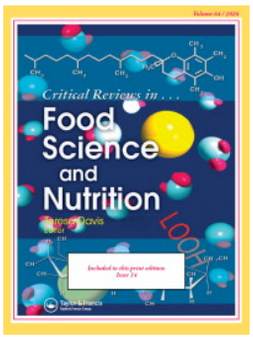


Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/bfsn20

Alzheimer, Parkinson, dementia, and phytochemicals: insight review

Basak Can & Nevin Sanlier

To cite this article: Basak Can & Nevin Sanlier (08 Jan 2024): Alzheimer, Parkinson, dementia, and phytochemicals: insight review, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2023.2299340

To link to this article: https://doi.org/10.1080/10408398.2023.2299340

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2023.2299340

Alzheimer, Parkinson, dementia, and phytochemicals: insight review

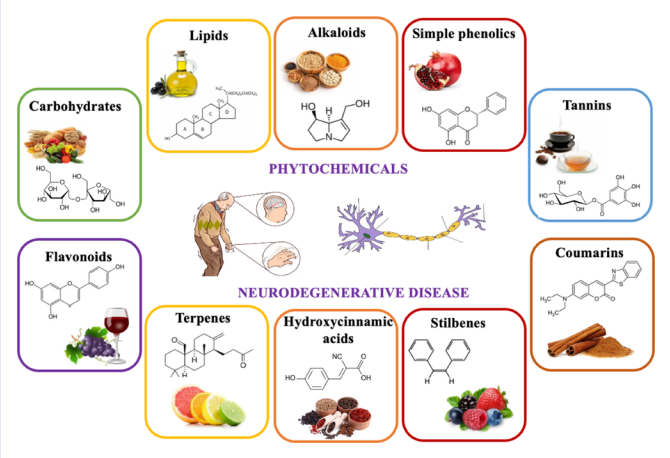
Basak Can[a] and Nevin Sanlier[b]

[a]Nutrition and Dietetics, School of Health Sciences, Istanbul Gelisim University, Istanbul, Turkey; [b]School of Health Sciences, Nutrition and Dietetics, Ankara Medipol University, Ankara, Turkey

ABSTRACT

Alzheimer's, Parkinson's, and dementia are the leading neurodegenerative diseases that threaten the world with the aging population. Although the pathophysiology of each disease is unique, the steps to be taken to prevent diseases are similar. One of the changes that a person can make alone is to gain the habit of an antioxidant-rich diet. Phytochemicals known for their antioxidant properties have been reported to prevent neurodegenerative diseases in various studies. Phytochemicals with similar chemical structures are grouped. Accordingly, there are two main groups of phytochemicals, flavonoid and non-flavonoid. Various *in vitro* and *in vivo* studies on phytochemicals have proven neuroprotective effects by increasing cognitive function with their anti-inflammatory and antioxidant mechanisms. The purpose of this review is to summarize the *in vitro* and *in vivo* studies on phytochemicals with neuroprotective effects and to provide insight.

GRAPHIC ABSTRACT



KEYWORDS

Alzheimer; dementia; Parkinson; phytochemical

Introduction

Age is determined to be a critical factor in the development of neurological diseases, and cognitive decline and memory impairment develop with increasing age (Scheiblich et al. 2020). The prevalence of neurodegenerative diseases (NDDs) increases as the population gets older because they are more common in the old age population. Neurodegenerative disorders prevalent in older adults include Parkinson's disease (PD), Alzheimer's disease (AD), AD-related dementias (ADRD), and movement disorders in PD patients (Velmurugan et al. 2018). Neuronal dysfunction, progressive loss of neurons, mitochondrial dysfunction, and accumulation of aggregated proteins are involved in the common pathogenesis of these diseases (Velmurugan et al. 2018; Wang et al. 2018a).

Inflammation and oxidative stress are also important factors that exacerbate nerve injury (Li, Feng, et al. 2021). Oxidative damage that accumulates in the body with increasing age is due to the increased production of free radicals. Production of oxidants increases under pathophysiological conditions and with age (George et al. 2022). The age-related increase and accumulation of oxidants can lead to an impairment of cellular functions due to a decrease in the intracellular level of adenosine triphosphate (ATP). It has been reported that the brain, which has a high level of oxygen consumption, is impressible to damage from reactive oxygen species (ROS) due to high concentrations of metals and iron and a low antioxidant capacity (Heitman and Ingram 2017). Neuronal systems are therefore among the first systems affected by oxidative damage (George et al. 2022).

CONTACT Nevin Sanlier nevintekgul@gmail.com, nevin.sanlier@ankaramedipol.edu.tr

Neuroinflammation is a pathological factor in Parkinson's and Alzheimer's diseases. And also neuroinflammation is mainly carried out by microglial cells, which are the macrophages of the central nervous system (Chesworth et al. 2021). Chronic inflammation is characterized by high circulating levels of inflammatory cytokines such as interferon (IFN), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, IL-8, IL-13, transforming growth factor-β (TGF-β), and c-reactive protein (CRP). It causes chronic diseases with molecular, cellular, and organ damage and accelerates the aging process (Zhu, Du, and Xu 2018; Zhang, Virgous, and Si 2019).

A neurodegenerative disease known as Alzheimer's disease (AD) is characterized by chronic neuroinflammation brought on by the buildup of the proteins amyloid beta protein (A) and hyperphosphorylated tau protein. Neuroinflammation and typical microglial activation have been identified as important mechanisms underlying AD, leading to neurological dysfunction and disease progression (Wang et al. 2023a). Neuronal inclusions in the form of Lewy bodies and Lewy neurites, which represent cell loss in the *Substantia Nigra* and other brain regions, are correlated with Parkinson's disease. Since aggregated and misfolded species of α-synuclein are the main constituents of Lewy bodies, Parkinson's disease is classified as a synucleinopathy (Tolosa et al. 2021).

During the aging process, chewing and swallowing problems, sensory loss and medication use can lead to differences in the nutritional needs of older people and inadequate nutrient intake. This makes older people more vulnerable to a variety of diseases, in particular neurodegenerative diseases, or to the progression of existing diseases (Mattioli et al. 2020). It has been shown that phytochemicals, which are naturally found in foods and known as bioactive compounds, have antioxidant and anti-inflammatory properties, as well as preventive or protective in the development of the aging process and neurodegenerative diseases (Hannan et al. 2020). The preventive and protective properties of the diet against neurodegenerative diseases may be due to antioxidant mechanisms (Kato et al. 2018). The Mediterranean diet which is associated with healthy aging and is a high source of antioxidants and rich in phytochemicals is one of the successful neuroprotective diets (Capurso, Crepaldi, and Capurso 2020). The Mediterranean diet is rich in bioactive compounds such as polyphenols, omega-3 fatty acids, fiber, phytosterols, and antioxidants, and includes fish, unrefined cereals (Alì et al. 2021), fruit, vegetable, nuts, milk, and legumes reported to be beneficial in the prevention of cognitive disorders (Román et al. 2019). It is defined as a diet rich in antioxidants with various phytochemicals (Capurso, Crepaldi, and Capurso 2020). The neuroprotective effects of the Mediterranean diet are explained by the following mechanisms: (i) its ability to decrease inflammation and oxidative stress with vascular properties; (ii) the superiority of vegetable, alcohol, fish, and monounsaturated fatty acids (MUFAs) over saturated fatty acids; (iii) cardiovascular protection, reducing the risk of comorbidities such as dyslipidemia, hypertension, coronary disease, metabolic syndrome and obesity (Dohrmann et al. 2019).

Phytochemicals have a protective role due to their antioxidant activity, which is associated with the overproduction of oxidants in the human body. Dietary non-enzymatic antioxidants and enzymatic antioxidants, which are biologically synthesized in the body, protect cells from oxidative damage by scavenging free radicals, quenching singlet oxygen, and chelating metal ions (Borsoi et al. 2022). Phytochemicals can fight neurodegenerative diseases due to aging with their antioxidant properties. For instance, polyphenols, characterized by the presence of cyclic benzene compounds, have antioxidant and anti-inflammatory effects and provide hormonal estrogen activity, metal chelation, and regulation of gene expression and cell signaling pathways (Román et al. 2019). Dietary antioxidants include sulfur-containing plant antioxidants of low molecular weight, such as carotenoids and phenols, or phenolic antioxidants of high molecular weight, such as tannins (Shunan et al. 2021). Remarkably, polyphenols are able to both modulate gene expression and alter epigenetic changes, suggesting that they play a critical role in preventing and/or developing certain pathologies (Borsoi et al. 2022). Therefore, this review examined the neuroprotective effects of dietary phytochemicals on neurological diseases such as Alzheimer's disease, Parkinson's disease, and dementia.

Phytochemicals

According to their chemical structures, phenolic compounds are divided into organo-sulfides, betalains, protein inhibitors, terpenes, indoles/glucosinolates/sulfur compounds, and other organic acids (Zhang, Virgous, and Si 2019). Phytochemicals contribute to the prevention of neurodegenerative diseases by reducing reactive oxygen species with the antioxidants they contain (Zheng et al. 2021). Figure 1 shows the classification of major phytochemicals (Wang et al. 2021; Alì et al. 2021; Santhiravel et al. 2022; Al-Khayri et al. 2023).

Flavonoids and non-flavonoids (phenolic acids, stilbenes, lignans, non-phenolic metabolites, and other polyphenols), which together make up more than 8000 different chemicals, are the two primary categories of polyphenols) (Singla et al. 2019). Flavonoids, such as flavonols, flavanonols, flavanones, flavones, isoflavones, flavonols, anthocyanins, and anthocyanidins, are natural antioxidants capable of scavenging free radicals (Durazzo et al. 2019; Singla et al. 2019). Phytochemicals may be present in foods as crude extracts or in complex forms. Examples of complex forms include phenolic acids, usually in the form of polyol esters, flavonoids, stilbenes, and lignans in the form of glycosides (Zamora-Ros et al. 2016). The leading phenolic acids found in food are p-coumaric, caffeic, ferulic, and synaptic acids. Quercetin, myricetin, and catechin are the most common phytochemicals in the flavonoid group, while resveratrol is the most studied stilbene structure (Griñán-Ferré et al. 2021). Table 1 shows detailed dietary sources of most phytochemicals.

Alzheimer's disease

Alzheimer's disease is an age-related evolving neurodegenerative disorder associated with mild cognitive impairment

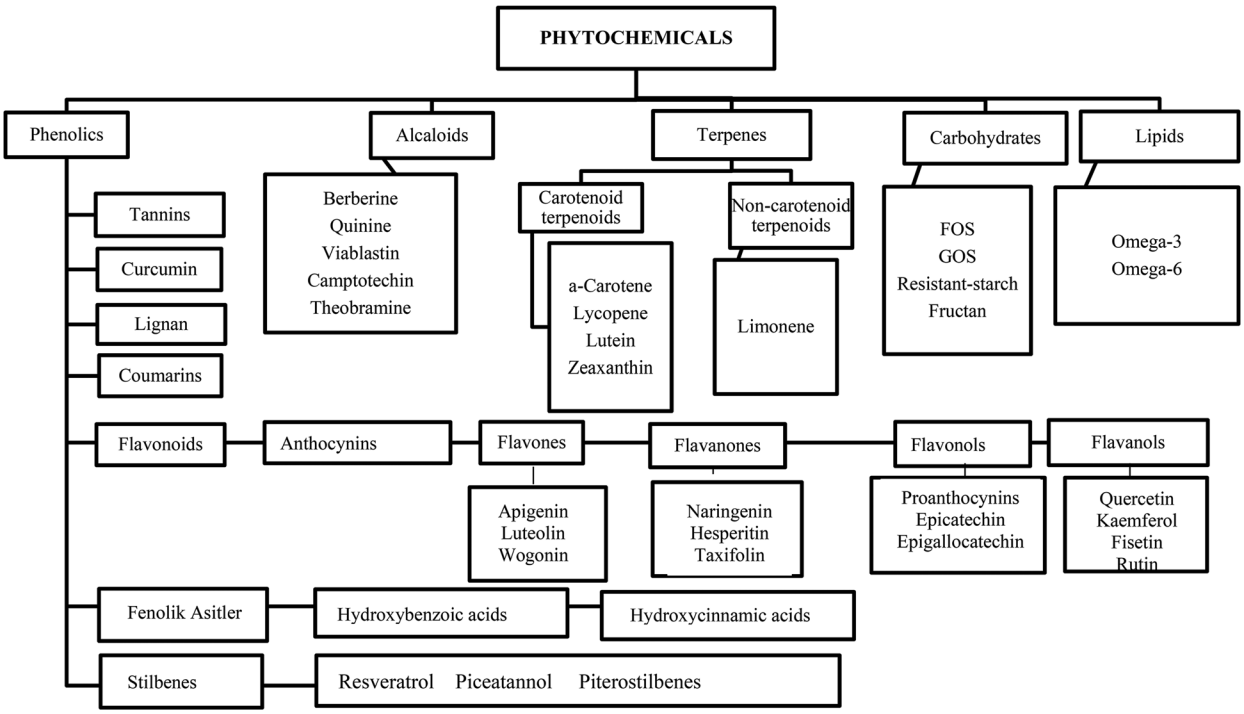


Figure 1. Classification of phytochemicals (Wang et al. 2021; Alì et al. 2021; Santhiravel et al. 2022).

and dementia (Voulgaropoulou et al. 2019; Taslimi et al. 2020), accounting for approximately 60–70% of dementia cases (WHO 2021a). The Alzheimer's Disease International (ADI) Association reports that 75% of patients with dementia are undiagnosed worldwide, and this figure is as high as 90% in some low- and middle-income countries. The latest estimates are that the number of people with dementia will rise to 139 million by 2050 (ADI. 2022). There is currently no known treatment for AD, the fifth leading cause of death worldwide, but several risk factors have been identified. Age is an important determinant in the incidence of AD. It is four times more common at age 80 than at age 70, and nine times more at age 65 (Kunkle et al. 2021).

Although the pathogenesis of AD remains incompletely understood, several mechanisms have been reported to have a role in this process. These mechanisms are neuritic plaques forming by the aggregation of Aβ protein and neurofibrillary tangles (NFTs) forming by the accumulation of phosphorylated tau protein (George et al. 2022; Li et al. 2023a). The Aβ protein is a peptide that is cleaved from the amyloid precursor protein (APP), an embedded protein at the plasma membrane. Aβ fibrils formed by misfolding then aggregate and accumulate into plaques that can disrupt effective synaptic signaling between neurons (Hartman and Ross 2018; Yang, Wang, and Zheng 2018; George et al. 2022). The production of Aβ peptides occurs through the cleavage of APP by β- and γ-secretases and is referred to as the amyloidogenic pathway (Wang et al. 2020; Yang et al. 2023). The Aβ monomers are produced to ensure the survival of neurons and protect mature neurons from excitotoxic death (Chen et al. 2018; Yang et al. 2023). APP is cleaved by α-secretase in the non-amyloidogenic pathway (Wang et al. 2020), so Aβ production does not occur (Wang et al. 2020). The inability to produce Aβ as a result of APPs that cannot be cleaved causes cellular damage. Free radicals have also been reported to contribute to this damage. Damaged neurons play a role in maintaining cognitive impairment (Yang, Wang, and Zheng 2018; Yang et al. 2023).

Tau is a highly soluble cytosolic protein commonly found in neurons. It is involved in axonal transport, DNA stabilization, and the stabilization of microtubules that support synaptic function. The accumulation of highly phosphorylated tau protein is expected to polymerize into insoluble neurofibrillary tangles. These tangles can affect many neuronal locations, including stabilizing the cytoskeleton, disrupting axonal transport and cell signaling, impairing protection against DNA damage, and damaging dendritic functions. These cellular perturbations are often associated with the reduced neuronal activity and cell death seen in AD, so reducing phosphorylated tau has been a therapeutic target (Naseri et al. 2019). Hyperphosphorylation of tau proteins causes the formation of neurofibrillary tangles, resulting in intramolecular fibrosis, inflammation, and oxidative damage in the brain. By reason of NFTs, which lead to disruption of axonal transport and microtubules, gliosis is induced and inflammatory damage is exacerbated (Li, Feng, et al. 2021). It has been reported that all of these pathological factors work together, NFTs and Aβ trigger the formation of pro-inflammatory processes and free radicals, and pro-inflammatory cytokines and free radicals trigger the formation of NFTs and Aβ. Thus, a vicious cycle between NFTs, Aβ, inflammation, and oxidative stress has been reported. Both inflammatory processes and oxidative damage are commonly observed at sites of neurodegeneration (Chen et al. 2018) and are among the factors that affect the onset and progression of neurodegeneration.

Table 1. Food sources of various phytochemicals (Zhu, Du, and Xu 2018; Al-Khayri et al. 2023).

Phytochemicals		Foods
Extract	Procyanindine extract	Grape seeds
	Citrus peel extract	Citrus
	Acetone extract	Black bean
	Ethanol extract	Bitter bean
	Ethyl acetate extract	Chinese pear
	Aqueous extract	Mung bean
Phenolic Acid	Capsaicin	Ginger, curry, leek, green onion
	Chlorogenic Acid	Coffee, most fruits, and vegetables
	Ferulic Acid	Grains such as oats, corn, rice
	Zerumbone	Ginger
	3-O-Methyl Kaempferol	
	Punicalagin, Punicalin, Strictin A	Pomegranate
	Garnet B	
	Narirutin	Citrus
	Flavon velutin	Acai berry
Triterpenoids	Monomeric compounds	Pear
	Pentacyclic triterpenoids	Apple
Flavonoids	Apigenin, Luteolin and Wogonin	Herbs such as parsley, rosemary, thyme, cereals, chamomile, celery, mint, and *Ginkgo Biloba*
	Quercetin	Red and yellow vegetables and fruits, onions, cabbage, cauliflower grapes, cherries, French bean, apples, and grains
	Naringenin	Citrus
	Taxifolin	
	Eriodictyol	
	Flavonols (Kaempferol, Fisetin, Myricetin, Isorhamnetin, Silymarin, Rutin)	Saffron, tomatoes, lettuce, apples, grapes, fruits, onions, cabbage, red wine, and tea
	Curcumin	Turmeric
	Flavanols (Catechins)	Green tea, cocoa fruit
	Epicatechin	Black and green tea and fruits, such as bananas, peaches, blueberries, apples, and pear
	Epigallocatechingallate (EGCG)	
	Gallocatechin	Some legumes, grapes, and wine seeds
	Anthocyanins and Glycosides	Fruits and vegetables, red wine, strawberries and red grapes
	Flavones	Leguminous crops, especially soy and soy products
	Malvidin	Merlot grapes, red grapes, blueberries, raspberries, strawberries, cranberries, blueberries, and blackberries
	Procyanidin	
	Cyanidin	
	Delphinidin	
	Peonidine	
Saponinler	Isoflavones (Genistein, Daidzein, Glycetein)	Tofu, roasted soybeans, miso
	Soy Saponins	Soybean
	Angularin A, Angulasaponins A-C And Azukisaponins III and VI	Adzuki bean
Lectin	Lectin	Butterfly bean
Stilben	Resveratrol	Grapes, wine
Lignans	Plant Lignans	Flaxseed has the highest content, whole grains, asparagus, vegetables, and tea
	Indole and Derivatives	Vegetables
Alkaloids	Caffeine	Coffee
Organic Sulfur	Isothiocyanate	Cruciferous vegetables such as cabbage, Brussels sprouts, broccoli, and cauliflower
	Glucosinolate, Isobisulfate	Some cruciferous sprouts (broccoli and cauliflower, bok choy, radishes)
	Allyl Sulfur	Onions, spring onions, leeks, and chives
	Coumarin Derivatives	Coumaric acid and chlorogenic acid in tomatoes, strawberries, pineapple, and green peppers
Carotenoids	β-Carotene	Orange and yellow vegetables and fruits
	Lutein and Zeaxanthin	Dark green leafy vegetables
	Lycopene	Tomato, watermelon, pink grapefruit, apricot, and pink guava
Phytosterol	Stigmasterol, Sitosterol and Campesterol	Oilseeds, unrefined vegetable oils, whole grains, nuts and legumes
Fiber	Cellulose, Hemicellulose, Lignin, Inulin	Whole Grains

The oxidation mechanisms of Aβ aggregates have been shown to include radical formation by iron or copper binding and superoxide stimulation. Superoxide anion (O_{2^-}), hydrogen peroxide (H_2O_2), and hydroxyl radical (HO) are important free radicals involved in neurodegeneration. In addition, nitric oxide, which reacts with hydrogen peroxide and contributes to the production of peroxynitrite (ONOO-), is also effective in the development of oxidative damage (Jurcau 2021).

The disease is associated with progressive neuronal loss, synaptic degeneration, brain atrophy, gliosis, and leukoaraiosis (Hartman and Ross 2018; Li, Hatano, and Hattori

2021; Wang et al. 2021). Also, several molecular changes are observed in aging individuals. These changes include a defect in the primary proteolytic mechanism for abnormal clearance proteins, including the ubiquitin-proteasome system (UPS), Aβ, and tau proteins. To ameliorate the defects in mechanisms in various AD models, phytochemicals may be critical agents for both the prevention and treatment of neurodegenerative diseases characterized by the accumulation of abnormal proteins. For example, resveratrol up-regulates the activity of the proteasome in AD models, restoring the functionality of the UPS and playing a crucial role in both the prevention and treatment of neurodegenerative diseases characterized by the accumulation of abnormal proteins (Griñán-Ferré et al. 2021). Besides age, several behavioral risk factors including excessive alcohol consumption, smoking, and physical inactivity have been regarded as behaviors causing the development of AD (Li et al. 2023a). Additionally, dietary studies have shown that a bad dietary pattern increases the incidence of obesity, hypertension, and diabetes, whereas a healthy dietary pattern may protect against AD and perhaps cause learning and memory impairment (Cremonini et al. 2019; Hill et al. 2019; Jin et al. 2021; Wesselman et al. 2021). It is predicted that phytochemicals, which have been proven in various studies in the literature, may be a therapeutic approach for Alzheimer's disease, considering that diet modulates the immune system and different nutrients and bioactive compounds may influence neuroinflammation (Wang et al. 2020; Decandia et al. 2023).

Phytochemicals and alzheimer's disease

Phytochemicals have a number of important biological and health-promoting effects. Polyphenols are the most abundant form of secondary metabolites and have a major antioxidant activity that prevents the progression of the disease. Phenolic acids, which are abundantly found in coffee, tea, whole cereals, strawberry, and nuts, are defined as one of the main classes of polyphenols (Szwajgier, Borowiec, and Pustelniak 2017). Phenolic acids and polyphenols, a group of plant-derived compounds widely represented in the common diet, have been reported to apply neuroprotective effects on the brain against oxidative stress, inflammation, abnormal protein aggregation, and chronic immune cell activation through a combination of antioxidant, anti-inflammatory, antiapoptosis and anti-aggregation activities (Caruso et al. 2022).

Capsaicin, one of the major phenolic acids, naturally occurs, is derived from plants of the genus Capsicum, known as chili peppers, and belongs to the *Vanilloid* compound family. It is a bioactive phytochemical abundant in red and chili peppers. 100 g of edible red pepper contains 8.81 g carbohydrate, 1.87 g protein, 88 g water, 1.50 g pulp, 534 µg beta-carotene, 1.24 mg niacin, 144 mg ascorbic acid, and 43 mg phosphorus (USDA. 2019; Batiha et al. 2020). Native to South America, it is reported that a quarter of the world's population consumes red pepper on a daily basis (Wang et al. 2022a). Capsaicin is absorbed from the stomach and intestine by inactive transport and serum concentrations peak approximately 1 h after ingestion (Pasierski and Szulczyk 2022). Capsaicin consumed with food is absorbed by non-active transport and approximately 5% of capsaicin passes into the portal vein and from there to the whole body and to brain tissue by crossing the blood-brain barrier (Wang et al. 2021). Transient receptor potential vanilloid 1 (TRPV1) channels are activated by capsaicin, according to a commonly reported mechanism of action (Pasierski and Szulczyk 2022). It has been reported that TRPV1 located in various parts of the brain (Liu et al. 2020) affects brain neurons and glial cells through dependent and independent mechanisms, and capsaicin, an agonist of TRPV1, has a role in increasing energy expenditure, vasodilator effect in vessels and scavenging of free radicals (Xu et al. 2017) protects against oxidative stress, which is responsible for the development of neurological and other age-related diseases. Many different beneficial effects of capsaicin in neurodegenerative diseases, epilepsy, stroke, and depression have been described in animal and human studies (Xia et al. 2021; Wang et al. 2022b). In one study, capsaicin was found to reduce excitotoxin-induced production of nerve growth factor A and the proinflammatory cytokines IL-1β and IL-6 in brain tissue (Kilinc et al. 2023). In another study, it was found that capsaicin intake reduced brain Aβ protein accumulation in APPswe/PS1dE9 (APP/PS1) mice by stimulating ADAM10 production by shifting the APP process toward α-cleavage. Capsaicin intake also inhibited neurodegeneration, hyperphosphorylation, and neuroinflammation of tau (Wang et al. 2020). The levels of phosphorylated tau protein were found to significantly reduce at Ser199, Ser202 and Ser396 sites in the hippocampus of type 2 diabetic rats fed a high-fat diet with capsaicin treatment, while no significant difference was reported in non-diabetic rats (Xu et al. 2017).

Other phenolic acids with neurodegenerative effects reported in the literature are chlorogenic acid and ferulic acid. Chlorogenic acid is a phenolic acid component and it has antioxidant, anti-inflammatory, and neuroprotective properties (Saitou et al. 2018; Yang, Wang, and Zheng 2018; Gao et al. 2020; Jurcau 2021). Both caffeinated and decaffeinated coffee contains high levels of chlorogenic acid. According to reports, one cup of coffee contains 70–350 mg of chlorogenic acid. The neuroprotective effects of regular coffee consumption have been attributed to chlorogenic acid, which is characterized as a polyphenol found at high levels in coffee (Saitou et al. 2018). In addition to chlorogenic acid, coffee also contains neuroprotective components. For example, chlorogenic acid lactones, caffeic acid, kahweol, and cafestol may also have neuroprotective effects (Kim, Robinson, and Newman 2022).

Chlorogenic acid and caffeine can reduce β-amyloid accumulation and prevent beta-amyloid-induced neurotoxicity in cerebral neurons (Socała et al. 2020). In addition, caffeine is said to have a therapeutic effect on Alzheimer's disease because it is a potent anti-inflammatory agent, antioxidant, mitochondrial activator, neuronal activator, and stimulator of glucose use (Ruiss, Findl, and Kronschläger 2022). Various studies have reported that treatment of 5-caffeoylquinic acid, the most abundant component of coffee polyphenols, significantly reduces Aβ plaque formation and neuronal loss in the hippocampus (Kim et al. 2019; Ishida et al. 2020a; Ishida

et al. 2020b). Another study revealed that coffee treatment reduced biochemical factors such as lipid peroxidation markers and TNF-α. In addition, the coffee treatment prevented the decrease in total antioxidant concentration levels (Sedaghat et al. 2019). Haller and colleagues also found that chronic coffee consumption provided beneficial cognitive performance and its moderate-to-heavy consumption provided cognitive cerebral blood flow (Haller et al. 2018). Macroautophagy (autophagy) refers to a catabolic process that is active in amyloid-β (Aβ) deposition and the clearance of hyperphosphorylated tau proteins. In an *in vivo* and *in vitro* study using APP/PS1 mice, chlorogenic acid treatment was found to inhibit $A\beta_{25-35}$ induced autophagy by modulating lysosomal function. It has also been reported to be effective in reducing cognitive damage through activation of the mTOR/TFEB pathway (Gao et al. 2020). Despite its health benefits, the bioavailability of chlorogenic acid is low and only one-third of it enters the circulation (Yang, Wang, and Zheng 2018).

Seed crops such as wheat, oat, rice, and corn bran, fruits such as orange and pineapple, and vegetables such as carrot, eggplant, artichoke, and tomatoes are known to be the main sources of ferulic acid (4-hydroxy-3-methoxycinnamic acid) (Mori et al. 2019). With a low molecular weight, ferulic acid has high cell permeability and bioavailability. It is absorbed from the gastric mucosa and transported to the hepatic portal vein and then to the liver for metabolism (Mori et al. 2019). Ferulic acid has been identified as an effective scavenger of ROS and RNS, reducing the possibility of radicals attacking proteins and thus preventing oxidative changes. This ability is predicted to be based on its antioxidant and anti-inflammatory potential, and its ability to suppress leukotriene synthesis and reduce oxidative stress in the brain (Singh et al. 2022). In another study using epigallocatechin-3-gallate, an A- secretase activator, and ferulic acid, a β-secretase modulator, transgenic mice (12 months old) expressing Aβ protein precursor and presenilin 1 (APP/PS1) were given EGCG and/or FA (30 mg/kg each) once daily for 3 months. The combined treatment reduced Aβ protein levels and brain parenchymal and cerebral vascular β-amyloid deposits. It also reduced synaptoxicity, oxidative damage, and neuroinflammation (Mori et al. 2019). Numerous models of neuroinflammation have been used to extensively illustrate the anti-inflammatory properties of ferulic acid in the nervous system. In Alzheimer's disease, activated microglia-mediated neuronal immunity causes neurodegeneration (Dong and Huang 2022). One study found that phosphodiesterase 4 activity stabilized LPS-induced upregulation and reversed LPS-induced downregulation of CREB and pCREB. Accordingly, it was reported that ferulic acid may be a therapeutic intervention tool for the treatment of neuroinflammatory diseases (Huang et al. 2016).

Resveratrol, catechins, berberine, and curcumin belong to the group of flavonoids, and epidemiological studies are increasing day by day showing a link between their consumption and the prevention of Alzheimer's disease (Calderaro et al. 2022; Sajad, Kumar, and Thakur 2022). Flavonoids are composed of a 15-carbon skeleton containing two benzene rings (A and B) connected to each other by a heterocyclic pyran ring (C). Among polyphenols, more than 8000 are classified as flavonoids (Al-Khayri et al. 2023). Subgroups of flavonoids include flavones (apigenin, chrysin, diosmetin and luteolin), flavonols (kaempferol, myricetin, quercetin and rutin), flavones (hesperidin, naringin and neohesperidin), flavols (catechin, epicatechin, gallocatechin epigallocatechin gallate, procyanidin and tea flavins), flavonolignans (silymarin), anthocyanidins (cyanidin, malvidin, pelargonidin) and isoflavones (genistein, daidzein) (Evans, Mendonca, and Soliman 2022). Anti-inflammatory flavonoids can reduce the activity of cytokine, chemokine, and inflammatory enzymes by interacting with many molecules involved in inflammatory pathways (Al-Khayri et al. 2023). Flavonoids have been shown to have positive effects on cognitive function by reducing synaptic dysfunction, preventing changes in protein processing, activating neurotrophic signaling pathways, and inhibiting oxidative and inflammatory processes (Maher 2019). An epidemiological study found that individuals who consumed the most flavonols, anthocyanins, and flavonoid polymers had a lower risk of ADRD than those who consumed the least. A similar trend for AD was found for flavonols and anthocyanins, but not for flavonoid polymers (Shishtar et al. 2020). Dietary intake of flavonoids is estimated to be 200–350 mg/day (Khan et al. 2019).

Apigenin (API), one of the major flavonoids, is naturally present in foods such as orange, parsley, onion, celery, thyme, basil, chamomile, wine, beer, and tea (Salehi et al. 2019). Many studies have reported that apigenin has potent anti-inflammatory, anti-carcinogenic, and antioxidant effects (Chen et al. 2017; Telange et al. 2017; Zhong et al. 2017). Several studies have shown that apigenin can prevent memory loss as a result of Alzheimer's disease. It has been reported that pretreatment with the API can significantly improve long-term memory, improve learning and memory abilities, and ameliorate neurovascular oxidative damage by reducing the levels of pCREB and tropomyosin receptor kinase B (TrkB) (Nabavi et al. 2018). Another study found that apigenin treatment did not affect the development of spatial memory, although it significantly reduced microglial activation (Chesworth et al. 2021). Ginwala et al. found that apigenin treatment decreased the mRNA and protein levels of RelB, an NF-κβ pathway protein, and controlled the regulation of dendritic cell activity (Ginwala et al. 2021).

Luteolin (3′,4′,5,7-tetrahydroxy flavones), found in vegetables such as celery, thyme, mint, and parsley, has been reported to have antioxidant, anti-inflammatory, and neuroprotective properties (Kwon 2017). Another study reported that luteolin treatment improved spatial learning and inhibited neuroinflammation (NO, TNF-α, IL-1β, IL-6, COX-) in rats with AD (Kou et al. 2022). The mechanism by which luteolin reduces neuroinflammation is due to its role as a scavenger of oxygen and nitrogen species, which are associated with a variety of pharmacological and antioxidant properties (Islam et al. 2022). In another study, it was found that luteolin activated neuronal cell-extracellular signal-regulated kinase (ERK1/2) and enhanced the Nrf2 pathway (Calis, Mogulkoc, and Baltaci 2020; Uddin et al. 2020). It also reduces neuroinflammation by suppressing the activation of

NF-kB, signal transducer and transcription 3 (STAT3), c-Jun N-terminal kinases (JNK), p38 and extracellular signal-regulated kinases 1/2 (ERK1/2), which play a role in glial cell activation and inflammatory mediator release (Kempuraj et al. 2021). Furthermore, luteolin has been reported to suppress lipopolysaccharide (LPS) -induced IL-1β expression by inhibiting endoplasmic reticulum (ER) stress, thus AD model ameliorating depression-like behaviors in mice (Nakagawa 2022). Similar to the current study, luteolin was found to protect dopaminergic neurons by inhibiting microglial activation in LPS-induced neuroinflammation in *in vitro* environment (Kempuraj et al. 2021).

Berberine is an isoquinoline alkaloid that can be extracted from the rhizome, stems, roots, and bark of the Berberis plants, *Hydrastis canadensis,* and *Coptis chinensis*. Berberine has the ability to pass through the blood-brain barrier and act directly on neurons, which can activate Akt/GSK-3/Nrf2-mediated regulation, which can safeguard neurons. It can also reduce TNF-α, COX-2, andIL-1 and induce NGF and brain-derived neurotrophic factor (BDNF) secretion (Islam et al. 2022). It also shows that berberine destroys misfolded proteins, which exert neurotoxic effects (Rusmini et al. 2020). In Alzheimer's disease, berberine has been shown to improve cognitive function in mice by reducing tau hyperphosphorylation and promoting autophagic clearance of tau (Chen et al. 2020). Berberine has the capability to regulate mitochondrial bioenergetics *in vitro*, reduce the malfunction of primary energy and glutathione metabolic pathways, inhibit basal respiration, and decrease the production of proinflammatory cytokines. In addition, berberine and pioglitazone (an oral antidiabetic drug) have similar binding affinity for the peroxisome proliferator-activated receptor gamma (PPARγ) protein and overlapping effects on Alzheimer's disease (Wong et al. 2021).

Quercetin, whose dietary intake is approximately 10–16 mg/day, is found in edible plants such as watercress, asparagus, coriander, onion, lettuce, various fruits, and nuts. The dose of quercetin aglycone, which has antioxidant properties and is recommended as a dietary supplement, is reported to be 1 g/day (Khan et al. 2019; Jurcau 2021). The antioxidant and chelating effects of quercetin are attributed to its A-ring free hydroxyl group and B-ring catechol groups (Zaplatic et al. 2019). Its capacity to lessen oxidative stress by scavenging free radicals has been shown to have neuroprotective effects (Wang et al. 2021). The blood-brain barrier is responsible for protecting brain integrity by regulating cell permeability in the brain endothelium (Zaplatic et al. 2019). The studies have reported that quercetin treatment at various amounts and durations improves memory loss (Nakagawa et al. 2016) and Aβ protein-induced learning impairment (Li et al. 2017) and alleviates neuroinflammation by inhibiting the expression of inflammatory markers such as TNF-α, IL-1β, IL-6, COX (Bahar, Kim, and Yoon 2017). In their study, Jain et al. found that quercetin treatment significantly reversed altered memory in mice, with reduced spontaneous changes in the Y and T maze tests and reduced exploration time in novel object recognition, increased immobility time, and reduced muscle strength in the forced swimming test (Jain et al. 2022). Another study reported that quercetin treatment attenuated pro-inflammatory mediators in the brain and reduced cell degeneration and death (Olayinka et al. 2022). As shown by various literature reviews, the possible beneficial effects of quercetin on memory are activation of Nrf2-ARE, ERK/CREB/BDNF, Akt, AMPK signaling pathways or NMDA receptors and inhibition of Ask/JNK/Jun, RAE signaling pathway and PP2Ca (Dong et al. 2017; Babaei, Mirzababaei, and Nassiri-Asl 2018; Zhang et al. 2020a). In a study using fibrillar Aβ1–40 ($fA\beta_{1-40}$) induced brain microvascular endothelial cells (hBMECs), the protective effects of quercetin were investigated and it was found that Aβ1-40 cytotoxicity, ROS generation, and lactate dehydrogenase release were reduced in a dose-dependent manner, superoxide dismutase (antioxidant enzyme) increased, nuclear damage was corrected and barrier integrity was improved (Li et al. 2015). A systematic review including animal studies revealed that quercetin showed consistent neuroprotective effects in AD models (Zhang et al. 2020b). This suggests that by reducing inflammation and free radical stress and promoting neurogenesis, quercetin may serve as a crucial therapeutic agent against multiple NDDs. The indirect and direct antioxidant activity and metal-chelating capacity of quercetin play an important role in attenuating neuronal damage. Its anti-inflammatory property has also been proven to be neuroprotective due to its tendency to modulate the expression of pro-inflammatory chemokines and cytokines (Chiang, Tsai, and Wang 2023). Furthermore, quercetin is a potential drug with minimal toxicity for the treatment of neurodegenerative diseases due to its potential to anti-aggregate and degrade defective proteins such as α-synuclein and Aβ-peptide. Finally, quercetin has been reported to have a beneficial effect in reversing or preventing memory loss associated with aging and NDD (Grewal et al. 2021).

Curcumin (phytopolylphenol) is a phytochemical with antioxidant, anticancer, anti-inflammatory, and anti-amyloidogenic properties from Curcuma longa (Zingiberaceae) (Choudhari et al. 2019; Sajad, Kumar, and Thakur 2022). In Alzheimer's disease, glial activation and cytokine production in the damaged area of the brain have been reported as a result of neuroinflammation, and curcumin has been reported as an anti-inflammatory compound with properties to inhibit these functions (Chen et al. 2018; Ullah et al. 2022). Its anti-inflammatory activities include inhibition of TNF-α or IL-1, −2, −6, −8, and −12, NF-κB, and suppression of inflammatory enzymes such as NOS and COX-2 (Voulgaropoulou et al. 2019). It promotes anti-inflammatory effects *via* a number of inflammatory signaling pathways, including the Toll-like receptor-4 (TLR-4) pathway. Activation of TLRs initiates the signaling cascade leading to activation of the NF-κB transcription factor, a transcription factor required for the expression of many inflammatory cytokines, including TNF-α and interleukin. Curcumin administration has been reported to attenuate the TLR4/NF-κB inflammatory signaling pathway (He et al. 2020; Ullah et al. 2022). It has also been reported to scavenge free radicals (ROS and RNS), regulate the activity of antioxidant enzymes such as superoxide dismutase (SOD), reduce ROS-generating

enzymes such as COX and xanthine oxidase (Jurcau 2021), and inhibit LPS-induced microglial activation (Zhang, Virgous, and Si 2019; Zhang et al. 2019b). Curcumin also plays a role in the clearance and inhibition of tau tangles and neurotoxicity (Sajad, Kumar, and Thakur 2022). In both *in vitro* and *in vivo* studies, curcumin has been found to significantly reduce oxidative stress and systemic inflammation and to inhibit pathways that activate transcription factors that increase these processes (Sarker and Franks 2018). Although it can cross the blood-brain barrier, its disadvantages include poor absorption, low solubility, rapid metabolism, and excretion (Voulgaropoulou et al. 2019). In animal models, curcumin's anti-Alzheimer's potential has been linked to its ability to cross the blood-brain barrier. Thus, it has been reported to prevent Aβ aggregation and protect neurons from Aβ-induced toxic insults (Reddy et al. 2018). The methoxyphenyl group in the structure of curcumin may help suppress pathogenic mechanisms in Alzheimer's disease by exhibiting chelating activity with iron and other metals (Sajad, Kumar, and Thakur 2022). In a study investigating the relationship between curcumin and gut microbiota in APP/PS1 double transgenic mice, curcumin reduced amyloid plaque burden and improved spatial learning and memory abilities in the hippocampus. It has also been shown that curcumin can partially correct gut microbiota dysbiosis and increase the number of certain bacterial species that may play a role in the development of AD. In addition, it was shown that the gut microbiota can biologically convert curcumin into a number of metabolites that have been reported to have neuroprotective effects (Sun et al. 2020). The neuroprotective effects of curcumin have been observed in both *in vitro* and *in vivo* models of Alzheimer's disease. It has been shown to protect against Ap-induced mitochondrial and synaptic toxicity in the human neuroblastoma cell model SH-SY5Y (Vaiserman et al. 2020). Curcumin derivatives were also shown to be beneficial in Alzheimer's disease and to be novel potent inhibitors of tau protein or β-amyloid (Chainoglou and Hadjipavlou-Litina 2020). In another study, curcumin was found to increase cognitive function in humans by reducing Aβ accumulation, oligomerization, and tau phosphorylation in Alzheimer's brain (Shakeri et al. 2019). All these findings suggest that curcumin may be one of the most promising compounds for the development of Alzheimer's disease treatment.

Epigallocatechin (EGCG) is a catechin found in small amounts in green tea, tea leaves, and carob flour (Mori et al. 2019; Choudhari et al. 2019; Luo et al. 2023). It is also found in trace amounts in nuts such as hazelnuts and walnuts, and fruits such as cranberries and apples. It has metal-chelating, anticarcinogenic, anti-inflammatory, anti-obesity, anti-diabetic, and antioxidant properties (Mori et al. 2019; Youn, Ho, and Jun 2022). In green tea production, steaming and roasting techniques prevent the formation of oxidation and thus preserve polyphenols (Xing et al. 2019). Green tea polyphenols (GTPs) consist of epigallocatechin-3-gallate (EGCG), epigallocatechin, epicatechin, epicatechin gallate, and catechin (Nan et al. 2021). GTPs have shown neuroprotective effects in Alzheimer's disease with anti-inflammatory and anti-amyloidogenic properties (Bao et al. 2020; Luo et al. 2023). Several experiments have demonstrated that EGCG regulates amyloid precursor protein (APP) processing and consequently reduces Aβ deposition (Zhang et al. 2020b; Dong et al. 2021; Khalil et al. 2022). EGCG administration at various doses improved learning and memory functions by reducing BACE1 expression, tau hyperphosphorylation, and AchE activity in the Aβ 25–35 solution-injected rat model. In addition, free radicals were scavenged, especially at high doses of EGCG, resulting in improved memory (Nan et al. 2021; Özduran, Becer, and Vatansever 2023; Luo et al. 2023).

Anthocyanins are the glucosides of anthocyanidins, which are flavonoid derivatives that are produced *via* the phenylpropanoid pathway. They are found in all tissues of higher plants, including leaves, stems, roots, flowers, and fruits. The six dominant anthocyanidins found in food are cyanidin, delphinidin, pelargonidin, peonidin, petunidin, and malvidin (Khoo et al. 2017; Mattioli et al. 2020). They are found in dark-colored foods such as purple vegetables, fruits, and black cereals (Bergland et al. 2019; Hein et al. 2019; Li, Feng, et al. 2021). Anthocyanins are absorbed in the stomach by binding to bilirubin reductase and in the small intestine by active transport and passive diffusion, mainly in the jejunum. After SI absorption, bilirubin enters the enterohepatic circulation (Li, Feng, et al. 2021). Anthocyanins may alleviate AD symptoms by reducing oxidative stress and inflammation and increasing microglial viability. Anthocyanins also have a beneficial role in brain cells by protecting against neurotoxicity and DNA damage through the prevention of lipid peroxidation (Nimse and Pal 2015; Li, Feng, et al. 2021). Typically in neurons, ROS are induced by excessive glutamate exposure, leading to excitotoxic neuronal damage. Anthocyanins can suppress oxidative stress in the nervous system by directly scavenging ROS (Thummayot et al. 2014).

Hesperidin is a substance used in traditional Chinese medicine that is also present in tea, olive oil, and particularly citrus fruits. In numerous models of illnesses of the central nervous system (CNS), hesperidin has been demonstrated to have considerable antioxidant, anti-inflammatory, and neuroprotective properties (Li et al. 2023b). As a neuroprotective agent, hesperidin inhibits NF-κB signaling by the receptor for advanced glycation end-products (RAGE) and activates Akt/Nrf2 to suppress inflammation and oxidative stress (Hong and An 2018). In neurodegenerative models both *in vitro* and *in vivo*, hesperidin has been shown to protect neurons against toxicity and caused oxidative stress, inflammation, and the production of neurotoxic chemicals (Evans, Mendonca, and Soliman 2022). Yıldız et al. (2022) found that hesperidin reduced lipid peroxidation and increased SOD, CAT, and GPx activities and GSH levels in brain tissue. Another study revealed that hesperidin treatment prevented $AlCl_3$-induced cognitive deficits, biochemical abnormalities, and apoptosis (Justin Thenmozhi et al. 2017). TLR4-mediated glial cell-mediated antioxidant mechanisms mediate neuroinflammation and neurodegeneration. Hesperidin treatment, by improving TLR4-mediated ionized calcium-binding adaptor molecule 1/glial fibrillary acidic protein (Iba-1/GFAP) expression, significantly reduced

the expression of inflammatory cytokines. It also improved cognitive dysfunction in mice according to the Y maze tests and Morris water maze (Muhammad et al. 2019). Javed et al. (2015) found that hesperidin improved the memory consolidation process, possibly by modulating acetylcholine esterase (AChE) activity, and modulated neuronal cell death by inhibiting the overexpression of inflammatory markers such as NF-κB, and NOX, COX-2, and glial fibrillary acidic protein-positive astrocytes. Hesperidin promotes spatial memory performance by two main mechanisms. These mechanisms directly improve the synaptic connections between cortical neurons and the hippocampus, and they also indirectly do so by increasing TGF-1 secretion, which increases the cortical astrocytes' synaptogenic activity (Matias et al. 2017; Li et al. 2023b).

Stilbenes have many effects such as anti-cancer, anti-inflammatory, anti-aging, antioxidant, and anti-atherogenic effects. Resveratrol and pterostilbene are familiar monomeric stilbenes (Teka et al. 2022). Resveratrol (3,5,4′-trihydroxy-trans-stilbene), a polyphenolic stilbenoid (phytoalexin), is an important constituent of grapes and red wine. It is also found in foods such as strawberries and peanuts (Choudhari et al. 2019; Alì et al. 2021; Jurcau 2021; Sarroca et al. 2021; Grau, Soucek, and Pujol 2023). Resveratrol has been reported to have anti-inflammatory, antioxidant, anti-cancer, anti-aging and neuroprotective properties (Griñán-Ferré et al. 2021; Sarroca et al. 2021). Long-term (5 months) low dose (1.25 mg/rat/day) resveratrol administration was found to regulate down reduce the production of compounds involved in inflammatory and oxidative processes such as IL-6, NF-κB and TNFR2, NO, and ROS in the brain (Garrigue et al. 2021). However, resveratrol is known to have little activity against tau protein, which is associated with neurodegenerative diseases such as Alzheimer's and Parkinson's (Grau, Soucek, and Pujol 2023). One of the primary neuroprotective effects of resveratrol is its ability to inhibit NF-κB activity. It can reduce microglia-dependent Aβ toxicity by activating SIRT1 and inhibiting NF-κB and exerts neuroprotective effects by inhibiting the over-activation of microglia through the regulation of these pathways (Huang et al. 2021). It may also counteract the progression of brain aging by inducing mild stress (i.e., a hormetic response) in neural cells (Corbi et al. 2016). Furthermore, in a model of C8-B4 glial cell neuroinflammation directly induced by LPS, resveratrol inhibited the inflammatory cascade and protected the neuronal-like Neuro2a cell line in co-cultures (Steiner et al. 2016). The beneficial effects of resveratrol were attributed in part to the inhibition of p-STAT1 and Keap1 and the upregulation of Nrf2 and SLC7A11. It has been reported to provide neuroprotective effects by reducing inflammation and oxidative stress (Li, Shen, et al. 2021). A negative relationship between wine drinking and the risk of Alzheimer's disease has been discovered in several epidemiologic research. Resveratrol may have therapeutic effects on Alzheimer's disease, according to this theory (Chan et al. 2019; Sajad, Kumar, and Thakur 2022).

Pterostilbene (PTS) (trans-3,5-dimethoxy-40-hydroxystilbene) is a natural polyphenol and dimethyl ether analog of resveratrol found in foods such as grape, blueberry, and peanut. It has been documented that as a natural component of the diet, PTS has a higher bioavailability when compared to other stilbene compounds (Seo, Fischer, and Efferth 2018; Nagarajan et al. 2022). Several lines of evidence have demonstrated the efficacy of PTS, which provides preventive and therapeutic benefits in experimental disease models, in counteracting oxidative damage and inflammation (Chan et al. 2019; Nagarajan et al. 2022; Xu et al. 2022). Pterostilbene has the ability to heal age-related cognitive impairment. In one study, rats showed improved behavioral performance and memory consolidation through the treatment of pterostilbene (La Spina et al. 2019). Pterostilbene has no effect on SIRT1 expression and activation. However, in contrast to resveratrol, pterostilbene has been shown to have an effect on cognitive status, as assessed by the radial arm water maze in mice. It has also been reported to decrease 1) cellular stress, including manganese superoxide dismutase, an endogenous antioxidant defense protein; 2) inflammation, including peroxisome proliferation-activated receptor α-receptor; and 3) AD markers, including phosphorylated tau (Freyssin et al. 2020). Activated microglia can secrete a variety of pro-inflammatory factors, including cytokines, chemokines, ROS, reactive nitrogen species, and prostaglandins. It is believed that the prolonged secretion of these factors can lead to neuronal damage, which can further activate microglia and lead to a condition known as microgliosis. Treatment with resveratrol and pterostilbene has been shown to protect neurons from neuroinflammation by inhibiting ROS production (Poulose et al. 2015; Li et al. 2022a).

Carotenes found in yellow-orange vegetables and fruit such as melon, tomato, carrot, and apricot are defined as fat-soluble compounds and are reported as rich sources of vitamin A (Torregrosa-Crespo et al. 2018; Davinelli et al. 2021). Xanthophylls (lutein, zeaxanthin, and A and β-cryptoxanthin) and carotenes (α-carotene, β-carotene, and lycopene) are composed of two subclasses (Kim et al. 2017) and more than 700 have been identified, with lutein, zeaxanthin, β-cryptoxanthin, β-carotene, α-carotene, and zeaxanthin being the most abundant in human diet and serum (Davinelli et al. 2021). A lower incidence of heart disease, cancer, macular degeneration, and other ophthalmological illnesses is linked to consuming foods high in carotenoids (Sauer, Li, and Bernstein 2019; Park et al. 2020; Manochkumar et al. 2021). Recently, carotenoids have been shown to have anti-inflammatory, neuroprotective, and antioxidant properties that may be used to reduce the progression of AD (Liu et al. 2018). Carotenoids have been shown to suppress the onset of neurodegenerative diseases through various mechanisms. They regulate Aβ neurotoxicity, Aβ aggregation, impaired lipid metabolism, long-term neuroinflammation, OS, and mitochondrial dysfunction. As a result, processes associated with AD pathogenesis improve (Mohammadzadeh Honarvar et al. 2017; Kabir et al. 2022; Abd Al Haleem, Ahmed, and El-Naga 2023). In neurodegenerative diseases, multiple mechanisms of action of carotenoids may occur simultaneously. For example, in the AD rat model, lycopene consumption reduced

caspase-3 function, several inflammatory cytokine mediators, and Aβ-mediated mitochondrial dysfunction (Sachdeva and Chopra 2015). In addition, astaxanthin administration reduced Aβ-mediated damage in cultured cells through multiple mechanisms, including reduction of ROS, suppression of inflammatory cytokine mediators, and reduction of apoptotic factors (Xiang et al. 2017). Another study revealed a negative correlation between higher carotenoid intake and the risk of Alzheimer's disease. In addition, intake of lutein/zeaxanthin and lycopene was associated with less AD pathology and AD diagnostic score (Yuan et al. 2021). Fucoxanthin, a xanthophyll, is a tetraterpene oxygen-containing compound (Li et al. 2022b). Fucoxanthin can directly inhibit the scopolamine-induced increase in AChE. Scopolamine is a muscarinic acetylcholine receptor antagonist and has been shown to stimulate inflammation and oxidative stress by attenuating cholinergic neurotransmission, resulting in decreased brain activity. In addition, fucoxanthin's hydrogen bond with BACE-1 inhibits enzymatic reactions. This results in the suppression of amyloid precursor protein cleavage and the blocking of amyloidogenic processing (Oliyaei et al. 2022). The role of fucoxanthin in the brain appears to mimic the action of macrophages in cleaning up the body's waste, preventing toxic oligomers from impairing synaptic communication and plasticity. However, fucoxanthin reverses cognitive impairment in rodents by down-regulating BDNF and choline acetyltransferase (ChAT) expression (Li et al. 2022b).

Lycopene is one of the red carotenoids. This carotenoid is most abundant in tomatoes and other red-colored fruits such as guava, grapefruit, watermelon, and papaya (Paul et al. 2020; Saini et al. 2020). Lycopene's antioxidant potential can be associated with its ability to improve brain SOD, CAT, and GSH levels and expression (Sachdeva and Chopra 2015). Lycopene prevented LPS-induced Aβ accumulation and amyloid precursor protein (APP) levels, suppressed the neuronal β-secretase BACE1 and increased the expression of the α-secretase ADAM10, according to a study by Wang et al. (2018a). Furthermore, lycopene downregulated the expression of IBA-1 (a marker of microglial activation), lowered the levels of inflammatory mediators, and inhibited oxidative stress in LPS-treated mice (Wang et al. 2018a).

Some phytochemicals prevent beta-amyloid and tau phosphorylation from aggregating, reduce the expression of various cytokines and increase the expression of various enzymes to restore the creation and function of various neurotransmitters. It shows this function with anti-Alzheimer activity. Furthermore, it has been proven that oxidative stress caused by Aβ and p-tau toxicity is an important factor in the development and progression of Alzheimer's disease and phytochemicals have antioxidant properties (Sajad, Kumar, and Thakur 2022).

Parkinson's disease

The second-most prevalent neurodegenerative condition after Alzheimer's disease is Parkinson's disease (Kim et al. 2017; Zhang et al. 2021), which is a neurological disorder characterized by progressive degeneration of nigrostriatal dopaminergic neurons (Chung et al. 2017). The disease involves the loss of *Substantia Nigra pars compacta* (SNpc) dopaminergic neurons and excessive accumulation of α-synuclein-positive cytoplasmic Lewy bodies (LBs) (Schirinzi et al. 2019). Despite the fact that Parkinson's disease is classified as a movement disorder, there are a number of non-motor symptoms (NMS) that are also present, such as hyposmia, constipation, urinary dysfunction, orthostatic hypotension, memory loss, depression, pain, and sleep disturbances in almost all patients (Chung et al. 2017; Schirinzi et al. 2019; Tolosa et al. 2021). Oxidative stress caused by reactive oxygen species may also contribute to damage in misfolded α-synuclein (α-syn) and dopamine (DA) neurons (Zhu, Zhuang, and Lu 2019), resulting in the accumulation of Lewy bodies (Kim et al. 2017). It has been stated that oxidase-derived reactive oxygen species and/or myeloperoxidase-derived reactive nitrogen species and proinflammatory cytokine production properties of reactive glia may cause oxidative damage and inflammation (Chung et al. 2017). A diet rich in fruits and vegetables, which are natural sources of antioxidants, is important to prevent disease progression and neuronal loss given that oxidative stress contributes to neurodegeneration. Fruit and vegetables exert their antioxidant properties mainly through the phytochemicals they contain (Schirinzi et al. 2019).

Phytochemicals and parkinson's disease

Phytochemicals, obtained from spice one of the most widely used plant-based food additives, prevent and halt neurodegenerative processes that correlate with aging. Aiswarya et al. found in the study that rosmarinic acid (RA), capsaicin (CAP), and curcumin (CUR) can inhibit phosphorylated PLA2 activity, which can initiate oxidative stress in the brain (Aiswarya et al. 2022; Wang et al. 2022a). Possible mechanisms of phytochemicals include the prevention of neuroinflammation, protein aggregation, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and oxidative stress. One study found that capsaicin treatment prevented the increase in malondialdehyde (MDA) and nitric oxide (NO) levels in brain tissue, prevented neuronal deterioration with neurotoxicity induced by rotenone administration, and restored GFAP-positive cells (Tyagi, Shekhar, and Thakur 2022). An *in vivo* study in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease investigated the effect of TRPV1 and its agonist capsaicin and showed that capsaicin improved nigrostriatal dopamine neurons and regulated striatal dopamine functions after 30 days of different capsaicin doses. The neuroprotective effects were associated with the expression of proinflammatory cytokines (TNF-α and IL-1β) and ROS/RNS, and TRPV1 was proven to play an important role (Chung et al. 2017). Another *in vitro* study conducted in a cell model showed that capsaicin can protect cells and reduce the rate of apoptosis by regulating the imbalance between ACTG1 and GSTA2, which are involved in PD (Liu et al. 2020). In a meta-analysis using animal models,

curcumin has been shown to have the antioxidant capacity to protect neurons in the substantia nigra and to improve striatal dopamine levels. Curcumin treatment was also reported to effectively reduce neuronal apoptosis and improve functional outcomes in animal models of Parkinson's disease (Wang et al. 2017). Curcumin has therapeutic effects on Parkinson's disease through its potent antioxidant effects and neuroprotective properties that target mitochondrial dysfunction and activate anti-apoptotic pathways that induce neurotrophic factors (Jung and Kim 2018). In mice with Parkinson's disease, curcumin treatment effectively improved glial cell activation and a-synuclein aggregation. Curcumin was also shown to significantly upregulate tyrosine, methionine, sarcosine, and creatine levels (Cui et al. 2022). In mice with PD, curcumin supplementation prevented LPS-induced upregulation of protein activity of the transcription factor NFκB, proinflammatory cytokines (TNF-α, IL-1β, and IL-1α), inducible nitric oxide synthase (iNOS), and intrinsic regulatory molecules. It also inhibited a-synuclein clusters in dopaminergic neurons, as observed from the α-synuclein gene and protein activity by RT-PCR and IHC (Sharma and Nehru 2018).

It has been reported that accumulation of damaged mitochondria leads to loss of dopaminergic neurons and mitophagy, known as selective autophagy *via* the lysosomal pathway, is important in removing damaged mitochondria. Impaired mitophagy and mitochondrial dysfunction are known to play a role in Parkinson's disease. In an *in vivo* study conducted with quercetin, progressive motor behaviors improved, and α-synuclein accumulation, mitochondrial damage, and neuronal loss were reduced. As *in vitro*, it reduced α-synuclein protein expression, oxidative stress, and mitochondrial damage. It increased levels of the mitophagy markers PINK1 and Parkin and showed a neuroprotective effect through 6-OHDA-induced activation of qPINK1-Parkin-dependent mitophagy in the same study (Wang et al. 2021). In another study, it was found that oral administration of quercetin ameliorated behavioral deficits and striatal dopamine depletion in mice (Ay et al. 2017). Josiah et al. (2022) found that catechin and quercetin treatment also alleviated striatal redox stress and neurochemical dysfunction, optimized impaired dopamine metabolism, and ameliorated rotenone-toxicity-induced neuronal density loss. Catechin administration created a more pronounced attenuating effect on IL-1β, TNF-α and p53 genes; whereas, the attenuating effect of quercetin was more pronounced on NF-κB and IκKB gene expression than the group (Josiah et al. 2022). These results support the study reporting significant neuroprotective effects of quercetin through iron-induced oxidative stress-related apoptotic pathways (Boyina et al. 2020).

To improve the clinical situation, some phytochemicals can be used as supplements in the treatment. One of these is carotenoids. Dirkse et al. (2022) found a clinically significant correlation between motor scores on the United Parkinson's Disease Rating Scale and lycopene intake in the study. In a study including Parkinson's disease patients, serum α-carotene, β-carotene, and lycopene levels were found to be significantly lower in advanced Parkinson's disease patients (Hoehn and Yahr stages III and IV) than in early Parkinson's disease patients (Hoehn and Yahr stages I and II). It was reported that these low levels of carotenoids may play a role in the pathogenesis and progression of the disease. No differences were observed in serum levels of lutein, zeaxanthin, β-cryptoxanthin, retinol, α-tocopherol, and γ-tocopherol (Kim et al. 2017; Wang et al. 2018b). Another cohort study showed that dietary intake of vitamins C and E may reduce the risk of Parkinson's disease (Hantikainen et al. 2021).

Epigallocatechin-3-gallate (EGCG) has shown neuroprotective effects in Parkinson's disease *in vivo* through immunomodulation by reducing TNF-α and IL-6 expression (Zhou, Zhu, and Liang 2018). Another study demonstrated the ability of EGCG to reduce oxidative stress in Parkinson's disease *in vivo* and *in vitro*. It also inhibited apoptosis by reducing caspase-3 activation and preserved mitochondrial membrane potential (Sánchez-Giraldo et al. 2020). Rotenone (ROT) is found in nature and is considered a natural pesticide and has been reported to play a role in the etiology of Parkinson's disease. In male Wistar rats, there was a decrease in NO levels and lipid peroxidation and an increase in ATPase, ETC enzyme, and succinate dehydrogenase enzyme activities and catecholamine levels. In Parkinson's disease, EGCG has been shown to have anti-apoptotic, anti-inflammatory, and antioxidant effects, as well as regulating neurochemical disorders and improving mitochondrial dysfunction (Tseng et al. 2020).

In the literature, coffee consumption has been associated with a reduced risk of developing PD. Several important studies have shown that increased coffee consumption significantly reduces the risk of PD in a dose-dependent manner (Cho et al. 2018; Carneiro, Oliveira, and Alves 2021; Li, Hatano, and Hattori 2021). Antioxidants such as caffeine-free compounds, quercetin, chlorogenic acid, ferulic acid, and kahweol in coffee play an important role in the neuroprotective effect (Li, Hatano, and Hattori 2021). Significant release of some pro-inflammatory mediators such as TNF-α and IL-1β and advanced expression of the anti-inflammatory cytokine IL-10 is inhibited by chlorogenic acid. In this way, it was found to significantly affect motor coordination and antioxidant defense in Parkinson's disease (Singh et al. 2023).

Another study reported that resveratrol increased dopamine levels and antioxidant activity, reduced motor dysfunction and α-synuclein expression, and also regulated TH protein levels. Another review demonstrated the anti-inflammatory and antioxidant effects of resveratrol in the brain and reported that it improved mitochondrial dysfunction (Su et al. 2021). Anthocyanins partially inhibit NF-κB translocation in PD and AD models (Ben Youssef et al. 2021). In a meta-analysis, the highest risk of PD was found for the lowest intake of anthocyanins; whereas, a significantly higher risk of PD was found for higher intakes of lutein. Overall, a lower risk of PD may be linked to eating more antioxidant-rich foods (Talebi et al. 2022).

Astaxanthin has been shown to protect against PD through multiple mechanisms, including attenuated dopaminergic neurodegeneration. Its effects have been shown to be mediated through the miR-7/SNCA axis, resulting in the inhibition of endoplasmic reticulum (ER) stress (Kohandel

Table 2. Neuroprotective effects *in vivo* and *in vitro* in alzheimer's, parkinson's disease, and dementia.

Category	Phytochemicals	Research Type	Neuroprotective effect	Reference
Alzheimer's Disease				
Phenolic Acid	Capsaicin	*In vivo*	Decreased tau protein hyperphosphorylation (diabetic rats) No significant difference in non-diabetic	(Xu et al. 2017)
		In vivo & in vitro	Shifting the APP process toward α-cleavage stimulating the maturation of a disintegrin and metalloproteinase 10 (ADAM10) Reducing Aβ accumulation	(Wang et al. 2020)
		In vivo	Decreased neurodegeneration, neuroinflammation, and impairment in spatial memory in the okadaic acid-induced AD model	(Çakır et al. 2023)
		In vivo	Reduction in oxidative stress, Aβ-peptide and IL-6 in the brain Improving grip strength and memory functioning Prevention of neuronal degeneration in the cerebral cortex, hippocampus, and *Substantia Nigra* of rats	(Abdel-Salam et al. 2023)
	Chlorogenic Acid	*In vivo & in vitro*	Aβ25-35-induced autophagy to modulate the lysosomal function Activation of the mTOR/TFEB signaling pathway	(Gao et al. 2020)
		In vivo & in vitro	Inhibiting Aβ25-35-induced autophagy by modulating lysosomal function Activation of mTOR (mechanistic target of rapamycin kinase) / TFEB (transcription factor EB) signaling pathways	(Nan et al. 2021)
Flavonoid	Curcumin	*In vivo*	Reducing amyloid plaque burden Improving microbiota dysbiosis Improving spatial learning and memory abilities in the hippocampus	(Sun et al. 2020)
		In vivo	Curcumin-treated AD mice had significantly reduced brain and plasma amyloid plaque (Aβ40 and Aβ42) levels compared to untreated AD mice	(Das et al. 2019)
	Apigenin	*In vivo & in vitro*	Reducing microglial activation characterized by inhibition of proliferation and modulation of microglia morphology Decreased expression of the M1 inflammatory marker CD68 Increasing mRNA expression of IL-6, IL-1β and CCL5 and decreasing mRNA expression of IL-10 Inducing an increase in brain-derived neurotrophic factor (BDNF) expression (an effect that can be associated with anti-inflammatory and neuroprotective effects)	(Dourado et al. 2020)
		In vivo	Reducing hyperphosphorylation of tau levels in the hippocampus Inhibition of β secretase (BACE1) and GSK-3β at the mRNA level	(Alsadat et al. 2021)
	Epigallocatechin-3-Gallate and Ferulic Acid	*In vivo*	Decreased number of amyloid β-proteins Reduction in parenchymal and cerebral vascular β-amyloid deposition Reduction in synaptoxicity, oxidative damage, and neuroinflammation	(Mori et al. 2019)
	Epigallocatechin-3-Gallate	*In vivo*	Inhibition of tau hyperphosphorylation Reduction of AchE activity Scavenging free radicals Improvement in learning and memory functions	(Nan et al. 2021)
	Quercetin	*In vitro*	Reduction in Aβ1–40 cytotoxicity Reduction in ROS formation Decreased release of lactate dehydrogenase Increase in superoxide dismutase (antioxidant enzyme) Recovery from nuclear damage Maintaining barrier integrity	(Li et al. 2015)
		In vivo	Revealing reduced transfer delay, high corrected score for spontaneous changes, low working and reference memory error, reduced escape delay, and normal locomotor activity	(Joseph and Ravi 2022)
		In vivo & in vitro	Making progress in behavioral studies Inhibition of AChE activity and decrease in oxidative stress parameters Quercetin combined with memantine treatment also enhances brain-derived neurotrophic factor (BDNF) expression and inhibits amyloid-β plaque formation	(Jadhav and Kulkarni 2023)
		In vivo	Alleviating dAGEs-induced cognitive impairment in aged mice	(Yang et al. 2020)
	Isoflavones	*In vivo*	Improving BACE1-induced cognitive decline	(Ahuja et al. 2021)
		In vivo	Inhibition of amyloidogenic pathways	(Sarroca et al. 2021).
Stilben	Resveratrol		Inhibition of the proteolytic activity of the ubiquitin-proteasome system Reducing abnormal protein deposition	
		In vivo & in vitro	Improve passive avoidance tasks alone Showing beneficial additive effects on recognition memory impairment in a mouse model of AD in co-treatment with melatonin	(Labban et al. 2021)
		In vivo & in vitro	Developing the spatial abilities of mice Increasing the expression of SOD, GSH-Px, CAT, and HO-1 at the mRNA level Reducing ERβ expression at mRNA and protein levels in brain tissue and Aβ expression at protein levels in brain tissue	(Kong et al. 2019)
	Pterostilbene	*In vivo & in vitro*	Improving neuronal plasticity and reducing neuronal loss Upregulation of Nrf2 expression and SOD level by SIRT1	(Zhu et al. 2022)
		In vivo & in vitro	Attenuating STZ-induced body weight loss, Aβ1-42 accumulation and Tau hyperphosphorylation, and memory impairment by regulating MAOB Reducing levels of ROS and MDA Attenuating STZ-induced oxidative stress in the hippocampus by increasing SOD and GSH levels Protection against STZ-induced neuroinflammation in the hippocampus by inhibiting TNF-α, IL-1β, IL-6, and p-NF-κB levels	(Li et al. 2022a)

(*Continued*)

Table 2. Continued.

Category	Phytochemicals	Research Type	Neuroprotective effect	Reference
Carotenoid	Lutein / Zeaxanthin and Lycopene	Prospective	Less AD pathology and AD diagnostic score	(Yuan et al. 2021)
	Xanthonoid	*In vivo*	Neuroprotective effect of mango seed extract and isolates showing beneficial effects in restoring cognitive abilities through anti-amyloid and anticholinesterase activities	(Ragheb et al. 2023)
	Lycopene	*In vivo & in vitro*	Improving cognitive deficits in water maze test with combination of HAEC transplantation and lycopene therapy Reducing the level of proinflammatory mediators (TNF-α and IL-1β) Increasing the level of anti-inflammatory mediators (IL-)	(Xu et al. 2021a)
		In vivo & in vitro	Attenuating astrocytosis and microgliosis Reducing malondialdehyde production Attenuated neuronal loss Inhibited amyloidogenic processing	(Guo et al. 2023)
Tannins	Ellagitannin	*In vivo & in vitro*	Activating autophagy by upregulating the SIRT1 signaling pathway and downregulating the mTOR signaling pathway Helping prevent D-galactose-induced brain aging through activation of the miR-34a-mediated SIRT1/mTOR signaling pathway	(Chen et al. 2019)
Cyanines	Betalain	*In vivo*	Suppression of lipid oxidation (MDA) through regulation of antioxidant content (SOD, CAT, and GSH) LDH, NO, AChE inhibition Decrease in NF-ƙB-related mRNA expression (TNF-α IL-6, Il 1β, iNOS, COX-2)	(Shunan et al. 2021)
Parkinson's Disease				
Flavonoid	Epigallocatechin-3-Gallate	*In vivo*	Reducing TNF-α and IL-6 expression	(Zhou, Zhu, and Liang 2018)
		In vivo & in vitro	Reducing oxidative stress Inhibiting apoptosis by reducing Caspase-3 activation Mitochondrial membrane potential preservation	(Sánchez-Giraldo et al. 2020)
		In vivo	Reduction in NO levels and lipid peroxidation (LPO) Increase in ATPase, ETC enzyme, and succinate dehydrogenase (SDH) enzyme activities Increased catecholamine levels Anti-apoptotic, anti-inflammatory, anti-oxidant effect	(Tseng et al. 2020)
	Catechin	*In vivo*	Alleviating striatal redox stress and neurochemical dysfunction Optimizing impaired dopamine metabolism and improving neuron density reduction caused by rotenone toxicity	(Josiah et al. 2022)
	Apigenin	*In vivo & in vitro*	Decreased upregulation of NF-κB gene expression in PD rats by apigenin treatment Prevention of neuroinflammation in the substantia nigra pars compacta (SNpc) Inhibiting the release of TNF-a, IL-6, and the proinflammatory enzyme iNOS-1	
	Quercetin	*In vivo & in vitro*	Improvement in progressive motor behavior in vivo Decreased accumulation of α-synuclein Reduction in mitochondrial damage Decreased loss of neurons Decreased expression of α-synuclein protein in vitro Reduction in oxidative stress Reduction in mitochondrial damage	(Wang et al. 2021)
		In vivo & in vitro	Attenuating motor deficiencies and biochemical and neurotransmitter changes induced by rotenone and iron supplementation in experimental rats	(Sharma, Raj, and Singh 2020)
	Kaempferol	*In vivo & in vitro*	Inhibiting lipid peroxidation and IL-6 and TNF-α Increasing monoamine levels in the striatum and substantia nigra of the brain More than 50% inhibition of ROS and apoptosis	(Pan et al. 2020)
Phenolic Acid	Capsaicin	*In vitro*	Regulating the imbalance between Actg1 (actin gamma 1) and Gsta2 (Glutathione S-transferase alpha 2) Scavenging free radicals	(Liu et al. 2020)
		In vitro	Improvement in nigrostriatal dopamine neurons Improvement in striatal dopamine functions Decreased secretion of proinflammatory cytokines (TNF-α and IL-1β) Decreased expression of ROS, RNS species	(Chung et al. 2017)
	Chlorogenic acid	*In vivo & in vitro*	Inducing GLP-1 secretion by CGA by increasing cAMP levels in GLUTag cells Preventing motor and cognitive impairments by rotenone-induced oxidative stress	(Sharma et al. 2022)
Terpenoid	Ruscogen	*In vivo & in vitro*	Reducing oxidative stress and inflammatory marker levels in microglial BV-2 cells Improving motor activities	(Wu et al. 2023)

(*Continued*)

Table 2. Continued.

Category	Phytochemicals	Research Type	Neuroprotective effect	Reference
Stilben	Resveratrol	*In vivo & in vitro*	Reducing microglia activation and M1 polarization in rotenone-induced BV-2 cells Free iron induced the production of ROS and MDA and inhibiting glutathione activity while its effects were hidden by resveratrol Also inhibiting the induction effect of rotenone on IL-6, IL-1β and TNF-α	(Li, Shen, et al. 2021)
		In vivo & in vitro	Demonstrate a beneficial effect on episodic-like memory and motor coordination by modulating neuroinflammation by acting on the SIRT1 and NF-κB signaling pathway in the hippocampus of aged mice	(Sarubbo et al. 2023)
Demans				
Flavonoids	Quercetin	*In vivo & in vitro*	Reduction in STZ-induced diabetes-induced deterioration in behavioral, endothelial, and biochemical parameters	(Sharma et al. 2021)
	Curcumin	*In vivo & in vitro*	Significantly ameliorate DM/CCH-induced cognitive deficits and attenuated neuronal cell death Suppressing neuroinflammation induced by microglial activation by regulating the triggering receptor expressed on the TREM2/TLR4/NF-κB pathway	(Zheng et al. 2021)
Stilben	Pterostilbene	*In vivo & in vitro*	Hippocampal neuronal death and decreased microglial activation in rats Inhibition in the expression of TLR4 and inflammatory cytokines	(Xu et al. 2022)
		In vivo & in vitro	Attenuating Aβ1-42, inducing cognitive dysfunction assessed using the Y-maze test, new object recognition task, Morris water maze test, and passive avoidance test Promoting Nrf2 nuclear translocation and increasing transcription and expression of antioxidant genes such as heme oxygenase-1 and superoxide dismutase both in vivo and *in vitro*	(Xu et al. 2021b)
	Resveratrol	*In vivo & in vitro*	Rats exhibit increased cognitive ability, decreased hippocampal MDA, Bax, and caspase-3 content, and increased SOD and Bcl-2 hippocampal expression (P<) Improving spatial learning and memory of rats	(Zhang et al. 2019a)
		In vivo	Improve cognitive decline Reversing diabetes-induced protein expression changes Preventing memory deficits, endothelial dysfunction, increased oxidative stress, inflammation, and impaired neurotrophin expression	(Gocmez et al. 2019)
Flavonoid	Quercetin	*In vivo & in vitro*	Attenuation of cognitive impairments in animals exposed to STZ during Morris water maze and Y maze tests	(Singh and Garabadu 2021)
		In vivo & in vitro	Facilitating the secretion of IL-4 and IL-10 and, in turn, reducing TNF-α and IL-1β production by regulating microglial phenotype transformation. Mediate microglial conversion to anti-inflammatory phenotype to reduce demyelination in the ventral hippocampus (vHIP) and subsequently attenuate neuropsychiatric deficits (including anxiety and depression)	(Tan et al. 2022)

*Rotenone is a pesticide, used to make animal models of Parkinson's disease. Parkinson Disease: PD; Alzheimer's disease: AD; malondialdehyde: MDA; reactive oxygen species:ROS; interleukin-1β: IL-1β ; tumor necrosis factor-α: TNF-α; monoamine oxidase B: MAOB; streptozotocin: STZ; β-secretase: BACE; nuclear factor kappa B: NF-κB; dietary advanced glycation end products: dAGEs; diabetes Mellitus: DM; chronic cerebral hypoperfusion: CCH; amyloid precursor protein: APP; amiloid beta: Aβ; transcription factor EB: TFEB; sirtuin-1: SIRT1; nuclear factor erythroid 2 associated factor 2: Nrf2; superoxide dismutase: SOD; Lactate dehydrogenase: LDH; nitric oxide: NO; acetylcholinesterase: AC.

et al. 2022). Xue et al. (2017) showed that astaxanthin ameliorated learning and memory deficits and reduced hippocampal neuronal degeneration and apoptosis after cerebral IR injury.

Administration of apigenin attenuated the histopathological changes induced by MPTP in brain tissue. Furthermore, apigenin reversed the changes in the expression and concentration of TNF-α, IL-1β, IL-6, IL-10, and TGF-β (Yarim et al. 2022). The anti-inflammatory activity derived from the regulation of transcription factors such as STAT3, nuclear factor kappa, and AP-1 is reported to be the main pharmacological mechanism of luteolin (Siddique 2021). Therefore, it can be said that luteolin is a therapeutic agent that can be used to treat PD and AD (Babaei, Mirzababaei, and Nassiri-Asl 2018; Dong et al. 2017). In one study, animals were infected with 6-hydroxydopamine (6-OHDA), an environmental neurotoxin that causes PD-like symptoms. Hesperidin supplementation was found to significantly reduce 6-OHDA-induced biomarkers of oxidative stress (Kesh et al. 2021). In addition, hesperidin was found to reduce cognitive dysfunction in mice using the Y maze test (Muhammad et al. 2019).

Dementia

Aging is defined as a natural process characterized by a decline in physical and cognitive functions (Kato et al. 2018). Dementia, which is most prevalent in the elderly, is a syndrome characterized by psychological and neurological changes associated with impaired memory and thinking, speech disorders, and difficulties in activities of daily living (Taslimi et al. 2020; WHO 2021b). Approximately 50 million people worldwide are reported to have dementia, with 10 million new cases reported each year (WHO 2021a). Cognitive function, the impairment of which threatens the quality of life and independence of older people, includes brain functions required for daily activities such as memory, speech, attention, executive function, and vigilance (Saitou et al. 2018). One study revealed that interventions targeting modifiable risk factors can potentially prevent or delay AD

(Livingston et al. 2020). The clinical spectrum of dementia is highly variable. Dementia caused by AD is divided into primary degenerative dementias, such as vascular dementia (VaD), frontotemporal dementia and dementia with Lewy bodies, and secondary dementia caused by another disease process, such as AIDS, Parkinson's disease or Huntington's disease (Molino et al. 2016). As there is no effective treatment for dementia, it has been emphasized that it is important to identify risk factors in order to prevent the onset or progression of dementia at an early stage (Yuan et al. 2020). Lifestyle factors, such as dietary habits, have been reported to influence cognitive function (Saitou et al. 2018).

Phytochemicals and dementia

A meta-analysis and systematic review demonstrated that blood lycopene was lower than α-carotene in patients with dementia. β-carotene, lutein, zeaxanthin, and β-cryptoxanthin were higher than in controls. Accordingly, blood levels of carotenoids were found to be significantly lower in patients with dementia than in controls (Wang et al. 2023b). In another study, D-galactose-induced Balb/c mice were treated with green tea EGCG and EGCG improved spatial memory function and oxidative stress in dementia (Gumay, Bakri, and Pudjonarko 2018). In another randomized controlled trial, healthy people were given quercetin-free and quercetin-enriched onions for 24 wk and quercetin was found to improve cognitive decline by increasing motivation and reducing depressive symptoms (Nishihira et al. 2021). Another randomized controlled trial showed that consumption of quercetin-enriched onions may improve cognitive function and prevent dementia (Nishimura et al. 2017). In a pilot study in elderly men, consumption of 330 mg of chlorogenic acid (CGA)-containing beverages every night for 6 months was shown to improve composite memory, verbal memory, complex attention, cognitive flexibility, and executive function (Kato et al. 2018). In another randomized controlled trial in elderly patients with mild cognitive impairment, a CGA intake of 553.6 mg/100 mLx2 for 28 wk was found to improve attention and executive function (Ochiai et al. 2019). In another study on the elderly, CGA supplementation resulted in improvements in motor speed, psychomotor speed, and executive function (Saitou et al. 2018). Compared two groups taking 75 mg of trans-resveratrol twice a day for 1 year with and without resveratrol, and the results showed a 33% improvement in cognitive performance in the resveratrol group compared with the control group, and a partial improvement in verbal memory in individuals aged 65 years and older compared with younger individuals (Zaw, Howe, and Wong et al. 2021). In a meta-analysis of clinical studies, it has been shown that carotenoid supplementation in healthy individuals aged 45–78 years has a significant effect on mental performance even in healthy individuals (Davinelli et al. 2021). Despite the positive results of these studies, the ESPEN guidelines on nutrition in dementia generally state that there is a significant lack of high-level evidence studies and there is insufficient clear evidence to recommend the use of any currently available nutritional supplement for the prevention or correction of cognitive decline in patients with dementia (Volkert et al. 2015). Table 2 shows the neuroprotective effects of preclinical studies in Alzheimer's and Parkinson's disease and dementia.

Conclusion and future perspectives

Although the antioxidant and anti-inflammatory effects of phytochemicals have been shown to improve cognitive performance, most of these results have been obtained from *in vivo* and *in vitro* studies. Although the results are promising, the main evidence for phytochemicals' neuroprotective mechanisms of action comes from animal studies, and evidence from human studies is still insufficient. In addition, it is not clear whether the phytochemicals that show neuroprotective effects act as single component or synergistically. The duration and dose of the phytochemicals administered in the trials varied. This led to uncertainty about the toxic or effective doses that would respond to treatment. In addition, the fact that their bioavailability is generally low and they are rapidly absorbed and excreted has made their effectiveness in treatment difficult. Larger and longer clinical trials are therefore needed to fill the gaps in the literature with dose-response studies and high-level evidence in the clinic.

Author contributions

Nevin Sanlier: Investigation, Writing-Original Draft, Visualization. Basak Can: Conceptualization, Resources, Visualization, Writing – Review & Editing, Supervision.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Basak Can http://orcid.org/0000-0002-0608-6496
Nevin Sanlier http://orcid.org/0000-0001-5937-0485

References

Abd Al Haleem, E. N., H. I. Ahmed, and R. N. El-Naga. 2023. Lycopene and chrysin through mitigation of neuroinflammation and oxidative stress exerted antidepressant effects in clonidine-induced depression-like behavior in rats. *Journal of Dietary Supplements* 20 (3):391–410. doi: 10.1080/19390211.2021.1988797.

Abdel-Salam, O. M. E., M. E. S. El-Shamarka, E. R. Youness, and N. Shaffie. 2023. Protective effect of hot peppers against amyloid β peptide and brain injury in AlCl3-induced Alzheimer's disease in rats. *Iranian Journal of Basic Medical Sciences* 26 (3):335–42. doi: 10.22038/IJBMS.2022.67871.14845.

ADI. 2022. Alzheimer's disease international world Alzheimer report 2022. Accessed April 3, 2023. https://www.alzint.org/u/World-Alzheimer-Report-2022.pdf.

Ahuja, A., P. K. Tyagi, S. Tyagi, A. Kumar, M. Kumar, and J. Sharifi-Rad. 2021. Potential of Pueraria tuberosa (Willd.) DC. to rescue cognitive decline associated with BACE1 protein of Alzheimer's disease on Drosophila model: An integrated molecular modeling and in vivo approach. *International Journal of Biological Macromolecules* 179:586–600. doi: 10.1016/j.ijbiomac.2021.03.0320141-8130.

Aiswarya, N., C. Remya, A. B. Remashree, C. Sadasivan, and K. V. Dileep. 2022. Binding of rosmarinic acid curcumin and capsaicin with PLA2: A comparative study. *Biochemical and Biophysical Research Communications* 626:187–91. doi: 10.1016/j.bbrc.2022.08.028.

Alì, S., S. Davinelli, G. Accardi, A. Aiello, C. Caruso, G. Duro, M. E. Ligotti, F. Pojero, G. Scapagnini, and G. Candore. 2021. Healthy ageing and Mediterranean diet: A focus on hormetic phytochemicals. *Mechanisms of Ageing and Development* 200:111592. doi: 10.1016/j.mad.2021.111592.

Al-Khayri, J. M., A. Banadka, M. Nandhini, P. Nagella, M. Q. Al-Mssallem, and F. M. Alessa. 2023. Essential oil from Coriandrum sativum: A review on its phytochemistry and biological activity. *Molecules (Basel, Switzerland)* 28 (2):696. doi: 10.3390/molecules28020696.

Alsadat, A. M., F. Nikbakht, H. H. Nia, F. Golab, Y. Khadem, M. Barati, and S. Vazifekhah. 2021. GSK-3β as a target for apigenin-induced neuroprotection against Aβ 25–35 in a rat model of Alzheimer's disease. *Neuropeptides* 90:102200. doi: 10.1016/j.npep.2021.102200.

Ay, M., J. Luo, M. Langley, H. Jin, V. Anantharam, A. Kanthasamy, and A. G. Kanthasamy. 2017. Molecular mechanisms underlying protective effects of quercetin against mitochondrial dysfunction and progressive dopaminergic neurodegeneration in cell culture and MitoPark transgenic mouse models of Parkinson's disease. *Journal of Neurochemistry* 141 (5):766–82. doi: 10.1111/jnc.14033.

Babaei, F., M. Mirzababaei, and M. Nassiri-Asl. 2018. Quercetin in food: Possible mechanisms of its effect on memory. *Journal of Food Science* 83 (9):2280–7. doi: 10.1111/1750-3841.14317.

Bahar, E., J. Y. Kim, and H. Yoon. 2017. Quercetin attenuates manganese-induced neuroinflammation by alleviating oxidative stress through regulation of apoptosis, iNOS/NF-κB and HO-1/Nrf2 pathways. *International Journal of Molecular Sciences* 18 (9):1989. doi: 10.3390/ijms18091989.

Bao, J., W. Liu, H. Y. Zhou, Y. R. Gui, Y. H. Yang, M. J. Wu, Y. F. Xiao, J. T. Shang, G. F. Long, and X. J. Shu. 2020. Epigallocatechin-3-gallate alleviates cognitive deficits in APP/PS1 mice. *Current Medical Science* 40 (1):18–27. doi: 10.1007/s11596-020-2142-z.

Batiha, G. E. S., A. Alqahtani, O. A. Ojo, H. M. Shaheen, L. Wasef, M. Elzeiny, M. Ismail, M. Shalaby, T. Murata, A. Zaragoza Bastida, et al. 2020. Biological properties, bioactive constituents, and pharmacokinetics of some *Capsicum* spp. and capsaicinoids. *International Journal of Molecular Sciences* 21 (15):5179. doi: 10.3390/ijms21155179.

Ben Youssef, S., G. Brisson, H. Doucet-Beaupré, A. M. Castonguay, C. Gora, M. Amri, and M. Lévesque. 2021. Neuroprotective benefits of grape seed and skin extract in a mouse model of Parkinson's disease. *Nutritional Neuroscience* 24 (3):197–211. doi: 10.1080/1028415X.2019.1616435.

Bergland, A. K., H. Soennesyn, I. Dalen, A. Rodriguez-Mateos, R. K. Berge, L. M. Giil, L. Rajendran, R. Siow, M. Tassotti, A. I. Larsen, et al. 2019. Effects of anthocyanin supplementation on serum lipids, glucose, markers of inflammation and cognition in adults with increased risk of dementia–a pilot study. *Frontiers in Genetics* 10:536. doi: 10.3389/fgene.2019.00536.

Borsoi, F. T., I. A. Neri-Numa, W. Q. de Oliveira, F. F. de Araújo, and G. M. Pastore. 2022. Dietary polyphenols and their relationship to the modulation of non-communicable chronic diseases and epigenetic mechanisms: A mini-review. *Food Chemistry Molecular Sciences* 6:100155. doi: 10.1016/j.fochms.2022.100155.

Boyina, H. K., S. L. Geethakhrishnan, S. Panuganti, K. Gangarapu, K. P. Devarakonda, V. Bakshi, and S. R. Guggilla. 2020. In silico and in vivo studies on quercetin as potential anti-Parkinson agent. *Advances in Experimental Medicine and Biology* 1195:1–11. doi: 10.1007/978-3-030-32633-3_1.

Çakır, M., F. Yüksel, M. Mustafa Özkut, M. Durhan, E. Kaymak, S. Tekin, and Y. Çiğremiş. 2023. Neuroprotective effect of transient receptor potential Vanilloid 1 agonist capsaicin in Alzheimer's disease model induced with okadaic acid. *International Immunopharmacology* 118:109925. doi: 10.1016/j.intimp.2023.109925.

Calderaro, A., G. T. Patanè, E. Tellone, D. Barreca, S. Ficarra, F. Misiti, and G. Laganà. 2022. The neuroprotective potentiality of flavonoids on Alzheimer's disease. *International Journal of Molecular Sciences* 23 (23):14835. doi: 10.3390/ijms232314835.

Calis, Z., R. Mogulkoc, and A. K. Baltaci. 2020. The roles of flavonols/flavonoids in neurodegeneration and neuroinflammation. *Mini Reviews in Medicinal Chemistry* 20 (15):1475–88. doi: 10.2174/1389557519666190617150051.

Capurso, A., G. Crepaldi, and C. Capurso. 2020. The Mediterranean diet: A pathway to successful aging. *Aging Clinical and Experimental Research* 32 (6):1187–8. doi: 10.1007/s40520-019-01160-3.

Carneiro, S. M., M. B. P. P. Oliveira, and R. C. Alves. 2021. Neuroprotective properties of coffee: An update. *Trends in Food Science & Technology* 113:167–79. doi: 10.1016/j.tifs.2021.04.052.

Caruso, G., J. Godos, A. Privitera, G. Lanza, S. Castellano, A. Chillemi, O. Bruni, R. Ferri, F. Caraci, and G. Grosso. 2022. Phenolic acids and prevention of cognitive decline: Polyphenols with a neuroprotective role in cognitive disorders and Alzheimer's disease. *Nutrients* 14 (4):819. doi: 10.3390/nu14040819.

Chainoglou, E., and D. Hadjipavlou-Litina. 2020. Curcumin in health and diseases: Alzheimer's disease and curcumin analogues, derivatives, and hybrids. *International Journal of Molecular Sciences* 21 (6):1975. doi: 10.3390/ijms21061975.

Chan, E. W. C., C. W. Wong, Y. H. Tan, J. P. Y. Foo, S. K. Wong, and H. T. Chan. 2019. Resveratrol and pterostilbene: A comparative overview of their chemistry, biosynthesis, plant sources and pharmacological properties. *Journal of Applied Pharmaceutical Science* 9 (7):124–9. doi: 10.7324/japs.2019.90717.

Chen, L., W. Xie, W. Xie, W. Zhuang, C. Jiang, and N. Liu. 2017. Apigenin attenuates isoflurane-induced cognitive dysfunction via epigenetic regulation and neuroinflammation in aged rats. *Archives of Gerontology and Geriatrics* 73:29–36. doi: 10.1016/j.archger.2017.07.004.

Chen, M., Z. Y. Du, X. Zheng, D. L. Li, R. P. Zhou, and K. Zhang. 2018. Use of curcumin in diagnosis, prevention, and treatment of Alzheimer's disease. *Neural Regeneration Research* 13 (4):742–52. doi: 10.4103/1673-5374.230303.

Chen, P., F. Chen, J. Lei, Q. Li, and B. Zhou. 2019. Activation of the miR-34a-mediated SIRT1/mTOR signaling pathway by urolithin A attenuates D-galactose-induced brain aging in mice. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics* 16 (4):1269–82. doi: 10.1007/s13311-019-00753-0.

Chen, Y., Y. Chen, Y. Liang, H. Chen, X. Ji, and M. Huang. 2020. Berberine mitigates cognitive decline in an Alzheimer's disease mouse model by targeting both tau hyperphosphorylation and autophagic clearance. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 121:109670. doi: 10.1016/j.biopha.2019.109670.

Chesworth, R., R. Gamage, F. Ullah, S. Sonego, C. Millington, A. Fernandez, H. Liang, T. Karl, G. Münch, G. Niedermayer, et al. 2021. Spatial memory and microglia activation in a mouse model of chronic neuroinflammation and the anti-inflammatory effects of apigenin. *Frontiers in Neuroscience* 15:699329. doi: 10.3389/fnins.2021.699329.

Chiang, M. C., T. Y. Tsai, and C. J. Wang. 2023. The potential benefits of quercetin for brain health: A review of anti-inflammatory and neuroprotective mechanisms. *International Journal of Molecular Sciences* 24 (7):6328. doi: 10.3390/ijms24076328.

Cho, B. H., S. M. Choi, J. T. Kim, and B. C. Kim. 2018. Association of coffee consumption and non-motor symptoms in drug-naïve, early-stage Parkinson's disease. *Parkinsonism & Related Disorders* 50:42–7. doi: 10.1016/j.parkreldis.2018.02.016.

Choudhari, A. S., P. C. Mandave, M. Deshpande, P. Ranjekar, and O. Prakash. 2019. Phytochemicals in cancer treatment: From preclinical

studies to clinical practice. *Frontiers in Pharmacology* 10:1614. doi: 10.3389/fphar.2019.01614.

Chung, Y. C., J. Y. Baek, S. R. Kim, H. W. Ko, E. Bok, W. H. Shin, S. Y. Won, and B. K. Jin. 2017. Capsaicin prevents degeneration of dopamine neurons by inhibiting glial activation and oxidative stress in the MPTP model of Parkinson's disease. *Experimental & Molecular Medicine* 49 (3):e298–e298. doi: 10.1038/emm.2016.159.

Corbi, G., V. Conti, S. Davinelli, G. Scapagnini, A. Filippelli, and N. Ferrara. 2016. Dietary phytochemicals in neuroimmunoaging: A new therapeutic possibility for humans? *Frontiers in Pharmacology* 7:364. doi: 10.3389/fphar.2016.00364.

Cremonini, A. L., I. Caffa, M. Cea, A. Nencioni, P. Odetti, and F. Monacelli. 2019. Nutrients in the prevention of Alzheimer's disease. *Oxidative Medicine and Cellular Longevity* 2019:9874159–20. doi: 10.1155/2019/9874159.

Cui, C., Y. Han, H. Li, H. Yu, B. Zhang, and G. Li. 2022. Curcumin-driven reprogramming of the gut microbiota and metabolome ameliorates motor deficits and neuroinflammation in a mouse model of Parkinson's disease. *Frontiers in Cellular and Infection Microbiology* 12:887407. doi: 10.3389/fcimb.2022.887407.

Das, T. K., P. Jana, P. S. K. Chakrabarti, and M. R. W. Abdul Hamid. 2019. Curcumin downregulates GSK3 and Cdk5 in scopolamine-induced Alzheimer's disease rats abrogating Aβ 40/42 and tau hyperphosphorylation. *Journal of Alzheimer's Disease Reports* 3 (1):257–67. doi: 10.3233/ADR-190135.

Davinelli, S., S. Ali, V. Solfrizzi, G. Scapagnini, and G. Corbi. 2021. Carotenoids and cognitive outcomes: A meta-analysis of randomized intervention trials. *Antioxidants (Basel, Switzerland)* 10 (2):223. doi: 10.3390/antiox10020223.

Decandia, D., F. Gelfo, E. Landolfo, F. Balsamo, L. Petrosini, and D. Cutuli. 2023. Dietary protection against cognitive impairment, neuroinflammation, and oxidative stress in Alzheimer's disease animal models of lipopolysaccharide-induced inflammation. *International Journal of Molecular Sciences* 24 (6):5921. doi: 10.3390/ijms24065921.

Dirkse, J., J. Ponce, J. Wuebker, M. Jackson, M. Timmerman, and C. Hanson. 2022. The impact of carotenoid intake on motor function in patients diagnosed with Parkinson's disease. *Journal of the Academy of Nutrition and Dietetics* 122 (9):A29. doi: 10.1016/j.jand.2022.06.111.

Dohrmann, D. D., P. Putnik, D. B. Kovačević, J. Simal-Gandara, J. M. Lorenzo, and F. J. Barba. 2019. Japanese, Mediterranean and Argentinean diets and their potential roles in neurodegenerative diseases. *Food Research International (Ottawa, Ont.)* 120:464–77. doi: 10.1016/j.foodres.2018.10.090.

Dong, F., S. Wang, Y. Wang, X. Yang, J. Jiang, D. Wu, X. Qu, H. Fan, and R. Yao. 2017. Quercetin ameliorates learning and memory via the Nrf2-ARE signaling pathway in d-galactose-induced neurotoxicity in mice. *Biochemical and Biophysical Research Communications* 491 (3):636–41. doi: 10.1016/j.bbrc.2017.07.151.

Dong, X., and R. Huang. 2022. Ferulic acid: An extraordinarily neuroprotective phenolic acid with anti-depressive properties. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 105:154355. doi: 10.1016/j.phymed.2022.154355.

Dong, X., Y. Tang, C. Zhan, and G. Wei. 2021. Green tea extract EGCG plays a dual role in Aβ42 protofibril disruption and membrane protection: A molecular dynamic study. *Chemistry and Physics of Lipids* 234:105024. doi: 10.1016/j.chemphyslip.2020.105024.

Dourado, N. S., C. D. S. Souza, M. M. A. de Almeida, A. Bispo da Silva, B. L. dos Santos, V. D. A. Silva, A. M. De Assis, J. S. da Silva, D. O. Souza, M. D. F. D. Costa, et al. 2020. Neuroimmunomodulatory and neuroprotective effects of the flavonoid apigenin in in vitro models of neuroinflammation associated with Alzheimer's disease. *Frontiers in Aging Neuroscience* 12:119. doi: 10.3389/fnagi.2020.00119.

Durazzo, A., M. Lucarini, E. B. Souto, C. Cicala, E. Caiazzo, A. A. Izzo, E. Novellino, and A. Santini. 2019. Polyphenols: A concise overview on the chemistry, occurrence, and human health. *Phytotherapy Research: PTR* 33 (9):2221–43. doi: 10.1002/ptr.6419.

Evans, J. A., P. Mendonca, and K. F. A. Soliman. 2022. Neuroprotective effects and therapeutic potential of the citrus flavonoid hesperetin in neurodegenerative diseases. *Nutrients* 14 (11):2228. doi: 10.3390/nu14112228.

Freyssin, A., G. Page, B. Fauconneau, and A. R. Bilan. 2020. Natural stilbenes effects in animal models of Alzheimer's disease. *Neural Regeneration Research* 15 (5):843–9. doi: 10.4103/1673-5374.268970.

Gao, L., X. Li, S. Meng, T. Ma, L. Wan, and S. Xu. 2020. Chlorogenic acid alleviates Aβ25-35-induced autophagy and cognitive impairment via the mTOR/TFEB signaling pathway. *Drug Design, Development and Therapy* 14:1705–16. doi: 10.2147/DDDT.S235969.

Garrigue, P., L. Mounien, S. Champion, Y. Mouhajir, L. Pechere, B. Guillet, J. F. Landrier, and E. Seree. 2021. Long-term administration of resveratrol at low doses improves neurocognitive performance as well as cerebral blood flow and modulates the inflammatory pathways in the brain. *The Journal of Nutritional Biochemistry* 97:108786. doi: 10.1016/j.jnutbio.2021.108786.

George, M., M. Tharakan, J. Culberson, A. P. Reddy, and P. H. Reddy. 2022. Role of Nrf2 in aging, Alzheimer's and other neurodegenerative diseases. *Ageing Research Reviews* 82:101756. doi: 10.1016/j.arr.2022.101756.

Ginwala, R., R. Bhavsar, P. Moore, M. Bernui, N. Singh, F. Bearoff, M. Nagarkatti, Z. K. Khan, and P. Jain. 2021. Apigenin modulates dendritic cell activities and curbs inflammation via RelB inhibition in the context of neuroinflammatory diseases. *Journal of Neuroimmune Pharmacology: The Official Journal of the Society on NeuroImmune Pharmacology* 16 (2):403–24. doi: 10.1007/s11481-020-09933-8.

Gocmez, S. S., T. D. Şahin, Y. Yazir, G. Duruksu, F. C. Eraldemir, S. Polat, and T. Utkan. 2019. Resveratrol prevents cognitive deficits by attenuating oxidative damage and inflammation in rat model of streptozotocin diabetes induced vascular dementia. *Physiology & Behavior* 201:198–207. doi: 10.1016/j.physbeh.2018.12.012.

Grau, L., R. Soucek, and M. D. Pujol. 2023. Resveratrol derivatives: Synthesis and their biological activities. *European Journal of Medicinal Chemistry* 246:114962. doi: 10.1016/j.ejmech.2022.114962.

Grewal, A. K., T. G. Singh, D. Sharma, V. Sharma, M. Singh, M. H. Rahman, A. Najda, M. Walasek-Janusz, M. Kamel, G. M. Albadrani, et al. 2021. Mechanistic insights and perspectives involved in neuroprotective action of quercetin. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 140:111729. doi: 10.1016/j.biopha.2021.111729.

Griñán-Ferré, C., A. Bellver-Sanchis, V. Izquierdo, R. Corpas, J. Roig-Soriano, M. Chillón, C. Andres-Lacueva, M. Somogyvári, C. Sőti, C. Sanfeliu, et al. 2021. The pleiotropic neuroprotective effects of resveratrol in cognitive decline and Alzheimer's disease pathology: From antioxidant to epigenetic therapy. *Ageing Research Reviews* 67:101271. doi: 10.1016/j.arr.2021.101271.

Gumay, A. R., S. Bakri, and D. Pudjonarko. 2018. The effect of green tea epigallocatechin-3-gallate on spatial memory function, malondialdehyde and TNF-α level in d-galactose-induced BALB/C mice. *Hiroshima Journal of Medical Sciences* 67:41–8.

Guo, Y., Z. Fan, S. Zhao, W. Yu, X. Hou, S. Nie, S. Xu, C. Zhao, J. Han, and X. Liu. 2023. Brain-targeted lycopene-loaded microemulsion modulates neuroinflammation, oxidative stress, apoptosis and synaptic plasticity in β-amyloid-induced Alzheimer's disease mice. *Neurological Research* 45 (8):753–64. doi: 10.1080/01616412.2023.2203615.

Haller, S., M. L. Montandon, C. Rodriguez, F. R. Herrmann, and P. Giannakopoulos. 2018. Impact of coffee, wine, and chocolate consumption on cognitive outcome and MRI parameters in old age. *Nutrients* 10 (10):1391. doi: 10.3390/nu10101391.

Hannan, M. A., R. Dash, A. A. M. Sohag, M. N. Haque, and I. S. Moon. 2020. Neuroprotection against oxidative stress: Phytochemicals targeting TrkB signaling and the Nrf2-ARE antioxidant system. *Frontiers in Molecular Neuroscience* 13:116. doi: 10.3389/fnmol.2020.00116.

Hantikainen, E., Y. T. Lagerros, W. Ye, M. Serafini, H. O. Adami, R. Bellocco, and S. Bonn. 2021. Dietary antioxidants and the risk of Parkinson disease: The Swedish National March Cohort. *Neurology* 96 (6):e895–e903. doi: 10.1212/WNL.0000000000011373.

Hartman, R. E., and D. M. Ross. 2018. Effects and mechanisms of actions of phytochemicals on Alzheimer's disease neuropathology.

Frontiers in Bioscience (Elite Edition) 10 (2):300–33. doi: 10.2741/e824.

He, W., K. Yuan, B. Ji, Y. Han, and J. Li. 2020. Protective effects of curcumin against neuroinflammation induced by Aβ25-35 in primary rat microglia: Modulation of high-mobility group box 1, toll-like receptor 4 and receptor for advanced glycation end products expression. *Annals of Translational Medicine* 8 (4):88– doi: 10.21037/atm.2019.12.147.

Hein, S., A. R. Whyte, E. Wood, A. Rodriguez-Mateos, and C. M. Williams. 2019. Systematic review of the effects of blueberry on cognitive performance as we age. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 74 (7):984–95. doi: 10.1093/gerona/glz082.

Heitman, E., and D. K. Ingram. 2017. Cognitive and neuroprotective effects of chlorogenic acid. *Nutritional Neuroscience* 20 (1):32–9. doi: 10.1179/1476830514Y.0000000146.

Hill, E., A. M. Goodwill, A. Gorelik, and C. Szoeke. 2019. Diet and biomarkers of Alzheimer's disease: A systematic review and meta-analysis. *Neurobiology of Aging* 76:45–52. doi: 10.1016/j.neurobiolaging.2018.12.008.

Hong, Y., and Z. An. 2018. Hesperidin attenuates learning and memory deficits in APP/PS1 mice through activation of Akt/Nrf2 signaling and inhibition of RAGE/NF-κB signaling. *Archives of Pharmacal Research* 41 (6):655–63. doi: 10.1007/s12272-015-0662-z.

Huang, H., Q. Hong, H. L. Tan, C. R. Xiao, and Y. Gao. 2016. Ferulic acid prevents LPS-induced up-regulation of PDE4B and stimulates the cAMP/CREB signaling pathway in PC12 cells. *Acta Pharmacologica Sinica* 37 (12):1543–54. doi: 10.1038/aps.2016.88.

Huang, J., N. Huang, S. Xu, Y. Luo, Y. Li, H. Jin, C. Yu, J. Shi, and F. Jin. 2021. Signaling mechanisms underlying inhibition of neuroinflammation by resveratrol in neurodegenerative diseases. *The Journal of Nutritional Biochemistry* 88:108552. doi: 10.1016/j.jnutbio.2020.108552.

Ishida, K., K. Misawa, H. Nishimura, T. Hirata, M. Yamamoto, and N. Ota. 2020b. 5-Caffeoylquinic acid ameliorates cognitive decline and reduces Aβ deposition by modulating Aβ clearance pathways in APP/PS2 transgenic mice. *Nutrients* 12 (2):494. doi: 10.3390/nu12020494.

Ishida, K., M. Yamamoto, K. Misawa, H. Nishimura, K. Misawa, N. Ota, and A. Shimotoyodome. 2020a. Coffee polyphenols prevent cognitive dysfunction and suppress amyloid β plaques in APP/PS2 transgenic mouse. *Neuroscience Research* 154:35–44. doi: 10.1016/j.neures.2019.05.001.

Islam, F., M. M. Islam, A. F. K. Meem, M. H. Nafady, M. R. Islam, A. Akter, S. Mitra, F. A. Alhumaydhi, T. B. Emran, A. Khusro, et al. 2022. Multifaceted role of polyphenols in the treatment and management of neurodegenerative diseases. *Chemosphere* 339 (Pt 3):139655. doi: 10.1016/j.chemosphere.2022.136020.

Jadhav, R., and Y. A. Kulkarni. 2023. Neuroprotective effect of quercetin and memantine against AlCl3-induced neurotoxicity in albino Wistar rats. *Molecules (Basel, Switzerland)* 28 (1):417. doi: 10.3390/molecules28010417.

Jain, J., W. Hasan, P. Biswas, R. S. Yadav, and D. Jat. 2022. Neuroprotective effect of quercetin against rotenone-induced neuroinflammation and alterations in mice behavior. *Journal of Biochemical and Molecular Toxicology* 36 (10):e23165. doi: 10.1002/jbt.23165.

Javed, H., K. Vaibhav, M. E. Ahmed, A. Khan, R. Tabassum, F. Islam, M. M. Safhi, and F. Islam. 2015. Effect of hesperidin on neurobehavioral, neuroinflammation, oxidative stress and lipid alteration in intracerebroventricular streptozotocin induced cognitive impairment in mice. *Journal of the Neurological Sciences* 348 (1-2):51–9. doi: 10.1016/j.jns.2014.10.044.

Jin, X., W. He, Y. Zhang, E. Gong, Z. Niu, J. Ji, Y. Li, Y. Zeng, and L. L. Yan. 2021. Association of APOE ε4 genotype and lifestyle with cognitive function among Chinese adults aged 80 years and older: A cross-sectional study. *PLoS Medicine* 18 (6):e1003597. doi: 10.1371/journal.pmed.1003597.

Joseph, L., and C. Ravi. 2022. Physalis minima L. fruit-a promising approach to Alzheimer's disease. *Pharmacological Research - Modern Chinese Medicine* 2:100038. doi: 10.1016/j.prmcm.2021.100038.

Josiah, S. S., C. D. Famusiwa, O. O. Crown, A. O. Lawal, M. T. Olaleye, A. A. Akindahunsi, and A. C. Akinmoladun. 2022. Neuroprotective effects of catechin and quercetin in experimental Parkinsonism through modulation of dopamine metabolism and expression of IL-1β, TNF-α, NF-κB, IκKB, and p53 genes in male Wistar rats. *Neurotoxicology* 90:158–71. doi: 10.1016/j.neuro.2022.03.004.

Jung, U. J., and S. R. Kim. 2018. Beneficial effects of flavonoids against Parkinson's disease. *Journal of Medicinal Food* 21 (5):421–32. doi: 10.1089/jmf.2017.4078.

Jurcau, A. 2021. The role of natural antioxidants in the prevention of dementia—Where do we stand and future perspectives. *Nutrients* 13 (2):282. doi: 10.3390/nu13020282.

Justin Thenmozhi, A., T. R. W. Raja, T. Manivasagam, U. Janakiraman, and M. M. Essa. 2017. Hesperidin ameliorates cognitive dysfunction, oxidative stress and apoptosis against aluminium chloride induced rat model of Alzheimer's disease. *Nutritional Neuroscience* 20 (6):360–8. doi: 10.1080/1028415X.2016.1144846.

Kabir, M. T., M. H. Rahman, M. Shah, M. R. Jamiruddin, D. Basak, A. Al-Harrasi, S. Bhatia, G. M. Ashraf, A. Najda, A. F. El-Kott, et al. 2022. Therapeutic promise of carotenoids as antioxidants and anti-inflammatory agents in neurodegenerative disorders. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 146:112610. doi: 10.1016/j.biopha.2021.112610.

Kato, M., R. Ochiai, K. Kozuma, H. Sato, and Y. Katsuragi. 2018. Effect of chlorogenic acid intake on cognitive function in the elderly: A pilot study. *Evidence-Based Complementary and Alternative Medicine: ECAM* 2018:8608497–8. doi: 10.1155/2018/8608497.

Kempuraj, D., R. Thangavel, D. D. Kempuraj, M. E. Ahmed, G. P. Selvakumar, S. P. Raikwar, S. A. Zaheer, S. S. Iyer, R. Govindarajan, P. N. Chandrasekaran, et al. 2021. Neuroprotective effects of flavone luteolin in neuroinflammation and neurotrauma. *BioFactors (Oxford, England)* 47 (2):190–7. doi: 10.1002/biof.1687.

Kesh, S., R. R. Kannan, K. Sivaji, and A. Balakrishnan. 2021. Hesperidin downregulates kinases lrrk2 and gsk3β in a 6-OHDA induced Parkinson's disease model. *Neuroscience Letters* 740:135426. doi: 10.1016/j.neulet.2020.135426.

Khalil, M. G., A. A. Ali, S. O. Hassanin, A. H. Al-Najjar, S. Ghosh, and M. O. Mahmoud. 2022. Comparative study on the effect of and grass together with mental and physical activities against induction of Alzheimer's disease in both isolated and socialized rats. *Phytomedicine Plus* 2 (1):100146. doi: 10.1016/j.phyplu.2021.100146.

Khan, H., H. Ullah, M. Aschner, W. S. Cheang, and E. K. Akkol. 2019. Neuroprotective effects of quercetin in Alzheimer's disease. *Biomolecules* 10 (1):59. doi: 10.3390/biom10010059.

Khoo, H. E., A. Azlan, S. T. Tang, and S. M. Lim. 2017. Anthocyanidins and anthocyanins: Colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food & Nutrition Research* 61 (1):1361779. doi: 10.1080/16546628.2017.1361779.

Kilinc, Y. B., M. Dilek, E. Kilinc, I. E. Torun, A. Saylan, and S. E. Duzcu. 2023. Capsaicin attenuates excitotoxic-induced neonatal brain injury and brain mast cell-mediated neuroinflammation in newborn rats. *Chemico-Biological Interactions* 376:110450. doi: 10.1016/j.cbi.2023.110450.

Kim, E., N. M. Robinson, and B. M. Newman. 2022. A brewed awakening: Neuropsychiatric effects of caffeine in older adults. *Clinics in Geriatric Medicine* 38 (1):133–44. doi: 10.1016/j.cger.2021.07.009.

Kim, J. H., J. Hwang, E. Shim, E. J. Chung, S. H. Jang, and S. B. Koh. 2017. Association of serum carotenoid, retinol, and tocopherol concentrations with the progression of Parkinson's Disease. *Nutrition Research and Practice* 11 (2):114–20. doi: 10.4162/nrp.2017.11.2.114.

Kim, J. W., M. S. Byun, D. Yi, J. H. Lee, S. Y. Jeon, G. Jung, H. N. Lee, B. K. Sohn, J. Y. Lee, Y. K. Kim, et al. 2019. Coffee intake and decreased amyloid pathology in human brain. *Translational Psychiatry* 9 (1):270. doi: 10.1038/s41398-019-0604-5.

Kohandel, Z., T. Farkhondeh, M. Aschner, A. M. Pourbagher-Shahri, and S. Samarghandian. 2022. Anti-inflammatory action of astaxanthin and its use in the treatment of various diseases. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 145:112179. doi: 10.1016/j.biopha.2021.112179.

Kong, D., Y. Yan, X. Y. He, H. Yang, B. Liang, J. Wang, Y. He, Y. Ding, and H. Yu. 2019. Effects of resveratrol on the mechanisms of antioxidants and estrogen in Alzheimer's disease. *BioMed Research International* 2019:8983752–8. doi: 10.1155/2019/8983752.

Kou, J. J., J. Z. Shi, Y. Y. He, J. J. Hao, H. Y. Zhang, D. M. Luo, J. K. Song, Y. Yan, X. M. Xie, G. H. Du, et al. 2022. Luteolin alleviates cognitive impairment in Alzheimer's disease mouse model via inhibiting endoplasmic reticulum stress-dependent neuroinflammation. *Acta Pharmacologica Sinica* 43 (4):840–9. doi: 10.1038/s41401-021-00702-8.

Kunkle, B. W., M. Schmidt, H. U. Klein, A. C. Naj, K. L. Hamilton-Nelson, E. B. Larson, D. A. Evans, P. L. De Jager, P. K. Crane, J. D. Buxbaum, et al. 2021. Novel Alzheimer disease risk loci and pathways in African American individuals using the African genome resources panel: A meta-analysis. *JAMA Neurology* 78 (1):102–13. doi: 10.1001/jamaneurol.2020.3536.

Kwon, Y. 2017. Luteolin as a potential preventive and therapeutic candidate for Alzheimer's disease. *Experimental Gerontology* 95:39–43. doi: 10.1016/j.exger.2017.05.014.

La Spina, M., G. Sansevero, L. Biasutto, M. Zoratti, R. Peruzzo, N. Berardi, A. Sale, and M. Azzolini. 2019. Pterostilbene improves cognitive performance in aged rats: An in vivo study. *Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology* 52 (2):232–9. doi: 10.33594/000000017.

Labban, S., B. S. Alghamdi, F. S. Alshehri, and M. Kurdi. 2021. Effects of melatonin and resveratrol on recognition memory and passive avoidance performance in a mouse model of Alzheimer's disease. *Behavioural Brain Research* 402:113100. doi: 10.1016/j.bbr.2020.113100.

Li, D., H. Yang, M. Lyu, L. Zhou, Y. Zhang, C. Kang, J. Wang, and Y. Wang. 2023a. Association between behavioural risks and Alzheimer's disease: Elucidated with an integrated analysis of gene expression patterns and molecular mechanisms. *Neuroscience and Biobehavioral Reviews* 150:105207. doi: 10.1016/j.neubiorev.2023.105207.

Li, F., T. Hatano, and N. Hattori. 2021. Systematic analysis of the molecular mechanisms mediated by coffee in Parkinson's disease based on network pharmacology approach. *Journal of Functional Foods* 87:104764. doi: 10.1016/j.jff.2021.104764.

Li, H., Y. Shen, H. Xiao, and W. Sun. 2021. Resveratrol attenuates rotenone-induced inflammation and oxidative stress via STAT1 and Nrf2/Keap1/SLC7A11 pathway in a microglia cell line. *Pathology, Research and Practice* 225:153576. doi: 10.1016/j.prp.2021.153576.

Li, N., X. Gao, L. Zheng, Q. Huang, F. Zeng, H. Chen, M. A. Farag, and C. Zhao. 2022b. Advances in fucoxanthin chemistry and management of neurodegenerative diseases. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 105:154352. doi: 10.1016/j.phymed.2022.154352.

Li, P., D. Feng, D. Yang, X. Li, J. Sun, G. Wang, L. Tian, X. Jiang, and W. Bai. 2021a. Protective effects of anthocyanins on neurodegenerative diseases. *Trends in Food Science & Technology* 117:205–17. doi: 10.1016/j.tifs.2021.05.005.

Li, Q., X. Li, B. Tian, and L. Chen. 2022a. Protective effect of pterostilbene in a streptozotocin-induced mouse model of Alzheimer's disease by targeting monoamine oxidase B. *Journal of Applied Toxicology: JAT* 42 (11):1777–86. doi: 10.1002/jat.4355.

Li, X., W. Huang, R. Tan, C. Xu, X. Chen, S. Li, Y. Liu, H. Qiu, H. Cao, and Q. Cheng. 2023b. The benefits of hesperidin in central nervous system disorders, based on the neuroprotective effect. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 159:114222. doi: 10.1016/j.biopha.2023.114222.

Li, Y. L., H. Guo, Y. Q. Zhao, A. F. Li, Y. Q. Ren, and J. W. Zhang. 2017. Quercetin protects neuronal cells from oxidative stress and cognitive degradation induced by amyloid β-peptide treatment. *Molecular Medicine Reports* 16 (2):1573–7. doi: 10.3892/mmr.2017.6704.

Li, Y., S. Zhou, J. Li, Y. Sun, H. Hasimu, R. Liu, and T. Zhang. 2015. Quercetin protects human brain microvascular endothelial cells from fibrillar β-amyloid1–40-induced toxicity. *Acta Pharmaceutica Sinica. B* 5 (1):47–54. doi: 10.1016/j.apsb.2014.12.003.

Liu, C. B., R. Wang, Y. F. Yi, Z. Gao, and Y. Z. Chen. 2018. Lycopene mitigates β-amyloid induced inflammatory response and inhibits NF-κB signaling at the choroid plexus in early stages of Alzheimer's disease rats. *The Journal of Nutritional Biochemistry* 53:66–71. doi: 10.1016/j.jnutbio.2017.10.014.

Liu, J., H. Liu, Z. Zhao, J. Wang, D. Guo, and Y. Liu. 2020. Regulation of Actg1 and Gsta2 is possible mechanism by which capsaicin alleviates apoptosis in cell model of 6-OHDA-induced Parkinson's disease. *Bioscience Reports* 40 (6):BSR20191796. doi: 10.1042/BSR20191796.

Livingston, G., J. Huntley, A. Sommerlad, D. Ames, C. Ballard, S. Banerjee, C. Brayne, A. Burns, J. Cohen-Mansfield, C. Cooper, et al. 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet (London, England)* 396 (10248):413–46. doi: 10.1016/S0140-6736(20)30367-6.

Luo, M., R.-Y. Gan, B.-Y. Li, Q.-Q. Mao, A. Shang, X.-Y. Xu, H.-Y. Li, and H.-B. Li. 2023. Effects and mechanisms of tea on Parkinson's disease, Alzheimer's disease and depression. *Food Reviews International* 39 (1):278–306. doi: 10.1080/87559129.2021.1904413.

Maher, P. 2019. The potential of flavonoids for the treatment of neurodegenerative diseases. *International Journal of Molecular Sciences* 20 (12):3056. doi: 10.3390/ijms20123056.

Manochkumar, J., C. G. P. Doss, H. R. El-Seedi, T. Efferth, and S. Ramamoorthy. 2021. The neuroprotective potential of carotenoids in vitro and in vivo. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 91:153676. doi: 10.1016/j.phymed.2021.153676.

Matias, I., L. P. Diniz, A. Buosi, G. Neves, J. Stipursky, and F. Gomes. 2017. Flavonoid hesperidin induces synapse formation and improves memory performance through the astrocytic TGF-β1. *Frontiers in Aging Neuroscience* 9:184. doi: 10.3389/fnagi.2017.00184.

Mattioli, R., A. Francioso, L. Mosca, and P. Silva. 2020. Anthocyanins: A comprehensive review of their chemical properties and health effects on cardiovascular and neurodegenerative diseases. *Molecules (Basel, Switzerland)* 25 (17):3809. doi: 10.3390/molecules25173809.

Mohammadzadeh Honarvar, N., A. Saedisomeolia, M. Abdolahi, A. Shayeganrad, G. Taheri Sangsari, B. Hassanzadeh Rad, and G. Muench. 2017. Molecular anti-inflammatory mechanisms of retinoids and carotenoids in Alzheimer's disease: A review of current evidence. *Journal of Molecular Neuroscience: MN* 61 (3):289–304. doi: 10.1007/s12031-016-0857-x.

Molino, S., M. Dossena, D. Buonocore, F. Ferrari, L. Venturini, G. Ricevuti, and M. Verri. 2016. Polyphenols in dementia: From molecular basis to clinical trials. *Life Sciences* 161:69–77. doi: 10.1016/j.lfs.2016.07.021.

Mori, T., N. Koyama, J. Tan, T. Segawa, M. Maeda, and T. Town. 2019. Combined treatment with the phenolics (−)-epigallocatechin-3-gallate and ferulic acid improves cognition and reduces Alzheimer-like pathology in mice. *The Journal of Biological Chemistry* 294 (8):2714–31. doi: 10.1074/jbc.RA118.004280.

Muhammad, T., M. Ikram, R. Ullah, S. U. Rehman, and M. O. Kim. 2019. Hesperetin, a citrus flavonoid, attenuates LPS-induced neuroinflammation, apoptosis and memory impairments by modulating TLR4/NF-κB signaling. *Nutrients* 11 (3):648. doi: 10.3390/nu11030648.

Nabavi, S. F., H. Khan, G. D'onofrio, D. Šamec, S. Shirooie, A. R. Dehpour, S. Argüelles, S. Habtemariam, and E. Sobarzo-Sanchez. 2018. Apigenin as neuroprotective agent: Of mice and men. *Pharmacological Research* 128:359–65. doi: 10.1016/j.phrs.2017.10.008.

Nagarajan, S., S. Mohandas, K. Ganesan, B. Xu, and K. M. Ramkumar. 2022. New insights into dietary pterostilbene: Sources, metabolism, and health promotion effects. *Molecules (Basel, Switzerland)* 27 (19):6316. doi: 10.3390/molecules27196316.

Nakagawa, T. 2022. Luteolin ameliorates depression-like behaviors by suppressing ER stress in a mouse model of Alzheimer's disease. *Biochemical and Biophysical Research communications* 588:168–174. doi: 10.1016/j.bbrc.2021.12.074.

Nakagawa, T., M. Itoh, K. Ohta, Y. Hayashi, M. Hayakawa, Y. Yamada, H. Akanabe, T. Chikaishi, K. Nakagawa, Y. Itoh, T., et al. 2016. Improvement of memory recall by quercetin in rodent contextual fear conditioning and human early-stage Alzheimer's disease patients. *Neuroreport* 27(9):671–76. doi: 10.1097/WNR.0000000000000594.

Nan, S., P. Wang, Y. Zhang, and J. Fan. 2021. Epigallocatechin-3-gallate provides protection against Alzheimer's disease-induced learning and

memory impairments in rats. *Drug Design, Development and Therapy* 15:2013–24. doi: 10.2147/DDDT.S289473.
Naseri, N. N., H. Wang, J. Guo, M. Sharma, and W. Luo. 2019. The complexity of tau in Alzheimer's disease. *Neuroscience Letters* 705:183–94. doi: 10.1016/j.neulet.2019.04.022.
Nimse, S. B., and D. Pal. 2015. Free radicals, natural antioxidants, and their reaction mechanisms. *RSC Advances* 5 (35):27986–8006. doi: 10.1039/C4RA13315C.
Nishihira, J., M. Nishimura, M. Kurimoto, H. Kagami-Katsuyama, H. Hattori, T. Nakagawa, T. Muro, and M. Kobori. 2021. The effect of 24-week continuous intake of quercetin-rich onion on age-related cognitive decline in healthy elderly people: A randomized, double-blind, placebo-controlled, parallel-group comparative clinical trial. *Journal of Clinical Biochemistry and Nutrition* 69 (2):203–15. doi: 10.3164/jcbn.21-17.
Nishimura, M., T. Ohkawara, T. Nakagawa, T. Muro, Y. Sato, H. Satoh, M. Kobori, and J. Nishihira. 2017. A randomized, double-blind, placebo-controlled study evaluating the effects of quercetin-rich onion on cognitive function in elderly subjects. *Functional Foods in Health and Disease* 7 (6):353–74. doi: 10.31989/ffhd.v7i6.334.
Ochiai, R., K. Saitou, C. Suzukamo, N. Osaki, and T. Asada. 2019. Effect of chlorogenic acids on cognitive function in mild cognitive impairment: A randomized controlled crossover trial. *Journal of Alzheimer's Disease: JAD* 72 (4):1209–16. doi: 10.3233/JAD-190757.
Olayinka, J., A. Eduviere, O. Adeoluwa, A. Fafure, A. Adebanjo, and R. Ozolua. 2022. Quercetin mitigates memory deficits in scopolamine mice model via protection against neuroinflammation and neurodegeneration. *Life Sciences* 292:120326. doi: 10.1016/j.lfs.2022.120326.
Oliyaei, N., M. Moosavi-Nasab, N. Tanideh, and A. Iraji. 2022. Multiple roles of fucoxanthin and astaxanthin against Alzheimer's disease: Their pharmacological potential and therapeutic insights. *Brain Research Bulletin* 193:11–21. doi: 10.1016/j.brainresbull.2022.11.018.
Özduran, G., E. Becer, and H. S. Vatansever. 2023. The role and mechanisms of action of catechins in neurodegenerative diseases. *Journal of the American Nutrition Association* 42 (1):67–74. doi: 10.1080/07315724.2021.1981487.
Pan, X., X. Liu, H. Zhao, B. Wu, and G. Liu. 2020. Antioxidant, anti-inflammatory and neuroprotective effect of kaempferol on rotenone-induced Parkinson's disease model of rats and SH-S5Y5 cells by preventing loss of tyrosine hydroxylase. *Journal of Functional Foods* 74:104140. doi: 10.1016/j.jff.2020.104140.
Park, H. A., M. M. Hayden, S. Bannerman, J. Jansen, and K. M. Crowe-White. 2020. Anti-apoptotic effects of carotenoids in neurodegeneration. *Molecules (Basel, Switzerland)* 25 (15):3453. doi: 10.3390/molecules25153453.
Pasierski, M., and B. Szulczyk. 2022. Beneficial effects of capsaicin in disorders of the central nervous system. *Molecules (Basel, Switzerland)* 27 (8):2484. doi: 10.3390/molecules27082484.
Paul, R., M. K. Mazumder, J. Nath, S. Deb, S. Paul, P. Bhattacharya, and A. Borah. 2020. Lycopene-a pleiotropic neuroprotective nutraceutical: Deciphering its therapeutic potentials in broad spectrum neurological disorders. *Neurochemistry International* 140:104823. doi: 10.1016/j.neuint.2020.104823.
Poulose, S. M., N. Thangthaeng, M. G. Miller, and B. Shukitt-Hale. 2015. Effects of pterostilbene and resveratrol on brain and behavior. *Neurochemistry International* 89:227–33. doi: 10.1016/j.neuint.2015.07.017.
Ragheb, A. Y., M. A. El-Ansari, O. A. Heikal, A. F. Galal, A. A. Salama, M. E. Kassem, and N. A. Saleh. 2023. Phenolic glycosides and bioactive Mangifera indica L. Kernel extract as neuroprotective agents against LPS-induced Alzheimer's disease in rats. *South African Journal of Botany* 157:37–43. doi: 10.1016/j.sajb.2023.03.045.
Reddy, P. H., M. Manczak, X. Yin, M. C. Grady, A. Mitchell, S. Tonk, C. S. Kuruva, J. S. Bhatti, R. Kandimalla, M. Vijayan, et al. 2018. Protective effects of Indian spice curcumin against amyloid-β in Alzheimer's disease. *Journal of Alzheimer's Disease: JAD* 61 (3):843–66. doi: 10.3233/JAD-170512.
Román, G. C., R. E. Jackson, R. Gadhia, A. N. Román, and J. Reis. 2019. Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. *Revue Neurologique* 175 (10):724–41. doi: 10.1016/j.neurol.2019.08.005.
Ruiss, M., O. Findl, and M. Kronschläger. 2022. The human lens: An antioxidant-dependent tissue revealed by the role of caffeine. *Ageing Research Reviews* 79:101664. doi: 10.1016/j.arr.2022.101664.
Rusmini, P., R. Cristofani, B. Tedesco, V. Ferrari, E. Messi, M. Piccolella, E. Casarotto, M. Chierichetti, M. E. Cicardi, M. Galbiati, et al. 2020. Enhanced clearance of neurotoxic misfolded proteins by the natural compound berberine and its derivatives. *International Journal of Molecular Sciences* 21 (10):3443. doi: 10.3390/ijms21103443.
Sachdeva, A. K., and K. Chopra. 2015. Lycopene abrogates Aβ (1–42)-mediated neuroinflammatory cascade in an experimental model of Alzheimer's disease. *The Journal of Nutritional Biochemistry* 26 (7):736–44. doi: 10.1016/j.jnutbio.2015.01.012.
Saini, R. K., K. R. Rengasamy, F. M. Mahomoodally, and Y. S. Keum. 2020. Protective effects of lycopene in cancer, cardiovascular, and neurodegenerative diseases: An update on epidemiological and mechanistic perspectives. *Pharmacological Research* 155:104730. doi: 10.1016/j.phrs.2020.104730.
Saitou, K., R. Ochiai, K. Kozuma, H. Sato, T. Koikeda, N. Osaki, and Y. Katsuragi. 2018. Effect of chlorogenic acids on cognitive function: A randomized, double-blind, placebo-controlled trial. *Nutrients* 10 (10):1337. doi: 10.3390/nu10101337.
Sajad, M., R. Kumar, and S. C. Thakur. 2022. History in perspective: The prime pathological players and role of phytochemicals in Alzheimer's disease. *IBRO Neuroscience Reports* 12:377–89. doi: 10.1016/j.ibneur.2022.04.009.
Salehi, B., A. Venditti, M. Sharifi-Rad, D. Kręgiel, J. Sharifi-Rad, A. Durazzo, M. Lucarini, A. Santini, E. B. Souto, E. Novellino, et al. 2019. The therapeutic potential of apigenin. *International Journal of Molecular Sciences* 20 (6):1305. doi: 10.3390/ijms20061305.
Sánchez-Giraldo, V., Y. Monsalve, J. Palacio, M. Mendivil-Perez, L. Sierra, C. Velez-Pardo, B. L. López, and M. Jiménez-Del-Rio. 2020. Role of a novel (−)-epigallocatechin-3-gallate delivery system on the prevention against oxidative stress damage in vitro and in vivo model of Parkinson's disease. *Journal of Drug Delivery Science and Technology* 55:101466. doi: 10.1016/j.jddst.2019.101466.
Santhiravel, S., A. E.-D A. Bekhit, E. Mendis, J. L. Jacobs, F. R. Dunshea, N. Rajapakse, and E. N. Ponnampalam. 2022. The impact of plant phytochemicals on the gut microbiota of humans for a balanced life. *International Journal of Molecular Sciences* 23 (15):8124. 23 doi: 10.3390/ijms23158124.
Sarker, M. R., and S. F. Franks. 2018. Efficacy of curcumin for age-associated cognitive decline: A narrative review of preclinical and clinical studies. *GeroScience* 40 (2):73–95. doi: 10.1007/s11357-018-0017-z.
Sarroca, S., A. Gatius, E. Rodríguez-Farré, D. Vilchez, M. Pallàs, C. Griñán-Ferré, C. Sanfeliu, and R. Corpas. 2021. Resveratrol confers neuroprotection against high-fat diet in a mouse model of Alzheimer's disease via modulation of proteolytic mechanisms. *The Journal of Nutritional Biochemistry* 89:108569. doi: 10.1016/j.jnutbio.2020.108569.
Sarubbo, F., M. R. Ramis, S. Tejada, M. Jiménez-Garcia, S. Esteban, A. Miralles, and D. Moranta. 2023. Resveratrol improves episodic-like memory and motor coordination through modulating neuroinflammation in old rats. *Journal of Functional Foods* 104:105533. doi: 10.1016/j.jff.2023.105533.
Sauer, L., B. Li, and P. S. Bernstein. 2019. Ocular carotenoid status in health and disease. *Annual Review of Nutrition* 39 (1):95–120. doi: 10.1146/annurev-nutr-082018-124555.
Scheiblich, H., M. Trombly, A. Ramirez, and M. T. Heneka. 2020. Neuroimmune connections in aging and neurodegenerative diseases. *Trends in Immunology* 41 (4):300–12. doi: 10.1016/j.it.2020.02.002.
Schirinzi, T., G. Martella, P. Imbriani, G. Di Lazzaro, D. Franco, V. L. Colona, M. Alwardat, P. Sinibaldi Salimei, N. B. Mercuri, M. Pierantozzi, et al. 2019. Dietary vitamin E as a protective factor for Parkinson's disease: Clinical and experimental evidence. *Frontiers in Neurology* 10:148. doi: 10.3389/fneur.2019.00148.
Sedaghat, G., M. A. Mirshekar, M. Amirpour, F. Montazerifar, S. Miri, and S. Shourestani. 2019. Sub-chronic administration of brewed cof-

fee on rat behavior and cognition and oxidative stress Alzheimer's disease model. *Clinical Nutrition Experimental* 28:62–73. doi: 10.1016/j.yclnex.2019.10.005.

Seo, E. J., N. Fischer, and T. Efferth. 2018. Phytochemicals as inhibitors of NF-κB for treatment of Alzheimer's disease. *Pharmacological Research* 129:262–73. doi: 10.1016/j.phrs.2017.11.030.

Shakeri, A., Y. Panahi, T. P. Johnston, and A. Sahebkar. 2019. Biological properties of metal complexes of curcumin. *BioFactors (Oxford, England)* 45 (3):304–17. doi: 10.1002/biof.1504.

Sharma, N., and B. Nehru. 2018. Curcumin affords neuroprotection and inhibits α-synuclein aggregation in lipopolysaccharide-induced Parkinson's disease model. *Inflammopharmacology* 26 (2):349–60. doi: 10.1007/s10787-017-0402-8.

Sharma, N., R. Soni, M. Sharma, S. Chatterjee, N. Parihar, M. Mukarram, R. Kale, A. A. Sayyed, S. K. Behera, and A. Khairnar. 2022. Chlorogenic acid: A polyphenol from coffee rendered neuroprotection against rotenone-induced Parkinson's disease by GLP-1 secretion. *Molecular Neurobiology* 59 (11):6834–56. doi: 10.1007/s12035-022-03005-z.

Sharma, P., K. Aggarwal, R. Awasthi, G. T. Kulkarni, and B. Sharma. 2021. Behavioral and biochemical investigations to explore the efficacy of quercetin and folacin in experimental diabetes induced vascular endothelium dysfunction and associated dementia in rats. *Journal of Basic and Clinical Physiology and Pharmacology* 34 (5):603–15. doi: 10.1515/jbcpp-2020-0159.

Sharma, S., K. Raj, and S. Singh. 2020. Neuroprotective effect of quercetin in combination with piperine against rotenone-and iron supplement–induced Parkinson's disease in experimental rats. *Neurotoxicity Research* 37 (1):198–209. doi: 10.1007/s12640-019-00120-z.

Shishtar, E., G. T. Rogers, J. B. Blumberg, R. Au, and P. F. Jacques. 2020. Long-term dietary flavonoid intake and risk of Alzheimer disease and related dementias in the Framingham Offspring Cohort. *The American Journal of Clinical Nutrition* 112 (2):343–53. doi: 10.1093/ajcn/nqaa079.

Shunan, D., M. Yu, H. Guan, and Y. Zhou. 2021. Neuroprotective effect of Betalain against AlCl3-induced Alzheimer's disease in Sprague Dawley Rats via putative modulation of oxidative stress and nuclear factor kappa B (NF-κB) signaling pathway. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 137:111369. doi: 10.1016/j.biopha.2021.111369.

Siddique, Y. H. 2021. Role of luteolin in overcoming Parkinson's disease. *BioFactors (Oxford, England)* 47 (2):198–206. doi: 10.1002/biof.1706.

Singh, N. K., and D. Garabadu. 2021. Quercetin exhibits α7nAChR/Nrf2/HO-1-mediated neuroprotection against STZ-induced mitochondrial toxicity and cognitive impairments in experimental rodents. *Neurotoxicity Research* 39 (6):1859–79. doi: 10.1007/s12640-021-00410-5.

Singh, S. S., S. N. Rai, H. Birla, W. Zahra, G. Kumar, M. R. Gedda, N. Tiwari, R. Patnaik, R. K. Singh, and S. P. Singh. 2023. Effect of chlorogenic acid supplementation in MPTP-intoxicated mouse. *Frontiers in Pharmacology* 14:1145172. doi: 10.3389/fphar.2023.1145172.

Singh, S., R. Arthur, S. Upadhayay, and P. Kumar. 2022. Ferulic acid ameliorates neurodegeneration via the Nrf2/ARE signalling pathway: A Review. *Pharmacological Research - Modern Chinese Medicine* 5:100190. doi: 10.1016/j.prmcm.2022.100190.

Singla, R. K., A. K. Dubey, A. Garg, R. K. Sharma, M. Fiorino, S. M. Ameen, M. A. Haddad, and M. Al-Hiary. 2019. Natural polyphenols: Chemical classification, definition of classes, subcategories, and structures. *Journal of AOAC International* 102 (5):1397–400. doi: 10.5740/jaoacint.19-0133.

Socała, K., A. Szopa, A. Serefko, E. Poleszak, and P. Wlaź. 2020. Neuroprotective effects of coffee bioactive compounds: A review. *International Journal of Molecular Sciences* 22 (1):107. doi: 10.3390/ijms22010107.

Steiner, N., R. Balez, N. Karunaweera, J. M. Lind, G. Münch, and L. Ooi. 2016. Neuroprotection of Neuro2a cells and the cytokine suppressive and anti-inflammatory mode of action of resveratrol in activated RAW264. 7 macrophages and C8–B4 microglia. *Neurochemistry International* 95:46–54. doi: 10.1016/j.neuint.2015.10.013.

Su, C. F., L. Jiang, X. W. Zhang, A. Iyaswamy, and M. Li. 2021. Resveratrol in rodent models of Parkinson's disease: A systematic review of experimental studies. *Frontiers in Pharmacology* 12:644219. doi: 10.3389/fphar.2021.644219.

Sun, Z. Z., X. Y. Li, S. Wang, L. Shen, and H. F. Ji. 2020. Bidirectional interactions between curcumin and gut microbiota in transgenic mice with Alzheimer's disease. *Applied Microbiology and Biotechnology* 104 (8):3507–15. doi: 10.1007/s00253-020-10461-x.

Szwajgier, D., K. Borowiec, and K. Pustelniak. 2017. The neuroprotective effects of phenolic acids: Molecular mechanism of action. *Nutrients* 9 (5):477. doi: 10.3390/nu9050477.

Talebi, S., S. M. Ghoreishy, A. Jayedi, N. Travica, and H. Mohammadi. 2022. Dietary antioxidants and risk of Parkinson's disease: A systematic review and dose–response meta-analysis of observational studies. *Advances in Nutrition (Bethesda, Md.)* 13 (5):1493–504. doi: 10.1093/advances/nmac001.

Tan, Z., G. Yang, J. Qiu, W. Yan, Y. Liu, Z. Ma, J. Li, J. Liu, and N. Shan. 2022. Quercetin alleviates demyelination through regulating microglial phenotype transformation to mitigate neuropsychiatric symptoms in mice with vascular dementia. *Molecular Neurobiology* 59 (5):3140–58. doi: 10.1007/s12035-021-02712-3.

Taslimi, P., E. Köksal, A. C. Gören, E. Bursal, A. Aras, Ö. Kılıç, S. Alwasel, and I. Gülçin. 2020. Anti-Alzheimer, antidiabetic and antioxidant potential of Satureja cuneifolia and analysis of its phenolic contents by LC-MS/MS. *Arabian Journal of Chemistry* 13 (3):4528–37. doi: 10.1016/j.arabjc.2019.10.002.

Teka, T., L. Zhang, X. Ge, Y. Li, L. Han, and X. Yan. 2022. Stilbenes: Source plants, chemistry, biosynthesis, pharmacology, application and problems related to their clinical application-A comprehensive review. *Phytochemistry* 197:113128. doi: 10.1016/j.phytochem.2022.113128.

Telange, D. R., A. T. Patil, A. M. Pethe, H. Fegade, S. Anand, and V. S. Dave. 2017. Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility, in vivo bioavailability, and antioxidant potential. *European Journal of Pharmaceutical Sciences: Official Journal of the European Federation for Pharmaceutical Sciences* 108:36–49. doi: 10.1016/j.ejps.2016.12.009.

Thummayot, S., C. Tocharus, D. Pinkaew, K. Viwatpinyo, K. Sringarm, and J. Tocharus. 2014. Neuroprotective effect of purple rice extract and its constituent against amyloid beta-induced neuronal cell death in SK-N-SH cells. *Neurotoxicology* 45:149–58. doi: 10.1016/j.neuro.2014.10.010.

Tolosa, E., A. Garrido, S. W. Scholz, and W. Poewe. 2021. Challenges in the diagnosis of Parkinson's disease. *The Lancet. Neurology* 20 (5):385–97. doi: 10.1016/S1474-4422(21)00030-2.

Torregrosa-Crespo, J., Z. Montero, J. L. Fuentes, M. Reig García-Galbis, I. Garbayo, C. Vílchez, and R. M. Martínez-Espinosa. 2018. Exploring the valuable carotenoids for the large-scale production by marine microorganisms. *Marine Drugs* 16 (6):203. doi: 10.3390/md16060203.

Tseng, H. C., M. H. Wang, K. C. Chang, H. S. Soung, C. H. Fang, Y. W. Lin, K. Y. Li, C. C. Yang, and C. C. Tsai. 2020. Protective effect of (−) epigallocatechin-3-gallate on rotenone-induced parkinsonism-like symptoms in rats. *Neurotoxicity Research* 37 (3):669–82. doi: 10.1007/s12640-019-00143-6.

Tyagi, S., N. Shekhar, and A. K. Thakur. 2022. Protective role of capsaicin in neurological disorders: An overview. *Neurochemical Research* 47 (6):1513–31. doi: 10.1007/s11064-022-03549-5.

Uddin, M. S., M. F. Hossain, A. A. Mamun, M. A. Shah, S. Hasana, I. J. Bulbul, M. S. Sarwar, R. A. Mansouri, G. M. Ashraf, A. Rauf, et al. 2020. Exploring the multimodal role of phytochemicals in the modulation of cellular signaling pathways to combat age-related neurodegeneration. *The Science of the Total Environment* 725:138313. doi: 10.1016/j.scitotenv.2020.138313.

Ullah, F., R. Gamage, M. K. Sen, and E. Gyengesi. 2022. The effects of modified curcumin preparations on glial morphology in aging and neuroinflammation. *Neurochemical Research* 47 (4):813–24. doi: 10.1007/s11064-021-03499-4.

USDA. 2019. FoodData central, peppers, hot chili, red, raw. Accessed April 18, 2023. https://fdc.nal.usda.gov/fdc-app.html#/food-details/170106/nutrients

Vaiserman, A., A. Koliada, A. Zayachkivska, and O. Lushchak. 2020. Curcumin: A therapeutic potential in ageing-related disorders. *PharmaNutrition* 14:100226. doi: 10.1016/j.phanu.2020.100226.

Velmurugan, B. K., B. Rathinasamy, B. P. Lohanathan, V. Thiyagarajan, and C. F. Weng. 2018. Neuroprotective role of phytochemicals. *Molecules (Basel, Switzerland)* 23 (10):2485. doi: 10.3390/molecules23102485.

Volkert, D., M. Chourdakis, G. Faxen-Irving, T. Frühwald, F. Landi, M. H. Suominen, M. Vandewoude, R. Wirth, and S. M. Schneider. 2015. ESPEN guidelines on nutrition in dementia. *Clinical Nutrition (Edinburgh, Scotland)* 34 (6):1052–73. doi: 10.1016/j.clnu.2015.09.004.

Voulgaropoulou, S. D., T. A. M. J. van Amelsvoort, J. Prickaerts, and C. Vingerhoets. 2019. The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. *Brain Research* 1725:146476. doi: 10.1016/j.brainres.2019.146476.

Wang, C., W. Huang, J. Lu, H. Chen, and Z. Yu. 2022b. TRPV1-mediated microglial autophagy attenuates Alzheimer's disease-associated pathology and cognitive decline. *Frontiers in Pharmacology* 12:763866. doi: 10.3389/fphar.2021.763866.

Wang, F., Y. Xue, L. Fu, Y. Wang, M. He, L. Zhao, and X. Liao. 2022a. Extraction, purification, bioactivity and pharmacological effects of capsaicin: A review. *Critical Reviews in Food Science and Nutrition* 62 (19):5322–48. doi: 10.1080/10408398.2021.1884840.

Wang, J., B. L. Sun, Y. Xiang, D. Y. Tian, C. Zhu, W. W. Li, Y. H. Liu, X. L. Bu, L. L. Shen, W. S. Jin, et al. 2020. Capsaicin consumption reduces brain amyloid-beta generation and attenuates Alzheimer's disease-type lipopolysaccharide-induced amyloidogenesis and mice. *Translational Psychiatry* 10 (1):230. doi: 10.1038/s41398-020-00918-y.

Wang, J., L. Li, Z. Wang, Y. Cui, X. Tan, T. Yuan, Q. Liu, Z. Liu, and X. Liu. 2018b. Supplementation of lycopene attenuates lipopolysaccharide-induced amyloidogenesis and cognitive impairments via mediating neuroinflammation and oxidative stress. *The Journal of Nutritional Biochemistry* 56:16–25. doi: 10.1016/j.jnutbio.2018.01.009.

Wang, J., Y. Song, Z. Chen, and S. X. Leng. 2018a. Connection between systemic inflammation and neuroinflammation underlies neuroprotective mechanism of several phytochemicals in neurodegenerative diseases. *Oxidative Medicine and Cellular Longevity* 2018:1972714–6. doi: 10.1155/2018/1972714.

Wang, L., T. Zhao, X. Zhu, and Q. Jiang. 2023a. Low blood carotenoid status in dementia and mild cognitive impairment: A systematic review and meta-analysis. *BMC Geriatrics* 23 (1):195. doi: 10.1186/s12877-023-03900-7.

Wang, M., G. Tang, C. Zhou, H. Guo, Z. Hu, Q. Hu, and G. Li. 2023b. Revisiting the intersection of microglial activation and neuroinflammation in Alzheimer's disease from the perspective of ferroptosis. *Chemico-Biological Interactions* 375:110387. doi: 10.1016/j.cbi.2023.110387.

Wang, W. W., R. Han, H. J. He, J. Li, S. Y. Chen, Y. Gu, and C. Xie. 2021. Administration of quercetin improves mitochondria quality control and protects the neurons in 6-OHDA-lesioned Parkinson's disease models. *Aging* 13 (8):11738–51. doi: 10.18632/aging.202868.

Wang, X. S., Z. R. Zhang, M. M. Zhang, M. X. Sun, W. W. Wang, and C. L. Xie. 2017. Neuroprotective properties of curcumin in toxin-base animal models of Parkinson's disease: A systematic experiment literatures review. *BMC Complementary and Alternative Medicine* 17 (1):412. doi: 10.1186/s12906-017-1922-x.

Wesselman, L. M. P., D. M. van Lent, A. Schröder, O. van de Rest, O. Peters, F. Menne, M. Fuentes, J. Priller, E. J. Spruth, S. Altenstein, et al. 2021. Dietary patterns are related to cognitive functioning in elderly enriched with individuals at increased risk for Alzheimer's disease. *European Journal of Nutrition* 60 (2):849–60. doi: 10.1186/s12906-017-1922-x.

WHO. 2021a. Dementia. Accessed June 6, 2021. https://www.who.int/news-room/fact-sheets/detail/dementia

WHO. 2021b. Ageing. Accessed May 5, 2021. https://www.who.int/health-topics/ageing#tab=tab_1

Wong, L. R., E. A. Tan, M. E. J. Lim, W. Shen, X. L. Lian, Y. Wang, L. Chen, and P. C. L. Ho. 2021. Functional effects of berberine in modulating mitochondrial dysfunction and inflammatory response in the respective amyloidogenic cells and activated microglial cells–in vitro models simulating Alzheimer's disease pathology. *Life Sciences* 282:119824. doi: 10.1016/j.lfs.2021.119824.

Wu, Q., M. Wang, W. Chen, K. Wang, and Y. Wang. 2023. Assessing neuroprotective efficacy of phytochemical saponin ruscogenin in both in vitro and in vivo model. *Arabian Journal of Chemistry* 16 (6):104693. doi: 10.1016/j.arabjc.2023.104693.

Xia, J., L. Gu, Y. Guo, H. Feng, S. Chen, J. Jurat, W. Fu, and D. Zhang. 2021. Gut microbiota mediates the preventive effects of dietary capsaicin against depression-like behavior induced by lipopolysaccharide in mice. *Frontiers in Cellular and Infection Microbiology* 11:627608. doi: 10.3389/fcimb.2021.627608.

Xiang, S., F. Liu, J. Lin, H. Chen, C. Huang, L. Chen, Y. Zhou, L. Ye, K. Zhang, J. Jin, et al. 2017. Fucoxanthin inhibits β-amyloid assembly and attenuates β-amyloid oligomer-induced cognitive impairments. *Journal of Agricultural and Food Chemistry* 65 (20):4092–102. doi: 10.1021/acs.jafc.7b00805.

Xing, L., H. Zhang, R. Qi, R. Tsao, and Y. Mine. 2019. Recent advances in the understanding of the health benefits and molecular mechanisms associated with green tea polyphenols. *Journal of Agricultural and Food Chemistry* 67 (4):1029–43. doi: 10.1021/acs.jafc.8b06146.

Xu, J., J. Liu, Q. Li, Y. Mi, D. Zhou, Q. Meng, G. Chen, N. Li, and Y. Hou. 2021b. Pterostilbene alleviates Aβ1-42-induced cognitive dysfunction via inhibition of oxidative stress by activating Nrf2 signaling pathway. *Molecular Nutrition & Food Research* 65 (2):e2000711. doi: 10.1002/mnfr.202000711.

Xu, J., J. Liu, Y. Mi, T. Zhao, D. Mu, Q. Meng, F. Wang, N. Li, and Y. Hou. 2022. Triad3A-Dependent TLR4 ubiquitination and degradation contributes to the anti-inflammatory effects of pterostilbene on vascular dementia. *Journal of Agricultural and Food Chemistry* 70 (19):5896–910. doi: 10.1021/acs.jafc.2c01219.

Xu, W., J. Liu, D. Ma, G. Yuan, Y. Lu, and Y. Yang. 2017. Capsaicin reduces Alzheimer-associated tau changes in the hippocampus of type 2 diabetes rats. *PloS One* 12 (2):e0172477. doi: 10.1371/journal.pone.0172477.

Xu, Z., C. Liu, R. Wang, X. Gao, C. Hao, and C. Liu. 2021a. A combination of lycopene and human amniotic epithelial cells can ameliorate cognitive deficits and suppress neuroinflammatory signaling by choroid plexus in Alzheimer's disease rat. *The Journal of Nutritional Biochemistry* 88:108558. doi: 10.1016/j.jnutbio.2020.108558.

Xue, Y., Z. Qu, J. Fu, J. Zhen, W. Wang, Y. Cai, and W. Wang. 2017. The protective effect of astaxanthin on learning and memory deficits and oxidative stress in a mouse model of repeated cerebral ischemia/reperfusion. *Brain Research Bulletin* 131:221–8. doi: 10.1016/j.brainresbull.2017.04.019.

Yang, L., N. Wang, and G. Zheng. 2018. Enhanced effect of combining chlorogenic acid on selenium nanoparticles in inhibiting amyloid β aggregation and reactive oxygen species formation in vitro. *Nanoscale Research Letters* 13 (1):303. doi: 10.1186/s11671-018-2720-1.

Yang, S., H. Zhou, G. Wang, X. H. Zhong, Q. L. Shen, X. J. Zhang, R. Y. Li, L. H. Chen, Y. H. Zhang, and Z. Wan. 2020. Quercetin is protective against short-term dietary advanced glycation end products intake induced cognitive dysfunction in aged ICR mice. *Journal of Food Biochemistry* 44 (4):e13164. doi: 10.1111/jfbc.13164.

Yang, Z., D. D. Zhou, S. Y. Huang, A. P. Fang, H. B. Li, and H. L. Zhu. 2023. Effects and mechanisms of natural products on Alzheimer's disease. *Critical Reviews in Food Science and Nutrition* 63 (18):3168–88. doi: 10.1080/10408398.2021.

Yarim, G. F., F. Kazak, M. Yarim, M. Sozmen, B. Genc, A. Ertekin, and A. Gokceoglu. 2022. Apigenin alleviates neuroinflammation in a mouse model of Parkinson's disease. *The International Journal of Neuroscience* :1–10. doi: 10.1080/00207454.2022.2089136.

Yıldız, M. O., H. Çelik, C. Caglayan, F. M. Kandemir, C. Gür, İ. Bayav, A. Genç, and Ö. Kandemir. 2022. Neuromodulatory effects of hesperidin against sodium fluoride-induced neurotoxicity in rats: Involvement of neuroinflammation, endoplasmic reticulum stress, apoptosis and autophagy. *Neurotoxicology* 90:197–204. doi: 10.1016/j.neuro.2022.04.002.

Youn, K., C. T. Ho, and M. Jun. 2022. Multifaceted neuroprotective effects of (-)-epigallocatechin-3-gallate (EGCG) in Alzheimer's dis-

ease: An overview of pre-clinical studies focused on β-amyloid peptide. *Food Science and Human Wellness* 11 (3):483–93. doi: 10.1016/j.fshw.2021.12.006.

Yuan, C., E. Fondell, A. Ascherio, O. I. Okereke, F. Grodstein, A. Hofman, and W. C. Willett. 2020. Long-term intake of dietary carotenoids is positively associated with late-life subjective cognitive function in a prospective study in US women. *The Journal of Nutrition* 150 (7):1871–9. doi: 10.1093/jn/nxaa087.

Yuan, C., H. Chen, Y. Wang, J. A. Schneider, W. C. Willett, and M. C. Morris. 2021. Dietary carotenoids related to risk of incident Alzheimer dementia (AD) and brain AD neuropathology: A community-based cohort of older adults. *The American Journal of Clinical Nutrition* 113 (1):200–8. doi: 10.1093/ajcn/nqaa303.

Zamora-Ros, R., V. Knaze, J. A. Rothwell, B. Hémon, A. Moskal, K. Overvad, A. Tjønneland, C. Kyrø, G. Fagherazzi, M.-C. Boutron-Ruault, et al. 2016. Dietary polyphenol intake in Europe: The European Prospective Investigation into Cancer and Nutrition (EPIC) study. *European Journal of Nutrition* 55 (4):1359–75. doi: 10.1007/s00394-015-0950-x.

Zaplatic, E., M. Bule, S. Z. A. Shah, M. S. Uddin, and K. Niaz. 2019. Molecular mechanisms underlying protective role of quercetin in attenuating Alzheimer's disease. *Life Sciences* 224:109–19. doi: 10.1016/j.lfs.2019.03.055.

Zaw, J. J. T., P. R. Howe, and R. H. Wong. 2021. Long-term effects of resveratrol on cognition, cerebrovascular function and cardio-metabolic markers in postmenopausal women: A 24-month randomised, double-blind, placebo-controlled, crossover study. *Clinical Nutrition (Edinburgh, Scotland)* 40 (3):820–9. doi: 10.1016/j.clnu.2020.08.025.

Zhang, J. F., X. X. Wang, Y. Feng, R. Fekete, J. Jankovic, and Y. C. Wu. 2021. Impulse control disorders in Parkinson's disease: Epidemiology, pathogenesis and therapeutic strategies. *Frontiers in Psychiatry* 12:635494. doi: 10.3389/fpsyt.2021.635494.

Zhang, J., Y. Zheng, Y. Luo, Y. Du, X. Zhang, and J. Fu. 2019b. Curcumin inhibits LPS-induced neuroinflammation by promoting microglial M2 polarization via TREM2/TLR4/NF-κB pathways in BV2 cells. *Molecular Immunology* 116:29–37. doi: 10.1016/j.molimm.2019.09.020.

Zhang, L., C. Virgous, and H. Si. 2019. Synergistic anti-inflammatory effects and mechanisms of combined phytochemicals. *The Journal of Nutritional Biochemistry* 69:19–30. doi: 10.1016/j.jnutbio.2019.03.009.

Zhang, S., Q. Zhu, J. Y. Chen, D. OuYang, and J. H. Lu. 2020b. The pharmacological activity of epigallocatechin-3-gallate (EGCG) on Alzheimer's disease animal model: A systematic review. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 79:153316. doi: 10.1016/j.phymed.2020.153316.

Zhang, X. W., J. Y. Chen, D. Ouyang, and J. H. Lu. 2020a. Quercetin in animal models of Alzheimer's disease: A systematic review of preclinical studies. *International Journal of Molecular Sciences* 21 (2):493. doi: 10.3390/ijms21020493.

Zhang, Y., Y. Li, Y. Wang, G. Wang, L. Mao, D. Zhang, and J. Wang. 2019a. Effects of resveratrol on learning and memory in rats with vascular dementia. *Molecular Medicine Reports* 20 (5):4587–93. doi: 10.3892/mmr.2019.10723.

Zheng, Y., J. Zhang, Y. Zhao, Y. Zhang, X. Zhang, J. Guan, Y. Liu, and J. Fu. 2021. Curcumin protects against cognitive impairments in a rat model of chronic cerebral hypoperfusion combined with diabetes mellitus by suppressing neuroinflammation, apoptosis, and pyroptosis. *International Immunopharmacology* 93:107422. doi: 10.1016/j.intimp.2021.107422.

Zhong, Y., C. Jin, J. Gan, X. Wang, Z. Shi, X. Xia, and X. Peng. 2017. Apigenin attenuates patulin-induced apoptosis in HEK293 cells by modulating ROS-mediated mitochondrial dysfunction and caspase signal pathway. *Toxicon: Official Journal of the International Society on Toxinology* 137:106–13. doi: 10.1016/j.toxicon.2017.07.018.

Zhou, T., M. Zhu, and Z. Liang. 2018. (-)-Epigallocatechin-3-gallate modulates peripheral immunity in the MPTP-induced mouse model of Parkinson's disease. *Molecular Medicine Reports* 17 (4):4883–8. doi: 10.3892/mmr.2018.8470.

Zhu, F., B. Du, and B. Xu. 2018. Anti-inflammatory effects of phytochemicals from fruits, vegetables, and food legumes: A review. *Critical Reviews in Food Science and Nutrition* 58 (8):1260–70. doi: 10.1080/10408398.2016.1251390.

Zhu, L., F. Lu, X. Zhang, S. Liu, and P. Mu. 2022. SIRT1 is involved in the neuroprotection of pterostilbene against amyloid β 25–35-induced cognitive deficits in mice. *Frontiers in Pharmacology* 13:877098. doi: 10.3389/fphar.2022.877098.

Zhu, Q., X. Zhuang, and J. Lu. 2019. Neuroprotective effects of baicalein in animal models of Parkinson's disease: A systematic review of experimental studies. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 55:302–9. doi: 10.1016/j.phymed.2018.09.215.