Neuroprotective Effects of Phytochemicals in Neurological Disorders

EDITORS

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Phytochemicals hold a special, elite place in the nutritional landscape.

Joel Fuhrman, MD

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Preface

The medicinal properties and health benefits of plant products (seeds, fruits, leaves, stems, and roots) are attributed to their non-nutritive bioactive components, known as "phytochemicals," which are classified into primary and secondary metabolites. Primary metabolites (carbohydrates, lipids, amino acids, and proteins) are necessary for the growth and basic metabolism of all plants. Secondary metabolites (phytochemicals), on the other hand, are not essential, but they provide vegetables, fruits, and herbs with their flavor and color. They not only play crucial roles in the well being of plants by interacting with their ecosystems, but also protect them from pathogens and absorb ultraviolet (UV), preventing DNA and photosynthetic apparatus damage. Consumption of phytochemicals by animals produces antioxidant, anti-inflammatory, antimicrobial, antitumor, analgesic, neuroprotective, and antiplatelet effects. In addition, they induce antiaging effects and improve poor blood circulation. These effects are mediated through the regulation of various receptors, transcription factors, growth factors, inflammatory cytokines, protein kinases, protein phosphatases, and other enzymes (phospholipases and cyclooxygenases). In brain, receptors, transcription factors, growth factors, and enzymes modulate the signal-transduction pathways critical in controlling synaptic plasticity and inducing neurogenesis in the hippocampus. The ability of many phytochemicals to activate the extracellular signal-regulated kinase (ERK)1/2 and protein kinase B (PKB/Akt) signaling pathways is associated with the activation of the cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), a transcription factor that plays an important role in memory formation. In recent years, the amount of research into phytochemicals has increased all over the world, and new terms such as "functional food" and "nutraceutical" have been introduced. There are several issues related to the use of phytochemicals, including concern about their dosage and activity and about the presence of contaminants.

Epidemiological studies have shown that incidences of neurological disorders among people living in Asia are lower than in the Western world. This may be due to the regular consumption of phytochemicals in the form of spices. Extensive research over the last 10 years has indicated that phytochemicals derived from various spices and oils (turmeric, black pepper, licorice, clove, ginger, garlic, green tea, and olive and flaxseed oils) target inflammatory and oxidative stress pathways and retard or delay the onset of neurological diseases. More than 7000 phytochemicals have been identified, which possess antiproliferative, anti-inflammatory, antioxidant, antiviral, and hypocholesterolemic properties. Unlike vitamins and minerals, phytochemicals are not necessary for

the maintenance of cell viability, but they play a vital role in protecting neural cells from the inflammation and oxidative stress associated with normal aging and brain diseases. Although many phytochemicals present in plant foods are poorly absorbed and undergo rapid excretion, they exert anti-inflammatory, antioxidant, and anticarcinogenic effects at realistic doses. Consumption of phytochemicals may also mediate neurohormetic response through the modulation of adaptive stress-resistance genes, which are responsible for encoding protein chaperones that favor resistance to cellular stress and modulate immune function. Thus, regular consumption of phytochemicals from childhood to adulthood may reduce the risk of age-related neurological disorders.

The chemical structures of phytochemicals are often used as "privileged structures" for the creation of synthetic analogues, which have improved pharmacological activities due to their optimized bioavailability and pharmacokinetic profile. Note that most studies on phytochemicals have been performed in animal models and cell-culture systems, and it is difficult to evaluate the significance of their effect in humans.

Information on the effects of phytochemicals on human health is scattered throughout the literature in the form of original papers and reviews, but few edited books. In this book, we provide the reader with a comprehensive and cutting-edge description of the metabolism of the molecular mechanism associated with the beneficial effects of phytochemicals in age-related neurological disorders, in a manner that is useful not only to students and teachers but also to researchers and physicians. The book has 29 chapters. Chapter 1 provides an introduction to the role of phytochemicals in protecting against neuroinflammation, which is typically associated with neurodegenerative diseases. Chapter 2 deals with the protective role of flavonoids in transgenic Alzheimer's disease (AD) mouse models. Chapters 3–15 describe the beneficial effects of phytochemicals (rich in flavonoids and polyphenols) against neurological disorders in model systems. Chapter 16 discusses the use of bee products (apitherapy) for the treatment of neurological disorders. Chapter 17 elegantly describes the mechanisms underlying the beneficial actions of polyunsaturated fatty acids (PUFAs) in brain diseases. Chapters 18–20 deal with the anti-inflammatory effects of resveratrol. Chapter 21 focuses on nobiletin, a flavonoid (an O-methylated flavone) that has the ability to rescue cognitive impairment in animal models. Chapters 22–25 discuss the potential neuroprotective effects of curcumin against brain diseases. Chapter 26 discusses polyphenols and protein misfolding. Chapter 27 describes the molecular mechanisms involved in the neuroprotective action of phytochemicals. Chapter 28 focuses on nutraceuticals (a food or a part of a food that provides health benefits, including the prevention or treatment of a disease) and their effect on cognitive dysfunction. Finally, Chapter 29 provides a perspective on the importance of phytochemicals in diet and on the direction for future research in phytotherapeutics. These topics fall in a fast-paced research area related to cell death in neurological disorders, which provides opportunities for target-based therapeutic intervention using phytochemicals. This book can be used as a supplemental text for a range of phytotherapeutics courses. Clinicians and pharmacologists will find it useful in understanding the molecular aspects of phytochemicals in chronic human diseases.

We have tried to ensure uniformity of presentation, as well as a logical progression of subject from one topic to another, and our authors have provided extensive bibliographies. For the sake of simplicity and consistency, a large number of figures showing the chemical structures of phytochemicals used for the treatment of chronic diseases and

signal-transduction pathways are also included. We hope that our attempt to integrate and consolidate the current knowledge on the molecular aspects of phytochemicals will provide the basis for more dramatic advances and developments in the area of the molecular mechanisms associated with the beneficial effects of phytochemicals in age-related neurological disorders.

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1

Use of Phytochemicals against Neuroinflammation

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1.1 Introduction

Neuroinflammation and oxidative stress are closely associated with the pathogenesis of neurotraumatic and neurodegenerative diseases, such as stroke and Alzheimer's disease (AD). During the inflammatory reaction, secretion of proinflammatory cytokines and chemokines amplifies and maintains inflammatory responses. It involves the enzymatic activity of cytosolic phospholipase A_2 ($cPLA_2$) and secretory phospholipase A_2 ($sPLA_2$), which release arachidonic acid from glycerophospholipids, and of cyclooxygenase (COX) and 5-lipoxygenase (5-LOX), which oxidize arachidonic acid to proinflammatory eicosanoids. This is followed by the formation of the prostaglandin D2 (PGD2) and of docosahexaenoic acid (DHA)-derived resolvins and protectins, which facilitate the resolution of inflammation. Acute neuroinflammation is a protective process that isolates the injured brain tissue from uninjured areas, destroys injured cells, and rebuilds the extracellular matrix. Without it, brain tissue would rapidly be damaged by the effects of injury and infections, including those of microbial, viral, and prion origin. Acute neuroinflammation involves the recruitment of lymphocytes, monocytes, and macrophages of the hematopoietic system and glial cells of the central nervous system (CNS). Microglia are recruited to the site of injury to protect and repair the injured tissue via the secretion of cytokines, chemokines, and lipid mediators such as resolvins and neuroprotectins, while astrocytes react by forming a glial scar. Chronic neuroinflammation, on the other hand, lingers for years, and causes damage to brain tissues. It is closely associated with the activity of microglia and astrocytes and with the assembly and activation of the inflammasome: a multiprotein oligomer consisting of caspase 1, PYCARD, NALP, and sometimes caspase 5 (also known as caspase 11 or ICH-3). Once activated, the inflammasome binds to and appositions together many p45

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pro-caspase-1 molecules to induce their autocatalytic cleavage to p20 and p10 subunits. Caspase-1 then assembles into its active form (consisting of two heterodimers with a p20 and p10 subunit each), in order to carry out a variety of processes, including cleavage of pro-interleukin (IL)-1β into IL-1β, cleavage of pro-IL-18 into IL-18 to induce interferon gamma (IFN-γ) secretion, and activation of lipid biosynthesis [1]. Inflammasomes orchestrate the activation of precursors of proinflammatory caspases, which, in turn, cleave precursor forms of IL-1β, IL-18, and IL-33 into their active forms. These lead to further stimulation of PLA_2, COX-2, and LOX; generation of eicosanoids, lysophosphatidylcholine (lyso-PtdCho), and platelet-activating factor (PAF); production of reactive oxygen species (ROS), proteinases, and complement proteins; and a potent inflammatory response. Alterations in the expression of inflammasome mediators may lead to neurodegeneration in neurotraumatic, neurodegenerative, and neuropsychiatric diseases. Based on this, it has been suggested that regulation of the inflammasome machinery may be better than suppression of all inflammation for the treatment of inflammatory conditions [1,2].

An emerging approach to the alleviation of neuroinflammation involves the use of medicinal plants and herbs. Epidemiological studies have indicated that the incidence of neurological disorders among people living in Asia is lower than that in the Western world. This may be due to the regular consumption of phytochemicals in the form of spices. Extensive research over the last 10 years has indicated that phytochemicals derived from various spices e.g., turmeric, red pepper, black pepper, licorice, clove, ginger, garlic, coriander, cinnamon, target inflammatory and oxidative stress pathways and retard or delay the onset of neurological diseases. More than 7000 phytochemicals, which possess antiproliferative, anti-inflammatory, antiviral, and hypocholesterolemic properties, have been identified (Figure 1.1). Unlike vitamins and minerals, phytochemicals are not required for the maintenance of cell viability, but play a vital role in protecting neural cells from neuroinflammation and oxidative stress associated with aging and brain diseases. Roots, stems, leaves, fruits, and seeds contain phytochemicals such as terpenoids, phenolic compounds, glucosinolates, betalains, and chlorophylls. Although many phytochemicals in plant foods are poorly absorbed and undergo rapid excretion, they exert anti-inflammatory, antioxidant, and anticarcinogenic effects at realistic doses. The effects of phytochemicals are mediated by their ability to counteract, reduce, and repair damage resulting from oxidative stress and

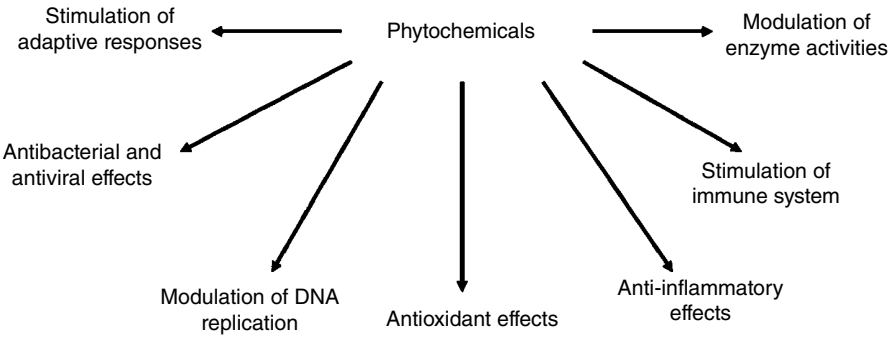

Figure 1.1 Effect of phytochemicals on various cellular activities.

neuroinflammation – processes that are modulated by the transcription factor, nuclear factor kappa B (NF-κB). Phytochemicals also stimulate the synthesis of adaptive enzymes and proteins that favor resistance to cellular stress [3].

1.2 Mechanism of Action of Phytochemicals

Plants and phytochemicals produce their beneficial effects not only through modulation of enzyme activities and regulation of gene expression, but also via the stimulation of adaptive cellular stress response pathways that protect cells against a variety of adverse conditions. Phytochemicals bind to neuronal cell-membrane or nuclear receptors as elective ligands and have signaling effects at concentrations much lower than is required for effective antioxidant activity [4]. They act on the NF-κB pathway to inhibit inflammation. NF-κB is predominantly localized in the cytoplasm in a complexed form that is inactive, but during oxidative stress it is released from the NF-κB–IκBα complex and migrates to the nucleus, where it initiates the transcription of a number of proinflammatory enzymes, including $sPLA_2$, COX-2, NADPH oxidase and inducible nitric oxide synthase (iNOS), as well as proinflammatory cytokines (tumor necrosis factor alpha (TNF-α), IL-1β, and IL-6). The latter stimulate the activities of PLA_2 and sphingomyelinases through a feedback loop involving cytokine-mediated phosphorylation. Other potential mechanisms through which NF-κB induces neuronal death include the induction of death proteins and an aborted attempt to re-enter the cell cycle. Phytochemicals such as curcumin, resveratrol, *Ginkgo biloba* (GB) retard inflammation by preventing the migration of NF-κB into the nucleus. In addition, many phytochemicals block the activation of NF-κB by inhibiting a protein kinase. *In vitro* studies indicate that phytochemicals inhibit both serine/threonine protein kinase and protein tyrosine kinase, supporting the view that phytochemicals may inhibit IκB kinaseβ (IKKβ) in the cytoplasm and nucleus, leading to a reduction in NF-κB activity. Phytochemicals have also been reported to modulate age-related decline in memory by upregulating signaling pathways that control synaptic plasticity. They activate both the extracellular signal-regulated kinase (ERK) 1/2 and protein kinase B (PKB)/Akt signaling pathways and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), a transcription factor that upregulates the expression of several neurotrophins that facilitate memory formation [5,6].

An important cellular antioxidant response that underlies the action of many phytochemicals is induction of antioxidative and anti-inflammatory enzymes through the cytoplasmic oxidative stress system (nuclear factor erythroid 2-related factor 2 (Nrf2)–kelch-like erythroid Cap'n'Collar homologue-associated protein 1 (Keap1)) (Figure 1.2) [7]. Under physiological conditions, Keap1 keeps the Nrf2 transcription factor in the cytoplasm, allowing it to be ubiquitinated and degraded by proteasomes, thus maintaining Nrf2 at low levels. This prevents Nrf2 from mediating the constitutive expression of its downstream genes. When cells are exposed to oxidative stress, a signal involving phosphorylation and/or redox modification of critical cysteine residues in Keap1 blocks the enzymatic activity of the Keap1–Cul3–Rbx1 E3 ubiquitin ligase complex, leading to a decrease in Nrf2 ubiquitination and degradation. As a result, free Nrf2 translocates into the nucleus, where it – along with other transcription factors (e.g., sMaf, ATF4, JunD, PMF-1) – transactivates the antioxidant response elements (AREs)

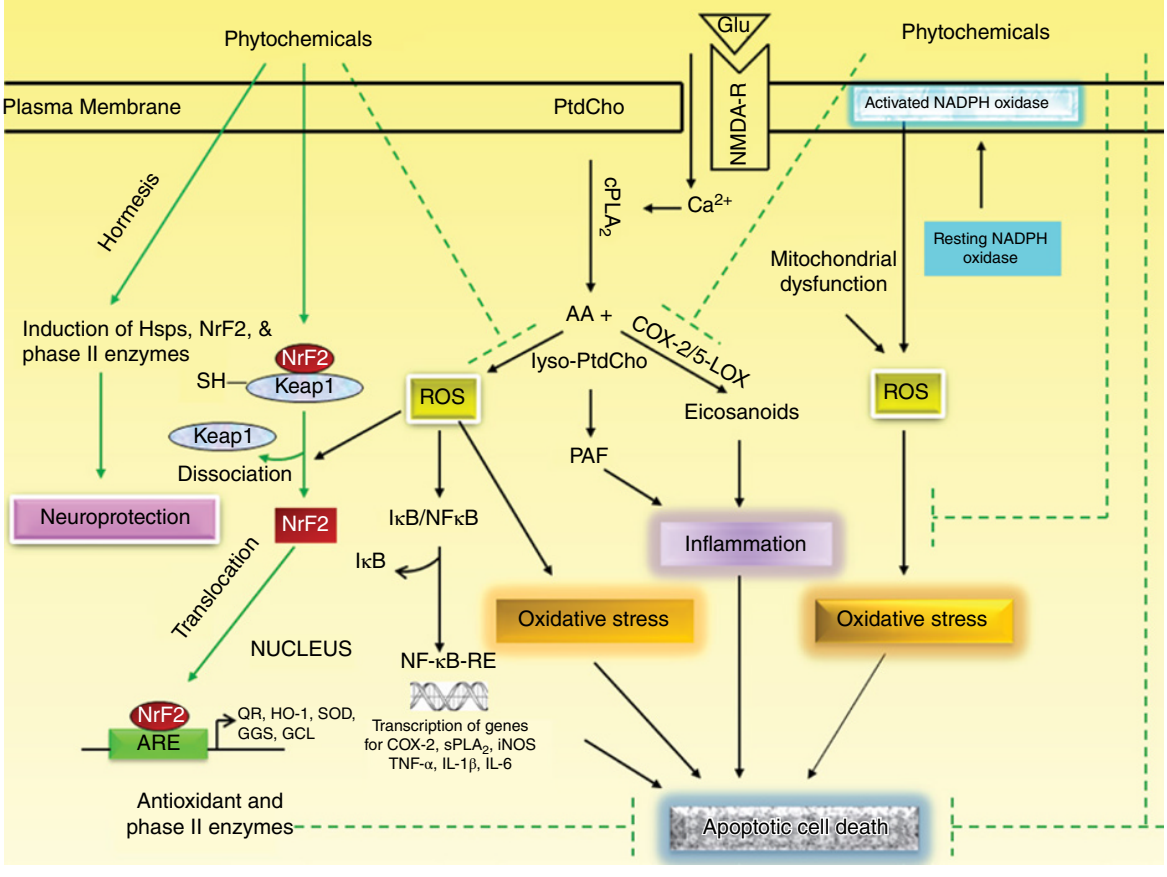

Figure 1.2 Hypothetical diagram showing the effects of phytochemicals on signal transduction processes in the brain. AA, arachidonic acid; COX-2, cyclooxygenase 2; $cPLA_2$, cytosolic phospholipase A_2; HO-1, hemeoxygenase 1; HSP, heat-shock protein; IL-1β, interleukin 1β; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; Keap1, kelch-like erythroid Cap'n'Collar homologue-associated protein 1; LOX, lipoxygenase; lyso-PtdCho, lyso-phosphatidylcholine; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; PAF, platelet-activating factor; PM, plasma membrane; PtdCho, phosphatidylcholine; QR, quinine oxidoreductase; ROS, reactive oxygen species; SOD, superoxide dismutase; $sPLA_2$, secretory phospholipase A_2; TNF-α, tumor necrosis factor alpha; γ-GCL, gamma glutamylcystein ligase. (*See insert for color representation of the figure.*)

of many cytoprotective genes. Microarray and biochemical analyses reveal the coordinated upregulation of several enzymes, such as HO-1, catalase, SOD, epoxide hydrolase, UDP-glucuronosyltransferases, and thioredoxin. In addition, Nrf2 induces the expression of enzymes related to glutathione biosynthesis and function (e.g., xCTcystine antiporter, gamma-glutamylcysteine synthetase, reduced glutathione (GSH) synthase, glutathione S-transferase (GST), glutathione reductase (GR)), leading to an increase in intracellular GSH and a decrease in oxidative stress. Upon recovery of cellular redox status, Keap1 travels into the nucleus and facilitates the dissociation of Nrf2 from ARE. Subsequently, the Nrf2–Keap1 complex is exported out of the nucleus by the nuclear export sequence in Keap1. Once in the cytoplasm, the Nrf2–Keap1 complex associates with the Cul3–Rbx1 core ubiquitin machinery, leading to degradation of Nrf2 and termination of the Nrf2/ARE signaling pathway [7].

Phytochemicals may also act through oxidant-mediated neural cell survival signaling pathways, together with histone deacetylases of the sirtuin family (sirtuin–FOXO pathway) and chaperones such as the heat-shock proteins (HSPs), antioxidant enzymes (SODs and glutathione peroxidase (GPx)), and growth factors (e.g., insulin-like growth factor (IGF), brain-derived neurotrophic factor (BDNF)) [8–10]. Low levels of phytochemicals crossing the blood–brain barrier (BBB) cause mild cellular inflammation and oxidative stress, involving the generation of low levels of ROS, which results in activation of transcription factors and synthesis of HSPs promoting the production of anti-inflammatory cytokines. In this scenario, responses to HSPs are considered an attempt to correct the inflammatory condition. The highly integrated and regulated processes are controlled by redox-sensitive genes called "vitagenes," which code for HSPs, thioredoxin, and sirtuin protein systems and modulate a complex network of intracellular signaling pathways for the preservation of cellular homeostasis.

A potential mechanism through which phytochemicals could exert their effect is via the inflammasome. *In vitro* studies have indicated that phytochemicals partially inhibit the release of TNF-α, IL-1β, and IL-6 in cultured neural cells [3]. TNF-α and IL-1β activate isoforms of PLA_2 and sphingomyelinases. It appears that phytochemicals prevent the formation of inflammasome by inhibiting the activities of NLRP3, NLRC4, AIM2, NLRP6, caspase-1, PLA_2, and sphingomyelinases, although more work needs to be carried out in this area.

1.3 Bioavailability of Phytochemicals

Bioavailability represents the fraction of an orally ingested or administered compound in food, beverages, or supplements that reaches the systemic circulation. The bioavailability of most phytochemicals in human tissues is very poor. Following oral administration, most phytochemicals are absorbed and metabolized to form glucuronide and sulfate conjugates, which are excreted in the urine [3,11]. The bioavailability of most phytochemicals in peripheral organs is higher than that in the brain as a result of the presence of the BBB. In order to enter the brain, a phytochemical must either be highly lipid-soluble or be subjected to uptake transport processes through adenosine triphosphate (ATP)-binding cassette (ABC) transporters. Many approaches have been taken in

an attempt to improve the bioavailability of phytochemicals, including the use of adjuvants that interfere with glucuronidation, the preparation of phytochemical liposomes and nanoparticles, the use of phytochemical–phospholipid conjugates, and the use of structural analogs of phytochemicals. These approaches have generally allowed phytochemicals to cross the BBB more effectively [12–14].

Green tea contains catechin flavonoid polyphenols. Catechin monomers can be easily absorbed through the gut, whereas large molecular-weight catechins, such as (–)-epigallocatechin-3-gallate (EGCG) (Figure 1.3), are poorly absorbed. Green-tea catechins undergo three degradation processes: decomposition to smaller molecules, polymerization to larger molecules, and oxidation to oxidized molecules under natural conditions. The digestive tract plays an important role in the metabolism and bioavailability of green-tea components before they enter the liver. Green-tea catechins and their metabolites formed in the small intestine are transported back into the intestinal lumen, where they reach the large intestine and are broken down to small phenolic acids and valerolactones by resident microflora. These metabolites are either reabsorbed or excreted in the feces [15].

The bioavailability of flavonoid polyphenols in berries is very low, and information on the molecular mechanisms of their action is still poorly understood. Dietary flavonoids enter the gastrointestinal tract in the form of esters and glycosides, which are not easily absorbed. Conversion of esters and glycosides into aglycones results in better bioavailability, because aglycones are lipophilic and more permeable across the cell membrane than the parent glycosides, and are more efficiently absorbed across the

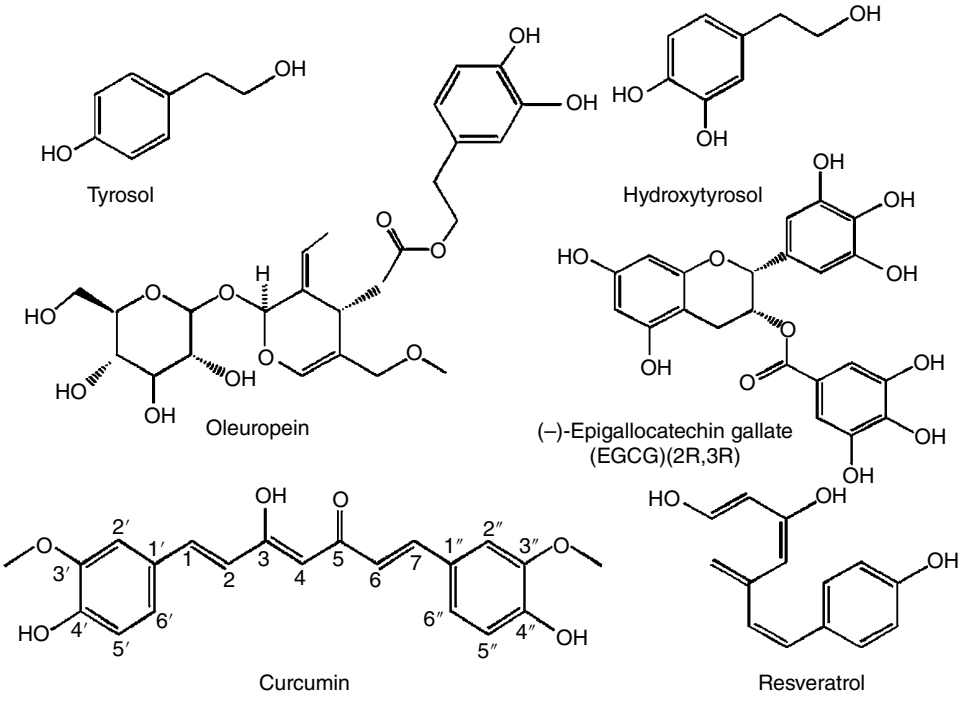

Figure 1.3 Chemical structures of phytochemicals.

gastrointestinal tract wall [16,17]. The conversion of glycosides into aglycones mainly occurs in the acidic environment of the stomach. Absorption of flavonoids by intestinal epithelial cells is accompanied by their extensive biotransformation, with the generation of different conjugated products (e.g., glucuronides, sulfates, O-methylated derivatives), first in the intestine and then in the liver, where conjugates are secreted into the bile. Favorable absorption across the gastrointestinal tract does not always result in improved bioavailability. One possible approach to improving the bioavailability of phytochemicals in the brain is the use of nanolipidic particles [18].

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) (Figure 1.3) is a member of the stilbenoid family of polyphenols. It is found in grapes, mulberries, peanuts, and other plants and food products, including raspberries, blueberries, Scots pine, Eastern white pine, and knotweed. Although transresveratrol is rapidly absorbed and distributed through the bloodstream in animals and humans, its bioavailability is low due to its rapid metabolism and elimination in the urine [19,20]; extensive metabolism in the intestine and liver results in an oral bioavailability of less than 1%. Resveratrol is well tolerated and metabolized through glucuronidation or sulfation reactions in the intestine and liver. The major glucuronidation derivatives of resveratrol are transresveratrol 3-O-glucuronide and transresveratrol-O-glucuronide, whereas the sulfated derivative is transresveratrol-3-O-sulfate. Kinetic analysis of resveratrol metabolism indicates that glucuronidation is favored over sulfation in the liver. *In vivo* studies indicate that free transresveratrol levels in the plasma are very low and short-lived. Intravenous administration of 15 mg/kg in rats results in a wide distribution of resveratrol in various tissues after 90 minutes. The highest concentrations are found in the kidney and lowest in the brain [21].

Curcumin is a member of the curcuminoid family of polyphenols (Figure 1.3). It has poor bioavailability, due either to (i) its poor absorption, (ii) its rapid metabolism, or (iii) its rapid systemic elimination and short biological half-life. In rodents, curcumin undergoes rapid metabolism by conjugation, reduction, and removal after oral dosing. Very little information is available on the pharmacokinetics of curcumin in humans. Phase I and II clinical trials have been performed for up to 4 months at several doses (500, 1000, 2000, 4000, 8000, and 12 000 mg/day) in patients with advanced colorectal cancer, without any toxicity [22,23]. The serum concentration of curcumin reaches a maximum at 1–2 hours after oral intake and gradually declines within 12 hours. Currently, an upper level of toxicity has not been established for curcumin. Studies have reported that a daily dose of as high as 12 g is safe and tolerable in humans, with few, mild side effects. Hybrid compounds of curcumin and melatonin have been designed, synthesized, and characterized, and one of these has been shown to cross the BBB and deliver a sufficient amount to brain tissue following oral administration. Results suggest the hybridization approach is an efficient strategy for identifying novel scaffolds with the desired pharmacology for use as neuroprotectants. In order to increase curcumin's bioavailability, a polymeric nanoparticle encapsulated curcumin (NanoCurc) has been formulated. NanoCurc injection at a dose of 25 mg/kg twice daily in mice results in significant curcumin levels in the brain (0. 32 μg/g) [24].

The bioavailability of flavonoids of GB extract EGb 761 is generally low due to limited absorption and rapid elimination [25]. Unabsorbed flavonoids that reach the colon are metabolized by colon microflora and absorbed. The flavonoids then reach the liver, where they are metabolized to conjugated derivatives. The bioavailability of EGb 761 has been studied in rats and humans. Oral administration or injection of acute and subacute doses of EGb 761 in rats results in the distribution of GB components in various

tissues and plasma that follows linear pharmacokinetics in rats and humans. In human volunteers, oral intake of EGb 761 (120 mg) results in bilobalide plasma levels of 0.05–0.15 μM [26,27]. In rats, oral administration of EGb 761 or pure bilobalide produces dose-dependent increases in bilobalide plasma levels of from 0.5 to 7.5 mM. It is increasingly evident that components of EGb 761 can cross the BBB and reach low micromolar concentrations in the brain. This allows efficient interaction with target molecules such as neurotransmitter receptors [28,29].

Studies on the bioavailability of a component of garlic, S-allyl cysteine (SAC), which belongs to the organosulfur family of glycosinolates, indicate that oral consumption results in rapid absorption in the gastrointestinal tract and distribution in the plasma, liver, and kidney of rats, mice, and dogs [30]. The bioavailability of SAC is about 100.0% in mice, 98.2% in rats, and 87.2% in dogs. N-acetyltransferases transform SAC into N-Acetyl-SAC, which can be detected in the urine of dogs and humans. Other oil-soluble organosulfur compounds of garlic, such as allicin, sulfides, ajoene, and vinyldithiins, are not found in the blood or urine even after consumption of large amounts of garlic. Incubation of allicin with liver homogenates results in its very rapid disappearance. No allicin was detected in either blood or urine 1–24 hours after ingestion of 25 g of raw garlic (approximately 90 mg allicin). In any case, allicin quickly disappears from the blood within a short period after ingestion, and its decomposition products diallyl sulfide and allylmercaptan are found in the blood [31].

1.4 Plants Effective against Neuroinflammation

Large number of plants around the world have been found to reduce inflammatory responses or stimulate antioxidant defenses, both in microglial cells and neurons *in vitro,* and in animal models of neurological diseases. On compiling literature reports of plants with antineuroinflammatory properties, we discovered that they are not randomly distributed throughout the plant kingdom but are **concentrated in a small number of orders, especially *Fabales*, *Lamiales*, *Rosales*, *Apiales* and *Sapindales*** (Table 1.1). These same orders of plants are associated with food allergy [32]. We hypothesize that plants that are useful against neuroinflammation are also those that are mildly proinflammatory or immunogenic.

Very low levels of phytochemicals that enter the brain due to limited absorption through the gastrointestinal tract and very limited passage across the BBB may cause a mild neuroinflammation and trigger the activation of transcription factors and the synthesis of HSPs, leading to an anti-inflammatory response. This may be a form of "inflammatory" hormesis (a process whereby a specific phytochemical induces biologically opposite effects at different doses).

Knowledge of the orders of plants that are most likely to be effective against neuroinflammation may help in the future discovery of novel phytochemicals. Low levels of phytochemicals are closely associated with the adaptive stress response, which confers resistance to severe inflammation and stress, through the activation of the Nrf2 pathway and antioxidant/drug-metabolizing enzymes, and through the generation of low levels of lipid mediators. These mediators maintain the cellular milieu and transfer messages between subcellular organelles, thereby inducing physiological functions (e.g., bioenergetics, growth, proliferation, remodeling). These

Table 1.1 Classification of plants with potential against neuroinflammation.

Common (Chinese) name	Order	Family	Genus	Species
Chinese ginseng/Korean ginseng	Apiales	Araliaceae	*Panax*	*ginseng*
Siberian ginseng	Apiales	Araliaceae	*Eleutherococcus/Acanthopanax*	*senticosus*
Asiatic/Indian pennywort (ji xue cao)	Apiales	Apiaceae	*Centella*	*asiatica*
Angelica dahuricae (bai zhi)	Apiales	Apiaceae	*Angelica*	*dahuricae*
Açaí palm	Arecales	Arecaceae	*Euterpe*	*oleracea*
African oil palm	Arecales	Arecaceae	*Elaeis*	*guineensis*
Garlic	Asparagales	Amaryllidaceae	*Allium*	*sativum*
Long yellow day lily (huang hua cai)	Asparagales	Xanthorrhoeaceae	*Hemerocallis*	*citrina*
Milk thistle	Asterales	Asteraceae	*Silybum*	*marianum*
Chinese mugwort (ai cao)	Asterales	Asteraceae	*Artemisia*	*argyi*
Lavender cotton	Asterales	Asteraceae	*Achillea*	*fragrantissima*
Coltsfoot	Asterales	Asteraceae	*Tussilago*	*farfara*
Thunder god vine (lei gong teng)	Celastrales	Celastraceae	*Tripterygium*	*wilfordii*
Bitter melon/bitter gourd	Cucurbitales	Cucurbitaceae	*Momordica*	*charantia*
Valeriana amurensis Smir. ex Kom. (hei shui xie cao)	Dipsacales	Caprifoliaceae	*Valeriana*	*amurensis*
Green tea (cha hua)	Ericales	Theaceae	*Camellia*	*sinensis*
Berry	Ericales	Ericaceae	*Vaccinium*	–
Walnut	Fagales	Juglandaceae	*Juglans*	*regia*
Yuan zhi	Fabales	Polygalaceae	*Polygala*	*tenuifolia*
Velvet bean	Fabales	Fabaceae	*Mucuna*	*pruriens*
Soybean	Fabales	Fabaceae	*Glycine*	*max*
Ku shen	Fabales	Fabaceae	*Sophora*	*flavescens*

(*Continued*)

Table 1.1 (Continued)

Common (Chinese) name	Order	Family	Genus	Species
Kudzu (gan ge teng)	Fabales	Fabaceae	*Pueraria*	*thomsonii*
Squirrel's claws/kuku tupai (hua nan yun shi)	Fabales	Fabaceae	*Caesalpinia*	*crista*
Jatobá-do-cerrado	Fabales	Fabaceae	*Hymenaea*	*stigonocarpa*
Ginkgo biloba (yin xing)	Ginkgoales	Ginkgoaceae	*Ginkgo*	*biloba*
Coffee	Gentianales	Rubiaceae	*Coffea*	*arabica*
Cryptolepis sanguinolenta	Gentianales	Apocynaceae	*Cryptolepis*	*sanguinolenta*
Olive	Lamiales	Oleaceae	*Olea*	*europaea*
Forsythia	Lamiales	Oleaceae	*Forsythia*	*koreana*
Brahmi/Indian pennywort	Lamiales	Plantaginaceae	*Bacopa*	*monnieri*
Sesame	Lamiales	Pedaliaceae	*Sesamum*	*indicum*
Devil's claw	Lamiales	Pedaliaceae	*Harpagophytum*	*procumbens*
Baikal skullcap (huang qin)	Lamiales	Lamiaceae	*Scutellaria*	*baicalensis*
Greek sage	Lamiales	Lamiaceae	*Salvia*	*fruticosa*
Cinnamon	Laurales	Lauraceae	*Cinnamomum*	*cassia*
Magnolia bark (hou po)	Magnoliales	Magnoliaceae	*Magnolia*	*officinalis*
Willow bark	Malpighiales	Salicaceae	*Salix*	–
Wild viola (bai hua di ding)	Malpighiales	Violaceae	*Viola*	*patrinii*
Cnestis ferruginea	Oxalidales	Connaraceae	*Cnestis*	*ferruginea*
Maritime pine/cluster pine	Pinales	Pinaceae	*Pinus*	*pinaster*
Thuja orientalis	Pinales	Cupressaceae	*Thuja*	*orientalis*
Black pepper	Piperales	Piperaceae	*Piper*	*nigrum*
Kava/kava-kava	Piperales	Piperaceae	*Piper*	*methysticum*

Black seed	Ranunculales	Ranunculaceae	*Nigella*	*sativa*
Cannabis/marijuana	Rosales	Cannabaceae	*Cannabis*	*sativa*
White mulberry	Rosales	Moraceae	*Morus*	*alba*
Cherokee rose (jin ying zi)	Rosales	Rosaceae	*Rosa*	*laevigata*
Nettle	Rosales	Urticaceae	*Urtica*	*dioica*
Hawthorn (shan zha)	Rosales	Rosaceae	*Crataegus*	*oxyacantha*
Myrrh	Sapindales	Burseraceae	*Commiphora*	*erythraea*
Mango	Sapindales	Anacardiaceae	*Mangifera*	*indica*
Mastic tree	Sapindales	Anacardiaceae	*Pistacia*	*lentiscus*
Chinese toon (xiang chun)	Sapindales	Meliaceae	*Toona*	*sinensis*
Mother-of-pearl-plant/ghost plant	Saxifragales	Crassulaceae	*Graptopetalum*	*paraguayense*
Chinese peony (bai shao)	Saxifragales	Paeoniaceae	*Paeonia*	*lactiflora*
Artic root/golden root (mei gui hong jing tian)	Saxifragales	Crassulaceae	*Rhodiola*	*rosea*
Wolfberry/goji berry (ning xia gou qi)	Solanales	Solanaceae	*Lycium*	*barbarum*
Sweet potato	Solanales	Convolvulaceae	*Ipomoea*	*batatas*
Grapevine	Vitales	Vitaceae	*Vitis*	*vinifera*
Turmeric	Zingiberales	Zingiberaceae	*Curcuma*	*longa*
Ginger	Zingiberales	Zingiberaceae	*Zingiber*	*officinale*
Brown algae	Fucales	Sargassaceae	*Myagropsis*	*myagroides*
Button mushroom/portobello mushroom	Agaricales	Agaricaceae	*Agaricus*	*bisporus*
Lingzhi mushroom (ling zhi)	Polyporales	Ganodermataceae	*Ganoderma*	*lucidum*

processes are partially controlled by the redox-sensitive vitagenes (see Section 1.2). At high doses, the same phytochemicals may elicit toxic effects through the activation of NF-κB, increased expression of cytokines and chemokines, activation of PLA_2s and COX, and generation of high levels of ROS and inflammatory eicosanoids. The amount of fruits and vegetables normally consumed by humans falls within the subtoxic stimulatory dose range of concentrations. However, some plants and fungi produce and concentrate toxins in amounts sufficient to cause illness or death in humans [33,34].

1.4.1 Order: Apiales

1.4.1.1 Family: Araliaceae, Genus: *Panax*, Species: *ginseng*

Panax ginseng is widely used as a health tonic. Ginsenoside remodulated phospho-p38, iNOS, and COX-2 signaling pathways in lipopolysaccharide (LPS)-stimulated BV-2 microglial cells. Ginsenoside Rg1 (50, 100 or 150 μM) decreased IL-1β, IL-8, and TNF-α levels in amyloid beta (Aβ)40-treated THP-1 monocytes [35].

1.4.1.2 Family: Araliaceae, Genus: *Eleutherococcus/Acanthopanax*, Species: *senticosus*

Acanthopanax senticosus (Siberian ginseng) extracts modulated nitric oxide (NO)/ROS production and induced translocation of Nrf2 to increase hemeoxygenase 1 (HO-1) expression in LPS-stimulated BV-2 microglial cells. Extracts also reduced infarct volume after cerebral ischemia in rats [36].

1.4.1.3 Family: Apiaceae, Genus: *Centella*, Species: *asiatica*

Centella asiatica is a medicinal herb commonly used in Ayurveda and traditional Chinese medicine. Asiaticoside, a triterpenoid isolated from *Centella asiatica*, modulated COX-2 expression in the brains of LPS-stimulated animals. Phenolic acids identified in *Centella asiatica* extracts also inhibited 5-LOX and were shown to have antioxidant and anti-inflammatory effects [37].

1.4.1.4 Family: Apiaceae, Genus: *Angelica*, Species: *dahuricae*

Angelica dahuricae radix extract modulated TNF-α, IL-1β, IL-6, iNOS, COX-2, and ROS in LPS-stimulated BV-2 microglial cells. Oral administration of the extract suppressed caspase-3 activation and apoptotic cell death of neurons and oligodendrocytes, and improved function after spinal cord injury (SCI) [38].

1.4.2 Order: Arecales

1.4.2.1 Family: Arecaceae, Genus: *Euterpe*, Species: *oleracea*

Euterpe oleracea Mart (açaí) fruit pulp has a high content of polyphenols. Açaí fractions modulated iNOS, COX-2, p38 mitogen-activated protein kinase (MAPK), TNF-α, and NF-κB expression in BV-2 microglial cells [39].

1.4.2.2 Family: Arecaceae, Genus: *Elaeis*, Species: *guineensis*

The oil palm (*Elaeis guineensis*) is an abundant source of water-soluble phenolics. In mice treated with oil palm phenolics, genes involved in brain development and activity were upregulated, while those involved in inflammation were downregulated [40].

1.4.3 Order: Asparagales

1.4.3.1 Family: Amaryllidaceae, Genus: *Allium*, Species: *sativum*

Intraperitoneal administration of a component of "Aged Garlic Extract" (AGE), SAC, modulated oxidative stress and decreased infarct volume after cerebral ischemia in rats. SAC also inhibited cell signaling pathways involved in synaptic degeneration and neuroinflammation in AD [41].

1.4.3.2 Family: Xanthorrhoeaceae, Genus: *Hemerocallis*, Species: *citrina*

Hemerocallis citrina, a traditional herbal medicine, has been used for the improvement of behavioral and emotional status in East Asian countries. It modulated IL-1β, IL-6, and TNF-α expression and indoleamine-2,3-dioxygenase (IDO) activity in the frontal cortex and hippocampus of rats exposed to chronic unpredictable mild stress [42].

1.4.4 Order: Asterales

1.4.4.1 Family: Asteraceae, Genus: *Silybum*, Species: *marianum*

Silybum marianum (milk thistle) contains silymarin, which modulated inhibitor κB-alpha (IκB-α) degradation and NF-κB nuclear translocation and reduced infarct volume after cerebral ischemia in rats. Silymarin has also been proposed as a neuroprotective agent in AD and Parkinson's disease (PD) [43].

1.4.4.2 Family: Asteraceae, Genus: *Artemisia*, Species: *argyi*

Artemisia argyi is a herbaceous perennial plant native to China, Japan, and Eastern Siberia. An extract modulated NO, prostaglandin E2 (PGE2), TNF-α, iNOS, COX-2, IL-1β, granulocyte-macrophage colony-stimulating factor, and macrophage inflammatory protein-1α levels in LPS-stimulated BV-2 microglial cells [44].

1.4.4.3 Family: Asteraceae, Genus: *Achillea*, Species: *fragrantissima*

Achillea fragrantissima is a desert plant used in traditional medicine. An extract modulated NO, IL-1β, TNF-α, matrix metallopeptidase 9, COX-2, and iNOS levels in LPS-stimulated primary microglial cells [45].

1.4.4.4 Family: Asteraceae, Genus: *Tussilago*, Species: *farfara*

Tussilago farfara L. (Compositae) flower buds are used in traditional oriental medicine for the treatment of bronchitis and asthma. Extracts modulated arachidonic acid metabolism, neuronal injury induced by an NO generator spermine (NONOate), and Aβ-induced neuronal injury [46].

1.4.5 Order: Celastrales

1.4.5.1 Family: Celastraceae, Genus: *Tripterygium*, Species: *wilfordii*

Triptolide is one of the major active components of the Chinese herb *Tripterygium wilfordii* Hook F, which has potent anti-inflammatory and immunosuppressive characteristics. Extracts modulated TNF-α and NO expression and reduced injury in LPS-stimulated primary mesencephalic neurons [47].

1.4.6 Order: Cucurbitales

1.4.6.1 Family: Cucurbitaceae, Genus: *Momordica*, Species: *charantia*

Momordica charantia, often called bitter melon or bitter gourd, is reported to have anti-inflammatory properties. Extracts modulated expression of neuroinflammatory markers NF-κB, IL-16, IL-22, and IL-17R in the brains of high-fat diet-treated mice [48].

1.4.7 Order: Dipsacales

1.4.7.1 Family: Caprifoliaceae, Genus: *Valeriana*, Species: *amurensis*

Valeriana amurensis extracts modulated iNOS, COX-2, and IκB-α levels, reduced neuronal injury, and improved spatial exploratory activity in a rat model of AD [49].

1.4.8 Order: Ericales

1.4.8.1 Family: Theaceae, Genus: *Camellia*, Species: *sinensis*

The beneficial effects of green tea result from interactions between green-tea catechins and cellular proteins. Teasaponin, a tea extract, has also been shown to have anti-inflammatory effects [50].

1.4.8.2 Family: Theaceae, Genus: *Vaccinium*

Fruits such as blueberries contain flavonoids, which have anti-inflammatory and antioxidant effects. Blueberry polyphenol supplementation for 8 weeks modulated IL-1β, TNF-α, and NF-κB levels, and reduced learning impairment after kainate-induced excitotoxic injury in rats [51].

1.4.9 Order: Fagales

1.4.9.1 Family: Juglandaceae, Genus: *Juglans*, Species: *regia*

Extracts of *Juglans regia* (English walnut) modulated NO and iNOS levels in LPS-stimulated microglial cells. Polyphenolic compounds in walnuts also reduced oxidant and inflammatory load on brain cells, and enhanced sequestration of toxic protein aggregates [52].

1.4.10 Order: Fabales

1.4.10.1 Family: Polygalaceae, Genus: *Polygala*, Species: *tenuifolia*

Polygala tenuifolia is a herb used in traditional Chinese medicine. Water extract of *Polygala tenuifolia* root modulated NO, PGE2, iNOS, COX-2, IL-1β, and TNF-α levels in LPS-stimulated BV-2 microglial cells [53].

1.4.10.2 Family: Fabaceae, Genus: *Mucuna*, Species: *pruriens*

Mucuna pruriens, a leguminous plant, is used as an anti-inflammatory drug in Ayurveda. Ethanolic extracts downregulated NO production, neuroinflammation, and microglial activation and modulated loss of TH-positive cells in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mouse model of PD [54].

1.4.10.3 Family: Fabaceae, Genus: *Glycine*, Species: *max*

Soybean isoflavones modulated inflammatory cytokines and Aβ42-induced upregulation of toll-like receptor 4 (TLR4) and NF-κB p65 mRNA in rats [55].

1.4.10.4 Family: Fabaceae, Genus: *Sophora*, Species: *flavescens*

Sophora flavescens Ait is a herb used in traditional Chinese medicine. One of its components, oxymatrine, modulated TLR4, NF-κB, TNF-α, IL-1β, IL-6, 12/15-LOX, phospho-p38 MAPK, and $cPLA_2$ levels and reduced neuronal injury after intracerebral hemorrhage in rats [56].

1.4.10.5 Family: Fabaceae, Genus: *Pueraria*, Species: *thomsonii*

Isoflavones of *Pueraria* flowers (genistein, tectorigenin, and irisolidone) inhibited NO levels in LPS-stimulated primary microglial cells [57].

1.4.10.6 Family: Fabaceae, Genus: *Caesalpinia*, Species: *crista*

Caesalpinia crista leaf extracts showed antioxidant effects and suppressed 5-LOX in polymorphonuclear leukocytes [37].

1.4.10.7 Family: Fabaceae, Genus: *Hymenaea*, Species: *stigonocarpa*

Hymenaea stigonocarpa extracts showed protective effects following 2,4,6-trinitrobenzenesulfonic acid-induced colon damage and modulated lipid peroxidation in rat brain membranes [58].

1.4.10.8 Family: Fabaceae, Genus: *Sutherlandia*, Species: *frutescens*

Sutherlandia frutescens is native to dry parts of southern Africa. It has been promoted as useful to people with HIV/AIDS, but there is no evidence of benefit, and it may interact adversely with antiretroviral drugs. *Sutherlandia* has been shown to have anti-neuroinflammatory properties in preliminary studies (W. Folk, unpublished).

1.4.11 Order: Ginkgoales

1.4.11.1 Family: Ginkgoaceae, Genus: *Ginkgo*, Species: *biloba*

GB is a unique species of tree, with no living relatives. The active compounds of the GB extract EGb 761 interact with gamma-aminobutyric acid (GABA) and glycine receptors on neurons that play an important role in memory formation, consolidation, and cognition. EGb 761 also enhanced cholinergic processes in the cerebral cortex [59,60].

1.4.12 Order: Gentianales

1.4.12.1 Family: Rubiaceae, Genus: *Coffea*, Species: *arabica*

A component of coffee, eicosanoyl-5-hydroxytryptamideeicosanoyl-5-hydroxytryptamide, attenuated neuroinflammatory response to MPTP, and improved neuronal integrity in the α-synuclein transgenic mouse model of PD [61].

1.4.12.2 Family: Apocynaceae, Genus: *Cryptolepis*, Species: *sanguinolenta*

Cryptolepis sanguinolenta extracts modulated TNF-α, IL-6, and PGE2 levels and suppressed NF-κB p65 nuclear translocation in IL-1β-stimulated SK-N-SH neuroblastoma cells [62].

1.4.13 Order: Lamiales

1.4.13.1 Family: Oleaceae, Genus: *Olea*, Species: *europaea*

Olive oil contains phenolic compounds that are well-known antioxidants. Long-term consumption of olive oil increased the proportion of monounsaturated fatty acids (particularly oleic acid) and reduced the level of arachidonic acid, suggesting its potential in modulating the production of proinflammatory eicosanoids [63].

1.4.13.2 Family: Oleaceae, Genus: *Forsythia*, Species: *koreana*

Forsythia is a genus of flowering plants in the olive family. Pinoresinol isolated from the fruits of *Forsythia koreana* Nakai modulated NO, PGE2, TNF-α, IL-1β, and IL-6 levels in LPS-stimulated primary microglial cells [64].

1.4.13.3 Family: Plantaginaceae, Genus: *Bacopa*, Species: *monnieri*

Bacopa monnieri (Indian pennywort or "Brahmi") is an important medicinal herb used in Ayurveda. Bacosides modulated proinflammatory cytokines and iNOS levels in aged rat brains. Extracts also restored Nrf2 and HO-1 expression, and improved memory dysfunction after okadaic acid treatment in rats [65].

1.4.13.4 Family: Pedaliaceae, Genus: *Sesamum*, Species: *indicum*

Sesamin, a constituent of sesame seeds, modulated extracellular signal, regulated kinase (ERK)1/2, p38 MAPK, caspase-3, and COX-2 expression in PC12 cells and BV-2 microglial cells, and reduced damage after kainate-induced excitotoxic injury in mice [66].

1.4.13.5 Family: Pedaliaceae, Genus: *Harpagophytum*, Species: *procumbens*

Harpagophytum procumbens (devil's claw) is a plant of the sesame family that is used in inflammatory diseases. Ethyl acetate extracts of *Harpagophytum procumbens* decreased lipid peroxidation and cellular damage in rat brain slices [67].

1.4.13.6 Family: Lamiaceae, Genus: *Scutellaria*, Species: *baicalens*

Scutellaria baicalens Georgia and its constituents are reported to have antioxidative and anti-inflammatory properties. Extracts modulated COX-2, iNOS, PGE2, and NO levels in LPS-stimulated Raw 264.7 and BV-2 microglial cells, and improved cognition in mice [68].

1.4.13.7 Family: Lamiaceae, Genus: *Salvia*, Species: *fruticosa*

Salvia fruticosa (Greek sage) is a perennial shrub in the eastern Mediterranean. Extracts modulated acetylcholinesterase (AChE) activity and C-reactive protein (CRP), NF-κB, and monocyte chemoattractant protein 1 (MCP-1) levels in the $AlCl_3$-induced rat model of AD [69].

1.4.13.8 Family: Acanthaceae, Genus: *Clinacanthus*, Species: *nutans*

Clinacanthus nutans Lindau (Sabah snake grass) leaves have been used in traditional medicine to treat snake bite. They are also used in the treatment of cancer and of kidney failure. Our recent studies have shown *C. nutans* leaves have the ability to inhibit $cPLA_2$ expression in SH-SY5Y cells.

1.4.14 Order: Laurales

1.4.14.1 Family: Lauraceae, Genus: *Cinnamomum*, Species: *cassia*

Cinnamomum cassia (cinnamon) extracts modulated NO, IL-1β, IL-6, and TNF-α levels in LPS-stimulated BV-2 microglial cells. Cinnamon's constituent, 2′-hydroxycinnamaldehyde (HCA), or its derivative, 2′-benzoyloxycinnamaldehyde (BCA), also modulated NO and TNF-α levels in LPS-stimulated microglial cells [70].

1.4.15 Order: Magnoliales

1.4.15.1 Family: Magnoliaceae, Genus: *Magnolia*, Species: *officinalis*

Oral administration of 4-O-methylhonokiol from Magnolia bark in drinking water for 12 weeks modulated β-secretase activity, Aβ deposition, oxidative lipid and protein damage levels, activation of glial cells, and memory impairment in the Tg2576 mouse model of AD [71]. *Magnolia officinalis* ethanol extract reduced amyloidogenesis and memory impairment in the LPS-induced mouse model of AD [72].

1.4.16 Order: Malpighiales

1.4.16.1 Family: Salicaceae, Genus: *Salix*

Willow bark contains salicin, which modulated immune activation and had a positive effect on the forced swim test (FST), suggesting antidepressant effects in rats [73].

1.4.16.2 Family: Violaceae, Genus: *Viola*, Species: *patrinii*

Viola patrinii extract modulated iNOS, COX-2, TNF-α, and IL-1β levels and upregulated Nrf2-dependent expression of HO-1 in hippocampal HT22 cells and BV-2 microglial cells [74].

1.4.17 Order: Oxalidales

1.4.17.1 Family: Connaraceae, Genus: *Cnestis*, Species: *ferruginea*

Amentoflavone isolated from *Cnestis ferruginea* modulated ROS, malondialdehyde (MDA), and TNF-α levels in LPS-stimulated C6 astrocytoma cells, and reduced nociceptive responses in the carrageenan-injection mouse model of inflammatory pain [75].

1.4.18 Order: Pinales

1.4.18.1 Family: Pinaceae, Genus: *Pinus*, Species: *pinaster*

Pinus pinaster (maritime pine) is native to the western and southwestern Mediterranean. An extract from the bark, Pycnogenol, modulated TNF-α and IL-1β levels in the striatum, and reduced behavioral impairment in MPTP-treated mice [76].

1.4.18.2 Family: Cupressaceae, Genus: *Thuja*, Species: *orientalis*

Thuja is a genus of coniferous trees in the cypress family. *Thuja orientalis* seed extracts modulated NO, PGE2, and IL-1β levels and iNOS, COX-2, and IL-1β expression in LPS-stimulated BV-2 microglial cells, and reduced infarct volume after cerebral ischemia in rats [77].

1.4.19 Order: Piperales

1.4.19.1 Family: Piperaceae, Genus: *Piper*, Species: *nigrum*

Piper nigrum (black pepper) extracts modulated AChE, CRP, NF-κB, and MCP-1 levels in the $AlCl_3$-induced rat model of AD [69].

1.4.19.2 Family: Piperaceae, Genus: *Piper*, Species: *methysticum*

Piper methysticum roots possess sedative and anesthetic properties. A chemically synthesized kavalactone derivative, 2′,6′-dichloro-5-methoxymethyl-5,6-dehydrokawain, modulated iNOS induction and NO production in LPS-stimulated BV-2 microglial cells, and reduced damage after oxidative stress-induced neuronal injury [78].

1.4.20 Order: Ranunculales

1.4.20.1 Family: Ranunculaceae, Genus: *Nigella*, Species: *sativa*

Nigella sativa is an annual flowering plant in South and South West Asia. Extracts modulated a scopolamine-induced increase in MDA and oxidative stress and reduced spatial memory impairment in scopolamine-treated rats [79].

1.4.21 Order: Rosales

1.4.21.1 Family: Cannabaceae, Genus: *Cannabis*, Species: *sativa*

The cannabis plant contains molecules (e.g., 2-arachidonoyl glycerol, anandamide) that bind to G-protein-coupled cannabinoid receptors, and have been reported to reduce the progression of neurodegeneration [80].

1.4.21.2 Family: Moraceae, Genus: *Morus*, Species: *alba*

Mulberry leaves have been reported to possess antiamyloidogenic effects. Mulberry leaf and silkworm excreta extracts modulated astrocyte and microglial reaction and reduced memory impairment in Aβ-treated mice [81].

1.4.21.3 Family: Rosaceae, Genus: *Rosa*, Species: *laevigata*

Rosa laevigata Michx fruit flavonoids modulated DNA and mitochondrial damage, activation of Jun kinase (JNK), ERK, and p38 MAPK, and expression of cytokines after hydrogen peroxide (H_2O_2)-induced oxidative stress. Oral administration of fruit extract reduced neuronal damage following cerebral ischemia in rats [82].

1.4.21.4 Family: Urticaceae, Genus: *Urtica*, Species: *dioica*

Urtica dioica (nettle) is reported to have anti-inflammatory and antioxidant effects. It modulated ROS levels and the DNA-binding activity of NF-κB and reduced neuronal injury after N-methyl-d-aspartate-induced excitotoxic injury in rats [83].

1.4.21.5 Family: Rosaceae, Genus: *Crataegus*, Species: *oxyacantha*

Hawthorn ethanolic extract pretreatment of 100 mg/kg for 15 days modulated proinflammatory cytokine and intercellular adhesion molecule 1 (ICAM-1) expression, and reduced the number of apoptotic cells after cerebral ischemia in rats [84].

1.4.22 Order: Sapindales

1.4.22.1 Family: Burseraceae, Genus: *Commiphora*, Species: *erythraea*

Plants in the myrrh family are reported to have anti-inflammatory effects. Extracts modulated ROS and NO levels in LPS-stimulated BV-2 microglial cells and NF-α and IL-1β levels in the brains of LPS-treated mice [85].

1.4.22.2 Family: Anacardiaceae, Genus: *Mangifera*, Species: *indica*

Mangifera indica is a species of mango. An aqueous extract, Vimang, is traditionally used in Cuba for its anti-inflammatory and antioxidant effects. Extracts modulated TNF-α-induced inhibitor κB (IκB) degradation, binding of NF-κB to DNA, and transcription of genes involved in oxidative stress [86].

1.4.22.3 Family: Anacardiaceae, Genus: *Pistacia*, Species: *lentiscus*

Pistacia lentiscus (essential oil), a mixture of terpenes and sesquiterpenes, prevented bilateral common carotid artery occlusion-induced loss of DHA. Treatment with *Pistacia lentiscus* extracts modulated an increase in COX-2 and decrease in DHA levels following cerebral ischemia in rats [87].

1.4.22.4 Family: Meliaceae, Genus: *Toona*, Species: *sinensis*

Toona sinensis leaf extract suppressed NO production, TNF-α secretion, and iNOS protein expression in LPS-stimulated microglia. Extracts also modulated nitrate, COX-1 and thromboxane levels, and reduced infarct volume after cerebral ischemia in rats [88].

1.4.23 Order: Saxifragales

1.4.23.1 Family: Crassulaceae, Genus: *Graptopetalum*, Species: *paraguayense*

Graptopetalum paraguayense E. Walther is reported to have anti-inflammatory and antioxidant effects. *Graptopetalum paraguayense* E. Walther leaf extracts modulated ERK expression, and reduced neuronal injury after cerebral ischemia in rats [89].

1.4.23.2 Family: Paeoniaceae, Genus: *Paeonia*, Species: *lactiflora*

A component of *Paeonia lactiflora* Pall, paeoniflorin, has anti-inflammatory effects. Paeoniflorin modulated IL-1β, TNF-α, ICAM-1, and MPO levels, and reduced neurological deficits after cerebral ischemia in rats [90].

1.4.23.3 Family: Crassulaceae, Genus: *Rhodiola*, Species: *rosea*

Extracts of *Rhodiola rosea* modulated iNOS and cytokine levels in LPS-stimulated BV-2 microglial cells and reduced iNOS, IL-1β, and TNF-α expression in the prefrontal cortex [91].

1.4.24 Order: Solanales

1.4.24.1 Family: Solanaceae, Genus: *Lycium*, Species: *barbarum*

Lycium barbarum is one of two species of boxthorn from which wolfberry is harvested. Extracts reduced oxidative stress and protected retinal ganglion cells from secondary injury after partial optic nerve transection in rats [92].

1.4.24.2 Family: Solanaceae, Genus: *Withania*, Species: *somnifera*

Ashwagandha (Sanskrit for "horse smell") is referred to in Ayurveda as "Indian ginseng." It had potent anti-inflammatory action against microglial cells and may have protective effects in a model of AD (G.Y. Sun, unpublished).

1.4.24.3 Family: Convolvulaceae, Genus: *Ipomoea*, Species: *batatas*

Purple sweet potato color (PSPC), a naturally occurring anthocyanin, modulated glial fibrillary acidic protein (GFAP) expression, iNOS, and COX-2 levels and improved performance in the open field and passive avoidance tests in D-galactose-treated mice [93].

1.4.25 Order: Vitales

1.4.25.1 Family: Vitaceae, Genus: *Vitis*, Species: *vinifera*

Red grapes contain resveratrol, which prevented nuclear translocation of NF-κB by inhibiting IκB kinase via activation of an enzyme of the NAD^+-dependent histone deacetylase, SIRT1; this enzyme deactivates NF-κB via deacetylation, leading to modulation of gene-expression changes associated with aging in mice [94].

1.4.26 Order: Zingiberales

1.4.26.1 Family: Zingiberaceae, Genus: *Curcuma*, Species: *longa*

Curcuma longa ("yellow ginger" in Chinese or "kunyit" in Malay) is reported to have anti-inflammatory and antioxidant effects. Curcumin modulated TNF-dependent activation of NF-κB through inhibition of p65 translocation to the nucleus and IκB-α degradation [95]. It also modulated tau phosphorylation and Aβ formation [96].

1.4.26.2 Family: Zingiberaceae, Genus: *Zingiber*, Species: *officinale*

Gingerols and shogaols in ginger modulated NF-κB, IL-1β, and TNF-α expression in microglial cells and human monocytic THP-1 cells, and reduced neuronal damage after 1-methyl-4-phenylpyridinium (MPP^+) treatment [97].

1.4.27 Order: Fucales

1.4.27.1 Family: Sargassaceae, Genus: *Myagropsis*, Species: *myagroides*

Myagropsis myagroides brown algae ethanolic extract modulated iNOS and COX-2 mRNA and protein expression in LPS-stimulated BV-2 microglial cells [98].

1.4.28 Order: Agaricales

1.4.28.1 Family: Agaricaceae, Genus: *Agaricus*, Species: *bisporus*

Agaricus bisporus (button mushroom, portobello mushroom) is abundant in ergosterol, which can be converted to vitamin D2 under ultraviolet (UV) light. Treatment with vitamin D2-enriched mushrooms resulted in improved learning and memory, in a mouse model of AD [99].

1.4.29 Order: Polyporales

1.4.29.1 Family: Ganodermataceae, Genus: *Ganoderma*, Species: *lucidum*

Ganoderma lucidum mushroom extracts modulated NO, TNF-α, and IL-1β levels in LPS-stimulated microglial cells, suggesting that *Ganoderma lucidum* is a promising agent for the treatment of neuroinflammation [100].

1.5 Use of Phytochemicals against Neuroinflammation

1.5.1 Catechin Flavonoid Polyphenols

The beneficial effects of green tea have been attributed to the interactions of green-tea catechins with cellular proteins. These interactions lead to changes in enzyme activity and ligand/receptor function. EGCG is converted to a catechol-quinone upon autooxidation, and the resultant quinone moiety rapidly reacts with the sulfhydryl group of proteins to form cysteinyl–flavonoid adducts [101]. In addition, EGCG binds to serum proteins such as fibronectin, fibrinogen, histidine-rich glycoproteins, 67-kDa laminin receptor, Bcl-2 proteins, and vimentin. EGCG interacts with growth factor receptors (e.g., epidermal growth factor, platelet-derived growth factor (PDGF), IGF-1, and vascular endothelial growth factor (VEGF) receptors) and alters signal transduction processes. The ability of EGCG to cross the BBB allows its use as a preventive treatment for neurodegenerative diseases. EGCG may work through a voltage-gated sodium channel signaling pathway. It also inhibits the activity of HSP90 by directly binding to HSP70-interacting protein. Green-tea components inhibit the arachidonic acid pathway (PLA_2, COX, and LOX) and decrease the production of prostaglandins and leukotrienes, key mediators of the acute inflammatory cascade. Together, results suggest that green-tea components inhibit inflammation by downregulating the expression of proinflammatory enzymes and cytokines [102].

Catechins in green tea have similar neuroprotective effects, and their antioxidant- and free radical-scavenging properties are well known [103,104]. Catechins function as metal chelators that quench copper (II) and iron (III) ions to form inactive complexes and prevent the generation of toxic free radicals. In addition, ultra-rapid electron transfer from catechins to ROS-induced radical sites on DNA can occur. The anti-inflammatory effects of catechins may involve downregulation of NO synthase activity and scavenging of NO. This can occur via attenuation of signal transducer and activator of transcription (STAT)-1α activation or through prevention of IκB degradation which inhibits NF-κB from binding to the promoter region of the NO synthase gene [105].

1.5.2 Anthocyanin Flavonoid Polyphenols

Fruits such as blueberries contain anthocyanin flavonoid polyphenols, which offer beneficial effects for memory [106,107]. Anthocyanins suppress apoptosis resulting from mitochondrial oxidative stress, while anthocyanin and pro-anthocyanin-rich extracts prevent death of dopaminergic neurons caused by rotenone, via an improvement in mitochondrial function. Blueberry extracts enhance microglial clearance of Aβ-inhibited aggregation of Aβ1–42 and suppress microglial activation via an effect on p44/42 MAPK signaling. Extracts also modulate inflammatory cytokine IL-1β and TNF-α expression, augment expression of the neurotrophic factor IGF-1 in the hippocampus, and improve cognitive performance in rats after excitotoxic injury induced by kainate [51].

1.5.3 Stilbenoid Polyphenols

The beneficial effects of resveratrol result from its antiaging, anticarcinogenic, cardioprotective, and neuroprotective activities, which are supported by its anti-inflammatory, antioxidant, and gene-modulating properties [108–110]. Due to its structural similarity

to diethylstilbestrol (a synthetic estrogen), resveratrol produces estrogenic effects by binding to estrogen receptors and evoking neurochemical effects that parallel those exerted endogenously. Many of these effects are associated with its ability to inhibit transcription factors such as MAPK, AP-1, and NF-κB. Resveratrol prevents nuclear translocation of NF-κB by inhibiting IκB kinase. This mechanism is postulated to occur via activation of an NAD + -dependent histone deacetylase, SIRT1, which deactivates NF-κB via deacetylation [94]. Resveratrol also induces antioxidant enzymes such as catalase, SOD, and GPx, as well as HO-1. The anti-inflammatory effects of resveratrol are mediated through downregulation of TNF-α, COX-2, iNOS, IFN-γ, and various interleukins. Resveratrol (5 mg/kg for males, 1 mg/kg for females) modulates IL-1β and TNF-α level, microglial activation, and ROS production in the ischemic cortex and reduces infarct volumes after ischemic stroke in mice. In addition, resveratrol (0.01% by weight in the diet for 1 year) reduces average Aβ plaque density and modulates the microglial activation in the transgenic amyloid beta protein protein/presenilin-1 (AβPP/PS1) mouse model of AD [111]. It also prevents the proinflammatory effect of fibrillary Aβ on macrophages by potently inhibiting the effect of Aβ on IκB phosphorylation, the activation of STAT1 and STAT3, and the secretion of TNF-α and IL-6 secretion [112].

1.5.4 Curcuminoid Polyphenols

The yellow curcumin pigment, bis-(4-hydroxy-3-methoxyphenyl)-1,6-diene-3,5-dione, in turmeric (*Curcuma longa*) is reported to have anti-inflammatory and antioxidant properties. Curcumin inhibits TNF-dependent activation of NF-κB by inhibiting p65 translocation to the nucleus and the degradation of IκB-α [95]. This may occur via quenching of reactive oxygen intermediates. In addition, curcumin blocks the DNA binding of JNK/AP-1 transcription factor and downregulates c-Jun by blocking its transcription. It also acts as a peroxisome proliferator-activated receptor gamma (PPARγ) agonist, inhibiting activation and inflammation of NF-κB. Curcumin reduces the levels of cytokines (e.g., IL-1β, TNF-α) and other inflammatory factors (e.g., iNOS) and inhibits various factors of the inflammatory pathway (e.g., COX-2 and LOX) at the transcriptional level. It activates Nrf2, leading to increased expression of HO-1, an enzyme that plays a pivotal role in cytoprotection against noxious stimuli. Curcumin modulates NF-κB activation and subsequent ICAM-1 gene expression in cultured brain microvessel endothelial cells. It also reduces neutrophil adhesion to the cerebrovascular endothelium and TNF-α and ICAM-1 expression in the brain after experimental stroke induced by middle cerebral artery occlusion in rats. It modulates Aβ-stimulated inflammatory responses in primary astrocytes and reduces GFAP expression and improved spatial memory in the Aβ1–40-induced rat model of AD. It also modulates COX-2 and GFAP in Aβ25–35-treated astrocytes and the anti-neuroinflammatory effects of a PPARγ antagonist, GW9662 [113].

1.5.5 *Ginkgo biloba* Polyphenols

The active compound of GB, EGb 761, possesses potent antioxidant, memory-enhancing, anti-inflammatory, and blood flow-promoting properties, which play important roles in modulating brain activities such as cognition, concentration, mental alertness, and mental fatigue. Many of these activities are mediated by interactions between constituents of EGb 761 (bilobalide) and GABA and glycine receptors located on neuronal

cell membranes. These receptors play an important role in memory formation, consolidation, and cognition [114,115]. EGb 761 also enhances cholinergic processes in various cortical regions. Together, results support the view that the psychological and physiological benefits of EGb 761 are partly due to modulation of neurotransmitters and neurotransmitter receptors. EGb 761 also benefits the microcirculation by improving blood flow in small vessels. It exerts its antioxidant and anti-inflammatory effects via activation of the HO-1/Nrf2 pathway, VEGF regulation, and downregulation of various inflammatory mediators. Its antioxidative action is suggested to work in concert with its antiapoptotic mechanism. The anti-inflammatory effects of the GB polysaccharide are shown by its suppression of NO production. Bilobalide (4, 8 mg/kg) extracted from GB leaves modulates TNF-α and Aβ1–40 expression, reduces neuronal damage in the frontal cortex and hippocampus, and protects against learning and memory impairments in a rat model of AD [116].

1.5.6 Aromatic Acid Class of Phenolic Compounds

Cinnamon (Figure 1.4) produces anti-inflammatory, antimicrobial, antioxidant, antitumor, cardiovascular, cholesterol-lowering, and immunomodulatory effects. *In vitro* studies have demonstrated that it may act as an insulin mimetic to potentiate insulin activity or stimulate cellular glucose metabolism [117,118]. Cinnamon not only scavenges ROS and NO, but also interacts with superoxide anion and peroxynitrite. Cinnamaldehyde is an anti-inflammatory constituent in cinnamon and together with 2-methoxycinnamaldehyde, are potent NF-κB inhibitors. They suppresses TLR4 oligomerization and attenuates LPS-induced intracellular signaling processes in peripheral macrophages. Cinnamaldehyde also reduces LPS-induced intracellular ROS formation, thereby attenuating oxidative stress-triggered signal transduction pathways such as the NF-κB-inducing kinase/IκB-α kinase, ERK, and p38 MAPK pathways. Cinnamic acid and its derivatives significantly (~12–63%) inhibit the formation of advanced glycation end products, in a concentration-dependent manner [119].

1.5.7 Phenylethanoid Class of Phenolic Compounds

Olive oil contains phenolic compounds that are well-known antioxidants. Extra-virgin olive oil fed to transgenic mice with memory impairments improves memory. This is associated with a reduction in oxidative stress, and increases in brain glutathione and GR levels [120]. Post-ischemic neuronal injury may be ameliorated by olive oil via the combination of its effects on the cholinergic system and its antioxidant effects. Long-term consumption of olive oil increases the proportion of monounsaturated fatty acids, particularly oleic acid, while reducing the level of arachidonic acid in the cell membrane, suggesting its potential to modulate the production of proinflammatory eicosanoids. Tyrosol and hydroxytyrosol isolated from olive oil decrease the nuclear translocation of the NF-κB subunits following Aβ exposure *in vitro*, suggesting the involvement of NF-κB in neuroprotective effects of olive oil [121].

1.5.8 Organosulfur Class of Glucosinolates

The beneficial effects of garlic in human health are due to its anti-inflammatory, antioxidant, anticancer, antifungal, and immune system-enhancing properties, as well as its inhibition of prostaglandin production. Organosulfur compounds in garlic target

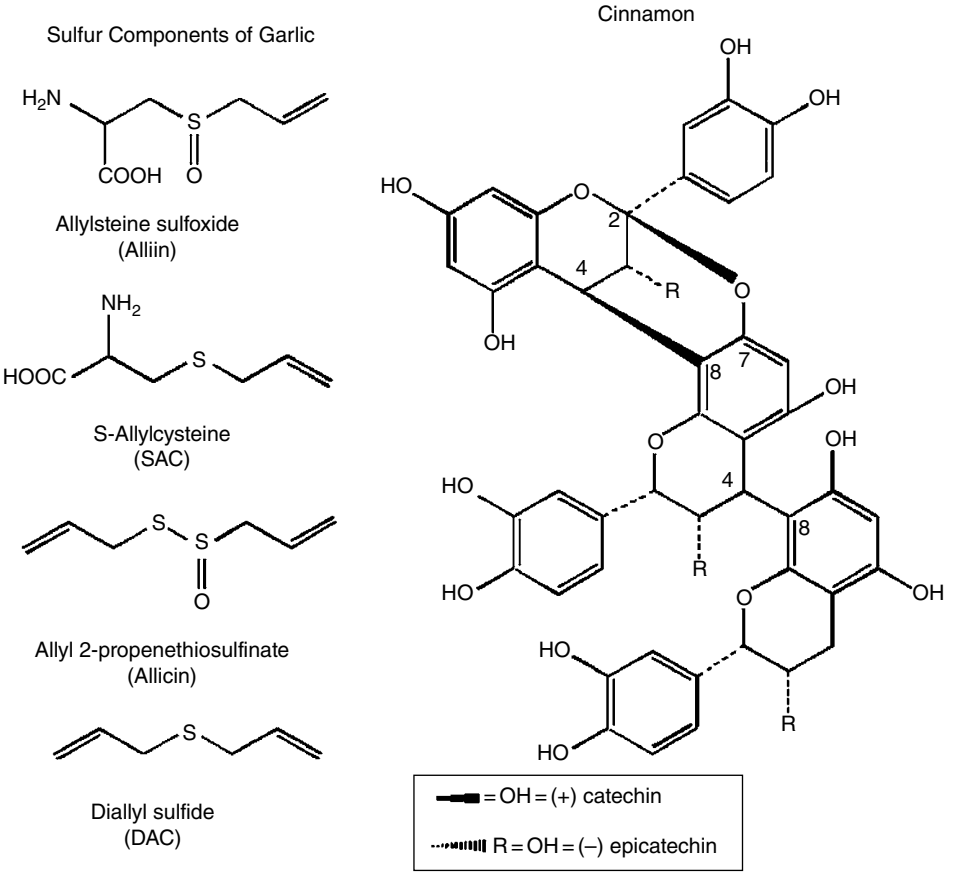

Figure 1.4 Chemical structures of components of garlic and cinnamon.

multiple signal transduction pathways and regulate the expression of many genes and the induction of many enzymes (e.g., arylamine N-acetyltransferase, SOD-like activity, H_2O_2-scavenging activity, GSH redox cycle enzymes, cytochrome P450 reductase, and lactate dehydrogenase) in the brain, liver, and other visceral tissues [122,123]. SAC (Figure 1.4) possesses neuroprotective properties, including antioxidant and radical scavenging effects [124]. SAC and AGE inhibit apoptosis by preventing caspase-3 activation. Garlic compounds modulate intracellular levels of GSH. Low levels of GSH are present in the Alzheimer's brain and are elevated by AGE. The antioxidant action of AGE is demonstrated by the preservation of expression of GPx and GR. This is partly caused by inhibition of NF-κB via interference with an intermediate of TNF-α. An alternative explanation for the antioxidant activity is that SAC inhibits NF-κB activation induced by TNF-α and H_2O_2. A sulfur compound isolated from garlic, thiacremonone, modulates phosphorylation of IκBα and NF-κB activation and reduces LPS-induced amyloidogenesis in cultured astrocytes and BV-2 cells. Results suggest the potential of thiacremonone for intervention in neuroinflammatory diseases, including AD [125].

1.5.9 n-3 Fatty Acids

n-3 fatty acids such as DHA are abundant in fish such as salmon, tuna, and whitefish. In plant products such as walnuts and flaxseed oil, the main n-3 fatty acid is alpha-linolenic acid (ALA), which is converted in the body to EPA and DHA [126]. The presence of ALA is crucial during periods of active growth around birth. Its conversion to EPA and DHA occurs in many body tissues, including the liver and brain – but at a restricted rate. The use of ALA labeled with radioisotopes suggests that with a background diet high in saturated fat, the conversion of ALA to long-chain metabolites is approximately 6% for EPA and 3.8% for DHA. This low rate of ALA to DHA conversion is due not only to a high percentage of ALA being directed toward β-oxidation, but also lower activities of enzymes that convert ALA to DHA in humans compared to rats. n-3 fatty acids are metabolized to lipid mediators, such as resolvins and neuroprotectins. These lipid mediators not only regulate inflammatory cytokines and chemokines (TNF-α, IL-1β, IL-10) but also block apoptotic cell death caused by inflammation and oxidative stress. DHA inhibits arachidonic acid metabolism and downregulates the expression of COX-2 via NF-κB. Mice fed with fish oil showed decreased production of TNF, IL-1β, and IL-6 by endotoxin-stimulated macrophages, and reduced serum levels of TNF, IL-1β, and IL-6 were found in mice injected with endotoxin. DHA is converted to neuroprotectin D1, which confers protection from apoptosis induced by oxidative stress and anti-inflammatory pathways. DHA also reduces oxidative stress by decreasing ROS production by mitochondria. A 3-month DHA supplementation significantly altered the n-3:n-6 polyunsaturated fatty acid ratio in the brain, increased levels of the antiapoptotic molecule Bcl-2 in the brain, modulated COX2 and IL-1β levels and microglial activation after ischemic injury, and decreased infarct volume following middle cerebral artery occlusion in rats. Results suggest that diet-induced accumulation of DHA in the brain may protect against immune response/brain damage in ischemic stroke. DHA and curcumin supplementation also improved cognitive function and modulates Aβ accumulation, oxidative damage, and synaptic deficits in mouse models of AD [127].

1.6 Phytochemicals and Stroke

1.6.1 Tea

Many preclinical studies have found that tea components are effective in reducing stroke volume following middle cerebral artery occlusion, and decrease in infarct volume are found with both tea extracts consumed orally and tea components introduced intraperitoneally in rodent models such as rats, mice, and gerbils. Epidemiological studies support this finding in humans, and are consistent across countries and types of tea [128]. Current evidence indicates beneficial effects of tea and cocoa on endothelial function and total and low-density lipoprotein (LDL) cholesterol [129]. Higher green tea and coffee consumption is inversely associated with risk of cardiovascular disease and stroke in the general population [130]. In addition, daily consumption of four or more cups of black tea is inversely associated with risk of stroke [131]. A significant decrease in ischemic stroke risk was observed for drinking at least one cup of tea weekly when compared with infrequent or

nondrinkers, the risk reduction being largest when drinking one to two cups of green or oolong (black) tea daily [132,133].

1.6.2 Flavonoids

Intake of polyphenols, especially from lignans, flavanols, and hydroxybenzoic acids, is associated with decreased cardiovascular disease risk [134]. High intake of flavonoids was associated with decreased risk of ischemic stroke and possibly with reduced cardiovascular disease mortality in one study [135], although another found that total flavonoid intake was not inversely associated with risk of stroke but that increased intake of citrus fruits/juices (the main dietary source of flavanones) was correlated with reduced ischemic stroke risk [136].

1.6.3 Resveratrol

Resveratrol has shown potential for treatment of stroke in animal and *in vitro* human cell studies [137]. Resveratrol improved memory performance in association with improved glucose metabolism and increased hippocampal functional connectivity in older adults [138].

1.6.4 *Ginkgo biloba*

Studies on the effect of GB on functional outcome in patients with acute stroke suggest that extracts may have protective effects in ischemic stroke [139]. In contrast, another study reported no convincing evidence to support the use of GB for promotion of stroke recovery [140].

1.6.5 Olive Oil

Studies support an inverse association of olive oil consumption with stroke, but not with coronary heart disease [141]. High olive oil consumption and high plasma oleic acid (as an indicator of olive oil intake) were associated with lower incidence of stroke in older adults [142]. One study reported that among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events [143].

1.6.6 n-3 Fatty Acids

Dietary supplementation with n-3 fatty acids did not reduce the risk of cardiovascular disease in elderly participants with age-related macular degeneration [144]. Similarly, there was no difference between n-3 fatty acids and placebo in end points such as mortality, nonfatal stroke, nonfatal acute myocardial infarction, systemic embolism, heart failure development, or recurrent atrial fibrillation [145,146]. In a large general-practice cohort of patients with multiple cardiovascular risk factors, daily treatment with n-3 fatty acids did not reduce cardiovascular mortality or morbidity, including nonfatal myocardial infarction and nonfatal stroke [147]. Meta-analyses showed no overall association between n-3 fatty acid intake and stroke [148], and no effect on cardiovascular biomarkers or mood was found following treatment of post-ischemic stroke patients with moderate-dose fish-oil supplements [149].

1.7 Phytochemicals and AD

1.7.1 Flavonoids

Intake of flavonols and of combined flavonoids (all five combined) were the two parameters among dietary factors that were inversely correlated with dementia in studies among 23 developed countries. Results suggest that higher consumption of dietary flavonoids (especially flavonols) is associated with lower population rates of dementia [150]. One study reported that regular cocoa flavonol consumption could reduce age-related cognitive dysfunction, possibly through an improvement in insulin sensitivity [151]. Flavonol consumption results in enhanced dentate gyrus (DG) function, as shown by functional magnetic resonance imaging (fMRI) and cognitive tests. Together, results suggest that dietary flavonols may be beneficial in modulating age-related cognitive deficits, through an effect on the DG [152].

1.7.2 Resveratrol

Recent epidemiological evidence has revealed the protective role of dietary polyphenols from grape products against AD-type cognitive deterioration, which stems in part from interference with the generation and assembly of Aβ peptides into neurotoxic oligomeric aggregated species. *In vivo* data have demonstrated the neuroprotective properties of resveratrol in animal models of stress and disease [11]. Resveratrol promotes nonamyloidogenic cleavage of amyloid precursor protein and clearance of Aβ [153], and recent studies have shown a role for grape-derived preparations in reducing tau aggregation, which may be useful in the prevention and treatment of AD [154].

1.7.3 Curcumin

Curcumin has antiamyloidogenic, anti-inflammatory, antioxidative, and metal-chelating properties that may result in potential neuroprotective effects. However, it exhibits very low bioavailability, mainly due to its poor aqueous solubility, poor stability in solution, and rapid intestinal first-pass effect and hepatic metabolism [155]. At present, four clinical trials concerning the effects of curcumin on AD have been conducted. Two of them (performed in China and the United States) report no significant differences in changes in cognitive function between curcumin and placebo, while results of the other two are not yet available. Additional trials are necessary to determine the potential usefulness of curcumin for the prevention and treatment of AD [156].

1.7.4 *Ginkgo biloba*

GB is one of the most investigated and adopted herbal remedies for AD. A 24-week randomized controlled trial was conducted to assess the efficacy of a 240 mg once-daily preparation of GB extract EGb 761 in 404 outpatients aged ≥50 years, diagnosed with mild to moderate dementia, AD, or vascular dementia with neuropsychiatric features [157]. Treatment with EGb 761 at a once-daily dose of 240 mg was safe and resulted in improvement in cognition, psychopathology, functional measures, and quality of life among patients and caregivers [158]. Significant changes in Mini-Mental State Examination (MMSE) score over a 12-month follow-up period were reported between patients on combined therapy and those taking only cholinesterase inhibitors,

suggesting that GB may provide some added cognitive benefits in AD patients already under cholinesterase inhibitor treatment [159]. EGb 761 240 mg once-daily was superior to placebo in treatment of patients with dementia with neuropsychiatric symptoms [160], and improvement in quality of life and cognitive function were noted with GB in irradiated brain-tumor patients [161]. A randomized, double-blind exploratory trial was undertaken to compare the treatment effects and tolerability of EGb 761, donepezil, and combined treatment in patients with AD and neuropsychiatric features. This study suggested no difference in the efficiency of EGb 761 and donepezil, and that combination therapy might be better than monotherapy due to having fewer side effects [162]. Another study directly compared a cholinesterase inhibitor with GB, and found no difference in efficacy of EGb 761 and donepezil for treatment of mild to moderate Alzheimer's dementia [163]. A meta-analysis looking at the prevention effect of ginkgo against AD suggests that GB may help established AD patients with cognitive symptoms but cannot prevent the neurodegenerative progression of the disease [164]. A trial of more than 2000 participants, of whom 1406 received at least one dose of GB extract and 1414 received at least one dose of placebo 2000 reported that long-term use of standardized GB extract did not reduce the risk of progression to AD [165].

1.7.5 n-3 Fatty Acids

Oral supplementation with n-3 fatty acids conferred changes in the n-3 fatty acid profile in the cerebrospinal fluid (CSF), suggesting transfer of these fatty acids across the BBB [166]. The effects of supplementation with n-3 fatty acids alone or with n-3 fatty acids plus α-lipoic acid were compared to placebo by MMSE, Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL), and Alzheimer Disease Assessment Scale – cognitive subscale (ADAS-cog). Results indicate that the n-3 plus lipoic acid group showed fewer declines in MMSE and IADL, and that the n-3 group had lower decline in IADL compared to placebo controls [167]. n-3 fatty acid supplementation for 6 months increased plasma levels of transthyretin in patients with AD. Transthyretin binds to Aβ and may influence Aβ deposition in the brain [168]. n-3 fatty acid supplementation also resulted in significant increases in DHA and EPA plasma concentrations and modulation of genes involved in inflammation and neurodegeneration (e.g., CD63, MAN2A1, CASP4, LOC399491, NAIP, and SORL1). Results suggest that dietary n-3 fatty acid supplementation affects the expression of inflammatory-related genes that might have an impact on AD [169]. The erythrocyte membranes of subjects on a DHA-phospholipids-, melatonin-, and tryptophan-supplemented diet showed significant increases in eicosapentenoic acid, docosapentenoic acid, and DHA concentrations, but decreases in arachidonic acid, MDA, and lipofuscin levels [170]. DHA also inhibited inflammatory cytokines in cells from subjects with AD [171]. One study reported the potential role of fish oil in improving memory function in mild cognitive impairment (MCI) subjects [172], while another reported that 24-week supplementation with 900 mg/d DHA improved learning and memory function in age-related cognitive decline [173]. Other studies, however, reported that supplementation with DHA did not slow the rate of cognitive and functional decline [174] or that supplementation with n-3 fatty acid did not result in marked effects on neuropsychiatric symptoms in patients with mild to moderate AD [175]. An intervention study reported that only ApoE4 non-carriers had increased concentrations of long-chain n-3 fatty acids in response to

supplementation. The mechanisms underlying this gene-by-diet interaction may involve impaired fatty acids and cholesterol transport or altered metabolism of n-3 fatty acids [176]. Studies using Souvenaid, a combination of uridine monophosphate, choline, EPA, DHA, phospholipids, vitamin C, vitamin E, selenium, vitamin B6, vitamin B12, and folic acid showed preservation of the organization of brain networks in patients with mild AD within 24 weeks, suggesting that this combination may be useful for modulating disease progression in AD [177].

1.8 Conclusion

Plants and phytochemicals not only provide beneficial effects in normal aging, but also modulate or delay the onset of neurodegenerative diseases. Phytochemicals produce actions on a wide spectrum of molecular targets. Many of these inhibit oxidative stress by scavenging free radicals and neuroinflammation, and by stimulating anti-inflammatory responses. They act via downregulation of proinflammatory enzymes through activation of PPARγ; inhibition of PI3K, tyrosine kinases, NF-κB, and c-Jun; modulation of cell survival/cell-cycle genes; and stimulation of ARE pathways. Phytochemicals disrupt the Nrf2–Keap1 association, thereby releasing Nrf2, which translocates to the nucleus and upregulates the expression of phase II detoxifying enzymes, such as HO-1 and GSTs, which have a protective effects on cells. Clinical evidence suggests the use of certain phytochemicals for the prevention of stroke and/or AD. Further work needs to be carried out to comprehensively evaluate each phytochemical in terms of its dose–response, bioavailability, safety, and effectiveness with regard to its anti-inflammatory and antioxidative properties, as well as its disease-prevention and therapeutic effects.

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Conflicts of Interest

The authors have no conflicts of interest.

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