Neuroprotective Compounds from Plant Sources and their Modes of Action: An Update

19

Sandra Gonçalves, Inês Mansinhos, and Anabela Romano

Contents

Abstract

Central nervous system diseases, particularly neurodegenerative maladies like Parkinson's and Alzheimer's diseases are the major public health concerns worldwide, since their prevalence has been increasing, and they are associated with social and financial problems. Owing the limited effectiveness and side effects of pharmacological treatments that are currently available and the fact that several factors are implicated in these diseases, novel treatments acting on multiple molecular targets are required. This chapter focuses on the beneficial effects of plant compounds against neurodegenerative diseases, specifically on

S. Gonçalves · I. Mansinhos · A. Romano (✉)
MED – Mediterranean Institute for Agriculture, Environment and Development, University of Algarve, Faculty of Sciences and Technology, Campus de Gambelas, Ed. 8, 8005-139 Faro, Portugal
e-mail: aromano@ualg.pt

M. K. Swamy (ed.), *Plant-derived Bioactives*,
https://doi.org/10.1007/978-981-15-2361-8_19

the main groups of compounds, their sources, and mode of action. Reviewed results showed that there are different plant compounds with the aptitude to target simultaneously several pathological pathways and to affect the activity of numerous enzymes or genes involved in neurological diseases. Nevertheless, the key ability of the reviewed compounds is their capacity to counteract oxidative stress damages and neuronal inflammations. The available results encourage more investigations and clinical trials aimed to develop new treatments for neurodegenerative disorders based on plant compounds.

Keywords
Alkaloids · Antioxidants · Cannabinoids · Flavonoids · Neuroinflammation · Polyphenols

19.1 Introduction

Many disorders of the nervous system are known, and among them epilepsy, stroke, headache disorders, and neurodegenerative diseases are the most prevalent ones. The latter include a heterogeneous group of diseases like Parkinson's (PD), Alzheimer's (AD), and Huntington's diseases (HD) and multiple sclerosis. The pathology of these diseases is complex, progressive, multifactorial, and with many targets and pathways (Hornedo-Ortega et al. 2018; Pohl and Lin 2018). They result in slow neuronal death, which is accompanied by the loss of cognitive functions, and therefore are associated with great social and financial problems. Aging and genetic, lifestyle, and environmental factors are implicated in the pathogenesis of many neurological conditions, and it is expected that their occurrence considerably increases in the coming decade (Peña-Altamira et al. 2017). For instance, it is anticipated that the amount of AD patients increase to 100 million by 2050 (Prince et al. 2013). No cure is currently available for neurodegenerative disorders, and the available treatments merely alleviate the symptoms and delay the disease progression. Moreover, the pharmacological treatments that are available today have limited efficacy and show some side effects. Owing to these limitations and the fact that several factors are implicated in these diseases, a multidimensional approach including lifestyle and dietary interventions seems to the most adequate approach for the management of these diseases (Wang et al. 2018).

Many investigations demonstrated that plant compounds, including dietary phytochemicals possess a multitude of biological features endowing some of these compounds with a great neuroprotective action (Arumugam et al. 2016; Mohanty et al. 2017; Velmurugan et al. 2018; Wang et al. 2019). Indeed, two important compounds currently used in neurodegenerative disease therapy are of natural origin: L-DOPA for PD and galantamine for AD. Phytochemicals can contribute to the control of neurodegenerative disorders not only with their neuroprotective effects, but also by enhancing gastrointestinal function and immunity improvement (Bhullar and Rupasinghe 2013). The correct understanding of plant compounds mechanism of action is fundamental in developing novel neuroprotective agents. Thus, extensive investigations have been

conducted in the last years to study the neuroprotective potentials of plant compounds and to elucidate their mode of actions involved. The purpose of this chapter is to make an outline of the valuable effects of phytocompounds for the management of neurodegenerative diseases and review the main plant compounds with neuroprotective effects, their sources, and mode of action based on the recent data.

19.2 Neurodegenerative Diseases and Main Therapies

Neurodegenerative disorders are more frequent in the elderly population, and their incidence is growing, since the proportion of older people is increasing; thus, they become a threat in this century (Prince et al. 2013; Pohl and Lin 2018). These diseases are caused by the degradation and subsequent loss of neurons, leading to cognitive or functional decline of the patient over time. AD is perhaps the most predominant and overwhelming neurodegenerative disorder, and it is the main reason of institutionalization in the old population (WHO 2017). It causes progressive and irreparable memory deficits, cognitive decline, and even behavior changes. PD is another most frequent of the neurodegenerative diseases related with age, which can also seriously disturb the quality of life. It is a movement disease being the characteristic signs the inactive tremors, bradykinesia, loss of walking and equilibrium, and extrapyramidal rigidity.

The pathogenesis of neurodegenerative diseases is multifactorial with many targets and pathways, although genetic and environmental factors are the most important responsible for their evolution. Oxidative stress associated with accumulation of some aggregated proteins, mitochondrial dysfunction, and neuroinflammation are some of the pathological features involved in these diseases (Farooqui 2012). Dopaminergic treatments, antipsychotic and brain stimulation drugs, and cholinesterase inhibitors are some of the treatments available for their control. In cases of AD, they include the use of exogenous antioxidants, N-methyl-D-aspartate (NMDA) receptor antagonists, and acetylcholinesterase, monoamine oxidase, Aβ, and tau aggregation inhibitors (Sanabria-Castro et al. 2017). After several decades of research, few drugs have been accredited for the management of many neurodegenerative diseases (Newman and Cragg 2012; Cummings et al. 2014). Furthermore, approved drugs merely alleviate the symptoms and delay the disease progression since no cure is currently available for these pathologies. The current research on therapies for neurodegenerative diseases focuses in different potential drug targets.

Mainly, the oxidative stress is the root cause of neurodegenerative disorders (Wang et al. 2018). Oxidative stress involves the disruption of cell redox status, resulting in a disproportion between the generation of reactive oxygen species (ROS) and the antioxidant response. Due to its high oxygen consumption, the brain is the organ more vulnerable to oxidative stress (Yin et al. 2016). Furthermore, the brain is especially disposed to lipid peroxidation owing the high quantity of polyunsaturated fatty acids in neuronal membranes. It is also known that ROS production increases with aging, while endogenous antioxidant defense mechanisms decrease. Additionally, inflammation, protein aggregation, and excessive presence of metal ions, such as iron and copper, can cause oxidative stress, leading to the damage of

biomacromolecules and creating a suitable environment for the pathology and evolution of neurodegenerative illnesses (Kim et al. 2015). The reduction of harmful ROS in the human body but allowing enough ROS to remain in the cell is a promising approach against these diseases. The exogenous supply of antioxidants to counteract the effect of oxidative stress and prevent neuron damage and loss is necessary, if the endogenous antioxidant system is not sufficient. Natural antioxidants, as those present in plants, including plant foods have revealed promising results and hence can be a good alternative to synthetic antioxidants.

Also, chronic inflammations play a vital role in the initiation and evolution of neurodegenerative disorders. Neuroinflammatory processes are implicated in successive events causing neuronal injury. During the inflammatory process, nuclear factor-kappa B (NF-κB) and inflammatory cytokines, like tumor necrosis factor (TNF)-α, IL-6, and IL-1β, are activated (Wang et al. 2018). Activated microglia in the brain releases unnecessary and detrimental ROS and reactive nitrogen species (RNS). Oxidative stress and neuroinflammation in association are both involved in neurodegenerative disorders. Furthermore, mitochondrial dysfunction is boosted by oxidative stress and neuroinflammation mediated by microglia. In fact, oxidative stress, neuronal inflammation, and mitochondrial impairment are interconnected in neuronal damage (Wang et al. 2018; Zheng et al. 2018a).

The search for effective tactics for neurodegenerative diseases using phytochemicals has augmented in the last years, due to the inefficacy and side effects of currently available therapies based on the use of synthetic compounds. Particularly, the supplement of dietary phytochemicals has demonstrated to be a hopeful nutritional intervention for the management of these disorders (Hornedo-Ortega et al. 2018). This is supported by many investigations, including preclinical trials that have demonstrated the neuroprotective effects of some phytochemicals mediated via different mechanisms, such as antioxidant, anti-inflammatory, anticholinesterase, anti-tauopathy, antiamyloidogenic, antiapoptotic, and neurotrophic effects (Fig. 19.1) (Velmurugan et al. 2018).

19.3 Main Sources of Plant Neuroprotective Compounds

Many studies have indicated that the risk of incidences of some diseases, including neurodegenerative ones depends on the dietary pattern followed by individuals. Many studies demonstrated that a broad range of phytochemicals can counteract the effects of oxidative stress and the neuronal inflammation process (Hornedo-Ortega et al. 2018; Velmurugan et al. 2018). Nutritional interventions, including a vast range of plant products are considered an effective approach against neurological conditions, particularly due to their anti-inflammatory and antioxidant capabilities (Wang et al. 2018) and their capacity to improve gastrointestinal and immunological functions (Bhullar and Rupasinghe 2013). Thus, diet intervention is beneficial for the ageing process, maintaining physical and cognitive health (Wang et al. 2018) and preventing and/or delaying the progression of neurological diseases (Hornedo-Ortega et al. 2018). Fruits and vegetables as well as aromatic herbs and spices are the main sources of antioxidants as they possess several neuroprotective

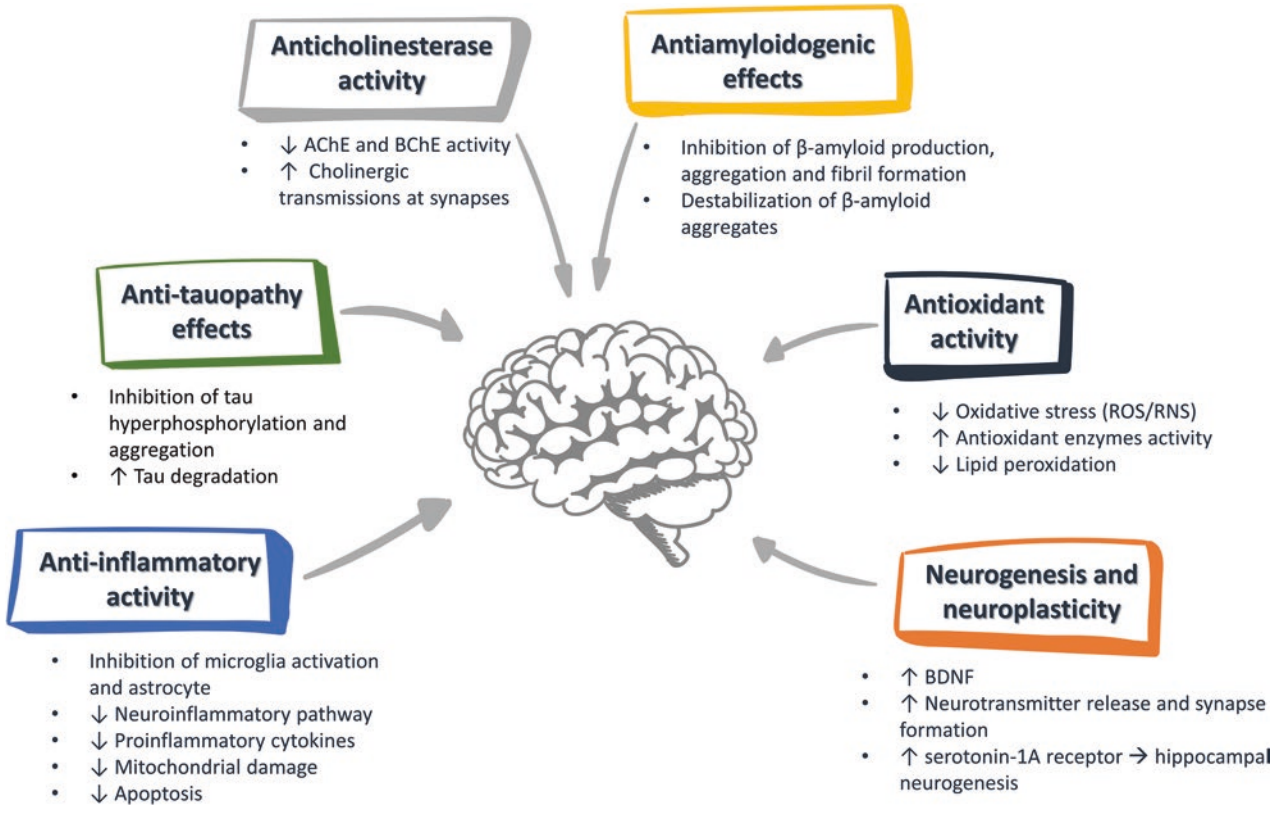

Fig. 19.1 Some of the multiple biological features of plant compounds contributing to their neuroprotective properties. *AChE* acetylcholinesterase, *BChE* butyrylcholinesterase, *BDNF* brain-derived neurotrophic factor, *ROS* reactive oxygen species, *RNS* reactive nitrogen species

phytochemicals. There are increasing evidences about the beneficial effects of Mediterranean diet against age-related pathological conditions (Hornedo-Ortega et al. 2018). This diet pattern is linked with a decrease in cognitive failure and dementia prevalence. The beneficial effects of this dietary pattern are associated with the high consumption of plant foods and plant-derived products as fruits, vegetables, aromatic herbs, olive oil, and adequate quantities of red wine that are all recognized sources of bioactive phytochemicals (Hornedo-Ortega et al. 2018). The protective role of food polyphenols in preventing neurodegenerative ailments is particularly well-documented and is mainly due to their strong free radicals scavenging capacity (Omar et al. 2017; Losada-Barreiro and Bravo-Díaz 2017). Fruits and vegetables contain several phenolic compounds, mainly high amounts of flavonoids, are well recognized to have antioxidant and anti-inflammatory activities (Spagnuolo et al. 2018). Among fruits, berries are probably the richest sources of neuroprotective phenolics (Kelly et al. 2018), and cruciferous are some of the vegetables recognized for their neuroprotective properties. Wine and olive oil are two of the main sources of important neuroprotective polyphenols among Mediterranean diet products. Olive oil is rich in hydroxytyrosol and oleuropein, as well as other bioactive phenolics (Casamenti and Stefani 2017), and red wine is rich in resveratrol, one of the most recognized neuroprotective compounds (Colica et al. 2018).

Herbs and spices used for food, cosmetic, and medicinal purposes are also rich sources of antioxidants (Embuscado 2015). They contain a great diversity of bioactive compounds, from which phenolics and essential oils are the most important. Among the great diversity of plants, Mediterranean species mainly from the Apiaceae and Lamiaceae families (e.g., *Coriandrum sativum* L., *Origanum vulgare* L., *Salvia* sp., *Mentha* sp., *Rosmarinus officinalis* L., *Thymus* sp.) are some of the most relevant ones (Benny and Thomas 2019). Essential oils from these plants inhaled or orally administered cross the blood-brain barrier and exert their psychological properties at the brain level, having beneficial effects in several neurological conditions (Benny and Thomas 2019). Data from many studies indicated that aromatic plant compounds including essential oil components and phenolics affect different pathological targets involved in neurodegenerative disorders (e.g., oxidative stress, Aβ deposition, neurofibrillary tangles, cholinergic hypofunction, glutamatergic abnormalities) (Ayaz et al. 2017). In addition to dietary plants, some well-known medicinal herbs are also important sources of neuroprotective compounds; some important examples are *Ginkgo biloba* L., *Panax ginseng* Meyer, and *Cannabis sativa* L.

19.4 Main Groups of Plant Compounds with Neuroprotective Effects

The most important phytochemicals with recognized preventive and/or therapeutic properties against neurodegenerative disorders belong to the group of polyphenols, isothiocyanates, alkaloids, and cannabinoids (Table 19.1). In addition to these four groups, there are some other chemical compounds with a remarkable action at the

Table 19.1 Main neuropharmacological properties and source(s) of selected plant compounds with neuroprotective effects

Classes	Subclasses	Compound	Neuropharmacological properties	Main source(s)	Reference(s)
Polyphenols	Flavonoid (Flavanol)	Catechin	Butyrylcholinesterase (BChE) inhibitor, ↓ β-amyloid accumulation	Fruits, green tea, leafy green or root vegetables, broad beans, and green beans	Omar et al. (2017), Hajialyani et al. (2019)
	Flavonoid (Flavanol)	Epigallocatechin-3-gallate	Antioxidant, anti-inflammatory, and antiapoptotic properties; ↓ β-amyloid accumulation; acetylcholinesterase (AChE) inhibitor; ↑ ATP levels in mitochondria; ↑ cognitive impairment	Green tea, berries, grapes, cocoa	Libro et al. (2016), Reglodi et al. (2017), Velmurugan et al. (2018), Manzinea et al. (2019)
	Flavonoid (Flavanone)	Hesperidin	Anti-inflammatory, antioxidant, and antiapoptotic properties; ↓ β-amyloid accumulation; AChE and lipid peroxidation inhibitor; ↑ catalase (CAT), glutathione (GSH), and superoxide dismutase (SOD) activities; corrects Aβ-induced mitochondrial abnormalities; ↓ depression symptoms in Parkinson's disease (PD); ↑ locomotion efficiency, learning and memory function in patients with Alzheimer's disease (AD)	*Citrus* spp., grapefruits	Hajialyani et al. (2019)
	Flavonoid (Flavonol)	Quercetin	Antioxidant, anti-proliferative, and antiapoptotic properties; ↑ GSH and SOD activities; prevents cytotoxicity induced by H_2O_2; ↑ biogenesis of mitochondria; ↓ motor deficits	Fruits, vegetables, tea, nuts, *Ginkgo biloba* L., *Hypericum perforatum* L., *Sambucus canadensis* L.	Li et al. (2016), Reglodi et al. (2017), Velmurugan et al. (2018), Hajialyani et al. (2019)

(continued)

Table 19.1 (continued)

Classes	Subclasses	Compound	Neuropharmacological properties	Main source(s)	Reference(s)
	Non-flavonoid (Curcuminoid)	Curcumin	Antioxidant and anti-inflammatory properties; prevents maturation of amyloid-β precursor protein (APP); reverses progression of tau/amyloid pathology in AD; helps in regeneration of neurons; ↑ brain-derived neurotrophic factor (BDNF) for maintenance of neurons in central nervous system (CNS); ↑ dopamine, norepinephrine, and 5-HT levels in CNS; ↑ cognitive functions; ↓ motor deficits	*Curcuma longa* L.	Reglodi et al. (2017), Wasik and Antkiewicz-Michaluk (2017), Maiti and Dunbar (2018), Velmurugan et al. (2018), Wang et al. (2018), Khazdair et al. (2019), Hatami et al. (2019), Manzinea et al. (2019)
	Non-flavonoid (phenolic acid, hydroxycinnamic acid)	Rosmarinic acid	Antioxidant and anti-inflammatory properties; AChE and BChE inhibitor; ↓ mitochondrial dysfunction and reactive oxygen species production; ↓ neuronal excitability; ↑ cholinergic tone	Lamiaceae species	Omar et al. (2017), Fachel et al. (2019)
	Non-flavonoid (Stilbene)	Resveratrol	Anti-inflammatory, antioxidant, and antiapoptotic properties; ↑ BDNF levels in the hippocampus; suppresses activation of glial cells; ↓ β-amyloid accumulation; prevents neurotoxicity in PD; ↑ SOD and CAT activities; ↓ malondialdehyde (MDA); normalizes mitochondrial function; ↓ anxiety and cognitive deficits; improves spatial learning and memory; activation of sirtuin 1	Grapes, berries, red wine, blueberries, peanuts, tea	Libro et al. (2016), Reglodi et al. (2017), Wasik and Antkiewicz-Michaluk (2017), Andrade et al. (2018), Colica et al. (2018), Velmurugan et al. (2018), Wang et al. (2018)

Alkaloids	Indole alkaloid	Isorhynchophylline	Antioxidant and antiapoptotic properties; ↓ β-amyloid accumulation; positive effects against dementia, amnesia, ischemia and epilepsy	*Uncaria rhynchophylla* (Miq.) jacks.	Hussain et al. (2018)
	Isoquinoline alkaloid	Berberine	Anti-inflammatory, antioxidant, and antiapoptotic properties; ↓ β-amyloid accumulation; AChE, BChE, and monoamine oxidase inhibitor; regulates neurotrophin levels; protects neuronal cells from neurotoxicity; improves learning deficits and long-term spatial memory; positive effects against depression and amnesia	*Hydrastis canadensis* L., *Coptis chinensis* Franch., *Berberis* spp.	Libro et al. (2016), Hussain et al. (2018), Lin and Zhang (2018), Velmurugan et al. (2018), Fan et al. (2019), Yuan et al. (2019)
	Isoquinoline alkaloid	Galantamine	Antioxidant properties; AChE inhibitor; ↓ β-amyloid accumulation; ↑ cognition, memory, and sleep quality; positive stimulation in hippocampal neurogenesis	Amaryllidaceae species	Libro et al. (2016), Hussain et al. (2018)
	Isoquinoline alkaloid	Morphine	Antioxidant properties; ↓ β-amyloid accumulation; ↑ GABA levels in synapse of brain; ↓ agitation behaviors and depression	*Papaver somniferum* L.	Libro et al. (2016), Hussain et al. (2018)
	Lycopodium alkaloid	Huperzine A	Anti-inflammatory, antioxidant, and antiapoptotic properties; AChE inhibitor; ↓ β-amyloid accumulation; improves mitochondrial energy metabolism and memory deficits	*Huperzia serrata* (Thunb.) Trevis.	Libro et al. (2016), Hussain et al. (2018)

(continued)

Table 19.1 (continued)

Classes	Subclasses	Compound	Neuropharmacological properties	Main source(s)	Reference(s)
	Methylxanthine derivative	Caffeine	Antioxidant and anti-inflammatory properties; ↓ neurotoxicity; ↓ β-amyloid accumulation and tau phosphorylation; ↑ cortical activity, metabolism of cerebral energy, and extracellular levels of acetylcholine; ↓ risk of dementia and memory decline	*Coffea arabica* L.	Libro et al. (2016), Hussain et al. (2018), Pohl and Lin (2018)
	Piperidine alkaloid	Piperine	Anti-inflammatory and antioxidant properties; AChE inhibitor; ↑ neuronal density in hippocampus in low concentrations; modulates the neurotransmitter systems in epilepsy; anticonvulsive agent	*Piper* spp.	Hussain et al. (2018)
	Pyridine alkaloid	Nicotine	Antioxidant, anti-inflammatory, and antiapoptotic properties; neuroprotective effect against Aβ toxicity; ↑ memory performance	*Nicotiana tobaccum* L.	Libro et al. (2016), Hussain et al. (2018)
	Pyrroloindole alkaloid	Physostigmine	AChE and BChE inhibitor, cognitive enhancer	*Physostigma venenosum* Balf.	Omar et al. (2017), Hussain et al. (2018)
Isothiocyanates		6-MSITC	Antioxidant, anti-inflammatory, and antiapoptotic properties; ↑ GSH activity; neuroprotective effects in PD; ameliorates Aβ-induced memory impairments	*Wasabia japonica* (Miq.) Matsum. (wasabi)	Sita et al. (2016), Morroni et al. (2018)
		Moringin	Antioxidant and anti-inflammatory properties; ↓ activity of MDA and AChE; ↑ SOD and CAT activities; ↑ cholinergic function; ↑ spatial memory	*Moringa oleifera* lam. (drumstick tree)	Giacoppo et al. (2015), Libro et al. (2016)

		Sulforaphane	Antioxidant and anti-inflammatory properties; ↓ β-amyloid accumulation and peroxidation in AD; AChE inhibitor; protects against rotenone-induced neurotoxicity in PD; ↑ proteasomal and autophagic activities in Huntington's disease; ↓ microglia activation and ↑ inflammatory markers	Brassica vegetable	Giacoppo et al. (2015), Libro et al. (2016), Sita et al. (2016), Pohl and Lin (2018)
Cannabinoids	Phytocannabinoid	Cannabidiol	Antioxidant, anti-inflammatory, and anti apoptotic properties; ↓ β-amyloid accumulation and tau phosphorylation; ↑ neurogenesis; regulates microglial cell migration; prevents the development of cognitive deficits in AD	*Cannabis sativa* L.; *Cannabis indica* lam.	Omar et al. (2017), Morales et al. (2017b), Watt and Karl (2017)
	Phytocannabinoid	Delta-9-tetrahydrocannabinol	Anti-inflammatory properties, mediates neuroprotection through PPARγ-dependent restoration of the mitochondrial material	*Cannabis sativa* L.	Maurya and Velmurugan (2018)

central nervous system, for instance, ginsenosides, terpenoids from essential oils, and polysaccharides (Aazza et al. 2011; Zheng et al. 2018b; Gao et al. 2018).

Polyphenols are probably the main and most investigated class of natural composites and are mostly present in vegetables and fruits, as well as in aromatic and medicinal plants. They include about 8000 structures and can be divided in non-flavonoids and flavonoids (Fig. 19.2) (Manach et al. 2004). Non-flavonoid chemical constituents comprise phenolic acids, stilbenes, lignans, and other compounds as displayed in Fig. 19.2. Flavonoids include about 4000 compounds and are divided in flavanols, flavones, flavonols, isoflavones, flavanones, and anthocyanins. Epidemiological studies indicated that intake of phenolic-rich products can be linked with a decreased risk of chronic diseases as is the case of neurodegenerative disorders (Renaud and Martinoli 2019). The biological properties of polyphenols are related to their structural characteristics, which include the presence of phenol rings in the molecule, variable hydroxylation patterns and conjugated double bonds. Polyphenols prevent and obviate neurodegenerative disorders by different mechanisms, e.g., by reducing oxidative stress, affecting amyloid aggregation, inhibiting enzyme activity, and reducing inflammation by regulating signaling pathways and cytokine expression (Table 19.1) (Renaud and Martinoli 2019).

The neuroprotective effect of flavonoids, the most abundant group of polyphenols in foods, has been frequently described, and is mainly associated with the antioxidant and anti-inflammatory features of these compounds (Spencer et al. 2012; Singh et al. 2017; Spagnuolo et al. 2018). The consumption of flavonoid-rich products is linked with the inhibition of biochemical processes involved in brain aging and in the prevention of neurodegenerative disease development (Spencer et al. 2012). The structure of flavonoids has in common a 15-carbon skeleton structured in 2 aromatic rings intertwined by another carbon chain. The antioxidant effects of these compounds are related to their ability to scavenge oxidants and free radicals (Singh et al. 2017) and reduce neuroinflammation by regulating microglial cells, particularly by modulating mitogen-activated protein kinases (MAPKs) and NF-κB signaling pathways (Spencer et al. 2012; Spagnuolo et al. 2018). Catechin, quercetin, hesperidin, and epigallocatechin-3-gallate (EGCG) present in tea, cocoa, and different fruits (mainly berries and citrus) and vegetables are some of the dietary flavonoids showing important neuroprotective properties (Table 19.1). Among flavonoids, EGCG is widely found in green tea and is one of the most reported compounds with neuroprotective properties. Recent studies suggest that green tea consumption decreases the occurrence of neurodegenerative diseases (Pervin et al. 2018). EGCG is the only polyphenolic compound that has reached the phase III of clinical testing (Levin et al. 2016).

Isothiocyanates are sulfur-containing compounds derived from myrosinase hydrolysis of glucosinolates and are mainly present in vegetables of the family *Brassicaceae*, although they can also occur in *Moringaceae* plants. Several studies indicated that regular consumption of *Brassicaceae* vegetables has positive effects in preventing certain chronic diseases including neurodegenerative diseases. These compounds can modulate oxidative stress and inflammatory processes interacting with the nuclear factor erythroid 2-related factor 2 (NrF2) pathway and therefore are

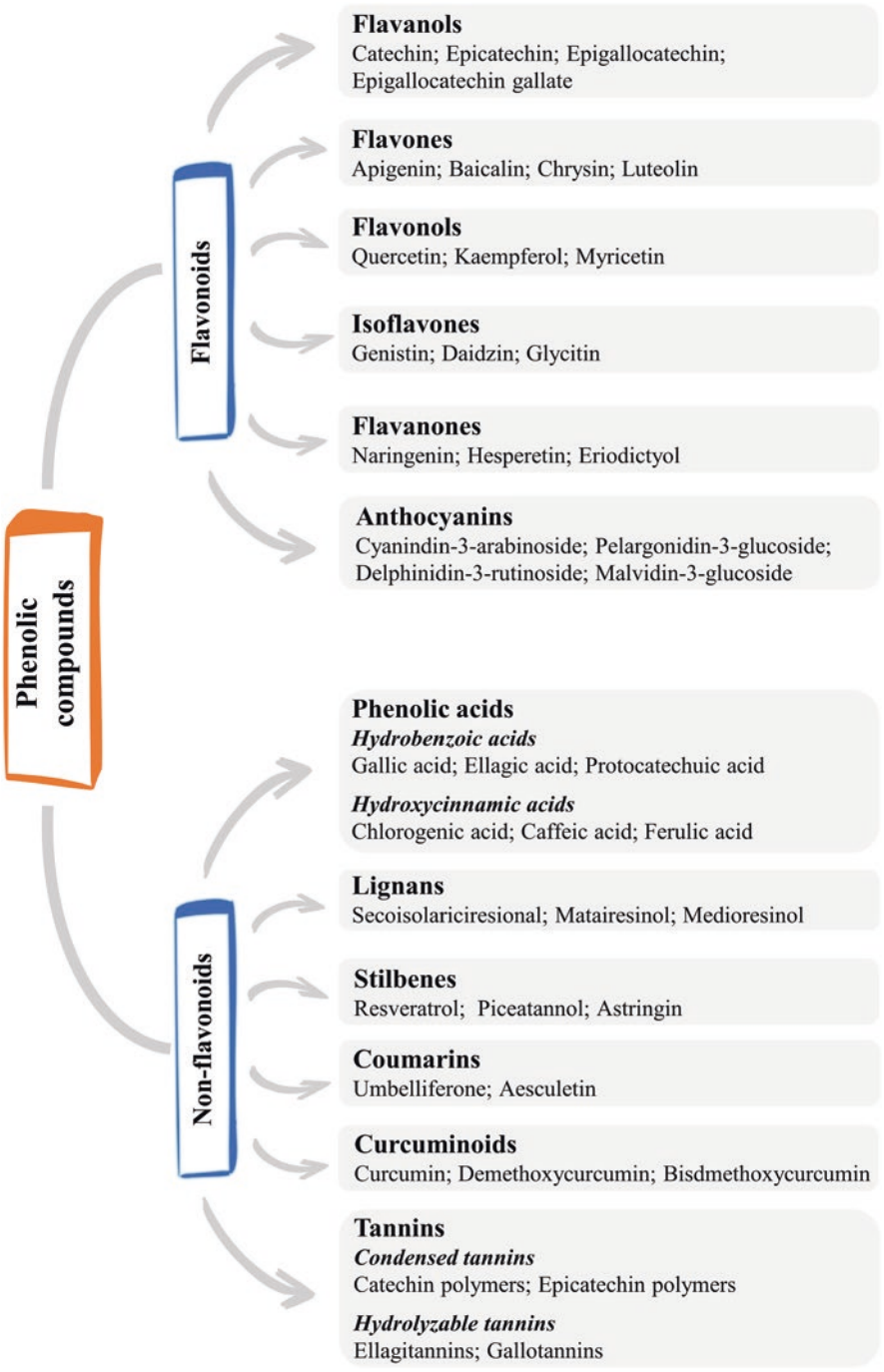

Fig. 19.2 Classification of polyphenols and some examples of each group. Based on Manach et al. (2004)

promising compounds in the deterrence and treatment of cognitive diseases, particularly AD (Giacoppo et al. 2015; Sita et al. 2016). Some important compounds of this class are isothiocyanate, sulforaphane, erucin, moringin, phenethyl isothiocyanate, and 6-(methylsulfinyl)hexyl.

Alkaloids are naturally found in several plant species, but plants of S*olanaceae*, *Papaveraceae*, *Ranunculaceae*, and *Amaryllidaceae* are a rich source of these compounds. These phytocompounds have showed a wide range of biological properties and are separated into several groups depending on their natural sources, pharmacokinetics, and chemodiversity. The role of these compounds in dementia has been expansively explored, and two alkaloid-based drugs, namely, rivastigmine and galantamine, were approved by the Food and Drug Administration (FDA, USA) for the treatment of AD, renewing the attention in alkaloids for dementia treatment. Alkaloids exert their beneficial effects against neurodegenerative diseases by several mechanisms as depicted in Table 19.1. In addition to their capacity to modulate the neurotransmitter system, alkaloids have antiamyloidogenic, antioxidant, anti-inflammatory, antidepressive, and anticonvulsive properties (Hussain et al. 2018). Galantamine, rivastigmine, berberine, morphine, physostigmine, piperine, and caffeine are some of the most important alkaloids among many bioactive compounds within this group.

Cannabinoids are a group of lipid-soluble compounds, present particularly in the plant, *Cannabis sativa* L., and have long been utilized for therapeutic purposes. The use of these compounds in human health increased exponentially in recent years, and the investigation in these compounds is focused on their neuroprotective potential and also on their capacity in attenuating AD-related symptoms. The main advantage of these compounds as neuroprotective agents is their broad-spectrum profile and activity at several molecular sites including within and outside the endocannabinoid system. By combining a broad range of effects, these compounds can regulate neuronal homeostasis and survival (Fernández-Ruiz et al. 2015). Delta-9-tetrahydrocannabinol (Δ^9–THC) is the most investigated compound; however, its psychotropic character limitits therapeutic usage. Cannabidiol, a non-psychotropic cannabinoid has been recently investigated for its effects in neurodegenerative diseases, showing promising results both in in vitro and in vivo models of dementia. Its neuroprotective properties are described comprehensively in the next section.

19.5 Neuroprotective Effects of Selected Plants/Plant Compounds

In this section, some plant species and their compounds showing remarkable neuroprotective properties are addressed in more detail.

19.5.1 *Ginkgo biloba*

Leaves and seeds of the Chinese tree, *Ginkgo biloba* L., belonging to Ginkgoaceae family have been used for centuries in the Chinese traditional medication for the treatment of different neurological conditions. Presently, standardized extracts from this plant are also used, principally in Germany and United States, mainly as a cognitive enhancer (Singh et al. 2017; Wąsik and Antkiewicz-Michaluk 2017). Four standardized extracts have been used in clinical trials, for instance, EGb-761 (*G. biloba* extract, Ginkor) contains mainly flavonol glycosides, such as kaempferol, isorhamnetin, and quercetin, ginkgoin acids, ginkgolin acids, and terpenes like bilobalides and ginkgolides A, B, C, and M (Singh et al. 2017). The antioxidant and neuroprotective properties of this extract have long been recognized. Different in vitro and in vivo investigations showed that this extract exerts its antioxidant effects through different mechanisms, such as free radicals scavenging activity, inhibition of ROS production, activity of antioxidant enzymes, and p-regulation of protein level (Wąsik and Antkiewicz-Michaluk 2017). Some studies also indicated that the mechanism involved in the neuroprotective properties of EGb-761 is related to its capability to inhibit monoamine oxidases A and B activity and to prevent the conversion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to 1-methyl-4-phenylpyridinium (MPP^+) ion (Sloley et al. 2000; Rojas et al. 2004). The compounds present in this extract can cross the blood-brain barrier and therefore induce their effects in the central nervous system (De Feudis and Drieu 2000). The available data demonstrated that the antioxidant and anti-inflammatory features of *G. biloba* standardized extract contribute to restore brain homeostasis in patients with anxiety, dementia or other neurodegenerative disorders, although more consistent clinical trials are still encouraged. The results available indicated that the extract from this plant is relatively safe even when consumed in parallel with other drugs (Singh et al. 2017).

19.5.2 *Panax ginseng*

Panax ginseng Meyer. is a medicinal plant, native to Korea and China and also cultivated in the eastern Asian countries. This plant roots have been employed in the folk medicines to treat several ailments. The beneficial effects of this plant are related to its several active components, particularly the ginseng saponins ginsenosides and also phenolic compounds, polyacetylenes, alkaloids, polysaccharides, sesquiterpenes, and oligopeptides (Kim et al. 2018a, b). This plant showed several biological properties like its capacity to improve the blood circulation, immune system, and memory as well as its antioxidant and other properties (Kim et al. 2018a, b). The activities of *P. ginseng* in preventing neurodegenerative disorders are mainly associated with the antioxidant and immunomodulatory properties of ginsenosides. The basic structure of these compounds is similar, i.e., they comprise 30 carbon atoms and are organized in four rings of steroid nuclei (Guo et al. 2014). As recently reviewed by Zheng et al. (2018a, b), ginsenosides have protective and therapeutic

effects on neurological disorders. These compounds exhibit anti-inflammatory action by interfering with various signaling pathways and antioxidant and anti-aging properties and have beneficial effects on depression, epilepsy, cerebral ischemia reperfusion injury, AD and PD (Zheng et al. 2018a, b). There are several research works on the beneficial effects of *Panax* extracts and its components in animal models of neurodegenerative diseases, mainly in AD and PD as reviewed by different authors (Ong et al. 2015; Kim et al. 2018a, b). For instance, *P. ginseng* extracts showed neuroprotective effects in rat models by counteracting the progressive glycation end product-induced memory loss and downregulating the receptor for advanced glycation end products (RAGE)/NF-kB pathway (Tan et al. 2015). *P. ginseng*, in particular ginsenosides, act not only as antioxidants and free iron scavengers but also as modulators of metabolism, intracellular neuronal signaling, both cell survival and cell death genes, and mitochondrial functions (Kim et al. 2018a). In a recent review, Kim et al. (2018b) concluded that the combination of ginseng compounds with conventional drugs used in AD therapy is more advantageous in the management of this disease than the monotherapy.

Many investigations proved the beneficial effects of *P. ginseng* and its compounds in controlling neurodegenerative disorders, and clinical results indicate no serious adverse effects, although it can modify anticoagulation with warfarin and blood hemostasis. However, data available is still inconclusive and more well-designed clinical studies are required.

19.5.3 Resveratrol

Resveratrol (3,5,4-trihydroxy-trans-stilbene) (Fig. 19.3a) is a stilbene (non-flavonoid polyphenol) that is the mainly found in red grapes and wine, although it is also found in other plants, namely, berries, peanuts, green tea, black tea, etc. This

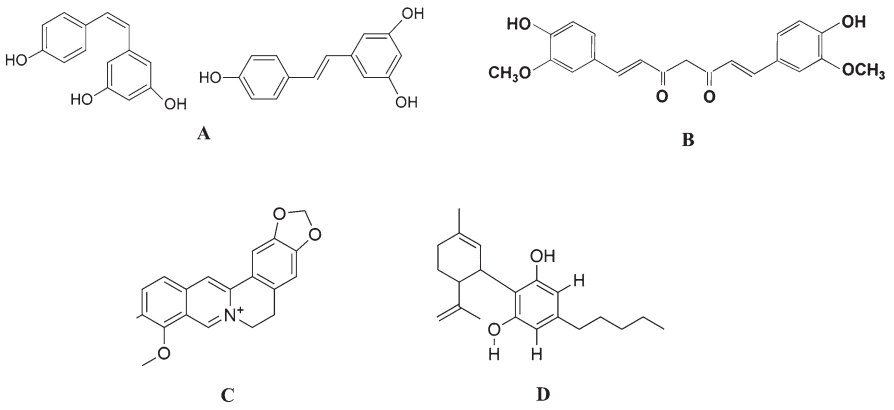

Fig. 19.3 Chemical structure of some important plant compounds with neuroprotective effects: *cis*- and *trans*-resveratrol (**a**) curcumin (**b**), berberine (**c**), and cannabidiol (**d**)

compound is a phytoalexin produced by plants as a response to several biotic and abiotic stimuli as fungal infections and UV radiation (Li et al. 2012). Some investigations showed that this compound has a positive effect on human health including on neurological conditions (Rauf et al. 2017). Indeed, this is one of the most investigated plant compounds concerning the neuroprotective properties. In addition to the properties related to the central nervous system and anti-aging, antioxidant, anti-inflammatory, and neuroprotective effects, this compound also shows several other biological properties including antiapoptotic, cardioprotective, antitumor, and antidiabetes.

This compound exerts its neuroprotective effects through different mechanisms (Table 19.1) but is mainly associated with the protection of neurons from oxidative damage and toxicity effects and to the deterrence of apoptotic neuronal death (Andrade et al. 2018). The antioxidant ability of resveratrol has also been extensively described (Colica et al. 2018) and is related to structural characteristics of the molecule, i.e., three hydroxyl groups attached to the aromatic rings confer the capacity to capture free radicals (Rege et al. 2014). Antioxidant capacity of this compound has been also attributed to its capacity to stimulate the expression of endogenous antioxidant enzymes as superoxide dismutase and catalase, decreasing the malondialdehyde content in mouse brain, reducing copper-catalyzed oxidation, and inhibiting lipid peroxidation (Mokni et al. 2007). Anti-inflammatory effects of resveratrol are mainly related to its capacity to inhibit cyclooxygenases and 5-lipoxygenase activities and consequently the suppression of prostaglandins, thromboxanes, and leukotriene (Kutil et al. 2014), to attenuate pro-inflammatory factors like platelet-activating factor (PAF), tumor necrosis factor (TNF), and histamine (Wiciński et al. 2018). The neuroprotective properties of resveratrol are also associated with its capacity to activate deacetylase enzymes like sirtuin 1 (SIRT1) (Sarubbo et al. 2018).

Although this compound has revealed promising properties against neurological diseases and is able to cross the blood-brain barrier, its pharmacokinetic properties limitits therapeutic applications. It is extensively metabolized and rapidly eliminated, showing a poor bioavailability and a great instability, in spite of its lipophilic nature. Thus, several investigations have been conducted concerning the use of several strategies to improve the pharmacokinetic characteristics, such as its encapsulation for delivery in the brain (Ethemoglu et al. 2017; Trotta et al. 2018). As recently reviewed by Chimento et al. (2019), these strategies showed promising results vitro and in vivo, but their efficacy must be investigated in preclinical and clinical studies.

19.5.4 Curcumin

Curcumin (Fig. 19.3b), 1,7-bis[4-hydroxy, 3-methoxy phenyl]-1,6-hepta-diene-3,5-dione, is a non-flavonoid polyphenol. This yellow pigment is the main component of curry spice (*Curcuma longa* L.) roots, which is a commonly used spice in Asian. Curry consumption has long been associated with cognitive function improvements

in the elderly. Indeed, some studies indicated that incidence of AD in India is lower than in the US population. Curcumin showed several biological effects including anti-inflammatory, antidiabetic, antioxidant, anticancer, and neuroprotective properties. The antioxidant, anti-inflammatory, and antiamyloidogenic effects of this compound, among other (Table 19.1), make it a promising candidate for neurological diseases therapy (Maiti and Dunbar 2018; Hatami et al. 2019). The antioxidant properties of this compound were confirmed in different in vitro and animal models and are mainly related to the presence of a phenolic group linked with two methoxy groups in its structure. This compound revealed radicals scavenging and metal-chelating capacities, improves brain antioxidant status, and protects cells from lipid peroxidation (Maiti and Dunbar 2018). It can attenuate the development and progression of neuroinflammatory disorders through different mechanisms as reducing inflammatory mediators (e.g., TNF-alpha, IL-1 beta, nitric, NF-kappa B gene expression, inhibition of cyclooxygenase 2, and NOS), affecting mitochondria dynamics and epigenetic changes (Hatami et al. 2019). Also, it has the aptitude to bind with amyloid plaques by inhibiting NF-κβ, thus diminishing AD pathogenesis. Research has revealed that curcumin derivatives have more lipophilic properties and higher capability to cross the blood-brain barrier and more affinity for amyloid plaques. Also, its association with lipophilic compounds was shown to improve its bioavailability (Mourtas et al. 2011). Nevertheless, well-ordered and randomized clinical trials are fundamental to completely evaluate its clinical prospective.

19.5.5 Berberine

Berberine (Fig. 19.3c) is an isoquinoline alkaloid found in various medicinal plants including the Chinese medical herb, *Coptis chinensis* Franch. This compound exhibits several pharmacological benefits, namely, antioxidant, anti-inflammatory, neuroprotective, antitumor, and antimalarial. Berberine has been reported to cross the blood-brain barrier and act on the central nervous system on several conditions, such as cerebral ischemic injury, AD, PD, depression, anxiety, HD, epilepsy, and convulsions (Lin and Zhang 2018). The regulation of protein kinase B (Akt/PKB)-related signaling, B-cell lymphoma 2 (Bcl-2), NF-κB, glycogen synthase kinase 3β (GSK3β), and also MAPK- and AMP-activated protein kinase (AMPK) pathways explain the antiapoptotic, anti-inflammation, and antioxidant properties of this compound (Lin and Zhang 2018).

Yuan et al. (2019) recently reviewed the data on neuroprotective activity by berberine against AD using animal models. It induced neuroprotective properties and memory-improving effects through different mechanisms by ameliorating intracellular oxidative stresses, mitigating neuroinflammations, triggering autophagy, guarding neurons against apoptotic cell death, and inhibiting enzyme (butyrylcholinesterase, acetylcholinesterase, monoamine oxidase A, and monoamine oxidase B) activity, hyper-phosphorylation of tau protein, and β-amyloid (Aβ) peptide production (Fan et al. 2019). The results available from studies in animal models encourage the development of clinical studies to effectively evaluate the effects of

berberine on AD human patients. However, some studies indicate that berberine has dual effect, neuroprotective and neurotoxic, in the treatment of nervous diseases depending on the dose, and therefore, the use of these compounds should be analyzed with caution.

19.5.6 Cannabidiol

Cannabidiol (Fig. 19.3d) is a non-psychotropic cannabinoid isolated mainly from *C. sativa*. The cannabis-based preparation Sativex®, which comprises equimolar contents of cannabidiol and Δ^9–THC, is currently used in the control of neuropathic symptoms of multiple sclerosis (Fernandez 2016). Cannabidiol recently attracts the interest of the scientific community due to its safe profile and vast range of bioactive effects including neuroprotective. It showed positive results in the management of several neurological conditions like HD, PD, AD, amyotrophic lateral sclerosis, and epilepsy (Watt and Karl 2017; Silvestro et al. 2019).

The neuroprotective action of this compound is mainly related to its anti-inflammatory and antioxidant properties. Most cannabinoids interact with cannabinoid receptors, but cannabidiol shows a low affinity for these receptors. The mechanisms by which these compounds exert its beneficial effects on neurological diseases are not totally known; however, the immunosuppressive and anti-inflammatory effects seem to be in part facilitated via the adenosine, serotonin, opioid, and non-endocannabinoid G protein-coupled receptors and other targets as ion channels and enzymes (Bih et al. 2015; Morales et al. 2017a). The anti-inflammatory potential of this compound has been demonstrated in mouse models and is modulated by different mechanisms, such as some pro-inflammatory cytokines and regulating cell cycle and immune cell functions. The strong antioxidant activity of cannabidiol is by modulating the expression of inducible nitric oxide synthase and nitrotyrosine as well as plummeting the production of ROS (Esposito et al. 2006). More controlled studies are essential to really assess the efficiency of this compound in neurodegenerative diseases (Morales et al. 2017b).

19.6 Concluding Remarks and Future Perspectives

The growing prevalence of neurodegenerative diseases worldwide, and the absence of effective treatments have led to extensive investigation in the last years concerning the search for new effective therapies. Plant compounds, including dietary phytochemicals have been widely studied in the last years concerning their beneficial effects for the prevention and treatment of these disorders. Furthermore, it is widely accepted that nutrition plays an important role in the occurrence and progression of many diseases. In the case of neurodegenerative diseases, lifestyle and diet intervention has been proposed as having positive effects to prevent and/or delay their progression. Among the diverse range of plant compounds, polyphenols, isothiocyanates, alkaloids, cannabinoids, and ginsenosides are some of the classes with

compounds showing relevant neuroprotective properties. Polyphenols, mainly present in fruits, vegetables, olive oil, wine, and tea, are the most important class of dietary phytochemicals. Several families of polyphenols from plants showed neuroprotective effects, due to a broad range of biological features. Resveratrol, curcumin, berberine, and cannabidiol are some of the most promising compounds with neuroprotective effects, and the extracts of *P. ginseng* and *G. biloba* are the most investigated. The protective role of phytochemicals includes several mechanisms of action including capacity of counteraction of oxidative stress, protection against neuronal damage caused by inflammation, and acetylcholinesterase, Aβ, and tau aggregation inhibitory capacities. Although there are many in vivo studies showing promising results, successful clinical trials in humans are scarce and in some cases with disappointing results. Also, the bioavailability and permeability across the blood-brain barrier of some plant compounds particularly of polyphenols is questionable. Anyway, the results obtained are sufficiently promising to justify future investigations aiming to translate the neuroprotective properties of plant compounds to the treatment of neurodegenerative diseases. Several strategies to overcome the limitations associated with plant compounds include the use of delivery systems and alternative administration routes and the engineering of structural analogues. Phytochemicals can be used in association with conventional therapies for the management of central nervous system disorders.

Acknowledgments This work was supported by the project INTERREG MD.Net: When Brand Meets People. Sandra Gonçalves is funded by national funds through Foundation for Science and Technology, under the Norma Transitória – DL 57/2016/CP1361/CT0022.

References

Aazza S, Lyoussi B, Miguel MG (2011) Antioxidant and anti-acetylcholinesterase activities of some commercial essential oils and their major compounds. Molecules 16:7672–7690

Andrade S, Ramalho MJ, Pereira MC, Loureiro JA (2018) Resveratrol brain delivery for neurological disorders prevention and treatment. Front Pharmacol 9:1261. https://doi.org/10.3389/fphar.2018.01261

Arumugam G, Swamy MK, Sinniah UR (2016) *Plectranthus amboinicus* (Lour.) Spreng: botanical, phytochemical, pharmacological and nutritional significance. Molecules 21:369

Ayaz M, Sadiq A, Junaid M, Ullah F, Subhan F, Ahmed J (2017) Neuroprotective and anti-aging potentials of essential oils from aromatic and medicinal plants. Front Aging Neurosci 9:168

Benny A, Thomas J (2019) Essential oils as treatment strategy for Alzheimer's disease: current and future perspectives. Planta Med 85:239–248

Bhullar KS, Rupasinghe HP (2013) Polyphenols: multipotent therapeutic agents in neurodegenerative diseases. Oxid Med Cell Longev 2013:891748

Bih CI, Chen T, Nunn AV, Bazelot M, Dallas M, Whalley BJ (2015) Molecular targets of cannabidiol in neurological disorders. Neurotherapeutics 12:699–730

Casamenti F, Stefani M (2017) Olive polyphenols: new promising agents to combat aging-associated neurodegeneration. Expert Rev Neurother 17:345–358

Chimento A, Amicis F, Sirianni R, Sinicropi MS, Puoci F, Casaburi I, Saturnino C, Pezzi V (2019) Progress to improve oral bioavailability and beneficial effects of resveratrol. Int J Mol Sci 20:1381

Colica C, Milanovic M, Milic N, Aiello V, De Lorenzo A, Abenavoli L (2018) A systematic review on natural antioxidant properties of resveratrol. Natural Prod Commun 13:1195–1203

Cummings JL, Morstorf T, Zhong K (2014) Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther 6:37

De Feudis FV, Drieu K (2000) *Ginkgo biloba* extract (EGb 761) and CNS functions: basic studies and clinical applications. Curr Drug Targets 1:25–58

Embuscado ME (2015) Spices and herbs: natural sources of antioxidants—a mini review. J Func. Foods 18:811–819

Esposito G, De Filippis D, Maiuri MC, De Stefano D, Carnuccio R, Iuvone T (2006) Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in β-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-B involvement. Neurosci Lett 399:91–95

Ethemoglu MS, Seker FB, Akkaya H, Kilic E, Aslan I, Erdogan CS, Yilmaz B (2017) Anticonvulsant activity of resveratrol-loaded liposomes *in vivo*. Neuroscience 357:12–19

Fachel FNS, Schuh RS, Veras KS, Bassani VL, Koester LS, Henriques AT, Braganhol E, Teixeira HF (2019) An overview of the neuroprotective potential of rosmarinic acid and its association with nanotechnology-based delivery systems: a novel approach to treating neurodegenerative disorders. Neurochem Int 122:47–58

Fan DH, Liu LP, Wu ZZ, Cao MQ (2019) Combating neurodegenerative diseases with the plant alkaloid berberine: molecular mechanisms and therapeutic potential. Curr Neuropharmacol 17:563–579

Farooqui AA (2012) Effect of lifestyle, aging, and phytochemicals on the onset of neurological disorders. In: Farooqui AA (ed) Phytochemicals, signal transduction, and neurological disorders. Springer, New York, pp 1–22

Fernandez O (2016) THC:CBD in daily practice: available data from UK, Germany, and Spain. Eur Neurol 75:1–3

Fernández-Ruiz J, Moro MA, Martínez-Orgado J (2015) Cannabinoids in neurodegenerative disorders and stroke/brain trauma: from preclinical models to clinical applications. Neurotherapeutics 12:793–806

Gao Q-HF, Zhang R, Wang Z, Guo M (2018) Neuroprotective effects of plant polysaccharides: a review of the mechanisms. Int J Biol Macromol 106:749–754

Giacoppo S, Galuppo M, Montaut S, Iori R, Rollin P, Bramanti P, Mazzon E (2015) An overview on neuroprotective effects of isothiocyanates for the treatment of neurodegenerative diseases. Fitoterapia 106:12–21

Guo C-L, Cui X-M, Yang X-Y, Wu S (2014) Advances in studies on biotransformation of ginsensides. Zhongguo Zhong Yao Za Zhi 39:3899–3904

Hajialyani M, Hosein Farzaei M, Echeverría J, Nabavi S, Uriarte E, Sobarzo-Sánchez E (2019) Hesperidin as a neuroprotective agent: a review of animal and clinical evidence. Molecules 24:648

Hatami M, Abdolahi M, Soveyd N, Djalali M, Togha M, Honarvar NM (2019) Molecular mechanisms of curcumin in neuroinflammatory disorders: a mini review of current evidences. Endocr Metab Immune Disord Drug Targets 19:247–258

Hornedo-Ortega R, Cerezo AB, Pablos RM, Krisa S, Richard T, García-Parrilla MC, Troncoso AM (2018) Phenolic compounds characteristic of the Mediterranean diet in mitigating microglia-mediated neuroinflammation. Front Aging Neurosci 12:373

Hussain G, Rasul A, Anwar H, Aziz N, Razzaq A, Wei W, Li X (2018) Role of plant derived alkaloids and their mechanism in neurodegenerative disorders. Int J Biol Sci 14:341–357

Kelly E, Vyas P, Weber JT (2018) Biochemical properties and neuroprotective effects of compounds in various species of berries. Molecules 23:26

Khazdair MR, Anaeigoudari A, Hashemzehi M, Mohebbati R (2019) Neuroprotective potency of some spice herbs, a literature review. J Tradit Complement Med 9:98–105

Kim GH, Kim JE, Rhie SJ, Yoon S (2015) The role of oxidative stress in neurodegenerative diseases. Exp Neurobiol 24:325–340

Kim H-J, Jung S-W, Kim S-Y, Cho I-H, Kim H-C, Rhim H, Kim M, Nah S-Y (2018b) *Panax ginseng* as an adjuvant treatment for Alzheimer's disease. J Ginseng Res 42:401–411

Kim KH, Lee D, Lee HL, Kim C-E, Jung K, Kang JS (2018a) Beneficial effects of *Panax ginseng* for the treatment and prevention of neurodegenerative diseases: past findings and future directions. J Ginseng Res 42:239–247

Kutil Z, Temml V, Maghradze D, Pribylova M, Dvorakova M, Schuster D, Vanek T, Landa P (2014) Impact of wines and wine constituents on cyclooxygenase-1, cyclooxygenase-2, and 5-lipoxygenase catalytic activity. Mediat Inflamm 2014:178931

Levin J, Maaß S, Schuberth M, Respondek G, Paul F, Mansmann U, Oertel WH, Lorenzl S, Krismer F, Seppi K, Poewe W, Wenning G, The PROMESA Study Group, Giese A, Bötzel K, Höglingeret G (2016) The PROMESA-protocol: progression rate of multiple system atrophy under EGCG supplementation as anti-aggregation-approach. J. Neural Transm 123:439–445

Li F, Gong Q, Dong H, Shi J (2012) Resveratrol, a neuroprotective supplement for Alzheimer's disease. Curr Pharm Des 18:27–33

Li Y, Yao J, Han C, Yang J, Chaudhry M, Wang S, Liu H, Yin Y (2016) Quercetin, inflammation and immunity. Nutrients 8:167

Libro R, Giacoppo S, Soundara Rajan T, Bramanti P, Mazzon E (2016) Natural phytochemicals in the treatment and prevention of dementia: an overview. Molecules 21:518

Lin X, Zhang N (2018) Berberine: pathways to protect neurons. Phytother Res 32:1501–1510

Losada-Barreiro S, Bravo-Díaz C (2017) Free radicals and polyphenols: the redox chemistry of neurodegenerative diseases. Eur J Med Chem 133:379–402

Maiti P, Dunbar GL (2018) Use of curcumin, a natural polyphenol for targeting molecular pathways in treating age-related neurodegenerative diseases. Int J Mol Sci 19:1637

Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L (2004) Polyphenols: food sources and bioavailability. Am J Clin Nutr 79:727–747

Manzinea PR, Ettcheto M, Cano A, Busquets O, Marcello E, Pelucchi S, Di Luca M, Endres K, Olloquequi J, Camin A, Cominettia MR (2019) ADAM10 in Alzheimer's disease: pharmacological modulation by natural compounds and its role as a peripheral marker. Biomed Pharmacother 113:108661

Maurya N, Velmurugan BK (2018) Therapeutic applications of cannabinoids. Chem Biol Interact 293:77–88

Mokni M, Elkahoui S, Limam F, Amri M, Aouani E (2007) Effect of resveratrol on antioxidant enzyme activities in the brain of healthy rat. Neurochem Res 32:981–987

Mohanty SK, Mk S, Sinniah UR, Anuradha M (2017) *Leptadenia reticulata* (Retz.) Wight & Arn. (Jivanti): botanical, agronomical, phytochemical, pharmacological, and biotechnological aspects. Molecules 22(6):1019

Morales P, Hurst DP, Reggio PH (2017a) Molecular targets of the phytocannabinoids: a complex picture. In: Kinghorn AD, Falk H, Gibbons S, Kobayashi J (eds) Progress in the chemistry of organic natural products: phytocannabinoids, unravelling the complex chemistry and pharmacology of *Cannabis sativa*. Springer, Berlin, pp 103–131

Morales P, Reggio PH, Jagerovic N (2017b) An overview on medicinal chemistry of synthetic and natural derivatives of cannabidiol. Front Pharmacol 8. https://doi.org/10.3389/fphar.2017.00422

Morroni F, Sita G, Graziosi A, Turrini E, Fimognari C, Tarozzi A, Hrelia P (2018) Protective effects of 6-(methylsulfinyl)hexyl isothiocyanate on Aβ1-42-induced cognitive ceficit, oxidative stress, inflammation, and apoptosis in mice. Int J Mol Sci 19:2083

Mourtas S, Canovi M, Zona C, Aurilia D, Niarakis A, La Ferla B, Salmona M, Nicotra F, Gobbi M, Antimisiaris SG (2011) Curcumin-decorated nanoliposomes with very high affinity for amyloid-beta 1-42 peptide. Biomaterials 32:1635–1645

Newman DJ, Cragg GM (2012) Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod 75:311–335

Omar SH, Scott CJ, Hamlin AS, Obied HK (2017) The protective role of plant biophenols in mechanisms of Alzheimer's disease. J Nutr Biochem 47:1–20

Ong W-Y, Farooqui T, Koh H-L, Farooqui AA, Ling E-A (2015) Protective effects of ginseng on neurological disorders. Front Aging Neurosci 7:129

Peña-Altamira E, Petralla S, Massenzio F, Virgili M, Bolognesi ML, Monti B (2017) Nutritional and pharmacological strategies to regulate microglial polarization in cognitive aging and Alzheimer's disease. Front Aging Neurosci 9:175

Pervin M, Unno K, Ohishi T, Tanabe H, Miyoshi N, Nakamura Y (2018) Beneficial effects of green tea catechins on neurodegenerative diseases. Molecules 23:1297

Pohl F, Lin PKT (2018) The potential use of plant natural products and plant extracts with antioxidant properties for the prevention/treatment of neurodegenerative diseases: in vitro, in vivo and clinical trials. Molecules 23:3283

Prince M, Guerchet M, Prina M (eds) (2013) World Alzheimer report 2013. Alzheimer's Disease International, London

Rauf A, Imran M, Suleria HAR, Ahmad B, Peters DG, Mubarak MS (2017) A comprehensive review of the health perspectives of resveratrol. Food Func 8:4284–4305

Rege SD, Geetha T, Griffin GD, Broderick TL, Babu JR (2014) Neuroprotective effects of resveratrol in Alzheimer disease pathology. Front Aging Neurosci 6:218

Reglodi D, Renaud J, Tamas A, Tizabi Y, Socías SB, Del-Bel E, Raisman-Vozari R (2017) Novel tactics for neuroprotection in Parkinson's disease: role of antibiotics, polyphenols and neuropeptides. Prog Neurobiol 155:120–148

Renaud J, Martinoli M-G (2019) Considerations for the use of polyphenols as therapies in neurodegenerative diseases. Int J Mol Sci 20:1883

Rojas P, Rojas C, Ebadi M, Montes S, Monroy-Noyola A, Serrano-Garcia N (2004) EGb761 pretreatment reduces monoamine oxidase activity in mouse corpus striatum during 1-methyl-4-phenylpyridinium neurotoxicity. Neurochem Res 29:1417–1423

Sanabria-Castro A, Alvarado-Echeverria I, Monge-Bonilla C (2017) Molecular pathogenesis of Alzheimer's disease: an update. Ann Neurosci 24:46–54

Sarubbo F, Esteban S, Miralles A, Moranta D (2018) Effects of resveratrol and other polyphenols on sirt1: relevance to brain function during aging. Curr Neuropharmacol 16:126–136

Silvestro S, Mammana S, Cavalli E, Bramanti P, Mazzon E (2019) Use of cannabidiol in the treatment of epilepsy: efficacy and security in clinical trials. Molecules 24:1459

Singh SK, Barreto GE, Aliev G, Echeverria V (2017) *Ginkgo biloba* as an alternative medicine in the treatment of anxiety in dementia and other psychiatric disorders. Curr Drug Metab 18:112–119

Sita G, Hrelia P, Tarozzi A, Morroni F (2016) Isothiocyanates are promising compounds against oxidative stress, neuroinflammation and cell death that may benefit neurodegeneration in Parkinson's disease. Int J Mol Sci 17:1454

Sloley BD, Urichuk LJ, Morley P, Durkin J, Shan JJ, Pang PKT, Coutts RT (2000) Identification of kaempferol as a monoamine oxidase inhibitor and potential neuroprotectant in extract of *Ginkgo biloba* leaves. J Pharm Pharmacol 52:451–459

Spagnuolo C, Moccia S, Russo GL (2018) Anti-inflammatory effects of flavonoids in neurodegenerative disorders. Eur J Med Chem 153:105–115

Spencer JPE, Vafeiadou K, Williams RJ, Vauzour D (2012) Neuroinflammation: modulation by flavonoids and mechanisms of action. Mol Asp Med 33:83–97

Tan X, Gu J, Zhao B, Wang S, Yuan J, Wang C, Chen J, Liu J, Feng L, Jia X (2015) Ginseng improves cognitive deficit via the RAGE/NF-kB pathway in advanced glycation end product-induced rats. J Ginseng Res 39:116–124

Trotta V, Pavan B, Ferraro L, Beggiato S, Traini D, Des Reis LG, Scalia S, Dalpiaz A (2018) Brain targeting of resveratrol by nasal administration of chitosan-coated lipid microparticles. Eur Pharm Biopharm 127:250–259

Velmurugan BK, Rathinasamy B, Lohanathan BP, Thiyagarajan V, Weng C-F (2018) Neuroprotective role of phytochemicals. Molecules 23:2485

Wang J, Song Y, Chen Z, Leng SX (2018) Connection between systemic inflammation and neuroinflammation underlies neuroprotective mechanism of several phytochemicals in neurodegenerative diseases. Oxid Med Cell Longev 2018:1972714

Wang D, Bădărau AS, Swamy MK, Shaw S, Maggi F, Da Silva LE, López V, Yeung AW, Mocan A, Atanasov AG (2019) Arctium species secondary metabolites chemodiversity and bioactivities. Front Plant Sci 10. https://doi.org/10.3389/fpls.2019.00834

Wąsik A, Antkiewicz-Michaluk L (2017) The mechanism of neuroprotective action of natural compounds. Pharmacol Rep 69:851–860

Watt G, Karl T (2017) *In vivo* evidence for therapeutic properties of cannabidiol (CBD) for Alzheimer's disease. Front Pharmacol 8:20

WHO (2017) Global action plan on the public health response to dementia 2017–2025. World Health Organization, Geneva. Accessed on 18 Sept 2019 at https://www.who.int/mental_health/neurology/dementia/action_plan_2017_2025/en/

Wiciński M, Socha M, Walczak M, Wódkiewicz E, Malinowski B, Rewerski S, Górski K, Pawlak-Osińska K (2018) Beneficial effects of resveratrol administration-focus on potential biochemical mechanisms in cardiovascular conditions. Nutrients 10:1813

Yin F, Sancheti H, Patil I, Cadenas E (2016) Energy metabolism and inflammation in brain aging and Alzheimer's disease. Free Radic Biol Med 100:108–122

Yuan N-N, Cai C-Z, Wu M-Y, Su H-X, Li M, Lu J-H (2019) Neuroprotective effects of berberine in animal models of Alzheimer's disease: a systematic review of pre-clinical studies. BMC Complement Altern Med 19:109

Zheng X, Liao Y, Wang J, Hu S, Rudramurthy GR, Swamy MK, Rohit KC, Wang Y (2018a) The Antineuroinflammatory effect of simvastatin on lipopolysaccharide activated microglial cells. Evid Based Compl Altern Med 2018:1–9. https://doi.org/10.1155/2018/9691085

Zheng M, Xin Y, Li Y, Xu, F, Xi X, Guo H, Cui X, Cao H, Zhang X, Han C (2018b) Ginsenosides: a potential neuroprotective agent. BioMed Res Int 2018:8174345