24 Use of Herbal Products/Alternative Medicines in Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease)

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24.1 Introduction

The most common neurodegenerative diseases are Alzheimer's disease (AD) characterized by a devastating memory loss and cognitive dysfunction and Parkinson's disease (PD), characterized by slowing and difficulty in initiating movements. The list also includes diseases such as Huntington's disease, fronto-temporal-dementia, amyotrophic lateral sclerosis, motor neuron disease, and other rare genetic forms of neurodegeneration. Alzheimer's disease and Parkinson's disease are age-related progressive disorders. Alzheimer's disease, the most common cause of dementia in the elderly [1] affects subjects over the age of 65 years with a prevalence of 11% and which increases to ~30% in those aged 85 and older in the United States [2]. Similarly, the prevalence of PD worldwide rises as age advances with 0.4% prevalence in subjects aged 65–74 years and 1.1% in those aged 70–79 years [3]. In these diseases, the process of neurodegeneration usually involves selective areas in the brain, e.g., the hippocampal region and cortical parenchyma, in AD [4], and the midbrain dopaminergic neurons in PD [5]. These disorders also share common pathogenetic mechanisms such as oxidative damage [6–8], neuroinflammation [9–11], and the presence of abnormal proteins; intracellular accumulation of α-synuclein in PD [12], and extracellular deposits of amyloid-β-peptide (Aβ) in the parenchyma (senile plaques) and neurofibrillary tangles made of hyperphosphorylated form of the microtubule associated protein (tau) in the neuronal cell body in AD [4]. Until now there is no treatment to stop either disease and although dopaminergic replacement therapy with L-dopa, the precursor of dopamine and dopamine receptor agonists have eased the life of many patients with PD, the natural history of the disease is not altered [13]. Similarly, in AD, the use of cholinesterase inhibitors to boost cholinergic neurotransmission results in modest improvements in memory [14].

In the search for novel therapies for these neurodegenerative disorders, research in the field of botanicals and phytochemicals suggested promising molecules. The most common of these herbal remedies are *Ginkgo biloba*, *Panax ginseng*, and curcumin. Other dietary components, e.g., polyphenols, black or green tea and their catechins, and coffee, have also been shown to exert beneficial effects. The aim of this chapter is to review the evidence pertaining to the action of these herbal preparations and some dietary components and their biologically active constituents.

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24.2 Dietary Polyphenols

There is evidence that some dietary patterns or specific components in diet are able to modulate the risk of PD. In a study on 805 subjects who developed PD over a period of 20–22 years, those with highest intake of total flavonoids showed 40% lower risk for PD compared with subjects with the lowest intake. The protective effect for flavonoids was significant in men but not in women. In particular, significant associations were found between increased intakes of berries (rich in anthocyanins) and apples (though not tea) and a lower PD risk [15]. In their study on 257 subjects with PD, Alcalay et al. [16] found that higher adherence to Mediterranean-type diet was associated with reduced risk for PD. In contrast, lower intake of such diet was associated with earlier PD age-at-onset. The study showed that PD subjects were less likely to adhere to Mediterranean-type diet compared with controls which might be associated with earlier age-at-onset. Such diet is rich in polyphenols and the antioxidants ascorbic acid and α-tocopherols derived from vegetables, fruits, cereals, and olive oil (contains unsaturated fatty acids) [17, 18]. Studies also indicated that consumption of specific nutrients or some dietary patterns might have a beneficial impact on the cognitive status of the individual. In this context, increased consumption of fish, mono- and polyunsaturated fatty acids was found to be associated with decreased risk for cognitive impairment and dementia [19]. Several studies also found that adherence to a Mediterranean-type diet delayed the development of cognitive dysfunction in the elderly [20–22]. Feart et al. [20] found that higher adherence to Mediterranean diet in older persons was associated with fewer errors on Mini-Mental State Examination (though not in other cognitive tests). The study included 1410 individuals, with average age of 75.9 years and a median follow-up of 4.1 years. In a follow-up study of 1393 cognitively normal subjects for 4.5 years, moderate and high intake of Mediterranean diet was associated with 17% and 28% less risk of developing mild cognitive impairment as compared to subjects with low intake. The risk for progression of mild cognitive impairment to AD was also decreased by 45% and 48% in subjects with moderate and high intake of Mediterranean diet compared with those with low intake [21]. In a randomized clinical trial of 334 cognitively healthy volunteers with a mean age of 66.9 years, participants allocated to a Mediterranean diet plus olive oil or nuts for 4.1 years showed better cognitive function compared with controls [23]. In the elderly, adherence to Mediterranean diet was also found to reduce the likelihood of developing depressive symptoms over an average follow-up of 7.2 years [24].

24.3 Tea Catechins

Tea is a water infusion from the dried leaves of *Camellia sinensis* (L.) and one of the most popular beverages worldwide. Green tea is made by steaming the leaves, preventing oxidation of the polyphenols. Polyphenols account for up to 40% of the dry weight of green tea. These are mostly flavanols, known as catechins of which (−)-epicatechin, (−)-epicatechin-3-gallate, (−)-epigallocatechin, and (−)-epigallocatechin-3-gallate are the most important. Epigallocatechin-3-gallate is the most abundant and most bioactive catechin of green tea. Other constituents of tea are caffeine, theophylline, theobromine, amino acids and phenolic acids, such as gallic acid. Black tea is a fermented tea where flavanols are oxidized to theaflavins and thearubigins [25, 26]. Studies in humans, however, showed limited bioavailability of black tea catechins with ~ 1.68% of the ingested catechins: (−)-epigallocatechin, (−)-epicatechin, (−)-epigallocatechin gallate, and (−)-epicatechin gallate being present in plasma. Moreover, bioavailability of the gallated catechins was lower than that of the non-gallated catechins [27]. In subjects given a single oral dose of a "decaffeinated green tea catechin mixture", epigallocatechin, epicatechin, were found in plasma mainly in their glucuronide/sulfate conjugates [28]. In subjects given single oral dose of green tea (20 mg tea solids/kg), the maximal plasma concentrations of (−)-epigallocatechin-3-gallate, (−)-epigallocatechin, and (−)-epicatechin were 77.9, 223.4, and

124.0 ng/ml, respectively. These concentrations were achieved 1.3–1.6 h following tea ingestion. In the plasma, (−)-epigallocatechin-3-gallate was present mainly in the free form, while (−)-epigallocatechin and (−)-epicatechin existed mostly in the conjugated form [29]. The effect of epigallocatechin gallate on brain activity was examined in a double-blind, placebo-controlled study. When given at 300 mg, the flavonoid increased overall electroencephalogram activity and calmness while reducing stress [30].

Consumption of tea has been associated with decreased risk for developing PD. Reduced risks were observed after consumption of 2 cups/day or more of tea [31]. A study among Chinese subjects suggested that intake of 3 cups of tea/day for 10 years would result in 28% decrease in the risk of developing PD [32]. Another study from Japan indicated an inverse relationship between intake of black tea, Japanese tea, or Chinese tea, and the risk for developing PD [33]. Similarly, Kandinov et al. [34] found in subjects with PD that consumption of more than 3 cups of tea/day delayed the age by which motor symptoms appear by 7.7 years. Studies also examined the effect of tea catechins on the response to antiparkinsonian drug therapy. (−)-epigallocatechin-3-gallate, (+)-catechin, and (−)-epicatechin were found to inhibit catechol-O-methyltransferase (COMT)-mediated O-methylation of L-DOPA in vitro [35]. In rats, only (+)-catechin significantly inhibited L-DOPA methylation in periphery and striatum, with this effect being attributed to better bioavailability [35].

Tea polyphenols are potent scavengers of reactive oxygen and nitrogen species and also inhibit redox-sensitive transcription factors such as nuclear factor-kappaB and activator protein-1 [36]. Tea polyphenols are also efficient chelators of Fe^{++}. In this latter study, the authors investigated the metal chelating and antioxidant properties of a number of dietary constituents thought to be of value to brain function. Phenolic compounds containing the pyrogalol moiety gallic acid, propylgallate, gallamide and epigallocatechin gallate were all strong chelators of Fe^{++}. Epigallocatechin gallate was also potent chelator of Cu^{++} and Zn^{++} [37]. The experimental data on the neuroprotective effect of tea or catechins are shown in Table 24.1.

Table 24.1 Neuroprotective effect of tea or tea constituents in models of Parkinson's disease and Alzheimer's disease

Model	Tea or individual constituents	Neuroprotection	Mechanism (s)	Study
6-hydroxydopamine (6-OHDA) toxicity in PC12 cells	(−)-epigallocatechins gallate (200 μM) (−)-epicatechin gallate (200 μM)	↓ Cell death	↓ Apoptosis	[38]
1-methyl-4-phenylpyridinium (MPP+) toxicity in embryonic rat mesencephalic dopaminergic neurons	Green tea polyphenols (10–30 μg/ml)	↓ Loss of tyrosine hydroxylase (TH)-positive cells Block MPP(+) uptake into dopaminergic neurons	Inhibitory effect on dopamine transporter	[39]
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- nonhuman primates model of Parkinson's disease	Tea polyphenols given orally	↓ Motor impairment ↓Dopaminergic neuronal injury in the substantia nigra	↓ α-synuclein oligomers	[40]
PC12 cells treated with Aβ (25–35) (10–50 μM)	Green tea extract (10–50 μg/ml)	↓Aβ (25–35) (50 μM)-induced cell death ↓ Intracellular reactive oxygen species ↓ 8-oxodG formation ↓ p53, Bax, and caspase-3 expression	↓Activation of NF-κB and ERK and p38 mitogen-activated protein kinase pathways	[41]

(continued)

Table 24.1 (continued)

Model	Tea or individual constituents	Neuroprotection	Mechanism (s)	Study
Aβ (25–35) toxicity in primary cultures of rat hippocampal cells	Green and black tea extracts (5–25 μg/ml) Gallic acid (1–20 μM) Epicatechin gallate (1–20 μM) Epigallocatechin gallate (1–10 μM)	↓Apoptosis (Epicatechin gallate and Epigallocatechin gallate)	↓Aβ aggregation (epigallocatechin gallate and gallic acid)	[42]
Aβ (1–42) (2 μg/mouse, i.c.v.) Alzheimer's disease mouse model	l-theanine (2 and 4 mg/kg) for 5 weeks in the drinking water	↓ Neuronal cell death in cortex and hippocampus ↓ Memory impairment	↓ ERK ↓ p38 mitogen-activated protein kinase ↓ NF-κB ↓ Oxidative damage	[43]
Neuroinflammation (LPS 1 μg/mouse, i.c.v.)	(−)-epigallocatechin-3-gallate 1.5 or 3 mg/kg in drinking water for 3 weeks	↓ Aβ levels ↓ Apoptotic neuronal cell death	↓ Brain β- and γ-secretase activities ↓ Inducible iNOS expression ↓ COX-2 expression	[44]
Aβ (1–42) (0.5 μg/mouse, i.c.v.) Alzheimer's disease mouse model	(−)-epigallocatechin-3-gallate 1.5 or 3 mg/kg in drinking water for 3 weeks	↓Apoptotic neuronal cell death ↓ Memory impairment	↑ Brain α-secretase activity ↓ Brain β- and γ-secretase activities ↓ ERK ↓ p38 mitogen-activated protein kinase ↓ NF-κB	[45]
Preseniline 2 (PS2) mutant Alzheimer's disease mouse model	(−)-epigallocatechin-3-gallate 3 mg/kg in drinking water for 3 weeks	↓ Aβ brain levels ↓ Memory impairment	↑ Brain α-secretase activity ↓ Brain β- and γ-secretase activities	[45]
Swedish double mutation in the APP gene (APPsw) transgenic Alzheimer's disease mouse model	(−)-epigallocatechin-3-gallate (50 mg/kg) in drinking water for 6 months	↓ Aβ levels in brain ↓ Memory impairment	↓ Phosphorylated tau isoforms	[46]
Primary neurons from APPsw transgenic mice	(−)-epigallocatechin-3-gallate	↓ Aβ brain levels	Enhanced non-amyloidogenic α-secretase proteolytic pathway	[47]
PSAPP transgenic Alzheimer's disease mouse model	Tannic acid (tea) orally for 6 months	↓ Cerebral vascular β-amyloid deposits ↓ Behavioral impairment ↓ Memory impairment	↓ Neuroinflammation	[48]
Transgenic Alzheimer's disease mouse model	Catechin (green tea) 1 mg or 10 mg for 6 months	↓ Aβ-42 production ↓ Behavioral impairment	↓ γ-secretase activity ↑ α-secretase activity	[49]
Neuroinflammation (lipopolysaccharide 250 μg/kg, i.p.) for 7 days	(−)-epigallocatechin-3-gallate 1.5 or 3 mg/kg in drinking water for 3 weeks	↓ Aβ levels ↓ Amyloid precursor protein (APP) expression ↓ Apoptotic neuronal cell death ↓ Memory impairment	↓ Astrocyte activation ↓TNF-α ↓ IL-1β ↓ Macrophage colony-stimulating factor ↓ Soluble intercellular adhesion molecule-1 ↓ IL-6 ↓ Inducible iNOS expression ↓ COX-2 expression	[50]

Abbreviations: *i.c.v.* intracerebroventricular, *NF-κB* nuclear factor kappaB, *ERK* extracellular signal-regulated kinase, *IL-1β* L interleukin-1beta, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-alpha, *COX-2* cyclooxygenase-2, *iNOS* inducible nitric oxide synthase, *i.p.* intraperitoneal

24.4 Coffee

Coffee is a popular beverage produced from the ground roasted beans. Coffee contains the alkaloids caffeine and trigonelline, chlorogenic acid, and the diterpenes cafestol and kahweol [51]. Coffee is the main source of caffeine (1,3,7-trimethylxanthine) intake in many parts of the world. In North America, coffee followed by tea provides most of caffeine in the adult diet. Brewed coffee contains 56–100 mg caffeine/100 ml while instant coffee and tea provide 20–73 mg caffeine/100 ml. Other sources of caffeine are cola, cocoa, and chocolate [52]. It is estimated that for adults consuming 3–4 cups of coffee/day, this will provide 300–400 mg of caffeine [53]. In the United States, studies suggested an average caffeine intake of 193 mg/day in caffeine consumers, with the highest intake being in men and women aged 35–64 years. In this group, coffee represented the major source of caffeine in the diet. Coffee also accounted for most of caffeine in diet (71%) to be followed by soft drinks (16%), and tea (12%) [54]. Data from a recent study indicated that 98% of the adult US population consumed caffeine. The prevalence was equal in men and women. The average caffeine intake was 211 and 183 mg/day for men and women consumers, respectively, with consumption being highest in men aged 31–50 years [55].

24.4.1 Coffee and the Risk of Parkinson's Disease

Studies indicated an inverse association between consumption of coffee and the risk of PD, with the effect of coffee being a dose-dependent one [56–66]. Sääksjärvi et al. [62] reported decreased risk for PD in subjects consuming 10 or more cups of coffee/day compared with non-drinkers. In a study on 304,980 participants, higher coffee intake in 1995–1996 was associated with lower PD risk in both men and women over about 10 years of follow-up [65]. In a study in 1808 patients with idiopathic PD, moderate intake of caffeine (3.1–5 cups/day) was associated with a lower risk for PD [66]. The effect of coffee in reducing the risk for PD appears to be limited to those who drink caffeinated coffee. Other sources of caffeine, e.g., soft drinks, hot tea, and iced tea, were not associated with the risk of PD [65]. The effect of coffee on PD could be observed for both men and women [58, 59, 62, 64, 65], but is likely to be attenuated in women by hormonal replacement therapy post-menopause. In their study on post-menopausal women, Ascherio et al. [58] found that caffeine reduces the risk for PD among those who do not use estrogen replacement therapy. In contrast, coffee increases risk among hormone users where the risk of PD increases by fourfold in women who consumed 6 or more cups of coffee/day compared with non-drinkers. In a prospective study on the relation between coffee consumption and Parkinson's disease mortality, coffee consumption was inversely associated with Parkinson's disease mortality in men but not in women. The failure of coffee to reduce mortality from PD in women was attributed to the use of estrogen replacement therapy after menopause [59]. In another prospective study of caffeine intake and risk of PD, high caffeine consumption was associated with a reduced risk of PD. Women who never used estrogen replacement therapy showed stronger association between coffee and decreased risk of PD compared with ever users [64].

In PD, dyskinesia refers to involuntary movements, most commonly chorea, that develops several years after treatment with L-dopa. It occurs at the time of peak L-dopa effect and the risk of developing dyskinesia is L-dopa dose-dependent [67]. In their study, Wills et al. [68] found that subjects who consumed >12 ounces of coffee/day were less likely to develop dyskinesia compared with those who consumed <4 ounces/day. Similarly, Nicoletti and Zappia [69] reported a negative association between coffee drinking and the presence of dyskinesia in subjects with PD on dopamine replacement therapy. The study also showed a dose-dependent effect for coffee in decreasing PD risk. It has also been shown in patients with idiopathic PD that caffeine improves L-dopa pharmacokinetics [70]. This is likely to reduce the development of dyskinesia due to L-dopa by decreasing the effective dose required.

The effect of coffee in PD could also be attributed to adenosine A2A receptor antagonism by the caffeine content. Istradefylline is a nonselective adenosine A2A receptor antagonist which can be used as adjunct to L-dopa [71].

24.4.2 Coffee and Cognition

Caffeine intake results in a decrease in mental fatigue and increased alertness while improving memory processes. These effects are observed in both habitual caffeine consumers and habitual non-consumers [72]. Coffee/caffeine intake has also been found to be associated with better cognitive performance in elderly. It was noted that in women with a mean age of 72.6 years, higher lifetime and current consumption of coffee resulted in better scores in many tests for cognitive functions. This effect of coffee was not observed in men with a mean age of 73.2 years or women aged 80 years or more. The study also found no effect for decaffeinated coffee on cognitive function in older men or women [73], thereby suggesting that caffeine content mediated the improvement in cognitive function. In their study, Eskelinen et al. [74] found that subjects who drink 3–5 cups of coffee/day at mid-life had 65% lower risk of dementia and AD in late-life compared with individuals who drink no or little coffee. This study included 1409 individuals aged 65–79 years. In a community-based sample of 4197 women and 2820 men aged 65 years and over, coffee consumption was associated with less degree of cognitive decline in women without dementia who consumed >3 cups of coffee/day. Verbal retrieval and visuospatial memory showed fewer declines over 4 years of follow-up compared to women consuming one cup or less of coffee. The cognitive protective effect of coffee was more evident as the age increases. The study found no association between coffee intake and cognitive decline in men [75]. In a cohort of 648 subjects aged 65 years or more, caffeine intake of >62 mg/day was associated with a lower risk for cognitive decline as compared with an intake of <22 mg/day. The effect of coffee was significant only in women but not in men [76]. Similarly, Vercambre et al. [77] observed slower rates of cognitive decline with increasing caffeine intake over 5 years in women. The study included 2475 women aged >65 years with vascular disorders.

The effects of caffeine on cognitive performance and mood would be also important for subjects with PD for they also suffer from fatigue [78], apathy [79], cognitive dysfunction [80], and depression which affect approximately 20–40% of patients [81, 82]. The effect of caffeine on day somnolence, motor activity, and other non-motor manifestations of PD were evaluated in a 6-week randomized placebo-controlled trial of 61 patients with PD. Caffeine improved somnolence and objective motor measures. There was no effect, however, on the quality of life, sleep, or depression [83].

Studies in a transgenic mouse model of AD showed that caffeine given from young adulthood till aging protected against memory impairment and reduced Aβ-peptide levels. Moreover, old transgenic mice showed improved memory and decreased Aβ-peptide burden upon giving caffeine [84, 85]. Table 24.2 summarizes the results on the protective effect of coffee or caffeine in models of Parkinson's disease or Alzheimer's disease.

24.5 Ginseng

Panax ginseng (*P. ginseng,* Fam. *Araliaceae*) is a perennial herbaceous plant widely cultivated in China, Korea, and Japan. The root of the plant is valued for its medicinal properties and has been used in traditional Chinese medicine since antiquity. Ginseng is usually described as being an adaptogen or restorative tonic [89]. There are several different *Panax* species, including *Panax ginseng* Meyer (Chinese or Korean ginseng), *Panax pseudo-ginseng* (Japanese ginseng), *Panax notoginseng* (China), *Panax vietnamensis* (Vietnamese ginseng), and *Panax quinquefolium* (American ginseng) [90]. The latter is native to eastern North America. It is currently grown in Eastern USA and Canada [91]. Siberian or Russian ginseng (*Eleutherococcus senticosus*) is

Table 24.2 Neuroprotective effect of coffee or caffeine in models of Parkinson's disease and Alzheimer's disease

Model	Coffee, tea, or individual constituents	Neuroprotection	Mechanism (s)	Study
APPsw transgenic mouse model of Alzheimer's disease	Daily caffeine (1.5 mg/mouse) in drinking water, starting from young adulthood to old age (equivalent to 500 mg of caffeine in humans or 5 cups of coffee/day)	↑ Memory performance ↑ Brain adenosine levels ↓ Aβ-peptide production ↓ Aβ-peptides in hippocampus	↓ Expression of Presenilin 1 (PS1) and β-secretase	[84]
Aged APPsw mice with cognitive impairment	Daily caffeine (1.5 mg/mouse) for 4–5 weeks	↓ Aβ-peptides in hippocampus and entorhinal cortex (40% and 46%). ↓ Soluble Aβ-peptides in brain	cRaf-1/ NF-κB mediated	[85]
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-toxicity in mice striatum	Caffeine (20 mg/kg, i.p.) daily for 9 days <MPTP	↓Loss of striatal dopamine ↓ Loss of dopamine transporter binding sites	–	[86]
SH-SY5Y cells exposed to lipopolysaccharide + interferon-γ or interferon-γ released from activated microglia and astrocytes	Quercetin, flavones, chlorogenic acid, and caffeine	↑ Cell viability (MTT assay)	↓ TNF-α, and ↓ IL-6 from the activated microglia and astrocytes. ↓ Activation of proteins from P38 mitogen-activated protein kinase ↓ NF-κB ↓ Oxidative/ nitrative damage (quercetin).	[87]
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-toxicity in mice striatum	Caffeine (20 mg/kg, i.p.) daily for 8 weeks <MPTP co-treatment once in a day for 2–4 weeks	↓ Loss of striatal dopamine ↑ Dopamine transporter mRNA expression	↓ Adenosine A2A receptor mRNA expression	[88]

Abbreviations: *NF-κB* nuclear factor kappaB, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-alpha

not a true ginseng but belongs to a different genus in the family *Araliaceae* and does not contain ginsenosides [92]. White ginseng refers to the air-dried root after being harvested while red ginseng is produced by steaming the fresh, unpeeled root at 98–100°C for 2–3 h before drying [93]. The chemical constituents of *P. ginseng* are polysaccharides, phenolics and flavonoids, mostly quercetin and kaempferol, and triterpene saponins known as ginsenosides which account for most of the biological activity of ginseng. The root contains 3–6% by weight of ginsenosides [94]. The ginsenoside content of American and Asian ginseng differs, e.g., Rf is absent in American ginseng while present in Asian ginseng. Siberian or Russian ginseng is devoid of ginsenosides [91]. *Panax notoginseng* is another species of the genus *Panax*. The root of *P. notoginseng* is a widely used traditional Chinese medicine. The major constituents are ginsenosides, notoginsenosides, gypenosides, flavonoids, cyclopeptides, and sterols [95]. Commercially available standardized extracts of ginseng are G115 from *P. ginseng* (Pharmaton

SA, Switzerland) and NAGE from *P. quinquefolius* (Canadian Phytopharmaceutical Corporation, Canada).

Whether ginseng would improve cognition in healthy subjects has been examined by several authors. One study that involved 3500 healthy volunteers found that neither ginseng nor *Ginkgo biloba* was able to enhance memory performance. The participants reported up to 2 years of regular use of either herb. The kind of herbal preparations used is, however, not specified in the study [96]. In this context, it should be noted that herbal preparation, especially those of ginseng vary widely in their content of ginsenosides [97]. Wesnes et al. [98], however, found the combination of ginseng and *Ginkgo biloba* to be superior to placebo in improving working and long-term memory. In this study, 256 healthy middle-aged volunteers received standardized extracts of *Ginkgo biloba* (GK501) and of *Panax ginseng* (G115) at doses of 60 mg and 100 mg, respectively, for 14 weeks. Similarly, in healthy, young adult volunteers, Kennedy et al. [99] reported improvements in memory function following 360 mg of *Ginkgo biloba*, 400 mg of *Panax ginseng*, or 960 mg of the two extracts as compared to placebo. In thirty healthy young adult volunteers, acute administration of G115® (400 mg) improved speed of attention tested 90 min after drug ingestion [100]. Sutherland et al. [101] used HT1001, a standardized North American ginseng (*Panax quinquefolius*) extract in healthy young adults and middle-aged volunteers. The extract is standardized to contain 13–20% of active ginsenosides. HT1001 given at 100 mg (equivalent to 500 mg of North American ginseng dried root) twice daily resulted in significant improvement of several aspects of memory. Scholey et al. [102] studied the effect of highly standardized extract of *P. quinquefolieus* (Cereboost™) on cognitive function in 32 healthy young subjects. Cereboost™ which is standardized to contain 10.65% ginsenosides was given at doses of 100, 200, and 400 mg. The authors reported significant improvement of working memory performance as well as an increase in calmness by ginseng. There was no change in blood levels of glucose after the intake of ginseng. In 52 healthy volunteers with a mean age of 51 years, Cereboost™ 200 mg improved working memory 3 h after dosing as compared to placebo. Cereboost™ at this dose showed no significant effects on mood or blood glucose levels [103]. Reay et al. [104], however, suggested a glucoregulatory mechanism to account for the effect of ginseng on cognitive performance. In their study, 27 healthy young adults received either 200 mg G115, 25 g glucose, or their combination. Interestingly, either ginseng or glucose increased the performance of a mental arithmetic task and alleviated the subjective mental fatigue in late stages of a sustained mental exercise.

In mice, memory impairment induced by the use of the cholinergic agent scopolamine could be prevented by pretreatment with a ginsenoside Rg3-enriched ginseng extract. Ginseng inhibited acetylcholinesterase activity and suppressed NF-κB signaling in the hippocampus [105]. Other mechanisms by which ginseng or individual ginsenosides enhance memory involve increased expression of choline acetyltransferase and trkA mRNAs in the basal forebrain and nerve growth factor mRNA in the hippocampus by ginsenoside Rb1 [106], and increased proliferation of hippocampal progenitor cells by Rg1 [107].

Ginseng exerts a number of important pharmacological effects which are likely to contribute to the observed neuroprotective effects of ginseng or ginsenosides and these include:

1. Antioxidant properties: inhibition of metal-induced lipid peroxidation (chelation of transitional metal ions Cu^{++} and Fe^{++}) by *P. quinquefolius* extract CNT2000 (standardized to 8% ginsenosides) [108]. Decreased intracellular reactive oxygen species and malondialdehyde, and increased glutathione and antioxidant enzyme activities of catalase, superoxide dismutase and glutathione peroxidase by ginsenoside Rd. [109].
2. Inhibition of caspase-3 mediated apoptosis by G115 [110], Rg1 [111], and ginsenoside Rd. [109].

3. Inhibition of cyclooxygenase-2 expression by panaxatriol saponins (P. notoginseng) [112] and Rg3 [113].
4. Inhibition of glia activation by G115 [114], ginsenoside Re [115], and ginsenoside Rg3 [113].
5. Increased BcL-2 expression and decreased Bax and HSP70 expression by ginsenoside Rg2 [116].
6. Increased expression and secretion of the neurotrophic factors nerve growth factor and brain-derived neurotrophic factor by ginsenosides Rb1 and Rg1 [107, 117].
7. Inhibition of glutamate-induced intracellular Ca^{++} influx by ginsenoside Rd. [118].
8. Decreased production of interleukin-6 by *P. notoginseng* (NotoG™) [119] and decreasd interleukin (IL)-1β and IL-6 mRNA by ginsenoside Rb1 [120].
9. Inhibition of tumor necrosis factor-alpha (TNF-α) release by ginsenoside Rg3 [113], ginsenoside Rb1 [120], and by *P. notoginseng* (NotoG™) [119].
10. Inhibition of nitric oxide release by ginsenoside Rd. [121] and *P. notoginseng* (NotoG™) [119].
11. Activation of phosphatidylinositol 3-kinase and Nrf2 signaling pathway by panaxatriol saponins from *P. notoginseng* [122].
12. Modulation of cerebral monoamine transmitters by ginsenoside Rb1 [123] and increased choline uptake by ginsenoside Rb1 by central cholinergic nerve endings [124].

Ginseng or individual ginsenosides were shown to exert protective effects in different experimental models of PD or AD (Table 24.3).

Table 24.3 Neuroprotective effect of ginseng or ginsenosides in models of Parkinson's disease and Alzheimer's disease

Model	Ginseng or ginsenosides	Neuroprotection	Mechanism (s)	Study
Scopolamine-induced memory impairment in mice	Ginsenoside Rg3-enriched ginseng extract (50 and 100 mg/kg) orally for 14 days	Alleviation of memory impairment	↓ Acetylcholinesterase activity ↓ NF-κB signaling in hippocampus	[105]
Parkinson's disease caused by feeding rats with dietary phytosterol glucoside β-sitosterol β-D-glucoside	G115 orally 100 mg/kg/day	↓ Locomotor deficits ↓ Tyrosine hydroxylase-immunoreactive cells loss in substantia nigra ↓ Microgliosis ↓ α-synuclein aggregates	↓ Caspase-3 activation ↓ Glia activation	[110]
1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-treated mice.	Ginsenoside Rg1 (5.0, and 10.0 mg/kg) 3 days prior to MPTP	↓ Apoptosis	↑ Bcl-2 expression ↓ Bax expression ↓ iNOS expression ↓ Caspase-3 activation	[111]
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity in mice	Panaxatriol saponins from *Panax notoginseng*	↓ Behavioral impairment ↓ Neuronal death in substantia nigra	↑ Thioredoxin-1 (Trx-1) expression ↓ COX-2 over-expression ↓Mitochondria-mediated apoptosis.	[112]
Systemic lipopolysaccharide injection in mice (3 mg/kg, i.p.)	Ginsenoside Rg3 20 and 30 mg/kg orally 1 h prior to the lipopolysaccharide	↓ Neuroinflammation	↓TNF-α, IL-1β, IL-6 mRNA ↓ COX-2 expression ↓ iNOS expression ↓ Microglia activation	[113]

(continued)

Table 24.3 (continued)

Model	Ginseng or ginsenosides	Neuroprotection	Mechanism (s)	Study
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice 1-methyl-4-phenylpyridinium (MPP+) in rats	G115 orally prior to and/or following exposure to MPP+	↓ Locomotor changes Prevented tyrosine hydroxylase-positive cell loss in the substantia nigra	–	[114]
Methamphetamine-induced dopaminergic toxicity in mice	Ginsenoside Re (10 and 20 mg/kg, p.o.)	↓ Behavioral changes ↓ Dopaminergic degeneration	↓ Oxidative stress ↓ Microglia activation (effects mediated by inhibition of protein kinase C (PKC) δ)	[115]
Mesencephalic primary cultures treated with lipopolysaccharide (100 microg/ml)	Ginsenoside Rd	↓ Cell death	↓ Neuroinflammation (↓ Nitric oxide and ↓ PGE2 synthesis)	[121]
Human SHSY5Y cells treated with MPP+ (1-methyl-4-phenyl-pyridinium)	Rg1(10 and 20 μM)	↓ Apoptosis	↓ Reactive oxygen metabolites ↓ c-Jun N-terminal kinase (JNK) activation ↓ Cleaved caspase-3 expression (anti-apoptotic effect)	[125]
Glutamate toxicity in embryonic mouse mesencephalic cells	Ginsenosides Rb1 and Rg1	↑ Number and length of neurites of surviving dopaminergic cells	Neurotrophic effect	[126]
Embryonic mouse mesencephalic cells treated with 1-methyl-4-phenylpyridinium-iodide (MPP).	Ginsenoside Rb1 (10 μM)	↑ Survival of dopaminergic neurons by 19%	Neurotrophic effect	[126]
6-hydroxydopamine (6-OHDA) toxicity in human neuroblastoma SK-N-SH cells	Ginsenoside Rg1	↑ Cell survival	↓ Bax ↑ Bcl-2 mRNA and protein expression ↑ Mitochondrial membrane potential (mediated by activation of insulin-like growth factor-I receptor-dependent pathway and estrogen receptor-dependent pathway).	[127]
6-hydroxydopamine (6-OHDA)-induced toxicity in MES23.5 cells	Ginsenoside Rg1	↑Cell viability	↑ Gene and protein expressions of Bcl-2 ↑Akt phosphorylation ↓ ERK1/2 phosphorylation induced by 6-OHDA	[128]
6-hydroxydopamine (6-OHDA)-treated MES23.5 cells	Ginsenoside-Rg1	↓ Cellular iron accumulation	↓ 6-OHDA-induced upregulation of iron importer protein divalent metal transporter 1 with iron responsive element.	[129]

Abbreviations: *Akt* Protein kinase B, *PGE2* prostaglandin E2, *IL-1β* L Interleukin-1beta, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-alpha, *COX-2* cyclooxygenase-2, *iNOS* inducible nitric oxide synthase

24.6 Ginko biloba

Extracts from the dried green leaves of *Ginkgo biloba* L. (Fam. *Ginkgoaceae*) have been used in traditional Chinese medicine over thousands of years. Ginkgo is one of the best-selling herbs in the United Sates, being used as a complementary therapy for cognitive impairment such as that associated old age or AD and vascular dementia [130]. Other uses of the extract are in the treatment of intermittent claudication, schizophrenia, and vertigo [131, 132]. EGb 761® is a water–acetone extract of the dried green leaves of *Ginkgo biloba*, standardized to contain 24% flavonoid glycosides (including quercetin, kaempferol, isorhamnetin), 6% terpene lactones (containing 3.1% ginkgolides A, B, C, and J and 2.9% bilobalide), and less than 9% proanthocyanidins and organic acids (<5 ppm ginkgolic acid) [131, 133]. When used to treat dementia syndromes, the dosage is 240 mg/day [134].

Studies in young healthy volunteers suggested that the administration of *Ginkgo biloba* extracts results in better performance in cognitive demanding tasks. When given to healthy young volunteers (mean age 19.9 years), GK501 (320 mg) increased cognitive function. GK501 (Pharmaton SA) is standardized to 24% ginkgoflavone glycosides and 6% terpene lactones [135]. In 78 healthy young volunteers aged ~20 years, compared with placebo, EGb at a low dose of 120 mg/day improved the quality of memory at 1 and 4 h post-dosing. This dose, however, was observed to impair performance on the "speed of attention" task performance [136]. Students (18–26 years) who received a single dose of standardized *Ginkgo biloba* extract (120 mg) and tested 4 h later demonstrated increased performance on the sustained attention and pattern recognition memory tasks. However, after 6 weeks of treatment, there was no effect for *Ginkgo biloba* for memory compared with controls who received placebo, suggesting that tolerance has developed. GK501 (Pharmaton SA) is standardized to 25% total ginkgoflavone glycosides and 6% terpene lactones [137].

The effect of *Ginkgo biloba* on cognitive decline in the elderly is somewhat less clear. Improvement in cognitive function has been reported after 24 weeks of treatment with EGb 761 (240 mg/day) in patients with dementia [138]. DeKosky et al. [139] found *Ginkgo biloba* (EGb761120-mg twice a day) to be no better than placebo in reducing the rate of progression to dementia or AD in elderly individuals with normal cognition or those with mild cognitive impairment. Moreover, an increasing rate of AD was noted in individuals with cerebrovascular disease given *Ginkgo biloba.* Similar observations were reported by Snitz et al. [140] who found that EGb761 (120-mg extract twice a day) did not lessen cognitive decline in the elderly with normal cognition or with mild cognitive impairment. In contrast, dementia patients with neuropsychiatric symptoms who received EGb761 for 22 weeks at the dose of 240 mg/day showed improvement in cognition as compared to placebo. The patients aged 50 years or above included those with AD and vascular dementia [141]. Patients with dementia and neuropsychiatric manifestations treated with EGb761 (240 mg/day) for 22 weeks exhibited improvements in apathy, indifference, anxiety, irritability, depression, dysphoria, and sleep [142]. In subjects with cognitive complaints and low functioning, EGb761 (240 mg/day) given for 12 weeks improved cognitive function and the quality of life compared with placebo. The subjects aged 45–65 years showed improvements in concentration and working memory as well as in memory tasks related to everyday life [143]. In a meta-analysis of nine trials on the use of ginkgo in patients with cognitive impairment and dementia, data favored EGb761 over placebo for maintaining cognitive performance and improving daily living activities. In these trials of 22–26 weeks duration, EGb761 administered at a dose of 240 mg/day was able to stabilize or slow the decline in cognitive function and behavior [134]. A recent fMRI study on the use of EGb761 (240 mg/day) in elderly with subjective memory impairment indicated increased cognitive flexibility without change in brain activation. The study found no effect for *Ginkgo biloba* on prefrontal dopaminergic function [144]. Rainer et al. [145] found that EGb 761R (240 mg/day) resulted

in a delay in activities of daily living deterioration by 22.3 months when compared to placebo. The cost of treatment with *Ginkgo biloba* extract to achieve treatment success was less than that of cholinesterase inhibitors. *Ginkgo biloba* and donepezil, however, could be used in combination. In this study, subjects aged 50 years or above, with probable AD were treated with EGb 761(R) (240 mg/day), donepezil (5 mg followed by 10 mg/day), or their combination for 22 weeks. The study found no significant difference in the efficiency between EGb 761(R) and donepezil but the combination seemed to be superior to either agent alone [146].

Several mechanisms are thought to account for the effect of *Ginkgo biloba* on cognition. Lowering Aβ-peptide deposition in brain is one goal of anti-AD therapy [147]. In transgenic mouse models of AD, treatment with EGb761 was found to decrease Aβ oligomers [148] and amyloid precursor protein (APP) protein levels [149]. Yao et al. [150] proposed reduction of free cholesterol level as the mechanism underlying inhibition of Aβ-peptide production by EGb761. In their study on aged rats, EGb761 given at 50 mg/kg/day for 28 weeks decreased circulating free cholesterol and both Aβ-peptide and APP protein levels. Colciaghi et al. [151] suggested that EGb761 directs the metabolism of APP towards the α-secretase pathway, the enzyme which regulates the non-amyloidogenic processing of APP. Increased alphaAPPs release was observed in hippocampal and cortical slices incubated with EGb761 and also after treating rats with 80 and 150 mg/kg of EGb761 daily for 5 days. EGb761 might regulate the phenotype of activated microglia, resulting in downregulation of pro-inflammatory cytokines and inducible nitric oxide synthase, and upregulation of anti-inflammatory cytokines [152]. EGb761 also increases Hsp70 expression [153]. Tchantchou et al. [148] showed that EGb761 increases neurogenesis in the hippocampus of a transgenic mouse model of Alzheimer's disease. This effect was observed in both young and old mice. Ma et al. [154] attributed the improvement of spatial memory in mice by effect of bilobalide to increased glucocorticoid receptor expression in the hippocampus. Alterations in brain neurotransmitter levels could also account for the memory enhancing action of *Ginkgo biloba*. Blecharz-Klin et al. [155] reported increased serotonin (5-HT) in hippocampus and norepinephrine in hippocampus and prefrontal cortex of rats given EGb761 50–150 mg/kg/day for 3 months. In another study, EGb 761 at 100 mg/kg/day for 2 weeks increased extracellular dopamine and noradrenaline levels in the prefrontal cortex of awake rats. These effects were mediated by the flavonol glycosides and ginkgolide fractions but not bilobalide [156]. Rats treated with EGb761 100–300 mg/kg/day for 2 weeks exhibited significant elevations in extracellular dopamine and norepinephrine levels in medial prefrontal cortex. When given orally at a dose of 10 mg/kg/day for 2 weeks, the acylated flavonol glycosides quercetin, and kaempferol markedly increased extracellular acetylcholine and dopamine in medial prefrontal cortex [157]. In treating dementia, boosting cholinergic neurotransmission with cholinesterase inhibitors tacrine, donepezil, and rivastigmine results in symptomatic benefit [14]. In their study, Stein et al. [158] found that EGb761 had no effect on basal acetylcholine release in the rat brain. There was no pharmacological interaction between donepezil and EGb761 on the hippocampal cholinergic system, suggesting that both drugs can be taken safely. Free radical mechanisms play an important role in different neurodegenerative diseases [6]. In vitro, exposure of human brain tissue to cobalt 60 irradiation and the subsequent generation of hydroxyl OH or superoxide radicals (O_2) resulted in oxidative protein degradation. This was prevented by the addition of *Ginkgo biloba* (and also *P. ginseng*) extract [159]. EGb761 also results in stabilization of mitochondrial membrane and maintenance of ATP production in PC12 cells exposed to the nitric oxide donor sodium nitroprusside [160]. The effects of *Ginkgo biloba* in PD or AD models are summarized in Table 24.4.

Table 24.4 Neuroprotective effect of *Ginkgo biloba* or its constituents in models of Parkinson's disease and Alzheimer's disease

Model	*Gingko biloba* extract or its constituents	Neuroprotection	Mechanism (s)	Study
APPswe/PS1-ΔE9 double transgenic mouse model of Alzheimer's disease.	Mice fed for 1 month a diet supplemented with EGb761 (100 mg/kg/day).	↑ Cell proliferation in hippocampus (↑ Neurogenesis) ↓ Aβ oligomers	↑ Phosphorylation of cyclic AMP response element binding protein	[148]
Mice transgenic for human APP (Tg2576).	EGb761 supplemented diet (300 mg/kg) for 1 and 16 months	↓ Human APP protein in cortex by 50% (EGb761 for 16 months) (No effect in young mice)	–	[149]
APP/PS1 transgenic mouse model of Alzheimer's disease. Two-month-old APP/PS1	EGb761 (50 mg/kg) daily for 6 months.	↑ Cognitive function ↓ Insoluble Aβ	↓ TNF-α, IL-β, and IL-6 in brain ↑ IL-4, IL-13, and TGFβ ↑ Arginase-1 ↓ iNOS ↑ mRNA levels of macrophage inflammatory protein-1α (MIP-1α) and MCP-1 in brain.	[152]
SH-SY5Y neuroblastoma cells incubated with Aβ (1–42)	EGb761 (100 μg/ml) for 2 h prior to Aβ1-42 oligomer for 24 h	↓ Neurotoxicity (↑ cell viability) ↓ Cell apoptosis-related protein expression.	↑ ER stress activation ↑ Hsp70 expression and subsequent Akt activation.	[153]
PC12 cells expressing APPsw mutation	EGb761	Lessened the decrease of mitochondrial membrane potential in APPsw-bearing PC12 cells and also after treatment with sodium nitroprusside.	↑ Function of mitochondrial respiratory chain. ↓ Caspase-3 activity	[160]
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-toxicity in mice	EGb761	↓ Impairment of locomotion ↓ Loss of striatal dopamine ↓ Loss of tyrosine hydroxylase immunostaining in striatum and substantia nigra pars compacta.	↓ Oxidative stress (↓ lipid peroxidation and ↓ superoxide radical production)	[161]
APPswe/PS1-ΔE9 double transgenic mouse model of Alzheimer's disease.	Bilobalide and quercetin	↑ Cell proliferation in hippocampus (↑ Neurogenesis) ↑ Aβ-induced synaptic loss (↑ Synaptogenesis)	↑ Phosphorylation of cyclic AMP response element binding protein ↑ BDNF	[162]

Abbreviations: *BDNF* brain derived neurotrophic factor, *ER* endoplasmic reticulum, *Hsp70* heat shock protein 70, *IL-β* L Interleukin-beta, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-alpha, *COX-2* cyclooxygenase-2, *iNOS* inducible nitric oxide synthase, *MCP-1* monocyte chemoattractant protein-1, *TGFβ* transforming growth factor beta

24.7 Curcumin

Curcumin is a major polyphenolic constituent of the spice *Curcuma longa*. Turmeric is used to add flavor and color to the food [163]. In recent years, curcumin has gained much interest as a potential remedy for AD. Hishikawa et al. [164] described symptomatic improvement in three patients with idiopathic AD following the administration of turmeric. Patients aged 83, 84, and 79 years, respectively, were treated with turmeric at a dose of 764 mg/day (curcumin 100 mg/day) for 12 weeks. The authors reported alleviation of agitated apathy, anxiety, irritability, hallucinations, and delusions. There was also evidence of an improvement in memory. To evaluate the effect of curcumin in persons with mild-to-moderate AD, a double-blind and placebo-controlled randomized trial using curcumin C3 Complex (®) was performed. In this study, 36 subjects with a mean age of 73.5 years received 4 g/day of oral curcumin or placebo, 2 g/day for 24 weeks. The study failed to demonstrate clinical or biochemical evidence of efficacy for curcumin, possibly due to limited bioavailability. Increased blood glucose and lowered hematocrit were observed following treatment with curcumin [165]. Potter et al. [166] suggested that poor oral bioavailability of curcumin and/or starting treatment after the development of substantial neuronal death in dementia might account for the lack of efficacy of curcumin in subjects suffering from Alzheimer's disease. In their study in healthy middle-aged subjects (40–60 years), DiSilvestro et al. [167] administered curcumin in a lapidated form to ensure good absorption. Curcumin 80 mg/day or placebo was given for 4 weeks. Curcumin but not placebo caused lowering of triglycerides and beta amyloid protein concentrations in plasma. There were also increases in plasma myeloperoxidase, nitric oxide, and decreased plasma alanine amino transferase activities. Cox et al. [168] used solid lipid curcumin formulation (Longvida®) to study its effect on cognitive function and mood in 60 healthy adults aged 60–85 years. In this randomized, double-blind, placebo-controlled trial, the authors reported improved performance on sustained attention and working memory tasks one hour after administering 400 mg of Longvida®. Four weeks of treatment with curcumin was associated with improvements in working memory and mood including fatigue and calmness. Curcumin also resulted in reduced total and low-density lipoprotein cholesterol. In another double-blind, placebo-controlled, randomized study on the efficacy of curcumin to prevent cognitive decline, subjects were given 1500 mg/day BiocurcumaxTM or placebo for 12 months. Curcumin but not placebo prevented the decline in cognitive at 6 months [169].

In rodent models of Alzheimer's disease, treatment with curcumin alleviated memory deficits and increased cholinergic neuronal function [170, 171]. APPSw mice fed curcumin exhibited decrements in insoluble Aβ and soluble Aβ plaque burden as well as decreased brain interleukin-1β [172]. Rats given intracerebroventricular injection of Aβ1-42 and treated with curcumin (50–200 mg/kg) for 5 days had their memory improved, possibly due to increased BDNF and phosphorylated ERK in hippocampus [171]. Aβ toxicity in neuronal/glial cultures is reduced by curcumin which decreased microglia and astrocyte activation [170]. It was suggested that curcumin acts by directing the Aβ aggregation pathway towards the formation of soluble oligomers and prefibrillar which are nontoxic aggregates and also by decreasing cell membrane permeabilization and membrane disruptions induced by Aβ aggregates [173, 174]. Liu et al. [170] found that curcumin alleviates neuroinflammation by directly binding to PPARγ and increases the transcriptional activity and protein level of PPARγ. In addition, Reddy et al. [175] showed that curcumin protects against Aβ toxicity by maintaining mitochondrial dynamics, mitochondrial biogenesis as well as synaptic activity.

Curcumin is also likely to benefit PD patients. Using PC12 cells that express the A53T α-synuclein mutation, Liu et al. [176] found that

curcumin protected against cell death by reducing intracellular reactive oxygen species and inhibiting the mitochondrial apoptotic cell death pathway. Mice over-expressing wild type of human α-synuclein had their gait improved by curcumin which resulted in increased phosphorylated α-synuclein at cortical presynaptic terminals [168]. Table 24.5 summarizes the results on the protective effect of curcumin in experimental models of AD and PD.

Table 24.5 Neuroprotective effect of curcumin in models of Parkinson's disease and Alzheimer's disease

Model	Curcumin	Neuroprotection	Mechanism (s)	Study
SH-SY5Y neuroblastoma cells incubated with oligomeric α-synuclein	Curcumin 4 μM	↓ Toxicity of pre-formed oligomeric α-synuclein ↓ Apoptosis Stabilized pre-formed α-synuclein fibrils	↓ Intracellular reactive oxygen species ↓ Caspase-3 activation	[178]
PC12 cells expressing mutant A53T α-synuclein	Curcumin	↓ Cell death	↓ Oxidative stress ↓ Mitochondrial cell death pathway (↓cytochrome c release, ↓ caspase-9, and ↓c aspase-3 activation)	[176]
6-hydroxydopamine rat model of Parkinson's disease.	Curcumin	↓ Loss of dopamine in striatum ↓ Loss of tyrosine hydroxylase-immunoreactive neurons ↓ Number of iron-staining cells.	Iron-chelating activity	[179]
Mice overexpressing wild type of human α-synuclein	Feeding with diet containing 500 ppm curcumin for 5 months	Improved gait impairment	↑ Phosphorylated α-synuclein at cortical presynaptic terminals	[177]
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-toxicity in mice	Long-term (7 weeks) dietary supplementation with curcumin at a concentration of 0.5% or 2.0% (w/w).	↓ Loss of dopaminergic cells in substantia nigra ↓ Loss of dopamine in striatum	↑ Expression of glial cell line-derived neurotrophic factor and transforming growth factor-β1 in striatum	[180]
PINK1 knock down SH-SY5Y neuroblastoma cells treated with paraquat	Curcumin	↓ Cell apoptosis	Preserved mitochondrial function (↑ mitochondrial membrane potential and ↑ maximal respiration)	[181]
Rotenone-treated rats	Curcumin	↑ Motor performance ↓ Loss of tyrosine hydroxylase-immunoreactive cells in substantia nigra	↓ Oxidative damage (↑ glutathione, ↓ reactive oxygen species activity, ↓ malondialdehyde) via activation of the Akt/Nrf2 signaling pathway	[182]

(continued)

Table 24.5 (continued)

Model	Curcumin	Neuroprotection	Mechanism (s)	Study
APPSw mice	Mice fed chow containing curcumin 160 ppm or 5000 ppm for 6 months.	↓ Oxidized proteins and IL-1β (160 ppm or 5000 ppm) in brain. ↓ GFAP (astrocytic marker), ↓ both insoluble and soluble Aβ (160 ppm only)	↓ Oxidative damage	[172]
Aβ (1–42) i.c.v. injection in rat	Curcumin (50, 100, and 200 mg/kg, i.p.) for 5 days	↑ Memory performance	↑ BDNF ↑ Phosphorylated ERK in hippocampus	[171]
APP/PS1 transgenic AD mouse model	Curcumin	↓ Spatial memory deficits ↑ Cholinergic neuronal function	↓ Neuroinflammation (partly PPARγ-mediated)	[170]
Aβ (1–42) toxicity in neuronal/glial cultures	Curcumin (10 μM)	↑ Cholinergic neuronal function ↓ Microglia and astrocyte activation	↓NF-κB signaling pathway ↓ Neuroinflammation	[170]
Aβ toxicity in SHSY5Y cells	Curcumin	↓ Mitochondrial and synaptic impairments Maintained cell viability	Preservation of mitochondrial function.	[175]

Abbreviations: *BDNF* brain derived neurotrophic factor, *NF-κB* nuclear factor kappaB, *ERK* extracellular signal-regulated kinase, *PPARγ* peroxisome proliferator-activated receptor gamma

Conclusions

Data from epidemiological studies suggest that dietary polyphenols could be of value in maintaining cognitive function and in decreasing the risk of progression to AD in the elderly. Benefits from tea and coffee, two widely consumed beverages could also be seen in patients with PD where there is a decrease in the risk for developing the disease. Coffee also improves the cognitive status in these individuals and decreases the risk of dyskinesia associated with dopaminergic replacement therapy. Coffee or caffeine also decreases the risk for developing dementia in late-life. While the administration of ginseng in healthy young subjects has been shown to improve working memory, a possible effect in PD or AD is yet to be determined. The weight of evidence is also in favor for a beneficial effect from *Ginkgo biloba* supplementation on cognitive decline and in preventing dementia. Clinical trials with curcumin suggest that using the herb might have an important role in preventing dementia or its progression. Studies conducted in vitro and in vivo indicated that the abovementioned herbal/dietary supplements and their biologically active constituents studies could reduce neuronal damage and are likely to have a positive impact in reducing neurodegeneration occurring in old age or in the context of disorders such as PD or AD.

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