Natural Products for Neurocognitive Disorders

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Doi: https://doi.org/10.36255/exonpublications.alzheimersdisease.2020.ch12

Abstract: Neurocognitive disorders are devastating. In 2016, 43.8 million people were estimated to have Alzheimer's disease worldwide. By 2050, this figure is expected to rise by 56%. Despite the extreme importance of the disease, the weapons available to us to combat it are very scarce. Natural substances may be a worthwhile option for the treatment and management of neurocognitive disorders. Some of these natural products have been shown to be capable of positively impacting memory, behavior, and functions of patients with Alzheimer's disease. These substances act on the disease mainly through antioxidant properties, the ability to eliminate oxygen radicals, the capacity to influence cell survival and programmed cell death, and the potential to condition amyloidogenesis. This chapter provides an overview of our current knowledge on the potential of natural products to be effective neuroprotective agents for Alzheimer's disease. Current evidence on Ginkgo biloba, bacopia, resveratol, curcumin, quercetin, kaempferol, capsaicin, and berberine, along with their adverse effects and drug interactions are discussed.

Keywords: bacopa; ginkgo biloba; natural products for Alzheimer's disease; neurocognitive disorders; resveratrol

INTRODUCTION

In 2013, the Diagnostic and Statistical Manual of Mental Disorders (DSM–5), introduced the term "Neurocognitive Disorders". It groups neurocognitive disorders into "major" and "mild" categories. A major neurocognitive disorder (MaND) is a disorder characterised by a decline in intellectual function due to disease of the brain, caused by a variety of acquired conditions such as cerebrovascular disease, Alzheimer's disease, infections, adverse drug reactions, and trauma. Alzheimer's disease is the most common form of MaND. The key distinction between a MaND and a mild neurocognitive disorder (MND) is that individuals with MaND experience substantial degradation in function resulting in loss of independence due to profound cognitive impairment, whereas subjects with MND experience only modest cognitive decline and can therefore function relatively independently. Reduced mental capacity may involve problems with complex attention, executive functioning, learning and memory, expressive and receptive language, perceptual-motor abilities, changes in behavior, and trouble performing everyday tasks (1).

A growing number of herbal remedies, dietary supplements, and "medical foods" are advertised as having beneficial neuroprotective effects. Compounds such as *Ginkgo biloba,* resveratrol, curcumin, capsaicin, berberine, kaeperol, quercetin as well as others are promoted as memory enhancers or as treatments to delay or prevent MaND (2). Many of these substances are found naturally in the diet, in vegetables and fruits, as well as in some spices. Some epidemiological investigations revealed that high consumption of certain foods was inversely associated with the incidence of Alzheimer's disease. These foods contain antioxidants, especially polyphenols. Polyphenols are excellent antioxidants both as reactive oxygen species (ROS) scavengers and transition metal chelators. While the neuroprotective effects of these foods in neurocognitive disorders are largely attributed to their antioxidant potential, some antioxidants derived from these foods go beyond modulating ROS (Figure 1). Several natural products are used alone or in combination with other treatment modalities to improve memory and cognition in both AD and MND (3). This chapter discusses the current scientific data on the potential of Ginkgo biloba, bacopa, resveratol, curcimun, quercetin, kaempferol, capsaicin, and berberine as effective neuroprotective agents for Alzheimer's disease along with their toxicities and drug interactions.

GINKGO BILOBA

Ginkgo biloba, also known as the Maidenhair tree, is an ancient plant whose origins date back to 250 million years ago to the Permian period. The extracts of its leaves have been used since antiquity in traditional Chinese medicine to treat various pathologies. Nowadays, extracts of this plant are used in Europe, especially in Germany and France, for the treatment of memory and concentration problems, depressive anxiety disorder, dizziness, headache, and many other issues. As highlighted by a systematic review and meta analysis, the extract of *Ginkgo biloba*, EGb761, which contains about 22% of glycosides
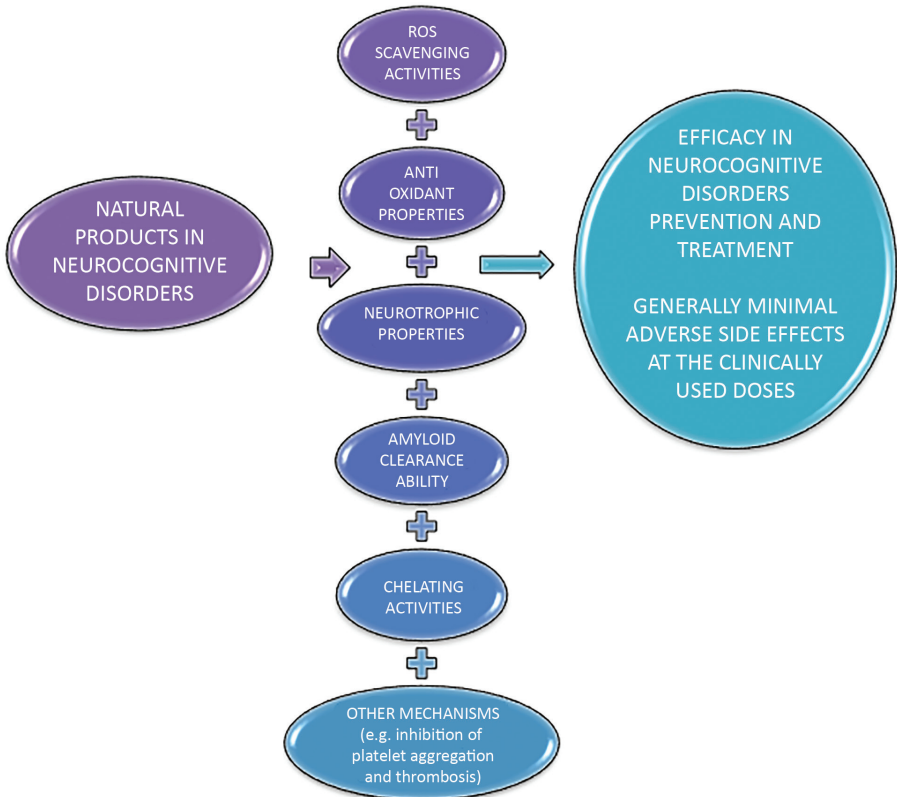
Figure 1. **Natural products for neurocognitive disorders.** The neuroprotective effects of natural products are largely attributed to their free radical scavenging abilities. In addition, they can chelate metals, inhibit amyolid beta formation, and enhance its clearance. In general, the natural products exert minimal or lower-grade adverse events.

and flavonoids and about 5–7% of terpene lactans (ginkgollids and biloballids), is capable of stabilizing or slowing down cognitive decline, functional decline, and behavior disorders at a dose of 240 mg/day. Furthermore, it is able to achieve global changes in cognitive impairment and neuro cognitive disorders in 22–26 weeks. These changes are significant for patients with neuropsychiatric symptoms (4, 5).

Neuroprotective Effects of Ginkgo Biloba

The *in vitro* effects of *Ginkgo biloba* extracts are manifold and are widely documented. They contain significant amounts of polyphenols. The effects of the extracts are largely attributed to their free radical scavenging abilities and metal chelation properties, especially chelation of copper and iron. *In vitro* studies conducted on PC12 cell lines have shown that *Ginkgo biloba* extracts

prevent the production of ROS and reduce the cytotoxicity of $A\beta_{(1-42)}$ by inhibiting apoptosis and cellular glucose absorption (6). *Ginkgo biloba* extracts were also found to prevent the formation of diffusible neurotoxic ligands derived from $A\beta_{(1-42)}$.

The *in vivo* activities of *Ginkgo biloba* have been studied in various animal models. In the nematode *Caenorhabditis elegans*, EGb761 alleviated the pathological behavior connected to the presence of $A\beta$, inhibited beta oligomerization and $A\beta$ deposits, and attenuated basal and induced levels of ROS in models of neurodegenerative pathology. In a trial conducted on TgCRND8 AD mice (mice that overexpress the amyloid precursor protein (APP) particularly at a neuronal level), treatment with EGb 761 for 5 months significantly improved cognitive function, as measured by Barnes Maze test. The results clearly showed inhibition of neuroinflammation, reduction in cognitive deficits, reduction in synaptic damage, improvement of autophagy, and inhibition of $A\beta_{1-42}$-induced microglial inflammatory activity (7). The doses given were designed to maintain plasma concentrations comparable to those reached by humans who take 240 mg of product per day (recommended dose).

The effects of the treatment with EGb761 extract of *Ginkgo biloba* have been the subject of a meta-analysis that collected data from three clinical studies. The meta-analysis showed that a dose of 240 mg per day of *Ginkgo biloba* extract is able to delay the deterioration of basal activities of daily life. An interesting fact that emerged from this analysis was that treatment with EGb761 had the same efficacy as acetylcholinesterase inhibitors, at a lower cost (8). The weak point of the cited meta-analysis was that it took into account only daily life activities and treatment costs, not the behavioral and psychological symptoms of dementia. The behavioral and neuropsychiatric effects were explored in a randomized controlled double-blind multicenter trial, which was designed to investigate the safety and efficacy of a daily dose of 240 mg of EGb761 in patients with mild to moderate neurocognitive disorders, using the neuropsychiatric inventory scale. Treatment with EGb761 improved cognitive function and the neuropsychological symptoms of dementia. Significantly, the quality of life of patients and their caregivers improved compared to placebo-treated patients (9). A randomized double-blind phase III trial conducted on 3069 community volunteers of at least 75 years of age with normal cognitive functions or mild cognitive impairment has shown that a dose of 120 mg twice daily of *Ginkgo biloba* is unable to prevent or delay the overall incidence rate of MaND or cases of Alzheimer's disease (10). On the contrary, a systematic review and meta-analysis investigating the clinical efficacy of EGb761 in minor and major cognitive decline, established that 240 mg per day was able to stabilize or slow down the decline in cognitive functions, functional skills, and behavior, resulting in overall positive effects, especially in patients with behavioral and psychological symptoms of dementia (11).

The Paquid study, a population-based cohort with a follow-up period of 22 years, examined the effect of *Ginkgo biloba* in the elderly. There were 3777 community participants, at least 65 years of age at the time of recruitment. The patients were visited at home by psychologists at baseline, and then every 2 years. They were grouped into three categories: consumers of *Ginkgo biloba* extracts, consumers of other medicines, and controls that did not receive any treatment. Consumers of *Ginkgo biloba* extracts showed lower mortality rates

and longer dementia-free lifespans than subjects taking other drugs for the same indications (12).

Ginkgo biloba extracts are mainly indicated for the treatment of "age-associated" cognitive decline and for improving the quality of life in patients with mild neurocognitive disorders (MND). Long-term use of these extracts is most effective in patients over 50 years of age. According to European Pharmacopoeia (Ph. Eur.), the extract should contain 22.0–27.0% of flavonoids, 2.8–3.4% of ginkgolides A, B, and C, and 2.6–3.2% of bilobalide (active constituents), and a maximum of 5 ppm ginkgoid acids (potential allergens) (13). Treatment with *Ginkgo biloba* extracts is safe, but close attention should be paid to patients being treated with anticoagulants, as the pharmacokinetics of some may be altered by certain plant extracts (14).

Adverse Effects of Ginkgo Biloba

Ginkgo biloba is currently considered to have one of the highest rates of adverse side effects and interaction (Table 1) with conventional drugs (15). Cases of intoxication have been reported in Japan and China, where Ginkgo seeds and nuts have been a common food since ancient times. Poisoning causes tonic–clonic epileptic seizures, vomiting, and loss of consciousness. These effects are mainly related to a neurotoxic compound known as ginkgotoxin. Rare cases of death related to Ginkgo poisoning have been described, especially in the years following the first and second World Wars, probably due to food shortages. Now-a-days, cases of *Ginkgo* poisoning are much rarer, perhaps due to an increase in knowledge of the toxicological profile of these substances. Another adverse effect attributable to *Ginkgo biloba* extracts is spontaneous bleeding, especially in patients taking Ginkgo and warfarin together. Rarer adverse effects include a proarrhythmic effect, nocturnal palpitations, cerebrovascular events (ischemic stroke and transient ischemic attacks), and allergic reactions such as contact dermatitis. Drug interactions of *Ginkgo biloba* with conventional medicinal substances have also been reported. It interacts with drugs widely used in clinical practice such as omeprazole, midazolam, and tolbutamide.

BACOPA

Brahmi or *Bacopa monnieri* is a plant used in Ayurvedic medicine with neuroprotective and nootropic properties. The neuroprotective effect of this plant seems to derive from numerous bioactive components such as bacoside A, bacoside B, bacosaponins, and betulinic acid. The mechanisms by which these compounds exert a neuroprotective effect and offer improvement of cognitive and learning abilities include reduction of ROS, anti-inflammation, and inhibition of beta amyloid aggregation. Bacopa seems to play a relevant role in the treatment of not only of Alzheimer's disease but also of other neurological pathologies (16).

TABLE 1	Interactions and side effects of natural products	
Natural product	**Indications**	**Drug interactions and side effects**
Ginkgo biloba	• Age associated cognitive decline • Mild neurocognitive disorder • Multi infarct dementia • Traumatic brain injury • Normal aging • Stroke • Tinnitus • Intermittent claudication • Senile macular degeneration	• Pay attention in association with anticoagulants • Intoxication: tonic clonic epileptic seizures, vomiting, loss of consciousness • Spontaneous bleeding (when administered with warfarin) • Rare: proarrhytmic effect, allergic reactions, acute generalized exhantematous pustolosis
Bacopa monnieri	• Improve cognition in the elderly and in patients with neuro cognitive disorders • Beneficial effects in Parkinson disease, depression, neoplastic pathologies • Beneficial properties on gastrointestinal tract	No significant harmful side effects is currently known
Resveratrol	• Improves adult cognitive abilities • Reduces cognitive decline in the healthy elderly • Slows down the decline in pathological states such as Alzheimer's and Parkinson's disease	• Leukopenia • Decreases circulating levels of TNF and IL 6 • Mild to moderate diarrhea, nausea, hypersensitivity and annoying itching in the anal area.
Curcumin	• Neurodegenerative diseases, multiple sclerosis, prion diseases, stroke • Autism, Down syndrome, Amyotrophic Lateral Sclerosis, depression, anxiety and aging • Beneficial properties in diabetes mellitus, arthritis, liver, kidney and cardiovascular pathologies	• High doses can produce toxic and even carcinogenic effects • Mild nausea and diarrhea • Subclinical iron deficiency
Quercetin	• Prevention and treatment of Alzheimer's disease and other types of dementia	• Adverse effects are rare and usually very mild • In animal models it shows toxic effects on kidney
Kaempferol	• Protective action against cognitive decline • Beneficial effects in experimental models of Alzheimer's disease	No significant harmful side effects is currently known

TABLE 1	Interactions and side effects of natural products (Continued)

Natural product	Indications	Drug interactions and side effects
Capsaicin	• Beneficial effects both on cognitive functions of middle aged adults and advanced age subjects • Beneficial effects on biomarkers of Alzheimer's disease • Anti cancer properties • Anti obesity properties • Osteoarthritic pain • Cannabinoid hyperemesis syndrome • Useful as a dermal patch in peripheral neurotrophic pain	• At very high doses, well above those clinically useful, capsaicin can lead to death due to respiratory paralysis • It is hypothesized that capsaicin may have carcinogenic effects linked to overdose • Capsaicin in the form of pepper spray is likely to induce a form of acute polyneuropathy that resembles Guillain Barrè syndrome
Berberine	• Neurodegenerative pathologies and, in particular, Alzheimer's disease • Ischemic stroke • Vascular dementia	• When administered for prolonged periods of time, causes a deterioration of dopaminergic neurons • Several drug interactions (tetrandine, levodopa, doxorubicin, beta lactam antibiotics and hydroxycamptotecin, Panax ginseng, cisplatin, fluconazole, cyclosporin A, warfarin and thiopental)

Neuroprotective Effects of *Bacopa*

Bacopa's mechanisms of action (Table 2) have been studied on the microglial cell line N9. Infusions, teas, and extracts of bacopa and bacoside A are able to significantly inhibit the release of mediators such as TNF-α and interleukin 6 by microglial cells *in vitro*. In cell-free systems, teas, infusions and alkaloid extracts of Bacopa can inhibit caspases 1 and 3, and matrix metalloproteinases 3. Thus the fundamental mechanism of action of bacopa appears to be inhibition of the release of pro-inflammatory cytokines by microglia cells and inhibition of enzymes that perform pro-inflammatory actions in the central nervous system. The net effect of all these pharmacological actions of bacopa evidently consists of keeping inflammation under control in the brain (17). In animal models, *Bacopa monnieri* extracts improve cognitive functions mainly through protective action on hippocampal neurons and partly through promoting neuroregeneration in the dentate gyrus (18, 19). Furthermore, studies on APP/PS1 mice have shown that *Bacopia monnieri* extracts can reduce plaque load and enhance plaque clearance, possibly via phagocytosis (20). *Bacopa monnieri* prevents senescence and has an anti-apoptotic effect in brain astrocytes and, therefore, is thought to combat brain pollution and age-related neurological disorders (21).

TABLE 2	Mechanism of action

Natural products	Mechanisms of action
Ginkgo biloba	• Antioxidant power • Copper chelating ability • Radicals scavenging properties • Prevents formation of diffusible neurotoxic ligands derived from $A\beta_{(1-42)}$ • Prevents apoptosis
Bacopa monnieri	• Inhibits the release by microglial cells *in vitro* of mediators such as TNF α and IL 6 • Inhibits caspases 1 and 3 and metalloproteinases 3 • Overall, keeps inflammation under control into the brain • Expresses amyloid clearance capacity • Prevents senescence and has anti apoptotic effect in brain astrocytes • Reduces the share of Reactive Oxygen Species
Resveratrol	• Improves metabolic functions • Acts as a neuroinflammation modulator • Shows protective effects against oxidative stress • Seems to inhibit the mechanism of apoptosis in brain cells • Anti aggregating activity against $A\beta_{(1-42)}$
Curcumin	• Powerful antioxidant, anti inflammatory, anti cancer, anti microbial actions • Neurotrophic properties • Stimulates amyloid clearance in Alzheimer's disease
Quercetin	• Anti inflammatory, anti oxidant, anti cancer properties • Beneficial properties for dyslipidemia, hypercolesterolemia, cardiovascular diseases, diabetes • ROS scavenging ability • Neuroprotective properties
Kaempferol	• Antiamyloidogenic activity • Destabilizing activity against amyloid fibrils • Chelates metal ions • Keeps oxidative stress under control • Inhibits platelet aggregation and thrombosis
Capsaicin	• Mitigates amyloid induced synaptic loss • Performs neuroprotective functions against stress induced cognitive impairment • Able to reduce the hyperphosphorylation degree of tau protein
Berberine	• Anti inflammatory activities • Anti oxidant properties • Inhibits acetyl cholinesterase • Inhibiting properties against amyloid formation

Taken together, the neuroprotective actions and positive effects of bacoside A on memory, mental, and intellectual functions can be largely attributed to its ability to reduce beta amyloid aggregation and toxicity (22), lower inflammation in the brain, scavenge ROS, and increase cerebral blood flow (23, 24). Promising indications for use in humans include improving cognition in the elderly and in patients with neurodegenerative disorders (25). Bacopa is considered by some authors as a kind of

"bulletproof vest" against Alzheimer's disease (26). It seems that *Bacopa monnieri* extracts are able to reduce the formation of transthyretin fibrils (TTR) by attenuating their disassembly from the tetrameric form to the monomeric form. This suggests bacopa has a role in preventing transthyretin amyloidosis, a very debilitating and often fatal disease in humans (27). The anti-inflammatory properties of bacopa have been beneficial in the treatment of many neurological diseases of the central nervous system. For example, they have shown promising results in some experimental models of Parkinson's disease (28). In addition, bacopa has proven beneficial in the treatment of depression, anhedonia, various inflammatory diseases, and neoplastic pathologies. In the rat, bacopa has exhibited beneficial properties on the gastrointestinal tract as an antidiarrheal, as a protector of the gastric mucosa, and as an anti-ulcer drug (29, 30). Currently, no significant harmful side effects of *Bacopa monnieri* are known.

RESVERATROL

Resveratrol is a phenol predominantly found in grapes and wine as well as in berries, peanuts, and soybeans (31). Resveratrol is effective in reducing the risk of dementia in mouse models; this perhaps is due to the fact that improving metabolic function improves brain health during senile age (32). Resveratrol acts as a brain neuroinflammation modulator (33), shows protective effects against oxidative stress (34), inhibits the mechanism of apoptosis in brain cells (35), and exerts anti-aggregating activity against $A\beta_{(1-42)}$ (36). Resveratrol is a promising molecule for improving cognitive abilities in adults, reducing cognitive decline in healthy elderly, and slowing decline in pathological states such as Alzheimer's and Parkinson's disease (37, 38). The toxic effects of resveratrol seem to be closely associated with a hormetic effect; low doses are generally associated with antioxidant effects while higher doses can have a pro-oxidant effect. Resveratrol can cause leukopenia, decrease circulating levels of TNF and interleukin 6, and increase plasma levels of alanine aminotransferase. In addition, it can cause mild to moderate diarrhea, nausea, hypersensitivity, and irritation of the anal area. Through the dose-dependent ROS increase, resveratrol can also cause proteolysis and DNA damage (39).

CURCUMIN

Curcumin is an extract of turmeric widely used in Asia, especially in the culinary sector. This substance seems to have multiple beneficial effects, particularly with respect to various neurological pathologies and cancer. Curcumin exerts its effects through powerful antioxidant, anti-inflammatory, anti-cancer and antimicrobial actions. In addition, the molecule has neurotrophic properties and appears to stimulate amyloid clearance in Alzheimer's disease (40). Curcumin shows beneficial effects in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's chorea (41), multiple sclerosis, prion diseases, and stroke. In addition, the molecule can attenuate age-related severity of autism and Down syndrome, and prevent the progression of amyotrophic lateral sclerosis, depression, anxiety, and pathological aging by reducing the expression of IL-1α, IL-6, and TNF-α, and by the activation of mitochondrial protection and anti-apoptotic

mechanisms (42). Currently, there is still insufficient clinical data to support the beneficial effects of curcumin in patients with Alzheimer's disease. In addition, curcumin administered orally is poorly bioavailable (43). The pharmacological effects, whether therapeutic or toxic, are dose-dependent. At high doses, the molecule can produce toxic and even carcinogenic effects (44). Sometimes curcumin, due to metabolic activation, can exert pro-oxidant effects (45). Other side effects include mild nausea and diarrhea (46). Curcumin also chelates iron and suppresses hepcidin, leading to a subclinical iron deficiency (47).

QUERCETIN

Quercetin is a flavonoid present in numerous plants, as well as in certain fruits and vegetables. It is also present in red wine and green tea. Quercetin has antioxidant, anti-inflammatory, anti-cancer, and ROS scavenging properties, and has been shown to be beneficial for the prostate, dyslipidemia hypercholesterolemia, cardiovascular diseases, diabetes, viral infections, kidney transplantation, asthma, and lung disease. Furthermore, it seems to have neuroprotective effects in schizophrenia, Alzheimer's disease, and other forms of dementia (48, 49). The adverse effects associated with the use of quercetin are rare and typically mild; however, animal studies have shown that quercetin has toxic effects on the kidney, promote tumor development especially in estrogen-dependent cancers, and can interact with various drugs to alter their bioavailability (50).

KAEMPFEROL

Kaempferol is a flavonoid present in many plants and in vegetables such as cabbage, spinach, beans, broccoli, and tea (51). Kaempferol has antiamyloidogenic activity. It can destabilize amyloid fibrils, chelate metals, and keep oxidative stress under control (52). Kaempferol has also been shown to inhibit platelet aggregation and thrombosis, an effect that could prove particularly interesting in vascular forms of cognitive decline (53). Like the other main dietary flavonoids (myricetin and quercetin), Kaempferol protects against cognitive decline (54). All flavonoids (myricetin, morin, rutin, quercetin, fisetin, kaempferol, apigenin, and glycitein) have shown beneficial effects in experimental models of Alzheimer's disease (55). There is currently insufficient data in the literature regarding the adverse effects of Kaempferol in humans.

CAPSAICIN

Capsaicin is a well-known alkaloid present in chilli pepper and is responsible for its spiciness. In experimental mouse models, capsaicin has been shown to mitigate amyloid-induced synaptic loss (56). Furthermore, capsaicin has proven to be capable of performing neuroprotective functions against stress-induced cognitive impairment (57). Finally, it has been shown in experimental animals that capsaicin is able to reduce the degree of hyperphosphorylation of the tau protein, a protein

involved in the pathogenesis of Alzheimer's disease (58). A capsaicin-rich diet has been shown to have beneficial effects both on the cognitive functions of middle aged adults and advanced age subjects, and on the blood biomarkers of Alzheimer's disease ($A\beta_{40}$, $A\beta_{42}$, and their ratio) (59). In addition to its neuroprotective properties, capsaicin has anti-cancer (60), antiobesity properties (61) and can counteract metabolic syndrome (62). It is useful as a topical applicant to ease osteoarthritic pain (63), particularly in that of the knee (64). It can be used in the treatment of cannabinoid hyperemesis syndrome (65), and as a dermal patch for peripheral neuropathic pain (66). At very high doses (well above those clinically useful), capsaicin can lead to death due to respiratory paralysis (67, 68). Capsaicin in the form of pepper spray can induce a form of acute polyneuropathy that resembles Guillain-Barrè syndrome (69).

BERBERINE

Berberine is an alkaloid extracted from various plants of the Berberis species and is widely used in Asia. Berberine exhibits anti-inflammatory, antioxidative, and anti-amyloid activities (70). It can also inhibit acetylcholinesterase (70). Berberine is useful in neurodegenerative pathologies such as Alzheimer's disease (71), stroke (72), and vascular dementia (73, 74).

Berberine, when administered for prolonged periods of time, causes a deterioration of dopaminergic neurons due to the cytotoxic effect exerted by 6 hydroxydopamine (75–77).

Berberine stimulates uterine contractions and should therefore be used with caution in pregnancy. It also appears to exacerbate jaundice and kernicterus (Kernicterus or Bilirubin encephalopathy or Nuclear jaundice) in infants with glucose-6-phosphate dehydrogenase deficiency. Berberine is likely to be able to cross the placenta and harm the developing fetus. It can be transferred to breast milk and should therefore also be used with caution when breastfeeding. However, berberine does not have known genotoxic, cytotoxic, mutagenic actions, or other adverse effects at clinically relevant doses.

Various drug interactions (Table 1) of berberine have been reported: (i), tetrandineh worsens the hypoglycaemic properties of berberine; (ii), the activity of levodopa is antagonized by berberine; (iii), with doxorubicin, Panax ginseng, cisplatin, and fluconazole berberine exerts synergistic effect; and (iv), berberine increases the circulating levels of cyclosporin A, warfarin, and thiopental (78).

CONCLUSION

Neurocognitive disorders are multifactorial pathological conditions that require a multidisciplinary therapeutic approach. The pharmacological weapons at our disposal are extremely limited and any aid is a welcome measure for the patients, their families, and caregivers. Given the available evidence, it is reasonable to assume that natural products will gain an increasingly important role in the future alongside traditional and experimental pharmacological therapies for the management of patients with neurocognitive disorders, including Alzheimer's disease.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this chapter.

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