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REVIEW

The neuroprotective effect of traditional Chinese medicinal plants—A critical review

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Abstract Neurodegenerative and neuropsychiatric diseases are increasingly affecting individuals' quality of life, thus increasing their cost to social and health systems. These diseases have overlapping mechanisms, such as oxidative stress, protein aggregation, neuroinflammation, neurotransmission impairment, mitochondrial dysfunction, and excitotoxicity. Currently, there is no cure for neurodegenerative diseases, and the available therapies have adverse effects and low efficacy. For neuropsychiatric disorders, such as depression, the current therapies are not adequate to one-third of the patients, the so-called treatment-resistant patients. So, searching for new treatments is fundamental. Medicinal plants appear as a strong alternative and complement towards new treatment protocols, as they have been used for health purposes for thousands of years. Thus, the main goal of this review is to revisit the neuroprotective potential of some of the most predominant medicinal plants (and one fungus) used in traditional Chinese medicine (TCM), focusing on their proven mechanisms of action and their chemical compositions, to give clues on how they can be useful against neurodegeneration progression.

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1. Introduction

Medicinal plants are species producing valuable bioactive compounds that have been cultivated and administered to prevent or treat several diseases. Around 35,000 plant species exert medicinal properties[1]. The commercialization of medicinal plants has raised with the increased global interest in natural products. In 2019, the traditional medicine market value was estimated at around 84.5 billion US dollars[2].

Neurodegenerative diseases belong to a group of pathologies of incurable and debilitating nature that affect people of all ages, mostly the elderly. These diseases are responsible for the progressive and irreversible degradation of neurons. According to the World Health Organization, the increase of the average life expectancy of the world population is one of the key factors for the prevalence of neurodegenerative diseases[3].

Neurodegenerative conditions are increasingly becoming a burden to society. As life expectancy increases with the overall improvement of quality of life, so do the periods of life where cognitive and motor abilities naturally decline. This is usually seen in the elderly, making older citizens more susceptible to developing abnormal levels of mental decline. Also, because of better knowledge amongst younger demographics, mental health has broken social stigma "barriers" with people suffering from major depression disorder (MDD) being less reluctant to seek help. Indeed, MDD is the main comorbidity affecting patients with dementia.

Using plants in treatment plans is seen controversial, as safe administration doses are hard to assess for different reasons. Nonetheless, some communities and demographics, like the elderly, tend to choose plant treatment over medical treatment, seeing it as natural, safe, and less costly. Besides, the pharmaceutical industry recognizes the promising potential of natural products, which have served as a source of inspiration for new bioactive molecular standards over the years.

This review summarizes the existing evidence on the comparative efficacy and safety of 21 medicinal plants and one fungus commonly used in traditional Chinese medicine (TCM), according to data collected from *in vitro* and *in vivo* studies and clinical trials performed. The safety assessment of these species was also considered. Species were selected based on information about having been utilized in TCM for neurodegenerative/neuropsychiatric treatment purposes, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), MDD and anxiety. Considering the growing increase in neurodegenerative/neurological diseases and the search for new therapeutic approaches, it is in the use of medicinal plants that certain sociodemographic groups have shown their preference. Thus, this area needs a continuous review that can be updated in the light of new emerging evidence, thus contributing to health policy planning.

Neurodegenerative diseases have a multifactorial nature whose symptoms may manifest and affect patients differently. Several patients may develop neuropsychiatric comorbidities like MDD and anxiety.

AD is the most common form of dementia, accounting for 50%−70% of all cases. According to the Organization for Economic Co-operation and Development, around 18.7 million people suffered from AD in 2017[4]. AD symptoms are related to progressive loss of intellectual and cognitive abilities, such as lack of attention and concentration, incapacity of recognizing visual space and verbal fluency, and the inability to interact with familiar objects.

PD is the second most prevalent progressive neurodegenerative disease that affects the CNS in adults. According to Parkinson's Foundation, around 10 million patients carried PD in 2018[5]. It affects all encephalic areas meant to regulate motor capacity. The main symptoms of this disease are movement disorders such as tremors, stiffness, bradykinesia, and postural instability.

HD is a rare, progressive, autosomal dominant neurodegenerative disease that usually manifests in adults and results in motor, cognitive and psychiatric symptoms. Estimates account for around 3.6 to 5.7 per 100,000 in regions mainly composed of Caucasian descendants[6]. HD originates from an excessive number of abnormal repeats of the trinucleotide cytosine-adenosine-guanine on the *IT15* gene on chromosome 4, encoding a protein called huntingtin[7].

MDD is a behavioral disorder that has a preponderant burden on individuals and society. Depressive states might develop as symptoms of other conditions, such as AD and PD[8]. Depression disorders are among the most prevalent forms of mental illness. The number of incident cases of depression worldwide increased from 172 million in 1990 to 258.16 million in 2017[9]. Depression is associated with sadness, lack of appetite, suicidal tendency, fatigue, social abstinence, and loss of interest in almost all activities.

The global population with anxiety disorders in 2015 was estimated to be 264 million people. Anxiety disorders are characterized by feelings of anxiety and fear and include pathologies such as generalized anxiety disorder, panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder[10].

Overlapping mechanisms, such as oxidative/nitrosative stresses, neuroinflammation, protein aggregation, and decreased neurotransmitter levels, complicate patient treatment.

The most well-documented mechanisms implicated in neurodegeneration/neuropsychiatric disorders are summarized in Fig. 1: (1) neurotransmitter system imbalance (such as cholinergic, monoaminergic, glutamatergic, GABAergic and endocannabinoid); (2) protein aggregation toxicity due to amyloid-β (Aβ) oligomers and plaques, Tau hyperphosphorylation, α-synuclein aggregation into Lewis bodies and mutant huntingtin protein; (3) oxidative stress-induced neuroinflammation and apoptosis. All the mechanisms possess different effects on cognition, motor capability, and general mood, wether it be by neuronal death (protein aggregation and oxidative stress) or stimulation blockage (neurotransmitter imbalance).

2. Chinese medicinal plants

There is a wide variety of molecular structures in nature that are essential for the development of new effective drugs against several diseases. Natural products play decisive roles in the

development of new drugs and can serve as skeletons for other synthetic molecules. In the development of new drugs, the great diversity of molecular skeletons is essential for the greater identification of unexplored macromolecular targets, allowing the possible identification of new prototypes of drugs with different modes of action[11].

The use of medicinal plants has a long history of clinical use, better tolerance, and, they have gained considerable interest in the treatment of neurodegenerative/neuropsychiatric diseases because of their therapeutic potential. However, these natural products can have some adverse effects such as allergies and hepatotoxicity[12].

Therefore, this review aims to demonstrate the role of plant extracts and their constituents in the discovery of new therapies to combat neurodegenerative and neuropsychiatric diseases, since they present a burden to the society due to the lack of appropriate therapies. For that, 21 plant species and one fungus were chosen and 260 original papers published between 2002 and 2022 were selected from databases based on the following keywords and their combination: "*Scutellaria baicalensis*", "*Ginkgo biloba*", "*Camellia sinensis*", "*Panax ginseng*", "*Glycyrrhiza glabra*", "*Curcuma longa*", "*Mucuna pruriens*", "*Gastrodia elata*", "*Paeonia lactiflora*", "*Centella asiatica*", "*Huperzia serrata*", "*Polygala tenuifolia*", "*Taraxacum officinale*", "*Bambusa vulgaris*", "*Cannabis sativa*", "*Coix lachryma-jobi*", "*Portucala oleracea*", "*Crataegus pinnatifida*", "*Gardenia jasminoides*", "*Poria cocos*", "*Citrus maxima*", "neurodegenerative disorders", "neuroinflammation", oxidative stress", "Alzheimer's disease", Parkinson's disease", "depression", anxiety", "Huntington's disease", "enzyme inhibition" and "brain receptors" (Fig. 2).

The structures of the bioactive compounds mentioned in Supporting Information Tables S1−S21 and Table 1 are shown in Supporting information Figs. S1 (phenolic acids and derivatives), S2 (flavonoids and bioflavonoids), S3 (other phenolic compounds), S4 (terpenoids), S5 (sterols), and S6 (other compounds).

2.1. *Scutellaria baicalensis Georgi*

S. baicalensis Georgi is a species belonging to the Lamiaceae family. The dried root has been used as a medicinal plant for a long time. It has been applied in the treatment of diarrhea, dysentery, hypertension, inflammation, respiratory infections, and neurodegenerative diseases[13]. The most characteristic compounds described in this plant species are baicalin, baicalein, wogonin and wogonoside (Table S1).

Recently, studies focusing on AD showed that an aqueous extract displayed moderate AChE inhibition (IC_{50} = 799.3 μg/mL)[14], and an ethanolic extract induced protection against oxidative damage and neuroinflammation by decreasing the levels of the expression of nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), and prostaglandin E2 in BV-2 and RAW 246.7 cells[15].

Regarding its constituents, baicalin is a flavonoid that promotes neural differentiation but inhibited glial formation in embryonic neural stem/progenitor cells (NPCs) from the cortex of E15-16 rats by regulating the expression of signal transducer and activator of transcription 3 (STAT3) and basic helix−loop−helix (bHLH)[16]. In the same study, it was also shown that due to the ability to cross the blood−brain barrier (BBB), baicalin can be developed as a therapeutic agent to promote neurogenesis[16].

Treatment with baicalein (Fig. 3) in isolated rat brain mitochondria promoted mitochondrial active respiration and prevented the production of reactive oxygen species (ROS), deficiency of ATP, and swelling of isolated brain mitochondria, thus reducing oxidative stress[17]. Furthermore, baicalein was also studied for its neuroprotective activity in 6-hydroxydopamine (6-OHDA)-induced cellular and animal models of experimental parkinsonism. Baicalein at 0.5 and 5 μg/mL promoted neurite outgrowth in rat pheochromocytoma cell line (PC12), which is derived from a rat pheochromocytoma tumor and has many properties similar to dopaminergic neurons, and significantly attenuated the 6-OHDA-induced cell apoptosis in SH-SY5Y cells. The neuroblastoma SH-SY5Y cell line is dopaminergic and is widely used in studies of neurodegenerative diseases[18].

In *in vivo* experiments, treatment with baicalein at 100−400 mg/kg (i.g.) significantly attenuated muscle tremor, mitigated astroglial response, and increased tyrosine-hydroxylase (TH) in the substantia nigra in 6-OHDA-lesioned rats. These results indicated that baicalein can increase the number of dopaminergic neurons, in part, caused by baicalein's anti-apoptotic, pro-differentiation and anti-inflammatory mechanisms[18]. In a similar research, baicalein was shown to improve spontaneous motor activity and rotarod performance in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP is a prodrug of the neurotoxin MPP^+, which causes permanent symptoms of PD and destroys dopaminergic neurons in the substantia nigra of the brain. Pretreatment with baicalein (200 mg/kg, i.g.) in a model of MPTP-induced loss of dopaminergic fibers in mice increased the levels of dopamine and serotonin in the striatum and inhibited both the oxidative stress and the astroglial response[19]. These results suggested that baicalein could protect dopaminergic neurons against MPTP-induced toxicity.

Moreover, baicalein in a dose-dependent manner was found to inhibit the oligomerization and decreased fibrillization of α-synuclein protein *in vitro* and in cellular systems. It inhibited the formation of α-synuclein oligomers in HeLa and SH-SY5Y cell lines and protected SH-SY5Y cells from α-synuclein oligomer-induced toxicity[20].

These results highlight the value of bioactive compounds from *S. baicalensis*, mainly baicalin and baicalein (Table S1)[21], as a valuable source of new drugs for the treatment of PD and other neurodegenerative diseases.

2.2. *Ginkgo biloba L.*

G. biloba L. (Ginkgoaceae family) is regarded as being one of, if not the oldest tree in the world, existing uninterruptedly for over 270 million years. The extract has beneficial properties for the treatment of several pathologies, like diabetic cardiomyopathy, neurodegenerative diseases, cataracts, hearing loss, myocardial lesion, hippocampus neuronal lesions, morphometry testicular changes, and liver damage[22].

One of the most commercially available forms of the extract is EGb 761, a standardized *G. biloba* leaves extract, whose combination of flavonoid and triterpenoid composition (24% and 6%, respectively) has been evidenced to promote free radical scavenging, neurotransmitter release, synaptic plasticity, as well as counteracting memory impairment[23,24].

Besides flavonoids, other compounds of *G. biloba* with neuroprotective effects are the terpenoids ginkgolides (ginkgolides A, B, C, J, K, L, and M) and bilobalide (Fig. 3, Table S2). Ginkgolides have been shown to protect cells from oxidative stress, improve cell viability, inhibit cell apoptosis and attenuate microglia activation, decreasing neuroinflammation. Bilobalide restores

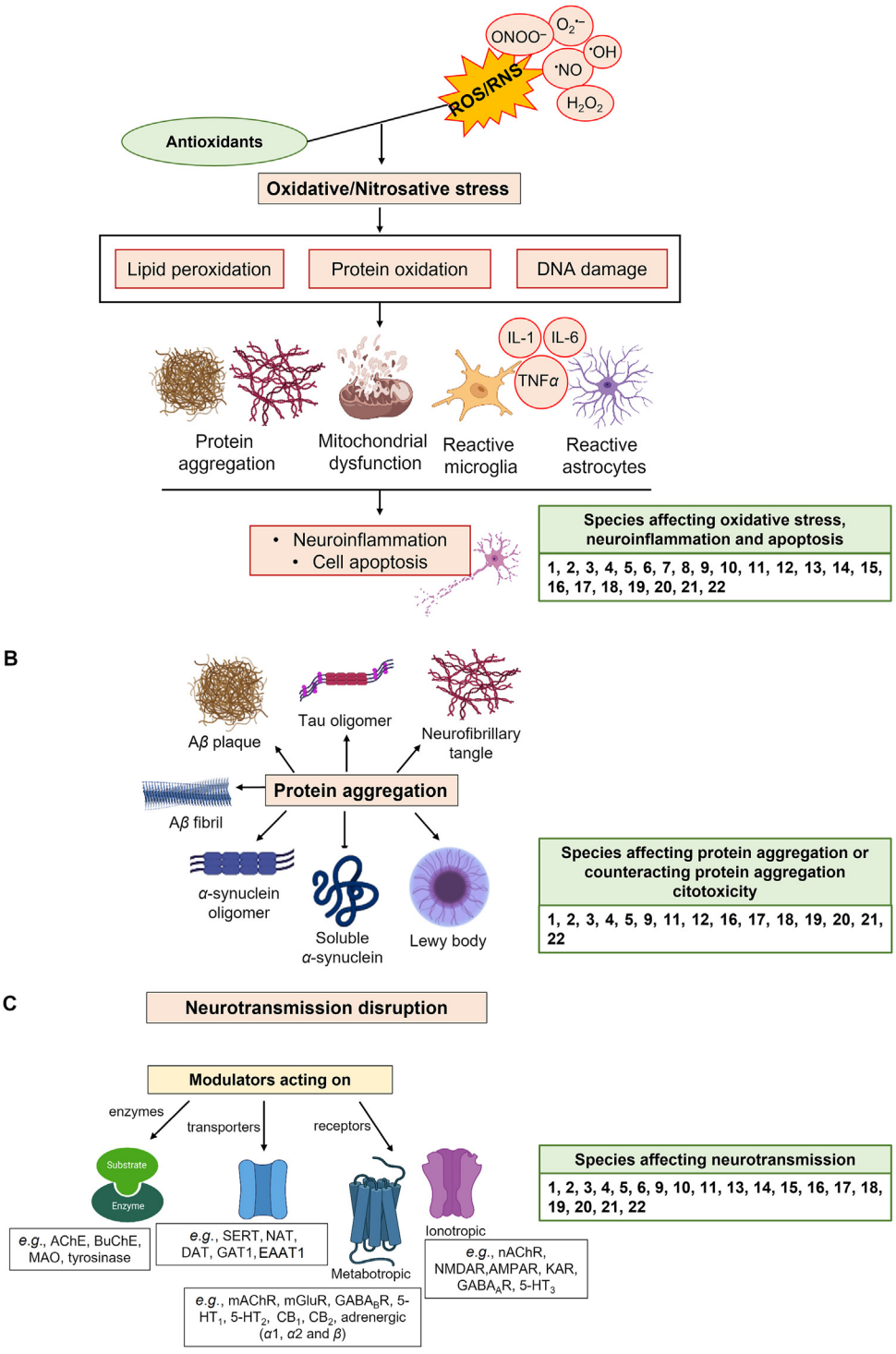

Figure 1 Neurodegeneration mechanisms of the reviewed Chinese medicinal plants: oxidative stress-induced neuroinflammation and apoptosis, protein aggregation toxicity and neurotransmitter system imbalance. ROS, reactive oxygen species; RNS, reactive nitrogen species; $ONOO^-$, peroxynitrite; $O_2^{\bullet-}$, superoxide anion radical; •NO, nitric oxide; •OH, hydroxyl radical; H_2O_2, hydrogen peroxide; IL, interleukin; Aβ, amyloid beta; AChE, acetylcholinesterase; BuChE, butyrylcholinesterase; MAO, monoamine oxidase; SERT, serotonin transporter; NAT, noradrenaline transporter; DAT, dopamine transporter; GAT1, GABA transporter; EAAT1, glutamate transporter; mAChR, metabotropic acetylcholine receptor; mGluR, metabotropic glutamate receptor; $GABA_AR$, metabotropic GABA receptors; 5-HT_1 and 5-HT_2, metabotropic serotonin receptors; CB1 and CB2, cannabinoid receptors; α1, α2 and β, metabotropic adrenergic receptors; nAChR, ionotropic acetylcholine receptor; NMDAR, *N*-methyl-D-aspartate receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; KAR, kainate receptors; 5-HT_3, ionotropic serotonin receptors; species 1−22, 21 medicinal plants and one fungus discussed in Section 2.

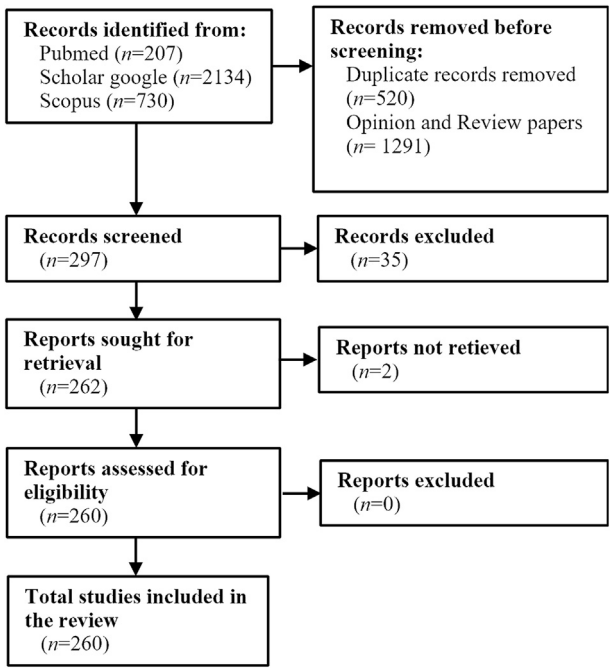

Figure 2 PRISMA flow diagram representing the original papers included in Section 2 "Chinese medicinal plants".

neurological function, increases antioxidant activity, inhibits apoptosis and reduces the production of cytokines such as TNF-α and IL-1β[25,26]. Naik et al.[27] have shown the capacity of *G. biloba* phytosomes (50 and 100 mg/kg) to increase superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase activities in cerebral cortex, cerebellum, hippocampus and striatum of Wistar rats. Another study indicated that the administration of EGb 761 to rats, at 100 mg/kg (i.p.) for 15 days, also had a neuroprotective role in HD, since it improved the 3-nitropropionic acid (3-NP)-induced neurobehavioral deficits and decreased the level of striatal malondialdehyde[28].

Concerning the anti-AD properties of this species, Ding et al.[29] evaluated AChE inhibition activities of 15 compounds isolated from the 80% methanolic extracts of *G. biloba* leaves. Fifteen compounds (13 flavonoids and 2 ginkgolides) were then isolated in a silica gel chromatography column. *G. biloba* leaf extract had moderate AChE inhibitory activity, with an IC_{50} = 252.1 μg/mL, while ginkgolides did not influence AChE activity. Quercetin-3-*O*-glucoside exhibited the strongest inhibitory activity, with an associated IC_{50} of 57.8 μg/mL.

EGb 761 has also beneficial effects in protecting neurons from toxicity of Aβ oligomerization *in vitro* and improving cognitive defects *in vivo*. In double transgenic mice expressing human mutant amyloid-beta precursor protein (APP) and presenilin-1 (PS1) (TgAPP/PS1 model), EGb 761 significantly increased cell proliferation in the hippocampus, which may be mediated by activation of cellular transcription factor cAMP response element-binding protein (CREB)[23]. Similarly, in another study[30] mouse N2a neuroblastoma cells of wild-type mice (control group) and APP/PS1 transgenic mice (test group) were cultured for 48 h with 100 μg/mL EGb 761 for an immunoblotting Aβ aggregation procedure. In addition, a cell-free *in vitro* assay was also conducted to evaluate the Aβ fibrillization suppression effects of EGb 761 and of bilobalide and ginkgolides A, B, C, and J. Transgenic cells expressed greater amounts of Aβ when compared with the control group, and EGb 761 was able to suppress the peptide aggregation. For the cell-free *in vitro* assay, the authors reported that 100 μg/mL of EGb 761 and 29 μg/mL bilobalide and ginkgolides A, B, C, and J inhibited Aβ aggregation by 82%, 73%, 35%, 20%, 42%, and 72%, respectively.

Zeng et al.[31] reported that EGb 761 also demonstrates neuroprotective effects against AD by attenuating the neurodegenerative effects induced by hyperphosphorylated tau protein. Sprague−Dawley mice were injected with 400 μg/kg/day doses of homocysteine and were compared with the control groups (saline). In the behavioral tests (open-field and Morris water maze tests), treatment with EGb 761 did not significantly alter the traveled distance in the box; however, it significantly reduced the escape latency time in the Morris water maze test. EGb 761 attenuated tau hyperphosphorylation induced by homocysteine, through activation of protein phosphatase 2 (PP2A) and inhibition of glycogen synthase kinase-3β (GSK-3β).

Regarding PD, Kuang et al.[32] evaluated the effects of *G. biloba* leaves on A57T mutant α-synuclein mice. Mice were divided into five groups: one saline control, three test groups that were administered different doses of *G. biloba* leaves (20−60 mg/kg), and a group treated with 75 mg/kg Madopa, for 21 days. After the administration period ended, the mice were subjected to a forced swimming test, a horizontal wire test, and a pole test. The mice were then sacrificed and *subtantia nigra* and striatum were dissected, cultured, and incubated with rabbit DAT-antibody for an immunochemistry assay to detect tyrosine hydroxylase and dopamine transporters expressing neurons. The administration of the highest dose of *G. biloba* leaves (60 mg/kg) exerted the best effects in the behavioral tests. For the immunochemistry assay, the results evidenced increased expression of both tyrosine hydroxylase and dopamine transporters, in a dose-dependent manner.

Shu et al.[33] investigated the potential tyrosinase inhibitory activity of 12 compounds isolated from *G. biloba* leaves. Ginkgolide B, 2-(3,4-dihydroxyphenyl) ethyl 3-*O*-β-D-glucopyranosyl-β-D-glucopyranoside, methyl hesperidin, cytidine, and genistin, moderately inhibited tyrosinase at a rate of 19.12%, 25.79%, 16.07%, 24.46%, and 18.64% (at 25 μmol/L), respectively.

G. biloba also affects other neurotransmitter systems, such as the glutamatergic, GABAergic and cannabinoid ones. One study investigated the effects of treating Sprague−Dawley mice hippocampal slices with micrometer and nanometer *G. biloba* leaf particle extracts, to evaluate their effects on the glutamatergic system. The results indicated that micrometer and nanometer *G. biloba* leaf particle extracts antagonized *N*-methyl-D-aspartate (NMDA) receptors, corresponding to IC_{50} of 21−26 μg/mL, respectively[30]. In addition, Ivic et al.[31] reported that treatment of test samples containing 30 μmol/L of $GABA_A$ receptors with 50 μmol/L of ginkgolide B and bilobalide was able to inhibit receptor activity at a rate of 63% and 46.8%, respectively. *G. biloba* has been evidenced to suppress the tetrahydrocannabinol (THC) effects on both short-term memory loss and reduced motor coordination. Abdel-Salam et al.[34] administered specific doses of different drugs, including 25 mg/kg of *G. biloba*, to different mice groups, already treated with 5−20 mg/kg doses of *C. sativa*, for one month. Then, the mice were subjected to a water maze test, with an escape glass platform hidden from sight. The group solely treated to 20 mg/kg *C. sativa* showed higher escape latency than the other groups, however, the group treated with *G. biloba* discovered the glass platform faster.

Table 1 Clinical trials conducted with plants species and compounds used in TCM to assess their neuroprotective potential.

ClinicalTrials.gov identifier	Title	Condition/disease	Plant preparation/plant species/compound	Number of participants	Starting date
NCT04846010	Recovering damaged cells for sequelae caused by COVID-19, SARS-CoV-2 (sequelae)	Several sequelae from COVID infection including anxiety, depression and post-infectious Parkinsonism	Several plant preparations. PurWet includes Poria and Glycyrrhizae Radix, among others; PurClo contains Curcumae Radix, among others; PurInf contains Scutellariae Radix and Gardeniae Fructus, among others; Smoliv includes Curcumae Radix and Paeoniae Radix rubra, among others	2000	March 2021
NCT03090516	Clinical efficacy of *Ginkgo Biloba* extract in the treatment of Alzheimer's disease	Alzheimer's disease	*Ginkgo biloba* dispersible tablets	240	August 2016
NCT00164749	A pilot study of curcumin and ginkgo for treating Alzheimer's disease	Alzheimer's disease	Curcumin and ginkgo extract	36	October 2004
NCT00010803	*Ginkgo biloba* prevention trial in older individuals	Dementia/Alzheimer's disease	*Ginkgo biloba*	3069	October 2000
NCT00814346	Effect of EGb761® on brain glucose metabolism in three groups of elderly defined by cognitive functions	Alzheimer's disease/ Cognitive impairment	EGb761®	49	October 2008
NCT00276510	A study of EGb 761® (Tanakan®) in dementia of Alzheimer type onset in patients suffering from memory complaints	Memory disorders, age-related/Retention disorders, cognitive	EGb 761® (Tanakan®)	2878	February 2002
NCT00042172	Treatment for early memory loss	Cognition disorders/ Alzheimer disease	*Ginkgo biloba* extract	40	June 2002
NCT01009476	Long-term use of galantamine *versus* nootropics (memory enhancing drugs) in patients with Alzheimer's dementia under conditions of daily routine	Dementia/Alzheimer disease/dementia, vascular	Nootropics (*Ginkgo biloba*, nicergoline, piracetam, or others)	1134	March 2006
NCT01416818	Treatment of depression in Parkinson's disease	Depression in Parkinson's disease	Bupleurum + Ginkgo	60	May 2008
NCT04279418	Non-pharmacological intervention for preclinical Alzheimer's disease	Alzheimer disease/ cognitive decline	Functional foods with main compositions of ginsenoside, green tea polyphenols and marine collagen peptide	60	April 2019
NCT00461942	Efficacy and safety of Green Tea polyphenol in *de novo* Parkinson's disease patients	Parkinson's disease	Green tea polyphenols (EGCG/ECG)	480	April 2006
NCT00391833	Effect of *Panax ginseng* on the cognitive performance in Alzheimer's disease	Alzheimer's disease/ memory decline	*Panax ginseng*	−	April 2004
NCT03221894	A retrospective study to investigate the additive effectiveness of Chinese herbal medicine in Alzheimer's disease	Alzheimer's disease	GRAPE granules containing Ginseng, *Polygala tenuifolia*, *Curcuma aromatica*, *Gastrodia elata*, among others	120	July 2017

(*continued on next page*)

Table 1 (*continued*)

ClinicalTrials.gov identifier	Title	Condition/disease	Plant preparation/plant species/compound	Number of participants	Starting date
NCT01496248	Efficacy study of Korean red ginseng to treat depression	Major depressive disorder	Korean red ginseng	35	August 2011
NCT01006460	A study with arctic root compared with the extract when combined with schizandra and russian root (adapt 232), standardized ginseng extract and placebo regarding impact on the level of energy, ability to work under stress, quality of life and wellbeing, in middle aged women who are still employed	Depression/stress	*Rhodiola rosea*, compared with *Rhodiola rosea* + *Eleutherococcus senticosus* + *Schisandra chinensis* compared with *Panax ginseng*	200	November 2009
NCT05570110	Enoxolone in major depression-biomarker-outcome relationship	Unipolar depression	Enoxolone (pentacyclic triterpenoid aglycone metabolite of glycyrrhizin)	60	September 2022
NCT01811381	Curcumin and yoga therapy for those at risk for Alzheimer's disease	Mild cognitive impairment	Curcumin	80	January 2014
NCT00099710	Curcumin in patients with mild to moderate Alzheimer's disease	Alzheimer's disease	Curcumin C3 complex	33	July 2003
NCT01022632	Effect of curcumin as nutraceutical in patients of depression	Major depressive disorder	Curcumin and curcumin + fluoxetine	60	March 2009
NCT04744545	RCT of adjunctive curcumin and the Meru Health Program	Depression	Curcumin	60	February 2021
NCT01875822	Open-label study of curcumin C-3 complex in schizophrenia	Schizophrenia/ Schizoaffective disorder/ depression	Dietary supplement: super-curcumin	17	June 2009
NCT05518019	An exploratory investigation of a CBD supplement's impact on sleep, stress, and focus	Anxiety/fear/stress/low mood/sleep	Organic broad spectrum Hemp extract 35 mg Bio-Terpene Complex 52 mg palm monoglycerides organic Hemp seed oil, clove bud oil, black pepper berry essential oil curcumin (turmeric root) essential oil	36	February 2022
NCT02680977	*Mucuna pruriens* therapy in Parkinson's disease	Parkinson's disease	*Mucuna pruriens*	18	February 2016
NCT00297245	Gastrodin prevents cognitive decline related to cardiopulmonary bypass	Cognitive decline	Gastrodin	200	February 2006
NCT03937908	Pharmacokinetics *Centella asiatica* product (CAP) in mild cognitive impairment	Cognitive impairment/ elderly	*Centella asiatica* water extract product	5	October 2019
NCT05591027	Safety and target engagement of *Centella asiatica* in cognitive impairment	Mild cognitive impairment/Alzheimer's disease	*Centella asiatica*	48	November 2022
NCT01012830	Huperzine-A to help with mental problems and the inability to care for onself in patients with schizophrenia	Schizophrenia/dementia	Huperzine A	15	December 2009

Table 1 (*continued*)

ClinicalTrials.gov identifier	Title	Condition/disease	Plant preparation/plant species/compound	Number of participants	Starting date
NCT03833206	A phase I/II study of PDC-1421 for treating depression in cancer patients	Major depressive disorder	PDC-1421 capsule is a botanical investigational new drug containing the extract of Radix Polygalae (*Polygala tenuifolia*) as active ingredient	12	October 2022
NCT02699086	A study of PDC-1421 treatment in adult patients with attention-deficit hyperactivity disorder (ADHD)	Attention-deficit hyperactivity disorder (ADHD)	PDC-1421 capsule	6	December 2019
NCT05202327	PDC-1421 treatment in adult patients with ADHD	Attention-deficit hyperactivity disorder (ADHD)	PDC-1421 capsule	99	April 2022
NCT02395978	A phase II study of PDC-1421 capsule to evaluate the safety and efficacy in patients with major depressive disorder	Major depressive disorder	PDC-1421 capsule	72	April 2015
NCT02752867	An fMRI study of Jianpi Yishen Huatan granules for cognitive impairment after acute cerebral infarction	Cognitive impairment	Jianpi Yishen Huatan granules containing *Polygala tenuifolia*, among others	40	December 2016
NCT02641886	The study of Jian Pi Yi Shen Hua Tan granules in cognitive impairment after acute cerebral infarction	Cognitive impairment	Jianpi Yishen Huatan granules containing *Polygala tenuifolia*, among others	300	March 2016
NCT01608217	Delta-THC in dementia	Behavioral disturbances/ pain/dementia/ Alzheimer's dementia/ vascular dementia	delta-9-Tetrahydrocannabinol	50	June 2012
NCT04075435	Cannabidiol solution for the treatment of behavioral symptoms in older adults with Alzheimer's dementia (CBD)	Alzheimer disease/ anxiety/agitation, psychomotor	High CBD/low THC sublingual solution	12	January 2021

The antidepressant activity of *G. biloba* is also recognized. The administration of the lipophilic extracts of *G. biloba* at 50 and 100 mg/kg (*p.o.*) in mice showed antidepressant activity since there was a decrease in the time of immobility in the behavioral despair test and in the number of escape failures. The activities were comparable to that of imipramine (15 mg/kg), a tricyclic antidepressant, and EGb 761 (50 mg/kg)[35]. In a related study, pretreatment with EGb 761 at 50 mg/kg (i.g.) for 14 days reversed depressive-like symptoms on lipopolysaccharide (LPS)-induced anhedonia in male rats, which might be associated with its MAO-B inhibitor property[24].

G. biloba is widely incorporated in supplements containing *P. ginseng*[36]. It was reported by Liang et al.[37] that the extracts of *G. biloba* are able of increasing the brain's ability to uptake ginsenosides. Kunming and Sprague−Dawley mice were randomly administered either with single doses *of P. ginseng* extract (500 mg/kg) or *P. ginseng* + *G. biloba* extracts (500 mg/kg + 400 mg/kg). Subsequently, the mice were sacrificed, and their brains were dissected to evaluate the presence of ginsenosides in the brain. Compared to the control sample, *G. biloba* extracts increased the uptake of ginsenosides Rg1, Re, Rd, and Rb1 by 12, 6, 5, and 6.5-fold, respectively.

2.3. *Camellia sinensis (L.) Kuntze*

Green tea (*C. sinensis* (L.) Kuntze, Theaceae family) is one of the most popular teas and the most widely consumed drink after water. Green tea possesses high levels of antioxidants and is used for its antiaging and neuroprotective effects, alongside treating or preventing several diseases such as cancer, cardiovascular conditions, obesity, and others[38].

C. sinensis is commercialized as green tea (unfermented), oolong tea (semi-fermented), and black tea (fully fermented). There is evidence that the concentration of catechins ((−)-epicatechin, (−)-epicatechin-3-*O*-gallate, (−)-epigallocatechin, and (−)-epigallocatechin-3-*O*-gallate, EGCG) (Fig. 3, Table S3) originally found in the leaves decreases with increasing degree of fermentation. In contrast, the leaves that are subjected to longer

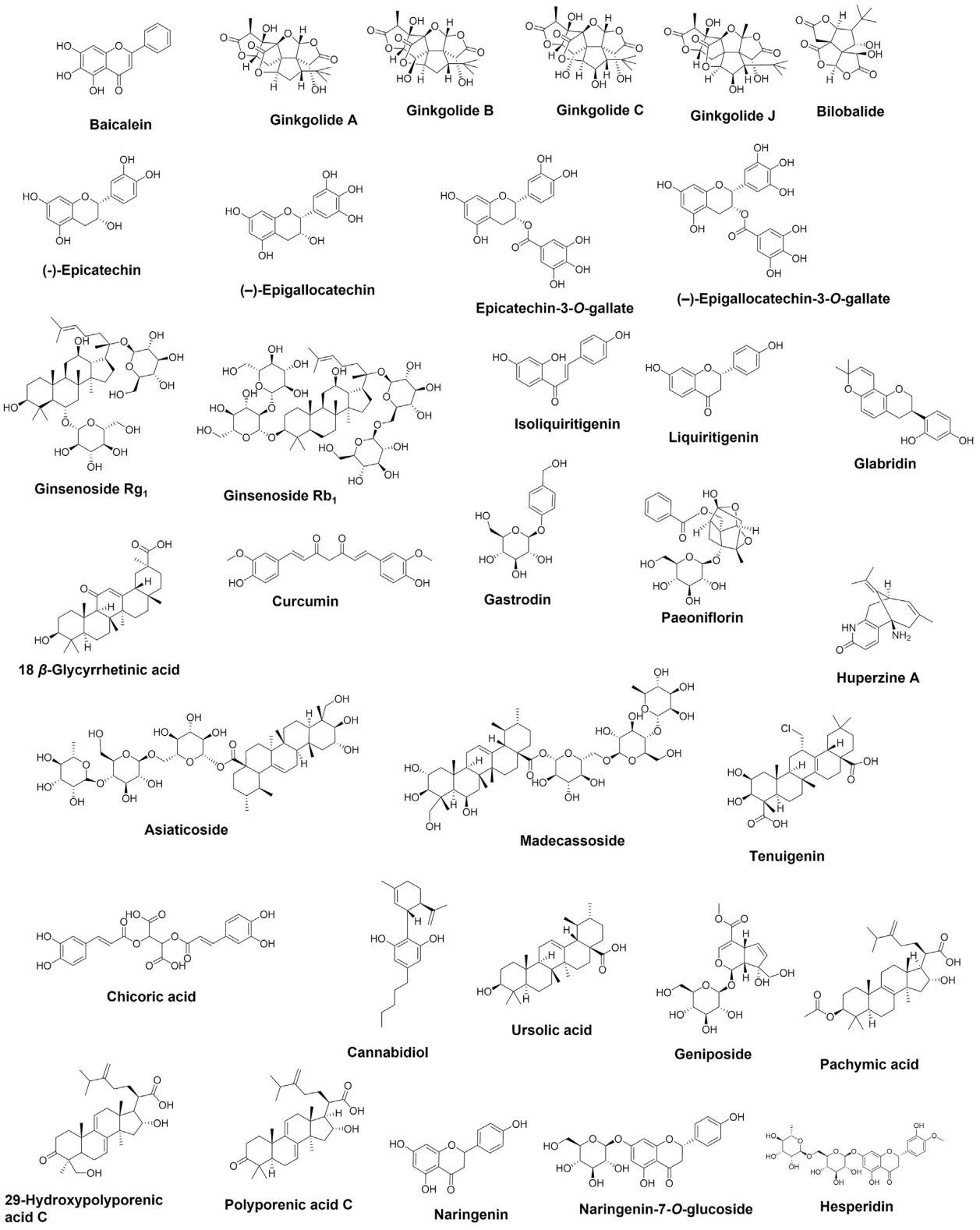

Figure 3 Neuroprotective compounds present in the 20 Chinese medicinal plants and one fungus reviewed in Section 2.

fermentation periods are richer in theaflavins (Table S3) and thearubigins[39].

High consumption of green tea was associated with a decreased prevalence of cognitive impairment and decreased risk of neurodegenerative diseases[40] as well as with an increase of the antioxidant defenses. Concerning the antioxidant activity, Nakagawa and Yokozawa[41] tested the free radical scavenging effects of green tea extract and green tea tannin mixture (composed by

EGCG (18.0%), (−)-gallocatechin-3-*O*-gallate (11.6%), epicatechin-3-*O*-gallate (4.6%), (−)-epigallocatechin (15.0%), (+)-gallocatechin (14.8%), (−)-epicatechin (7.0%) and catechin (3.5%)) and its components against $O_2^{\bullet -}$ and •NO. Green tea extract directly scavenged both radicals but green tea tannin mixture, at the same concentration, showed higher scavenging activity. By comparing the activities of seven pure compounds isolated from green tea tannin mixture, the results demonstrated that EGCG, (−)-gallocatechin-3-*O*-gallate and (−)-epicatechin-3-*O*-gallate were more active than (−)-epigallocatechin, (+)-gallocatechin, (−)-epicatechin and (+)-catechin, showing the importance of the structure of flavan-3-ol linked to gallic acid for this activity. Moreover, Xu et al.[42] studied the influence of the fermentation process on the antioxidant activity. While in *in vitro* •NO scavenging assay all three tea samples (green tea, black tea and Pu-erh tea) exhibited similar activities (30%−40% at a concentration of 1000 μg/mL, respectively), green tea (125 μg/mL), among the three teas, showed the best inhibition of ROS formation in Raw 264.7 cells exposed to H_2O_2. On the other hand, Pu-erh tea was the most effective in inhibiting •NO production in LPS-activated Raw 264.7 cells. These authors also investigated the role of catechins, theabrownins and caffeine against ROS and •NO. They concluded that all components in tea showed the same effect as •NO scavengers; catechins had a better effect on scavenging intracellular free radical than more polymerized theabrownins and caffeine, but none of the classes of compounds alone was able to suppress intracellular •NO production. Nonetheless, caffeine also contributes to the neuroprotective effect of *C. sinensis*, since it possesses other properties including its ability to inhibit AChE[43] and tyrosinase[44], as well as, to selectively scavenge •HO radicals[45].

C. sinensis and its components have been shown to inhibit several brain enzymes. Ray and De[46] carried out a study in which AChE extracted from 3−4-week-old mice brains were treated with infusions and decoctions prepared from different varieties of black tea. The results noted that all aqueous extracts exerted anti-AChE activity, with one black tea decoction sample having an IC_{50} value of 30.49 μg/mL. *C. sinensis* has also been evidenced to inhibit MAO-B showing its protective effect against PD. In particular, EGCG was found to simultaneously inhibits MAO-B and boasts antioxidant activity[47,48]. *C. sinensis* is also known to regulate the activity of brain tyrosinase. Black tea has been reported to possess a strong inhibitory effect against tyrosinases, mostly due to the presence of theaflavins. Kim et al.[49] showed that white, green, and black tea water extracts reduced the activity of tyrosinase in the cells in a dose-dependent manner. Black tea also affects the accumulation of neuromelanin[49].

EGCG can modulate the accumulation of proteins like huntingtin, Aβ, and α-synuclein[50]. EGCG at 1.5 and 3 mg/kg (*p.o.*) was shown to have neuroprotective effects against systemic LPS-induced memory-deficiency-like behavior in mice. The administration of this flavonoid prevented the loss of memory, and decreased cellular apoptosis and microglial activation[51]. In a similar study transgenic mouse model, which expresses APP, was orally fed with EGCG at 2 and 6 mg/kg and showed a significant reduction in the expression of APP and Aβ in the hippocampus of mice[52]. In addition, Rho et al.[53] conducted a thioflavin-T fluorescence assay to determine the inhibitory rates of isolated compounds. The results showed that EGCG, (−)-epicatechin-3-*O*-gallate, and (−)-catechin-3-*O*-gallate exerted the lowest fluorescence values (78.0, 62.8, and 46.4%, respectively), meaning that these catechins had the highest inhibitory rate on Aβ aggregation.

Chesser et al.[54] evaluated the effects of EGCG extracted from *C. sinensis* on the potential amelioration of neurodegenerative conditions mediated by tau protein. Three tauopathy epitope (p-S396/404, p-S262, and p-T231) samples of cortical Sprague−Dawley mice embryo neurons were isolated, cultured, and treated with 25 μmol/L and 50 μmol/L of EGCG, followed by 24 h incubation and subsequent tau level measurement. EGCG (50 μmol/L) reduced the phosphorylated tau levels of around 60% (p-S396/404 and p-S262 epitopes) and 80% (p-T231 epitope).

Green tea also affects GABAergic, glutamatergic and cannabinoid systems. Wang et al.[55] evaluated the stimulating potential of green tea extracts by conducting an assay where Xenopus cells were treated with (−)-epicatechin and EGCG to determine the inhibitory effects of the tea catechins on GAT1 (GABA transporter) and EAAT1 (glutamate transporter). Results indicated that (−)-epicatechin did not register significant inhibition for GAT1, while EGCG revealed a 50% inhibition rate at around 100 μmol/L. For EAAT1, (−)-epicatechin showed an $IC_{50} \approx 5$ μmol/L, while EGCG did not register any effects. Moreover, Kakuda et al.[56] evaluated the possible inhibitory effects of L-theanine, an important amino acid found in *C. sinensis*, on glutamate receptors α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and NMDA by treating Wistar mice cortical membrane samples with 1 μmol/L of L-theanine and L-glutamic acid. L-Theanine exhibited IC_{50} values of 24.6, 41.5, and 347 μmol/L, for AMPA, kainate, and NMDA receptors, respectively. However, Theanine bound the three receptors, but its IC_{50} values were 80- to 30,000-fold lower than that of L-glutamic acid.

Korte et al.[57] evidenced that green tea catechins exerted a modest endocannabinoid system modulatory activity. Recombinant human cells containing CB1 and CB2 receptors were treated with 10 μL of EGCG, (−)-epigallocatechin, and (−)-epicatechin-3-*O*-gallate. Results indicated that the inhibition constant for CB1 was overall inferior to that registered for CB2 receptors. This suggests that *C. sinensis* catechins have a more predominant effect on the CNS cannabinoid system than in the PNS.

Grelle et al.[58] showed the effects of *C. sinensis* theaflavins against the neurotoxic effects of α-synuclein. A 50 μmol/L aqueous solution of monomeric α-synuclein was mixed with different solutions (5 mmol/L) of theaflavin, theaflavin-3-monogallate, theaflavin-3′-monogallate and theaflavin-3,3′-digallate. Results showed that the control sample formed α-synuclein fibrils, whereas theaflavins suppressed fibrilization. The positive effect of theaflavins on brain was also pointed out by Anandhan et al.[59,60]. *In vivo* studies have shown that theaflavins (Table S3) (5−20 mg/kg, *p.o.*, for seven days), reduced oxidative stress, motor deficits and increased the expression of dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) in mice nervous system[59]. Another study also showed that treatment with theaflavin (10 mg/kg, *p.o.*) decreases cell apoptosis and increases dopamine levels, given that there is an increase in tyrosine hydroxylase (TH)[60].

2.4. *Panax ginseng C.A. Meyer*

Commercial ginseng originates from the roots of *P. ginseng* C.A. Meyer (Araliaceae family) and has been used as a medication for thousands of years in East Asian countries, such as Japan, China, and Korea[61]. Ginseng is widely used for its anti-aging, anti-diabetic, immunoregulatory, anti-cancer, neuroregulation, wound and ulcer healing activities, among others[62].

The protective effect of ginseng is mainly due to the role of more than 180 ginsenosides (Table S4). These compounds also have pharmacological effects on the CNS, being able to strengthen brain function, prevent neuroinflammation and oxidative stress, modulate nerve growth factors expression, and reduce or weaken a variety of neurodegenerative disorders[62].

Regarding oxidative stress protection, *P. ginseng* extracts have been indicated as possessing modest antioxidant activity. Kim et al.[63] have shown the potential of aqueous *P. ginseng* extracts in scavenging $O_2^{\bullet -}$, •OH, •NO, DPPH, and carbon radicals. The results were the following: a 2 mg/mL extract sample completely scavenged DPPH•; 0.5 mg/mL quenched 80% of all carbon-free radicals; at 0.1 mg/mL, around 40% of total •OH radicals were scavenged; at 2 mg/mL, $O_2^{\bullet -}$ was completely scavenged; the extract was documented to possess no •NO scavenging activity.

The neuroprotective potential of ginseng extracts and ginsenosides against AD, PD, HD and depression have been extensively studied. For instance, black, red and white ginseng displayed IC_{50} values of 1.72, 6.30 and 5.89 mg/mL against AChE and 1.88, 1.84 and 2.56 mg/mL against BuChE, respectively[64]. Moreover, Cao et al.[65] evidenced that 200 μmol/L of ginsenoside Re inhibited Aβ production by 26.82% by inhibiting β-secretase in N2a/APP695 cells. Fang et al.[66] administered 10 mg/kg Rg1 samples to transgenic AD mice overexpressing APP/Aβ for three months. The authors found that this compound improved Aβ pathology, modulated the APP process, and improved cognition levels. The anti-AD effects of *P. ginseng* also expand to the neurodegenerative impact of tau protein, specifically to the toxic effects of its aggregation. An aqueous extract of Korean red ginseng (10−500 μg/mL) has been evidenced to both inhibit recombinant K_{18} tau fragment aggregation (IC_{50} = 545 μg/mL) and dissociation (IC_{50} = 713 μg/mL)[67]. Among the Korean red ginseng fractions, the rich polysaccharide fraction was the most potent to inhibit tau aggregation (IC_{50} = 179.3 μg/mL), while the saponin fraction was the most effective on aggregated tau dissociation (DC_{50} = 100.2 μg/mL)[67].

Recent *in vivo* and *in vitro* studies also investigated the potential of Rb1 and Rg1 (Fig. 3) to treat PD. Rb1 was shown to enhance cell viability and reduce apoptosis in PC12 cells[68]. It was also demonstrated that dopaminergic cell loss was reduced after rats were administered with Rg1 at 5−20 mg/kg (i.p.)[68]. Ardah et al.[69] evidenced that 100 μmol/L Rb1 DMSO solution exerted the most significant α-synuclein aggregation inhibition, at around 80%, while Rg3 inhibited around 25% of total aggregation. The authors also conducted a western blotting assay, where α-synuclein fibrils were treated solely by Rb1 for an incubation period of 2 days. The results evidenced fibrils dissociation in the presence of this ginsenoside, in a dose-dependent manner.

Another study in mice demonstrated that the loss of dopamine neurons, motor deficits, and abnormal ultrastructural changes in the SNpc were significantly improved by oral administration of Rg1 at 10, 20, and 40 mg/kg and that the antineuroinflammatory properties of Rg1 may be involved in neuroprotection[70]. These results highlighted the neuroprotective effect of Rg1 was not only in *in vitro* but also in *in vivo* PD models[68−70].

Other PD related targets are also influenced by ginsenosides. Different components found in ginseng have been reported to interact in the production of neuromelanin, such as phenolic acids and ginsenosides[71]. Moreover, the administration of ginsenosides Rg1, Re, and Rd, has shown to prevent dopaminergic cell death, boosting the expression of tyrosine-hydroxylase, which in turn augments dopamine production and limits locomotor dysfunction[72], and suppressing free radical generation and the related injuries in the brain[73]. The levels of dopamine are also influenced through MAO inhibition. Hao et al.[74] reported that ginsenoside Rb1 was capable of inhibiting both isoforms of MAO in mice brains, increasing dopamine and serotonin levels. Hao et al.[74] also evidenced that the activity of both tryptophan hydroxylase and L-aromatic amino acid decarboxylase, meaning that the production rates of dopamine and serotonin increased.

To evaluate the neuroprotective activity against HD, an *in vitro* model of the mouse medium-sized multispinous striatum nerve YAC128 was exposed to glutamate stimulation. This study demonstrated that pretreatment with ginsenoside Rb1, Rc, and Rg5 at low concentrations (0.01, 0,1 and 1 μmol/L) attenuated neuronal apoptosis and this protective effect was associated with an inhibition of Ca^{2+}[75]. In addition, the *in vitro* and *in vivo* effects of ginsenosides were evaluated at different doses (6.25−50 mg/kg, i.p.) on striatal neurotoxicity induced by 3-NP treatment in rats. The study demonstrated that these compounds increased the survival rate of HD animals, inhibited intracellular Ca^{2+} elevation, and reduced behavioral disorders after toxin administration[76].

GABAergic, adenosine and glutamatergic systems are also targeted by ginsenosides. Radad et al.[77] conducted an assay where the dopaminergic neurons of pregnant OF1/SPF mice were cultured with excess glutamate and samples of ginsenosides Rb1 and Rg1 (0.1−20 μmol/L) for 4 days. Exposure to glutamate decreased the dopaminergic cells by around 58% and reduced the total neurite length by 24%. When neurons were pre-treated for 4 days or post-treated for 2 days with Rb1 or Rg1 following glutamate exposure, they significantly increased the numbers and lengths of neurites of surviving dopaminergic cells but were unable to counteract cell loss induced by glutamate. The authors concluded that cell loss prevention occurred due to Rb1 and Rg1 inability to antagonize NMDA receptors overactivation induced by glutamate. On the other hand, ginsenosides are able to target GABA and adenosine A_{2A} receptors.

Concerning GABAergic system, Yin et al.[78] evaluated the effects of aqueous extracts of Korean red ginseng (0.3−10 μmol/L) on $GABA_A$ receptor-induced ion flow, resorting to tetrodotoxin, a sodium-channel blocker. The obtained results evidenced ion inward flow on the extracts on the brain cells, suggesting that the ginsenosides in the extracts target the GABA receptors.

Shin et al.[79] reported that the administration of ginsenosides could regulate the excitotoxic activation of adenosine A_{2A} receptors by kainate. Sprague−Dawley mice were orally administered two ginsenoside extracts (50 and 100 mg/kg) and 10 mg/kg kainate[80]. Mice that were solely administered kainate exhibited robust seizures during the 4-h timeframe, while the mice treated to the 100 mg/kg ginsenoside extract developed lesser seizure activity. Two days after documenting these results, the hippocampus of the test subjects was dissected and analyzed through micrographs. The obtained micrographs evidenced well-preserved cells in the hippocampus sample of the ginsenoside-treated mice. The authors suggested that ginsenosides interact with adenosine A_{2A} receptors as antagonists.

Finally, the antidepressant activity of ginseng is also evidenced. Unlike conventional antidepressants, which have many adverse reactions, especially peripheral anticholinergic side effects, *P. ginseng* does not affect the monoaminergic systems significantly but can promote neurogenesis, mediated by the brain-derived neurotrophic factor (BDNF) signal pathway[81]. It was shown that Rg1 (5−20 mg/kg, i.g., 28 days) alleviated the

depression-like behavior in rats exposed to chronic unpredictable stress (CUS)[82].

2.5. *Glycyrrhiza glabra L.*

G. glabra L., or licorice, is one of the most popular medicinal plants belonging to the Fabaceae family and is cultivated in Southern Europe and parts of Asia[83]. The plant has been documented to display anti-inflammatory, antitussive, expectorant, anti-hepatic, anti-asthma, anti-ulcerative, and antimicrobial properties, being glycyrrhizin its main active compound[84].

The flavonoids present in licorice roots (Table S5) stand out for their inherent antioxidant activity. Tohma and Gulçin[85] extracted *G. glabra* root and aerial parts with distilled water and ethanol to determine the $O_2^{\bullet -}$, H_2O_2, and DPPH• scavenging activity, Fe^{2+} chelating activity, and Fe^{3+} and Cu^{2+} reduction activity of the extracts. The aqueous root extract exhibited the most potent $O_2^{\bullet -}$ and H_2O_2 scavenging activities, displaying 41.0% and 51.2% at 30 μg/mL, respectively. At the same concentration, all samples exerted similar DPPH• scavenging activity, ranging from 50% to 60% total quenching, apart from the aqueous extract of *G. glabra* aerial part, which was lesser. The authors also concluded that all extracts had exhibited strong metal-reducing activity and electron-donor properties. According to Jong et al.[86], *G. glabra* extracts also can suppress nitric oxide synthase, thus suppressing nitric oxide radical formation.

Regarding its direct effect against AD, cortical neural cells were exposed to Aβ (25−35)-neurotoxicity and isoliquiritigenin (Fig. 3), a chalcone extracted from licorice, was found to reduce the effects of neurotoxicity, by decreasing the expression of Bax and caspase-3 as well as decreasing the levels of inflammatory markers such as Ca^{2+} and ROS[87]. Moreover, the extracts of licorice roots have been reported to ameliorate the cognitive ability of scopolamine-induced mice, by inhibiting AChE. Scopolamine is a muscarinic cholinergic receptor blocker that causes memory deficits and a decrease in cholinergic activity on behavioral performance. Dhingra et al.[88] evaluated the effects of root aqueous extract administration on the brain tissue of Swiss male albino mice. Consecutive administration of 150 mg/kg licorice root aqueous extract for 7 days decreased the overall AChE activity by 25.4%. Despite this, glycyrrhizin is known to dose-dependently enhance the activity of AChE, as reported by Li and Zhou[89]. The inhibitory activity of ChEs by licorice roots is attributed to glycyrrhizin aglycones, such as glycyrrhetinic acid and its derivatives.

The extracts of *G. glabra* have also been found to suppress Aβ production. Zhu et al.[90] conducted an assay where APP-PS1 Tg mice were divided into three groups, with two groups subjected to daily intraperitoneal injection of 2,2′,4-trihydroxychalcone, a compound found in *G. glabra* at doses of 3 and 9 mg/kg/day, for 106 days, while the other was treated with a control vehicle. After the administration period, the mice were subjected to a Morris water maze. The group which was administered with the highest concentration registered the shortest periods in the maze. After the test, the mice were sacrificed, and the brain tissue was cultured to assess Aβ content and β-secretase activity. The results showed that 2,2′,4-trihydroxychalcone inhibited 50% of β-secretase at a concentration of 4.75 μmol/L, which correlated with the reduced Aβ contents in the brain tissue.

Regarding their anti-PD potential, isoliquiritegenin and liquiritin (Fig. 3), have been evidenced to inhibit α-synuclein aggregation[91]. Liao et al.[91] evidenced that, at a concentration of 250 μmol/L, isoliquiritegenin and liquiritin inhibited α-synuclein aggregation by 36.9% and 62.5%, while 1 mg/mL of the lyophilized *Glycyrrhiza uralensis* extract inhibited α-synuclein aggregation by 66%. Moreover, isoliquiritigenin disaggregated preformed deposits of this protein.

The inhibition of tyrosinase was also studied by Nerya et al.[92] These authors evaluated the potential inhibitory activity of licorice root extract against tyrosinase, along with three isolated compounds [glabridin (Fig. 3), isoliquiritigenin, and glabrene]. When tyrosine or L-DOPA were used as the substrate, the IC_{50} values were, respectively, 0.9 and 53 μg/mL for the extract, 0.09 and 3.94 μmol/L for glabridin, 3.5 and 47 μmol/L for isoliquiritigenin, and 8.1 and 7600 μmol/L for glabrene.

Hwang et al.[93] treated mouse dopaminergic cell line cultures with 6-OHDA, which is known to induce stress and apoptosis signals in neurons and is a cell model to study PD. The addition of isoliquiritigenin suppressed 6-OHDA-induced upregulation of Bax, p-c-Jun N-terminal kinase (JNK), p-p38 mitogen-activated protein (MAP) kinase, cytochrome c release, and caspase 3 activation and attenuated the reduction of 6-OHDA-induced Bcl-2, BDNF, and mitochondrial membrane potential[93].

The effects of *G. glabra* on depression were investigated in animal models. In one study, extracts of *G. glabra* were administrated at 75−300 mg/kg (*p.o.*) for 7 days in mice and they showed production of antidepressant-like effect in mice in forced swimming test (FST) and tail suspension test (TST), by interaction with adrenergic and dopaminergic system[94]. Moreover, Dhingra and Sharma[95] evaluated the effects of consecutive oral administration aqueous licorice root extract, control sample, fluoxetine, and imipramine by intravenous injection for 7 days in Swiss male mice by analyzing the test subject's performance in both FST and TST tests. The results after 7 days evidenced that 150 mg/kg licorice aqueous extracts exerted the most significant antidepressant effects in the mice, although the effects were less potent than those observed for fluoxetine. The authors suggested that the phytochemical components of the licorice extracts interact with dopamine receptors as agonists.

In addition, the cannabinoid and the GABAergic systems are also affected by licorice. Park et al.[96] examined the inhibitory activity of licorice and 18β-glycyrrhetinic acid (0.1−100 μg/mL) (Fig. 3) on human CB_1-expressing Chem-1 cells. The control sample activated the influx of calcium ions, with an EC_{50} of 0.91 μmol/L; on the other hand, licorice extract and 18β-glycyrrhetinic acid exerted inhibitory activity towards the CB_1 receptor (IC_{50} of 9.17 and 1.96 μmol/L, respectively).

Glabridin one of the most well-studied flavonoids found in *G. glabra*, was found to stimulate $GABA_A$ receptors, thus inhibiting the neurotransmission, which was evidenced by Hoffman et al.[97] Glabridin was found to strongly potentiate the $GABA_A$, $\alpha 1\beta 2\gamma 2$ receptor subtype, which registered an EC_{50} of 6.30 ± 1.70 μmol/L.

2.6. *Curcuma longa L.*

C. longa L. (Zingiberaceae family), commonly known as turmeric, is an original species of Southeast Asia. The turmeric, besides its main use as a food additive and cosmetic, has antioxidant, antimicrobial, and antiinflammatory properties[98].

The pharmaceutical activity of *C. longa* is mainly attributed to its polyphenolic fraction, which comprises curcumin (Fig. 3), bisdemethoxycurcumin, and demethoxycurcumin (Table S6)[99].

Curcumin, the major bioactive component of curcuminoids, has revealed its bioactivities, including anti-inflammatory,

antioxidant, proapoptotic, chemotherapeutic, antiproliferative, wound healing, antinociceptive, antiparasitic, and antimalarial properties[100].

In animal experiments related to AD, curcumin at 12 mg per day (*p.o.*) improved spatial and non-spatial memory in the Morris water maze and in the social recognition test, respectively. The results also indicate that prolonged treatment with curcumin could promote neurogenesis and cognition, which may be due to its effects on genes expressed in the hippocampus and cortex related to growth and plasticity like NeuroD1 (that is fundamental in neurogenesis), and NeuroD6 (that regulates neuronal differentiation and promotes neuron survival). Other genes altered by curcumin are the *Fezf2*, *Wnt2*, *Nnat*, *Tiam1*, and *Unc5d* genes which are also very important in neuronal development[101].

In a study focusing on PD, curcumin at concentrations below 5 μmol/L was observed to decrease α-synuclein-induced intracellular ROS generation, inhibit caspase-3 activation, and ameliorate signs of apoptosis in SH-SY5Y neuroblastoma cells[102].

Studies using MPTP- and OHDA-induced mouse models of PD also showed the protective effect of curcuminoids. For instance, oral pre-treatment with curcuminoids at 150 mg/kg/day significantly prevented loss of tyrosine hydroxylase (TH)-positive neurons and depletion of dopamine, and mitigated cytokines, generation of total nitrite, and the expression of protein inflammatory markers, such as glial fibrillary acidic protein (GFAP) and iNOS, in the striatum of MPTP-intoxicated mice[103]. Tyrosine hydroxylase (TH) is a marker for dopamine, noradrenaline, and adrenalise-containing neurons. In a similar study, curcumin at 50 mg/kg (i.p.) per day protected dopaminergic neurons from apoptosis and ameliorated the loss of dopaminergic axons in the striatum of MPTP-treated mice[104]. Moreover, posttreatment of 6-OHDA-treated mice with curcumin (200 mg/kg (i.p.)) was found to decrease the induced loss of striatal TH fibers and nigral TH-immunoreactive neurons. The neuroprotection was accompanied by a significant weakening of astroglial and microglial reaction in the striatum and the SNpc, indicating that the protective effect may be mediated *via* curcumin anti-inflammatory properties, or direct protection on nigral dopaminergic neurons[105].

A study on HD have proven that chronic administration of curcumin (10, 20, and 50 mg/kg, *p.o.*) once daily for a period of 8 days consistently improved body weight, reversed motor deficits, and increased the mitochondrial enzyme succinate dehydrogenase activity in 3-NP treated rats. The improvement of the 3-NP-induced motor and cognitive impairment along with a strong antioxidant property indicates that curcumin could be useful and can act as a lead molecule in the treatment of HD[106].

Finally, the antidepressant effect of *C. longa* and curcumin was evidenced by Yu et al.[107] and Xu et al.[108] The extract of *C. longa* 560 mg/kg (*p.o.*) for 14 days significantly decreased the duration of immobility in TST and FST in mice, indicating that the activity of this herb in depression may be mediated in part through MAO-A inhibition in mouse brain[107]. Curcumin at various doses (1.25−10 mg/kg, *p.o.*) also reversed depression-induced low levels of serotonin, noradrenaline, 5-hydroxyindoleacetic acid (5-HIAA), and 3,4-dihydroxyphenylacetic acid (DOPAC) in rats brain[108].

2.7. *Mucuna pruriens (L.) D.C.*

M. pruriens (L.) D.C. is a tropical legume (Fabaceae family) native to eastern India and western regions of China and widely naturalized and cultivated[109]. *M. pruriens* is a rich source of L-DOPA (Table S7) and has been used traditionally as an effective remedy for several brain-related maladies, including reducing tremors (as seen in PD)[110]. Zandopa (HP-200), a commercial preparation of *M. pruriens*, is also available for the treatment of PD[111]. This plant showed positive effects on PD patients in clinical trials, with a quick onset of action and without a concomitant increase in dyskinesia, suggesting that this herb has advantages over conventional L-DOPA preparations in the long-term management of this disease[112,113].

At laboratory level, the neuroprotective effects of the *M. pruriens* extract were evaluated in murine microglia BV-2 and neuroblastoma SH-SY5Y cells. Treatment with the extract at 12.5−50 μg/mL reduced BV-2 and SH-SY5Y cytotoxicity induced by oxidative stress and inflammation, and also decreased ROS production and cell apoptosis. In addition, *in vivo* models using MPP^+-induced *Caenorhabditis elegans* and *Drosophila melanogaster* indicated that the extract of *M. pruriens* at 20 or 40 μg/mL ameliorated dopaminergic neurotoxin-induced lethality in *C. elegans* and at 40 μg/mL recovered climbing ability in *D. melanogaster*.[114] This herb has also been reported to show protective properties against PD the in 6-OHDA-lesioned rat model by increasing the activity of brain mitochondrial complex-I and reducing motor dysfunction[115].

2.8. *Gastrodia elata Blume*

G. elata Blume is an herb belonging to the family of Orchidaceae and has been used as a folk medicine in oriental countries for many years due to its therapeutic properties[116]. The main compounds in *G. elata* are gastrodin (Fig. 3), vanillyl alcohol, 4-hydroxybenzaldehyde, and vanillin (Table S8). These compounds are known to cross the BBB and have several biological activities, such as antioxidant, antiasthmatic, antimicrobial, and antimutagenic activities[117]. To investigate the influence of gastrodin on the inflammatory response, murine microglial BV-2 cells were pretreated with gastrodin (30, 40, and 60 μmol/L) for 1 h and then stimulated with LPS. In this study, gastrodin significantly attenuated the expression levels of neurotoxic pro-inflammatory mediators, including iNOS, COX-2, and proinflammatory cytokines (TNF-α and IL-1β), indicating that it has an anti-inflammatory effect[118].

Several studies highlight *G. elata* potential against PD. A study demonstrated that pretreatment with *G. elata* at 10−200 μg/mL significantly improved cell viability in MPP^+-treated SH-SY5Y cells and reduced the proportion of apoptotic cells, ROS, and Bax/Bcl-2 ratio[119]. Similar results were obtained with the application of vanillyl alcohol at 10−200 μg/mL to MPP^+ toxicity-induced dopaminergic MN9D cells[117]. Furthermore, gastrodin at 10, 30, and 60 mg/kg (*p.o.*) for 15 days also shows neuroprotective effects by ameliorating bradykinesia and motor impairment in a subchronic MPTP mouse[116].

These results indicate that the compounds of *G. elata* have protective effects in experimental PD models and might be suitable for development as a clinical candidate to ameliorate PD symptoms.

2.9. *Paeonia lactiflora Pall.*

Paeoniae alba Radix is the white root of *P. lactiflora* Pall. (Paeoniaceae family) and is one of the most well-known herbs in China[120]. It is used extensively as a component of traditional Chinese prescriptions to treat amenorrhea, traumatic injuries,

epistaxis, inflammation, boils, and sores and to relieve pain in the chest and back regions[121].

The main bioactive component of *P. alba* Radix is paeoniflorin (Fig. 3, Table S9), a monoterpene glycoside, and it has exhibited many pharmacological effects, such as anti-inflammatory, anti-allergic, anti-hyperglycemic, analgesic, neuromuscular blocking, cognition-enhancing, antioxidant, etc.[120,121].

Concerning PD, recent studies have shown that pre-treatment with paeoniflorin at 2.5 and 5 mg/kg (s.c.) for 11 days protected striatal nerve fibers and TH-positive substantia nigra neurons from death and decreased bradykinesia in the MPTP mouse model of PD. Posttreatment with paeoniflorin at 5 mg/kg significantly ameliorated the dopaminergic neurodegeneration and decreased the neuroinflammation[121]. Another similar study indicates that paeoniflorin at 2.5, 5 and 10 mg/kg (s.c.) twice daily for 11 days alleviated the effects induced by 6-OHDA in rats. Since this compound had no direct action on the dopamine D1 or dopamine D2 receptors, these indicate that paeoniflorin might provide an opportunity to develop nondopaminergic management of PD[122].

In a recent report, paeoniflorin 50 μmol/L was observed to protect PC12 cells from MPP^+- and acid-induced damage *via* an autophagic pathway and decreased the release of lactate dehydrogenase and apoptotic rate. These results indicate that paeoniflorin is an effective compound in the modulation of autophagic activity and has neuroprotective effects[123].

Paeoniflorin also affects α-synuclein. Sun et al.[124] described that paeoniflorin (50 μmol/L) increased the autophagic degradation of α-synuclein by regulating the expression and activity of acid-sensing ion channels and thus eliciting protective effects against its cytotoxicity in PC12 cells.

P. lactiflora is also commonly used to treat depression. Animal studies have found that extract from *P. alba* Radix at 80 and 160 mg/kg/day (i.g.) produces antidepressant effects in CUS-induced depression models in mice and rats. The antidepressant effects are mediated by neuroprotection, inhibition of the MAO activity and oxidative stress, modulation of the function of the hypothalamus−pituitary−adrenal (HPA) axis, and the upregulation of neurotrophins including BDNF and nerve growth factor (NGF)[125].

2.10. *Centella asiatica (L.) Urban*

C. asiatica (L.) Urban, commonly known as Asiatic Pennywort belongs to the Umbelliferae family and has neuropharmacological effects[126].

Many studies have shown various neuropharmacological effects of *C. asiatica* which comprises antioxidant properties, memory enhancement, increased neurite elongation, and acceleration of nerve regeneration[126−128]. The main compounds from *C. asiatica* are triterpenoid saponins including asiaticoside, asiatic acid, madecassoside, and madecassic acid, as depicted in Table S10[126].

Studies assessing the potential beneficial effect of asiaticoside to treat PD indicate that this compound (15−45 mg/kg, i.g.) protect dopaminergic neuron, alleviate oxidative stress and improve motor dysfunction in rats with MPTP-induced parkinsonism[129].

In addition, *C. asiatica* may be useful in the treatment of HD. At 5 mg/kg (*p.o.*) for 10 days, it attenuated the 3-NP-induced depletion of glutathione (GSH) levels, total thiols, and endogenous antioxidants in the striatum and other brain regions of mice. It also exhibited protection against mitochondrial dysfunctions, reduction in the activity of mitochondrial enzyme succinic dehydrogenase, electron transport chain enzymes, and decreased mitochondrial viability (since mitochondrial dysregulation is associated with this disease)[130]. The results of this study clearly indicate that *C. asiatica* can be helpful in controlling HD-related impairments.

Other studies have shown that *C. asiatica* at 3, 10, 30 mg/kg (*p.o.*) have also the ability to induce antidepressant effects in rats and mice. A standardized extract of *C. asiatica* leaves showed reversal of physiological changes (like body weight, heart rate, and others) and behavioral changes in rats with induced depression[131]. In another study, total triterpenes from *C. asiatica* reduced the immobility time in FST and improved the imbalance of amino acid levels[132]. Moreover, total triterpenes significantly reduced the corticosterone level and increased the contents of serotonin, noradrenaline, dopamine, and their metabolites 5-HIAA and 3-methoxy-4-hydroxyphenylglycol (MHPG) in the rat brain. The antidepressant effect of total triterpenes of *C. asiatica* may be involved in ameliorating the function of the HPA axis and increasing the contents of monoamine neurotransmitters[133].

2.11. *Huperzia serrata (Thunb.) Trev.*

H. serrata (Thunb.) Trev. is a plant that belongs to the Lycopodiaceae family and is used in Chinese medicine to treat schizophrenia, swelling, strains, bruises, myasthenia gravis, and poisoning by organophosphates[134].

This herb presents as an active principle huperzine A (Fig. 3), which displays multiple neuroprotective effects. Huperzine A is an alkaloid capable of inhibiting in a potent, selective, and reversible way the enzyme responsible for the degradation of acetylcholine, AChE[135]. Due to the ability to cross the BBB, huperzine A can increase concentrations and action of ACh in certain brain regions, such as the medial prefrontal cortex (mPFC) and hippocampus[135]. Beside, huperzine A in PC12 cells, HEK293sw cells, and rats demonstrated a neuroprotector effect preventing the progress of AD, including the alleviation of Aβ (25−35)-induced oxidative stress, Aβ (1−40)-induced apoptosis effect, improvement of the mitochondrial function and antiinflammatory effect[136]. Huperzine A also promotes hippocampal neurogenesis through activation of MAPK/ERK signaling pathway[137]. Nguyen et al.[138] have quantified huperzine A in a methanolic extract (155 μg/g DW).

With these results, it is possible to conclude that the administration of the alkaloid huperzine A, is a valuable source of new drugs for the treatment of AD.

2.12. *Polygala tenuifolia Willdenow*

P. tenuifolia Willdenow, also known as yuan zhi, is an herb that belongs to the Polygalaceae family and its dried root (Polygalae Radix) is widely used in TCM to improve memory, combat forgetfulness and aging, treat amnesia, neurasthenia, insomnia, and cognitve dysfunction[139,140].

To evaluate the effects of Polygalae Radix in the treatment of PD, tests were performed on PC12 cells and in a mouse model of PD. In *in vitro* studies, polygalae radix (0.05−1 μg/mL) protected PC12 cells from neurotoxicity induced by 6-OHDA, by decreasing the production of ROS and •NO and reducing caspase-3, thus decreasing cell apoptosis. In *in vivo* studies, the administration of this compound (100 mg/kg/day, 3 days, *p.o.*) increased the number

of TH-positive cells and the length of dendrites, protecting dopaminergic neurons[141].

One of the main compounds extracted from the dried root of *P. tenuifolia* is tenuigenin (Fig. 3, Table S11), a triterpenoid saponin, which has several pharmacologic properties such as antioxidant, antiaging and anti-inflammatory[142].

Tenuigenin was investigated for its neuroprotective effect in 6-OHDA-induced cytotoxicity in SH-SY5Y cells. It was demonstrated that pre-treatment with tenuigenin at 10 μmol/L significantly increased cell viability, reduced cell death, and exhibited antioxidant activity[143].

Moreover, *in vivo* assays have demonstrated the protective role of tenuigenin against PD and AD. To study the neuroprotective effect of tenuigenin in neuroinflammation, adult male rats were induced with LPS as a model of PD. This study demonstrated that treatment with this compound at 300 mg/kg/day (i.g.) for 14 weeks decreased dopaminergic degeneration and prevented the loss of dopaminergic neurons. In addition, treatment with tenuigenin attenuated the release of inflammatory cytokines such as TNF-α and IL-1β, in LPS-treated primary cultured microglia[139].

P. tenuifolia can also be used to treat AD, as it has a therapeutic effect on Aβ (1−40)-induced neurotoxicity. In a study using an AD rat model, tenuigenin at 18.5, 37.0 and 74.0 mg/kg (i.g.) inhibited Aβ aggregation, decreased phosphorylation level of Tau by down-regulating ubiquitin expression, and up-regulated the activity of ubiquitin ligase E3 and 26S proteasome. This result indicates that the role of tenuigenin in combating AD may be related to the ubiquitin-proteasome pathway[144].

With these results, it can be concluded that this plant can be used in the treatment of PD and AD since it has neuroprotective effects.

2.13. *Chrysanthemum sp.*

The flowers of chrysanthemum (Asteraceae family) are one of the most used plant components in traditional Chinese medicine. In nature, numerous chrysanthemum subspecies are found, with *Chrysanthemum indicum* L. and *Chrysanthemum morifolium* (Ramat.) Hemsl. as the predominant species cultivated in gardens[145]. The primary health benefits of the flower range from anti-inflammatory, immunomodulatory, antibacterial, anti-tumor, and antioxidant properties[146,147]. Regarding its protection against oxidative stress, the antioxidant properties of chrysanthemum are due to the plant's vast phytochemical composition, which ranges from caffeoylquinic acids, flavonoids (Table S12), and terpenes[148,149]. According to the available literature, Kim and Lee[150] showed that 3,5-dicaffeyol-*epi*-quinic acid and 1,3-dicaffeyol-*epi*-quinic acid, isolated from *C. morifolium*, scavenged $O_2^{\bullet -}$ radicals with an associated IC_{50} of 2.9 μg/mL and 2.6 μg/mL, respectively; Zeng et al.[151] reported that the aqueous extracts of *C. indicum* and *C. morifolium* possessed •HO free radical scavenging activity of 54.45% and 33.51%, respectively, at 1 mg/mL.

The study of the neuroprotective effects of *C. indicum* petal tea has been growing in recent years, mostly due to the number of different flavonoids in its composition. To assess its potential in AD treatment, Sun et al.[152] conducted an assay where mice were administered with 1 mg/kg of scopolamine, a cognitive diminishing drug, and aqueous extracts of chrysanthemum petals, to evaluate the mice's performance in passive avoidance, a stress-inducing test, and a Morris water maze test. The authors concluded that the extracts prevented a deficit in the cognitive ability of the mice, as well as improved the memory of mice with amnesia. It was reported that the main phenolics responsible for these results were luteolin and acacetin. Further investigation of the effects on AChE was conducted. The scopolamine-induced mice and scopolamine-chrysanthemum-induced mice were sacrificed after the cognitive tests, and their brains were prepared for a colorimetric method with acetylcholine iodide. The obtained results evidenced that the mice treated with aqueous *C. indicum* extract registered a lower AChE activity than that registered for scopolamine-treated mice, of around 20%.

Besides AChE inhibition, *Chrysanthemum* species also exert inhibitory activity towards monoamine oxidases and tyrosinase. Chang et al.[153] tested the 80% methanolic extract and the ethyl acetate fraction obtained from *C. indicum* against MAO-A, obtaining IC_{50} values of 240 and 50 μg/mL. However, IC_{50} values were much higher when assayed against MAO-B. Regarding tyrosinase inhibition, Choi et al.[154] evaluated the effects of *C. indicum* flower extracts on the activity of this enzyme. At 100 μg/mL, the methanol extract inhibited mushroom tyrosinase activity by 60%, while the water extract, at the same concentration, exhibited an inhibition rate of about 50%.

The effects of this species on the GABAergic system were also assessed by Hong et al.[155] Male ICR mice were separated into groups and administered with bicuculline (0, 0.3, and 1 mg/kg) 30 min before administration of 0.1 mL of *C. indicum* aqueous extracts (125, 350, and 500 mg/kg). Bicuculline is a $GABA_A$ receptor antagonist. The anxiety levels in the mice were then measured with an elevated maze structure with barriers in some sections. The group which was only administered the chrysanthemum extracts registered increased time spent in the open arms section of the maze in a dose-dependent manner. Since bicuculline is a selective $GABA_A$ receptor antagonist, these findings suggest that chrysanthemum can suppress the anxiety-induced effects of bicuculline.

2.14. *Taraxacum officinale F.H. Wigg*

T. officinale F.H. Wigg, or dandelion (Asteraceae family), is a widely used remedy in both Asia and Europe throughout the years. Both the roots and leaves are used in clinical treatment, although they are usually mixed with other plants since, by itself, dandelions are applied in very specific conditions. They are usually administrated to patients suffering from diuretic and gastrointestinal conditions, while other properties have been suggested, but not fully agreed upon[156].

The activity of *T. officinale* against brain enzymes was already studied by several authors. *T. officinale* bioactive compounds include luteolin and other luteolin derivatives and chicoric (Fig. 3) and monocaffeoyltartaric acids (Table S13)[157,158], molecules that were previously proven to inhibit AChE; however, *T. officinale* has been found to not influence the activity of this enzyme. Jukic et al.[159] screened different plants for possible AChE inhibition and antioxidant activity, including *T. officinale*. While all samples of *T. officinale* (methanol, ethyl acetate, and chloroform leaf extracts) possessed different phenolic content, AChE inhibitory activity was not affected. Mazzio et al.[47] screened the MAO-B inhibition activity of the roots of *T. officinale*. They found that the extract from the roots of *T. officinale* was a weak MAO-B inhibitor since the IC_{50} value was about 7 mg/mL. Xie et al.[160] investigated different *Taraxacum mongolicum* Hand.-Mazz extracts on their potential to inhibit mushroom tyrosinase. It was found that the IC_{50} values for the leaf extracts were similar, with the aqueous extract possessing a more potent tyrosinase inhibitory rate (IC_{50} = 0.97 mg/mL),

while the 50% ethanol stem extract exerted a higher inhibitory rate of IC_{50} = 0.48 mg/mL.

On the other hand, chicoric acid has shown its antidepressant activity. Kour and Bani[161] conducted an assay, where stressed-induced mice were subjected to the FST and a passive avoidance test. The results showed that the levels of despair-induced stress were diminished by chicoric acid treatment in the test subjects.

Dandelion leaf extracts have been reported to successfully scavenge various ROS and RNS. Hu and Kitts[162] conducted assays to determine the scavenging activity of a *T. officinale* flower extract. The results showed a dose-dependent scavenging ability of free radicals, with the 150 μg/mL of *T. officinale* flower extract scavenging around 63.6% of $O_2^{\bullet -}$ and 200 μg/mL displaying 54.6% of •HO scavenging. In addition, the extract was able of suppressing the production of •NO in RAW264.7 cells, with an associated IC_{50} value of 130 μg/mL of extract.

2.15. Bamboo

Bamboo is one of the most common plants spread throughout Asian countries, and the fastest growing plants known to date. Bamboo refers to any of a group of plants in the subfamily Bambusoideae, which is a part of the Poaceae Family, and include species such as *Phyllostachys edulis* (Carrière) J. Houz, *Phyllostachys nigra* (Lodd.) Munro, *Sasa senanensis* (Franch. & Sav.) Rehder, *B. vulgaris* Schrad, *Bambusa arundinacea* (Retz.) Willd., among others. Bamboo is a woody grass that was used in ancient civilizations for decorative and day-to-day tasks, due to its durability and sturdiness, such as construction. The bamboo grass/leaves/shoots, still to this day, are implemented in the dietary intake of several communities with assess to it and have been a common component in TCM[163]. Bamboo leaves are rich in flavonoids, such as luteolin, vitexin, and orientin, as well as some phenolic acids, like caffeic, ferulic, and cholinergic acid (Table S14), among other important compounds. The upper section of bamboo shoots has been proven to possess unusually high levels of ACh[164]. The administration of the leaves, either by infusion or direct consumption, has exerted anti-inflammatory, antioxidant, diuretic, expectorant, and anticarcinogenic properties[165,166].

The influence of bamboo extracts on cholinergic, monoaminergic, glutamatergic and GABAergic systems was already assessed. Liu et al.[167] evaluated both the behavioral and biochemical effects of dementia-induced mice through intraperitoneal injection of D-galactose. The behavioral assay was determined by subjecting three groups of mice (one control, one with senile demented mice, and one group with senile demented mice, treated with bamboo leaf extract) to a daily Morris water navigation test, recording the path length and escape latency. By the second day of testing, the treated mice had completed the test in less time than the untreated group. Complementary assays on ACh content and AChE activity indicated that the levels of the neurotransmitter in the hippocampus and the cortex of the mice group treated with bamboo extract were the highest. The neurotransmitter production rate did not suffer alteration. Liu et al.[167] also evaluated the effects of the administration of bamboo leaf extracts on the brain levels of glutamate and GABA. Compared with the control group, no significant changes were evidenced, however, glutamate and GABA levels were higher than those observed in the senile mice group. These results suggest that the leaf extracts of bamboo possess a role in the regulation of spatial memory. The authors also evaluated the levels of dopamine, as well as the activity of MAO-B. The levels of dopamine in the hippocampus and cortex rose in the treated mice brain, as MAO-B activity lowered.

Bamboo leaves are known to contain several phenolic compounds capable of preventing neuromelanin accumulation in the *substantia nigra*. Choi et al.[168] examined the inhibitory activity of an ethyl acetate fraction of 80% ethanol *P. nigra* leaf extract on mushroom tyrosinase, with melanin as a substrate. The authors reported that the bamboo leaf extract has an associated IC_{50} value of 243.7 μg/mL. The anti-melanogenic effects of this extract have been evidenced to depend on the presence of important phenolic compounds, such as *p*-coumaric acid, caffeic acid, chlorogenic acid, luteolin, rutin, and catechin.

Finally, Choi et al.[168] attested for the antioxidant capability of *P. nigra* leaves in different mechanisms, such as inhibiting superoxide dismutase. The authors also reported a scavenging potential of •HO scavenging (IC_{50} = 509.17 μg/mL). Khatun et al.[169] showed that a 0.1 g/mL of an 80% methanolic *S. senanensis* leaf extract had a $O_2^{\bullet -}$ scavenging activity of about 10%. Macwan et al.[170] evaluated the •NO scavenging potential of three *B. arundinacea* leaf extracts obtaining IC_{50} values of 644 μg/mL (water extract), 433 μg/mL (methanolic extract), and 664 μg/mL (butanol extract), respectively.

2.16. Cannabis sativa L.

C. sativa L. (Cannabaceae family) is a plant most known for its psychoactive effects and its use as a recreational drug throughout the world. Cannabinoids are the predominant phytochemical components found in *C. sativa* and they hold a significant role in our daily lives. These types of phytochemicals can be synthesized in the body (endocannabinoids) or administered (plant cannabinoids). Cannabinoids have been documented to alleviate inflammation, chronic pain, and cancer growth[171].

The social stigma around this plant is due to the presence of THC, a psychoactive cannabinoid. Today, many countries have slowly increased the restrictions surrounding this plant, which allowed only for the legal medicinal use in cancer patients. Several sources throughout the years attested to the medicinal properties of *C. sativa* and attributed these effects to cannabidiol (CBD) (Fig. 3, Table S15). When compared with THC, CBD shows no psychoactive effects in the body, while maintaining other properties attributed to cannabinoids. CBD has been reported as being a nonselective compound binding to both cannabinoid CB_1 and CB_2 receptors[172,173].

In vitro assays have shown that hemp seed extracts have potential beneficial effects against AD. Yan et al.[174] isolated several compounds from *C. sativa* and evaluated each compound's inhibition activity on *Torpedo californica* AChE. The authors reported overall modest AChE inhibitory rates, with compounds 3,3′-demethyl-grossamide, *N-trans*-caffeoyltyramine, and 3,3′-dimethyl-heliotropamide exhibiting a 50% inhibitory rate at 38.7, 216, and 46.2 μmol/L respectively. In addition, Iuvone et al.[175] evidenced the neuroprotective effects of CBD against Aβ toxicity. The authors treated PC12 cells with Aβ (1 μg/mL) and CBD (10^{-7}–10^{-4} mol/L). In the control sample, Aβ was responsible for reducing cell viability by 38.8%. With the increase in CBD concentration, the total cell death decreased, with the 10^{-4} mol/L dose registering cell death just above 10%. In addition, Esposito et al.[176] studied the possible effects of CBD in inhibiting tau protein hyperphosphorylation in Aβ-stimulated

PC12 cells. CBD was found to suppress the levels of hyperphosphorylated tau protein in a dose-dependent manner.

Cannabinoids have been shown to inhibit both MAO isoforms as well as tyrosinase, highlighting their potential use for PD treatment. Fišar[177] tested THC, anandamide (endocannabinoid) and WIN 55212-2 (synthetic cannabinoid receptor agonist) against both MAO-A and MAO-B, showing that THC was a potent inhibitor (IC_{50} (MAO-A) = 24.7 μmol/L and IC_{50} (MAO-B) = 22.6 μmol/L), with IC_{50} values close to those of WIN 55212-2. However, CBD had no effect on MAO inhibition[178]. Moreover, Manosroi et al.[179] reported an IC_{50} of the leaf and seed hemp extracts, of 0.049 and 0.07 mg/mL against tyrosinase, respectively.

CBD has been reported to enhance the cognitive ability of mice. Murillo-Rodríguez et al.[180] conducted an assay where the Wistar mice forebrain was collected and treated with CBD (5−30 mg/kg) or vehicle, 6 times across 6 h. Compared with the control, the 5 mg/kg dose increased acetylcholine levels by 25%, while the 10 mg/kg and 30 mg/kg dose increased neurotransmitter levels around 100% and 167%, respectively. The authors suggested that CBD interacts with CB_1 receptors in the forebrain as an antagonist.

Although the relaxing effects of CBD consumption are primarily related to the compound's interaction with the CB_1 receptors, other non-cannabinoid related systems have been evidenced in the past to exert similar behavioral properties, like the GABAergic system. For example, Lile et al.[181] evidenced that THC augmented the interaction between GABA and its receptors by specifically inhibiting transporter proteins involved in cellular uptake. Moreover, Castillo et al.[182] reported that CBD exerts anti-excitatory effects on cannabinoid receptors, which in turn affect adenosine receptor-induced glutamate release to the synapse. For that, the brains of newborn C57BL6 mice were sliced and incubated in a culture medium with 1000 μmol/L CBD solution or vehicle (control). The obtained results reported that the administration of CBD to the brain samples decreased cell death and reduced extracellular glutamate levels in the extracellular domain.

Finally, the antioxidant effects of a hemp seed meal protein hydrolyzate in spontaneously hypertensive rats were studied, demonstrating that hemp seed extracts promoted an increase of superoxide dismutase and catalase activities[183]. This result reinforces the role of hemp against oxidative stress.

2.17. *Coix lachryma-jobi L.*

Adlay (*C. lachryma-jobi* L., Poaceae family) is a tall grass that contains important nutrients and proteins that, to this day, serve as a source of food in some Asian countries, like China and Japan. From all the plant's parts, seeds are the most consumed. Adlay seeds are a well-established botanical medicine in TCM, with its application dating back to thousands of years ago to treat patients with various ailments, mostly cancer. Adlay seeds exert many properties, such as anti-inflammatory, antimutagenic, anti-tumor, anti-allergic, anti-glycemic, anti-microbial, anti-cancer, hormone modulating, diuretic, among others[184] due to the presence of several phenolic compounds (Table S16).

Adlay seeds extracts have been proven to display anti-AD properties, mostly affecting AChE activity and Aβ. Seo et al.[185] evaluated the anti-cholinesterase effects of an unnamed compound, referenced as AChE inhibitor, isolated from a methanol extract of adlay seed hull. The extract was then fractioned with different solvents, including *n*-hexane, chloroform, ethyl acetate, butanol, and water. The results indicated that the *n*-hexane fraction showed the highest inhibitory activity among all fractions (IC_{50} = 176 μg) and the isolated AChE inhibitor displayed an IC_{50} value of 0.608 μg.

No reports were yet conducted to assess the Aβ inhibitory activity of adlay seed extracts in the brain. However, in a study assessing the effects of adlay extracts on antidiabetic ICR mice, Chen et al.[186] found that these extracts significantly reduced Aβ levels in the blood.

Concerning the protection against melanogenesis, Huang et al.[187] evaluated the effects of a supercritical fluid extract of adlay seed extracts on mushroom tyrosinase. The results showed that mushroom tyrosinase activity was reduced in a dose-dependent manner, with the 100 and 250 mg/mL samples exhibiting reduced tyrosinase activity to 46.68% and 38.85%, respectively.

Adlay seed extracts are also capable of inhibiting inflammation-inducing enzymes, such as nitric oxide synthase, preventing the production of the radicals •NO and $ONOO^-$[188,189].

2.18. *Portulaca oleracea L.*

Portulaca oleracea L. (Portulacaceae Family), or purslane, is a fast-growing weed used around the world for medicinal and food purposes. Its global distribution and fast growth in both arable and arid soils make it one of the most common plants, with some estimates pointing it as the eighth-most distributed plant in nature. The interest in purslane was renewed when it was determined to contain high levels of melatonin, adenosine, catecholamines, fatty acids, alkaloids, phenolic acids, anthocyanins, flavonoids, lignans, terpenoids and betalains (Table S17)[190].

Purslane extracts intake has been documented to exert antimicrobial, neuroprotective, anti-inflammatory, anti-diabetic, hepatoprotective, immune-modulatory, antiarthritic, among others[191].

Agrawal et al.[192] evaluated the cognitive effects of melatonin in scopolamine-induced amnesia adult male Swiss albino mice. The authors subjected the mice to a passive avoidance test: in the first trial, the mice that entered the dark chamber were locked and punished with a light foot shock; in the second trial, the passage to the dark chamber is opened, but mice are free from foot shock. The second trial acts as a memory retention test. Different mice groups were treated with 10 and 20 mg/kg melatonin doses, 5 mg/kg donepezil, and 0.5 mg/kg insulin, 1 h before the first trial, with the intake of 3 mg/kg scopolamine 5 min before the first trial. The observed effects in the mice groups revealed that donepezil and melatonin increased transfer latency time to cross from the initial section to the dark chamber. Afterward, the mice were sacrificed to assess AChE activity. All studied drugs inhibited AChE activity in the hippocampus and hypothalamus, when compared to the control group. These results suggest that melatonin can help suppress amnesiac effects in patients by inhibiting AChE.

The effect of melatonin against Aβ and tau toxicity was also addressed. According to Cheng et al.[193], melatonin (10^{-5}, 10^{-6}, and 10^{-7} mol/L) was evidenced to possess a deeper role in AD suppression, by suppressing Aβ neurotoxicity (apoptosis) induced in PC12 cells. Moreover, Das et al.[194] evidenced that melatonin (1000 μg/mL) is also capable of inhibiting tau protein aggregation

in Neuro2A and N9 cell lines, showing mild anti-aggregation and cytoprotective effects.

The ethanolic extract from purslane has also been found to weakly inhibit MAO-B, displaying an $IC_{50} = 7$ mg/mL[47].

Purslane extracts are often reported as possessing anxiolytic effects in patients, which are normally derived from the activation of the GABAergic system. Lee et al.[195] investigated the effects of purslane extracts (50−400 mg/kg) on ICR mice groups and compared them with the control group. The mice were then subjected to an elevated maze test, a horizontal wire, and open field tests. The results evidenced that: the 200 mg/kg dose had the best effects in the elevated maze test, as this group of mice spent more time in the open areas; all samples of purslane did not harm the mice's ability to grasp the horizontal wire; and no significant changes were registered in the locomotor activity levels of mice, as the measured distance traveled by the mice groups were similar. In a separate group, mice were administered with 400 mg/mg purslane extract and 10 mg/kg doses of flumazenil, a GABA receptor antagonist, to evaluate the compound's effects on the elevated maze test. As expected, flumazenil administration induced shorter periods spent by the mice in the open arms section. This suggests that the purslane extracts induced their anxiolytic effects by interacting with the GABA receptors in the brain.

Finally, purslane demonstrated significant antioxidant activity, hence it has a strong basis of the diet for several populations. Kashef et al.[196] documented the free radical scavenging effects of purslane leaf extracts (80% ethanol, 80% methanol, cold water, and boiling water). The authors conducted •NO and OH• scavenging assays. The results were as follows: for •NO assay, the ethanol extract exhibited the highest scavenging rate (75.69%) at a concentration of 7500 ppm; for the OH• assay, the methanol extract exhibited the highest scavenging rate (57.95%) at a concentration of 980.39 ppm. Melatonin was also shown to protect dopaminergic neurons in mice brains, by inhibiting the production of the toxic 6-OHDA in the brain, thus protecting against the reduction of dopamine production and release to the synapse[197].

2.19. *Crataegus pinnatifida Bunge*

Crataegus sp. (Rosaceae family), also known as hawthorn, is a flowering tree whose berries have been utilized in the production of pre-historic fermented beverages since 7000 B.C. Hawthorn berries have a characteristic sweet and sour taste, due to the high levels of sugar and tartaric acid[198]. The denomination "Chinese hawthorn" comprises 18 different species, including *C. pinnatifida* Bunge and *Crataegus cuneata* Siebold & Zucc. Hawthorn berries are known for their high phenolic content, which comprises primarily flavonoids (epicatechin and quercetin-3-*O*-rutinoside, mostly) and 5-*O*-caffeoylquinic acid (Table S18)[199]. The fruit has been attributed to significant properties, such as digestive, antibacterial, antiviral, anti-inflammatory, anti-tumor, immunoregulative, and antioxidant properties, among others[200].

Numerous assays have proved that *Crataegus* berries possess neuroprotective abilities with potential against AD. Tohtahon et al.[201] performed an AChE inhibition assay with six extracted terpenoids from *C. cuneata* berries. Ursolic acid (Fig. 3), maslinic acid, corosolic acid, pomolic acid, tormentic acid, and 2α,19α-dihydroxy-2-oxo-urs-12-en-28-oic acid were isolated. The obtained results indicated that ursolic acid, maslinic acid, pomolic acid, and tormentic acid exerted the highest inhibitory activities, with IC_{50} values of 0.62, 0.88, 0.56, and 0.91 mmol/L, respectively. Moreover, Lee et al.[202] reported that the administration of berry extracts to Aβ-induced dementia mice helped in improving memory impairment. ICR mice were separated into groups, one being assigned as a control. The other groups were orally administered with two doses (30 and 300 mg/kg) of *C. pinnatifida* berry ethanol extracts, as well as 30 mg/kg curcumin ethanol extract. Behavioral tests were conducted showing that *C. pinnatifida* berry extracts were able to prevent short-term Aβ-induced dementia, as the treated mice groups registered both increased spontaneous alternation in the Y maze test and latency time in the passive avoidance test. Shortly after, the mice were sacrificed and their brains were isolated and cultured for a Aβ aggregation assay, revealing that the berry extracts were also able to suppress the formation of fibrils.

C. pinnatifida seeds have also a role in preventing tyrosinase activity. Huang et al.[203] isolated four lignan glycosides (pinnatifidaninsides A−D) and two other compounds, 7*R*,8*S*-dihydrodehydrodiconiferyl alcohol-9-*O*-β-D-glucoside and 7*R*,8*S*-dihydrodehydrodiconiferyl alcohol-9′-*O*-β-D-glucoside from fractioned 70% ethanol *C. pinnatifida* seed extracts. The results showed weak tyrosinase activity from pinnatifidaninsides A, B, C, and D (37.58%, 34.54%, 31.15%, and 32.97%, respectively), with the other two compounds exerting modest inhibition at rates of 46.00% and 58.15%, respectively.

Concerning MDD, Lim et al.[204] investigated the effects of administrating lyophilized *C. pinnatifida* berry ethanol extracts (300 mg/kg) and chlorogenic acid extracted from the berries (30 mg/kg) to ICR mice, to assess if they were able to reverse corticosterone or dexamethasone behavioral changes in TST, open field, passive avoidance, and FST tests. As a complement to this procedure, a MAO inhibition assay was conducted in cultured C8-D1A cells treated with chlorogenic acid (1 and 10 μmol/L) and *C. pinnatifida* berry (100 and 200 μg/kg). Compared with control mice (which only received corticosterone or dexamethasone to induce depressive states), behavioral tests showed that the administration of either chlorogenic acid or *C. pinnatifida* berry extract was able to reduce the immobility time of the mice in all tests, with the 30 mg/kg chlorogenic acid dose inducing more mobility. Regarding MAO inhibition, there was not any significant changes in the activity of MAO-A, while MAO-B was significantly inhibited by both chlorogenic acid and *C. pinnatifida* berry extract. When compared to the control sample, which was attributed a 100% MAO-B activity, 1 and 10 μmol/L chlorogenic acid reduced the MAO-B activity to 23.36% and 22.13%, while 100 and 200 μg/kg *C. pinnatifida* berry extract inhibited MAO-B activity to 19.84% and 20.02%, respectively.

Due to their phenolic composition, *C. pinnatifida* berries possess antioxidant properties. For instance, the aqueous extract of *C. pinnatifida* berries (100 μg/mL) have been reported to possess a $O_2^{\bullet -}$ scavenging activity of 82%[205], while methanolic extracts displayed an IC_{50} value of 554.2 μg/mL against H_2O_2[206] and, at 1 mg/mL, scavenge 40% of •NO[207]. Other antioxidant properties of these extracts include the upregulation of superoxide dismutase, and catalase, and the inhibition of lipid peroxidation[205].

2.20. *Gardenia jasminoides J. Ellis*

Cape jasmine, also known as *G. jasminoides* J. Ellis (Rubiaceae family), is a fragrant shrub cultivated in Asian countries, like China, Taiwan, India, Japan, and distributed around the world, mostly for decorating and coloring purposes. However, the plant has been

cultivated in China for, at least, a thousand years, for medicinal purposes[40]. The fruits of cape jasmine have been used in TCM to alleviate inflammation and prevent thrombosis and arteriosclerosis. The main components found in *G. jasminoides* fruits are iridoid glycosides, like geniposide (Fig. 3) and genipin, crocin, and its derivatives (Table S19), which are water-soluble pigments. These phytochemicals are responsible for providing the fruit's characteristic antioxidant activity, as well as an antidepressant, antidiabetic, anti-insomnia, antihypertensive, anti-AD, and anti-PD properties[208].

The extracts of *Gardenia* fruits have been documented to possess different anti-AD properties, such as cholinesterase inhibitory activity and Aβ aggregation suppression. Li et al.[209] conducted various neuroprotective assays to evaluate the potential effects of 26 plants used in TCM, including *G. jasminoides* fruits, in inhibiting *in vitro* AChE and butyrylcholinesterase (BuChE), Aβ aggregation suppression, antioxidant and scavenging activities. 20 g powder plant samples were extracted with 200 mL 95% ethanol in an ultrasonic bath at room temperature. The 95% ethanolic extracts inhibited 34.50% and 43.74% of AChE activity at 100 and 200 mg/mL, respectively, and 14.66% and 23.50% of BuChE activity at the same concentrations. For the Aβ aggregation suppression assay, 50 mmol/L Aβ solution was treated to different concentrations of *G. jasminoides* fruit extracts and incubated for 48 h. At 100 mg/mL, the extract suppressed Aβ aggregation by 32.63%. Further studies have demonstrated that not only Aβ aggregation is affected by *G. jasminoides*, but also tau protein hyperphosphorylation, and GSK-3β activity. Gao et al.[210] investigated the potential therapeutic effect of geniposide on streptozotocin-induced AD model in rats. A single injection of geniposide (50 μmol/L, 10 μL) to the lateral ventricle prevented streptozotocin-induced spatial learning deficit by about 40% (in the Morris water maze test) and reduced tau phosphorylation by about 30%. Geniposide was also able to reduce streptozotocin-induced GSK-3β hyperactivity.

G. jasminoides fruit also affect the serotonergic, dopaminergic and GABAergic systems. Kim et al.[211] fractioned an 80% methanolic extract, and several compounds were isolated, namely, protocatechuic acid, geniposide, 6′-*O*-*trans*-*p*-coumaroylgeniposide, 3,5-dihydroxy-1,7-bis(4-hydroxyphenyl) heptane, and ursolic acid. Each isolated compound was tested MAO-A or MAO-B inhibitors. All compounds were more potent MAO-B inhibitors than MAO-A. 3,5-Dihydroxy-1,7-bis(4-hydroxyphenyl) heptane was the strongest MAO-A inhibitor (IC_{50} = 400 μmol/L) For MAO-B, some compounds were reported as displaying strong inhibition rates, with 6′-*O*-*trans*-*p*-coumaroylgeniposide having an IC_{50} of 127 μmol/L, followed by 3,5-dihydroxy-1,7-bis(4-hydroxyphenyl) heptane (IC_{50} = 196 μmol/L) and geniposide (IC_{50} = 223 μmol/L). In addition, Liu et al.[212] evaluated the effects of geniposide administration in the behavior of mice under FST and TST. The results showed that geniposide significantly reduced the recorded immobility time in both tests, with no abrupt changes to the locomotive action of the mice. Further investigation on the neuronal mechanisms showed that geniposide increased serotonin levels in the hippocampus and cortex.

Choi et al.[213] subjected ICR mice to different behavioral tests after orally administering 100 and 200 mg/kg doses of *G. jasminoides* fruit, as well as intraperitoneally injecting both genipin and geniposide, at doses of 2−20 mg/kg, for 1 week. The control group was administered with saline solution, while the positive control group was administered with diazepam. The mice were subjected to locomotor activity, horizontal wire, and elevated maze tests. *G. jasminoides* fruit extract administration decreased locomotor activity, falling frequency in the horizontal wire test, and increased the total time spent on the open arms of the elevated maze test. For the isolated compounds, geniposide only increased the time spent in the elevated maze test's open arms. In addition, human IMR-32 cells were treated with the *G. jasminoides* fruit extracts, as well as the isolate compounds, to measure intracellular chloride ion influx. Geniposide and *G. jasminoides* fruit extracts were reported to significantly increase the intracellular influx in a dose-dependent manner. The authors concluded that *G. jasminoides* fruit extracts could induce relaxation and calmness and suggested that the intracellular chloride influx effects were mediated by $GABA_A$ receptor interaction.

Geniposide has also been documented as displaying a role in preventing the progression of synucelinopathies. Uddin et al.[214] divided C57BL/6N mice into five groups: a saline control, a geniposide positive control, an MPTP negative control, and two test groups. The test groups were injected with 100 mg/kg doses of geniposide (i.g.) and with 20 mg/kg doses of neurotoxin MPTP (i.p.) or miR-21 (i.c.), a micro-RNA capable of reducing LAMP2A receptor expression in the brain, thus blocking α-synuclein clearance. The mice group treated with MPTP or miR-21 revealed that the α-synuclein levels were increased, compared to the saline control group, as well as had reduced LAMP2A receptors. However, when treated with geniposide, these effects were suppressed.

The folkloric use of *G. jasminoides* fruits in medicine is typically derived from the antioxidant activity that the fruits exert. Kang et al.[215] reported the free radical scavenging activities of *G. jasminoides* fruit methanol extracts fractioned with n-hexane, butanol, water, and ethyl acetate. In the $O_2^{\bullet -}$ scavenging assay, the aqueous extracts (100 and 200 μg/mL) exerted the most significant scavenging activity, at 54.6% and 68.8%, respectively. The ethyl acetate fraction exerted the highest •HO scavenging activity displaying 32.1% (at 100 μg/mL) and 46.7% (at 200 μg/mL). Additionally, Gardenia fruit aqueous extracts have been reported to mimic the activity of both superoxide dismutase and catalase[216].

2.21. *Poria cocos fungus*

Wolfiporia extensa, or *P. cocos*, is a fungus that typically grows in the rotten bark of pine trees. The *P. cocos* sclerotium is an edible and medicinal component that has been cultivated and implemented in TCM for more than two thousand years. The fungus does not possess flavonoids or phenolic acids in its composition, rather, it is rich in terpenes and polysaccharides. The fungus has been reported to exert a lot of bioactivities, including anticancer, anti-inflammatory, antioxidant, antiviral and neuroprotective, among others[217].

The consumption of *P. cocos* extracts has been documented to improve cognitive abilities, showing its potential for AD treatment. Lin et al.[218] evaluated the cognitive effects of an herbal mixture containing *P. cocos* sclerotium, *Atractylodes macrocephala* Koidz Rhizome, and *Angelica sinensis* root, as well as the effects of each plant on ICR mice's cognitive performance and AChE and BuChE activity. The two tested mice groups were injected with 4 mg/kg scopolamine dose, along with 200 mg/kg and 600 mg/kg of herbal mixture aqueous extract. The herbal mixture-treated groups reported less total swimming time compared to the negative control group (only 4 mg/kg scopolamine dose), while the latency time in the passive avoidance test

increased compared to the scopolamine group. *In vivo* assays also showed that the herbal mixture was also able to inhibit 71.4%−85.7% at 200 and 600 mg/kg, respectively, reversing the effect of scopolamine. In addition, Park et al.[219] reported the importance of *P. cocos* extracts in preventing Aβ-induced cell death. The authors evaluated the effect of the aqueous extract of *P. cocos* sclerotium (5−125 μg/mL) on Aβ-induced toxicity in PC12 cells. The administration of *P. cocos* water extracts induced the attenuation of the cytotoxic effects of Aβ in a dose-dependent manner, with the 125 μg/mL sample enabling cell viability over 85%.

P. cocos protection against depressive states was also investigated. Huang et al.[217] evaluated the effects of administering *P. cocos* extracts (100, 300 and 900 mg/kg, o.g.) on rats subjected to a FST and unpredicted chronic mild stress (UCMS), for 28 days and 5 weeks, respectively, with subsequent measurement of the dopamine and serotonin levels in the frontal cortex. The results showed that sucrose preference during the UCMS paradigm was increased and immobility time in the FST was reduced with the administration of *P. cocos* aqueous extract. Moreover, the extract also attenuated UCMS-induced turnover rate of dopamine and serotonin in the frontal cortex. Finally, the extract also inhibited the inflammatory response activated by UCMS, by reducing the expression of p38, NF-κB and TNF-α in the frontal cortex.

Hu et al.[220] evaluated the anti-tyrosinase activity of the poricoic acid A and total triterpene extracts. At 200 μg/mL, they exerted good inhibitory rates, approximately 40%, and 60%, respectively, with the latter exhibiting similar inhibition rates to the arbutin (positive control).

Pachymic acid (Fig. 3, Table S20) has been described as an anxiolytic agent, which is an underlying effect mediated by the GABAergic system. Shah et al.[221] evaluated the effect of muscimol (0.2 mg/kg), a $GABA_A$ agonist, or pachymic acid (1, 3, and 5 mg/kg) in pentobarbital (40 mg/kg, i.p.)-treated ICR mice. The administration of pachymic acid (5 mg/kg) significantly decreased the latency of sleep and increased total sleep time of the test subjects. in a similar manner to muscimol After these tests, the mice were sacrificed, and their hypothalamus were cultured to investigate the role of the compounds in intracellular chloride influx and $GABA_A$ receptor expression assays. The treatment of the hypothalamic cells with 10 μmol/L pachymic acid significantly increased the inward flow of chloride ions at a rate almost three times that observed in the control, while the treatment with 5 μmol/L pachymic acid over-expressed protein levels for α- and β-subunits, but no γ-subunits, of $GABA_A$ receptors. Althogether, these results suggest that pachymic acid is an agonist of $GABA_A$ receptors.

Due to the phytochemical composition of *P. cocos*, several studies regarding its antioxidant activity have also been conducted. Pachymaran, a derivative from *P. cocos* polysaccharide, was reported to moderately scavenge $O_2^{\bullet -}$, •OH, and H_2O_2 radicals, with IC_{50} of 2.57, 7.66, and 4.56 mg/mL, respectively[222]. Moreover, 29-hydroxypolyporenic acid C and polyporenic acid C (Fig. 3, Table S21) are strong •NO scavengers, with an associated IC_{50} of 16.8 ± 2.7 and 18.2 ± 3.3 μmol/L, respectively[223].

2.22. *Citrus maxima L. and other citrus fruits*

C. maxima L., or pummelo or shaddock (Rutaceae Family), is a citrus fruit cultivated mostly in South Asian countries, such as Malaysia and southern China. The fruit, like most citrus, is rich in vitamin C. In recent years, the commercialization of pummelo has gained attraction in several countries' domestic markets, either as beverages or sweets. The peel's composition differs from that of the pulp, exhibiting a higher alkaloid, phenolic acid, and flavonoid content (Table S21)[224]. Most studies on pummelo peel extracts attest to their favorable antioxidant and free radical scavenging activity, which can delay the oxidative stress impact in neurodegenerative diseases. Moreover, other species from *Citrus* genus have been studied due to their flavanone content.

For instance, Ademosun and Oboh[225] tested orange, grapefruit and pummelo peels against AChE activity. All extracts displayed inhibitory activity around 80%−90% at 400 μg/mL.

Moreover, Odemosum and Oboh[226] reported that pummelo peel aqueous extract behaved as a weak BuChE (IC_{50} = 4.42 mg/mL) and MAO-B (IC_{50} = 1.93 mg/mL) inhibitor, and Abirami et al.[227] evidenced strong tyrosinase (ranging from 76.95% to 80.79%) and AChE ((75.71%−79.74%) inhibitory rates from pummelo juice samples.

In vivo studies have demonstrated the protective effect of citrus peels and flavanones against amnesia and cognitive impairment. Heo et al.[228] reported that the administration of naringenin (Fig. 3) (4.5 mg/kg) isolated from *Citrus junos* Siebold ex Tanaka improved the short-term memory loss in scopolamine-induced ICR mice. While treatment with scopolamine (1 mg/kg) significantly shortened the latency time in the retention trial and displayed significantly impaired spatial working memory in the Y-maze test, naringenin reverted these effects. Moreover, the authors also verified that the ethyl acetate fraction prepared from *C. junos* methanolic extract (the one containing naringenin) displayed anti-AChE activity.

The pummelo peel contains naringin (naringenin-7-*O*-glucoside, Fig. 3). Its precursor, naringin dihydrochalcone, has been reported to suppress Aβ aggregation and plaque formation. Yang et al.[229] subjected APP/PS1 transgenic and wild-type mice to a behavioral test (Morris Water Maze test). The transgenic group was orally administered with 200 μL of 100 mg/kg daily doses of naringin dihydrochalcone, or 200 μL vehicle solution, for 3−4 to 6−7 months. The observed performances of the mice revealed that the vehicle-treated group took more time to locate the platform because of cognitive decline; however, the naringin dihydrochalcone-treated group did not show any significant decreased cognitive impairment when compared to the wild-type group. After the behavioral tests, the mice were sacrificed and the brain tissue was removed for Aβ-amyloid plaque and astrocyte, microglia, and neuron screening. It was shown that Aβ plaque deposits and neuroinflammation were significantly reduced in the naringin dihydrochalcone-treated group when compared to the vehicle-treated group.

As a citrus fruit, pummelo shows great antioxidant activity. Abirami et al.[227] reported that samples of juice from red and white pummelo were able to scavenge 20.50% and 18.70% of total $O_2^{\bullet -}$ radicals, respectively, and 46.43% and 48.09% of total •HO radicals.

3. Recent clinical trials

In the last few years, several clinical trials have been conducted with plant preparations containing the species reviewed in this paper, as well as with species alone or their marker compounds.

For instance, a 6-month trial (NCT00164749) showed that there were not differences between curcumin treatment and placebo in terms of cognitive decline, but curcumin was able to raise Vitamin E in plasma and increased serum Aβ40, possibly by

promoting Aβ deposits disaggregation in the brain. The authors suggested longer and larger trials to test the efficacy of curcumin for treating AD in order to investigate whether there are greater deterioration on placebo than in curcumin group[230].

A randomized, double-blind, placebo-controlled clinical trial (NCT00010803) conducted in 6 academic medical centers in the USA between 2000 and 2008. Three thousand sixty-nine community volunteers aged 72−96 years with normal cognition (n = 2587) or mild cognitive impairment (n = 482) were assessed every 6 months for incident dementia. Treatments consisted of administration of twice-daily dose of 120-mg extract of *G. biloba* (n = 1545) or placebo (n = 1524). From those, 523 individuals developed dementia (246 receiving placebo and 277 receiving *G. biloba*) with 92% of the dementia cases classified as possible or probable AD, or AD with evidence of vascular disease of the brain. In this study, *G. biloba* was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with mild cognitive impairment[231,232]. Similarly, in the clinical trial No. NCT00276510, 2854 participants aged 70 years or older who spontaneously reported memory complaints to their primary-care physician in France were followed-up for 5 years. Participants were randomly allocated to a twice daily dose of 120 mg EGb761 (1406 participants) or placebo (1414 participants). At the end of 5 years, 61 participants in the ginkgo group had been diagnosed with probable AD compared with 73 participants in the placebo group. The authors of the study concluded that long-term use of EGb761 extract did not reduce the risk of progression to Alzheimer's disease compared with placebo[233].

On the other hand, *P. ginseng* enhanced the cognitive performance in Alzheimer disease patients as shown in clinical trial nr. NCT00391833. In this study, AD patients were randomly distributed by the ginseng (n = 58) or the control group (n = 39), and the ginseng group was treated with *P. ginseng* powder (4.5 g/day) for 12 weeks. After ginseng treatment, the cognitive subscale of Alzheimer's Disease Assessment Scale (ADAS) and the Mini Mental State Examination (MMSE) score began to show improvements.

In an eight-week prospective study (NCT01496248), Korean red ginseng at doses of 3 g/day were given to 35 female outpatients (18−65 years, 45.1 ± 9.5), who were remitted from major depression with residual symptoms. Patients showed significant improvements but no comparison with a placebo group was made[234].

Ringman et al.[235] conducted a 24-week randomized, double blind, placebo-controlled study of Curcumin C3 Complex® with an open-label extension to 48 weeks (NCT00099710). Thirty-six persons (mean age = 73.5 years) with mild-to-moderate AD were randomly divided into 3 groups: placebo; 2 g/day, or 4 g/day of oral curcumin for 24 weeks. For weeks 24 through 48, patients receiving curcumin continued with the same dose, while subjects previously belonging to placebo group were randomized in a 1:1 ratio to 2 g/day or 4 g/day. Five subjects from the curcumin group left the study due to gastrointestinal problems. No differences were verified between curcumin and placebo groups concerning clinical (ADAS-Cog) and biomarkers (levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ in plasma and levels of $A\beta_{1-42}$, t-tau, p-tau181 and F2-isoprostanes in cerebrospinal fluid).

The safety of single-dose intake of *M. pruriens* powder from roasted seeds was investigated in a double-blind, randomized, controlled, crossover study (NCT02680977). Eighteen patients with advanced PD were randomized into 6 groups: (1) marketed levodopa/benserazide at 3.5 mg/kg (reference treatment); (2) high-dose of *M. pruriens* (17.5 mg/kg); (3) low-dose of *M. pruriens* (12.5 mg/kg); (4) pharmaceutical preparation of levodopa (17.5 mg/kg) without benserazide; (5) *M. pruriens* plus benserazide (3.5 mg/kg); (6) placebo. Changes in motor response at 90 and 180 min, side effects, alterations in blood pressure and heart rate, and the severity of dyskinesias were recorded. Subjects in groups 3 and 2 had fewer diskynesias and side effects than those in the group receiving the reference treatment. Moreover, similar motor response was recorded between groups 1 and 3 while greater motor improvement was found in group 2 than in group 1[113].

Wright et al.[236] investigated the pharmacokinetics and pharmacodynamics of key components (triterpenes and caffeoylquinic acids) of a standardized aqueous extract of *C. asiatica* in 5 subjects (between 67 and 77 years old) with mild cognitive impairment receiving donepezil (NCT03937908). One participant left the trial due to SARS-CoV-2 restrictions and the remaining four were divided into two groups: 2 participants receiving 2 g of extract and then 4 g of extract; and 2 participants receiving 4 g and then 2 g of extract. The triterpene and phenolic acid profile of plasma and urine was studied showing that the triterpene aglycones, asiatic acid and madecassic acid, were identified in plasma and urine, while the parent glycosides (asiaticoside and madecassoside, Fig. 3), present in higher amount in the extract, were absent in plasma and had limited renal excretion. Concerning phenolic acids, monocaffeoylquinic acids (3-, 4-, and 5-*O*-caffeoylquinic acids) and di-caffeoylquinic acids (1,3-, 1,5-, 3,4-, 3,5-, and 4,5-di-*O*-caffeoylquinic acids) showed delayed absorption and limited presence in plasma or urine, while their metabolites (caffeic, dihydrocaffeic, dihydroferulic, ferulic, 3-(3-hydroxyphenyl)propionic) and isoferulic acids) were detected in plasma and urinary excretion products. Moreover, the extract was able to activate *NRF2* gene expression, thus protecting against toxic and oxidative insults.

A randomized controlled trial (NCT01608217) was developed to study the efficacy and safety of a low dose of THC (1.5 mg) in the treatment of neuropsychiatric symptoms in dementia. Twenty-four patients received THC and 26 received placebo, three times daily for three weeks. Participants were 78.4 years old (mean value), 50% male and 50% women. Oral THC showed no benefit in neuropsychiatric symptoms, since there was no difference between THC and placebo groups, but was well tolerated[237].

Table 1 summarizes 35 clinical trials searched in https://clinicaltrials.gov/, where the neuroprotective effect of the TCM plant species was investigated.

Some of these clinical trials have shown that there are no differences between the treatment group and the placebo group. However, some of the limitations pointed out in these studies are the small size of participants, the short duration of the study and the advanced stage of disease progression of the participants; so, future clinical trials should be designed to avoid these factors.

4. Plant toxicological studies

As reported in the preceding sections, all plants (and fungus) displayed anti-AD, anti-PD, anti-HD, anti-depression properties with different rates. However, traditional medicine acceptance suffers both from a lack of knowledge on the plant's specific beneficial properties and a misconception of the benefits and denial of side effects of a plant because of it being a "natural

product", which makes this area a controversial one. According to Feng et al.[238] the toxicity caused by TCMs has now become a serious problem not only in China but globally, being responsible for several adverse effects including drug-induced liver injury, kidney failure, cardiotoxicity, neurotoxicity and reproduction toxicity.

Many compounds found in herbal medicines exhibit low bioavailability. For instance, the bioavailability of polyphenols (ubiquitous in medicinal plants) and ginsenosides (characteristics from *P. ginseng*) is usually less than 10% and 0.1%, respectively. Therefore, the unabsorbed compounds can easily cross small intestine and target colon, where they will directly interact with gut microbiota[238]. Then, gut microbiota will transform the parent compounds into metabolites with higher bioavailability. Polysaccharides will be transformed into oligosaccharides, short-chain fatty acid (SCFAs) and other secondary metabolites; flavonoids will lose glycosyl moieties; polyphenols will lose organic acids, glucuronides and glucosides groups to be transformed into their correspondent aglycones; and saponins will lose the glycosyl moiety[239]. Several studies have shown that the enzymes released by gut microbiota can increase or decrease the toxicity of TCM compounds. Khanal et al.[240] showed that fecalase transforms baicalin (a glycosylated flavone from *S. baicalensis*) to baicalein (aglycone), and that baicalein display less toxicity on HepG2 cells than the parent compound. On the other hand, geniposide (found in *G. jasminoides*) is transformed into genipin (aglycone), which shows higher toxicity on HepG2 cells[241] as well as daidzin (an isoflavone from *G. glabra*) which is transformed by gut microbiota into daidzein and calycosin, metabolites with much more toxic than the parent compound[242]. Moreover, the direct contact between TCMs and gut microbiota can also lead to changes in gut microbiota composition, which is not only promoted by the natural products as well as by TCM contaminants, such as insecticides, herbicides, fungicides and heavy metals[238].

Regarding specifically the plant species reviewed in this paper, the adverse effects of *C. sinensis* are due to two main factors: the presence of caffeine, and the effects on metal bioavailability[243]. During the fermentation process, black tea leaves lose weight, which gives the consumer the perspective that a higher dose of leaves is necessary to counteract this loss in plant mass. This correlates to an increase in caffeine consumption, which can lead to insomnias, nervousness, restlessness, motor agitation, cardiac arrhythmia, and gastrointestinal disturbance[244]. *C. sinensis* has also been reported to be a viable option in soil treatment methods or phytoremediation. Karak et al.[245] evidenced the plant's potential in the extraction of aluminum from municipal waste to the aerial parts. Aluminum overexposure has been linked with cognitive impairment effects, and in severe cases, to dementia and cancer[246]. The consumption of black tea has also been associated with reduced absorption of dietary iron. It has been suggested that both tannins and catechins found in *C. sinensis* absorb non-heme iron. This property suggests that patients suffering from anemia should avoid any sort of *C. sinensis*-based tea[243].

Ginseng is a relatively safe plant to consume moderately for vast periods[247]. The negative effects of ginseng are mostly associated with high dose intake, also known as "ginseng abuse disorder". Siegel[248] evaluated 133 patients that ingested high doses of ginseng for two years. Most of the subjects reported excitatory effects, such as sleeplessness, euphoria, and a feeling of well-being. However, other effects included diarrhea, nausea, skin eruptions, edema, and in some cases, hypertension, hypotension, appetite loss, and depression.

Chrysanthemum has been classified as a safe plant to ingest chronically. Li et al.[249] conducted a case study, where the effects of chronic administration of chrysanthemum extracts for 2 and 26 weeks to mice were evaluated. The results showed that no toxicological changes were found in any group in terms of body weight, food, and water consumption, hematologic examination, blood biochemical examination, organ weight, and microscopic histopathologic examination. The main side effect of chrysanthemum is derived from pyrethrin, which is a natural insecticide produced in the flower. This compound has been reported to exert allergy-related symptoms, such as skin irritation, as well as nausea, headaches, vomiting, among others[250].

Dandelion is classified as an allergen, which usually includes symptoms such as skin irritation and eczema[251]. Posadzki et al.[252] classified dandelion as a moderately severe plant, evidencing its reported effects, such as gastrointestinal upset, vomiting, lack of appetite, liver damage, and platelet aggregation. Another consideration regarding dandelion is the plant's phytoremediation properties. Bini et al.[253] reported the ability of dandelion to absorb and translocate iron and zinc from the soil to the aerial parts of the plant.

Licorice is considered safe, however, excessive consumption of glycyrrhizin can lead to cardiovascular problems, such as hypertension, hypokalemia, and hypoglycemia. Glycyrrhizin is metabolized in the body into glycyrrhetinic acid, which increases the levels of cortisol in the kidneys. Cortisol activates renal mineralocorticoid receptors, which in turn deregulates sodium reabsorption and potassium release[254]. The excessive intake of glycyrrhizin salts has also been reported to cause hypoglycemia[255].

Bamboo leaf extracts are safe to ingest in regular doses. Lu et al.[256] confirmed the overall safety of ingesting bamboo leaf extracts, by reporting no significant adverse effects on mice who were chronically administered bamboo leaf tea. Overconsumption of bamboo leaf extracts has been reported by Yakubu et al.[257] to damage the kidneys and the liver. Bamboo leaf tea was also found to decrease hormone levels in the ovaries of pregnant rabbits, which increases the probability of a failed pregnancy occurring. No studies were conducted yet on the potential side effects of bamboo leaf tea on the thyroid, however, bamboo shoots have been evidenced to inhibit thyroid peroxidase, a crucial enzyme involved in the production of thyroid hormones[258].

From all the plant components of *C. sativa*, the seeds are the safest for consumption, in moderate doses. Hemp seeds have been associated with some mild adverse effects, mostly related to gastrointestinal upset, bloating, and abdominal pain[259]. Hemp seed has been reported as a potential therapeutic agent to integrate hypertensive treatment methods[260]. This is mainly due to the seeds content of linoleic and α-linoleic acids, at a 2/1 ratio, which has been linked with preventing several chronic diseases, such as diabetes, coronary artery disease, inflammation, cancer, hypertension, among others.

No major adverse effects on adlay seed extracts administration were reported. Adlay seeds have been evidenced to prevent cancer, metastasis, hypertension, arthritis, asthma[261] and reduce blood glucose levels[262].

The dietary intake of purslane has been recommended for its multiple health benefits since it is rich in vitamin C and fatty acids, aside from the effects against neurodegenerative diseases[263]. However, overconsumption can cause kidney problems due to its high content of insoluble oxalates. Oxalates are known to bind to calcium ions and form deposits, or kidney stones. Kidney overexposure to oxalate-calcium deposits can lead to

nephropathic effects, such as renal tubular atrophy and interstitial fibrosis[264].

Chinese hawthorn berries have been documented as safe treatment agents in various cardiovascular diseases, such as cholesterol reduction, blood pressure reduction, chronic heart failure prevention, among others. Studies suggest that hawthorn berry intake should be intermittent[265], as periodic consumption may lead to hypotension.

Cape jasmine berries have been considered non-toxic to human patients, however, there have been no reports on the plants' adverse effects. *Gardenia* species have been reported to induce toxic effects on domesticated animals, such as diarrhea[266]. Tian et al.[267] evidenced that geniposide may cause health problems. Four groups of mice were administered with 3 geniposide samples (25−100 mg/kg/day) plus a control group for 26 weeks. The results showed that the group that consumed 100 mg/kg sample had significant liver and kidney damage, as well as anemia. Cape jasmine berries have also been reported to alleviate hypertension[268].

There is a lack of studies that thoroughly assess the adverse effects of *P. cocos* intake. To date, only the potential benefits have been investigated. The polysaccharides of *P. cocos* were reported as non-toxic[269]. In TCM, *P. cocos* is administered freely, with excessive doses, which can allude to its safety. *P. cocos* polysaccharides have the ability to remove calcium-oxalate deposits from the kidneys[269].

Various citrus peels, including pummelo, have been reported to be safe for consumption and nontoxic. Citrus peels are usually composed of the same phytochemicals of their respective fruit. Currently, no assays on the potentially toxic effects of pummelo peel were conducted. The primary adverse effects of citrus peel consumption derive from the pesticides spread in the peels to prevent microbial-induced degradation. Ortelli et al.[270] evaluated the presence of 38 different fungicides, insecticides, and acaricides across 240 citrus fruits, including pummelo. The authors indicated that the regulated levels of metalaxyl found in citrus fruits are lower in pummelo, which indicates that this is a recurrent fungicide applied in the fruit. Exposure to this kind of fungicides involves carcinogenic, mutagenic, reproductive, and organ failure effects.

Despite the numerous neuroprotective effects of *G. biloba*, several reports indicate that the plant is associated with some adverse effects. According to the Committee on Herbal Medicinal Products[271], health risks include gastrointestinal problems, headaches, and hypersensitive reactions. The leaves also contain dangerous components, such as ginkgolic acids, whose excessive consumption has been linked with neuronal death by increasing phosphatase activity[272], and 4′-*O*-methylpyridoxine, a neurotoxin found in the seeds and leaves of *G. biloba* that has been evidenced to inhibit $GABA_A$ receptor synthesis[273].

5. Conclusions

The increase in average life expectancy in recent decades makes age-related neurodegenerative diseases an increasingly common reality in clinical practice now and in the future. Today, neurodegenerative and neuropsychiatric diseases affect millions of people around the world. These diseases are a problem in society due to the growing number of individuals affected by these pathologies and the lack of proper cure.

In this context, natural products are gaining importance in the pharmaceutical industry as a source of inspiration for new bioactive molecular patterns. As demonstrated in this review, plants have been shown to be preventive of various neurological, cardiovascular, and carcinogenic diseases and also to have the potential to improve memory, learning and cognitive skills, due to mainly their antioxidant properties, interaction with enzymes and receptors, activation of genes and signaling pathways.

With the increasing commercialization and consumption of these species, health authorities must guarantee that safe and well-characterized standardized extracts are supplied to the consumers and must also certify health claims based on clinical trials. In our opinion, although there is a huge number of papers published on Chinese medicinal plants, there is still scarce information about their chemical composition, exact mechanism of action, effective and potentially toxic doses, their bioavailability and metabolism and future studies should focus on these topics. Moreover, many of the reviewed clinical trials also pointed out limitations that must be overcome in future studies, such as a reduced number of participants and short duration, which hampered comparisons with the placebo groups.

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Author contributions

João Moreira and Mariana Machado have selected the published information to be included in this review paper and have prepared the first draft of the manuscript. Mónica Dias-Teixeira and Clara Grosso have selected the plant species to be covered in this review paper. Mónica Dias-Teixeira, Clara Grosso, Ricardo Ferraz and Cristina Delerue-Matos have critically reviewed and edited the manuscript draft. All authors have approved the final version of the manuscript.

Conflict of interest

We declare no conflict of interest.

Appendix A. Supporting information

Supporting data to this article can be found online at https://doi.org/10.1016/j.apsb.2023.06.009.

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