Nat. Volatiles & Essent. Oils, 2021;8(6): 6733-6760

NVEO
Natural Volatiles & Essential Oils

Herbal Treatments For Dementia And The Role Of Natural Products

Joshi Ankur [1*], Malviya Neelesh [1,2]

1. Mandsaur University, Rewas Dewda Road, SH - 31, Mandsaur, Madhya Pradesh- 458001
2. Smriti College of Pharmaceutical Education, MR-11, Dewas Naka, Indore, Madhya Pradesh-452010

***Corresponding Author:** Joshi Ankur
ankurpharmacology@gmail.com

Abstract
Dementia is a disease that causes mental and cognitive decline. It's often linked to neurodegenerative diseases including Alzheimer's, Huntington's, and Parkinson's, and involves cerebral blood flow, toxins, mitochondrial malfunction, and oxidative damage. Most (semi-)synthetic Alzheimer's and dementia drugs have considerable adverse effects. It supplies a varied variety of plant-derived lead molecules for future medicinal research. Around the world, ethnomedicinal herbs are utilised to treat dementia. Using well-known databases, we compiled a list of 90 medicinal plants used to treat dementia. We also study five essential therapeutic plants or plant genera' physiological effects and method of action. We also studied mitochondrial dysfunction and dementia. We conclude that some plant-derived drugs may be effective dementia treatments, although more research is needed.

Keywords: Alzheimer’s disease, amyloid fibrils, β-amyloid, dementia, ethnopharmacology, herbal drugs

Introduction

Alzheimer's disease is a progressive loss of mental and cognitive ability. Memory loss lowers an individual's independence (1,2,3). Distinct causes of dementia exist. All reversible causes: substance addiction, subdural hematoma, malignancies, and CNS infections (4). Alzheimer's, Parkinson's, and Huntington's diseases are incurable dementia causes (5).
The most important risk factor and predisposing condition for dementia is ageing (6,7). Alzheimer's, Parkinson's, and Huntington's are the most common dementias (ALS). Vascular dementia is another frequent dementia. They often accompany neurodegenerative dementias (8). Destruction of the blood-brain barrier (BBB) and neurovascular units in hemispheric white matter causes vascular cognitive deficits (8). Other illnesses can cause dementia. Afebrile infections, such as AIDS, which causes indirect brain damage via immune activated macrophages (9,10). Environment can aggravate dementia. Toxicants such mismanaged medicines (11,12) and pesticides cause oxidative stress and neuronal cell death (13). Along with the other parts, dementia is heritable. Alzheimer's disease and gene polymorphisms (14). For example, EOAD is linked to mutations in PSEN1, PSEN2, and APP on 21q (15). Spontaneous lead-onset AD is caused by the apolipoprotein E (APOE) gene at 19q13.2 (16,15,17). In Alzheimer's disease, the most prevalent APOE alleles are 2, 3, and 4. (18,15,17). Inheritance of APOE 4 genotype and Alzheimer's disease pathology (15). Patients with APOE 4 have a 3-to-12-fold greater risk of LOAD and dementia. PSEN1 mutation reduces LOAD risk, although APOE2 mutation reduces LOAD risk (19,15). Other A-independent mechanisms that contribute to AD development include neurovascular, synaptic plasticity, cholesterol homeostasis, and neuroinflammation (15). Having the APOE4 4 allele increases the risk of cerebral amyloid angiopathy and age-related cognitive impairment (20).

Dementia is a very common condition. Despite its prevalence, some research suggests that only 10% to 50% of all dementia patients are diagnosed in low-middle-income countries and high-income ones, respectively (21). Furthermore, because dementia primarily affects the elderly, and the number of individuals over the age of 65 is fast increasing due to global increases in life expectancy, the number of dementia cases will rise in consecutive years. According to Quaglio G et al.2016 (22), dementia affects 1.5–2% of Europeans nowadays. In a similar vein,(21) projected that 47 million people worldwide suffered from dementia in 2015. By 2050, this number may have risen to almost 131 million (21). Dementia will impact one million people in the United Kingdom alone by 2021. (23). The G7 meeting in December 2014 emphasised the significance of developing new dementia treatments. Dementia should be handled as a global priority, with the main goal of introducing effective therapy by 2025, according to the forum attendees (24).

Dementia is a substantial societal burden, both in terms of human suffering and financial costs. In high-income countries, dementia is the sixth leading cause of mortality (25). The health status of the patients had a negative impact on their caretakers, who had fairly high levels of depression symptoms (26). According to the World Alzheimer Report 2016 (21), people with dementia have inadequate access to healthcare not only in low-income nations, but also in high-income countries, due to high costs and insufficient diagnostic methods. Dementia management is particularly costly due to the patients' need for long-term and expensive care (27). In the UK, various dementia-related costs, such as health services, social services, unpaid careers, and others, total roughly e23 billion per year (28). The fact that the current yearly cost of dementia in the United Kingdom is larger than the present annual cost of heart disease and cancer combined exemplifies this economic burden (28). According to another estimate, dementia and Alzheimer's disease will cost the United States roughly USD 1 trillion by 2050. (25).

This article provides a broad overview of ethnomedicine's use in dementia care. We also focus on five well-known plants used to treat dementia and highlight the chemicals responsible for the plant's bioactivity. There is presently no effective treatment for dementia (29). Learn about various plants' active chemicals and how to use them. Their method of action may lead to the creation of novel dementia medicines. The natural product pool continues to be an important drug discovery source (30). In this perspective, the present review may help create ethnomedicine-derived medicines for dementia treatment.

Table No. 1 Most common forms of dementia (29).

Dementia form	**Neuropathology**	**Symptoms**	**Dementia cases (%)**
AD-related dementia	Aβ plaques, neurofibrillary tangles	Memory deficits, depression, poor judgment or evidence of mental confusion	50–80
Vascular dementia	Decreased or interrupted blood flow to the brain, hypoperfusion, oxidative stress	Similar to AD, but less affected memory	20–30
Dementia with Lewy bodies	α-Synuclein aggregates in neurons and glial cells (cortical Lewy bodies)	Similar to AD and less to PD, hallucinations, tremors, impaired attention	<5
Frontotemporal dementia	Accumulation of MAP tau, atrophy of frontal and temporal lobes	Changes in social behavior, difficulties with language	5–10

Frequent forms of dementia

Most dementia cases are Alzheimer's (50–80% of cases) (31,29), followed by vascular dementia (20–30%) (29, 8) (between 15 percent and 5 percent) (29). These illnesses cause abnormal protein buildup in the brain. For example, A peptides create amyloid plaques in AD, while TDP-43 protein accumulates in FTD (32). The frontal and anterior temporal lobes of FTD patients show significant atrophy, with microvacuolar degeneration and pyramidal neuron loss (33,34). (35). Pathologic tau accumulation is frequent in AD and FTD (36). Hyperphosphorylated tau protein causes intraneurial neurofibrillary tangles (37). Hypoperfusion, oxidative stress, and inflammation are connected to cognitive decline (8). Synuclein aggregates in neurons

and glia define Lewy body dementia (38). It might also be claimed that dementia symptoms are extremely similar (29). Its pathophysiology is necessarily more complicated (6). Many AD markers are seen in AD brains (6). Memory-related neurotransmitter acetylcholine (ACh) is one of these markers, as is vascular injury (39, 40). As a result, mitochondrial dysfunction may be a target for treating Alzheimer's disease and associated dementias (41). This is described in the section Mitochondrial Dysfunction and Neurodegeneration.

Mitochondrial dysfunction and neurodegeneration

Mitochondria are double membrane-enclosed organelles that perform numerous cellular functions, including adenosine triphosphate (ATP) production (energy conversion), calcium handling, and apoptosis-programmed cell death (42). Moreover, mitochondria are vital in many other metabolic activities (42). Thus, mitochondrial abnormalities are predictable in energy-dependent disruptions, inflammation, and ageing (43,44). Dementia-associated dementia has mitochondrial malfunction as one of the pathogenic characteristics, due to mitochondria's crucial involvement in neuronal cell survival or death (45). For example, mitochondrial network remodelling may be important in neurodegeneration (46,47). The mitochondrial cascade concept proposed mitochondrial dysfunction as an AD pathogenesis episode (45,48). Furthermore, mitochondrial dysfunction causes an increase in reactive oxygen species (ROS) and alters mitochondrial dynamics (49,50,51). A recent study found a link between ROS and mitochondrial dynamics in early neurodegeneration (52). The buildup of A in mitochondria causes mitochondria-mediated toxicity (50). Recent research shows that mitochondrial malfunction regulates ROS and intracellular calcium levels in neuronal cells (53). The NAD-dependent deacetylase sirtuin-3 (SIRT3) protein is linked to mitochondrial and neuronal damage, as demonstrated by Lee et al. utilising AD human brain tissues (54). Thus, mitochondrial failure is a pathological hallmark of neurodegenerative illnesses including Alzheimer's and dementia (50,42). Figure 1 shows detailed information on mitochondrial activity related with dementia.

The foregoing highlights the role of oxidative stress and mitochondrial dysfunction in the aetiology of AD and dementia. Thus, natural antioxidants and mitochondria targeting compounds can help treat AD in the elderly (55). In transgenic mice models, antioxidants including Ginkgo biloba and curcumin inhibited age-dependent spatial cognitive behaviour and enhanced A-degrading enzymes (56,57).

Additionally, ferulic acid, alpha-lipoic acid, R-lipoic acid, vitamin E and C were found to be helpful in AD transgenic mouse models (55). They also boosted synaptic activity and reduced A levels and mitochondrial dysfunction while increasing phosphorylated tau and microglial activation (55). So many of them are available as supplements or alternative treatments for neurological disorders like Parkinson's, Alzheimer's, and other clinical conditions..

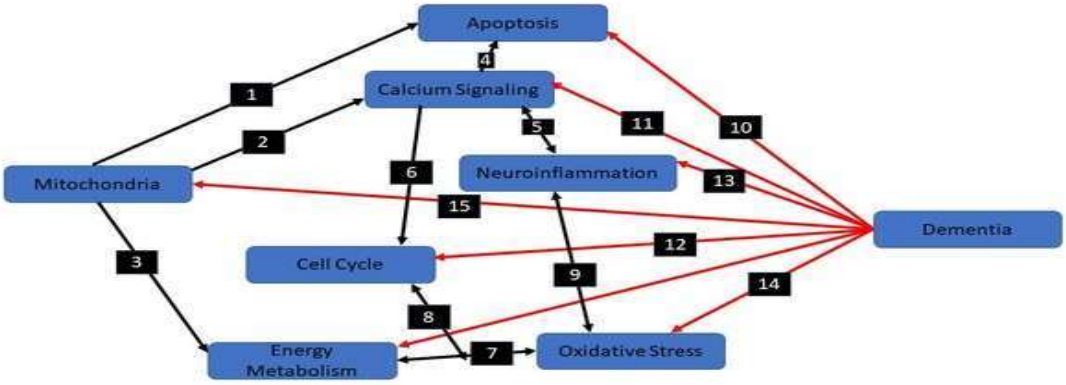


FIGURE 1 | Overview of mitochondrial activity and dementia: apoptosis (58); mitochondria regulate calcium signaling pathway (59); mitochondrial electron transport chain undergoes oxidative phosphorylation (60); 6 calcium signaling in cell cycle (61) Reactive oxygen species are produced by mitochondrial oxidative phosphorylation (62); Oxidative stress and neuroinflammation are strongly

interrelated processes (63,9); Alterations in the cell cycle (64,65,12); Increased oxidative stress (66,41,13,67,49).

Current dementia medications

Synthetic Drugs Approved

Worldwide, several (semi-)synthetic medicines are available to treat AD and certain dementias. Some of the most extensively used medications for AD-associated dementia are donepezil, rivastigmine, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (68). Some of these medications, such rivastigmine, are approved to treat other d,ementias, like PD-related dementia (68). Table 2 lists the most commonly prescribed medications for Alzheimer's disease and other dementias. The FDA authorised NamzaricXR in 2014 for the treatment of moderate-to-severe Alzheimer's disease in persons taking donepezil hydrochloride at the clinically effective dose of 10 mg/day (http://www.alz.org). DA report This combination drug may induce muscle pain, slow heartbeat, fainting, increased stomach acid, nausea, vomiting, and seizures. Moreover, some research suggests that these medicines do not treat agitation in patients with severe behavioural symptoms (69,71). Some neuroleptic/antipsychotic medicines, like haloperidol, risperidone, and olanzapine, are being used to treat BPSD, however their usage is contentious (70). Thus, the FDA has not approved such medications for BPSD treatment. They are still prescribed off-label because there is no effective treatment for BPSD (72).

The current generation of (semi-)synthetic dementia medications reduce symptoms but do not reverse the disease's progression (73). Thus, the search for naturally occurring chemicals with therapeutic qualities for dementia is of vital medical and socioeconomic value.

Galantamine—the Only Current Drug of Plant Origin against Dementia

Galantamine is a plant-based medication used to treat mild to moderate Alzheimer's disease and dementia (74). Several clinical investigations have proven galantamine's efficacy (75). Galantamine (Figure 2) is an isoquinoline alkaloid found in Amaryllidaceae plants. In 1956, Bulgarian chemist D. Paskov and his team identified and extracted it from Galanthus nivalis (common snowdrop) bulbs. The same research group developed the first industrial phytopreparation of pure galantamine extract (NivalinXR) in the late 1950s (76).

Galantamine was first used to treat poliomyelitis, then neuropathic pain, and finally as an anaesthetic (77). In modern times, galantamine is obtained from Galanthus woronowi Losinsk and Galanthus alpines Sosn. bulbs, as well as synthetically (78)

Galantamine affects the brain's cholinergic system in two ways (Figure 2). It is an allosteric activator of the nicotinic acetylcholine receptor (nAChR) and a competitive inhibitor of AChE. (79).

Galantamine also protects mitochondrial dysfunction by restoring MMP and morphological alterations caused by A25/35 or hydrogen peroxide therapy (80,81). Toxic reactive oxygen species (ROS) are produced during electron transport in mitochondria, causing oxidative stress. Galantamine protects mitochondria and inhibits AChE activity, reducing oxidative cell damage and promoting neuroprotection (82).

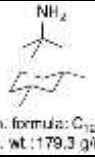
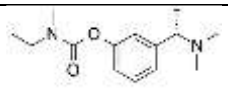
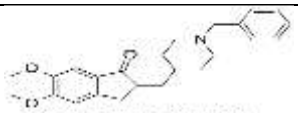
A multi-drug resistance transporter found in the brain's vascular endothelium, P-glycoprotein, may also interact with other brain-targeted medications (83). It prevents medications from entering into the brain by aggressively effluxing them back into the bloodstream (83). Galantamine may thereby facilitate the absorption of medications co-administered with it. Furthermore, galantamine increases rofecoxib (an anti-inflammatory COX-2 inhibitor) and caffeic acid (a phytophenol) protection against neurotoxic neurodegeneration in rats (84). Similarly, galantamine enhances melatonin's antioxidant action (85). Combining galantamine and memantine may also be a unique therapy for schizophrenia (86).

Anxiety, euphoria, depression, irritability, delusions, and aberrant motor behaviour have all been demonstrated to be delayed by galantamine use (87). reviewed 10 clinical trials involving 6,805 demented individuals treated with galantamine. The majority of patients tolerated galantamine satisfactorily. Treatment groups experienced dose-dependent common side effects (78).

The medicine is recommended by both the US and European Alzheimer's disease/dementia therapy standards (88,89). Canada, the European Union (save for the Netherlands under the name NivalinXR in 2000), Japan, Korea, Mexico, Singapore, South Africa, Thailand, etc. In 2001, the FDA approved galantamine

(RazadyneXR) for the treatment of Alzheimer's disease and associated dementias. For treating dementia, plant-derived galantamine works by modulating cholinergic signalling and inhibiting oxidative damage.

TABLE 2 | Approved (semi-)synthetic drugs used for the treatment of dementia.

	Memantine	**Rivastigmine**	**Donepezil**
Brand name	Namenda® (USA) Axura® (Europe) Ebixa® (Europe) Memando® (Ger)	Exelon® (USA, Europe)	Aricept® (USA, Europe)
Chemical structure	 Chem. formula: $C_{12}H_{21}N$ Mol. wt.:179.3 g/mol	 Chem. formula: $C_{14}H_{22}N_2O_2$ Mol. wt.: 250.3	 Chem. formula: $C_{24}H_{29}NO_4$ Mol. wt.: 379.5 g/mol
Indications	Moderate-to-severe AD, AD-related dementia	Mild-to-moderate AD, AD-related dementia	Mild-to-moderate AD, early-to-mid AD dementia
Mode of action	Non-competitive NMDA-receptor antagonist	Slowly reversible, non-selective AChE and BuChE inhibitor	Reversible, selective AChE inhibitor
Side effects (http://www.alz.org)	Confusion, dizziness, constipation, and headache	Nausea, vomiting, loss of appetite,increased frequency of bowel movements	Nausea, vomiting, loss of appetite, increased frequency of bowel movements
Half-life (6)	60–100 h (long)	1 h (very short)	70 h (long)
Doses per day (6)	One (first week)	Two	One
Initial dose (6)	5 mg/day	3 mg/day (2 × 1.5mg)	5 mg/day
Recommended clinically efficient dose (6)	20 mg/day	6–12 mg/day	10 mg/day

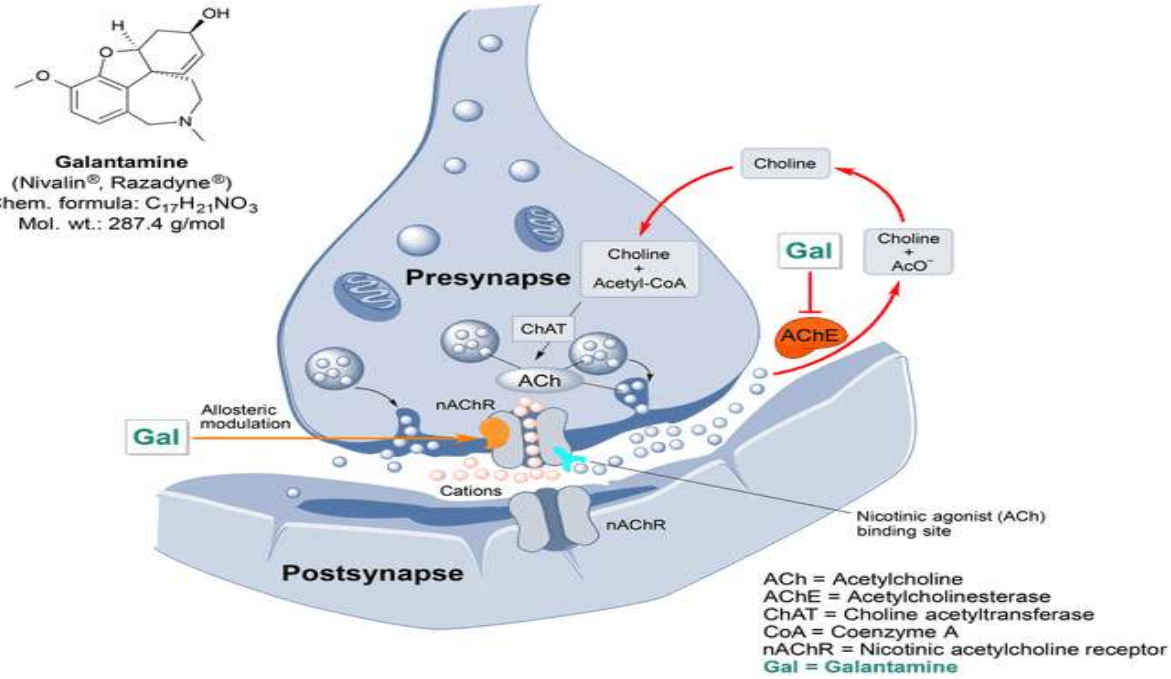


FIGURE 2 | Galantamine (Gal): structure and target mechanisms against AD and dementia. Gal's main biological effects include neuroprotection via dual AChE inhibition and allosteric nAChR stimulation.

An overview of dementia-friendly plants

Dementias are complicated diseases with various biological processes involved in aetiology. This insight ushered in a new paradigm for treating these diseases: treatments for dementia should target numerous biological targets rather than just one. Similarly, plants and plant extracts contain various compounds that may act on multiple molecular targets in an additive or synergistic manner (90). Many herbal remedies already cure dementia.

Sadly, these herbs' active components are inadequately characterised. Similarly, we don't know how these diverse chemicals interact with one other or with prescription drugs (91). This research is vital for generating medicines with no adverse side effects and compounds that enhance each other's activity.

We tried to compile dispersed material from numerous ethnopharmacological papers. We searched ScienceDirect, Pubmed, Scopus, and Google Scholar for articles mentioning dementia, Alzheimer's, traditional medicine, ethnopharmacology, and ethnobotany. The plant name was used using the “AND” operator (92) followed by “dementia” or “Alzheimer's.” Table 3 lists the recognized medicinal plants used to treat dementia or Alzheimer's.

Medicinal plants and plant genera used to cure dementia

Following a comprehensive web search for medicinal plants used to treat dementia in diverse places globally, the five plants or plant genera listed below were chosen for further discussion.

Plant (Plant family)	**References for the use of the plants for dementia treatment in ethnomedicine**
Acorus calamus L. (Acoraceae)	(93)
Aframomum melegueta (Roskoe) K. Schum. (Zingiberaceae)	(94)
Agapanthus africanus (Agapanthaceae)	(95)
Ammocharis coranica (Ker-Gawl.) Herb. (Amaryllidaceae)	(95)
Ananas comosus (Bromeliaceae)	(96,97)
Angelica sinensis (Oliv.) Diels (Apiaceae)	(98)
Angelica archangelica (Apiaceae)	(99, 93)
Angelica species (Apiaceae)	(100)
Annona senegalensis Pers. (Annonaceae)	(95)
Artemisia absinthium L. (Asteraceae)	(93,97)
Asparagus africanus Lam. (Asparagaceae)	(95)
Asparagus concinnus (Baker) Kies (Asparagaceae)	(95)
Bacopa monnieri (L.) Wettst. (Plantaginaceae)	(101)
Barbieria pinnata (Pers.) Baill. (Fabacea)	(102,103,97)
Platycladus orientalis (L.) Franco (Syn. *Biota orientalis* (L.)Endl.) (Cupressaceae)	(104, 93)
Boophone disticha (L.f.) Herb. (Amaryllidaceae)	(95)

Brugmansia ×*candida* Pers. (Solanaceae)	(105,97)
Butea monosperma (Fabaceae)	(264)
Bupleurum species (Apiaceae)	(100)
Camellia sinensis Kuntze (Theaceae)	(100)
Cannabis sativa L. (Cannabaceae)	(100)
Carum carvi L. (Apiaceae)	(106)
Caryophyllus spp. (Caryophyllaceae)	(107,97)
Cassia lucens Vog. (Fabaceae)	(102,103, 97)
Celastrus paniculatus Willd. (Celastraceae)	(93)
Centella asiatica (L.) Urb (Apiaceae)	(95)
Dysphania ambrosioides (L.) Mosyakin&Clemants (Amaranthaceae) {Syn. *Chenopodium ambrosioides* L.(Chenopodiaceae)}	(108,109,110,97)
Clitoria ternatea L. (Fabaceae)	(93)
Codonopsis pilulosa (Franch.) Nannf. (Campanulaceae)	(93)
Coffea arabica L. (Rubiaceae)	(94)
Convallaria majalis L. (Convallariaceae)	(107, 97)
Coriandrum sativum L. (Apiaceae)	(107, 97)
Corydalis cava (L.) Schw. et K. (Papaveraceae)	(106, 97)
Corydalis intermedia (L.) M'erat (Papaveraceae)	(106,97)
Corydalis solida (L.) Swartz ssp. *laxa* (Papaveraceae)	(106, 97)
Corydalis solida (L.) Swartz ssp. *slivenensis* (Papaveraceae)	(106, 97)
Crinum bulbispermum (Burm.f.) Milne-Redh. & Schweick. (Amaryllidaceae)	(95)
Crinum moorei Hook.f (Syn.*Crinum imbricatum* Baker) (Amaryllidaceae)	(95)
Crinum macowanii Baker (Amaryllidaceae)	(95)
Crocus sativus L. (Iridaceae)	(100)
Curcuma longa L. (Zingiberaceae)	(93,100)
Euphrasia nemorosa (Pers.) Wallr. (Scrophulariaceae)	(106)
Tetradium ruticarpum (A.Juss.) T.G.Hartley (Syn.	(98,100)
Ferula gummosa Boiss. (Apiaceae)	(107,97)
Galanthus woronowii Losinsk. (Amaryllidaceae)	(100)
Galanthus alpinus Sosn. (Syn. *Galanthus caucasicus*) (Amaryllidaceae)	(100)
Ginkgo biloba L. (Ginkgoaceae)	(111,100)
Glycyrrhiza species (Leguminosae)	(100)
Huperzia serrate (Thunb.) Trevis. (Lycopodiaceae)	(93,97, 100)

Hydrolea glabra Schum. and Thonn. (Hydrophilaceae)	(94, 97)
Hypericum perforatum L. (Clusiaceae)	(100)
Lactuca sativa L. (Asteraceae)	(112,97)
Lannea schweinfurthii Engl. (Anacardiaceae)	(95)
Lantana camara L. (Verbenaceae)	(113, 97)
Lavandula angustifolia Miller (Lamiaceae)	(106,100)
Leucojum aestivum L. (Amaryllidaceae)	(100)
Lycoris radiata Herb. (Amaryllidaceae)	(93)
Magnolia officinalis Rehder and Wilson (Magnoliaceae)	(93)
Matricaria recutita L. (Asteraceae)	(107,97)
Medicago sativa L. (Fabaceae)	(114, 97)
Melissa officinalis L. (Lamiaceae)	(78, 115,116,98,106,97,100)
Mentha spicata L. (Lamiaceae)	(106)
Narcissus spp. (Amaryllidaceae)	(100)
Nicotiana species (Solanaceae)	(100)
Ocimum basilicum L. (Lamiaceae)	(63,117,97)
Origanum majorana Moench (Lamiaceae)	(63, 97)
Origanum vulgare L. (Lamiaceae)	(106)
Paeonia ×suffruticosa Andrews (Paeoniaceae)	(98)
Panax ginseng C.A.Mey. (Araliaceae)	(100)
Paullinia cupana Kunth ex. H. B. K (Sapindaceae)	(118,97)
Petroselinum crispum (Mil.) Nym.exA.W.Hill. (Apiaceae)	(106)
Physostigma venenosa Balf.f. (Leguminosae)	(98)
Pimpinella anisum L. (Apiaceae)	(106)
Piper methysticum G.Forst. (Piperaceae)	(100)
Polygala tenuifolia Willd. (Polygalaceae)	(119,93)
Pteroselinum vulgare (Mill.) Nym. and A.W. Hill (Apiaceae)	(97)
Rosmarinus officinalis L. (Lamiaceae)	(120,121,116,98 ,97)
Rosmarinus officinalis L. (Lamiaceae)	(106)
Ruta graveolens L. (Rutaceae)	(106)
Salvia lavandulifolia Vahl. (Lamiaceae)	(100)
Salvia miltiorrhiza Bung. (Lamiaceae)	(93)
Salvia officinalis L. (Lamiaceae)	(117,107,122,93,123,97)
Scadoxus multiflorus (Martyn) Raf. (Amaryllidaceae)	(95)
Syzygium aromaticum (L.) Merrill and Perry (Myrtaceae)	(107,97)
Tagetes lucida Cav. (Asteraceae)	(124,97)
Terminalia chebula Retz. (Combretaceae)	(125,101,93)
*Terminalia catappa (*Combretaceae)	(265)
Theobroma cacao L. (Sterculiaceae)	(126,97)
Thymus vulgaris L. (Lamiaceae)	(106)
Valeriana officinalis L. (Valerianaceae)	(94)
Vinca minor L. (Apocynaceae)	(94)
Vitis vinifera L. (Vitaceae)	(94)

Ginkgo biloba L.

Ginkgo biloba is one of the most unusual plants on the planet, and it is one of the world's oldest tree species (127). It's a living fossil with a morphology that hasn't changed in over 200 million years (128). The

Ginkgoaceae family, which first arose during the Mesozoic epoch, is the final extant member. Due to its several therapeutic benefits, Gb was cultivated in ancient China. This plant's extracts were used to cure a variety of diseases and symptoms, including poor circulation, tiredness, vertigo, and tinnitus (129). Gingko extract is sold as a herbal supplement called Gingium in various countries (for example, China). It is indicated for the treatment of some age-related cognitive impairments, including as memory loss, as well as the symptoms of dementia and Alzheimer's disease (130). Terpene lactones (ginkgolides and bilobalides) and flavonoids (flavonols and flavone glycosides) are the two main chemical phytoconstituents responsible for Gingko's neuro-therapeutic potential (Figure 3: 131,127).

Ginkgolides A, B, and C are triterpenes that are only found in Gb (131). Other compounds, such as ginkgotoxin (found in Ginkgo biloba seeds) and the phenolic type lipid bilobol (found in Ginkgo biloba fruits), have particular biological effects (127). Ginkgotoxin, for example, is neurotoxic (causes epileptic convulsions) (127), but bilobol and its derivatives are cytotoxic and antimicrobial (127). (132).

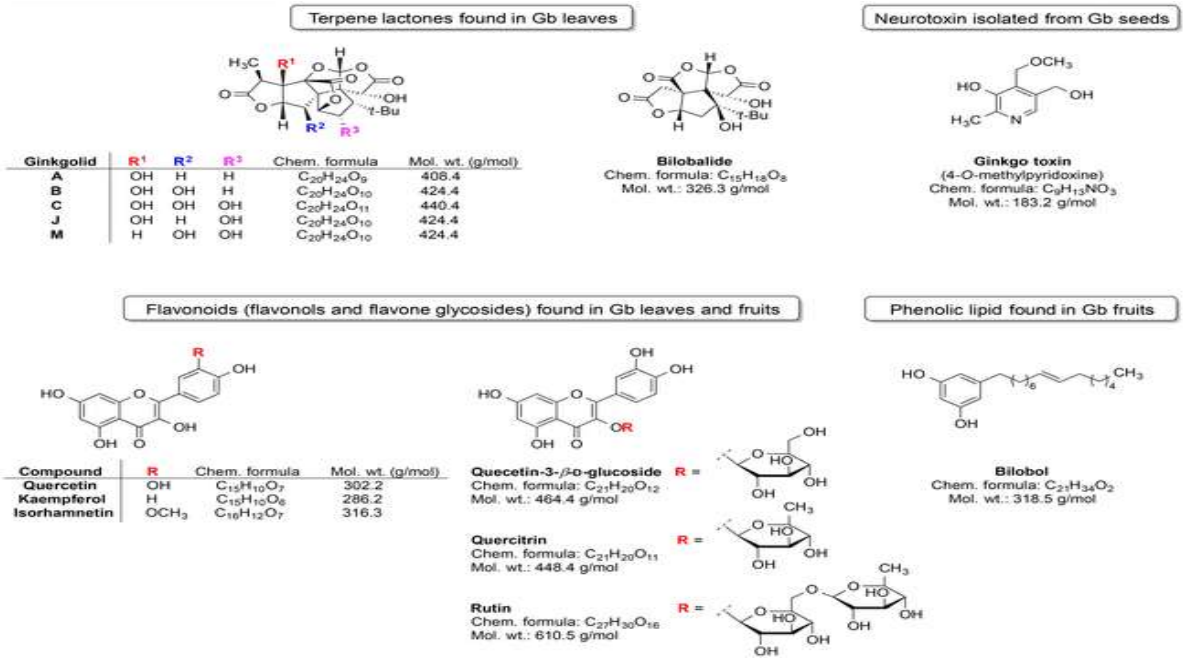


FIGURE 3 | Most prominent phytochemical constituents found in *Gingko biloba* (Gb).

In Germany, ginkgo leaf extract was developed for therapeutic purposes for the first time in 1965. (133). The first commercially accessible extract, EGb761, was registered in France in 1974 and contains around 24% flavonoids and 6% terpene lactones (133). The standardised Gb extract (EGb761) is one of the most thoroughly studied herbal treatments for cognitive impairment, Alzheimer's disease, and dementia caused by Alzheimer's disease (131). EGb761 has an effect on a number of systems involved in normal brain function (130,Figure 4).

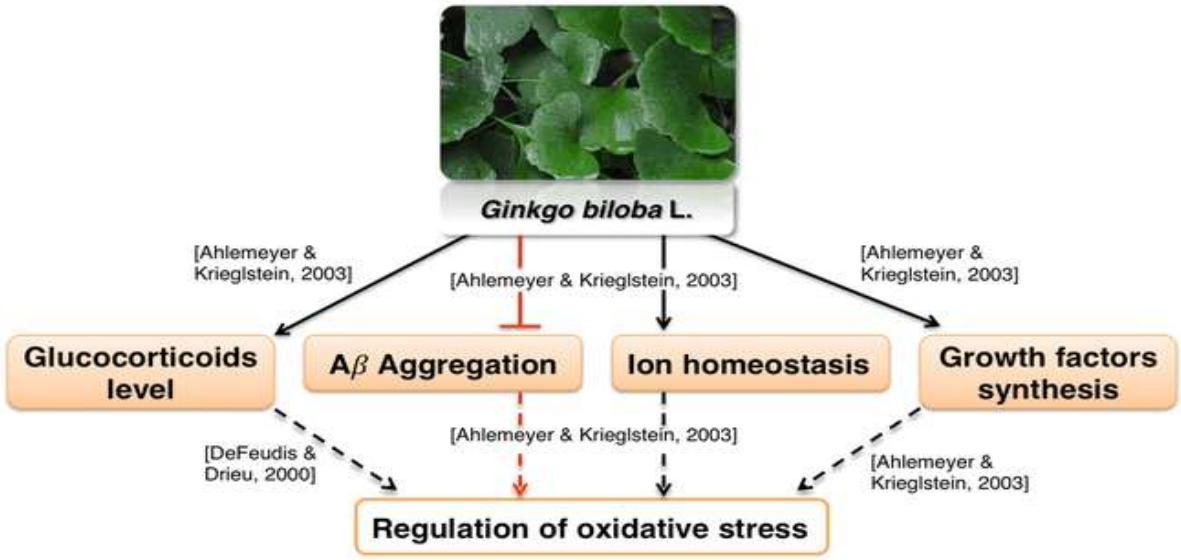


FIGURE 4 | Neuroprotective effects of Gingko biloba L.

It was found to modulate circulating glucocorticoid levels, as well as A aggregation, ion homeostasis, and growth factor production, to mediate neuroprotection (134.135). These processes are likely involved in oxidative stress regulation (136,137,138,139,140), which is consistent with various reports showing antioxidative activity of Gb extract (136,137 (141,142). Furthermore, the impact of Ginkgo components on mitochondrial activity has long been known. Ginkgo components have been shown to protect MMP against a variety of toxicants and oxidative stress in a number of in vitro investigations (143,144,145). Many features of mitochondrial morphology are affected by gingko extract, including fission (146), swelling (147), and coupling (147). (148). Gingko extract also interacts with the electron transport chain in the mitochondria (144). Surprisingly, it was discovered that cells overexpressing APP improved their oxidative phosphorylation efficiency more than control cells (148). This shows that Ginkgo extract could be useful in the treatment of Alzheimer's disease. Rodent neurons and glial cells were also protected from ischemia/reperfusion and scopolamine-induced toxicity by the extract (142,149,150,151,152). Furthermore, EGb761 improved the functional integrity of cerebral microvascular endothelial cells cultivated in vitro and protected them from harm (153,154). These effects could be linked to Gingko extract's antiplatelet action (155). Antiplatelet drugs have been suggested as a potential treatment for vascular disorders (156,157). As a result, EGb761 may be used to treat neurovascular dysfunction, which is one of the diseases linked to Alzheimer's disease (158,159).

Ginkgo has a long history of being used to treat a variety of cerebral dysfunctions linked to neurodegenerative dementia and brain ageing (160). Gingko extract appears to improve cognitive and behavioural abilities in elderly people and Parkinson's disease patients, according to animal studies (161,162,163). Aside from animal studies, multiple clinical trials have also revealed that EGb 761 has no significant side effects and is beneficial in the treatment of Alzheimer's disease and vascular dementia (164,165,166). Although gingko extract appears to be helpful in the treatment of cognitive deficits, more research is needed to determine whether it interacts with other medications. Such research could lead to improved gingko extract therapy efficacy and safety. There are now just a few relevant interactions between Ginkgo components and medications that are known (167). Nonetheless, single people have reported major neurological side effects when taking Ginkgo herb in combination with risperidone, valproic acid/phenytoin, or trazodone (167). In conclusion, Ginkgo extract has a neuroprotective effect that could be attributed to its antioxidative and/or antiplatelet properties. Ginkgo extract has been shown to be useful in the treatment of dementia in clinical studies. As a result, we believe that certain Ginkgo-based medications will be available in the near future.

Panax ginseng C.A. Meyer (Ginseng)

Ginseng is widely utilised in nutritional supplements and pharmaceuticals. It's an adaptogen, a drug that promotes homeostasis and protects against biological stresses. This plant's dried root was utilised in traditional Chinese and Korean medicine (168). Panax species include P. ginseng, P. japonicus, P. quinquefolius, P. trifolius, P. notoginseng (Burkill), and P. major (169). ginseng CA Meyer ginseng is the most

widely used and investigated (170). The species is widespread throughout northeastern China. Tonic for weariness, weakness, and ageing, utilised in Chinese medicine for almost 2000 years (171). Some ginseng components, like ginsenosides Rg1 and Rg3 (Figure 5), have been studied for their medicinal potential (172,173,174). For example, 20(S)-ginsenoside Rg3 (Figure 5) has a steroidal backbone structure with carbohydrate component and an aliphatic side chain (175). Rg3 is produced by heating the roots (176,177).

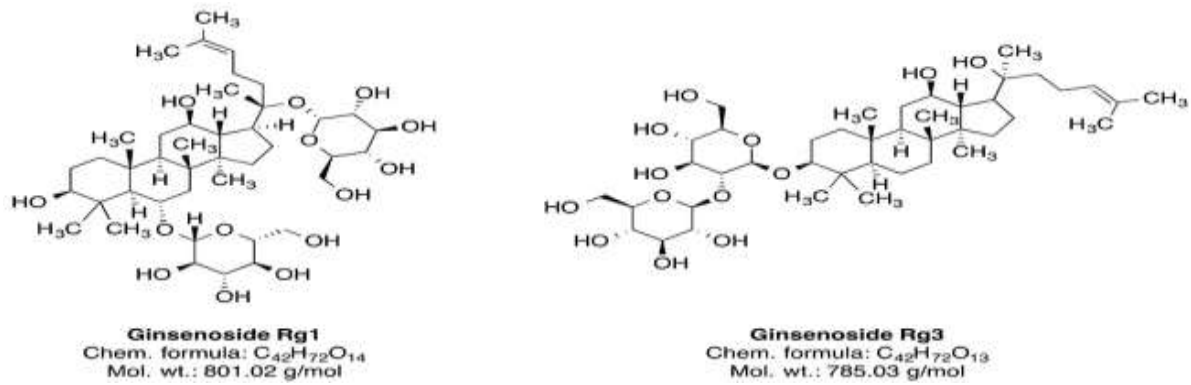


FIGURE 5 | Phytochemical constituents of ginseng

The ginsenoside Rg3 therapy significantly reduced amyloid-40 and amyloid-42 levels in the brains of transgenic mice (Tg2576 line) and in cultured cells (178). Neuroprotective effects of ginsenoside Rg3 in cultured cortical neurons (179). Similarly, ginsenoside Rg1 (GRg1) reduced A-induced neurotoxicity in neuroblastoma cells via activating the p38 pathway (180). Ginsenosides also control nicotinic acetylcholine receptor activation (181). Modulation of acetylcholine receptor activation may be implicated in the compound's effectiveness against dementia (182,183). A ginseng extract high in ginsenoside Rg3 improves memory in mice through modulating AChE activity and the NF-B signalling pathway (184). NF-B is a protein complex that is activated by ROS (185). GRg1 also lowers A-induced ROS production and cell death (186). Many papers suggest protective effects of ginseng components on brain mitochondrial activity under hazardous conditions, such as ischemia (187), calcium therapy (188,189), and even incubation of cells with A in vitro (188).

Gingseng's effect on Alzheimer's disease was inconclusive in a recent (145). The trials had tiny sample sizes and poor design, including no placebo groups (145). Larger trials are needed to determine ginseng's efficacy in AD.

In summary, ginseng components may influence amyloid metabolism, oxidative stress, neuroinflammation, and cholinergic transmission. Despite considerable efforts, the effect of gingseng on dementia sufferers is yet unknown.

Curcuminoids from Genus Curcuma

Curcuma (Turmeric) is one of the largest Zingiberaceae genera, with roughly 80 species (190). Typical yellow turmeric hue comes from curcumin and its curcuminoid analogues demethoxycurcumin and bisdemethoxycurcumin (191). Curcumin is the major bioactive phytoconstituent of Curcuma (Figure 6).

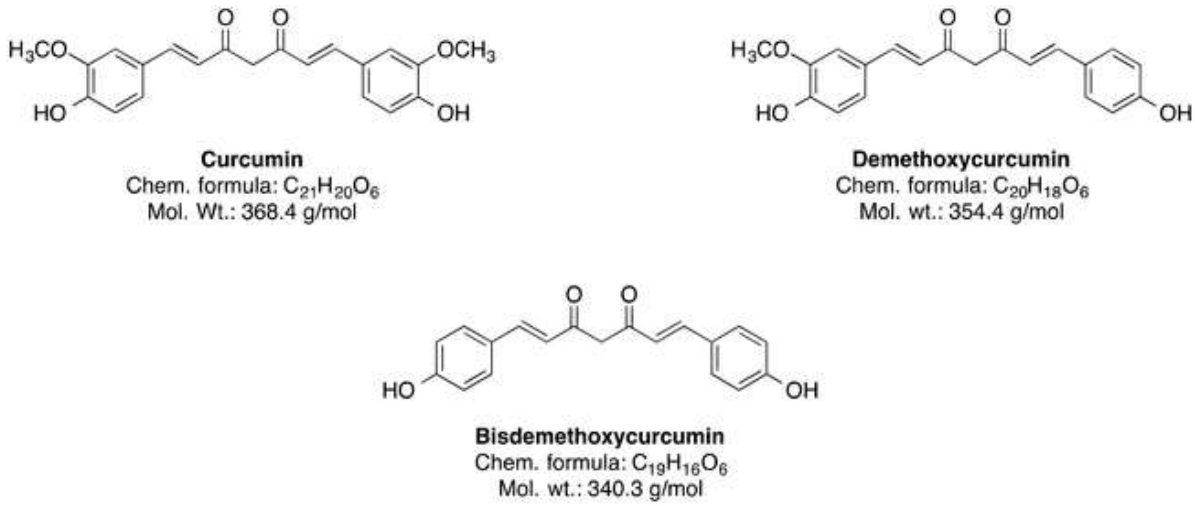


FIGURE 6 | Chemical structures of curcuminoids.

To acquire it from turmeric, simply extract it with a solvent and crystallise it (191). It is also used in traditional Indian medicine to treat anorexia, hepatitis, and other ailments (191,192). Curcumin has been shown to have antioxidant, anti-inflammatory, antiproliferative, anti-amyloidogenic, and neuro-regulatory activities in vivo (191). This may be linked to the increased curcumin consumption in the Indian population (191), although correlation does not suggest causation.

2 Feruloyl moieties with 3-methoxy-4-hydroxy substituents (Figure 7A; 193). Curcumin is virtually symmetrical due to an unsaturated seven-carbon spacer that includes a -diketo function. Curcumin can exist in two tautomeric forms: enol and diketo, depending on pH. (193). The keto form dominates in acidic and neutral (pH 7.4) conditions, while the enol form dominates in non-polar and basic (pH 8.0) media (193). A second enol tautomer undergoes intramolecular hydrogen transfer (Figure 7B;194). When curcumin reaches physiological pH (7.4), it is in its 1,3-keto-enol form. Curcumin's antioxidant capabilities and ability to scavenge ROS are linked to the stability and antioxidative ability of the methoxy phenolic type groups present. Figure 7 shows curcumin's structural properties, including tautomeric forms and pharmacophores.

Curcumin inhibits TNF activity, prevents A plaque development, and protects brain cells from toxins (195). Natural polyphenols have recently been used to treat several neurological illnesses (196, 197).

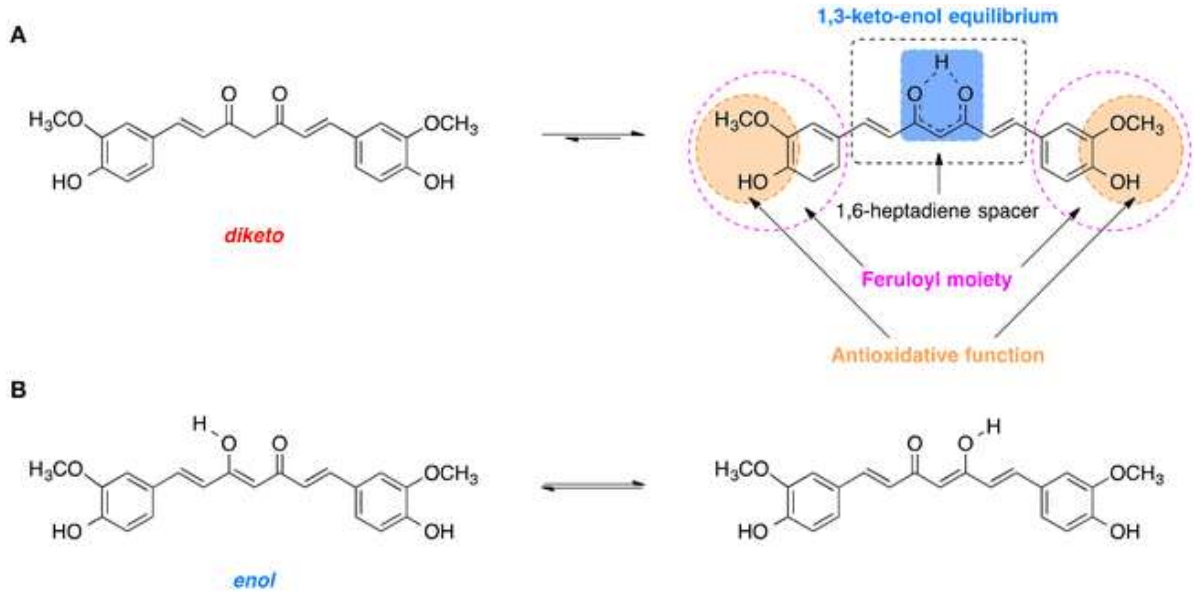


FIGURE 7 | Tautomerism of curcumin: (A) Diketo and 1,3-keto-enol equilibrium form of curcumin with its biologically relevant structural units. (B) Hydrogen transfer in the most stable enol form

Curcumin improves memory and hippocampus neurogenesis in elderly rats (198). Curcumin may exert this action through modulating gene expression involved in cell proliferation and synaptic plasticity (198).

Curcumin's neuroprotective characteristics include anti-inflammatory, antioxidant, and lipophilic qualities (199). Infusion of curcumin-loaded lipid-core nanocapsules (but not free curcumin) reversed the increased hippocampus production of pro-inflammatory proteins TNF- and IL-1 beta produced by intracerebroventricular A42 peptide solution infusion (200). Curcumin also reduced the activity of the pro-inflammatory complex NF-B in neuroblastoma cells (201). Curcumin inhibited the activity of NF-B, Nrf2, and Sirt1 in human neuroblastoma cells (202). Curcumin lowers ROS in neuroblastoma cells treated with acrolein and in rat primary neurons treated with Ab42 hyper-expression (203,202). In vitro, curcumin protects mitochondria from oxidative stress and rotenone (an electron transport chain inhibitor) (204,205). It also slows the ageing of rodent brain mitochondrial and oxidative activities (206,207). It also increased Sirt1 and Bcl-2 expression and decreased brain cell death in experimental strokes (208). Curcumin also binds A peptides, inhibiting their aggregation into A plaques (203). (209). Curcumin can penetrate the BBB, bind to plaques, and reduce amyloid plaques in AD by stimulating phagocytosis of A. (199). Some curcumin pyrazoles and isoxazoles bind to A42 (Figure 8; 210).

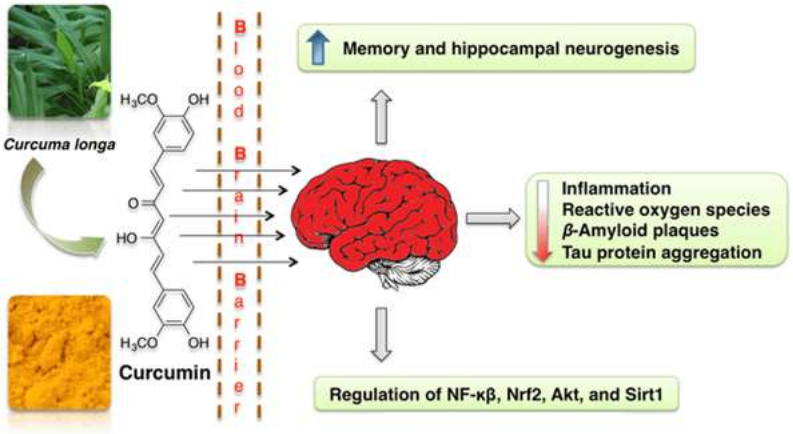


FIGURE 8 | Neuroprotective effects of curcumin.

It reduces A40/42 and PSEN1 protein and mRNA levels in APP+ neuroblastoma cells (211). Curcumin derivatives enhanced A absorption by AD macrophages isolated from blood and cultured in vitro (212). This is significant since peripheral macrophages are known to infiltrate AD patients' brains and help remove amyloid plaques (213). Curcumin also suppresses A-induced tau phosphorylation in neuroblastoma cells via the PTEN/Akt/GSK-3 pathway (214). Others report that curcumin protects against A-induced memory deficits via the Akt/GSK-3 and ERK pathways (215,216). Curcumin improved A-infused rats' hippocampal-dependent memory (215).

According to Brondino et alsystematic .'s review, the few clinical trials evaluating curcumin's effect on AD were equivocal (217). Although curcumin was confirmed to be safe in short-term usage, long-term safety and efficacy in humans must be determined (217). Since the comprehensive review was released, another clinical trial on the topic showed improvement in working memory and mood in a small group of older volunteers treated with curcumin (218). A study also found a link between curcumin-rich curry and improved cognitive function in the elderly (219). The curcumin concentration in curry is modest (220), and the amount of physiologically accessible curcumin consumed with curry is debated. A synergistic effect of curcumin and donepezil on cognition and oxidative stress (221). The donepezil/curcumin combination demonstrated good BBB permeability (222). Curcumin protects brain cells from oxidative stress and A disease. Curcumin's positive effects on dementia symptoms in animal models may be due to these qualities. Curcumin appears to be a good possibility for a novel dementia therapy, however clinical evidence to back this up is still missing. Also, researchers have only studied curcumin's efficacy against AD-associated dementia, excluding other dementias.

Glycyrrhiza Genus

Glycyrrhiza, or licorice, is a member of the Fabaceae family, which includes more than 30 species. These plants are perennial and native to the Mediterranean, Asia, southern Russia, and Iran (223). Glycyrrhiza species can be found all throughout Europe and Asia (224,223). The roots of the licorice plant have been

proven to have anti-inflammatory, anti-cancer, and anti-microbial properties, among other things (223,225,226). The principal bioactive phytoconstituents are the sweet-tasting triterpene saponin glycyrrhizin (glycyrrhizic acid) and isoliquiritigenin (a phenolic type molecule) (Figure 9). Other ingredients include shinpterocarpin, glabrone, glabridin, galbrene, and lico-isoflavones A and B. Please see the following link for more details (223).

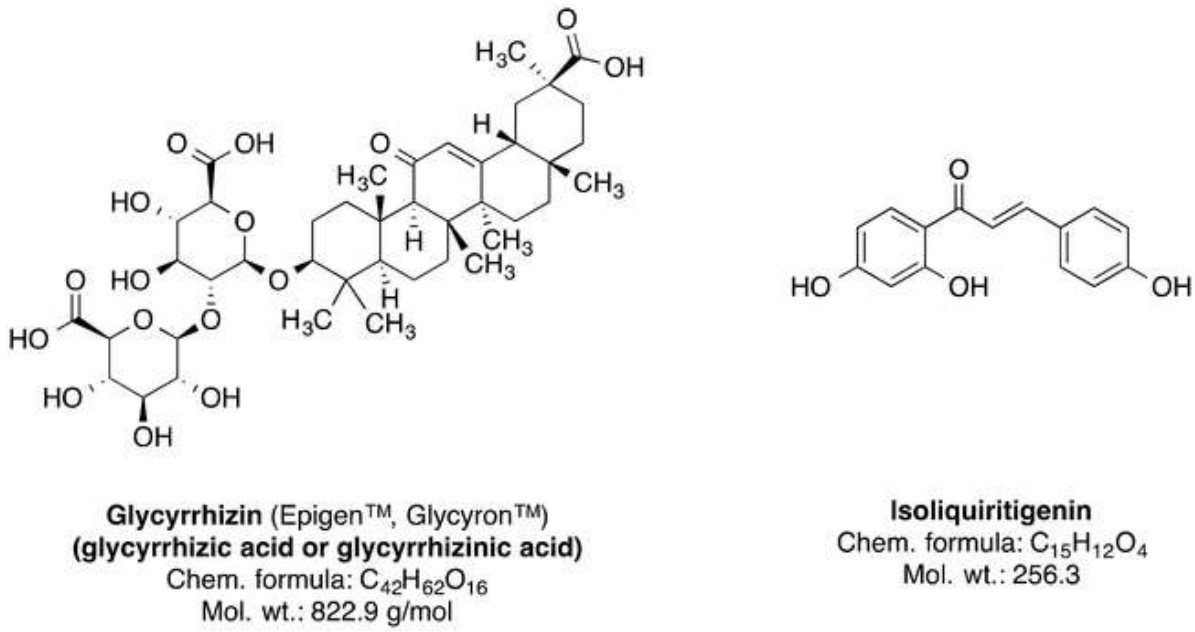


FIGURE 9 | Chemical structures of the major phytoconstituents of Glycyrrhiza glabra.

The antioxidant capabilities of Glycyrrhiza species have been connected to neurodegenerative illnesses such as Parkinson's disease, Alzheimer's disease, and dementia. Tau misfolding is prevented by inflata extract, according to in vitro experiments (227). As a result, this plant's extract could be beneficial in the treatment of tauopathies and Alzheimer's disease. G. inflata extract reduced oxidative stress in spinocerebellar ataxia type 3 (SCA3) cells by activating PPARGC1A and the NFE2L2-ARE pathway (228). 1-methyl-4-phenylpyridinium (MPP+) causes cellular toxicity, ROS production, and GSH downregulation (229). MPP+, a neurotoxin, inhibits mitochondrial oxidative phosphorylation (MOP) (229).

GSH is an important antioxidant in the brain, hence its downregulation is critical (230). A reduction in GSH levels in dementia exacerbates oxidative stress (229,231). In vitro, G. inflata extract was also discovered to have an anti-oxidant effect (232). Oxidative stress has an effect on brain cells. The potential of licorice extract to protect against oxidative stress may be attributed to isoliquiritigenin's mitochondrial action (233). Licorice may minimise brain cell damage, improve neuronal function, and prevent memory loss by reducing oxidative stress linked with various dementias (234,235).

The use of licorice root extract in the treatment of dementia and/or Alzheimer's disease has been proven (see Figure 10). According to certain research, licorice root extract can boost memory by lowering inflammation (236,235). Inflammation and oxidative stress, according to past research, go hand in hand (237). Glycyrrhiza Polyherbal is a component. Glycyrrhiza uralensis Fisher, a 2A adrenoceptor antagonist, is a component of the yokukansan formula, which incorporates seven distinct plants (238). When used in yokukansan, the glycyrrhiza phytoconstituents glycyrhizin, liquiritin, and isoliquiritigenin have neuroprotective effects (238). The NMDA receptor's firing rate was lowered by isoliquiritigenin (238). Memantine, a popular anti-dementia medication, works by blocking NMDA receptors (239). The potential of glycycoumarin to reduce caspase-3 activity may also play a role in its neuroprotective properties (240, 238).

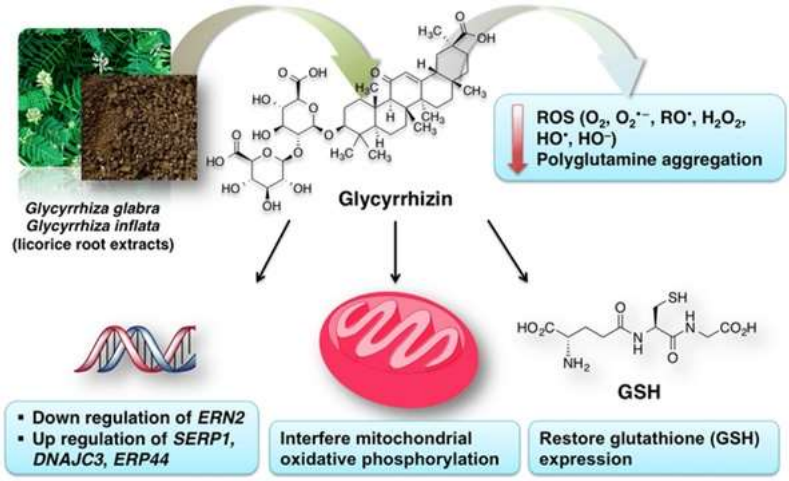


FIGURE 10 | A simplified representation of the neuroprotective effects of licorice for dementia treatment.

Glycyrrhiza glabra extract increased mice's learning abilities after seven days of oral administration (241). A second trial, however, found that the extract was sedative (242). To avoid sedative effects, however, the dosage of G. glabra extract should be carefully monitored. Diammonium-glycyrrhizinate, on the other hand, was able to offset A42's effects on mitochondria and cognitive performance in rats (243). Licorice compounds may interact with other medications because they change P450 proteins, which are important regulators of xenobiotic metabolism (244). Glycyrrhiza extracts have been shown to have anti-inflammatory, antioxidant, and apoptotic properties. Unlike curcumin and ginseng, glycyrrhiza has not been investigated as a dementia treatment in humans.

Camellia sinensis Kuntze

One of the most popular drinks in the world is green tea (Camellia sinensis Kuntze) (245). Green tea use has been linked to obesity, diabetes, inflammation, coronary artery disease, stroke, and different cancers (246,247). Animal and human cognitive processing and memory are boosted by green tea-related chemicals [e.g. (-)- epigallocatechin-3-gallate] (248,246,249).

Polyphenols are one of almost 4,000 bioactive chemicals found in C. sinensis (250). Excessive expression and activity of metalloendopeptidase genes and enzymes were enhanced by green tea extract (MME). A peptides can be broken down by many MME (251). When green tea leaf extract was pretreated with AlCl3, it averted cognitive deficits, alterations in superoxide dismutase activity, and uncontrolled activity of pro-inflammatory enzyme COX and AChE in the same brain area (252). L-theanine from C. sinensis, administered intravenously, protects against ischemia-induced memory loss and cell death (253,254). Intriguingly, rats fed L-theanine showed improved cognition and reduced levels of oxidative stress (255). Research by Nishida et al. in a transgenic AD mouse model, epigallocatechin-3-gallate corrected the dysregulated ROS generation, mitochondrial respiration, and MMPs (256). L-theanine is a proteinogenic neurotransmitter L-N-amino-ethylated glutamine's derivative (Figure 11). Inhibits A42-induced memory loss and cell death, perhaps through lowering ERK/p38 and NF-B signalling pathways and decreasing oxidative stress (257).

Alzheimer's disease and dementia may be reduced by drinking green tea (258). The combination of L-theanine and coffee has been shown to have a positive effect on cognitive and emotional well-being in healthy persons (259, 260). The results of studies on L-theanine alone on mood have been mixed, though (261; 259). The P- glycoprotein activity can be altered by green tea catechins, which may have an impact on medication availability (262). To sum up, green tea extract is anti-apoptotic, anti-oxidant, and may directly prevent the development of A plaques in the bloodstream. Human studies have also shown that green tea components may be beneficial in the treatment of dementia.

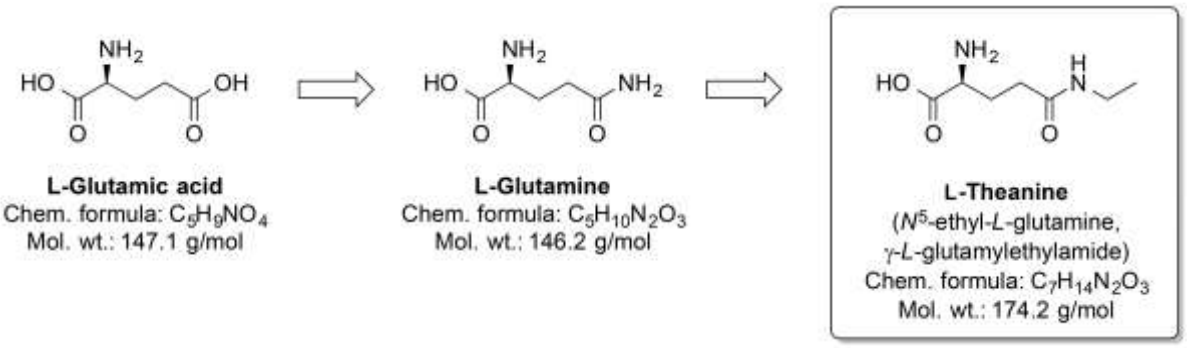


FIGURE 11 | Chemical structures of the nootropic drug L-Theanine and its proteinogenic amino acid analogs

CONCLUSIONS

In this study, we explain how plants have been utilised to treat dementia all across the world. The neuroprotective benefits of these plants or their bioactive ingredients are predominantly connected with anti-inflammatory, antioxidative, and antiapoptotic activity. Some of these naturally occurring chemicals show promise as alternative therapeutics. Curcumin, when combined with the authorised reversible ChE inhibitor donepezil, demonstrated notable synergetic effects on cognition, oxidative stress, and BBB permeability. Moreover, donepezil/curcumin administration may help treat dementia symptoms in animal models. It has also been proven that supplementing with mitochondrial antioxidants like -lipoic acid and acetyl-L-carnitine can help minimise physical and mental fatigue, and even improve memory function in age-related disorders like Alzheimer's and other dementias. However, there are numerous unknowns in this research area that need to be clarified. The scientific community requires more extensive research on plant active components and their mechanisms of action. This research will help clinical trials evaluate the herbal items' efficacy in treating dementia. Research on plants used in traditional and ethnomedicinal medicine could lead to the creation of novel dementia treatments, which is quite exciting.

REFERENCES

1. Burgess L, Page S, and Hardman P. Changing attitudes in dementia care and the role of nurses. Nurs. Times 2002;99:18–19.
2. Damasio A.R, and Gabrowski T.J. Definition, clinical features and neuroanatomical basis of dementia, in The Neuropathology of Dementia, eds M. M. Esiri, V. M.-Y. Lee, and J. Q. Trojanowski 2004;1–34
3. Grand J.H, Caspar S, Macdonald S.W. Clinical features and multidisciplinary approaches to dementia care. J Multidiscip Heal 2011;4:125-47.
4. Tripathi M, Vibha D. Reversible dementias. Indian J. Psychiatry 2009;51:S52.
5. Mehan S, Sharma D, Sharma G, Arora R, Sehgal V. Dementia-A Complete Literature Review on Various Mechanisms Involves in Pathogenesis and an Intracerebroventricular Streptozotocin Induced Alzheimer's Disease. INTECH Open Access Publisher. Available online at: http://www.intechopen.com/books/inflammatory-diseases-immunopathology-clinical-and-pharmacologicalbases/alzheimer-s-disease-an-updated-review-on- pathogenesis-and-intracerebroventricular-streptozotocin-ind 2012
6. Blennow K, de Leon M.J, Zetterberg. Alzheimer's disease. Lancet (London, England) 2006;368:387–403.
7. Corrada M.M, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas C.H. Dementia incidence continues to increase with age in the oldest old: the 90+ study. Ann. Neurol 2010;67:114–121.
8. Iadecola C. The pathobiology of vascular dementia. Neuron 2013;80(4):844-66.
9. Navia B.A, Rostasy, K. The AIDS dementia complex: clinical and basic neuroscience with implications for novel molecular therapies. Neurotoxicity Research 2005;8:3–24.
10. Lim S.L, Rodriguez-Ortiz C.J, Kitazawa M. Infection, systemic inflammation, and Alzheimer's disease. Microbes Infect. 2015;17:549–556.

11. Ridley N.J, Draper B, Withall, A. (2013). Alcohol-related dementia: an update of the evidence. Alzheimer's Research & Therapy 2013;5:3.
12. Power M.C, Adar S.D, Yanosky J.D, Weuve, J. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: a systematic review of epidemiologic research. Neurotoxicology 2016;56:235–253
13. Yan D, Zhang Y, Liu L, Yan H. (2016). Pesticide exposure and risk of Alzheimer's disease: a systematic review and meta-analysis. Scientific Reports 2016;6:32222.
14. Weksler M.E, Szabo P, Relkin N.R, Reidenberg M.M, Weksler B.B, Coppus A.M.W. Alzheimer's disease and Down's syndrome: treating two paths to dementia. Autoimmun Rev. 2013;12(6):670–673.
15. Giri M, Zhang M, Lu Y. Genes associated with Alzheimer's disease: an overview and current status. Clin Interv Aging 2016; 11:665–681.
16. Corder E.H, Saunders A.M, Strittmatter W.J, Schmechel D.E, Gaskell P.C, Small G.W, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families.Science 1993;261 (5123):921–923.
17. Swerdlow R.H, Koppel S, Weidling I, Hayley C, Ji Y, Wilkins H.M. Mitochondria, cybrids, aging, and Alzheimer's disease. Prog Mol Biol Transl Sci. 2017;146:259–302.
18. Mahley R.W, Rall S.C. Jr. Apolipoprotein E: far more than a lipid transport protein. Annual Review of Genomics and Human Genetics 2000;1:507–537.
19. Pastor P, Roe C.M, Villegas A, Bedoya G, Chakraverty S, Garcia G, et al. Apolipoprotein Eepsilon4 modifies Alzheimer's disease onset in an E280A PS1 kindred. Ann. Neurol.2003;54:163–169.
20. Liu Chia-Chen, Kanekiyo Takahisa, Xu Huaxi, Bu Guojun. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nature reviews neurology (2013);9(2): 106-18.
21. Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M.World Alzheimer Report 2016: Improving Healthcare for People Living with Dementia: Coverage, Quality and Costs Now and in the Future. London: Personal Social Services Research Unit; London School of Economics and Political Science.2016;1-131.
22. Quaglio G, Brand H, Dario C. Fighting dementia in Europe: the time to act is now. Lancet Neurol.2016;15:452–454.
23. Rabinovici G.D, Miller B.L. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. CNS Drugs 2010;24(5):375–398.
24. Knapp M, Prince M, Albanese E, Banerjee S, Dhanasiri S, Fernandez, J.L.Dementia UK: The Full Report. London: Alzheimer's Society.2007;1-91.
25. Cummings J, Aisen P.S, DuBois B, Frölich L, Jack C.R, Jones R.W, et al. Drug development in Alzheimer's disease: the path to 2025. Alzheimer's Research and Therapy 2016;8:39.
26. Dolgin E. (2016). How to defeat dementia. Nature 539, 156–158. doi: 10.1038/539156a
27. Schulz R, McGinnis K.A, Zhang S, Martire L.M, Hebert R.S, Beach S.R et al. Dementia patient suffering and caregiver depression. Alzheimer Dis. Assoc. Disord.2008; 22:170–176.
28. Hurd M.D, Martorell P, and Langa K.M. (2013). Monetary costs of dementia in the United States. N. Engl. J. Med.2013; 369:489–490.
29. Luengo-Fernandez R, Leal J, and Gray A. Dementia 2010: The Economic Burden of Dementia and Associated Research Funding in the United Kingdom. Oxford: Cambridge Alzheimer's Research Trust 2010.
30. Abbott A. Dementia: a problem for our age. Nature 2011;475:S2–S4.
31. Atanasov A.G, Waltenberger B, Pferschy-Wenzig E.-M, Linder T, Wawrosch C, Uhrin P et al. Discovery and resupply of pharmacologically active plant-derived natural products: a review. Biotechnol. Adv. 2015;33:1582–1614.
32. Qiu C, Kivipelto M, and von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin. Neurosci. 2009;11:111–128.
33. Baloh R.H. TDP-43: the relationship between protein aggregation and neurodegeneration in amyotrophic lateral sclerosis and frontotemporal lobar degeneration. FEBS J. 2011;278:3539–3549.
34. Brun A.Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. Arch. Gerontol. Geriatr.1987;6:193–208.

35. McKhann G.M, Albert M.S, Grossman M, Miller B, Dickson D, and Trojanowski J.Q. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch. Neurol.2001;58:1803–1809.
36. Rabinovici G.D, and Miller B.L. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. CNS Drugs 2010;24:375–398.
37. Iqbal K, Liu F, and Gong C.-X. Tau and neurodegenerative disease: the story so far. Nat. Rev. Neurol.2016;12:15–27.
38. Iqbal K, Liu F, Gong C.-X, and Grundke-Iqbal, I. Tau in Alzheimer disease and related tauopathies. Curr. Alzheimer Res.2010;7:656–664.
39. Zupancic M, Mahajan A, and Handa K. Dementia with lewy bodies: diagnosis and management for primary care providers. Prim. Care Companion CNS Disord. 2011;13(5).
40. Franzblau M, Gonzales-Portillo C, Gonzales-Portillo G.S, Diamandis T, Borlongan M.C, Tajiri, N, et al.Vascular damage: a persisting pathology common to Alzheimer's disease and traumatic brain injury. Med. Hypotheses 2013;81:842–845.
41. Shankar G.M, and Walsh D.M.Alzheimer's disease: synaptic dysfunction and Aβ. Mol. Neurodegener.2009;4:48.
42. Kumar A, and Singh A. A review on mitochondrial restorative mechanism of antioxidants in Alzheimer's disease and other neurological conditions. Front. Pharmacol. 2015;6:206.
43. Van Horssen J, van Schaik P, and Witte M. Inflammation and mitochondrial dysfunction: a vicious circle in neurodegenerative disorders? Neurosci. Lett.2017;710:132931.
44. Chan D.C. Mitochondria: dynamic organelles in disease, aging, and development. Cell 2006;125(7):1241–1252.
45. Banasch M, Ellrichmann M, Tannapfel A, Schmidt W.E, and Goetze O. The non-invasive (13)C-methionine breath test detects hepatic mitochondrial dysfunction as a marker of disease activity in non-alcoholic steatohepatitis. Eur. J. Med. Res.2011;16:258.
46. Moreira P.I, Carvalho C, Zhu X, Smith M.A, and Perry G. Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. Biochim. Biophys. Acta 2010;1802:2–10.
47. Zhu X, Perry G, Smith M.A, and Wang X.Abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. J. Alzheimers. Dis.2013;33(Suppl. 1):S253–S262.
48. Burte F, Carelli V, Chinnery P.F, and Yu-Wai-Man P.Disturbed mitochondrial dynamics and neurodegenerative disorders. Nat. Rev. Neurol. 2015;11(1):11–24.
49. Swerdlow R.H, Burns J.M, and Khan S.M. The Alzheimer's disease mitochondrial cascade hypothesis. J. Alzheimers. Dis. 2010;20(Suppl.2):S265–S279.
50. Beal M.F. Mitochondria take center stage in aging and neurodegeneration Ann. Neurol.2005;58:495–505.
51. Lin M.T, and Beal M.F. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature2006;443:787–795.
52. Hung C.H.-L, Cheng S.S.-Y, Cheung Y-T., Wuwongse S, Zhang, N.Q, Ho,Y.-S, et al. A reciprocal relationship between reactive oxygen species and mitochondrial dynamics in neurodegeneration. Redox Biol. 2018;14:7–19.
53. Chen J.X and Yan S.S. Role of mitochondrial amyloid-beta in Alzheimer's disease. J. Alzheimers.Dis.2010;20(Suppl.2):S569–S578.
54. Aminzadeh M, Roghani M, Sarfallah A and Riazi, G.H. TRPM2 dependence of ROS-induced NLRP3 activation in Alzheimer's disease. Int. Immunopharmacol.2018;54:78–85.
55. Lee J, Kim Y, Liu T, Hwang Y.J, Hyeon S.J, Im H et al. SIRT3 deregulation is linked to mitochondrial dysfunction in Alzheimer's disease. Aging Cell 2017.
56. Reddy A.P., and Reddy P.H. mitochondria-targeted molecules as potential drugs to treat patients with Alzheimer's disease. Prog. Mol. Biol. Transl. Sci.2017;146:173–20.
57. Stackman R.W, Eckenstein F, Frei B, Kulhanek D, Nowlin J, and Quinn J.F. Prevention of age-related spatial memory deficits in a transgenic mouse model of Alzheimer's disease by chronic Ginkgo biloba treatment. Exp. Neurol.2003;184:510–520.
58. Ma B, Meng X, Wang J, Sun J, Ren X, Qin M, et al. Notoginsenoside R1 attenuates amyloid-beta-induced damage in neurons by inhibiting reactive oxygen species and modulating MAPK activation. Int. Immunopharmacol.2014;22:151–159.

59. Wang C, and Youle R.J. The Role of Mitochondria in Apoptosis. Annu.Rev. Genet.2009; 43:95–118.
60. Walsh C, Barrow S, Voronina S, Chvanov M, Petersen O.H, and Tepikin A.(Modulation of calcium signalling by mitochondria. Biochim. Biophys. Acta 2009;1787:1374–1382.
61. Hajnoczky G, Davies E, and Madesh M. Calcium signaling and apoptosis. Biochem. Biophys. Res. Commun. 2003; 304:445–454.
62. Berridge M.J. Calcium signalling and cell proliferation. Bioessays1995;17:491–500.
63. Dai D-F, Chiao Y.A, Marcinek D.J, Szeto H.H, and Rabinovitch P.S.Mitochondrial oxidative stress in aging and healthspan. Longev. Heal.2014;3:6.
64. Fuchs L. Kräuterbuch Michael Isingrin. Basel Gao H.-M., Zhou H., and Hong J.-S. Oxidative stress, neuroinflammation, and neurodegeneration, in Neuroinflammation, and Neurodegeneration, eds P. K. Peterson and M. Toborek (New York, NY: Springer New York),2014;81–104.
65. Raina A.K, Zhu X, Rottkamp C.A, Monteiro M, Takeda A, and Smith MA. (2000). Cycling toward dementia: cell cycle abnormalities and abortive oncogenesis in Alzheimer disease. J. Neurosci. Res. 2000;61:128–133.
66. Katsel P, Tan W, Fam P, Purohit D.P, and Haroutunian V. (2013). Cell cycle checkpoint abnormalities during dementia: a plausible association with the loss of protection against oxidative stress in Alzheimer's disease [corrected]. PLoS ONE 2013;8(7).
67. Bennett S, Grant M.M, and Aldred S. Oxidative stress in vascular dementia and Alzheimer's disease: a common pathology. J. Alzheimers. Dis. 2009;17:245–257.
68. Spano M, Signorelli M, Vitaliani R, Aguglia E, and Giometto B. (2015). The possible involvement of mitochondrial dysfunctions in Lewy body dementia: a systematic review. Funct. Neurol.2015;30:151–158.
69. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. (2016). Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol. 2016;15:455.
70. Howard R.J, Juszczak E, Ballard C.G, Bentham P, Brown R.G, Bullock R, et al. Donepezil for the treatment of agitation in Alzheimer's disease. N. Engl. J. Med.2007; 357:1382–1392.
71. Ballard C, and Howard R. Neuroleptic drugs in dementia: benefits and harm. Nat. Rev. Neurosci.2006;7:492–500.
72. Fox C, Crugel M, Maidment I, Auestad B.H, Coulton S, Treloar A, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. PLoS ONE 2012;7.
73. Ibrahim F, Knight S.R, and Cramer R.L. Addressing the controversial use of antipsychotic drugs for behavioral and psychological symptoms of dementia. J. Pharm. Technol.2012;28;3–9.
74. Tzvetkov N.T, and Antonov L. (2017). Subnanomolar indazole-5-carboxamide inhibitors of monoamine oxidase B (MAO-B) continued: indications of iron binding, experimental evidence for optimised solubility and brain penetration. J. Enzyme Inhib. Med. Chem.2017;32:960–967.
75. Lilienfeld S. Galantamine–a novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer's disease. CNS Drug Rev.2002;8:159–176.
76. Olin J, and Schneider L. Galantamine for Alzheimer's disease. Cochrane database Syst. Rev.2002;3:CD001747.
77. Chrusciel M, and Varagic V. The effect of galantamine on the blood pressure of the rat. Br. J. Pharmacol.1996;26:295–301.
78. Ng Y.P, Or, T.C.T and Ip N.Y .Plant alkaloids as drug leads for Alzheimer's disease. Neurochem. Int. 2015;89:260–270.
79. Lonicerus A. Kräuterbuch, Matthias Wagner. Ulm.Loy, C., and Schneider, L. Galantamine for Alzheimer's disease and mild cognitive impairment. Cochrane database Syst. Rev. 2006;25:CD001747.
80. Albuquerque E.X, Santos M.D, Alkondon M, Pereira E.F, and Maelicke A. Modulation of nicotinic receptor activity in the central nervous system: a novel approach to the treatment of Alzheimer disease. Alzheimer Dis. Assoc. Disord.2001;15(Suppl. 1): S19–25.
81. Ezoulin M.J.M, Ombetta J.-E, Dutertre-Catella H, Warnet J-M, and Massicot F. Antioxidative properties of galantamine on neuronal damage induced by hydrogen peroxide in SK-N-SH cells. Neurotoxicology 2008;29:270–277.

82. Liu X, Xu K, Yan M, Wang Y, and Zheng X. (2010). Protective effects of galantamine against Aβ-induced PC12 cell apoptosis by preventing mitochondrial dysfunction and endoplasmic reticulum stress. Neurochem. Int.2010;57:588–599.
83. Tsvetkova D, Obreshkova D, Zheleva-Dimitrova D, and Saso L.Antioxidant activity of galantamine and some of its derivatives. Curr. Med. Chem.2013;20:4595–4608.
84. Namanja H.A, Emmert D, Pires M.M, Hrycyna C.A, and Chmielewski J. Inhibition of human P-glycoprotein transport and substrate binding using a galantamine dimer. Biochem. Biophys. Res. Commun. 2009;388:672–676.
85. Kumar A, Prakash A, and Pahwa D. Galantamine potentiates the protective effect of rofecoxib and caffeic acid against intrahippocampal Kainic acid-induced cognitive dysfunction in rat. Brain Res. Bull. 2011;85:158–168.
86. Romero A, Egea J, Garcia A.G, and Lopez M.G. (2010). Synergistic neuroprotective effect of combined low concentrations of galantamine and melatonin against oxidative stress in SH-SY5Y neuroblastoma cells. J. Pineal Res.2010;49:141–148.
87. Koola M.M, Buchanan R.W, Pillai A, Aitchison K.J, Weinberger D.R, Aaronson S.T, et al. Potential role of the combination of galantamine and memantine to improve cognition in schizophrenia. Schizophr. Res.2014;157:84–89.
88. Monsch A.U, and Giannakopoulos P. Effects of galantamine on behavioral and psychological disturbances and caregiver burden in patients with Alzheimer's disease. Curr. Med. Res. Opin.2004;20:931–938.
89. Doody R.S, Stevens J.C, Beck C, Dubinsky R.M, Kaye J.A, Gwyther L, et al. Practice parameter: management of dementia (an evidence- based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56: 1154–1166.
90. Waldemar G, Dubois B, Emre M, Georges J, McKeith I.G, Rossor M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur. J. Neurol.2007;14:e1–e26.
91. Long F, Yang H, Xu Y, Hao H, and Li P. A strategy for the identification of combinatorial bioactive compounds contributing to the holistic effect of herbal medicines. Sci. Rep. 2015;5:12361.
92. Zhou X, Seto S.W, Chang D, Kiat H, Razmovski-Naumovski V, Chan K, et al. Synergistic effects of chinese herbal medicine: a comprehensive review of methodology and current research. Front. Pharmacol. 2016b;7:201.
93. Pohl S, Zobel J, and Moffat A. Extended boolean retrieval for systematic biomedical reviews, in Proceedings of the Thirty-Third Australasian Conferenc on Computer Science -Volume 102 ACSC'10. (Darlinghurst, NSW: Australian Computer Society, Inc.)2010;117–126.Available online at: http://dl.acm.org/citation.cfm?id=1862199.1862212
94. Howes M.-J.R, and Houghton P.J. Plants used in Chinese and Indian traditional medicine for improvement of memory and cognitive function. Pharmacol. Biochem. Behav.2003; 75:513–527.
95. Fatumbi P.V.P. Ewé: The Use of Plants in Yoruba Society. Salvador:Oderbrecht.1995
96. Stafford G.I, Pedersen M.E, van Staden, J, and Jäger, A.K. Review on plants with CNS-effects used in traditional South African medicine against mental diseases. J. Ethnopharmacol. 2008;119:513–537.
97. Wolters B. Drogen, Pfeilgift und Indianermedizin: Arzneipflanzen aus Südamerika. Greifenberg: Urs Freud Verlag GmbH 1994.
98. Adams M, Gmünder F, and Hamburger M.Plants traditionally used in age related brain disorders—a survey of ethnobotanical literature. J. Ethnopharmacol.2007;113:363–381.
99. Mantle D, Pickering A.T., and Perry E.K.Medicinal plant extracts for the treatment of dementia. CNS Drugs 2000;13:201–213.
100. Ross I.A.Medicinal Plants of the World: Chemical Constituents, Traditional and Modern Medicinal Uses. New York, NY: Humana Press 2001.
101. Howes M.-J.R, and Perry E. The role of phytochemicals in the treatment and prevention of dementia. Drugs Aging 2011;28:439–468.
102. Manyam B,V. Dementia in ayurveda. J. Altern. Complement. Med. 1999;5:81–88.
103. Schultes R.E. Plants in treating senile dementia in the Northwest Amazon.J. Ethnopharmacol.1993;38:121–128.

104. Schultes R.E.Amazonian Ethnobotany and the Search for New Drugs BT - Ciba Foundation Symposium 185. Chichester: Wiley.1994.
105. Nishiyama N, Chu P.J, and Saito H.Beneficial effects of Biota, a traditional Chinese herbal medicine on learning impairment induced by basal forebrain-lesion in mice. Biol. Pharm. Bull.1995;28:1513–1517.
106. González Ayala J.C.Botánica Medicinal Popular: Etnobotánica Medicinal de El Salvador. Jardín Botànico La Laguna.1994.
107. Adsersen A, Gauguin B, Gudiksen L, and Jäger A.K. Screening of plants used in Danish folk medicine to treat memory dysfunction for acetylcholinesterase inhibitory activity. J. Ethnopharmacol.2006;104:418–422.
108. Tabernaemontanus D.I.T. Kräuterbuch, Johann Ludwig König/Johann Brandmüller. Basel.1987.
109. De Barradas J.P. Plantas Mágicas Americanas. Consejo Superior de Investigaciones Científicas, Instituto Bernardino de Sahagún.1957.
110. CESA. Usos Tradicionales de las Especies Forestales Nativas en el Ecuador. Tomo II.1992
111. CESA (1993). Usos Tradicionales de las Especies Forestales Nativas en el Ecuador.
112. Gurib-Fakim A.Medicinal plants: traditions of yesterday and drugs of tomorrow. Mol. Aspects Med. 2006;27:1–93.
113. Schweitzer de Palacios D.Cambiashun. Las prácticas médicas tradicionales y sus expertos en San Miguel del Común, una comuna indígena en los alrededores de Quito. Berlin: Holos-Verlag; Free University of Berlin.1994.
114. Müller-Ebeling C, and Rätsch C. Heilpflanzen der Seychellen.VWB-Verlag für Wissenschaft und Bildung. Berlin.1989.
115. Finkler K.Spiritualist Healers in Mexico: Successes and Failures of Alternative Therapeutics. Salem, WI: Praeger Publishers.1985.
116. Mills S.Y.Out of the Earth: The Essential Book of Herbal Medicine. London: Viking.1991.
117. Perry E.K., Pickering A.T., Wang W.W., Houghton P., and Perry N.S.L.Medicinal plants and Alzheimer's disease: integrating ethnobotanical and contemporary scientific evidence. J. Altern. Complement. Med.1998;4:419–428.
118. Sfikas G.Heilpflanzen Griechenlands. P. Efstathiadis & Söhne AG. Athen.1980.
119. Taylor L. Herbal Secrets of the Rainforest: The Healing Power of over 50 Medicinal Plants You Should Know About. Rocklin, CA: Prima Publishing.1998.
120. Duke J.A., and Ayensu E.S. Medicinal Plants of China. Algonac: Reference Publications.1985.
121. Price S, and Price L. Aromatherapy for Health Professionals. Edinburgh: Churchill Livingston.1995.
122. Chevallier A.The Encyclopedia of Medicinal Plants. London: Dorling Kindersley publishers.1996.
123. Akhondzadeh S, Noroozian M, Mohammadi M, Ohadinia S, Jamshidi A.H., and Khani M. Salvia officinalis extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind,randomized and placebo-controlled trial. J. Clin. Pharm. Ther.2003;28:53–59.
124. Savelev S.U., Okello E.J., and Perry E.K. Butyryl-and acetyl- cholinesterase inhibitory activities in essential oils of Salvia species and their constituents. Phyther. Res.2004;18:315–324.
125. Ortiz de Montellano B.R. Aztec Medicine, Health and Nutrition. New Brunswick: Rutgers University Press.1990.
126. Misra R. Modern drug development from traditional medicinal plants using radioligand receptor-binding assays. Med. Res. Rev. 1998;18:383–402.
127. Roeder B.A. Chicano Folk Medicine from Los Angeles. Berkeley; Los Angeles: CA: University of California Press.1988.
128. IARC Working Group. Some Drugs and Herbal Products. Lyon: Ginkgo Biloba. International Agency for Research and Cancer (IARC) Monographs, WHO.2016.
129. Guan R., Zhao Y., Zhang H., Fan G., Liu X., Zhou W., et al. Draft genome of the living fossil Ginkgo biloba. Gigascience 2016;5:49.
130. Sun Z.-K, Yang H.-Q., and Chen S.-D.Traditional Chinese medicine: a promising candidate for the treatment of Alzheimer's disease. Transl. Neurodegener.2013;2:6.
131. Zhou X., Cui G., Tseng H.H.L., Lee S.M.-Y, Leung G.P.H., Chan S.W., et al. Vascular contributions to cognitive impairment and treatments with traditional chinese medicine. Evid. Based. Complement. Alternat. Med.2016a;9627258.

132. Solfrizzi V., and Panza F. Plant-based nutraceutical interventions against cognitive impairment and dementia: meta-analytic evidence of efficacy of a standardized Gingko biloba extract. J. Alzheimers. Dis. 2015;43:605–611.
133. Tanaka A., Arai Y., Kim S.-N., Ham J., and Usuki, T.Synthesis and biological evaluation of bilobol and adipostatin A. J. Asian Nat. Prod. Res. 2011;13:290–296.
134. Isah T. Rethinking Ginkgo biloba L.: medicinal uses and conservation. Pharmacogn. Rev.2015;9:140–148.
135. Amri H., Ogwuegbu S.O., Boujrad N., Drieu K., and Papadopoulos, V.In vivo regulation of peripheral-type benzodiazepine receptor and glucocorticoid synthesis by Ginkgo biloba extract EGb 761 and isolated ginkgolides. Endocrinology1996;137: 5707–5718.
136. Ahlemeyer B., and Krieglstein J.Neuroprotective effects of Ginkgo biloba extract. Cell. Mol. Life Sci. C. 2003;60:1779–1792.
137. Butterfield D.A., Swomley A.M., and Sultana R. Amyloid beta- peptide (1-42)-induced oxidative stress in Alzheimer disease: importance in disease pathogenesis and progression. Antioxid. Redox Signal.2013;19:823–835.
138. Ruttkay-Nedecky B., Nejdl L., Gumulec J., Zitka O., Masarik M., Eckschlager T., et al. The role of metallothionein in oxidative stress. Int. J. Mol. Sci.2013;14:6044–6066.
139. Dávila D., Fernández S., and Torres-Alemán I.Astrocyte resilience to oxidative stress induced by insulin-like growth factor I (IGF-I) involves preserved AKT (protein kinase B) activity. J. Biol. Chem. 2016;291:12039.
140. Alam M.M., Okazaki K, Nguyen L.T.T., Ota N, Kitamura H, Murakami S, et al. Glucocorticoid receptor signaling represses the antioxidant response by inhibiting histone acetylation mediated by the transcriptional activator NRF2. J. Biol. Chem.2017;292: 7519–7530.
141. Gómez-Sámano M.Á., Grajales-Gómez M., Zuarth-Vázquez J.M., Navarro- Flores M. F., Martínez-Saavedra M., Juárez-León Ó.A., et al. Fibroblast growth factor 21 and its novel association with oxidative stress. Redox Biol.2017;11:335–341.
142. Bridi R, Crossetti F.P, Steffen V.M., and Henriques A.T.The antioxidant activity of standardized extract of Ginkgo biloba (EGb 761) in rats. Phytother. Res.2001;15:449–451.
143. Chandrasekaran K., Mehrabian Z., Spinnewyn B., Chinopoulos C., Drieu K., and Fiskum G.Neuroprotective effects of bilobalide, a component of Ginkgo biloba extract (EGb 761Ⓧ R) in global brain ischemia and in excitotoxicity-induced neuronal death. Pharmacopsychiatry 2003;36:89–94.
144. Eckert A, Keil U, Scherping I., Hauptmann S., and Muller W.E. Stabilization of mitochondrial membrane potential and improvement of neuronal energy metabolism by Ginkgo biloba extract EGb 761. Ann. N.Y. Acad. Sci. 2005;1056:474–485.
145. Abdel-Kader R., Hauptmann S., Keil U., Scherping I, Leuner K., Eckert A., et al. Stabilization of mitochondrial function by Ginkgo biloba extract (EGb 761). Pharmacol. Res.2007;56:493–502.
146. Wang C., and Wang B. Ginkgo biloba extract attenuates oxidative stress and apoptosis in mouse cochlear neural stem cells. Phytother. Res. 2016;30:774–780.
147. Zhou X, Wang H.-Y, Wu B, Cheng C.-Y, Xiao W., Wang Z.-Z, et al. Ginkgolide K attenuates neuronal injury after ischemic stroke by inhibiting mitochondrial fission and GSK-3beta-dependent increases in mitochondrial membrane permeability. Oncotarget 2017;8: 44682–44693.
148. Schwarzkopf T.M., Koch K.A, and Klein J. Neurodegeneration after transient brain ischemia in aged mice: beneficial effects of bilobalide. Brain Res.2013;1529:178–187.
149. Rhein V, Giese M., Baysang G., Meier F., Rao S., Schulz K.L., et al. Ginkgo biloba extract ameliorates oxidative phosphorylation performance and rescues abeta-induced failure. PLoS ONE 2010;5:e12359.
150. Domoráková I, Burda J, Mechírová E, and Feriková M. Mapping of rat hippocampal neurons with NeuN after ischemia/reperfusion and Ginkgo biloba extract (EGb 761) pretreatment. Cell. Mol. Neurobiol.2006;26:1191–1202.
151. Paganelli R.A, Benetoli A, and Milani H. Sustained neuroprotection and facilitation of behavioral recovery by the Ginkgo biloba extract, EGb 761, after transient forebrain ischemia in rats. Behav. Brain Res. 2006;174:70–77.

152. Jahanshahi M., Nickmahzar E.G., and Babakordi F.Effect of Gingko biloba extract on scopolamine-induced apoptosis in the hippocampus of rats. Anat. Sci. Int.2013;88:217–222.
153. Jahanshahi M., Nikmahzar E., Yadollahi N., and Ramazani K. Protective effects of Ginkgo biloba extract (EGB 761) on astrocytes of rat hippocampus after exposure with scopolamine. Anat. Cell Biol. 2012;45:92–96.
154. Yan F.-L., Zheng Y., and Zhao F.-D. Effects of Ginkgo biloba extract EGb761 on expression of RAGE and LRP-1 in cerebral microvascular endothelial cells under chronic hypoxia and hypoglycemia. Acta Neuropathol. 2008;116;529–535.
155. Wan W., Cao L., Liu L., Kalionis B., Chen C., Tai X., et al. EGb761 provides a protective effect against Aβ(1-42) oligomer-induced cell damage and blood-brain barrier disruption in an in vitro bEnd.3 endothelial model. PLoS ONE 2014;9:e113126.
156. Kim J.M., Ryou S.H, Kang Y.H., and Kang J.S. Effect of Ginkgo biloba leaf powder and extract on plasma and liver lipids, platelet aggregation and erythrocyte Na+ efflux in rats fed hypercholesterolemic diet. FASEB J.2011;25:980–988.
157. Geeganage C., Wilcox R., and Bath P.M.W. Triple antiplatelet therapy for preventing vascular events: a systematic review and meta-analysis. BMC Med. 2010;8:36.
158. Heim C., Khan M.A., Motsch B., Gocht A., Ramsperger-Gleixner M., Stamminger T., et al. microvascular integrity can be preserved by anti-platelet therapy and in combination with mTOR inhibitor. J. Hear. Lung Transplant.2017;36:S376.
159. Farkas E., and Luiten P.G. Cerebral microvascular pathology in aging and Alzheimer's disease. Prog. Neurobiol. 2001;64:575–611.
160. Zlokovic B.V. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat. Rev. Neurosci.2011;12:723–738.
161. Abdou H.M., Yousef M.I., El Mekkawy D.A., and Al-Shami A.S.Prophylactic neuroprotective efficiency of co-administration of Ginkgo biloba and Trifolium pretense against sodium arsenite-induced neurotoxicity and dementia in different regions of brain and spinal cord of rats. Food Chem. Toxicol.2016;9:112–127.
162. Kim M.-S., Lee J.-I., Lee W.-Y., and Kim S.-E. Neuroprotective effect of Ginkgo biloba L. extract in a rat model of Parkinson's disease. Phytother. Res.2004;18:663–666.
163. Takuma K., Hoshina Y., Arai S., Himeno Y., Matsuo A., Funatsu Y., et al.Ginkgo biloba extract EGb 761 attenuates hippocampal neuronal loss and cognitive dysfunction resulting from chronic restraint stress in ovariectomized rats. Neuroscience 2007;149: 256–262.
164. Ribeiro M.L., Moreira L.M., Arcari D.P., Dos Santos L.F., Marques A.C., Pedrazzoli J. J., et al. Protective effects of chronic treatment with a standardized extract of Ginkgo biloba L. in the prefrontal cortex and dorsal hippocampus of middle-aged rats. Behav. Brain Res.2016;313:144–150.
165. Kanowski S., Herrmann W.M., Stephan K., Wierich W., and Horr R. Proof of efficacy of the Ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. Pharmacopsychiatry 1996;29:47–56.
166. Napryeyenko O., Sonnik G., and Tartakovsky I.Efficacy and tolerability of Ginkgo biloba extract EGb 761 by type of dementia: analyses of a randomised controlled trial. J. Neurol. Sci.2009;283:224–229.
167. Ihl R., Tribanek M., and Bachinskaya N.Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761(R) in Alzheimer's disease and vascular dementia: results from a randomised controlled trial. Pharmacopsychiatry 2012;45:41–46.
168. Izzo A.A.Interactions between herbs and conventional drugs: overview of the clinical data. Med. Princ. Pract. 2012;21:404–428.
169. Yun T.K. Brief introduction of Panax ginseng C.A. Meyer. J. Korean Med.Sci. 2001;16(Suppl.):S3–S5.
170. Ngan F., Shaw P., But P., and Wang J. Molecular authentication of Panax species. Phytochemistry 1999;50,787–791.
171. Lee T.-K., Johnke R.M., Allison R.R., O'Brien K.F., and Dobbs, L.J.J. Radioprotective potential of ginseng. Mutagenesis2005;20:237–243.
172. Liu X., Xu K., Yan M., Wang Y., and Zheng X. Protective effects of galantamine against Aβ-induced PC12 cell apoptosis by preventing mitochondrial dysfunction and endoplasmic reticulum stress. Neurochem. Int. 2010;57:588–599.

173. Yin S.Y., Kim H.J., and Kim H.-J. A comparative study of the effects of whole red ginseng extract and polysaccharide and saponin fractions on influenza A (H1N1) virus infection. Biol. Pharm. Bull. 2013;36:1002–1007.
174. Song L., Xu M.-B., Zhou X.-L., Zhang D.-P., Zhang S.-L., and Zheng G.-Q. A Preclinical systematic review of ginsenoside-Rg1 in experimental Parkinson's disease. Oxid. Med. Cell. Longev. 2017:2163053.
175. Sun M., Ye Y., Xiao L., Duan X., Zhang Y., and Zhang H. Anticancer effects of ginsenoside Rg3 (Review). Int. J. Mol. Med. 2017;39,507–518.
176. Yang L., Hao J., Zhang J., Xia W., Dong X., Hu X., et al. Ginsenoside Rg3 promotes beta-amyloid peptide degradation by enhancing gene expression of neprilysin. J. Pharm. Pharmacol. 2009;61:375–380.
177. Popovich D.G., and Kitts D.D. Generation of ginsenosides Rg3 and Rh2 from North American ginseng. Phytochemistry 2004;65:337–344.
178. Sun S., Wang C.-Z., Tong R., Li X.-L., Fishbein A., Wang Q., et al. Effects of steaming the root of Panax notoginseng on chemical composition and anticancer activities. Food Chem. 2010;118:307–314.
179. Chen F., Eckman E.A., and Eckman C.B. Reductions in levels of the Alzheimer's amyloid beta peptide after oral administration of ginsenosides. FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.2006;20:1269–1271.
180. Kim Y.C., Kim S.R., Markelonis G.J., and Oh T.H. Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration. J. Neurosci. Res. 1998;53:426–432.
181. Li W., Chu Y., Zhang L., Yin L., and Li L. Ginsenoside Rg1 attenuates tau phosphorylation in SK-N-SH induced by Abeta-stimulated THP-1 supernatant and the involvement of p38 pathway activation. Life Sci. 2012;91:809–815.
182. Nah S.-Y.Ginseng ginsenoside pharmacology in the nervous system: involvement in the regulation of ion channels and receptors. Front. Physiol. 2014;5:98.
183. Bartus R.T., Dean R.L.III., Beer B., and Lippa A.S.The cholinergic hypothesis of geriatric memory dysfunction. Science1982;217:408–414.
184. Giacobini E. Cholinesterase inhibitors: new roles and therapeutic alternatives. Pharmacol. Res.2004;50:433–440.
185. Kim J., Shim J., Lee S., Cho W.-H., Hong E., Lee J.H., et al. Rg3-enriched ginseng extract ameliorates scopolamine-induced learning deficits in mice. BMC Complement. Altern. Med.2016;16:66.
186. Kaur U., Banerjee P., Bir A., Sinha M., Biswas A., and Chakrabarti S. Reactive oxygen species, redox signaling and neuroinflammation in Alzheimer's disease: the NF-kappaB connection. Curr. Top. Med. Chem. 2015;15:446–457.
187. Wang Y.-H., and Du G.-H.Ginsenoside Rg1 inhibits beta-secretase activity in vitro and protects against Abeta-induced cytotoxicity in PC12 cells. J. Asian Nat. Prod. Res.2009; 11:604–612.
188. Ye R., Zhang X., Kong X., Han J., Yang Q., Zhang Y., et al.Ginsenoside Rd attenuates mitochondrial dysfunction and sequential apoptosis after transient focal ischemia. Neuroscience 2011;178:169–180.
189. Tian J., Zhang S., Li G., Liu Z., and Xu B.20(S)-ginsenoside Rg3, a neuroprotective agent, inhibits mitochondrial permeability transition pores in rat brain. Phytother. Res.2009;23:486–491.
190. Zhou J.-S., Wang J.-F., He B.-R., Cui Y.-S., Fang X.-Y., Ni J.-L.,et al. Ginsenoside Rd attenuates mitochondrial permeability transition and cytochrome c release in isolated spinal cord mitochondria: involvement of kinase-mediated pathways. Int. J. Mol. Sci.2014;15:9859–9877.
191. Sirirugsa P., Larsen K., and Maknoi C. The genus Curcuma L.(zingiberaceae): distribution and classification with reference to species diversity in Thailand. Gard. Bull. Singapore 2007;59:203–320.
192. Chin D., Huebbe P., Pallauf K., and Rimbach G.Neuroprotective properties of curcumin in Alzheimer's disease–merits and limitations. Curr. Med.Chem.2013;20: 3955–3985.
193. Huminiecki L., Horbanczuk J., and Atanasov A.G. The functional genomic studies of curcumin. Semin. Cancer Biol. 2017;46:107–118.
194. Sahne F., Mohammadi M., Najafpour G.D., and Moghadamnia A.A.Enzyme-assisted ionic liquid extraction of bioactive compound from turmeric (Curcuma longa L.): isolation, purification and analysis of curcumin. Ind. Crops Prod.2017;95:686–694.

195. Anjomshoa S., Namazian M., and Noorbala M.R. The effect of solvent on tautomerism, acidity and radical stability of curcumin and its derivatives based on thermodynamic quantities. J. Solution Chem.2016;45:1021–1030.
196. Belkacemi A., Doggui S., Dao L., and Ramassamy C.Challenges associated with curcumin therapy in Alzheimer disease. Expert Rev. Mol. Med.2011;13:e34.
197. Pathak L., Agrawal Y., and Dhir A. Natural polyphenols in the management of major depression. Expert Opin. Investig. Drugs 2013;22:863–880.
198. Hügel H.M., and Jackson N. Polyphenols for the prevention and treatment of dementia diseases. Neural Regen. Res. 2015;10: 1756–1758.
199. Dong S., Zeng Q., Mitchell E.S., Xiu J., Duan Y., Li C., et al.urcumin enhances neurogenesis and cognition in aged rats: implications for transcriptional interactions related to growth and synaptic plasticity. PLoS ONE 2012;7:e31211.
200. Mishra S., and Palanivelu K.The effect of curcumin (turmeric) on Alzheimer's disease: an overview. Ann. Indian Acad. Neurol.2008;11:13–19.
201. Hoppe J.B., Coradini K., Frozza R.L., Oliveira C.M., Meneghetti A.B., Bernardi A., et al.Free and nanoencapsulated curcumin suppress beta-amyloid-induced cognitive impairments in rats: involvement of BDNF and Akt/GSK-3beta signaling pathway. Neurobiol. Learn. Mem.2013a;106:134–144.
202. Aravindan N., Madhusoodhanan R., Ahmad S., Johnson D., and Herman T.S. Curcumin inhibits NFκB mediated radioprotection and modulate apoptosis related genes in human neuroblastoma cells. Cancer Biol. Ther. 2008;7:569–576.
203. Doggui S., Belkacemi A., Paka G. D., Perrotte M., Pi R., and Ramassamy C.Curcumin protects neuronal-like cells against acrolein by restoring Akt and redox signaling pathways. Mol. Nutr. Food Res.2013;57:1660–1670.
204. Ye J., and Zhang Y.Curcumin protects against intracellular amyloid toxicity in rat primary neurons. Int. J. Clin. Exp. Med.2012;5:44–49.
205. Daverey A., and Agrawal S.K. Curcumin alleviates oxidative stress and mitochondrial dysfunction in astrocytes. Neuroscience 2016;333:92–103.
206. Ramkumar M., Rajasankar S., GobiV.V., Dhanalakshmi C., Manivasagam T., Justin Thenmozhi A., et al. Neuroprotective effect of Demethoxycurcumin, a natural derivative of Curcumin on rotenone induced neurotoxicity in SH-SY 5Y Neuroblastoma cells. BMC Complement. Altern. Med. 2017;17:217.
207. Eckert G.P., Schiborr C., Hagl S., Abdel-Kader R., Muller W.E., Rimbach G., et al. Curcumin prevents mitochondrial dysfunction in the brain of the senescence-accelerated mouse-prone 8. Neurochem. Int.2013;62:595–602.
208. Rastogi M., Ojha R. P., Sagar C., Agrawal A., and Dubey G.P. Protective effect of curcuminoids on age-related mitochondrial impairment in female Wistar rat brain. Biogerontology 2014;15:21–31.
209. Miao Y., Zhao S., Gao Y., Wang R., Wu Q., Wu H., et al. Curcumin pretreatment attenuates inflammation and mitochondrial dysfunction in experimental stroke: the possible role of Sirt1 signaling. Brain Res. Bull. 2016;121:9–15.
210. Yanagisawa D., Taguchi H., Yamamoto A., Shirai N., Hirao K., and Tooyama I. Curcuminoid binds to amyloid-beta1-42 oligomer and fibril. J. Alzheimers. Dis. 2011;24(Suppl. 2): 33–42.
211. Narlawar R., Pickhardt M., Leuchtenberger S., Baumann K., Krause S., Dyrks T., et al. Curcumin-derived pyrazoles and isoxazoles: swiss army knives or blunt tools for Alzheimer's disease? ChemMedChem 2008;3:165–172.
212. Xiong Z., Hongmei Z., Lu S., and Yu L. Curcumin mediates presenilin activity to reduce beta-amyloid production in a model of Alzheimer's Disease. Pharmacol. Rep. 2011;63:1101–1108.
213. Zhang L., Fiala M., Cashman J., Sayre J., Espinosa A., Mahanian M., et al. Curcuminoids enhance amyloid-beta uptake by macrophages of Alzheimer's disease patients. J. Alzheimers. Dis.2006;10:1–7.
214. Gate D., Rezai-Zadeh K., Jodry D., Rentsendorj A., and Town T. Macrophages in Alzheimer's disease: the blood-borne identity. J. Neural Transm. 2010;117:961–970.
215. Huang H.-C., Tang D., Xu K., and Jiang Z.-F.Curcumin attenuates amyloid-beta-induced tau hyperphosphorylation in human neuroblastoma SH-SY5Y cells involving PTEN/Akt/GSK-3beta signaling pathway. J. Recept. Signal Transduct. Res. 2014;34:26–37.

216. Hoppe J.B., Haag M., Whalley, B.J., Salbego C.G., and Cimarosti, H.Curcumin protects organotypic hippocampal slice cultures from Abeta1-42-induced synaptic toxicity. Toxicol. In Vitro 2013b;27:2325–2330.
217. Zhang L., Fang Y., Xu Y., Lian Y., Xie N., Wu T., et al. Curcumin improves amyloid beta-peptide (1-42) induced spatial memory deficits through BDNF-ERK signaling pathway. PLoS ONE 2015;10:e0131525.
218. Brondino N., Re S., Boldrini A., Cuccomarino A., Lanati N., Barale F., et al. Curcumin as a therapeutic agent in dementia: a mini systematic review of human studies. Sci. World J. 2014:174282.
219. Cox K.H.M., Pipingas A., and Scholey A. B.Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. J. Psychopharmacol.2015; 29:642–651.
220. Ng T.-P., Chiam P.-C., Lee T., Chua H.-C., Lim L., and Kua E.-H. (2006).
221. Tayyem R.F., Heath D.D., Al-Delaimy W.K., and Rock C.L. Curcumin content of turmeric and curry powders. Nutr. Cancer 2006;55:126–131.
222. Akinyemi A.J., Oboh G., Oyeleye S.I., and Ogunsuyi O.Anti-amnestic effect of curcumin in combination with donepezil, an anticholinesterase drug: involvement of cholinergic system. Neurotox. Res.2017;31: 560–569.
223. Yan J., Hu J., Liu A., He L., Li X., and Wei H. Design, synthesis, and evaluation of multitarget-directed ligands against Alzheimer's disease based on the fusion of donepezil and curcumin. Bioorg. Med. Chem. 2017;25:2946–2955.
224. Asl M.N., and Hosseinzadeh H. Review of pharmacological effects of Glycyrrhiza sp. and its bioactive compounds. Phyther. Res.2008;22:709–724.
225. Blumenthal M., Goldberg A., and Brinkmann J.Herbal Medicine, Expanded Commission E Monographs Cd-Rom. Austin, TX: American Botanical Council/Integrative Medical.2000
226. Callender V.D., St Surin-Lord S., Davis E.C., and Maclin M.Postinflammatory hyperpigmentation: etiologic and therapeutic considerations. Am. J. Clin. Dermatol.2011; 12:87–99.
227. Tewari D., Mocan A., Parvanov, E.D., Sah A.N., Nabavi S.M., Huminiecki L., et al. Ethnopharmacological approaches for therapy of jaundice: Part II. Highly used plant species from Acanthaceae, Euphorbiaceae, Asteraceae, Combretaceae, and Fabaceae families. Front. Pharmacol. 2017;8:519.
228. Chang K.-H., Chen I.-C., Lin H.-Y., Chen H.-C., Lin C.-H., Lin T.-H.,et al.The aqueous extract of Glycyrrhiza inflata can upregulate unfolded protein response-mediated chaperones to reduce tau misfolding in cell models of Alzheimer's disease. Drug Des. Devel. Ther.2016;10:885–896.
229. Chen C.-M., Weng Y.-T., Chen W.-L., Lin T.-H., Chao C.-Y., Lin C.-H., et al. Aqueous extract of Glycyrrhiza inflata inhibits aggregation by upregulating PPARGC1A and NFE2L2-ARE pathways in cell models of spinocerebellar ataxia 3. Free Radic. Biol. Med.2014;71: 339–350.
230. Yim S.B, Park S.E, and Lee C.S. Protective effect of glycyrrhizin on 1-methyl-4-phenylpyridinium-induced mitochondrial damage and cell death in differentiated PC12 cells. J. Pharmacol. Exp. Ther 2007;321:816–822.
231. Dringen R. Metabolism and functions of glutathione in brain. Prog. Neurobiol.2000;62:649–671.
232. Saharan S., and Mandal, P.K.The emerging role of glutathione in Alzheimer's disease. J. Alzheimers. Dis. 2014;40:519–529.
233. Chang K.-H., Chen I.-C., Lin H.-Y., Chen H.-C., Lin C.-H., Lin T.-H.,et al.The aqueous extract of Glycyrrhiza inflata can upregulate unfolded protein response-mediated chaperones to reduce tau misfolding in cell models of Alzheimer's disease. Drug Des. Devel. Ther. 2016;10:885–896.
234. Yang E.-J., Min J.S., Ku H.-Y., Choi H.-S., Park M., Kim M.K., et al. Isoliquiritigenin isolated from Glycyrrhiza uralensis protects neuronal cells against glutamate-induced mitochondrial dysfunction. Biochem. Biophys. Res. Commun.2012;421:658–664.
235. Ju H.S., Li X.J., Zhao B.L., Han Z.W., and Xin W.J. Effects of glycyrrhiza flavonoid on lipid peroxidation and active oxygen radicals. Yao Xue Xue Bao 1989;24:807–812.
236. Dhingra D., Parle M., and Kulkarni S.K.Memory enhancing activity of Glycyrrhiza glabra in mice. J. Ethnopharmacol. 2004;91:361–365.
237. Yokota T., Nishio H., Kubota Y., and Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. Pigment cell Res.1998;11:355–361.
238. Dandekar A., Mendez R., and Zhang K. Cross talk between ER stress, oxidative stress, and inflammation in health and disease. Methods Mol. Biol.2015;1292:205–214.

239. Ikarashi Y., and Mizoguchi K. Neuropharmacological efficacy of the traditional Japanese Kampo medicine yokukansan and its active ingredients. Pharmacol. Ther.2016; 166:84–95.
240. Danysz W., and Parsons C.G. The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence. Int. J. Geriatr. Psychiatry 2003;18:S23–S32.
241. Kanno H., Kawakami Z., Tabuchi M., Mizoguchi K., Ikarashi Y., and Kase Y. Protective effects of glycycoumarin and procyanidin B1, active components of traditional Japanese medicine yokukansan, on amyloid beta oligomer-induced neuronal death. J. Ethnopharmacol.2015;159:122–128.
242. Parle M., Dhingra D., and Kulkarni S.K. Memory-strengthening activity of Glycyrrhiza glabra in exteroceptive and interoceptive behavioral models. J. Med. Food2004;7:462–466.
243. Hikino H. Recent research on oriental medicinal plants. Econ. Med. Plant.Res.1985;1: 53–85.
244. Zhu X., Chen C., Ye D., Guan D., Ye L., Jin J., et al.Diammonium glycyrrhizinate upregulates PGC-1α and protects against Aβ 1–42-induced neurotoxicity. PLoS ONE2012;7:e35823.
245. Qiao X., Ji S., Yu S.-W., Lin X.-H., Jin H.-W., Duan Y.-K., et al. .Identification of key licorice constituents which interact with cytochrome P450: evaluation by LC/MS/MS cocktail assay and metabolic profiling. AAPS J.2014;16:101–113.
246. Goenka P., Sarawgi A., Karun V., Nigam A.G., Dutta S., and Marwah N.Camellia sinensis (Tea): implications and role in preventing dental decay. Pharmacogn. Rev.2013; 7:152–156.
247. de Mejia E.G., Ramirez-Mares M.V., and Puangpraphant S. Bioactive components of tea: cancer, inflammation and behavior. Brain. Behav. Immun.2009;23:721–731.
248. Chacko S.M., Thambi P.T., Kuttan R., and Nishigaki I. Beneficial effects of green tea: a literature review. Chin. Med.2010;5:13.
249. Rezai-Zadeh K., Arendash G. W., Hou H., Fernandez F., Jensen M., Runfeldt M., et al. Green tea epigallocatechin-3-gallate (EGCG) reduces beta-amyloid mediated cognitive impairment and modulates tau pathology in Alzheimer transgenic mice. Brain Res. 2008;1214:177–187.
250. Mandel S.A., Amit T., Weinreb O., and Youdim M.B.H.Understanding the broad-spectrum neuroprotective action profile of green tea polyphenols in aging and neurodegenerative diseases. J. Alzheimers. Dis. 2011;2:187–208.
251. Mahmood T., Akhtar N., and Khan B.A.The morphology, characteristics, and medicinal properties of Camellia sinensis tea. J. Med. Plants Res.2010;4:2028–2033.
252. Wang D.-S., Dickson D.W., and Malter J.S. beta-Amyloid degradation and Alzheimer's disease. J. Biomed. Biotechnol. 2006:58406.
253. Jelenkovic A., Jovanovic M.D., Stevanovic I., Petronijevic N., Bokonjic D., Zivkovic J., et al. Influence of the green tea leaf extract on neurotoxicity of aluminium chloride in rats. Phytother. Res. 2014;28:82–87.
254. Egashira N., Hayakawa K., Osajima M., Mishima K., Iwasaki K., Oishi R., et al. Involvement of GABA(A) receptors in the neuroprotective effect of theanine on focal cerebral ischemia in mice. J. Pharmacol. Sci. 2007;105:211–214.
255. Egashira N., Ishigami N., Pu F., Mishima K., Iwasaki K., Orito K., et al. Theanine prevents memory impairment induced by repeated cerebral ischemia in rats. Phytother. Res. 2008;22,:65–68.
256. Yamada T., Terashima T., Honma H., Nagata, S., Okubo T., Juneja L.R., et al. Effects of theanine, a unique amino acid in tea leaves, on memory in a rat behavioral test. Biosci. Biotechnol. Biochem. 2008;72:1356–1359.
257. Dragicevic N., Smith A., Lin X., Yuan F., Copes N., Delic, V., et al.Green tea epigallocatechin-3-gallate (EGCG) and other flavonoids reduce Alzheimer's amyloid-induced mitochondrial dysfunction. J. Alzheimers. Dis.2011;26:507–521.
258. Kim T.I., Lee Y.K., Park S.G., Choi I.S., Ban J.O., Park H.K., et al.l-Theanine, an amino acid in green tea, attenuates beta-amyloid-induced cognitive dysfunction and neurotoxicity: reduction in oxidative damage and inactivation of ERK/p38 kinase and NF-kappaB pathways. Free Radic. Biol. Med.2009;47:1601–1610.
259. Ayoub S., and Melzig M. F. Induction of neutral endopeptidase (NEP) activity of SK-N-SH cells by natural compounds from green tea. J. Pharm. Pharmacol. 2006;58:495–501.
260. Haskell C.F., Kennedy D.O., Milne A.L., Wesnes K.A., and Scholey A.B.The effects of L-theanine, caffeine and their combination on cognition and mood. Biol. Psychol. 2008;77:113–122.

261. Owen G.N., Parnell H., De Bruin E.A., and Rycroft J.A.The combined effects of L-theanine and caffeine on cognitive performance and mood. Nutr. Neurosci. 2008;11:193–198.
262. Kimura K., Ozeki M., Juneja L.R., and Ohira H. L-Theanine reduces psychological and physiological stress responses. Biol. Psychol. 2007;74:39–45.
263. Zhou S., Lim L.Y., and Chowbay B. Herbal modulation of P-glycoprotein.Drug Metab. Rev.2004;36:57–104.
264. Joshi A, Malviya N, Anti-Alzheimer Activity of Hydroalcoholic Extract of Butea monosperma leaves, Journal of Drug Delivery and Therapeutics. 2019; 9:62-67
265. Joshi A, Malviya N, Memory enhancing activity of hydroalcoholic extract of Terminalia catappa leaves, Journal of Drug Delivery and Therapeutics. 2017; 7:197-199