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Medicinal plants and their derivatives with amyloid beta inhibitory activity as potential targets for drug discovery

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that primarily affects the elderly population. Its management has been a long-standing challenge and area of interest. One of the pathological features of the disease is the formation of senile plaques which are made up of amyloid beta (Aβ) peptides. Aβ causes neurodegeneration by a complex interaction of processes that involves increasing the extracellular concentration of glutamate, intracellular Ca^{2+} and apoptosis. The Aβ peptide is therefore a prime target for developing therapies for AD, and inhibition of the peptide has been explored as a possible approach toward treatment of AD. A potential source of Aβ inhibitors is provided by the abundance of medicinal plants in nature. Several extracts from medicinal plants and isolated compounds have been tested in animal and cellular models of AD with promising results. The present work constitutes a review of the literature on medicinal plants and isolated compounds which have been tested for their inhibitory activity against Aβ. The plant species and compounds listed are potential inhibitors of Aβ and may aid researchers in their further studies on the development of treatments for AD from natural products.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by impairment in learning and memory, followed by cognitive deficits and behavioural disturbances, which progressively become more severe[1]. It is the most common cause of dementia affecting approximately 10%-15% of the elderly population over 65 years, with an estimated 30 million sufferers worldwide[2]. The clinical symptoms result from the deterioration of selective cognitive domains, particularly those related to memory. Memory decline initially manifests as a loss of episodic memory, which impedes recollection of recent events including autobiographical activities[3].

Histopathologically, AD is characterized by progressive degeneration and loss of neurons in the brain, and this has been correlated with the formation of senile plaques and neurofibrillary tangles[4,5]. The major component of senile plaques is amyloid beta (Aβ) peptide. Both *in vitro* and *in vivo* studies have reported its toxic effects, suggesting an important role of Aβ in the pathogenesis of AD[6,7]. Aβ is an amino acid peptide which consists of 39-43 amino acid residues. These residues are derived from amyloid precursor protein (APP) which aggregates into a fibrillar and β-sheeted structure[7]. In brains of AD patients, the Aβ peptide aggregates and forms insoluble fibrils that are the major component of the senile plaques. According to Cummings and Cotman, the extent of brain Aβ deposition correlates with the degree of cognitive deficit in patients with AD[8]. Aβ causes neurodegeneration in AD by a complex interaction of neurodegenerative processes that involves increasing the extracellular concentration of glutamate, intracellular Ca^{2+} and apoptosis[5,9]. Aβ increases Ca^{2+} influx by

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the impairment of membrane Ca^{2+} pumps and formation of amyloid channels[10]. Ca^{2+} overload can activate Ca^{2+}-dependent proteases and nitric oxide synthase and destroy mitochondria[10,11]. It can also cause neuronal excitotoxicity by promoting recruitment of other ion channels[12]. Aβ also facilitates generation of free radicals, which cause peroxidation of membrane lipids and increase the production of reactive oxygen species (ROS), resulting in cell damage and apoptosis[13,14]. In addition, DNA damage and increased activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) are associated with degenerating neurons in the brains of AD patients, and occur as a consequence of oxidative stress by Aβ deposition in the brain[15,16]. Cumulative ROS induces oxidative stress, membrane damage and increases the permeability of ions including Ca^{2+}. Resultant Ca^{2+} influx, in turn, induces further ROS accumulation. Thus, Aβ either directly or through excessive Ca^{2+} influx and ROS accumulation, alters cellular function, leading to neuronal apopotosis[10,17-19].

The Aβ peptide is a prime target for developing therapies for neurodegenerative diseases including AD[20]. Therefore, modulating the chain of events starting from the production of Aβ fragments from APP to its deposition in the form of extracellular plaques is believed to be possible approach toward the treatment of AD[1].

Plants have been used since antiquity in traditional medicinal systems for the treatment of memory dysfunction and several other age-related diseases. It has been shown that natural products have the potential not only to prevent Aβ toxicity but also to prevent the production of Aβ. These studies have involved ethnopharmacological approaches as well as bio-assay guided isolation research[1,21]. This article highlighted the plants and compounds that have been isolated from medicinal plants, to date, which have demonstrated inhibition of Aβ.

2. Experimental approaches

$Aβ_{1-42}$ and $Aβ_{25-35}$ are two commonly used forms of Aβ. $Aβ_{1-42}$, an antiparallel β-pleated sheet peptide, is a major constituent of diffused plaques in the brain of AD patients. $Aβ_{1-42}$, after cleavage from APP, has been shown to be an important factor in the pathogenesis of AD[14,22,23]. Also, the increased production of $Aβ_{1-42}$ in AD patients accelerates neurodegeneration, possibly due to the higher propensity of the peptide for amyloid fibrillogenesis, resulting in formation of bioactive amyloid plaque species[14,24-26]. The shorter length $Aβ_{25-35}$ peptide is the core fragment of the full length $Aβ_{1-42}$ peptide, and it is also highly toxic. Although it cannot be found naturally in brains of AD patients, several studies have shown that it triggers neurotoxicity similar to that caused by $Aβ_{1-42}$ peptide[27-31].

3. *In vitro* assays

Several cell lines have been used as neuronal cell models to determine the Aβ inhibitory activity of plant extracts and isolated compounds. However, the most commonly used cell lines from literature include the rat pheochromocytoma (PC12) cell line, primary cortical neurons and the human neuroblastoma (SH-SY5Y) cell line (Tables 1 and 2). The PC12 cells have been widely used in both neurobiological and neurotoxicological studies as a model of neuronal differentiation[32]. They are clonal cells which originated from a transplantable rat pheochromocytoma and exhibit the phenotypic properties associated with pheochromocytomas. PC12 cells respond to nerve growth factors and acquire several properties common to sympathetic neurons[32,33].

The SH-SY5Y cell line is a thrice-cloned sub-line of SK-N-SH cells which were originally established from a bone marrow biopsy of a neuroblastoma patient with sympathetic adrenergic ganglial origin in the early 1970s[34]. It has been widely used as a model of neurons since the early 1980s, as the cells possess many biochemical and functional properties of neurons. The cell line is a comparatively homogenous neuroblast-like cell line, and it exhibits neuronal marker enzyme activity. In addition, the SH-SY5Y cells possess the capability of proliferating in cultures for long periods without contamination, which is a prerequisite for the development of an *in vitro* cell model. The cell line has therefore, been widely used in experimental neurological studies including analysis of neuronal differentiation, metabolism and function related to neurodegenerative and neuroadaptive processes, neurotoxicity and neuroprotection[35].

The primary cortical neurons, also referred to as primary culture of foetal rat cortical neurons, are widely used in cell models of various neurological disorders[36]. The cortical neurons are usually obtained from embryos of Sprague-Dawley rats[10]. The neurons can be co-cultured with endotheliocytes and astrocytes to mimic neurovascular units *in vitro*, to study the blood-brain barrier[36-38]. The cell line is widely applied in studying cell function, neurodevelopment and neurological diseases[36].

Several biochemical assays including 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide, neutral red uptake, lactate dehydrogenase (LDH)-release assays, measurement of apoptotic cell death, intracellular calcium concentration, glutamate concentration, intracellular ROS level and caspase-3 activity are usually carried out using established methodology[7,14,39,40].

4. *In vivo* models

Several animal models have been used to determine the effect of medicinal plants and isolated compounds on Aβ-induced neurodegeneration. The preferred model seems to be the Institute of Cancer Research (ICR) mice (Tables 1 and 2). The experimental animals are injected with Aβ peptide either before or after administration of the test drug and several *in vivo* behavioural tests are performed. Commonly used behavioural tests include the Y-maze test, Morris water maze test, passive avoidance test and open-field tests.

The Y-maze is made of black painted plastic, and each arm is 33 cm long, 15 cm high and 10 cm in width and positioned at an equal angle[41]. The Morris water maze consists of a circular water tank (diameter of 4.5 cm and height of 14.5 cm) containing water (28°C) with a depth of 15 cm and rendered opaque by adding powdered milk. It also consists of an escape platform (height of 14.5 cm and diameter of 4.5 cm) which is submerged 0.5 cm below the water surface[42,43]. The apparatus for the passive avoidance test consists of two adjoining compartments,

Table 1
Medicinal plants with inhibitory activity against Aβ.

Plants	Families	Extracts and fractions	Assays	Models or assays	Mechanism of actions	References
Achyranthes bidentata B.	Amaranthaceae	Ethanol extract	*In vitro*	Thioflavin T fluorescence	Reduction of Aβ polymerization	Luo *et al*.[56]
Alpinia galanga (L.) W.	Zingiberaceae	*n*-Hexane, chloroform and ethyl acetate fractions	*In vivo*	Swiss albino mice	Free radical scavenging activity, increased Na^+/K^+-ATPase activity and cholinesterase inhibition	Hanish Singh *et al*.[43]
A. gigas	Umbelliferae	Ethanol extract	*In vivo*	ICR mice	Antioxidant activity and inhibition of acetylcholinesterase	Yan *et al*.[57]
Bacopa monnieri (L.) P.	Plantaginaceae	95% Ethanol extract	*In vitro*	Primary cortical neurons	Regulation of neuronal protein transcription and inhibition of amyloid peptide-activated intracellular acetylcholinesterase activity	Limpeanchob *et al*.[58]
Bambusae concretio S.	Gramineae	Water extract	*In vitro*	Cortical astrocyte cells	Inhibition of lipid peroxidation and protection of antioxidant enzymes	Jeong *et al*.[59]
Caesalpinia crista L.	Fabaceae	Water extract	*In vitro*	Thioflavin T assay	Inhibition of Aβ aggregation and disaggregation of preformed fibrils	Ramesh *et al*.[60]
Carica papaya L.	Caricaceae	Fermented papaya preparation	*In vitro*	Neuroblastoma cell line	Reduction of intracellular calcium, ROS generation and nitric oxide accumulation; prevention of apoptosis through the bax/Bcl-2 pathway	Zhang *et al*.[61]
Centella asiatica (L.) U.	Mackinlayaceae	Standardised extract of leaves NS	*In vitro* *In vivo*	Neuroblastoma cell line, primary cortical cell culture, PSAPP mice	Enhancement of the phosphorylation of the cyclic AMP response element binding protein, inhibition of hydroxyl radical induced membrane damage, alteration of the extracellular matrix composition of Aβ	Xu *et al*.[62], Dhanasekaran *et al*.[63]
Cinnamomum zeylanicum L.	Lauraceae	Material tested based on aqueous extract	*In vitro* *In vivo*	Thioflavin T binding fluorescence, PC 12 cells transgenic flies, 5XFAD mice	Inhibition of fibril formation and destabilization of pre-formed fibrils, reduction of Aβ deposition	Frydman-Marom *et al*.[55]
C. sativus	Iridaceae	Hydroalcoholic extract	*In vitro*	Thioflavine T-based fluorescence assay and DNA binding shift assay	Binding to the hydrophobic regions of the Aβ via the hydrophobic carotene backbone and inhibiting fibril formation	Dastmalchi *et al*.[1], Papandreou *et al*.[64]
D. asper	Dipsacaceae	Water extract and saponin fraction	*In vitro*	PC 12 cells	Inhibition of excessive Ca^{2+} influx, reduction of LDH leakage and prevention of loss of cell viability	Zhou *et al*.[65]
Ecklonia cava K.	Lessoniaceae	Butanol extract	*In vitro*	Primary cortical neurons, HEK293 cells	Antioxidant activity, prevention of Aβ oligomer and fibril formation	Kang *et al*.[66]
E. senticosus	Araliaceae	Ethyl acetate, *n*-butanol and water fractions from the methanol extract	*In vitro*	Primary cortical neurons	Prevention of $Aβ_{25-35}$-induced axonal atrophy	Bai *et al*.[67]
Eriobotrya japonica (T.) L.	Rosaceae	Ethanol extract	*In vitro* *In vivo*	PC 12 cells, ICR mice	Free radical scavenging activity	Kim *et al*.[54]
Eucommia ulmoides O.	Eucommiaceae	Aqueous extract	*In vivo*	ICR mice	Inhibition of acetylcholinesterase activity	Kwon *et al*.[68]
F. macrophylla	Leguminosae	Ethanol fraction, ethyl acetate-butanol fraction (EA-74) and butanol-methanol fraction (B50M)	*In vitro*	swAPP-N2a cells	Inhibition of β-secretase and activation of insulin degrading enzyme	Lin *et al*.[69]
Ganoderma lucidum (C.) P. K.	Ganodermataceae	Aqueous extract	*In vitro*	Primary cortical neurons	Attenuation of Aβ-induced synaptotoxicity, inhibition of Aβ-induced DEVD cleavage activity and reduction of the phosphorylation of c-Jun n-terminal kinase, c-Jun and p38 MAP kinase	Lai *et al*.[70]
Gastrodia elata B.	Orchidaceae	Ethyl ether fraction	*In vitro*	IMR-32 neuroblastoma cells	Antioxidant activity	Kim *et al*.[71]
G. biloba	Ginkgoaceae	Standardised extract rich in flavonoids and terpenoids (EGb 761)	*In vitro*	Hippocampal primary cultured cells	Attenuation of $Aβ_{25-35}$ induced apoptosis	Bastianetto *et al*.[72]
G. uralensis	Fabaceae	Aqueous extract	*In vitro*	PC 12 cells	Suppression of Aβ-induced apoptosis and ROS generation	Ahn *et al*.[5]
Houttuynia cordata T.	Saururaceae	Water extract	*In vitro*	Primary cortical neurons	Inhibition of $Aβ_{25-35}$-induced elevation of intracellular calcium, ROS, mitochondrial membrane disruption and caspase-3 activation	Park and Oh[73]
H. perforatum	Hypericaceae	50% Ethanol extract	*In vitro*	Microglial cell line BV2	Reduction of Aβ-induced ROS generation and membrane fluidity increase	Kraus *et al*.[40]
Ipomoea batatas (L.) Lam	Convolvulaceae	Ethanol extract	*In vivo*	ICR mice	Increased catalase activity and reduction of lipid peroxidation	Kim *et al*.[53]
Juglans regia L.	Juglandaceae	Ethyl acetate extract	*In vitro*	PC 12 cells	Free radical scavenging activity, inhibition of membrane damage and attenuation of DNA damage	Muthaiyah *et al*.[74]
Lycium barbarum L.	Solanaceae	Alkaline extract	*In vitro*	Primary cortical neurons	Reduction of caspase-3 activity triggered by Aβ and stimulation of the Akt survival pathway	Ho *et al*.[31]
M. officinalis	Magnoliaceae	Ethanol extract	*In vivo*	ICR mice	Inhibition of $Aβ_{1-42}$-induced ROS generation and neuronal death	Lee *et al*.[42]
P. suffruticosa	Paeoniaceae	Water, methanol and ethanol extracts	*In vitro* *In vivo*	Thioflavin T method, transgenic 2576 mice	Inhibition of fibril formation and destabilization of pre-formed fibrils, inhibition of Aβ plaque formation	Fujiwara *et al*.[75]
Phellodendron amurense R.	Rutaceae	Ethanol extract	*In vitro*	PC 12 cells	Increase in the ratio of protein and mRNA levels of Bcl-2/Bax and reduction of cytochrome *c* release and expression of caspase-3	Xian *et al*.[2]
Phellodendron chinense S.	Rutaceae	Ethanol extract	*In vitro*	PC 12 cells	Increase in the ratio of protein and mRNA levels of Bcl-2/Bax and reduction of cytochrome *c* release and expression of caspase-3	Xian *et al*.[2]
Polygonum multiflorum T.	Polygonaceae	Aqueous extract	*In vivo*	ICR mice	Antioxidant activity and inhibition of acetylcholinesterase	Um *et al*.[76]
Pterocarpus erinaceus P.	Fabaceae	Aqueous extract	*In vitro*	CHO-K1 cells overexpressing human neuronal β-amyloid peptide precursor	Inhibition of γ-secretase activity at the γ-site where Aβ is produced	Hage *et al*.[77]
Ptychopetalum olacoides Benth.	Olacaceae	Ethanol extract	*In vivo*	CF1 albino mice	Anticholinesterase activity and inhibition of Aβ-induced cytotoxicity	Figueiró *et al*.[78]
R. acori	Acoraceae	Water extract	*In vitro*	PC 12 cells	Inhibition of cytotoxic action of $Aβ_{1-40}$	Irie and Keung[79]
Rosa laevigata M.	Rosaceae	Methanol extract	*In vitro* *In vivo*	PC12 cells, ICR mice	Protection of mitochondria and antioxidant activity	Choi *et al*.[41]
S. officinalis	Labiatae	Hydroalcohol extract	*In vitro*	PC 12 cells	Antioxidant activity	Iuvone *et al*.[80]
Salvia sahendica B. et B.	Lamiaceae	Methanol extract	*In vivo*	Wistar rats	Attenuation of levels of Ca^{2+}/cAMP-response element binding protein, c-fos and peroxisome proliferator-activated receptor gamma coactivator-1α levels in Aβ-injected rats	Khodagholi and Ashabi[81]
Schisandra chinensis (T.) B.	Schisandraceae	*n*-Hexane: ethanol (9:1)	*In vivo*	ICR mice	Inhibition of acetylcholinesterase, increasing levels of glutathione in cortex and hippocampus and reduction in levels of β-secretase	Jeong *et al*.[82]
Smilax china L.	Liliaceae	Methanol extract	*In vitro*	Rat cerebral cortical neurons	Blockage of $[Ca^{2+}]_c$ increase, glutamate release, ROS generation and caspase-3 activation	Ban *et al*.[7]
Tabernaemontana divaricata L.	Apocynaceae	Ethanol extract	*In vivo*	ICR mice	Anti-acetylcholinesterase properties resulting in increased acetylcholine level in the neuronal synaptic cleft	Nakdook *et al*.[83]
U. rhynchophylla	Rubiaceae	Aqueous extract	*In vitro*	Thioflavin T-binding assay, atomic force microscopic imaging and electrophoresis	Inhibition of Aβ fibril formation	Fujiwara *et al*.[84]

NS: Not specified; Bcl-2: B-cell lymphoma 2; *G. uralensis*: *Glycyrrhiza uralensis* F.; *A. gigas*: *Angelica gigas* N.; *P. suffruticosa*: *Paeonia suffruticosa* A.; *M. officinalis*: *Magnolia officinalis* R. et W.; *C. sativus*: *Crocus sativus* L.; *D. asper*: *Dipsacus asper* W.; *E. senticosus*: *Eleutherococcus senticosus* (R. et M.) M.; *F. macrophylla*: *Flemingia macrophylla* (W.) M.; *H. perforatum*: *Hypericum perforatum* L.; *R. acori*: *Rhizoma acori* G.; *S. officinalis*: *Salvia officinalis* L.; *G. biloba*: *Ginkgo biloba* L. *U. rhynchophylla*: *Uncaria rhynchophylla* (M.) J.

Table 2
Bioactive compounds with inhibitory activity against Aβ.

Compounds	Phytochemical classes	Plant sourcees	Assays	Models and assays	Mechanism of actions	References
Acteoside	Glycoside	*Verbascum sinuatum* L.	*In vitro*	SH-SY5Y cells	Modulation of the apoptotic signal pathway through Bcl-2 family, cytochrome *c* and caspase-3 and attenuation of ROS production	Wang *et al*.[93]
Ageconyflavone A	Phenol	*E. ferruginea*	*In vitro*	PC 12 cells	NS	Na *et al*.[94]
Akebia saponin B	Saponin	*D. asper*	*In vitro*	PC 12 cells	Inhibition of excessive Ca^{2+} influx, reduction of LDH leakage and prevention of loss of cell viability	Zhou *et al*.[65]
Apigenin	Flavonoid	*Elsholtzia rugulosa* H.	*In vitro*	APPsw cells	Reduced intracellular ROS generation, preserved mitochondrial function and regulation of apoptotic pathways	Zhao *et al*.[95]
Alpha-asarone	Phenylpropanoid	*Acori graminei*	*In vivo*	Wistar rats	Inhibition of effects of nitric oxide overproduction in the hippocampus and temporal cortex	Limón *et al*.[96]
Beta-asarone	Phenylpropanoid	*R. acori*	*In vitro*	PC 12 cells	Inhibition of basal Ca^{2+} intake	Irie and Keung[79]
Berberine	Alkaloid	*Coptis chinensis* F.	*In vivo* *In vitro*	TgCRND8 mice	N2a-SwedAPP cells regulation of the processing of amyloid precursor protein	Durairajan *et al*.[87]
Bisdemethoxycurcumin	Curcuminoid	*C. longa*	*In vitro*	PC 12 cells	Antioxidant activity	Kim *et al*.[97], Park and Kim [98]
Caffeic acid	Phenolic acid	*Solanum tuberosum* L.	*In vitro*	PC 12 cells	Reduction of levels of intracellular calcium and tau phosphorylation	Friedman[99], Sul *et al*.[100]
Calebin-A	Curcuminoid	*C. longa*	*In vitro*	PC 12 cells	Antioxidant activity	Kim *et al*.[97], Park and Kim[98]
(+)-Catechin	Flavonoid	*H. perforatum*	*In vitro*	Microglial cell line BV2, N11 cells	Reduction of Aβ-induced ROS generation and increase of membrane fluidity	Kraus *et al*.[40]
Cannabidiol	Cannabinoid	*Cannabis sativa* L.	*In vitro*	PC 12 cells	Inhibition of phosphorylated form of p38 MAP kinase and NF-κB activation	Esposito *et al*.[101]
(-)Clausenamide	Amide	*Clausena lansium* (L.) S.	*In vitro*	PC 12 cells	Inhibition of calcium overload, prevention of ROS generation, inhibition of activation of p38 MAPK and expression of P53 and cleaved caspase 3	Hu *et al*.[102]
Cryptotanshinone	Diterpenoid	*S. miltiorrhiza*	*In vivo* *In vitro*	APP/PS1 transgenic mice	Swe/APP cortical neurons increased release of sAPP and reduction in levels of Aβ	Mei *et al*.[86]
Curcumin	Polyphenol	*C. longa*	*In vivo*	Tg2576 mice	Inhibition of oligomer and fibril formation	Anekonda and Reddy[103], Yang *et al*. [104]
Decursinol	Coumarin	*A. gigas*	*In vivo*	ICR mice	Inhibition of acetylcholinesterase	Yan *et al*.[57]
Dehydroevodiamine	Quinazoline alkaloid	*Evodia rutaecarpa* B.	*In vivo*	ICR mice	Inhibition of acetylcholinesterase	Wang *et al*.[105]
Demethoxycurcumin	Curcuminoid	*C. longa*	*In vitro*	PC 12 cells	Antioxidant activity	Kim *et al*.[97], Park and Kim [98]
3,4-Dihyroxybenzoic acid	Phenol	*Smilacis chinae*	*In vitro*	Primary cortical neurons	Attenuation of increase in $[Ca^{2+}]_c$ and inhibition of glutamate release, caspase-3 activity and generation of ROS	Ban *et al*.[106]
Dimethylcrocetin	Crocin	*C. sativus*	*In vitro*	Thioflavine T-based fluorescence assay and DNA binding shift assay	Inhibition of Aβ aggregation and fibrillogenesis	Papandreou *et al*.[64]
Eleutheroside B	Phenylpropanoid	*E. senticosus*	*In vitro*	Primary cortical neurons	Prevention of $Aβ_{25-35}$-induced axonal and dendritic atrophy	Bai *et al*.[67]
Eleutheroside E	Phenylpropanoid	*E. senticosus*	*In vitro*	Primary cortical neurons	Prevention of $Aβ_{25-35}$-induced axonal atrophy	Bai *et al*.[67]
Emodin	Anthraquinone	*Polygonum cuspidatum* S. et Z.	*In vitro*	Cultured cortical neurons	Up-regulation of B-cell lymphoma-2, activation of ER/P13K/Akt pathway and inhibition of JNK1/2 phosphorylation	Liu *et al*.[90]
(-)-Epicatechin	Flavonoid	*H. perforatum*	*In vitro*	Microglial cell line BV2, N11 cells	Reduction of Aβ-induced ROS generation and increase of membrane fluidity	Kraus *et al*.[40]
(-)-Epigallocatechin-3-gallate	Flavonol	*Camellia sinensis* (L.) K.	*In vivo*	ICR mice	Reduction of LPS-induced β- and γ-secretase activity, expression of inflammatory proteins, inducible nitric oxide synthetase and cyclooxygenase-2	Lee *et al*.[107]
Eugenol	Phenylpropanoid	*R. acori*	*In vitro*	PC 12 cells	Inhibition of Aβ-induced Ca^{2+} intake	Irie and Keung[79]
ε-Viniferin	Polyphenol	*Vitis vinifera* L.	*In vitro*	PC 12 cells	Scavenging of ROS and inhibition of Aβ fibrillization	Richard *et al*.[108]
Fucoidan	Sulfated polysaccharide	*Laminaria japonica* A.	*In vivo*	Sprague-Dawley rats	Reduction of oxidative stress and inhibition of acetylcholinesterase	Gao *et al*.[109]
Gallic acid	Phenolic acid	*Sanguisorba officinalis* L.	*In vitro*	Primary cortical neurons	Inhibition of $Aβ_{25-35}$-induced elevation of cytosolic Ca^{2+} concentration ($[Ca^{2+}]_c$), ROS and glutamate release	Ban *et al*.[110]
[6]-Gingerol	Gingerol	*Z. officinale*	*In vitro*	SH-SY5Y cells	Inhibition of intracellular accumulation of ROS and/or reactive nitrogen species and subsequent oxidative and/or nitrosative damages	Lee *et al*.[111]
Ginkgolide A	Ginkgolide	*G. biloba*	*In vitro*	SH-SY5Y cells, primary cortical neurons	Reduction of Aβ-induced caspase-3 and inhibition of platelet activating factor	Bate *et al*.[112]
Ginkgolide B	Ginkgolide	*G. biloba*	*In vitro*	SH-SY5Y cells, primary cortical neurons	Reduction of Aβ-induced caspase-3 and inhibition of platelet activating factor	Bate *et al*.[112]
Ginsenoside Re	Glycoside	*P. ginseng*	*In vitro*	PC 12 cells	Reduction of Aβ-induced cell death	Ji *et al*.[92]
Hibifolin	Flavonol glycoside	*Abelmoschus manihot* (L.) M.; *Melochia corchorifolia* L.	*In vitro*	Primary cortical neurons	Reduction of Aβ-induced caspase-3 and caspase-7 activation, DNA fragmentation and Ca^{2+} mobilization	Zhu *et al*.[113]
Huperzine A	Alkaloid	*Huperzia serrata* (T. ex M.) T.	*In vivo*	Sprague-Dawley rats	Inhibition of Aβ-induced down regulation of APP secretion and protein kinase C	Zhang *et al*.[114], Anekonda and Reddy [103]
Icariin	Flavonoid	*Epimedium herba* L.	*In vivo*	Wistar rats	Decreased production of insoluble fragments of Aβ through suppression of β-secretase expression	Nie *et al*.[115]
Isofraxidin	Phenylpropanoid	*E. senticosus*	*In vitro*	Primary cortical neurons	Prevention of $Aβ_{25-35}$-induced axonal and dendritic atrophy	Bai *et al*.[67]
Isorhynchophylline	Alkaloid	*U. rhynchophylla*	*In vitro*	PC 12 cells	Reduction of intracellular calcium overloading and tau protein hyperphosphorylation	Xian *et al*.[116]
Lespedezaflavanone B	Flavonoid	*F. macrophylla*	*In vitro*	swAPP-N2a cells	Modification of Aβ accumulation by activation of insulin degrading enzyme	Lin *et al*.[69]
L-Theanine	Amino acid	*Camellia sinensis* (L.) K.	*In vivo*	SIc:ICR mice	Suppression of extracellular signal-regulated kinase/p38 and NF-κB induced by $Aβ_{1-42}$ and lipid damage in the brain	Kim *et al*.[117]
Luteolin	Flavonoid	*Elsholtzia rugulosa* H.	*In vitro*	SH-SY5Y cells	Reduction of Aβ protein precursor expression, regulation of redox imbalance and attenuation of caspase family-related apoptosis	Liu *et al*.[118]
4-Ketopinoresinol	Phenol	*E. ferruginea*	*In vitro*	PC 12 cells	NS	Na *et al*.[94]
α-Mangostin	Xanthone	*Garcinia mangostana* L.	*In vitro*	Primary rat cerebral cortical neurons, thioflavin T fluorescence assay	Dissociation of toxic β-sheet-rich aggregated Aβ oligomers and later stage fibrils and inhibition of fibril formation	Wang *et al*.[119]
4-*O*-methylhonokiol	Lignan	*M. officinalis*	*In vivo* *In vitro*	ICR mice PC 12 cells, thioflavin T fluorescence assay, primary cortical neurons	Inhibition of $Aβ_{1-42}$-induced ROS generation and neuronal death Inhibition of Aβ aggregation/fibrillization, $Aβ_{1-42}$-induced ROS generation	Lee *et al*.[42]
Myricetin	Flavonoid	*Moringa oleifera* L., *Ficus religiosa* L.	*In vitro*	Primary cortical neurons	Activation and up-regulation of levels of α-secretase	Sultan and Anwar[120], Shimmyo *et al*.[121]

NS: Not specified; iNOS: inducible nitric oxide synthase; *Z. officinale*: *Zingiber officinale* R.; *P. ginseng*: *Panax ginseng* L.; *E. ferruginea*: *Eragrostis ferruginea* (T.) P. B.; *C. longa*: *Curcuma longa* L.; *S. miltiorrhiza*: *Salvia miltiorrhiza* B.

Table 2, continued

Bioactive compounds with inhibitory activity against Aβ.

Compounds	Phytochemical classes	Plant sources	Assays	Models and assays	Mechanism of actions	References
Nectandrin B	Phenol	*E. ferruginea*	*In vitro*	PC 12 cells	NS	Na *et al*.[94]
Nobiletin	Flavonoid	*Citrus depressa* H.	*In vivo*	APP-SL 7-5 transgenic mice	Increased extracellular signal-regulated kinase phosphorylation and inhibition of Aβ-induced inflammation	Onozuka *et al*.[44]
Oroxylin A	Flavonoid	*Scutellaria baicalensis* G.	*In vivo*	ICR mice	Reduction of $A\beta_{25-35}$-induced astrocyte and microglia activation, iNOS expression and lipid peroxidation	Kim *et al*.[122]
Panaxydol	Polyacetylene	*Panax notoginseng* W.	*In vitro*	Primary cortical neurons	Inhibition of extracellular calcium overload and intracellular free radical generation	Nie *et al*.[10]
Panaxynol	Polyacetylene	*Panax notoginseng* W.	*In vitro*	Primary cortical neurons	Inhibition of extracellular calcium overload and intracellular free radical generation	Nie *et al*.[10]
Penta-o-galloyl-beta-D-glucopyranose	Polyphenol	*P. suffruticosa*	*In vitro* *In vitro* *In vivo*	Thioflavin T SK-N-SH cells Transgenic 2576 mice	Inhibition of fibril formation and destabilization of pre-formed fibrils Inhibition of neurotoxic Aβ oligomer formation Inhibition of Aβ production in the rat brain	Fujiwara *et al*.[75]
Pomiferin	Flavonoid	*F. macrophylla*	*In vitro*	swAPP-N2a cells	Modification of Aβ accumulation by activation of insulin degrading enzyme	Lin *et al*.[69]
Prunetin	Flavonoid	*F. macrophylla*	*In vitro*	swAPP-N2a cells	Modification of Aβ accumulation by activation of insulin degrading enzyme	Lin *et al*.[69]
Purple sweet potato anthocyanins	Anthocyanin	*Ipomoea batatas* (L.) Lam	*In vitro*	PC 12 cells	Inhibition of oxidative damage, intracellular calcium influx and mitochondria dysfunction	Ye *et al*.[123]
Rhaponticin	Stilbene	*Rhei rhizome* (*Rheum* spp.)	*In vitro*	IMR-32 cells	Reduction of the pro-apoptotic Bax/Bax homodimers through the formation of Bcl-2/Bax heterodimers	Misiti *et al*.[124]
Rhapontigenin	Stilbene	*Rhei rhizome* (*Rheum* spp.)	*In vitro*	IMR-32 cells	Reduction of the pro-apoptotic Bax/Bax homodimers through the formation of Bcl-2/Bax heterodimers	Misiti *et al*.[124]
Rhynchophylline	Alkaloid	*U. rhynchophylla*	*In vitro*	PC 12 cells	Reduction of intracellular calcium overloading and tau protein hyperphosphorylation	Xian *et al*.[116]
Rosmarinic acid	Phenolic acid	*S. officinalis*	*In vitro*	PC 12 cells	Reduction of Aβ-induced ROS formation, lipid peroxidation, DNA fragmentation, csapase-3 activation and tau protein hyperphosphorylation	Iuvone *et al*.[80]
Salidroside	Glycoside	*Rhodiola rosea* L.	*In vitro*	SH-SY5Y cells	Induction of antioxidant enzymes, downregulation of pro-apoptotic protein Bax and upregulation of anti-apoptotic protein Bcl-extra large	Zhang *et al*.[125]
Salvianolic acid B	Phenolic acid	*S. miltiorrhiza*	*In vivo*	ICR mice	Reduction of $A\beta_{25-35}$-induced nitric oxide synthase, cyclooxygenase-2 expression and thiobarbituric acid reactive substance	Lee *et al*.[126]
Sesaminol glucosides	Glucoside	*Sesamum indicum* L.	*In vitro*	PC 12 cells	Reduction of $A\beta_{25-35}$- induced ROS generation and intracellular calcium	Lee *et al*.[16]
Silibinin	Flavonoid	*Silybum marianum*	*In vitro* *In vivo*	SH-SY5Y cells, thioflavin T binding assay ICR mice	Inhibition of Aβ aggregation and attenuation of Aβ-induced H_2O_2 production Prevention of oxidative damage in the hippocampus	Yin *et al*.[89], Lu *et al*.[88]
Sinapic acid	Phenylpropanoid	*Sinapis alba* L.	*In vivo*	ICR mice	Attenuation of iNOS expression, glial cell activation and nitrotyrosine expression induced by $A\beta_{1-42}$	Lee *et al*.[127]
Sinomenine	Alkaloid	*Sinomenium acutum* (T.) R. et W.	*In vitro*	BV2 microglial cells	Inhibition of Aβ-induced increase in levels of ROS, nitric oxide and inflammatory molecules	Shukla and Sharma[128]
Tanshinone IIA	Diterpene	*S. miltiorrhiza*	*In vitro*	Primary cortical neurons	Reduction of caspase-3 activity and cytochrome *c* translocation from the mitochondria into the cytosol. Amelioration of $A\beta_{25-35}$-induced Bcl-2/Bax ratio reduction in cortical neurons	Liu *et al*.[90]
Tenuigenin	Saponin glycoside	*Polygala tenuifolia* W.	*In vitro*	SH-SY5Y cells	Inhibition of β-secretase	Jia *et al*.[129], Anekonda and Reddy [103]
Tetrandrine	Alkaloid	*Stephania tetrandra* (S.) M.	*In vivo*	Sprague-Dawley rats	Inhibition of NF-κB activity and downregulation of interleukin-1β and tumor necrosis factor-α expression	He *et al*.[130]
Trans-crocin-4	Crocin	*C. sativus*	*In vitro*	Thioflavine T-based fluorescence assay and DNA binding shift assay	Inhibition of Aβ aggregation and fibrillogenesis	Papandreou *et al*.[64]
Tricin	Phenol	*E. ferruginea*	*In vitro*	PC 12 cells	NS	Na *et al*.[94]
Ursolic acid	Triterpene	*Origanum majorana* L.	*In vitro*	PC 12 cells	Free radical scavenging activity	Heo *et al*.[131]
Withanamide A	Withanamide	*Withania somnifera* (L.) D.	*In vitro*	PC 12 cells	Inhibition of free radical generation and fibril formation	Jayaprakasam *et al*.[20]
Withanamide C	Withanamide	*Withania somnifera* (L.) D.	*In vitro*	PC 12 cells	Inhibition of free radical generation and fibril formation	Jayaprakasam *et al*.[20]
Xylocoside G	Glycoside	*Itoa orientalis* H.	*In vitro*	SH-SY5Y cells	Downregulation of cyclooxygenase-2, attenuation of release of inflammatory factors and repression of caspase-3 activation	Yu *et al*.[132]
Z-ligustilide	Phthalide	*Angelica sinensis* (O.) D.	*In vivo*	SPF Wistar rats	Inhibition of the tumor necrosis factor-α-activated NF-κB signalling pathway	Kuang *et al*.[133]

NS: Not specified; iNOS: Inducible nitric oxide synthase; *Z. officinale*: *Zingiber officinale* R.; *P. ginseng*: *Panax ginseng* L.; *E. ferruginea*: *Eragrostis ferruginea* (T.) P. B.; *C. longa*: *Curcuma longa* L.; *S. miltiorrhiza*: *Salvia miltiorrhiza* B.

one illuminated and the other dark (each 20.3 × 15.9 × 21.3 cm) which is linked by a small gate with a grid floor[42]. The open field test is usually carried out in a wooden box (50 × 50 × 40 cm), with the floor of the field divided into 25 identical squares to ensure easy measurement of the ambulation of the animals[44]. Other behavioural tests employed are the contextual fear conditioning, the delayed-matching to position paradigm and the probe trial test. The detailed experimental protocol involved in carrying out the latter behavioural tests have been reported[41-45].

5. Medicinal plants with inhibitory activity against Aβ

Extracts obtained from several medicinal plants have been reported to confer protection against Aβ-induced toxicity in various cell culture systems and animal models. Some studies have focused on screening extracts obtained from a combination of several medicinal plants, for possible anti-Aβ activity.

Seonghyangjeongkisan, a Korean traditional medicine, used for treatment of cerebral infarction is reported to be a decoction made up of several traditional herbs, which include *Agastache rugosa, Perilla frutescens, Atractylodes macrocephala, Atractylodes chinensis, Citrus reticulata, Pinellia ternata, Areca catechu, Cinnamomum cassia, Z. officinale, Alpinia oxyphylla, G. uralensis, Zizyphus jujuba, Aucklandia lappa* and *Arisaema erubescens*. The neuroprotective effects of the decoction were assessed using both *in vitro* and *in vivo* tests[46]. Administration of seonghyangjeongkisan of 10 μg/mL, 100 μg/mL and 1000 μg/mL protected neuroblastoma cells from Aβ-induced cytotoxicity. The decoction also reduced Aβ-induced apoptosis and ROS. The extract was reported to improve memory impairment in Aβ-treated mice. In addition, it was shown

to suppress the activation of several stress-related kinases and the phosphorylation of tau protein, a known marker of AD. The authors concluded that seonghyangjeongkisan could be useful as a potential complementary therapy to delay or improve cognitive impairments associated with AD[46].

Tohda *et al*. determined the neuroprotective properties of zokumeito[47], a Kampo formula, consisting of *Prunus armeniaca, Ephedra sinica, Cinnamomum cassia, P. ginseng, Angelica acutiloba, Cnidium officinale, Z. officinale, G. uralensis* and *Gypsum fibrosum*. Zokumeito (500 mg/kg/day) was reported to reverse synapses and memory loss in ddY mice and prevent neuronal death and Aβ deposition.

The neuroprotective effect of ESP-102, a standardised extract containing *A. gigas, Saururus chinensis* and *Schizandra chinensis* was investigated using the passive avoidance and Morris water maze tasks in $A\beta_{1-42}$ injected mice[48]. Single administration of 100 mg/kg of ESP-102 was found to significantly attenuate memory impairment. It also attenuated $A\beta_{1-42}$-induced increase in the expression of glial fibrillary acidic portein (a marker of astrocyte) and iNOS. ESP-102 was thought to exert its effects by inhibiting acetylcholinesterase activity in the hippocampus, due to its antioxidant and anti-inflammatory activity[48].

A decoction of *P. ginseng, Acorus gramineus, Poria cocos, A. gigas, Ophiopogon japonicas, Scrophularia buergeriana* and *Thuja orientalis* is known as LMK02-Jangwonhwan. The decoction, administered at a dose of 400 mg/kg/day for three months, was found to suppress $A\beta_{1-42}$ and $A\beta_{1-40}$ levels and plaque deposition in the brains of transgenic-APPswe/PS1 dE9 mice[49]. In addition, it was shown to prevent oxidative stress and Aβ-induced neurotoxicity in (SH-SY5Y) neuroblastoma cells[49]. The authors ascribed the observed neuroprotective effect of the decoction to its antioxidant activity. Liu *et al*. treated Sprague-Dawley rats with naoweikang, a combination of *G. biloba* and *P. ginseng*[50]. Naoweikang was reported to increase the level of acetylcholinesterase in the rat brain following injection with $A\beta_{1-40}$.

Fujuwara *et al*. conducted *in vivo* studies in APP transgenic mice (a model of AD), to determine the neuroprotective properties of Yokukansan[51]. This traditional Japanese medicine is made up of seven medicinal plants, which include *Atractylodes lancea, Poria cocos, Cnidium officinale, Angelica acutiloba, Bupleurum falcatum, G. uralensis* and *U. rhynchophylla*. Powdered chow of Yokukansan administered at concentrations of 0.3% and 1%, was observed to inhibit $A\beta_{1-40}$ and $A\beta_{1-42}$ aggregation in a concentration dependent manner. In addition, the administered doses of Yokukansan inhibited accumulation of $A\beta_{1-42}$ in the cerebral cortex of the mice.

The reported activity for these polyherbal preparations is likely due to the various compounds in the extracts interacting in an additive or synergistic manner[52]. Most of the reviewed publications (71%) focused on screening medicinal plants for anti-Aβ activity using an *in vitro* model, while only a few authors (29%) investigated the activity of the medicinal plants in animal models. In four studies both *in vitro* and *in vivo* tests were used to screen for activity[41,53-55]. A list of the medicinal plants which have been screened individually and are reported to contain inhibitory activity against Aβ is provided in Table 1.

6. Bioactive compounds with inhibitory activity against Aβ

The importance of plant-derived compounds in drug discovery is evident from the fact that 35 natural product related drugs, originally discovered from vascular plants, were among the 150 top selling drugs in 1993[85]. This provides validity for the ethno-medicinal use of the plants and the subsequent development of drugs for the treatment of the specific disease[1]. Bioactivity guided isolation has led to discovery of new bioactive compounds from medicinal plants which are useful in protecting against Aβ-induced neuronal cell death.

In vitro assays were mostly (76%) used to assess activity of the isolated compounds. Only four authors demonstrated the activity of the compounds using both cell based and animal based models[42,75,86,87]. A list of bioactive compounds with Aβ inhibitory activity is provided in Table 2.

It is observed that most of the compounds with anti-Aβ activity are phenolic compounds, glycosides or alkaloids. Their good activity is possibly due to their antioxidant activity and lipophilicity, making it easy for them to cross the blood brain barrier.

Penta-o-galloyl-beta-D-glucopyranose isolated from *P. suffruticosa*, was shown to inhibit formation of Aβ fibrils and to destabilise pre-formed fibrils in the thioflavin T assay[75]. It was also reported to inhibit formation of neurotoxic oligomers of Aβ in SK-N-SH cells and to prevent its production in transgenic 2576 mice[75]. Lee *et al.* reported that 4-*O*-methylhonokiol, a lignin isolated from *M. officinalis*, inhibited Aβ aggregation and ROS generation[42]. The authors carried out further tests with the compound in ICR mice and found that 4-*O*-methylhonokiol inhibited Aβ-induced ROS generation and neuronal death. Berberine, an alkaloid isolated from *Coptis chinensis*, has been shown to exert its neuroprotective effect by regulation of the processing of APP in both N2a-SwedAPP cells and TgCRND8 mice[87]. The neuroprotective effect of the flavonoid, silibinin, has been demonstrated by Lu *et al.*[88] and Yin *et al*[89]. *In vivo* studies in ICR mice showed that silibinin exerts its activity by prevention of oxidative damage in the hippocampus. Further tests using the thioflavin T binding assay and neuroblastoma cells indicated that silibinin inhibits Aβ aggregation and attenuates Aβ-induced H_2O_2 production.

The genus *Salvia* has been shown to contain several compounds with Aβ inhibitory activity. Rosmarinic acid, isolated from *S. oficinalis* has been reported to protect PC 12 cells from $A\beta_{1-42}$-induced cell death[80]. The neuroprotective activity of this compound was attributed to its reduction of the formation of ROS, lipid peroxidation, DNA fragmentation, caspase-3 activation and tau protein hyperphosphorylation[80]. Salvianolic acid

B, cryptotanshinone and tanshinone IIA, all isolated from *S. miltiorrhiza*, have also been reported to possess anti-Aβ activity both in animal models of AD and in rat cortical neurons[86,90,91].

Ji *et al*. discovered that ginsenoside Re, a glycoside isolated from *P. ginseng*, protects PC 12 cells from Aβ-induced cell death[92]. Other compounds isolated from the *Panax* genera include the polyacetylenes, panaxynol and panaxydol[10]. Both compounds are reported to exert their neuroprotective activity by inhibition of extracellular calcium overload and intracellular free radical generation[10].

7. Concluding remarks

Many researchers focused more on *in vitro* cell based assays in assessing the neuroprotective effect of medicinal plants and isolated compounds. This is probably due to the ease and reproducibility of cell cultures and the high cost involved in setting up animal models. However, it is necessary to subject these plants and compounds to animal models to determine their efficacy in metabolic environments. Clinical trials in human subjects should also not be neglected when a compound has demonstrated promising activity and substantially low toxicity. Many of the plants reported to contain good anti-Aβ activity (Table 1) have not been subjected to further tests to identify the bioactive compounds. Ten studies were identified from literature where the authors isolated bioactive compounds from the plants after initial screening of the plant extracts for anti-Aβ activity. These include studies carried out on *A. gigas*, *C. sativus*, *D. asper*, *E. senticosus*, *F. macrophylla*, *H. perforatum*, *M. officinalis*, *P. suffruticosa*, *R. acori* and *S. officinalis*[40,42,57,64,65,67,69,75,79,80]. However, most of the researchers did not carry out any animal or human studies possibly due to the reasons highlighted above.

It is also important to establish suitable formulations that retain the efficacy demonstrated in the *in vitro* screening procedures[52]. Formulations such as tinctures, concoctions, teas, ointments and incorporating plant material need to be developed to determine feasibility and bio-availability. In addition, clinical efficacy and possible toxicity of plants and compounds with promising activity require attention before the much needed development of novel drugs with minimal side effects is taken further.

Conflict of interest statement

We declare that we have no conflict of interest.

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