Neuroprotective role of herbal alternatives in circumventing Alzheimer’s disease through multi-targeting approach - a review

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ABSTRACT
Alzheimer’s disease (AD) is a common form of dementia affecting the elderly worldwide. It is a multifactorial neurodegenerative disorder with no known preventive therapy. Many of the drugs used in the treatment of AD, such as galantamine, rivastigmine, and donepezil, have unpleasant side effects, and hence physicians are keen to find alternatives. Research has shown that plants and their phytochemicals can alleviate AD. These plant products can act through various modes, such as inhibition of amyloid β, acetylcholine, and γ-secretase, modulation of antioxidants, and α-secretase activation, which are known to involve in the improvement of brain functions. A recent approach that has garnered the attention of many researchers in designing a drug against AD is the multi-target-directed ligand (MTDL), wherein the same molecule act on multiple targets. Many studies have reported the potential of herbs to act on multiple targets and display biological properties. The current review summarizes the ongoing evidence on the use of herbs and their derived bioactive molecules in the treatment of AD and in relieving disease-associated pathological events. Currently available plant-derived MTDLs for the treatment or slowing down of the progression of AD are also discussed.

Introduction
Alzheimer’s disease (AD) is an irreversible, chronic neurodegenerative disorder characterized by deterioration of cognitive functions and behavioral disturbances [1]. Globally, AD is the most common cause of dementia, affecting approximately 46.8 million people and expected to increase up to 131.5 million by 2050 [2]. The probability of AD aggressively increases with age, more particularly after the age of 65. Thus, age is the primary risk factor for AD development [3]. AD developed after 65 years of age is referred to as ‘sporadic’ (or late-onset), whereas AD developed before 65 is classified as ‘familial’ (or early-onset). Several complex pathogenic pathways are involved in the progression and development of the disease, including plaque formation, inflammatory cascade, oxidative stress, and cholinergic deficit [4]. These cognitive deficits lead to memory-related clinical symptoms, such as loss of episodic and newly learned memories [5].
Acetylcholine- and glutamate-producing neurons are known to be damaged during AD, thereby affecting the synapses associated with them. This is in agreement with the early cognitive symptoms observed in AD [6]. The main factor for the degeneration of neurons is due to the increased activity of cholinesterases (ChEs), which leads to a decrease in acetylcholine (ACh) levels, which in turn stops the neuronal transmission signals [7]. Studies have also established that acetylcholinesterase (AChE) promote Aβ aggregation and a notable increase in the cortical levels of butyrylcholinesterase (BuChE), which is related to the formation of Aβ plaques and neurofibrillary tangles (NFTs) [8–10].

Many natural compounds are known to have neuroprotective effects during AD. A large family of plant isolates has proven to be a modality for treatment by their inhibitory effect on Aβ, cholinesterase, beta, and gamma secretases. Potent activation of alpha secretases by plant products also substantiates the neuroprotective effect. This review gives a detailed insight into the list of plants and their isolates as neuroprotective agents during AD.

**Molecular mechanism of AD**

The formation of NFTs and senile plaques are the main histopathological hallmarks of AD [11]. The senile plaques contain amyloid-beta (Aβ) peptide, which consists of 37–49 amino acid residues and are formed by the extracellular and transmembrane domains of amyloid precursor protein (APP) [12]. In plaques, the oligomers might be trapped in fibrillar aggregates. Oligomers may be the hazardous Aβ species that contribute to signaling pathway deregulation (Fyn, FAK, GSK3b, and CDK5), causing changes in cytoskeletal and synaptic proteins, as well as synaptic and neural damage [13] (Figure 1). During sporadic AD, APP is cleaved by gamma and beta secretases to form 4 kDa Aβ peptide. The cleavage product has a strong tendency to form aggregates. Aβ

![Figure 1. Formation of neurofibrillary tangles (NFTs) and senile plaques. The senile plaques contain amyloid beta (Aβ) peptide, which consists of 37–49 amino acid residues and are formed by the extracellular and transmembrane domains of amyloid precursor protein (APP). Oligomers may be the hazardous Aβ species that contribute to signaling pathway deregulation (Fyn, FAK, GSK3b, and CDK5), causing changes in cytoskeletal and synaptic proteins, as well as synaptic and neural damage.](image-url)
accumulation has been one of the major pathological events resulting from an imbalance between production and clearance [14]. The Aβ aggregation process initiates by self-assembling of Aβ monomers into low molecular weight oligomers, which in turn results in the formation of high molecular weight oligomers known as soluble aggregation intermediates. These further aggregate to form fibrils and accumulate in the brain [15,16]. It is believed that microglia and astrocytes then mount an inflammatory response to clear the amyloid aggregates, and this inflammation likely causes the destruction of adjacent neurons and their neurites.

Other than plaques, the presence of NFTs is considered another characteristic feature in the neuropathological event of AD [17]. These NFTs are insoluble twisted fibers formed by abnormal hyperphosphorylation of a microtubule-associated protein called ‘tau’. NTF in normal form serves as a microtubule-stabilizing protein and plays a role in intracellular (axonal and vesicular) transport [18]. NFT may interfere with the regular axonal transport of components necessary for proper neuronal function and survival, eventually causing neurons to die. In addition, Aβ is thought to trigger neuronal cell death via controlling apoptosis inducers, generating oxidative stress, and increasing free radical-mediated pathways[11].

Methodology

A detailed literature survey was performed using both offline and online resources. Data were mainly collected from various journal publishers, including Elsevier, Springer Nature, Taylor & Francis, Cambridge University Press, Oxford University Press, BioMed Central, and PLOS (Public Library of Science). The online databases such as Google Scholar, Pubget, Medline, PubMed, EMBASE, Mendeley, ScienceDirect, Scopus, and SpringerLink were also used to retrieve literature. The results were then cross-referred to generate the list of references (up to 2018) cited in this review. The Current review methodically summarizes the neuroprotective effects of phytochemicals in various models. Herbal extracts, bioactive constituents, and herbal formulations were included to provide references in the future.

Natural products in AD

Since time immemorial, natural products have been used as medicine for many ailments. Natural products are molecules with diverse functions and have been the source of most active constituents in medicine [19,20]. They are said to be the most successful basis of drug leads with lesser toxicity [21,22]. Natural products may be derived from plants, animals, or microorganisms. Most herbal medicines are complex and constitute many chemical components, which possess diverse biological and pharmacological activities.

Medicinal plants are nature’s gift that remains unexplored. The active component present in herbal medicine may serve as the basis for preparing synthetic drugs [22]. Plants can synthesize chemical compounds involved in preventing or curing various diseases, including memory dysfunction and age-related disorders. In modern medicine, plants occupy a very significant place as a source of raw material for synthetic drugs [23].

Cholinesterase inhibitors

The important etiological factor in the pathogenesis of memory deficit in AD is the impairment in cholinergic transmission [24]. The inhibition of AChE increases the levels of acetylcholine in the brain and thus improves the cholinergic functions in AD patients 25. Hence, cholinesterase inhibitors are currently used as standard drugs for treating AD. Tacrine was the first AChE inhibitor drug approved for AD treatment [26]. Later, many other AChE inhibitors such as rivastigmine, galantamine, and donepezil were also developed and approved by the
FDA. These drugs alleviate the symptoms but are associated with side effects when used for an extended period [27]. As AD has reached a state of public health burden, the ever-increasing reports of side effects from these synthetic and hybrid drugs have driven the research for a novel and safe AchE inhibitors from plant sources.

Plants continue to be the unvaryingly abundant source of therapeutic drugs for AD treatment because of their AchE inhibitory activity. Several plant extracts of various solvents have been reported to show anticholinesterase activity. Aqueous and methanolic root extracts of *Acacia nilotica* and *Withania somnifera* possessed moderate anticholinesterase activity (IC50 values of 0.079 and 33.38 µg/ml, respectively) [28,29]. Much lesser inhibitory activity was observed in hydroethanolic seed extracts of *Myristica fragrans*, which showed 50% enzyme inhibition at a concentration range between 100 and 150 µg/mL [30]. Also, *Pinus nigra* was used to extracting essential oils possessing 94.4 µg/mL activity [31]. Similarly, different extracts of plants belonging to varied plant families have shown considerable cholinesterase inhibitory activity, which is listed in (Table 1).

Alkaloids derived from various plant extracts show immense potential for AchE inhibitory activity. However, significantly few isolated compounds have been utilized for research and therapeutic purposes. Many isolated compounds from different classes of alkaloids have been considered and tabulated in (Table 2).

### γ- and β-secretase inhibitors

Many plant extracts and their derived compounds are found to influence the Aβ production pathways, mainly by interacting with brain enzymes like β- and γ-secretases [112,113]. As explained earlier, both β- and γ-secretases are involved in the synthesis of Aβ. β-secretase cleaves the APP to form a transmembrane C-99 fragment with the N-terminus of the Aβ peptide (Figure 2) followed by the action of γ-secretase, which cleaves C-99 fragment in the transmembrane domain to make the C-terminus of Aβ [112].

In addition to β-APP processing, γ-secretase also plays a vital role in the cleavage of the Notch family of cell-surface receptors, a protein mainly required for transcriptional regulation during neuron development [114]. As a result, the use of γ-secretase inhibitors has provided insights into proteolytic activity and suggests that such inhibition might be a useful strategy for AD therapeutics [115]. A triterpene isolated from *Actaea racemosa* reduced the formation of Aβ toxicity through the modulation of γ-secretase activity. Thus, it suggests that the isolated compound may bind to γ-secretase APP complex, modulating the cleavage of APP and hence lowering the formation of Aβ peptides. 116, demonstrated that the use of green tea polyphenol epigallocatechin-3-gallate (EGCG) inhibited LPS-induced Aβ elevation levels through the suppression of LPS-induced β- and γ-secretase activities [116]. However, the inhibition of Notch protein by γ-secretase inhibitors affects neuronal development, as Notch has multiple substrates that are involved in neuronal development [117]. Hence, β-secretase, also referred to as β-site APP cleaving enzyme 1 (BACE-1), a transmembrane aspartic protease secreted in almost all tissues but present in higher amounts in neurons of the brain [115], is considered as the most promising target for pharmaceutical research on AD, compared to γ-secretase.

### α-secretase activators

α-secretase enzyme proteolytically cleaves the APP via the non-amyloidogenic pathway at L688 residue located within the Aβ sequence and thereby preventing the formation of Aβ (Figure 2). The first enzyme for α-secretase was proposed in 1998, when ADAM17, also known as tumor necrosis factor-converting enzyme (TACE), was reported to possess α-secretase activity [118]. Later, ADAM9 and ADAM10
Table 1. Plants with potential AChE inhibitory activity.

| Plant Family and Botanical Name | Type of Extract | Plant’s parts | References |
|----------------------------------|-----------------|---------------|------------|
| Acanthaceae                      |                 |               |            |
| Acanthus ebracteatus             | MeOH            | Aerial        | [32]       |
| Andrographis paniculata          | H₂O:EtOH        | Aerial        | [30]       |
| Amaranthaceae                    |                 |               |            |
| Salsola oppositifolia            | Alkaloids       | Aerial        | [33]       |
| Salsola soda                     |                 |               |            |
| Salsola tragu                    |                 |               |            |
| Amaryllidaceae                   |                 |               |            |
| Crinum jagus                     | MeOH            | Leaf          | [34]       |
| Crinum jagus                     | MeOH            | Bulb          | [35]       |
| Crinum bulbispermum              |                 |               |            |
| Hippeastrum barbatum             |                 |               |            |
| Hippeastrum puniceum             |                 |               |            |
| Zephyranthes carinata            |                 |               |            |
| Crinum moorei                    | MeOH            | Bulb          | [36]       |
| Sternbergia candida              | MeOH, CHCl₃    | Root, Bulb    | [37]       |
| Anacardiaceae                    |                 |               |            |
| Harpephyllum caffrum             | MeOH, DCM      | Leaf, Stem, bark | [Moy38] |
| Sclerocarya birrea               |                 |               |            |
| Pistacia atlantica               | H₂O            | Leaf          | [39]       |
| Pistacia lentiscos               |                 |               |            |
| Semecarpus anacardium            | MeOH           | Seed, Bark    | [29]       |
| Spindias mombin                  | MeOH           | Root, Bark    | [34]       |
| Araliaceae                       |                 |               |            |
| Acanthopanax henryi              | MeOH           | Leaf          | [40]       |
| Eleutherococcus sessiliflorus    | EtOH, CHCl₃    | Root          | [41]       |
| Eleutherococcus gracilistylus    |                 |               |            |
| Eleutherococcus senticosus       |                 |               |            |
| Eleutherococcus setchuenensis    |                 |               |            |
| Emmenopterys henyi               |                 |               |            |
| Eurybia divaricatus              |                 |               |            |
| Asteraceae                       |                 |               |            |
| Arnica chamissonis               | MeOH, Hexane   | Flower        | [42]       |
| Artemisia annua                  | EtOH           | Leaf, twig    | [43]       |
| Chromolaena tequendamensis       | MeOH           | Whole plant   | [44]       |
| Schistocarpa sinforosi           | MeOH           | Whole plant   | [44]       |
| Pulicaria stephanocarpa          | CHCl₃          | Leaf          | [45]       |
| Caprifoliaceae                   |                 |               |            |
| Nardostachys jatamansi           | Methanolic      | Rhizome       | [29]       |
| Scabiosa arenaria                | EtOH, Butanol   | Fruit, stem, leaf | [29]     |
| Chenopodiaceae                   |                 |               |            |
| Atriplex lacinaria               | MeOH, CHCl₃, H₂O, Ethyacetate | Whole plant | [47]       |
| Convolvulaceae                   |                 |               |            |
| Evalvulus alsinoides             | H₂O:EtOH       | Whole plant   | [30]       |
| Ipomoea asarifolia               | MeOH           | Leaf          | [48]       |
| Elaeocarpaceae                   |                 |               |            |
| Aristotelia chilensis            | H₂O:EtOH       | Leaf          | [49]       |
| Ericaceae                        |                 |               |            |
| Cephalocroton socotranus         | CHCl₃          | Bark          | [45]       |
| Euphorbia characias              | H₂O, EtOH      | Leaf, stem    | [50]       |
| Jatropha gossypifolia            | DCM, MeOH      | Stem, bark roots | [51]    |
| Rhododendron luteum              | CHCl₃:MeOH (1:1)| Whole plant | [52]       |
| Rhododendron ponticum            |                 |               |            |
| Euphorbiaceae                    |                 |               |            |
| Alchornea laxiflora              | MeOH           | Leaf          | [34]       |
| Fabaceae                         |                 |               |            |
| Acacia nilotica                  | H₂O            | Root          | [28]       |
| Acacia raddiana                  | H₂O            | Bark          | [39]       |

(Continued)
| Plant Family and Botanical Name | Type of Extract | Plant's parts | References |
|---------------------------------|-----------------|---------------|------------|
| Albizia adianthifolia          | MeOH, Ethylacetate, CHCl₃ fraction | Leaf          | [53]       |
| Albizia procera                | MeOH            | Bark          | [32]       |
| Cassia obtusifolia             | EtOH            | Seed          | [54]       |
| Genista tenera                 | EtOH            | Aerial        | [55]       |
| Lathyrus cicero                | MeOH            | Aerial        | [56]       |
| Lathyrus digitatus             | EtOH            | (Except seed) |            |
| Senna alata                    | EtOH            | Leaf          | [48]       |
| Trigonella foenum-graecum      | EtOH            | Seed          | [57]       |
| Fumariaceae                    |                 |               |            |
| Fumaria capreolata             | CHCl₃:MeOH (1:1) | Whole plant   | [52]       |
| Fumaria cilica                 |                 |               |            |
| Fumaria judiaca                |                 |               |            |
| Fumaria vailantii              |                 |               |            |
| Hypericaceae                   |                 |               |            |
| Hypericum ambysepalum          | MeOH            | Flower, fruit, seed | [58]       |
| Hypericum humifusum            | MeOH            | Aerial        | [59]       |
| Lamiaceae                      |                 |               |            |
| Cyclotrichium niveum           | EtOH, DCM      | Whole plant   | [52]       |
| Hyssopus officinalis           | Hexane          | Whole plant   | [42]       |
| Leonurus sibiricus             | MeOH            | Aerial        | [60]       |
| Mentha longifolia,             | EtOH            | Leaf          | [61]       |
| Mentha x piperita,             |                 | Aerial        |            |
| Salvia officinalis             |                 | Leaf          |            |
| Satureja montana,              |                 | Aerial        |            |
| Teucrium arduini,              |                 | Aerial        |            |
| Teucrium chamaedrys            |                 | Aerial        |            |
| Teucriumpolium                 |                 | Aerial        |            |
| Thymus vulgaris                |                 | Aerial        |            |
| Tsentonis montanum             |                 | Aerial        |            |
| Mimosa pudica                  | MeOH            | Whole         | [32]       |
| Pycnostachys reticulata        | MeOH:EtOH (1:1) | Leaf          | [62]       |
| Salvia fruticose               | DCM             | Whole plant   | [63]       |
| Salvia millionhiza             | H₂O₂, EOH       | Root          | [64]       |
| Salvia officinalis             | EtOH            | Whole plant   | [27]       |
| Salvia tiliifolia              | MeOH            | Whole plant   | [126]      |
| Stachys guayoniana             | MeOH, CHCl₃, Butanol, Ethylacetate | Aerial | [65]       |
| Mentha aquatica                |                 | Aerial        |            |
| Leguminosae                    |                 |               |            |
| Butea superba                  | MeOH            | Root, bark    | [32]       |
| Cassia fistula                 |                 | Root          |            |
| Cassia obtusifolia             | MeOH            | Seed          | [66]       |
| Chamaecrista mimosoides        | MeOH            | Root          | [126]      |
| Liliaceae                      |                 |               |            |
| Habranthus tubispathus         | Alkaloid        | Aerial        | [67]       |
| Habranthus jamesonii           |                 |               |            |
| Lycopodiaceae                  |                 |               |            |
| Huperzia squarrosa             | EtOH fraction   | Aerial        | [68]       |
| Menispermaceae                 |                 |               |            |
| Stephania pierrei              | EtOH            | Tuber         | [69]       |
| Stephania suberosa             | MeOH            | Root          | [32]       |
| Tiliacora triandra             | CHCl₃:MeOH (1:1)| Root          | [29]       |
| Tinospora cordifolia           | MeOH            | Stem          | [29]       |
| Moraceae                       |                 |               |            |
| Ficus religiosa                | MeOH            | Stem, bark    | [29]       |
| Morus alba                     | EtOH, MeOH, H₂O | Aerial        | [70]       |
| Streblus asper                  | MeOH            | Seed          | [32]       |

(Continued)
| Plant Family and Botanical Name | Type of Extract | Plant's parts | References |
|---------------------------------|-----------------|---------------|------------|
| Myristicaceae Myristica fragrans | H2O:EtOH       | Seed          | [30]       |
| Myrsinaceae Embelia ribes       | Methanolic     | Root          | [29]       |
| Myrtaceae Eugenia dysenterica   | H2O            | Leaf          | [71]       |
| Nymphaeaceae                   |                |               |            |
| Nelumbo nucifera               | H2O:EtOH       | Rhizome       | [30]       |
| Orchidaceae Vanda roxburghii    | Methanol       | Root          | [72]       |
| Paeoniaceae Paonia lactiflora   | H2O, EtOH      | Root          | [64]       |
| Papaveraceae                   |                |               |            |
| Corydalis intermedia           | MeOH, H2O      | Whole plant,  | [73]       |
| Corydalis solida               |                | Tuber         |            |
| Pedaliaceae Harpagophyton procumbens | MeOH    | Hairy root    | [74]       |
| Pinaceae Pinus halepensis      | EtOH           | Needle        | [75]       |
| Pinus nigra                    | Essential oil  | Needle        | [31]       |
| Poaceae Cymbopogon schoenanthus | Hexane, DCM,  | Shoot         | [76]       |
| Polypalmaeae Polygala tenuifolia | H2O          | Root          | [27]       |
| Olax subscropioidea            | H2O            | Leaf          | [77]       |
| Securidaca longipendunculata    |                |               |            |
| Polygonaceae Rheum palmatum    | H2O, EtOH      | Root, Rizhome | [64]       |
| Fallopia multiflora            | EtOH           | Aerial        | [78]       |
| Ruprechtia apetala             |                |               |            |
| Rosaceae                       |                |               |            |
| Crataegus pinnatifida          | EPHF extract   | Fruit         | [79]       |
| Rubus coreanus                 | EtOH           | Whole plant   | [80]       |
| Rubiaceae                      |                |               |            |
| Paedaria linearis              | MeOH           | Whole plant   | [32]       |
| Sarcopodium latifolius         | EtOH           | Bark          | [81]       |
| Rutaceae                       |                |               |            |
| Aegle marmelos                 | MeOH           | Fruit pulp    | [32]       |
| Ruta graveolens                | MeOH, Hexane   | Whole plant   | [42]       |
| Sapotaceae                     |                |               |            |
| Mimusops elengi                | MeOH           | Flower        | [32]       |
| Scrophulariaceae Bacopa Monniera | Ethanol       | Whole plant   | [82]       |
| Solanaceae                     |                |               |            |
| Withania somnifera             | MeOH           | Root          | [29]       |
| Tamaricaceae                   |                |               |            |
| Valerianaceae                  |                |               |            |
| Nardostachys jatamansi         | H2O:EtOH, MeOH | Rhizome       | [30]       |
| Zingiberaceae                  | EtOH           | Rhizome       | [69]       |
| Kaempfera parviflora           |                |               |            |
| Isolated compound | Classification       | Plants                  | Family          | References |
|-------------------|----------------------|-------------------------|-----------------|------------|
| 1-epi-malycorin A | Lycopodium alkaloids | *Phlegmariurus henryi* | Lycopodiaceae   | [83]       |
| 1-epi-17S-hydroxymalycorin A |                      |                         |                 |            |
| 16-hydroxylycodine |                      |                         |                 |            |
| 1-epi-17S-hydroxymalycorin A | Steroidal alkaloids | *Buxus macowanii*      | Buxaceae        | [84]       |
| 6α-hydroxyphlegmariurine |                      |                         |                 |            |
| 16α-hydroxymacowanitriene |                      |                         |                 |            |
| Macowanamine      |                      |                         |                 |            |
| 31-hydroxybuxatrienone | Quinoline alkaloids | *Skimmia laureola*     | Rutaceae        | [Atta-ur 85] |
| 3,4,5,6-tetrahydro-2 H-pyano(3,2-c) quinoline-5-one, |                      |                         |                 |            |
| 3-hydroxy-2,2,6-trimethyl- |                      |                         |                 |            |
| 7-O-angeloyllycopsamined | Pyrrolizidine alkaloids | *Echium confusum* | Boraginaceae  | [39]       |
| 7-O-angeloyllycopsamine N-oxide |                      |                         |                 |            |
| Echimid N-oxide, |                      |                         |                 |            |
| Echimid 7-O angeloyltronecine = |                      |                         |                 |            |
| Berberine         | ISOquinoline alkaloids | *Coptis Chinensis* | Ranunculaceae  | [27]       |
| Palmatine         | ISOquinoline alkaloids | *Coptis chinensis* | Ranunculaceae  | [86]       |
| Columbamine       | ISOquinoline alkaloids | *Coptis chinensis* | Ranunculaceae  | [86]       |
| Jatroprhizine     | ISOquinoline alkaloids | *Coptis chinensis* | Ranunculaceae  | [86]       |
| Coptisine         | ISOquinoline alkaloids | *Coptis chinensis* | Ranunculaceae  | [86]       |
| Coronarine        | ISOquinoline alkaloids | *Coptis chinensis* | Ranunculaceae  | [86]       |
| Voacangine        | ISOquinoline alkaloids | *Coptis chinensis* | Ranunculaceae  | [86]       |
| Voacangine hydroxyindolenine | ISOquinoline alkaloids | *Coptis chinensis* | Ranunculaceae  | [86]       |
| Dehydroevodiamine- | Quinazolinocarboline alkaloids | *Evodia rutaecarpa* | Rutaceae        | [88]       |
| Fumaricine        | ISOquinoline alkaloids | *Fumaria officinalis*  | Papaveraceae    | [89]       |
| Fumarostrejidine  | ISOquinoline alkaloids | *Fumaria officinalis*  | Papaveraceae    | [89]       |
| Geissospermine    | Indole alkaloid       | *Geissospermum vellosii* | Apocynaceae     | [90]       |
| Hookerianamide H and I | Steroidal alkaloids | *Sarcococca hookeriana* | Buxaceae       | [91]       |
| Isotalatazidine hydrate | Diterpenoid alkaloid | *Delphinium denudatum* | Ranunculaceae  | [92]       |
| Juliflorine       | Pipieridinum alkaloid | *Prosopis juliflora*   | Papilionaceae   | [93]       |
| Kokusaginine      | Furoquinoline Alkald | *Evodia lepta*         | Rutaceae        | [94]       |
| Melineurine       | Furoquinoline Alkald | *Evodia lepta*         | Rutaceae        | [94]       |
| Lycorine          | Pyrralo(de) phenanidine alkaloid | *Narcissus pseudonarcissus* | Amaryllidaceae | [95]       |
| Mulberrofuran G   | Benzyl isoquinoline alkaloids | *Morus alba* | Moraceae        | [70]       |
| Albanol B         | ISOquinoline alkaloids | *Morus alba* | Moraceae        | [70]       |
| Kuwanon G         | ISOquinoline alkaloids | *Morus alba* | Moraceae        | [70]       |
| Berberine         | ISOquinoline alkaloids | *Morus alba* | Moraceae        | [70]       |
| Physostigmine     | Indole alkaloid       | *Physostigma venenosum* | Fabaceae       | [96]       |
| Rauwolfine C      | Indole alkaloids      | *Rauwolfia reflexa*    | Apocynaceae     | [97]       |
| 3-methyl-10,11-dimethoxy-6-methoxycarbonyl-β-carboline |                      |                         |                 |            |
| Saligenanamides-C, E and F, Axillarine-C | Steroidal alkaloids | *Sarcococca saligna* | Buxaceae       | [91]       |
| Saligcinamidate   |                      |                         |                 |            |
| Vaganine-A        |                      |                         |                 |            |
| 5,6-dehydroasarconidine |                    |                         |                 |            |
| 2-hydroxysaligamine-E |                    |                         |                 |            |
| 2-hydroxysaligamine-E |                    |                         |                 |            |
| Epipachysamine-D  |                    |                         |                 |            |
| Dictyophlebine    |                    |                         |                 |            |
| Iso-H-formylichomorphine |            |                         |                 |            |
| Axillaridine-A    |                    |                         |                 |            |

(Continued)
were also shown to have α-secretase activity [119]. These three proteins belong to the ADAM (a disintegrin and metalloprotease) family. It is reported that mutations in ADAM10 alter the processing of APP and lead to AD by increasing Aβ levels [120]. Thus, a promising yet underestimated approach to overcome AD would be, activating α-secretase processing of βAPP.

Moderate overexpression of ADAM10 in an APP mouse model showed a decreased level of Aβ, and prevented its accumulation. Such
decreased levels of Aβ are found to alleviate cognitive deficits [121,122]. Various studies have corroborated that several drugs currently used in the treatment of AD promote α-secretase activity by activating associated signaling cascades. Thus, it has been considered as one of the best therapeutic approaches in AD [123–125].

**Aβ inhibitors**

Bioactivity-guided isolation has led to the discovery of novel bioactive compounds from plants, which are useful in preventing Aβ-induced neuronal cells [126]. *In vitro* assays were widely used to assess the activity of isolated compounds. It is observed that phenolic compounds, alkaloids, and glycosides comprise the major part of the isolated compounds with Aβ inhibitory activity. Their antioxidant activity and lipophilicity make it easy for them to cross the blood-brain barrier [126]. A list of compounds with Aβ inhibitory activity is provided in (Table 3 and 4).

**Antioxidants in AD**

Oxidative stress is a process of ROS generation, which plays a central role in cellular injuries and various clinical disorders, including neurodegen

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**Figure 2.** β- and γ-secretases are involved in the synthesis of Aβ. β-secretase cleaves the APP to form transmembrane C-99 fragment with the N-terminus of the Aβ peptide. This is followed by the action of γ-secretase, which cleaves C-99 fragment in the transmembrane domain to make the C-terminus of Aβ.
| Plants                      | Families         | Type of extract           | Models or assays                        | Key mechanism                                                                 | References |
|-----------------------------|------------------|---------------------------|-----------------------------------------|-------------------------------------------------------------------------------|------------|
| *Alpinia galanga*           | Zingiberaceae    | CHCl₃, Hexane, Ethyl acetate fractions | *In vivo* Swiss albino mice            | Increased Free radical scavenging activity, Na⁺/K⁺ ATPase activity and exhibit AChE inhibition | [127]      |
| *Angelica gigas*            | Umbelliferae     | EtOH                      | *In vivo* ICR mice                     | Inhibition of AChE and possesses rich antioxidant activity                    | [128]      |
| *Bacopa monnieri*           | Plantaginaceae   | Ethyl                        | *In vitro* Primary cortical neurons     | Inhibition of amyloid peptide activated intracellular AChE activity and Regulation of neuronal transcription protein | [129]      |
| *Bambusae concretio*        | Gramineae        | H₂O                        | *In vitro* Cortical astrocyte cells     | Attenuation of lipid peroxidation product and protection of antioxidant enzymes | [130]      |
| *Caesalpinia cristata*      | Fabaceae         | H₂O                        | *In vitro* ThT and microscopic analysis | Inhibition of Aβ aggregation and disaggregation of preformed fibrils           | [131]      |
| *Capsicum annum*            | Solanaceae       | MeOH                       | *In vitro* MC65 and SH-SYSY neuroblastoma cells | Significantly inhibited β-secretase and unveil dis-aggregation of preformed Aβ₄₀ fibrils | [132]      |
| *Centella asiatica*         | Apiaceae         | H₂O                        | *In vitro* PC 12 cells In vivo SXFAD mice | Prevented Aβ-induced decreases in ATP and induced the expression of mitochondrial genes and proteins in both cell lines | [133]      |
| *Cinnamomum zeylanicum*     | Lauracea         | H₂O                        | *In vitro* ThT, PC 12 cells In vivo SXFAD mice | Inhibition of fibril formation and destabilization of pre-formed fibrils, reduction of Aβ deposition | [134]      |
| *Crocus sativus*            | Iridaceae        | H₂O:EtOH                   | *In vitro* ThT, DNA binding shift assay In vivo SXFAD mice | Binding to the hydrophobic regions of the Aβ through the hydrophobic carotene backbone and inhibiting fibril formation Increased Aβ cleavage across the BBB through up-regulation Pgp and LRP1, NEP, and up-regulation of the ApoE-Clearance pathway | [135,136] |
| *Ecklonia cava*             | Lessoniaceae     | Butanol                    | *In vitro* Primary cortical neurons, HEK293 cells | Exhibit rich antioxidant activity, prevention of Aβ oligomer and fibril formation | [137]      |
| *Eleutherococcus senticosus*| Araliaceae       | Ethyl acetate, Butanol H₂O fractions from the MeOH extract | *In vitro* Primary cortical neurons    | Prevention of Aβ₂₅₋₃⁵ induced axonal atrophy                                 | [138]      |
| *Ficus macrophylla*         | Leguminosae      | EtOH, Ethylacetate, MeOH fraction, | *In vitro* swAPP-N2a cells             | Inhibition of β-secretase and activation of insulin degrading enzyme            | [139]      |
| *Ganoderma lucidum*         | Ganodermataceae  | H₂O                        | *In vitro* Primary cortical neurons     | Reduction of Aβ-induced synaptotoxicity, inhibition of Aβ-induced DEVD cleavage activity and reduction of the phosphorylation of c-Jun and p38 MAP kinase and c-Jun n-terminal kinase | [140]      |
| *Ginkgo biloba*             | Ginkgoaceae      | flavonoids and terpenoids extract (EGb 761) | *In vitro* Hippocampal primary cultured cells | Attenuation of Aβ₂₅₋₃⁵ induced apoptosis                                        | [141]      |
| *Glycyrrhiza uralensis*      | Fabaceae         | H₂O                        | *In vitro* Primary cortical neurons     | Suppression of Aβ induced apoptosis and ROS generation                          | [11]       |
| *Grewia tiliaefolia*        | Tiliaceae        | MeOH                       | *In vitro* ThT, microscopic analysis   | Preventing the oligomerization of Aβ₂₅₋₃⁵                                       | [142]      |

(Continued)
| Plants                        | Families         | Type of extract | Models or assays                      | Key mechanism                                                                 | References |
|------------------------------|------------------|-----------------|---------------------------------------|-------------------------------------------------------------------------------|------------|
| *Houttuynia cordata*         | Saunuraceae      | H₂O             | In vitro Primary cortical neurons      | Attenuation of Aβ<sub>25-35</sub> induced elevation of intracellular ROS, calcium, caspase-3 activation and mitochondrial membrane disruption | [143]      |
| *Humulus japonicus*          | Cannabaceae      | MeOH            | In vivo Tg-APP/PS1 mice                | Decreased the Aβ and neurofibrillary tangles and also decreased mRNA expression (TNF-α, IL-1β, IL-6) levels | [144]      |
| *Hypericum perforatum*       | Hypericaceae     | H₂O:EtOH (1:1)  | In vitro Microglial cell line BV2      | Attenuation of Aβ-induced ROS generation and membrane fluidity increase       | [145,146] |
|                             |                  | H₂O             | In vivo Aβ143 induced rat              |                                                                               |            |
| *Lycium barbaryum*           | Solanaceae       | Alkaline extract | In vitro Primary cortical neurons      | Attenuation of caspase-3 activity triggered by Aβ and stimulation of the Akt survival pathway | [147]      |
| *Melissa officinalis*        | Magnoliaceae     | EtOH            | In vivo ICR mice                      | Inhibition of Aβ<sub>1-42</sub> induced ROS generation and neuronal cell death | [148]      |
| *Mansonnia angustifolia*     | Geraniaceae      | EtOH            | In vitro HeLa cells and In vivo in vivo Tg2576 mice | Reduced the level of insoluble Aβ<sub>42</sub> in brain regions and increased memory function. | [149]      |
| *Paeonia suffruticosa*       | Paeonaceae       | EtOH, MeOH, H₂O | In vitro ThT                           | Inhibition of fibril formation and destabilization of pre-formed fibrils, Inhibition of Aβ plaque formation | [150]      |
| *Piper nigrum*               | Piperaceae       | MeOH            | In vivo Aβ<sub>1-42</sub> induced AD model | improves amyloid beta(1-42)-induced spatial memory impairment by inhibiting oxidative stress in the rat hippocampus | [151]      |
| *Pterocarpus erinaceus*      | Fabaceae         | H₂O             | In vitro CHO-K1 cells                 | Inhibition of γ-secretase activity at the γ-site where Aβ is produced          | [152]      |
| *Psychotropia olacoides*     | Orlaceaee        | EtOH            | In vivo CF1 albino mice               | Inhibition of Aβ<sub>1-42</sub>-induced cytotoxicity and AChE activity         | [153]      |
| *Rhodanac acori*             | Acoraceae        | H₂O             | In vitro PC12 cells                   | Inhibition of cytoxic action of Aβ<sub>1-40</sub>                          | [154]      |
| *Salvia sahendica*           | Lamiaceae        | MeOH            | In vivo Aβ micro injected rats         | Decrease in levels of Ca²⁺/cAMP-response element binding                      | [155]      |
| *Satureja bachtiarica*        | Lamiaceae        | MeOH            | In vivo Aβ microinjected rat model     | Improved Aβ induced cognitive impairment and cholinergic loss and decreased oxidative stress | [156]      |
| *Schisandra chinensis*       | Schisandraceae   | Hexane: EtOH (9:1) | In vivo ICR mice                     | Inhibition of AChE increasing levels of glutathione in cortex and hippocampus and reduction in the levels of β-secretase | [157]      |
| *Smilacis chinensis*         | Liliaceae        | MeOH            | In vivo Rat cerebral cortical neurons  | Blockage of (Ca²⁺) increase, glutamate release, ROS generation and caspase-3 activation | [158]      |
| *Trigonella foenum-graecum*  | Fabaceae         | Seed powder     | In vivo Aβ143 induced rat model        | Suppresses aluminium overload, Aβ accumulation, and apoptosis through activating Aβ/GSK3β pathway | [159]      |
| *Uncaria rhynchophylla*      | Rubiaceae        | H₂O             | In vitro ThT                           | Inhibition of Aβ fibril formation                                              | [160]      |
| *Zingiber officinale*        | Zingiberaceae    | Seed            | In vitro ThT and primary hippocampal neuron | Prevented the formation of oligomers and dis-aggregated the pre formed fibrils. Also, inhibited AChE activity and increased Aβ induced cell survival | [161]      |

(Continued)
| Plants                  | Families   | Type of extract | Models or assays | Key mechanism                                           | References |
|------------------------|------------|-----------------|------------------|---------------------------------------------------------|------------|
| Ziziphus mucronata     | Rhamnaceae | EtOH            | In vitro neuroblastoma SH-SY5Y cells | Attenuated the effects of Aβ induced neuronal cell death | [162]      |
| Lannea schweinfurthii  | Anacardiaceae Combretaceae |                  |                  |                                                         |            |
| Terminalia sericea     | Amaryllidaceae |                  |                  |                                                         |            |
| Cinnum bulbispernum    |            |                 |                  |                                                         |            |
| Compounds          | Plants and Family     | Models/assays              | Key mechanism                                                                 | References |
|--------------------|-----------------------|----------------------------|-------------------------------------------------------------------------------|------------|
| Alkaloid Berberine | *Coptis chinensis*    | *in vivo* TgCRND8 mice     | N2a-SwedAPP cells regulation of the processing of amyloid precursor protein. | [163]      |
| Caffeine           | *Coffee arabica*      | *in vitro* neuroblastoma 2a cells *in vivo* APP transgenic mice | Reduces levels of Aβ in neuroblastoma 2a cells stably expressing human Swedish mutant Prevents and reverses cognitive impairment in young and aged Swedish mutant APP transgenic mice. | [95,164]  |
| Dehydroevodiamine  | *Evodia rutaecarpa*    | *in vivo* Aβ1-42 infused rat model | Rescued Aβ induced neurotoxicity decreased ROS, and intracellular calcium levels | [88]       |
| Huperzine A        | *Huperzia serrata*    | *in vitro* Sprague Dawley rats | Inhibition of Aβ induced down regulation of APP secretion and protein kinase C | [165]      |
| Nicotine           | *Nicotiana tabacum*   | *in vivo* mice model       | Enhances cholinergic function, and it binds to Aβ and blocks its aggregation. | [166]      |
| Rhynchophylline    | *Uncaria rhynchophylla* | *in vitro* PC12 cells     | Rescue PC12 cells from cell death after Aβ challenge. Inhibits caspase-3, increases the ratio of Bcl-2/Bax protein expression, and stabilizes mitochondrial membrane potential. Also, reduction of Ca^{2+} overload and tau protein hyperphosphorylation. | [167,168] |
| Tetrandrine        | *Stephania tetrandra* | *in vivo* Sprague Dawley rats | Inhibition of NF-κB activity and downregulation of IL-1β and TNF-α expression. | [169]      |
| Vincamine          | *Vinca minor*         | *in vitro* PC12 cells     | Protects Aβ25-35 induced cell death via upregulation of SOD and activation of PI3K/Akt pathway. | [170]      |
| Z-ligustilide      | *Umbellifers*         | *in vitro* Aβ induced PC12 and SH-SYSY human neuroblastoma cells | Protects against Aβ fibrils-induced neurotoxicity via inhibition of p38 and activation of PI3-K/Akt signaling pathways. | [171]      |
| Amino acids        | *Camellia sinensis*   | *in vivo* S1cICR mice      | Suppression of extracellular signal-regulated kinase/p38 and NF-κB induced by Aβ1-42 and prevents lipid damage in the brain. | [172]      |
| L-Theanine         | (Theaceae)            |                             |                                                                              |            |
| Cannabinoids       | *Cannabis sativa*     | *in vitro* PC12 cells     | Attenuation of phosphorylated form of p38 MAP kinase and NF-κB activation. | [173]      |
| Cannabidiol        | (Cannabaceae)         |                             |                                                                              |            |
| Carotenoids        | *Crocus sativus*      | *in vitro* ThT, DNA binding shift assay | Inhibition of Aβ aggregation and fibrillogenesis. | [135]      |
| Dimethylcrocetin   | (Iridaceae)           |                             |                                                                              |            |
| Fucoxanthin        | *Sargassum horneri*   | *in vitro* ThT and microsopical studies *in vivo* Aβ1-42 microinjected mice | Effectively inhibited Aβ assembly, Reversed cognitive impairments through inhibiting oxidative stress, increasing BDNF expression and elevating cholinergic system. | [174]      |
| Flavonoids         | *Smilacis chiniae*    | *in vitro* Primary cortical neurons | Reduced increase in (Ca2+) and inhibition of glutamate release, caspase-3 activity and ROS generation. | [175]      |

(Continued)
Table 4. (Continued).

| Compounds                        | Plants and Family           | Models/assays       | Key mechanism                                                                                     | References |
|----------------------------------|----------------------------|---------------------|--------------------------------------------------------------------------------------------------|------------|
| 7-Demethylageconylavone A, Tricin, Ageconylavone A, Corylin, Nectandrin B, 4-Ketopinoresinoside | *Eragrostis ferruginea* (Poaceae) | PC12 cells | Protects Aβ induced toxicity                                                                   | [176]      |
| Aceragenin A                     | *Acer maximowiczianum* (Sapindaceae) | *In vitro* HT22 cells | Prevents glutamate-induced oxidative damage. HO-1 induction through PI3K/Akt and Nrf2 pathways | [177]      |
| Apigenin                         | *Elsholtzia rugulosa* (Lamiaceae) | *In vitro* APPsw cells | Attenuation of intracellular ROS generation, preserved mitochondrial function and regulation of apoptotic pathways | [178]      |
| Biochanin A                      | *Trifolium pretense* (Fabaceae) | PC12 cells          | Protective effect against Aβ25–35 and attenuated PC12 cell injury and apoptosis by preventing mitochondrial dysfunction. Also, estoration of Bcl-2/Bax and Bcl-xl/Bax ratio. | [179]      |
| Caffeic acid                     | *Solanum tuberosum* (Solanaceae) | *In vitro* PC12 cells | Reduced levels of intracellular calcium and tau phosphorylation                                  | [180]      |
| Catechin                         | *Hypericum perforatum* (Hypericaceae) | *In vitro* Microglial cell line BV2, N11 cells | Reduction of Aβ induced ROS generation and increase of membrane fluidity                       | [146]      |
| Chlorogenic acid                 |                            | PC12 cells          | Attenuates Aβ-induced neurotoxicity by reducing apoptotic effect and inhibiting calcium influx by Aβ | [181]      |
| Curcumin                         | *Curcuma longa* (Zingiberaceae) | *In vivo* APPswe/PS1dE9dtg mice | Reduced the expressions of hippocampal Aβ40, Aβ42 and ADDLs in brains                          | [182]      |
| Decursin                         | *Angelica gigas* (Apiaceae) | PC12 cells          | Significantly inhibited Aβ25–35-induced cytotoxicity and apoptosis                              | [183]      |
| Ellagic acid                     | *Rubus idaeus* (Rosaceae) | *In vivo* Aβ25–35 microinjected rats | Atenuated oxidative stress and modulation of NF-κB/Nrf2/TLR4 signaling pathway.                | [184]      |
| Emodin                           | *Polygonum cuspidatum* (Polygonaceae) | *In vitro* Cultured cortical neurons | Up regulation of B-cell lymphoma-2, activation of ER/P13 K/Akt pathway and inhibition of JNK1/2 phosphorylation | [83]       |
| Epicatechin                      | *Hypericum perforatum* (Hypericaceae) | *In vitro* Microglial cell line BV2, N11 Cells | Inhibition of Aβ induced ROS generation and increase of membrane fluidity                      | [146]      |
| Epigallocatechin-3-gallate       | *Camellia sinensis* (Theaceae) | *In vivo* ICR mice | Attenuation of LPS induced β- and γ-secretase activity, expression of inflammatory proteins, inducible cyclooxygenase-2 and nitric oxide synthetase | [116]      |
| Eugenol                          | *Rhizoma aconi* (Anaceae) | *In vitro* PC12 cells | Inhibition of Aβ induced Ca2+ intake                                                             | [154]      |
| -Viniferin                       | *Vitis vinifera* (Vitaceae) | *In vitro* PC12 cells | ROS Scavenging activity and inhibition of Aβ fibrilization                                       | [185]      |
| Ferulic acid                     |                            | PSAPP mouse model   | Significantly decreased Aβ production and reduced amyloidogenic APP proteolysis. Also acts as β-secretase modulators. | [186]      |
| Compounds          | Plants and Family           | Models/assays       | Key mechanism                                                                 | References |
|--------------------|----------------------------|---------------------|-------------------------------------------------------------------------------|------------|
| Gallic acid        | *Sanguisorba officinalis* (Rosaceae) | *In vitro* Primary cortical neurons | Attenuation of Aβ25–35 induced elevation of cytosolic Ca²⁺ concentration, ROS and glutamate release | [187]       |
| Gingerol           | *Zingiber officinalis* (Zingiberaceae) | *In vitro* SH-SYSY human neuroblastoma cells | Attenuation of intracellular ROS and/or reactive nitrogen species and subsequent oxidative and/or nitrosative damages | [181]       |
| Isofraxidin        | *Eleutherococcus senticosus* (Analiaceae) | *In vitro* Primary cortical neurons | Prevention of Aβ25–35 induced axonal and dendritic atrophy                      | [138]       |
| Justicidin A       | *Mansonia angustifolia* (Geraniaceae) | *In vitro* HeLa cells | Decreased formation of Aβ in APPsw-transfected cells                            | [149]       |
| Luteolin           | *Elsholtzia rugulosa* (Lamiaceae) | *In vitro* SH-SYSY human neuroblastoma cells | Suppression of Aβ protein precursor expression, regulation of redox imbalance and attenuation of caspase family related apoptosis | [188]       |
| Methyl 3,4-Dihydroxybenzoate | *Kalimeris indica* (Asteraceae) | *In vitro* SH-SYSY human neuroblastoma cells | Attenuate neuronal cell death, reduce oxidative stress and inhibit apoptosis in cells. | [189]       |
| Nobiletin          | *Citrus depressa* (Rutaceae) | *In vivo* APP-SL 7–5 transgenic Mice | Increased extracellular signal regulated kinase phosphorylation and attenuation of Aβ-induced inflammation | [190]       |
| Oroxylin A         | *Scutellaria baicalensis* (Lamiaceae) | *In vivo* ICR mice | Suppression of Aβ25–35 induced astrocyte and microglia activation, iNOS expression and lipid peroxidation | [191]       |
| Paeoniflorin       | *Paeoniae alba* (Paeoniaceae) | PC12 cells | Attenuated neuronal cell death induced by Aβ25–35 via preventing mitochondrial dysfunction, increased cytochrome c as well as caspase 3 and 9 activity | [192]       |
| p-Coumaric acid    | *Corni fructus* (Cornaceae) | PC12 cells | Attenuated Aβ25–35 induced toxicity via NF-κB signaling pathway                | [193]       |
| Penta-o-gallyl-beta-D glucopyranose | *Paeonia suffruticosa* (Paeoniaceae) | *In vitro* ThT, and neuroblastoma SK-N-SH cells *In vivo* Transgenic 2576 mice | Inhibition of oligomer and fibril formation from monomer and destabilization of pre-formed fibrils Inhibition of Aβ production in the rat brain | [150]       |
| Phenolics           |                            |                     |                                                                               |            |
| Pomiferin          | *Ficus macrophylla* (Moraceae) | *In vitro* swAPP-N2a cells | Modification of Aβ accumulation by activation of insulin degrading enzyme       | [139]       |
| Puerarin           | *Pueraria lobata* (Fabaceae) | PC12 cells | Protect against Abeta25–35 induced neuronal cell death. Also, found to increase the Bcl-2/Bax ratio and reduce caspase-3 activation | [194]       |
| Rosmarinic acid    | *Salvia officinalis* (Lamiaceae) | *In vitro* PC12 cells | Inhibition of Aβ-induced ROS formation, lipid peroxidation, DNA fragmentation, caspase-3 activation and tau protein hyperphosphorylation | [195]       |
| 4-O-methylhonokiol | *Melissa officinalis* (Lamiaceae) | *In vivo* ICR mice, *In vitro* PC 12 cells | Inhibition of Aβ1–42 induced ROS generation and neuronal cell death. Also attenuated the formation of Aβ aggregation/fibrillization | [148]       |
| Rutin              | *Ginkgo biloba* (Ginkgoaceae) | *In vitro* SH-SYSY human neuroblastoma cells | Inhibit Aβ42 fibrillization and attenuate Aβ42-induced cytotoxicity dose dependently | [196]       |
| Salvianolic acid B | *Salvia miltiorrhiza* (Lamiaceae) | *In vivo* ICR mice | Reduced levels of Aβ25–35 induced nitric oxide synthase, cyclooxygenase-2 expression and lipid peroxidation product | [197]       |

(Continued)
| Compounds                | Plants and Family | Models/assays | Key mechanism                                                                 | References |
|-------------------------|-------------------|---------------|--------------------------------------------------------------------------------|------------|
| Silybinin               | *Silybum marianum* (Asteraceae) | *In vitro* SH-SYSY human neurobloma cells | Prevention of oxidative damage in the hippocampus, Inhibition of Aβ aggregation and attenuation of Aβ-induced H$_2$O$_2$ Production | [198,199] |
| Sulfuretin              | *Albizia julibrissin* (Fabaceae) | *In vitro* SH-SYSY human neurobloma cells | Protection against Aβ induced neurotoxicity. nuclear factor erythroid 2-related factor 2 (Nrf2), a downstream target of PI3K/Akt | [200]     |
| Tannic acid             | *Plantago Lanceolata* (Plantaginaceae) | *In vitro* PSAPP mouse model | Significantly reduced both Aβ$_{40}$ and Aβ$_{42}$ production and inhibited β-Secretase activity. | [186]     |
| α-Mangostin             | *Garcinia mangostana* (Clusiaceae) | *In vitro* primary cortical neurons | Reduction in the Aβ production via inhibiting β-secretase γ-secretase | [201]     |
| Saponins                |                    |               |                                                                                 |            |
| Akebia saponin B        | *Dendrocalamus asper* (Poaceae) | *In vitro* PC12 cells | Inhibition of excessive Ca$^{2+}$ influx, reduction of LDH leakage and prevention of loss of cell viability | [202]     |
| Cotalinoside A          | *Polaskia chichipe* (Cactaceae) | *In vitro* SH-SYSY human neurobloma cells | Inhibited Aβ aggregation in Aβ$_{40}$ and Aβ$_{42}$ | [203]     |
| Chikusetsusaponin V     |                    |               |                                                                                 |            |
| Sugars                  |                    |               |                                                                                 |            |
| Bajjiasu (β-D-fructofuranosyl (2→2) β-D-fructofuranosyl) | *Marinda officinalis* (Rubiaceae) | PC12 cells | Neuroprotective against Aβ$_{25–35}$ induced neurotoxicity in PC12 cells, likely by protecting against oxidative stress and ensuing apoptosis likely by expression levels of p21, CDK4, E2F1, Bax, NF-jB p65, and caspase-3 | [204] |
| Fucoidan                | *Laminaria japonica* (Laminariaceae) | *In vivo* Sprague-Dawley rats | Decrease in oxidative stress and inhibition of acetylcholinesterase | [205]     |
| α-D-(1→4)-glucan        | *Loniceria japonica* (Caprifoliaceae) | *In vitro* TH and human neurobloma cells | Inhibited Aβ42 aggregation, Also, attenuate the cytotoxicity induced by Aβ42 aggregation in cell type. | [206]     |
| Steroids                |                    |               |                                                                                 |            |
| Acteoside               |                    |               |                                                                                 |            |
| Eleutherococcus senticosus (Atalilaeae) | *Verbascum sinuatum* (Scrophulariaceae) | *In vitro* human neurobloma cells | Modulation of the apoptotic signal pathway via Bcl-2 family, caspase-3 cytochrome c inhibition of ROS production | [207] |
| Eleutherococcus senticosus (Atalilaeae) | *Eleutherococcus senticosus* (Atalilaeae) | *In vitro* Primary cortical neurons | Prevention of Aβ(25–35) induced axonal and dendritic atrophy | [138] |
| Ginkgolide               |                    |               |                                                                                 |            |
| Rhaponticin             | *Panax ginseng* (Araliaceae) | *In vitro* PC12 cells | Reduction of Aβ-induced cell death | [208]     |
| Rhamnoligoside          | *Rhizome rhei* (Polygonaceae) | *In vitro* IMR-32 cells | Reduction of the pro-apoptotic Bax/Bax homodimers through the formation of Bcl-2/Bax heterodimers | [209] |
| Salidroside             | *Rhodiola rosea* (Crassulaceae) | *In vitro* SH-SYSY human neurobloma cells | Induction of antioxidant enzymes, downregulation of pro-apoptotic protein Bax and upregulation of anti-apoptotic protein Bcl-extra large | [194] |
| Withanamide C           | *Withania somnifera* (Solanaceae) | *In vitro* PC12 cells | Inhibition of free radical generation and fibril formation | [210]     |

(Continued)
| Compounds   | Plants and Family       | Models/assays                      | Key mechanism                                                                 | References |
|------------|-------------------------|-----------------------------------|-------------------------------------------------------------------------------|------------|
| Xylocoside G | *Itoa orientalis* (Flacourtiaceae) | *In vitro* SH-SYSY human neuroblastoma cells | Downregulation of cyclooxygenase-2, attenuation of release of inflammatory factors and repression of caspase-3 activation | [211]      |
| Terpenoids  |                         |                                   |                                                                               |            |
| Alantolactone | *Inula helenium* (Asteraceae) | *In vitro* cortical neurons        | Attenuated intracellular ROS and superoxide anion in Aβ25−35 induced cortical neurons. Reversed cognitive deficit induced by scopolamine | [212]      |
| Isoalantolactone |                         | *In vivo* scopolamine induced Nrf2−/− mice |                                                                               |            |
| Carnosic acid | *Rosmarinus officinalis* (Lamiaceae) | Aβ induced toxicity rats          | Increased the learning and behavior and increased healthy neurons in CA region in brain | [213]      |
| Cryptotanshinone | *Salvia miltiorrhiza* (Lamiaceae) | *In vivo* APP/PS1 transgenic mice | Swe/APP cortical neurons increased release of sAPP and reduction in levels of Aβ | [214]      |
| Eugenol     | *Acorus calamus* (Acoraceae) | *In vitro* PC12 cells             | Inhibition of Aβ-induced Ca²⁺ intake                                           | [154]      |
erative diseases [215]. The brain cells are continuously exposed to a surplus of free radicals, which leads to oxidative stress. Thus, ROS-induced oxidative stress in the brain is one of the most common etiologies of neurodegenerative disorders, including AD [216,217]. The oxidative stress not only mediates neurotoxicity induced by Aβ, but also enhances the production of Aβ [218]. Thus, oxidative stress is a prime contributing factor for AD development, and antioxidants can be considered therapeutic approaches.

**MTDL: A new therapeutic approach for AD**

For 15 years, AD had been treated symptomatically, and the therapeutic approaches are of modest efficacy [219]. The approved drugs fall into two categories: AChE inhibitors and N-methyl D-aspartate (NMDA) receptor antagonists, with four and one drug in each group, respectively [220,221]. These cholinergic drugs increased cholinergic system deficiency by inhibiting the AChE enzyme, which degrades acetylcholine. One of the important drugs belonging to this class is donepezil. Many evidence infers that AChE inhibition reinstates the cholinergic system and mediates the disease progression [222].

On the other hand, the excessive NMDA glutamate receptor activity observed in AD was inhibited by a low-affinity, non-competitive and open channel blocker, memantine, which is frequently used with AChE inhibitors [219]. These drugs are insufficient for AD therapy, and this warrants more research towards finding drugs against AD. 223, suggested that identification of Aβ or tau proteins as a target in AD created two groups of researchers, referred to as ‘baptists’ and ‘tausists’ [223]. However, both these groups failed to develop the potential drugs which can cure the disease. Moreover, along with Aβ, antagonistic AChE also targets other aspects of AD.

Over the past nine decades, researchers have been targeting one factor at a time, which did not result in any drug to cure AD. Efficient pharmacotherapy may require simultaneous action on several targets involved in its pathogenesis due to the complexity of AD. Such effects may be achieved by administering a drug cocktail or a multicomponent drug. Besides AD, other neurological disorders such as depression, allergies, hypertension, schizophrenia, inflammation, and metabolic diseases can also be treated by this combination of drugs [224]. But, this approach carries the risk of potentially hazardous drug-drug interactions caused by specific pharmacokinetic and pharmacodynamic properties of individual components. It would be ideal if a single molecule could simultaneously act on multiple targets with greater efficacy and safety profile. In 2005, Morphy and Rankovic proposed this innovative strategy to develop MTDLs as potential drug candidates. This approach can be more relevant and practical since AD is a complex neurological disorder with multiple causative factors.

Further, to reduce the side effects, many reports suggest using herbal alternatives to enhance the efficacy of the therapy in the future [225]. Thus, identifying novel pharmacological neuroprotective MTDLs from plants is the new hope for treating AD. These natural products can simultaneously act on multiple targets associated with AD (enhance α-secretase activity; decrease β- and γ-secretase activity; inhibit Aβ; prevent oxidative stress and inflammation). Some plant products possessing multiple targets against AD are presented in tabulated in Table 5. The summary of the role of plant extracts and their phytochemicals in circumventing AD is represented in Figure 3.

**Conclusion and prospects**

Natural products have tremendous potential to act against AD and have given hope to the scientific fraternity as sources of drugs. Though the cause of AD is not clearly understood, natural products with multiple activities like AChE inhibition, NMDAR antagonist, antioxidant ability, amyloid inhibition, and anti-inflammation have the potential to be used as drugs. The healing power of culinary herbs and medicinal plants
Table 5. Plant products with multiple targets against AD.

| Compounds            | Mechanisms                                                                                   | References          |
|----------------------|----------------------------------------------------------------------------------------------|---------------------|
| Asiatic acid         | BACE-1 inhibitor, anti-inflammatory, anti-apoptotic, kinase modulator, α-secretase inhibitor | [226–228]          |
| Berberine            | IMAO, anti-neuroinflammatory, cholesterol regulator, insulin regulator                       | [229,230]          |
| Curcumin             | Anti-inflammatory, BACE-1 inhibitor, tau dimerization inhibitor, NMDA receptor modulator (antagonistic), α-secretase inhibitor, metal chelator | [231–236]          |
| Enscalin             | Serotonin 5-HT1A agonist, NMDA receptor modulator (antag.), dopamine D2 receptor antagonist | [237,238]          |
| Epigallocatechin gallate | BACE-1 inhibitor, α-secretase inhibitor, kinase modulator, metal chelator, α-synuclein inhibitor, anti-inflammatory | [239–242]          |
| Ferulic acid         | BACE-1 inhibitor, protective against PSEN1 expression                                          | [186,243,244]      |
| Honokiol, Magnolol   | Anti-apoptotic, neuroprotective                                                               | [245]               |
| Myricetin            | Anti-neuroinflammatory, NMDA receptor modulator, BACE-1 inhibitor                            | [246,247]          |
| Nicotine             | Adenosine A2 receptor antagonist, IMAO-B                                                     | [230]               |
| Osmotin              | BACE-1 expression, phosphorylation of p-PI3K, p-Akt and p-GSK3β                               | [248,249]          |
| Quercetin            | Inhibitors of NF-κB induced cytokine production, potential anti-AChE activity                 | [71,250]           |
| Resveratrol          | SIRT1-ROCK1 signaling pathway regulatoBACE-1 in, hibitor, apoptosis modulator, anti-inflammatory | [251; 236, 252–254]|
| Tannic acid          | BACE-1 inhibitor, apoptosis modulator, anti-inflammatory                                       | [255]               |
| Vincamine            | SOD and activation of PBK/Akt pathway, brain circulation modulator, voltage Na+ channel modulator | [170]               |
has attracted the researcher’s attention to study natural products as a potentially valuable resource for drug discovery against AD. Several natural products are used alone or in combination with some other neuroprotective agents to enhance memory and cognitive dysfunction and prevent AD.

Theoretically, phytochemical-based treatments against cognitive deficit could prove beneficial in clinical trials on humans due to their low toxicity and high bioavailability. The use of recent pharmaceutical technologies and developments in medicinal chemistry is to design novel drugs based on natural templates, which act on multiple targets, opens up a new window to using natural products in therapeutics against AD.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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