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Review Article

The pathophysiological signaling and efficacy of medicinal herbal compounds in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a high prevalence worldwide. It is associated with annoying and debilitating cognitive and memory deficits. For many years, various herbs have been consumed to boost memory and other dementia-related complications. Acetylcholinesterase (AChE) inhibitory, antioxidant properties, and neuroprotective effects of medicinal plants have broadened their application in the treatment of neurodegenerative diseases. Among them, compounds of *T. grandiflora*, including the methanol extract, depicted antioxidant and hydroxy radical scavenging properties. Likewise, *Zingiber officinale* and resveratrol have been suggested to demonstrate a neuroprotective effect. Besides, there is a long list of herbal medicines with AChE inhibitory action listed as follows: *T. grandiflora, A. paniculata, S. officinalis, G. nivalis, A. calamus, N. jatamansi, M. Allemão, C. sativum, C. tubulosa*, and silymarin a flavonoid derived from *Silybum marianum (L.) Gaertn. Moreover, Ginkgo biloba L., Curcuma longa L*, and natural bioactive compounds including silymarin, and resveratrol, can inhibit the formation and progression of amyloid-beta (Aβ), increase synaptic accumulation of acetylcholine, modulate the degree of tau protein phosphorylation, provide oxidative stress protection, and attenuate neuroinflammation. Herbal compounds involved in AD signaling pathways could affect various pathological processes related to AD and may be beneficial for AD treatment. In this review, the impact of medicinal herbs in alleviating AD symptoms is discussed, for which three databases including PubMed, Web of Science, and Scopus were selected with the keywords of Alzheimer's disease, medical herbs, signaling pathway, and plants.

Keywords:
Alzheimer Disease
Antioxidants
Cognition
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Herb-Drug Interactions

Introduction

Dementia, as the leading cause of disability in old age, has comprehensively become an intricate and urgent social problem (Tiwari et al., 2019). Regarding the

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Global Alzheimer's Report, today about 46.8 million people live with dementia, and it is conceptualized that the number of these patients will reach a peak of 131.5 million, by 2050 (Reitz and Mayeux 2014). Alzheimer's disease (AD), known as one of the dementia subgroups, is manifested by progressive neurodegenerative conditions with cognitive impairment symptoms (Shah-Abat di et al., 2023).

AD typical progress could be summarized into: the preclinical stage without prominent symptoms, subsequently the mild cognitive impairment (MCI) stage, and eventually the AD stage with the signs of dementia. Amnestic mild cognitive impairment (aMCI), the most prevalent type of MCI, has a high probability of leading to AD. Studies have indicated the relation of amyloid-beta (Aβ) peptide accumulation, to the onset of AD. Along with "downstream" pathological changes, including unrestrained tau protein phosphorylation, inflammatory degeneration is promoted. The two common pathological changes in AD are: 1- substantial deposition of amyloid protein in senile plaques (SP) and 2- Abnormal phosphorylation of tau protein, which causes neurofibrillary tangles (NFTs) (Ariaei and Ramezani 2023; Goedert and Spillantini 2006). In addition, neuroinflammation, atypic immune regulation, oxidative stress (OS), genes, calcium ions, central cholinergic system dysfunction, and insulin signaling pathway malfunction, are closely associated with the pathogenesis of AD. Unfortunately, despite the multiple drug developments, no promising treatment has been suggested to impede or hinder the progression of AD (Mohammadi et al., 2024).

AD and memory-impaired patients could benefit from medicinal herbs since several studies mentioned their efficacy in improving their quality of life. Medical herbs bioactive extracts such as flavonoids, polyphenols, and alkaloids, demonstrated diverse pharmacological activities. These activities were highlighted by anti-inflammatory, anticholinesterase, anti-amyloidogenic, and antioxidant effects, which effectively manage AD symptoms (Bordoloi et al., 2024).

AD is a progressive and lethal disease that imposes additional socioeconomic consequences on patients, families, and communities. Unfortunately despite multiple conducted research, the underlying cause of AD remains unknown, and no effective treatment or specific prevention is defined (Crous-Bou et al., 2017).

In this review, the effects of active medicinal herbs compounds in the molecular pathological signaling pathways of AD, are compared and demonstrated. Moreover, the most effective biological compounds in the management of AD, are reported.

Material and Methods

This review article was conducted by the following methodology: three databases including PubMed, Web of Science, and Scopus were used. Moreover, the search query was developed based on AD, medical herbs, and plants by utilizing a combination of AND/OR Boolean. Subsequently, the inclusion criteria were applied based on mentioning certain and clear results, peer-reviewing processed journals, and relevance to the research concept. We reported studies mentioning the potent benefits of medical herbs in the treatment or prevention of AD. There was no specific restriction on the time of article publication. From an immense number of articles, only articles which were accessible and clearly described their results, were selected. Since the current study is a narrative review, no specific guideline was applied to the study.

Pathology and signaling pathways of AD

Amyloid-beta (Aβ)

Aβ peptide isoforms are formed by different sequential cleavage of β-secretase and γ-secretase, on the amyloid precursor protein (APP) (Chen et al., 2017). $Aβ_{1-40}$ and $Aβ_{1-42}$ are two Aβ isoforms. $Aβ_{1-42}$, remarkably found as aggregated fibrils in the extracellular space due to its hydrophobic properties, is the main biomarker of AD (Perl 2000). The Aβ accumulation can be classified into two main causes: genetic factors and Aβ receptor involvement. The PSEN1 and PSEN2 genes are associated with the APP cleavage pathway (Barage and Sonawane 2015). Another genetic factor associated with AD is Apolipoprotein E (APOE), which leads to inflammation induced by glial cells, especially microglia, resulting in dysfunction of the APOE-mediated clearance pathway (Husain et al., 2021; Kloske and Wilcock 2020; Sato and Morishita 2015). The other reason is the role of receptors and protein transporters. Low-density lipoprotein receptor-related protein-1 (LRP-1) plays a crucial role in Aβ clearance by transporting from the interstitial fluid to the blood. Moreover, astrocytes can uptake Aβ via endocytosis, potentially mediated by LRP1 in an APOE-dependent manner (Koistinaho et al., 2004). The

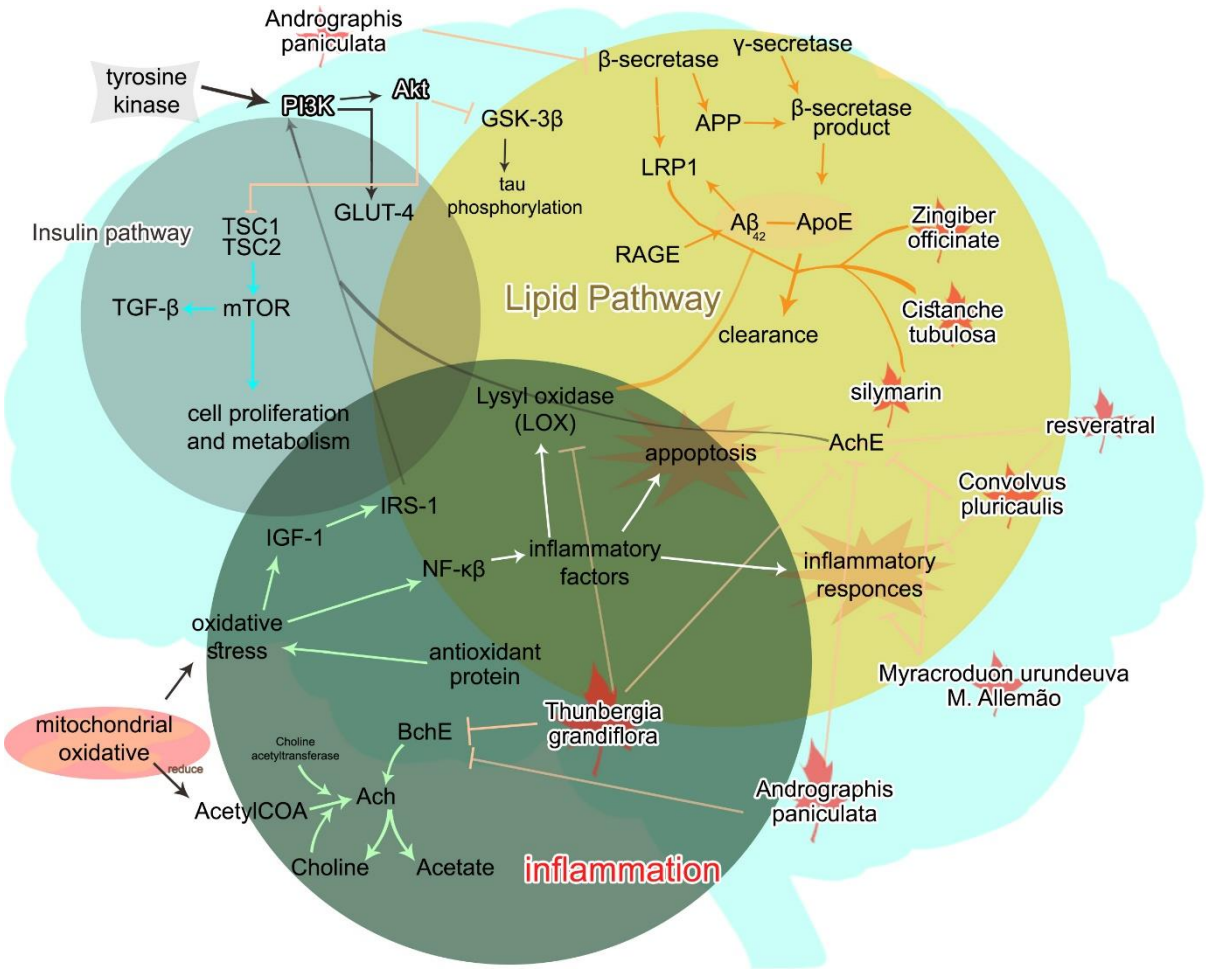

FIGURE 1. An overview of the cellular and molecular mechanisms of Alzheimer's pathology and the effect of medicinal herbs.

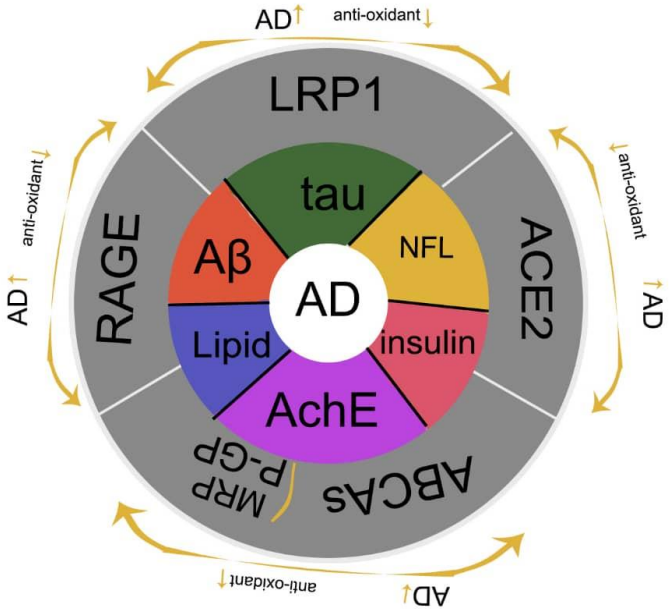

FIGURE 2. Antioxidant mechanisms restricting AD-related molecular signaling. As shown, the amounts of LRP1, RAGE, and ACE2 increased at the onset of AD, and anti-oxidants can compensate for these effects. In contrast, the amounts of ABCAs, including MRP and P-GP, decreased in AD, and antioxidants can enhance them.
LRP1: Low-density lipoprotein receptor-related protein-1
RAGE: Receptor for advanced glycation end products
ACE2: angiotensin-converting enzyme 2
ABCA: ATP binding cassette A
MRP: multidrug resistance proteins
P-gP: P-glycoprotein

receptor for advanced glycation end-products (RAGE) binds to Aβ (Yan et al., 2000). In AD brains, RAGE is found in neurons, astrocytes, and microglia, and is theorized to be involved in the formation of Aβ plaques and neurofibrillary tangles. The ATP-binding cassette (ABC) transporters, including P-glycoprotein (P-gp), multidrug resistance proteins (MRPs), and breast cancer resistance protein (BCRP), are known to be transporters mainly located in blood plasma or on the luminal side of enterocytes (Behl et al., 2021). P-gp has been shown to transport Aβ out of the brain (Wang et al., 2016). Eventually, the ACE2 protein is reported to be linked with Aβ levels (Ding et al., 2021). (Fig 2).

Tau

AD is characterized by the presence of paired helical filaments (PHF) and neurofibrillary tangles (NFTs), resulting from an increase in tau phosphorylation (Kolarogva et al., 2012; Maeda et al., 2006). Subsequently, the pathologic form of tau is detected in the cerebrospinal fluid (CSF), with levels gradually increasing over time (Blennow and Zetterberg, 2009). Multiple enzymes are known to be involved in tau phosphorylation (Iqbal et al., 2009). For instance, GSK-3 and CDK5 are among well-known enzymes. Their activities can be counteracted by BTA-EG4, which has dephosphorylation properties (Hashiguchi et al., 2002; Liu et al., 2005). Tau solubility mainly relies on Tau-tubulin kinase 1, which phosphorylates Ser422, subsequently reducing tau's solubility (Sato et al., 2006). CK1 δ with three phosphorylated residues, considerably influences tau phosphorylation, while PKA has only one phosphorylated residue (Hanger et al., 2007). PP1, PP2A, PP2B, and PP5 are a group of enzymes with multiple targets for tau protein (Liu et al., 2005). Tauopathy causes axonal instability. Similarly, one of the important components in neural growth and axon stability is neurofilaments (especially NFL). As neurofilaments are key elements of the neuron's cytoskeleton, various types of neural damage can cause their release into the extracellular fluid (Uddin et al., 2021).

Akt pathway

Phosphoinositide 3-kinases (PI3Ks) activate protein kinase B (PKB), also known as Akt, leading to the inactivation of GSK-3β, a protein involved in tau phosphorylation. On the other hand, when the PI3K signaling pathway is impaired, the GSK-3β enzyme is activated, resulting in tau hyperphosphorylation and the formation of NFTs (Lee et al., 2003). Integrating findings from various molecular techniques, the role of PI3K in converting phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3) is elucidated, along with the involvement of Akt in several pathological pathways associated with Alzheimer's disease. Notably, Akt overexpression has been shown to alleviate symptoms of AD. Moreover, the activation of Akt triggers a signaling cascade that regulates various cellular processes, including metabolism, transcription, protein synthesis, proliferation, and growth. Receptor tyrosine kinases (RTKs) are the primary initiators of Akt signaling pathway activation. However, other molecules such as integrins, cytokine receptors, G-protein-coupled receptors, and B and T cell receptors can similarly influence Akt activity (Chen et al., 2012).

mTOR and insulin pathway

The mammalian target of the rapamycin (mTOR) signaling pathway has a significant role in regulating glucose metabolism and energy consumption, stimulated by various signaling components like hormones (Cai et al., 2012). As regulating energy consumption is crucial for neurons, impairment in this system causes serious problems, including mitochondrial dysfunction, autophagy, dysregulation in cellular survival, and apoptosis (Buller et al., 2008). Cell proliferation and growth are due to the activation of p70S6K1, which is mediated by mTOR through the phosphorylation of multiple serine and threonine sites (Tramutola et al., 2017). The PI3K signaling pathway, activated by the insulin receptor (IR), regulates the GLUT-4 gene and the trafficking of GLUT4 storage vesicles (GSVs) (Akhtar and Sah, 2020). Genome analysis has corroborated the influence of proinflammatory factors and insulin resistance on the downregulation of the GLUT-4 gene (Arnold et al., 2018).

Neuroinflammation

Neuroinflammation is the result of peripheral T cells and microglia activation by the innate immune system (Mietelska-Porowska and Wojda 2017). Microglia and astrocytes are stimulated by the accumulation of pathological forms of tau protein. Additionally, insoluble forms of Aβ interact with Toll-like receptors, while soluble forms activate mitogen-activated protein kinases,

stimulating the production of cytokines and proinflammatory genes. This leads to chronic inflammation, with cytokines that affect the permeability of the blood-brain barrier (BBB). Cytokines have a significant role in mediating the immune response of AD patients' central nervous system (CNS), including interleukins (IL-1, IL-4, IL-6, and IL-10), interferon-gamma (IFNγ), and tumor necrosis factor-alpha (TNFα) (Gezen-Ak et al., 2013; Tatebe et al., 2017).

Nrf2 pathway

Another signaling pathway involved in AD is nuclear factor erythroid-2-related factor 2 (Nrf2), which mediates the expression of antioxidant proteins. This factor interacts with Kelch-like ECH-associated protein 1 (KEAP1), and its stability depends on E3 ligase activity. In the normal state of the cell, Nrf2 levels remain low due to degradation through the ubiquitin-proteasome system (Katoh et al., 2005). OS and reduced insulin sensitivity are two main factors that cause the downregulation of the Nrf2. In the AD due to an excess amount of ROS and other active molecules, the Nrf2 pathway is activated through spatial conformational changes in the KEAP1 molecule. Subsequently, Nrf2 migrates to the nucleus and binds to the Maf protein. The binding of the Nrf2-Maf complex to the antioxidant-responsive element (ARE) increases the transcription of antioxidant proteins. Translocation of Nrf2 from the nucleus to the cytoplasm occurs when the redox balance is restored (Zhang et al., 2021). The NF-κB signaling pathway, as a regulator of a wide range of proinflammatory cytokines, is impeded by the inhibitor of kB (IkB) and activated by IKK. IKK activation is triggered by OS either from mitochondrial stress or other sources. When the NF-κB signaling pathway is activated, various pro-inflammatory cytokines released by neurons, including IL-6, TNF-α, and IL-1β, initiate a secondary molecular cascade that leads to short-term resistance to insulin or IGF-1 (Scassellati et al., 2021). Oxidative stress also activates PI3K through the IGF-1 pathway, in which IGF-1 activates Insulin Receptor Substrate 1, resulting in the activation of PI3K (Ebrahimpour et al., 2020).

Gut-Brain Axis

There is clear evidence that AD is associated with chronic inflammation in both CNS and PNS (Le Page et al., 2018). Researchers have recently suggested a potential role for the gut microbiome in the onset and exacerbation of AD, and have shown that the composition of the microbiota in Alzheimer's patients is less diverse compared to healthy individuals (Vogt et al., 2017). The gut microbiota produces many metabolites that directly or indirectly affect brain function. Among these, short-chain fatty acids (SCFAs), which are abundantly present in medicinal herbs, including acetate, propionate, and butyrate, are known to be beneficial in modulating CNS and PNS.

Acetate crosses the BBB and modulates brain signals to regulate food absorption (Frost et al., 2014). It also reduces BBB permeability by influencing microglia (Deelchand et al., 2009; Frost et al., 2014). In addition, Butyrate is a multifaceted compound that is not only the preferred source of energy for gut cells but also inhibits histone deacetylase to alter the expression of several genes and proteins in the gut and neuronal cells (Walsh et al., 2015). Accordingly, Butyrate significantly improves learning and memory, by replicating the expression of learning-related genes in the AD mouse model and restoring histone acetylation (Govindarajan et al., 2011). This evidence suggests that restoring the production of SCFAs in the gut may help prevent AD. In addition, the metabolism of medical herbs extracts via gut microbiota and the interaction of bioactive compounds with drug transporters like P-gp and liver enzymes such as cytochrome P450 could alter the pharmacokinetics and pharmacodynamics of the therapeutic agents (John et al., 2022).

Other pathways

Choline acetyltransferase and AChE, the two main enzymes in AD symptoms, are diagnosed to be hypoactive in multiple areas of the brain, including the cerebral cortex (Chen et al., 2022; Schliebs and Arendt 2006). Furthermore, the AChE enzyme can trigger the PI3K signaling cascade and be portrayed as a suitable mediator of PI3K, since various types of active components influence it (Cai et al., 2012; Lazarevic-Pasti et al., 2017). Acetylcholine, as a major neurotransmitter involved in AD, is synthesized and degraded by various enzymes (Kummer et al., 2008). Calcium is asserted to be involved in both tau hyperphosphorylation and Aβ accumulation (Kutluer et al., 2020; Shin et al., 2012). APP cleavage by BACE1 causes Aβ42 (more toxic than Aβ40) accumulation (Arbor Ph D 2017), and activates

the lysyl oxidase pathway in astrocytes, resulting in accelerated senile plaque formation in the hippocampus of AD patients (Gilad et al., 2005) (Fig 1&2).

Synthesized drugs available for AD

Available drugs only alleviate symptoms in AD patients and cannot obstruct the progression of it. Based on common AD symptoms, multiple medications have been developed which include four drugs: Donepezil (Aricept), Rivastigmine (Exelon or Galantamine and Reminyl), Memantine (Namenda), and a combination drug called Namzaric (memantine + donepezil), all approved by the FDA (Yiannopoulou and Papageorgiou 2020). The traditional medicinal approach for AD patients is based on cholinesterase inhibitors (such as rivastigmine, donepezil, and galantamine) and N-methyl-D-aspartate antagonists (memantine) (Yiannopoulou and Papageorgiou 2020). Cholinesterase inhibitors are commonly prescribed for mild to moderate symptoms, while memantine is rigidly prescribed for moderate to severe ones. In addition to these AD-specific medications, doctors prescribe various supplements such as coenzyme Q_{10}, alpha-lipoic acid, Ginkgo Biloba, Omega-3, and acetyl-L-carnitine to maintain the patient's health. Although the FDA has approved a specific list of drugs, none of them are recommended, unless clinical manifestations are observed for a long time (Geun Kim and Sook Oh 2012). In the following part different types of medicinal plants, their active compounds, their involvement in modulating or protecting, and finally their interaction in the pathogenesis of AD are examined.

Herbal medicines and their compound's effect on memory

1. Thunbergia Grandiflora Roxb (T. grandiflora): belongs to the Acanthaceae family and contains iridoids, glycosides, isounedoside, and grandifloric acid. These compounds have anti-AChE, antioxidant, and anti-arthritis properties (Kamran et al., 2020; Uddin et al., 2016; Uddin et al., 2021). The methanolic extract derived from the leaf of this plant revealed tangible results in anti-AChE, antioxidant, and inhibition activity of lipid peroxidation, which makes it a potential candidate for the treatment of AD. The main factor in antioxidant capacity and slowing the lipid peroxidation processes was mentioned as the power of reducing the ferricyanide complex to the ferrous form (Uddin et al., 2016) (Table 1).

2. Andrographis paniculata (Burm.f.): belongs to the Acanthaceae family. Diterpene glycans, diterpenoids, flavonoids, lactones, and flavonoid glycosides are contained in its extracts (Gu et al., 2020; Hossain et al., 2014) Studies have shown that the presence of many useful bioactive compounds in this plant led to a broad range of pharmacological impacts such as anti-inflammatory (Bosco et al., 2023; Sheeja et al., 2006; Shen et al., 2000; Shen et al., 2002), anti-cancer (Harjotaruno et al., 2007; Zhou et al., 2006), antihyperglycemic (Yu et al., 2003), and antioxidant (Gu et al., 2020; Sheeja et al., 2006) properties. Its neuroprotective activity is mainly due to three compounds named 3,4-Di-O-caffeoylquinic acid, apigenin, and 7-O-Methylwogonin, with a high binding affinity to cholinesterase and β-Site APP cleaving enzyme 1 (1-BACE) (Das et al., 2017). Their extracts indicate powerful inhibition of AChE, butyrylcholinesterase (BChE), and BACE-1. Thus, the formation of amyloid plaques, as a main cause of neurotoxicity, is reduced (Panche et al., 2019) (Table 1). Apigenin upregulates the ATP binding cassette A1 (ABCA1) via decreasing the level of microRNA 33 (miR33) and Toll-like receptor (TLR-4) that alleviates inflammation (Bok sco et al., 2023; Gu et al., 2020; Ren et al., 2018). On the other hand, apigenin diminishes the level of tau hyperphosphorylation in the hippocampus as well as mitigates the Aβ load via suppressing the expression of GSK-3β and BACE1 (Alsadat et al., 2021; Das et al., 2017).

3. Acorus Calamus L.: belongs to the Acoraceae family. Molecular techniques reveal five key components including flavonoids, triterpenes, alkaloids, phenols, and saponins responsible for antioxidant attributes (He et al., 2023). The phenolic potential of this plant was determined by the Folin-Siocalcite method and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) antioxidant test, unveiling the capability of treating AD. Animal research conducted on male Wistar rats confirmed its anti-AChE activity (Ahmed et al., 2009) (Table 1). Studies showed different fractions of *A. calamus* can attenuate memory impairment and modulate oxidative stress via suppressing PERK signaling and inflammatory processes. Moreover, it prevents neuronal loss in the hippocampus. These researches also suggest the neuroprotective role of *A. calamus* in AD treatment (Esfandiari et al., 2018; Khwairakpam et al., 2018; Mikami et al., 2021).

4. Myracrodruon Urundeuva M. Allemão: belongs to

TABLE 1: The most important substances in medicinal plants, along with their mechanisms of action in modulating or protecting the molecules involved in the pathogenesis of AD.

Row	Plant name	Type of Research	Main part	Active ingredients	Dose-dependent	Mechanism of action	Side effects/ Adverse effects
1	Thunbergia grandiflora	In vitro	methanol extract from leaves	Iridoids, glycosides	IC_{50} value for BChE 94.30 ± 3.17 µg/mL IC_{50} value for AChE 80.81 ± 3.02 µg/mL	Antioxidant, Anti-lysyl oxidase (LOX), AChE inhibitor, BChE inhibitor	Not reported
2	Andrographis paniculata (Burm.f.)	In silico & In vitro	Active composition	Grandifloric acid, phenolic acids, Eserine, Quercetin	IC_{50} value for AChE: 1.10 µg/mL IC_{50} value for BChE: 0.743 µg/mL IC50 value for BACE-1: 1.709 µg/mL	Inhibitor AChE, BChE, BACE-1	Not reported
3	Acorus calamus L.	In vitro	Methanolic extract from leaves	Phenolics, Flavonoids	IC_{50} DPPH Radical Scavenging 703.9 ± 22.29 µg/mL AChE inhibitor IC_{50} 791.35 ± 77.67 µg/mL	Antioxidant and AChE inhibitor	Not reported
4	Myracrodruon urundeuva M. Allemão	In vitro and animal study on mice	Leaf extract	Phenols tannins and Dimeric chalcones	10 mg/kg body wt., i.p. has 70% inhibition in Analgesic and anti-inflammatory AChE inhibitory effect IC_{50} inhibitor: 10.75 ± 0.15 µg/mL	Anti-inflammatory and AChE inhibitor	Decrease in hemocyte values and bone formation
5	Ferula asafoetida H. Karst	In vitro & In vivo	Aqueous extract of whole plant and resins	Ferulic acid, Umbelliferone, Coumarins, and other terpenoids	IC_{50} value of top four extracts for hMAO-B: 1.3 to 3.8 µg/mL	AChE inhibitor Antioxidants	Not reported
6	Crocus sativus L.	In silico & In vitro & Clinical trial	Flower extract	Crocin, Crocetin	30 mg/day, p.o. human	Anti-amyloidogenic activity and AChE inhibitor	Not reported
7	Cistanche tubulosa	Animal study on rat	Whole plant extract	Echinacoside, Acteoside	200 mg/kg	Anti-accumulation activity of Aβ	Not reported
8	Zingiber officinale	In vitro & animal research	Aqueous extract of rhizome	Phenolic compounds	Antioxidant Properties 200–500 µg/mL in hepatoma cell line 100 and 200 mg/kg to Wistar rats	Anti-accumulation activity of Aβ	Not reported
9	Agrimonia pilosa	In vitro	Flavonoids	Quercitrin, Tiliroside	30 µg/mL	AChE inhibitor	Photodermatitis
10	Salvia officinalis	In vitro	Leaves	Rosmarinic acid	IC_{50} value for DPPH radical scavenging activity: 4.81 ± 0.30 µg/mL	Anti-inflammatory, Antioxidant, and AChE inhibitor	tachycardia, vomiting, vertigo, and allergic reactions

Row	Plant name	Type of Research	Main part	Active ingredients	Dose-dependent	Mechanism of action	Side effects/ Adverse effects
11	Prunella vulgaris	Animal study on rat	Plant extract	Oleic acid, Ursolic acid, Butyric acid, Flavonoids and Rosmarinic acid	1 mg/kg for rat	Antioxidant, Anti-inflammatory, Acetylcholine-like effects, Increased cholinergicneurotransmitters	Nausea, vomiting, hyperthyroidism, and endocrine disorders
12	Galanthus nivalis	Animal study on mice	Flower	Alkaloids (Galantamine)	-	AChE inhibition Tau clearance	Nausea
13	Curcuma longa	Clinical Trial and animal research on mice	Rhizome polyphenolic compounds	Curcumin (diferuloylmethane)	IC_{50} for Aβ aggregation inhibition: 1.98 ±0.11 μg/mL IC_{50} for tau aggregation inhibition: 1.10 ±0.14 μg/mL	Inhibition of Aβ accumulation, OS, and inflammation Decrease Tau phosphorylation level	Not reported
14	Silymarin	In vitro & animal study on mice & In silico & human experiment	Seed	Flavonolignans of silybin, Isocilibin, Silydianin, and Silycristine	200 mg/kg for mice IC50 values of AChE and BChE 118.19±23.63 μg/mL and 255.69±10.61 μg/mL	Reduced toxicity induced by Aβ, protein oxidation, lipid peroxidation, and apoptosis, Reduce aging plaques and reduce memory and learning disabilities	Not reported
15	grapes	Animal study on mice & Clinical Trial	Bark, seeds, and leaves	Resveratrol	0.02 mg/kg daily for human	Inhibition of amyloid-induced neuronal apoptosis Improving learning memory deficits caused by Aβ Reduce MM9 Modulation of neuronal inflammation	Gastrointestinal disturbance and nephrotoxicity
16	Genista tinctoria, Glycine max	Animal model of rat & In vitro	Rhizome and seeds	Genistein	150 mg/kg/day for rat	Decreased Aβ levels in the brain Improve learning, cognitive memory, and odor detection and discrimination Degradation of Aβ and hyperphosphorylation of tau protein	Not reported
17	Green tea	In vitro & animal study & human study	Leaves	(Catechins (EGCG	and 3 mg/kg for rat 1.5 mg/kg for human 2	Inhibition of tau accumulation as toxic oligomers Increased clearance of phosphorylated tau related to Alzheimer's Increased expression of autophagic adapter proteins NDP52 and p62 Inhibition of amyloid synthesis and memory degradation	palpitation, neurological and gastrointestinal disturbance

Row	Plant name	Type of Research	Main part	Active ingredients	Dose-dependent	Mechanism of action	Side effects/ Adverse effects
18	Ginkgo biloba	In vitro	Leaf extract	,Terpene Lactones Flavonoids	-	Antioxidant and anti-inflammatory effects Increased neurogenesis and increased memory	vomiting, vitamin B6 deficiency, and spontaneous bleeding
19	Allium sativum	Animal study on rats & In vitro	Modified leaves	Organosulfur compounds: S-allyl-cysteine, S-allyl-mercaptocysteine	-	Anti-Aβ accumulation	allergic reaction, and changing the behavior of breast-feeding infants
20	Coriandrum sativum	In vitro	Fruit	Terpenoids: Linalool Biophenols: Quercetin, Isoquercetin, Rutin, Caffeic Acid	-	Antioxidants nootropic	Mutagenicity and Congenital malformations
21	Ferula asafoetida .Linn	Animal study on rat	Gum extract	-	mg/kg and 400 mg/kg 200	Reduction of Aβ levels by induction of autophagy by activating the AMPK / mTOR signaling pathway	Gastrointestinal disturbance
22	Punica granatum	Animal study on rat	Flowers and fruits	Anthocyanin compounds	to 500 mg/kg/day 300	Neuroprotective And antioxidants Improve learning ability and reduce memory	flu-like symptoms, gastrointestinal problems, allergic reaction , and urinary problems
23	Withania somnifera ((ashwagandha	Animal study & In vitro	Root	IX, Sitoindoside ,Sitoindoside X Withanolides, Withanols	mg/kg/day. in rat 100 µg/mL in cell culture 0.25	Anti-inflammatory AChE inhibitor Antioxidants Aβ inhibitor Reconstruction of damaged axons of dendrites and synapses	somnolence, gastrointestinal disturbance, vertigo, allergy symptoms, and nausea
24	Convolvulus pluri- (caulis (Shankhpushpi	Animal research on rat	Aqueous methanol	Flavonoids Tannins and Phenolics	mg/kg in the rat 100	altering AChE Antidepressant activity Anxiolytic activity	gastrointestinal disturbances, serious bleeding, allergic skin reactions, and headache

the Anacardiaceae family. The high phenolic content in this plant is vital for AChE inhibition and essential in treating AD. Its high anti-inflammatory properties are due to the existence of tannins and dimeric chalcones (Viana et al., 2003). Since the extract of this plant compensates for dopamine levels in pathological conditions, it could be a possible candidate for neurodegenerative diseases (Calou et al., 2014; Penido et al., 2017). A decrease in hemocyte values and bone formation was mentioned as the adverse effect of this herbal medicine (Machado et al., 2016) (Table 1).

5. Ferula asafoetida H. Karst: belongs to the Apiaceae family. Its AChE inhibitory properties were disclosed by in vitro and in vivo examinations of the snail nervous system and the rat brain. The resins of this plant have the inhibitory potential of monoamine oxidase B (MAO-B) (Zarmouh et al., 2016). The antioxidant and AChE inhibitory properties of this plant could improve cognitive symptoms of AD (Vijayalakshmi et al., 2012) (Table 1).

6. Crocus sativus: belongs to the Iridaceae family. Its antioxidant and AChE inhibitory properties are because of Crocin, Crocetin, and Safranal. The mechanism of its effect on memory is due to its anti-amyloidogenic activity. As mentioned in multiple studies, the accumulation of Aβ peptides serves as a trigger for AD. Therefore, impeding Aβ fibril formation attenuates AD symptoms. Multiple aspects of the extract from this plant have been investigated using in vitro models. The results of enzymatic assays and molecular studies demonstrate that crocetin has a high binding affinity to the catalytic center and peripheral anionic sites of the AChE enzyme, leading to inhibition, unlike safranal.Hence, the acetylcholine level increases, which plays a major role in memory function (Geromichalos et al., 2012) (Table 1).

7. Cistanche tubulosa: belongs to the Orobanchaceae family and is prescribed by traditional Chinese physicians for treating cognitive impairment. Its extract contains significant amounts of echinacoside and acteoside, which inhibit Aβ formation. Moreover, it upregulates dopaminergic and cholinergic neuronal activity, leading to an increase in acetylcholine levels (Wu et al., 2014). A clinical trial on this plant was conducted on AD patients; however, it resulted in insignificant changes in cognitive test scores. Due to the limited sample size and the improvement seen in a portion of the participants, a definitive conclusion regarding the plant's effects could not be established (Guo et al., 2013) (Table 1).

8. Zingiber officinale: belongs to the Zingiberaceae family and contains two main active compounds: 6-Gingerol and 6-Shogaol, both of which are vital for preventing OS and inflammation, making them effective in treating AD (Mohd Sahardi and Makpol 2019). Moreover, its effect on increasing the expression of nerve growth factor (NGF) and promoting synaptogenesis through the chronological activation of cyclic AMP response element-binding protein (CREB) and extracellular signal-regulated kinases (ERK) has been highlighted in neurodegenerative diseases (Talebi et al., 2021) (Table 1).

9. Agrimonia pilosa: belongs to the Rosaceae family. The main chemical compounds present are coumarin, tannin, and flavonoids. The flavonoids extracted from this plant, namely, quercitrin and tiliroside, exhibit AChE inhibitory properties and could serveas an alternative for the treatment of AD (Jung and Park 2007). Moreover, its flavonoid extracts were highlighted for antioxidant activity, DPPH scavaging activity, and Hydroxyl radical scavenging activity. In addition, anti-inflammatory and NO scavenging have been mentioned for the agrimonolide extract of A. pilosa (Jin et al., 2022). However, photodermatitis has been reported as a potential adverse effect of this medication(Paluch et al., 2020) (Table 1).

10. Salvia officinalis: belongs to the Lamiaceae family. It has a noticeable effect on the brain and has long been used to improve memory. The leaves of this plant are well known for their antioxidant traits. The therapeutic properties related to AD include antioxidant, anti-inflammatory, and weak inhibitory effects of AChE. Rosmarinic acid (the main active ingredient of the plant) reduces pathogenic cascades of AD induced by Aβ, including the formation of ROS, DNA fragmentation, lipid peroxidation, caspase-3 activity, and changing tau phosphorylation pattern. Based on clinical evidence, this plant may help to ameliorate AD symptoms (Vladimir-Knežević et al., 2014). Among the side effects and adverse effects of this medicine tachycardia, vomiting, vertigo, allergic reactions, hot flushes, cyanosis, tongue swallowing, and convulsion could be mentioned (Ghorbani and Esmaeilizadeh 2017) (Table 1).

11. Prunella vulgaris: belongs to the Lamiaceae familyus. The active compounds of this plant comprised of oleic acid, uric acid, butyric acid, rosmarinic acid, and flavonoids with antioxidant activity. In addition, this plant has anti-inflammatory, anti-allergic, and antimi-

crobial activities. Its effects on memory are attributed to the structure of the active compounds, which create an acetylcholine-like effect, influencing the cholinergic signaling pathway without interacting with AChE. P. vulgaris, besides its effect on increasing cholinergic neurotransmitters, can enhance memory function by binding to the NMDA (N-methyl-D-aspartate) receptor (Vladimir-Knežević et al., 2014). Nausea, vomiting, hyperthyroidism, and endocrine disorders are mentioned as the adverse effects (Han et al., 2021) (Table 1).

12. Galanthus nivalis: belongs to the Amaryllidaceae family. Alkaloids, especially galantamine, extracted from this plant are regularly used as a medicine for treating AD. One of the most common adverse effects is nausea. The molecular mechanism of galantamine is known to specifically inhibit the AChE enzyme (Heinrich and Teoh 2004). The mechanism underlying galantamine is increasing the concentration of acetylcholine in the synaptic cleft and enhancing nicotinic receptor concentration. In addition, it was stated that it could affect AD pathology by decreasing the early deposition of Aβ plaques (Zhang et al., 2020) (Table 1).

13. Curcuma longa: belongs to the Zingiberaceae family. Its polyphenolic compounds, especially Curcumin, are remarkably found in the rhizome. This plant has antioxidant, anti-inflammatory, anti-cancer, and neuroprotective properties (Sarker and Franks 2018). Curcumin has a protective effect on synaptic and mitochondrial toxicity, induced by Aβ accumulation (Reddy et al., 2016). The pharmacokinetic properties of this drug include BBB penetration and a high rate of distribution, resulting in higher neural protection (Reddy et al., 2018). Moreover, it could accelerate tau and Aβ clearance and diminish oxidative damage and inflammation levels (Okuda et al., 2016). In addition, due to the potential of inhibiting lipid peroxidation and reducing protein oxidation, AD symptoms could be managed (Bhat et al., 2022) (Table 1).

14. Silymarin: A powerful antioxidant extracted from a plant called Silybum Marianum (milk thistle). Appearance features of Silybum Marianum were first documented in Europe, in the first century. This plant contains 6 flavonolignans, including silybin A, silybin B, isosilybin A, isosilybin B, silychristin, and silydianin (Porwal et al., 2019). Administration of 100 mg/kg silymarin and 100 mg/kg silybin daily for 15 days, reduces memory impairment and dwindles the clump of amyloid plaques in the brains of APP/PS1 mice (Shen et al., 2019). Silymarin modifies gut microbiota diversity and regulates bacterial species, including Verrucomicrobia, Butyricicoccus, Enterorhabdus, and Mucispirillum, which are closely associated with AD pathogenesis. Administration of silymarin has more advantages than silybin because silymarin has a wide range of lignan-derived flavonols and it is expected to have a synergetic neuroprotective effect (Jiang et al., 2016; Shen et al., 2019). Administration of 200 mg/kg silibinin daily for 28 days in vitro converts the features of Aβ and AChE in a way that Aβ concentrations and AChE activity are reduced, while cholinergic synaptic activity is increased. Cognitive tests like MWM, point out spatial learning ability improvement in APP / PS1 transgenic mice that received silibinin. Moreover, silibinin, by crossing the BBB, can stimulate gliogenesis (microglia and astrocytes), neurogenesis, and differentiation of neuronal progenitor cells. The dual inhibitory trait of silibinin for the accumulation of Aβ and AChE makes it a potential therapeutic strategy for AD (Duan et al., 2015) (Table 1).

15. Resveratrol: A type of polyphenol compound found in berries, especially grape peels and seeds. Multiple functions have been linked to resveratrol, like activating silent information regulator sirtuin 1 (SIRT1), as a transcription factor, and modulation of important cellular messenger molecules, including cytokines, matrix metalloproteinases (MMPs), caspases, Nuclear factor kappa B (NF-κB), peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), AMP-activated protein kinase (AMPK), IGF-1, endothelial growth factor, phosphorylated Akt (pAkt), Forkhead box O (FOXO), etc (Singh et al., 2019; Zhao et al., 2015a). The potential effect of resveratrol in the management of AD has been declared in numerous studies (Moussa et al., 2017; Rege et al., 2014). Mechanisms include dampened toxicity and accumulation of Aβ peptides in the hippocampus of AD patients, thus enhancing neurogenesis and preventing hippocampal degeneration (Gomes and Silva 2018), in which SIRT1 plays a key role. Moreover, Resveratrol has anti-inflammatory effects by inhibiting the microglia M1, which is known to initiate neuronal apoptosis (Yang et al., 2017). Gastrointestinal disturbance and nephrotoxicity are mentioned as the adverse effects of resveratrol (Shaito et al., 2020) (Table 1).

16. Genista tinctoria and Glycine max: belong to the

Fabaceae family. Genistein, as a polyphenolic isoflavone, is their main composition. This category of isoflavones attenuates many pathological conditions associated with aging, such as OS, inflammation, etc (Devi et al., 2017; Saha et al., 2014). Genistein is suitable for AD, due to its ability to manage disorders caused by abnormal Aβ accumulation and Alzheimer-related OS (Devi et al., 2017; Uddin and Kabir 2019). Moreover, the neuroprotective effect of Genistein was explored in ApoE-/- mice illustrated by the potential suppression of oxidative stress and neuroinflammation. In addition, by inhibiting the Glycogen synthase kinase 3 (GSK-3) and c-Jun N-terminal kinase (JNK) potential effect on reducing tau hyperphosphorylation was observed (Park et al., 2016) (Table 1).

17. Green tea: belongs to the Theaceae family. In vitro and animal studies highlighted its function in preventing aging-related neurodegenerative disorders including AD, mainly because of catechins, as an active polyphenol ingredient. Pharmacological traits of catechins are as follows: improving the internal antioxidant defense system, modulating neuronal growth factors, hindering neuroinflammatory pathways, and regulating apoptosis (Cascella et al., 2017; Dragicevic et al., 2011). Epigallocatechin gallate (EGCG) is a type of catechin extensively studied for its neuroprotective potential either by inhibiting tau aggregation, resulting in NFTs (Wobst et al., 2015), or hastening the clearance of hyperphosphorylated tau (Chesser et al., 2016). In addition, EGCG treatment results in abating Aβ accumulation (Abbas and Wink 2010). In addition to cardiovascular effects, including palpitation, neurological and gastrointestinal side effects were mentioned as the result of caffeine (Schönthal 2011) (Table 1).

18. Ginkgo biloba: belongs to the Ginkgoaceae family. It contains two major classes of phytochemicals, including terpene lactones (consisting of ginkgolides and bilobalide) and flavonoids (consisting of kaempferol, quercetin, isorhamnetin, and myricetin) (Nagori et al., 2023; Shi et al., 2010; Solfrizzi and Panza 2015). Moreover, isoginkgetin, and flavonols, like The medical constituents of this plant cause salutary neurochemical effects in the brain, including modulation of neurotransmission, memory enhancement, inhibition of apoptosis, antioxidant and anti-inflammatory effects, neurogenesis escalating, cerebrospinal fluid circulation, and cognitive activity improvement (Sochocka et al., 2022; Yoo et al., 2010; Zuo et al., 2017). Multiple adverse effects were mentioned as a result of seed and leaf extract toxicity including, vomiting, tonic and clonic convulsion, loss of consciousness, vitamin B6 deficiency, and spontaneous bleeding (Mei et al., 2017) (Table 1).

19. Allium sativum: belongs to the Alliaceae family. It contains active organosulfur compounds that reduce brain inflammation and dwindle both soluble and aggregated species of Aβ. The influence of this plant on the regulation of tau protein phosphorylation is demonstrated by in vitro studies, which show its interaction with GSK-3β (Gupta et al., 2009). Some adverse effects were mentioned as allergic reactions, increasing the effect of anticoagulant agents, altering the function of platelets, and changing the behavior of breast-feeding infants (Borrelli et al., 2007) (Table 1).

20. Coriandrum sativum: belongs to the Apiaceae family. According to the results, OS markers (including Superoxide dismutase (SOD)) and Lactate dehydrogenase (LDH) activity were diminished because of the plant's active compounds, namely, terpenoids and biophenols. Moreover, it is asserted that its oil ameliorates Aβ induced spatial memory/cognition decline, via attenuation of the OS in the rat hippocampus. Besides anti-apoptotic activity, the extract increases glutathione peroxidase activity (Cioanca et al., 2013). Mutagenicity and congenital malformations are among the adverse effects of this compound (Laribi et al., 2015) (Table 1).

21. Radix Polygalae: belongs to the Polygalaceae family. Its active compounds, including saponins and xanthones, have been shown to possess a wide range of medicinal properties, such as neuroprotective, anti-depressant, anti-inflammatory, anti-tumor, antioxidant, and anti-aging effects (Qiong et al., 2021). Its aqueous extract reduces autophagy by activating the AMPK/mTOR signaling pathway, resulting in a reduction of Aβ levels (Zhao et al., 2015b). Gastrointestinal disturbances are the primary side effect of this medication (Zhao et al., 2020) (Table 1).

22. Punica granatum: belongs to the Punicaceae family. Its flower is a rich source of biologically active compounds, including gallic acid, oleanolic acid, ursolic acid, ellagic acid, and triterpenoids. These compounds possess powerful antioxidant properties, helping to counteract reactive oxygen and nitrogen species as well as oxidation-induced free radicals affecting proteins and lipids. Therefore, it could play a major role in improving

memory and learning function (Cambay et al., 2011). Among the side effects flu-like symptoms, gastrointestinal disturbance, allergic reactions, and urinary problems have been mentioned (Zare et al., 2023) (Table 1).

23. Withania somnifera: belongs to the Solanaceae family. Vitalonides are the active compounds responsible for maintaining endothelial function, modulation of apoptosis, as well as inflammatory damage (Dar 2020; Das et al., 2021; Sehgal et al., 2012). An in vitro research conducted on neuronal cells revealed the inhibitory activity of AChE and retrieving Aβ toxicity (Kurapati et al., 2013). Furthermore, the active ingredient of this plant downregulates beta-secretase enzyme while upregulating disintegrin and metalloproteinase 10, which are involved in Aβ clearance (Patil et al., 2010). Some adverse effects mentioned include somnolence, gastrointestinal disturbance, vertigo, allergy symptoms, nausea, hyperactivity, blurring of vision, and nocturnal cramps (Tandon and Yadav 2020) (Table 1).

24. Shankhpushpi (Convolvulus pluricaulis): Using cellular and molecular methods, the role of this herb in inhibiting acetylcholine esterase activity was clarified, mainly in the CA1 and CA3 regions of the rat hippocampus. Hence, this plant can alleviate cognitive dysfunctions by reducing hippocampal Aβ deposition, enhancing glutathione peroxidase activity, improving the function of cholinergic neurons, and mitigating anticholinesterase activity (Chaudhari et al., 2017; Dubey and Chinnathambi 2019). Reported side effects include gastrointestinal disturbances, serious bleeding, allergic skin reactions, and headaches (Jatwa et al., 2014) (Table 1).

Discussion

Molecular techniques have demonstrated a high antioxidant potential (IC_{50} value of 10.50 ± 0.68 μg/mL) for the bioactive compounds of *T. grandiflora*, indicating significant DPPH scavenging activity compared to well-known antioxidants like ascorbic acid (IC_{50} value of 4.41 ± 0.27 μg/mL). Moreover, its hydroxyl radical scavenging property, with an IC_{50} value of 24.98 ± 1.39 μg/mL, is higher than *Catechin*, with a value of IC_{50} 12.68 ± 0.63 μg/mL. The methanol extract of this plant has an inhibitory action on AChE (IC_{50} 80.81 ± 3.02 μg/mL) and lipid peroxidation enzymes (IC_{50} 21.84 ± 0.91 μg/mL) (Uddin et al., 2016). The efficacy of AD medications depends on the absorption and penetration of bioactive compounds through the BBB. *Andrographis paniculata* bioactivity properties were examined by spectrophotometry developed by Ellman, in vitro studies, and bioinformatics methods. As the results depicted, inhibition of AChE and BChE was predicted along with a low absorption rate, in which human oral absorption is about 1-3 percent, as well as neglecting Lipinski's rule of five. The results of pkCSM data suggested poor BBB permeability, while molecular dynamic data revealed a stability state in inhibiting enzymes (Panche et al., 2019). In contrast, FDA-approved drugs including donepezil and memantine have a high potential of penetrating BBB (0.157 and 0.603 log BB, respectively) and distributing in the CNS (Shah-Abadi et al., 2023). Animal research did not depict oral administration of *Myracrodruon urundeuva Allemão* completely effective, since it only causes 33 to 50% inhibition. Nevertheless, injecting the extract into the peritoneum at doses of 5 and 10 mg/kg, caused 57 and 70% inhibition, respectively (Penido et al., 2017; Viana et al., 2003). Moreover silibinin, as a main active constituent of *silymarin* stimulated by in-silico molecular techniques, seemed to have considerable merit in the penetration of BBB. Meanwhile, molecular dynamics data reveals a high binding affinity of silibinin in counteraction with Aβ1-42, resulting in the stabilization of the Aβ1-42 structure and reduction of plaque formation (Duan et al., 2015). Accordingly, a clinical trial on the efficacy of Silymarin on AD reveals a beneficial result in ameliorating the effect of Aβ aggregation measured through magnetic resonance spectroscopy (Ebrahimi Shah-abadi et al., 2023; Rustamzadeh et al., 2023). In comparison, Lecanemab, an FDA-approved drug, has shown promising results in reducing brain amyloid burden through its interaction with Aβ (Van Dyck et al., 2023). AD is a multifactorial neurodegenerative disorder driven by dysregulated enzymatic pathways. Targeting these pathways through the identification of selective enzyme inhibitors holds promise for developing novel therapeutic strategies to mitigate disease progression and improve clinical outcomes. *C. pluricaulis* has two separate pathways affecting the pathological mechanisms of AD. Firstly, it adjusts the level of acetylcholine in the synaptic cleft, by interfering with the synthesis or catalysis pathway of AChE enzyme. Secondly, it indirectly intervenes in Aβ formation by acting as a muscarinic agonist (Malik et al., 2011). Active compounds may have a healing process through simple pathways, even by inhibiting spe-

cific enzymes or acting on a particular receptor, while some active compounds produce noticeable effects by activating signaling cascades resulting in multiple molecular incidents. Since the AChE enzyme has a considerable impact on the pathology of AD, even in Aβ formation or tau hyperphosphorylation, inhibiting the activity of this enzyme ameliorates the cognitive symptoms of the disease. Some medicinal herbs indicate a satisfactory level of AChE activity, including *T. grandiflora, A. paniculata, S. officinalis, G. nivalis, A. calamus, N. jatamansi, M. Allemão, C. sativum, C. tubulosa, and silymarin. Cistanche tubulosa*, besides its AChE inhibitory action, could act on nicotinic receptors as an agonist. Meanwhile, because of various active compounds, it can mediate the PI3k/Akt pathway, one of the significant pathways in AD. Its neuroprotective action is due to antioxidant compounds named Echinacoside and acteoside (Wu et al., 2014). In a meta-analysis exploring the efficacy of different drugs on AD, it was mentioned that donepezil in doses of 5 mg and 10 mg and Galanthamine derived from *G. nivalis*, in doses of 24 mg and 32 mg were effective agents in the management of AD symptoms (Zhang et al., 2020). The antioxidant effects of *Zingiber officinale* are not limited to neuroprotective properties. The active compounds of ginger can improve heart and respiratory system function, by impeding 5-lipooxygenase synthetase. Moreover, in vitro and animal research depicted the inhibition traits of gingerol and shogaol in the leukotriene and prostaglandin biosynthesis (Mohd Sahardi and Makpol 2019; Talebi et al., 2021). By conducting animal and human research, the role of other molecules and genes was scrutinized for better consideration of molecular interactions and drug development of AD. Molecular and cognitive tests, including the Morris water maze (MWM) and long-term potentiation (LTP), portray CREB and SIRT1 as two molecular factors whose interaction is involved in synaptic plasticity. The results demonstrate the inhibitory role of $A\beta_{1-42}$ on CREB activation. Meanwhile, SIRT1 expression is downregulated during the onset of AD. Furthermore, the toxicity effects of $A\beta_{1-42}$ can be adjusted by CREB phosphorylation. Resveratrol can partially retrieve SIRT1 expression and CREB phosphorylation, resulting in cognitive improvement (Gomes and Silva 2018; Moussa et al., 2017).

Conclusion

Neurodegenerative diseases are a major health concern, due to high mortality rates and high healthcare costs. In addition, current treatments for AD could partly palliate symptoms and are unable to impede neurodegeneration (Crous-Bou et al., 2017; Yiannopoulou and Papageorgiou 2020). Recent studies link nutrition with aging and neurodegeneration since some compounds comprise neurogenic properties (Dohrmann et al., 2019; Naoi et al., 2017). Particular compounds such as polyphenols (e.g., flavonoids, curcuminoids, acetylbones, phenolic acids, and carotenoids), abundant in various nutrition sources (including tea, herbs, seeds, and fruits), are essential for maintaining mental health. Some of these herbal compounds can induce neurogenesis along with reducing OS and neuroinflammation (Gómez-Pinilla 2008), and enhance cellular signaling as well as synaptogenesis (Poulose et al., 2012). Herbal compounds due to antioxidant properties, could be used as an inhibitor of free radicals activity, leading to the formation of more stable compounds (Rossi et al., 2008). Moreover, active herbal compounds could enhance neurons' survival rate energy consumption, as well as decrease AD pathophysiological characteristics including mitochondrial dysfunction, and misfolded protein accumulation. Interventions derived from medicinal herbs involved in the pathophysiology processes of AD can be useful to impede the progression of neurodegenerative diseases or even modulate and retrieve them. Consequently, medicinal herbal compounds (mainly polyphenols) involved in AD signaling pathways, in particular flavonoids with negligible antioxidant properties, could affect various pathological processes related to AD and may be beneficial for AD treatment.

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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Ethics approval

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