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THERAPEUTIC PHYTOCONSTITUENTS FOR ALZHEIMER'S DISEASE: AN OVERVIEW

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive decline and behavioural changes. This review explores the potential of phytoconstituents derived from medicinal plants as alternative treatments for AD. It provides an overview of currently approved medications and disease-modifying immunotherapies but highlights the need for improved therapeutic options due to limitations and side effects. The review focuses on key phytoconstituents, including baicalein, quercetin, and berberine, discussing their pharmacological properties in mitigating oxidative stress, reducing inflammation, promoting neuronal health, and inhibiting protein aggregation. However, challenges related to bioavailability and metabolisms hinder their efficacy. The use of targeted nanocarrier systems shows promise in enhancing their delivery and bioactivity. By combining. traditional knowledge with modern advancements, this review emphasizes the therapeutic potential of phytoconstituents in AD management. Further research, including rigorous preclinical and clinical trials, is crucial to validate their effectiveness, optimize delivery strategies, and advance neurodegenerative disease treatment. In conclusion, investigating phytoconstituents as complementary treatments to conventional AD medications offers new possibilities in the battle against Alzheimer's disease.

KEYWORDS: Alzheimer's, Phytochemicals, Alternative therapy, Neurodegenerative.

INTRODUCTION

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder affecting people above 65 years. The progressive increase in the severity of the disorder is alarming and current treatments aim to control the progression of the disease. The consequent impact on the afflicted persons and their loved ones is immeasureable. The symptoms of AD were first documented by Aloysius Alzheimer in 1907.[1] AD is a neurodegenerative condition that is distinguished by two primary indicators: the build-up of β-amyloid plaques and the development of neurofibrillary tangles. In a comprehensive survey conducted in Zhejiang province, Eastern China, a group of 2,015 individuals aged 65 years or older underwent examination, revealing prevalence rates of dementia, AD, and vascular dementia that were standardized at 13.0%, 6.9%, and 0.5% respectively.[2] India is not lagging behind in prevalence of AD. **(Fig.1)**

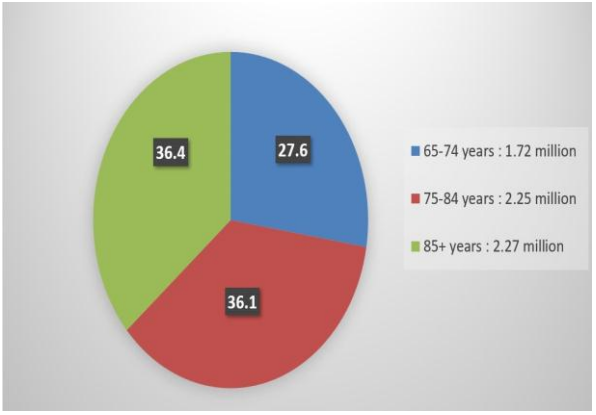

Fig. 1: Alzheimer's disease in india.

AD presents clinical features such as cognitive decline, memory loss, behavioural and emotional changes, loss of motor coordination, and psychological impairments **(Fig.2).** It is a progressive condition marked by cognitive impairment, memory loss, personality changes, and behavioural alterations.

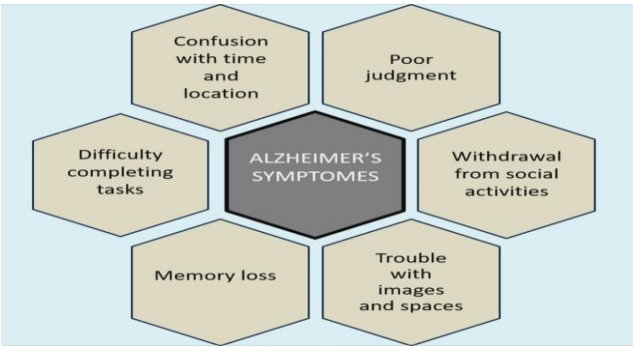

Fig. 2: Symptoms of AD.

The primary hypotheses explaining the neurodegeneration and neurological impairments in AD involve the deposition of cytotoxic β-amyloid plaques and the abnormal processing and hyperphosphorylation of tau protein, which are the pathological hallmarks of AD. These plaques and tangles may lead to oxidative stress, inflammation, synaptic failure, neuronal apoptosis (particularly in cholinergic neurons of the basal forebrain, hippocampus, and cortex), and brain atrophy].**(Fig.3).**[3]

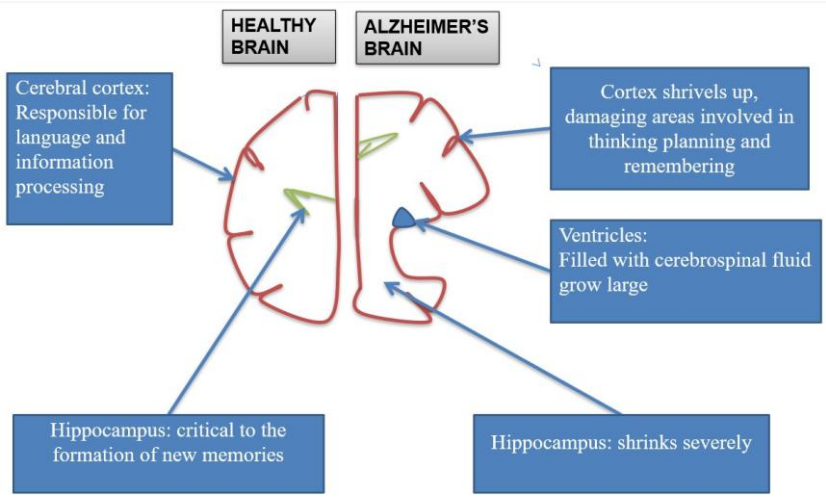

Fig. 3: Brain damage in AD.

These mechanisms can interact and create cascades of pathological changes, involving various protein signalling pathways and gene regulation pathways.[4] Diet plays a significant role in AD, with the Mediterranean diet being particularly noteworthy. This diet consists of high consumption of vegetables, fruits, legumes, fish, cereals, and unsaturated fats, particularly olive oil. The Mediterranean diet has been found to reduce the risk of neurodegenerative diseases. It involves consuming natural plant-based foods, emphasizing green leafy vegetables, while decreasing the intake of animal-based foods high in saturated fats.[5] Moreover, the prevalence of AD is expected to rise significantly in the coming years. Currently, there are approximately 35 million people worldwide suffering from AD and dementia, and this number may reach around 65 million by 2030 and multiply further to 106.2 million by 2050. Several factors, including reduced physical activity, infections, smoking, and the prevalence of diseases like obesity and diabetes, pose a threat to the emergence of AD.[6]

Conventional treatment modalities

Current treatments focus on symptomatic relief which is temporary. There is a high demand for discovery of novel therapeutic agents and treatment modalities. Transcranial magnetic

stimulation has been used as an imaging technique to understand the neurological and cortical functions. Non pharmacological techniques like physical activity and music therapy have also yielded good results in improving the quality of life. Conventional therapeutic agents have undesirable side effects which have led scientists to explore phytoconsitutents for therapy. The following is an overview of US-FDA approved medications used for the treatment of AD.

1. **Donepezil:** Donepezil is a cholinesterase inhibitor that helps to reduce the severity of AD symptoms at various stages (mild, moderate, and severe) by preventing the breakdown of acetylcholine in the brain. Common potential side effects include nausea, vomiting, diarrhoea, insomnia, muscle cramps, fatigue, and weight loss. It is taken orally once a day in the form of a dissolvable tablet.[7]

2. **Rivastigmine:** Rivastigmine is a cholinesterase inhibitor that prevents the degradation of acetylcholine and butyrylcholine (a similar molecule) in the brain, thus treating AD in its mild, moderate, and severe forms. Possible side effects may include weight loss, indigestion, decreased appetite, anorexia, muscle weakness, nausea, vomiting, and diarrhoea. It can be administered orally as a twice-daily tablet or through a daily replacement skin patch.[8]

3. **Galantamine:** Galantamine is a cholinesterase inhibitor that is used for mild to moderate AD. It works by preventing the breakdown of acetylcholine and stimulating nicotinic receptors to release more acetylcholine in the brain. Common side effects may include nausea, vomiting, diarrhoea, decreased appetite, weight loss, dizziness, and headache. Galantamine is available in extended-release capsules, tablets, or liquid forms. The extended-release capsule is taken once a day, while the tablet and oral solution are taken twice a day.[9]

4. **Memantine:** Memantine is a medication used to treat moderate to severe AD by blocking the harmful effects caused by excessive glutamate and regulating its activation. It acts as an NMDA antagonist. Some possible side effects of memantine include dizziness, headaches, diarrhoea, constipation, and confusion. This medication is available in extended-release capsules, tablets, or liquid forms and is taken orally. The extended-release capsule is typically taken once daily, while the tablet and oral solution are also taken once a day.[10]

5. **Memantine and Donepezil** (combination medication): This medication combines memantine, an NMDA antagonist, with donepezil to treat moderate to severe AD. Donepezil prevents the breakdown of acetylcholine in the brain. Possible side effects of this combination medication may include headaches, nausea, vomiting, diarrhoea, dizziness, loss of appetite, and minor bruising (ecchymosis) due to small blood vessel leakage. It is taken orally in the form of an extended-release capsule, once a day.[11]

6. **Aducanumab:** Aducanumab is a disease-modifying immunotherapy used for the treatment of mild cognitive impairment or mild AD. It works by removing abnormal beta-amyloid plaques in the brain, reducing their quantity. Potential side effects of aducanumab may include ARIA (amyloid-related imaging abnormalities), headaches, dizziness, falls, diarrhoea, and confusion. This medication is administered intravenously over one hour every four weeks.[12]

7. **Lecanemab:** Lecanemab is a disease-modifying immunotherapy used to treat mild cognitive impairment or mild AD. Similar to aducanumab, lecanemab works by eliminating abnormal beta-amyloid plaques in the brain, reducing their presence.[13] Potential side effects of lecanemab may include headaches, cough, diarrhoea, nausea, vomiting, fever, chills, body aches, fatigue, high blood pressure, low blood pressure, and low oxygen levels. It is administered intravenously over one hour every two weeks.[14]

Introduction to phytoconstituents

Throughout history, herbs have been widely utilized in traditional treatments to enhance cognitive function and address age-related memory decline. Various studies have highlighted the presence of active components in medicinal plants, which are employed in the management of cognitive disorders and related conditions. Herbal remedies have played a significant role in the progression of medical practices. Numerous studies have explored the utilization of phytoconstituents for treating AD.[15] The objective of this article is to emphasize the potential of herbal remedies in the future management of AD and similar ailments. Herbal remedies offer promising avenues for the discovery and development of drugs, thereby opening up new possibilities for addressing neurodegenerative diseases such as AD. While several phytochemicals have shown efficacy in managing AD, their therapeutic claims are often limited due to low solubility and metabolism. To overcome these limitations, targeted nanocarrier systems have been introduced. This article aims to present both

traditional remedies and the progress made in developing herbal remedies for managing AD.[16]

Table 1: Therapeutic potential of phytoconstituents.[14,15]

Botanical Source	Phytoconstituent	Mechanism of action
Ginkgo biloba	Terpenetrilactones, ginkgolides, fumaric acid	Cell damage in Alzheimers decrease in fluid behaviour of membrane
Salvia officinalis	Oleic acid, cornsole, caffeic acid, rosmarinic acid	Inhibition of acetylcholinesterase
Rosmarinus officinalis	Ursolic acid, betulinic acid	Inhibitor of lipid peroxidation
Curcuma longa	Curcumin, polyphenol	Involves inhibition of articular NF-B, a transcription factor activated in vascular endothelium
Zingiber officinale	Sesquiphellandrene, bisabolene, cineol	Inhibit the synthesis of prostaglandin-PGE2 and B2, act on serotonin receptor
Urticadioica	5-hydroxy tryptamine, fiber, amino acids	Boosting up cholinergic system in the brain
Lepidium meyenii	Phenylalamine, threonine, tyrosine	It provides its antioxidant and AChE inhibitory activities 82
Huperzia serrate	11α-O-acetyllycopodine, huperzine A.	Acetylcholinesterase, inhibitory activity
Terminalia chebula	Chebulinic acid, gallic acid, ethyl gallate	Acetylcholinesterase inhibition
Ganoderma lucidum	Heteropolysaccharides, triterpenoids, ganoderic acid	Neuroprotective effects against oxidative stress-induced neuronal apoptosis

Phytoconstituents against alzheimer's disease

1. Baicalein

Baicalein, a major bioactive flavone found in the root of *Scutellaria baicalensis Georgi*, has long been used in traditional Chinese medicine to treat central nervous system disorders.

Modern pharmacokinetic studies have confirmed its therapeutic potential for AD.[16] Baicalein exhibits various important pharmacological properties, including the reduction of oxidative stress, anti-inflammatory effects, and inhibition of disease aggregation. Recently, studies have demonstrated its neurotrophic and neurogenic actions, along with the molecular mechanisms underlying its neurogenic effects. Baicalein has been shown to mitigate radiation-induced impairment of hippocampal neurogenesis by modulating oxidative stress and enhancing the signalling of brain-derived neurotrophic factor (BDNF).[17]

2. Quercetin

Quercetin, a polyphenolic flavonoid chemically known as 3,3,3,5,7-pentahydroxyflavone, is abundantly found in various vascular plants like onions, tea, coffee, and berries. This natural compound exhibits remarkable pharmacological effects,[18] including anticancer properties, antioxidation, blood pressure reduction, radiation protection, neuroprotection, and inhibition of platelet aggregation and capillary permeability. It's potential in the treatment of neurodegenerative diseases has gained considerable attention.[19] In the context of AD, quercetin has shown therapeutic efficacy in enhancing learning, memory, and cognitive function. Prolonged administration of quercetin has been found to improve cognition and ameliorate mitochondrial dysfunction in individuals with AD.[20] The pathophysiology of AD involves the binding of soluble amyloid-beta oligomers (Aβo), contributing to AD progression, to cellular prion protein (PrPc). At the postsynaptic density (PSD), extracellular Aβo binds to lipid-anchored PrPc, activating intracellular Fyn kinase and disrupting synapses. PrPc interacts with metabotropic glutamate receptor 5 (mGluR5)[21] and cytoplasmic Fyn forms a complex with mGluR5. The Aβo-PrPc-mGluR5 pathway leads to elevated levels of intracellular calcium, as observed in *Xenopus oocytes* and neurons, and is also seen in the presence of extracts from human AD brains. Furthermore, the signalling mediated by Aβo-PrPc-mGluR5 complexes results in the phosphorylation of eukaryotic elongation factor 2 (eEF2) and the loss of dendritic spines.[22]

3. Apigenin derivatives

Plant extracts containing apigenin derivatives have shown promise in the treatment of AD.[23] Apigenin, also known as 4',5,7-trihydroxyflavone, is a yellow crystalline powder classified as a flavone. It acts as the aglycone component in various naturally occurring glycosides. Apigenin, a relatively safe and non-mutagenic flavone compound, is commonly found in fruits, vegetables like cabbage, celery, and bell peppers, as well as medicinal herbs such as

Elsholtzi arugulosa and *Carduus crispus*.[24] Although it is insoluble in water, it can dissolve in organic solvents. Apigenin exhibits a range of pharmacological activities, including anti-inflammatory, anti-toxicant, and anti-cancer properties.[24] AD is characterized by the accumulation of amyloid-β peptides (Aβ), which contribute to disease progression. Apigenin has been shown to protect against Aβ-induced toxicity in rat cerebral microvascular endothelial cells. It achieves this by regulating redox balance and enhancing the barrier function. Additionally, apigenin has the potential to prevent cognitive decline by preserving the function of EF2 (eukaryotic elongation factor 2) and preventing the loss of dendritic spines.[25]

4. Rosmarinic Acid

Lemon balm, scientifically known as *Melissa officinalis*, has a long history of traditional use due to its antioxidant and neuroprotective properties. One of its key components, rosmarinic acid, has demonstrated the ability to scavenge free radicals and prevent cell death.[26] Studies have shown that rosmarinic acid derived from *Rosmarinus officinalis* can stimulate the differentiation of cells and enhance cholinergic activity, mimicking the effects of neurotrophic factors in PC12 cells through the activation of ERK1/2 signalling pathways. Furthermore, rosmarinic acid has been recognized as a potent antioxidant molecule, proven effective both in laboratory experiments and animal models.[27] It has also been investigated as a mediator for copper-induced neurotoxicity. Additionally, studies have compared the pro-neurogenic effects of rosmarinic acid and its active compounds to those of donepezil, a drug used in the treatment of AD, in a mouse model induced by Aβ1-42. Lemon balm extracts, such as its oil, contain various compounds like citronellal, geraniol, geranyl acetate, iso geranial, caryophyllene, caryophyllene oxide, germacrene D, and carvacrol.[28] These compounds have demonstrated neuroprotective effects by protecting against neuronal damage caused by proinflammatory cytokines and suppressing the activity of caspase 3 through the inhibition of hypoxia-inducible factor-1 (HIF-1) expression. In summary, the studies indicate that rosmarinic acid derived from *M. officinalis* and its derivatives play a crucial role in memory enhancement by improving cholinergic activity through various mechanisms.[29]

5. Berberine

Emerging evidence suggests that berberine may offer potential benefits in the context of AD by mitigating the development of extracellular amyloid plaques and intracellular neurofibrillary tangles.[30] Berberine, an isoquinoline alkaloid, is the primary active

component found in *Coptis chinensis*, a plant belonging to the *Ranunculaceae* family. In traditional Chinese medicine, this plant has been utilized to treat skin inflammation, diarrhoea, liver disease, and microbial infections.[31] Several studies using models of neurodegenerative diseases have indicated that berberine possesses multiple neuroprotective effects, including the promotion of neurotrophic factors that aid in safeguarding neuronal health.[32]

6. Diosgenin

Diosgenin is primarily found in plants such as *Dioscorea* species, *Heterosmilax* species, and Trigonella Foenum-graecum. However, it can also be obtained commercially from tubers of various *Dioscorea* species**.** Diosgenin is synthesized from cholesterol through the isoprenoid pathway in several plant species.[33] In Korean traditional medicine, Diosgenin is an important component of *Dioscorea nipponica*, a medicinal plant used for treating diabetes, inflammation, and neurodegenerative diseases. Researchers investigated the effect of an ethanol extract of *D. nipponica* on NGF secretion in a C6 glioma cell line, which contained 17 different fractions.[34] Among the compounds identified were 3,7-dihydroxy-2,4,6-trimethoxy-phenanthrene and diosniposide B. The sapogenins present in the extract demonstrated strong induction of NGF secretion, reduction of NO production, and significant promotion of neurite outgrowth in the N2a cell line. Additionally, studies have shown that diosgenin can induce NGF expression in a mouse model of diabetic neuropathy. This induction led to improved nerve conduction velocity, accompanied by structural changes and stimulation of neural regeneration.[35]

7. Spicatoside A.

Spicatoside A is a compound found in *Liriope platyphylla*, a medicinal plant commonly used in certain regions of Korea. It is known for its powerful effect against sortase enzymes found in gram-positive bacteria and its anti-inflammatory properties. Extracts from *L. platyphylla* contain a steroidal saponin called spicatoside A, which has been shown to have neurotrophic effects. It promotes the growth of neurites in PC12 cells and stimulates the synthesis of nerve growth factor (NGF) in astrocytes through the activation of the TrkA receptor, PI3-kinase, and ERK1/2, which in turn activates CREB—a protein that regulates neuronal function and long-term potentiation (LTP).[36] Recent research indicates that spicatoside A, derived from *L. platyphylla* extract, can increase the levels of brain-derived neurotrophic factor (BDNF) mRNA in mice. This compound has also been found to facilitate recovery from cognitive

impairment.[37] By regulating the secretion of NGF and BDNF, which are two crucial neurotrophins responsible for promoting neuronal survival and playing important functional roles in the central nervous system of individuals with neurodegenerative diseases, Spicatoside A offers potential therapeutic benefits.[38]

8. Oleuropein

Oleuropein, a constituent of the *Oleaceae* family, contains a polyphenolic compound called oleuropein. It is used in traditional therapy and herbal tea preparations. Additionally, oleuropein has been recognized for its role as an epigenetic modulator. In conditions related to memory and learning disorders like AD, abnormal acetylation occurs. This abnormal acetylation involves a significant increase in histone deacetylase 2 ($HDAC_2$), which hampers gene expression at specific sites, including autophagy markers.[39] The Mediterranean diet has long been acknowledged for its positive effects on AD and cognitive impairment. These effects are attributed to various polyphenols found in extra virgin olive oil, including oleuropeinaglycone (OLE). OLE has the ability to induce autophagy, leading to a reduction in aggregated proteins and improved cognitive function *in vivo*.[40]

9. Curcumin

Curcumin, an essential component found in turmeric, a widely used spice in Indian cuisine, possesses significant medicinal properties. It has been utilized in the treatment of various conditions such as diabetes, biliary disorders, cough, and hepatic disorders.[41] Among its many potential mechanisms, curcumin has been suggested to bind to amyloid plaques by inhibiting NF-κβ, thereby reducing the progression of AD.[42] Furthermore, curcumin is believed to reduce levels of TNF-α and caspase while simultaneously increasing Brain-derived neurotrophic factor levels. The mechanisms by which curcumin operates can be summarized as follows: i. Binds to small Aβ species, effectively impeding Aβ aggregation, fibril formation, and self-assembl y of Aβ. ii. It decreases the size of senile plaques and can even reverse the structural changes observed in atrophied dendrites. iii. It destabilizes preformed fibrillar Aβ. By utilizing these mechanisms, curcumin shows potential in combating the pathology of AD.[43]

10. Resveratrol

Resveratrol, a phenolic compound present in grapes, peanuts, wine, and tea, is often referred to as a "miracle" molecule due to its antioxidant and anti-inflammatory properties in relation to neurodegenerative diseases (ND). Extensive research suggests that red wine, which

contains various bioactive molecules like quercetin, myricetin, catechins, and tannins, holds neuroprotective effects.[44] During ND, the activation of glial cells leads to the release of inflammatory cytokines and neurotoxic molecules such as nitric oxide and superoxide.[45] Resveratrol plays a crucial role in protecting neurons by inhibiting glial cell activation.[46] A study demonstrated that administering resveratrol successfully restored cognitive functions in a prepared model.[47] It has also been found to destabilize plaques and prevent their formation. Recent research showed that resveratrol effectively prevented neurotoxicity induced by 6-OHDA by activating SIRT-1, which was otherwise inhibited by a SIRT1 inhibitor.[48]

11. Limonoids

Limonoids are natural compounds that are found in limited quantities in various plants. One such plant, *Meliatoo sendan* from the *Meliaceae* family, contains an abundance of limonoids, which contribute to its bitter taste. Researchers have discovered that the extract derived from this plant can stimulate the growth of neurons in a manner similar to NGF (nerve growth factor), a protein that plays a crucial role in neuronal development.[49] This neuronal growth is facilitated through the activation of ERK (extracellular signal-regulated kinase) and PKA (protein kinase A) pathways.[50] In one study, three specific limonoid compounds (dregeanin DM4, rohituka 3, and trichilia lactone D5) were isolated from the seeds of *Trichilia welwitschii* and investigated. Previous research has shown that these limonoids can enhance neuronal differentiation and growth by increasing the levels of NGF in PC12 rat cells. Despite causing changes in the conformation of tau protein, which is associated with tau pathology, the cytological studies conducted in this research demonstrated that the basic limonoids actually protected cells from death. This dual action of limonoids, inhibiting tau aggregation and disintegrating matured aggregates, suggests their potential as effective molecules in combating tau-related disorders.[51] However, it was observed in this study that inhibiting the PKA pathway, along with ERK, in the PC12 rat cell line hindered the neuronal growth process. The activation of ERKs and PKA by limonoids is critical for promoting neuronal differentiation. Interestingly, the extract derived from *Meliatoo sendan* exhibited greater success in promoting neuronal growth compared to NGF alone.[52] By harnessing the properties of limonoids and their ability to stimulate neuronal growth through ERK and PKA pathways, researchers are exploring their potential as therapeutic agents in addressing tau pathology and related conditions.[53]

CONCLUSION

The conclusion of this review article highlights natural phytochemicals that are commonly used to treat neurodegenerative diseases.[54] These phytochemicals are effective in protecting neurons against damage, and the review provides insight into the various mechanisms by which they offer protection against NDs. While the potential benefits of these compounds have been studied, more comprehensive research is needed to establish their long-term effects and efficacy as therapeutics for neurodegenerative diseases.[55]

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REFERENCES

1. Pervin M, Unno K, Ohishi T, Tanabe H, Miyoshi N, Nakamura Y. Beneficial Effects of Green Tea Catechins on Neurodegenerative Diseases. Molecules, 2018; 29, 23(6): 1297.
2. Zu G, Sun K, Li L, Zu X, Han T, Huang H. Mechanism of quercetin therapeutic targets for Alzheimer disease and type 2 diabetes mellitus. Sci Rep, 2021; 25, 11(1): 22959.
3. Ayaz M, Nawaz A, Naz F, Ullah F, Sadiq A, Islam Z.U. Phytochemicals-based Therapeutics against Alzheimer's Disease: An Update. C.T.M.C., 2022; 22(22): 1811–20.
4. Bakrim S, Aboulaghras S, E.l. Menyiy N, E.l. Omari N, Assaggaf H, Lee L.H., et al. Phytochemical Compounds and Nanoparticles as Phytochemical Delivery Systems for Alzheimer's Disease Management. Molecules, 2022; 19, 27(24): 9043.
5. Vaiserman A, Koliada A, Lushchak O. Neuroinflammation in pathogenesis of Alzheimer's disease: Phytochemicals as potential therapeutics. Mechanisms of Ageing and Development, 2020; 189: 111259.
6. Venkatesan R, Ji E, Kim S.Y. Phytochemicals That Regulate Neurodegenerative Disease by Targeting Neurotrophins: A Comprehensive Review. BioMed Research International, 2015; 2015: 1–22.
7. Birks J.S, Harvey R.J. Donepezil for dementia due to Alzheimer's disease, 2018, 19; (6).
8. Chong L.Y, Grimley Evans J. Rivastigmine for Alzheimer's disease, 2015; 22(9).
9. Razay G, Wilcock G.K. Galantamine in Alzheimer's disease. Expert Review of Neurotherapeutics, 2008; 8(1): 9–17.
10. Atri A, Molinuevo J.L, Lemming O, Wirth Y, Pulte I, Wilkinson D. Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for

combination therapy. Alzheimers Res Ther, 2013; 5(1): 6.

11. Guo J, Wang Z, Liu R, Huang Y, Zhang N, Zhang R. Memantine, Donepezil, Combination Therapy, 2020; 10(11).
12. Tolar M, Abushakra S, Hey JA, Porsteinsson A, Sabbagh M. Aducanumab, gantenerumab, BAN2401, and ALZ-801—the first wave of amyloid-targeting drugs for Alzheimer's disease with potential for near term approval. Alz Res Therapy, 2020; 12(1): 95.
13. Griffin W.S.T, Liu L, Li Y, Mrak R.E, Barger S.W. Interleukin-1 mediates Alzheimer and Lewy body pathologies. J Neuroinflammation, 2006; 3(1): 5.
14. Van Dyck C.H, Swanson C.J, Aisen P, Bateman R.J, Chen C, Gee M, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med, 2023; 5, 388(1): 9–21.
15. Singh A.K, Rai S.N, Maurya A, Mishra G, Awasthi R, Shakya A, et al. Therapeutic Potential of Phytoconstituents in Management of Alzheimer's Disease, 2021; 8, 2021: 1–19.
16. Sharma A, Lee HJ. Loniceracaerulea: An updated account of its phytoconstituents and health-promoting activities. Trends in Food Science & Technology, 2021; 107: 130–49.
17. Li Y, Zhao J, Hölscher C. Therapeutic Potential of Baicalein in Alzheimer's Disease and Parkinson's Disease. CNS Drugs, 2017; 31(8): 639–52.
18. Khan H, Ullah H, Aschner M, Cheang W.S, Akkol EK. Neuroprotective Effects of Quercetin in Alzheimer's Disease. Biomolecules, 2019; 30, 10(1): 59.
19. Moreno L.C.G.E.I, Puerta E, Suárez-Santiago J.E, Santos-Magalhães N.S, Ramirez M.J, Irache J.M. Effect of the oral administration of nanoencapsulatedquercetin on a mouse model of Alzheimer's disease. International Journal of Pharmaceutics, 2017; 517(1–2): 50–7.
20. Albasanz J.L, Dalfó E, Ferrer I, Martín M. Impaired metabotropic glutamate receptor/phospholipase C signaling pathway in the cerebral cortex in Alzheimer's disease and dementia with Lewy bodies correlates with stage of Alzheimer's-disease-related changes. Neurobiology of Disease, 2005; 20(3): 685–93.
21. Rusznyák St, Szent-Györgyi A. Vitamin P: Flavonols as Vitamins. Nature, 1936; 138(3479): 27–27.
22. Zu G, Sun K, Li L, Zu X, Han T, Huang H. Mechanism of quercetin therapeutic targets for Alzheimer disease and type 2 diabetes mellitus. Sci Rep, 2021; 25, 11(1): 22959.
23. Salehi B, Venditti A, Sharifi-Rad M, Kręgiel D, Sharifi-Rad J, Durazzo A, et al. The Therapeutic Potential of Apigenin. IJMS, 2019; 15, 20(6): 1305.
24. Venigalla M, Sonego S, Gyengesi E, Münch G. Curcumin and Apigenin - novel and

promising therapeutics against chronic neuroinflammation in Alzheimer′s disease. Neural Regen Res, 2015; 10(8): 1181.

25. Nabavi SF, Khan H, D'onofrio G, Šamec D, Shirooie S, Dehpour AR, et al. Apigeninas neuroprotective agent: Of mice and men. Pharmacological Research, 2018; 128: 359–65.
26. Mirza F.J, Amber S, Sumera, Hassan D, Ahmed T, Zahid S. Rosmarinic acid and ursolic acid alleviate deficits in cognition, synaptic regulation and adult hippocampal neurogenesis in an Aβ1-42-induced mouse model of Alzheimer's disease. Phytomedicine, 2021; 83: 153490.
27. Stelzmann R.A, Norman Schnitzlein H, Reed Murtagh F. Rosmarinic acid uded in alzheimers diseas, 1995; 8(6): 429–31.
28. Sawda C, Moussa C, Turner R.S. Rosmarinic acid for Alzheimer's disease: Alzheimer's disease. Ann NY Acad Sci, 2017; 1403(1): 142–9.
29. Yi T, Fan L.L, Chen H.L, Zhu G.Y, Suen H.M, Tang Y.N, et al. Comparative analysis of diosgenin in Dioscorea species and related medicinal plants by UPLC-DAD-MS. BMC Biochem, 2014; 15(1): 19.
30. Singh A.K, Singh S.K, Nandi M.K, Mishra G, Maurya A, Rai A, et al. Berberine: A Plant-derived Alkaloid with Therapeutic Potential to Combat Alzheimer's disease. CNSAMC, 2019; 31, 19(3): 154–70
31. Cheng Z, Kang C, Che S, Su J, Sun Q, Ge T, et al. Berberine: A Promising Treatment for Neurodegenerative Diseases. Front Pharmacol, 2022; 20, 13: 845591.
32. Wu Y, Chen Q, Wen B, Wu N, He B, Chen J. Berberine Reduces Aβ42 Deposition and Tau Hyperphosphorylation via Ameliorating Endoplasmic Reticulum Stress. Front Pharmacol, 2021; 19, 12: 640758.
33. Chaudhary S, Chikara S, Sharma M, Chaudhary A, Alam Syed B, Chaudhary P, et al. Elicitation of Diosgenin Production in Trigonellafoenum-graecum (Fenugreek) Seedlings by Methyl Jasmonate. IJMS, 2015; 15, 16(12): 29889–99.
34. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi H.M. Forecasting the global burden of Alzheimer's disease. Alzheimer's & Dementia, 2007; 3(3): 186–91.
35. Tohda C, Urano T, Umezaki M, Nemere I, Kuboyama T. Diosgenin is an exogenous activator of 1,25D3-MARRS/Pdia3/ERp57 and improves Alzheimer's disease pathologies in 5XFAD mice. Sci Rep, 2012; 26, 2(1): 535.
36. Angus W.G.R, Contreras M.L. Aroclor 1254 alters the binding of 125I-labeled nerve growth factor in PC12 cells. Neuroscience Letters, 1995; 191(1–2): 23–6.
37. Ramalingam M, Kim SJ. Pharmacological Activities and Applications of Spicatoside A.

Biomolecules & Therapeutics, 2016; 1, 24(5): 469–74.

38. Kwon G, Lee HE, Lee DH, Woo H, Park SJ, Gao Q, et al. Spicatoside A enhances memory consolidation through the brain-derived neurotrophic factor in mice. Neuroscience Letters, 2014; 572: 58–62.
39. Cordero J.G, García-Escudero R, Avila J, Gargini R, García-Escudero V. Benefit of OleuropeinAglycone for Alzheimer's Disease by Promoting Autophagy. Oxidative Medicine and Cellular Longevity, 2018; 2018: 1–12.
40. Velmurugan B, Rathinasamy B, Lohanathan B, Thiyagarajan V, Weng C.F. Neuroprotective Role of Phytochemicals. Molecules, 2018; 27, 23(10): 2485.
41. Hamaguchi T, Ono K, Yamada M. REVIEW: Curcumin and Alzheimer's Disease: Curcumin and AD. CNS Neuroscience & Therapeutics, 2010; 16(5): 285–97.
42. Chen M, Du ZY, Zheng X, Li DL, Zhou RP, Zhang K. Use of curcumin in diagnosis, prevention, and treatment of Alzheimer's disease. Neural Regen Res, 2018; 13(4): 742.
43. Ringman J, Frautschy S, Cole G, Masterman D, Cummings J. A Potential Role of the Curry Spice Curcumin in Alzheimers Disease. CAR, 2005; 1, 2(2): 131–6.
44. Anekonda TS. Resveratrol—A boon for treating Alzheimer's disease, Brain Research Reviews, 2006; 52(2): 316–26.
45. Kim J, Lee H.J, Lee K.W. Naturally occurring phytochemicals for the prevention of Alzheimer's disease. Journal of Neurochemistry, 2010; 112(6): 1415–30.
46. Ahmed T, Javed S, Javed S, Tariq A, Šamec D, Tejada S, et al. Resveratrol and Alzheimer's Disease: Mechanistic Insights. MolNeurobiol, 2017; 54(4): 2622–35.
47. Karuppagounder SS, Pinto JT, Xu H, Chen HL, Beal MF, Gibson GE. Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease. Neurochemistry International, 2009; 54(2): 111–8.
48. Ma T, Tan MS, Yu JT, Tan L. Resveratrol as a Therapeutic Agent for Alzheimer's Disease. BioMed Research International, 2014; 2014: 1–13.
49. Tang XH, Luo RC, Ye MS, Tang HY, Ma YL, Chen YN, et al. Harpertrioate A, an A,B,D-*seco* -Limonoid with Promising Biological Activity against Alzheimer's Disease from Twigs of *Harrisoniaperforata* (Blanco) Merr. Org Lett, 2021; 15, 23(2): 262–7.
50. Gorantla NV, Das R, Chidambaram H, Dubey T, Mulani FA, Thulasiram HV, et al. Basic Limonoid modulates Chaperone-mediated Proteostasis and dissolve Tau fibrils. Sci Rep, 2020; 4, 10(1): 4023.
51. Moya K.L, Benowitz L.I, Schneider G.E, Allinquant B. The Amyloid Precursor Protein Is Developmentally Regulated and Correlated with Synaptogenesis. Developmental

Biology, 1994; 161(2): 597–603.

52. Sun JB, Jiang N, Lv MY, Wang P, Xu FG, Liang JY, et al. Limonoids from the root bark of Dictamnusangustifolius: potent neuroprotective agents with biometal chelation and halting copper redox cycling properties. RSC Adv, 2015; 5(31): 24750–7.
53. Calfio, Camila et al. 'The Emerging Role of Nutraceuticals and Phytochemicals in the Prevention and Treatment of Alzheimer's Disease', 2020; 1: 33 – 51.
54. Ardura-Fabregat A, Boddeke E.W.G.M, Boza-Serrano A, Brioschi S, Castro-Gomez S, Ceyzériat K, et al. Targeting Neuroinflammation to Treat Alzheimer's Disease. CNS Drugs, 2017; 31(12): 1057–82.
55. Zhong K.L, Chen F, Hong H, Ke X, Lv YG, Tang S.S, et al. New views and possibilities of antidiabetic drugs in treating and/or preventing mild cognitive impairment and Alzheimer's Disease. Metabolic Brain Disease, 2018; 33(4): 1009–18.