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Therapeutic Implication of Herbal Phytoconstituents in Alzheimer's Disease

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ABSTRACT

Introduction: Herbal plants have been widely used in traditional medicines for improving cognitive decline and age-related loss of memory since ancient times. Medicinal plants, it is claimed, contain various active components, and they have a widely used synthetic medication option for treating cognitive and associated issues. Herbal medicines have aided in advancing medicine, and several innovative pharmaceuticals have already developed. For example, much research has backed the use of phytoconstituents in herbal medicines to treat Alzheimer's disease (AD). Progressive memory loss, linguistic difficulties, melancholy, anxiety, mood swings, and psychosis are some of these symptoms.

Objective: A systemic literature review of Bentham, Scopus, PubMed, Medline, and EMBASE (Elsevier) database was carried out to understand the study till March 2021. Conclusion: Although neurofibrillary tangle and cholinergic dysfunction, -amyloid plaquesdevelopment are critical features of AD, it is also linked to oxidative damage, disruption of other neurotransmitters, high levels of AGEs, neuroinflammation, hereditary and environmental variables. On the one hand, because of this complex etiology, responses to routinely used medications like memantine, donepezil, galantamine, and rivastigmine are unpredictable and frequently poor. On the other hand, their nonspecific anti-inflammatory and antioxidant effect and particular cholinesterase inhibitory activity support the use of herbal medications. Herbal drugs are also gaining popularity as a result of their supposed efficacy, safety, and accessibility.

1. Introduction

Alzheimer's disease (AD) is a substantial health concern for persons with the illness and their carers worldwide, with a significant economic impact. It is a typical kind of dementia. It accounts for around 70 percent to 85 percent of all forms of dementia (Singh et al., 2019). AD causes unalterable degeneration and gradual neuronal loss in the hippocampus entorhinal and cortex and various cognitive dysfunctions, such as problems remembering designations, continuing events, and concomitant behavioral dysfunctions such as depression. In addition, motor nerve degeneration happens in advanced stages, resulting in difficulties speaking, swallowing, and walking, leading to the person's death (Singh et al., 2019, Herrup 2015). Reduced physical activity, illness, smoking, and the occurrence of conditions like diabetes and obesity all present a risk to the onset of AD(Ardura-Fabregat et al., 2017). Furthermore, BBB disruption (Zhong et al., 2018), impaired brain metabolism (Zhong et al., 2018), cellular autophagy distress (Friedman et al., 2015), the unsettling effects of calcium homeostasis, increased oxidative stress, increasingly widespread neuroinflammation (Jevtic et al., 2017), and nerve cell death (Sanabria-Castro et al., 2017; Ghosh et al., 2017) are some of the possible mechanism. As a result, AD may be caused by one of the described pathologies. Less than 1% of instances are classed as early-onset AD, a genetic kind of AD, which is a strange sort of AD that most patients have. The mutant amyloid precursor protein (APP) and presenilin-1 (PS-1) and presenilin-2 (PS-2) genes are linked to genetically linked AD. The mutation in PS genes is triggered by a grouping of hereditary and natural factors and recognizing polymorphism in the apolipoprotein E (APOE) gene.

2. Pathophysiology of Alzheimer's Disease

Amyloid plaques and neurofibrillary tangles (NFTs) are the major pathological markers of AD that are usually employed for confirmation diagnosis. Outside neurons, amyloid plaques are mostly made of β-amyloid peptides, produced by incorrect cleavage of APP. NFTs develop inside of neurons, and their main constituent is hyperphosphorylated tau, a protein related to microtubules with a growing number

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of potential functions (figure 1). β-amyloid buildup and neurofibrillary tangles, that frequently start in the mesial temporal lobe, induces breakdown of neurons and synapse, leading to significant atrophy of the affected brain regions. The precise mechanism by which neurofibrillary tangles and β-amyloid peptide harm the brain is unknown. The accumulation of β -amyloid in the brain, based on the amyloid hypothesis, sets off a complicated series of events that cause synapse loss, neuronal cell death, and progressive neurotransmitter shortages, which all contribute to the dementia symptoms. Alzheimer's patients' brains have been revealed to exhibit ongoing inflammation and an immune response. According to several experts, inflammation is the third core pathologic symptom of AD (Kinney et al., 2018). According to the Alzheimer's Association, brain disorders and cardiovascular disease comorbidities are significant pathogenic characteristics of AD. Brain atrophy and neurochemical alterations are two other pathogenic substrates (Yaari & Corey-Bloom, 2007). Reduced cholinergic activity and alterations in glutamate, norepinephrine (NE), serotonin, and biomarkers, are all examples of neurochemical abnormalities (Rapoport & Nelson, 2011). Augmented β-amyloid synthesis and immune system phagocytosis deficiencies and impaired β-amyloid breakdown and clearance contribute to β-amyloid buildup and soluble Amyloid beta-induced Inflammation in AD (Chagas et al., 2012; Mizwicki et al., 2013).

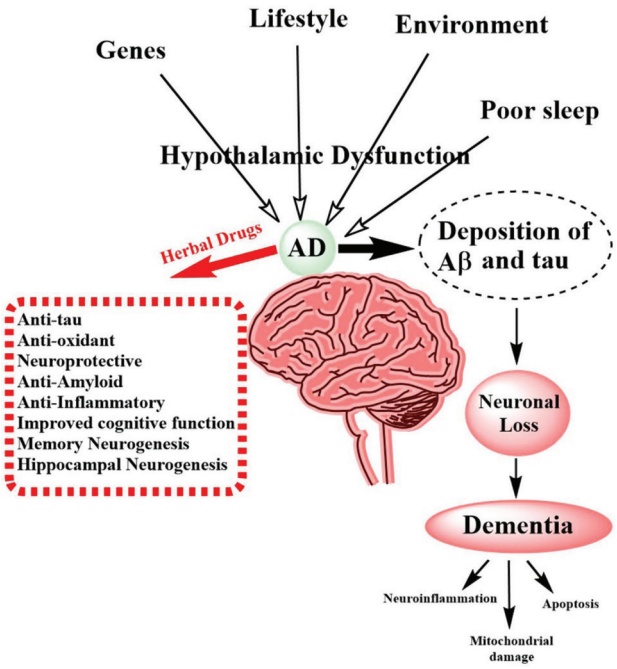

Figure 1: Figure depicting the pathophysiology of Alzheimer's Disease.

3. Herbal Plants Against Alzheimer's Disease

Table 1: Different types of Plant species and their active constituents with a specific mechanism of action.

S.NO.	*PLANT NAME*	ACTIVE CONSTITUENTS	MOA	REFERENCES
1.	*Bacopa monnieri*	D mannitol, Bacoside A, stigmastanol, bacoside, betulinic acid	Improved cognition and decreased cholinergicdegeneration.	(Jayaprakasam et al., 2010)
2.	*Withania somnifera*	Dehydrowithanolide R, Withanolides, withasomidienone, withasomniferin A, withaferinA, withasomniferols A to Cand withanone	Amyloid plaque-induced nerve cell damage is prevented.	(Sancheti et al., 2010; Matsuda et al., 2001)
3.	*Terminalia chebula*	Arjunglucoside I, arjungenin, Gallic acid, Ethyl gallate, Punicalagin, Chebuloside I and II, Chebulinic acid	Inhibition of Acetylcholinesterase.	(Rafii et al., 2011; Wang et al., 2009)
4.	*Huperziaserrata*	Lycoposerramine-H, obscurumine A,11α-O-acetyllycopodine, Lycodine, Serratidine, Huperzine A, Huperzine B, Huperzinine	Acetylcholinesterase (AChE) inhibited.	(Gonzales et al., 2005; Gonzales et al., 2002)
5.	*Lepidium meyenii*	Alkaloids, histidine, Amino acids, Arginine, threonine, Phenylalanine, Glucotropaeolin, Tyrosine, Anthocyanins	Antioxidant and AChE inhibition.	(Safarinejad et al., 2005)
6.	*Urtica dioica*	Acetylcholine, Histamine,,Fat, Fiber, 5-Hydroxytryptamine, Protein	Increasing the cholinergic system in the brain.	(Rhode et al., 2007; Abdel-Aziz et al., 2006; Nievergelt et al., 2010)

7.	*Zingiber officinale*	Zingerone, Shogaols, Gingerols, Farnesene, β-sesquiphellandrene, Bisabolene, Citral, Cineol	Prostaglandin-E2 (PGE2) and thromboxane B2 production are inhibited.	(Tawab et al., 2003; Cho, 2012)
8.	*Curcuma longa*	polyphenol and Curcumin	Inhibits the vascular endothelium-active transcription factor articular NF-κB.	(Henrotin et al., 2010)
9.	*Rosmarinus officinalis*	Rosmarinicacid, Carnosic acid, caffeic acid, Camphor, Ursolicacid, Betulinicacid, Rosmaridiphenol	Inhibition of lipid Peroxidation.	(Katerinopoulos et al., 2005)
10.	*Salvia officinalis*	Borneol, Cineole, chlorogenic acid Thujone, Fumaric acid, Tannic acid, Oleic acid, Nicotinamide, Ursolicacid, Cornsole, Caffeic acid,	Acetylcholinesterase inhibited.	(Spiridonov et al., 2003)
11.	*Ginkgo biloba*	Terpene trilactones, Proanthocyanidins, Alkylphenols, Ginkgolides A, B, C, J and Bilobalide, Polyprenolsbiflavones	Reduced red cell accumulation, increased nitric oxide production, and alienation of platelet-activating factor receptors occur.	(Le Bars et al., 1997)
12.	*Convolvulus pluricaulis*	Convolvine	It improved the memory-boosting effects of arecoline, decreased oxidative stress and AChE activity, and preserved ChAT and Nerve Growth Factor-Tyrosine Kinase A receptor activity to diminish cognitive impairment in Alzheimer's disease (NGF-TrkA)	(Bihaqi et al., 2009)
13.	*Moringa oleifera*	Glucosinolates, Isothiocyanates, Tannins, Polyphenols, Alkaloids, and Saponins	Antioxidant effect	(Sutalangka et al., 2013)
14.	*Eclipta alba*	Coumestans, Alkaloids, Triterpenoid saponins Flavonoids, Sterols, and Volatile oil.	Augmented ACh content reduced MAO-B activity and oxidative stress, anti-inflammatory	(Kim et al., 2008)
15.	*Desmodiumgangeticum*	Alkaloids (tryptamines and phenylethylamines), Phospholipids, Sterols, Pterocarpanoids(gangetin and desmodin), , Flavone andGlycosides	AChE inhibitory, anti-inflammatory, and antioxidant activities.	(Rastogi et al., 2011)
16.	*Evolvulusalsinoides*	Octadecanoic acid, Piperine, Squalene, n-hexadecanoic acid, Ethyl oleate, and Cholesterol	Enhancing memory, correcting neural dysfunctions, and reducing ROCK II expression and oxidative stress.	(Mehla et al., 2012)
17.	*Celastrus paniculatus*	Malkanguniol, Palmitic, Malkangunin, Agarofuran, Polyalcohol A–D and celapnin, oleic, Linoleic, Stearic and Lignoceric acid	Reduced AChE enzyme activity in the frontal cortex, hypothalamus, and hippocampus.	(Lekha et al., 2010)
18.	*Clitoriaternatea*	Taraxerol, Kaempferol, p-coumaric acid, Teraxerone, Ternatins, Delphinidin-3,	Increase in hippocampus acetylcholine content.	(Rai et al., 2002)
19.	*Centella asiatica*	Asiaticosides, Madasiatic acid, Asiatic acid and Madecassoside	A decrease in malondialdehyde and an elevation in glutathione, SOD and catalase levels are indications of antioxidant activity.	(Rao et al., 2005)

4. Herbal Drugs: Issues and Challenges

Herbal medication quality control: Variations in the number of active ingredients might be caused by extraction techniques and processing steps, necessitating quality control of herbal medicines. Herbal medications should assess their macroscopic and microscopic properties for quality control (figure 2). Herb-drug interactions: Combining herbal remedies with prescription medications can have dangerous side effects. Herbal medications have a lot of undisclosed ingredients, which makes determining the nature of interactions difficult.

Furthermore, while herbal medicines are often thought to be harmless because they come from nature, many of them have lately been discovered to have severe pharmacological reactions (Zhou et al., 2007). The herbal drug interaction has also been linked to adverse outcomes in several studies (Zhou et al., 2007; Kennedy&Seely, 2010; Izzo&Ernst, 2009). Drug interactions are also complicated by heterogeneity in dosage and frequency of usage. The enzyme CYP450 is involved in the metabolism of medications used to treat AD. The herbal medication inhibition of CYP450 should be evaluated to predict possible herbal drug interactions. Due to additive cholinergic activity, ginkgo Biloba and donepezil produce an enhanced effect in Alzheimer's disease. Due to the induction of CYP2C19, it induces breakthrough seizures when administered with phenytoin. Curcumin increases celiprolol oral bioavailability by inhibiting CYP450 enzymes and p-glycoprotein in the intestine (Wilson&Maulik, 2018). donepezil and curcumin(reversible cholinesterase inhibitor) coadministration demonstrated a synergistic effect on cognition, oxidative stress (Akinyemi et al., 2017), and good BBB permeability (Yan et al., 2017). More experimental and clinical research is needed to assess the herbal drug interaction. Such interactions can be avoided if patients are informed about their concurrent medications and physicians are aware of them. The older population already compromised drug absorption, metabolism, and elimination. The use of herbal medicines at the same time may exacerbate the impairment.

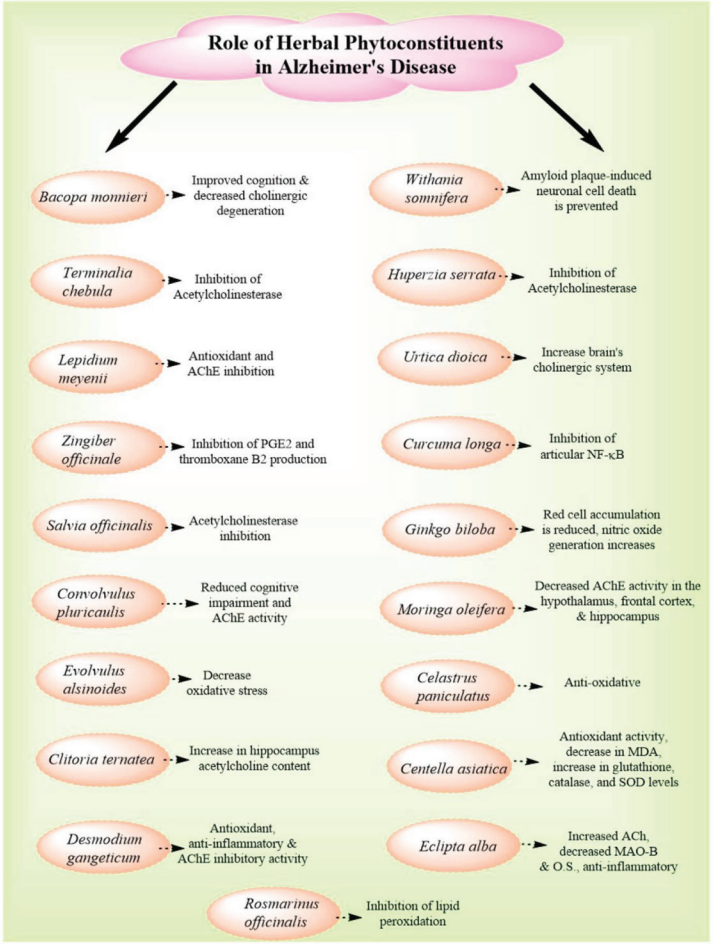

Figure 2: The figure summarizes the herbal phytoconstituents used in Alzheimer's Disease.

Conclusion

Alternative medicine has been practised since the beginning of humanity, and several extracts of herbal combinations and medicinal plantshave shown promise in treating Alzheimer's disease. Due to their wide range of chemical components and ability to interact with a variety of biological targets, medicinal plants are a rich source of potential new drug candidates. However, considerable work is still to be done to turn this possibility into a practical drug. In herbal medication research, standardization of plant extracts is critical. Pharmacologically active phytoconstituents should be extracted, identified, and carefully tested. Multicenter clinical trials should be carried out to confirm the effectiveness of these herbal remedies either used alone or as part of preparations for the treatment of Alzheimer's disease. Herbal treatments are considered to have the potential to create some unique chemicals in the drug development process to treat Alzheimer's disease.

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Conflict of Interest

There is no conflict of interest.

Authorship Contribution

Conceptualization Conceived and Designed the Experiments: Thakur Gurjeet Singh, Heena Khan.
Analyzed the Data: Heena Khan, Thakur Gurjeet Singh.
Wrote the Manuscript: Vivek Rihal, Heena Khan.
Editing of the Manuscript: Thakur Gurjeet Singh.
Critically Reviewed the Article: Amarjot Kaur Grewal, Thakur Gurjeet Singh.
Supervision: Thakur Gurjeet Singh.

References

Abdel-Aziz, H., Windeck, T., Ploch, M., &Verspohl, E. J. (2006). Mode of action of gingerols and shogaols on 5-HT3 receptors: binding studies, cation uptake by the receptor channel and contraction of isolated guinea-pig ileum. *European Journal of Pharmacology*, *530* (1-2), 136-143. https://doi.org/10.1016/j.ejphar.2005.10.049

Akinyemi, A. J., Oboh, G., Oyeleye, S. I., & Ogunsuyi, O. (2017). Anti-amnestic effect of curcumin in combination with donepezil, an anticholinesterase drug: involvement of cholinergic system. *Neurotoxicity Research*, *31*(4), 560-569. https://doi.org/10.1007/s12640-017-9701-5

Ardura-Fabregat, A., Boddeke, E. W. G. M., Boza-Serrano, A., Brioschi, S., Castro-Gomez, S., Ceyzériat, K., & Yang, Y. (2017). Targeting neuroinflammation to treat Alzheimer's disease. *CNS Drugs*, *31*(12), 1057-1082. https://doi.org/10.1007/s40263-017-0483-3

Bihaqi, S. W., Sharma, M., Singh, A. P., &Tiwari, M. (2009). Neuroprotective role of Convolvulus pluricaulis on aluminium induced neurotoxicity in rat brain. *Journal of Ethnopharmacology*, *124*(3), 409-415. https://doi.org/10.1016/j.jep.2009.05.038

Chagas, C. E., Borges, M. C., Martini, L. A., & Rogero, M. M. (2012). Focus on vitamin D, Inflammation and type 2 diabetes. *Nutrients*, *4*(1), 52–67. https://doi.org/10.3390/nu4010052

Cho, I. H. (2012). Effects of Panax ginseng in neurodegenerative diseases. *Journal of Ginseng Research*, *36*(4), 342. https://doi.org/10.5142/jgr.2012.36.4.342

Friedman, L. G., Qureshi, Y. H., & Yu, W. H. (2015). Promoting autophagic clearance: viable therapeutic targets in Alzheimer's disease. *Neurotherapeutics*, *12*(1), 94-108. https://doi.org/10.1007/s13311-014-0320-z

Ghosh, A., Chen, F., Wu, F., Tang, S. S., Hu, M., Long, Y., & Hong, H. (2017). CysLT1R downregulation reverses intracerebroventricular streptozotocin-induced memory impairment via modulation of neuroinflammation in mice. *Progress in Neuro- Psychopharmacology and Biological Psychiatry*, *73*, 19-30. https://doi.org/10.1016/j.pnpbp.2016.10.001

Gonzales, G. F., Córdova, A., Vega, K., Chung, A., Villena, A., Góñez, C., & Castillo, S. (2002). Effect of Lepidiummeyenii (MACA) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. *Andrologia*, *34*(6), 367-372. https://doi.org/10.1046/j.1439-0272.2002.00519.x

Gonzales, G. F., Miranda, S., Nieto, J., Fernández, G., Yucra, S., Rubio, J., ... &Gasco, M. (2005). Red maca (Lepidiummeyenii) reduced prostate size in rats. *Reproductive Biology and Endocrinology*, *3*(1), 1-16. https://doi.org/10.1186/1477-7827-3-1

Henrotin, Y., Clutterbuck, A. L., Allaway, D., Lodwig, E. M., Harris, P., Mathy-Hartert, M., & Mobasheri, A. (2010). Biological actions of curcumin on articular chondrocytes. *Osteoarthritis and Cartilage*, *18*(2), 141-149. https://doi.org/10.1016/j.joca.2009.10.002

Herrup, K. (2015). The case for rejecting the amyloid cascade hypothesis. *Nature Neuroscience*, *18*(6), 794-799. https://doi.org/10.1038/nn.4017

Izzo, A. A., & Ernst, E. (2001). Interactions between herbal medicines and prescribed drugs. *Drugs*, *61*(15), 2163-2175. https://doi.org/10.2165/00003495-200161150-00002

Jayaprakasam, B., Padmanabhan, K., & Nair, M. G. (2010). Withanamides in Withania somnifera fruit protect PC- 12 cells from β-amyloid responsible for Alzheimer's disease. *Phytotherapy Research*, *24*(6), 859-863. https://doi.org/10.1002/ptr.3033

Jevtic, S., Sengar, A. S., Salter, M. W., & McLaurin, J. (2017). The role of the immune system in Alzheimer disease: etiology and treatment. *Ageing Research Reviews*, *40*, 84-94. https://doi.org/10.1016/j.arr.2017.08.005

Katerinopoulos, H. E., Pagona, G., Afratis, A., Stratigakis, N., & Roditakis, N. (2005). Composition and insect attracting activity of the essential oil of Rosmarinus officinalis. *Journal of Chemical Ecology*, *31*(1), 111-122. https://doi.org/10.1007/s10886-005-0978-0

Kennedy, D. A., & Seely, D. (2010). Clinically based evidence of drug–herb interactions: a systematic review. *Expert Opinion on Drug Safety*, *9*(1), 79-124. https://doi.org/10.1517/14740330903405593

Kim, D. I., Lee, S. H., Choi, J. H., Lillehoj, H. S., Yu, M. H., & Lee, G. S. (2008). The butanol fraction of Ecliptaprostrata (Linn) effectively reduces serum lipid levels and improves antioxidant activities in CD rats. *Nutrition Research*, *28*(8), 550-554. https://doi.org/10.1016/j.nutres.2008.05.003

Kinney, J. W., Bemiller, S. M., Murtishaw, A. S., Leisgang, A. M., Salazar, A. M., & Lamb, B. T. (2018). Inflammation as a central mechanism in Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *4*, 575-590. https://doi.org/10.1016/j.trci.2018.06.014

Le Bars, P. L., Katz, M. M., Berman, N., Itil, T. M., Freedman, A. M., &Schatzberg, A. F. (1997). A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. *Jama*, *278*(16), 1327-1332. https://doi.org/10.1001/jama.278.16.1327

Lekha, G., Kumar, B. P., Rao, S. N., Arockiasamy, I., & Mohan, K. (2010). Cognitive enhancement and Neuroprotective effect of Celastrus paniculatus Willd. seed oil (Jyothismati oil) on male Wistar rats. *Journal of Pharmaceutical Science and Technology*, *2*(2), 130-138.

Matsuda, H., Murakami, T., Kishi, A., & Yoshikawa, M. (2001). Structures of withanosides I, II, III, IV, V, VI, and VII, new withanolide glycosides, from the roots of Indian Withania somnifera DUNAL. and inhibitory activity for tachyphylaxis to clonidine in isolated guinea-pig ileum. *Bioorganic & Medicinal Chemistry*, *9*(6), 1499-1507. https://doi.org/10.1016/S0968-0896(01)00024-4

Mehla, J., Pahuja, M., Dethe, S. M., Agarwal, A., & Gupta, Y. K. (2012). Amelioration of intracerebroventricular streptozotocin induced cognitive impairment by Evolvulusalsinoides in rats: in vitro and in vivo evidence. *Neurochemistry International*, *61*(7), 1052-1064. https://doi.org/10.1016/j.neuint.2012.07.022

Mizwicki, M. T., Liu, G., Fiala, M., Magpantay, L., Sayre, J., Siani, A., & Teplow, D. B. (2013). 1α, 25-dihydroxyvitamin D 3 and resolvin D1 retune the balance between amyloid-β phagocytosis and Inflammation in Alzheimer's disease patients. *Journal of Alzheimer's Disease*, *34*(1), 155-170. https://doi.org/10.3233/JAD-121735

Nievergelt, A., Huonker, P., Schoop, R., Altmann, K. H., &Gertsch, J. (2010). Identification of serotonin 5-HT1A receptor partial agonists in ginger. *Bioorganic & Medicinal Chemistry*, *18*(9), 3345-3351. https://doi.org/10.1016/j.bmc.2010.02.062

Rafii, M. S., Walsh, S., Little, J. T., Behan, K., Reynolds, B., Ward, C., & Aisen, P. S. (2011). A phase II trial of huperzine A in mild to moderate Alzheimer disease. *Neurology*, *76*(16), 1389-1394. https://doi.org/10.1212/WNL.0b013e318216eb7b

Rai, K. S., Murthy, K. D., Karanth, K. S., Nalini, K., Rao, M. S., & Srinivasan, K. K. (2002). Clitoriaternatea root extract enhances acetylcholine content in rat hippocampus. *Fitoterapia*, *73*(7-8), 685-689. https://doi.org/10.1016/S0367-326X(02)00249-6

Rao, S. B., Chetana, M., & Devi, P. U. (2005). Centella asiatica treatment during postnatal period enhances learning and memory in mice. *Physiology & Behavior*, *86*(4), 449-457. https://doi.org/10.1016/j.physbeh.2005.07.019

Rapoport, S. I., & Nelson, P. T. (2011). Biomarkers and evolution in Alzheimer disease. *Progress in Neurobiology*, *95*(4), 510-513. https://doi.org/10.1016/j.pneurobio.2011.07.006

Rastogi, S., Pandey, M. M., & Rawat, A. K. S. (2011). An ethnomedicinal, phytochemical and pharmacological profile of Desmodiumgangeticum (L.) DC. and Desmodiumadscendens (Sw.) DC. *Journal of Ethnopharmacology*, *136*(2), 283-296. https://doi.org/10.1016/j.jep.2011.04.031

Rhode, J., Fogoros, S., Zick, S., Wahl, H., Griffith, K. A., Huang, J., & Liu, J. R. (2007). Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells. *BMC complementary and Alternative Medicine*, *7*(1), 1-9. https://doi.org/10.1186/1472-6882-7-44

Safarinejad, M. R. (2005). Urtica dioica for treatment of benign prostatic hyperplasia: a prospective,

randomized, double-blind, placebo-controlled, crossover study. *Journal of Herbal Pharmacotherapy*, *5*(4), 1-11. https://doi.org/10.1080/J157v05n04_01

Sanabria-Castro, A., Alvarado-Echeverría, I., & Monge-Bonilla, C. (2017). Molecular pathogenesis of Alzheimer's disease: an update. *Annals of Neurosciences*, *24*(1), 46-54. https://doi.org/10.1159/000464422

Sancheti, S., Um, B. H., & Seo, S. Y. (2010). 1, 2, 3, 4, 6-penta-O-galloyl-β-D-glucose: A cholinesterase inhibitor from Terminalia chebula. *South African Journal of Botany*, *76*(2), 285-288. https://doi.org/10.1016/j.sajb.2009.11.006

Singh, A. K., Mishra, G., Maurya, A., Awasthi, R., Kumari, K., Thakur, A., & Singh, S. K. (2019). Role of TREM2 in Alzheimer's Disease and its Consequences on β-Amyloid, Tau and Neurofibrillary Tangles. *Current Alzheimer Research*, *16*(13), 1216-1229. https://doi.org/10.2174/1567205016666190903102822

Spiridonov, N. A., Arkhipov, V. V., Foigel, A. G., Shipulina, L. D., &Fomkina, M. G. (2003). Protonophoric and uncoupling activity of royleanones from Salvia officinalis and euvimals from Eucalyptus viminalis. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *17*(10), 1228-1230. https://doi.org/10.1002/ptr.1403

Sutalangka, C., Wattanathorn, J., Muchimapura, S., & Thukham-mee, W. (2013). Moringa oleifera mitigates memory impairment and neurodegeneration in animal model of age-related dementia. *Oxidative Medicine And Cellular Longevity, 2013,* Article ID 695936. https://doi.org/10.1155/2013/695936

Tawab, M. A., Bahr, U., Karas, M., Wurglics, M., & Schubert-Zsilavecz, M. (2003). Degradation of ginsenosides in humans after oral administration. *Drug Metabolism And Disposition*, *31*(8), 1065-1071. https://doi.org/10.1124/dmd.31.8.1065

Wang, B. S., Wang, H., Wei, Z. H., Song, Y. Y., Zhang, L., & Chen, H. Z. (2009). Efficacy and safety of natural acetylcholinesterase inhibitor huperzine A in the treatment of Alzheimer's disease: an updated meta-analysis. *Journal of Neural Transmission*, *116*(4), 457-465. https://doi.org/10.1007/s00702-009-0189-x

Wilson, V., & Maulik, S. K. (2018). Herb-drug interactions in neurological disorders: a critical appraisal. *Current drug metabolism*, *19*(5), 443-453. https://doi.org/10.2174/1389200218666171031123738

Yaari, R., & Corey-Bloom, J. (2007). Alzheimer's disease. *Seminars in Neurology*, *27*(1), 32–41. https://doi.org/10.1055/s-2006-956753

Yan, J., Hu, J., Liu, A., He, L., Li, X., & Wei, H. (2017). Design, synthesis, and evaluation of multitarget-directed ligands against Alzheimer's disease based on the fusion of donepezil and curcumin. *Bioorganic & medicinal chemistry*, *25*(12), 2946-2955. https://doi.org/10.1016/j.bmc.2017.02.048

Zhong, K. L., Chen, F., Hong, H., Ke, X., Lv, Y. G., Tang, S. S., & Zhu, Y. B. (2018). New views and possibilities of antidiabetic drugs in treating and/or preventing mild cognitive impairment and Alzheimer's Disease. *Metabolic brain disease*, *33*(4), 1009-1018. https://doi.org/10.1007/s11011-018-0227-1

Zhou, S. F., Zhou, Z. W., Li, C. G., Chen, X., Yu, X., Xue, C. C., & Herington, A. (2007). Identification of drugs that interact with herbs in drug development. *Drug Discovery Today*, *12*(15-16), 664-673. https://doi.org/10.1016/j.drudis.2007.06.004

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