MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Open Access Journal of Pharmaceutical Research
ISSN: 2574-7797

Perspectives for Treating Alzheimer's Disease: A Review on Indigeous Plants for Alzheimer Disease

Meher PS, Rao J* and Kumar D

Department of Pharmaceutical Chemistry, Poona College of Pharmacy, India

***Corresponding author:** Janhavi R Rao, Vice principal, HOD pharmaceutical Chemistry, Poona College of Pharmacy, Pune, Jijau Masaheb Marg, Rambaug Colony, Erandwane, Pune, Maharashtra 411038, India, Tel: +919822532662; Email: janrao61@gmail.com

Review Article

Volume 5 Issue 2

Received Date: March 19, 2021

Published Date: May 07, 2021

DOI: 10.23880/oajpr-16000237

Abstract

Alzheimer's disease (AD) is one of the most common forms of dementia. The salient pathological hallmarks of AD are extracellular accumulation of amyloid β peptide (Aβ) forming senile plaques (SP), the aggregates of intracellular neurofibrillary tangles (NFTs) and microglial changes in the brain. N-Methyl-D-aspartate receptor (NMDAR), a member of ionotropic glutamate receptor (iGluR), plays an indispensable mantle in maintaining calcium homeostasis and synaptic plasticity. Activation of NMDAR requires co-binding of glycine and glutamate along with postsynaptic depolarization. Upon activation it facilitates the entry of calcium ion into the neurons. The GluN2B subunit of NMDAR has been involved into the direct interaction with Aβ and tau protein and also in the activation of microglia, thus leading to pathophysiology of AD. N-methyl-d-aspartate receptors (NMDARs) mediated excitotoxicity has been implicated in multi-neurodegenerative diseases. Owing to dearth of efficacy and adverse effects of NMDA receptor antagonists, search for herbal remedies acting like salutary agents is a dynamic expanse of investigation to contest neurodegenerative disease. In this review we have delved deep into different NMDA antagonist and their pivotal role in preventing Aβ-mediated synaptic plasticity and their potential role as therapeutic target to curtail AD.

Keywords: Therapeutic TARGET; Excitotoxicity; NMDA Receptor; Medicinal Plants; Alzheimer's Disease

Introduction

Alzheimer disease (AD) is neurodegenerative disease which affect nearly 36 million people today and will goes on increasing up to 131 million by 2050. The most common cause is dementia but other factors like cholinergic dysfunction, amyloid-B (A B) deposits, tau protein aggregation and metal ion disorder are considered in pathology of AD [1]. There are various FDA approved drugs for treatment of disease such as donepezil, rivastigmine and galantamine as ACE inhibitors but having certain side effects bradycardia, excessive salivation, GI disturbance. AD characterize by loss of both short term and long-term memory due to neuronal loss, disorientation, loss of reasoning skills, difficulty in speaking or writing, delusions like symptoms [2].

Due to perturbed synaptic calcium handling leads to over activation of glutamate receptors like N-methyl-D-aspartate receptors (NMDARs). Primary excitatory neuroreceptor in brain is glutamate, acting at ionotropic and metabotropic receptors. The structure of receptor is as shown in figure 1. Subunits of NMDARs are GluN2A and GluN2B, but excitotoxicity in AD is due to extra synaptic GluN2B [3]. For researchers it is an interesting strategy to synthesize GluN2B

antagonists to prevent dysfunction in AD. NMDARS have seven different subunits-GluNI, four distinct GluN2 (GluN2A, GluN2B, GluN2C and GluN2D), pair of GluN3 (GluN3A and GluN3B) respectively. All subunits have common tropology with four discrete domains as extracellular amino-terminal domain (ATD), extracellular ligand-binding domain (LBD), the transmembrane domain (TMD) and intracellular carboxyl-terminal domain (CTD) [4,5].

NMDA receptors are heterotetrametric cation channels. Currently there are eight different splice variants known for the NR1 subunit and NR2 and NR3 subunits are each encoded by families of different genes. The receptor itself has an extracellular N-terminus and can be manipulated by protons or polyamines. The NMDA receptor is permeable to both Na+ and Ca2+, but during the resting state the channel is blocked by Mg2+.

AD pathology basically includes three speculation named as cholinergic, amyloid and tau theory. These speculations depend on the different lacks, commencement of different neurodegenerative systems and event of related unfavorable impacts.

Cholinergic hypothesis is related to depleted level of acetylcholine neurotransmitter. It is because of increased action of acetylcholinesterase, an enzyme responsible for the hydrolytic metabolism of the neurotransmitter acetylcholine into choline and acetate, located in presynaptic vesicles. Increased acetylcholinesterase activity causes reduced level of acetylcholine, accordingly hindered neural transmission which subsequently changes the various physiological responses mainly information-based circuits.

Amyloid theory portrays the collection of amyloid β (Aβ) which at first influences the proficiency and capacity of neurotransmitter and later lead to neuronal misfortune and causes dementia. The arrangement of Aβ is the consecutive endoproteolytic measure which starts with the cleavage of amyloid forerunner protein (Application) at three distinctive locations. The extracellular deposits of Aβ in the grey matter of the brain forms the senile plaques, called as neurite plaques.

Another AD related hypothesis is tau hypothesis. Tau is a microtubule associated protein tau (MAPT) that stimulates tubulin and establishes its assembly in microtubule to facilitate axoplasmic transport and provide the integrity to neuronal network. This protein is predominantly found in neurons which affect the stability of axonal microtubule and contribute in recruitment of the signaling protein and microtubule mediated transport through phosphorylation. Kinases mediated hyperphosphorylation of the tau protein results in self-assembly of tangles which are very well associated with AD pathology.

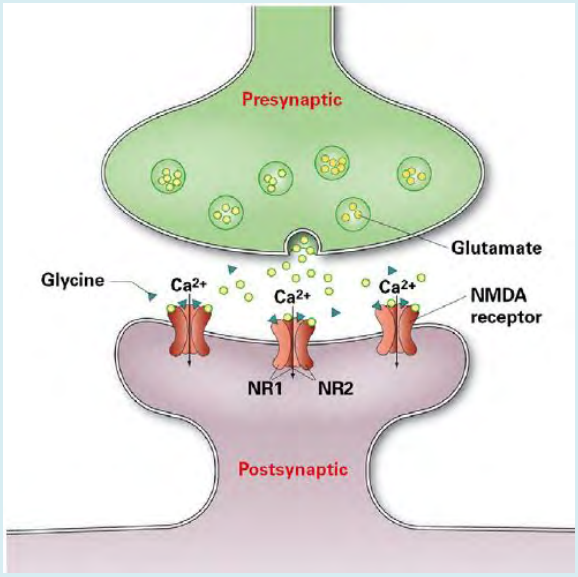


Figure 1: Structure of NMDA receptor.

Symptoms

The side effects of AD get more regrettable with time, in spite of the fact that the pace at which the illness advances is variable. Changes within the brain related to AD commence a long time some time recently any related clinical appearances emerge. The progression of AD happens in three stages, to be specific Early stage (mild AD), Middle stage (moderate AD), Last stage (Severe AD). The symptoms related with each stage are given in (Table 1) [6].

Early stage (mild AD)	Middle stage (moderate AD)	Last stage (Severe AD)
· Functioning independently	· Mood swing	· Loss in movements
· Some memory lapses may be felt	· Slurring of word	· Loss in capability to converse properly
	· Difficulty in expression of thoughts	
	· Acting in an unexpected manner	

Table1: Sstages of AD progression and related symptoms.

Factors for Alzheimer's Disease

Genetic abnormalities cause the AD is rare cases. Specialists accept that Alzheimer's, like other common inveterate infections, creates as a result of multiple factors instead of a single cause. The most prominent chance factors for late-onset Alzheimer's are family history, Age and APOE-e4 gene. Age is the most noteworthy of these three risk components, with the vast larger part of individuals with Alzheimer's dementia being age 65 or more seasoned [7]. A family history of Alzheimer's isn't fundamental for a person to develop the illness [7]. The APOE gene gives the outline for a protein that transports cholesterol within the bloodstream [8]. Everybody inherits one of three forms of the APOE gene—e2, e3 or e4 — from each parent. Having the e4 form increments one's chance of creating Alzheimer's compared with having the e3 form, whereas having the e2 shape may diminish one's chance compared with having the e3 shape [9].

Hereditary variations from the norm that cause Alzheimer disease:

Genetic Mutations

A small percentage of Alzheimer's cases create due to transformations to any of three specific genes. A hereditary change is an unusual alter within the arrangement of chemical sets that make up genes. These changes include the gene for the amyloid precursor protein (APP) and the genes for the presenilin 1 and presenilin 2 proteins. Those acquiring a change to the APP or presenilin 1 genes are ensured to create Alzheimer's. Those acquiring a transformation to the presenilin 2 gene have a 95 percent chance of creating the infection.12.

Down Syndrome

Individuals with down disorder are at high chance of developing a sort of dementia that's either the same as or comparative to that caused by Alzheimer's infection. Researchers are not certain why individuals with down disorder are at higher chance, but it may be related to the extra full or partial duplicate of chromosome 21. This chromosome incorporates a gene that encodes for the generation of APP, which in individuals with Alzheimer's is cut into beta-amyloid parts that go on to construct up into the hallmark amyloid plaques of Alzheimer's.

Treatment

All the existing medications work by directing the levels of certain neuro- transmitters in brain, basically ACh and glutamate. They may be supportive within the cognitive functions, communication skills, maintenance of thinking and may diminish certain behavioural issues to a few percent. A few drugs are being showcased beneath the endorsement of the U.S. Food and Drug Administration (US-FDA) to provide symptomatic relief in AD [10].

Pharmacotherapy of AD

The existing drugs utilized in treatment of AD can be broadly classified as:

a. Acetylcholinesterase inhibitors: Galantamine, Rivastigmine, tacrine, Donepezil.

b. Glutamate inhibitor (NMDA antagonist): Memantine.

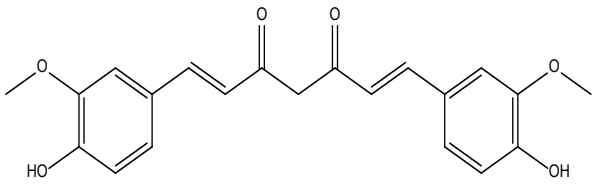
Despite of advancement in knowledge regarding AD pathology and development of specific medicine, the successful disease-preventing / disease-modifying drugs are still lacking. This review suggested that most of the indicated herbs could be utilized in prophylactic mode as well as could be excellent adjunct therapeutic option in treatment of AD patients. Use of herbal drugs is helpful to utilize them in clinics and adapt their traditional and neuro protective effects specifically in AD therapeutics with no or minimal side effects.

Herbal Plants to Treat Alzheimer

The present survey puts together inquire about on different therapeutic plants that have appeared promise in in turning around the Ad pathology. The information concerning report summarizes of Biological, photochemical and clinical application of these various plant gave sufficient information that could be used in drug discovery and development processes, this manner giving unused useful leads for AD. Below we depict the different therapeutic plants that are prescribed for AD.

Turmeric: Curcumin (Curcuma longa - Haldi) belongs to family Zingiberaceae, the source of the spice Turmeric and is used in curries and other spicy dishes from India, Asia and the Middle East. In Ayurvedic medicine it is known as a "cleanser of the body." The process through which AD degrades the nerve cells is believed to involve certain properties: inflammation, oxidative damage and most notably, the formation of beta-amyloid plaques, metal toxicity which reduced by use of turmeric in daily routine of life. Curcumin has a potential role in the prevention and treatment of AD. Because, Curcumin as an antioxidant, anti-inflammatory and lipophilic action improves the cognitive functions in patients with AD. But it is not recommended for persons with biliary tract obstruction because it stimulates bile secretion. And thee lipophilic nature of curcumin, it can cross the blood brain barrier and binds to plaques. Curcumin was a better A-beta 40 aggregation inhibitor and it destabilizes the A-beta polymer. Curcumin helps to reduce inflammation

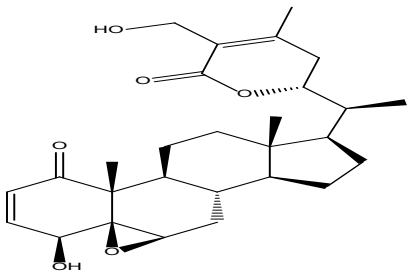
which is one of the symptoms of AD. Curcumin (C21H20O6) or diferuloylmethane (bis-α, β-unsaturated β-diketone) is a hydrophobic polyphenolic compound (mol mass of 368.38) present in turmeric (an ingredient in curry powder) [11,12]. It is a polyphenolic molecule extracted from turmeric, the spice consisting of the powdered rhizome of the plant Curcuma longa Linn. Turmeric contains about 5% curcumin, which gives the spice its yellow color and is used widely as yellow food coloring. It has also a medical history that date back 5000 years. It has been extensively used to treat various ailments for centuries in Ayurveda, the traditional Indian system of medicine, such as arthritis, gastric ulcer, jaundice, fever, liver disease, urinary tract disease, skin disease, and as a "blood purifier. "Turmeric helps remove beta-amyloid that's already built up in the neurons. Turmeric helps maintain healthy brain cellular metabolism, helps the cells repair themselves, and keeps the cells connected to each other. In other words, turmeric helps brain cells stay healthy.



Curcumin

Withania Somniferous: The common name Ashwagandha belonging to family of Solanaceae, its Shrubs play important role in indigenous ayurvedic system. There are 23 different species distributed in dryer parts. The biologically active chemical constituents are alkaloids: (isopelletierine, anaferine), steroidal lactones (withanolides, withaferin's), saponins containing an additional acyl group (sitoindoside VII and VIII), and withanolides with a glucose at carbon 27 (sitoindoside IX and X). WS is also rich in iron. Traditional systems of medicine, such as Ayurveda, offer a knowledge base that can be drawn on to develop novel therapeutic strategies. Withania somnifera (WS), also known as Ashwagandha, is a nootropic agent that promotes cognition, including memory. A semi purified extract of the root of Withania somnifera consisting predominantly of withanolides and withanosides reversed behavioral deficits, plaque pathology, accumulation of β-amyloid peptides (Aβ) and oligomers in the brains. Ashwagandha root contains a large variety of compounds including 12 alkaloids, 40 withanolides, and several sitoindosides and flavonoids.

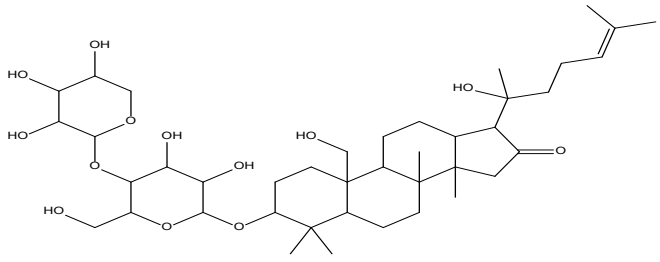
Eextract of Ashwagandha root exhibited a calming effetc. On the central nervous system (CNS) in several mammalian. Neuronal cell death triggered by amyloid plaques was also blocked by withanamides. Ashwagandha has been reported to increase memory and learning. Recent reports have provided exciting information on the ability of this herb to stimulate neurite out growth. Treatment with the methanol extract of Ashwagandha caused neurite outgrowth in a dose- and time-dependent manner in human neuroblastoma cells [13,14].



withaferins

Brahmi: It also known as Bacopa monniera of family Scrophulariaceae. It contains Bacoside A, Bacoside, Betulinic acid, D Mannitol, Stigmastanol, bSitosterol, Stigmasterol as chemical constituents. Bacopa monnieri is a nootropic ayurvedic herb known to be effective in neurological disorders from ancient times. Numerous approaches including natural and synthetic compounds have been applied against Alzheimer's disease. Bacopa monnieri belongs to the family Scrophulariaceae and is found throughout the Indian subcontinent in wet, damp, and marshy areas. It has many branches with small oblong leaves and purple flowers. This plant is not only used for the treatment of a number of nervous system disorders such as insomnia, anxiety, and epilepsy, but also used for enhancing memory.

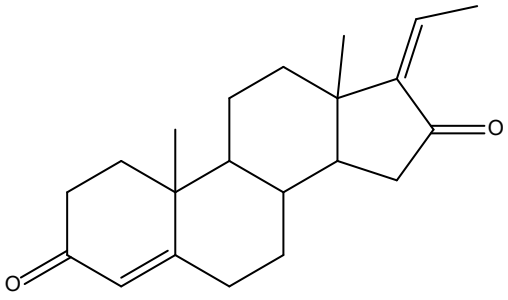
Mechanism of action involves the inhibition of cholinergic degeneration and displayed a cognition-enhancing effect in a rat model of AD. The triterpenoid saponins and their bacosides are responsible for Bacopa's ability to enhance nerve impulse transmission. The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, and restoration of synaptic activity, and ultimately nerve impulse transmission. It is used in the treatment of memory loss, its potential benefit in the treatment of Alzheimer's disease [15,16].



Bacoside A

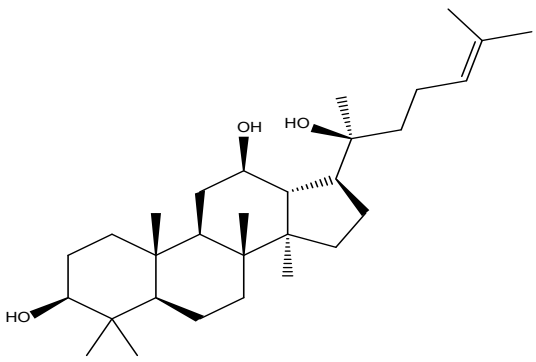
Guggulu: Commiphora mukul (*Burseraceae family)* is useful for treatment of various diseases due to its essential chemical constituents like terpenes, sesquiterpenoids, cuminic aldehyde, eugenol, and the ketone steroids Z-and E guggulsterone, and guggul sterols I, II, and III. It contains ferulic acids, phenols, and other non-phenolic aromatic acids that are potent scavengers of superoxide radicals and could potentially be of importance for the treatment of AD [17]. The main mechanism of action includes Decreased neuronal cholesterol levels, in turn, inhibit the beta-amyloid forming amyloidogenic pathway, possibly by antiacetylcholine esterase activity [18]. It is used as anti-dementia drug, cholesterol-lowering, antioxidant, Alzheimer's disease [19]. Gugguls is an oleogum resin exuding from cracks and fissures or incisions in the bark of several plant species including Commiphora Mukul, Commiphora molmol, Commiphora abyssinica, Commiphora Burseraceae, and Commiphora wightii. It is pale yellow or brown in color with an aromatic odor and bitter astringent taste. guggul preparations contain 30% to 60% water-soluble gum, 20% to 40% alcohol-soluble resins, and about 8% volatile oils, which have many biological activities. Water-soluble extracts of guggul contain mucilage, sugars, and proteins.

Alcohol-soluble extracts of guggul contain commiphoric acids, commiphorinic acid, and heerabomyrrhols. The volatile constituents of guggul include terpenes, sesquiterpenoids, cuminic aldehyde, eugenol, the ketone steroids Z- and E-guggulsterone, and guggulsterols I, II, and III. It is likely that beneficial effects of guggul on AD may be due to its cholesterol-lowering effects. Decreased neuronal cholesterol levels, in turn, inhibit the Aβ-forming amyloidogenic pathway, possibly by removing amyloid precursor protein from cholesterol and sphingolipid-enriched membrane microdomains. These intriguing relationships raise hopes that cholesterol-lowering strategies may influence the progression of dementia associated with AD



guggulsterone

Ginseng: Ginseng is also known as Asian ginseng belong to family Araliaceae. It is obtained from panax ginseng, this plant mostly found in mountains of East Asia. Biological active chemical constituents are saponins, ginsenosides, 20(S)-protopanaxatriol (PPT) and protopanaxadiol (PPD). [20]. Mechanism includes enhancement of the evacuation of Aβ from the neurons and inhibition of accumulation or generation of amyloid beta (Aβ) also carried out intrusion of tau hyperphosphorylation. And this is most effective in treatment of AD [21]. Ginseng (Panax ginseng Meyer) root has been widely used in the far eastern countries such as China, Japan, and Korea for thousands of years as a traditional tonic for longevity. In traditional medicine, ginseng was simply decocted with water and prepared as a drink. Recent studies demonstrated that Panax ginseng extract improves AD symptoms in patients with AD, and the two main components of ginseng might contribute to AD amelioration. Gintonin is a newly identified ginseng constituent that contains lysophosphatidic acids and attenuates AD-related brain neuropathies. Ginsenosides decrease amyloid β-protein (Aβ) formation by inhibiting β- and γ-secretase activity or by activating the nonamyloidogenic pathway, inhibit acetylcholinesterase activity and Aβ-induced neurotoxicity, and decrease Aβ-induced production of reactive oxygen species and neuroinflammatory reactions. Oral administration of ginsenosides increases the expression levels of enzymes involved in acetylcholine synthesis in the brain a Curcumin (C21H20O6) or diferuloylmethane (bis-α, β-unsaturated β-diketone) (Figure 2) is a hydrophobic polyphenolic compound (mol mass of 368.38) present in turmeric (an ingredient in curry powder). alleviates Aβ-induced cholinergic deficits in AD models. Similarly, gintonin inhibits Aβ-induced neurotoxicity and activates the nonamyloidogenic pathway to reduce Aβ formation and to increase acetylcholine and choline acetyltransferase expression in the brain through lysophosphatidic acid receptors. Oral administration of gintonin attenuates brain amyloid plaque deposits, boosting hippocampal cholinergic systems and neurogenesis, thereby ameliorating learning and memory impairments. It also improves cognitive functions in patients with AD. Ginsenosides and gintonin attenuate AD-related neuropathology through multiple routes.



protopanaxadiol (PPD)

Neem: A large number of small molecules have been isolated from Azadirachta indica with varied medicinal applications. The intermediate and final limonoids, nimbin and salannin respectively, isolated from Azadirachta indica, were screened against tau aggregation. The axonal tau and trans-membrane amyloid- are the two majorly effected proteins. And the limonoids from Neem were non-toxic to HEK293T cells thus, substantiating limonoids as a potential lead in overcoming Alzheimer's disease. Limonoids are tetranortriterpenoid class of molecules with large number of biological activities that includes, anti-fungal, anti-bacterial, anti-inflammatory, anticancer, and anti-feedant. Limonoids in presence of nimbin and salanin prevent the formation of -sheet structure in tau. Nimbin and salannin are one of the major constituents of Azadirachta indica, and tauopathy includes cellular toxicity and mitochondrial dysfunction.

Ginco biloba: Ginkgo biloba specific terpenic lactones, i.e. Bilobalide and ginkgolides, could be the CNS function modulating components, and that it could be, pharmacologically, a novel type of so-called 'noo-tropic' agent with cognitive function modulating as well as neuro-protective properties. Ginkgo leaf extracts are useful remedies for coping with several age-related mental health problems of the elderly, including those associated with AD. Bilobalide, a constituent of Ginkgo biloba was successful in inhibiting phospholipid breakdown and choline release under hypoxic conditions. This group has further established that bilobalide also inhibited glutamatergic excitotoxic membrane breakdown both in vitro and in vivo, an effect which may be beneficial in the treatment of brain hypoxia and/or neuronal hyperactivity. Ginkgolides A, B, C and J were also effective blockers of glycine-activated chloride channels. Also showed that bilobalide inhibited an NMDA-induced chloride flux through glycine/GABA-operated channels, thereby preventing NMDA-induced breakdown of membrane phospholipids.

New Drug in the Chain of Clinical Preliminaries

Due to the constrained alternatives for the therapeutic specialists, a few unused molecules have come within the later a long time claiming to have a corrective potential for AD. Right now, there are a few molecules which are beneath the method of clinical trials, some of these (Table 2). Approximately 2085 clinical studies being carried out for AD around the world [22].

Name of entity / under Clinical Trial Phase	Description
AXS-05 / Phase 3	A combination of Bupropion (enhancer of bioavailability of nicotinic cholinergic antagonist, dextromethorphan, norepinephrine and dopamine reuptake inhibitor,) and and serotonin transporters) [23].Dextromethorphan (NMDA receptor antagonist, sigma1receptor antagonist, inhibitor of norepinephrine
ALZ-801 / Phase 1	Amyloid beta-protein inhibitor [24]
Solanezumab / Phase 3	Alfa-Beta inhibitor [25]
Brexpiprazole / Phase 3	Partly dopaminergic agonist [26]
CPC-250 / Phase1	Acetylcholinesterase inhibitor [27]

Table2: Some currently registered entities in clinical trial worldwide for AD [28,29].

Advancement and Breakthroughs

In this work, authors made an endeavour to appear curiously summative survey of the accessible data of the medicinal plants utilized within the treatment of learning and memory impairments.

Applications

This work can be advance connected in pharmaceutical inquire about and it can moreover be assist referenced in tropical biomedicine.

References

1. Muhammad A, Ullah F, Sadiq A, Ok Kim M, Ali T (2019) Editorial: Natural Products-Based Drugs: Potential Therapeutics Against Alzheimer's Disease and Other Neurological Disorders. Front Pharmacol 10: 1417.

2. Elmahdi BZ, Sughir A, Senthil Kumar A (2014) Role Of Medicinal Plants In Neurodegenerative Diseases With Special Emphasis to Alzheimer's 5(6): 454-462.

3. Daniela C, Colotta V, Varano F (2006) Competitive Gly / NMDA Receptor Antagonists Curr Top Med Chem 6(8): 809-821.

4. Liu J, Chang L, Song Y, Li H, Wu Y (2019) The Role of NMDA Receptors in Alzheimer's Disease. Frontiers in Neuroscience 13: 43.

5. Kim D, Stein IS, Brock JA, Castillo PE, Zito K, et al. (2017) Unconventional NMDA Receptor Signaling. Journal of Neuroscience 37(45): 10800-10807.

6. Parul A, Alok S, Fatima A, Singh PP (2015) Herbal Remedies for Neurodegenerative Disorder (Alzheimer's Disease): A Review. IJPSR 4(9): 3328-3340.

7. Alzheimer A (2018) 2018 Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia 14(3): 367-429.

8. Robert CG, Cupples LA, Go R, Benke KS, Edeki T, et al. (2015) Risk of Dementia Among White and African American Relatives of Patients With Alzheimer Disease Robert. JAMA 287(3): 329-336.

9. Robert WM, Rall SC (2000) Apolipoprotein E: Far More than a Lipid Transport Protein. Annual Review of Genomics and Human Genetics 1: 507-537.

10. Abhinav A, Patience AA, Sharma N, Khurana N (2017)The Present and Future of Pharmacotherapy of Alzheimer's Disease: A Comprehensive Review. European Journal of Pharmacology 815: 364-375.

11. Amjad HB, Bazzari FH (2018) Medicinal Plants for Alzheimer's Disease: An Updated Review. Journal of Medicinal Plants Studies 6(2): 81-85.

12. Rammohan RV, Descamps O, John V, Bredesen DE (2012) Ayurvedic Medicinal Plants for Alzheimer ' s Disease : A Review. Alzheimers Res Ther 4(3): 22.

13. Vikas K, Amitabha D, Tatjana M, Mila E, Hadimani MB (2015) Chemistry and Pharmacology of Withania Somnifera: An Update. Tang [Humanitas Medicine] 5(1): 1.1-1.13.

14. Tomoharu K, Tohda C, Komatsu K (2014) Effects of Ashwagandha (Roots of Withania Somnifera) on Neurodegenerative Diseases. Biological and Pharmaceutical Bulletin 37(6): 892-897.

15. Arpita R (2018) Role of Medicinal Plants against Alzheimer's Disease. Int J Complement Alt Med 11(4): 205-208.

16. Vivek Kumar S (2010) Herbal Help in Alzheimer's Type of Cognitive Disorders : A Comprehensive Review. Drug Invention Today 2(7): 320-324.

17. Philippe SO, Wolfe ML, Bloedon LT, Cucchiara AJ, Der Marderosian AH, et al. (2003) Guggulipid for the Treatment of Hypercholesterolemia: a randomized controlled trial. Jama 290(6): 765-772.

18. Tiago BR, Ballesteros P (2007) Journal of Neuroscience Research 85:3244–3253 (2007). Journal of Neuroscience Research 3253: 3244-3253.

19. Eckert GP, Wood WG, Mu WE (2005) Statins: Drugs for Alzheimer's Disease ?. J Neural Transm (Vienna) 112(8): 1057-1071.

20. Zhen Y, Wang JR, Niu T, Gao S, Yin T, et al. (2012) Inhibition of P-Glycoprotein Leads to Improved Oral Bioavailability of Compound K, an Anticancer Metabolite of Red Ginseng Extract Produced by Gut Microflora. Drug Metabolism and Disposition 40(8): 1538-1544.

21. Bruno PI (2008) Therapeutic Potential of Secretase Inhibitors and Modulators. Current Topics in Medicinal Chemistry 8(1): 54-61.

22. Michael DH, Martorell P, Delavande A, Mullen KJ, Langa KM (2013) Monetary Costs of Dementia in the United States. New England Journal of Medicine 368(14): 1326-1334.

23. Alzforum (2017a) Therapeutics. Azeliragon.

24. Bexarotene (2017b) Therapeutics. Bexarotene.

25. Alzheon Preserving Future Memories (2017) Pipeline

26. Lilly (2017) Clinical Development Pipeline.

27. Lundbeck (2017) Pipeline

28. Adis Insight (2017a) CPC 250. Springer International Publ. AG.

29. Cull-Candy S, Brickley S, Farrant V (2001) NMDA Receptor Subunits : Diversity, Development and Disease. Current Opinion in Neurobiology 11(3): 18-20.