EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 6
170-175
Year: 2018

AN OVERVIEW OF TREATMENT FOR ALZHEIMER'S DISEASE

Deepali J. Mane*[1], Dr. Mrs. Vanita Kanase[2] and Mr. Imtiyaz Ansari

[1]Oriental College of Pharmacy, Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai, Maharashtra 400705.
[2]HOD Pharmacology, 1Oriental College of Pharmacy, Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai, Maharashtra 400705.

***Corresponding Author: Deepali J. Mane**
Oriental College of Pharmacy, Sector 2, Behind Sanpada Railway Station, Sanpada West, Navi Mumbai, Maharashtra 400705.

Article Received on 25/03/2018 **Article Revised on 15/04/2018** **Article Accepted on 06/05/2018**

ABSTRACT
Alzheimer's is a type of dementia that causes problems with memory, thinking and behavior. Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks. Alzheimer's is the most common form of dementia, a general term for memory loss and other cognitive abilities serious enough to interfere with daily life. Alzheimer's disease accounts for 60 to 80 percent of dementia cases.

KEYWORDS: Rivastigmine, Donepezil, Glantamine, Memantine, Alternative treatments, herbal drugs.

INTRODUCTION

Alzheimer's disease (AD), also referred to simply as Alzheimer's, is a chronic neurodegenerative disease that usually starts slowly and worsens over time.[1][2] It is the cause of 60% to 70% of cases of dementia.[1][2] The most common early symptom is difficulty in remembering recent events (short-term memory loss).[1] As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care, and behavioural issues.[1][2] As a person's condition declines, they often withdraw from family and society.[1] Gradually, bodily functions are lost, ultimately leading to death.[8] Although the speed of progression can vary, the average life anticipation following diagnosis is three to nine years.[5][6]

The cause of Alzheimer's disease is poorly understood.[1] About 70% of the risk is believed to be genetic with many genes usually involved.[3] Other risk factors include a history of head injuries, depression, or hypertension.[1] The disease process is associated with plaques and tangles in the brain.[3] A probable diagnosis is based on the history of the illness and cognitive testing with medical imaging and blood tests to rule out other possible causes.[4] Initial symptoms are often mistaken for normal ageing.[1] Examination of brain tissue is needed for a definite diagnosis.[3] Mental and physical exercise, and avoiding obesity may decrease the risk of AD; however, evidence to support these recommendations is not strong.[3][10] There are no medications or supplements that decrease risk.[11]

No treatments stop or reverse its progression, though some may temporarily improve symptoms.[2]Affected people increasingly rely on others for assistance, often placing a burden on the caregiver; the pressures can include social, psychological, physical, and economic elements.[12] Exercise programmes may be beneficial with respect to activities of daily living and can potentially improve outcomes.[13] Treatment of behavioural problems or psychosis due to dementia with antipsychotics is common, but not usually recommended, as there is little benefit with an increased risk of early death.[14][15]

In 2015, there were approximately 29.8 million people worldwide with AD.[2] It most often begins in people over 65 years of age, although 4% to 5% of cases are early-onset Alzheimer's which begin before this.[9] It affects about 6% of people 65 years and older.[1]In 2015, dementia resulted in about 1.9 million deaths.[16] It was first described by, and later named after, German psychiatrist and pathologist Alois Alzheimer in 1906.[17] In developed countries, AD is one of the most financially costly diseases.[18][19]

SIGN AND SYMPTOMS

Early

- Memory problems, particularly remembering recent events.
- Increasing confusion.
- Reduced concentration.
- Personality or behaviour changes.
- Apathy and withdrawal or depression.

- Loss of ability to do everyday tasks.

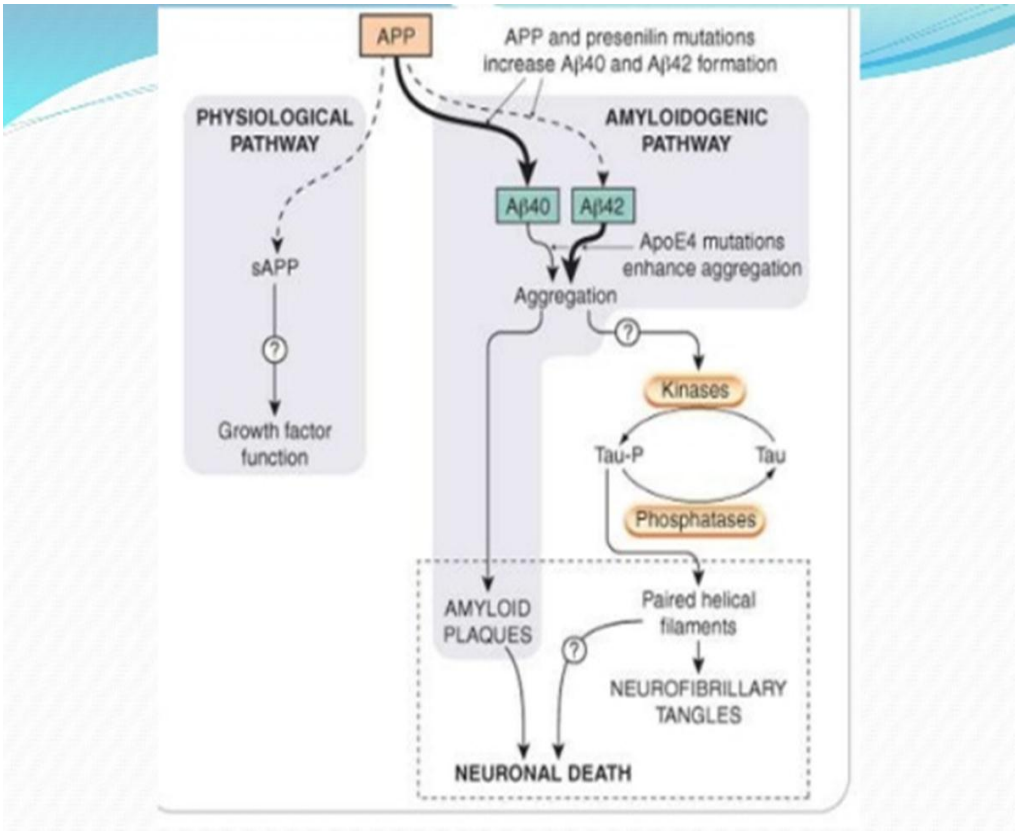
Moderate

- Unable to perform most common activities of daily life.[20]
- Speech difficulties.
- Reading and writing skills are also progressively loss.[20][21]
- Behavioural and neuropsychiatric changes[20]
- Common manifestations are wandering, irritability and labile affect, leading to crying, outbursts of unpremeditated aggression, or resistance to caregiving
- Urinary incontinence can develop.[20]

Advanced

- The patient is completely dependent upon caregivers
- complete loss of speech.
- apathy and exhaustion.[20]

MECHANISM



Tau hypothesis

The hypothesis that tau is the primary causative factor has long been grounded in the observation that deposition of amyloid plaques.[24] A mechanism for neurotoxicity has been proposed based on the loss of microtubule-stabilizing tau protein that leads to the degradation of the cytoskeleton.[25] However, consensus has not been reached on whether tau hyperphosphorylation precedes or is caused by the formation of the abnormal helical filament aggregates.[27] Support for the tau hypothesis also derives from the existence of other diseases known as tauopathies in which the same protein is identifiably misfolded.[26] However, a majority of researchers support the alternative hypothesis that amyloid is the primary causative agent.

Amyloid hypothesis

In 1991, the amyloid hypothesis postulated that extracellular amyloid beta (Aβ) deposits are the fundamental cause of the disease.[28][29] Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit at least the earliest symptoms of AD by 40 years of age.[30][31] Also, a specific isoform of apolipoprotein, APOE4, is a major genetic risk factor for AD. While apolipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE4), leading to excess amyloid buildup in the brain.[32] These toxic oligomers, also referred to as amyloid-derived diffusible ligands (ADDLs), bind to a surface receptor on neurons and change the structure of the synapse, thereby disrupting neuronal communication.[33] One receptor for Aβ oligomers may be the prion protein, the same protein that has been linked to mad cow disease and the related human condition, Creutzfeldt–Jakob disease, thus potentially linking the underlying mechanism of these

neurodegenerative disorders with that of Alzheimer's disease.[34]

In 2009, this theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal connections in the brain in the fast-growth phase of early life may be triggered by ageing-related processes in later life to cause the neuronal withering of Alzheimer's disease.[35] N-APP, a fragment of APP from the peptide's N-terminus, is adjacent to beta-amyloid and is cleaved from APP by one of the same enzymes. N-APP triggers the self-destruct pathway by binding to a neuronal receptor called death receptor 6 (DR6, also known as TNFRSF21).[35] DR6 is highly expressed in the human brain regions most affected by Alzheimer's, so it is possible that the N-APP/DR6 pathway might be hijacked in the ageing brain to cause damage.

ALREADY USED DRUGS

1. Acetylcholine esterase Inhibitors

This drugs are inhibit the AchE enzyme & increase the conectration of Ach in brain.

There is evidence for the efficacy of these medications in mild to moderate Alzheimer's disease,[37][38] and some evidence for their use in the advanced stage.[36] The use of these drugs in mild cognitive impairment has not shown any effect in a delay of the onset of AD.[39] The most common side effects are nausea and vomiting, both of which are linked to cholinergic excess. These side effects arise in approximately 10–20% of users, are mild to moderate in severity, and can be managed by slowly adjusting medication doses.[40] Less common secondary effects include muscle cramps, decreased heart rate (bradycardia), decreased appetite and weight, and increased gastric acid production.[38]

AchE are commonly prescribe

- Donepezil (Aricept) is approved to treat all stages of Alzheimer's.
- Rivastigmine (Exelon) is approved to treat mild to moderate Alzheimer's.
- Galantamine (Razadyne) is approved to treat mild to moderate Alzheimer's.

2. NMDA antagonist

Memantine, the fifth Alzheimer's drug, is an NMDA (N-methyl-D-aspartate) receptor antagonist, which works by regulating the activity of glutamate, an important neurotransmitter in the brain involved in learning and memory. Attachment of glutamate to cell surface "docking sites" called NMDA receptors permits calcium to enter the cell. This process is important for cell signaling, as well as learning and memory. In Alzheimer's disease, however, excess glutamate can be released from damaged cells, leading to chronic overexposure to calcium, which can speed up cell damage. Memantine helps prevent this destructive chain of events by partially blocking the NMDA receptors.

ALTERNATIVE TREATMENTS

- **Caprylic acid (clinically tested as Ketasyn [AC-1202], marketed as a "medical food" called Axona®) and coconut oil.**

Caprylic acid is the active ingredient of Axona, which is marketed as a "medical food." Caprylic acid is a medium-chain triglyceride (fat) produced by processing coconut oil or palm kernel oil. The body breaks down caprylic acid into substances called "ketone bodies." The theory behind Axona is that the ketone bodies derived from caprylic acid may provide an alternative energy source for brain cells that have lost their ability to use glucose (sugar) as a result of Alzheimer's.

Ketasyn was tested in a Phase II clinical study with mild to moderate Alzheimer's.

- **Coenzyme Q10**

Coenzyme Q10, or ubiquinone, is an antioxidant that occurs naturally in the body and is needed for normal cell reactions. This compound has not been studied for its effectiveness in treating Alzheimer's. A synthetic version of this compound, called idebenone, was tested for Alzheimer's disease but did not show any benefit. Little is known about what dosage of coenzyme Q10 is considered safe, and there could be harmful effects if too much is taken.

- **Ginkgo biloba**

Ginkgo biloba is a plant extract containing several compounds that may have positive effects on cells within the brain and the body. Ginkgo biloba is thought to have both antioxidant and anti-inflammatory properties, to protect cell membranes and to regulate neurotransmitter function.

The Ginkgo Evaluation and Memory (GEM) Study enrolled 3,000 individuals age 75 or older who had no signs of dementia or had mild cognitive impairment (MCI). Participants were randomly assigned to receive twice daily doses of either a placebo or 120 milligrams of ginkgo biloba extract. They were followed up every six months for six years.

- **Omega-3 fatty acids**

Omega-3s are a type of polyunsaturated fatty acid (PUFA). Research has linked certain types of omega-3s to a reduced risk of heart disease and stroke. Research has also linked high intake of omega-3s to a possible reduction in risk of dementia or cognitive decline.

- **Tramiprosate (clinically tested as Alzhemed, marketed as a "medical food" called ViviMind™)**

Tramiprosate is a modified form of taurine, an amino acid found naturally in seaweed. Amino acids are the chemical building blocks of proteins. Tramiprosate was

tested in a large Phase 3 clinical study as a possible Alzheimer's treatment.[41]

HERBS

1. Ashwagandha (Withania somnifera)

500 mg/day was more effective.[42] Withanamides A and C bind to the active beta-amyloid (Aβ 25-35) and prevent fibril formation.[43][44] It is used to increase memory and learning.[45] Aqueous extracts of this herb have been found to increase cholinergic activity, including increases in the acetylcholine content and cholineacetyl transferase activity in rats and this might partly explain the cognition-enhancing and memory-improving effects.[46][47]

2. Turmeric (Curcuma longa)

Oral supplementation with up to 4 g/day of curcumin was safe.[51] Curcumin reduced the amount of plaque deposition.[47][48][50] It reduced oxidative damage and reversed the amyloid pathology in an AD.[49][50] Direct injection of curcumin into the brains reduced the plaque levels.[50]

3. Gotu kola (Centella asiatica)

Asiaticoside derivatives, including asiatic acid and asiaticoside, were shown to reduce hydrogen peroxide-induced cell death, decrease free radical concentrations, and inhibit beta-amyloid cell death in vitro.[52]

4. Jyotishmati (Celastrus paniculatus)

Jyotishmati extracts also protected neuronal cells against glutamate-induced toxicity by modulating glutamate receptor function. In addition, the CP extracts protected neuronal cells by virtue of their free radical scavenging properties, reducing lipid peroxidation, and also by their ability to induce the antioxidant enzyme catalase.[68,72-75] In addition, aqueous extracts of CP seed have dose-dependent cholinergic activity, thereby improving memory performance.

5. Jatamansi (Nardostachys jatamansi)

This plant may prove to be useful in restoring memory in older individuals as well as in patients with age-associated dementia.

6. Guggulu

Gugulipid as a potential anti-dementia drug. It also inhibit the beta-amyloid-forming amyloidogenic pathway.[53]

CONCLUSION

In the future, it is anticipated that advances in the fields of molecular biology and genetic engineering will assist in the management of Alzheimer's disease. These new treatments and therapies increases the quality of life of patients.

REFERENCES

1. Burns A, Iliffe S. "Alzheimer's disease". The BMJ, 5 February, 2009; 338: b158. doi:10.1136/bmj.b158. PMID 19196745. (Subscription required (help)).
2. "Dementia Fact sheet N°362". World Health Organization. March 2015. Archived from the original on 18 March 2015. Retrieved 13 January 2016.
3. Ballard C, Gauthier S, Corbett A, et al. "Alzheimer's disease". Lancet, 19 March, 2011; 377(9770): 1019–31. doi:10.1016/S0140-6736(10)61349-9. PMID 21371747.
4. "Dementia diagnosis and assessment" (PDF). National Institute for Health and Care Excellence (NICE). Archived (PDF) from the original on 5 December 2014. Retrieved 30 November 2014.
5. Querfurth HW, LaFerla FM. "Alzheimer's disease". The New England Journal of Medicine, 28 January, 2010; 362(4): 329–44. doi:10.1056/NEJMra0909142. PMID 20107219.
6. Todd S, Barr S, Roberts M, Passmore AP. "Survival in dementia and predictors of mortality: a review". International Journal of Geriatric Psychiatry, November, 2013; 28(11): 1109–24. doi:10.1002/gps.3946. PMID 23526458.
7. Systematic Review of Information and Support Interventions for Caregivers of People with Dementia. BMC Geriatrics, 2007; 7: 18. doi:10.1186/1471-2318-7-18. PMID 17662119.
8. "About Alzheimer's Disease: Symptoms". National Institute on Aging. Archived from the original on 15 January 2012. Retrieved 28 December 2011.
9. Mendez MF. "Early-onset Alzheimer's disease: nonamnestic subtypes and type 2 AD". Archives of Medical Research, November, 2012; 43(8): 677–85. doi:10.1016/j.arcmed.2012.11.009. PMC 3532551 Freely accessible. PMID 23178565.
10. "So, What Can You Do?". National Institute on Aging. 29 July 2016. Archived from the original on 3 April 2017.
11. "More research needed on ways to prevent Alzheimer's, panel finds". National Institute on Aging. 29 August 2006. Archived from the original (PDF) on 28 January 2012. Retrieved 29 February 2008.
12. Systematic Review of Information and Support Interventions for Caregivers of People with Dementia. BMC Geriatrics, 2007; 7: 18. doi:10.1186/1471-2318-7-18. PMID 17662119.
13. Forbes, Dorothy; Forbes, Scott C.; Blake, Catherine M.; Thiessen, Emily J.; Forbes, Sean. "Exercise programs for people with dementia". The Cochrane Database of Systematic Reviews, 2015-04-15; 4: CD006489. doi:10.1002/14651858.CD006489.pub4. ISSN 1469-493X. PMID 25874613.
14. National Institute for Health and Clinical Excellence. "Low-dose antipsychotics in people with dementia". National Institute for Health and Care Excellence (NICE). Archived from the original on 5 December 2014. Retrieved 29 November 2014.

15. "Information for Healthcare Professionals: Conventional Antipsychotics". US Food and Drug Administration. 16 June 2008. Archived from the original on 29 November 2014. Retrieved 29 November 2014.
16. GBD 2015 Mortality and Causes of Death, Collaborators. "Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015". Lancet, 8 October, 2016; 388(10053): 1459–1544. doi:10.1016/S0140-6736(16)31012-1. PMID 27733281.
17. Evolution in the Conceptualization of Dementia and Alzheimer's Disease: Greco-Roman Period to the 1960s. Neurobiology of Aging, 1998; 19(3): 173–89. doi:10.1016/S0197-4580(98)00052-9. PMID 9661992.
18. Impact économique de la démence (English: The Economical Impact of Dementia). Presse Médicale, 2005; 34(1): 35–41. French. doi:10.1016/s0755-4982(05)83882-5. PMID 15685097.
19. Economic Considerations in Alzheimer's Disease. Pharmacotherapy, 1998; 18(2 Pt 2): 68–73. discussion 79–82. doi:10.1002/j.1875-9114.1998.tb03880.x. PMID 9543467.
20. Clinical Features of Alzheimer's Disease. European Archives of Psychiatry and Clinical Neuroscience, 1999; 249(6): 288–90. doi:10.1007/s004060050101. PMID 10653284.
21. Frank EM. Effect of Alzheimer's Disease on Communication Function. Journal of the South Carolina Medical Association, 1994; 90(9): 417–23. PMID 7967534.
22. Sundowning and Circadian Rhythms in Alzheimer's Disease. The American Journal of Psychiatry, 2001; 158(5): 704–11. doi:10.1176/appi.ajp.158.5.704. PMID 11329390.
23. When Home Caregiving Ends: A Longitudinal Study of Outcomes for Caregivers of Relatives with Dementia. Journal of the American Geriatrics Society, 1995; 43(1): 10–16. doi:10.1111/j.1532-5415.1995.tb06235.x. PMID 7806732
24. Schmitz C, Rutten BP, Pielen A, et al. "Hippocampal neuron loss exceeds amyloid plaque load in a transgenic mouse model of Alzheimer's disease". Am. J. Pathol, 1 April, 2004; 164(4): 1495–502. doi:10.1016/S0002-9440(10)63235-X. PMC 1615337 Freely accessible. PMID 15039236.
25. Gray EG, Paula-Barbosa M, Roher A. "Alzheimer's disease: paired helical filaments and cytomembranes". Neuropathol. Appl. Neurobiol, 1987; 13(2): 91–110. doi:10.1111/j.1365-2990.1987.tb00174.x. PMID 3614544.
26. Williams DR. "Tauopathies: classification and clinical update on neurodegenerative diseases associated with microtubule-associated protein tau". Internal medicine journal, 2006; 36(10): 652–60. doi:10.1111/j.1445-5994.2006.01153.x. PMID 16958643.
27. Mudher A, Lovestone S. "Alzheimer's disease-do tauists and baptists finally shake hands?". Trends Neurosci, 2002; 25(1): 22–6. doi:10.1016/S0166-2236(00)02031-2. PMID 11801334
28. Amyloid Deposition as the Central Event in the Aetiology of Alzheimer's Disease. Trends in Pharmacological Sciences, 1991; 12(10): 383–88. doi:10.1016/0165-6147(91)90609-V. PMID 1763432.
29. Alzheimer's disease-do tauists and baptists finally shake hands?. Trends in Neurosciences, 2002; 25(1): 22–26. doi:10.1016/S0166-2236(00)02031-2. PMID 11801334.
30. Alpha- and Beta-secretase Activity as a Function of Age and Beta-amyloid in Down Syndrome and Normal Brain. Neurobiology of Aging, 2007; 28(10): 1493–506. doi:10.1016/j.neurobiolaging.2006.06.023. PMID 16904243.
31. Alzheimer Disease and Down Syndrome: Factors in Pathogenesis. Neurobiology of Aging, 2005; 26(3): 383–89. doi:10.1016/j.neurobiolaging.2004.08.005. PMID 15639317.
32. Apolipoprotein E, Dementia, and Cortical Deposition of Beta-amyloid Protein. The New England Journal of Medicine, 1995; 333(19): 1242–47.
33. Aß Oligomer-Induced Aberrations in Synapse Composition, Shape, and Density Provide a Molecular Basis for Loss of Connectivity in Alzheimer's Disease. The Journal of Neuroscience, 2007; 27(4): 796–807. doi:10.1523/JNEUROSCI.3501-06.2007. PMID 17251419.
34. Cellular Prion Protein Mediates Impairment of Synaptic Plasticity by Amyloid-β Oligomers. Nature, 2009; 457(7233): 1128–32. doi:10.1038/nature07761. PMID 19242475.
35. Nikolaev A. APP Binds DR6 to Cause Axon Pruning and Neuron Death via Distinct Caspases. Nature, 19 February, 2009; 457(7232): 981–89. doi:10.1038/nature07767. PMID 19225519.
36. Donepezil for dementia due to Alzheimer's disease. The Cochrane Database of Systematic Reviews, 25 January, 2006; 1: CD001190. doi:10.1002/14651858.CD001190.pub2. PMID 16437430.
37. Birks, Jacqueline S.; Grimley Evans, John. "Rivastigmine for Alzheimer's disease". The Cochrane Database of Systematic Reviews, 2015-04-10; 4: CD001191. doi:10.1002/14651858.CD001191.pub3. ISSN 1469-493X. PMID 25858345.
38. Birks J. Cholinesterase inhibitors for Alzheimer's disease. The Cochrane Database of Systematic Reviews, 2006; 1: CD005593. doi:10.1002/14651858.CD005593. PMID 16437532.
39. Cholinesterase inhibitors in mild cognitive impairment: a systematic review of randomised trials. PLoS Medicine, 2007; 4(11): e338.

doi:10.1371/journal.pmed.0040338. PMID 18044984.

40. al.], edited by Brian K. Alldredge ... [et (2013). Applied therapeutics : the clinical use of drugs (10th ed.). Baltimore: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2385. ISBN 978-1609137137.
41. https://www.alz.org/alzheimers_disease_treatments.asp
42. Auddy B, Hazra J, Mitra A, Abedon B, Ghosal S. A standardized Withania somnifera extract significantly reduces stress-related parameters in chronically stressed humans: a double-blind randomized, placebo-controlled study. J Am Nutra Assoc, 2008; 11: 50–56.
43. Jayaprakasam B, Padmanabhan K, Nair MG, Phytother Res., Jun, 2010; 24(6): 859-63. Withanamides in Withania somnifera fruit protect PC-12 cells from beta-amyloid responsible for Alzheimer's disease.
44. Kumar S, Harris RJ, Seal CJ, Okello EJ, Phytother Res., Jan, 2012; 26(1): 113-7. An aqueous extract of Withania somnifera root inhibits amyloid β fibril formation in vitro.
45. Tohda C, Kuboyama T, Komatsu K, Neurosignals, 2005; 14(1-2): 34-45. Search for natural products related to regeneration of the neuronal network.
46. Kuboyama T, Tohda C, Zhao J, Nakamura N, Hattori M, Komatsu K, Neuroreport, Oct 7, 2002; 13(14): 1715-20. Axon- or dendrite-predominant outgrowth induced by constituents from Ashwagandha.
47. Begum AN, Jones MR, Lim GP, Morihara T, Kim P, Heath DD, Rock CL, Pruitt MA, Yang F, Hudspeth B, Hu S, Faull KF, Teter B, Cole GM, Frautschy SA. Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. J Pharmacol Exp Ther., 2008; 326: 196–208. doi: 10.1124/jpet.108.137455.
48. Cole GM, Lim GP, Yang F, Teter B, Begum A, Ma Q, Harris-White ME, Frautschy SA. Prevention of Alzheimer's disease: omega-3 fatty acid and phenolic anti-oxidant interventions. Neurobiol Aging, 2005; 26(1): 133–136. [PubMed]
49. Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J Neurosci, 2001; 21: 8370–8377.
50. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem., 2005; 280: 5892–5901.
51. Baum L, Lam CW, Cheung SK, Kwok T, Lui V, Tsoh J, Lam L, Leung V, Hui E, Ng C, Woo J, Chiu HF, Goggins WB, Zee BC, Cheng KF, Fong CY, Wong A, Mok H, Chow MS, Ho PC, Ip SP, Ho CS, Yu XW, Lai CY, Chan MH, Szeto S, Chan IH, Mok V. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. J Clin Psychopharmacol, 2008; 28: 110–113. doi: 10.1097/jcp.0b013e318160862c.
52. Dhanasekaran M, Holcomb LA, Hitt AR, Tharakan B, Porter JW, Young KA, Manyam BV. Centella asiatica extract selectively decreases amyloid beta levels in hippocampus of Alzheimer's disease animal model. Phytother Res., 2009; 23: 14–19. doi: 10.1002/ptr.2405.
53. Rammohan V Rao, Olivier Descamps, Varghese John, and Dale E Bredesen. Ayurvedic medicinal plants for Alzheimer's disease: a review. Alzheimers Res Ther., 2012; 4(3): 22. Published online 2012 Jun 29. doi:10.1186/alzrt125.