

An Overview Pharmacological Approaches and Herbal Intervention for Alzheimer Disease

Sakshi Parjane¹, Vikas Nighot², Tejas Maharse³, Avishkar Pawar⁴, Akshada Suryawanshi⁵

Final Year B. Pharmacy Students, Department of Pharmaceutical Quality Assurance^{1,2,3,4}

Guide, Department of Pharmaceutical Quality Assurance⁵

Shri Swami Samarth Institute of Pharmacy, Malwadi (Bota), MH, India

*Corresponding author: Ms. Parjane Sakshi Rajesh

sakshiparjane67@gmail.com

Abstract: *The most prevalent kind of dementia, Alzheimer's disease (AD), is a progressive neurodegenerative illness that has a major impact on memory and cognitive function. As the condition advances to more advanced stages, it results in behavioral issues like aggression, depression, and verbal and visuospatial impairments. Alzheimer's has no known cure, however symptomatic treatment helps with memory loss and other symptoms. Natural goods provide a therapeutic alternative for many ailments, effectively halting their progression, and alleviating the symptoms of many different types of diseases. Traditionally, memory diseases including dementia and amnesia have been treated with medicinal plants and plant derivatives. Although there is little scientific backing for the claims made in numerous research regarding the effectiveness of plants in treating Alzheimer's disease. However, reports indicate that an early start to usage*

Keywords: Alzheimer's disease, Dementia, Acetylcholine, Memory, Medicinal plants

I. INTRODUCTION

Herbs

Herb is a plant or plant part used for its scent, flavor, or therapeutic properties. Herbal medicines are one type of dietary supplement. Herbs are sold as tablets, capsules, powders, teas, extracts, and fresh Nior dried plants. People use herbal medicines to try to maintain or improve their health. Herbs have been used for thousands of years to add flavour to meals, as medicine and as a preservative.

- Plants with green and tender stems are called herbs.
- They are usually short and have branches that are present uniformly throughout the stem.
- For example: Coriander, Bay leaves, Basil, Tomato plant, etc.

Alzheimer disease –

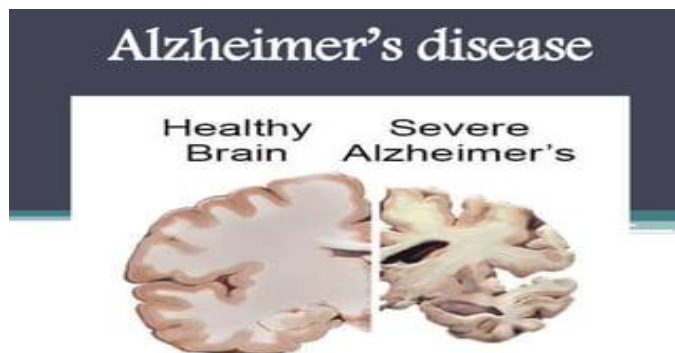
Alzheimer's disease (AD) is the most common cause Of severe mental deterioration (dementia) in the elderly. While Alzheimer's disease was known to run in families on occasion, it was not always assumed that this condition was connected to the more common occurrence of cognitive decline in later life. Alzheimer's disease cases and prevalence increased. As people get older, particularly those who are above 65. The annual incidence of Alzheimer's disease is between 1 and 4 percent of the population; rates peak between the ages of 65 and 70, and for people over 85, they may even exceed 6 percent. Progressive memory loss, a decline in almost all intellectual abilities, heightened apathy, diminished speech function, disorientation, and abnormalities in gait are the hallmarks of this Alzheimer's disease. Even years before they encounter obvious signs like language problems and memory loss, Alzheimer's patients are unable to recognize the changes in their brains.

Even after the illness has been present for at least 20 years, the AD is still undetected. The profound irreversible damage to the brain's neurons connected to thinking, memory, and learning is the cause of the symptoms. As the illness worsens, it begins to damage neurons in other areas of the brain, impairing daily functioning including walking,

swallowing, and sitting up straight, to mention a few. Patients grow bedridden and become dependent on others to perform simple tasks, requiring care around-the-clock, which makes them very weak and finally leads to death.

Stages of Alzheimer disease

1. There are three main phases to the progression of Alzheimer’s disease: 12
2. Preclinical (still without symptoms or indications)
3. Mild cognitive impairment
4. Dementia
5. These three phases can be divided into seven more stages.



Alzheimer Disease

The Differences between normal brain and brain of AD patients

Normal human brain	Alzheimer brain
1.The normal human brain is consists of billions of healthy neurons.	1.The Alzheimer brain consists of injured and dead neurons.
2. Continuous communication between neurons of different parts of the brain and from the brain.	2.Communication process among neurons is distributed with the loss of functions results in cell death.
3.Good capacity to transmit information through electrical and chemical signals.	3.Capacity to transmit information through electrical and chemical signals is substantially lost.
4.In Connection between neurons network are strong.	4.connection between neurons network genrally break.

Herbal Approach for Alzheimer’s Disease

Herbal remedies are regarded as being extremely safe, reasonable, and possibly clinically effective. They may also have interactions between drugs that are synergistic. Ayurveda and Chinese traditional medicine prescribe a variety of medications to treat a range of illnesses. Numerous scholarly investigations have proven the significant function of medicine.

Botanicals in the treatment of nervous system illnesses, memory enhancement, and overall nervous system improvement. Herbal therapy has the potential to improve patients’ quality of life by offering more benefits than current pharmacological treatments for AD, which inevitably include adverse effects. Herbal medications are useful for treating a wide range of illnesses, but they are particularly useful for treating psychiatric and neurological problems where patients are dissatisfied with their present course of treatment and want to make decisions about their care that align with their values and beliefs. Numerous papers and studies point to the novel application of herbal remedies in the management of AD.

Compounds like tannins, lignans, polyphenols, flavonoids, sterols, triterpenes, and alkaloids are found in herbal medications used to treat AD. These compounds may have anti-amyloidogenic, anti-inflammatory, anti-cholinesterase, hypolipidemic, and antioxidant effects.

Herbal Drugs for the Treatment of AD

Many researchers have found that herbal plants can effectively treat dementia and Alzheimer's disease. Herbal medications primarily reduce the signs and symptoms of illness without or with little adverse effects.

Phytochemicals for treating AD

In addition to reporting on the herbal plants, numerous researchers assessed the potency of the active ingredients in these plants in treating AD.

Epidemiology

According to the WHO, there are over 55 million dementia sufferers globally, and approximately 10 million new cases are reported year. According to reports, 51.6 million individuals worldwide—or 0.7% of the total population—have dementia, and by the middle of the century, that number is expected to rise to 152 million. Among all diseases, it ranks as the seventh most common cause of death.

Every five years, there is an almost thirty percent increase in reported instances of AD, according to a World Health Organization (WHO) report. Globally, there has been a sharp rise in the prevalence, incidence, mortality, and disability-adjusted life years (DALYs) associated with AD. Projections show that by 2040, the number of fatalities linked to AD will rise from the current 2.4 million to 5.8 million annually.

Given that AD increases progressively with age, age is a significant prevalence factor. AD affects about 5% of those over 65 and 20% of people over 80, meaning that the prevalence rate doubles every five years. High-income areas like Western Europe exhibit greater incidence than Asia and Africa.

The presented data comes from medical records, it may be misleading. Many developing nations do not record all health issues, particularly those pertaining to dementia among the elderly. Improvements must be made to the search and registration processes for unregistered or underdiagnosed AD patients in order to obtain the maximum amount of accurate data.

II. PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Neurotransmitters are not the only brain and nerve cells that are attacked by Alzheimer's disease.

The destruction of these parts causes clumps of protein to form around the brain's cells. These clumps are known as 'plaques' and 'bundles'. The presence of the 'plaques' and 'bundles' start to destroy more connections between the brain cells, which makes the condition worse.

Numerous factors, including cholinergic dysfunction, amyloid/tau toxicity, and oxidative stress/mitochondrial dysfunctions, are linked to Alzheimer's disease. Patients exhibit inflammation and amyloid plaque deposition due to temporo-frontal brain atrophy and neuronal death. One of the main characteristics of AD is the existence of twisted fiber bundles and an uneven cluster of protein fragments. It raises the number of microglial cells in the parenchyma and monocytes and macrophages in the cerebral cortex.

The hippocampal, amygdala, and entorhinal cortex all lose neurons as a result of AD. Neurons are also lost in the cholinergic basal nucleus and the cortical connection of the frontal, temporal, and parietal cortices and sub-cortical nuclei. The deposited tangles exhibit a distinct pattern that begins in the trans-entorhinal cortex and extends to the entorhinal cortex, the hippocampal CA1 region, and finally the cortical association area, which is the meeting point of the frontal, parietal, and temporal lobes. The quantity of amyloid plaques is less of an indicator of dementia severity than tangle development. Amyloid β deposition and the development of hyperphosphorylated tau proteins are associated with hippocampal shrinkage and cognitive impairment. In addition, AD patients exhibit decreased cholinergic receptor binding in particular brain regions and elevated amounts of redox transition metals in the brain.

Alzheimer's disease symptoms

1. Confusion with time and location.
2. Memory loss.
3. Poor judgement.
4. Difficulty complying familiar tasks.

5. Misplacing items.
6. Difficulty in solving problems.
7. Trouble with images and space.
8. Withdrawal from social activities.
9. Change in mood.
10. Change in vision

Causes of Alzheimer Disease

1. Age
2. Smoking
3. Genetics
4. Diabetes
5. Head injury
6. Depression
7. Obesity
8. High BP and high cholesterol.

Management of AD

At the moment, the following elements of a multifactorial individualized management of AD are being tried:-

Communication

When a patient, doctor, and caregiver communicate openly and honestly, symptoms are typically recognized and confirmed, AD is correctly diagnosed and evaluated, and an appropriate course of action and treatment plan are developed. The effective management and treatment of AD depend on these three parties having open lines of communication.

Caregiver support

Support and care are crucial to the management of AD. Better management and control may come from preparing and teaching people about potential hazards and conditions that may arise from AD getting worse as well as how to handle them. Being aware of and ready for the consequences of Alzheimer's disease-related dementia on expectancies, normal function and behavior, and cognition. Effective care and management may arise from knowing which circumstances can exacerbate the symptoms or provide risks to safety and well-being.

Behavioral approaches

Techniques that improve their mood and aid in management include pleasant and calm conversations, straightforward language, limiting only when safety is at risk, and engaging in enjoyable activities. Frequent physical activity also has positive impacts on symptoms and control of AD. Regular physical activity, scheduled routines, and predictable, basic surroundings can all be very helpful.

Sleep

Sleep disturbance is one of the main causes of AD. Sleep habits may have a direct or indirect impact on AD. Insufficient sleep causes Amyloid- β ($A\beta$) to build up, which in turn causes memory loss and eventually leads to AD. In order to effectively manage and treat AD and reap its therapeutic and prophylactic effects, getting enough sleep is essential.

Depending on the patient's circumstances and the severity of the disease, further alternatives for reducing the symptoms of AD include cognitive behavioral treatment, light therapy, music therapy, exercise, etc.

Challenges in Alzheimer Therapy

AD can proceed from asymptomatic to circumstances with significant impairments. It is difficult to distinguish between preclinical AD symptoms and those of normal aging, which makes diagnosing these diseases difficult. Additionally, the causes of women's comparatively higher incidence of AD remain poorly understood. Numerous uncertainties regarding AD may eventually be resolved by future study.

NSAID use lowers the chance of acquiring AD suggesting that an important focus for AD may be inflammation. However, definitive results have not yet been obtained. It might be because anti-inflammatory medications work on

general targets rather than on particular neuro-inflammatory elements of AD. To investigate the efficacy of addressing inflammation in neurodegeneration, early AD control and therapy of inflammation is required.

More understanding of the intricate characteristics of AD, such as inflammation, mood, metabolic, and behavioral abnormalities, could lead to the development of effective new treatments. Monoclonal antibodies and immunoglobulins are promising novel treatments that are presently being tested. For AD therapy to be successful, earlier intervention with repurposed medications, combination therapy, anti-inflammatory agents, or medications that can change underlying problems may be helpful.

Herbal Approach for Alzheimer's Disease

Since conventional AD medicines are ineffective and have several negative consequences, there is an urgent need for alternative AD treatments that have little or no side effects. Herbal medications are regarded as being incredibly safe, reasonably priced, and maybe clinically effective. They may also interact synergistically with other drugs. Ayurveda and Chinese traditional medicine prescribe a number of medications to address different ailments.

Use Numerous scientific investigations have documented the significant role that medicinal herbs play in improving the nervous system overall, improving memory, and treating neurological illnesses. Herbal treatment for AD appears to offer more benefits than current medication therapies, which inevitably have side effects and lower patient quality of life.

Herbal remedies are useful for treating a wide range of illnesses, but they are particularly useful for mental and neurological conditions if patients are dissatisfied with their present course of therapy and want to make decisions about their care that align with their values and beliefs. Numerous scholarly investigations and records demonstrate the remarkable efficacy of herbal remedies in the management of AD.

Compounds such as tannins, lignans, polyphenols, flavonoids, sterols, triterpenes, and alkaloids are found in herbal medications used to treat AD. These compounds may have anti-amyloidogenic, anti-inflammatory, anti-cholinesterase, hypo-lipidemic, and antioxidant effects.

Limitations of Herbal Drugs

Herbal medications for AD should target many processes, including fibrillation, A β -mediated oxidative stress, neuro-inflammation, and A β generation. Herbal medications have several drawbacks, such as low BBB crossing ability, lack of statistically meaningful clinical efficacy, and liver and other damage at greater concentrations.

Processing restrictions include the inability to get the active components in significant amounts, the impact of erratic environmental conditions on the efficacy of herbal medications, and preparations that are made without strictly adhering to GMP rules.

Clinical trial on Alzheimer diseases based on herbal drugs

In 2016, phase II and III clinical trials examining the effectiveness of Ginkgo biloba extract (GBE) in treating Alzheimer's disease were carried out. Promising findings from the research indicated alterations in the 1.5 T MRI, ADAS-cog electroencephalography P300, and MMSE. Additionally, GBE enhanced everyday functioning, liver, kidney, and neuropsychiatric states, and decreased depression.

In order to determine the efficacy of coconut oil in treating AD patients with mild to moderate symptoms, phase III clinical trials were carried out. Due to its high content of medium-chain fatty acids and medium-chain triglycerides, coconut oil has been shown to significantly reduce AD symptoms.

In order to assess the effectiveness of Salvia officinalis extract, a double blind, randomized, placebo-controlled experiment was conducted in 2003. The Alzheimer's disease assessment scale, or ADAS-cog CDR-SB, was used to measure the outcome. A similar study involving extract of Melissa officinalis was also published. The results demonstrate both medications' substantial therapeutic benefits in treating AD, and in the case of Melissa officinalis, a notable reduction in agitation episodes in AD patients was noted.

Chinese traditional medicine In a randomized, controlled study, Yi-Gan San's efficacy in treating behavioral and psychological symptoms as well as the impact it has on dementia patients' quality of life was assessed. The NPI Barthel Index MMSE (mini-mental state examination scale; NPI, neuropsychiatric) was used to measure the results.

Additionally, a randomized, double-blind, placebo-controlled investigation on the Chinese herbal remedy “Ba Wei Huang Wan” has been carried out. Both studies showed improvements in participants diagnosed with AD more than a year ago.

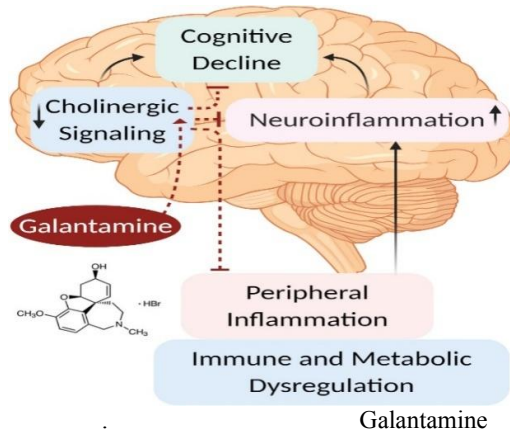
Pharmacological treatment

Agents that block the breakdown of Ach within the synapses are the cornerstone of treatment for AD, despite the fact that no medication has been demonstrated to fully protect neurons.

The only medications that have been approved by the Food and Drug Administration for the treatment of AD are memantine and acetylcholinesterase/cholinesterase inhibitors. Although studies have been done on other medications, including selegiline, vitamin E, estrogen, and anti-inflammatory medicines, their use is still debatable. Ginkgo biloba is among the numerous medications that have been tried to alter the course of AD or alleviate its symptoms. Because it requires frequent laboratory testing and may be harmful to the liver, the cholinesterase inhibitor tacrine is not used very often. While galantamine, rivastigmine, and donepezil have low rates of significant reactions, they frequently cause cholinergic side effects like nausea, vomiting, diarrhea, and anorexia.

Approximately 200 years ago, herbal pharmaceuticals dominated the major pharmacopoeias. Today, many synthetic drugs have their origins in the kingdom of plants. Following the establishment of basic and clinical pharmacology as dominant fields within medicine, herbal medicine experienced a sharp fall. However, herbal therapy continues to be of interest for treating a wide range of illnesses, including neurological and psychiatric conditions. This problem has several causes: 1) They feel that it aligns with their philosophical values and views; 2) they want to have control over their healthcare decisions; and 3) they are dissatisfied with conventional treatment. Numerous scholarly investigations and records suggest that herbal remedies have a special place in the management of AD.

Galantamine



Synonyms–Galantamin, Galantamine, Galanthamine , Galantamine Hydrobromide , Lycoremine , Nivalin.

Biological source-Galantamine is found in various plant sources, mainly from the genera Amaryllis, Lycoris, Hippeastrum, Ungernia, Leucojum, Zephyranthes, Narcissus, Galanthus, Hymeneals’, and Haemanthus and is a naturally occurring alkaloid

Family-Amaryllidaceae

Information

This medication, an alkaloid cholinesterase inhibitor, is a competitive and selective acetyl-cholinesterase inhibitor that was first made from common snowdrops or European daffodils. Additionally, galantamine increases the potency of the presynaptic response to Ach by allosterically altering nicotinic Ach receptors. Galantamine exhibits brain selectivity, similar to donepezil and rivastigmine. Galantamine is metabolized by the same CYP-450 enzymes that break down

donepezil, with a half-life of five to six hours. In clinical trials, galantamine has not been linked to hepatotoxicity. The patients who took galantamine 24 mg/d for six months had better cognition more often than those who received a placebo, and a higher proportion of those who received galantamine showed global improvement, according to pooled data from four randomized studies of patients with moderate AD. This implies that galantamine therapy is beneficial for persons with mild AD

Ginkgo biloba



Ginkgo biloba

Synonyms–Maiden hair tree, kew tree

Biology source–Ginkgo (Ginkgo biloba), deciduous gymnosperm tree .native to china.

Family–Ginkgoaceae.

Information

China has been using ginkgo biloba, a herbal remedy, for thousands of years to treat a wide range of illnesses. Numerous studies have shown that ginkgo biloba extract helps with AD symptoms and slows the disease’s progression. A study including 309 individuals with moderate dementia was conducted. For a maximum of one year, the patients received either 120 mg of Ginkgo biloba extract (GBE) or a placebo daily. When it came to a range of cognitive tests, 27% of Ginkgo biloba users reported moderate improvement at six months. On these exams, just 14% of the placebo group showed improvement.

In an independent study, 120 mg/d of GBE was administered to 112 individuals with chronic cerebral insufficiency. Researchers discovered that using this extract significantly improved blood and oxygen flow. Reduced oxygen and blood supply to the brain could have a significant role in the onset of AD.

Huperzine A



Huperzine A

Synonyms – Huperzine A , selagine.

Biological source – Huperzine A is a naturally occurring sesquiterpene alkaloid found in the extracts of the firmoss *Huperzia serrata*.

Family–Lycopodiales.

Information

Huperzine A is a compound that comes from a specific kind of club moss called *Huperzia serrata*. Huperzine A, like cocaine and caffeine, is an alkaloid—a kind of chemical produced from plants that has therapeutic properties. Although this item is marketed as a dietary supplement for memory loss and mental impairment, it is actually more of a medicine than a herb.

Huperzine A has been shown to dramatically reduce AD and other dementia symptoms in three Chinese double-blind trials with a total of over 450 participants. A comparatively tiny amount of evidence of benefit was found to be absent in one double-blind trial.

Vinpocetine



Vinpocetine

Synonyms–Apovincaminic acid ethyl ester,cavinton,ceractin, Intellectol.

Biological source–vinpocetine is a synthetic ethyl ester of apovincamine, a vinca alkaloid obtained from the leaves of the lesser periwinkle (*vinca minor*).

Information

Vinpocetine is a chemical that is produced from vincamine, which is a component of seeds from a variety of African plants and the leaves of the common periwinkle (*Vinca minor*). It is applied in the treatment of mental illness and memory loss.

Vinpocetine, a medication developed in Hungary more than 20 years ago, is marketed as

Cavinton in Europe. It is sold in the US under the name “dietary supplement,” though by any stretch of the imagination, the chemical probably does not fall into that category. Vinpocetine is not found in nature in any appreciable amount. Its production necessitates extensive laboratory chemistry activity.

Vinpocetine has been studied in multiple double-blind trials to assess its efficacy in treating AD and associated disorders. Regrettably, the majority of these studies had serious problems with reporting and design. Three studies with a total enrollment of 728 participants were deemed to be of acceptable quality by a review of the literature. The finest of these was probably a 16-week double-blind, placebo-controlled study that included 203 participants with mild to moderate dementia and shown a substantial improvement in the group that received treatment. Even yet, there were a number of technical issues with this research, leading the review’s authors to conclude that vinpocetine is not yet a proven treatment. Many higher-quality trials are currently being conducted.

Melissa officinalis and Salvia officinalis



Melissa officinalis

Synonyms – Melissa officinalis – Balm, Balm mint, common balm, lemon balm.

Salvia officinalis – sage, common sage.

Biological source -lemon balm (*Melissa officinalis* L., Lamiaceae), sage (*Salvia officinalis* L., Lamiaceae) and spearmint (*Mentha spicata* L., Lamiaceae) are among the various plants widely used in traditional Mediterranean cuisine and medicine.

Family–It is a member of the Lamiaceae (mint) family, and lemon balm (*Melissa officinalis*) belongs to a genus that includes 5 species of perennial herbs native to Europe, Central Asia, and Iran.

Information

Lemon balm, or *Melissa officinalis*, has been shown to help people with mild to moderate AD by lowering agitation and improving cognitive performance. It is known that *M. officinalis* exhibits both nicotinic and muscarinic binding characteristics when it comes to Ach receptor activation in the central nervous system. According to a recent study, giving this plant to young, healthy volunteers affects their mood and cognitive function. Furthermore, 42 individuals with mild to moderate AD participated in a parallel, randomized, placebo-controlled study that evaluated the safety and effectiveness of *M. officinalis*. Four months were spent treating the subjects.

By adding together the ratings from six domains—memory, orientation, judgment, problem solving, community affairs, home and hobbies, and personal care—the CDR-SB generates a consensus-based global clinical assessment. After 16 weeks of treatment, the results showed that patients receiving *M. officinalis* extract had significantly improved cognition. Both the CDR-SB and the ADAS-cog scores showed improvements.

Between the groups receiving the herb extract and the placebo, the researchers found no discernible variation in the frequency of adverse events. On the other hand, agitation occurred more frequently in the placebo group than in the active treatment group. Furthermore, after ingesting *Salvia officinalis* (sage) extract for 16 weeks, patients with mild to moderate AD demonstrated statistically significant improvements in their cognitive function. The improvements in the ADAS-cog and CDR-SB measures in the *S. officinalis* extract group on both observed case and intention-to-treat analyses highlighted the therapeutic importance of these findings.

III. CONCLUSION

The review discusses basic pathophysiology and epidemiology of AD including risk factors and management. There aren't many options for medical intervention, therefore finding new medications to treat AD is necessary. You can accomplish this by looking into herbal remedies. Herbal medications are typically thought to be safe and to have fewer adverse effects. Numerous plants exhibit neuronal activity and may be used to treat AD. In addition to helping Alzheimer's patients with their memory loss, the plants and phytoconstituents described in this review can be utilized to

treat a number of other conditions. To enable the development of safer and more effective treatments for AD, the scientific community ought to play a leading role in the identification of the plants and the understanding of their mode of action. Studies on these herbal remedies and other forms of Ayurvedic medicine may yield new useful insights and efficient

REFERENCES

- [1]. Mohamed T, Shakeri A, Rao PPN. Amyloid cascade in Alzheimer's disease: recent advances in medicinal chemistry. *Eur J Med Chem.* 2016;113:258-72. [CrossRef] | [Google Scholar]
- [2]. Chase TN, Farlow MR, Clarence-Smith K. Donepezil plus solifenacin (CPC-201) treatment for Alzheimer's disease. *Neurotherapeutics.* 2017;14(2):405-16. [CrossRef] [Google Scholar]
- [3]. Kim DH, Lee SB, Young LD, VYang HD. Hist Alzheimers Dis Dem Neurocognitive Disord. 10.3390/geriatrics6010005. 2016;15(4):115- 21. [CrossRef] [Google Scholar]
- [4]. Soria Lopez JA, Gonzalez HM, Leger GC. Chapter 13. Alzheimer's disease. In: *Handbook of clinical neurology.* 2019;167:231-55. [CrossRef] [Google Scholar]
- [5]. Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun.* 1984;120(3):885-90. [CrossRef] | [Google Scholar]
- [6]. WHO <https://www.who.int/news-room/fact-sheets/detail/dementia> [CrossRef] | [Google Scholar]
- [7]. Bondi MW, Edmonds EC, Salmon DP. Alzheimer's disease: Past, present, and future. *J Int Neuropsychol Soc.* 2017;23(9-10) 81831 <https://doi.org/10.1007/s00127-017-1183-1> [CrossRef] | [Google Scholar]
- [8]. Alzheimer report. 2015 <http://alz.co.uk/research/worldreport-2015> (World Accessed May 02, 2016) [CrossRef] | [Google Scholar]
- [9]. Wimo A, Guerchet M, Ali G, Wu Y, Prina AM. World alzheimer report. *Alzheimer's and Dementia.* 2017;13(1):1-7. [CrossRef] | [Google Scholar]
- [10]. Manual diagnostico e Estatistico de transtornos mentais-DMS-5. 5rd Artmed, editor. Porto Alegre, 2014. Available from:.. [CrossRef] | [Google Scholar]
- [11]. Javed SF, Giebel C, Khan MA, Hashim MJ. Epidemiology of Alzheimers disease and other dementia:rising global burden and forecasted trends *F1000Research;* 2021.10.25. [Cross [Google Scholar]
- [12]. Prakash A, Dhaliwal GK, Kumar P, Majeed ABA. Brain biometals and Alzheimer's disease boon or bane?. *Int J Neurosci.* 2017;127(2):99-108. [CrossRef] | [Google Scholar]
- [13]. Feldman H, Woodward M. The staging and assessment of moderate to severe Alzheimer disease. *Neurology.* 2005;65:10-7. [CrossRef] [Google Scholar]
- [14]. Brayne C. Elephant in the room-healthy brains in later life, epidemiology and public health. *Nat Rev Neurosci.* 2007;8:233-9. [CrossRef] | [Google Scholar]
- [15]. Nestor PJ, Scheltens P, Hodges JR. Advances in the early detection of Alzheimer's disease. *Nat Rev Neurosci.* 2004;5:34-41. [CrossRef] | [Google Scholar]
- [16]. Chong MS, Sahadevan S. An evidence-based clinical approach to the diagnosis of dementia. *Ann Acad Med Singapore.* 2003;32:740-8. [CrossRef] | [Google Scholar]
- [17]. Katzman R: The prevalence and malignancy of Alzheimer's disease. A major killer. *Arch Neurol.* 1976; 33: 217-218.
- [18]. Evans DA, Funkenstein HH, Albert MS: Prevalence of Alzheimer's disease in a community population of older persons: Higher than previously reported. *JAMA.* 1989; 262: 2551-2556.
- [19]. Geldmacher DS, Whitehouse PJ: Differential diagnosis of Alzheimer's disease. *Neurology.* 1997; 48(Suppl 6): S2-S9.
- [20]. World Health Organization: *The ICD-10 Classification of Mental and Behavioral Disorders.* Geneva: World Health Organization, 1992.
- [21]. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC: American Psychiatric Association, 1994.

- [22]. McKhann G, Drachman D, Folstein M, et al.: Clinical diagnosis of AD: Report of NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on AD. *Neurology*. 1984; 34: 939-944.
- [23]. Schneiders LS: An overview of rating scales used in dementia. *Alzheimer Insights*. 1996; 2: 1-7.
- [24]. Selkoe DJ: Amyloid beta-protein and genetics of Alzheimer's disease. *J Biol Chem*. 1996; 271: 18295-18298.
- [25]. Lue LF, Kuo YM, Roher AE: Soluble amyloid beta peptide concentration as a predictor of synaptic changes in Alzheimer's disease. *Am J Pathol*. 1999; 155: 853-862.