Available online on 15.09.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

Alzheimer Disease: Cognizance and Potential Aspect of Disease Pathophysiology & Recently Developed Therapeutic Drug Strategies

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Article Info:

Article History:

Received 08 June 2024
Reviewed 02 August 2024
Accepted 26 August 2024
Published 15 Sep 2024

Cite this article as:

Kumar R, Saini M, Bhattacharya T, Deepika. Kumari A, Alzheimer Disease: Cognizance and Potential Aspect of Disease Pathophysiology & Recently Developed Therapeutic Drug Strategies, Journal of Drug Delivery and Therapeutics. 2024; 14(9):232-239

DOI: http://dx.doi.org/10.22270/jddt.v14i9.6790

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Abstract

Alzheimer's disease (AD) is a multifactorial neuron-degenerative old age disease which has no cure. AD causes degeneration of the neuronal cells in the brain which is the main reason of dementia, characterized by a decline in the thinking and independence in daily routine activities. In most of the cases, AD is suspected to be caused by a combination of genetic, lifestyle and environmental factors, affecting the brain over time. The currently approved therapy, which includes cholinesterase inhibitors, NMDA-receptor antagonists and their combinations provides only temporary symptomatic relief. Nowadays, the clinical research is targeting on understanding of Alzheimer pathology[1]. These are targeting the abnormal tau protein metabolism, removal of beta-amyloid, inflammatory response, cholinergic neuron and free radical damage treatments which can either that stop or modify the course of Alzheimer. Global efforts are continued to identify new targets to develop novel therapeutic agents for the treatment of AD.

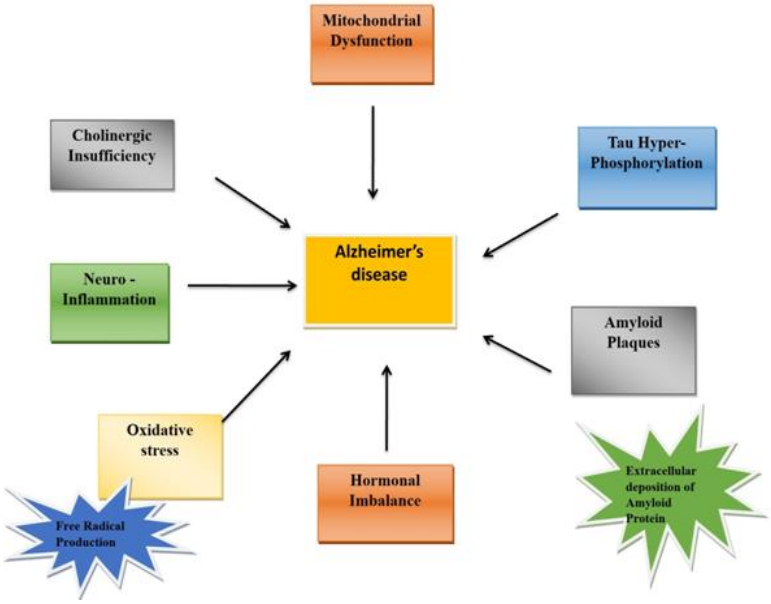
Keywords: Alzheimer disease, Dementia, Drug therapy, Drug effect, Amyloid, Amyloid precursor protein, Tau proteins, Acetyl cholinesterase enzyme

Introduction

In terms of dementia, Alzheimer's disease (AD) is the most prevalent. It's described as a gradually worsening neuro-degenerative illness, caused by amyloid-beta peptide (Aβ) buildup in the brain's most affected region - medial temporal lobe and cortical structures, which results in neuritis plaques and neuroibrillary tangles. Alzheimer is age-related neuro-degenerative diseases such as Alzheimer's disease (AD) and Patients and caregivers with Parkinson's disease face significant challenges. In older people, Alzheimer disease is the most prevalent type of dementia. Patients have a range of neuropathological changes[2]. According to Tifratene et al. (2012)[3], this caused people to experience memory loss, disorientation, poor judgment, confusion, and trouble communicating. Alzheimer's disease (AD) is characterized by a progressive loss of cognitive functions that may be caused by cerebral disorders. Additional factors that could contribute to this include infections, intoxication's, abnormalities in the pulmonary and circulatory systems that reduce the amount of oxygen reaching the brain, deficiencies in nutrition, low levels of vitamin B12, tumors, and other conditions[1]. Two percent of people in developed nations suffer from AD, a progressive disorder. AD affects more than 10% of people over 65 and 50% of people over 85. This figure will double every 20 years as the population ages, and by 2040, it is expected to have surpassed 80 million cases. Thus, in order to manage AD, the right care is required. According to Ladner et al. (2020)[4], the current article examines the pathological mechanism of AD, the medications used to treat AD, and their efficacy and drawbacks.

Pathophysiology of Alzheimer's disease

According to Gillette-Guyonnet et al. (2012)[5], Alzheimer's disease is thought to be a multifunctional illness linked to a number of risk factors, including advancing age, genetics, head trauma, vascular disorders, infections, and environmental factors (such as heavy metals and trace metals). It is currently unknown what causes the pathological changes associated with Alzheimer's disease (Aβ, NFTs, and synaptic loss)[6]. Although many theories have been put forth to explain AD, two are thought to be the primary culprits: According to[6], a significant risk factor for AD is impairment of cholinergic function. According to Tifaraene et al. (2012)[7], the primary initiating factor is alteration in the production and processing of amyloid β-protein. Nevertheless, there aren't any recognized postulates as of yet which can explain the AD pathogenesis. Alzheimer's disease causes with numerous risk factors and different stages as shown in figure[1].



Causes of Alzheimer (Breijyeh et al 2020) [17]

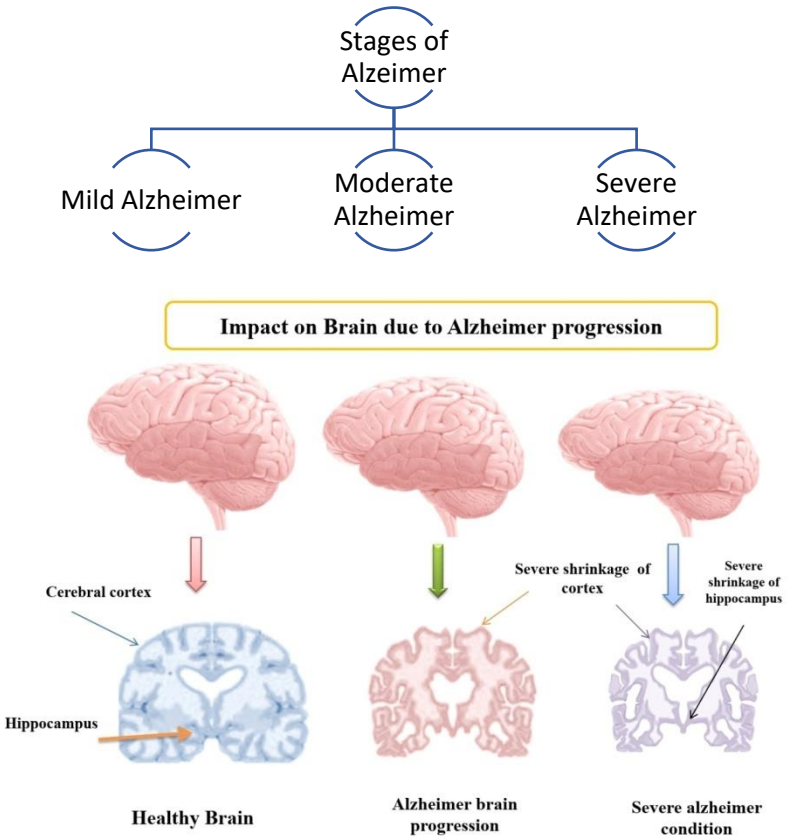


Figure: 1 Progression of Alzheimer disease (Yang et al 2024)[25]

Alzheimer is characterized into three categories. Usually in Alzheimer, there is continuous and gradual impairment in learning and memory. Memory issues are less common in a small percentage of cases than difficulties with language, executive functions, perception (agnosia), or movement execution (apraxia). According to Briggs R et al. (2016)[1], language disorders are primarily characterized by a declining vocabulary and a decrease in word fluency, which impairs oral and written language generally. At this point, the Alzheimer's patient can typically express fundamental concepts clearly. AD is a serious issue everywhere for a number of reasons, such as:

An aging population

Increasing life span

Inadequate pharmacotherapy options[8].

The moderate stage is characterized by worsening memory problems and a possible inability to identify close relatives. Changes in behavior and neuropsychiatry are becoming more common. Wandering, irritability, and labile affect, which can result in sobbing fits[1], unplanned violent outbursts, or resistance to receiving care are common symptoms[2].

In the last stages of severe illness, the patient is totally reliant on caregivers. Individuals suffering from Alzheimer's may:

1) Habituated to repeat statements and questions over and over.
2) Forget previous conversations, appointments or events.
3) Misplace things, frequently placing them in odd locations.
4) Become lost in locations they used to be familiar with, like his house.
5) Eventually, you forget the names of your loved ones and commonplace items.
6) Find it difficult to articulate ideas, describe objects, or participate in conversations when using the appropriate words[9]

Neuropathology of Alzheimer's disease

Some studies suggest that areas of the brain linked to memory and learning, including the hippocampus, nucleus basalis of Meynert, and cortex, are typically where cholinergic neurons are lost.The brains of people with Alzheimer's disease have incredibly low levels of acetylcholine (ACh). Thus, the decline in cholinergic activity raises concerns about potential cognitive function impairment. this decreased activity has an impact on synaptic transmission and starts inflammatory processes. Cell death may result from productive reactive oxygen species. Furthermore, cholinergic acetyltransferase, which inhibits the production of ACh, can be stopped by Aβ, which can also prevent cholinergic neurons from absorbing choline[10]. Consequently, the concentration of ACh dropped as shown in figure[2]

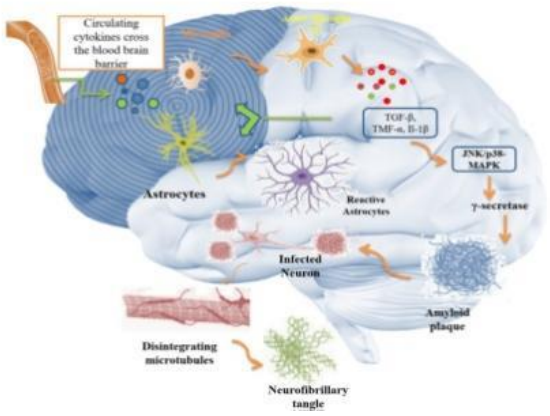


Figure 2: Degeneration of neurons during Alzheimer (Spoleti et al 2024)[26]

Amyloid precursor protein (APP)

The APP is a trans-membrane glycoprotein that consists of 695-770 of amino acids. It is widely occurrs in human histiocytosis; and it is found in the brain and acts as a membrane receptor. It is cleaved by three types of enzymes[8]

- α-secretase,
- β-secretase
- γ-secretase

Aβ function

Some studies have demonstrated that over-production of Aβ cause the neurotoxicity in neurons. It causes synaptic dysfunction and the formation of intraneuronal fibrillary tangles, which eventually results in neuron loss. Soluble A can stimulate neuritis growth in a short amount of time, increasing the survival rate of neurons. The deposited A, on the other hand, has the opposite effect on neurons. It has the potential to cause neuritis shrinkage and neuron denaturation. Although excessive A production is detrimental to nerve cells, low levels of A can improve memory and increase hippocampal long-term potentiation[11].

Neuroinflammation in Alzheimer Disease

One of the long-term consequences of Aβ deposition is persistent inflammation. It is typified in the brain by important inflammatory mediators being expressed and glial cells becoming activated. The majority of the cells involved in the activity are astrocytes and microglia[12]. They release cytotoxic molecules, including complement proteins, proteases, reactive oxygen intermediates, and pro-inflammatory cytokines, which contribute to the development and progression of neurological disorders. One attack method involves the activated glial cells releasing reactive oxygen species, NO, and protease that causes neurotoxicity, which in turn kills nearby neurons[9]. In an additional assault, an inflammatory response may trigger the production of Aβ, intensifying the inflammation and creating a vicious cycle[11].

Drugs used for treatment of Alzheimer disease

Most drugs that are approved to treat AD at different stages of the disease are only partially effective[13]. There

appears to be a linear correlation between the AD process and the pathological alterations in the human brain, suggesting that medication that disrupts the various stages of the disease can prevent it from progressing further. The following medications are shown in below figure[3]

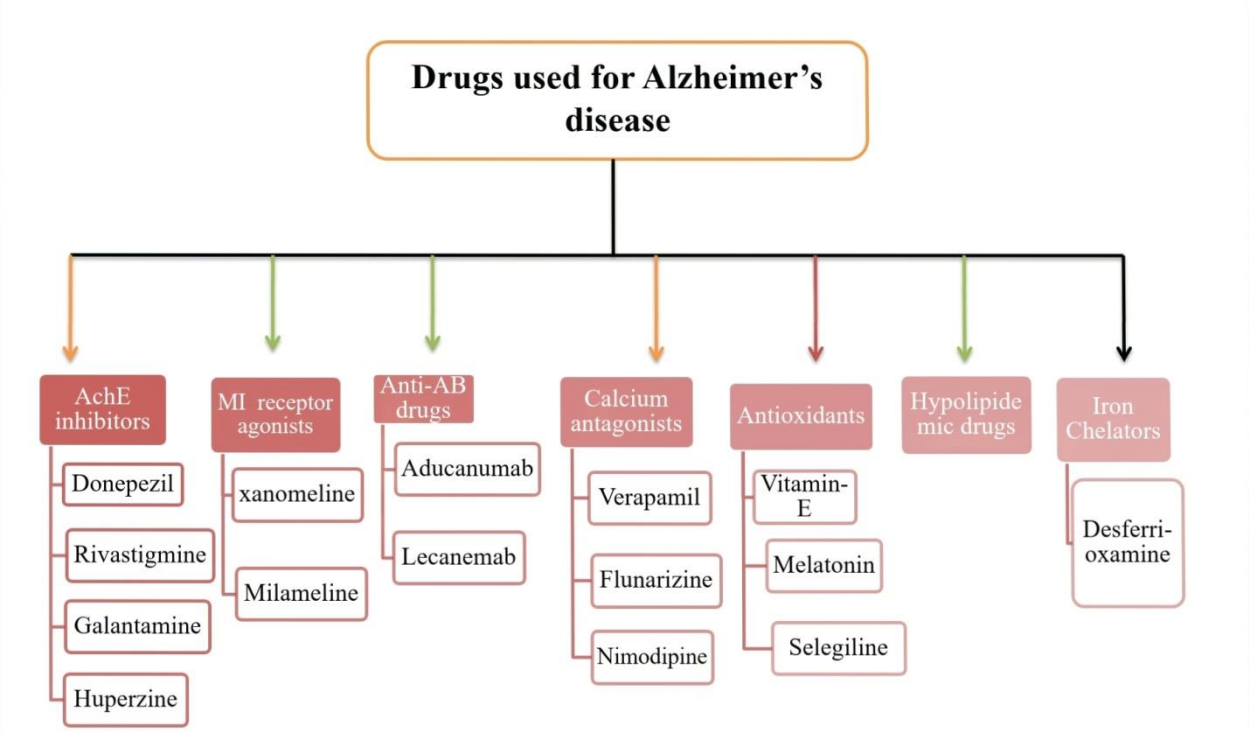


Figure 3: Drugs used for Alzheimer Disease (Noetzli et al 2013)[13]

1. **Acetyl cholinesterase inhibitors**

Acetyl cholinesterase inhibitors were the first medications authorized to treat AD.

- As an acetyl cholinesterase inhibitor, tacrine was the first medication used to treat AD in 1993. Because of its hepatotoxicity, tacrine is no longer frequently used to treat AD. Another inhibitor of acetyl cholinesterase is donepezil. When taken orally, it is quickly absorbed. Its effects are more enduring than those of tacrine. Patients respond to it better and experience fewer side effects. Nausea, vertigo, diarrhea, and anorexia are the most common adverse drug reactions. Each of these is dependent on the dose. It may be able to stabilize patients' functional ability and enhance cognitive performance, according to several clinical trials. It is used on cases of moderate to mild AD[9].
- As a derivative of carbamate, rivastigmine. It can reversibly inhibit butyryl- and acetyl-cholinesterase (BuChE and AChE, respectively). When administered orally, it takes an hour to reach its peak plasmatic concentration. It is the only medication that can reduce drug-drug interactions because cytochrome P450 isoenzymes are not involved in its metabolism[14]. There is evidence from numerous clinical trials that rivastigmine significantly affects memory and the praxis domains of cognition. The language domain is significantly affected by rivastigmine patches, in contrast to capsules. According to Noetzli et al. (2013)[11], patients with mild to moderate AD may benefit from these patches.
- The flower and bulb parts of lilies, daffodils, and related plants are extracted to produce galantamine. This inhibitor of acetyl cholinesterase is specific. It reduces cognitive dysfunction and protects neurons from cytotoxicity brought on by Aβ aggregation. It is thought to improve central neurotransmission as well. According to Deardorff et al. (2016)[9], galantamine's clinical efficacy is nearly identical to donepezil's.
- One plant-based alkaloid called Huperzine A is derived from the Huperzia serrate plant. It is a potent AChE inhibitor that is able to pass through the blood-brain barrier (BBB). Huperzine offers neuroprotection against harm to neurons. Compared to tacrine and galantamine, it exhibits stronger inhibition and better selectivity[15]. AD is treated with a variety of acetyl cholinesterase inhibitors, including metrifonate, physostigmine, and its derivatives, in addition to the medications already mentioned[16]. Acetyl cholinesterase inhibitors have increased synaptic transmission, but they also have certain drawbacks[9]. They are costly and typically offer few advantages. More advice is required regarding their clinical use because they have the potential to harm the neuronal membrane.

2. M1 receptor agonists

In AD patients' brains, M1 muscarinic receptors are largely unaltered. For this reason, M1 receptors are

thought to be a promising therapeutic target for the treatment of AD[11]. Adverse events are lessened and the disease's advancement is slowed down by M1 receptor agonists. Drugs like xanomeline and milameline are among those used to treat AD. It is able to pass through the BBB. According to Deardorff et al. (2019)[17], numerous clinical studies have shown that patients with AD have significantly improved in terms of cognitive performance.

3. Anti-Aβ drugs

The primary pathogenic factor in AD is B-amyloid peptides. According to Kabir M. T. et al. (2021)[18], deposited Aβ can result in denaturation of neurons and shrinkage of neuritis. Aβ can cause the calcium channels in the cell membrane to become disrupted, which increases Ca2+ influx and causes the calcium to become out of balance. According to Lipton et al. (2004)[10], anti-Aβ medications may therefore be the most beneficial for treating AD.Aducanumab and Lecanemab is a monoclonal antibody (a protein that helps your immune system target specific proteins for removal), and it is designed to remove a protein called amyloid beta from the brain. Amyloid beta is an important protein involved in the progression of Alzheimer's disease. Lecanemab is given intravenously (infused through a vein) every 2 weeks. Lecanemab does not cure Alzheimer's disease, but it does modestly slow the rate of progression in the earliest stages of Alzheimer's disease

4. Calcium antagonists

Neurotransmitters are produced, transmitted, and released in response to either an excess or a deficiency of calcium in nerve cells[13]. Tetrandrine, verapamil, flunarizine, and nimodipine are common medications used as calcium antagonists in the treatment of AD. Nimodipine is an antagonist of the L-type calcium channel. It is very lipophilic, easily passes through the blood-brain barrier, and blocks calcium influx to improve cerebral blood flow. Patients seem to tolerate it well and experience fewer side effects[19].

5. Antioxidants

By removing or inhibiting the production of active oxygen, antioxidants can stop the deterioration of nerve cells. The most widely used antioxidant is vitamin E, a lipophilic vitamin[14]. Numerous clinical studies have revealed that it may be able to stop oxidative damage. It can lessen neuroblastoma cell toxicity and reduce cellular death brought on by Aβ. Other popular clinical antioxidant medications include melatonin and selegiline. Patients' mood, behavior, and cognitive function do improve to some extent[22]. Nonetheless, it does not improve behavior, functional ability, or cognition worldwide. Moreover, it exhibits strong anti-amyloidogenic properties[14,]

6. Hypolipidemic drugs

Amyloid precursor protein metabolism is regulated by Apo lipoprotein E expression, which may result in Aβ deposition and amyloid plaque formation. These days, amyloid plaque development can be successfully inhibited by using Apo lipoprotein E isomers [9].

7. Iron chelators

Both SP and NTFs in the brain have been shown to contain high amounts of iron. Ions may play a role in the generation of free radicals and the degeneration of neurons. They might attach themselves firmly to Aβ, potentially harming neurons. The goal of iron chelator treatment is to eliminate excess iron from brain tissue that causes neurotoxicity[9]. Iron is highly affinized for iron chelators. As an illustration, the natural iron scavenger desferrioxamine is a particular chelator that has a strong affinity for copper, zinc, and aluminum. A common treatment for AD is desferrioxamine[2].

8. Vaccines

One of the most promising methods to stop Aβ deposition may be immunotherapy. Denaturation of neurons and shrinking of neuritis can be brought on by the deposited Aβ. The first AD vaccination therapy was created in 1999 by Dale Schenk and colleagues[10]. AN-1792, a combination of adjuvant QS21 and synthetic Aβ, was the first vaccine to undergo clinical trials. This vaccination was used to treat patients with mild-to-moderate AD.

All these types of drugs used in treatment of Alzheimer disease shown in given table[1]

Table 1: Drugs used in treatment of Alzheimer Disease (Cacabelos et al 2022)[8]

Drugs	Class and indication	Mechanism of action	Uses
Galantamine (ACh inhibitors)	Cholinesterase inhibitor prescribed To treat symptoms of mild to moderate and moderate to severe	Prevent the breakdown of acetylcholine in the brain	Reduce Sleepiness
Rivastigmine (ACh inhibitors)	Cholinesterase inhibitor prescribed To treat symptoms of mild to moderate and moderate to severe	Prevent the breakdown of acetylcholine and butrylcholine in the brain	Cognitive neuropsychatric improvement

Huperzine (ACh inhibitors)	AChE inhibitor prescribed to provides neuroprotection against neuronal damage	provide protection against oxidative stress and Aβ toxicity	Improvement in memory, language and memory
Donepezil (ACh inhibitors)	Inhibitor prescribed to treat symptoms of mild-to-moderate AD	Prevent the breakdown of acetylcholine in the brain	Improvement in memory and language
Memantine (ACh inhibitors)	N-methyl-D-aspartate antagonist prescribed to treat symptoms of moderate to severe AD	Block the toxic effect associated with excess glutamate and regulate glutamate activation	Improvement in flight performance
Xanomeline (ACh inhibitors)	M1 receptor agonist and Improvement of Cognition function and behavioral disturbances	Cholinergic transmission at muscarinic acetylcholine receptors implicated in higher brain functions	Improvement of Cognition function and behavioral disturbances
Milameline (ACh inhibitors)	M1 receptor agonist and Cognition enhancing drug	Cholinergic transmission at muscarinic acetylcholine receptors implicated in higher brain function	Cognition enhancing drug
Nimodipine Verapamil Diltiazem (Calcium Antagonist)	Calcium channel antagonist that block the flux of extracellular calcium through L-type, voltage-gated calcium channel	Calcium channel blocker prevent the AD cells from A-beta oligomer production	Decreased risk of cognitive impairment or dementia in patients
Antioxidants	Reduce the amount of DNA damage, nueronal cell death and reduce the aggregation of B-anyloid with in the brain	Counteracting the negative effect of oxidative stress and protect the cells from certain type of molecular damage	Reduce the risk of dementia in AD patients
Hypolipidaemic	Decrease the plasmatic concentration of lipoproteins, LDL	Mediate lipid transport in the brain and periphery	Decreased risk of cognitive impairment or dementia in patients
Aβ drugs (Aducanumab and lecanemab)	Against amyloid-beta directed monoclonal antibody	Lecanemab selectively binds to soluble Aβ aggregate species and is selective for Ab protofibrils	Amyloid beta is an important protein involved in the progression of Alzheimer's disease

New therapeutic candidates for the treatment of Alzheimer's disease

1. Resveratrol (3, 4, 5-trihydroxystilbene): It is a phytochemical that occurs in nature. According to Tifratene et al. (2012)[7], it can be found in peanuts, chocolate, berries, grapes, and red wine. Resveratrol has anti-inflammatory, antiviral, antioxidant, and anti-cancer effects. After being isolated in 1940, it came to be known for its possible therapeutic benefit in lowering the chances of neurodegeneration in general and Alzheimer's disease (AD) specifically. Numerous in vitro and in vivo models of AD have shown neuroprotective effects of resveratrol[21]. In addition to its strong anti-inflammatory and antioxidant properties, research indicates that resveratrol helps the amyloid precursor protein (APP) break down non-amyloidogenesis and encourages the removal of neurotoxic amyloid beta (Aβ) peptides, which is a vital step in preventing and delaying AD pathology.

2. Bisnorcymserine: It is a derivative of drug Cymserine, which is related to physostigmine. Bisnorcymserine is highly selective for BuChE[11]. It has potential to improve the symptoms of patients with severe AD. It lowers the amyloid plaque-associated protein, amyloid-beta peptide.

3. Huperzine A (HupA): It is an alkaloid of Lycopodium that was separated from Huperzia serrate, a Chinese medicinal herb. It is a highly selective, reversible, and potent AChE inhibitor that is used to treat memory deficitHupA and HupB are the two varieties. Hup A's natural homologue is called Hup B. AChE has been shown to be effectively and reversibly inhibited by huperzine B (HupB)[20]. Although HupB has a higher therapeutic index and other advantageous properties, it is less selective and potent than HupA.

4.. Phenserine: Physostig'sphenylcarbamate derivative selectively and non-competitively inhibits amyloid precursor protein (APP) by reducing APP translation

through interaction with the 5'-untranslated region of the APP gene. It also modulates the amount of beta-mine[22]. This new cholinesterase inhibitor is called phenserine.

5. Naringenin: The beneficial effect of naringenin on improvement of learning and memory was evaluated in an Alzheimer's disease rat model.In addition to decreasing apoptosis, naringenin pretreatment of Aβ-injected rats also decreased hippocampus malondialdehyde (MDA) without significantly affecting nitrite and superoxide dismutase (SOD) activity. According to these findings, naringenin pretreatment reduces the damage that Aβ causes to learning and memory by reducing lipid peroxidation and apoptosis. This beneficial effect is partially mediated by the estrogenic pathway[1].

6.Cymserine: It acts as a reversible BuChE inhibitor and useful for treating AD without producing side effects like tremor, lacrimation and salivation[20]. These were found to increase brain ACh levels, and did not produce tropic effects. Furthermore, these were found to decrease the levels of amyloid precursor protein and amyloid beta, the known biomarkers for the development of AD.

7. Aptiom (Eslicarbazepine acetate): It has been approved by the Food and Drug Administration as a supplemental medication to help treat adults experiencing partial seizures of epilepsy. Regardless of food intake, the gut absorbs at least 90% of eslicarbazepine acetate[14]. It is swiftly converted to eslicarbazepine, preventing the bloodstream from detecting the original drug (Ladner et al., 2020). After 2-4 hours, eslicarbazepine reaches its peak plasma levels, and less than 40% of plasma proteins bind to the drug. After four to five days from the beginning of treatment, steady-state concentrations are reached, with a biological half-life of ten to twenty hours.

8. Fetzima: It is chemically known as levomilnacipran. It might act as a potent inhibitor of BACE-1 and expected to form the basis of a future therapy against AD. It is approved by Food and Drug Administration in July 2013.

Conclusion

Numerous theories that attempt to explain the pathophysiology of AD have been defined, leading to the development of specific strategies for the prevention and treatment of this dangerous neuron-degenerative illness[21]. Of all the theories, the amyloid cascade hypothesis has had the greatest influence on current research and the development of experimental treatment plans. It is generally believed that AD can be prevented by inhibiting Aβ production, improving the clearance of Aβ deposition, or inhibiting Aβ aggregation[15].Numerous prospective studies are presently being conducted, and retrospective studies have demonstrated the significance of these substances and methods for reducing the chances of Alzheimer disease[21]. All of these fundamental biochemical pathways may also highlight the overall significance of APP processing and amyloid proteins in cell physiology, necessitating additional research into the physiological function of amyloid[23].It is possible that treatment options for AD may evolve beyond the amyloid cascade theory[20].Depending on the specific needs of each patient, future preventative methods may include a combination of medications, such as hormones, anti-inflammatory drugs, cholesterol-lowering medications, and antioxidants[21].

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