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A REVIEW ON ACETYLCHOLINESTERASE INHIBITING THERAPEUTICS AND RECENT BREAKTHROUGHS IN THE FIELD OF ALZHEIMER`S DISEASE

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ABSTRACT: Alzheimer's disease (AD) is one of the most well-studied neurodegenerative conditions. It is a debilitating chronic disease of the central nervous system (CNS). Almost 131.5 million individuals are predicted to be affected by the disease by 2050. The main effects of AD are cognitive decline and language problems. One of the factors contributing to AD is the gradual decrease in the brain's concentrations of the neurotransmitter acetylcholine. The breakdown of acetylcholine is carried out by the increased activity of the acetylcholinesterase (AChE) enzyme within the brain. Many natural and synthetic acetylcholinesterase inhibitors (AChEIs) have been created in order to slow down the progression of the disease over the years. Currently, there are two potential AChEIs (Donepezil and Galantamine) that have shown positive clinical advantages. Furthermore, Rivastigmine is claimed to be an anti-AChE molecule showing the effects similar to Donepezil and Galantamine. The knowledge of specific as well as multitargeted molecules to treat or cure AD is the ultimate route to reach achievements in the field of AD medication. The intention of this review article is to give an overview of different types of cholinesterase Inhibitors (ChEIs) such as single and multi-target inhibitors and natural organic compounds used in curing AD. Furthermore, the recent breakthroughs in the field of AD are also discussed.

INTRODUCTION: In today's world, Alzheimer's disease (AD), due to its prevalence, is one of the most researched neurodegenerative diseases. AD was first identified by Dr. Alois Alzheimer who was a German psychiatrist. He saw the symptoms (memory loss and language disorder) of AD in one his patients in 1901 [1].

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The Global Alzheimer Survey 2016 estimates that there are currently 46.8 million AD patients worldwide. Almost 131.5 million individuals are predicted to be affected by the disease by 2050. All global regions will experience a sharp rise in dementia prevalence as a result of population ageing.

After cardiovascular disorders, AD is now the major contributor to disability and mortality in the older population [2]. It often begins at age 65 and is defined by a gradual decline in mental abilities. Disease development differs from patient to patient, possibly due to concomitant conditions that

contribute to the intensity of symptoms. The specific reasons of AD onset and progression are yet unknown. Based on what we know so far, this disease can be classified as a multifaceted disease depending on the factors like hereditary and environmental conditions [3]. There are now seven contending hypotheses related with the onset of AD [4].

Changes in the cholinergic system [5]. Improper disintegration of the precursor protein of amyloid causes the formation of beta-amyloid clumps [6]. Development of intracellular neurofibrillary tangles [7]. Oxidative stress [8] neuro-inflammation [9]. Heavy metal concentrations are high [10]. Disorders of the metabolism arising from the interruption in cholesterol homeostasis [11] and obesity [12].

In this paper, only the first hypothesis *i.e.;* changes in the cholinergic system and the recent breakthroughs in AD field will be thoroughly discussed. According to this hypothesis, a significant decline in the levels of acetylcholine (ACh) neurons is thought to be the primary factor behind the normal slowdown of learning and memory functions observed in AD [5]. As a result, numerous pharmaceutical methods have been developed with the goal of slowing AD signs and restoring ACh concentration in the synaptic cleft by using cholinergic agonists to improve the synthesis of neurotransmitter ACh. Unfortunately, due to severe side effects, such tactics were mainly ineffectual in the treatment of AD. Many mechanisms, including decreased activity of the enzyme choline O-acetyltransferase, which produces ACh, and increased catalytic activity of the acetylcholinesterase enzyme, which destroys it, could be to blame for the drop in ACh concentration [4].

Therapeutic treatments aimed at the inhibition of the acetylcholinesterase (AChE) enzyme were frequently chosen as a target. AChE inhibitors (AChEIs) are found to be highly effective in the increment of ACh concentration which improves cholinergic neurotransmission and allows patients with AD to regain cognitive abilities [13]. AChEIs, on the other hand, are not without side effects. They can be non-selective in inhibition [14]. The human body has also other types of cholinesterase besides AChE. AChE is present in the neural synapses while butyrylcholinesterase (BuChE) is present in the liver and neurotic plaques.15They both have different physiological substrates. Acetylcholine (ACh) is the physiological substrate for AChE while butyrylcholine (BuCh) is the physiological substrate for BuChE [16]. Some ChEIs lack sufficient selectivity since they can't tell the difference between AChE and BuChE. Therefore, there were a need of designing and producing some novel specific inhibitors [4].

Acetylcholinesterase: AChE has been demonstrated to be the primary treatment target for the clinical relief of AD. It is a key enzyme found in the peripheral and the central nervous system. Its principal function is to catalyse ACh hydrolysis, which results in the production of choline and acetate ions. AChE can also be present in the red blood cells where it forms the antigen of the Yt blood group. It facilitates identifying a person's blood type [17]. It can be found in two distinct molecular forms such as homomeric and heteromeric oligomers. Homomeric form of AChE is typically exists in soluble form within the cells. These oligomers are secreted or connected with the exterior membrane *via* glycol-phospholipid attachment. Heteromeric oligomers are more commonly detected in the neural synapses. These oligomers are found on the cell membrane`s outer surface where they are present in the form of catalytic subunits consisting of tetramers subunits joined with the next subunits.

AChE is one of the most efficient enzymes ever examined in terms of kinetics. AChE has an average turnover period of 100 microseconds and a molecule of this enzyme can hydrolyse 6×10^5 ACh molecules each minute. The majority of ACh degradation occurs at the nerve level, where AChEs are found in the postsynaptic membrane of cholinergic junctions [5]. BuChE also hydrolyses ACh but its affinity for ACh is very less [18].

Acetylcholinesterase Inhibitors: Inhibition of the acetylcholinesterase (AChE) enzyme is a commonly chosen target and is achieved by AChE inhibitors (AChEIs). AChEIs inhibit the cholinesterase enzyme from degrading ACh, hence they extend the neurotransmitter activity. According to their structure and method of action, inhibitors that affect ChE activity can be

categorised into two groups: (i) Inhibitors that can form covalent bonds with the enzyme such as organophosphates; (ii) Inhibitors that can form reversible bonds with the enzyme, typically containing aminic groups [19].

These inhibitors mainly inhibit the enzyme's action and keep ACh available in the brain. During the moderate phase of the disease, they can also help with cognitive (memory, concentration) and behavioural (disinterest, aggression, hallucinations) symptoms [20]. Unfortunately, as the neurodegenerative condition progresses, this capacity deteriorates. AChE inhibitors have side effects too. The most prevalent side effects are nausea and cardiac arrhythmia in some circumstances [21, 22].

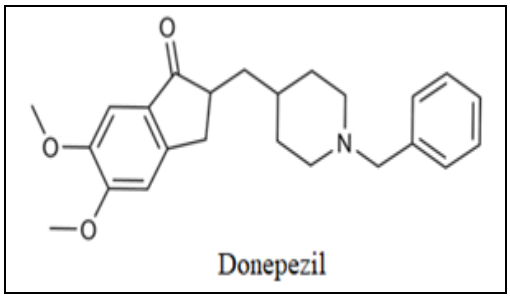
Despite the fact that only a small percentage of patients react to therapy, these inhibitors are the first choice in curing AD. The Cholinesterase inhibitors are classified into two groups: (i) single-target (ii) multi-target inhibitors. Single-target inhibitors especially inhibit AChE or BuChE while multi-target inhibitor influences other enzymatic pathways and alter various biological processes which are responsible for AD [4].

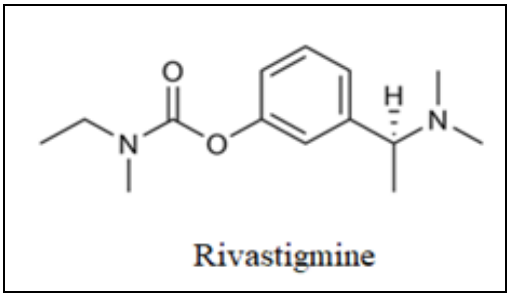
Single-Target AChEIs: Single-target AChEIs are the most frequently prescribed drugs for treating early to moderate AD. The drugs which are currently available in the market for curing early to mid-stage AD are Donepezil, Rivastigmine and Galantamine [14]. Some general characteristics of these drugs are discussed below:

Donepezil: Donepezil (shown in **Fig. 1**) was licenced in 1996 and is usually given at a daily dose of 5 mg for the first month of therapy. The dose of this drug can be raised to 10 mg for curing moderate AD. Donepezil was also authorised for severe Alzheimer disease in 2010 with a posology of 23 mg/day [23]. Diarrhoea, muscular cramps, and tiredness are the most commonly reported side effects.

Rivastigmine: Rivastigmine (shown in **Fig. 1**) was approved for the treatment of AD in 2000. It inhibits both AChE and BuChE in a non-competitive, pseudo-irreversible manner. It is used to treat mild to severe AD at a starting dose of 3 mg per day and can be increased up to 12mg per day. In comparison to donepezil, rivastigmine treatment usually results in a more global rehabilitation of cognitive functions. Nausea, vomiting and diarrhoea are the most common side effects of this medicine [24, 25].

Galantamine: Galantamine (shown in **Fig. 1**) was approved for the treatment of AD in 2001. It is a strong AChE inhibitor that is competitive and reversible. It's usually taken at a dose of 16 mg each day. Galantamine improves the quality of sleep. Nausea, diarrhoea, asthenia, and fatigue are the most common side effects of this medicine [26].





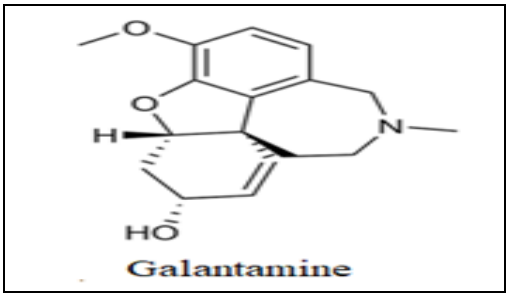


FIG. 1: STRUCTURES OF SINGLE-TARGET ACHEIS (CURRENTLY AVAILABLE IN THE MARKET)

Single-Target Natural AChEIs:

Huperzine A (HupA): HupA (shown in **Fig. 2**) is a Lycopodium alkaloid derived from the herb *Huperzia serrata*. It has a higher penetration through the blood-brain barrier than classic inhibitors. In comparison to donepezil, HupA is 8 times more effective at raising cortical ACh levels while having a more enduring effect [27]. It is a highly selective AChE inhibitor that has been studied for its low toxicity [28].

Huperzine B (HupB): HupB (shown in **Fig. 2**) is the minor lycopodium alkaloid derived from the herb *Huperzia serrata*. Compared to HupA, it is less effective and selective in inhibiting AChE [27]. HupB restored the disturbance of memory retention caused by sodium nitrite and cycloheximide in mice during behavioural trials, and it enhanced memory retention in aged mice. Subsequent investigations also showed that HupB had neuroprotective effects by lessening damage brought on by hydrogen peroxide [29].

Physostigmine Derivatives: Physostigmine (shown in **Fig. 2**) derivatives were employed as a model for the development of new potential ligands. It is a natural alkaloid derived from the Calabar bean that affects the activity of the enzyme ChE. It was never employed in therapy due to its negative impacts [30]. Tolserine and eseroline are two physostigmine derivatives.

Tolserine: Tolserine (shown in **Fig. 2**) has been shown in experiments to be a more effective inhibitor of erythrocytic Ache than physostigmine. In reality, with a partial non-competitive inhibitory mechanism, its IC_{50} value was discovered to be 8.13 nM. However, no information about preclinical research on this drug is currently available [31].

Eseroline: Eseroline (shown in **Fig. 2**) is a derivative of physostigmine. It is a reversible cholinesterase inhibitor. It is hard to figure out potential dangers and benefits of Eseroline in preclinical and clinical trials due to the lack of sufficient studies about this compound. The cyclic alkyl carbamate derivative of this compound was found to be a very potential inhibitor of the cholinesterase enzyme [32].

Cardanol Derivatives: Cardanol (shown in **Fig. 2**) development is attractive due to the availability of the raw material. It is a lipid derived from the nutshell of the Anacardium occidentale. The N, N-dimethycarbamoyl substitution exhibited similarities to rivastigmine in theoretical investigations, suggesting that they could be future AChE inhibitors [33].

Tacrine Analogues: Many artificial analogues containing the key functional moieties generated from various chemotype like acridine showed their pharmacological effects. Many tacrine (shown in **Fig. 2**) analogues, such as7-methoxytacrine (shown in **Fig. 2**), were found to have significant AChE inhibitory action [34].

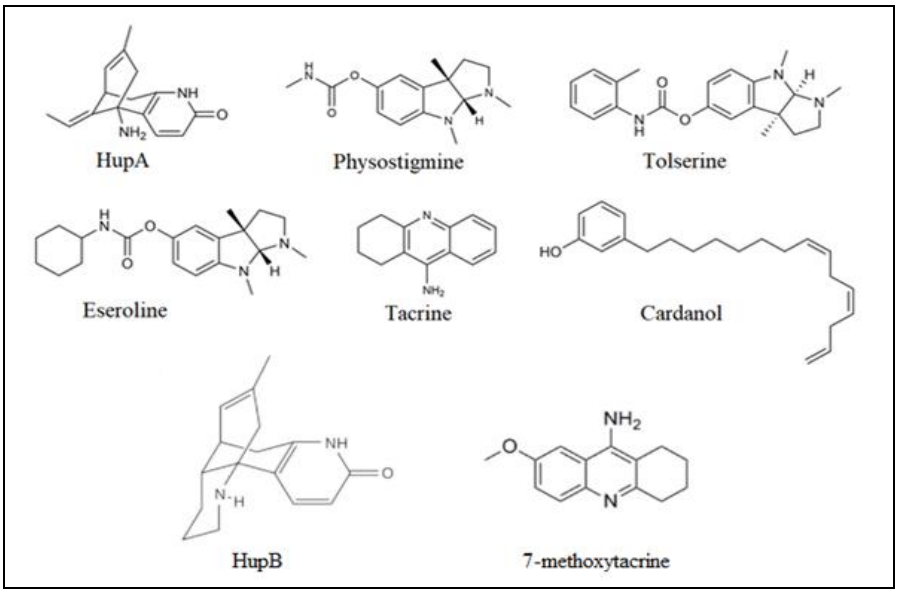


FIG. 2: STRUCTURES OF SINGLE-TARGET NATURAL AChEIs

Multi-Target AChEIs: Since, AD is a complex disorder there is a need of "one compound, multi targets" strategy. As the name suggests multi-target AChE inhibitors target more than one enzymatic pathway at a time to combat AD. Some multi-target AChE inhibitors are discussed below:

Ladostigil: Current development in pharmacology have enabled the creation of multifunctional molecules that work at several levels and may allow for improved control of the progression of AD. Ladostigil (shown in **Fig. 3**) has MAO-A/-B and ChE inhibiting property. This compound's dual effect made it particularly attractive for clinical trials [35].

Hybrid Compounds: Researchers chose to study the prospect of synthesising hybrid compounds in their search for effective AChE inhibitors. These ligands were created with the goal of binding to the peripheral sites in AChE as well as having a secondary effect on β-amyloid aggregation.

The hybrid compound, donepezil-AP2238 (shown in **Fig. 3**), was found to inhibit Aβ-mediated toxicity more effectively than donepezil, while being capable of binding to both anionic spots in AChE [36, 37].

Other hybrid ChEIs such as tacrine-ferulic acid (T6FA, shown in **Fig. 3**) and tacrine-8-hydroxyquinoline (shown in **Fig. 3**) found more efficient in inhibiting the cholinesterase *enzyme in-vitro* [38, 39]. Donepezil-tacrine composites (shown in Figure 3) were also discovered to inhibit AChE and beta amyloid aggregation. They were found to be more effective than their parent compounds [40].

Remarkable results were shown by the compound, donepezil-chromone-melatonin, by exhibiting strong inhibition of cholinesterase enzyme as well as antioxidant capabilities [41]. In addition, tacrine-acridine hybrids are being studied as multi-target medicines in the treatment of AD [42].

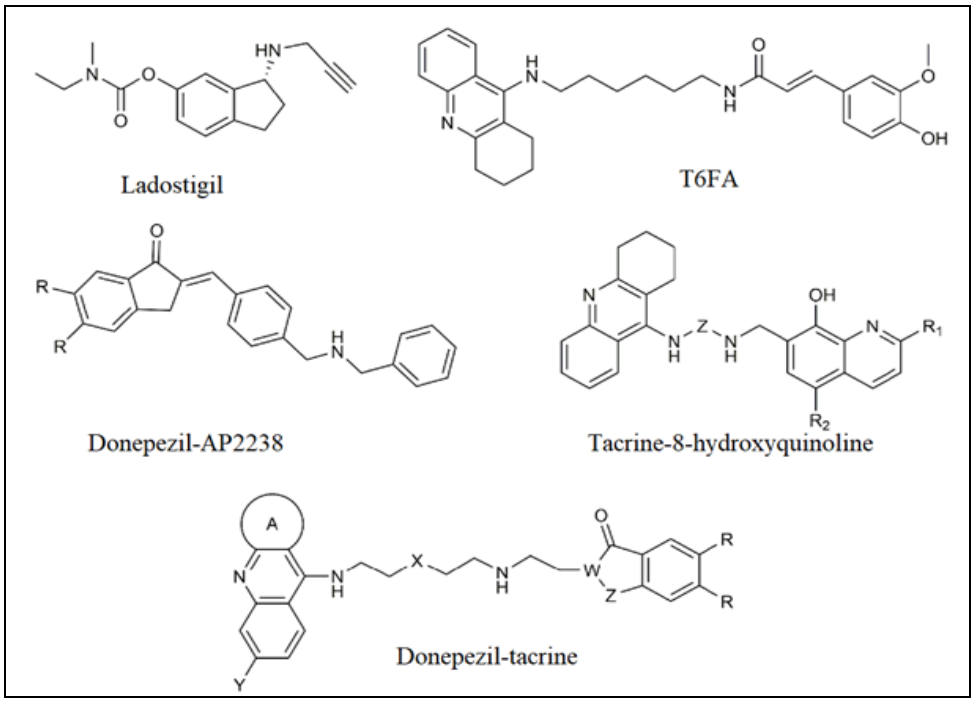


FIG. 3: STRUCTURES OF MULTI-TARGET ACHEIS (LADOSTIGIL AND HYBRID COMPOUNDS)

Multi-Target Natural AChEIs:

Flavonoids: It is well recognised that phytochemicals, particularly flavonoids, can be used to prevent and treat disease. Flavonoids can be found naturally in fruits and vegetables. It is a class of natural chemicals which is recognised for their ability to scavenge free radicals. They were widely utilised in traditional Chinese medicine and can be derived from plants. Galangin (shown in **Fig. 4**), a flavonol, demonstrated a 55 percent AChE inhibitory action in vitro with an IC_{50} of 120 µM [43].

Phenserine: Phenserine (shown in **Fig. 3**) also exhibits neuroprotective effects. It is a phenylcarbamate of physostigmine. When compared to standard anti-ChEs, it is a highly

selective AChE inhibitor with fewer side effects. It was utilised to treat cognitive problems caused by traumatic brain damage in mice and can be regarded as a multi-target medication because of its capacity to prevent Aβ-aggregation [44, 45]. Phenserine was also evaluated in Phase II tests, and it was found to be somewhat effective [46]. Indeed, after 12 weeks of treatment with phenserine (10 and 15 mg) patients' cognitive capabilities improved significantly. These results corroborated phenserine's potential efficacy in the treatment of AD symptoms. Further research is being carried out in order to understand its mechanism of action [47].

Algal Metabolites: Numerous researchers around the world have focused their attention on numerous algal metabolites such as alkaloids, polysaccharides and carotenoidsover the last decade [48]. Several preclinical investigations have verified such drugs' neuroprotective effect in metabolic ailments. Furthermore, algal metabolites have anti-inflammatory characteristics, as well as the ability to participate in defence processes [49, 50].

Fucoxanthin (shown in **Fig. 4**), a carotenoid, binds to the AChE anionic site in a non-competitive manner with an IC_{50} of 81.2 µM.[51]Different types of ChEs are inhibited by fucosterol (shown in **Fig. 4**) isolated from different algae species. The most effective is one from *Ecklonia stolonifera,* which has an IC_{50} of about 422 µM for BuChE [52]. When fucosterol and fucoxanthin are evaluated *in-vitro* and *vivo* experiments both resulted in an improvement in inflammation *via* MAPK mediated pathway [53, 54]. Fucosterol decreases the neurotoxicity in hippocampal neurons induced by Aβ-aggregation [55].

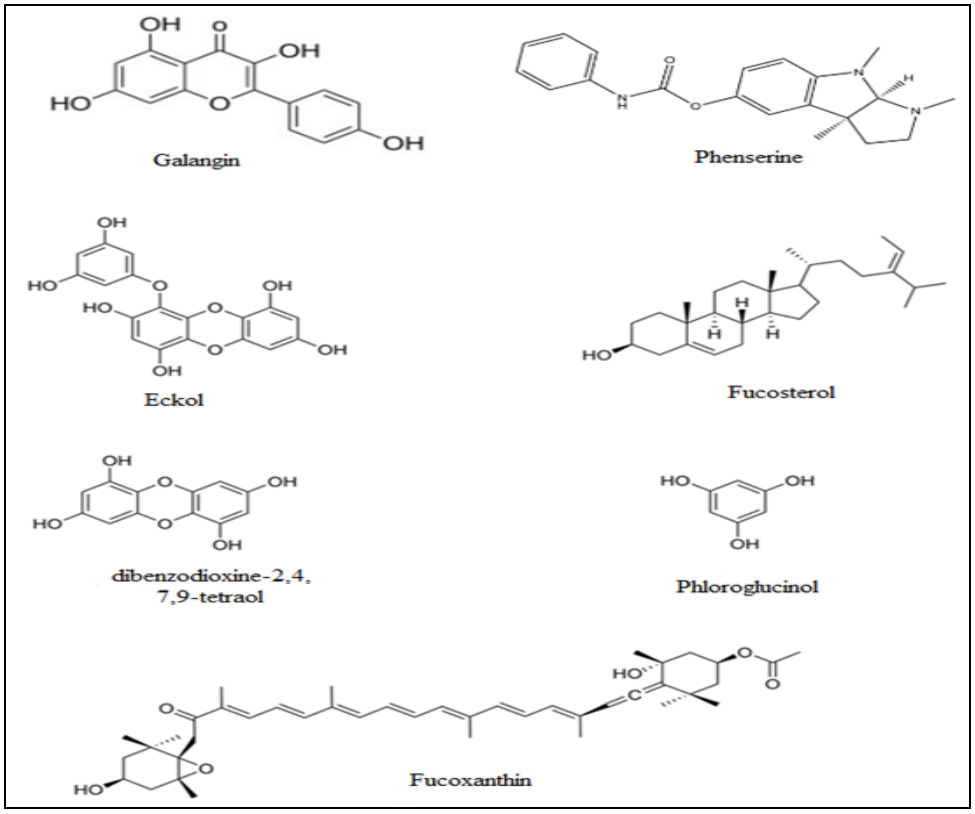


FIG. 4: STRUCTURES OF MULTI-TARGET NATURAL ACHEIS

With IC_{50} values ranging from 76.7 to 579.3 M, Phloroglucinoland Ecklonia maxima (both shown in **Fig. 4**) are considered to be powerful and selective inhibitors.

Dibenzodioxine-2,4,7,9-tetraol (shown in **Fig. 4**) is also found to be an effective anti-AChE molecule [56].

Recent Breakthroughs in the Field of Alzheimer`s Disease: The scientific community has long been perplexed by Alzheimer's disease, which was identified in 1906 and is currently the second biggest cause of mortality worldwide [2]. The best technique to treat it in a clinically precise manner has not yet been determined, despite

decades of research identifying the disease's hallmarks, such as the drop in acetylcholine concentration in the brain and the existence of amyloid plaques between neurons. Several scientists now concur that Alzheimer's disease precursors start to build up in the brain ten or more years before its signs appear. Over time, amyloid plaques can accumulate and eventually set off an inflammatory reaction that can quickly kill brain cells. A variety of factors, including family history, environmental factors etc. can have an impact on these impairments. Thus, the possibility of treating Alzheimer's disease can be increased by a combination of therapies. Now a days, targeting the amyloid plaques has become a major area of pharmacological research.

Lecanemab, a drug, is the latest breakthrough in the field of Alzheimer`s disease. Lecanemab was given accelerated approval by the Food and Drug Administration of the United States (FDA) on January 6, 2023. It may help people with early Alzheimer's disease to slow down their mild cognitive loss and diminish amyloid- plaques of the effected neurons within the brain cells [57]. It is a humanized IgG1 monoclonal antibody having more selectivity (>1000-fold) for large soluble amyloid clusters than small (monomers) amyloid clusters [58].

Another monoclonal antibody, Aducanumab, was granted a provisional approval by the FDA on June 7, 2021. It is a highly selective monoclonal antibody for amyloid aggregates. Some professionals voiced concern with the FDA's decision after it was approved. The insufficient data about phase III trials of this compound was the main reason of the controversy [59]. Another anti-amyloid plaque compound, Sodium oligomannate (GV-971), a marine oligosaccharide, received its first conditional approval on 2 November, 2019 in China for the treatment of mild to moderate AD. Shanghai Green Valley Pharmaceuticals in China made the initial discovery of this compound. They obtained the licensing rights for this compound in 2009. In phase III clinical trials performed in China, GV-971 dramatically decreased beta-amyloid plaque aggregates inside the brain cells. The phase III trial of GV-971 is still ongoing in US and Canada [60]. Docosahexaenoic acid (DHA), an omega-3 fatty acid, has recently been created by the researchers that can penetrate into the retina of the eye to prevent the loss of vision associated with Alzheimer's disease. The DHA that is generally included in fish oil capsules and other dietary supplements is known as triacylglycerol (TAG) DHA. TAG-DHA has advantages in other regions of the body, but it cannot enter the retina from the bloodstream. Thus, LPC-DHA, a brand-new lysophospholipid version of DHA, was produced for the study. LPC-DHA successfully raised DHA level in the retina and decreased eye related issues in a trial involving mice. The amount of LPC-DHA employed in this study was comparable to 250 to 500 mg of omega-3 fatty acids consumed by an adult daily. To confirm that LPC-DHA is safe for usage in people, additional research is required as these trials were carried out in mice [61].

Conclusion and Future Prospective: AD is one of the most well-studied neurodegenerative conditions; with more than 60% of individuals progressing to dementia. Recent research has revealed the molecular pathways behind the pathology as well as the development of reliable procedures of accurate diagnosis and efficient treatments. Alteration developed in the cholinergic system and the formation of amyloid plaques in the brain neurons are the major cause of progression of this disease.

Donepezil, rivastigmine, and galantamine are three anti-AChE medicines currently available in the market. Such chemicals have shown to be effective in lowering AD-related clinical symptoms, such as cognitive and behavioural impairments, as well as increasing the quality of life. Studies have revealed that AChE inhibitor therapy is beneficial in the initial phases of the illness, when symptoms are minor to mild.

New generation of ChE inhibitors have been designed and explored in this area, although only a few have entered clinical trials thus far. AChEIs can also act as multi-targeted medicines that can affect ChE as well as other enzymatic processes that take place in the person having AD. Numerous studies have been conducted in an effort to find more potent AChE inhibitors since the recognition of the very first inhibitor, physostigmine. AD is a serious aging-related health issue that places a significant burden on the world's healthcare systems. Though some symptomatic medications

have been approved, they have no effect on the development of the disease and only offer moderate clinical benefits. The FDA granted fast approval to one anti-amyloid antibody (aducanumab); however, it did not completely address the deserving need for AD treatment. As a result, Lecanemab, a second antibody, is discovered which shows the higher beta-amyloid plaque resistance property than Aducanumab. Hence, the development of disease-modifying medicines is essential to both enhancing the quality of life for AD patients and reducing the disease's overall burden.

More research is needed to understand the link between the various components involved in AD aetiology and development at the molecular level. Preclinical AD research may one day lead to effective medicines to treat the disease in its early stages and slow its progression. However, in order to identify patients with preclinical AD, it is important to set up inexpensive screening globally with the support of AD specialists and neurologists. Since AD progression depends upon various factors, researchers should develop a particular molecule capable of targeting several AD-related factors. Therefore, the challenge before researchers is to develop new effective drugs for the treatment of different phases of AD.

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