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Review

An update on the novel and approved drugs for Alzheimer disease

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ABSTRACT

Introduction: Given the severity of the condition and the increasing number of patients, developing effective therapies for Alzheimer's disease has become a significant necessity. Aggregation of Amyloid-Beta (Aβ) plaques and Tau Protein Tangles in the brain's nerve tissue are two of the most histopathological/pathophysiological symptoms. Another important element involved in the etiology of Alzheimer's disease is the reduction in acetylcholine (ACh) levels in the brain. Currently available medications for Alzheimer's disease treatment, such as cholinesterase inhibitors and an antagonist of the *N*-methyl-D-aspartate receptor, can temporarily reduce dementia symptoms but not stop or reverse disease development. In addition, several medicinal plants have been shown to diminish the degenerative characteristics associated with Alzheimer's disease, either in its crude form or as isolated chemicals.

Aim: This review summarises the results from previous studies that reflect an array of novel therapies underway in various phases of clinical trials. Many are discontinued due to non-adherence to the designed endpoints or the surfacing of unavoidable side effects. The present piece of article focuses on the approved drugs for the treatment of Alzheimer's disease and their related mode of action as well as the promising therapies for the treatment of the said disease. Special attention has been placed on the researched herbal drugs, with the pipeline of novel therapies underway in various phases of clinical trials.

Result: The current article includes a list of approved pharmaceuticals for treating Alzheimer's disease, prospective therapies for the illness's treatment, and a pipeline of novel therapies in various stages of clinical trials.

Conclusion: The results suggest that the drugs under clinical trials may open new pathways for the effective treatment of patients with Alzheimer's disease while improving their quality of life.

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1. Introduction

Alzheimer's disease (AD) seems to be the most prevalent cause of dementia and one of the major healthcare challenges of the present century. In summary, 40 million individuals are expected to suffer from dementia globally, and this figure is predicted to double in every 2 decades until around 2050 (Prince et al., 2013). AD is marked by gradual memory loss, language dysfunction, visual-spatial impairment, and personality abnormalities, all of which necessitate extensive caregiving (Wagner et al., 2012).

Extracellular amyloid plaques and intracellular Tau neurofibrillary tangles are the most common histopathologic lesions in AD. The pathophysiological feature of AD is depicted in Fig. 1 while representation of Tau Protein tangles is shown in Fig. 2**.** The core component of amyloid or senile plaques (SPs) is exceedingly insoluble and proteolysis-resistant peptide fibrils formed by -amyloid (A) cleavage. After the sequential breakdown of the big precursor protein amyloid precursor protein (APP) by the β- and γ-e -secretase, Aβ peptides with A38, A40, and A42 being the most prevalent forms are generated (Yiannopoulou et al., 2013). β- amyloid (Aβ) cleavage produces highly insoluble and proteolysis-resistant peptide fibrils, which make up amyloid or senile plaques (SPs).. However, if APP is first interacted on and broken by the enzyme α-secretase rather than β-secretase, Aβ is not generated. According to the "amyloid hypothesis," Aβ production in the brain sets off a chain of events that leads to the clinical symptoms of AD. The formation of amyloid oligomers is primarily responsible for neurotoxicity and commences the amyloid cascade. Local inflammation, oxidation, production of excess glutamate known as exitootoxicity, and tau hyperphosphorylation are all components of

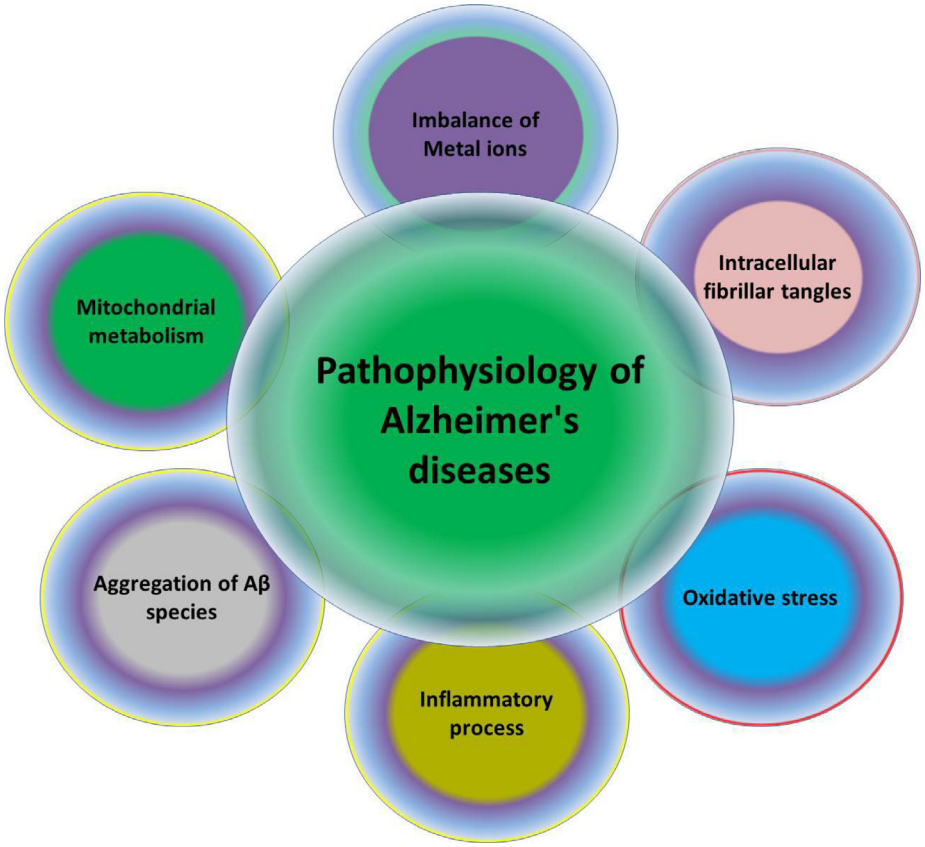

Fig. 1. Pathophysiological features of Alzheimer's disease.

Fig. 2. Representation of Tau Protein tangles.

the cascade [Anand et al., 2017]. Further another theory suggests the mitochondrial dysfunction hypothesis for AD pathogenesis posits that amyloidosis, cell cycle re-entry, and tau phosphorylation are all caused by mitochondrial failure in the AD brain (Swerdlow et al., 2014).

There is pertinent evidence to support the fact that that both cholinergic and glutamatergic neurochemical systems are involved in the genesis of AD. Acetylcholine (ACh) is a neurotransmitter involved in cognitive and learning functioning. Both concentration and function are reduced in brains of AD sufferers. The cholinergic theory of AD is supported by this impairment and other presynaptic cholinergic limitations, such as loss of cholinergic neural network and diminished acetylcholinesterase activity. The *N*-Methyl d-aspartate (NMDA) mediated glutamatergic hypothesis is another neurochemical explanation for the genesis of AD. Glutamate is an excitatory neurotransmitter that binds to NMDA receptors, which are important for memory and learning. Overstimulation of NMDA receptors by glutamate, on the other hand, can induce neuronal injury owing to excitotoxicity in some cases (Francis, 2005).

With the ever-increasing number of people being afflicted with AD, it is evident that effective treatments are vitally essential. Currently, symptomatic treatments for AD include acetylcholinesterase inhibitors such as donepezil, rivastigmine, and metrifonate and NMDA receptor blockers such as memantine [Reisberg et al., 2003]. Therapeutics that slow or stop disease progression are the need of the hour. The amyloid cascade theory is highly corroborated by pathology, genetics, and biochemistry; therefore, exploration of these therapies has been mostly designed to target A peptide or clumps in AD (Hardy and Selkoe., 2002).

The emergence of various approved drugs and the ones in clinical pipeline are elaborated upon with an additional insight on the potential therapies for the disease along with the pre-clinical research being undertaken by group of researchers for the treatment of AD.

2. FDA approved drugs for AD and their MOA

Though AD has no cure, one treatment may assist to slow clinical degeneration and enhance cognition and function. Others may be able to aid with alleviating symptoms like memory loss and confusion. The Food and Drug Administration (FDA) in the United States has approved pharmaceuticals that fall into two categories: drugs that may slow down clinical decline in patients with AD and therapies that may momentarily alleviate some of the associated symptoms of the disease. It is critical to speak with a health care expert before beginning any treatment to establish whether it is relevant. Patients who are using these drugs need to be monitored by a clinician who is familiar with them and guarantee that the specified guidelines are rigorously followed.

2.1. Drugs that may decrease the evolution of Alzheimer's disease

Drugs in this category may benefit individuals with AD halt clinical degeneration and improve cognition and function. On June 7, 2021, the FDA gave Aducanumab expedited approval [FDA Approved Drug Products: Aduhelm (Aducanumab-avwa) Intravenous Injection].

Aducanumab (AduhelmTM) is an anti-amyloid antibody and is an intravenous (IV) infusion medication for AD. An FDA-approved diagnostic test is often recommended prior to the start of the therapy. It is a high-affinity, completely human monoclonal antibody (mAb) that attaches to aggregated forms of Aβ and predominantly binds parenchymal amyloid as compared to vascular amyloid. It was produced via a reverse translational medical strategy, in which the antibody was obtained from older people who had not yet acquired AD, with the hope that they could have an exceptional resistance to the disease. Intraperitoneal injection of aducanumab into Tg2576 mice was reported to demonstrate parenchymal plaques and facilitate in their clearance without generating microhemorrhages (Dunstan et al., 2011). The researchers also noticed a build-up of brain macrophages encircling the residual plaques suggesting phagocytosis as a plausible clearance pathway.

According to the ‘‘amyloid cascade hypothesis,” the etiology of AD is driven by the aggregation of amyloid-oligopeptides in the brain (Arndt et al., 2018). Aducanumab is a monoclonal IgG1 antibody that binds to the amino acids 3–7.1,6 of amyloid-. Phe4, His6, Glu3, and Arg5 are the amyloid residues accounting for the bulk of the engagement between amyloid and aducanumab's Fab region. Acurenumab treatment lowers amyloid-, according to reports from animals and while human trials revealed no substantial improvements in amyloid-40 and amyloid-42 (Ferrero et al., 2016).

2.2. Conventional pharmacotherapy for AD

The drugs now used to treat AD can be divided into the following categories:

Rivastigmine, Donepezil, Galantamine, and Tacrine are acetylcholinesterase inhibitors.

Memantine is an NMDA antagonist (glutamate inhibitor).

2.2.1. Acetylcholinesterase inhibitors

The FDA has approved donepezil and rivastigmine for mild, moderate, and severe AD, respectively, while galantamine has been approved for mild and moderate AD (Rountree et al., 2013). Conventional class of drugs for the treatment of AD is shown in Fig. 3.

The action of acetylcholinesterase is enhanced in AD patients, which contributes to higher acetylcholine breakdown and decreased acetylcholine concentrations in the brain. In addition, the enzyme plays a role in the production of amyloid plaques and neurofibrillary tangles. The enzyme acetylcholinesterase also

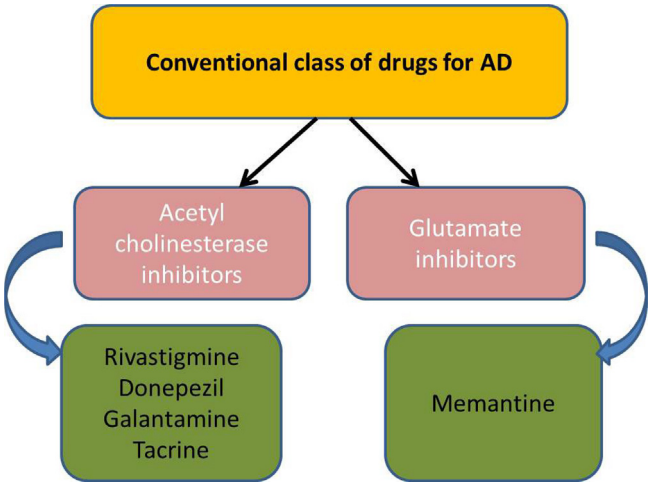

Fig. 3. Conventional class of drugs for the treatment of AD.

acts as a promoter, facilitating the development of -amyloid peptide fragments by forming complexes with the growing fibrillar structures. Individual -amyloid fibrils are found to confer more cytotoxicity than the resultant complexes. (Singh et al., 2013). These medications work by blocking the enzyme acetylcholinesterase, which is crucial for the metabolic breakdown of acetylcholine, which results in boosting its level in the brains of individuals with mild to moderate AD. In most patients, these classes of drugs were noted to be well tolerated (Tabet, 2006).

AChEIs action on the gastro-intestinal tract (git) causes the most common side effects, which include diarrhea, nausea, and vomiting (Yiannopoulou et al., 2020). The predominant route of elimination for donepezil and galantamine is reported to be hepatic metabolism, whereas those for rivastigmine is both hepatic and intestinal metabolism. Donepezil and galantamine are known to block acetylcholinesterase specifically and reversibly, but rivastigmine is a "pseudo-irreversible" acetylcholinesterase and butyrylcholinesterase inhibitor. The "pseudo irreversible" acetylcholinesterase activity of rivastigmine refers to the fact that it forms a covalent carbamoyl-AChE complex after reacting with the crucial active site serine, preventing it from catalyzing the synthesis of acetylcholine. Galantamine has a $t_{1/2}$ of 6 to 8 h, while donepezil has a 70-hour elimination half-life. Rivastigmine has a short elimination half-life, but it has a prolonged duration of effect (Atri 2019).

2.2.2. Glutamate inhibitor

Excitotoxicity is a condition caused by glutamatergic overstimulation, which causes neuronal injury by raising neuronal calcium burden. Memantine is known to be a non-competitive NMDA receptor antagonist that counteracts the negative effects of high glutamate concentrations in the brain (Yiannopoulou et al., 2013). It has made a way as a helpful therapeutic drug in people with AD because of the said attribute. Memantine, an approved drug for the treatment of moderate to severe AD, has been shown to enhance cognitive capacities and the resultant outcomes in people with AD (Reisberg et al., 2003). The said drug is well tolerated by most people. However, there may be minor and transitory side effects. It may interact with other medications according to its pharmacological nature. Concurrent treatment with levodopa, other dopamine agonists, and anticholinergics may enhance their biological activity according to their mode of action.

Memantine can be used in conjunction with an AChEI because their modes of action are complimentary. The said combinatorial therapy is usually beneficial to patients, with cumulative results and no rise in side effects (Kishita et al., 2020). In intermediate or advanced dementia, the duration and durability of monotherapy or combinatorial treatment modality with greater doses is linked to better overall functioning and therapeutic outcomes (Calvó-Perxas et al., 2017). Combining memantine with other chemically related NMDA receptor antagonists such as amantadine, budipine, ketamine, and dextrometorphan can lead to pharmacotoxic psychosis. Dizziness, agitation, hallucinations, headache, and exhaustion were the most common symptoms that arose in clinical trials. Anxiety, emesis, urinary tract infections, and increased sweating were among the less commonly reported symptoms (Molinuevo et al., 2005).

3. Potential therapeutic approach for the treatment of AD

3.1. Anti-amyloid therapy

According to the amyloid cascade hypothesis, AD is linked to monomeric Aβ aggregation. The development of harmful oligomers can be caused by an increase and buildup of Aβ in the synaptic synapse. These oligomers form protobrils, which eventually lead to amyloid deposits (Bondi et al., 2017). The "Amyloid hypothesis" proposes that Aβ generation in the brain propagates a series of pathophysiologic events that culminate in the clinical manifestation of AD The formation of amyloid oligomers, which eventually trigger the amyloid cascade, is primarily responsible for neurotoxicity (Yiannopoulou et al., 2013). The key pathophysiologic cornerstones of the cluster are oxidation, inflammation, excessive glutamate, and tau hyperphosphorylation.

To circumvent the said condition, anti-amyloid therapy acts by two major mechanisms either by reducing of Aβ42 production and Aβ-plaque burden or by promoting Aβ clearance (Atri 2019).

3.1.1. Reducing of Aβ42 production

3.1.1.1. α-secretase modulators. The non-amyloidogenic process is increased when APP is broken down by α-secretase, based on the current amyloid hypothesis. As a result, the modulation of the enzyme has been suggested as a major drug strategy. Clinical trials for APH-1105 and ID1201, two -secretase modulators that stimulate the PI3K/Akt pathway, are now underway. APH-1105 is an intranasal therapy for mild to moderate AD while ID1201 also activates α -secretase and is studied in subjects with mild AD (Cho et al., 2014).

Etazolate (EHT0202) is listed as another α-secretase modulators which acts as a selective GABA receptor modulator. The agent was reported to have a safety profile with a good tolerance in AD patients (Vellas et al., 2011).

3.1.1.2. BACE inhibitors. Due to unanticipated challenges, clinical studies with BACE inhibitors such as lanabecestat, verubecestat, and atabecestat have lately been terminated (Egan et al., 2019; Henley et al., 2019). The lanabecestat phase 3 investigation was halted due to a lack of efficacy, and the verubecestat and atabecestat trials were halted as well owing to inefficacy and safety concerns, respectively. All the treatments reduced cerebrospinal fluid (CSF) Aβ42 in a dose-dependent manner, but without providing any cognitive or functional benefits, and several of them were inadequately tolerated and ineffective in subjects with prodromal AD. These findings back the idea that stopping the formation of Aβ may not be enough to avoid the disease from progressing.

Elenbecestat (E2609) and umibecestat (CNP520) are the two agents which are in different phases of clinical trials (Cummings et al., 2019).

3.1.1.3. γ-secretase inhibitors. γ secretase inhibitors are no longer regarded a suitable target for the treatment of AD due to major safety concerns (Lopez et al., 2019). Additional investigations on this essential enzyme may assist to safely target -secretase therapeutically. There are no γ-secretase effectors in clinical trials right now. Semagacestat was linked to a deterioration of everyday activities as well as greater infections incidences and incidence of skin cancer, while avagacestat was linked to a higher percentage of cognitive decline as well as adverse dose-limiting effects such as the incidence of skin cancer while tarenflurbil had little blood–brain barrier penetration (Doody et al., 2013; Coric et al., 2015; Muntimadugu et al., 2016).

3.1.2. Reducing Aβ-plaque burden

Anti-amyloid aggregation drugs directly communicate with the Aβ peptide to prevent the production of Aβ42 fibers, making them a possible therapy for AD.

The oral drug, scyllo-inositol is a Aβ42 aggregation inhibitor that was studied in AD subjects (ELND005). A clinical study (phase 2) in patients with AD found no confirmation of ELND005′s clinical benefit, and the study was stopped due to severe toxicity concerns (Salloway et al., 2011).

Another promising treatment is KLVFF, a peptide sequence that mimics the hydrophobic center region of the Aβ and eventually replaces natural polypeptides. The KLVFF compound, which is resistant to proteolytic degradation and can also break down oligomerics to a limited level, is the final compound, can also break down oligomerics to a minor amount. (Stark et al., 2017).

3.1.2.1. Promoting Aβ clearance. Passive and active immunization are the 2 key immunotherapeutic methods for promoting Aβ clearance that are presently under investigation in various phases of analyses (Wisniewski et al., 2015).

3.1.2.1.1. Passive immunization. The most efficient and prospective class is passive Ab immunotherapy using mAbs. The chief disadvantages of this class of medicines are cerebral microhemorrhages and vasogenic edema (Yiannopoulou et al., 2013).

Crenezumab, gantenerumab, and solanezumab are the major therapies that are enrolled for preclinical studies or for at-risk populations, while crenezumab, gantenerumab, and solanezumab are the drugs that are for studies in prodromal and very mild AD patients (Yang et al., 2019). The preliminary results from the BAN2401 studies revealed a treatment-afflicted effect of a reduction in cerebral amyloid load in AD patients, together with a slowing of cognitive deterioration (Panza et al., 2018). Conversely, the preliminary trial of gantenerumab in patients with prodromal AD was untimely halted due to a lack of therapeutic efficacy, but research findings imply that relatively high gantenerumab dosing may be required to attain clinical effectiveness (Ostrowitzki et al., 2017) To achieve this an open-label addition for engaged patients with mild AD is being pursued concurrently with a double-blind, placebo-controlled study in AD patients. Similarly, until today, solanezumab had not been shown to slow the progression of brain atrophy.

3.1.2.1.2. Active immunization. A phase 2 research using UB-311, a synthetic peptide utilized as an Aβ vaccine, is now underway in individuals who are experiencing mild or moderate episodes of AD. It produced a total response rate in AD patients during the phase 1 of clinical trial. Swelling at the injection site and agitation were the most common side effects. Patients with mild AD had a slower rate of cognitive decline (Hull et al., 2017). The high rate of encephalitis in previous experiments (AN-1792) inspired the development of more potent anti-active immunotherapy drugs that are more specific to Aβ sites and less prone to activate T cells and are currently being tested in clinical trials. ABvac40 is being assessed as the first active vaccine. AD Patients with aged 50 to 85 years old participated in a phase one trial. There was no evidence of incident vasogenic edema or microhemorrhages. Antibodies specific to Aβ40 were generated in 92 % who had ABvac40 injections (Lopez et al., 2019).

3.2. Chelation therapy

Metal ion imbalance in the brain is among the primary triggers in the etiology of AD and hence it is appropriate to tackle this said illness with a chelation therapy technique employing metal ions (Pfaender et al., 2014). A metal chelator as an ideal drug for AD should meet essential qualities including moderate binding for metals, effective transit through biological membranes (particularly the BBB) and thereby lower toxicity (Bendova et al., 2010). Furthermore, determining the selectivity of prospective metal chelators is a significant complexity. The chelating capacity of metal chelators for AD treatment needs to be powerful enough to trap either free metal ions or Ab linked metal ions, but not substantial enough to participate with metal ions coupled to other metalloproteins that could perform a role in human health.

Even though there are many chelating agents, only some have desirable pharmacological effects and could be employed as a drug for AD. Clioquinol (CQ) and deferiprone (DFP) have been identified as promising AD drugs due to their lower MW and robust scaffolding attributes.

3.2.1. Clioquinol (CQ) and its derivatives

Metal ions can be chelated with CQ, decreasing Aβ aggregation. It also has the capability to chelate metal ions from metal–Aβ species into CQ–Cu(II) or CQ–Zn(II) complexes in a 2:1 ratio, preventing metal ions from adhering to Ab and dispersing brain aggregates in vitro [Ferrada et al., 2007]. These exciting findings give insights on the possibility of using metal chelating drugs to partially reverse the progression of AD. CQ indicated promising results in a phase IIa clinical trial in Alzheimer's patients and slowing cognitive decline [Ritchie et al., 2003]. Consequently, the emergence of CQ as an anti-AD drug has been halted due to potential neurotoxicity and undesirable mutagenic contaminants (Budimir et al., 2011).

In the presence of Cu(II), Zn(II), and Fe(III), a bis-8-hydroxyquinoline ligand, allowed huge rise in the potential to safeguard against b-amyloid peptide precipitation compared to CQ in vitro (Deraeve et al., 2007). It is known to inhibit Cu–Aβ from causing H2O2 generation, which is linked to harmful oxidative stress in AD.

Mohamed et al. synthesized (2,20-(1E,10 E)-(1,2- phenylenebis (methan-1-yl-1-ylidene)) bis (azan-1-yl-1-ylidene) dibenzoic acid), which is coordinated to metal ions with the azomethine-N and carboxylate-O as binding sites in a 1: 1 ratio. Magnetic and solid reflectance confirmed the geometrical structure of the formed complexes with the metal ions (Abdallah et al., 2010).

3.2.2. Deferiprone (DFP) and its derivatives

The iron chelator deferiprone (DFP, 3-hydroxy-1,2-dimethylpyridin-4(1H)-one) is known to treat thalassaemia (Telpoukhovskaia et al., 2013). It has a strongly positive and significant affinity for metals such as iron, copper, and zinc in its scaffold (Clarke et al., 1992). Even though DFP has a C log P value of 1.4, which is too negligible to cross the BBB, its low molecular weight as well as its suitable structure render it relatively easy to optimize, and it has been used as a lead compound in the development of multi-target directed ligands (MTDL) for the treatment of AD (Santos 2008).

Free radicals can also be scavenged by the Zn (II)–curcumin complex and the Cu(II)–curcumin complex. Furthermore, as compared to curcumin and Zn (II)–curcumin combination, Cu(II)–cur-

Table 1
List of herbal compounds for AD treatment.

Active compound	Source	Therapeutic attribute	Therapeutic efficacy	Ref
Berberine	*Coptis chinensis*	Antioxidant activity, butyrylcholinesterase and AChE inhibition, monoamine oxidase inhibition, and cholesterol-lowering effect	Berberine has been shown to improve memory, lower Aβ and APP concentration, and diminish Aβ plaque accumulation.	Huang et al., 2017
			Berberine treatment on BV2 microglia cells significantly suppressed the IL-6, COX-2, and iNOS expressions induced by β -amyloid.	Zhu et al., 2006
Curcumin	*Curcuma longa*	Anti-inflammatory, antioxidant, antitumor, antibacterial activities	By lowering oxidative damage, PC12 cells were found to be protected from Aβ induced neurotoxicity. and tau hyperphosphorylation with a dose of 5–10 μM.	Veldman et al., 2016
			In an Alzheimer's transgenic mouse model, curcumin has been reported to reverse amyloid etiology.	Lim et al., 2001
			Curcumin's antioxidant and anti-inflammatory qualities also helped to alleviate certain symptoms of Alzheimer's disease.	Yang et al., 2005
triterpenoids, flavonol glycosides, anthocyanins, and steroids	Convolvulus pluricaulis	Reducing the induction of tau and APP protein and mRNA levels	The neurotoxic action of scopolamine was substantially reduced when C. pluricaulis was administered orally.	Bihaqui et al., 2012
Bilobalide	Ginkgo biloba		When tested on neurons and Schwann cells, it showed substantial protective properties.	Defeudis 2002
			Increased the amounts of the transcription factor phosphorylated CREB and the neurotrophin BDNF in neuronal cells, which boosted neurogenesis and synaptogenesis.	Tchantchou et al., 2009
Epigallocatechin-3-gallate	Camellia sinensis	Antioxidant activity	In streptozotocin-induced dementia in mice, glutathione peroxidase activity was increased, AChE activity was inhibited, and NO metabolite production and ROS generation were also observed to be inhibited.	Biasibetti et al., 2013
			In mutant PS2 Alzheimer mice, enhanced memory retention and inhibited -secretase enzyme activity was noted	Lee et al., 2009
			In senescence-accelerated P8 animals, minimized Aβ accumulation and increased neprilysin enzyme expression was showcased.	Chang et al., 2015
Biflavonoid	*Chamaecyparis obtusa*		The biflavonoid have shown to protect HT22 mouse hippocampus cells from glutamate-induced oxidative damage by activating antioxidant enzymes and/or inhibiting ERK1/2.	Jeong et al., 2014
Ginsenoside Rg1	*Panax ginseng*	Physical stress reliever and stamina enhancer	Following oxygenglucose deprivation (OGD) therapy, it protected cultured hippocampal cells from ischemia-reperfusion injury by reducing neuronal nitric oxide synthase (nNOS) function and avoiding calcium overinflux into neural cells	He et al., 2014.
			Ginsenoside Rb1 was found to protect neurons against glucose-induced neurotoxicity, which has been linked to cognitive impairment in hippocampus neurons caused by diabetes.	Liu et al., 2014a
Catalpol	*Rehmannia glutinosa*	Antioxidation, anti-inflammatory, anti-apoptotic activity	It provided neuroprotection against cerebral ischaemia/reperfusion injury by reducing ROS, inhibiting lipid peroxidation, and increasing endothelin-1 production.	(Liu et al., 2014d).
			Modifying protein kinase C (PKC) and caveolin-1 (Cav-1) expression and limiting oxidative damage in diabetic rats was found to restore spatial memory loss.	(Zhou et al., 2014a).
Genistein	*Glycine* max	inhibited NF-κB, JNK and ERK signaling pathways	Genistein protected C6 glial cells from Aβ25-35-induced inflammation via altering the NF-B signaling cascade.	Zhao et al., 2014b
			It also reduced apotosis and improved antioxidation reaction in A (25–35)-induced cultured hippocampal neurons.	Zeng et al., 2004
Crocin	Crocus sativus		It worked by reducing stress-related oxidative damage to the brain and other organs in the tested rat model.	Bandegi et al., 2014
			Trans-crocetin, was observed to pass the BBB and enter the CNS when evaluated in Caco-2 monolayer cell culture, although crocin bioavailability was likely limited after oral treatment.	Lautenschläger et al., 2015
Huperzine A	*Huperzia serrata*	a natural inhibitor of acetylcholinesterase	It aided in ymptomatic treatment for AD. However, the chemical had no substantial impact.	Rafii et al., 2011
Glabridin	*Glycyrrhiza glabra*	brain cholinesterase inhibitory activity	The said study found that Liquorice's memory-improving effects were attributable to its antioxidant and antiinflammatory properties.	Chakravarthi and Avadhani, 2013
Honokiol and magnolol	*Magnolia officinalis*	Reactive oxygen species production is reduced, intracellular calcium levels are reduced, and caspase-3 activation is inhibited.	It significantly ameliorated Aβ induced neuronal apoptotic cell death.	Hoi et al., 2010

cumin complex had a better potential to scavenge free radicals. The findings could help researchers better understand the role of curcumin in the treatment of AD (Krishnankutty et al., 2003).

3.3. Natural drugs for AD treatment

Medications have been shown to reduce progression and associated symptoms of many diseases, including AD. Numerous studies have been conducted to look at the benefits of complete extraction of plants on AD, as well as to identify the functional factors involved in achieving the necessary therapeutic benefits (Ansari et al., 2013). Many molecules, including lignans, flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids, have been shown to have anti-inflammatory, anti-amyloidogenic, anti-cholinesterase, and anti-inflammatory properties. An array of substances has been used in people with AD which has produced promising results. (Olajide et al., 2017). Table 1 presents an array of herbal compounds that are being researched upon for AD.

4. Clinical trials of novel drugs for AD

Considering the complexity of the condition and the expanding number of patients, finding effective treatments for AD has risen to the top of the priority list. Currently available treatments for AD, such as cholinesterase inhibitors and the *N*-methyl-D-aspartate receptor antagonist, can temporarily reduce psychiatric symptoms but not stop or cure the progression of the disease. From an amyloid perspective, many international pharmaceutical companies have conducted numerous clinical trials in the treatment based on amyloid cleansing, but none have been successful. Researchers have developed and tested a variety of therapies, including anti-amyloid and anti-tau interventions, neurotransmitter mutations, anti- neuroinflammation and neuroprotection interventions, cognitive enhancement, and behavioral submission (Huang et al., 2020) An array of novel therapies is underway in various phases of clinical trials (Table 2).

Bapineuzumab was the first monoclonal antibody to target Aβ in AD using a passive immunotherapy technique. Following

Table 2
List of novel drugs in various phases of clinical trials for AD.

Drug entity	Trial Number	Study title	Description	Status
MEDI1814(anti-amyloid beta mAb)/ Phase I	NCT02036645	"SAD/MAD Study to Assess Safety, Tolerability, PK & PD of MEDI1814 in Subjects With Mild-Moderate Alzheimer's Disease"	Antibody binds to monomeric Aβ42	Completed
TPI 287 (next-generation taxane) / Phase 1	NCT01966666	"A Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Preliminary Efficacy Study of TPI-287 in Alzheimer's Disease"	It functions as a microtubule stabilizing and tubulin binding agent. Because it can pass across the blood–brain barrier, unlike other taxanes, it is being researched for tauopathies.	Completed
NGP 555/Phase 1	NCT02534480	"Neurogenetic Pharmaceuticals (NGP) 555 in Healthy Young Volunteers (Single-ascending Dose)"	By regulating the gamma secretase complex, it was shown to pass the BBB and efficiently reduce Aβ 42 and Aβ40	Completed
ALZT-OP1a and ALZT-OP1b/Phase1/2	NCT04570644	"Randomized I/II Phase Study of ALZT-OP1 Combination Therapy in Alzheimer's Disease and Normal Healthy Volunteers"	Mast cell stabilizer, anti-inflammatory	Recruiting
PF-06648671/Phase 1	NCT02316756	"A Single Ascending Dose Study To Evaluate Safety And Pharmacokinetics Of Compound PF-06648671 In Healthy Subjects"	Gamma secretase modulator	Completed
SUVN-502 / Phase 2a	NCT02580305	"SUVN-502 With Donepezil and Memantine for the Treatment of Moderate Alzheimer's Disease- Phase 2a Study"	5-HT4 antagonist	Completed
AC-1204(glucose stimulant) / Phase 3	NCT01741194	"AC-1204 26-Week Long Term Efficacy Response Trial With Optional Open-label Ext (NOURISH-AD)"	Caprylic triglyceride is an oral formulation that promotes a mild persistent ketosis, which enhances mitochondrial metabolism. In people with Alzheimer's disease, it provides a fueling substitute to glucose.	Completed
IIdalopirdine / Phase 3			Selective 5-HT6 antagonist	
Posiphen / Phase 1	NCT04524351	"Posiphen® Dose-Finding, Biomarker Study in Early Alzheimer's and Parkinson's Patients"	A small, lipophilic, orally available chemical that easily passes the BBB. Iron promotes neurotoxic aggregating protein mRNA translation, but iron regulatory protein-1 prevents it (IRP-1). This drug decreases the amount of free mRNA accessible for translation by increasing IRP-1 binding to the iron response element stem loop in the 5′UTR of the mRNAs in issue.	Active, not recruiting
Rilapladib / Phase 2a	NCT01428453	"A Phase 2a Study to Evaluate the Effect of Rilapladib (SB-659032) in Alzheimer's Disease"	Lipoprotein-associated phospholipase A2 inhibitor	Completed
Nilvadipine / Phase 3	NCT02017340	"A Phase III Trial of Nilvadipine to Treat Alzheimer's Disease (NILVAD)"	This dihyropyridine calcium channel blocker is being evaluated for its efficacy in the treatment of AD, based on epidemiological research associating hypertension to dementia.	Completed
Elenbecestat (E2609)/ Phase 3	NCT02956486	"A 24-Month Study to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Participants With Early Alzheimer's Disease"	BACE inhibitor	Terminated
MK-7622 / Phase 3	NCT01852110	"Efficacy and Safety of MK-7622 as Adjunct Therapy in Participants With Alzheimer's Disease (MK-7622–012)"	Muscarinic M4 receptor modulator	Terminated
Tau Mab / Phase 1	NCT04619420	"A Study of JNJ-63733657 in Participants With Early Alzheimer's Disease (Autonomy)"	A monoclonal antibody that binds to human tau and has been shown to be effective in the treatment of AD and other tauopathies.	Recruiting

the completion of the first two studies, which revealed no treatment efficacy on either cognitive or functional outcomes, further trials were halted (Salloway et al., 2014). A phase 2b study of E2609 (elenbecestat), a BACE-1 inhibitor, in amyloid-PET people with MCI, prodromal AD, or mild AD was performed and reduced dose-dependent in CSF A levels was noted. There is no significant change in AD. Composite Score or CDR-SB score (Murakami et al., 2019). In a 24-month study to evaluate the efficacy and safety of elenbecestat in studies on Alzheimer's Disease (MISSION AD1) and MISSION AD2 trials of prodromal AD, elenbecestat therapeutic efficacy was tested. The said trials are expected to run until December 2023. GV-971 (sodium oligo-mannurarate) binds to several amyloid sites, further destabilizes, and prevents Aβ synthesis, and increases the elimination of Aβ (Wang et al., 2019). The effects of GV-971 on mild to severe form of AD were tested in a phase 3 study that started in April 2014 and the results of this study highlighted the fact that GV-971 has significant cognitive benefits.The dihydropyridine calcium channel blocker nilvadipine with a capacity of lowering Aβ production and increasing clearance Aβ was evaluated for neuroprotective and anti-inflammatory properties (Lawlor et al., 2018).

The NILVAD trial, which took place in 2013, examined the effectiveness of nilvadipine in people with AD. ADAS-Cog was the main outcome measure, but there was no difference in the primary or secondary end point measures according to a published report (Bishop et al., 2004).

The effectiveness of suvorexant in patients with mild to severe AD with insomnia was studied in a phase 3 trial. Merck pointed out that the first and second objectives of the case were fulfilled. It can therefore be said that Suvorexant can be an effective treatment for the behavioral and psychological symptoms associated with AD (Herring et al., 2019). EVP-6124, an antagonist of 5-HT3 receptor and a agonist of 7 nicotinic acetylcholine receptor a has a central role in regulating the release of various neurotransmitters (Ahmed et al., 2019). It enhances cholinergic neurotransmission, which increases cognitive abilities. A trial (phase 3) to assess its safety was initiated but FDA issued a clinical hold owing to its gastrointestinal side effect.

Apiprazole works to stabilize the dopamine system (DSSs). It helps to improve the reduction of neurite-induced neuropathy. In AD-related psychosis, this treatment has the potential to remove the neurotoxicity induced by Aβ (Coleman et al., 2017). A phase 3 clinical study examined the effectiveness of different doses of aripiprazole in people AD who were agitated. Because it was difficult to hire volunteers, the attempt was completed in March 2016.

In the year 2018, two phase 3 clinical trials involving azeliragon for patients with mild AD were initiated and its the study (phase 3) in individuals with AD and poor glucose tolerance started in the year 2019 which is expected to be completed in 2023 (Galimberti et al., 2017).

Due to the shortage of anti-AD drugs, experiments with various drugs, such as anti-amyloid and anti-tau, neurotransmitter flexibility and neuroprotective benefits, and mental enhancement, require planning that can provide promising results.

5. Significance of work

Several options for treating AD are currently being researched. Phytopharmaceuticals and nutraceuticals are also gaining popularity in the fight against Alzheimer's disease. The current article includes a list of approved pharmaceuticals for the treatment of AD, as well as prospective therapies for the illness's treatment and a pipeline of novel therapies in various stages of clinical trials. The drugs under clinical trials may open new pathways for effective treatment of patients with AD while improving their quality of life.

6. Conclusion

A slew of ongoing clinical trials is focusing on numerous therapy targets in AD. Considering the recent knowledge of a high percentage of failed AD clinical trials on therapeutics, more recent trials appear to be bolstered by the convergence of advances in AD biomarkers, the positioning of a single primary outcome and fabrication of novel trial designs. At the same time, cutting-edge research is focusing on the generation of more comprehensive diagnostic tools as well as disease prevention investigations. Framing a compelling therapeutic affiliation of the patient with healthcare providers through a comprehensive and integrated strategy that uses psychoeducation, behavioral, and environmental methodologies, innovative prepping for future healthcare demands along with relevant pharmaceutical treatment would add substantial value in the treatment regime for AD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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