REVIEW

Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease

Teeba Athar[1] · K. Al Balushi[1] · Shah Alam Khan[1]

Abstract

Alzheimer's disease (AD) is a neurodegenerative old age disease that is complex, multifactorial, unalterable, and progressive in nature. The currently approved therapy includes cholinesterase inhibitors, NMDA-receptor antagonists and their combination therapy provides only temporary symptomatic relief. Sincere efforts have been made by the researchers globally to identify new targets, discover, and develop novel therapeutic agents for the treatment of AD. This brief review article is intended to cover the recent advances in drug development and emerging therapeutic agents for AD acting at different targets. The article is compiled using various scientific online databases and by referring to clinicaltrials.gov and ALZFORUM (alzforum.org) websites. The upcoming therapies act on one or more targets including amyloids (secretases, $A\beta_{42}$ production, amyloid deposition, and immunotherapy), tau proteins (tau phosphorylation/aggregation and immunotherapy) and neuroinflammation in addition to other miscellaneous targets. Despite the tremendous improvement in our understanding of the underlying pathophysiology of AD, only aducanumab was approved by FDA for the treatment of AD in 18 years i.e., since 2003. Hence, it is concluded that novel therapeutic strategies are required to discover and develop therapeutic agents to fight against the century old AD.

Graphic Abstract
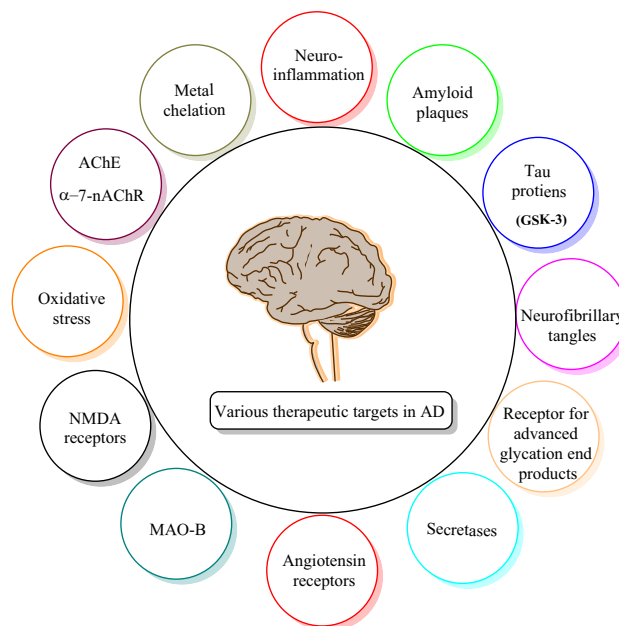
Keywords Acetylcholine · Alzheimer's disease · Beta-Amyloid · Neurodegeneration · Tau proteins

Extended author information available on the last page of the article

Abbreviations

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ACh	Acetylcholine
AD	Alzheimer's disease
ApoE4	Apolipoprotein E4
APP	Amyloid precursor protein
Aβ	Beta amyloid
BBB	Blood brain barrier
BACE	Beta secretase
ChE	Cholinesterase
CSF	Cerebrospinal fluid
DMD	Disease modifying drugs
EOAD	Early onset AD
FDA	Food and drug administration
GABA	Gamma aminobutyric acid
GSK3	Glycogen synthase kinase 3
GWASs	Genome-wide association studies
Ig	Immunoglobulins
LOAD	Late onset AD
mAB	Monoclonal antibodies
MAO	Mono amine oxidase
MSC	Mesenchymal stem cell
MTD	Multi target drugs
nAChR	α7-Nicotinic ACh Receptor
NFT	Neurofibrillary tangles
NID	New investigational drug
NMDA	N-Methyl D-aspartate
NSAID	Non-steroidal anti-inflammatory drug
ODOT	One drug one target
OLE	Open label extension
PSEN1	Presenilin 1
RAGE	Receptor for advanced glycation end products
TKI	Tyrosine kinase inhibitor

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease. It severely affects cognitive abilities of a person causing loss of memory and conscience. It is complex, unalterable, and progressive in nature. AD is the prevalent cause of dementia in late adult life and is linked with high morbidity and mortality rate in the elderly [1]. In 1906, the first case of AD was reported by a German psychiatrist and pathologist Alois Alzheimer after whom the disease is named [2]. It is associated with both genetic and environmental factors but the most prominent risk factor is age, and thus it is most prevalent in the older groups [3]. It is one of the most widespread neurodegenerative diseases affecting around 40 million people around the globe and it is expected that more than 100 million people will live with AD by 2050. AD is a progressive and a devastating brain disorder that places a considerable financial burden on the government, families, and individuals. Some of the common symptoms of mild AD

include a decline in memory, change in personality, impaired reasoning, poor judgments, and inability to perform normal daily tasks, etc. [4]. The key clinical co-pathological indicators (Fig. 1) of AD are the formation of amyloid plaques or senile plaques formed through the accumulation of amyloids in extracellular regions while aggregated hyperphosphorylated tau proteins in the intracellular regions form neurofibrillary tangles (NFT) in affected neurons [5]. Accumulation of amyloid plaques, which primarily contains amyloid beta$_{40/42}$ peptides, further leads to neuroinflammation and misprocessing of tau proteins. The MRI scan of the brains of AD patients shows shrinkage of the hippocampus and entorhinal cortex regions in comparison to the normal brain (Fig. 1).

AD can be classified typically into two types: sporadic and familial. Sporadic AD affects people above 65 years and is often referred to as late-onset AD (LOAD). Familial forms of AD are influenced by genetic factors and inheritance, the affected group lies between 30–65 years of age and is referred to as early-onset AD (EOAD) [6]. The Familial type of AD is originated through a rare autosomal dominant mutation occurring in three genes: Amyloid Precursor Protein (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2) [7]. The majority of AD cases are sporadic and are driven by environmental factors and few genetic influences. A genetic risk factor found in sporadic AD cases through detailed genome-wide association studies (GWASs) is the presence of epsilon 4 allele in Apolipoprotein E4 (ApoE4).

The symptomatic treatment with cholinesterase inhibitors, NMDA-receptor antagonists, and combination therapy are currently approved strategies for AD. However, there are other mechanisms also that contribute to the pathogenesis of AD such as neuroinflammation, oxidative stress, hypoglycemia and vascular dysfunction, metal dyshomeostasis, protein misfolding, clearance of abnormal proteins, etc., and thus are the potential targets for the treatment of AD [8]. The new
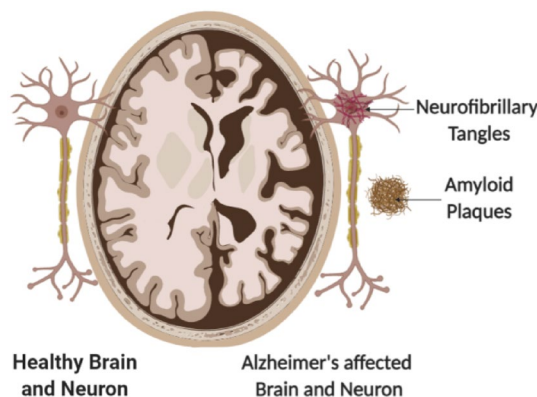
Fig. 1 Illustration showing the comparison between the brain of a healthy and an affected one

disease-modifying drug (DMF) strategies are emerging that target the pathogenic culprits of the disease i.e., extracellular amyloid plaques and intracellular neurofibrillary tangles in addition to other miscellaneous mechanisms. This brief review article is intended to review the approved symptomatic therapies, upcoming therapies targeting amyloids, tau proteins, neuroinflammation, mitochondrial dysfunction, and miscellaneous targets.

Therapeutic strategies for the development of anti-AD drugs

AD exhibits complicated multifactorial pathophysiology which is responsible for the disease being difficult to handle. The AD pathogenesis is associated with several complex pathways including deficiency in cholinergic neurotransmission, defective beta-amyloid (Aβ) protein metabolism (Aβ aggregation), tau protein deposition and phosphorylation (NFT), and the involvement of inflammatory and oxidative pathways [9]. The currently approved drugs act on one target (one drug one target; ODOT) but lately, attention has been paid to multiple therapeutic strategies to design and develop drugs capable of hitting at more than one target [8, 10]. Multi-target drugs (MTDs) are designed by incorporating two or more pharmacophoric structural features of bioactive drugs acting at different targets in a single molecule. These pharmacophoric structural scaffolds can be connected directly (fused), through a tether/linker or merged together. ANAVAX 2–73 and ladostigil are examples of the drugs acting at multiple targets. Ladostigil, a hybrid conjugate (merged) of carbamate rivastigmine and N-propargyl, is a dual inhibitor of cholinesterase (ChE) and monoamine oxidase (MAO) enzymes (Fig. 2). This drug failed to meet its primary endpoint of delaying progression from mild cognitive impairment to AD in second phase 2 clinical trials [11].

Lumateperone is an example of another multi-target drug that could regulate the levels of several neurotransmitters (Fig. 2). It was evaluated for its efficacy in the phase 3 trial. But, the drug did not meet the primary endpoint and the trial was discontinued in 2018 [12]. Idalopirdine (2-(6-fluoro-1H-indol-3-yl)-ethyl]-[3-(2,2,3,3-tetrafluoro-propoxy)-benzyl]-amine) is a hybrid molecule designed to inhibit AChE and to target 5-HT6 receptors (Fig. 2). It was prepared by incorporating tryptamine moiety, a pharmacophore from 5-HT and a benzylamine pharmacophore from an AChE inhibitor. It received a fast-track designation by FDA in 2016, however it showed weak efficacy in the phase 3 trials and therefore was discontinued [13]. In our opinion, the hybridization approach should be used to fuse, merge or link two or more pharmacophoric motifs acting at more than

one target but through the same pathway to obtain MTDs possessing synergistic therapeutic effects.

Though MTD strategy is a promising rational approach but an approved drug progressing from clinical trials to market is yet to be developed. As of 4th March 2021, more than 140 agents with the diverse mechanisms of action have been registered in the clinical trials for AD. The result of a search done on clinical trials by entering the term "Alzheimer's" in the disease field and selecting interventional studies revealed that there are currently 111 clinical studies in phase 2/3 and 29 in phase 3 clinical trials. These interventional studies are evaluating the safety and efficacy of new molecules and repurposed drugs acting on different targets. Majority of the therapeutic agents in the pipeline target amyloids (AChEI, BACE inhibitors) tau proteins, mitochondrial dysfunction, oxidative stress, metal dysregulation, neuroinflammation and at some miscellaneous targets to reverse the progression of AD. Various therapeutic approaches used to develop agents for AD are illustrated in Fig. 3 and the status of some selected agents tested in clinical trials is presented in Table 1.

Drug repositioning and repurposing are the strategies to accelerate the drug discovery and development process. Drug repurposing involves the use of an approved existing drug for some new therapeutic indication, for example, use of remdesivir in COVID-19 [14] while drug repositioning occurs during the development process in biopharmaceutical industries and refers to the development of a drug for an indication different than its original intended indication [15]. Applications of drug repurposing and repositioning to identify novel molecules for the treatment of AD have been reviewed [15–20]. One study reported that approximately 40% of drugs currently undergoing clinical trials for the development of anti-AD drugs belong to the repurposed drugs. More than 3/4th of these drugs are disease-modifying agents with the highest representation from hematologic-oncologic agents (20%), cardiovascular drugs (18%), antipsychotic agents (14%) and antidiabetic agents (12%). Some of the repurposed drugs in the pipeline for AD in the phase 3 clinical trials include escitalopram (SSRI, antipsychotic), brexipiperazole (Dopamine D_2 partial receptor agonist, schizophrenia), masitinib (anti-cancer), metformin (antidiabetic), guanfacine and losartan (cardiovascular) [16]. Corbett et al., in 2012 published an expert Delphi consensus review listing five potential classes of prioritized drugs for repurposing namely, minocycline (tetracycline antibiotic), losartan (angiotensin receptor blocker), nivaldipine (calcium channel blocker), liraglutide or semaglutide (glucagon- like peptides 1) and retinoid therapy for the treatment of AD [21]. Clinical trials of minocycline, nivaldipine, and losartan did not reveal significant benefits in AD patients [22–24]. A recent Delphi consensus process conducted in 2018–19

Fig. 2 Chemical strategy used to synthesize ladostigil and idalopiridine as multi-target drugs
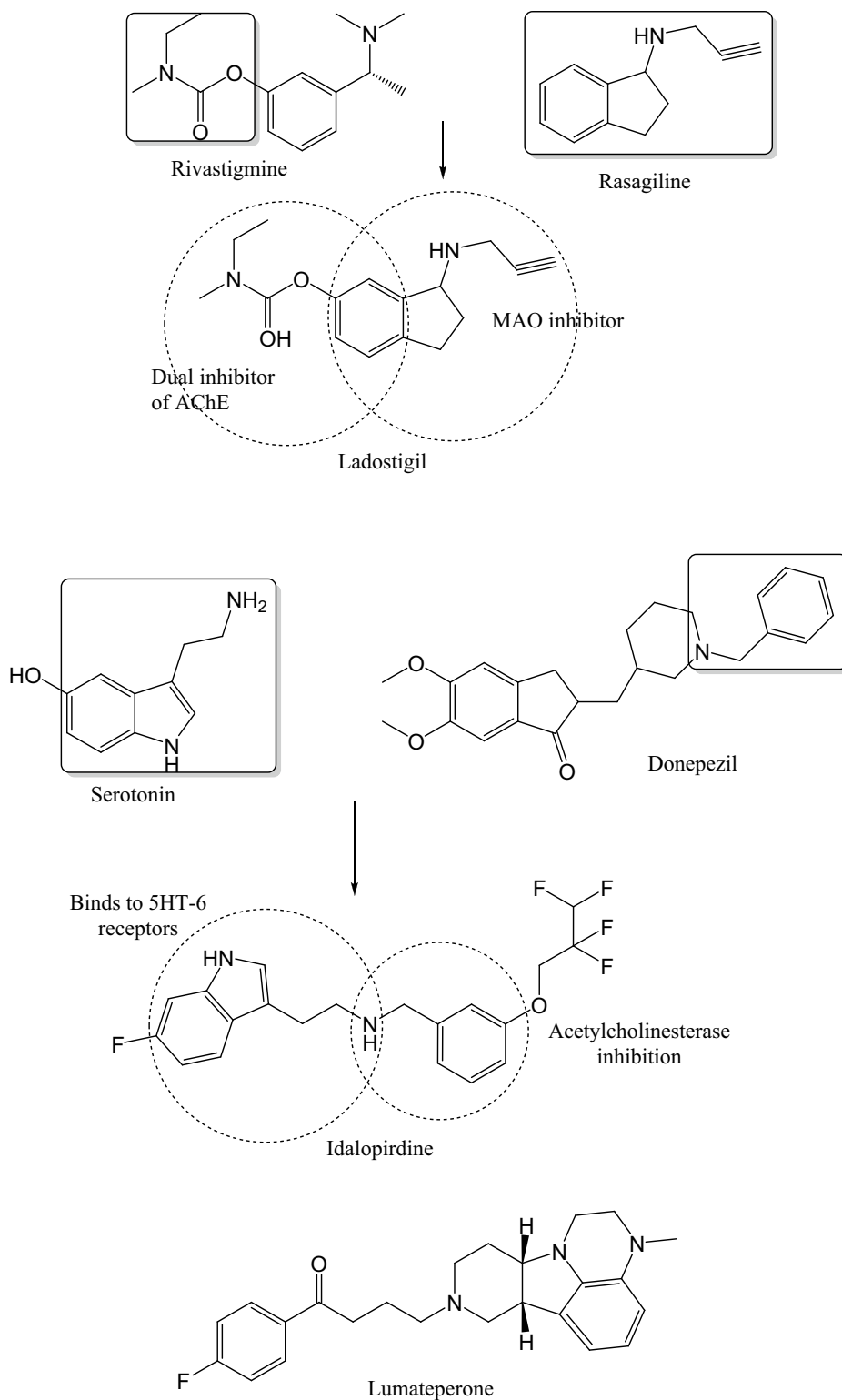
further identified three new high priority repurposed drug candidates for clinical trials in AD patients. These molecules were shortlisted based on the preclinical data and include fasudil (a selective inhibitor of rho kinase; ROCK inhibitor), phenserine (AChE inhibitor) and valaciclovir,

acyclovir, foscarnet and famciclovir (antiviral drugs). The non-shortlisted compounds included ACE inhibitors (captopril, ramipril, perindopril) and some disease-modifying antirheumatic drugs (chloroquine/hydroxychloroquine, methotrexate, cyclosporine, etc.) [15]. Preclinical studies
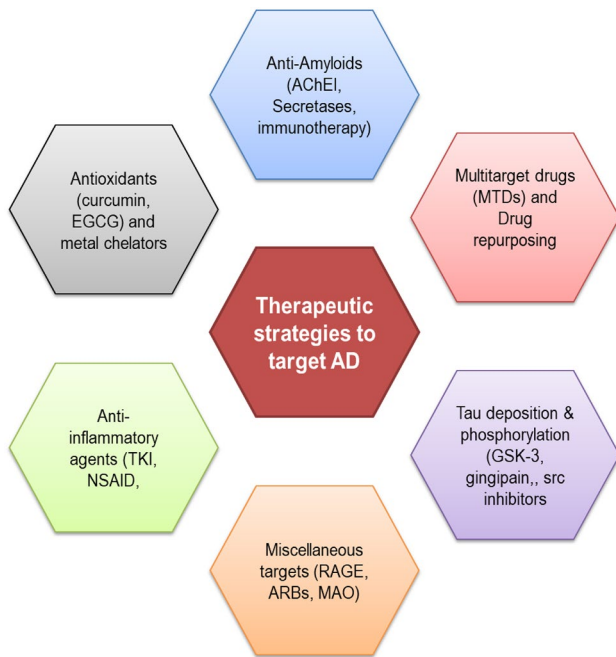
Fig. 3 Various therapeutic approaches used to develop agents for AD

indicated that fasudil acts by decreasing the Aβ levels, neuroinflammation and by preventing synaptic damage [25–27]. Antiviral drugs might inhibit Aβ aggregation and abnormal tau phosphorylation induced by herpes simplex virus [28, 29].

Kumar et al., used in silico approach combined with in vitro investigation to identify repurposed drugs as AChE inhibitors among the pool of FDA-approved drugs (2369) to treat AD. Based on the virtual screening and in vitro analysis, they identified three classes of repurposed drugs viz., thiazolidinedione antidiabetic (rosiglitazone), aminoquinoline antimalarial (hydroxychloroquine), and antifungal drugs (miconazole) as mild to moderate AChE inhibitors [17].

Stem cell (SC) therapy is another upcoming field that has received considerable attention in recent years to treat cancer, blood-related diseases and neurodegenerative diseases including AD [30, 31]. It has shown promising results in AD animal models, preclinical and in early clinical studies especially with regard to reduction in neuroinflammation, increase in neurotransmission, neuronal growth and clearance of proteins, etc. Different type of stem cells such as embryonic SC can mitigate ACh levels [32], induced pluripotent SC can help in regeneration of depleted neural network [33, 34] while umbilical cord blood/placenta and mesenchymal SC can reduce Aβ, tau phosphorylation and reverse microglial neuroinflammation [35]. Several clinical trials (phase1/2) involving autologous adipose tissue-derived mesenchymal stem cells (MSC), human MSC, leukemia MSC, bone marrow MSC and human umbilical cord

blood-derived MSC have been conducted in the AD patients to evaluate their safety and efficacy [36, 37]. Undoubtedly stem cell therapy has the potential to produce disease-modifying effects in AD and therefore cast a ray of hope in a battle against the devastating AD. Though numerous challenges and hurdles (safety, efficacy, genomic instability, reproducibility of cell types, route of administration, optimization of clinical outcome, ethical issues, etc.) are to be overcome before the introduction of this innovative technique into clinical practice.

FDA approved symptomatic therapies to treat AD

Pathways and exact mechanisms leading to AD are still not completely understood resulting in a high rate of failed therapeutic strategies. Presently the symptomatic treatment of the disease to slow the progression of AD is concentrated on three therapies: (a) Cholinesterase inhibitors; (b) *N*-methyl D-aspartate (NMDA) receptor antagonists, and c) combination therapy. The prime cause of AD is the depletion of the neurotransmitter, hence the cholinesterase inhibitors aimed at increasing the amount of ACh, this is achieved through the application of cholinergic inhibitors (viz., rivastigmine, donepezil, tacrine, galantamine). These inhibitors limit the reduction of ACh concentration in the brain (Fig. 4) [38].

Ideally, the NMDA-receptor functions by permitting calcium ions entry for neurotransmission. But in the case of AD, the receptor manifests high activity resulting in overabundance of Ca^{2+} leading to excitotoxicity and cell death [39]. The high activity of the receptor is controlled by an anti-AD drug called memantine that binds to the open state of the NMDA-receptor and functions as a non-competitive antagonist [3].

In combination therapy, a mixture of memantine and donepezil (28 mg and 10 mg, respectively once daily) has shown effective results in treating symptoms like cognitive judgment, language, and behavioral problems in the moderate to severe group of AD patients. The results were significantly better than placebo comprising a combination of memantine and placebo [40]. However, the combination was not effective in patients with mild to moderate disease [41].

Unfortunately, the currently approved agents offer temporary relief from the symptoms of this complex disease and therefore search is on to discover and develop novel agents for AD therapy.

Upcoming AD therapies targeting amyloids

The amyloid hypothesis describes beta amyloid (Aβ) formation to be one of the major culprits in the pathogenesis of AD [42]. A sequence of proteolysis of APP forms Aβ. This is achieved through two metabolic pathways: the non-amyloidogenic pathway and the amyloidogenic pathway.

Table 1 Status and mechanism of action of some selected anti- AD drugs tested in clinical trials

S. no	Name of the drug	Mechanism of action	Status of the clinical trial
1	Lanabecestat	BACE1 reversible inhibition	phase 3 (terminated in 2018)
2	Umibecestat	BACE1 reversible inhibition	Phase 2/3 (terminated in 2019)
3	Tramiprosate[a]	Aβ aggregation inhibition	Phase 3 (discontinued in 2007)
4	ALZ-801	Aβ aggregation inhibition	Phase 3 (ongoing)
5	Verubecestat	BACE1 reversible inhibition	Phase 3 (discontinued in 2017)
6	Elenbecestat	BACE1 reversible inhibition	Phase 3 (discontinued in 2019)
7	Atabecestat	BACE1 reversible inhibition	Phase 2/3 (ongoing)
8	Semagacestat	γ-secretase inhibitor	Phase 3 (terminated in 2011)
9	Avagacestat	γ-Secretase inhibitor	Phase 2 (discontinued in 2012)
10	Etazolate	α-Secretase stimulator	Phase 2 (ongoing)
11	Acitretin[a]	α-Secretase stimulator	Phase 2 (ongoing)
12	Epigallocatechin-gallate[a]	α-Secretase stimulator	Phase 2/3 (ongoing)
13	Tarenflurbil (MPC-7869)	γ-Secretase inhibitor	Phase 3 (terminated in 2009)
14	GV 971	Aβ aggregation inhibitor	Phase 3 (undergoing)
15	Colostrinin	Aβ aggregation inhibitor	Phase 2 (terminated in 2009)
16	Bapineuzumab	Anti-amyloid mAB	Phase 3 (discontinued in 2012)
17	Solanezumab	Anti-amyloid mAB	Phase 3 (ongoing)
18	Gantenerumab	Anti-amyloid mAB	Phase 3 (ongoing)
19	Aducanumab[a]	Anti-amyloid mAB	Approved (7th June 2021)
20	Lecanemab	Anti-amyloid mAB	Phase 3 (ongoing)
21	LMTM	*tau* aggregation inhibitor	Phase 3 (ongoing)
22	Blarcamesine	Sigma-1 receptor activator	Phase 2b/3 (ongoing)
23	Saracatinib[a]	Src kinase inhibitor	Phase 2a (terminated in 2018)
24	Thiamet G	*O*-GlcNAcase enzyme inhibitor	Phase 1 (ongoing)
25	Telmisartan[a]	Angiotensin II receptor blocker	Phase 2 (ongoing)
26	ALZT-OP1[a]	Aβ clearance promotor	Phase 3 (ongoing)
27	Atuzaginstat	Irreversible inhibitor of gingipain	Phase 2/3 (ongoing)
28	Masitinib[a]	Tyrosine kinase inhibitor	Phase 2b/3 (completed)
29	Azeliragon	Receptor for advanced glycation end products (RAGE) inhibitor	Phase 3 (Ongoing)
30	Encenicline	Partial α7-nAChR Agonist	Phase 3 (on clinical hold)
31	J-147	MAO-B inhibitor	Phase 1 (ongoing)
32	Escitalopram[a]	Selective serotonin reuptake inhibitor	Phase 3 (ongoing)
33	Brexipiperazole[a]	Partial agonist of 5-HT$_{1A}$ and dopamine D2 and D3 receptors	Phase 2/3 (ongoing)
34	Pioglitazone[a]	Peroxisome proliferator-activated receptor-γ agonist	Phase 3 (terminated in 2018)
35	Guanfacine[a]	α_{2A} adrenergic receptor agonist	Phase 3 (ongoing)
36	Losartan[a]	Angiotensin II receptor blocker	Phase 2/3 (ongoing)
37	Minocycline[a]	Anti-inflmmatory, inhibits microglial inactivation	Phase 2 (discontinued in 2019)
38	Nivaldipine[a]	Calcium channel blocker	Phase 3 (Inactive since 2018)
39	Liraglutide[a]	Glucagon-like peptide 1 agonist	Phase 2b (ongoing)
40	Semaglutide[a]	Glucagon-like peptide 1 agonist	Phase 3 (ongoing)
41	Aripiprazole[a]	Dopamine D2 agonist	Phase 3 (terminated in 2016)
42	Lumateperone (ITI-007)	5HT$_{2A}$ antagonist, SSRI, glutamate GluN2B receptor phospho-protein modulator	Phase 3 (terminated in 2018, failed to meet the primary end point objectives)
43	Idalopirdine	AChE inhibitor and 5HT-6 antagonist	Phase 3 (discontinued in 2017)
44	AVP-786	NMDA receptor antagonist	Phase 3 (ongoing)

[a]Marketed drug/US-FDA approved

Fig. 4 Chemical structures of FDA approved anti-AD drugs; **a** rivastigmine, **b** donepezil, **c** galantamine and **d** memantine

Rivastigmine

Donepezil

Galantamine

Memantine
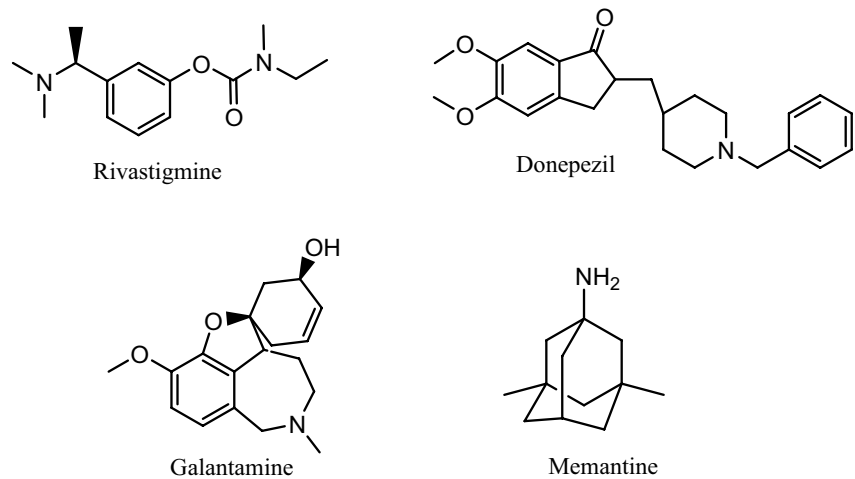
First, APP is proteolyzed by an enzyme α-secretase forming α-APP and an 83 amino acids peptide. The latter peptide is then cleaved by γ-secretase resulting in the formation of two non-amyloidogenic peptides [43]. In the amyloidogenic pathway, enzyme β-secretase (BACE) cleaves APP into β-APP and a 91 amino acids peptide which comes under the action of γ-secretase forming amyloidogenic peptides namely $A\beta_{40}$, $A\beta_{42}$ and $A\beta_{43}$ [44].

Therapeutics targeting secretases

Inhibition of BACE is understood to limit the production of $A\beta_{42}$ [45]. Several agents targeting secretase entered into the clinical trials including CTS-21166 (CoMentis), PF-05297909 (Pfizer), LY2886721 (Lilly), AZD3293 (AstraZeneca) [46]. CTS-21166 in the phase 1 clinical trial conducted in young healthy men showed depletion in the amount of Aβ in human plasma [47]. AZD3293 was also reported to exhibit promising results under a combined clinical trial phase 2/3 [48].

β-secretase (BACE) inhibitor Lanabecestat is another orally active BACE-1 inhibitor (AZD3293 or LY3314814). This drug showed excellent results in the preclinical phase. Lilly and Astra Zeneca obtained an FDA track designation for this drug in 2016 and in the same year it was advanced to the phase 3 clinical trials. Unfortunately, the two ongoing trials were terminated in June 2018 by the pharmaceutical companies because it was found to be ineffective [49].

Clinical trials of verubecestat (MK-8931) and elenbecestat (E2609) were also stopped in between due to their efficacy concerns as these drugs did not show any improvement in cognition scores in the subjects [50, 51]. However, the efficacy and safety of oral atabecestat (JNJ-54861911) are currently being evaluated in phase 2/3 clinical trials [52, 53]. It is a thiazine-based small molecule with good blood–brain barrier (BBB) permeability. It inhibits APP cleavage by the enzyme BACE and thus reduces Aβ level in cerebrospinal fluid (CSF). Results of long-term safety and tolerability of atabecestat in the early AD patients evaluated through a randomized, double-blind, placebo-controlled study and a two-period extension study showed it to be associated with a trend toward declines in cognition, and elevation of liver enzymes [54].

Umibecestat (CNP520) is a BACE inhibitor developed by Novartis for the treatment of early stages of AD [55]. The ongoing GENERATION clinical trial was prematurely stopped in 2019 due to cognitive worsening in the participants [56].

γ-Secretase inhibitors γ-Secretase is an important target in the pharmacotherapy of AD as inhibition of this enzyme results to a reduction in the production of Aβ. Semagacestat (LY450139) is a nonselective γ-secretase inhibitor developed by Lilly. It showed a dose-dependent decrease in the production of Aβ in healthy subjects [57]. Two clinical trials under phase 3 of the same drug were also prematurely interrupted as patients suffering from mild to moderate AD started to show a significant deterioration of cognitive functions besides the risk of skin cancer and weight loss [58]. This unfortunate event was caused because γ-secretase also catalyze other transmembrane proteins, one of them being the Notch receptor. Inhibition of notch receptor caused severe hepatic and splenic side effects [59]. Avagacestat, another γ-secretase inhibitor, also failed to show promising results in AD [60, 61].

α-Secretase stimulators α-Secretase stimulation through activating protein kinase C has shown depletion in the levels of Aβ [62]. Etazolate (EHT 0202; ExonHit Therapeutics, Paris, France) a pyrazolopyridine derivative having anxiolytic properties is currently being investigated in clinical trials. It is a promising α-secretase stimulator that has been shown to inhibit Aβ induced cell death and also

exhibit a relief in AD symptoms [59, 63]. Acitretin also enhances the α-secretase secretion and is thought to help in the non-amyloidogenic APP pathway [64].

Epigallocatechin-gallate (EGCG, Sunphenone) is a polyphenolic flavonoid phytoconstituent found in green tea. It possesses a broad spectrum of bioactivities including anti-inflammatory and neuroprotective properties [65]. Experimental studies have provided the evidence that it acts by increasing α-secretase cleavage of APP

thereby improving cognitive defects in APP/PS1 Mice [66, 67]. It is used as a dietary supplement to combat AD and Down syndrome. It was studied in phase 2/3 clinical trials, but the results were not published. Researchers in Spain started a trial to evaluate the ability of EGCG in the prevention of cognitive decline in ApoE4 carriers with subjective cognitive impairment through a one-year multimodal intervention study [68]. The chemical structure
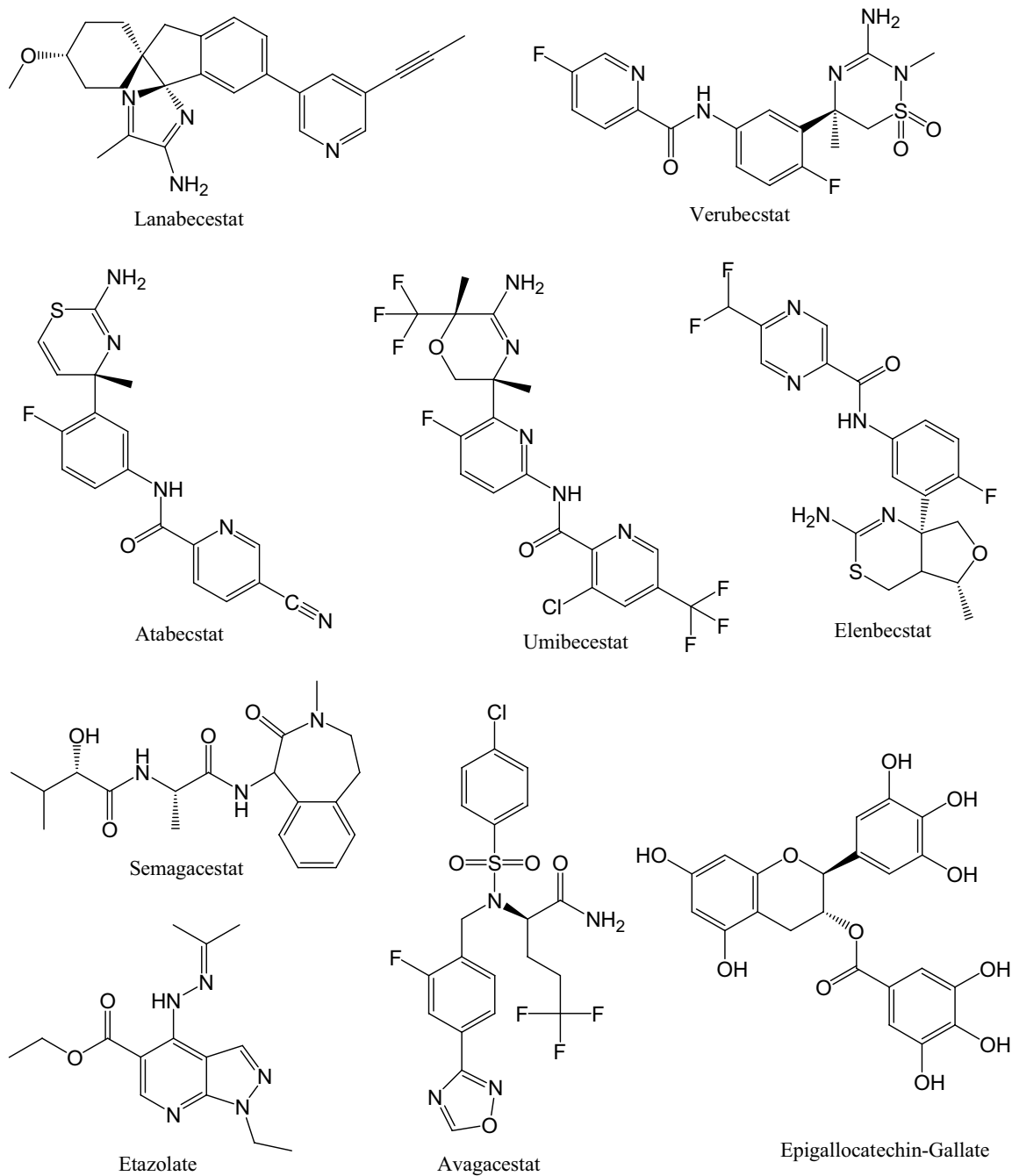
Fig. 5 Chemical structure of drugs targeting secretases in AD

of drugs targeting secretases in AD have been shown in Fig. 5.

Therapeutics targeting Aβ$_{42}$

As discussed above, Aβ$_{42}$ is produced under the proteolytic activity of enzymes BACE-1 and γ-secretase. Agents working on these two enzymes would help in the reduction of Aβ$_{42}$ production. Tarenflurbil is an anti-inflammatory drug chemically related to ibuprofen (Fig. 6). It acts on γ-secretase by allosterically modifying its catalysis of AP and in place of Aβ$_{42}$, Aβ$_{38}$ is produced that manifests lower neurotoxicity compared to Aβ$_{42}$ [62]. The phase 2 trial showed encouraging results, but the agent because of poor brain penetrability and low efficacy failed miserably in the phase 3 trial as well as in its subsequent phase 3 trials [69, 70].

Therapeutics targeting formation of amyloid deposition/ aggregation A number of therapeutic agents have been developed to target and inhibit amyloid aggregation. Two drugs namely tramiprosate and colostrinin showed encouraging results in the early phases of clinical trials. Tramiprosate (3-amino-1-propanesulfonic acid; 3-APS; homotaruine) is an example of a naturally occurring amino acid in seaweed (Fig. 6). It is a structural analog of taurine and GABA. It exerts neuroprotective activity via modulation of GABA receptors. It inhibits Aβ aggregation by hindering the binding of glycosaminoglycan to Aβ and thereby prevents the formation of β-sheet [59]. The phase 2 clinical trials comprising patients with mild to moderate AD showed a reduction in cognitive loss and an increase in CSF Aβ$_{42}$ concentration [71]. The phase 3 clinical trials of tramiprosate couldn't show promising results as were expected, however, the agent limited the hippocampal volume reduction and cognitive loss. In 2018, Hey et al., described the discovery, identification and promising results of an ALZ-801, a prodrug of tramiprostate, in AD [72]. GV 971 (Sodium oligo-mannurarate) derived from brown algae is an Aβ aggregation inhibitor developed by Shanghai Green Valley Pharmaceuticals, China [73]. This small molecule (acidic linear oligosaccharide) possessing anti-inflammatory activity is approved in China for the treatment of mild to moderate AD. However, in US-FDA, it is undergoing phase 3 clinical trials [74]. Results of a 24-week multicenter, randomized, double-blind, placebo parallel controlled clinical trial of sodium oligomannate in Alzheimer's dementia showed it to be safe and well tolerated by AD subjects [75].

Colostrinin is a polypeptide affluent in proline, it is derived from ovine colostrum. It has been demonstrated to inhibit the Aβ aggregation by modulating an innate immune response [76]. Szaniszlo et al., highlighted its clinical potential in AD therapy [77]. Colostrinin in Phase 2 clinical trials conducted on patients with mild to moderate AD showed recovery in Mini Mental State Evaluation scores after a treatment period of 15 months. But the same results were not obtained after 15 months of consecutive treatment [78].

Immunotherapy targeting inhibition of Aβ aggregation Immunotherapy targeted against amyloids is one of the approaches being considered by the concerned authorities to tackle AD. So far, two mechanisms have been elucidated to tackle AD: active immunization and passive immunization. Active immunization is aiming to produce a vaccine against Aβ$_{42}$ targeting the production of amyloid plaques. Phase 2 clinical trials of a vaccine exhibited better cognitive results as well as reduction of Aβ$_{42}$ levels and tau levels, however, the trial was terminated because a number of subjects suffered from meningo-encephalitis after getting vaccinated [79]. Passive immunization is focused upon monoclonal antibodies (mAB) and the administration of immunoglobulins (Ig). Bapineuzumab, solanezumab, and gantenerumab are currently under investigation and are assumed to show promising results.

Bapineuzumab is a humanized monoclonal antibody (*h*mAB). The agent entered phase 3 trials. It showed efficacy in the improvement of cognitive ability in mild to moderate groups of patients.

Solanezumab is another anti-amyloid mAB that binds to soluble Aβ peptides. The phase 3 clinical trials lasted 80 weeks in mild AD carriers. The study showed a significant reduction in cognition and functionality loss, moreover, biomarker findings in CSF showed solanezumab association with its target [80].

Gantenerumab, an anti-amyloid IgG1 *h*mAB functions by removing aggregated Aβ plaques through phagocytosis. A phase 2 clinical study (DIAN-TU) was aborted in the early stages as it showed no significant results. The results of randomized and placebo-controlled trials showed that high doses might exhibit some efficacy based on few clinical and biomarker endpoints [81]. The results of GRADUATE studies on the efficacy of a higher gantenerumab dose that most patients received in the DIAN-TU trial are expected in 2022 [81–83].

Aducanumab (BIIB037; Aduhelm®), an Aβ-targeting drug, has been approved on 7th June 2021 by US-FDA to
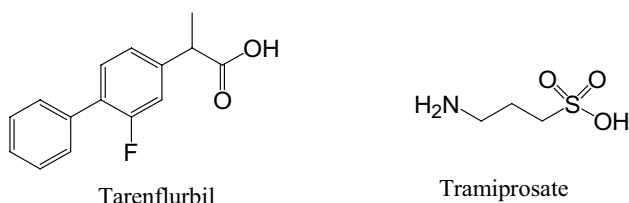
Fig. 6 Chemical structure of drugs targeting Aβ$_{42}$ and inhibiting amyloid aggregation

treat AD patients. It was approved using an accelerated approval process making it the first approved therapy for AD since 2003. It is a fully human IgG1 mAB that binds selectively to aggregated Aβ fibrils and reduces the Aβ plaques in the brain of AD patients in a dose and time dependent manner [84]. Biogen carried out a phase 3 randomized, double-blind, placebo-controlled, parallel-group study (2015–2019; NCT02484547) on aducanumab to evaluate the efficacy and safety in subjects with early AD. However, the study was discontinued due to safety concerns. However, Biogen® initiated another phase 3b open-label study in Jan 2020 for three more years. They recruited 2,400 previous aducanumab trial participants to study only safety and tolerability parameters as primary outcomes (EMBARK). The company also submitted a biologics license application to the U.S. FDA in July 2020 [85, 86]. One of the two phase 3 clinical trials met the primary endpoint having shown a significant reduction in Aβ plaques and clinical decline. The outcome of this study led to accelerated approval of aducanumab for the treatment of AD in 18 years. However, FDA will continue to monitor the drug after marketing. Biogen is also required to conduct a post approval clinical trial to verify the drug's clinical benefit. The approval may be withdrawn in case the trials fail to verify the drug's clinical benefits [84].

Lecanemab (BAN2401; mAb 158), a humanized mAB, binds selectively to soluble Aβ protofibrils [87]. Initial clinical studies conducted revealed it to have potential disease-modifying properties as it significantly slows down the progression of the disease by reducing the Aβ accumulation in the brain. Isai Inc., in collaboration with Biogen® is testing the anti- Aβ protofibril antibody in phase 3 interventional study in the subjects with early AD (CLARITY AD). The study will run till 2024.[88]. Another phase 3 clinical study (AHEAD 3–45) has also been started in US, Europe and several other countries to evaluate its therapeutic efficacy in pre-clinical AD subjects [89].

Upcoming therapies targeting tau proteins

Neurofibrillary tangles (NFT) formation is a key indicator of AD pathogenesis; therefore, it becomes imperative for treatment therapies to target *tau* proteins as well. Strategies so far have targeted *tau* deposition and phosphorylation along with *tau* immunotherapy.

Therapeutics targeting tau deposition and phosphorylation *Tau* deposition and phosphorylation are the two processes that are the culprits in the formation of NFT as well as for the increased neuronal loss. The surged phosphorylation could be controlled through inhibition of enzyme glycogen synthase kinase 3 (GSK3) [90]. Lithium is being considered to act as an inhibitor but failed to show efficacy in clinical trials [91]. PKC is stimulated by M1 receptor can also

inhibit the enzyme GSK3, studies have shown this might decrease *tau* phosphorylation and aggregation [92–94].

LMTM (LMTX, TRx0237) is an improved derivative of the reduced form of MB (leuco-methylene blue, LMT) in terms of absorption, bioavailability, and tolerability. Leuco-methylenthyonium bis hydromethanesulfonate is a second-generation, cysteine independent *tau* aggregation inhibitor. In addition, several studies indicated to inhibit MAO and diminish nitric oxide production. It is currently evaluated in the phase 3 [95, 96].

A phase 3 clinical trial with 588 enrolled subjects is currently underway to determine the safety and efficacy of TRx0237 at two doses (16 mg/day and 8 mg/day) for AD treatment [97].

Gandini et al., in 2018 identified 2,4-thiadiazolidinedione derivatives to be dual GSK-3β and tau-aggregation inhibitors. The two most potent multitarget compounds were compound T_1 ((Z)-5-((5-methoxy-1-methyl-1*H*-indol-3-yl)methylene)thiazolidine-2,4-dione) and T_2 (Z)-5-((1*H*-Indol-3-yl) methylene)thiazolidine-2,4-dione (IC_{50} of 0.89 and 4.93 μM for GSK-3β inhibition). Both compounds also improved cell viability, possessed good BBB penetrability and were nontoxic [98].

Blarcamesine (ANAVEX2-73) is chemically Tetrahydro-*N,N*-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride and is an experimental investigational drug against AD. It is a muscarinic receptor agonist and a sigma-1 receptor activator that targets protein misfolding and reduces tau hyperphosphorylation, oxidative stress, and neurodegeneration in AD [99]. It has been shown to exhibit anti-apoptotic and antioxidant activity. The results of the phase 1 clinical trial conducted in Germany determined 55 mg to be the maximum tolerated dose in healthy male volunteers. In a phase 2a study, it demonstrated dose-dependent improvement in MMSE ADCS-ADL. Its single daily dose in capsule form is currently being studied in phase 2b/3 for 48-weeks in 450 patients with early AD in Australia at 16 different sites. This open-label extension (OLE) study might expand to include UK and Canada and the results would be available by December 2023 [100].

Saracatinib (AZD0530) is a dual kinase inhibitor of Src and Abl family kinases1. It is a repurposed drug originally developed to treat cancer. This small molecule in the preclinical studies was shown to block Fyn in brain slices, prevented synaptic depletion and helped to overcome spatial memory deficits in APP/PS1 mice [101]. In the same mouse line, it boosted hippocampal synaptic density [102]. Van Dyck et al. [103] published the results of a randomized clinical trial (NCT02167256) conducted to evaluate the safety, tolerability and effect of AZD0530 on cerebral metabolic decline in AD. The treatment failed to show a significant reduction in cerebral metabolic rate for glucose (CMRgl) level [103].

Thiamet G (LY3372689) is a promising O-GlcNAcase (OGA) enzyme inhibitor. It has been demonstrated to reduce tau phosphorylation in tau transgenic model TG4510 [104]. It is currently undergoing phase 1 clinical trials [105].

Telmisartan is an angiotensin II receptor blocker (ARB) currently being investigated as a repurposed drug against AD. Scientific evidence indicated that use of ARB in AD may reduce the incidence of cognitive impairment and dementia [106]. It is proposed that it controls cerebral blood flow, protects the cerebral microvasculature, and decreases plaque formation and CSF tau in the brain [107]. It is undergoing phase 2 clinical trials in mild-moderate AD subjects (NCT02085265 and NCT02471833) [108].
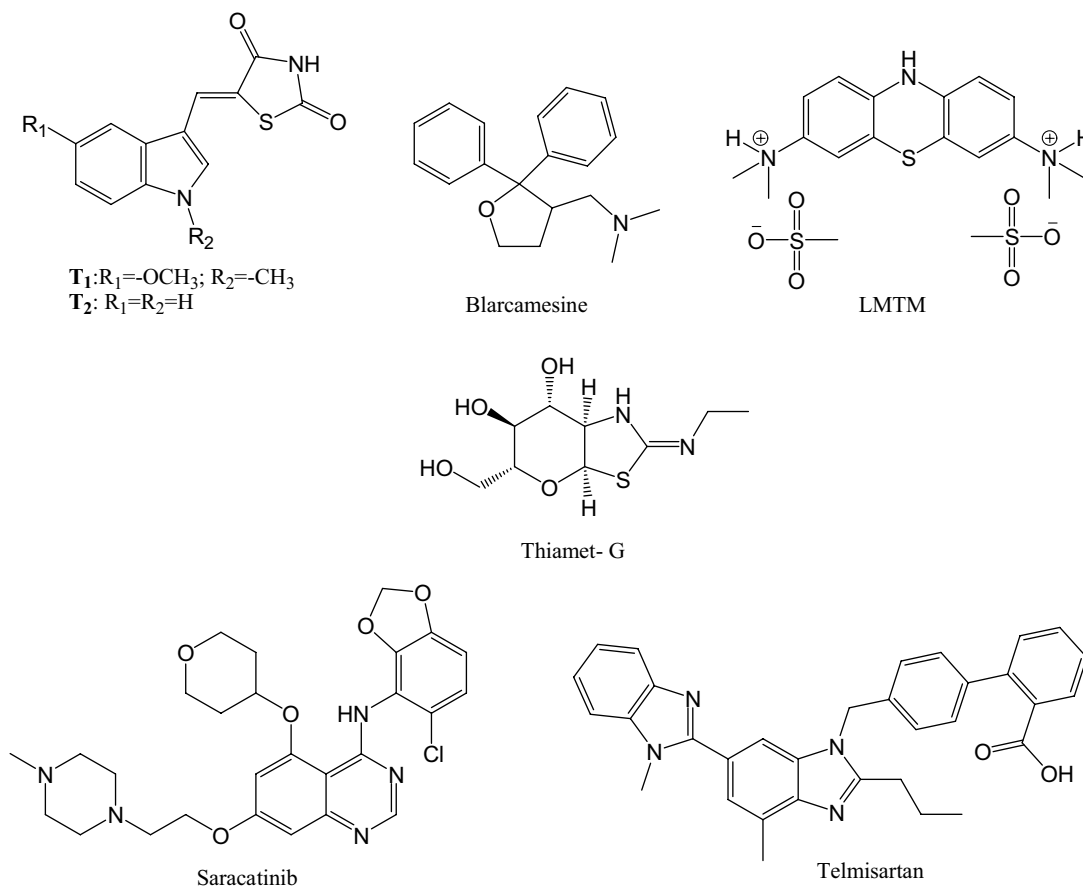
Atuzaginstat (COR388) is an irreversible inhibitor of lysine-gingipain, the virulence factor proteases found in a *P. gingivalis* periodontal pathogen detected in the brain of AD patients. *P. gingivalis* infection in cultured human neurons can cause tau phosphorylation and degradation, synapse loss, and cell death [109]. It's twice-daily dosing is currently being tested in a large phase 2/3 clinical study (GAIN) in subjects with mild-to-moderate AD. Results are expected by the end of Dec 2022 [110, 111]. Recently, in Feb 2021, a partial clinical hold on GAIN was imposed by

FDA because few participants developed liver abnormalities. However, it was found that the liver effects are reversible and pose no risk of long-term effects [112]. Chemical structures of several new molecules targeting tau proteins are shown in Fig. 7.

Immunotherapy A vaccine named AADvac1 is currently under clinical trials. It functions by promoting the generation of antibodies that attack the conformational epitopes regions of *tau*, resulting in the reduction of *tau* deposition. The vaccine in humans showed higher efficacy than in experimental animals as the antibodies produced were able to identify *tau* proteins in mild to moderate AD patients. The vaccine is currently under phase 2 trial [113].

Drugs targeting neuroinflammation

Several independent observational studies have demonstrated that anti-inflammatory drugs use is associated with a lower risk of developing AD. A recent prospective, population-based study reported that non-steroidal anti-inflammatory drugs (NSAIDs) use in elderly people was associated with 71% decreased risk of AD mortality [114].

T₁:R$_1$=-OCH$_3$; R$_2$=-CH$_3$
T₂: R$_1$=R$_2$=H

Blarcamesine

LMTM

Thiamet- G

Saracatinib

Telmisartan

Fig. 7 Chemical structure of new molecules targeting tau proteins

ALZT-OP1 is a combination regimen of a mast cell stabilizer (cromolyn) and an NSAID to reduce neuroinflammation and to promote Aβ clearance through phagocytosis of Aβ [112]. A phase 3 clinical trial (COGNITE), a randomized, double-blinded, placebo-controlled study is evaluating the potential of ALZT-OP1 in slowing down, arrests, or reverse cognitive and functional decline on the CDR-SB in the early-stage AD subjects (NCT02547818).

Masitinib (Masivet, Kinavet, AB1010) is a selective tyrosine kinase inhibitor (TKI) known to modulate neuroinflammation mediated by mast cells. Li et al., in 2020 demonstrated that chronic treatment with masitinib could restore spatial learning and synaptic density in the hippocampus in the APP/PS1 mouse model of amyloidosis [115]. AB Science® conducted a phase 2b/3 clinical trial from 2012 to 2020 to compare masitinib 4.5 or 6 mg/kg/day dosing with placebo in 721 confirmed mild to moderate AD subjects receiving a ChE inhibitor and/or memantine in twenty one mostly European countries. The company announced that the study met its primary goal [116].

Minocycline a tetracycline repurposed drug possessing anti-inflammatory activity failed to improve the cognitive and functional ability in mild AD patients during 2 years period in a randomized clinical trial The plausible explanations given by the authors for the failure of this drug in the phase 3 clinical trials were (i) neuroinflammation "may be a reaction to pathologic characteristics of the disease rather than an important factor in neurodegeneration"; (ii) complex association between microglial activation and neurodegeneration and (iii) "minocycline did have some efficacy against AD, but treatment effects were too small to be detectable" [22]. Gyengesi and Münch recommended that future trials should focus on anti-inflammatory drugs capable of decreasing the formation of cytotoxic cytokines [117].

Miscellaneous targets in AD

Azeliragon (TTP488) is an orally active inhibitor of receptor for advanced glycation end products (RAGE). RAGE is over expressed in the brain tissues of AD patients. Azeliragon has been shown to slow down the progression of AD [118]. It was developed by vTv Therapeutics® (Originator) and was studied in the phase 3 clinical trials for the treatment of Alzheimer's type dementia (STEADFAST). The trial was terminated in 2019 due to the lack of efficacy of 5 mg dose of Azeliragon [119].

Encenicline (EVP-6124) is a new potent molecule capable of activating α7-nicotinic ACh Receptor (nAChR) in the brain at very low concentration and thereby exhibits memory enhancing properties [120]. The drug showed promising results in mild-to-moderate AD patients with respect to placebo on functional and cognitive skills. However, in 2015 FDA imposed a clinical hold based on the outcome of two phase 3 trials owing to its gastrointestinal side effects [121].

J-147 is a new investigational drug (NID) in US for the treatment of AD. It is a curcumin derivative and its chemical name is; *N*-(2,4-dimethylphenyl)-2,2,2-trifluoro-*N*'-[(*E*)-(3-methoxyphenyl)methylene]acetohydrazide. The experimental drug is orally active, able to cross BBB with ease and was demonstrated to enhance memory in aged AD mice [122]. It also inhibits MAO-B ($IC_{50} = 1.88$ μM). It is currently being tested in phase 1 clinical trial. Chemical structures of agents acting at miscellaneous targets in AD are presented in Fig. 8.

Fig. 8 Chemical structure of molecules **a** acting as RAGE inhibitor; **b** α7-nAChR agonist and **c** MAO-B inhibitor

J-147

Encenicline

Azeliragon
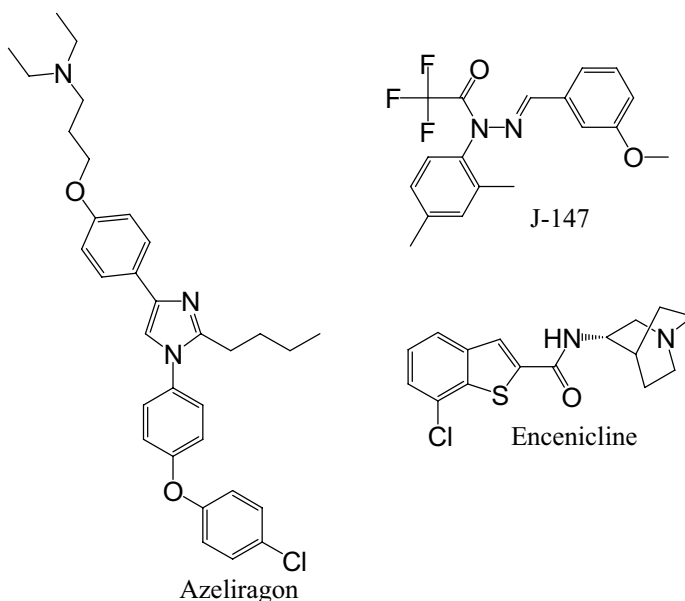
Conclusion

AD is a complex neurodegenerative disease affecting millions of people worldwide. Numerous biochemical and pharmacological studies conducted in the past couple of decades have tried to unwind the complexities of this progressive disease. We now have a better understanding of the pathogenesis of AD at the molecular level that has enabled the researchers to discover and develop novel therapeutic agents to treat this devastating disease. A number of therapeutics based on the identified targets were developed from 2010 to 2020 for the treatment of AD and several of these molecules are currently under investigation in clinical studies. Data indicated that over the last decade, the majority of the agents that reached in the phase 2 failed to show a drug-placebo difference and therefore could not make it to phase 3. On the other hand, more than 50 molecules successfully progressed from phase 2 to phase 3 but unfortunately, only one agent could pass the phase 3 clinical trial since 2003. Most of the studies were discontinued/terminated as these agents were found to be toxic and ineffective and thus failed to meet the primary and secondary endpoints of the studies.

In the ongoing clinical trials, anti-amyloid immunotherapy, Aβ aggregation inhibitors, BACE inhibitors, SALA (Selective $A\beta_{42}$ lowering agents), tau aggregation inhibitors, α-secretase enhancers, anti-tau immunotherapy and anti-inflammatory agents, etc., have exhibited encouraging results in the initial phases. However, the outcome of these clinical studies would shed more light on the safety and effectiveness of therapeutic agents. Currently, more than 140 drug candidates, mostly drug modifying agents, are being tested in various phases of clinical trials but it is yet to be seen how many of these would progress from the clinical testing phase to the clinical practice.

In our opinion, newer therapeutic strategies to design, discover and develop anti-AD agents should focus on (i) repositioning and repurposing of existing drugs for AD; (ii) multitarget directed ligands capable of acting on multiple key molecular targets involved in the pathogenesis of AD (iii) minimizing the toxicity of drugs failed in phase 3 (iv) improving the pharmacokinetic profile of the promising candidates by structural modification, (v) exploring the natural products to identify the lead molecule for AD, (vi) stem cell therapy, and (vii) identification of novel molecular targets including development of immunotherapy.

Author contributions SAK, AK and TA carried out the literature review and wrote the manuscript.

Declarations

Conflicts of interest Authors declare no conflict of interest.

Consent for publication All authors have read and approved the manuscript prior to submission.

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Authors and Affiliations

Teeba Athar[1] · K. Al Balushi[1] · Shah Alam Khan[1]

✉ Shah Alam Khan
    shahalam@nu.edu.om

[1] Department of Pharmaceutical Chemistry,
     College of Pharmacy, National University
     of Science and Technology, Bousher, PO Box 620,
     Postal code 130 Muscat, Sultanate of Oman