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Review Article

Molecular scaffold and biological activities of anti-Alzheimer agents

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Abstract

Alzheimer's disease (AD) is an age-associated and neurodegenerative illness which results in progressive dementia and severe cognitive malfunctions. The pathogenesis of AD is affected by some factors such as accumulation of β-amyloid, aggregation of tau protein, cholinergic insufficiency, neuro-inflammation, oxidative stress and apoptosis. Factors such as gene mutation, as well as environmental, psychical and other co-existing diseases influence the pathogenesis of AD to varying extents. While there are no available drugs for arresting AD-associated neurodegeneration, the characteristics that result from AD treatment are considered as indexes of symptomatic cure. Several medications with varied scaffolds have been used for the treatment of many cognitive syndromes, including AD. These medications act as anti-inflammatory and antioxidant agents, and as inhibitors of cholinesterase and β-secretase. Moreover, these drugs suppress the accumulation of β-amyloid and its fibril. This review is an update and compilation of various scaffolds of anti-AD medications used to ameliorate the deleterious effects of the disease, based on their pharmacologic characteristics.

Keywords: *Alzheimer's disease, Dementia, Beta-amyloid plaques, Protein tau tangles, Neuro-degeneration, Anti-AD medication*

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INTRODUCTION

In 1906, the first human case of Alzheimer's disease (AD) was discovered by Alois Alzheimer. He investigated the brain of a woman who lost her life due to unusual symptoms such as unpredictable behavior, loss of memory, and cognitive impairment. He attributed her death to the presence of neurofibrillary tangles and neuritic plaques, and he named these disorders AD. Over the years, improved healthcare worldwide has resulted in marked increase in the population of elderly people. However, this demographic shift poses certain concerns due to a rise in instances of AD and other dementias among the elderly. Alzheimer's disease (AD) is a brain disease and a neurodegenerative disorder which gets worse with time. It is said that it takes more than 20 years for the symptoms to manifest. The disease results in unnoticeable deleterious changes in the brain which take several years to manifest in obvious symptoms

such as memory loss and language problems. Late-onset AD develops after the age of 65. Alzheimer's disease causes deterioration of the patient's functionality over time, resulting in substantial and long-term incapacity over the course of 7 to 10 years from diagnosis, and eventually resulting in death. In situations where delirium lasts for at least 6 months in the absence of other symptoms, the diagnosis of AD is highly likely [1]. Alzheimer's disease (AD) is categorized based on the age of onset, and on whether it was acquired spontaneously, or as a consequence of genetic mutations. Familial AD (FAD) is an early-onset (at 40 years of age) disease which is affected by genetic mutations, and it accounts for approximately 2 % of AD cases. Sporadic AD is the major category which is sub-divided into early- and late-onset types. The early-onset type is diagnosed in individuals less than 65 years of age (3 – 5 % prevalence), while the late-onset type accounts for 95 – 97 % prevalence.

A study has reported that 4.6 million new cases of dementia are expected to be recorded each year, at a rate of one patient every seven seconds, and the number of patients is expected to double every 20 years by 2040, reaching 81.1 million [2]. Reports from the World Health Organization (WHO) indicate that cases of AD in the world are expected to double in the future, achieving 114 million individuals by 2050. Not only will this have an incalculable social impact, it will also increase the financial burden on healthcare systems around the world. In 2010, it was projected that 46.8 million individuals worldwide would suffer from dementia, resulting in a global healthcare cost estimated at US $818 billion [3]. Antipsychotics and antidepressants are used to ameliorate neuropsychiatric symptoms, whereas cholinesterase inhibitors (CIs) and N-methyl-D-aspartate (NMDA) receptor antagonists are used to prevent excitotoxicity in mild-to-moderate instances. The future treatment of AD rests on the targeting of neurofibrillary tangles (NFTs) and neuritic plaques (NPs) that potentially exacerbate neurodegeneration [4]. There are various scaffolds of anti-AD medications based on their pharmacologic characteristics in the treatment of AD (Table 1).

HYPOTHESES-BASED THERAPIES OF AD

Cholinergic hypothesis

Davies and Maloney first proposed the cholinergic theory in 1976. Cholinergic neurons create ACh by the catalytic effect of choline acetyl transferase. The Ach is stored in vesicles, while choline esterase catalyzes postsynaptic breakdown or hydrolysis of ACh. However, under disease conditions, the activities of cholinesterases (ChEs) are up-regulated, resulting in decreased levels of ACh and impairment of neurotransmission. Furthermore, the increased levels of AChE enhance Aβ aggregation. In addition, high cortical levels of BuChE have been reported to be linked to neurofibrillary tangles and neuritic plaques which are the chief neuropathological characteristics of AD. Therefore, inhibitors of AChE and BuChE have been proposed as potential therapeutic targets for AD. These inhibitors improve cholinergic neurotransmission by extending the time ACh neurotransmitters remain in the synaptic cleft (Figure 1) [5]. In less than half of AD patients, cholinesterase inhibitor (CI) medications produce substantial effects, indicating the presence of major additional risk factors in the pathogenesis of the illness.

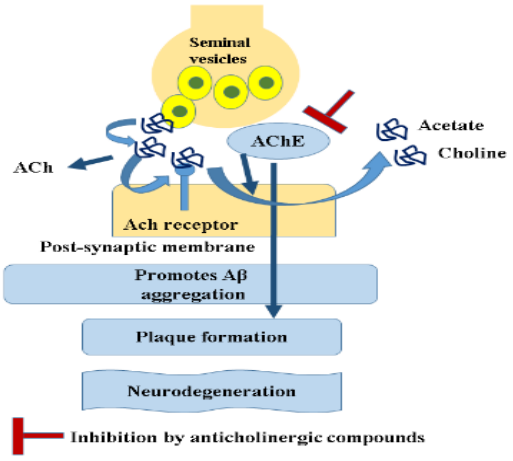

Figure 1: Neurodegenerative effect of acetylcholinesterase in AD. Aβ = amyloid beta; ACh = acetylcholine; AchE = acetylcholinesterase

Acridine-based therapies for AD

Tacrine (**1**), an inhibitor of AChE and BChE (Figure 2) was first synthesized in the 1930s, and was approved by FDA for treatment of AD in 1993. However, the clinical use of tacrine was discontinued in 2013 due to its side effects such as vomiting, nausea, loss of appetite, clumsiness, diarrhea and hepatotoxicity. Tacrine analogue (**2**) (Figure 2) produces better AChE-inhibitory activity than the parent drug tacrine [6].

Carbamate-linked therapies for AD

Rivastigmine (**3**) was approved in year 2000 for the treatment of mild or moderate AD (Figure 2). Rivastigmine targets both BChE and AChE [7].

Table 1: Therapeutic agents for Alzheimer's disease

Pharmacology based classes	Scaffold based classes	Representative drug/chemical compounds	References
Cholin esterase inhibitors	Acridines.	Tacrine and tacrine analogues.	[6]
	Carbamates.	Rivastigmine, phenserine and tolserine	[7,8]
	Benzothiazoles.	(E)-2-(benzo[d]thiazol-2-yl)-3-(pyridin-3-yl)acrylonitrile	[9]
	Indanes	Donepezil	[10,11]
	Indane-Carbamate Hybrid	Ladostigil	[12]
	Coumarines	Decursinol, mesuagenin B, Bergamottin compounds	[16-18]
	Sesquiterpenes	Huperzine-A and huperzine-B	[19]
β-Secretase (BACE) inhibitors as modulators of Aβ production	Peptidomimetics	Hydroxyethylenes, hydroxyethylamines, carbinamines, and macrocycles.	[23-26]
	Acyl Guanidines	2-(2-(2,5-diphenyl-1, H-pyrrol-1-yl)acetyl)guanidine	[27]
	2-Aminopyridines	6-(3-(3-methoxyphenyl)phenethylpyridin-2-amine	[28]
	Aminoimidazoles	4-(5-fluoro-2,3-dihydro-6-methoxy-1-(p-tolylmethyl)-1H-inden-1-yl)-1-methyl-1H-imidazol-2-amine	[29]
	Aminohydantoins	2-amino-1-methyl-4,4-diphenyl-1H-imidazol-5(4H)-one	[30]
	Aminooxazolines	2-aminooxazoline 3-azaxanthenes hybrid	[31]
	Dihydroquinazolines	(S)-4-(2-amino-6-phenoxyquinazolin-3(4H)-yl)-N,4-dicyclohexyl-N-methylbutanamide	[32]
	Aminoquinolines	(R)-2-((2-amino-6-(2-chlorophenyl)quinolin-3-yl)methyl)-N-(3,3-dimethylbutyl)propanamide	[33]
	Pyrrolidines	Pyrrolidine tetrahydroquinoline hybrid	[34]
γ-Secretase inhibitors (GSIs) of Aβ production	Peptidomimetic	Semagacestat, avagacestat [35]	
γ-secretase modulators (GSMs) of Aβ production	Non-NSAID	NGP555, E2012, E2212	[36]
Tau protein modifications compounds	Adamantane	1-Aminoadamantane	[37]
	Thiadiazolidines	Tideglusib	[38]
Tau Deglycosylation Inhibitors	Salicylsalicylic	Salsalate	[39]
	Pyranothiazoline	MK-8719	[40]
Tau aggregation Inhibitors	Curcumin	Curcumin	[41]
Microtubule Stabilizers	Macrocyle	Epithilone D, abeotaxane	[42]
Tau-protein Degradation Modulators	Phenylacetic Acid	BPN14770	[43]
	Antioxidant drugs	Vitamin E, vitamin C, and β-carotene	[45]
	Antioxidant Enzymes	Glutathione peroxidases, superoxide dismutase SOD enzyme-copper-zinc (CuZnSOD), a prosurvival mitochondrial antioxidant enzyme-MnSOD, repair enzymes such as lipases, proteases, and DNA repair enzymes	[45]
Antioxidant Anti-neuroinflammatories Chelators	Flavonoids	Quercetin, isorhamnetin, isoflavones, (calycosin), and flavans ((2S)-5,7,3′,5′-tetrahydroxy flavanone, 5,4′-dihydroxy-7-methoxy-6-methylflavane	[46]
Mitochondrial Therapies	***Hydroxyquinoline***	CQ	[47, 48]
	Triazoles	Deferasirox	[49]
	Pyridones	***Deferiprone***	[50]
	Quinone	CoQ10, MitoQ, SkQ1	[51]
	Keto-Carotenoids	Astaxanthin	[52]
	Indole	Melatonin	[53]
	Carboxylic acid	α-lipoic acid (LA), Acetyl-cysteine	[54,55]
	Hormone	Insuline	[56]
	Biguanide	Metformin	[57]
Antidiabetic	Thiazolidinediones	Pioglitazone	[58]
	Amylin Analog	Pramlintide	[60]

The physostigmine derivatives phenserine (**4**) and tolserine (**5**) (Figure 2) have been used as ChE inhibitors. Phenserine not only inhibits AChE, it also reduces the generation of APP *in vitro* and *in vivo*. Phenserine is a promising AD therapy because of its dual anti-AChE and anti-A β effects. It has been used for the treatment of cognitive impairments in mice, and clinical trials are on-going [8]. In 2000, preclinical studies indicated that tolserine was 200-fold more specific as inhibitor of human AChE (hAChE) than BChE.

Benzothiazoles therapies in AD

Compound (**6**) has been developed as AChE inhibitor (Figure 2) and was found more potent and selective than galantamine natural compound [9].

Indane-linked therapies for AD

Donepezil (**7**) (Figure 2) was approved as a therapy for mild-to-moderate AD in 1996 [10]. Apart from its molecular target AChE, donepezil has cellular targets associated with the pathogenesis AD. These include inhibition of glutamate-induced excitotoxicity, down-regulation of the expression levels of inflammatory cytokines, reduction of oxidative stress-induced effects, and initiation of a neuroprotective isoform of AChE. Indenyl compound (**8**; Figure 2) was developed as a moderate AChE-inhibitor in 2009 [11].

Indane-carbamate hybrid therapies for AD

Ladostigil (**9;** Figure 2), an AchE inhibitor with potent anti-AD and neuroprotective activities, is currently in Phase IIb clinical trial [12]. Ladostigil inhibits the activities of AChE and MAO-B. It is used as a novel treatment of neurodegenerative disorders such as AD and Parkinson's disease.

Coumarin-based therapies for AD

Compound **10** with 2-methoxyanilino moiety linked to coumarin fused benzofuran has been shown to be a potent inhibitor of AChE, with IC_{50} of 0.19 ± 0.01 μM [13]. The coumarin compound which was designed as a novel AChE inhibitor (**11**) produced IC_{50} of 0.236 nM and AChE/BChE selectivity >300,00038 [14] (Figure 2). In another study [15], two coumarin-based compounds (**12** & **13**) with moderate inhibitory effect on AChE (IC_{50} ~ μM) were developed. Decursinol (**14**) and mesuagenin B (**15**; Figure 2) are natural coumarins with potent AChE inhibitory activities (IC_{50} values = 0.28 μM and 0.7 μM respectively) [16, 17]. Bergamottin compounds (**16** & **17;** Figure 2) are potent AChE inhibitors with IC_{50} values of 11.2 ± 0.1 and 15.4 ± 0.3 μM, respectively [18].

Sesquiterpene-linked AD therapies

Huperzine-A (**18**) and huperzine-B (**19**) (Hup-A and Hup-B, respectively; Figure 2) are lycopodium alkaloids extracted from *Huperzia serrata*, and they are used for treating AD based on their highly selective and potent inhibition of AChE [19].

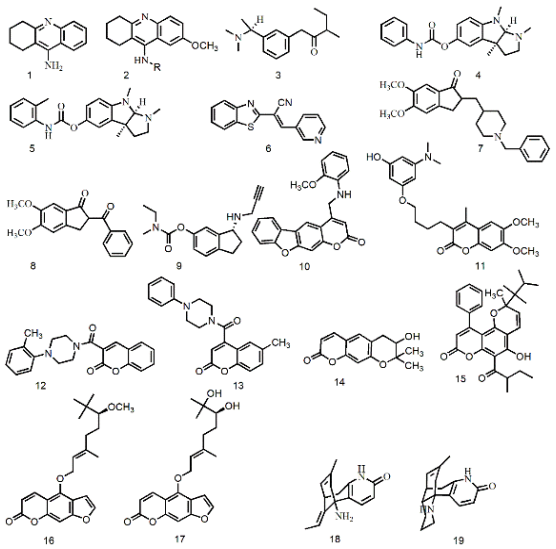

Figure 2: Chemical structures of agents used for AD treatment: Choline esterase inhibitors

B-amyloid cascade hypothesis

Deposition of neurofibrillary tangles (NFTs) and amyloid plaques are the principal neuropathological hallmarks of AD. In the brains of AD patients, the accumulated β-amyloid (Aβ) peptides self-assemble into oligomers (Figure 3). The toxicity of these oligomers cause synaptic deterioration which leads to inflammation and oxidative stress. Non-covalent interactions of the oligomers form protofibrils which, upon maturation, lead to the generation of amyloid-like fibrils (Figure 4) [20]. The toxic β-amyloid (Aβ) peptides accumulate as a result of proteolytic cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase. β-Secretase is a type 1 member of the pepsin family and a transmembrane aspartic acid protease. β-Site amyloid precursor protein cleaving enzyme 1 (BACE-1) is involved in the production of Aβ. Therefore, it is seen as a drug target macromolecule that modulates Aβ generation. The levels of BACE1 mRNA are increased in AD patients, and in AD animal models [21].

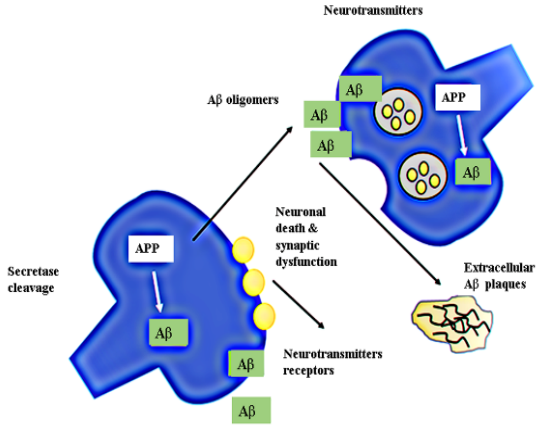

Figure 3: Formation of β-amyloid plaques

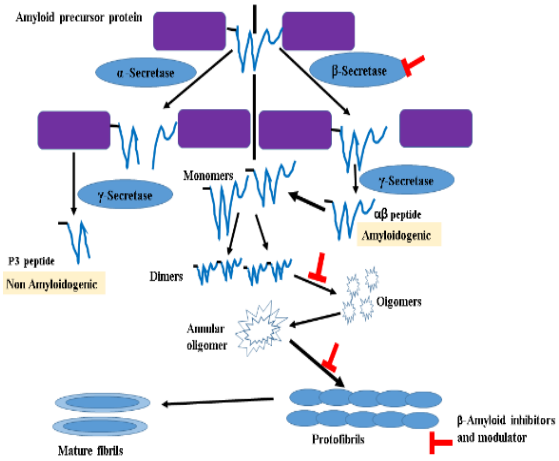

Figure 4: Formation of toxic Aβ peptides, and their aggregation into fibrils

β-Secretase (BACE) inhibitors as modulators of Aβ production

Peptidomimetics

The design of numerous potent small molecular weight peptidomimetic inhibitors with drug-like properties was facilitated by X-ray structural studies of substrate-based inhibitors. The reduction of peptidyl characteristics could improve *in vitro* and *in vivo* characteristics of some designed inhibitors, and could increase selectivity of other inhibitors. Representative classes of these peptidomimetic inhibitors include hydroxyethylene-based inhibitors (**20-25)** [22] (Figure 5), hydroxyethylamine-based inhibitors (**26** & **27;** Figure 5) [23], carbinamine-based Inhibitors (**28)** [24] (Figure 5), reduced amide-based inhibitors (**29)** (Figure 5) [25], and macrocyclic peptidomimetic inhibitors (**30)** [26] (Figure 5).

Guanidine-based AD therapies

The catalytic residues i.e., Asp32 and Asp228 in the active site of BACE1 interact with the acyl guanidine pharmacophore. Compound **31** is a representative structure of these inhibitors (Figure 5) [27].

2-Aminopyridine-based AD therapies

The binding of 2-aminopyridine inhibitors to BACE1 results in a flap-open conformation due to the dislocation of Tyr71 to a position above the pyridine scaffold. A substituted 2-aminopyridine compound (**32**) [28] is shown in Figure 5.

Aminoimidazole-based therapies for AD

High-throughput screening (HTS) and the resultant optimization of the scaffold led to the discovery of an aminoimidazole compound (**33**; Figure 5) with a BACE1 inhibitory activity (IC_{50} = 63 nM) [29].

Aminohydantoin-linked therapies for AD

Laboratory screening of BACE1 inhibitors resulted in the discovery of a potent and selective BACE1 inhibitor and a hit compound (**34**; Figure 5) with an aminohydantoin scaffold [30].

Therapies for AD based on aminooxazolines

Inhibitors of BACE1 with aminooxazoline scaffolds (**35**; Figure 5) had IC_{50} of 12 nM and showed better specificity than other common aspartic acid proteases with IC_{50} > 200 μM) [31].

Dihydroquinazoline-based therapies for AD

The development of dihydroquinazolinse as BACE1 inhibitors and subsequent optimization led to identification of an inhibitor (**36**) which had IC_{50} of 11 nM (Figure 5) and moderate specificity, relative to common aspartate-bearing proteases e.g., renin (IC_{50} = 2.7 μM) [32].

AD therapies based on aminoquinolines

Initial screening studies identified a 2-aminoquinoline with BACE1 kd of 900 μM which was later optimized to produce a more potent and selective BACE1 inhibitor (**37**; Figure 5) with IC_{50} of 11 nM [33].

Pyrrolidine-based AD therapies

High-throughput screening has revealed BACE1 inhibitors with pyrrolidine scaffolds, and SAR

analyses and optimization resulted in the development of a BACE1 inhibitor (**38**; Figure 5) which had IC_{50} of 29 nM [34].

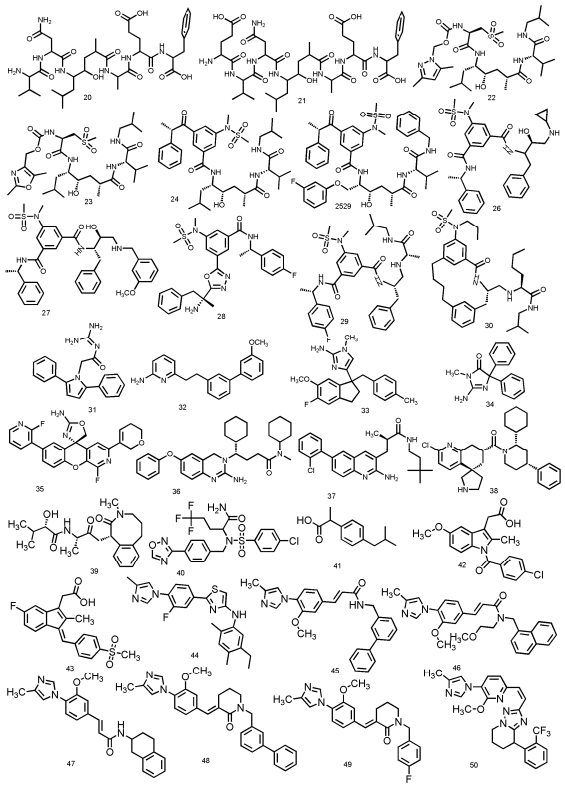

Figure 5: Chemical structures of anti-AD compounds: β-secretase inhibitors and γ-secretase inhibitors and modulators

γ-Secretase inhibitors (GSIs) of Aβ production

Semagacestat (**39**), a peptidomimetic, and avagacestat (**40**; Figure 5) are GSIs in clinical trials for AD. Unfortunately, GSIs also block the ε-cleavage of γ-secretase in the Notch signaling pathway, resulting in several side effects such as decreased lymphocyte count, skin cancer and memory loss. Notch is a type I transmembrane receptor involved in neuritic growth, neurogenesis, and long-term memory. These side effects led to discontinuation of the use of GSIs as therapeutic strategy for AD [35].

γ-Secretase modulators (GSMs) of Aβ production

Non-NSAID-derived GSMs (**41-50**; Figure 5) decrease the levels of Aβ42 peptide and increase those of Aβ38 isoform, indicating that NSAIDs modulate γ-secretase activity without perturbing APP processing or Notch pathway. The NGP555-diarylcinnamide derivatives (**45-50**; Figure 5) have been used led to discovery of clinically useful cinnamide compounds NGP555 (**45**), E2012 (**49**) and E2212 (**50**; Figure 5) [36].

Tau protein and neurofibrillary tangle (NFT) hypothesis

Neurofibrillary tangles (NFTs) are aggregates of hyperphosphorylated tau protein which are biomarkers of AD. It has been observed that soluble tau clump together into helical filaments which subsequently generate intracellular NFTs, a process that results in neuronal cell damage. Currently, tau protein-targeting medicines are used to stabilize, decrease, or prevent hyperphosphorylation or aggregation of the proteins [37].

1-Aminoadamantane phosphatase modifier therapies for AD

Memantine (**51**; Figure 6), a blood sugar level-lowering agent, was discovered as an antagonist of N-methyl-D-aspartate receptor. It produced minor short-term cognitive gains, but it may be more beneficial when used in conjunction with cholinesterase enzyme inhibitors [37].

Thiadiazolidine kinase inhibitor-based therapies for AD

Tideglusib (**52**; Figure 6) is an irreversible inhibitor of glycogen synthase kinase (GSK3β). In an *in vivo* study of AD, tideglusib decreased tau phosphorylation, Aβ plaque formation, cell death, memory shortfalls and astrocytosis. In a phase II study, tideglusib produced cognitive improvement in patients with mild AD, while another tideglusib phase II trial revealed no clinical improvements [38].

Salicylsalicylic tau acetylation inhibitor therapies for AD

Preclinical studies have shown that salsalate (**53**; Figure 6), a small-molecule NSAID, inhibited p300 HAT acetylation of tau at Lys174 in transgenic mice, leading to diminished tau pathology, preserved hippocampal volume, and repaired cognition. In 2017, a phase I trial of salsalate in patients with PSP was performed, although the results are not yet published [39].

Pyranothiazoline tau de-glycosylation inhibitor therapies for AD

The compound MK-8719 (**54**; Figure 6) is a small molecule and an inhibitor of O-GlcNAcase (OGA) enzyme. In 2016, the FDA granted orphan drug

status to MK-8719, and plans are ongoing to develop MK-8719 for the treatment of PSP [40].

Curcumin tau aggregation inhibitor therapies for AD

Curcumin (**55**; Figure 6) is a natural compound that stops protein aggregation by binding to β-sheets. *In vivo*, it reduces tau and Aβ pathology and improves cognitive impairment. A phase II study on curcumin in AD patients is currently ongoing [41].

Macrocycle microtubule stabilizer therapies for AD

Epithilone D (**56**; Figure 6) is an anti-fungal agent at preclinical testing stage. It was discovered that epithilone stabilized and increased the number of microtubules, while reducing the number of abnormal axons in a mouse model. Moreover, epithilone D increased cognition, and also reduced tau pathology and tau-associated alterations in microtubule dynamics. Abeotaxane (**57**; Figure 6) is being tested in patients with mild-to-moderate AD [42].

Therapies for AD based on phenylacetic acid tau-protein degradation modulators

The compound BPN14770 (**58**; Figure 6), a phosphodiesterase inhibitor E4 PDE4, has produced promising results in phase II trial in AD patients [43].

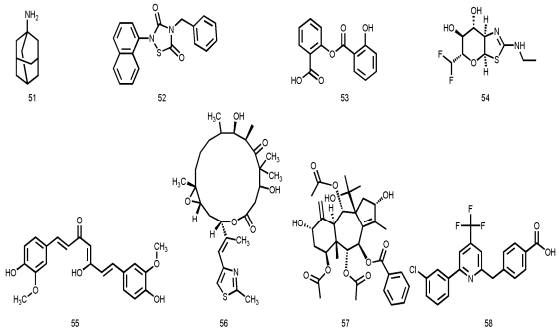

Figure 6: Chemical structures of anti-AD compounds: Tau proteins inhibitors

Oxidative stress hypothesis

In recent studies, free radical generation and the oxidative stress have been proposed as major risk factors in the pathogenesis of AD. The generated free radicals promote nitration, formation of glycation products, lipid peroxidation, and carbonyl-modified neurofilament proteins and free carbonyls which ultimately result in neuronal damage (Figure 7). Moreover, the resultant oxidative stress may induce amyloidogenic processing of β-APP, resulting in buildup of neurotoxic Aβ species [44].

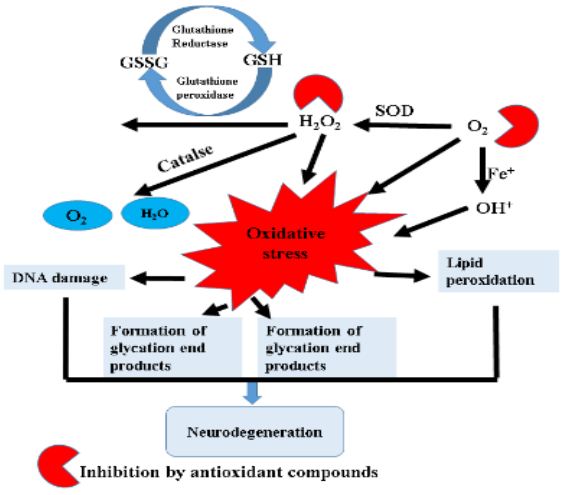

Figure 7: Role of oxidative stress in neurodegeneration (GSH = glutathione; GSSG = glutathione disulfide; SOD = superoxide dismutase)

Antioxidant therapies for AD, and AD therapies based on vitamins and carotene

Antioxidant drugs reduce free-radical-induced damage caused by toxic chain reactions in neuronal cells, and inhibit the pathogenesis of dementia in AD patients. In 1997, it was reported that α-tocopherol (vitamin E; **59**; Figure 8) therapy (at a daily dose of 2000 IU) in patients with moderate-to-severe disabilities from AD decreased neuronal death and reduced the severity of AD, suggesting a clinical delay in AD-induced deterioration of neuronal function. A 2004 study showed that when given prior to AD, α-tocopherol suppressed brain lipid peroxidation and decreased Aβ production and senile plaque formation in animal models. It has been found that patients who take vitamin E supplements live longer than those who do not. Vitamins C and E (**59** & **60),** and β-carotene (**61**; Figure 8) synergistically inhibit lipid peroxidation [45].

Antioxidant enzyme therapies for AD

The antioxidant enzymes are glutathione peroxidase, superoxide dismutase (SOD) comprising copper-zinc SOD (CuZnSOD) and MnSOD (a pro-survival mitochondrial antioxidant enzyme); lipases, proteases, and DNA repair enzymes. These enzymes are essential for neuronal survival and protection against oxidative lesions, and it has been suggested that they may be beneficial in the treatment of cognitive and behavioral symptoms of AD [45].

Neuroinflammation hypothesis

Neuroinflammation normally protects the central nervous system (CNS) from infectious diseases or injuries through the activation of endogenous immunity of the brain. Neuroinflammation is central to the degenerations associated with tauopathies. In brain stem and spinal cord, cycolooxygenase-2 (COX-2) enzymes and proinflammatory cytokines (e.g., IL-1B) are up-regulated in tau-positive nerve cells. In animal model of AD, suppression of neuroinflammation mitigated behavioral and cognitive deficits, and decreased levels of Aβ plaques and hyperphosphorylated tau in brain tissue. Moreover, treatment with anti-tumor necrosis factor-α (anti-TNF-α) or interleukin-1β (IL-1β) antibodies reduced AD pathology in an animal model of the disease. It has been suggested that anti-inflammatory agents may be used for suppressing neuroinflammation in order to prevent cognitive decline and memory in AD. Some flavonoid-containing traditional herbal extracts have been shown to exert inhibitory effects on over-activation of microglia. Some flavonoids such as quercetin (**62**), isorhamnetin (**63**), isoflavone (**64**) (calycosin), and flavan [(2S)-5,7,3′,5′-tetrahydroxy flavanone] (**65**), and 5,4′-dihydroxy-7-methoxy-6-methylflavane (**66**) (Figure 8), produced significant anti-neuroinflammatory effects [46].

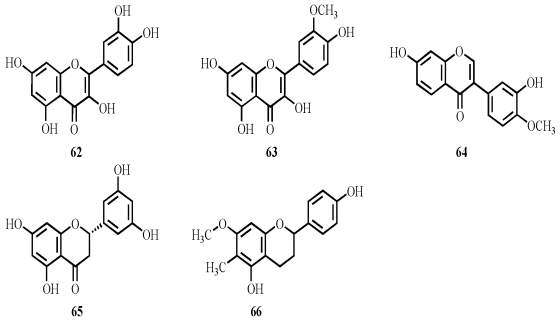

Figure 8: Chemical structures of anti-AD compounds: Anti-neuroinflammatory agents

Metal toxicity hypothesis

Although copper, iron and zinc are needed for neuronal function, their accumulation in the brain contributes to neurodegeneration. These metals do not accumulate inside the core and periphery of senile plaques, and they are involved in Aβ aggregation and oxidative degeneration. As a result, development of drugs that improve mineral balance is an attractive area in ongoing AD research. A metal chelator and anti-AD drug with moderate affinity for metal ions and low toxicity should have the property of passing through the blood-brain barrier (BBB). It should also selectively mop up free metal ions or metal ions bound to Aβ, rather than competing for binding to metal ions attached to other metalloproteins with important biological functions.

Hydroxyquinoline chelator therapies for AD

The compound CQ (**67**; Figure 9), an antiprotozoal drug, has the ability to chelate copper and zinc ions from metal–Aβ species, and to dissolve brain deposits *in vitro*. In AD patients, phase IIa clinical trial of CQ showed reduced level of cognitive deterioration and decreased plasma levels of Aβ42. Unfortunately, the use of CQ as an anti-AD agent was discontinued due to its neurotoxic and mutagenic side effects [47]. *In vitro*, bis-8-hydroxyquinolines (**68-70**; Figure 9) were found to be more effective in preventing amyloid peptide precipitation in the presence of Cu (II), Zn (II), and Fe (III), than CQ (**67**). In addition, it inhibited H_2O_2 generation due to Cu–Aβ as a result of the toxic oxidative stress in AD.

Therapies for AD based on hydroxyquinoline-bioisosteres chelators

Based on CQ (**67**), bioisosterism was applied to design compounds **71** & **72** (Figure 9) as core scaffolds. Compound **71** has a similar chelation potential for Cu (II), Fe (III), and Zn (II) ions, but compound **(72)** preferentially chelates Cu (II). Database virtual screening using compound **72** as query, identified compound **73** as metal chelator for AD, and it was shown to have potential for passing through the BBB [48].

Triazole chelator-based therapies for AD

Deferasirox (**74**) is an old drug used for the treatment transfusion iron overload in thalassemia patients. It selectively binds Fe (II) and Fe (III) [49].

Pyridone chelator-based therapies for AD

Deferiprone (DFP, **75**; Figure 9) ***and DFP analogues*** are used as iron chelators for the treatment of thalassaemia [50]. However, these compounds do not cross the BBB.

Mitochondrial cascade hypothesis

In 2004, Swerdlow and Kan proposed that mitochondrial malfunction occurs early in AD, leading to NFT production, Aβ deposition, and synaptic loss. Oxidative stress and mitochondrial dysfunction are intrinsically linked. The increased

concentrations of reactive oxygen species (ROS) produced during mitochondrial activity cause oxidative stress that results in the mutation of mitochondrial DNA and subsequently results in mitochondrial damage and mitochondrial dysfunction.

Quinone mitochondrial therapies for AD

In a rat model of AD, CoQ10 (**76**; Figure 9) inhibited cognitive decline. However, its low systemic bioavailability is not consistent with its significant pharmacological effects, a quality which makes the drug unsuitable for clinical use. The compounds MitoQ (**77**) and SkQ1 (**78**; Figure 9) are antioxidants, and they are conjugates of ubiquinone and triphenylphosphonium (TPP) cation. A conjugated lipophilic triphenylphosphonium cation (TPP+) induces MitoQ10 accumulation within the mitochondria [51].

Keto-carotenoid-based mitochondrial therapies for AD

The conjugated double bonds of astaxanthin (**79**; Figure 9) are responsible for its antioxidant function, and its lipophilic properties enhance its crossing of the BBB which is required in the treatment of AD [52].

Mitochondrial therapies for AD based on indoles

Melatonin (80; Figure 9) is a neuroprotective hormone generated by the pineal gland. It is involved in the etiology of AD. At mitochondrial level, melatonin prevents cardiolipin oxidation, ROS production, and opening of MPTP; it reduces the levels of caspase-3 and caspase-9, and restores calcium homeostasis [53].

Mitochondrial therapies for AD based on α-lipoic acid

In clinical trials on AD patients, α-lipoic acid (81; Figure 9), an important coenzyme, improved cognitive function. α-Lipoic acid affected the generation of Aβ peptide fibrils and enhanced protection against Aβ peptide toxicity in cultured hippocampal neurons [54].

Mitochondrial therapies for AD based on acetyl-cysteine

N-Acetyl-cysteine (NAC, 82; Figure 9) is a glutathione (GSH) precursor and an endogenous antioxidant that is important for the maintenance of mitochondrial functions. In two clinical trials, AD patients with memory loss received long-time treatment with NAC, resulting in beneficial effects on Aβ peptide, as well as recovery of cognitive and behavioral functions [55].

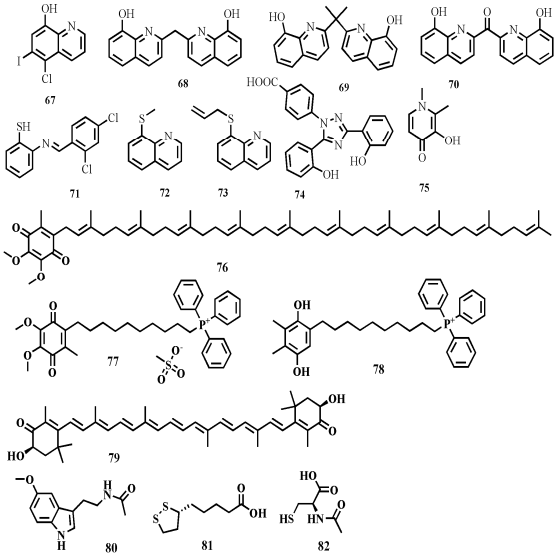

Figure 9: Chemical structures of anti-AD compounds: Mitochondrial therapies

Diabetes mellitus hypothesis

There are insulin receptors in the cognition areas of the brain such as cerebellum, cerebral cortex, hypothalamus, olfactory bulb and hippocampus. In AD, there are impairments in insulin signaling and brain glucose utilization, as well as decreased insulin levels in the cerebrospinal fluid (CSF), decreased insulin/plasma insulin ratio in CSF, reduced expression of insulin receptor, and increased level of fasting plasma insulin. The pathogenesis of AD is affected by impaired insulin signaling via tau hyperphosphorylation, Aβ metabolism, and acetylcholine signaling. Insulin increases the expression of choline acetyltransferase, an enzyme responsible for acetylcholine production. Thus, low insulin levels or severe insulin resistance in AD brains can lead to low acetylcholine levels [56].

Insulin-based therapy for AD

Early clinical investigations in adult AD patients demonstrated that hyperinsulinemia without hyperglycemia improved memory, implying that insulin is vital for memory enhancement. In order to overcome the hypoglycemic effect of injectable insulin, intranasal spray of insulin is used to allow the hormone to bypasses the BBB and reach to

brain in its active form. In patients with early AD, 21-day administration of 20 or 40 IU of intranasal insulin improved verbal memory, attentiveness, and neuronal functions, and also increased plasma levels of short β-amyloid peptide, resulting in higher Aβ 40/42 ratio [56].

Biguanide therapy for AD

Metformin suppresses hepatic gluconeogenesis and re-sensitizes insulin signaling in peripheral tissues. In a mouse model of AD, metformin therapy reduced tau phosphorylation which is the main pathological characteristic of AD. However, in diabetic patients, metformin use resulted in poorer cognitive performance which was mitigated by combining metformin with vitamin B12 and calcium supplementation [57].

Thiazolidinedione-based therapies for AD

Thiazolidinediones are agonists of peroxisome proliferator-activated receptor-gamma (PPARγ). Pioglitazone is the only thiazolidinedione approved for DM therapy, and its application in AD is due to its up-regulation of the expression of PPARγ in the temporal cortex. A recent meta-analysis on PPARγ agonists showed that pioglitazone mitigated the early stages of mild-to-moderate AD [58].

Therapies for AD based on glucagon-like peptide receptor agonists and dipeptidyl peptidase-4 inhibitors

The peptide hormone glucagon-like peptide-1 (GLP-1) is released by the intestine in response to food intake. The GLP-1Rs are receptors present on pancreatic cells, and they stimulate insulin production in response to elevated blood glucose levels. Dipeptidyl peptidase-4 (DPP4) degrades GLP-1, leading to the production of DPP4-resistant GLP-1 analogs (exendin-4, liraglutide and lixisenatide) for clinical use.

However, CNS tissues such as the hypothalamus, hippocampus, cerebral cortex, and olfactory bulb, are rich in GLP-1Rs. Thus, activation of GLP-1Rs in CNS prevents apoptosis, stimulates neurite outgrowth especially in the hippocampus, and exerts neuroprotective effect, particularly in AD. In a mouse model of AD, administration of liraglutide for 8 weeks prevented neuronal loss, memory impairment, and deterioration of synaptic plasticity in the hippocampus. Liraglutide may also lower deposition of Aβ plaque by 40 – 50 %, and decrease inflammatory response. Liraglutide reduced tau hyperphosphorylation, promoted neurogenesis, and had positive effects on the cerebral and systemic microvasculature in AD transgenic mice. Liraglutide is unique in that it produced both preventive and curative effects against the pathological hallmarks of late-stage AD in mice. Other GLP-1 analogs (e.g., exenatide) have showed promising results in preclinical trials involving their application in the treatment of neurodegenerative illnesses. Moreover, a clinical trial on early-stage AD or moderate cognitive impairment is currently underway. Gliptins are DPP4 inhibitors which block the degradation of GLP-1, resulting in decreased fasting and postprandial glucose levels. Preclinical investigations on the DM-approved AD medications i.e., saxagliptin and vildagliptin have also been conducted. The results showed reductions in tau phosphorylation, Aβ deposition, and inflammatory markers, as well as increases in hippocampus GLP-1 levels and memory retention [59].

Amylin analog therapies for AD

Amylin is a hormone co-secreted with insulin by the pancreatic β-cells. The β-sheet structure of amylin, and its degradation by insulin-degrading enzyme, are comparable to those of Aβ. Amylin has the ability to pass the BBB, and it may play a role in regulation of mood, memory, and anxiety. The FDA has approved pramlintide, an amylin analog, for use in the management of type 1 and type 2 diabetes. Plasma amylin levels are markedly reduced in AD patients. Indeed, preclinical data in a mouse model of AD suggest that pramlintide drug might reduce AD symptoms [60]. However, there is need for more research into the potential significance of amylin and its analogs in AD.

CONCLUSION

Alzheimer's disease (AD) is a growing challenge worldwide due to lack of clear understanding of the exact pathophysiology associated with the disease. Several compounds of natural or synthetic origin have been found to be effective in the treatment of AD, either as whole molecules, or as lead compounds. There are many successful efforts towards the development and discovery of novel compounds with potential activity against AD. In addition, many efforts have been made in the synthesis of chemical derivatives with enhanced pharmacokinetic characteristics and improved efficacies. As a result, several molecules have been identified as potential therapeutic candidates for AD, with focus on their safety and clinical benefits.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

The authors declare that this work was done by them and all liabilities pertaining to claims relating to the content of this article will be borne by them. FK Alanazi, AA Radwan and H Abu-Auda conceptualized the study, collected data and contributed in manuscript writing. All authors read and approved the manuscript.

REFERENCES

1. *Bouchard RW, Rossor MN. Typical clinical features. In: Gauthier S; editor. Clinical diagnosis and management of Alzheimer's disease. 3rd Ed. 2006; p. 39-52.*
2. *Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005; 366: 2112-2117.*
3. *American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (5th edition). Arlington; Va.: American Psychiatric Publishing; 2013.*
4. *Martinez A. Emerging drugs and targets for Alzheimer's disease; Volume 1: Beta-Amyloid; Tau protein and glucose metabolism. Cambridge: The Royal Society of Chemistry 2010.*
5. *Lleó A. Current therapeutic options for Alzheimer's disease. Curr Genomics 2007; 8: 550–558.*
6. *Oset-Gasque MJ, Marco-Contelles JL. Tacrine-Natural-product hybrids for Alzheimer's Disease therapy. Curr Med Chem 2020, 27: 4392-4400.*
7. *Onor ML, Trevisiol M, Aguglia E. Rivastigmine in the treatment of Alzheimer's disease: An update. Clin Interv Aging 2007; 2: 17-32.*
8. *Becker RE, Greig NH, Lahiri DK, Bledsoe J, Majercik S, Ballard C, Aarsland D, Schneider LS, Flanagan D, Govindarajan R, et al. (-)-Phenserine and inhibiting apoptosis: In pursuit of a novel intervention for Alzheimer's disease. Curr Alzheimer Res 2018; 15: 883-891.*
9. *De la Torre P, Saavedra LA, Caballero J, Quiroga J, Alzate-Morales JH, Cabrera MG, Trilleras J. A novel class of selective acetylcholinesterase inhibitors: Synthesis and evaluation of (E)-2-(benzo d.thiazol-2-yl)-3-heteroarylacrylonitriles. Molecules 2012; 17: 12072-12085.*
10. *Jacobson SA, Sabbagh MN. Donepezil: Potential neuroprotective and disease-modifying effects. Expert. Opin. Drug Metab Toxicol 2008; 4: 1363-1369.*
11. *Ali MA, Yar MS, Hasan MZ, Ahsan MJ, Pandian S. Design; synthesis and evaluation of novel 5;6-dimethoxy-1-oxo-2;3-dihydro-1H-2-indenyl-3;4-substituted phenyl methanone analogues. Bioorg Med Chem Lett 2009; 19: 5075-5077.*
12. *Weinreb O, Amit T, Bar-Am O, Youdim MBH. A novel anti-Alzheimer's disease drug; ladostigil; neuroprotective; multimodal brain-selective monoamine oxidase and cholinesterase inhibitor. Int Rev Neurobiol 2011; 100: 191-215.*
13. *Shen Q, Peng Q, Shao J, Liu X, Huang Z, Pu X, Ma L, Li YM, Chan AS, Gu L. Synthesis and biological evaluation of functionalized coumarins as acetylcholinesterase inhibitors. Eur J Med Chem 2005; 40: 1307-1315.*
14. *Leonetti F, Catto M, Nicolotti O, Pisani L, Cappa A, Stefanachi A, Carotti A. Homo- and hetero-bivalent edrophonium-like ammonium salts as highly potent, dual binding site AChE inhibitors. Bioorg Med Chem 2008; 16: 7450-7456.*
15. *Zhou X, Wang XB, Wang T, Kong LY. Design, synthesis, and acetylcholinesterase inhibitory activity of novel coumarin analogues. Bioorg Med Chem 2008; 16: 8011-8021.*
16. *Kang SY, Lee KY, Sung SH, Park MJ, Kim YC. Coumarins isolated from Angelica gigas inhibit acetylcholinesterase: structure-activity relationships. J Nat Prod 2001; 64: 683-685*
17. *Awang K, Chan G, Litaudon M, Ismail NH, Martin MT, Gueritte F. 4-Phenylcoumarins from Mesua elegans with acetylcholinesterase inhibitory activity. Bioorg Med Chem 2010; 18: 7873-7877.*
18. *Youkwan J, Sutthivaiyakit S, Sutthivaiyakit P, Citrusosides AD. Citrusosides A–D and furanocoumarins with cholinesterase inhibitory activity from the fruit peels of Citrus hystrix. J Nat Prod 2010; 73: 1879-1883.*

19. Camps P, El Achab R, Morral J, Muñoz-Torrero D, Badia A, Baños JE, Vivas NM, Barril X, Orozco M, Luque FJ. New tacrine-huperzine A hybrids (huprines): Highly potent tight-binding acetylcholinesterase inhibitors of interest for the treatment of Alzheimer's disease. J Med Chem 2000; 43: 4657-4666.
20. Estrada LD, Soto C. Disrupting β-Amyloid aggregation for Alzheimer Disease treatment. Curr Top Med Chem 2007; 7: 115–126.
21. Kandalepas PC, Sadleir KR, Eimer WA, Zhao J, Nicholson DA, Vassar R. The Alzheimer's beta-secretase BACE1 localizes to normal presynaptic terminals and to dystrophic presynaptic terminals surrounding amyloid plaques. Acta Neuropathol 2013; 126: 329–352.
22. Ghosh AK, Kumaragurubaran N, Hong L, Lei H, Hussain KA, Liu CF, Devasamudram T, Weerasena V, Turner R, Koelsch G, et al. Design; synthesis and x-ray structure of protein-ligand complexes: important insight into selectivity of memapsin 2 (-β-secretase) inhibitors. J Am Chem Soc 2006; 128: 5310–5311.
23. Stachel SJ, Coburn CA, Steele TG, Jones KG, Loutzenhiser EF, Gregro AR, Rajapakse HA, Lai MT, Crouthamel MC, Xu M, et al. Structure based design of potent and selective cell-permeable inhibitors of human β-secretase (BACE-1). J Med Chem 2004; 47: 6447–6450.
24. Rajapakse HA, Nantermet PG, Selnick HG, Munshi S, McGaughey GB, Lindsley SR, Young MB, Lai MT, Espeseth AS, Shi XP, et al. Discovery of oxadiazoyl tertiary carbinamine inhibitors of β-secretase (BACE-1). J Med Chem 2006; 49: 7270–7273.
25. Coburn CA, Stachel SJ, Jones KG, Steele TG, Rush DM, DiMuzio J, Pietrak BL, Lai MT, Huang Q, Lineberger J, et al. BACE-1 inhibition by a series of ψCH2NH. reduced amide isosteres. Bioorg Med Chem Lett 2006; 16: 3635–3638.
26. Stachel SJ, Coburn CA, Sankaranarayanan S, Price EA, Wu G, Crouthamel M, Pietrak BL, Huang Q, Lineberger J, Espeseth AS, et al. Macrocyclic inhibitors of β-secretase: functional activity in an animal model. J Med Chem 2006; 49: 6147–6150.
27. Cole DC, Manas ES, Stock JR, Condon JS, Jennings LD, Aulabaugh A, Chopra R, Cowling R, Ellingboe JW, Fan KY, et al. Acylguanidines as small-molecule β-secretase inhibitors. J Med Chem 2006: 49: 6158–6161.
28. Congreve M, Aharony D, Albert J, Callaghan O, Campbell J, Carr RA, Chessari G, Cowan S, Edwards PD, Frederickson M, et al. Application of fragment screening by X-ray crystallography to the discovery of aminopyridines as inhibitors of β-secretase. J Med Chem 2007; 50: 1124–1132.
29. Hills ID, Holloway MK, de Leon P, Nomland A, Zhu H, Rajapakse H, Allison TJ, Munshi SK, Colussi D, Pietrak BL, et al. A conformational constraint improves a β-secretase inhibitor but for an unexpected reason. Bioorg Med Chem Lett 2009; 19: 4993–4995.
30. Malamas MS, Erdei J, Gunawan I, Turner J, Hu Y, Wagner E, Fan K, Chopra R, Olland A, Bard J, et al. Design and synthesis of 5,5'-disubstituted aminohydantoins as potent and selective human β-secretase (BACE1) inhibitors. J Med Chem 2010; 53: 1146–1158.
31. Low JD, Bartberger MD, Chen K, Cheng Y, Fielden MR, Gore V, Hickman D, Liu Q, Sickmier AE, Vargas HM, et al. Development of 2-aminooxazoline 3-azaxanthene β-amyloid cleaving enzyme (BACE) inhibitors with improved selectivity against Cathepsin D Med Chem Commun 2017; 8: 1196-1206.
32. Ghosh AK, Pandey S, Gangarajula S, Kulkarni S, Xu X, Rao KV, Huang X, Tang J. Structure-based design; synthesis; and biological evaluation of dihydroquinazoline-derived potent β-secretase inhibitors. Bioorg Med Chem Lett 2012; 22: 5460–5465.
33. Cheng Y, Judd TC, Bartberger MD, Brown J, Chen K, Fremeau RT Jr, Hickman D, Hitchcock SA, Jordan B, Li V, et al. From fragment screening to in vivo efficacy: optimization of a series of 2-aminoquinolines as potent inhibitors of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1). J Med Chem 2011; 54: 5836–5857.
34. Stachel SJ, Steele TG, Petrocchi A, Haugabook SJ, McGaughey G, Katharine HM, Allison T, Munshi S, Zuck P, Colussi D, et al. Discovery of pyrrolidine-based β-secretase inhibitors: lead advancement through conformational design for maintenance of ligand binding efficiency. Bioorg Med Chem Lett 2012; 22: 240–244.
35. Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, He F, Sun X, Thomas RG, et al. A Phase 3 Trial of Semagacestat for Treatment of Alzheimer's Disease. N Engl J Med 2013; 369: 341–350.
36. Kimura T, Kawano K, Doi E, Kitazawa N, Shin K, Miyagawa T, Kaneco T, Ito K, Takaishi M, Sasaki T, et al. Cinnamide Compound. Patent Application Publication No. WO 2005115990 A1; 8 December 2015.
37. Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. PloS ONE 2015; 10: e0123289.
38. Tolosa E, Litvan I, Höglinger GU, Burn D, Lees A, Andrés MV, Gómez-Carrillo B, León T, Del Ser T. TAUROS Investigators. A phase 2 trial of the GSK-3 inhibitor tideglusib in progressive supranuclear palsy. Mov Disord 2014; 29: 470–478.
39. Min SW, Chen X, Tracy TE, Li Y, Zhou Y, Wang C, Shirakawa K, Minami SS, Defensor E, Mok SA, et al. Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits. Na Med 2015; 21: 1154–1162.
40. Alectos Therapeutics announces FDA orphan drug designation for MK-8719: an investigational small-molecule OGA inhibitor for treatment of progressive supranuclear palsy (2016).
41. Hu S, Maiti P, Ma Q, Zuo X, Jones MR, Cole GM, Frautschy SA. Clinical development of curcumin in

neurodegenerative disease. Expert Rev Neurother 2015; 15: 629–637.

42. *Zhang B, Carroll J, Trojanowski JQ, Yao Y, Iba M, Potuzak JS, Hogan AM, Xie SX, Ballatore C, Smith AB, et al. The microtubule-stabilizing agent; epothilone D; reduces axonal dysfunction; neurotoxicity; cognitive deficits; and Alzheimer-like pathology in an interventional study with aged tau transgenic mice J Neurosci 2012; 32: 3601–3611.*
43. *US National Library of Medicine. ClinicalTrials.gov (2017).*
44. *Devi P, Syad A. Botanics: a potential source of new therapies for Alzheimer's disease? Botanics: Targets and Therapy 2014; 11: 10.2147/BTAT.S33554.*
45. *Nunomura A, Castellani RJ, Zhu X, Moreira PI, Perry G, Smith MA. Involvement of oxidative stress in Alzheimer disease. J Neuropathol Exp Neurol 2006; 65: 631–641.*
46. *Kim DH, Li H, Han YE, Jeong JH, Lee HJ, Ryu JH. Modulation of inducible nitric oxide synthase expression in LPS-stimulated BV-2 microglia by prenylated chalcones from cullen corylifolium (L.) medik. through Inhibition of I-κBα Degradation. Molecules 2018; 23: 109–117.*
47. *Budimir A. Metal ions, Alzheimer's disease and chelation therapy. Acta Pharm 2011; 61: 1–14.*
48. *Rodríguez-Rodríguez C, Rimola A, Alí-Torres J, Sodupe M, González-Duarte P. In silico strategies for the selection of chelating compounds with potential application in metal-promoted neurodegenerative diseases. J Comput Aided Mol Des 2011; 25: 21–30.*
49. *Nick H. Iron chelation, quo vadis? Curr Opin Chem Biol 2007; 11: 419–423.*
50. *Telpoukhovskaia MA, Patrick BO, Rodríguez-Rodríguez C, Orvig C. Exploring the multifunctionality of thioflavin- and deferiprone-based molecules as acetylcholinesterase inhibitors for potential application in Alzheimer's disease. Mol Biosyst 2013; 9: 792–805.*
51. *Ng LF, Gruber J, Cheah IK, Goo CK, Cheong WF, Shui G, Sit KP, Wenk MR, Halliwell B. The mitochondria-targeted antioxidant MitoQ extends lifespan and improves healthspan of a transgenic Caenorhabditis elegans model of Alzheimer disease. Free Radic Biol Med 2014; 71: 390–401.*
52. *Lobos P, Bruna B, Cordova A, Barattini P, Galáz JL, Adasme T, Hidalgo C, Muñoz P, Paula-Lima A. Astaxanthin protects primary hippocampal neurons against noxious effects of Aβ-oligomers. Neural Plast 2016; 2016: 3456783.*
53. *Shukla M, Govitrapong P, Boontem P, Reiter RJ, Satayavivad J. Mechanisms of melatonin in alleviating Alzheimer's disease. Curr Neuropharmacol 2017; 15: 1010–1031.*
54. *Dos Santos SM, Romeiro CFR, Rodrigues CA, Cerqueira ARL, Monteiro MC. Mitochondrial Dysfunction and Alpha-Lipoic Acid: Beneficial or harmful in Alzheimer's disease. Oxid Med Cell Longev 2019; 2019: 8409329.*
55. *Remington R, Bechtel C, Larsen D, Samar A, Page R, Morrell C, Shea TB. Maintenance of cognitive performance and mood for individuals with Alzheimer's disease following consumption of a nutraceutical formulation: A one-year; open-label study. J Alzheimers Dis 2016; 51: 991–995.*
56. *Wilkinson CW, Baker LD, Cholerton B, Fishel MA, Plymate SR, Breitner JC, DeGroodt W, Mehta P, Craft S. Intranasal insulin improves cognition and modulates β-amyloid in early AD. Neurol 2008; 70: 440–448.*
57. *Moore EM, Mander AG, Ames D, Kotowicz MA, Carne RP, Brodaty H, Woodward M, Boundy K, Ellis KA, Bush AI, et al. Increased risk of cognitive impairment in patients with diabetes is associated with metformin. Diabetes Care 2013; 36: 2981–2987.*
58. *Cheng H, Shang Y, Jiang L, Shi TL, Wang L. The peroxisome proliferators activated receptor-gamma agonists as therapeutics for the treatment of Alzheimer's disease and mild-to-moderate Alzheimer's disease: a meta-analysis. Int J Neurosci 2016; 126: 299–307.*
59. *Calsolaro V, Edison P. Novel GLP-1 (glucagon-like peptide-1) analogues and insulin in the treatment for Alzheimer's disease and other neurodegenerative diseases. CNS Drugs 2015; 29: 1023–1039.*
60. *Mousa YM, Abdallah IM, Hwang M, Martin DR, Kaddoumi A. Amylin and pramlintide modulate γ-secretase level and APP processing in lipid rafts. Sci Rep 2020; 10: 3751-3784.*