Review Article
An overview on therapeutics attenuating amyloid β level in Alzheimer’s disease: targeting neurotransmission, inflammation, oxidative stress and enhanced cholesterol levels

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Abstract: Alzheimer’s disease (AD) is the most common underlying cause of dementia, and novel drugs for its treatment are needed. Of the different theories explaining the development and progression of AD, “amyloid hypothesis” is the most supported by experimental data. This hypothesis states that the cleavage of amyloid precursor protein (APP) leads to the formation of amyloid beta (Aβ) peptides that congregate with formation and deposition of Aβ plaques in the frontal cortex and hippocampus. Risk factors including neurotransmitter modulation, chronic inflammation, metal-induced oxidative stress and elevated cholesterol levels are key contributors to the disease progress. Current therapeutic strategies abating AD progression are primarily based on anti-acetylcholinesterase (AChE) inhibitors as cognitive enhancers. The AChE inhibitor, donepezil, is proven to strengthen cognitive functions and appears effective in treating moderate to severe AD patients. N-Methyl-D-aspartate receptor antagonist, memantine, is also useful, and its combination with donepezil demonstrated a strong stabilizing effect in clinical studies on AD. Nonsteroidal anti-inflammatory drugs delayed the onset and progression of AD and attenuated cognitive dysfunction. Based upon epidemiological evidence and animal studies, antioxidants emerged as potential AD preventive agents; however, clinical trials revealed inconsistencies. Pharmacokinetic and pharmacodynamic profiling demonstrated pleiotropic functions of the hypolipidemic class of drugs, statins, potentially contributing towards the prevention of AD. In addition, targeting the APP processing pathways, stimulating neuroprotective signaling mechanisms, using the amyloid anti-aggregants and Aβ immunotherapy surfaced as well-tested strategies in reducing the AD-like pathology. Overall, this review covers mechanism of inducing the Aβ formation, key risk factors and major therapeutics prevalent in the AD treatment nowadays. It also delineates the need for novel screening approaches towards identifying drugs that may prevent or at least limit the progression of this devastating disease.

Keywords: Donepezil, memantine, antioxidants, statins, screening

Introduction

Dementia is a neurodegenerative condition marked by diminished cognitive and thinking ability, altered personality and loss of reasoning [1]. Alzheimer’s Disease (AD) is the best known and the most prevalent cause of dementia, accounting for about 60-80% of all dementia cases [2]. Owing to the increasing average life span, the prevalence of AD is sharply on the rise, with the WHO predicting above 20 million cases by 2020, and Delphi consensus study projecting about 70-80 million AD sufferers by 2050 [3-5]. Though AD is an aging-associated disorder mainly reported in patients aged 65-85 years, it can affect younger people too, with environmental and genetic factors playing a leading contributory role in such cases [6, 7].

Presence of several pathophysiologic mechanisms in the progression of AD hinders development of a single potential treatment for the disease [8]. Although, a few therapeutic agents have gained prominence in the recent years and have reached the late stages of clinical trials [9], an overall lack of any suitable disease-modifying therapy prevents its effective management. This leads to severe damage and death of the functioning brain cells, which ultimately proves fatal [10]. In this review, we will...
briefly discuss the current mechanisms, rationales and targets for therapeutic interventions in AD. We will focus on the drugs that are known to suppress AD symptoms, specifically the neurotransmitter modulators, anti-inflammatory compounds, antioxidants and cholesterol-lowering statins. We also highlight the need for new drugs that may slow the disease progression, overcoming the deficiencies of existing therapies. Unlike earlier reviews that generally focus on either causes of AD or its treatment, we concisely provide a comprehensive idea about all the essential factors promoting AD pathogenesis, as well as potential approaches to the disease prevention and therapy.

AD hypotheses and Aβ Generation

Although the molecular mechanisms of AD pathogenesis are well-investigated, the key reason that governs the pathology is yet contentious. The most accepted “amyloid hypothesis” points to the deposition of amyloid beta (Aβ) in the neurons and parenchyma as major reason for synaptic, axonal and neural dysfunctions and the consecutive cognitive impairment in patients [11-13] (Figure 1). Aβ formation is largely regulated by a shift in the balance between amyloidogenic and non-amyloidogenic amyloid precursor protein (APP) processing [14]. The APP, predominant in the brain as 695, 751 and 770 amino acid isoforms, undergoes non-amyloidogenic cleavage at the α-secretase site at position 17 of the 40-42-Aβ amino acid domain. This results in the formation of two fragments, sAPPα and a C-terminal fragment (CTFα). sAPPα, proved to be neuroprotective, is secreted. CTFα undergoes further proteolysis by γ-secretase, yielding p3 peptide and a C-terminal fragment, CTFγ. A down-regulation of this non-amyloidogenic processing or a shift towards the amyloidogenic pathway causes β-secretase to cleave APP before the Aβ amino acid site, releasing CTFβ and sAPPβ. CTFβ is further cleaved by γ-secretase, generating Aβ40 and Aβ42. The Aβ42 isoform is deemed more toxic, participating more in the plaque formation [15, 16]. Intracellular accumulation of hyperphosphorylated and aggregated tau in the form of neurofibrillar tangles is also closely

Figure 1. APP processing pathway stimulating Aβ plaque deposition and AD pathology.
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Figure 2. Major risk factors promoting Aβ plaque deposition in AD.

Table 1. Important publications on Neurotransmitter Modulators as AD therapeutics

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related to neuronal death in AD [17, 18]. It is believed that Aβ deposition precedes tau tangle formation, with the latter triggered by Aβ-activated calpain and an increased tau pro-
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An association of AD with several vascular and mitochondrial risk factors, e.g., diabetes mellitus, hypertension, atherosclerosis, hypercholesterolemia, metabolic syndrome and obesity, led to a view that vascular pathologies may trigger AD [21]. It is believed that apolipoprotein E (Apop E) genotype is linked with hypercholesterolaemia [22]. Amyloid and vascular mechanisms are closely related and both culminate in Aβ deposition via disruption and perturbation of Aβ transporters, especially in the blood-brain barrier (BBB) [23]. Familial AD is governed by the autosomal, dominantly inherited, rare mutations in APP and its processing molecules, such as the γ-secretase components, presenilin (PSEN)1 and PSEN2, and accounts for less than 1% of AD cases overall [24]. The present review will focus specifically on the amyloid-based Aβ concept of AD, highlighting the major risk factors and therapeutics.

AD therapeutics

Risk factors, such as neurotransmitter modulation, chronic inflammation, metal-induced oxidative stress and elevated cholesterol, primarily contribute to AD progression (Figure 2). Altered neurotransmission involving cholinergic dysfunction, increased glutamate release and N-methyl-D-aspartate (NMDA) receptor action, and aberrant gamma-aminobutyric acid (GABA), histamine and serotonin functioning participate in the pathogenesis [25-29]. Elevated levels of brain-specific inflammatory cytokines and a pronounced increase in the metals, iron, copper and zinc, in the amyloid plaques of the AD brain suggest inflammation and metal-induced oxidative stress as key mechanisms in AD pathology [30, 31]. Hypercholesterolemia and cholesterol-linked pathways play an important role in AD [32]. Thus, here we elaborate on these risk factors and their mitigation approach in reducing the Aβ generation and, thereby, AD pathology.

**Targeting neurotransmitters (Table 1)**

**Cholinesterase inhibitors**: Cholinergic hypothesis of AD development focuses on the increased hydrolysis of acetylcholine by acetylcholinesterase (AChE). This leads to a reduction in synaptic acetylcholine levels detected in AD brain [33]. The resulting modulation in cholinergic neurotransmission and functions prompts learning-memory impairments and altered intellectual, behavioral and emotional responses. Clinical findings reveal significant cortical and hippocampal atrophy associated with the cholinergic modulations [33]. This cholinergic damage is promoted by butyrylcholinesterase (BuChE) that functions as a co-regulator and enhancer of AChE. However, since the effect of BuChE is more prominent at peripheral tissues, AChE gains predominance as the cholinergic neuro-modulator in AD [34]. Of the known clinically-used AChE drugs, tacrine, donepezil, rivastigmine and galantamine (Figure 3) are the most commonly used and considered promising for AD treatment. Further, these drugs have been derivatized to improve their efficacy and potency and reduce toxic side effects [35]. Tacrine (Figure 3) is the foremost approved of the first-
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generation AChE and BuChE inhibitors that has cholinomimetic properties [36]. Owing to tacrin’s hepatotoxic effects, ring structure-modified derivatives of tacrine were synthesized [37]. Dual-binding site, homo- and heterodimeric derivatives capable of binding to both active and peripheral AChE sites were generated based on homodimers of two tacrine moieties linked by oligomethylene chains [38]. Of these, linkers with a heptamethylene tether were found to be significantly more potent than tacrine [39]. Incorporation of a protonable amino group in the middle of the tether enhanced AChE selectivity and activity, and an amide group in place of the central methylene group of a heptamethylene linker increased BuChE selectivity [40]. Some derivatives with chloro and iodo moieties were also designed [41]. Heterodimeric derivatives with indane and phthalimide tagged to tacrine also proved suitable [42]. Tacrine heterodimers were designed by connecting the tacrine moiety with imidazole, piperidine and ferulic acid. A potent tacrine heterodimer, carbcrine, was generated by combining tacrine with the carbazole moiety of carvedilol that had IC50 values of 2.15 nM and 296 nM for AChE and BuChE respectively [43]. Combination of tacrine with the hepatoprotective nitric oxide (NO) donors appeared safe [44]. Interestingly, to reduce Ca2+ toxicity, Ca2+ channel blockers, such as 1,4-dihydropyridine (DHP) were inserted forming tacripyrines, of which the one with a cycloheximide ring in DHP moiety appeared the most potent as AChE inhibitor (IC50 = 0.37 µM) [45]. Tacrine-phenyl-benzoheterocyclic derivative demonstrated AChE inhibitory property. Moreover, this benzo derivative functioning was also dependent on the methylene linker chains [46]. Donepezil (IC50 = 5.7 nm) (Figure 3) is considered less toxic and physiologically well-accepted and was the second FDA-approved drug for treating AD. The drug enhances cholinergic transmission and attenuates neuronal damage [47]. Interaction of its benzyl piperidine and indane groups with the indole rings at the peripheral anionic site (PAS) proved useful. N-benzylpiperidine derivatives with aroylthiourea, fluoro and a chloro incorporation at indane system were also designed and demonstrated to have 30-50% of donepezil’s IC50 value of [48]. A combination of 3-amino-6-phenylpiridazine with N-benzylpiperidine units yielded a compound that was several times more potent than donepezil. Combining piperidine, indanone and methylene groups resulted in a compound with the highest potency, with an IC50 of 0.0018 µM [49]. Galanthamine (IC50 = 800 nM) (Figure 3), a tertiary alkaloid drug, manifests AChE activity reduction and modulates nicotinic acetylcholine receptors (nAChR) towards enhancing acetylcholine generation [50]. The drug is a proven allosteric modulator of nAChR [51]. Though less toxic, its reduced potency for acetylcholine release compared to tacrine led to the designing of few derivatives using alkyl linkers, especially eight to ten methylene groups, and a terminal ammonium or phthalimido group with several fold increased efficacy [52]. N-substituted galanthamine derivatives with incorporated benzylpiperidines and alkyl linkers, specifically with six methylene units, appeared to have highest AChE efficacy amongst all derivatives [43]. Rivastigmine (IC50 = 4.15 µM) (Figure 3), with a carbamate moiety, emerged as a new generation of AChE inhibitor which is long-acting and reversible. Benzopyrano[4,3-b]pyrrole carbamate derivatives with further methyl derivatization at carbamoyl nitrogen showed a potent inhibitory property [53]. A combination of donepezil and rivastigmine linked through 5,6-dimethoxy-indan-1-one and dialkyl-benzylamine moieties demonstrated significantly higher AChE rather than BuChE inhibition, indicating selectivity towards the former [54]. For these compounds, variations in the meta- and para-substituted derivatives were evident [54]. A heterodimer of rivastigmine and the serotonin transport inhibitor, fluoxetine, appeared as a potent second-generation dual AChE-SERT inhibitor, emphasizing the importance of incorporating dual functions in drugs [55]. Xanthostigmine derivatives possess the amyloid pro-aggregatory property due to their binding at the AChE peripheral site. Its aryldenebenzocycloalkanone derivative targeted both the active and peripheral sites, and a further incorporation of three or seven methylene units alkoxy spacer chain and aryldiene moiety into the aryldiene aryl ring moiety enhanced contact with PAS [56]. Of the tested meta- and para-isomers, the para-aminobenzoic acid derivative possessed a K value of 53 nM (AChE). Further molecular dynamics and docking studies confirmed their efficacy as AChE inhibitors. Cis-isomers of pyrrolo-isoxazole derivatives with methoxy substitution, especially at the para-position were deemed...
highly potent, claiming an anti-amnestic and AChE inhibitory abilities higher than that of donepezil [57]. The polyphenolic compounds, coumarin and its derivatives, such as ensaculin (KA-672 HCl) containing a benzoxyran ring and a piperazine substitution [58] and AP2238 having benzylamino group linked to coumarin via phenyl ring, are rising as AChE/BuChe inhibitors with peripheral and catalytic site-binding capacities [59]. Flavonoid derivatives linking flavonoid and benzylpiperidine through oxygen atom or alkoxy group (-OCH2) spacers proved effective [60]. A replacement of benzyl piperidine moiety with amino alkyl or the conformationally restrained hydrophobic groups, pyrrolidine or piperidine at the meta- or para-positions was more potent, whith the latter two demonstrateing greater effect [60]. Carbamate-substituted 5,7-dimethoxyflavanone, having an IC50 of around 10 nM or several folds greater respectively [61].

However, cholinesterase inhibitors are not recommended for patients with advanced AD and are prescribed rather for moderate or mild AD cases. Other side effects of these drugs include unwanted cholinergic stimulation in the intestine, heart, muscle, kidney, and other organs. Thus, AChE inhibitors specifically targeting the cholinergic system of the brain are desired.

Glutametargic alteration: Modulation in the functioning of glutamatergic neurons is generally viewed as a property of mature AD pathology, mediated strongly by the altered levels of the synaptic glutamate neurotransmitter [62]. NMDA receptor activation inducing excitotoxicity by enhanced synaptic glutamate accumulation damages the glutamatergic neurons and adversely impacts the neuronal proliferation and differentiation, causing learning, memory and cognitive impairments [62]. Further, a direct interaction between the NMDA receptors and APP is also reported, indicating the importance of glutamatergic synaptic transmission in AD [63]. Memantine (1-amino-3,5-dimethyladamantane) (Figure 3), an adamantane derivative, is the most used and cost-effective drug targeting the NMDA receptor for AD treatment, especially in the USA and Europe [64, 65]. It is proved through clinical studies that the drug has symptomatic effectiveness and is known to treat moderate to severe AD [66]. As detected through cultured neuronal whole-cell patch clamp recordings, memantine has a modest affinity of about 1 mM at 70 mV [67]. The proposed mechanism appears uncompetitive, fast, voltage-dependent and with reduced tendency for entrapment in the receptor channel [67]. Memantine is capable of blocking the NMDA receptor channel and in preventing glutamate-mediated excitotoxicity by interacting with Mg2+ or binding to NMDA channel close to the magnesium-binding site, and thereby reducing Ca2+ entry in the post-synaptic neurons [68]. Other than NMDA receptor-mediated functioning, memantine also reduced Aβ-induced neuronal apoptosis, marked by an attenuated DNA fragmentation and altered Bcl-2 immunostaining [69]. A non-specific neurotransmitter targeting is also detected with memantine, via its ability to antagonize human α7nAChR, indicating a concern for studies involving the co-existence of NMDA and nACh receptors [70]. However, for situations that involve aberrant functioning of both nAChR and NMDAR in AD, memantine appears very effective. A modulation of dopaminergic and serotonergic/histaminergic neurotransmission is also reported with memantine [71, 72]. Interestingly, it was claimed that a combination of memantine and cholinesterase inhibitor with different and interconnected activities is preferred: the former takes care of agitation/aggression and delusions, and the latter reduces depression, anxiety and apathy thus indicating complementary activities [73, 74].

GABAergic alteration: It is proven that transgenic mice with early-stage amyloid pathology manifest modulations in the cholinergic neurons, followed by glutamatergic and lastly the inhibitory GABAergic neurons [75]. By inducing GABAa receptor subunit endocytosis, Aβ impedes synaptic inhibition [76]. GABAa undergoes a compensatory increase in a few hippocampal regions and sub-regions where the NMDA and non-NMDA type α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)-receptors are reduced at the late AD stages, probably in order to maintain hippocampal functions [77]. The pyrazolopyridine compound etazolate with anxiolytic-like properties at nanomolar to low micromolar pharmacological doses selectively affected the GABAa receptor and enhanced the propagation of α-secretase pathway towards sAPPα [78]. Another anticonvulsant drug, gabapentin, structurally related to GABA demonstrated prominent positive responses to treatment at low
doses in mixed vascular/Alzheimer dementia patients [79]. However, the drug caused sedation at a high dose, and appears to affect other neurotransmitter systems, including serotonin and glutamate [80].

Serotonergic alteration: The hippocampal serotonin 5-hydroxytryptamine (5-HT) receptor, especially 5-HT1A receptor, and the cortical 5-HT6 serotonergic receptors and their metabolites, particularly 5-HIAA, play key role in the memory and cognition [81]. Post-mortem AD brain demonstrated a decrease in 5-HT, and its reduction in the cortex correlated with the neuronal loss at the raphe nuclei [82]. This serotonergic dysfunction is a property of the early-onset AD, reportedly with the mis-regulation of α-secretase processing [83]. Given the location of many of these receptors on terminals of other neurons, it is possible that these changes reflect the loss of cholinergic synapses as well [84, 85]. Thus, preclinical studies on 5-HT1A receptor antagonists reported pro-cognitive effects with the significant abetment of glutamatergic and cholinergic transmission [86]. The 5-HT1A receptor antagonist lecozotan (SRR-333) initially appeared promising, safe and well tolerated in clinical pharmacokinetic studies at a single drug dose [87]. However, adverse side effects prevented its progress into phase II clinical trials. Few partial agonists, such as tandospirone and buspirone, are being considered useful in preventing dementia [88, 89]. Agonists of the 5-HT4 G-protein-coupled receptor, such as PRX-3140, PF-04995274 and RQ-00000009 (RQ-9), that act by enhancing Ca2+ influx, involving store-operated calcium entry (SOCE) [103]. Aβ-dependent alteration in T helper cell memory with altered expression of cytokines and chemokines clearly indicated a link with histidine. An aberrant postreceptor signaling in AD involving phosphoinositide hydrolysis and adenylate cyclase pathways that are constitutively suppressed by the cortical H3R substantiated association between histidine and AD [102]. Inverse agonists of histidine receptor, carebastine and mepyramine, suppressed H1R and also histamine generation, and prevented an alteration in Ca2+-signaling via alteration of protein kinase A (PKA) and cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) [104]. The H3R agonist, R-(alpha)-methylhistamine, was found to distinctly attenuate muscarinic

Histaminergic modulation: It is reported that short-term and long-term memory is regulated by histamine, and a degeneration of histaminergic neurons impairs the cognition [98]. Studies on null-mutations of the excitatory receptors, H1R and H2R, in frontal cortex, amygdala and hippocampus revealed histidine participation in maintaining the normal synaptic plasticity and learning-memory [99]. For the histaminergic synaptic functioning, an interaction with aminergic and peptidergic systems was also reported [100]. An enhanced activity of the inhibitory H3Rs attenuated the cholinergic system as well [101]. Histamine is known to contribute to dendritic cell (DC) functioning and regulates immune responses via increased interleukin IL-6 and IL-10, decreased IL-12, and enhanced secretion of chemokines and matrix metalloproteases-9 and -12, the latter participating in DC migration via the H2R binding [102]. H1R and H4R triggered the T helper 2 (Th2)-type immune responses and modulated Ca2+ influx, involving store-operated calcium entry (SOCE) [103]. Aβ-dependent alteration in T helper cell memory with altered expression of cytokines and chemokines clearly indicated a link with histidine. An aberrant postreceptor signaling in AD involving phosphoinositide hydrolysis and adenylate cyclase pathways that are constitutively suppressed by the cortical H3R substantiated association between histidine and AD [102]. Inverse agonists of histidine receptor, carebastine and mepyramine, suppressed H1R and also histamine generation, and prevented an alteration in Ca2+-signaling via alteration of protein kinase A (PKA) and cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) [104]. The H3R agonist, R-(alpha)-methylhistamine, was found to distinctly attenuate muscarinic
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Acetylcholine receptor-dependent phospholipase C (PLC) activity and calcium-calmodulin- and cAMP-induced protein kinases, thereby predicting an attenuation of the presynaptic excitatory functions of acetylcholine in AD [105]. The H3R antagonists that promote the generation of histamine, acetylcholine, dopamine and norepinephrine, and suppress the adenyl cyclase-PKA pathways are being promoted as drug targets for AD. The H1R antagonist, pyrilamine, inactivated His-dependent STAT6 hyperphosphorylation, while H2R antagonist, ranitidine, and H3R/H4R antagonist, thioperamide, failed to do so [106]. Rather, H3R antagonists that stimulate the cognitive domains were proposed as new therapeutic agents for AD treatment. Chlorpheniramine, an H1R antagonist, that functioned as a serotonin-norepinephrine reuptake inhibitor altered the cortical and hippocampal cholinergic tone and affected learning and memory in AD [107]. Furthermore, the H3R antagonist, thioperamide, and 5-HT3 antagonist, ondansetron, healed cholinergic deficits, suggesting their probable role in inhibiting the AD pathogenesis [108].

Adenosine receptor: Activation of adenosine receptor of A2A subtype induced the anti-inflammatory IL-10 and prevented Aβ deposition [109, 110]. An interaction of Aβ with β2-adrenergic receptors induced internalization and degradation of the latter, causing adrenergic and glutamatergic aberrations and reduction in β2-adrenergic-stimulated cAMP [111, 112]. It was found that both caffeine and adenosine receptor antagonists averted Aβ build-up via increased striatal PKA activity and p-CREB levels, and decreased p-JNK and p-ERK [113, 114]. The reduction in A2a adenosine receptors, therefore, stimulated pro-survival anti-apoptotic cascades and cognitive impairments induced by Aβ [115]. A selective adenosine A2A receptor antagonist SCH58-261 also demonstrated a similar effect [116].

Targeting inflammation

(Table 2)

Neuroinflammation is established as intricately associated with AD, involving the participation of complement, cytokines, chemokines and acute phase proteins [117]. Chronic complement activation leading to membrane blebbing and endocytosis, and neutrophil opsonization was observed in the vicinity of Aβ [117]. Activated microglia and astrocyte-generated cytokines, such as the pro-inflammatory IL-1 and tumor necrosis factor alpha (TNFα), regulate cyclooxygenase (COX) activity and extensively participate in APP metabolism [118, 119]. Supportively, cytokine and Transforming Growth factor beta polymorphism is observed in the AD brain [120]. In addition, these cytokines, alongside chemokine IL-8, intracellular adhesion molecule-1, macrophage colony stimulating factor and acute phase proteins such as C-reactive protein, serum amyloid A, and transthyretin coordinate the acute phase mechanisms [121-125]. The inflammatory mediators evidently activate the AChE enzyme activity and thereby aggravate the cholinergic dysfunction in AD [126]. Thus, targeting inflammation to reduce AD pathology appears to be advantageous.

Microglial generation of superoxides and oxidative intermediates is an early feature of AD [127]. Thus, therapeutics that target microglia and prevent microglial activation are being designed. Small molecules directed towards the 13-16 site of Aβ (HHQK domain) that binds within the microglia [128], and SD-282 that targets microglial P38-MAPK mechanism of inflammation [129] are also being assessed. Drugs aiming at the plaque-linked complement C3 and neurotoxic C5b-9 [130] and the brain osonins integrated to the inflammatory cascade are hypothesized to suppress the membrane attack complex that mediate the complement cascade-mediated neuronal killing [131].

Table 2. Important publications on anti-inflammatory agents as AD therapeutics

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<td></td>
<td>Targeting PPAR</td>
<td>Nenov et al., 2014</td>
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However, the most well-studied compounds are the non-steroidal anti-inflammatory drug (NSAID) that had undergone epidemiological studies. The studies revealed that consistent use of NSAID has a positive effect in attenuating the AD risk [132]. Indomethacin inhibited astroglial IL-1-dependent IL-6 secretion involving a reduction in the prostaglandin-2 [133]. A specific cyclooxygenase-2 (COX-2) inhibitor, BF389, followed almost a similar IL mechanism [134]; however, the COX-2 inhibitors failed to prevent cognitive decline. Cognitive restoration and reduction in the AD pathological features in triple transgenic mice by the anti-inflammatory COX-1 inhibitor, SC-560, appeared hopeful [135]. Ibuprofen, rather than adopting the COX inhibition pathway, suppressed γ-secretase activity and reduced Aβ levels, as found in APP-transgenic mice [136]. A nitro-derivative of ibuprofen, nitro-flurbiprofen, released NO that promoted microglial Aβ clearance and also prevented the reduction of plasticity-related genes [137, 138]. Very interestingly, the anti-inflammatory mode of action of nitro-ibuprofen was different from SD-282, that is used for suppressing microglial activation in AD [129]. Thus, a suitable NSAID tha balances the two opposing properties in terms of microglial activation is essential. Via targeting the BACE activity, the peroxisome proliferator-activated receptor gamma agonists, pioglitazone, prevented cytochrome-dependent Aβ production, while the antagonists, GW0072, prevented NSAID-mediated amyloid formation [139-141]. NSAID regulated Rho-GTPases and restrained the reduction in axonal functioning and astroglial migration and activation in AD [142]. Another very interesting aspect is that the targeting of the IL-1 responsive element of 5’-untranslated region (5’UTR) of APP proved responsible for driving APP translation [143]. These drugs are also conjectured to target the interaction of AU-rich protein with the 3’-UTR of IL-1 and TNFα, or the thalidomides that block the cytokine translation [143]. Thus, targeting the NSAID-dependent cytokines as well as APP translation appears quite promising. However, long duration treatments with COX inhibitors were found to cause damage to heart, kidney, intestine and other organs [144-146]. Moreover, the belief that NSAIDs function in the ApoEε4-carrying AD population restricts the use of NSAID in other AD patients [147]. Thus, these limitations associated with the anti-inflammatory targets enlighten the need for newer compounds and drugs for AD.

Targeting metals and oxidative stress (Table 3)

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<th>Anti-Oxidative stress agents</th>
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<td>Resveratrol</td>
<td>Joseph et al., 2003; Ho et al., 2009</td>
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<td>Curcumin</td>
<td>Yang et al., 2005, Ringman et al., 2012</td>
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<td>Neu-P11</td>
<td>He et al., 2013</td>
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<td>Green tea and food additives</td>
<td>Kim et al., 2009; Zhao et al., 1989; Goodman et al., 1994; Iuvone et al., 2006</td>
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<td>Coenzyme Q10 (CoQ10)</td>
<td>Lee et al., 2009</td>
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<td>a-lipoic acid</td>
<td>Siedlak et al., 2009</td>
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<td>MitoQ and plastoquinone</td>
<td>Kapay et al., 2011; McManus et al., 2011</td>
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<td>Calkins et al., 2011</td>
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<td>Nrf2/ARE pathway targets</td>
<td>Tertbutylhydroquinone</td>
<td>Ramsey et al., 2007; Kanninen et al., 2008; Dumont et al., 2012</td>
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<td>Adenovirus-dependent gene delivery</td>
<td>Kanninen et al., 2008; Dumont et al., 2012</td>
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<tr>
<td>Metal Chelation</td>
<td>Desferrioxamine, EDTA and Clioquinol</td>
<td>Mandel et al., 2007; Amiat et al., 2008; Hegle et al., 2009</td>
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Trapping of Fe, Cu and Zn ions within the amyloid plaques and their interactions with APP and Aβ are prominent mechanisms accelerating the amyloid pathology [143]. Several experimental techniques, such as proton-induced X-ray emission, epifluorescence microscopy, immersion autometallography [148], synchrotron X-ray fluorescence (SXRF), magnetic resonance imaging (MRI), susceptibility weighted MR (SWI), and laser capture microdissection coupled with X-ray fluorescence microscopy confirmed the metal localization in concentrations of ~15 μM for Cu²⁺ and about 1 mM for iron and zink [149-152]. Aluminium is another
metal that has emerged as an important participant in AD [152]. Catalytic reactions involving the generation of neurotoxic hydrogen peroxide (H₂O₂) and superoxide ion generation are the major metal-mediated mechanism of Aβ generation. Thus, superoxide dismutase-1 and co-enzyme Q that possess endogenous antioxidant properties are assessed for their usefulness in animal models exposed to oxidative stress, and are also being tested for efficacy in AD [153]. In the current review section, we will discuss the specific participation of these heavy metals in the AD pathogenesis, followed by the therapeutics targeting the metals and their induced mechanism.

Fe: Cortical and hippocampal over-expression of hemeoxygenase (HO-1) promotes heme conversion to Fe²⁺ inducing the mitochondrial insufficiency, enhancing cytochrome C oxidase activity and H₂O₂ generation [154]. Furthermore, an involvement of Fenton reaction (Fe²⁺ + H₂O₂ → Fe³⁺ + OH⁻ + OH⁻) in neurons and astroglia triggers free radical generation and oxidative stress, which then activates neurotoxic mechanisms associated with nuclear factor-kB, p53, c-Jun transcription factors, DNA damage and apoptosis [155]. These oxidative stress mechanisms culminate in BBB disruption [156], myelin breakdown and eventually cognitive decline in AD [157]. An IRE-IRP binding that regulates APP translation is also altered due to excess iron accumulation via formation of an IRP-1 and [4Fe-4S] cluster that deregulate iron uptake andAPP translation [143]. A resemblance of APP 5'-UTR sequence with the ferritin IRE stemloop strongly supports the intense participation of iron in the pathology. Moreover, an iron binding site was also found in the APP 5'-UTR, corroborating the concept of Fe-regulated APP and thereby Aβ generation [158, 159]. Furthermore, the iron-mediated down-regulation of α-secretase activator furin was also shown to participate in iron homeostasis [160].

Cu: The fact that copper ions bind to histidine, aspartate and tyrosine- residues in Aβ with a dissociation constant at the attomolar levels, and the Cu-promoted stimulation of Fenton reaction strongly support the participation of Cu in oxidative stress-mediated AD pathogenesis [161]. The released H₂O₂ interacts with copper tyrosinate that cross-links with Aβ, further enhancing Aβ generation [162]. The process of Cu-mediated toxicity during AD pathogenesis was proven to be stimulated by an interaction of copper ions with membrane lipid rafts, altering endocytosis of APP that bears the features of a Cu transporter [163].

Zn: A Micro-PIXE study revealed the Zn(II) levels of around 70-90 μg/g, amounting to about 1020-1060 μM concentration in the plaque rim, core and the total plaques [143]. The zinc level as high as 1 mM was also reported in cerebral amyloid plaques, with a pre-synaptic vesicle to postsynaptic neuronal discharge [164]. The APP was found to have a Zn-binding domain located between the amino acids 181 and 200, leading to its binding to the amino acid 6-8 in Aβ [165]. The alteration in Zn release involves an enhanced expression of zinc transporter proteins (ZNTs, ZnT2-8) that further promotes abnormal Zn deposition in the AD brain [166]. This change in Zn homeostasis alters its normal functions, influencing APP interaction with heparin-like molecules or laminin that participates in the biological process of neurite outgrowth [167]. Zinc deposition in Aβ promotes γ-secretase activity via enhanced presenilin formation, and also activates transcription factors nuclear factor kapp-B and Specificity protein-1 that bind to APP promoter, thereby promoting amyloidogenic APP synthesis [168].

Al: Studies in APP transgenic Tg2576 mice revealed an increase in insoluble Aβ deposition upon dietary Al supplementation and consumption of Al-treated drinking water [169]. This was supported by an increased Al levels within Aβ core plaques peptides of aluminium dust-exposed workers [170]. Apart from inducing oxidative stress, aluminium disrupts neuronal intracellular Ca²⁺ release and stimulates DNA damage during AD pathology [171]. Because of the explicit role of transition metals in AD, metal chelation in modifying the AD progression is being widely accepted. Desferrioxamine, EDTA and clioquinol were found to be effective in attenuating AD pathogenesis in transgenic AD mice, which also proved successful in clinical trials [172-174]. The metals function via an oxidative stress mechanism, and hence antioxidant treatments are deemed as a promising preventive approach in mitigating AD.

Oxidative stress attenuation: antioxidant treatment

Animal studies on APP and PS1 transgenic models, and Aβ over-expressing animals re-
revealed an anti-oxidant-mediated cognitive restoration associated with a reduction in hippocampal and cortical Aβ deposition. The antioxidants mainly studied include the vitamins (carotenoids, vitamins C and E, lipoic acid, coenzyme Q10, N-acetylcysteine, polyphenols and Ginkgo biloba extract [175]). An attenuation in reactive oxygen species (ROS) generation and Aβ-induced neurotoxicity in cultured primary neuronal cultures and cell lines, such as PC12 cells, as well as in Tg 2576 AD transgenic mice, was observed using vitamin E [176, 177]. The effect of vitamin E was more pronounced when combined with anti-inflammatory agents, as reported for indomethacin [178]. Patient studies revealed tocopherol-mediated attenuation in AD pathology, and its combination with vitamin C augmented the preventive effect [179, 180]. Combining vitamin E with memantine and donepezil, however, failed to add to the protective effect of vitamin E alone [181, 182]. Mitochondrial targeting aimed at mitigating the ROS generation appeared as a pertinent anti-oxidant mechanism, where coenzyme Q10 (CoQ10, ubiquinone) played a potent role [183]. However, the effect of ubiquinone or its water-soluble cognate, idebenone, though appealing in the pre-clinical studies, failed to prove effective in clinical trials [184, 185]. Treatment with the mitochondrial antioxidant, α-lipoic acid, significantly improved cognition in Tg2576 transgenic AD mice [186]. This was supported by patient data, at a level comparable to AChE drug therapy [187]. A combination of lipoic acid with the anti-oxidant, omega-3-fatty acid, appeared potent in slowing down the functional cognitive decline [188]. In vitro effect of lipoic acid in inhibiting the Aβ oligomerization was also reported [189]. Other mitochondrial antioxidants, such as MitoQ and plastoquinone, prevented oxidative stress, the astroglia-induced neuroinflammation and, ultimately, AD pathology [190, 191]. Plastoquinone also prevented hippocampal modulations of Long Time Potentiation in rats [191], and SS31 prevented alterations in the mitochondrial dynamics of transgenic AD mice neurons [192]. MitoVitE was found to be an advanced and more effective form of MitoQ [193]. Mitochondrial permeability transition pore (mPTP), that regulated mitochondrial functions, was also targeted. Dimebon, which appeared to be promising in this context, failed in clinical trials, probably because of its complex mechanism of action, which involves AChE reduction and 5-HT4 stimulation on one hand, and 5-HT6 and 5-HT3 activations that impairs cognition [194]. N-acetylcysteine (NAC) is another antioxidant that reduced malondialdehyde, increased glutathione and restored the LTP [195, 196]. Interestingly, a study revealed that a combination of NAC and lipoic acid, along with curcumin, epigallocatechin gallate and the anti-oxidant vitamins is a prominent inducer of normal cognitive functioning in Tg2576 mice [197]. Flavonoids and carotenoids themselves were also widely studied as preventive agents in AD [194]. Natural flavonoid and carotenoid, namely rutin and lutein, prevented dementia [198, 199]. Curcumin proved important in reducing Aβ and AChE in animal studies; however, the human studies were not so promising [200, 201]. Resveratrol containing blueberry [202] and red grape [203] caused attenuation in Aβ plaque deposition, with epidemiological surveys proving the red wine-induced reduced memory loss in AD [204]. However, all these natural antioxidants could be claimed effective after completion of clinical trials [194]. Supplementation with the antioxidant melatonin that quenches free radicals reduced fibrillar amyloid burdens and prevented neurodegeneration via reduction of Aβ-induced neuronal apoptosis, with observed protection in human studies [205]. A melatonin agonist Neu-P11 was found to be effective in rats [206]. Alkaloid and a flavonoid derivative, Silibinin, Ginkgo biloba and a long-term caffeine intake proved useful against Aβ-induced damage in transgenic animals [207-210]. Green tea and food additives, such as theanine, rosamarinic acid and nordihydroguaiaretic acid had both antioxidant properties and anti-amyloid features as well [211-214]. An endogenous antioxidant mechanism targeting the nuclear receptor factor 2 (Nrf2)/antioxidant response element (ARE) pathway also seems to be a potential alternative approach to attenuate the AD pathology [215]. Tertbutylhydroquinone or adenovirus-dependent gene delivery along with the triterpenoid CDDO-methylamide that stimulated Nrf2 expression and translocation protected against AD pathology [216, 217]. Overall, the general prevailing view is that although oxidative stress is a major risk factor for AD, the therapeutic effects of antioxidants alone in clinical trials appear less promising. Probably, the antioxidants bioavailability, water and lipid solubility,
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Mechanism of action, time and duration of treatment, and combined use are to be taken into consideration for further preclinical and clinical studies.

**Targeting hypercholesterolemia (Table 4)**

APP is a transmembrane protein, and cholesterol is an integral component of the lipid membrane. Hence, the changes in cholesterol level affect the lipid raft proteins, thereby impacting the APP as well [218]. The binding of cholesterol to CTFβ through the GXXXG motif is an important factor that brings APP, γ- and β-secretases close together and enhances the amyloidogenic cleavage [219]. Since the major non-amyloidogenic component, α-secretase, is not a part of the lipid raft, cholesterol contributes greater to the amyloidogenic cleavage pathway of APP [219]. Noticeably, APP is also closely associated with the cholesterol biosynthesis regulatory enzymes - sterol receptor element binding protein (SREBP) and HMG-CoA reductase [220]. Participation of cholesterol in Aβ aggregation was also reported through its interaction with the ganglioside GM1 found in lipid rafts of CNS [221]. Furthermore, localization of Aβ degrading enzymes, insulin-degrading enzyme (IDE) and neprisynin (NPE) and plasmin in the lipid rafts points towards the role of cholesterol in influencing the Aβ degradation [222]. Aβ clearance is also influenced by ApoE polymorphic alleles, ε4, ε3 and ε2, that participate in the cholesterol transport and impact the brain cholesterol homeostasis [223]. ApoE participates in neuroinflammation by modulating the toll like recetor and the nuclear factor kappaB pathways [224]. In fact, it is believed that the effect of APOE on BBB is inflammation-mediated, since its integral cell component, astrocytes, induce inflammation when activated [225]. Increased levels of oxysterols interact with APP and Aβ, with several hydroxylated cholesterol forms identified in the AD brain [226].

Cholesterol lowering drugs/statins: Because of the well-proven link between cholesterol and AD, statins are believed to be therapeutic for the disease. Simvastatin, via increased PI3K/AKT activity and endothelial NO synthase pathway, contributes towards inhibiting the learning and memory impairment in the Tg2576 mice [229]. However, simvastatin has no effect on the Aβ level in brain. Rather, administration of simvastatin to Aβ-immunized mice exacerbat-ed the amyloid angiopathy [230]. The suppression of cholesterol metabolism with the help of HMG-CoA reductase inhibitor lovastatin, or its active metabolite lovastatin acid at 10-60 mg once-daily dose, caused dose-dependent Aβ reduction in human subjects [231]. Epidemiological studies have demonstrated that hypercholesterolemia was a risk factor for AD, and lovastatin caused a delayed AD onset and attenuated AD development [231, 232]. Atorvastatin was reported to prevent the neuronal degeneration following Aβ induction. The effects of both atorvastatin and pitavastatin were mediated by attenuation of inflammation and oxidative stress and increase in the glutamatergic transporters [229, 233]. Statins were also found to suppress inflammation and microglial iNOS synthesis and NO generation in

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<tr>
<th>Anti-cholesterol agents</th>
<th>Therapeutics</th>
<th>References</th>
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<tr>
<td>Statin</td>
<td>Simvastatin</td>
<td>Shinohara et al., 2014</td>
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<td></td>
<td>Lovastatin</td>
<td>Friedhoff et al., 2001; Buxbaum et al., 2002</td>
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<td>Atorvastatin, Cerivastatin, Fluvastatin, Pravastatin, Rosuvastatin</td>
<td>Barone et al., 2014</td>
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AD via pleiotropic actions involving isoprenyl intermediates [234]. The neuroprotective pleiotropic effects of statin included an increase in SOD activity, activation of PKC, augmentation of endothelial nitric oxide synthase (eNOS) and reduction of CoQ10 levels [235, 236]. The effects observed in clinical trials were analyzed for atorvastatin, cerivastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin and were found to be independent of apoE genotype [237]. There were several controversies in regards to the statins’ beneficial role, however. It was later deduced that, despite lower reported AD incidence among the statin-treated users, there is no direct link between statins and the AD risk and development. Moreover, contradicting the phase II study, phase III randomized clinical trials showed a less beneficial role of statins [237]. Thus, it is suggested that clinical trials with a large patient population, different duration and different stages of disease are needed to find out the exact role of the cholesterol-reducing agents in AD. An upregulation of the heme oxygenase/biliverdin reductase system, probably via inhibition of BACE1, is a likely possible pathway for inhibiting the AD progression. It is hypothesized that the effects of simvastatin, lovastatin, atorvastatin and rosuvastatin and simvastatin are based on this mechanism [238]. Although still debatable, the use of statins may provide a useful strategy for suppressing the AD progression.

Future directions and conclusion

The present review gives an insight into the major pathophysiological risk factors promoting AD. Overall, it is observed that despite elaborate knowledge of the risk factors and mechanism of AD, only a modest choice of therapeutic tools is available for management, prevention, mitigation and treatment of the disease. Presently, symptomatic treatments are the most prevalent, and multiple studies are in progress to identify specific drugs targeting AD. With all the progress made so far, clinical trials have accepted the AChE inhibitors and a single NMDA receptor agonist as the probable AD therapeutics. AChE inhibitors, donepezil, galantamine and rivastigmine are used in mild to moderate AD. In severe AD or in patients not responding to AChE inhibitors, memantine can be used as an alternative (Table 5). A combination of cholinesterase inhibitors, with memantine is also accepted as a treatment option, where the cholinergic drugs appeared more clinically beneficial even at the late stage of the disease [239]. Yet, it remains unclear at which stage of the disease the drugs should be started and which sequence of treatments should be used. A lack of knowledge on the AD-specific pharmacokinetics and bioavailability has led to a reasonably low acceptance of the antioxidants, statins and anti-inflammatory agents as AD therapeutics. An understanding of their usage-dose, latency period, stage at which efficacy is at the peak and the genetic impact may help in proceeding with the agents reducing oxidative stress, inflammation and hyperlipidemia. Targeting BACE1 and presenilin, the components of the γ-secretase pathway, is envisaged as a reasonable approach for inhibiting the amyloidogenic pathway of APP processing. Alternatively, stimulation of signaling pathways triggering the α-secretase-based non-amyloidogenic pathway appears as a reasonable strategy. A very optimistic approach is the targeting of APP 5’-UTR. Worldwide, the drug libraries are being screened for that purpose, with the aim of identifying both the inhibitors of amyloidogenic and the promoters of non-amyloidogenic pathways of Aβ. Vaccine-based approaches are also designed, bringing the attention to the usefulness of Aβ immunotherapy. The use of amyloid anti-agregant strategies is also being investigated. Though clinical trials for the immunotherapies are in progress, detailed clinical studies on patients are yet awaited. However, we look forward to further research and clinical trials towards understanding and identifying novel independent and interdependent strategies that modulate amyloid metabolism in attenuating Aβ in AD.

Disclosure of conflict of interest

None.

Table 5. FDA-approved drugs as AD therapeutics

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<thead>
<tr>
<th>Drugs</th>
<th>Mode of action</th>
<th>AD symptoms</th>
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<td>Donepezil</td>
<td>AChE inhibitor</td>
<td>Mild to severe AD</td>
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<tr>
<td>Memantine</td>
<td>NMDAR antagonist</td>
<td>Moderate to severe AD</td>
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<tr>
<td>Rivastigmine</td>
<td>AChE and BuChE inhibitor</td>
<td>Alzheimer-like pathology</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Cholinergic inhibitor</td>
<td>Alzheimer-like pathology</td>
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