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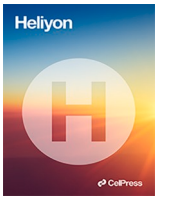

Review article

Recent advances in potential enzymes and their therapeutic inhibitors for the treatment of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD), a chronic neurodegenerative disease, is clinically characterized by loss of memory and learning ability among other neurological deficits. Amyloid plaques, hyperphosphorylated tau protein, and neurofibrillary tangles involve in AD etiology. Meanwhile, enzymes and their inhibitors have become the focus of research in AD treatment. In this review, the molecular mechanisms involved in the pathogenesis of AD were overviewed and various enzymes such as acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), β-secretase, γ-secretase, monoamine oxidase (MAO), and receptor of advanced glycation end products (RAGE) were highlighted as potential targets for AD treatment. Several hybrid molecules with essential substructures derived from various chemotypes have demonstrated desired pharmacological activity. It is envisioned that the development of new drugs that inhibit enzymes involved in AD is a future trend in the management of the disease.

1. Introduction

Alzheimer's disease (AD) is the common cause of dementia with huge implications for the elderly. This slowly progressive neurodegenerative disease is currently becoming a global health crisis that lacks effective treatment [1,2]. Memory decline, neuropsychiatric symptoms, and cognitive dysfunction are some symptoms observed in AD patients [3].

The main pathological features of AD are characterized by the presence of senile plaques and neurofibrillary tangles (NFTs), which are formed due to the extracellular of amyloid-beta (Aβ) and hyperphosphorylated tau protein, respectively [1].

AD can be divided into two different forms, sporadic or late-onset (LOAD) which accounts for over 95 % of cases, and early onset or familial AD (FAD) which usually manifests by age 60.

Microglial activation, overproduction of reactive oxygen species, cerebral amyloid angiopathy, associated astrogliosis, and dystrophic neurites are some abnormalities detected in LOAD [3]. S. Samanta *et al* highlighted the multifactorial nature of AD. Mitochondrial dysfunction, insulin resistance, calcium dyshomeostasis, and impaired brain glucose metabolism are some other factors involved in AD progress [4,5].

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At FAD, dysregulation in tangle-bearing and non-tangle-bearing neurons is found at different levels of protein folding and myelination in autophagy, apoptosis, and stress response. Altered expression of some genes including apolipoprotein E (APOE), β -secretase, homology and U-box containing protein 1 STUB1 (STIP1) (CHIP), FYN, Golgi Associated, Gamma Adaptin Ear Containing, ARF Binding Protein 1(GGA1), and Sortilin Related Receptor 1 (SORL1) is one of the neuropathological hallmarks of AD, particularly FAD [6]. The change in gene expression could be varied in two genders. While the specific genes are overexpressed in females in comparison to males, the degree of pathophysiological and cognitive weakening remains similar in both genders [7]. It has been shown that several other factors like key enzymes could involve in AD development and progression [8]. β-site amyloid precursor protein cleaving enzyme 1 (BACE-1) and γ-secretase are related to amyloid-β (Aβ) accumulation. BACE-1 is essential for all monomeric forms of Aβ, including Aβ42. Aβ42 aggregates into bioactive conformational types and likely causes toxicity in FAD. From the BACE family, BACE-1 and the homolog BACE-2 have other substrates that can be important for synaptic plasticity and synaptic hemostasis. However, data show that BACE-2 does not contribute to the amyloid precursor protein (APP). On the other hand, the enhanced expression of BACE-1 invokes scientists to find out whether AD-associated factors such as oxidative stress, radicals, and unfolded proteins may induce BACE-1 transcription in LOAD [9].

Mutations in the Presenilin1 (PSEN1), the catalytic component of γ-secretase, lead to elevated Aβ products at the γ-secretase complex. Early inhibitors were used for characterizing and labeling the γ-secretase complex containing PSEN1. But poor drug qualities of these compounds lead scientists to use a wide variety of small molecule γ-secretase modulators (GSMs). Two important groups of GSMs are nonsteroidal anti-inflammatory drugs (NSAIDs)-derived carboxylic acid GSMs and heterocyclic non-NSAIDs-derived GSMs. All these GSMs bind to the PS subunit of γ-secretase and reduce the aggregation-prone peptide. The important challenge about the new drugs is the lack of information about the structure of GSMs- γ-secretase complex. Nowadays, efficient Aβ-degrading enzymes such as neprilysin (NEP), endothelin-converting enzyme-1(ECE-1), plasmin, angiotensin-converting enzyme (ACE), matrix metalloproteinase (MMP)-9, and insulin-degrading enzymes (IDE) have become the main targets in novel pharmacotherapies for AD treatment [7,8]. An upregulation of NEP in reactive astrocytes surrounding amyloid plaques in AD transgenic mice, suggests its role in the development of cerebral amyloid angiopathy. At earlier stages of AD progression, histone deacetylase (HDAC) 1 inhibitors such as trichostatin A and valproic acid (VA) upregulate the NEP level and increase its activity. In endothelial cells, high glucose level increases the expression level of ECE-1c mRNA, one of the two close homologs of NEP, which reduced cellular Aβ [10]. Several unexpected candidates have been introduced as potential enzyme inhibitors. Homocysteine is a sulfur-containing amino acid that plays a key role in transferring activated methyl groups from tetrahydrofolate to S-adenosylmethionine. It also contributes to the synthesis of Tau protein and the formation of amyloid plaques. Recent research reveals a biological connection between homocysteine (Hcy) and detoxifying enzymes such as PON1, BLMH, and BPHL, suggesting their involvement in AD [11].The significance of this topic is highlighted by a recent study focusing on bioactive compounds produced by microalgae and cyanobacteria, which exhibit enzyme inhibitory effects to AD [12]. There are over 3000 articles related to AD and cholinesterase (ChE), and approximately 3600 articles on sirtuins. However, there are only a few notable studies on other specific enzymes involved in AD.

We conducted a thorough literature search using databases such as PubMed, Scopus, and Web of Science. Our search terms included "Alzheimer's disease," "Target enzymes in AD", "Enzyme inhibitors," "Clinical studies in AD", "Multi-target drugs in AD". We focused on articles published in the last 20 years to ensure the relevance and currency of the information presented. The inclusion criteria comprised review articles that explain the pathogenesis of AD. Original research articles exploring the role of enzymes in AD and studies discussing various inhibitors targeting these enzymes. The exclusion criteria included articles not published in peer-reviewed journals and studies reporting the non-enzymatic mechanisms of AD.

In this article, we overview the key molecular mechanisms involved in the pathogenesis of AD. Additionally, we provide a comprehensive review of the enzymes associated with AD and the latest advancements in developing enzyme inhibitors for therapeutic applications, highlighting several recent studies and clinical trials focused on these inhibitors.

2. Molecular mechanisms involved in the pathogenesis of AD

The major cause of AD is generally attributed to the increased production of senile plaques, Aβ accumulation, and NFTs formation [13]. Research on the two main classifications of AD indicates that FAD is linked to complete or partial genetic mutations in the APP, PSEN1, and presenilin 2 (PSEN2) genes [14]. Some studies suggested that gene duplication increases Aβ concentration [15]. SAD or LOAD is believed to be linked to genetic predispositions in the APOE ε4 allele, as well as mutations in genes such as CLU, SORL1, and TREM2. These genetic factors are associated with synaptic dysfunction, which can disrupt communication between neurons and contribute to cognitive impairment [16]. Both FAD and SAD are distinguished by the presence of Aβ in the brain. However, FAD has a more correlation with Aβ plaques, while SAD encompasses other pathological alterations including neurofibrillary tangles and neuronal depletion [17]. Furthermore, Aβ overproduction is not always observed in SAD. For instance, plasma Aβ42 levels are consistently elevated in FAD, while such increases are rarely seen in cases of SAD. In FAD, mutations lead to Aβ42 deposition, whereas in SAD, a reduction in aminopeptidase activity results in impaired Aβ catabolism and subsequent deposition [18]. Some other pathogenic AD hypotheses are explained below.

2.1. The amyloid-β pathway in AD

One of the main pathological hallmarks of AD is Aβ protein and senile plaques. One notable development is the inclusion of Aβ oligomers in the amyloid hypothesis. According to the amyloid cascade hypothesis, AD results from a "machine failure" due to the accumulation of Aβ amyloid deposits in the brain. Understanding the mechanisms of Aβ aggregation involves examining primary and

secondary nucleation points, where amyloid fibrils catalyze the formation of oligomers. This connects oligomers to the entire process of Aβ aggregation [19]. The amyloid cascade hypothesis has been revitalized by the effectiveness of antibodies such as Lecanemab and Donanemab in individuals affected by AD. Lecanemab shows promising results against Aβ amyloid deposits and provides hope for AD patients, having been proven to slow cognitive decline [20]. Another successful anti-amyloid therapy in phase 3 clinical trials is Donanemab, which specifically targets pyroglutamated Aβ [21]. Recent studies over the last decade suggest that extracellular Aβ may be benign and potentially even physiologically protective. This perspective paves the way for considering intraneuronal Aβ (iAβ) as a potential stimulant in the development of AD [22]. Studies using transgenic animal models of AD reveal the impact of molecular factors on Aβ formation. Zinc, produced by glutamatergic synapses, binds to Aβ and accelerates its aggregation. Another significant factor is isomerized Asp7 (isoD7-Aβ), which accounts for a substantial portion of Aβ deposits in amyloid plaques. The cytotoxicity of isoD7-Aβ is linked to the induction of oxidative stress, actin polymerization, and the formation of stress fibers. Additionally, isoD7-Aβ can serve as a nucleation seed for Aβ aggregation in the presence of high concentrations of free zinc in vivo [23].

The principal component of amyloid plaques is Aβ protein and is made by different transcriptional splicing of APP. Soluble APPs (sAPP)β which are the products of APP cleavage are related to essential upstream pathophysiological events in AD. Although proteins that are targeted by sAPPβ remain enigmatic, some evidence shows sAPPβ regulates Cdk5 and P25 hyperactivity which have been detected in neurofilament and tau tangles of AD's brain [24]. Aβ can be generated through different pathways including amyloidogenic and non-amyloidogenic ways (Fig. 1). Amyloidogenic processing results in the formation of two common variants of APPsβ, namely Aβ40 and Aβ42, in AD. Aβ42 is the initiator of plaque formation in the cerebral spinal fluid (CSF) [25] Aβ42/Aβ38 ratio is a specific marker of AD that can be used to discriminate AD from dementia. In the non-amyloidogenic pathway, α-secretase, mainly A disintegrin and metalloprotease (ADAM) 17 and ADAM10 cut the APP and retain the C-terminal of APP to further make γ-secretase complex, including PSEN1 and PSEN2 [26]. Low-density lipoprotein receptor-related protein 1 (LRP1) is a factor that has been found to increase APP endocytosis and sAPP β generation. This evidence shows that LRP1 specifically downregulates BACE1 and increases APP [27]. It has been found that Aβ plaques in the mitochondria of the AD brain led to low energy production in mitochondria. Aβ accumulation in mitochondria stimulates ROS production and induces appoptosin, a pro-apoptotic protein that led to mitochondrial dysfunction and cell death [24,28].

2.2. The role of tau (τ) protein in pathology of AD

Tau proteins play an important role in cytoskeleton integration and stability by binding to microtubules [29]. Tau also regulates axonal transport in the mammalian brain and influence synaptic plasticity and insulin signaling in dendrites. Most of the tau species except tau tangles are assumed to be neurotoxic although the exact mechanism is not clear. Some studies show the role of other proteins in the neurotoxicity of the tau species. One of the proteins is Fyn kinase which stabilizes its interaction with N-methyl D-aspartate (NMDA) receptors at postsynaptic densities [30]. According to several studies, post-translational modifications (PTMs) control the tau function. Under certain conditions, the monomeric tau aggregates into NFTs. According to the tau propagation theory, the intracellular pathological tau protein is released from donor cells to extracellular space and accumulated in the recipient cells of CSF. Several studies confirmed the tau-containing exosome as a biomarker in AD pathology [31]. Hyperphosphorylation in the paired helical filaments (PHFs) is one of the early events in AD onset (Fig. 2). Hyperphosphorylation dissociates tau protein from microtubules. In contrast, phosphorylation distributes tau in dendritic spines. Tau phosphorylation is regulated by various Ser/Thr and Tyr kinases. Many studies aim to target tau hyperphosphorylation by inhibiting these kinases and phosphatases [32,33]. Moreover, in the AD sample, N- and O- glycation of Lys are identified in the microtubule-binding domain of PHF-tau [34]. The O-linked-N-acetylglucosaminylation (O-GlcNAcylation) of Ser and Thr sites is supposed to be the reason for abnormal glucose metabolism in

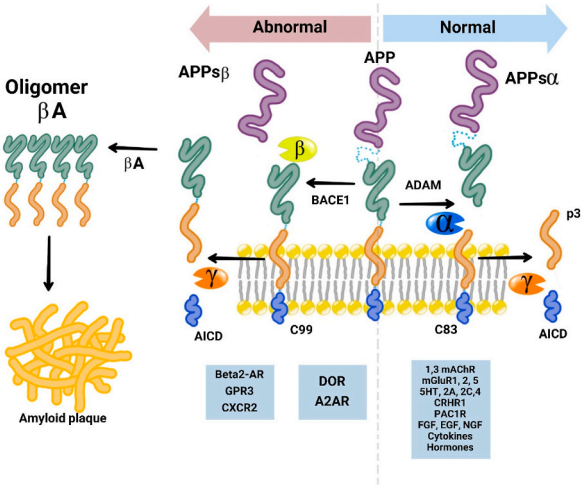


Fig. 1. Amyloidogenic and non-amyloidogenic pathways in Aβ production.

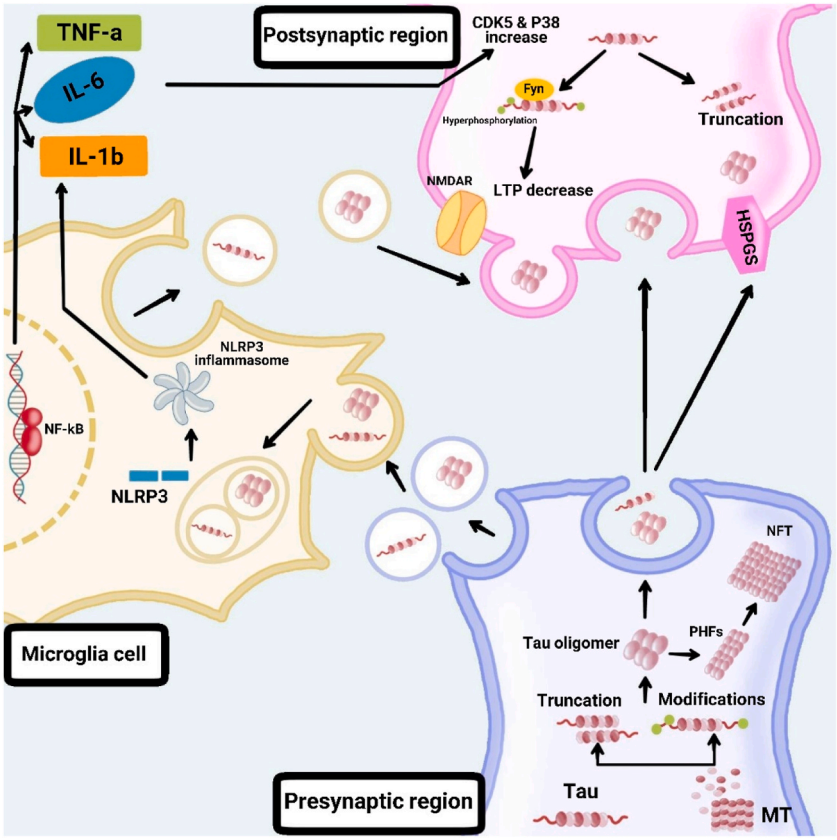


Fig. 2. Tau processing. In AD, tau oligomer undergoes aberrant post-translational modifications which lead to NFTs or any presynaptic dysfunction. Hyperphosphorylation and truncation of tau oligomers are two common post-translational modifications that can corporate the formation of the postsynaptic Fyn/NMDAR complex. Extracellular tau species can enter microglia and activate NF-κB and NLRP3 in inflammasome pathways.

AD [35]. In proteolytic processing, tau proteases like ADAM10, cathepsins, caspase, and endopeptidase truncate tau species. Caspase 2, 3, and 6 cleave tau products in AD. Before NFTs formation, tau is cleaved by caspase 3 and disassociated from the microtubule. New studies introduce appoptosin as a regulator for caspase 3 function which increases tau aggregation [36]. Some other post-translational modifications like auto-acetylation and ubiquitination of tau were found in AD brains [37]. The study of Al Mamun et al. suggests that the shape-shifting form of the tau is associated with toxic protein accumulation and even could be a symptom of early diagnosis in AD patients [38].

2.3. The interplay between neuroinflammation, amyloid-β, and tau in AD pathogenesis

The Aβ plaques induce cytokine secretion such as IL-1β resulting in high inflammation [39]. Inflammation is the hallmark of AD pathology which is induced by glial cells including microglia and astrocytes. Therefore, the inactivation of microglia cells can decrease the Aβ plaques in CNS. Microglia cells can induce oxidative stress, secretion of IL-1β, IL-6, and tumor necrosis factor-α (TNFα) in AD. The new subtype of microglia cells called disease-associated microglia (DAM), upregulates APOE, TREM2, progranulin, and TYROBP (DAP12) which are essential genetic risk factors in AD progression [40]. Numerous studies have confirmed the same mechanism of tau and Aβ in microglia activation. Tau can stimulate the release of IL-1β, IL-6, and TNF-α. Aβ also activates NF-κB signaling and NLRP3-ASC inflammasome [41].

The inflammation can even initiate the high blood sugar in the brain, leading to a hyperglycemic where necroptosis is then initiated. Necroptosis can lead to an acute cycle in AD treatment. So It could be an important therapeutic target for Alzheimer's disease [42]. Necroptosis is a non-apoptotic, being regarded as a genetically programmed and regulated pattern of necrosis. Tau pathogenesis is likely started by Aβ, where pathogenic tau and Aβ contribute to gliosis and neuroinflammation. Reactive glial cells together with inflammation further promote Aβ and tau pathogenesis to aggravate the neurodegeneration [40,43].

3. Enzymes involved in AD

It is accepted that neurodegeneration is a consequence of several detrimental conditions such as protein aggregation and neuro-inflammation which finally results in the loss of neuronal functions. There has been a wide study on enzyme inhibition to treat the

above-mentioned conditions or to elucidate the involved mechanisms. Many target enzymes related to the pathogenesis mechanisms of AD such as Aldolase, AChE, phosphofructokinase, and triosephosphate isomerase have been reported (Fig. 3). From analyzed data, the correlation between APOE4 and reduction of neprilysin, plasmin, plasminogen activators (uPA and tPA), and ECE-2 insulin-degrading enzyme (IDE) has been suggested as markers in the AD onset [44]. Various processes have been proposed regarding the major causes of AD. Key enzymes such as neprilysin, insulin-degrading enzyme, and ADAM10 play crucial roles in degrading Aβ in the brain. Numerous medical approaches targeting these pathological processes have shown promise in preclinical and clinical trials, particularly those involving ChE inhibitors, monoamine oxidase inhibitors, secretase modulators, xanthine oxidase inhibitors, and sirtuins. In this discussion, we will highlight these enzymes implicated in AD and explore their potential mechanisms of action [45–47].

3.1. Secretases

Senile plaques are associated with cognitive deficits which are initiated by secretase activity. That is the reason why secretase inhibitors are widely used in AD drug development. As previously mentioned, ADAMs mediate cleavages of APP in amino acids 16 and 17 in cooperating with α-secretase. Some findings have indicated an increase in α-secretase and ADAM10 levels, which might lead to a low level of aβ plaque processing in AD's brain. Wnt/MAP kinase signaling and (−)-Epigallocatechin-3-gallate (EGCG) cooperate in APP processing by upregulating ADAM10 [48]. Riluzole, a glutamate modulator, could be considered a new treatment modality that enhances the activity of Wnt/MAP kinase signaling and decreases amino acid neurotransmission. Although the positive effect of MAP kinase on ADAM10 has been identified also the main mechanism underlying this effect is still unclear [49]. C Shi et al. studied estrogen receptor α in N2s cells as an AD cell model. The study showed that high expression of Wnt agonists reduced the level of BACE1 in N2 cells. Some hormones like estrogen and serotonin type4 receptors also interact with AdAM10 resulting in APP elevation. Some reports show the effect of rivastigmine on the activity of α-secretase. Rivastigmine is a pseudo irreversible carbamate inhibitor which stimulates the activation of both the extracellular-signal-regulated kinase (ERK) and protein kinase B (Akt) which regulate ADAM-9, -10, and −17 and also reduces Aβ production [50]. There should be peculiar coordination among ADAM10 and α-secretase activity which is quite unclear in the case of ADAM9 species. Given ADAM10's role in AD and the low level of ADAM10 in CSF, researchers have focused to discover the reason. In 2019 Steve et al. showed a high rate of secreted-frizzled-related protein 1 (SFRP1) in detergent extracts of entorhinal and frontal cortex from AD patients which are common as endogenous ADAM10 inhibitors. No evidence has shown the connection between SFRP1 and Wnt/MAP signaling [51]. Acitretin is a vitamin A analog that decreases Aβ levels and hepatotoxicity through the effect on the BBB [52]. The other enhancer of α-secretase is Etazolate which is a $GABA_A$ modulator. It increases non-amyloidogenic APP and α-secretase secretion. Furthermore, ryostatin-1, a lactone, cause sAPPα and protein kinase C secretion. α-7-nicotinic acetylcholine receptor agonists, 5-hydroxytryptamine receptor 4 agonists, and a γ-aminobutyric acid receptor stimulate the α-secretase activity indirectly. However, the functional mechanism of the α-secretase in the attenuation of AD symptoms is needed for more extensive studies [53].

Theoretically, increased β-secretase should be a pivotal part of the APP processing. New studies also offer the effect of BACE1 as an endogenous β-secretase in the low generation of cerebral aβ and cognition deficit in mice brains. MK8931 is a BACE1 inhibitor that reduces Aβ peptide production in animal models. Although MK8931 didn't have any side effects on the CNS its efficiency in clinical trials III was unsuccessful. The great efficiency of TTP-854 (HPP854), the other inhibitor of mild AD, has been approved in phase I of a clinical trial. Other inhibitors like AZD3839 (LY3314814) interact with the ion channel and decrease levels of CSF [54,55]. AM-6494 and CNP-520 show sufficient ligand binding to BACE1 at the atomistic level and could be considered new potential drugs in AD treatment [56]. Cleavage in the cytoplasmic terminal of APP (CT31) induces the neuroprotective effect of neuregulin-1 (NRG1) and decreases apoptosis and cytotoxicity in SH-SY5. NRG1 is a trophic growth factor and its tyrosine kinase receptor, ErbB4, is abundantly expressed in the hippocampus and induces $Aβ_{1-42}$ impairment in CNS. With this nonpeptidergic effect, NRG1 would be used as a

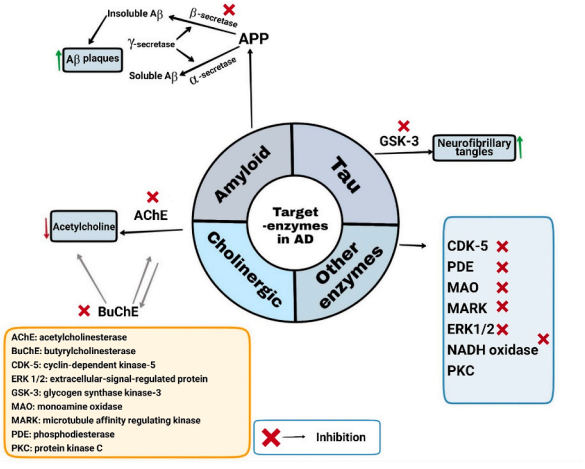


Fig. 3. Targets enzymes linked to the cause of AD.

potential drug for BACE1 inhibition in AD. These drugs also can inhibit BACE1 by connecting to the small part on the surface of cells, but also a large active site is a challenge in designing nanopeptidergic drugs [57].

γ-Secretase involved in the processing APP is a suitable target for therapeutic applications. γ-Secretase, a complex enzyme, has four subunits including PS, nicastrin (Nct), anterior pharynx defective-1 (Aph-1), and presenilin enhancer-2 (Pen-2). Mutations in the related genes are associated with Aβ48 or Aβ49 formation in FAD [58]. PSEN1 and PSEN2 are the catalytic parts of γ-secretase and made C and N terminal fragments. But the main activity of the γ-secretase is related to the GXXXG motif in the transmembrane domain of Aph-1 which meditates the protein-protein interaction between PS and γ-secretase. γ-secretase small-molecule inhibitors (GSIs) effectively decrease Aβ production in vivo but high toxicity is the main concern of using these drugs. Two common examples of GSIs are avagacestat (BMS-708163) and semagacestat (LY-450149) which inhibit Notch signaling and cause several side effects such as skin cancer and low lymphocyte count reported in phase III trials. Besides, due to the failures of GSIs in late-stage clinical trials, researchers have focused on GSMs for AD treatment. GSMs stimulate the Aβ42→ Aβ38 trimming step and decrease the aggregation-prone peptide. The first NSAIDs based GSMs are ibuprofen, tarenflurbil, sulindac sulfide, and indomethacin which have poor brain penetration. So, they have been withdrawn from clinical trials. The other study about GSMs shows that the E2012-BPyne binding protein, IFITM3, involved in innate immune responses binds to the γ-secretase and cleavage recombinant APP substrate to Aβ40 and Aβ42 [59,60].

3.2. Sirtuin

Sirtuin (SIRT), a highly conserved HDAC enzyme, belongs to the nicotinamide adenine dinucleotide (NAD^+) group and has 7 isoforms in mammals like rodents and yeast. Mammalian SIRT is a multidirectional catalytic enzyme involved in DNA repair, transcription, neuronal signaling, and inflammation. Each SIRT has a particular role, and despite the best-understood role of some SIRTs like SIRT3 in Krebs (TCA) regulation and urea cycle, the role of the other classes has remained to be cleared [61].

3.2.1. SIRT1

The gene encoding SIRT1 is located on the 10q21.3 chromosome. SIRT1 regulates many cellular processes such as transcription, stress response, and DNA repair. SIRT1 is also involved in diabetes, memory and learning, anxiety, and neurodegenerative disorders, including AD and Huntington's disease. Glyceraldehyde-derived advanced glycation end products (AGEs) are crucial factors in the neurotoxicity of APP and SIRT1 via ROS in the frontal cortex, which leads to cell death. Some new investigations recognized the role of SIRT1 in the regulation of AGEs [62]. SIRT1 leads ADAM10 stimulation to release APP-α. APP-α is generated by α-secretase and has neurotrophic and neuroprotective properties [63]. In the apoptosis process, Pin1 and SIRT1 act as neuroprotective factors in amyloid deposition, reducing and recreating amyloid surrogate protein. Increasing cytochrome *c*, and Bax translocation in mitochondria and inhibition of prion protein (PrP106–126) in neurotoxicity through adenoviral Sirt1 activation are some other processes of apoptosis [64]. R Manjula et al. discovered the low expression of SIRT1 in the animal model of AD. Multiple activators of SIRT1 are being tested for a variety of pathologies. One of these natural activators of SIRT1 is a polyphenol that is present in virgin olive oil, oleuropein aglycone (OLE). OLE keeps Poly [ADP-ribose] polymerase 1 (PARP1) at a low rate and induces autophagy through overexpression of SIRT1 [65]. Resveratrol is a common drug that activates Sirt1.On the other hand, Forkhead transcription factors of the O class (FoxOs) act in cooperation with SIRT1. FoxOs are involved in some signaling pathways in cells such as Wnt pathway and growth factors signaling pathways. Resveratrol is known as a drug which enhances the expression of SIRT1/FoxOs factors [66,67].

According to some studies, HDAC and SIRT levels are in contrast with each other in AD. Overexpression of ApoE4 and HDAC leads to the reduction of the amount of SIRT and NFTs formation. That is the reason HDAC inhibitors have shown promising results in clinical trials [68]. Humic acid (HA) is a potential pathogenic factor in vascular diseases and AD. HA contributes to Aβ cytotoxicity through the induction of endoplasmic reticulum stress leading to the suppression of the Sirt1/proliferator-activated receptor coactivator 1 (PGC1α) pathway. Recent research shows that HA and Aβ decrease the viability of cells by increasing SIRT1 expression [69]. Aβ 1–42 induces toxic effects on neurons when neurons and astrocytes are co-cultured. Aβ 1–42 downregulates peroxisome proliferator-activated receptor (PPAR), over-expresses PGC1α, mitochondrial transcription factor A (TFAM), and SIRT1 expression. Taurine, a naturally occurring β-amino acid in the brain, has been demonstrated to have neuroprotective properties. Q Sun et al. treated SK-N-SH cells with taurine which significantly attenuated Aβ1–42-induced neuronal death and recovered SIRT1 expression [70]. The other natural cysteine protease inhibitor is Cystatin C (CysC) which inhibits SIRT1 and decreases Aβ40 secretion in microvascular endothelial brain cells. The CysC-induced Aβ40 reduction was caused by SIRT1-mediated ADAM10 upregulation and degradation of BACE1 through the ubiquitin/proteasome pathway [71]. Some neural stem cells (NSCs) are derived from EVs like exosomes. B Li et al. investigated the effect of NSCs-derived EVs on mitochondrial function and SIRT1 level in a transgenic mouse model of AD (Tg-NSCs-ev). The high expression of SIRT1 level was found in the cerebral cortex of the Tg-NSCs-ev group. This high expression of SIRT1 and its role in mitochondrial function indicates the possible role of SIRT1 in the recovery of cognitive function in AD [72].

3.2.2. SIRT2

The expression of SIRT1 and SIRT2 are tissue-specific and vary in different physiological conditions. SIRT2 is a highly conserved deacetylase (19q13.2) that mediates the amplification of the centrosome in the cell cycle and acetylation of the microtubule network in AD pathogenesis. SIRT2 is mainly located in the cytoplasm and also accumulates in CNS. Moreover, a high level of *SIRT2* mRNA is reported in the peripheral blood of patients with AD. SIRT2 deacetylates Reticulon (RTN) family, mainly RTN4B, in lysine residues. RTN family has the main interaction with BACE1 [73,74]. Y Wang et al. studied the role of SIRT2 in the deacetylation of RTN4B and its negative effect on BACE1 in 293T cells. SIRT2 acts as a regulator for RTNB4 deacetylation and ubiquitination which influences the

expression of BACE1. When RTN4B was knocked down, the effects of SIRT2 inhibition on the BACE1 level, Aβ pathology, and AD-liked behaviors were also blocked. However, to strengthen this result, the certain acetylation sites of RTN4B and the interaction of SIRT2 and RTNB4 should be determined [72]. This evidence suggested that SIRT2 inhibitors could play a vital role as a potential drug target for AD. For example, Allosteric modulators with hydrophobic pockets might potentially be a new drug in the design of SIRT2 inhibitors. AGK2 is a type of this new drug that prevents aggregation by inhibiting NF-κB and decreasing TNF-α and IL-6 mRNA levels. In the sporadic rat model, the AK-1 inhibitor increases α-tubulin acetylation and degrades the Aβ aggregates. It is the general inhibitor of SIRT2 [75,76].

3.2.3. SIRT3

The third member of the SIRT family is mono-ADP-ribosyltransferases (11p15.5) that control lipid beta-oxidation and ROS detoxification [77]. SIRT3 decreases ROS levels by deacetylating manganese superoxide dismutase (MnSOD) and FoxO3a in the ameboid microglial cells [78]. Downregulation of SIRT3 expression is detected in the brain of AD patients and correlates with the levels of tau tangles and amyloid plaques. Moreover, it was reported that SIRT3 controls many neuroprotective factors, such as ketones, sesamin, and resveratrol [79]. Nicotinamide riboside is one of the activators of SIRT3 that reduces DNA damage in hippocampal neurons by decreasing tau protein [80]. S Li *et al* showed that overexpression of Sirtuin3 causes tau acetylation. However, the pathophysiological mechanisms of this process are still unclear [81].

3.2.4. SIRT4

SIRT4 is an ADP-ribosyltransferase located on the 12q24.23-q24.31 chromosomes with weak deacetylase ability but also with high inhibitory effects on glutamate dehydrogenase (GDH) of mitochondria and pyruvate dehydrogenase (PDH) complex. It is assumed that SIRT4 manages mitochondrial uncoupling and nucleus signaling via AMPK, PGC1α, and acetyl-CoA carboxylase [82]. SIRT4 was found to negatively regulate insulin secretion in response to glucose. It is also suggested that the SIRT4 may control insulin levels in β-cells by interactions with GDH and adenine nucleotide transporter (ANT). Mitochondrial trifunctional protein α-subunit (MTPα) is the other substrate of SIRT4 in lipid metabolism to inhibit fatty acid oxidation. Many interacting proteins with SIRT4 have been detected in mitochondria. For example, SIRT4 provokes ROS by inhibiting MnSOD. No specific enzymatic activity has been reported for SIRT4 which makes it hard to identify SIRT4 regulation mechanisms [83,84].

3.2.5. SIRT5

SIRT5 (6p23) is an efficient lysine desuccinylase and demalonylase with low deacetylase activity when subjected to PTM. In mitochondria Sirt3 expression inhibits Sirt5. It was suggested that sirtuins can regulate the level of each other [82]. SIRT5 removes a series of newly-discovered negatively charged acyl modifications including succinylation, malonylation, and glutarylation.SIRT5 catalyzes lysine deglutarylation. Zhou *et al* have reported carbamoyl phosphate synthase-1 (CPSEN1) as the main target of Sirt5. Sirt5 can reverse CPSEN1 activity [85]. They suggested that the crystal structures targeting SIRT5 with bicyclic intermediate can be novel tools in the treatment of SIRT-related diseases. Glas *et al* demonstrated that balsalazide could be a selective drug as SIRT5 inhibitor in AD [50]. Da Kalbas *et al* found 3-arylthiosuccinylated and 3-benzylthiosuccinylated peptide derivatives as the new SIRT5 inhibitors [84].

3.2.6. SIRT6

An NAD + -dependent, histone H3 lysine 9 (H3K9) deacetylase is SIRT6 which has a pivotal role in genome integrity, gene silencing, and neurogenesis ability in the hippocampus [86]. AE Pukhalskaia et al. showed a low rate of SIRT3, SIRT6, and SIRT1 in the hippocampus and saliva of humans. They recommended SIRT6 concentration of saliva as a marker for aging [87]. SIRT6 inhibits Aβ-42 activity, a DNA damage inducer, through the cysteine monoubiquitination process. SIRT6 decreases the nuclear factor kappa B (NF-κB) by upregulating IκBα and binding to histone methyltransferase, Suv39h1. SIRT6 also enhances the GSK3α/β kinase activity and directs the phosphorylation and stability of the tau protein. Nutlin-3 and p53 upregulation decrease SIRT6 levels and DNA damage while inducing Aβ-42 [88]. Regarding the role of SIRT6 in controlling neuroinflammation, SIRT6 inhibition increases the anti-inflammatory cytokine, interleukin-10 (IL-10), and IL-8 by decreasing autoimmunity-promoting cytokines. It stabilizes heterochromatin in the sub-telomeric region by silencing the transcription of telomere-proximal genes. Several natural products such as Quercetin, Luteolin, Delphinidin, and Fucoidan are SIRT6 activators. Further research should be performed to characterize these natural compounds and their derivatives for the treatment of AD [89]. The role of other SIRTs (SIRT4, 5, and 7) in AD is unclear but some research has continued (Table 1).

Table 1
The effect of SIRTs on AD.

SIRTs type	Effect	Refencesses
SIRT4	Deactylate adenine nucleotide transport 2(ANT2), Promote autophagy realated proteins	[90]
SIRT5	Promote autophagy, Suppress microglia and astrocytes activity	[91,92]
SIRT7	Knockdown $A\beta_{42}$,Suppress NOX4 upregulation	[93]

3.3. Monoamine oxidase

MAOs are a family of intramitochondrial flavoenzymes that catalyze the metabolism of monoamines like dopamine and serotonin in the peripheral and central nervous system and also are expressed in different organs like the liver and intestine [94]. The products of oxidative deamination cause harmful effects on the biochemical neurotransmitter in neurological disorders like Parkinson's disease and AD [95]. Activated MAOs are also involved in the aggregation of neurofibrillary tangles and cognitive destruction through cholinergic neuronal damage. In AD, activated MAOs cause high oxidative stress which aggregates neurofibrillary tangles in the cholinergic system [96]. In most mammalian tissues, two isoforms of MAOs, monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B), have been determined in the human brain and peripheral nervous system (PNS). MAO-A metabolizes catecholamines, serotonin, and melatonin preferentially, but phenylethylamine and benzylamine are oxidized by MAO-B. Norepinephrine (NE) is the other main chemical neurotransmitter distributed by MAOs in cognitive destruction. NE is the MAO-A substrate and acts as an electron donor for neural transition [97]. Both of these enzymes deaminase tyramine, dopamine, octopamine, and tryptamine [98]. In the mouse model of AD, the rate of some MAOs mediators such as homovanillic acid (HVA) and 5-hydroxyindole-3-acetic acid (5- HIAA) change the level of MAOs [99]. The wide range of primary, secondary, and tertiary MAOs was recognized through Fourier transform infrared spectroscopy- Attenuated total reflectance (FTIR-ATR). Different MAOs are unique in their active sites and their oligomerization manners. The inhibitor or substrate bind to the active site located at the b-sheet and helix-rich domain [95].

The difference between MAO-A and MAO-B is in anatomic distribution and substrate specificity. In addition, a bipartite outer chamber of MAO-B with an inner cavity causes more selectivity than MAO-A in reaction with inhibitors [100]. Recently three amine oxidation mechanisms of MAOs catalysis have been introduced: The polar nucleophilic mechanism, the radical transfer mechanism or single electron transfer (SET), and the hydrogen atom transfer (HAT). It was found that MAOs enzymes catalyze the oxidative deamination of biogenic amines resulting in poisonous metabolic products like ammonia, hydrogen peroxide, and aldehydes, which may be involved in the progression of AD [95]. For decades, researchers have been focused on the role of MAOs in various metabolic disorders like diabetic heart and cardiometabolic syndrome, but the main systematic mechanism of MAOs in AD has not yet been proved [101]. All of these characteristics of MAOs, inspire scientists to find MAOs inhibitors for various disorders such as AD. Hydrozine-based inhibitors like iproniazid and phenelzine were first studied as an antidepressant. Rasagiline and safinamide, the irreversible MAO-B inhibitors, and resveratrol as the MAO-A inhibitor were used in phase II clinical trials of AD. However, no recent progress has been made regarding their actual effect on AD [102]. However, ladostigil and diphenyl pyrimidines, the combination of MAO and AChE inhibitors, influence antidepressant and anxiolytic activity [103].

Several natural products are used as MAO-A and MAO-B inhibitors for the treatment of AD [104]. AM Kimura et al. proved that myricetin prevents Aβ1-42 oligomer that induced neurotoxicity in AD. To assess the effect of myricetin on HMW-Aβo-induced oxidative stress, the level of membrane oxidative damage was measured by cell membrane lipid peroxidation, membrane fluidity, and cell membrane potential. The results showed that Myricetin has antioxidant activity inhibiting HMW-Aβo-induced mitochondria

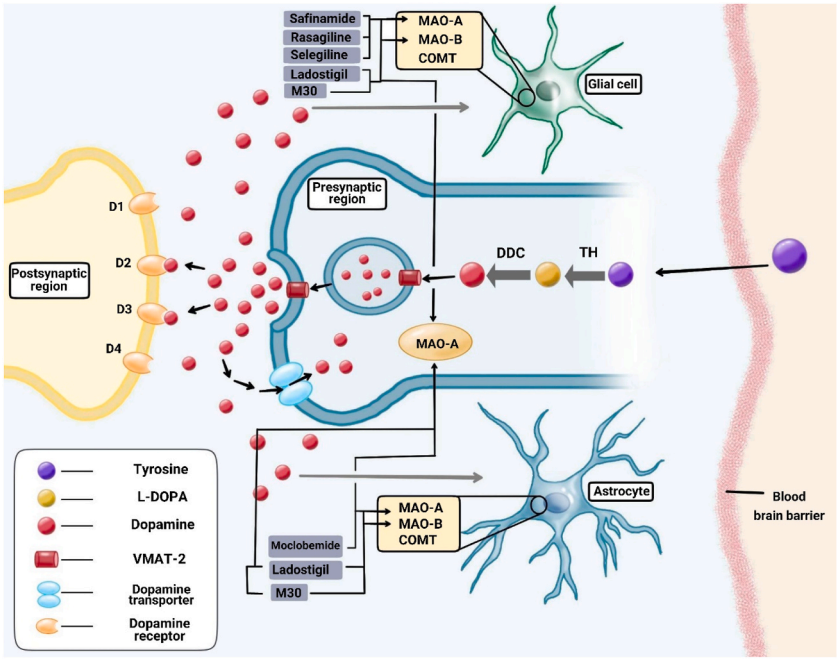


Fig. 4. Dopamine synthesis in the brain by MAO-A and MAO-B. The dopamine pathway starts from tyrosine, which proceeds through BBB. Vesicular monoamine transporter 2 (VMAT-2) transports dopamine transporters into synaptic vesicles and finally, MAO-A and MAO-B enzymes metabolize them in neurons.

dysfunction and suppress HMW-Aβo-induced neurotoxicity. Therefore Myricetin could be considered as an effective agent against AD [105]. Quercetin is the other flavonoid glycoside that decreases lipid peroxidation and prevents fibril formation. Also, it has been shown that quercetin protects neurons from oxidative damage. In addition, it inhibits the fibril formation of Aβ proteins and inflammatory cascade pathways. A combination of natural inhibitors affects different enzymes. For example, coumarin/tacrine hybrids are natural effective inhibitors of AchE and MAO [106]. YR Qin et al. focused on the mechanism of bilobalide in cognitive functions of APP/PSEN1 in AD mice. Bilobalide is a terpenoid which suppresses neuroinflammation and promotes autophagy by upregulating lincRNA-p21 levels [107]. On the other hand, the use of a significant number of structurally distinct synthetic inhibitors, like minerals with fewer side effects and selective inhibition, is increasing [95]. The interaction between MAOs and free iron-chelating activity in the brain shows some positive effects in increasing the rate of endogenous neurotrophins. Related to these studies MAO inhibitors have broad-reaching cellular and pericellular effects (Fig. 4). The plan of either repurposing existing or developing novel synthetic MAO inhibitors is a promising and exciting area of investigation [108].

3.4. Xanthine oxidase

There are different types of enzymes in the xanthine oxidase family [109]. Xanthine oxidoreductase (XOR), the main enzyme in this category, is highly distributed in prokaryotic and mammalian tissues like epithelial cells of the lactating mammary gland, and vascular endothelial cells of the kidney, and liver [110,111]. Moreover, XOR is a dimeric metalloflavoprotein, which induces the gene expression in active dehydrogenase type and includes two similar subunits with about 145 kDa molecular weight. Each subunit is containing a flavin adenine dinucleotide and molybdopterin cofactor (Moco), and also two non-identical iron-sulfur redox centers which catalysis the reaction of hypoxanthine to xanthine and xanthine to uric acid [112]. Uricase converts uric acid into allantoin, a water-soluble molecule excreted in the urine [113]. In both steps, molecular oxygen is reduced, forming the superoxide anion. This superoxide anion is the subsequent generation in uric acid production which generates hydrogen peroxide and superoxide [114].

Free radicals ($OH^{\cdot}$) and non-radicals derivatives of oxygen (H_2O_2) contribute to oxidative stress. The level of XO increases in CSF of AD's brian [115]. XO-derived oxidants are a current target for the synergic treatment of many diseases. The inhibition of XO is the most desirable as it interferes with the catabolism of natural purines (hypoxanthine and xanthine), by directly preventing uric acid biosynthesis. Two classifications of xanthine oxidase inhibitors, purine-like and non-purine XO inhibitors, affect XO activity. Allopurinol is the class of purine-like XO inhibitors that decreases high levels of uric acid in cancer medication and reduces endothelial dysfunction and platelet aggregation in cardiovascular diseases [116]. Febuxostat and topiroxostat are two non-purine inhibitors that are used currently for the treatment of hyperuricemia [117–119]. Allopurinol reduced p53 level and high glucose-induced ROS [120]. The brain is rich in oxidizable lipids, which are affected by ROS and cause DNA-protein crosslinking in AD [121].

The hydroxylation product of oxypurinol (XOD), also known as alloxanthine, effectively inhibits the oxidized form of XOD. Natural inhibitors are vastly studied about XOD inhibition [122–124]. Hydroxylation, glycosylation, hydrogenation, and methylation of the phenyl ring in flavonoids are necessary for XOD inhibition. About flavonols, quercetin - 3 -Me, persicarin, and apigenin, without glycosyl group, show a strong XOD inhibitory effect [125].

3.5. Choline esterase

ChE is an effective serine α, β-hydrolases that hydrolyze acetylcholine in CNS. In the vertebrates, two forms of ChE were identified encoded by two distinct genes including AChE and BuChE [126]. AChE is found in plasma, nervous tissue, blood, and muscles, while BuChE is found in the liver. The primary distinction between the two cholinergic enzymes is their specific substrates, hydrodynamic parameters, and ionic and hydrophobic interactions. Acetylcholine modulates muscarinic or nicotinic receptors activating in the CNS. 5 subtypes of muscarinic receptors are located in the postsynaptic and presynaptic membrane of CNS which regulate adenylate cyclase and phospholipase C pathways [127].Three types of acetylcholine nicotinic receptors (nAChR) are composed of five subunits that are found in the CNS and muscles and may play a role in calcium concentration and the aging process. The activity of AChE in the AD brain is linked to pre-amyloid diffuse deposits and mature senile plaques in A deposits [128]. BuChE plays a similar role in the formation of senile plaques. The three major nAChR subtypes in the hippocampus are composed of α7-, α4β2-, and α3β4-nAChRs. Wang and Khan found that Aβ selectively affects the α7-and α4β2-nAChRs, but not the α3β4-nAChRs in hippocampal neurons, resulting in neuronal hyperexcitation [129].On other hand, Sabri et al. quantified the number of radioligands, α4β2*-nAChR, which is decreased in AD patients [130]. Miwa et al. demonstrated that lynx1 (Ly6/Neurotoxin 1) affects positively Aβ toxicity by competing in binding Aβ to nAChRs [131]. Donepezil (derived from indanone base), galantamine, and physostigmine are three traditional AchE inhibitors. Galantamine (Razadyne), particularly inhibits AchE and modulate nicotinic cholinergic receptors. Moreover, Rivastigmine and tacrine inhibit AchE and BuChE [132–134]. Two important advantages of tacrine in compared to physostigmine and donepezil are tacrine capacity in greatly enhancing cerebral blood flow and preventing of β-precursor proteins' release from the intestinal tract [135]. However, the use of all these drugs is limited due to many side effects, like nausea, vomiting, loss of appetite, and diarrhea. To diminish the side effects of tacrine, new derivatives of hybrids such as homo/heterodimer or hybrids of two moieties have been synthesized. These two compound lead to high ligand efficiency and beneficial inhibitory effect in both in vivo and in vitro. The main structure of these inhibitors include condensed aromatic cores with quaternary ammonium or nitrogen [136]. One of the first successful achievements in the synthesis of hybrid compounds was the development of heptylene linked bis- (6-chloro)-which has a potency 3000 times higher than the tacrine in inhibiting AChE [137]. G. Fancellu et al. designed the hybrids tacrine - benzofuran derivatives which showed great capacity in AChE inhibition and Aβ aggregation [138]. E Uliassi et al. designed the effective quinolinrone-tacrine compound by replacing naphthoquinone scaffold with 2, 5, 8-quinolinetrione. This new compound showed low hepatotoxicity and

good anti-amyloid aggregation properties [139]. Tolserine and phenserine are new generations of ChE inhibitors. Tolserine selectively inhibits AchE [140]. Phenserine reduces APP production and inhibits AchE. But, their side effects or advantageous in clinical trials are still unclear [141]. Huperzine A is an alkaloid derived from a chinese herb called Huperzia serrata which inhibits AchE by forming an H-bond between Gly117 and Ala201 [142,143]. Galangin is a flavonoid with a potent inhibitory effect on AchE, but human clinical trials are required. L Huang et al. found that galangin regulates the Akt/GSK3β/mTOR pathway and decreases Aβ42 and p-tau levels [144]. In hybrid groups, donepezil-tacrine and tacrine-ferulic acid (T6FA) have shown a great inhibitory effect on both AchE and BuChE activity [145,146]. Ladostigil and tacrine analogs are recently developed as multi-target therapeutic agents for AD treatment [147,148].

3.6. Other related enzymes

There is increasing interest in identifying new enzymes associated with AD symptoms, such as Aβ accumulation in the central nervous system, some of which are summarized in Table 2.

Eukaryotic initiation factor 2α kinase 2 (PKR), a ubiquitous 551 amino acid enzyme, has been implicated in many molecular pathways that lead to AD brain lesions. PKR also accumulates in degenerating neurons of cerebrospinal fluid and is activated by Aβ1-42 neurotoxicity [149]. PKR is activated during three cellular processes: apoptosis, inflammation, and tau phosphorylation. PKR is involved in the production of IL-1β and the expression of the inflammatory cytokine TNFα. Tunicamycin as PKR inhibitor attenuates neural cell apoptosis. It induces PKR in human neuroblastoma cells and can trigger GSK3β activation, as well as tau phosphorylation [163].

In the research study conducted in 2020, researchers showed the connection between mutation in Val158/108Met the Catechol-O-methyltransferase (COMT) gene and decreasing Aβ42 levels [164]. COMT degrades catecholamines and forms Dopamine. Some studies have demonstrated that COMT inhibitors, such as Entacapone and Tolcapone, can block Aβ fibril formation in the treatment of AD [165]. Src family kinase Fyn is a non-receptor tyrosine kinase activated by Aβ via PrPC in the central nervous system. Fyn phosphorylates the NR2A and NR2B subunits of the NMDA receptor, which increases synaptic expression and enhances receptor transmission [150]. Fyn phosphorylates tau near its amino terminus, and this interaction influence the pathogenesis of AD. Research has indicated that Saracatinib and Masitinib can inhibit Fyn across the BBB [166]. In recent years, the role of ACE activity in increasing the risk of AD has become clearer, as ACE is responsible for degrading Aβ [167,168]. Eicosanoids are inflammation mediators which are generated by 5 lipoxygenases (5-LOs) mediating in Arachidonic Acid (AA) metabolism. The first result is *5*-hydroperoxyeicosatetraenoic acid (5-HPETE) which metabolizes to form Leukotrienes (LTA4) and 5-HETE eicosanoid receptors to trigger inflammation [169]. A new study shows that 12/15-LO inhibition suppress neuroinflammation [170].

One of the key lipid peroxidizing enzymes is 5-LOX, part of the LOfamily, which is involved in the biosynthesis of lipoxins. Analysis of human brain tissue has shown that the levels of 5-LOX are significantly elevated in the hippocampus of AD-affected brains [171]. One of the main product of 5-LOX is 5-HETE, which activates CREB and promotes γ-secretase complex. The impact of 5-LOX on Aβ is also linked to the γ-secretase-activating protein (GSAP), which plays a critical role in Aβ production. 5-LOX modulates GSAP's function by cleaving it to produce the active fragment, GSAP 16 kD. Inhibitors of 5-LOX may prove effective in AD treatment by reducing Aβ deposits [172].

4. Enzymes inhibitors in AD

In 2012, it was demonstrated that natural inhibitors such as curcumin can inhibit the activation of c-Jun NH2-terminal kinase (JNK), the protein kinase responsible for phosphorylating c-Jun at Ser-63 and Ser-73, induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) lesions. Additionally, curcumin has been shown to restore dopaminergic terminals from degeneration [173].

Table 2
Enzymes involved in AD and their mechanisms.

Enzyme	Mechanism of effect	References
Eukaryotic initiation factor 2α kinase 2 (PKR)	Cascade tau phosphorylation	[149]
Tyrosine kinase Fyn	Activate by Aβ via protein cellular prion (PrPC)	[150]
Sterol O-acyltransferase	Reduction of Aβ generation	[151,152]
PARP-1	Reduction of Aβ accumulation	[153]
Catechol-O-methyltransferase (COMT)	Effects on the metabolism of catecholamine neurotransmitters and estrogen	[154]
Cdc2-like kinases (CLKs)	Phosphorylation of the serine residue in serine arginine rich -family (SR) proteins	[155]
Aminopeptidases A, B, and N (ApA, ApB & ApN) and insulin-regulated aminopeptidase (IRAP)	Involved in the brain renin-angiotensin system	[156]
Lipoxygenases (LO)	Induction of Aβ formation	[157]
Alkaline phosphatase	involved in anti-inflammatory function	[158]
Plasmin, endothelin converting enzymes ECE-1 and -2; matrix metalloproteinases MMP-2, -3 and -9; and angiotensin-converting enzyme (ACE)	Degradation of Aβ aggregation	[159,160]
Ubiquitin-proteasome (E2-25K, E3 ligase)	Aβ toxicity, Enhancement of BACE1 level	[161]
Rho GTPases	Involved in tau pathology	[162]

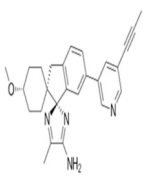
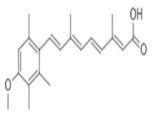
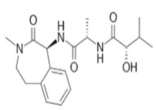
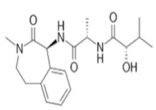
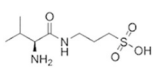
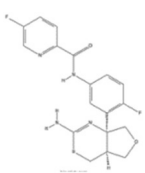
Furthermore, another study identified JNK-IN-8 as a selective JNK inhibitor that prevents the phosphorylation of c-Jun, a direct substrate of JNK [174]. J Jun *at al.* studied a new JNK 3 inhibitor, 2-aryl-1-pyrimidinyl-1*H*-imidazole-5-yl acetonitrile, which is able in improving cognitive memory in APP/PSEN1 and the 3xTg mouse model [175].

Tideglusib is a non-ATP competitive, irreversible inhibitor of GSK3β, representing a significant challenge in the treatment of AD [176].

Non-peptidic anti-aggregate drugs, including tramiprosate, clioquinol (PBT1), and second-generation inhibitors of metal-induced Aβ aggregation (PBT2), have demonstrated promising results in Phase II clinical trials by enhancing Aβ degradation [177]. On the other hand, few studies mentioned to glycosaminoglycans (GAGs) biomimetics blocking β-pleated sheet formation [178]. It has been found that a group of phosphatidylinositol including Myo-inositol and scylloinositol prevents plaque formation [179]. Further, colostrinin and proline-rich polypeptide complex (PRP) regulate the redox system and decrease oxidative damage and Aβ fibrils aggregation in AD patients [180].

Martin et al. studied the role of tau protein kinases including proline-directed protein kinase (PDPK) and tyrosine-protein kinase (TPK) in AD. PDPK is a large proline residues family, consisting of GSK3, Erk1/2, cyclin-dependent protein kinase-5 (CDK5), MAPK, and JNK. GSK3 is well known for inducing tau phosphorylation and also the regulation of signaling pathways including Wnt/β-catenin, NFκB, and insulin pathways [181]. Tau protein can be phosphorylated by P38 activity. SB-239063 reduces the inflammatory response in AD brains by inhibiting P38 function. Moreover, PSEN1 and PSEN2 regulate extracellular signal-regulated kinases 1/2 (ErK1/2) that phosphorylate tau. The only inhibitor for Erk1/2 is FR-180204. JNK1/2/3 phosphorylates tau in stress. It can be activated by MKK4. It has a role in Aβ accumulation through increasing ϒ-secretase. Reduction of Aβ levels are obtained with secretase inhibitors in line with exogenous monomeric Aβ show neuroprotective potential by decreasing cell death. Aducanumab targets amyloid in patients with early AD. ALZ-801 and 3-SPA are some small-molecules drugs which target Aβ42 monomer at specific sites and inhibit aggregation into Aβ oligomers (Table 3). It even gives opportunity to effectively test the refined amyloid oligomer to treat in APOE4/4 homozygous patients with early AD [182]. Numerous studies have also confirmed the positive effect of sodium selenite on the reduction of tau phosphorylation [183]. Moreover, Tau-tubulin kinase 1/2 (TTBK1/2), casein kinase 1ϒ/1ε/1ɑ/2 (CK1ϒ/1ε/1ɑ/2), DYRK1A/2, microtubule affinity-regulating kinases, phosphorylase kinase (PhK), PKA, PKB/Akt, PKC, protein kinase N (PKN), and Ca2+/calmodulin-dependent protein kinase II (CaMKII) belong to the non-PDK group which cooperates in tau hyper-phosphorylation.

Table 3
The Secretases' inhibitors.

NO	Molecule Name	Target	Clinical Trails ID	Structure	Clinicla trails Statutes	Side effects
1	Lanabecestat (AZD3293, LY3314814	CSF Aβ levels decreasing	NCT02245737		Phase 3 trials terminated	Headache, dizziness, Nausea, Vomiting, Diarrhea, and pruritus
2	Acitretin	increased CSF APPSα	NCT01078168		Phase 2 trails terminated	Chapped, red, or swollen lips, Difficulty in wearing contact lenses, Dry or runny nose, Dryness of the eye
3	Umibecestat(CNP520)	CSF Aβ levels decreasing	NCT02576639		Phase 2 and 3 completed	Dizziness, Headache
4	Semagacestat (LY450139)	Decrease β-amyloid and amyloid plaques	NCT00594568		Phase 3	Skin lesions and bloody stool
5	Valiltramiprosate (ALZ-801)	Effect on Aβ42 monomer	NCT04693520		Phase 2	Transient and mild nausea, Loss of appetite
6	LY2886721	Inhibit BACE-1	NCT01561430		Phase 1/2 terminated	Procedural headache

TPK phosphorylate tyrosine residues in tau protein through mediating Src family kinase (SFK) and Fyn. The high tau phosphorylation causes tau dissociation in microtubules and tau aggregation in AD brains. However, more studies will be needed to find out the contribution of each tau phosphorylation site in tau pathology. Some medicinal compounds may act on multiple tau kinases, providing a good opportunity as AD inhibitors [184,185].

Commercial kinase inhibitors are used for the treatment of AD [186]. For instance, Masitinib, a tyrosine kinase inhibitor, blocks Fyn kinase and the stem cell factor (SCF/c-Kit) signaling pathway through mast cell-microglia interactions, playing a role in the neuro-inflammatory process [187]. Inhibitors of the Src/abl family of kinases (Saracatinib and thiamet-G) show the same inhibitory effect on Fyn kinase for mild-to-moderate AD [188].

Various in vivo and in vitro studies highlighted the role of sirtuin on the activity of amyloid β, tau protein, and oxidative stress, in some particular parts of AD's brain like the prefrontal cortex and hypothalamus. A group of sirtuin-activating compounds (STACs) (e.g., resveratrol, polyphenol, quercetin, curcumin, and kaempferol) causes a significant increase in sirtuin ratios. Furthermore, while SIRT1 expression increased in AD, its activity decreased due to a decrease in NAD + levels [189]. According to the association between caloric restriction and overexpression of SIRT1, the main role of SIRT1 is to decrease histone H3-Lys79 methylation and H1-Lys26H3-Lys9, Lys14, and H4-Lys16 deacetylation. In one study, following resveratrol treatments and calorie restriction in Fischer 344 rats, the Ku70 is deacetylated and apoptosis is decreased. Ku70 has a major role in the pathway of double-strand breaks (DSBs) in neurons. Ku70 phosphorylation recruits DNA-PKcs to the DSB and activates its kinase function.

Leptin is an adipokine in the hypothalamus and its resistance is correlated with gain weight and aging. On the other hand, SIRT1 increases leptin sensitivity and upregulates BACE1. This process inhibits NFκB signaling and decreases β-amyloids. Manipulating SIRT1 activity will likely aid in AD therapy [190]. Anekonda et al. suggested that SIRT2 deacetylates p53 and controls the expression of insulin/IGF-1 receptor in olfactory sensory neurons of AD. The deacetylation ability of other sirtuins, such as SIRT4, SIRT5, SIRT6, and SIRT7, has not been approved by other studies. As a result, the precise cellular function remains unknown and more research on this subject is required [191].

Table 4
The inhibitors of various enzyme isoforms.

Enzyme family	Enzyme Isoforms	Enzyme Inhibitors	References
PDPK	GSK3	6-BIDECO (6-bromoindirubin-3_-[O-(N,Ndiethylcarbamyl)- oxime), lithium, Paullone, Anilinomaleimides, Thiadiazolidinones, 6-BIMYEO (6-bromoindirubin-3_-[O-(2-morpholin-1- ylethyl) oxime] Hydrochloride)	[176]
	CDK5	(R)-CR8 (2-(R)-(1-ethyl-2-hydroxyethylamino)-6- (4-(2-pyridyl)benzyl)-9 isopropylpurine trihydrochloride) and (R)-roscovitine or CYC202 or Seliciclib (6 benzylamino-2[(R)-(1_-ethyl-2_- hydroxyethylamino)]-9 isopropylpurine)	[200]
	P38	SB 239063 (trans-4-[4-(4-fluorophenyl)-5-(2- methoxy-4-pyrimidinyl)-1H-imidazole yl]cyclohexanol)	[201]
	ErK1/2	FR 180204 (5-(2-Phenyl-pyrazolo[1,5-_]pyridin-3- yl)-1H-pyrazolo [3,4-c]pyridazin-3- ylamine)	[202]
	JNK	SP 600125 (Anthra [1-9-cd]pyrazol-6(2H)-one)	[203]
TPK	SFK	AP23846	[204]
	c-AbL	STI571 or Gleevec® (4-[(4-methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)- 2-pyrimidinyl] amino]-phenyl]benzamide methanesulfonate)	[205]
Non-PDK	CK1	IC261 (3-[(2,3,6 trimethoxyphenyl)methylidenyl] indolin- 2-one)	[206]
	CK2	TBCA (Tetrabromocinnamic acid)	[207–209]
	DYRK1A	Harmine (7-methoxy-1-methyl-_-carboline)	[210]
	PKA	H-89 (N-[2-(p-bromocinnamylamino) ethyl]-5-isoquinolinesulfonamide dihydrochloride)	[211]
	PKB	Akt inhibitor VIII (1,3-dihydro-1-(1-((4-(6-phenyl-1Himidazo[4,5 g]quinoxalin-7- yl)phenyl)methyl)-4-piperidinyl)-2Hbenzimidazol- 2-one trifluoroacetate)	[212]
	CAMKII	GF-109203X (Bisindolylmaleimide I)	[213]
	PKC	KN62 (4-[(2S)-2-[(5 isoquinolinylsulfonyl)methylamino]-3-oxo-3- (4-phenyl-1-piperazinyl)propyl phenyl isoquinolinesulfonic acid ester	[214]
Sirtuin	SIRT1	Eurochevalierine, hyperforin, Ex-527, Donepezil, 3′-(3-fluoro-phenethyloxy)-2-anilinobenzamide, SirReal2, ethoxymalonyl, Nε-thioacetyl- lysine, UBCS0137, ELT-11c	[215–219]
	SIRT2	ELT-11c, UBCS0137, Nε-thioacetyl- lysine, SirReal2, 3′-(3-fluoro-phenethyloxy)-2-anilinobenzamide, Ex-527, AGK2, hyperforin, Peperovulcanone A, Tanikolide, Eurochevalierine	[220]
	SIRT3	Ex-527, Cambinol, SirReal2, Nε-thioacetyl- lysine, UBCS0137, ELT-11c,	[221]
	SIRT4	SirReal2	[222]
	SIRT5	Thiosuccinyl penta peptide, SirReal2, 3-methyl-3-phenylsuccinyl, UBCS0137	[223]
	SIRT6	SirReal2	[224]
ChE	AChEI	Tacrine, Phenserin, Donepezil–tacrine hybrid, Tolserine and Donepezil (noncompetitive reversible), Rivastigmine, Eseroline (irreversible), Galantamine, Thiazolyl-pyrazoline and 2(benzo[d]thiazol- 2-yl)-3- heteroarylacryloni triles (Competitive reversible), Tacrine–ferulic acid (T6FA) hybrid, THA–phenothiazine heterodimers	[225–229]
	BuChEI	Tacrine, Donepezil–tacrine hybrid and 2-pheynlbenzofuran (noncompetitive reversible), Rivastigmine, Eseroline and N-alkylpiperidine carbamates (irreversible)	[230–232]
MAO	MAO-A	Clorgyline- LY-51641(irreversible selective), Methamphetamine- Amiflamine- Cimoxatone- Maclobemide- Isatin (reversible selective), Ladostigil- M30(reversible nonselective), Isocarboxazide- Tranycvpromine- Pargyline (irreversible nonselective)	[192,233,234]
	MAO-B	Selegiline- Rasagiline(irreversible selective), Safinamide- Sembragiline- N-alkylpiperidine carbamates(reversible selective), Ladostigil- M30(reversible nonselective), Isocarboxazide- Tranylcypromine- Pargyline(irreversible nonselective)	[235–238]

Both reversible and irreversible inhibitors of MAOs are currently used as therapeutics of AD. The long-lasting irreversible inhibitors as antidepressant agents such as isocarboxazid and tranylcypromine increase NE in neurons but inevitably induce hypertensive reactions. Ladostigil and rasagiline are two novel drugs that are applied in adjuvant therapy with donepezil, in the treatment of Parkinson's disease and AD [192,193]. L-deprenyl (selegiline) is effective inhibitor which inhibit MAO-B activity, exclusively effecting distance between phenolic group and N-terminal of c-Jun in JNK1 [194]. Numerous studies indicate that oxidative stress plays a role in brain disorders like ischemia and AD. Research has shown that Cabergoline, an agonist of dopamine D2-like receptors, offers neuroprotective benefits against oxidative stress. It protects cortical neurons through a receptor-mediated process that involves inhibiting ERK1/2 activation and reducing the accumulation of extracellular glutamate caused by H2O2 [195].

Hydrangea, another noncompetitive inhibitor, inhibits AChE and BuChE activity [196]. Further, the inhibitory effect of hybrid donepezil–AP2238 has been shown on AChE and A toxicity, but human toxicology studies are still being conducted. (4- (pent-4-yn-1-yloxy)phenyl)-2-phenylpyrimidine derivatives inhibit MAO-A, MAO-B, and AChE [140]. Some natural product-based inhibitors like Thymohydroquinone and Carvacrol are two constituents of aromatic plants that have a strong AChE inhibitory effect and their related clinical trials have been successfully performed.

Multi-target drugs (MTDs) are therapeutic agents designed to interact with multiple biological targets, rather than focusing on a single target. This approach is particularly beneficial in treating complex diseases, such as AD, cancer, and cardiovascular disorders, where multiple pathways and mechanisms contribute to disease progression. MTDs drugs not only reduce drug toxicity and drug-drug interactions but also have synergistic effects. In multitarget drugs, at least two pharmacophoric moieties are linked together using fusion (forming a covalent bond), conjugation (designing a cleavable linker), or hybridization (merging). Current AD therapeutics utilizing MTDs, such as AChE inhibitors and NMDA receptor antagonists, are expected to provide a more effective approach by binding to various enzymes and receptors. New compounds based on 1,2,4-thiadiazole combined with tacrine demonstrate efficient inhibition of ChEs, particularly exerting a dominant effect on BuChE, while simultaneously blocking two binding sites on the NMDA receptor [197]. Caproctamine is a typical example of MTDs which has synergistic cholinergic action against AD. Caproctamine antagonizes presynaptic muscarinic acetylcholine M2 auto receptors and inhibits AChE. Blocking Aβ aggregation, metal chelation, and antioxidant activity are additional therapeutic approaches of MTDs that act by binding to specific receptors. Ladostigil is an advanced example of an MTDs currently in Phase II clinical trials, demonstrating inhibitory effects on both MAO-B and AChE enzymes simultaneously [198]. In 2023, Vicente-Zordo et al. developed Rivastigmine–Benzimidazole hybrids (RIV–BIM) as multi target-directed ligands for potential treatment of AD. This newly developed series of multifunctional RIV–BIM hybrids exhibited significant capacity to inhibit ChE and to reduce Aβ peptide aggregation. The ChE inhibitory activity is primarily attributed to the Rivastigmine (RIV) moiety, while the anti-Aβ aggregation and antioxidant effects are mainly ascribed to the Benzimidazole (BIM) moiety [199]. The inhibitor of various enzyme isoforms are listed in Table 4.

5. Conclusion and future perspective

In this article, we explore the essential molecular mechanisms that contribute to the pathogenesis of AD. Furthermore, we offer a detailed review of the enzymes linked to AD and the recent progress in creating enzyme inhibitors for therapeutic use. This study has several limitations. The scope of the literature reviewed may not include all relevant studies, particularly those published in languages other than English, which could restrict the comprehensiveness of the findings. Furthermore, our emphasis on specific enzymes may lead to the omission of other potential therapeutic targets and emerging treatment strategies.

Targeting various enzymes, including secretase, SIRT, MAOs, and ChE, presents effective and innovative opportunities for recent therapeutic approaches in AD. Several studies show that new groups of enzymes like lipoxygenase and PARP-1 affect Aβ formation in AD's brain. Meanwhile, enzyme inhibitors with the most effective in AD have shown important challenges in therapeutic strategies. The serious toxicities associated with synthetic inhibitors have resulted in the discontinuation of several clinical studies. Consequently, specific compounds are being developed to mitigate the adverse effects of these inhibitors. Meanwhile, researchers have been focused to optimize the potency and penetration of new drugs to the target sites of the brain. The conflicting studies on the role of various inhibitors in the progression of AD remain clinically unconfirmed. Therefore, further preclinical and clinical studies are necessary to clarify these findings. On the other hand, the positive results recently obtained with different drugs, suggesting that AD may be considered a curable diseases in near future. However, significant efforts are needed to identify and thoroughly characterize other drug pathways, as well as to develop multi-target therapeutic strategies that can effectively halt or modify this devastating disease.

CRediT authorship contribution statement

Zahra Farajzadeh Vahid: Writing – review & editing, Writing – original draft. **Morteza Eskandani:** Writing – review & editing, Conceptualization. **Hamed Dadashi:** Writing – original draft. **Somayeh Vandghanooni:** Writing – review & editing, Supervision, Conceptualization. **Mohammad-Reza Rashidi:** Writing – review & editing, Supervision.

Ethics statement

This review article adheres to ethical standards in research and publication, ensuring that all sources are properly cited and that the integrity of the information presented is maintained. Furthermore, the authors have addressed all relevant ethical considerations, in compliance with the guidelines outlined in Elsevier's Publishing Ethics Policy.

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Declaration of competing interest

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

Abbreviation

Alzheimer's disease AD
Histone deacetylase HDAC
Paired helical filaments PHFs
γ-secretase small-molecule inhibitors GSIs
APP amyloid precursor protein
amyloid-β: Aβ Cholinesterase: ChE
Acetylcholinesterase AChE
Valproic acid VA
O-linked-N-acetylglucosaminylation O-GlcNAcylation
nicotinamide adenine dinucleotide: NAD^+
Butyrylcholinesterase BuChE
K + -Cl-cotransporter KCC2
Protein kinase G PKG
Sirtuin SIRT
Monoamine oxidase MAO
γ-aminobutyric acid-ergic GABAergic
interleukin 1β: IL-1β
Krebs TCA
Receptor of advanced glycation end products RAGE
APPs sAPPβ
Tumor necrosis factor-α: TNFα
Advanced glycation end products AGEs
Neurofibrillary tangles NFTs
cerebral spinal fluid CSF
Disease-associated microglia DAM
Poly [ADP-ribose] polymerase 1 PARP1
β-amyloid Aβ
A disintegrin and metalloprotease ADAM
Apolipoprotein E APOE
Factors of the O class FoxOs
Late-onset AD LOAD
Low-density lipoprotein receptor-related protein 1 LRP1
TYRO protein tyrosine kinase binding: TYROB
Proliferator-activated receptor coactivator 1 PGC1α
Familial AD FAD
Sorting nexin SNX
Gasdermin D GSDMD
Neural stem cells NSCs
Apolipoprotein E4 APOE4
Manganese superoxide dismutase MnSOD
Presenilin PS
Synaptic vesicle SV
ECE-2insulin-degrading enzyme IDE
Adenine nucleotide transporter ANT
Post-translational modifications PTMs

Epigallocatechin-3-gallate EGCG
Histone H3 lysine 9 H3K9
β-site APP cleavage enzyme 1 BACE-1
Nicastrin Nct
Secreted-frizzled-related protein 1 SFRP1
Src family kinase SFK
Tacrine-ferulic acid T6F
blood-brain barrier BBB
interleukin-10 IL-10
γ-secretase modulators GSMs
Eukaryotic initiation factor 2α kinase 2 PKR
Neuregulin-1 NRG1
Peripheral nervous system PNS
Nonsteroidal anti-inflammatory drugs NSAIDs
Catechol-O-methyltransferase COMT
Cytoplasmic terminal of APP CT31
Norepinephrine: NE
Acetylcholine nicotinic receptors nAChR
Protein cellular prion PrPC
Vesicular monoamine transporter 2 VMAT-2
Single electron transfer SET
Cdc2-like kinases CLKs
Protein kinase N PKN
Serine arginine rich family SR
Insulin-regulated aminopeptidase IRAP
Proline-directed protein kinase PDPK
Tyrosine-protein kinase TPK
Glycosaminoglycans GAGs
Cyclin-dependent protein kinase-5 CDK5
Tau-tubulin kinase 1/2 TTBK1/2
Casein kinase 1ϒ/1ε/1α/2 CK1ϒ/1ε/1α/2
Phosphorylase kinase PhK
Ca2+/calmodulin-dependent protein kinase II CaMKII
Sirtuin-activating compounds STACs
Multi-target drugs MTDs
Protein cellular prion PrPC
Double-strand breaks: DSBs
Multi-target drugs: MTDs
Vesicular monoamine transporter 2: VMAT-2
Tacrine-ferulic acid: T6FA
5 lipoxygenases: 5-LO
Leukotrienes LTA4
Extracellular signal-regulated kinases 1/2 ErK1/2
Arachidonic Acid AA
Umibecestat CNP520
Semagacestat LY450139
Valiltramiprosate ALZ-801
γ-secretase-activating protein GSAP
Intraneuronal Aβ iAβ
Designed multi-target ligand: DML,
Amyloid precursor protein APP
Homocysteine: Hcy
Presenilin2 PSEN2
Presenilin1 PSEN1
N-methyl D-aspartate: NMDA
extracellular-signal-regulated kinase ERK
Nicastrin Nct
Anterior pharynx defective-1 Aph-1
Presenilin enhancer-2: Pen-2
Homovanillic acid: HVA
5-hydroxyindole-3-acetic acid: 5- HIAA

5-HPETE 5-hydroperoxyeicosatetraenoic acid.
JNK c-Jun NH2-terminal kinase
MPTP 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine.
ACE angiotensin-converting enzyme
STIP1 homology and U-box containing protein 1 STUB1
Golgi Associated, Gamma Adaptin Ear Containing, ARF Binding Protein 1 GGA1
Sortilin Related Receptor 1 SORL1

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