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Recent Advances in the Quest for Treatment and Management of Alzheimer and Other Dementia

Sameena E. Tanwir, Ajay Kumar*

School of Science, Technology and Environment, Universidad Ana G. Mendez, San Juan, PR, USA
Email: *ajkumar@suagm.edu

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease distinguished by progressive cognitive deterioration along with declining activities of daily living and behavioral changes. It is the commonest type of pre-senile and senile dementia. Many new therapeutic strategies have been developed in the last few years. We aimed at reviewing the evidence supporting these new therapeutic targets, including anti-amyloid and anti-Tau strategies. This review is focused on important future direction in investigation of potential therapeutic targets for AD drug discovery. Medical advances have improved treatment of many diseases but still there is a need to establish new tools for early diagnosis of AD. A thorough comprehensive understanding of the unexplored mechanism can ameliorate the diagnostic and therapeutic management of AD. There have been several disease-modifying therapeutic strategies for AD in the last few years and are presently at various phases of investigation. Few of them have shown promising results, but their safety and efficacy need to be further explored.

Keywords

Alzheimer, β Amyloid, Tau, Acetylcholinesterase, Amyloid Precursor Protein, Plaques, Tangles, Neurodegeneration

1. Introduction

Dementia is used to describe a broad range of symptoms that impact memory, thoughts, performance of everyday routine activities, and difficulty in learning and communication abilities. The most common type of dementia is Alzheimer's Disease (AD) which gets worse with time; irreversible dementia is becom-

ing a major threat for the aging people [1]. AD is considered as the sixth leading cause of death in USA. It is the only disease in America in the top ten that cannot be prevented, cured or slowed. It causes the degeneration of loss of neurons in the brain particularly in the cortex. Despite decades of research on the etiology, the precise cause appears to be unclear. AD destructs the patients mind, makes significant burdens for their families and caregivers and outlays the United States billions of dollars every year. According to the Alzheimer's Association today, more than 5 million Americans are living with Alzheimer's disease. As per estimations Alzheimer's and other dementias may cost the U.S. health care system for more than $259 billion during 2017, which will potentially increase approximately 4-fold to $1.1 trillion by 2050 [2]. The early stage of AD short-term memory loss appears [3], as it progresses through the different stages of dementia, cognitive impairment such as forgetfulness with daily activities, remembering names of familiar people or thing becomes increasingly noticeable and severe [4] [5].

Current approaches for drug development are basically therapeutic. Due to the complex etiology of AD, its pathogenesis has not been fully interpreted, and numerous pathogenesis hypotheses for AD have been explained, such as cholinergic hypothesis [6], amyloid cascade hypothesis [7] [8], oxidative stress hypothesis [9], and metal dyshomeostasis hypothesis [10] [11]. Despite continuous efforts towards unraveling the brain complexities and recognizing the keystones of Alzheimer's, the effective treatment foundation remains an unnerving challenge [12]. There is currently no cure to stop or reverse the advancement of AD. However, medications presently available treat the disease symptoms like memory loss, confusion and problems with thinking. Nevertheless, there are presently five FDA-approved medications Donepezil (Aricept), Galantamine (Reminyl), Rivastigmine (Exelon), Tacrine (Cognex) and Memantine (Namenda) which are available that temporarily improve symptoms, but the benefits are not so potent and none is capable to halt the progression of this disease (**Figure 1**) [13] [14]. This review summarizes the therapeutic agents discovered so far, which could lead to the development of an effective drug for AD.

General structure of the review is:

1) Etiology of Alzheimer's Disease;

2) Current strategy for Alzheimer's Disease treatment;

3) Strategies in drug discovery for Alzheimer's Disease;

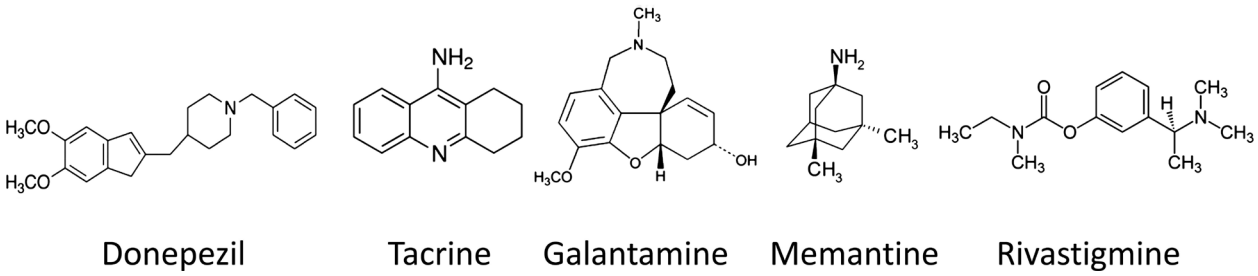

Figure 1. Medications approved by FDA for AD treatment.

4) Conclusion.

2. Etiology

The initiation of pathogenic process is explained by the formation of amyloid plaques, which starts either because of mutations in the amyloid precursor protein (APP), or due to other mutations and environmental factors [7]. These changes lead to the formation of amyloidogenic peptides that first aggregate into oligomers, which can interfere with synaptic neurotransmission (e.g. cholinergic neurotransmission), and then into amyloid plaques, which are thought to cause intracellular metabolic alterations that lead to the hyperphosphorylation of tau proteins [15]. Thus hyperphosphorylated tau proteins aggregate to form neurofibrillary tangles that alter intracellular metabolism to a sufficient degree to cause neuronal death. Both β-amyloid plaques and neurofibrillary tangles are thought to cause an excessive release of glutamate in certain cortical and sub-cortical structures [16] [17] [18] that can lead to neuronal death through N-methyl-D-aspartate (NMDA) receptor mediated excitotoxicity [19].

3. Current Strategy

Present research to treat AD is focused on either to impede or slow down disease progression by directing one or more of the brain changes instigated by AD. These targets of treatment are β-amyloid plaques that occur between the cells of the nerve, tangles of tau protein that damage and kill cells of the brain by disabling the nerve transport system and a receptor that decreases a neurotransmitter required for the brain to think and function normally. Potential medications also intend to decrease neuro-inflammation that is accompanied with Alzheimer's and targets the immune system to empower it to fight the disease.

Intensifying the central cholinergic movement and ameliorating acetylcholine level in the brain, for example, by prohibiting the activity of acetylcholinesterase (AChE) have been believed to be a powerful approach AD therapy [20] [21]. Presently, the first-line drugs for AD treatment are primarily AChE inhibitors such as donepezil, rivastigmine, galantamine, and huperzine A (Hup A, approved by CFDA [13] [22]. These drugs functions only to enhance the memory and cognitive capabilities of AD patients but do not serve as curative treatment [23] [24].

4. Strategies in Drug Discovery for Alzheimer's

4.1. Biomarkers

A biomarker is a measurable indicator of some biological or pathological state or condition that is objectively measured to evaluate normal biological or pathological processes. They can be used for diagnosis as well as monitoring the success of a therapy (**Figure 2**). Present diagnostic techniques for AD are quiet expensive-magnetic resonance imaging (MRI) or positron emission tomography (PET), invasive cerebrospinal fluid (CSF) biomarkers, genetic markers, serum

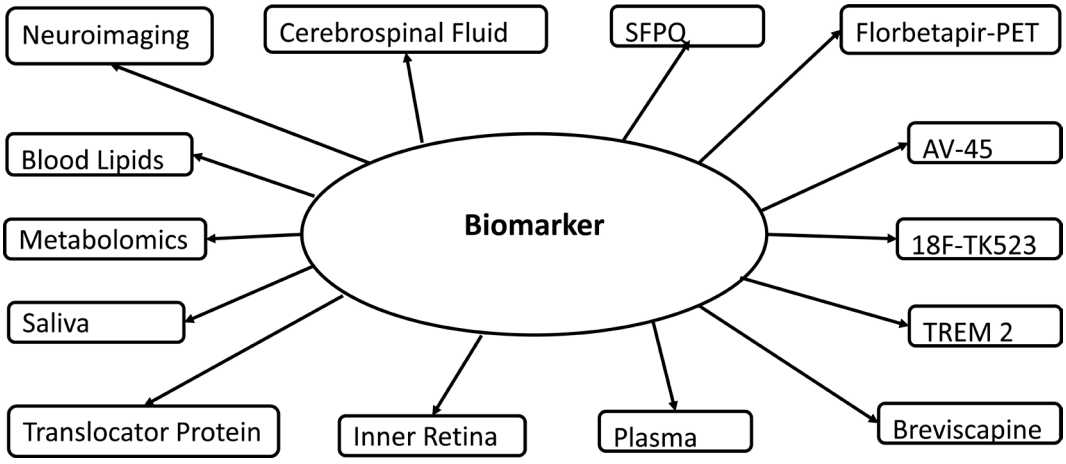

Figure 2. Various biomarkers used in diagnosis of AD.

amyloid within significant specificity and reactivity [25]. However, neuropsychological analysis is considered to be the "gold standard" for pre-mortem detection of AD [26], but the screening is tedious, and may demand manifold assessment.

Most of the AD drug development relevant biomarkers presently used are brain imaging, plasma and cerebrospinal fluid (CSF) measures; microarray and spectroscopic examination of multiple genes, proteins, lipids, metabolites. Florbetapir-PET (an imaging agent which has high binding specificity for β amyloid) images demonstrates that amyloid-β load associates with the cognitive function [27]. Another biomarker Aβ amyloid can also be analyzed using commercially available imaging agent (AV-45), for further research to understand AD; but still there is no imaging agent commercially available for tau. However, Victor Villemagne's research group is engaged in developing a tau imaging agent 18F-THK523 in patients [27] with Alzheimer and Jeff Kuret is also working on biomarkers for tau imaging for early analysis, differential analysis, and monitoring response to various treatments but selectivity and the binding potential are the key challenges in the development of tau imaging agents. In the frontotemporal dementia, enhanced sensitivity of a TDP-43 was observed during Cerebro Spinal Fluid (CSF) measurement [27]. Neuroimaging and CSF measures of β-amyloid and neuronal injury demonstrates the importance of the heterogeneity of the definition of neuronal injury, and has significant consequences for clinical trials exploiting biomarkers as substitute endpoint measures [28].

Other major biomarkers developed so far include blood lipids [29], saliva and metabolomics [30], amyloid blood biomarker [31] [32] [33] [34], retinal ganglion cell-inner plexiform layer (GCIPL) and nerve fiber layer (NFL) [35]. Plasma biomarkers have also been found to be very helpful in the detection of AD [35]. These biomarkers are economic and scalability bonus over existing techniques, facilitating broader clinical approach and productive population screening. Several proteins have been reported to play a significant role in the early detection of AD. A18kDatranslocator protein (TSPO) is known to have a promi-

nent role in neuroinflammation in dementia pathogenesis and can aid in monitoring disease succession [36]. Another major protein Splicing factor proline- and glutamine-rich (SFPQ) which aids in transcription, pre-mRNA splicing, and DNA damage repair, was found to be dysregulated and dislocated in the development of AD and FTD [37]. Modifications in extracellular matrix proteins ameliorate hippocampal IL6 level and iron in the initial phases of AD and show inflammation-mediated iron dyshomeostasis in the initial phases of neurodegeneration. Besides, the level of iron in the hippocampus was calculated by preliminary coupled plasma-mass spectrometry as IL6 is cited in many studies to take part in iron homeostasis and inflammation and known to be elevated in 5XFAD mice hippocampus [38]. Further, Flavonoids-breviscapine biomarkers were investigated and were found to enhance the learning and memory deficits of AD mice chiefly by regulating phospholipids metabolism, promoting level of serotonin and reducing cholesterols content *in vivo* [39]. Noncoding MicroRNA (miR)-34a acts as a promising biomarker for early detection and intervention which contribute to the pathological development of AD [40] [41].

4.2. Multi-Target-Directed Ligand (MTDL) Design Strategy

Multi-target-directed-ligands (MTDLs) are found to be an innovative form of polypharmacology, which are compounds that influence two or more biological targets and processes [42]. This strategy has evolved vigorously over the past few years, mainly in the context of multifactorial diseases such as AD [43] [44] [45] [46]. A variety of promising multifunctional anti-AD molecules has been developed and synthesized by incorporating chemical fragments accountable for interaction with desirable biological targets [47]-[52]. Further MTDL for AD has been developed with multifunctional roles such as antioxidant property, blood-brain barrier penetration, biometal chelation, Aβ aggregation modulation and neurotrophic and neuroprotective properties [53]. It also revealed hippocampal cell proliferation activity in living adult mice. The role of ASS234 was identified as multi-target directed compound for AD [54]. Presently, the most effective therapeutic strategy for drug designing for AD is aiming the cholinergic system. It has been proposed that the decline of acetylcholine (ACh) level causes the cognitive and memory deficits [55] [56] [57]. Hence, targeting cholinergic function by preventing cholinesterase's (ChEs), which control the hydrolysis of ACh, is valuable for the treatment of AD [58] [59]. Two types of ChEs, exits namely, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Normally, AChE is a ruling factor for ACh metabolism (80%), thus, acetylcholinesterase inhibitors (AChEIs) can proficiently stops the hydrolysis of ACh and offers capable therapeutic effects [60]. The level of AChE decreases to 90% in AD patients, causing the loss of function of AChEIs [61]. Whereas BuChE continues the standard level or are upregulated for the metabolism of ACh. Suppression of BuChE forms a favorable target for drug discovery of progressed AD [62]. So, clinical use of inhibitors of both AChE and BuChE can be applied for a powerful

therapeutic strategy for AD. But, presently ChEs suppressors in clinical use, such as donepezil and rivastigmine, only allow a comforting treatment [63]. Therefore, designing multi-target-directed ligands (MTDLs) that can instantaneously control multiple targets in the advancement of AD, has developed as a novel strategy [64] [65] [66], and several of MTDLs have shown favorable pharmacological impacts on AD [67] [68] [69] [70] [71]. A novel series of sixteen multifunctional N-benzyl-piperidine-aryl-acylhydrazones hybrid derivatives were assessed for multi-target activities associated with AD by Dias *et al.* [72]. Among them, one compounds showed excellent AChEI activity, also had anti-inflammatory activity *in vitro* and *in vivo*, against amyloid beta oligomer (AβO) induced neuroinflammation. The target compound also exhibited the best *in vitro* and *in vivo* neuroprotective activity against AβO-induced neurodegeneration. Furthermore, the target compound also revealed a similar binding mode to donepezil in both acetylated and free forms of AChE enzyme in molecular docking studies and did not express toxic effects on *in vitro* and *in vivo* assays. Hence, all these consequences authenticated the target compound to be a potent and novel multi-target drug candidate for AD treatment. Furthermore, novel TDMQ (TetraDentate MonoQuinolines) ligands based on an 8-aminoquinolinewere designed [73]. Their affinity for Cu (II) has been reported, and their competency to suppress oxidative stress encouraged by copper-amyloids initiated by a reductant. These metal ligands can be assessed as potent anti-AD agents; can monitor the homeostasis of copper in brains.

4.3. Targeting β-Amyloid: Attractive Therapeutics for AD

Deposits of insoluble proteins: β-amyloid (Aβ) and hyperphosphorylated tau are regarded as the primary cause of AD. Aβ is the product of enzymatic cleavage of amyloid precursor protein (APP) by β-secretase (BACE-1) and γ-secretase (**Figure 3**). Various forms of Aβ, primarily Aβ1–42 and Aβ1–40, have the ability to aggregate and create extracellular neurotoxic senile plaques [74]. Amyloid precursor protein (APP) undergoes sequential cleavages by β-secretase and γ-secretase and gives rise to the β-amyloid (Aβ) that is known to instigate soluble oligomers, insoluble fibrils, and assembled plagues. APP can be processed by α-secretase within the Aβ region and produce a longer C-terminal fragmenting the first cleavage. For controlling Aβ production, the three important enzymes processing in APP have been therapeutic targets in AD drug development. The strategy is the inhibition of β-/γ-secretase while stimulating the α-secretase activity. Beta-site APP-cleaving enzyme 1 (BACE1) is the protease in charge for the preliminary cleavage of APP, giving rise to neurotoxic suspect Aβ [75] [76] [77]. BACE1 knock-out mice marked a close correlation between the BACE1 inhibition and the Aβ decline [77] [78]. It is outlined that BACE1 inhibition enhanced memory deficits [79] and released Aβ-driven cholinergic dysfunction [80] in APP transgenic mice. Nuclear peroxisome proliferator activated receptor gamma (PPARγ) act as a transcription factor regulating gene expression [81],

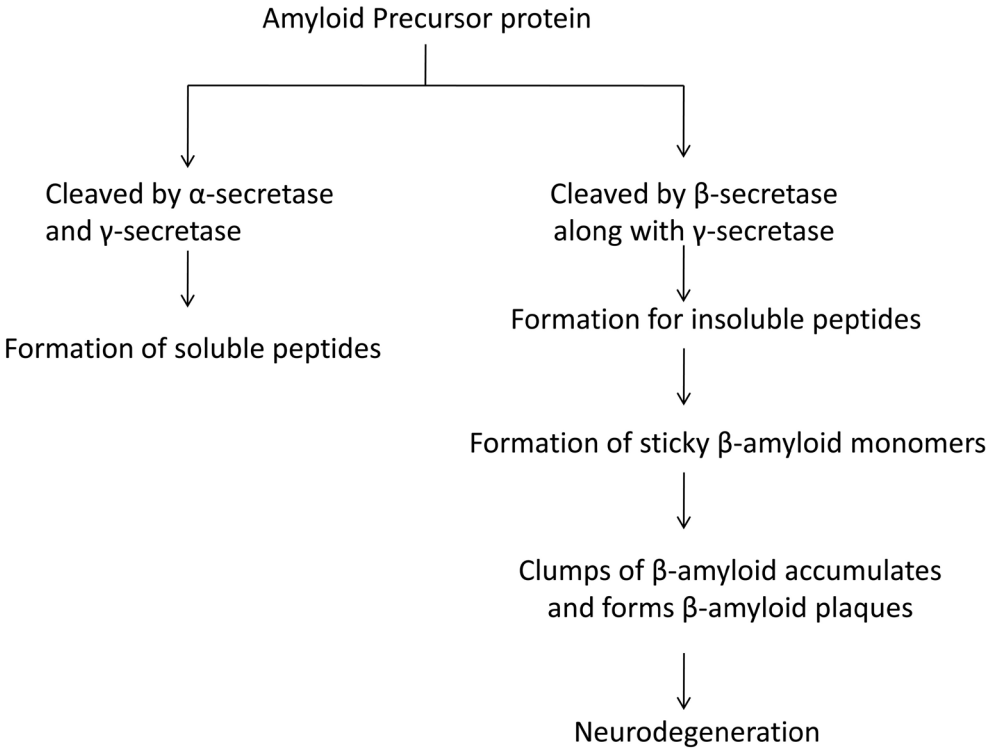

Figure 3. β-amyloid pathology.

regulating inflammation response, encouraging microglia-mediated Aβendocytosis, and decrease cytokine secretion [82]. It was noticed that thiazolidinediones stimulated PPARγ to inhibit β-secretase and promoted ubiquitination to deteriorate amyloid load [83]. PPARγ agonists like thiazolidinediones derivatives rosiglitazone and pioglitazone lessen the peripheral insulin resistance [84], which provoked AD neuropathology, and this decline of insulin sensitivity aids in Aβproteolysis. The study of rosiglitazone has been enhanced to a large phase; still, it has been terminated due to cardiac risk concerns [85]. Pioglitazone has recently been developed into a phase 3 clinical trials after preventing an earlier reported bladder risk. Development of small nonpeptidic BACE1 inhibitors, compared to older agents, have enhanced molecular weight, beneficial pharmacokinetic (PK) guidelines, and adequate lipophilicity to cross the blood-brain barrier (BBB) [86] [87]. Lately, orally bioavailable BACE1 inhibitors have been evolved that can cross the BBB and have shown strong cerebral Aβ reduction in preclinical animal models [86]. Many of these compounds have been explored in clinical trials [86] [87] [88] [89]. Anti-inflammatory properties of donepezil were studied and its neuroinflammatory effects were also explored [90] [91] [92] [93]. It was observed that donepezil notably reduced the release of inflammatory intermediaries (prostaglandin E2, tumor necrosis factor-a, interleukin-1 beta, and nitric oxide) from microglia. It was further established that donepezil inhibits activated microglia-mediated toxicity in primary hippocampal cells. In intrahippocampal Af30-injected mice, donepezil inhibited microgliosis and astrogliosis. Moreover, behavioral tests showed that donepezil remarkably improved

Aβ0-induced cognitive impairment. Thus, it was concluded that donepezil straight away prevents microglial activation induced by Aβ via obstructing MAPK and NF-KB signaling. This further, brings about the amelioration of neurodegeneration and cognitive impairment. The dosage and duration of treatment of Memogain, another drug, was screened on behavior and amyloid-β (Aβ) plaque deposition in the brain of AD patients [94]. Their experiments revealed that nasal administration of Memogain efficiently transported the drug to the brain with the possibility to inhibit deposition of plaque and enhance behavioral symptoms in AD. Another novel sequence of flavonoid based compound was designed and produced which showed AChEI activity along with advanced glycation end products (AGEs) inhibitory properties and antioxidant potential as well [95]. One compound 6-methyluracil derivative was found capable of passing through the blood-brain barrier, enhanced working memory in transgenic mice with amyloid precursor protein/PS1 and considerably decreased the Aβ plaques number and area in the brain [96]. Another compound, β-asarone notably enhanced the learning and memory of APP/PS1 transgenic mice by suppressing Beclin-1-dependent autophagy via the PI3K/Akt/mTOR pathway [97]. Besides, there was decline in AChE and $A\beta_{42}$ levels, improved p-mTOR and p62 expression, reduced p-Akt, Beclin-1, and LC3B expression, reduced the number of autophagosomes and decline in levels of APP mRNA and Beclin-1 mRNA after treatment with β-asarone. A natural extract from black sesame (*Sesamum indicum* L.) known as black sesame pigment (BSP) shows strong inhibition of AChE-induced accumulation of β-amyloid Aβ1-40 and inhibition of self-induced Aβ1-42 aggregation and activity of BACE-1 [98].

The cellular mechanism of Bis (propyl)-cognitin (B3C) and bis (heptyl)-cognitin effect on the impairments of cognitive function, synapse formation, and synaptic plasticity induced by soluble amyloid-β protein (Aβ) oligomers in AD patients has been unraveled [99] [100]. AβO-induced synaptotoxicity was inhibited by Bis (heptyl)-cognitin in primary hippocampal neurons. Further, it was identified that bis (heptyl)-cognitin changed Aβ assembly via directly preventing AβO formation and decreasing the amount of preformed AβO's. Previous research has proved B3C to be a capable therapeutic anti-AD drug. The effect of a compound, named baicalein on synaptic function both *in vitro* and *in vivo* in AD model was found that baicalein prohibited Aβ-induced impairments in hippocampal LTP via initiation of serine threonine Kinase (Akt) phosphorylation. These findings fortified the flavonoid baicalein effect as potent bioactive therapeutics that avoids memory deficit in AD patients [101]. This compound was also found to enhance scopolamine induced memory deficit in mice. An interesting fact about folic acid is that it prohibited the Aβ deposition due to folate deficiency in APP/PS1 mice. Folic acid decreased the accumulation of Aβ42 in APP/PS1 mice brain by reducing the mRNA and protein expressions of β-secretase BACE1 and γ-secretase complex catalytic component-presenilin 1 (PS1)-in APP/PS1 mice brain [102]. A compoundα7 nicotinic acetylcholine receptor (α7-nAChR) was

studied for its binding, Aβ deposition, and mitochondrial complex I (MC-I) effect in the aged monkeys (Macaca mulatta) brain [103]. The results showed significant upregulation of α7-nAChR caused by neurodegeneration by Aβ accumulation as well as disabled MC-I activity in brain. Later, Nakaizumi *et al.* unraveled the association between α7-nAChR presence in the specific cholinergic region and cognitive decline in the AD patients [104]. Relation among Aβ burden and α7-nAChR decrease in the basal forebrain cholinergic system was underlined in accordance to AD cognitive decline. Furthermore, a series of 15 drug-like derivatives of 2-(benzylamino-2-hydroxyalkyl) isoindoline-1,3-diones were identified with β-secretase inhibitory activities [105]. Another compound, (2-(5-(benzyl amino)-4-hydroxypentyl) isoindoline-1, 3-dione), presented inhibitory potency against *ee*AChE, *h*BACE-1, and Aβ-aggregation. Kallikrein-related peptidase 7 (KLK7) was explored as an astrocyte derived degrading enzyme [106]. There was reduced expression of KLK7 mRNA in the of AD patient's brain. It was found that the FDA approved anti-dementia drug memantine elevated the Klk7 expression and degradation of β amyloid precisely in the astrocytes. Thus, KLK7 is a significant target enzyme in the deposited β amyloid degradation and clearance in AD patients. Some spiropyrrolidine heterocyclic hybrids in 1-butyl-3-methylimidazoliumbromide ([bmim] Br) were identified and reported as promising agents for treating AD [107]. Pitt *et al.* speculated CNS factors in physiologically defending neurons from the deleterious effect of AβOs [108]. Neurons in the presence of astrocytes exhibited decreased AβO binding and synaptopathy. Insulin and insulin-like growth factor-1 (IGF1) were identified as the defensive factors released by astrocytes. The shielding mechanism involved liberation of newly bound AβOs into the extracellular medium dependent on trafficking that was delicate to exosome pathway inhibitors. Transmembrane Post-synaptic density (PSD) proteins were scrutinized heterologously for the capability to bind AβO-PrP(C) with Fyn [109]. Coexpression of the metabotropic glutamate receptor, mGluR5, permitted PrP(C)-bound AβO to activate Fyn. PrP(C) and mGluR5 communicate physically, and cytoplasmic Fyn establishes a complex with mGluR5. AβO-PrP(C) multiplexes at the neuronal surface activate mGluR5 to damage neuronal function. Further, Haas group reported that the PrP(C) segment of amino acids 91 - 153 facilitates the interaction with mGluR5 [110]. mGluR5 agonists intensify the mGluR5-PrP(C) interaction, whilemGluR5 antagonists inhibit protein association. In brain homogenates with AβO, the interaction of PrP(C) and mGluR5 was reversed by mGluR5-directed competitor or antibodies administered against the PrP(C) segment of amino acids 91-153. It was seen that silent allosteric modulators of mGluR5 did not alter Glu or basal mGluR5 property; instead they disrupted the AβO-induced interaction of mGluR5 with PrP(C). The findings described here has the prospective to detect novel compounds that prevent the interaction of PrP(C) and mGluR5, which is very crucial for AD pathogenesis. Stress-inducible phosphoprotein 1 (STI1), an Hsp90 cochaperone released by astrocytes in AβO toxicity was stu-

died [111]. The precise binding of AβOs and STI1 to the cellular Prion protein (PrP(C)) was validated and displayed that STI1 capably repressed AβO binding to PrP *in vitro* and reduced AβO binding to cultured mouse primary hippocampal neurons. Significantly, TPR2A inhibited both AβO binding to PrP(C) and PrP(C)-dependent AβO toxicity, the PrP(C)-interacting domain of STI1. Furthermore, PrP(C)-STI1 stimulated α7 nicotinic acetylcholine receptors, thereby contributing in neuroprotection against AβO-induced toxicity. Furthermore, Maciejewski *et al.* explored the molecular interactions between AβO and STIP1 attachment to PrP(C) and their consequences on neuronal cell death [112]. They reported that residues situated in the short region of PrP (90 - 110) facilitate AβO binding. PrP binding was caused because of multiple binding sites on STIP1. The TPR2A (one of the binding site on STIP1) interface was found to be very vast and moderately overlayed with the Hsp90 binding site. Thus, there is a likelihood of a PrP, STIP1 and Hsp90 ternary complex, which may impact AβO-mediated cell death.

It is known that proteolysis of APP is vital for β-amyloid peptides (Aβ) production which deposits as disorientated plaques in brains of patients with AD. The BACE1 is the rate determining enzyme in the formation of Aβ from APP. Dai *et al.* used the inhibition of BACE1 strategy for the development of drug for AD [113]. Chitosan oligosaccharides (COS) has been known to hold numerous biological activities. The experimental data showed that COS reduced the cell apoptosis, and strongly suppressed the secretion of both Aβ40 and Aβ42. Furthermore, COS treatment reduced the BACE1 mRNA and protein expression level, eIF2α phosphorylation as well as the enzymatic activity of BACE1. They concluded that COS contained properties that could ameliorate Aβ-associated neurodegeneration, thereby contributing to drops in BACE1 enzymatic activity and expression.

Wang *et al.* conducted an AD mice vaccine development experiment where they immunized the mice with AOE1 vaccine comprising mimotope L2 induced antibodies that precisely identified Aβ42 oligomers and found that it decreased the levels of Aβ oligomers and activation of glial in the AD mouse brains [114]. Aβ-specific T cells were not activated in their brains and no microhemorrhages activation was detected in their brains after AOE1 vaccination. A different approach of disease modification was used by Giannoni *et al.* to combat AD [115]. They identified a potent 5-HT4 receptor agonist RS67333 which reduced Aβ production level which led to decline in hippocampal astrogliosis and microgliosis. Jung *et al.* revealed the neuroprotective effects of Cassiae obtusifolia semen which could be promising therapeutic anti-AD agents as it possessed the inhibitory activity against AChE, BChE and BACEl [116]. Earlier it has been reported that the Cassiae obtusifolia seeds extracts, have memory ameliorating properties and anti-AD activity to enhance amyloid β-induced synaptic dysfunction [117] [118]. Xu *et al.* evaluated the function of SNX3 in Aβ production and processing of APP. Their findings suggested that overexpression of SNX3 in

HEK293T cells reduces the Aβ level and soluble N-terminal APP fragments (sAPPβ) [119]. SNX3 overexpression decreased APP internalization, and formed increased level of APP on the cell surface. Further, SNX3 overexpression ameliorated the level of APP.

Esmaeili *et al.* concluded that obstruction of K_{ATP} channels with glibenclamide reduced depression- and anxiety-related behaviors by regulating HPA axis activity in Aβ25-35-treated rats [120]. Ge *et al.* reported that soluble islet amyloid polypeptide (IAPP) encouraged the accumulation of Aβ42 by binding-induced conformational modification of Aβ42 in its amyloidogenic core and hence decreased aggregation free energy barrier [121]. Hall group reported the M1/sigma-1 activity and long-lasting disease-modifying properties of a compound AF710B, as a potent anti-AD agent [122]. The cognitive deficits related with progressive Alzheimer-like amyloid neuropathology were reverted in transgenic rats after long term treatment with AF710B. AF710B was reported as capable to induce the binding and efficacy of carbachol on M1 receptors and their downstream effects (phopho-ERK1/2, phospho-CREB) at low concentrations. In accord with its anti-amnesic effect, AF710B, via activation of M1 and a possible involvement of σ1 receptors, retrieved mushroom synapse loss in PS1-KI and APP-KI neuronal cultures. There were decrease in amyloid pathology and markers of neuroinflammation and elevation in amyloid cerebrospinal fluid clearance and levels of a synaptic marker. Wang *et al.* designed and created a series of new 4-isochromanonecompounds having *N*-benzyl pyridinium moiety and biological assessment displayed that most of the target compounds revealed potent AChEI activities [123]. Fisher *et al.* reported AF710B, to be an effective and selective allosteric M1 muscarinic and σ1 receptor agonist [124]. In female transgenic AD mice AF710B reduced cognitive impairments, also reduced BACE1, GSK3β activity, p25/CDK5, neuroinflammation, soluble and insoluble Aβ40, Aβ42, plaques and tau pathologies. Clemens *et al.* validated the co-relation between inflammation, retinoic acid (RA) signaling, and Apolipoprotein E (ApoE) homeostasis in origin and development of AD [125]. Microglia is an important source of ApoE, and is known to be pathologically stimulated in AD. RA signaling is known to be inhibited by these microglia and proinflammatory stimulation reduces synthesis of ApoE, due to an effect blocked by RA. Sans *et al.* demonstrated the cellular model for evaluating apoE proteolysis, which showed that serine peptidase A1 (HtrA1) controlled apoE 25-kDa fragment production under physiological conditions, and depicts a novel neurotrophic effect for the apoE fragment [126]. Studies on CSF have shown that levels of CSF of amyloid-beta 1-42 (Aβ42) are decreased and tau levels ameliorated earlier to the commencement of cognitive decline related to AD. Leon *et al.* noticed that the prognosis of cognitive decline was enhanced by taking into account both high and low levels of Aβ42 [127]. Their data proposed a preliminary preclinical stage, manifested by CSF increase in tau and escorted by elevations or diminution in Aβ42. Chen *et al.* designed and analyzed a series of tacrine-cinnamic acid

hybrids as novel ChEIs [128]. All target compounds are assessed for their *in vitro* ChEI activities. Those compounds which revealed effective ChEI activity were further screened for the Aβ-protein self-accumulation inhibition and *in vivo* assays. Three compounds were found to be helpful in enhancing the scopolamine-induced cognition impairment and preliminary safety in hepatotoxicity assessment and claimed as potential novel therapeutic anti-AD agents.

Several findings have shown that monoamine oxidase (MAO) plays a vital role in the pathogenesis of AD because the elevation of MAO in the brain may produce a cascade of biochemical events resulting in neuronal dysfunction [129] [130]. MAOs are flavin adenine dinucleotide (FAD)-containing enzymes that are accountable for the oxidative deamination of endogenous and exogenous monoamine substances. There are two functional isozymic forms of MAOs, mainly, MAO-A and MAO-B [131]. MAO-A inhibitors are applied in clinical antidepressants and antianxiety, while MAO-B inhibitors are used as a remedy for neurodegenerative disorders such as AD and Parkinson's diseases (PD) [132] [133]. Based on previous research [134] [135], MAO-B action in the brain and blood platelets of AD patients were high, while increased expression levels of MAO-B could result in the enhanced level of free radicals that portrayed a significant role in AD pathogenesis. MAO-B inhibitors can decrease the oxidative stress response and guard the nerve cells from oxidative damage and neurotoxicity, hence, MAO-B could be a significant target for AD treatment [136] [137]. Selegiline, an irreversible and selective MAO-B inhibitor, has been described as a potent anti-AD agent because of its neuroprotective attribute in cellular and animal models of AD [138]. The elevated levels and dysregulation of biometal ions such as Cu^{2+}, Zn^{2+} and Fe^{2+} were found to be closely involved in AD pathogenesis [139] and was reported to promote Aβ aggregation, resulting in the production of toxic Aβ oligomers [140]. Redox-active Cu (I/ II) and Fe (II/III) are involved in the creation of reactive oxygen species (ROS) causing an increase in oxidative stress [141] [142] [143] [144]. Biometal chelators, particularlyCu^{2+} chelators, decrease the metal-induced Aβ aggregation and also minimize the ROS level generated by the redox metal and metal-Aβ complex [145] [146]. Hence, biometal chelators have been believed to be a potent therapeutic strategy for AD treatment. Moreover, neurotoxic ROS and oxidative damage of neuronal cells are also related to AD, so the compounds with antioxidant properties could be favorable for AD treatment [147] [148]. Vilella *et al.* screened altered zinc-levels in the AD brain via zinc loaded nanoparticles which can deliver zinc into the brain across the BBB for favorable effect on AD patients [149]. *In vivo* studies were conducted with wild type (WT) and APP23 mice to evaluate plaque load, inflammatory status and synapse damage. Besides, behavioral analyses were undertaken. A remarkable decrease in plaque size and impact on the pro-inflammatory cytokines 11-6 and IL-18 was seen after administering these nanoparticles for 14 days. In case of behavioral changes there was no negative result of increased brain zinc levels in APP23 mice and treatment with g7-NP-Zn

standardized the detected hyperlocomotion of APP23 mice.

Mitochondria association has been revealed in the disease pathogenesis of AD [150]. The member of quinone family is key mitochondrial targets used as the curative against ROS-mediated impairment. To avoid oxidative injury in AD, Mitoquinone mesylate or MitoQ, a ubiquinone derivative has been applied [151]. Zhang *et al.* discovered novel Phosphodiesterase-9 (PDE9) inhibitors [152]. This PDE9is a promising target for AD treatment. AD is marked by continuous cognitive decline, progressively associated with neuronal dysfunction caused by amyloid-β oligomers (AβOs). Diniz *et al.* reported that AβOs interact with astrocytes, triggers astrocyte activation and causes abnormal production of reactive oxygen species (ROS), which is accompanied by damage of astrocyte neuroprotective potential *in vitro* [153]. They demonstrated that astrocyte stops the synapse damage induced by AβOs, through formation of transforming growth factor-β1 (TGF-β1). AβOs also causes morphological and functional modifications in astrocytes, and weaken their neuroprotective potential. These findings outline a new strategy unrevealed the toxicity of AβOs and specify a novel therapeutic target for AD, primarily focused on TGF-β1 and astrocytes.

Yu *et al.* earlier reported that the inhibition of histone deacetylase 3 (HDAC3) enhances spatial memory deficits and reduces the Aβ accumulation in the 9-month-old APP/PS1 mice brain [154]. Recently, they opened new frontiers for AD drug development by proposing HDAC3 to be a promising target because of their effect of reducing spatial memory deficits and preventing oxidative stress in APP/PS1 mice. HDAC3 is mainly present in the neurons; its inhibition notably attenuates production of ROS and enhanced primary cortical neuron viability. Researchers determined a molecular association between aging and dementia via the identification of J147 a molecular target for the AD drug [155]. Mitochondrial a-F1-ATP synthase (ATP5A) was identified as a target fora potential drug candidate J147.It was found that J147 ameliorated intracellular calcium level which induced calcium/calmodulin-dependent protein kinase kinase b (CAMKK2)-dependent activation of the AMPK/mTOR pathway, an established longevity procedure. Hence, ATP synthase prove to be a potential target which could be further explored for AD drug development. Xu *et al.* synthesized new propargyl amine-modified pyrimidinylthiourea derivatives (1e3) for AD treatment, and evaluated their potential through numerous biological experiments [156]. These derivatives showed good selective inhibitory activity against acetylcholinesterase (AChE) and monoamine oxidase (MAO-B). Molecular studies displayed that the pyrimidinylthiourea moiety of 1b possibly bind to the catalytic active site (CAS) of AChE, and the propargylamine moiety cooperated directly with the flavin adenine dinucleotide (FAD) of MAO-B. Furthermore, 1b confirmed significant antioxidant capability, good copper chelating property, effective inhibitory activity against Cu2þ-induced Aβ1-42aggregation, moderate neuroprotection, little cytotoxicity, and suitable blood brain barrier permeability

in vitro and was found to be able of ameliorating scopolamine-induced cognitive impairment in mice. Their findings showed that 1b has the possible potential to act as a multifunctional candidate for the treatment of AD. Monoamine oxidase inhibitors (MAOIs) are potential drug candidates for the treatment of various neurological disorders like Parkinson's disease, AD and depression. Kumar *et al.* evaluated MAO-A and MAO-B inhibitory activities of two series of 4-substituted phenylpiperazine and 1-benzhydrylpiperazine derivatives, and found them to be strong MAO inhibitors [157]. Birnbaum *et al.* reported that improved production of ROS may have an integral role in the advancement of sporadic AD prior to the emergence of amyloid and tau pathology [158].

4.4. Targets and Small Molecules against Tauopathies

Tau accumulation association with neurodegeneration in AD and associated tau-positive neurological disorders collectively known as tauopathies directs the involvement of tau aggregates to neurotoxicity (**Figure 4**). Delrieu *et al.* aimed at developing a new third phase 3 clinical trials for solanezumab, called expedition 3, in patients with minor AD and sign of amyloid accumulation has been started. Previously designed drug solanezumab seems to be more successful when used in early stages of amyloid accumulation, showing the importance of detecting AD as early as possible and undergoing clinical trials at this stage [159]. Gibbons *et al.* identified novel tau monoclonal antibodies (mAbs) that allowed the selective recognition of AD tau pathology by selectively binding to an AD-specific tau conformation [160].

Lo *et al.* developed Azure C (AC), which is competent of regulating tau oligomer accumulation pathways at minimal concentrations and releases tau oligomers-induced toxicity in cell culture [161]. Remarkably, AC inhibited toxicity by transforming the oligomers into groups of aggregates with non-toxic conformation.

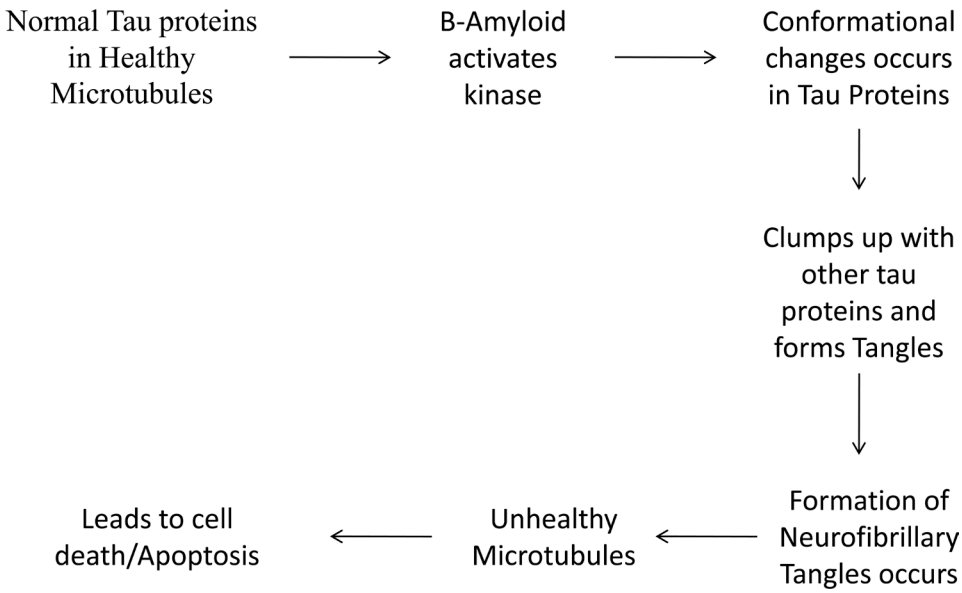

Figure 4. Tau pathology.

Tiernan *et al.* revealed the spatiotemporal progression of oligomeric tau accumulation within the highly vulnerable cholinergic neurons of the nucleus basalis of Meynert (nbM) in AD [162]. They concluded that toxic tau oligomers multiply in selectively susceptible nbM neurons through the progression of AD. Yang *et al.* designed the reagent for assessing plasma phosphorylated tau protein (p-tau181) with immunomagnetic reduction (IMR) and classified its analytic performances [163]. Their findings revealed that the level of plasma p-tau181 is associated more to AD severity than plasma T-tau.

4.5. Other Strategies

The anti-AD activities of different parts of Nelumbo nucifera (leaves, de-embryo seeds, embryos, rhizomes, and stamens) were explored to assess the selectivity and resourceful usage of its specific components [164]. It was noticed that the embryo extract act as a potent suppressor of BACEl and BChE and also has scavenging activity against $ONOO^-$. Further evaluation showed that dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc), and n-butanol (n-BuOH) fractions showed promising ChEI and BACEl inhibitory activities. Similar activities were shown by compounds obtained from Corni Fructus: loganin, morroniside, and 7-0-galloyl-o-sedoheptulose [165], these compounds had triple inhibitor activity for AChE, BChE, and BACE1 suggesting it to be a potent therapeutic class of agents for AD treatment. Further, the anti-AD activities of ginsenosides (Rbt, Rb2, Re, Re, Rg1, and Rg3) conferring to $ONOO^-$ scavenging activity and suppressor activity of $ONOO^-$mediated nitrotyrosine formation was reported [166]. Various *in vitro* enzyme assays established that ginsenosides possess substantial inhibitory activity against AChE, BChE, and BACE1 as well as $ONOO^-$ and nitrotyrosine formation. Inula japonica, a member of the Asteraceae plant family and its flowers has been used as a healthy tea and a traditional Chinese medicine. Liu *et al.* reported two new sesquiterpenes and ten known terpenes from the flowers of I. japonica [167]. Their findings revealed the flowers of I. japonica to be a healthy tea and potentially helpful for AD and related neuroinflammatory diseases. Baicalin is known to possess anti-inflammatory and neuroprotective properties. Chen *et al.* studied the neuroprotective influence of baicalin and found that baicalin enhanced Aβ (1-42) protein-related pathology and cognitive dysfunction through its anti-neuroinflammatory property [168].

Astrocytes have shown to play a vital role in CNS homeostasis and neuronal function maintenance. Tg astrocytes presented many prominent effects such as basal inflammatory status, with heightened reactivity and improved expression of the inflammatory cytokine interleukin-1 beta (IL-1β), the hexose monophosphate shunt was stimulated, also the initiation of hypoxia inducible factor-1 alpha (HIF-1α), which aids in insulation against Aβ toxicity [169]. Furthermore, Pantethine, the vitamin B5 precursor, has a neuroprotective and anti-inflammatory effect, improved the pathological pattern in Tg astrocytes as well as WT astrocytes treated with Aβ. Their findings showed the dual defensive role of astrocytes

in AD and the shielding effect of pantethine. The dietary vitamin D addition in female AD-like mice decreased cognitive decline only when applied in the symptomatic phase [170]. It was proposed that transcranial ultrasound can securely and efficiently modify the brain interstitium and enhance the diffusion of large therapeutic drug carriers, which has a promising potential to develop the therapeutic uses of MRgFUS [171]. Neurons with hyperphosphorylated tau in AD has the profile of metabolically active cells including amplified exportin-5 and importin-β mRNA and proteins which signifies that immunohistochemistry evaluation of these proteins may assist in the early diagnosis of AD [172].

Compounds comprising a benzofuran ring have been defined to have a vital role in reducing Aβ-induced toxicity, though, till date only synthetic benzofurans have been inspected. González *et al.* explored *in vitro* neuroprotective properties of fomannoxin (Fx), a natural benzofuran isolated from the Andean-Patagonian fungi Aleurodiscus vitellinus cultures, and noted its neuroprotective effect against Aβ peptide toxicity [173]. Paley *et al.* previously proposed that tryptophan metabolites lead to neurotoxicity and neurodegeneration in AD patients [174]. Tryptophan is known to be a product of Shikimate pathway (SP). There is no SP in human cells, instead human gut bacteria use SP to yield aromatic amino acids (AAA). Recently, gene-targeted investigation of human gut microbiota in AD fecal samples was carried out by this group of scientists. The remarkable variance in the gut microbial genotypes between the AD and control human populations was a significant achievement. Research was carried out on the function and role of pro-opio melanocortin (POMC)-derived neuropeptides and melanocortin 4 receptor (MC4R) in hippocampus-dependent synaptic plasticity, whose damage leads to cognitive deficits in AD [175]. It was seen that proinflammatory peripheral blood mononuclear cell (PBMC)-derived cytokines level was ameliorated in AD patients as compared with healthy controls and donepezil treatment minimized proinflammatory cytokines [176]. Atorvastatin treatment notably enhanced cognitive deficits of rats, diminished microglia and activation of astrocyte, prevented apoptosis, and down-regulated the expression of TLR4, TRAF6, and NF-κB, at the mRNA and protein levels as well [177]. TLR4 signaling pathway is therefore vigorously involved in Aβ-induced neuroinflammation and treatment with atorvastatin can exert therapeutic effects for AD. A nonselective β-adrenergic receptor blocker, Carvedilol, applied in the treatment for heart failure and hypertension, and has exhibited neuroprotective property due to its antioxidant attribute. Liu and Wang reported that Carvedilol restrained apoptosis signals by decreasing cytochrome C release and cleaved caspase-3 level [178]. Thus, favourable use of Carvedilol in AD treatment can be further explored. Simvastatin is known to be a cholesterol-lowering statin drug that has been employed to control blood cholesterol level, mainly in cases of hypercholesterolemia. Hu *et al.* proposed that Simvastatin may be helpful in enhancing the clinical consequences of AD patients [179]. Batista *et al.* identified means of neuroprotection by liraglutide, and suggested that glucagon-like pep-

tide-1 (GLP-1) receptor activation may be utilized to defend receptors of brain insulin and synapses in AD [180].

The role of erythropoietin-producing hepatocellular A4 (EphA4) in mediating hippocampal synaptic dysfunctions in AD was explored and it was seen that synaptic impairment is altered by the blockade of the ligand-binding domain of EphA4 in AD mouse models [181]. Their studies disclosed an anonymous role of EphA4 in facilitating AD-associated synaptic dysfunctions, indicating it to be a novel therapeutic target for treatment of AD.

5. Conclusions

AD attributes a vigorous progression of β-amyloid accumulation, neurodegeneration, and cognitive impairment. It is the most widespread age-related neurodegenerative disturbance influencing millions of people worldwide. Thus, discovery of an effective intervention and therapies is extremely important. Medications are immediately needed for the treatment of AD and unfortunately nearly entire clinical trials of AD drug candidates in the past have failed or have been obsolete to date. A number of available tools such as mathematical, computational or statistical tools can be employed for the clinical trial simulators development for the advancement of trial design and thus aid in the success of possible novel therapies. Drugs aimed at more than one target could reduce an excessive impact in the intricate nerve network, this combination procedure known as multi target-directed ligands (MTDLs) might lead to the discovery of novel therapeutics for AD [182] [183]. Previously designed multitarget compounds include, dual binding AChE and BACE1 inhibitors [184], AChE inhibitors and antioxidants [185]. Presently, multiple-pharmacology natural products can be employed in the drugs designing of AD treatment [186], Herbal formulae like Kai-Xin-San (consisting of Ginseng Radix, Poria, Polygalae Radix, and Acori Tatarinowii Rhizoma) also found to be effective in the treatment of AD [187] [188]. Novel strategies, such as quantitative systems pharmacology [189], chemogenomics knowledgebase [190], metabolomics [191]-[196] and chinmedomics [197]-[202] can be further explored for the finding of new generation drugs for AD. Several reviews on different strategies employed for potential target have been reported [1] [203] [204] [205] [206]. The impact of understanding Alzheimer pathogenesis can aid in developing novel therapeutic strategies with the objective of moving from treatment to prevention.

AD, the commonest dementia, is a rising worldwide health concern in today's world with immense implications for patients and societies as well. In this review, we have demarcated the current knowledge of the epidemiology, genetics, pathology and pathogenesis of AD, which is a prerequisite for the successful development of an effective therapy for the treatment of AD. Because the deposition of β-amyloid protein is a consistent pathological hallmark of brains affected by AD, the inhibition of Amyloid-β generation, prevention of Amyloid-β fibril formation, destabilization of pre-formed Amyloid-β would be an attractive the-

rapeutic strategy for the treatment of AD. Finally, the review discusses the various strategies which can be applied for an effective treatment for AD. Given the diverse strategies employed to develop potent therapeutic approach, there is hope that a viable drug targeting key components will be developed in our fight against AD in the not too distant future.

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Conflicts of Interest

The authors declare no conflict of interest, financially or otherwise.

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