Alzheimer's Disease & Treatment

Chapter 1

Therapeutic Strategies for the Treatment of Alzheimer's Disease-Recent Advances and Future Perspective

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Abstract

Alzheimer's disease (AD) a progressive and fatal neurodegenerative disorder is considered as scourge of 21st century, as it acts as a biggest health challenge and socioeconomic burden for the developed countries. Neuropathological hallmarks of AD involves extracellular deposition of senile plaques composed of fibrillar β amyloid peptide (Aβ) in the synaptic junction and presence of neurofibrillary tangles (NFT) in the axon leading to impairment of neurotransmission causing neuronal death. AD is multifactorial disorder, with complex biochemical pathways leading to its pathogenesis; hence single targeted drugs will not be efficient for the treatment of AD. Current symptomatic treatment for AD includes cholinesterase inhibitors and N-methyl-D aspartate receptor antagonist, which are poorly effective for mild to moderate AD and also possess severe side effects. Recent research on pathogenesis of AD unfolded several therapeutic strategies for the treatment of AD which includes (1) drugs interfering with Aβ deposition such as β and γ secretase inhibitors, attenuators of Aβ aggregation, deaggregators of β amyloid plaque, metal chelators, active and passive vaccination against Aβ peptide (2) drugs modulating Tau protein phosphorylation and deposition like glycogen synthase kinase 3β inhibitors (GSK-3β), vaccination against τ-protein (3) Anti-inflammatory and antioxidant drugs which attenuates the oxidative/nitrosative stress induced by Aβ peptide (4) modulators of cholesterol and vascular risk factor. The present review focuses on summarizing the recent findings and advances in the therapeutic strategies for the treatment of AD.

Keywords: β-amyloid peptide; Oxidative stress; Neuroinflammation; Tau protein; Immunotherapy; Traditional medicine

Abbreviations: Aβ: β amyloid; ACE I: Angiotensin converting enzyme I; AChE: Acetylcholinesterase; ACh: Acetylcholine; AD: Alzheimer's disease; ApoE: Apolipoprotein E; APP: Amyloid precursor protein; BACE1: β Secretase; BDNF: Brain-derived neurotrophic factor; BuChE: Butyrylcholineesterase; CDK5: Serine/threonine cyclin dependent kinase; ChAT: Choline acetyl transferase; CNS: Central nervous system; CSF: Cerebrospinal fluid; CREB: cAMP response element-binding protein , ECGC: Epigallocatechin gallate; GSK-3β : Glycogen synthase kinase 3β; IDE: Insulin degrading enzyme; IL-1β: Interleukin 1 beta; IL-6: Interleukin-6; IF-γ: Interferon gamma; LRP: Low-density lipoprotein; MAPT: Microtubule-associated protein Tau; MAPK: mitogen activated protein kinase; NFT: Neurofibrallary tangles (NFT); NGF: Neuronal growth factor; NSAIDs: Nonsteroidal anti-inflammatory drugs; PKC: protein kinase C; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor alpha.

1. Introduction

Alzheimer's disease is an irreversible degenerative brain disorder comprising 60-80% of dementia cases affecting particularly the elderly persons above the age of 60. AD is one of the fifth leading causatives of death creating huge socioeconomic burden to the developed countries [1]. Clinically, AD is characterized by progressive loss of cognitive function mostly memory and learning affecting the daily activities of life with death occurring within 9 years of incidence [2]. Epidemiological studies reported that worldwide approximately 36 million (3 per 1000 individuals) people are suffering from AD and this expected to quadruple to 115 million by 2050, if no effective therapy intervenes [3,4]. Alzheimer's disease is classified as familial and sporadic AD, both of which share similar clinical and pathological features such as deposition of abnormal protein aggregates, defects in axonal transport, synaptic loss ultimately leading to neuronal death. Familial type AD also termed as early onset AD constitute 5% of the total AD cases affecting people aged between 30-60 years. Mutation in gene encoding for amyloid precursor protein (APP; chromosome 21), Presenillin 1 and 2 encoding for γ secretase enzyme (PSEN 1, 2; Chromosome 1 and 14) and patient suffering from Down's syndrome (21^{st} trisomy) have high risk of familial type AD. About 95% of the total AD cases are sporadic type (late onset), which is incident in elderly population above the age of 65 [5]. Several reversible and irreversible factors such as aging, nutrition, life style, environmental factors, increased expression of ApoE4 gene and chronic metabolic disorders provokes the incidence of late onset AD. Among the etiological factors, aging is the major risk factor as incidence of AD increases exponentially with age [6].

Neuropathological hall marks of AD include both positive and negative lesions leading to neuronal death. Classical positive lesion includes extracellular deposition of amyloid plaques composed of Aβ (1-42) peptide in the synaptic junction and intracellular accumulation of neurofibrallary tangles (NFT) containing hyperphosphorylated tau protein in the axonal region. Deposition of amyloid plaques and NFT is accompanied by activation of astrocytes and microglial cells causing impairment in the synaptic junction leading to neuronal death, the core negative features of AD. Unique lesions like amyloid plaques are widely found in the cortical mantle, while the NFT are present in limbic and associated cortices. Degeneration

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of neurons occurs early in the entorhinal/peirhinal cortex followed by hippocampus region, the associated cortex, finally in the primary cortex causing neuronal loss leading to cognitive impairment. The disease primarily affects cognitive function like learning and memory initially, while in the advanced stages patient suffer from loss of motor functions, which are essential for the basic activities of daily life [7]. As etiological factors leading to AD are not well defined, multiple hypotheses were proposed as causatives for the pathophysiology of AD, among, which amyloidogenic pathway that causes deposition of the amyloid-β peptide (Aβ) in the brain is a considered as central event. Other pathways including oxidative stress, inflammation, tau aggregation and cholinergic dysfunction are the secondary pathways triggered as a result of amyloidogenic pathway [8].

2. Processing of Amyloid Precursor Protein (APP)

Amyloid precursor protein is a ubiquitous transmembrane protein of about 639-770 amino acid long, highly expressed in the nervous system. APP exists in three isoforms, APP695 expressed in neurons, while APP751 and APP770 isoforms are highly expressed in non-neuronal cells. APP plays significant role in differentiation of neurons, neurogenesis, maintenance of synaptic plasticity, regulation of apoptosis and cell proliferation. About 90% of APP is processed by non-amyloidogenic, while 10% enters into the amyloidogenic pathway (**Figure 1**) the ratio may vary according to environmental factors, mutation and aging [9]. In the non-amyloidogenic pathway, γ-secretase cleaves APP between aminoacids 16(Lys) and 17(Leu) forming N-terminal secreted APP (sAPPα) exhibiting neurotrophic effect and 83- aminoacid containing C-terminal fragment (CTF), which plays crucial role in neurotrophic and calcium regulation. CTF will be further cleaved by γ secretase to form 3kDa product (P3) and APP intracellular domain (AICD), which is involved in nuclear signaling via transcriptional regulation, as well as axonal transport through its ability to associate with different proteins [10].

In the amyloidogenic pathway, APP is cleaved by β-secretase yielding N-terminal fragment (sAPPβ) and membrane bound C-terminal fragment (CTF-β) comprising of 99 amino-acid. CTFβ is further cleaved by γ secretase forming AICD and soluble Aβ fragment, which tends to accumulate into microscopic plaques. Level of Aβ in the extracellular space is influenced by several factors like neural activity and synaptic release, aging, and high cholesterol level. Length of Aβ peptides varies from 38 to 42 amino acids, among, which Aβ acts as major species deposited as plaques [11].

3. Pathogenesis Leading to AD

Presence of high concentration of transition metal ions like Cu^{2+}, Zn^{2+} and Fe^{2+} in the brain alleviates the aggregation of Aβ fragment formed in amyloidogenic pathway to oligomers, proto-fibrils and mature plaques. Deposition of mature plaques in the synaptic junction disrupts the cholinergic neurotransmission leading to neuronal death. In addition, plaques acti-

vate the associated astrocytes and microglial cells initiating inflammatory mechanism provoking death of neurons. Furthermore, reactive oxygen species (ROS) released during Aβ aggregation causes peroxidation of neuronal membrane lipids forming neurotoxic 4hydroxynonenal (4HNE), which alters the calcium homeostasis. Enhanced intracellular calcium activates kinases promoting hyperphosphorylation of tau protein forming neurofibriallary tangles (NFT), which gets deposited in the axonal region, affecting microtubules leading to neuronal death. Increased Ca^{2+} level also induce glutamate excitotoxicity, endoplasmic reticulum stress, mitochondrial dysfunction triggering caspase dependant apoptosis ultimately leading to neuronal death [12,13]. All these multiple cascade of events occurs primarily in the cholinergic neurons of hippocampal region of brain leading to impairment in cognitive function such as learning and memory (**Figure 2**).

4. Therapeutic Strategies for AD

Although genetical, biochemical and neuropathological evidences strongly illustrate Aβ and amyloid plaque formation as a central event in AD pathogenesis, the etiopathology of AD still remains unclear. Considerable evidences suggest AD as multifactorial disorder and metabolism of Aβ influences multiple pathways, which shift towards the pathogenic pathway under unfavorable condition leading to AD [12]. Several biochemical pathways including amyloidogenic pathway, cholinergic pathway, mitochondrial cascade, oxidative stress and neuroinflammation were implicated in the pathogenesis of AD. Hence current treatment strategies are focusing on therapeutic molecules targeting these pathways to prevent AD. Drug molecules targeting multiple pathways (**Figure 2**), which are under clinical trials, are tabulated in **Table 1**.

4.1. Cholinesterase inhibitors

According to cholinergic hypothesis decline in cognitive function in AD patients are caused due to deficit in cholinergic neurotransmission due to loss of acetylcholine level (ACh). The enzyme choline acetyltransferase (ChAT) plays a significant role in the synthesis of ACh, and the degradation of ACh is catalysed by cholinesterase. Deterioration of synaptic junction of cholinergic neurons together with decline in ChAT leads to reduction in level of ACh ultimately leading to impairment in cognitive function in AD patients [14]. In addition scientific evidences illustrated that acetylcholinesterase (AChE) interacts with Aβ peptide forming AChE-Aβ complex inducing the aggregation of Aβ peptide to form oligomers and mature plaques. This AChE-Aβ complex in the synaptic junction triggers neurotoxicity by dysregulating the calcium homestasis leading to mitochondrial dysfunction culminating to apoptosis [15,16]. Butyrylcholinesterase (Pseudocholinesterase) primarily localized in glial cells and subcortical neurons are also involved in the extra synaptic cleavage of ACh. Recent evidences s illustrated that BuChE with Aβ in senile plaques promotes its maturation from benign to ma

lignant plaques [17,18]. Based on these evidences, current therapeutic approach focuses on enhancing the cognitive function by inhibiting cholinesterase, thereby restoring the level of ACh necessary to stimulate nicotinic and muscarinic receptors within the brain [19]. Moreover, inhibition of ChE might block the aggregation of Aβ peptide attenuating the pathological casacade of AD [20]. FDA approved drugs like Galanthamine (Razadyne), Rivastigmine (Exelon) for mild to moderate AD and Donepezil (Aircept) for all stages of AD. Systemic reviews and clinical trials illustrated these drugs possess severe side effects and were effective only for mild to moderate and not for longer progressive disease [21]. Despite of FDA approved drugs, several drug molecules with potent AChE and BuChE activities were identified from natural source which are under clinical trials. One such drug Huperzine A, an alkaloid isolated from Huperzine serrata with potent AChE inhibitory activity has been commercialized as a dietary supplement for the treatment of AD in china [22]. Ladostigil (TV3326) which exhibits dual inhibition of AChE and monoamine oxidase are currently used for the treatment of AD [23].

4.2. N-methyl-D-aspartate antagonist (NMDA)

N-methyl-D-aspartate (NMDA) receptors have received must attention nowadays, despite of several post synaptic neuronal receptors as they play major role in neurodegenerative mechanism. L- Glutamate the predominant excitatory neurotransmitter of mammalian central nervous system plays important role in establishing new neural networks, maintaining synaptic plasticity, learning and memory. Glutamate binds to NMDA receptor in the post synaptic terminal transmitting neurosignals via the entry of calcium, which gets terminated by the uptake of glutamate by the excitatory aminoacid transporter in glial cells and astrocytes around the synapse. Increased glutamate level in the post synaptic cleft of AD causes hyperpolarisation of neurons leading to synaptic loss and neuronal shrinkage [24]. NMDA receptor antagonist binds to the receptor blocking the action of glutamate thereby preventing neuronal excitotoxicity and damage. Currently memantine the FDA approved glutaminergic NMDA receptor antagonist has been used for the treatment of moderate to severe AD. Memantine exhibits mild to moderate affinity to NMDA receptor in uncompetitive mode of inhibition. Experimental studies illustrated that memantine also showed protective effect against Aβ induced toxicity by attenuating neuronal apoptosis and increased synaptic density in the hippocampus. Randomized clinical trial showed improvement in cognition, behavior and ADL in people suffering from moderate to severe AD [25]. Administration of memantine caused certain adverse effects such dizziness, headache and confusion [26]. Clinical trials were attempted for combination therapy of donepezil and memantine, which was effective for severe AD and not for mild to moderate AD [27,28].

4.3. Therapeutic strategy modulating Aβ formation and amyloid deposition

4.3.1. Modulation of secretase enzymes

APP is processed by two competing proteases, α and β secretase to form sAPPα/sAPPβ followed by γ secretase activity to form P3/Aβ fragment. Formation of Aβ peptide in AD is regulated by β secretase (BACE1/memapsin 2) followed by γ-secretase cleavage, hence inhibiting β secretase and γ secretase or by promoting α-secretase cleavage can reduce Aβ load [29].

4.3.1.1. β secretase inhibitors/modulators

β secretase (BACE1) also termed as Asp2, and memapsin 2 is transmembrane aspartic protease comprising of 501 amino acid closely related to the pepsin family of aspartic proteases. BACE1 is the key enzyme involved in the formation of Aβ (1-42) peptide fragment in the amyloidogenic pathway. Scientific evidences illustrated that inhibition of BACE1 effectively reduced 90% Aβ production in cerebrospinal fluid (CSF) in human. BACE1 in addition to APP processing are involved in other biological function such as processing neuregulin -1 involved in maintaining synaptic plasticity, neurogenesis, so inhibition of BACE1 might cause severe secondary effects [30,31]. Second major limitation is poor oral bioavailability and obstacles like blood brain barrier permeability and efflux system P-glycoprotein, which acts as hurdle for the entry of BACE1 inhibitors in to brain. Current researches are focusing on selective BACE 1 modulators, which blocks APP processing without interfering its other signaling pathways [32]. Structure based design has led to identification of several peptide and nonpeptidomimetic compounds with BACE 1 inhibitory/modulating activity, which are still under preclinical and clinical trials. KMI-429 when administered in to the hippocampal region of APP transgenic mice significantly reduced Aβ production [33]. BACE1 inhibitor CTS-21166 reported to reduce the level of human plasma Aβ is under phase I clinical trials [34]. MK8931 (Verubecestat - Merck laboratories) entered in to Phase II clinical trials in 2012 effectively reduced the Aβ levels in human CSF., however it was discontinued due to lack of cognitive and clinical efficacy in mild to moderate AD patients (Kennedy et al., 2016). Similarly, AZD3839 from AstraZeneca and LY2811376 from Eli Lill, which entered in to phase IIa/b clinical trials in 2012, ended in 2013 due to anamolous finding in hepatic biochemical parameters of participants [35,36]. Ultimately the next move will be to develop inhibitors with better pharmaceutical properties and well defined clinical trials to rescue cognitive decline in patients with AD.

4.3.1.2. γ- secretase inhibitors/ modulators

γ Secretase is a nucleoprotein complex comprising four different proteins, among which Presenilin PS-1 and PS-2 are involved in the cleavage of α/β secretase cleaved fragments. As γ-secretase acts as therapeutic target in AD, a plethora of γ-secretase inhibitors (GSIs) have been developed that effectively inhibit γ-secretase cleavage of APP in humans [37]. Moreover γ-secretase in addition to APP are also involved in processing Notch receptor 1 necessary for

cell growth and development, so inhibition of γ secretase causes notch-related side effects hampering its pharmacological action. Current scientific investigation focuses on search for GSI with oral bioavailability, BBB permeability and substrate specificity [38]. Semagacestat (LY-450139) the potent γ-secretase inhibitor, decreases the generation of Aβ in concentration dependant manner in CSF of the healthy volunteers. However phase III clinical trial with semagacestat at higher dose (140 mg) was discontinued due to its unfavorable effects on cognition and brain function when compared to control due to the inhibition of Notch signaling pathway [39]. Other side effects such as weight loss, increased incidence of skin cancer and high risk of infection were also observed [40,41]. BMS-708163 (Avagacestat; Bristol-Myers Squibb, New York, NY, USA) a GSI showed decrease in level of CSF Aβ 40 and 42, following daily intake of 100 mg [42]. Phase II clinical trials with Avagacestat (100 and 125 mg) was interrupted due to its lack of efficacy in cognitive enhancement and adverse effects in gastrointestinal tract and skin [43]. Administration of LY450139 di-hydrate for 6 weeks in about 70 patients during RCT decreased the plasma Aβ 1-40 level with no significant toxicity [44]. Mayer et al. [45] identified two notch sparing GSIs Begacestat BMS-708163 and ELN-475516, which lowered the Aβ level in transgenic mice Tg257 mice at dosage of 100 mg/kg bw. Clinical trials with γ - secretase inhibitors are closely scrutinized because these agents might affect other protein like Notch causing deleterious effect in gastrointestinal tract and thymus. To avoid adverse effects, investigations are underway for search of γ - secretase modulators (GSM), which modulates the PSEN1 and 2 proteins, with notch sparing activity, BBB permeability without affecting other signaling pathway. Several nonsteriodal anti-inflammatory drugs (NSAIDs) such as ibuprofen, sulindac, indomethacin and flurbioprofen, which exhibited cylooxygenase (COX) inhibitory activity also showed decline in the level of Aβ (1-42) peptide under *in vitro* and *in vivo* condition [46]. Tarenflurbil (or R-flurbiprofen), a NSAID devoid of COX inhibitory activity acts as GSM, reducing Aβ level in preclinical studies, however Phase III clinical trials showed negative effect due to its low potency and brain penetration difficulty [47] CHF 5074 another NSAID devoid of COX inhibition with GSM activity, on chronic treatment in AD transgenic mice model system reduced brain β- amyloid burden, associated microglia inflammation and attenuated spatial memory deficit [48]. Phase I clinical studies with 144 volunteers reported CHF 5074 as safe and tolerable drug, but caused mild diarrhea. Similarly, Phase II was performed in 96 patients with amnestic / nonamnestic mild cognitive impairment (MCI) and the results of the study showed enhancement in cognitive function and memory [49]. Naturally occurring NSAID NIC-15 also known as pinitol a cyclic sugar alcohol, which modulates γ - secretase activity, reduced Aβ load, improving cognitive function, without affecting Notch signaling pathway in preclinical AD model system [50]

4.3.1.3. *α*-secretase activator

α-secretase a disintegrin and metalloproteinase (ADAM) cleaves at L688 residue lo-

cated within the Aβ peptide sequence preventing Aβ formation and its cleavage product sAPP α exhibits neuroprotective potential [51]. Mounting evidences indicated that activation of non-amyloidogenic pathway by stimulating α- secretase activity is one of the promising therapeutic strategy for the treatment of AD. Some potential therapeutics and lead compounds such as benzolactam derivative, TPPB [(2S,5S)-(E,E)-8-(5-(4-(trifluoromethyl)phenyl)-2,4-pentadienoylamino) benzolactam] and green tea polyphenol (-)-epigallocatechin-3-gallate activates α-secretase shifting towards nonamyloidogenic pathway reducing the level of Aβ in brain [52]. Etazolate (EHT 0202, ExonHit Therapeutics, Paris, France) a GABA receptor modulator stimulates the neurotrophic α-secretase attenuating Aβ induced neuronal death providing symptomatic relief for AD. Phase II clinical trials of EHT0202 with 159 randomized patients with mild to moderate AD was found to be safe, generally well tolerated except the fact it cause adverse events in the central nervous system at high dose [53]. Drug showed no significant difference in cognitive function between the treated and control group, which led to the discontinuation of drug [54]. Selective monoamine oxidase inhibitor selegiline slowed down the progression of AD by enhancing the activity of α-secretase via a protein trafficking related mechanism [55]. Atorvastatin the lipid lowering drug used to treat AD induced the activation of α-secretase [56]. PRX-03140, a serotonin type receptor (5-HT4) agonist stimulated α-secretase activity improving cognition in AD patients in phase II clinical trials, which was terminated as results were not declared (http://clinicaltrials.gov/show/NCT00693004). Bryostatin, a powerful PKC modulator showed increased sAPP α level in Phase II clinical trials indicating enhanced activity of α secretase activity [57].

4.3.2 Antiamyloid therapy

4.3.2.1. Compounds with antiaggregation potential

The production of Aβ from APP and its aggregation to toxic oligomers, protofibrils and mature plaques are the crucial step in the pathogenesis of AD [29]. Based on these facts, recent investigation focuses on identifying compounds, which prevent the aggregation of Aβ and disaggregates the preformed mature plaques [58]. 3-amino-1-propaneosulfonic acid (3-APS, Alzhemed, tramiprosate) designed as antagonist to prevent the interaction of Aβ with glycosaminoglycans, which promotes Aβ aggregation showed negative results in Phase III clinical trials [59]. Assessment of clinical efficacy, safety and disease modification of tramiprostate in mild to moderate AD showed slowing down of decline in Alzheimer's disease cognitive scale with no effect in clinical dementia illustrating the clinical inefficacy of tramiprosate for the treatment of heterogeneous dementia [60]. Colostrinin a proline-rich polypeptides distributed in ovine, bovine, and human colostrum inhibited aggregation of Aβ and its neurotoxicity under *in vitro* condition, improved cognitive function in AD mice model system, however phase II clinical trials showed only mild improvement in patients with mild AD [61]. Oral administration of scyllo-inositol (ELND005) halted the aggregation of Aβ reducing its toxicity in mouse

hippocampus. Phase II clinical trials with ELND005 for 18 months did not meet the primary clinical efficiency outcomes [62]. Metal chelating compounds such as 8-hydroxiquinolines (8-HQ), clioquinol and PBT2 blocks the interaction of metals with brain Aβ peptide attenuating oxidative stress mediated damage restoring cellular metal homeostasis. However, Phase I and II clinical trials lack the clinical efficacy of drug [63]. Sulfated glycosaminoglycan mimetic tramiprosate (NC-531) attenuated Aβ induced toxicity in cell lines and reduced amyloid plaques in transgenic mice. Phase II clinical trials in about 58 patients with mild to moderate AD showed reduction in Aβ (1-42) level in CSF in concentration dependant manner. Moreover the treatment was well tolerated with no adverse effect. Two RCT in phase III for 18 month to evaluate the safety and efficacy of drug are underway [59].

4.3.2.2. Compounds promoting removal of amyloid plaques

As deposition of amyloid plaques in the synaptic junction impairs the synaptic plasticity leading to neuronal death, clearance of amyloid plaques might act as one of the promising therapeutic strategies for AD. Different strategies used for disaggregation of plaques are

- Activation of multiple proteases enzyme, which degrade amyloid plaques such as neprilysin, insulin degrading enzyme, plasmin, endothelin converting enzyme, angiotensin converting enzyme and metalloproteinases, which are effective only under *in vitro* condition and not under clinical trials due to lack of specificity [64].

The transport of Aβ between the CNS and pheripheral circulation is mediated by (i) apoplipoprotein which transport Aβ from the blood to brain, (2) low-density lipoprotein receptor-related protein (LRP-1), which increases Aβ outflow from the brain to the blood, (3) receptor for advanced glycation end products (RAGE), which facilitates the transport of Aβ across the blood-brain barrier (BBB). The ultimate aim of the treatment is to reduce the amyloid load by regulating the transport of Aβ between CNS and peripheral circulation. Azeliragon is a small molecule inhibitor of RAGE, which was discovered by TransTech Pharma as TTP488 and licensed to Pfizer as PF-04494700. Phase II clinical trials in 67 people suffering from mild to moderate AD for 10 weeks showed safe and well tolerated results in treatment groups [65]. Phase II clinical trials with oral administration of TTP488 (60 mg for 6 days followed by 20 mg/day; 15 mg for 6 days followed by 5 mg/day) in 399 patients of mild to moderate AD for 18 months showed negative results with respect to safety and efficacy, hence the usage of drug was halted [66]. In April 2015, Phase III clinical trials of azeliragon (5mg/day daily) was initiated in 800 patients with mild to moderate AD for 18 months and yet to complete in 2018.

- Immunotherapy with active (Aβ (1-42) peptide) and passive immunisation (Anti Aβ antibodies) acts as one of the novel approach for the clearance of amyloid plaque. Active immunisation with synthetic full length Aβ (1-42) peptide AN1792 with adjuvant in phase II clinical trial decreased amyloid load, but caused cerebral inflammation like meningoencephalitis, led

to discontinuation of the drug [67]. A second-generation vaccine was designed with Aβ (1-6) to reduce nonspecific immune response. CAD106 (Novartis) was the first second generation vaccine, which reached clinical phase of development [68]. ACC-001 (Janssen) has recently completed two phase II trials (NCT01284387 and NCT00479557) with an additional phase II trial still ongoing (NCT01227564). Other vaccines like tetra-palmitoylated Aβ(1-15) reconstituted in liposome (ACI-24), MER5101 and AF205 are currently used in various stages of preclinical studies [69,70]. Passive immunisation deals with intravenous administration of monoclonal or polyclonal antibodies directed against Aβ. Benefit of passive immunization when compared to active immunisation is that no proinflammatory T cell mediated immune response was observed. Experimental evidence of passive immunisation of transgenic animals illustrated reduced cerebral amyloid load with improvement in cognitive function. Bapineuzumab and solanezumab are monoclonal antibodies against Aβ (1-6) and Aβ (12-28), which entered into phase III clinical trials, however bapineuzumab declined the brain amyloid plaques in the CSF with no significant improvement in cognitive function [71,72] Administration of 400 mg of solanezumab for 80 weeks in patients with mild to moderate AD showed improvement in cognition in mild AD [39]. Eli Lilly and Company (NYSE: LLY) performed EXPEDITION phase III clinical trials of solanezumab with 2100 patients with mild to moderate AD in 2015 for 18 months, which was discontinued in November 2016 as it did not meet the primary endpoint in people with mild dementia due to AD (NCT01900665 ; INDIANAPOLIS, Nov. 23, 2016 /CNW/ -- Eli Lilly and Company (NYSE: LLY). Several other monoclonal antibodies, which recognizes Aβ oligomeric and fibrillar species such as MABT5102A (Crenezumab, Genentech, San Francisco, California, USA), PF-04360365 (Ponezumab, Pfizer), R1450 (Hoffman-LaRoche, Basel, Switzerland), GSK933776A (GlaxoSmithKline, London, UK) which are effective in clearing amyloid plaques have successfully completed Phase I clinical trials related to safety [66,73,74] . Crenezumab (MABT5102A) a humanized monoclonal antibody with IgG4 backbone was subjected to phase II clinical trial to evaluate the safety and efficacy in E280A **autosomal dominant** mutation of PSEN1 (NCT01998841), which failed to reach its primary endpoints [75]. Hoffmann-La Roche initiated Phase III clinical trials in 750 people with MCI or prodromal AD (NCT02670083) termed as CREAD, which is expected to run until 2020 [76]. Ponezumab (PF-04360365) was subjected to two phase 2 clinical trials with 198 (NCT00722046)and 36 patients (NCT00945672) of mild to moderate AD which showed no effect on primary endpoints such as change in CSF Aβ burden, hence it was discontinued. Phase II open label trials of GSK933776A was performed with different doses (1,3 or 6 mg/kg bw) in patients with mild to moderate AD in Germany and Sweden. Trial showed decrease in CSF Aβ level with increase in plasma Aβ level and no significant change in CSF tau protein level [77]. However there are no current plan of developing the drug for the treatment of AD. Gantenerumab (R1450 - Hoffman-LaRoche, Basel, Switzerland) human IgG1 antibody specific to conformational epitope on β-amyloid fibres binds to amyloid plaque recruits microglial cells inducing phagocytosis mediated amyloid plaque clearance. Phase 2 clinical trial

(NCT01224106) was carried out with different doses of gantenerumab in 360 participants, which was later expanded to Phase2/3 study in 799 people (Roche) and this study was discontinued due to lack of efficiency in primary and secondary endpoints. Phase III clinical trials (NCT02051608) with 1000 patients of mild AD was initiated by Roche, which is actively ongoing till 2018 [78]. In addition, other passive immunotherapies mostly in phase I clinical development include NI-101, SAR-228810, and BAN-2401 [70,79,80]. SAR228810 a monoclonal antibody directed primarily against soluble protofibrillar and fibrillar species of Aβ. Phase I clinical trials was carried out in patients with mild to moderate AD to assess the safety, tolerability and the pharmacokinetic properties of SAR228810, which was discontinued due to lack of reports (NCT01485302). Gammagard a small fraction of polyclonal antibodies against Aβ peptide, which possess immunomodulatory and microglial cells mediated amyloid clearance, was reported to be safe and effective in phase II clinical trials [81]. Phase III trials in gammagard was carried out in two doses 400 mg/kg and 200 mg/kg doses for 18 months in 390 patients with mild to moderate AD. Primary endpoints showed no difference between study drug and placebo. Benefits were observed in higher dose treatment in moderate AD with insufficient power in other AD patients. Baxter international terminated phase III clinical trials of gammagard, which was started in 2012 due to adverse effects and inefficient results (NCT00818662; May 2013 press release).

4.4. Tau based therapeutics

Tau proteins are highly soluble microtubule stabilizing protein present abundantly in the axonal region of the neurons essential to maintain the morphology of neurons. Upregulated expression of kinase enzyme like CDK5, GSK3β, Fyn, stress activator protein kinase JNK, p38 and mitogen activated protein kinase and downregulated expression of phosphatase leads to hyperphosphorylation of tau protein, which tends to aggregate forming NFT [82,83]. Formation of NFT affects the microtubule binding capacity leading to neuronal death. Development of drugs, which inhibit phosphorylation and aggregation of tau protein, microtubule stabilizing drugs and immunomodulation are the possible disease modifying strategy for the treatment of AD [84].

4.4.1. Drugs attenuating tau hyperphosphorylation

As imbalance between the expression of phosphatase and kinase leads to hyperphosphorylation of tau protein, drug, which modulate these expression can act as potential therapeutic drug for AD. Among the kinases, GSK3β (Glycoge synthase kinase), CDK5 (serine/threonine cyclin dependent kinases) were the key enzymes involved in the tau pathology, hence inhibition of these kinases can prevent tau hyperphosrylation. Lithium exhibited GSK3β inhibitory activity and Aβ peptide accumulation in AD transgenic mice model and in MCI patients; however toxicity in adults limits its usage [85]. Compounds like pyrazolopyrazines, pyrazolopyri-

dines, the aminothiazole AR-A014418, and sodium valproate exhibited GSK3β inhibitory activity under *in vitro* and *in vivo* condition and the clinical trial is ongoing [86]. Tideglusib, an irreversible inhibitor of GSK3β showed negative results in phase II clinical trials in mild to moderate AD. Roscovitine and flavopiridol showed potent CDK5 inhibitory activity under in vitro and in vivo model system, clinical trials are yet to be carried out [87].

Activation of phosphatase also acts one of the possible drug targets, till date only one protein phosphatase 2 (PP2A)agonist has been developed. Experimental evidences reported that sodium selenite (VEL015) effectively reduced tau phosphorylation under in vitro condition and improved cognitive function in AD mouse model system. Sodium selenite is under phase II clincical trails in Australia (ACTRN12611001200976) [88].

4.4.2. Inhibitors of tau aggregation

Several compounds inhibiting tau aggregation were identified under in vitro condition. Methylene blue and its derivatives showed promising results disrupting the aggregation of both tau protein and Aβ peptide, attenuating oxidative stress and improving mitochondrial function in AD model system [89]. Rember the first generation of methylene blue stabilized AD progression in clinical trials for 50 weeks. Positive results led to the development of second generation of methylene blue, TRx 0237 which not only attenuated tau protein aggregation, but also dissolved NFT [90] . Three phase III trials have been carried out with TRx0237. First phase III study (NCT01689233) deals with administration of single dose (200 mg/day) to placebo in 800 patients with dementia or AD mild enough to score above an MMSE of 20. Trial began in 2012, its outcome have not been presented yet. Second Phase III trial (NCT01689246) deals with comparison of 150 and 250 mg/day dose in 891 patients with mild to moderate AD with MMSE of 14 or higher. Clinical, cognitive and safety outcomes showed negative results. Third Phase 3 clinical trials (NCT01626378) was carried out in 180 patients with fronto-temporal dementia administrating 200 mg/day and the outcome was observed to be negative. Overall all the phase III clinical trials with TRX0237 showed negative results in terms of safety and cognitive outcomes [91], https://clinicaltrials.gov/ct2/show/NCT02245568.

4.4.3. Stabilizers of microtubule

Microtubule stabilization may provide similar effect as that of drugs interfering tau hyperphosphorylation and aggregation. Paclitaxel an anticancer drug have been reported for microtubule-stabilizing ability, however inability to cross BBB and adverse side effects limited its usage in AD [92,93]. Another anticancer drug TPI 287 a derivative of taxane stabilized the microtubules by binding to tubulin . TPI287 has entered into clinical trials to assess its safety in mild to moderate AD patients (ClinicalTrials.gov identifier: NCT01966666) which is under way [94,95]. MT-stabilizing agent from the taxane family, TPI-287, has entered clinical testing

in patients with AD and PSP/CBD (ClinicalTrials.gov identifier: CT02133846). Epothilone D a microtubule-stabilizing compound, which showed improvement in axonal transport, reduced tau neuropathology and hippocampal neuronal loss in AD model system, was discontinued from drug development after its failure in clinical trials [22].

4.4.4. Anti-Tau immuntherapy

Active and passive immunization to prevent the aggregation of tau protein and dissolving the preformed NFT is one of the current areas of research to prevent tau pathology. AADvac-1 (Axon neuroscience) a synthetic peptide derived from the tau sequence was coupled with adjuvant keyhole limpet hemocyanin and was subjected to preclinical studies which showed good preclinical safety profile for a period of 3 months for rats, rabbits and dogs. Phase I clinical trials of AADvac1 was carried out in 30 patients for 12 weeks in which 24 patients were assigned as AADvac 1 group and six as placebo groups (NCT01850238). No cases of meningoencephalitis or vasogenic oedema were observed, except two patients who withdrew due to adverse events such as a viral infection followed by epileptic seizure. Results showed positive IgG response in 29 patients illustrating the safety profile and excellent immunogenicity, in Phase I clinical trials [96]. To substantiate the clinical efficacy of AADvac1, phase II clinical trial (24 months) was initiated in 185 patients with mild to moderate AD on March 2016 and it is slated to run up to February 2019 (clinical trial no. NCT0257952) .

4.5. Antinflammatory drugs

Biochemical and neuropathological studies in the brain of AD patients provided clear evidence of activation of inflammatory pathway and its destructive effect. In AD, deposition of amyloid plaques in the synaptic junction activates microglial cells and reactive astrocytes promoting enhanced expression of phospholipase A2 with subsequent release of proinflammatory mediators leading to inflammation mediated neuronal death. Evidences showed that long term usage of anti-inflammatory drugs such as NSAIDs reduced the risk of AD [97]. Inflammation and AD are interlinked as certain components of this molecular machinery promote AD pathology, while other components exhibit protective effect to the neuron via amyloid plaque clearance. Despite of successful preclinical studies of glucocorticoid therapy, hydroxychloroquine, and non-steroidal anti-inflammatory drugs with AD models system, results of clinical trials are still disappointing. The challenge with anti-inflammatory drug is to find ways of fine tuning inflammation to delay, prevent, or treat AD [98].

Certain NSAIDs have been reported to modulate γ-secretase activity decreasing the production of Aβ (1-42), which has been prevented from clinical trials due to toxicity [99]. Another possible mode of action of NSAIDs is to block COX-2 expression in brain, as COX-2 is upregulated in AD brain mainly in pyramidal neurons in the cerebral cortex and the hippocampal formation [100]. NSAIDS such as ibuprofen, indomethicin, and sulindac sulphide reduce

the level of Aβ1-42 peptide up to 80% in cultured cells [101]. Ibuprofen treatment in AD mice model system showed reduction in amyloid plaque in the cortex attenuating microglial activation in the mice [102]. Neurons treated with COX-1 inhibitors, such as ibuprofen and acetyl salicylic acid, were observed to be more resistant to the effects of Aβ than neurons that were treated by COX-2 inhibitors [103]. Treatment with COX-1 and COX-2 inhibitors reduced the production of prostaglandin E2. NSAIDs may also function by activating the peroxisomal proliferators-activated receptors (PPARs) which act negatively inhibiting the transcription of proinflammatory genes. *In vitro* studies illustrated that PPARα agonist inhibited microglial activation and proinflammatory mediators like NOS, COX-2 and IL-6 [104]. RCT of COX-2 inhibitor rofecoxib and naproxen showed no change in cognitive decline in patients with mild to moderate AD. Unfortunately clinical trials of NSAID in AD patients were not fruitful, particularly in the case of COX-2 inhibitors [105]. Recent hypothesis illustrated that NSAIDS reduces the incidence of the disease and are ineffective after the incidence of disease. Glucocorticoids like prednisone inhibited Aβ induced chemokines and cytokines in the CNS of animal models; however RCT showed no difference in cognitive decline in AD patients [106]. Among the plant derived polyphenols, flavonoids play crucial role in down regulating proinflammatory mediators of innate immune system [107]. Green tea rich in flavonoids like EGCG modulated T- cell response, NF-κB signaling, TNF-α production in vascular endothelial cells and improvement in cognitive function in mice model system. Results were inconsistent with the clinical trial reports, in which no significant improvement in cognition was observed in AD patients [109]. Recent report revealed that tumour necrotic factor (TNF) one of the glial transmitters play key role in glial activation mediating inflammation and synaptic dysfunction. Administration of FDA approved TNF inhibitor Etanercept (used for rheumatoid arthritis) for 6 months in 15 patients with AD provided sustained improvement in cognitive function for patients with AD. Nevertheless, etanercept merits further study in RCTs [110].

4.6. Antioxidants in AD therapy

Brain is highly vulnerable to oxidative insults because it is rich in polyunsaturated fatty acids, high demand for oxygen and relative scarcity for antioxidant systems. Aβ peptide together with altered mitochondrial function and increased level of transition metal ions in brain are the potential source of oxidative stress in brain. In AD primarily oxidative stress is induced by the Aβ aggregation, which is considered as crucial factor in the early pathogenesis of AD, leading to neuronal cell injury and death [111]. Epidemiological investigations revealed that intake of food rich in antioxidants reduced the incidence of AD [112]. Antioxidant therapy includes direct acting antioxidants (ROS scavenging and chain breakers) and indirect antioxidants (metal chelators) which are further classified as enzymatic and nonenzymatic antioxidant system [113]. Naturally occurring antioxidants such as Glutathione (GSH), ascorbate (vitamin C), α- tocopherol (vitamin E), β-carotene, NADPH, uric acid, bilirubin, sodium selenite, di-

hydrolipoic acid, melatonin and plasma protein thiol are direct acting antioxidants which attenuated ROS mediated oxidative stress in AD model system [114]. Other antioxidant such as mitoquinone, Ginkgo biloba and natural polyphenols like green tea, blue berries, curcumin, ω3 fatty acids, folate, vitamin B_6 and vitamin B_{12} supplementation showed positive results under in vivo AD model system. However clinical trials with these antioxidants showed conflicting results for AD patients. In placebo controlled trials, daily administration of Vitamin E (2000 IU for 2 years) in about 341 patients of moderate to severe AD showed significant delay in progression of AD suggesting vitamin E as prophylactic medicine [115]. High intake of vitamin E and C supplements in combination also reduced the risk of AD. But the main disadvantage of these studies are the dose of antioxidant used are low and the studies were carried out in patient who are affected by neurodegenerative diseases in which the full potency of antioxidant cannot be observed. In addition the cardiovascular risk of vitamin E reduced the usage of vitamin E for AD. Most commonly studied antioxidant curcumin, which showed positive results under in vitro conditions, is under clinical trials with AD patients. Current research focus on developing antioxidant that target the mitochondria such as lipophilic triphenylphosphonium cation conjugated to an antioxidant moiety, such as the ubiquinol moiety of coenzyme Q (mitoquinone; MitoQ), α-tocopherol (MitoVitE) [116,117]. MitoQ is a recycling antioxidant which can revert back to its active form after ROS neutralization, similarly SOD mimetic MitoSOD and MitoTEMPOL, and peroxidase mimetic MitoPeroxidase exhibit antioxidant activity [118, 119]. Szeto-Schillertetra peptides a novel class of small-cell permeable peptide concentrates in the inner mitochondrial membrane and protects against mitochondrial oxidative damage attenuating further ROS production [120]. Antioxidant therapy might be beneficial in early phase of AD or people with risk of AD incidence. BBB permeability acts as major hurdle for the smaller antioxidant molecules, hence naturally occurring small antioxidant molecules with ability to cross the BBB offers much promise for the treatment of AD.

4.7. Cholesterol lowering drugs

Human brain contains approximately 25% of total body cholesterol which are distributed in myelin sheath, glial cells (astrocytes and microglia) and in other parts of neurons. Cholesterol plays key role in signal transduction, neurotransmitter release, synaptogenesis, membrane trafficking [121]. Increased cholesterol level enhances BACE-1 activity leading to accumulation of Aβ 1-42 peptide forming amyloid plaques. In addition reports suggested that cholesterol alters the conformation of Aβ leading to the generation of amyloid seeds. ApoE is the lipid carrier protein in the CNS released by astrocytes to supply neurons with cholesterol and it exist in three isoforms. ApoE2 and ApoE3 are involved in lipid clearance, recycling particularly after injury than ApoE4. Increased expression of ApoE4 promotes the aggregation of Aβ leading to AD [122]. Enhanced level of ApoE4 together with Aβ impairs the cholesterol transport from the astrocytes to neuron affecting the neurotransmission [123]. Evidences il-

lustrated that intake of hypocholestermic drugs reduced the risk of developing AD. Statin a hypocholestermic drug exhibited safe efficacy during long term treatment and also exhibited delayed onset of AD in mice model system [124]. Statins reduces the Aβ level by enhancing APP metabolism by α -secretase activity [125]. Clinical trials of atorvastatin with 63 individual with normal cholesterol levels and mild to moderate AD exhibited clinical benefit for a period of 6 months and 1 year. Large scale Phase III clinical trials with atorvastatin in mild to moderate AD is under progress U.S. National Institute on Aging (NIA) sponsored conducted survey on cholesterol lowering agent simvastatin to slow the progression of AD in mild to moderate AD patients [126,127].

4.7. Other treatment strategies

- Presence of activated astrocytes around the Aβ plaques led to the development of astrocyte modulating agent to reduce AD pathology. Arundic acid (ONO-2506) reduced infarct size, enhanced neurologic outcome, prevented motor abnormalities and protected the dopaminergic neurons in AD and parkinson's mice model system by modulating the activation of astrocytes. This compound is under phase II clinical trial with mild to moderate AD [128,129].

- Increased concentration of sulfur containing amino acid homocysteine was observed in AD patients, which will hamper the DNA repair in neurons making the neurons more vulnerable to Aβ induced damage. Therefore lowering of homocysteine might reduce the pathology of AD. Clinical trial on homocysteine lowering vitamin combination in AD is under progress [130]

- Neuronal growth factor play significant role in maintaining neuronal integrity, lack of endogenous NGF leads to memory deficit in AD. Hence treatment with NGF and NGF-related agents were attempted to enhance the neuroprotective effect [131]. But the major limitation with exogenous NGF administration is BBB permeability, which acts as a significant challenge for AD therapy. Recently surgical implantations of NGF expressing cells (gene therapy) or administration of agents, which potentiate production of NGF were carried out [132]. Neurotrophic enhancing agent like xaliproden (SR-57746) cerebrolysin (FPF 1070), activated the endogenous neurotrophin synthesis including BDNF and NGF, enhanced the synaptic regeneration, ameliorated memory deficit in APP transgenic mice [133,134]. RCT investigation showed cerebrolysin infusions significantly improved the activities of daily living and cognitive function, while xaliproden is under phase III clinical trials with mild to moderate AD patients [135,136]. Results of phase I study on genetically modified, autologous fibroblasts producing human NGF implanted into the forebrains of six patients showed no post surgical adverse effects and moreover improvement in cognitive function was observed [137]. Clinical investigation of this approach is expected to continue.

5. Conclusion

Multiple evidences suggest AD as complex multifactorial disorder caused by several etiological factors and multiple biochemical pathways, which prompted the search for disease modifying drugs for AD therapy. This review summarizes the various therapeutic strategies available and under research for the treatment of AD. For the past 20 years, amyloid hypothesis have been considered as pathogenic pathway and enormous number of studies have been carried out on inhibition and removal of Aβ and senile plaques. Unfortunately, the amyloidogenic approaches have failed to demonstrate defects that clearly contribute to cognitive decline in AD. Mechanism underlying the pathogenesis of AD must be assessed before the development of disease modifying compounds. Understanding the events occurring in the synapse and associated microglial cells and the relationship between tau and Aβ will be instrumental in developing successful disease modifying drugs. Novel pharmacotherapies should not be limited to amyloid cascade hypothesis; it should be multitargeted focusing on other pathways involved in the pathogenesis. Early diagnosis, nutritional diet coupled with combinatorial pharmacotherapy targeting multiple pathways and change in life style will help in successful eradication of AD. As BBB acts as a major obstacle for the treatment of AD recent research focuses on improving drug delivery systems such as nanoencapasulation and microemulsion to enhance the bioavailability and blood brain permeability.

Table 1: Disease modifying drugs under clinical trials for the Alzheimer's therapy

S. No:	Mode of action	Modulating Agents/compounds	Clinical trials	Results
	Beta secretase inhibitors	Lilly AZD 3293 (Astrazeneca)	Phase II/III	
		CTS-21166 (CoMentis)	Phase I	+
		E2609 (Eisai/Biogen Idec)	Phase II	
		HPP854 (High point)	Phase I	
		LY2886721 (Lilly)	Phase II	-
		MK-8931 (Merck)	Phase II/III	-
		PF-05297909 (Pfizer)	Phase I	
		RG7129 (Roche)	Phase I	
		TAK-070(Takeda)	Phase I	
		VTP-37948 (vitae/Boehringer Ingelheim)	Phase I	
	Gamma secretase inhibitors	Semagacestat	Phase III	-
		Tarenflurbil	Phase III	-
		LY450139 (Avagacestat)	Phase II	-
	Gamma secretase modulators	Ibuprofen, sulindac, indomethacin, and R-flurbiprofen (Tarenflurbil)		
		NIC5-15		
	Alpha secretase modulators	Etazolate	Phase II	-

	Nonsteroidal inhibitory of cyclooxygenase activity (NSAIDs)	CHF5074	Phase IIa	+
	Drugs attenuating aggregation of Aβ Peptide/Anti Aβ immunotherapy	Glycosaminoglycans 3-amino acid, 1-propanesulfonic synthetic (3APS, Alzhemed, tramiprosate)	Phase III	-
		Colostrinin	Phase II	+/-
		Scyllo-inositol compound (ELND005)	Phase II	+/-
		PBT1 (clioquinol) and PBT2 (metal chelators)	Phase IIa	+
		Active immunization (vaccination)		
		AN-1792	Phase II	-
		CAD-106	Phase II	+
		ACC-001	Phase II	
		MER5101, AF205	Preclinical trials	
		Passive immunization (Monoclonal antibodies)		
		Bapineuzumab	Phase III	-
		Solanezumab	Phase III	-
		Crenezumab (MABT5102A)	Phase II	-
		Gammagard	Small number of AD patients	-
		PF-04360365 (Ponezumab), NI-101, SAR-228810, GSK933776A, and BAN-2401	Phase I Phase II	+ -
Modulators of tau pathology				
	GSK 3β inhibitor	Lithium Tideglusib Sodium selenite (VEL015)	Phase I Phase II Phase II	+ -
	CDK5 inhibitor	Roscovitine and flavopiridol	Preclinical trials	+-
	Immunotherapy	AADvacI vaccine	Phase I	Ongoing
	Inhibitors tau aggregation	Methylene blue derivatives - RemberTM, TRx0237	Preclinical trials Phase III	+ -
	Microtubule stabilizers	Paclitaxel Epothilone D TPI 287 (taxane)	Phase I Phase III	- -
	Anticholinesterase inhibitors	Donepezil, Rivastigmine, Galanthamine Ladostigil (TV3326)	FDA approved drugs	-
	N-methyl-D-aspartate antagonist	Memantine Dimebon	Treatment of mild to moderate AD Phase III	+

	Antioxidants	α-Tocopherol	Phase III	+
	Nicotinic receptor activator	AZD1446/TC-6683	Phase II/IIa/ IIb	
	Nerve growth factor	CERE-110	Phase II/IIa	

+ = Positive results, +/- = Partially positive, - = Negative results.

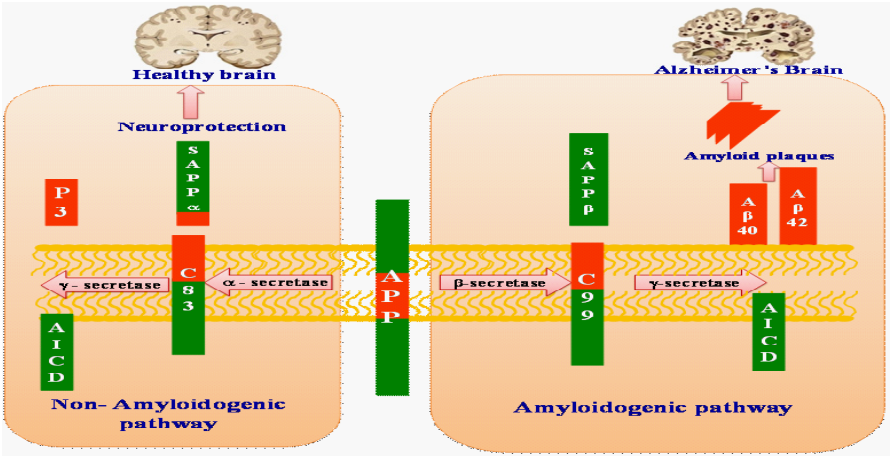

Figure 1: Sequential cleavage of Amyloid precursor protein

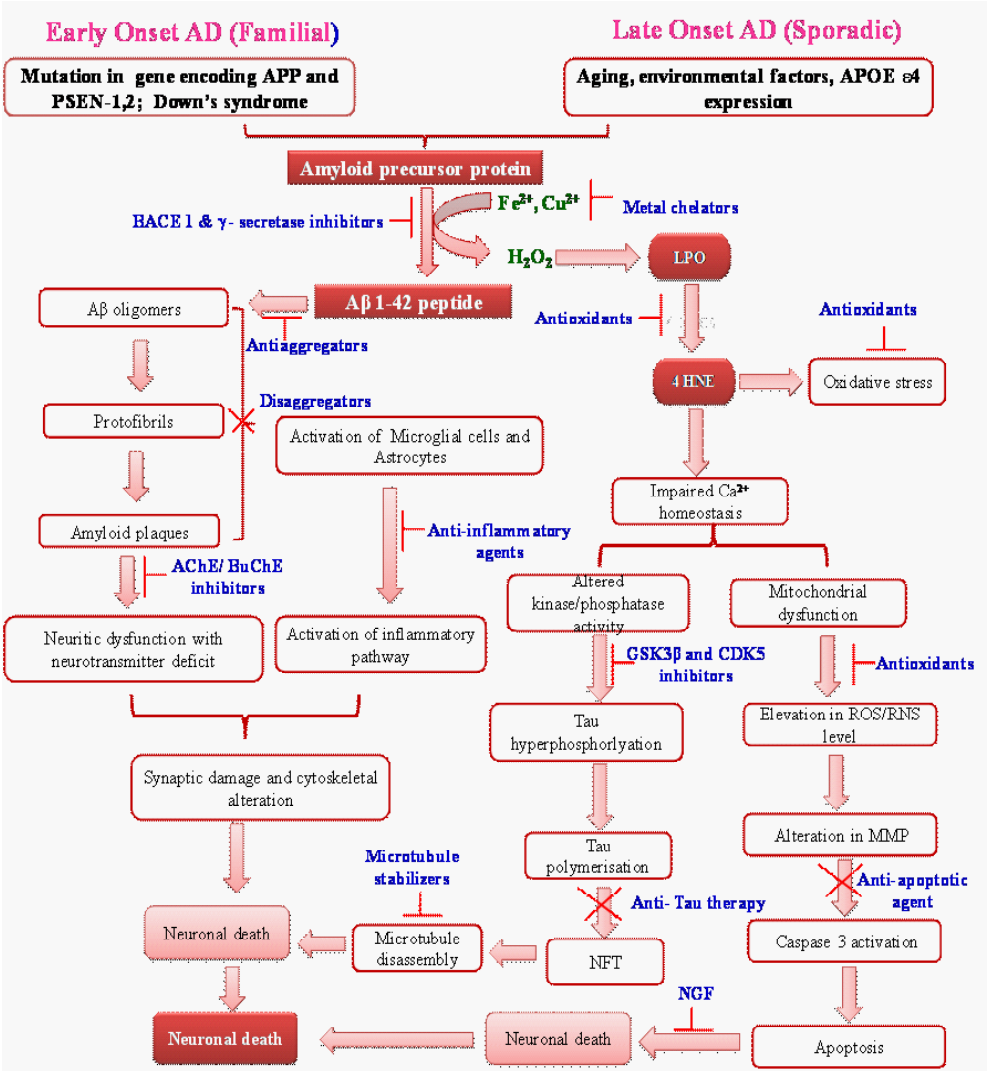

Figure 2: Pathogenesis of AD and Therapeutic strategies for AD

6. References

1. Gu Y, Brickman AM, Stern Y et al. (2015). Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology 85(20), 1744-1751.

2. Yiannopoulou KG, Papageorgiou SG (2013). Current and future treatments for Alzheimer's disease. Ther. Adv. Neurol. Disord. 6(1), 19–33.

3. Prince M, Wimo A, Guerchet M, Ali GC, Wu Y, Prina M (2015). World Alzheimer Report 2015: The global impact of dementia. An analysis of prevalence, incidence, costs and trends. Alzheimer's disease International, London.

4. Alzheimer's Association (2016). 2016 Alzheimer's disease Facts and Figures. Alzheimer's & Dementia, 12(4).

5. Lanoisele´e H-M, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, et al. (2017). APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med 14(3): e1002270

6. Bu G (2009). Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. Nat. Rev. Neurosci. 10: 333–344.

7. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological Alterations in Alzheimer Disease. Cold Spring Harbor Perspectives in Medicine: 2011; 1(1): a006189

8. Persson T, Popescu BO, Cedazo-Minguez A (2014). Oxidative Stress in Alzheimer's Disease: Why Did Antioxidant Therapy Fail? Oxid. Med. Cell. Longev. 2014, Article ID 427318, 11 pages.

9. Chow VW, Mattson MP, Wong PC, Gleichmann M (2010). An Overview of APP Processing Enzymes and Products. Neuromolecular Med. 12(1): 1-12.

10. Kojro E, Fahrenholz F(2005). The non-amyloidogenic pathway: structure and function of alpha-secretases. Subcell Biochem 38: 105-127.

11. Selkoe DJ, Hardy J (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 8: 595–608

12. Godoy JA, Rios JA, Zolezzi JM, Braidy N, Inestrosa NC (2014). Signaling pathway cross talk in Alzheimer's disease. Cell Communication and Signaling : CCS. 12: 23.

13. Lo Vasco VR (2017). The Phosphoinositide signal transduction pathway in the pathogenesis of Alzheimer's disease. Curr Alzheimer Res. 28

14. Nunes-Tavares N, Santos LE, Stutz B et al. (2012). Inhibition of Choline Acetyltransferase as a Mechanism for Cholinergic Dysfunction Induced by Amyloid-Peptide Oligomers. JBC, 287(23) 19377–19385

15. Butini S, Brindisi M, Brogi S, et al. (2013). Multifunctional Cholinesterase and Amyloid Beta Fibrillization Modulators. Synthesis and Biological Investigation. ACS Med. Chem. Lett. 4(12): 1178-1182

16. Lushchekina S., Kots E., Novichkova D., Petrov K., Masson P (2017). Role of Acetylcholinesterase in β-Amyloid Aggregation Studied by Accelerated Molecular Dynamics. BioNanoScience 7 : 396-402.

17. Darvesh S, Cash MK, Reid GA, Martin E, Mitnitski A, Geula C (2012). Butyrylcholinesterase is Associated with β-Amyloid Plaques in the Transgenic APPSWE/PSEN1dE9 Mouse Model of Alzheimer Disease. J. Neuropathol. Exp. Neurol. 7 (1): 2–14.

18. Nordberg A, Ballard C, Bullock R, Darreh-Shori T, Somogyi M (2013). A review of Butyrylcholinesterase as a therapeutic target in the treatment of Alzheimer disease. Prim. Care Companion CNS Disord. 15(2), PCC.12r01412

19. Mehta M, Adem A, Sabbagh M (2012). New acetylcholinesterase inhibitors for Alzheimer's disease. Int. J. Alzheim-

ers Dis. 728983: 8

20. Castro A, Martinez A (2006). Targeting beta-amyloid pathogenesis through acetylcholinesterase inhibitors. Curr. Pharm. Des. 12(33): 4377-4387.

21. Blanco-Silvente L, Castells X, Saez M, et al.(2017). Discontinuation, Efficacy, and Safety of Cholinesterase Inhibitors for Alzheimer's Disease: a Meta-Analysis and Meta-Regression of 43 Randomized Clinical Trials Enrolling 16 106 Patients. Inter J. Neuropsychopharmacol. 20(7): 519-528.

22. Diaz N, Refolo L, Buxbaum JD et al. (2012). The microtubulestabilizing agent, epothilone D, reduces axonal dysfunction, neurotoxicity, cognitive deficits, and alzheimer-like pathology in an interventional study with aged tau transgenic mice. J. Neurosci. 32(11): 3601–3611.

23. Weinreb O, Amit T, Bar-Am O, Youdim MB (2012). Ladostigil: a novel multimodal neuroprotective drug with cholinesterase and brain-selective monoamine oxidase inhibitory activities for Alzheimer's disease treatment. Curr. Drugs Targets 13(4): 483-494

24. Ezza HAS, Khadrawyb YA (2014). Glutamate Excitotoxicity and Neurodegeneration. J. Mol. Genet. Med. 8: 141

25. McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. Cochrane Database Syst Rev (2): CD 003154.

26. Alva G, Cummings J (2008). Relative tolerability of Alzheimer's disease treatments. Psychiatry (Edgmont) 5: 27–36.

27. Farlow M, Alva G, Meng X, Olin J (2010). A 25-week, open label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis. Curr. Med. Res. Opin. 26: 263–269.

28. Howard R, McShane R, Lindesay J et al. (2012). Donepezil and Memantine for Moderate-to-Severe Alzheimer's disease. N Engl J Med. 366 : 893-903.

29. Cummings J (2008a). Optimizing phase II of drug development for disease-modifying compounds. Alzheimers Dement. 4(1): 15–20.

30. Vassar R, Kandalepas PC (2011). The β-secretase enzyme BACE1 as a therapeutic target for Alzheimer's disease. Alzheimer's Res. Ther. 3(3): article 20

31. Menting KW, Claassen JAHR (2014). β-secretase inhibitor; a promising novel therapeutic drug in Alzheimer's Disease. Front. Aging Neurosci. 6: 165, 2014.

32. May PC, Willis BA, Lowe SL et al. (2015). The potent BACE1 inhibitor LY2886721 elicits robust central Aβ pharmacodynamic responses in mice, dogs, and humans. J. Neurosci. 35(3): 1199–1210.

33. Asai M, Hattori C, Iwata N et al. (2006). The novel beta-secretase inhibitor KMI-429 reduces amyloid beta peptide production in amyloid precursor protein transgenic and wild-type mice. J. Neurochem. 96(2): 533-540.

34. Hey JA, Koelsch G, Bilcer G et al. (2008). Single dose administration of the β-secretase inhibitor CTS21166 (ASP1720) reduces plasma Aβ40 in human subjects. International Conference on Alzheimer's Disease (ICAD), Chicago, IL.

35.Ghosh AK, Osswald HL (2014).. BACE1 (β-Secretase) Inhibitors for the Treatment of Alzheimer's Disease. Chem. Soc. Rev. 43(19): 6765-6813

36. Folch J, Ettchetoc M, Petrovc D, Abadc S,et al. (2017). Review of the advances in treatment for Alzheimer disease: strategies for combating -amyloid protein. Neurología, 1-12

37. Wolfe MS (2012). Gamma-secretase as a target for Alzheimer's disease. Adv. Pharmacol. 64: 127–153

38. Zhang X, Li Y, Xu H, Zhang Y (2014). The γ-secretase complex: from structure to function. Front. Cell.Neurosci. 8: 427

39. Doody RS, Raman R, Farlow M et al (2013). A phase 3 trial of semagacestat for treatment of Alzheimer's disease. N. Engl. J. Med. 369(4): 341-350

40. Henley DB, May PC, Dean RA, Siemers ER (2009). Development of semagacestat (LY450139), a functional gamma-secretase inhibitor, for the treatment of Alzheimer's disease. Expert Opin. Pharmacother. 10(10): 1657-64

41. Henley DB, Sundell KL, Sethuraman G, Dowsett SA, May PC (2012). Safety profile of semagacestat, a gamma-secretase inhibitor: IDENTITY trial findings. Curr. Med. Res. Opin. 30(10): 2021-2232

42. Tong G, Wang J, Sverdlov O et al. (2012). Multicenter, randomized, double-blind, placebo-controlled, singleascending dose study of the oral γ-secretase inhibitor BMS-708163: tolerability profile, pharmacokinetic parameters, and pharmacodynamic markers. Clin. Ther. 34: 654–667.

43. Coric V, van Dyck CH, Salloway S et al. (2012). Safety and tolerability of the γ-secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease. Arch. Neurol. 69(11): 1430-1440.

44. Siemers E, Skinner M, Dean R et al. (2005). Safety, tolerability, and changes in amyloid β concentrations after administration of a γ-secretase inhibitor in volunteers. Clin. Neuropharmacol. 28: 126–132.

45. Mayer SC, Kreft AF, Harrison B et al. (2008). Discovery of Begacestat, a Notch-1-sparing gamma secretase inhibitor for the treatment of Alzheimer's disease. J. Med. Chem. 51 (23): 7348–7351.

46. Pasqualetti P, Bonomini C, Dal Forno G et al. (2009). A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease. Aging Clin. Exp. Res. 21(2): 102–110.

47. Imbimbo BP, Giardina GAM (2011). γ-secretase inhibitors andmodulators for the treatment of Alzheimer's disease: disappointments and hopes. Curr. Topics Med. Chem. 11(12): 1555–1570.

48. Sivilia S, Lorenzini L, Giuliani A et al. (2013). Multi-target action of the novel anti-Alzheimer compound CHF5074: in vivo study of long term treatment in Tg2576 mice. BMC Neurosci. 14: 44

49. Ross J, Sharma S, Winston J et al. (2013). CHF5074 reduces biomarkers of neuroinflammation in patients with mild cognitive impairment: a 12-week, double-blind, placebo-controlled study. Curr. Alzheimer Res. 10(7): 742–743.

50. Pitt J, Thorner M, Brautigan D, Larner J, Klein WL (2013). Protection against the synaptic targeting and toxicity of Alzheimer's-associated Aβ oligomers by insulin mimetic chiroinositols. The FASEB J. 27(1): 199–207.

51. Fahrenholz F (2007). Alpha-secretase as a therapeutic target. Curr Alzheimer Res 4(4): 412-417.

52. Obregon DF, Rezai-Zadeh K, Bai Y et al. (2006). ADAM10 activation is required for green tea (-)-epigallocatechin-3-gallate-induced alpha-secretase cleavage of amyloid precursor protein. J. Biol. Chem. 281(24): 16419-16427

53. Marcade M, Bourdin J, Loiseau N et al. (2008). Etazolate, a neuroprotective drug linking GABA(A) receptor pharmacology to amyloid precursor protein processing. J. Neurochem. 106: 392–404.

54. Vellas B, Sol O, Snyder PJ et al. (2011). EHT0202 in Alzheimer's disease: a 3-month, randomized, placebo-controlled, double-blind study. Curr. Alzheimer Res. 8(2): 203–212.

55. Filip V, Kolibás E (1999). Selegiline in the treatment of Alzheimer's disease: a long-term randomized placebo-controlled trial. Czech and Slovak Senile Dementia of Alzheimer Type Study Group. J Psychiatry Neurosci. 24(3): 234-243.

56. Parvathy S, Ehrlich M, Pedrini S et al. (2004). Atorvastatin-induced activation of Alzheimer's alpha secretase is

resistant to standard inhibitors of protein phosphorylation-regulated ectodomain shedding. J. Neurochem. 90(4): 1005-1010.

57. Nelson TJ, Sun M-K, Lim, C et al. (2017). Bryostatin Effects on Cognitive Function and PKCε in Alzheimer's Disease Phase IIa and Expanded Access Trial. J. Alzheimers Dis. 58(2): 521–535.

58. Griffin W (2006). Inflammation and neurodegenerative diseases. Am .J. Clin. Nutr. 3(l): 470–474.

59. Gauthier S, Aisen P, Ferris Set al. (2009). Effect of tramiprosate in patients with mild-to-moderate Alzheimer's disease: exploratory analyses of the MRI sub-group of the Alphase study. J. Nutr. Health Aging. 13: 550–557.

60. Aisen PS, Gauthier S, Ferris SH. (2011). Clinical research Tramiprosate in mild-to-moderate Alzheimer's disease – a randomized, double-blind, placebo-controlled, multi-centre study (the Alphase Study). Arch. Med. Sci. 7(1): 102-111

61. Bilikiewicz A, Gaus W (2004). Colostrinin (a naturally occurring, proline-rich, polypeptide mixture) in the treatment of Alzheimer's disease. J Alzheimers Dis. 6: 17–26.

62. Salloway S, Sperling R, Fox NC et al. (2014). Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N. Engl. J. Med. 370(4): 322–333, 2014.

63. Faux N, Ritchie C, Gunn A et al. (2010). PBT2 rapidly improves cognition in Alzheimer's disease: additional phase II analyses. J. Alzheimers Dis. 20: 509–516.

64. Nalivaeva NN, Fisk LR, Belyaev ND, Turner AJ (2008). Amyloid-degrading enzymes as therapeutic targets in Alzheimer's disease. Curr. Alzheimer Res. 5(2): 212–224.

65. Sabbagh MN, Agro A, Bell J, Aisen PS, Schweizer E, Galasko D. (2011). PF-04494700, an oral inhibitor of receptor for advanced glycation end products (RAGE), in Alzheimer disease. Alzheimer Dis. Assoc. Disord.25 (3): 206-212.

66. Burstein AH, Grimes I, Galasko DR, Aisen PS, Sabbagh M, Mjalli AM. (2014). Effect of TTP488 in patients with mild to moderate Alzheimer's disease. BMC Neurol.14: 12

67. Gilman S, Koller M, Black RS et al. (2005). Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial. Neurology 64(9):1553–1562.

68. Wiessner C, Wiederhold K-H, Tissot AC et al. (2011). The second generation active Aβ immunotherapy CAD106 reduces amyloid accumulation in APP transgenic mice while minimizing potential side effects. J. Neurosci. 31(25): 9323–9331.

69. Liu B, Frost JL, Sun J et al. (2013). MER5101, a novel Aβ1- 15:DT conjugate vaccine, generates a robust anti-Aβ antibody response and attenuates Aβ pathology and cognitive deficits in APPswe/PS1ΔE9 transgenic mice. J. Neurosci. 33(16): 7027–7037.

70. Panza F, Solfrizzi V, Imbimbo BP, Logroscino G (2014). Amyloid-directed monoclonal antibodies for the treatment of Alzheimer's disease: the point of no return? Expert Opin. Biol. Ther. 14(10): 1465–1476.

71. Salloway S, Sperling R, Fox NC et al. (2014). Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N. Engl. J. Med. 370(4): 322–333, 2014.

72. Tayeb HO, Murray ED, Price BH, Tarazi FI (2013). Bapineuzumab and solanezumab for Alzheimer's disease: is the 'amyloid cascade hypothesis' still alive? Expert Opin. Biol. Ther. 13(7): 1075–1084.

73. Galimberti D, Scarpini E (2011). Disease modifying treatments for Alzheimer's disease.Ther. Adv. Neurol. Disord. 4(4): 203–216

74. Adolfsson O, Pihlgren M, Toni N et al. (2012). An effector-reduced anti-β-amyloid (Aβ) antibody with unique Aβ binding properties promotes neuroprotection and glial engulfment of Aβ. J. Neurosci. 32(28): 9677- 9689.

75. Jindal H,Bhatt B, Sk S, Malik JS (2014). Alzheimer disease immunotherapeutics: then and now. Hum. Vaccin. Immunother. 10(9): 2741–2743.

76. Blaettler T. (2016). Clinical trial design of CREAD: a randomized, double-blind, placebo-controlled, parallel-group Phase-3 study to evaluate crenezumab treatment in patients with prodromal-to-mild Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association 12.7 (2016): P609.

77. Leyhe T, Andreasen N, Simeoni M et al. (2014). Modulation of β-amyloid by a single dose of GSK933776 in patients with mild Alzheimer's disease: a phase I study. Alzheimers Res Ther. 6(2): 19.

78. Novakovic D, Feligioni M, Scaccianoce S et al. (2013). Profile of gantenerumab and its potential in the treatment of Alzheimer's disease. Drug Des. Devel. Ther. 7: 1359–1364.

79. Bohrmann B, Baumann K, Benz J et al. (2012). Gantenerumab: a novel human anti-Aβ antibody demonstrates sustained cerebral amyloid-β binding and elicits cell-mediated removal of human amyloid-β. J. Alzheimer's Dis. 28(1): 49– 69.

80. Jacobsen H, Ozmen L, Caruso A (2014). Combined treatment with a BACE inhibitor and anti-Aβ antibody gantenerumab enhances amyloid reduction in APPLondon mice.J. Neurosci. 34(35): 11621–11630.

81. Dodel R, Rominger A,. Bartenstein P et al. (2013). Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial. Lancet Neurol. 12(3): 233–243.

82. Kimura T, Ishiguro K, Hisanaga S-I (2014). Physiological and pathological phosphorylation of tau by Cdk5. Front. Mol. Neurosci. 7: 65

83. Gourmaud S, Paquet C, Dumurgier J et al. (2015). Increased levels of cerebrospinal fluid JNK3 associated with amyloid pathology: links to cognitive decline. JPN 40(3): 151–161.

84. Iqbal K, Gong C-X, Liu F (2014). Microtubule-associated protein tau as a therapeutic target in Alzheimer's disease. Expert Opin.Therap. Targets 18(3): 307–318

85. de la Torre AV, Junyent F, Folch J et al. (2012). GSK3β inhibition is involved in the neuroprotective effects of cyclin-dependent kinase inhibitors in neurons. Pharmacol. Res. 65(1): 66–73.

86. Martinez A, Perez D (2008). GSK-3 inhibitors: a ray of hope for the treatment of Alzheimer's disease? J Alzheimers Dis. 15: 181–191.

87. Jorda EG, Verdaguer E, Canudas AM et al. (2003). Neuroprotective action of flavopiridol, a cyclin-dependent kinase inhibitor in colchicine-induced apoptosis. Neuropharmacology 45(5): 672–683.

88. Corcoran M, Martin D, Hutter-Paier B et al. (2010). Sodium selenite specifically activates PP2A phosphatase, dephosphorylates tau and reversesmemory deficits in an Alzheimer's disease model. J. Clin.Neurosci. 17(8): 1025–1033.

89. Hochgr¨afe K, Sydow A, Matenia D et al. (2015). Preventive methylene blue treatment preserves cognition in mice expressing fulllength pro-aggregant human Tau. Acta Neuropathol.Commun. 3: 25

90. Baddeley C, McCaffrey J, Storey JMD et al. (2015). Complex disposition of methylthioninium redox forms determines efficacy in tau aggregation inhibitor therapy for Alzheimer's disease.J. Pharmacol. Exp. Therap. 352(1): 110–118.

91. Panza F, Solfrizzi V, Seripa D, et al. (2016). Tau-Centric Targets and Drugs in Clinical Development for the Treatment of Alzheimer's Disease. BioMed. Res. Internat. 2016: 3245935

92. Wischik CM, Staff RT, Wischik DJ et al. (2015). Tau aggregation inhibitor therapy: an exploratory phase 2 study in mild or moderate Alzheimer's disease. J Alzheimer's Dis. 44(2): 705–720.

93. Shemesh OA, Spira ME (2011). Rescue of neurons fromundergoing hallmark tau-induced Alzheimer's disease cell pathologies by the antimitotic drug paclitaxel. Neurobiol. Dis. 43(1): 163–175.

94. Fitzgerald DP, Emerson DL, Qian Y et al. (2012). TPI-287, a new taxane family member, reduces the brain metastatic colonization of breast cancer cells. Mol Cancer Ther. 11(9): 1959-67.

95. Makani V, Zhang B, Han H et al. (2016). Evaluation of the brain-penetrant microtubule-stabilizing agent, dictyostatin, in the PS19 tau transgenic mouse model of tauopathy. Acta Neuropathol. Commun. Neurosci.Dis.4: 106

96. Novak P, Schmidt R, Kontsekova E et al. (2017). Safety and immunogenicity of the tau vaccine AADvac1 in patients with Alzheimer's disease: a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet Neurol. 16(2):123-134.

97. McGeer PL, McGeer EG (2007). NSAIDs and Alzheimer disease: Epidemiological, animal model and clinical studies. Neurobiol Aging. 28(5): 639-647.

98. Rubio-Perez JM, Morillas-Ruiz JM (2012). A Review: Inflammatory Process in Alzheimer's Disease, Role of Cytokines. Sci. World J 2012: 756357.

99. Weggens (2001). A subset of NSAIDs lower amyloidogenic Aβ42 independently of cyclooxygenase activity. Nature. 414: 212-216

100. Ajmone-Cat MA, Bernardo A, Greco A, Minghetti L (2010). Non-Steroidal Anti-Inflammatory Drugs and Brain Inflammation: Effects on Microglial Functions. Pharmaceuticals. 3(6): 1949-1964

101. Calvo-Rodríguez M, Núñez L, Villalobos C (2015) Non-steroidal anti-inflammatory drugs (NSAIDs) and neuroprotection in the elderly: a view from the mitochondria. Neural Regen Res 10(9):1371-1372

102. Lim GP, Yang F, Chu T et al. (2000). Ibuprofen Suppresses Plaque Pathology and Inflammation in a Mouse Model for Alzheimer's Disease. J. Neurosci. 20(15): 5709–5714.

103. Bate C, Veerhuis R, Eikelenboom P, Williams A (2003). Neurones treated with cyclo-oxygenase-1 inhibitors are resistant to amyloid-beta1-42. Neuroreport 14(16): 2099–2103.

104. Landreth GE, Heneka MT (2001). Anti-inflammatory actions of peroxisome proliferator-activated receptor gamma agonists in Alzheimer's disease. Neurobiol Aging 22(6): 937-944.

105. Aisen PS (2002). The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease. Lancet Neurol. 1(5): 279–284.

106. Aisen PS, Davis KL, Berg JD, et al. (2000). A randomized controlled trial of prednisone in Alzheimer's disease: Alzheimer 's disease Cooperative Study. Neurology 54: 588–593.

107. Serafini M, Peluso I, Raguzzini A (2010). Flavonoids as anti-inflammatory agents. Proc. Nutr. Soc. 69(3):273-278

108. Singh BN, Shankar S, Srivastava RK (2011). Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochem. Pharmacol. 82(12):1807-1821.

109. Singh BN, Shankar S, Srivastava RK (2011). Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochem. Pharmacol. 82(12):1807-1821.

110. Griffin W (2008). Perispinal etanercept: potential as an Alzheimer therapeutic. J Neuroinflammation 5:3.

111. Chakrabarti S, Sinha M, Thkurta IG, Banerjee P, Chattopadhyay M (2013). Oxidative Stress and Amyloid Beta Toxicity in Alzheimer's Disease: Intervention in a Complex Relationship by Antioxidants. Curr. Med. Chem. 20(37).

112. Thapa A, Carroll NJ (2017). Dietary Modulation of Oxidative Stress in Alzheimer's disease. Int. J. Mol. Sci. 18: 1583.

113. Galasko DR, Peskind E, Clark CM, et al. (2012). Antioxidants for Alzheimer Disease: A Randomized Clinical Trial With Cerebrospinal Fluid Biomarker Measures. Arch. Neurol. 69(7): 836-841.

114. Lee HP, Zhu X, Casadesus G, Castellani RJ et al. (2010). Antioxidant approaches for the treatment of Alzheimer's disease. Expert Rev. Neurother. 10(7): 1201-1208.

115. Sano M, Ernesto C, Thomas RG et al. (1997). A controlled trial of selegiline, a-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. N. Engl. J. Med. 336: 1216–1222.

116. James AM, Cochemé HM, Smith RA et al. (2005). Interactions of mitochondria-targeted and untargeted ubiquinones with the mitochondrial respiratory chain and reactive oxygen species. Implications for the use of exogenous ubiquinones as therapies and experimental tools. J. Biol. Chem. 280: 21295–21312.

117. Reddy PH (2006). Mitochondrial oxidative damage in aging and Alzheimer's disease: implications for mitochondrially targeted antioxidant therapeutics. J. Biomed. Biotechnol. (3): 31372.

118. Salvemini D, Wang ZQ, Zweier JL et al. (1999). A nonpeptidyl mimic of superoxide dismutase with therapeutic activity in rats. Science 286: 304–306.

119. Filipovska A, Kelso GF, Brown SE et al. (2005). Synthesis and characterization of a triphenylphosphonium-conjugated peroxidase mimetic: insights into the interaction of ebselen with mitochondria. J. Biol. Chem. 280: 23113–23126.

120. Zhao K, Zhao GM, Wu D et al. (2004). Cellpermeable peptide antioxidants targeted to inner mitochondrial membrane inhibit mitochondrial swelling, oxidative cell death, and reperfusion injury. J. Biol. Chem. 279(33): 34682–34690.

121. Dietschy JM, Turley SD (2004). Cholesterol metabolism in the central nervous system during early development and in the mature animal. J. Lipid Res. 45: 1375–1397.

122. u G (2009). Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. Nat. Rev. Neurosci. 10: 333–344.

123. Liu B, Frost JL, Sun J et al. (2013). MER5101, a novel Aβ1- 15:DT conjugate vaccine, generates a robust anti-Aβ antibody response and attenuates Aβ pathology and cognitive deficits in APPswe/PS1ΔE9 transgenic mice. J. Neurosci. 33(16): 7027–7037.

124. McGuinness B, Passmore P (2010). Can statins prevent or help treat Alzheimer's disease? J. Alzheimers Dis. 20(3): 925-933

125. Pedrini S, Carter TL, Prendergast G, Petanceska S, Ehrlich ME, Gandy S (2005). Modulation of Statin-Activated Shedding of Alzheimer APP Ectodomain by ROCK. 2(1):e18.

126. Sun Y, Wang G, Pan Z, Chen S (2012). Systematic review of atorvastatin for the treatment of Alzheimer's disease. Neural Regen.Res. 7(17): 1344-1351

127. Gamboa CM, Safford MM, Levitan EB, et al. (2014). Statin under-use and low prevalence of LDL-C control among U.S. adults at high risk of coronary heart disease. Am. J. Med. Sci. 348(2): 108-114

128. Kato H, Kurosaki R, Oki C, Araki T (2004). Arundic acid, an astrocytemodulating agent, protects dopaminergic neurons against MPTP neurotoxicity in mice. Brain Res. 1030: 66-73.

129. Asano T, Mori T, Shimoda T et al. (2005).Arundic acid (ONO-2506) ameliorates delayed ischemic brain damage by preventing astrocytic overproduction of S100B. Curr. Drug Targets CNS Neurol. Disord. 4: 127-142.

130. Clarke R, Smith Ad, Jobst Ka, Refsum H, Sutton L, Ueland Pm (1998). Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch. Neurol. 55: 1449-1455.

131. Cattaneo A, Calissano P (2012). Nerve growth factor and Alzheimer's disease: new facts for an old hypothesis. Mol. Neurobiol. 46(3): 588-604.

132. Tuszynski Mh, Thal L, Pay M, Salmon Dp, U Hs, Bakay R, Patel P (2005). A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat Med. 2005; 11: 551-555.

133. Duong Fh, Warter Jm, Poindron P, Passilly P (1999). Effect of the nonpeptide neurotrophic compound SR 57746A on the phenotypic survival of purified mouse motoneurons. Br. J. Pharmacol. 128: 1385-1392.

134. Dong H, Jiang X, Niu C, Du L, Feng J, Jia F (2016). Cerebrolysin improves sciatic nerve dysfunction in a mouse model of diabetic peripheral neuropathy. Neural Regen. Res. 11(1): 156-162

135. Douillet P, Orgogozo JM (2009). What we have learned from the Xaliproden Sanofi-aventis trials. J. Nutr. Health Aging. 13(4): 365-366.

136. Gauthier S, Proano JV, Jia J, Froelich L, Vester JC, Doppler E (2015). Cerebrolysin in mild-to-moderate Alzheimer's disease: a meta-analysis of randomized controlled clinical trials. Dement. Geriatr. Cogn. Disord. 39(5-6): 332-347.

137. Gu H, Long D (2012). Application of Nerve Growth Factor in Alzheimer’s disease. Clinic. Pharmacol. Biopharm. 1:e109.