IJPIHS
An Open Access Peer Reviewed Journal
(A Project of Superior University)

International Journal of Pharmacy & Integrated Health Sciences

ISSN (online): 2789-2840; ISSN (print): 2958-1656

REVIEW ARTICLE

ADVANCEMENT IN THE TREATMENT OF ALZHEIMER'S DISEASE, 2023

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DOI: https://doi.org/10.56536/ijpihs.v5i1.114

Submitted on: 14-08-2023 **Revised on:** 10-12-2023 **Published on:** 01-03-2024

ABSTRACT

Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by extracellular amyloid β deposition and intercellular neurofibrillary tangles. AD is a complex disease with a strong genetic component, and it is classified into three phases by the Food and Drug Administration (US-FDA): pre-pathology, plaque formation, and neural destruction. A number of therapeutic agents have been developed to reduce AD pathology and improve cognition. **Objectives:** The objective of this paper was to review recent advancements in AD treatment and cure. **Methodology:** A literature search was conducted using the keywords "therapeutic developments for AD" and "natural products as a drug for AD." Publications related to AD were retrieved, and the NCBI Clinical trial database was also searched to check drug status. **Results:** Monoclonal antibodies against amyloid β plaques, tau protein, and microtubule-associated protein have shown positive results in animal models, but they have failed in clinical trials. This is likely due to the fact that these antibodies are designed to target specific proteins that are not always present in the human brain. **Conclusion:** Based on the findings of this review, it is suggested that medicines based on natural extracts and combination therapy would be least toxic and more effective than single therapy. This is because combination therapy targets multiple pathways involved in AD pathogenesis. There is also a dire need to initiate AD research in Pakistan and facilitate the Pakistani community in early diagnosis and cure.

Keywords: Alzheimer's disease, Amyloid precursor protein, Neurodegeneration, Aducanumab, Clinical trials, Plaque clearance, Natural extracts

INTRODUCTION

Alzheimer's Disease was first discovered in 1907 by Alois Alzheimer after he performed a brain autopsy of a dementia patient (1). Neurodegeneration due to amyloid accumulation is more prevalent in people above the age of 60, but early onset of this disease has also been observed (2). The degeneration of neurons is caused either by the accumulation of extracellular amyloid plaques or intracellular neurofibrillary tangled formation (3). Mutation in the amyloid precursor protein (APP) gene alters the cleavage pattern of APP by secretase enzyme. Alteration in APP cleavage produces insoluble 42 amino acids long amyloid protein, amyloid β (Aβ42), in the extracellular matrix. Dimerized amyloid plaque inhibits neural glutamate receptors and affects synaptic plasticity. Another protein associated with neurodegeneration is tau. It is a soluble microtubule-associated protein having several posttranslational modifications, especially phosphorylation. A shift in phosphorylation patterns accelerates intracellular neurofibrillary tangle formation (4). Similar to amyloid plaque, neurofibrillary tangles block glutamate receptors (5, 6).

Amyloid β plaque formation and microtubule disassembly initiate an immune response in the brain by activating ameboid microglial cells (7). Activation of the brain microglial has also been associated with an altered gut microbiome as it acts as a stimulator for the production of T-helper 1 cells which cross the blood-brain barrier and cause microglial activation in the brain (8). It is reported that microglial activation disrupts cellular homeostasis which ultimately leads to neurodegeneration (9, 10).

Alzheimer's disease being a complex neuro-disorder, is influenced by both genetic as well as environmental factors. Over the last decades, many antibodies-based amyloid and tau-directed therapies have been developed but only two drugs have gained FDA approval. Most antibodies show positive responses in animal models, but they fail when introduced to the human body. This drug failure is either due to differences in genetics or the complexity of the human brain. The aim of writing this review is to understand Alzheimer's disease and the drug development efforts of the scientific community.

LITERATURE REVIEW

Genetic association of Alzheimer

Genetic studies are important for early diagnosis and prevention of disease. The genetic database http://www.alzgene.org has been developed to report all genomic variation. Approximately data from 1365 studies reported mutation in 695 genes (11) . Genetic variations in PSEN1, PSEN2, APP, APOE-ε2/3/4, BINI, CLU, ABCA7, CRI, PICALM, CD33, MS4A4E, and CD2AP genes have been strongly associated with Alzheimer's disease (12). The PSEN1, PSEN2, and APP are associated with early onset whereas the APOE gene has a strong association with late onset of disease (13).

Mutation in presenilin genes (PSEN1 and PSEN2) is associated with the early onset of disease. Both genes encode the catalytic domain of γ-secretase. The amyloid precursor protein is a glycosylated membrane protein that is cleaved by α, β, and γsecretase (14). Amyloid pathology is observed in patients with a missense mutation in APP at codons 665, 670, 671, 692, 716, and 717 (15). Due to these mutations γ-secretase that cleaves amyloid fragments at the C-terminal releases a toxic 42 amino acid long insoluble β pleated rich amyloid protein (16).

History of therapeutic development for AD

During the 1990's tacrine, donepezil, and rivastigmine, cholinesterase inhibitors, were approved by US FDA to reduce the symptoms of dementia. In 2003 memantine was approved for severe AD to reduce AD-related symptoms (17). Chemically this drug is the antagonist to NMDA receptors. The NDMA receptors are glutamatergic and involved in long-term memory development as the strong stimulus allows the removal of magnesium ion from the receptors and initiate the influx of calcium ions which ultimately initiate gene expression (18, 19). These receptors are more highly sensitive toward calcium ions than a neurotransmitter. Overexpression of NDMA receptors causes intracellular calcium toxicity and cause neurodegeneration (20).

For therapeutic development, AD has been divided into three phases. In the first pre-clinical

phases, clinical biomarkers are identified in blood and cerebrospinal fluid (CSF). In the second phase, amyloid plaque formation is observed under PET imaging. The third and last phase of AD is the symptomatic phase in which neurofibrillary tangles and neurodegeneration are commonly observed (21). Previously approved FDA drugs for AD show effectiveness as symptomatic control but are ineffective to reduce disease pathology. In the year 2021, about 126 drugs for AD were the focus of clinical trials, and 82.5% of them have targeted agents to reduce the pathophysiology of the disease either by acting on the amyloid peptide or tau protein while other drugs target cognitive abilities, neuropsychiatry, and behavioral symptoms (22, 23). Other targets selected for drug development are secretase enzymes, neuroinflammation, oxidation stress, NDMA receptors, neuroinflammation, and angiotensin receptors (24).

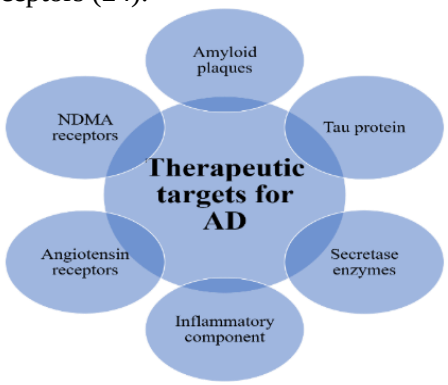

Figure 1. Commonly selected therapeutic target for AD treatment

Antibodies targeting amyloid plaques

Aducanumab is the first class of drug that has been approved by the FDA to target amyloid plaques (25). It is an intravenous drug that contains recombinant immunoglobin gamma1 (IgG1) antibodies against amyloid plaque. Its molecular weight is approximately 146kDa and has N-glycosylation at its residue 304 (26). The entrance of the drug is facilitated by brain parenchymal cells where it is specifically bound to the oligomeric and fibril of amyloid plaque. This binding is facilitated by residue Phe4 and His6, at the N-terminal of amyloid-β plaques (27). The binding of antibody (AB) initiates the activation of ameboid microglial cells (brain macrophages) which induce plaque clearance via phagocytosis.

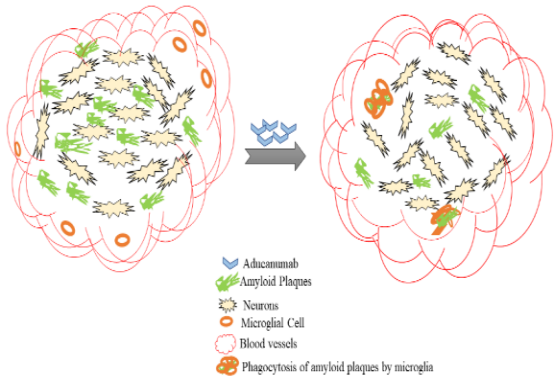

Figure 2. Mechanism of action of Aducanumab: Monoclonal antibodies can cross the blood-brain barrier and enter into brain parenchymal tissues. Here it activates microglial cells and initiates amyloid clearance by phagocytosis.

The effectiveness of a drug is highly dependent on the time of administration and dosage of the drug (28). Brain autopsy of an 84-year-old woman, treated with aducanumab, shows effective clearance of amyloid plaques (29). During the phase1 clinical trial, named PRIME, no drug toxicity was observed. After phase 1, two independent phases 2 trials were begun with the name ENGAGE and EMERGE. In 2019 it was observed that this antibody was able to remove amyloid plaque efficiently but did not affect cognitive progression. Amyloid-related imaging abnormalities (ARIA) were also observed, which may be due to poor penetration of the drug, to the target area and it causes vasogenic edema (30). Based on these observations both trials were halted. In June 2021 US FDA approved this drug for marketing for controlled observation (23, 28, 31). Now this antibody is marketed under the name of Aduhelm (32).

The human version of mouse monoclonal antibodies, mAb158, has also been developed against amyloid protofibrils (33). In 2010 this humanized monoclonal G1 antibody, named BAN2401, was approved for clinical trials. These antibodies effectively clear amyloid from the brain and CSF when administered biweekly10mg/kg dose to patients.ARIA is the

most commonly observed toxicity with monoclonal antibodies (34, 35). In 2021 Rofo *et al.* modify the drug structure by adding a variable chain of immunoglobin at the N-terminal of mAb158 to enhance drug affinity toward protofibrils. This hexavalent antibody exhibits 40 times more affinity than the previous analog (36). PET imaging of volunteers under clinical trial shows positive amyloid clearance while only 10 percent of patients show ARIA-E and ARIA-H (37). Considering these findings FDA approved this antibody for AD treatment under the name Leqembi (38).

Antibodies targeting Tau protein

Neurofibrillary tangles formation is another contributing factor to AD progression. Antibodies against tau are also under clinical trials (39). Tau is a soluble microtubule-associated acidic protein have a proline-rich microtubule-binding domain (40). It has more than 85 different sites for phosphorylation which is facilitated by tau kinases. Inappropriate phosphorylation of tau protein causes the disassembly of microtubules which results in fibrilization in the medial or temporal lobe of the brain. Biochemical analysis reveals that shifts in phosphorylation cause blockage of glutamate receptor and shift in glucose metabolism hence play important role in cognitive loss (41).

Anti-tau antibodies 43D (targeting 6-18 tau residues) and 77E9 (targeting 184-195 residues) are under the animal model testing phase. Animal testing shows a positive response against tangles removal in the hippocampus region after six doses and overall cognitive improvement (42). Recombinant anti-tau AV-1980R/A has a significant effect on short-term memory improvement and phosphate removal at Ser396 of tau (43). Another antibody, named anti-prion protein antibody (TW1), shows a significant effect on cognitive improvement (39). Similar results have been observed by Veronica *et al* when they inject a transgenic mouse with a 12A12 monoclonal antibody that targets 26-36 residues (44). Another approach to clear tau deposition is the development of antibody isotypes that can ensure the formation of antibody-tau complex and microglial Fc-receptors. One group of scientists developed an RN2N antibody and cloned it into murine IgG1/k and IgG2a/k framework to study tau clearance and cognitive improvement in mouse models. Their results indicate that the former antibody complex has a higher affinity toward tau clearance (39). Studies indicate that the VQIINK region can be the critical target for epitope development. Acetylated K280 was targeted using anti-tau Y01 antibodies via the intracerebroventricular or intraperitoneal route of drug delivery (45). The therapeutic activity of 22- residue immunotherapeutic peptide has also been designed against 68 and 69 tau residues. This therapeutic peptide shows significant memory improvement (44).

Semorinemab, an anti-tau IgG4 antibody, was approved by FDA for clinical trials and it is under phase II clinical trial. Animal testing results suggest that this antibody equally binds to all tau isoforms at doses of 3, 10, and 30 mg/kg concentration (46). Clinical trials commenced in 2016 on AD patients and healthy volunteers. During one year of investigation, no serious complications were observed. A successful initial trial shifted that antibody toward phase II placebo 18-month-long open-labeled extension trials in more than 100 regions. No tau clearance was observed with 1500mg, 4500mg, and 8100mg concentrations (47). Bepranemab is another tau-directed humanized monoclonal antibody IgG4 specific for the microtubule-binding domain. This antibody is supposed to target tau seeding and inhibit hyperphosphorylation (48). The trial of these antibodies is supposed to end in 2025. This antibody may be the best possible therapy to target disease pathology.

Secretase directed therapy

Successive cleavage of amyloid precursor protein by secretases releases two peptides *i.e.*, soluble α amyloid and C terminal fragment α (CTFα). CTFα is further cleaved into the amyloid intracellular domain and soluble peptide 3 (P3) (49). This P3 peptide influence transcriptional activities to enhance neuroprotection and neuronal outgrowth (50). The amyloidogenesis pathway is initiated because of a lethal mutation in the APP gene. This mutation weakens the binding and cleavage activity of α-secretase and introduces a site for β-secretase. Cleavage with β secretase produces

insoluble amyloid peptide which accumulates in the form of plaque (49).

Another crucial enzyme in amyloid pathology is γ-secretase. It is aspartyl intramembrane protease which, upon activation, cleaves C99 fragments at multiple sites producing diverse amyloid β fragments. Mutation in PS1 and PS2 genes affects the assembly of γ-secretase subunits. These mutated enzymes produce Aβ42 which is more pathogenic (15). The clinical trials for γ-secretase inhibitor, irrespective of better Aβ clearance, were ceased in phase III because patients on Semagacestat, a γ-secretase inhibitor, suffered from the sudden decline in lymphocytes (especially CD19 cells), increased risk of squamous cell carcinoma, and elevated urine pH. The decline in lymphocytes and other immune cell populations may be due to the interference of the drug with the Notch receptor as these receptors are involved in cellular communication in hemopoietic stem cells (51).

Adverse effects of γ-secretase inhibitors shift AD research toward the development of non-steroidal γ-secretase modulators (GSMs) that were approved for clinical trials. First-generation GSMs, tarenflurbil, work better to reduce cognitive decline rate but were not able to pass phase III. The trials were halted because of frequent anemia, pneumonia, gastric ulcer, and increased eosinophil count. During the trial, 24/42 deaths were observed in patients taking tarenflurbil (52). New drugs were developed by carboxylation of NSAID and hetero-cyclization non-NSAID. Both these components can bind catalytic pores of γ-secretase. Second-generation GSMs were developed by substituting nitrogen of piperidine in NSAID and yielded multiple piperidine acetic acid analogs. Another drug from second-generation GSMs is JNJ-40418677 an analog of flurbiprofen, itanapraced and EVP-0015962 has also been used for AD treatment. All these compounds show an active reduction of $A\beta_{42}$ reduction (53).

Natural extracts for AD therapeutics

Natural products are thought to be multi-targeted agents and can be promising treatments for AD. A plenty of bioactive compounds with complex structures and unique pharmacological properties could be found in natural sources such as plants, microorganisms, animals and marine ecosystems (54). Natural products (especially plants) and their isolated compounds have extensively been investigated as one of the major source of drug discovery in an effort to develop more potent drugs to manage AD (55). In fact, a commonly used Cholinesterase Inhibitor, galantamine, derived from *Galanthus nivalis* (56), is a natural extract of plant (57) and rivastigmine, comonly known for its activity against Parkinson Disease Dementia and Alzheimer's Disease (58), is a semi-synthetic drug derived from natural product physostigmine (59).

Natural products have ability to improve and prevent neurodegeneration in AD because of their anti-oxidant activities and anti-inflammatory properties, with fewer side effects as compared to synthetic drugs (60). The expression of an antioxidant gene is regulated by the transcription factor "nuclear factor E2-related factor 2 (Nrf2)" in response to oxidative stress. The upregulated expression of Nrf2 is found in neurons of AD patients due to oxidative damage. The *Rosmarinus officinalis* is a medicinal plant from which the phenolic acid was isolated which shows a neuroprotective effect in vitro by diminishing RNS/ROS levels and suppressing the Nrf2 expression. While the Carotenoids partially prevent the AD symptoms by the reduction of ROS/RNS (61) .

Physostigmine is an alkaloid that was isolated from *Physostigma venenosum*. The first discovered AChE inhibitor was Balf which laid the foundation for use and discovery in clinics. The template for the synthesis of AChE inhibitors like rivastigmine was provided by the chemical structure of Physostigmine. In the UK, rivastigmine has been licensed for clinical use as a treatment for moderate to mild AD due to the presence of carbamate moiety, which is a cholinesterase inhibitor (62) .

The protection against neurotoxicity induced by Aβ in neurons can be protected by the activation of the signaling pathway, P3IK/AKT. Some natural products like salidroside, dihydromyricetin, and curcumin show preventive effects against AD through the PI3K pathway (63). Grapes and red wine contain Resveratrol which is non-flavonoid polyphenol. In vitro studies reported that resveratrol has

reduced the formation of Aβ fibrils and initiated the Aβ disaggregation by intracellular proteasomal action. As a result, resveratrol diminishes the plaque and Aβ level in the brain of rates with AD. Some in Vivo studies also reported the anti-inflammatory and anti-oxidant role of this compound (64).

An alkaloid Tetrandra, derived from Radix Stephania tetranda has shown promising activity against neuro-inflammation in a rat model of AD by the inhibition of NF-κB activation (65). Similarly, Cryptolepis sanguinolenta-derived crytolepine alkaloid has been reported to alleviate the levels of IL-1β, TNFα, NO, IL-6 and PGE2 in the lipopolysaccharide-stimulated microglia in rat model by blocking the activation of p38 MAPK and NF-κB in the microglial cells (66). Furthermore, a systematic literature survey conducted by Xin Chen et al reported that natural product extracts and their mixtures have effective neuroprotective results, targeting various pathological mechanisms associated with AD (61).

Some of the natural products successfully reached phase 3 clinical trials. ALZ-801 is an orally administered disease-modifying molecule that shows a significant effect on patients suffering from apolipoprotein ε4 (APOE4) mediated disease pathology (34). Invitro studies on ALZ-801 indicate the inhibition of amyloid β aggregation without being bound to it (67). Tramiprosate was a glycosaminoglycan, a variant of amino acid taurine abundantly found in red algae, that was used to reduce the symptoms of AD (68). Due to gastric intolerability, it has been modified, ALZ-801, with 3-(L-valyl) amino-1-propane sulfonic acid (69). During the primary stage of phase 1, this drug show the least toxicity and during phase 3 it was found to have good cerebral penetration (70). This study was designed to assess drug availability in CSF and plasma. The sulfonic acid group in this tablet forms a multi-ligand envelope around amyloid β42 plaques and leads to the inhibition of aggregate formation (71). This prodrug has shown brain penetration of more than 25% while no ARIA has been observed during clinical trials (72).

In silico studies have shown the effectiveness of curcumin against amyloid β accumulation. Syaban *et al.* reported that curcumin has a strong binding affinity with glycogen synthase kinase 3β (GSK-3β) (73). GSK3β plays an integral role in the hyperphosphorylation of tau protein when the concentration of amyloid plaque is increased (74). GSK3β inhibition in mice model shows positive effects toward plaque clearance and reduction in tau hyperphosphorylation (75). Curcumin can be used in drugs as a potential therapeutic agent against AD (73).

Sodium oligomannate, a mixture of the acidic oligomer, has been isolated from brown algae and can be used for the treatment of moderate AD. It got its first approval in China in 2019 (76). The clinical trial indicates cognitive improvement, reduction in neuroinflammation, and amyloid plaque reduction (77). Phase 2 clinical trials were performed to identify the tolerable dose of GV-971. It was observed that the oral dose of 900mg/day was slowing the rate of cognitive impairment and least or no toxicity was observed (78). Similar findings have been observed under 36-week phase 3 trials (79). These natural extracts can have a more promising effect than synthetic chemicals.

COMBINATION THERAPIES

Natural compounds or extracts have extensively been explored alongside the synthetic drugs to increase their efficiency while treating AD. Some of the examples include:

Donepezil with curcumin

Donepezil, an acetylcholinesterase inhibitor drug, combined with a natural compound Curcumin has been studied for potential therapeutic effects against AD and studies report the improvement of cognitive functions and memory in the model animals of AD (80). The combination increases the inhibition of butyrylcholiesterase, acetylchonesterase and adenosinedeaminase, thus improving learning and memory activities (81).

Memantine with resveratrol

Several studies have investigated the potential of Memantine in combination with Resveratrol in context of AD. A study by Samah Labban et al investigated the Memantine and Resveratrol effects on passive avoidance and recognition memory in mouse models. The findings demonstrated resveratrol enhanced the passive

avoidance ability and memantine considerably restored memory deficiencies (82).

Ashwagandha *(Withania somnifera)* with donepezil

Ashwagandha and Donepezil, in combination, are a subject of interest for many researchers as ashwagandha has already been used in ayurvedic medicine due to its cognitive enhancing and neuroprotective potentials (83), while there is a limited research on this combination. Ashwagandha has extensively been studied in relation to cognitive functions and has been demonstrated to be a potent free-radical scavenger and antioxidant (83, 84).

Given the potential antioxidant, free-radical scavenging and neuroprotective properties of various plant extracts, further clinical investigations and research is required to evaluate the safety, efficiency and efficacy of combining synthetic drugs with natural products and extracts for treating Alzheimer's disease.

CONCLUSION

Alzheimer's disease is characterized by neurodegeneration due to extracellular amyloid β deposition, intercellular formation of neurofibrillary tangles, and neuroinflammation due to microglial activation. A strong association between gut microbiota dysbiosis and neuroinflammation has been found. Based on the findings and conclusions of clinical trials it is suggested that natural medicines and combination therapy would be least toxic and more effective than single therapy.

ACKNOWLEDGEMENT

None

DECLARATIONS

Authors' Contributions

AS supervised and designed the study concept; AS, MUG and MFS contributed to the study design, data collection, and manuscript write-up. MUK, MH, KA and TH contributed to data analysis and interpretation and critically reviewed the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Ethical Approval

Not applicable

Conflict of Interest

The authors declared no conflict of interest among them.

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