Iran J Public Health, Vol. 54, No.7, Jul 2025, pp.1399-1410

Review Article

Regenerative Medicine in the Treatment of Alzheimer's Disease: A Narrative Review

Mana Shojapour [1], ****Samira Asgharzade*** [2,3]

1. *Molecular and Medicine Research Center, Arak University of Medical Sciences, Arak, Iran*
2. *Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran*
3. *Department of Molecular Medicine, School of Advanced Technologies, Shahrekord University of Medical Sciences, Shahrekord, Iran*

***Corresponding Author:** Email: Asgharzade2336@gmail.com

(Received 15 Jan 2025; accepted 05 Apr 2025)

Abstract

Alzheimer's disease (AD) is one of the progressive neurodegenerative diseases, memory impairments and multiple cognitive and behavioral deficits characterize that. We aimed to evaluate the molecular mechanisms involved in the pathogenesis of AD. It introduces the regenerative medicine approach as a novel therapeutic strategy based on the pathogenesis of AD that would be efficient. Our data was collected using databases such as the Web of Science, PubMed, Scopus, and Google Scholar. We summarized the available therapeutic strategies to induce neurodegeneration that can increase the number of neurons and their survival and improve the plasticity of synapses and synaptic activity. There is a different approach to treatment. In first-line treatment, focusing declines the amyloid beta and hypophosphorylated tau protein accumulation. It inhibits acetylcholinesterase, but in regenerative medicine focusing on treatment via gene therapy, cell therapy, and tissue engineering. As a proposed solution for AD in recent years, the use of inhibitors of the pathogenesis of AD is known as a supportive therapeutic approach, but the multi-potential treatment of regenerative medicine has been able to provide promising results in treating neurodegenerative patients.

Keywords: Alzheimer's disease; Molecular basis; Regenerative medicine; Treatment

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that is known for different disabilities such as memory loss, cognitive dysfunction, and behavioral instability (1).

Various factors are involved in the molecular base of AD, such as disruption of the cholinergic system, amyloid beta (Aß) 42 protein accumulation, and tau phosphorylation. The accumulation of Aß42 is one of the most important causes of AD pathogenesis, which leads to the formation of senile plaques, these plaques attract microglia. Activated microglia generated a huge amount of pro-inflammatory cytokines in the brain that could stimulate astrocyte-neuron cells to produce higher amounts of oligomer Aß42, than secondary damage into nerve cells induced by the starting of inflammation and oxidative stress pathway (2).

DOI: https://doi.org/10.18502/ijph.v54i7.19146

Tau protein stabilizes microtubules, but excessive phosphorylation leads to its detachment, causing microtubule cohesion loss and impairing axonal transport. This ultimately results in nerve cell death, contributing to AD pathology (3).
Different mechanisms involved in Alzheimer's pathogenesis, make effective treatment challenging. Currently, memantine and cholinesterase inhibitors are the only FDA-approved therapies for AD. This review aims to explore proposed treatments based on the molecular basis of Alzheimer's and regenerative medicine for preventing disease progression (4).

Molecular basis of AD

AD is a complex and multifactorial disorder. Many hypotheses are important in the pathogenesis of Alzheimer's.

Amyloid beta hypothesis

Over the past 20 years, extensive research in laboratory conditions or using genetically modified animal models has confirmed that Aß plays a role in the development of Alzheimer's and is considered a major goal for therapeutic interventions (5). The Aß peptide is produced through the cleavage of a primary precursor known as amyloid precursor protein (APP) by β- and γ-secretase enzymes. The APP is a gene on chromosome 21. The three most common APP isoforms include 659 amino acids (aa) (APP695), 751aa (APP751), and 770aa (APP770) expressed in neurons and glial cells (5-7).
Alzheimer's genetic basis involves mutations in genes like APP and PSEN1-2, accumulating toxic Aβ oligomers. These oligomers are the primary causes of neurodegeneration, interacting with membrane receptors and activating neurotoxic pathways, including mitochondrial dysfunction and inflammatory responses (8).
Alpha-secretase under physiological conditions (non-amyloidogenic processing) produces dissolved Appα (sAPPα). sAPPα modulates neural excitability, increases neural resistance to metabolic and oxidative stresses, and improves synaptic, learning, and memory formation. The amyloid pathway involves the cleavage of APP by β-secretase, resulting in sAPPβ and a C-terminal fragment of 99 amino acids (C99); C99 is subsequently cleaved by γ-secretase into Aß [1-40] or Aß [1-42] peptides. Aβ42 is more neurotoxic because of its strong hydrophobicity and increased propensity to aggregate (9).
One of the main goals of AD treatment is to eliminate or inhibit Aß peptide development. Therapeutic strategies targeting Aß include inhibiting Aß accumulation, modulating Aß production, immunotherapy targeting Aß, and increasing Aß decomposition (6).

Tau hypothesis

Tau as a microtubule-associated protein is predominantly distributed in neuron cells. The C-terminal (repetitive elements Pro-Gly-Gly-Gly) of tau binds to microtubulin, assembles microtubules, and maintains the balance between stable and dynamic states which plays a crucial role in keeping the integrity of the cytoskeleton, synaptic structure, optimal communication of cells and regulation of neuronal signaling (10,11). Some post-translational modifications (PTMs) in tau such as hypophosphorylation could cause a change of configuration and the loss of its function. Therefore, tau instability and abnormal aggregation are caused form the neurofibrillary tangle (NFT). NFT abnormal accumulation causes death and degenerative of nerve cells. This phenomenon has been observed in different neurological disorders such as Amyotrophic lateral sclerosis and Parkinson's disease (12,13).

Stress oxidative hypothesis

Oxidative stress is another critical factor in the pathogenesis of AD, occurring when there is an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses. When mitochondria lose their function, they release huge amounts of ROS that damage in brain cells of neurodegenerative disease patients and healthy elderly individuals (14). Abnormal accumulation of Aβ could be inhibited by different mitochondrial enzymes evolved in apoptotic cascades (cytochrome c oxidase) and Krebs cycle (alpha-ketoglutarate and pyruvate dehydrogen-

ase). As a result, there are some malfunctions in mitochondria such as reduced ATP production, impaired electron transport, and oxygen metabolism. Excessive free radicals imitate oxidative stress in nerve cells caused by DNA and cell membranes. Also, ROS alters antioxidant enzyme activity including enzymes like catalase and superoxide dismutase (15). This results in a positive feedback loop, where oxidative stress induces Aβ accumulation, which subsequently amplifies oxidative stress, ultimately leading to the development and progression of AD.

Modulation of neurotransmitter

Cholinergic nerve cells are the primary neurotransmitters involved in AD, with confirmed loss in the post-brainstem region of patients. These cells play crucial roles in learning, memory, cerebral cortex development, and regulating the sleep-wake cycle (16, 17).

Cholinergic dysfunction in Alzheimer's patients involves decreased acetylcholine transferase activity, reduced choline absorption, lower acetylcholine synthesis, and altered acetylcholine receptor levels (18). Different FDA-approved cholinesterase inhibitors such as tacrine, galantamine, donepezil, and rivastigmine were shown to stimulate markedly symptomatic improvement in patients with AD (19).

Tau-based therapies

In AD, hyperphosphorylated tau collects in paired spirals, leading to the destruction of neurons. Targeting tau phosphorylation is one of the therapeutic mechanisms. One of the main enzymes involved in tau phosphorylation is glycogen synthase kinase 3 (GSK3), targeted in several experimental studies (20). Lithium inhibited GSK3ß activity leading to a decrease in amyloid production and tau phosphorylation in transgenic mouse models (Aßppswe/PS1A246E). Chronic lithium therapy reduces precursor γ-separation of amyloid-β protein, decreases amyloid-β production, and the formation of aging plaque, which has been associated with improved spatial and memory learning abilities (21).

Tideglusib is an irreversible GSK3 inhibitor whose oral administration in AD animal models reduces tau hyperphosphorylation and amyloid plaque in the brain and improves animal learning and memory. The application of this drug is underway in phase two clinical trial study (NP031112-10b04) in individuals with mild to moderate AD (22). Also, several small GSK3 inhibitors such as SB216763, CHIR-98014, and SRN-003-556 are currently in preclinical studies. SB216763 reduced tau phosphorylate levels through GSK3 inhibition but side effects included induction of neurodegenerative markers and behavioral defects (23). Activating phosphatase proteins for tau dephosphorylation is another strategy under evaluation, with phosphatase 2A (PP2A) being a key enzyme. Studies indicate that activating PP2A has positive effects on AD. Sodium selenite, a PP2A activator, is currently in phase IIa clinical trials in Australia (24).

Microtubule stabilization

Tau phosphorylation changes microtubules' structure and function, eventually leading to axon transfer defects. Thus, microtubule-stabilizing drugs such as paclitaxel (anti-cancer drug), Epothilone NAP (NAPVSIPQ), and SAL (SALLRSIPA) are suitable therapeutic solutions for AD (25). Intra-nasal administration of paclitaxel in tracheotomy mice (3xTg-AD) reduced tau pathology, reduced neuronal inflammation, improved axon transmission, as well as cognitive function in mice (26).

Preventing the oligomerization of tau

Compounds that prevent the interaction of tau and the accumulation of NFT can be highly beneficial in treating AD. Drugs like lansoprazole and astemizole (benzimidazole derivatives) exhibit strong binding affinity the binding to the tau protein, thus, indirectly reducing the interaction of tau proteins (27).

Tau and nerve fiber destruction

The Hsp90 facilitates aberrant aggregation and accumulation of tau and can even increase its toxicity. The use of the Hsp90 inhibitor is anoth-

er treatment (28). Curcumin, a polyphenol and ingredient in turmeric, has various functions, including HSP90 inhibition. Oral administration of curcumin in transgenic mice reduces Aβ plaque size, inhibits dissolved tau dimers, and disrupts tau accumulation. This therapy has been shown to reduce tauopathy (29). EC102 is the Hsp90 inhibitor capable of crossing the blood-brain barrier (BBB). It has reduced the accumulation of tau in the brains of transgenic mice with AD (30).

Reduced production of Aß-secretase modifiers

Posiphen, an enantiomer of phenserine, directly reduces levels of APP by inhibiting ribosome access and interfering with the 5' untranslated region of APP mRNA, effectively acting as an APP synthesis inhibitor. Additionally, posiphen and its metabolites inhibit the synthesis of interleukin, beta-secretase, and acetylcholinesterase (AChE) (31).

Modulation of Aß transmitters

Apolipoproteins have a significant role in the metabolism and transport of Aß. However, they do not cross the BBB, but regulate the movement of Aß between the central and peripheral nervous systems. Apolipoprotein 34E (ApoE34) increases the passage of Aß from the BBB (4).

Reduced Aß accumulation

Tramiprosate is a glycosaminoglycan that binds to Aß monomers and prevents oligomerization and their accumulation. Taking this drug in a phase II clinical trial study showed that tramiprosate caused improvement in cognitive effects reported in patients but no decrease in clinical dementia was observed (32). Scyllo-inositol is another anti-oligomerization drug that effectively reduces insoluble Aß and cognitive decline in transgenic mice (33).

Increased Aß clearance

Some proteases that break down Aß plaques include plasmin, angiotensin, insulin-degrading enzyme, neprilysin, endothelin converting enzyme, metalloproteinase converting enzyme, and several other proteases (34).

Amyloid targeted immunotherapy

Animal studies have demonstrated the negative effects of anti-amyloid immunization strategies. AN1792 was the first active vaccine tested in humans, but about 6% of patients developed meningoencephalitis, leading to the study's discontinuation (35). To avoid non-specific immune responses, new vaccines targeting small epitopes were developed. CAD106, which includes the first six amino acids of Aβ (Aβ1-6) as immunogenic sequences, showed no side effects after 52 weeks of consumption, with over 75% of participants demonstrating a proper antibody response (36). The vaccine has recently completed phase II clinical trials (NCT00956410) and (NCT01097096) (37). ACC-001, the second-generation vaccine, is currently in the second phase of the clinical trial (NCT01284387, NCT01227564, and NCT00479557) (38). Bapinuzumab is an anti-Aβ monoclonal antibody targeting the N terminal. This is the first passive immunization therapy for AD, although the results from a phase II trial were inconclusive (39).

Overcome stress oxidative

Exogenous antioxidants

Since the activation of oxidative stress pathways is involved in AD pathology, antioxidant administration is one of the preventive factors and supportive treatments. Flavonoids and carotenoids are antioxidants with protective properties of the neuronal system (40).

Routine, a bioflavonoid compound, protects mice from stress damage and streptozotocin-derived neuronal inflammation (41). Curcumin has multiple beneficial roles (antioxidants, anti-inflammatory properties, and amyloid decomposition properties). In experimental studies, curcumin administration reduces inflammation caused by Aß, β-secretase inhibition, and AChE (42). Melatonin is another powerful antioxidant compound that is involved in the correcting of diseases by numerous mechanisms including inhibiting Aß production, accumulation formation

of amyloid fibers, reducing tau phosphorylation, protecting mitochondria from free radicals, and anti-apoptosis effect (43). Of course, in animal studies, antioxidant compounds generally exhibit promising results, but their use in the clinical phase is unsuccessful.

Targeting of mitochondrial pathway

Although antioxidants destroy ROS, controlling the source of ROS production is the most important. Drugs aimed at targeting mitochondria are used for various neurodegenerative disorders. Coenzyme Q10 (CoQ10), commonly known as ubiquinone, is a protein that displaces electrons from complex I to complex II in the electron transfer chain (ETC). Supplementing with CoQ10 may offer neuroprotective benefits by suppressing ROS and enhancing the stability of mitochondrial function (44,45). Other mitochondrial antioxidants comprise R-α-lipoic acid and acetyl-L-carnitine. Nevertheless, this positive impact on oxidative stress has led to a significant reduction in Aß levels in CSF, as well as total levels and their phosphorylation (46).

Cell therapy

Cell therapy using neural stem cells (NSCs) for AD is a significant branch of NSC transplantation for various neurological disorders (47). The basis of cell therapy is the prevention of cell death or the regeneration of damaged tissue (48). Because of their high survival rate and capacity to differentiate into neurons and glial cells after being transplanted into injured tissue, human NSCs are viewed as a highly effective resource for genetic manipulation and gene transfer to the central nerve system (CNS) in ex vivo conditions. Identifying an unlimited source of transplantable cells could represent a breakthrough in cell therapy. In this regard, the infinite ability of stem cells to renew and differentiate into neurons makes cell therapy very important for clinical applications (47). In an AD model, a neurotoxin (Ethylcholine Mustard Aziridinium ion (AF64A)) was stereotaxically injected into the mouse brain (49). This resulted in the loss of cholinergic neurons and memory deficits. This model exhibits many of the salient features of AD. After NSC grafting, it was reported to have increased expression of acetylcholine transferase in AD mice, improved learning and memory function, and increased levels of acetylcholine in cerebrospinal fluid. NSC is associated with improved cognitive function in AD model animals through increased hippocampal synaptic density, mediated by brain-derived neurotrophic factor (BDNF). The excessive expression of nerve growth factor (NGF) in NSC lines leads to improved cognitive impairments in the AD model (50).

Combining neurotransmitter and growth factor secretion in engineered cells enhances cell therapy for AD, which involves multiple cell death pathways. Mesenchymal stem cells (MSCs) are accessible and effective for this multifaceted approach (51). MSCs transplantation to aging models in rats resulted in the differentiation of these cells into neuronal cells, accompanied by an increase in local concentrations of neurotransmitter acetylcholine transporter, vascular endothelial growth factor (VEGF), BDNF, and NGF, leading to improved motor and cognitive function. However, only a few reports have documented the functional or synaptic maturity of neurons derived from MSCs under **in** vivo conditions after transplantation. MSCs exhibit abundant neuroprotective properties, and by secreting these factors, they stimulate the proliferation, differentiation, and survival of neurons in cellular and animal models of AD (51).

Similarly, in the AD mouse model, MSC transplantation has inhibited cell death associated with Aβ and tau, reduced Aβ aggregation and plaque formation, and promoted neurogenesis, and neural differentiation, thereby improving spatial learning and memory deficits (52).

Injection of extracellular vesicles from human umbilical cord mesenchymal stem cells (HUC-MSCs) into AD mouse models improves cognitive function and promotes the clearance of Aβ. It reduces inflammatory microglial cells, increases immunoregulatory microglial cells, and lowers pro-inflammatory cytokines (interleukin (IL)-1β and tumor necrosis factor-α (TNF-α) while raising anti-inflammatory cytokines (IL-10) and tu-

mor growth factor- β (TGF-β) (53). Placenta-derived MSCs (PD-MSCs) transplantation in the Aβ 1-42 mouse model improves cognitive impairment by reducing the expression of BACE1, APP, Aβ, and β-secretase and γ-secretase activity (47).

Activated microglia have two phenotypes M1 microglia typically produce high levels of pro-inflammatory cytokines including IL-1β, IL-12, TNF-α, and induced nitric oxide (iNOS), often causing damage to the CNS. M2 microglia respond to IL-4, IL-10, IL-13, and TGF-β, which have anti-inflammatory effects in AD. While microglia change from phenotype M2 to M1 in AD. MSCs regulate microglia activation and convert them from the M1 phenotype to the M2 phenotype (54). As a result, they are involved in suppressing inflammatory cytokines, and while inactivating microglia, they prevent the accumulation of Aß and tau phosphorylation, thereby improving learning deficits and spatial memory.

Gene therapy

The first strategy in AD gene therapy is to inhibit secretase activity to reduce amyloid production. Anti-BACE1, given BACE1's pivotal role in producing Aß, is an obvious therapeutic target. BACE1 small molecule inhibitors are being developed and used in various stages of clinical trials (55). The decrease in BACE1 levels using siRNA-expressing lentiviral vectors caused a reduction in amyloid production and neurodegeneration, accompanied by decreased behavioral defects in AD mice (56).

However, recent results showed unexpected and undesirable effects of BACE1 inhibition on synaptic function. Inhibition of BACE1 in animals without disease caused endogenous Aß production to decrease to the point that its neurotrophic and synaptic properties were lost. Inhibition of γ-secretase activity, along with an increase in amyloid-degrading enzymes such as neprilysin enzymes (NEP), endothelin-converting enzyme (ECE), and insulin-degrading enzyme (IDE) using viral vectors is another strategy employed in animal AD models (57).

The second strategy is to increase the levels of neuronal protective factors. BDNF is reduced in AD patients. Administration of BDNF using a lentiviral vector to the entorhinal cortex in an AD mouse model improved learning and memory, increased synaptic protein expression of synaptophysin, and prevented neuron loss (57).

The clinical trial targeting AD involved the administration of cDNA NGF to individuals in the early stages of the disease. Fibroblasts were extracted from dermal tissue and subsequently engineered to express NGF via retroviral vector transformation in vitro. These modified cells (engineered to express NGF) were then implanted into the nucleus basalis of Meynert as part of the therapeutic intervention. In the following year, no adverse effects were observed in the patients after the implantation. Evaluation of the overall cortical metabolic activity demonstrated improvement, which was accompanied by enhanced basal nucleus performance. All patients exhibited a trophic response to NGF, as evidenced by axonal sprouting toward the NGF source (59).

Furthermore, hypertrophy of cholinergic neurons was observed in this case. Activation of cellular signaling and functional markers was reported in two patients undergoing AAV2-NGF gene transfer. Overall, a decline in cognitive function and an increase in glucose uptake in the brain cortex were reported. Additionally, subcortical hemorrhage was noted in two patients during cell implantation. However, no adverse cognitive effects related to NGF were observed. The phase II clinical trial of this study involving 49 patients with mild to moderate AD, utilizing the AAV-NGF vector delivering the NGF gene (CERE-110), revealed that AAV2-NGF was safe and well-tolerated over 24 months. However, a significant difference between the treatment and placebo groups regarding the primary outcome, AD assessment scale, and cognitive scale, was not observed (59).

Nanotechnology offers potential applications in the treatment of AD

To treat AD, drugs must cross the BBB. Effective small lipophilic molecules should have less

than 8-10 hydrogen bonding sites and weigh under 400 DA. Patients often require high doses to ensure enough drug reaches the brain, but this can cause significant side effects from the remaining drug in the bloodstream. Current AD treatments mainly focus on symptom relief due to the challenges of drug penetration through the BBB. Delivery of drugs using nanotechnology-based nanocarriers aims to overcome current limitations by precisely targeting the brain through conjugation with proteins and antibodies. This facilitates effective passage through the BBB via receptor-mediated transcytosis, carrier-mediated transcytosis, absorption-mediated transcytosis, or paracellular diffusion, providing advanced biological access and prolonged retention. Research is ongoing into nanomaterials for managing AD (60). Nanoencapsulation of antioxidants is a strategy to protect them from enzymatic metabolism in the gastrointestinal tract, liver absorption and plasma concentration, and brain targeting ability. In a study on a mouse model of AD in Wistar albino rats, the combined effect of nanocurcumin as an antioxidant and donepezil as an acetylcholinesterase inhibitor was investigated. Histological studies in the hippocampus of mice showed that treatment with nanocurcumin improved memory, movement, and neuronal differentiation by activating the PI3K/AKT/GSK-3β pathway (61). Liposomes are spherical nanoparticles that contain one or more phospholipid bilayers. The ability of liposomes to encapsulate hydrophilic or lipophilic drugs has made these vesicles useful and highly effective drug delivery systems for the brain, recent findings have uncovered the role of apolipoprotein E (APO E) isoforms in clearing toxic Aβ proteins from the brain. In a study, liposomes carrying a plasmid encoding ApoE2 (pApoE2) were specifically targeted using GLUT-1 and CPP.. ApoE2 has prevented AD development, while ApoE4 is a major contributor to the disease. Active liposomes could safely and effectively deliver significant concentrations of the ApoE2 gene to target tissues for AD treatment (62). Researchers utilized intranasal lipid-based nanocarriers loaded with PEGylated glucocorticoids for direct drug delivery from the nasal activity to the brain. Pioglitazone, as an anti-diabetic drug has been shown to improve AD in animal models. However, its success in clinical trials has been limited due to poor BBB penetration and serious environmental side effects.

Nanocarriers of pioglitazone, act as agonists of the peroxisome proliferator-activated receptor (PPARγ). Lead to a reduction in oxidative stress, decreased formation of Aβ plaques and NFT, and neuroinflammation by activating the PI3/AKT pathway and reducing the activity of the p38 MAPK pathway (4).

Gold nanoparticles (Au-NPs) possess the ability to penetrate the BBB and exhibit neuroprotective properties. When combined with glutathione, Au-NPs have demonstrated anti-Alzheimer effects by inhibiting the accumulation of Aβ plaques (63). Solid lipid nanoparticles (SLNs) form colloidal drug delivery systems shown in a study to be suitable carriers for transferring donepezil drugs from the nasal cavity to the brain (64).

polymeric materials have gained significant importance and a special position in drug delivery to the brain. AnjiReddy and Karpagam investigated chitosan nanofibers as carriers of donepezil for AD treatment in animal models and in vitro. The results demonstrated that the chitosan nanofibers as drug carriers reached maximum concentration within 3.5 hours. Additionally, the chitosan nanofibers exhibited significantly faster absorption rates (65).

Huperzine A is a reversible inhibitor of acetylcholinesterase, which effectively aids in the treatment of memory impairment and memory enhancement by affecting the levels of acetylcholine. Meng and colleagues synthesized chitosan-conjugated lactoferrin nanoparticles as carriers of huperzine for the treatment of AD, aiming to facilitate the nasal-to-brain drug delivery of huperzine. In vitro drug release and cell viability studies using the 16HBE cell line support controlled drug release and the safety of nanoparticles for intranasal administration. Studies in kunming mice showed that the

nanosystem efficiently targeted the brain and distributed over a prolonged period through targeted lactoferrin delivery (66).

Wilson and colleagues evaluated the ability of Sitagliptin-loaded chitosan nanoparticles (SIT-CS-NPs) as an approach to deliver SIT to the brain following intranasal administration. Animal studies demonstrated that SIT-CS-NPs increased SIT levels in the brain by 5.07-fold compared to free SIT after intranasal administration (67).

Another study reported that the potential of poly lactic-co-glycolic acid (PLGA) nanoparticles loaded with memantine for targeting the BBB after oral administration in AD treatment was investigated. The results demonstrated that MEM-PEG-PLGA nanoparticles were non-cytotoxic to brain astrocyte cell lines. Behavioral experiments conducted on transgenic APPswe/PS1dE9 mice showed that the use of nanoparticles, compared to free drug solution, reduced memory impairment. Histological studies also confirmed that the nanoparticles reduced beta-amyloid plaque and AD-associated inflammation (68).

Challenges of Regenerative Medicine

Despite the promising potential of regenerative medicine for treating AD, several challenges and limitations must be considered. Cost is a significant barrier, as therapies involving gene editing, cell transplantation, or tissue engineering often require substantial financial investment, making them less accessible to a broader patient population. Safety is another critical concern; the long-term effects of such interventions are not yet fully understood, and potential risks, such as tumorigenicity, mutagenesis, contamination, immune rejection, or immune activation necessitate thorough clinical evaluation. Additionally, the widespread applicability of regenerative therapies is limited by factors such as variability in patient responses, the complexity of AD pathology, and the need for individualized treatment approaches (69, 70).

Conclusion

AD is the most common cause of dementia and the most prevalent neurodegenerative disease in developed countries, affecting over 50 million people worldwide. Despite this, the pathophysiological mechanisms of AD remain largely unknown. Regenerative medicine and traditional medicine offer distinct approaches to treating AD, each with its advantages and limitations. Traditional medicine primarily focuses on symptomatic relief through pharmacological interventions, such as acetylcholinesterase inhibitors and amyloid-beta-targeting therapies. However, these treatments often fail to address the underlying pathophysiology of AD. The positive effects of these drugs are usually temporary, and their effectiveness decreases as the disease progresses. Many of these drugs may cause undesirable side effects, including nausea, diarrhea, allergic reactions, and cardiovascular issues. In contrast, regenerative medicine aims to restore neuronal function and promote neuroregeneration through innovative strategies like gene therapy, cell therapy, and tissue engineering. These approaches target the molecular mechanisms involved in AD and enhance neuroplasticity and neuronal survival (71, 72). Overall, the potential of regenerative medical therapy shows promising results in treating neurodegenerative patients. To improve the outcomes of future research in the field of Alzheimer's, it is suggested to consider personalized treatment protocols, the use of new technologies, and interdisciplinary collaboration.

Journalism Ethics Considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely was approved by the authors.

Acknowledgements

This study was supported by the Deputy of Shahrekord University of Medical Sciences and Arak University of Medical Sciences.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Aisen P, Briand R, Saumier D, Laurin J, Duong A, Garceau D (2008). Targeting amyloid with tramiprosate in patients with mild-to-moderate Alzheimer disease. *Progress in Neurotherapeutics and Neuropsychopharmacology*,3 (1):111-25.
2. Rabiei Z AS, Bigdeli M.R. (2015). Medical herbs effective in the treatment of the Alzheimer disease. *Journal of Babol University of Medical Sciences*,17 (3):51-9.
3. Hampel H, Mesulam M-M, Cuello AC, et al et al (2018). The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. *Brain*,141 (7):1917-33.
4. Conejero-Goldberg C, Gomar J, Bobes-Bascaran T, et al (2014). APOE2 enhances neuroprotection against Alzheimer's disease through multiple molecular mechanisms. *Mol Psychiatry*,19 (11):1243-50.
5. Matsui T, Ingelsson M, Fukumoto H, et al (2007). Expression of APP pathway mRNAs and proteins in Alzheimer's disease. *Brain Res*,1161:116-23.
6. O'brien RJ, Wong PC (2011). Amyloid precursor protein processing and Alzheimer's disease. *Ann Rev Neurosci*,34:185-204.
7. Zheng H, Koo EH (2011). Biology and pathophysiology of the amyloid precursor protein. *Mol Neurodegener*,6 (1):27.
8. Hampel H, Hardy J, Blennow K, et al (2021). The Amyloid-β Pathway in Alzheimer's Disease. *Mol Psychiatry*,26 (10):5481-503.
9. Zhang Y-w, Thompson R, Zhang H, Xu H (2011). APP processing in Alzheimer's disease. *Mol Brain*,4 (1):3.
10. Kadavath H, Hofele RV, Biernat J, et al (2015). Tau stabilizes microtubules by binding at the interface between tubulin heterodimers. *Proceedings of the National Academy of Sciences*,112 (24):7501-6.
11. Goedert M, Jakes R (1990). Expression of separate isoforms of human tau protein: correlation with the tau pattern in brain and effects on tubulin polymerization. *EMBO J*,9 (13):4225-30.
12. Lindwall G, Cole RD (1984). Phosphorylation affects the ability of tau protein to promote microtubule assembly. *J Biol Chem*,259 (8):5301-5.
13. Dubey J, Ratnakaran N, Koushika SP (2015). Neurodegeneration and microtubule dynamics: death by a thousand cuts. *Front Cell Neurosci*,9:343.
14. Zhao Y, Zhao B (2013). Oxidative stress and the pathogenesis of Alzheimer' s disease. *Oxid Med Cell Longev*,2013 (1):316523.
15. Yan X, Hu Y, Wang B, Wang S, Zhang X (2020). Metabolic dysregulation contributes to the progression of Alzheimer's disease. *Front Neurosci*,14:530219.
16. Bezerra da Silva C, Pott A, Elifio-Esposito S, et al (2016). Effect of donepezil, tacrine, galantamine and rivastigmine on acetylcholinesterase inhibition in Dugesia tigrina. *Molecules*,21 (1):53.
17. Asgharzade S, Rabiei Z, Rafieian-Kopaei M (2015). Effects of Matricaria chamomilla extract on motor coordination impairment induced by scopolamine in rats. *Asian Pacific J Trop Biomed*,5 (10):829-33.
18. Zahra R, Shiva M, Samira A, Mostafa G, Samira R, Mahmoud R-k (2015). Inhibitory effect ofThymus vulgaris extract on memory impairment induced by scopolamine in rat. *Asian Pacific J Trop Biomed*:806-11.
19. Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE (2008). Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clin Interv Aging*,3 (2):211-25.
20. Amin J, Paquet C, Baker A, et al (2015). Effect of amyloid-β (A β) immunization on hyperphosphorylated tau: a potential role for glycogen synthase kinase (GSK)-3β. *Neuropathol Appl Neurobiol*,41 (4):445-57.

21. Zhang X, Heng X, Li T, et al (2011). Long-term treatment with lithium alleviates memory deficits and reduces amyloid-β production in an aged Alzheimer's disease transgenic mouse model. *J Alzheimer's Dis*,24 (4):739-49.
22. Domínguez JM, Fuertes A, Orozco L, del Monte-Millán M, Delgado E, Medina M (2012). Evidence for irreversible inhibition of glycogen synthase kinase-3β by tideglusib. *J Biol Chem*, 287 (2):893-904.
23. Boutajangout A, Wisniewski T (2014). Tau-based therapeutic approaches for Alzheimer's disease-a mini-review. *Gerontology*,60 (5):381-5.
24. Malpas CB, Vivash L, Genc S, et al (2016). A phase IIa randomized control trial of VEL015 (Sodium Selenate) in mild-moderate Alzheimer's disease. *J Alzheimer's Dis*,54 (1):223-32.
25. Bhargava S, Kulkarni R, Dewangan B, et al (2023). Microtubule stabilising peptides: new paradigm towards management of neuronal disorders. *RSC Med Chem*,14 (11):2192-205.
26. Brunden KR, Trojanowski JQ, Smith III AB, Lee VM-Y, Ballatore C (2014). Microtubule-stabilizing agents as potential therapeutics for neurodegenerative disease. *Bioorg Med Chem*,22 (18):5040-9.
27. Badiola N, Alcalde V, Pujol A, et al (2013). The proton-pump inhibitor lansoprazole enhances amyloid beta production. *PloS One*, 8 (3):e58837.
28. Blair LJ, Sabbagh JJ, Dickey CA (2014). Targeting Hsp90 and its co-chaperones to treat Alzheimer's disease. *Expert Opin Ther Targets*,18 (10):1219-32.
29. Ma QL, Zuo X, Yang F, et al (2013). Curcumin suppresses soluble tau dimers and corrects molecular chaperone, synaptic, and behavioral deficits in aged human tau transgenic mice. *J Biol Chem*,288 (6):4056-65.
30. Kasibhatla AKS, Biamonte M, Zhang H, et al (2007). Small-molecule HSP90 Inhibitors: Applications in Cancer and Neurodegenerative Diseases. *Heat Shock Proteins in Cancer*:275-94.
31. Lahiri DK, Chen D, Maloney B, et al (2007). The experimental Alzheimer's disease drug posiphen [(+)-phenserine] lowers amyloid-β peptide levels in cell culture and mice. *J Pharmacol Exp Therap*,320 (1):386-96.
32. Aisen PS, Gauthier S, Ferris SH, et al (2011). 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):102-11.
33. Ma K, Thomason LA, McLaurin J (2012). Scyllo-inositol, preclinical, and clinical data for Alzheimer's disease. *Adv Pharmacol*,64:177-212.
34. Barker R, Love S, Kehoe PG (2010). Plasminogen and plasmin in Alzheimer's disease. *Brain Res*,1355:7-15.
35. Pride M, Seubert P, Grundman M, Hagen M, Eldridge J, Black RS (2008). Progress in the active immunotherapeutic approach to Alzheimer's disease: clinical investigations into AN1792-associated meningoencephalitis. *Neurodegener Dis*,5 (3-4):194-6.
36. Robinson SR, Bishop GM, Lee H-g, Münch G (2004). Lessons from the AN 1792 Alzheimer vaccine: lest we forget. *Neurobiol Aging*, 25 (5):609-15.
37. Vandenberghe R, Riviere ME, Caputo A, et al (2017). Active Aβ immunotherapy CAD106 in Alzheimer's disease: A phase 2b study. *Alzheimers Dement (N Y)*,3 (1):10-22.
38. Hull M, Sadowsky C, Arai H, et al (2017). Long-Term extensions of randomized vaccination trials of ACC-001 and QS-21 in mild to moderate alzheimer's disease. *Cur Alzheimer Res*,14 (7):696-708.
39. Panza F, Frisardi V, P Imbimbo B, et al (2011). Anti-β-amyloid immunotherapy for Alzheimer's disease: focus on bapineuzumab. *Curr Alzheimer Res*,8 (8):808-17.
40. Moradi Z, Rabiei Z, Anjomshoa M, et al (2021). Neuroprotective effect of wild lowbush blueberry (Vaccinium angustifolium) on global cerebral ischemia/reperfusion injury in rats: Downregulation of iNOS/TNF-α and upregulation of miR-146a/miR-21 expression. *Phytother Res*,35 (11):6428-40.
41. Habtemariam S (2016). Rutin as a natural therapy for Alzheimer's disease: Insights into its mechanisms of action. *Cur Med Chem*, 23 (9):860-73.
42. Mishra S, Palanivelu K (2008). The effect of curcumin (turmeric) on Alzheimer's disease: An overview. *Ann Indian Academy Neurol*,11 (1):13.

43. Lin L, Huang QX, Yang SS, et al (2013). Melatonin in Alzheimer's disease. *Int J Mol Sci*,14 (7):14575-93.
44. Dumont M, Kipiani K, Yu F, et al (2011). Coenzyme Q10 decreases amyloid pathology and improves behavior in a transgenic mouse model of Alzheimer's disease. *J Alzheimer's Dis*,27 (1):211-23.
45. Yang X, Zhang Y, Xu H, et al (2016). Neuroprotection of coenzyme Q10 in neurodegenerative diseases. *Curr Top Med Chem*,16 (8):858-66.
46. Montgomery SA, Thal L, Amrein R (2003). Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol*,18 (2):61-71.
47. Yun H, Kim H, Park K, et al (2013). Placenta-derived mesenchymal stem cells improve memory dysfunction in an Aβ1–42-infused mouse model of Alzheimer's disease. *Cell Death Dis*,4 (12):e958-e.
48. Asgharzade S, Talaei A, Farkhondeh T, Forouzanfar F (2020). A review on stem cell therapy for neuropathic pain. *Curr Stem Cell Res Ther*,15 (4):349-61.
49. Walsh TJ, Chrobak JJ (2013). *Animal Models of Alzheimer's Disease: Role of Hippocampal Cholinergic Systems in Working Memory. Current Topics in Animal Learning*. Psychology Press; 2013. p. 359-92.
50. Park D, Lee HJ, Joo SS, et al (2012). Human neural stem cells over-expressing choline acetyltransferase restore cognition in rat model of cognitive dysfunction. *Exp Neurol*,234 (2):521-6.
51. Zhang L, Dong ZF, Zhang JY (2020). Immunomodulatory role of mesenchymal stem cells in Alzheimer's disease. *Life Sci*, 246:117405.
52. Lee HJ, Lee JK, Lee H, et al (2010). The therapeutic potential of human umbilical cord blood-derived mesenchymal stem cells in Alzheimer's disease. *Neurosci lett*,481 (1):30-5.
53. Ding M, Shen Y, Wang P, et al (2018). Exosomes isolated from human umbilical cord mesenchymal stem cells alleviate neuroinflammation and reduce amyloid-beta deposition by modulating microglial activation in Alzheimer's disease. *Neurochem Res*,43:2165-77.
54. Danielyan L, Beer-Hammer S, Stolzing A, et al (2014). Intranasal delivery of bone marrow-derived mesenchymal stem cells, macrophages, and microglia to the brain in mouse models of Alzheimer's and Parkinson's disease. *Cell Transplant*,23 (1_suppl):123-39.
55. Vassar R (2014). BACE1 inhibitor drugs in clinical trials for Alzheimer's disease. *Alzheimer's Res Ther*,6 (9):89.
56. Singer O, Marr RA, Rockenstein E, et al (2005). Targeting BACE1 with siRNAs ameliorates Alzheimer disease neuropathology in a transgenic model. *Nat Neurosci*,8 (10):1343-9.
57. Li Y, Wang J, Zhang S, Liu Z (2015). Neprilysin gene transfer: A promising therapeutic approach for A lzheimer's disease. *J Neurosci Res*,93 (9):1325-9.
58. Tanila H (2017). The role of BDNF in Alzheimer's disease. *Neurobiol Dis*,97:114-8.
59. Tuszynski MH, Thal L, Pay M, et al (2005). A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. *Nat Med*,11 (5):551-5.
60. Cao Y, Zhang R (2022). The application of nanotechnology in treatment of Alzheimer's disease. *Front Bioengin Biotechnol*,10: 1042986.
61. Beltagy DM, Nawar NF, Mohamed TM, Tousson E, El-Keey MM (2024). The synergistic effect of nanocurcumin and donepezil on Alzheimer's via PI3K/AKT/GSK-3β pathway modulating. *Prostaglandins Other Lipid Mediat*,170:106791.
62. Arora S, Layek B, Singh J (2021). Design and Validation of Liposomal ApoE2 Gene Delivery System to Evade Blood-Brain Barrier for Effective Treatment of Alzheimer's Disease. *Mol Pharm*,18 (2):714-25.
63. Hou K, Zhao J, Wang H, et al (2020). Chiral gold nanoparticles enantioselectively rescue memory deficits in a mouse model of Alzheimer's disease. *Nat Commun*,11 (1):4790.
64. Topal GR, Mészáros M, Porkoláb G, et al (2020). ApoE-Targeting Increases the Transfer of Solid Lipid Nanoparticles with Donepezil Cargo across a Culture Model of the Blood-Brain Barrier. *Pharmaceutics*,13 (1):38.

65. AnjiReddy K, Karpagam S (2017). Chitosan nanofilm and electrospun nanofiber for quick drug release in the treatment of Alzheimer's disease: In vitro and in vivo evaluation. *Int J Biol Macromol*,105:131-42.
66. Meng Q, Wang A, Hua H, et al (2018). Intranasal delivery of Huperzine A to the brain using lactoferrin-conjugated N-trimethylated chitosan surface-modified PLGA nanoparticles for treatment of Alzheimer's disease. *Int J Nanomed*,13:705-18.
67. Wilson B, Mohamed Alobaid BN, Geetha KM, Jenita JL (2021). Chitosan nanoparticles to enhance nasal absorption and brain targeting of sitagliptin to treat Alzheimer's disease. *J Drug Delivery Sci Technol*,61:102176.
68. Sánchez-López E, Ettcheto M, Egea MA, et al (2018). Memantine loaded PLGA PEGylated nanoparticles for Alzheimer's disease: in vitro and in vivo characterization. *J Nanobiotechnolgy,* 16 (1):32.
69. Wang ZB, Wang ZT, Sun Y, Tan L, Yu JT (2022). The future of stem cell therapies of Alzheimer's disease. *Ageing Res Rev*, 80:101655.
70. Ortega A, Chernicki B, Ou G, Parmar MS (2024). From Lab Bench to Hope: Emerging Gene Therapies in Clinical Trials for Alzheimer's Disease. *Mol Neurobiol*, 62(1):1112-1135.
71. Bhatt A, Bhardwaj H, Srivastava P (2024). Mesenchymal stem cell therapy for Alzheimer's disease: A novel therapeutic approach for neurodegenerative diseases. *Neurosci*,555:52-68.
72. Ataei B, Hokmabadi M, Asadi S, et al (2024). A review of the advances, insights, and prospects of gene therapy for Alzheimer's disease: A novel target for therapeutic medicine. *Gene*,912:148368.