Review Article

Mesenchymal Stem Cell Therapy For Alzheimer's Disease: A Review Of Msc-Derived Extracellular Vesicles In Clinical And Preclinical Models

Mahdi Rezaei[1], Amir Tahavvori[2], Nadia Doustar[3], Armin Jabraeilipour[4], Amirreza Khalaji[5], Ali Shariati[6], Reza Mosaddeghi Heris[7], Erfan Golshan Shali[8], Farima Fakhri[9], Fariba Mirakhori[10], Hossein Tahernia[11], Hamed Rahmani Youshanlouei[12*]

[1,6,8] School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Faculty of Internal Medicine, Urmia University of Medicine, Urmia, Iran
[3]Faculty of Internal Medicine, Ardabil University of medical sciences, Ardabil, Iran
[4]Faculty of Internal Medicine, Islamic Azad University of Ardabil, Ardabil, Iran
[5]Connective Tissue Diseases Research Center Tabriz University of Medical Sciences Tabriz Iran.
[5]Immunology Research Center Tabriz University of Medical Sciences Tabriz Iran
[6,7]Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[9]Department of Neurology, University of Chicago Medical Center, Chicago, IL, USA
[10]General practitioner, Zanjan University of medical sciences
[11]Molecular Medicine Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[12*]Department of Internal Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

*Corresponding Author: Hamed Rahmani Youshanlouei

*MD, Tabriz University of Medical Sciences, Tabriz, Iran. E-mail:Hamed.Rahmani284@gmail.com
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Abstract

Alzheimer's disease (AD) is a frequent dementia form that impacts central nervous system (CNS) areas implicated in higher cognitive functions, including memory and learning and is defined by behavioral disturbances, memory loss, and progressive cognitive decline. Because of the heterogeneity and complexity of AD, effective methods are needed to address this epidemic. Mesenchymal stem cell (MSC)-based treatments have illustrated positive outcomes in several disorders experimental models such as those impacting CNS, as well as are being found in neurological disorders clinical trials. Extracellular vesicles (EVs), like micro vesicles and exosomes, are heterogeneous membrane structures containing numerous proteins, nucleic acids, and lipids. In comparison to management with stem cells, EVs have lower tumorigenicity and immunogenicity, and their managements are easier. This review is an overview of the available knowledge of the essentials of MSCs and MSC-derived EVs from many sources in clinical and preclinical AD models. This study includes the various MSCs types' examination, like induced-pluripotent stem cells-MSCs and Bone marrow-MSCs Wharton's jelly-MSCs.

Keywords: Dementia, Alzheimer’s disease, AD, Exosomes, Micro vesicles, Regeneration, Mesenchymal Stem cells, MSCs, mild cognitive impairment

INTRODUCTION

Alzheimer's disease (AD) origins are possibly traced back to also Alzheimer's seminal work, a neuropathologist who recognized in the brain the characteristic pathological indication of the condition, namely amyloid-beta plaques presence of neurofibrillary tangles (1). An AD hallmark is the misfolded protein accumulation which identifies plaques of Aβ, which possess neurotoxic properties and are detected in the extracellular space, which can result in neuronal loss. *Tau* is a misfolded protein that is correlated with AD. *Tau* is a microtubule protein associated with accumulation inside cells. This phenomenon's pathological characteristics are closely correlated with AD cognitive decline (2, 3). Tau gene encoding mutations result in frontotemporal dementia rather than AD typically (3). Tau protein hyper phosphorylation is aggregated by insoluble neurofibrillary tangles, which are both conditions' hallmark features. However, the correlation between Tau neurofibrillary tangles and Aβ plaques has not been fully understood. Also, their synergistic function is believed to lead to synaptic and neuronal losses in many of the brain cortical areas, resulting in cognitive decline and memory loss. AD is known as the main cause of frailty and dementia worldly (4). This debilitating disease frequently manifests firstly as mild memory difficulties, which develop into disruptions in complex daily activities, more severe cognitive impairment, and numerous other cognitive deficits (1). The diagnosis of AD is clinical; neuropathological lesions and extensive neuronal loss have already developed in the brain in multiple regions (5, 6).

AD is the sixth most frequent death cause in the United States. Currently, AD incidence is 36 million cases worldwide (7). The U.S. Food and drug administration (FDA) has approved medications such as memantine, galantamine, rivastigmine, and donepezil in AD management. In the early AD stages, these medications have been illustrated to have therapeutic advantages (8-11). Also, for moderate to severe AD, Memantine received FDA approval in the USA, which

is an N-methyl-D-aspartate receptor antagonist (12). Prevention of dementia trials utilizing Ginkgo biloba, antihypertensive drugs, Nonsteroidal anti-inflammatory drugs (NSAID), and vitamin E and selenium did not have effective in diminishing AD risk (13-17). Since 1991 the cascade of the amyloid hypothesis has been put forth, and medications developing that target researchers have focused on the amyloid cascade (18).

Currently, many ongoing clinical trials are focusing on targeting specific steps in the amyloid cascade via many interventions, including amyloids vaccines, Beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1) inhibitors, and secretase inhibitors anti-tau approaches. To this end, several compounds have been investigated, including tramiprosate (19) and Scylla-inositol (20), which are amyloid aggregation inhibitors, tarenflurbil (21), amyloid-secretase modulator, semagacestat (22), amyloid-secretase inhibitor, avagacestat (23), a receptor for advanced glycation end products (RAGE) inhibitor, bapineuzumab, solanezumab both, immunoglobulins and amyloid antibodies, in the amyloid cascade hypothesis context. These interventions hold significant potential for effective therapy development for conditions related to amyloid deposition in the brain (24).

Because of the null outcomes observed in previous research, researchers have begun conducting trials with larger sample sizes and longer durations (25). Additionally, studies are now focusing on AD's preclinical or prodromal phase (25). To ensure the subjects with AD inclusion pathology and facilitate disease modification interventions, measurements and interpretation are being implemented using well-established scales like the clinical dementia rating (CDR), the Alzheimer's disease cooperative study-activities of daily living (ADCS-ADL), and Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog), as well as biomarkers such as cerebrospinal fluid A and amyloid positron emission tomography before and after the study (26).

Recent studies have shown no significant changes in using solanezumab in the CDR-sum or ADCS-ADL baseline-to-endpoint scores of boxes for cases with mild AD (18). Also, data supporting the intravenous immunoglobulin using decreasing preventing cognitive decline, brain atrophy, or the conversion from mild cognitive delaying impairment to cases with AD was limited. (27). These adverse outcomes have led researchers to adopt a multifaceted method containing neuroregeneration and stem cells to address the AD therapy clinical benefits (28).

Stem cells have a noticeable capacity to differentiate into numerous types of cells by self-renewal and are capable to categorize according to their differentiation potential (26). The omnipotent or totipotent stem cells can be differentiated into extraembryonic and embryonic cells and possess the unique potential of a fertilized egg to produce a complete organism (29). However, totipotent stem cells have a slightly higher potency than pluripotent stem cells. In contrast, pluripotent stem cells can still differentiate into the three types of germ cell layers mesoderm, endoderm, and ectoderm (30).

Stem cells (SC) have different potency degrees, which range from unipotent to Oligo potent to multipotent. Multipotent SC can vary into closely related cells, like mesenchymal SC (31). However, Oligo potent SC have feature to self-renew into closely related cells only, including hematopoietic stem cells. Also, unipotent SC is capable to vary into one kind of cell like muscle stem cells and the least potent SC (32).

SCs are grouped into many categories according to their source (33). Blastocyst derives embryonic stem cells (ESCs), the embryo developmental stage after fertilization for about 5-6 days. ESCs are highly potent and can vary to any type ofcell in the body. However, after abortion, fetal stem cells are gained from fetal tissue and have less potential than ESCs (34, 35).

Perinatal SCs, such as those gained from the umbilical cord, placenta, and amniotic fluid, offer a remarkable change to ESCs. On the other hand, the amniotic fluid SC use is limited because of the invasive gathering nature via procedures like amniocentesis (36, 37). However, the perinatal SCs availability suggests significant potential for therapeutic applications and research, and ongoing studies are exploring their unique potential and properties' clinical advantages.

Additionally, epithelial flakes derived from fetal skin are commonly used for research. At the same time, placental SCs are extracted from the placental villi and amnion of the depleted placenta, but unfortunately, when cultured in vitro, they cannot divide indefinitely. However, SCs of the umbilical cord preserved in umbilical cord blood (UCB) banks often show the most frequent SCs used type (35, 38). Though the applications range for SCs of the umbilical cord is comprehensive, robust data considering their effectiveness needs improvement (38).

Recently, Wharton's jelly took remarkable attention because of its mesenchymal constituents. Typically known as tissue-restricted or resident SCs, adult SCs frequently undergo self-renewal occasionally and are unipotent in numerous tissues, including endometrial epithelium, gastrointestinal, and human epidermis. This has made them an exciting research area, especially in regenerative medicine, for their utilizing potential (35, 39).

Moreover, induced pluripotent stem cells (iPSCs) illustrated a noticeable option because of their potential in vitro differentiation into all cell types in the body. On the other hand, it is worth noting that many management limitations correlate with iPSC use (40, 41).

MSCS AND THEIR EXTRACELLULAR VESICLES

Multipotent adult SCs, known as MSCs, have been widely studied in clinical and preclinical trials for various disorders in the last 30 years (42). MSCs can vary into multiple lineages, including chondrocytes, adipocytes, and osteocytes. It is possible to detect in numerous postnatal organs, such as dental follicles, human placental, bone marrow, human-induced pluripotent stem cell, human cord blood, Wharton's Jelly, adipose tissue, human amniotic membrane, and umbilical cord (43-45). These cells show surface markers like CD73, CD90, and CD105 but not CD11b, CD14, CD19, CD34, and CD45)49-46(. MSCs present broad regenerative, immunoregulatory, and anti-inflammatory properties (50-52).

It has been shown that MSCs secrete EVs and have an essential role in handling biological processes, including angiogenesis, regeneration, blood coagulation, immunomodulation, and stem cell differentiation (53, 54). Evs have two

major subtypes: micro vesicles and exosomes, which are produced by direct budding from the plasma membrane and secretion of micro vesicular bodies into the extracellular space, and both are Nano-sized (55, 56).

Various Mesenchymal stem cells in treatment Alzheimer's disease

Mesenchymal stem cells (MSCs) derived from numerous sources, such as Wharton's jelly, human induced pluripotent stem cells, and bone marrow, in managing and regenerating AD. Mainly, researchers have found MSCs efficacy in dental follicles, human placentas, human amniotic membrane, adipose tissue, umbilical cord, and cord blood. The following sections of this review will delve into this topic in greater detail (57, 58).

BONE MARROW-MSCS

According to the SC tissue sources, therapeutic SCs are possible to classify into two groups: allogenic and autologous SCs. Allogenic SCs are derived from embryonic tissue, umbilical cord, or placenta, while autologous SCs are gathered from tissues including bone marrow, dental pulp, fat, or brain (59, 60). iPSC-derived stem cells, in some cases, have been used (61). On the other hand, some research has been conducted on different kinds of SC tissue sources. Allogeneic SCs' immunogenicity and ethical issues soon make them unsuitable for AD management (62). The autophagy mechanism analysis involved in the transplantation of Bone Marrow Mesenchymal Stem Cells (BMMSCs) has illustrated the enhancement in the behavioral and cognitive impairments in AD animal models (63). Transplanted BMMSCs can decrease neurogenesis stimulation and neuronal apoptosis, thus suggesting a significant management avenue for AD (64). In addition, the crosstalk between apoptosis and autophagy showed a novel target for therapeutic drug development aimed at increasing the SC treatment's beneficial effects. The autophagy utilizing and/or apoptosis modulators is possible to amplify the BMMSC's therapeutic potential (65).

In the AD cases clinical management, SCs of autologous cells derived from fat or bone marrow are chosen (66). Interestingly, bone marrow SCs have better outcomes than SCs isolated from adipose tissue (67). In the pre-clinical study, BMMSCs have certain advantages while many problems, including poor homing into injured tissue, low viability, and heterogeneity still complicated (68). Furthermore, the SCs' therapeutic efficiency is likely impacted by cell viability, preconditioning, and delivery approach (68, 69).

Various SC transplantation approaches exist, such as intracerebroventricular, intrahippocampal, intravenous, or autologous MSCs intranasal delivery (70).Various research has found that BMMSCs can improve memory decline, neuropathology, and behavioral impairments such as cognitive impairment, as demonstrated by many tests like the social recognition test, plus-maze discriminative avoidance task, Y-maze alternation test, Morris water maze test, open-field evaluation (71). Additionally, positive results were detected even by a bone marrow-derived mononuclear cell transplantation (72, 73). Currently, in the autologous BMMSCs, technical improvements ensure their clinical application (74).

Despite these positive results, the beyond-action mechanism has yet to elucidate fully. Current high-profile research provided evidence that supported the notion that transplanted BMMSCs activate autophagy, as data by alternations in the signal molecules expressions levels like mTOR, LC3-II, Atg5, and Beclin-1 (75). The functional autophagy induction contributes to mitigating neuronal apoptosis, as reflected by changes in caspase-3, Bcl-2, IAPs, and other markers. Moreover, enhancing autophagy, the BMMSCs transplantation has been detected that diminish tau aggregates and aberrant amyloid-beta peptides, blocking stimulating synaptogenesis and neuroinflammation (75, 76).

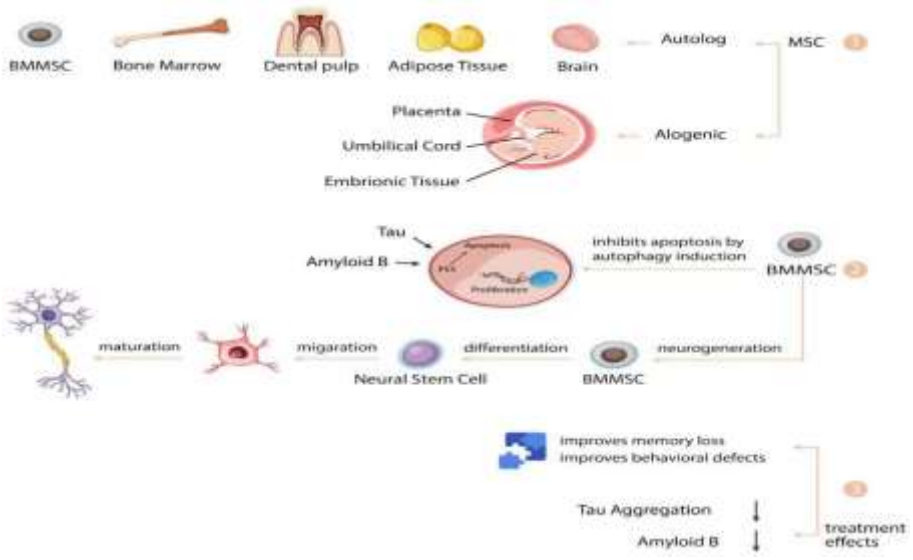

Figure 1. The Bone Marrow-derived Mesenchymal Stem Cells impacts on Alzheimer's disease management: A Summary of Current Findings.

In addition, there appears to be a signal crosstalk between apoptosis and autophagy that may be mediated to generate a synergistic impact in the SCs preconditioning. Thus, the transplanted BMMSCs' therapeutic effect could be increased by

autophagy modulators and/or apoptosis. Via a comprehensive review and meta-analysis of relevant literature, these data underscore the BMMSCs transplantation potential as an effective method for AD treatment (76, 77).

INDUCED-PLURIPOTENT STEM CELL-MSCS

The iPSCs emergence technology has illustrated remarkable potential in AD research in overcoming many challenges (78). These cells that induce pluripotency are formed from somatic cells utilizing specific transcription factors. iPSCs closely resemble ESCs, can self-renew indefinitely, and vary into any kind of cell type, such as glial cells and neurons, which are relevant to research on AD (78, 79).

One of the noticeable iPSCs benefits is that they are capable of being formed from their own somatic cells case, which eliminates immune rejection issues correlated with ESCs and ethical concerns (80). Cases-specific iPSCs derived from either sporadic or familial AD, in vitro, is possible to recapitulate the disease's pathological characteristics, and modeling AD plays a valuable tool (78, 81).

Moreover, isogenic iPSCs of AD-iPSCs are possible to gather utilizing the technology of genetic repairing like CRISPR/Cas- or TALEN- mediated genome editing (78, 82). For transplantation studies and disease modeling, genetically repaired AD-iPSCs have a role appropriate to control cells (1, 83). Although in iPSCs clinical technology applications have numerous challenges, recently, in this field, advancements made remarkable Capacities for promoting clinical therapy and unraveling the AD molecular mechanisms (84). In this review, we discuss the recent progress in iPSCs research and its potential applications, as well as the major challenges and future directions in disease modeling and cell-replacement therapy for AD.

Wharton's Jelly-derived mesenchymal stem cells

Wharton's Jelly-derived mesenchymal stem cells (WJ-MSCs) have demonstrated potential therapeutic benefits for neurological illnesses (85-87). A study shown four weeks after administering WJ-MSCs intravenously to APP and PS1 mice showed a memory decline and discernible improvement in the animals' spatial learning (86). Following WJ-MSC treatment, the levels of A deposition and soluble A were also significantly decreased (86, 88, 89). Also, WJ-MSCs increase the anti-inflammatory cytokine IL-10 expression, although pro-inflammatory cytokines expression, TNF and IL-1, and activation of pro-inflammatory microglial were decreased. These data suggest that WJ-MSCs, through modifying neuroinflammation, could positively impact the management and prevention of AD (86, 90).

Human umbilical cord mesenchymal stem cell

A study found that human umbilical cord mesenchymal stem cell (HUC-MSC) administration to AD PS1 and APP model in the hippocampus and cortex mice decreased the amyloid beta burden, associated with a decline in cognitive impairment (91).

As we mentioned in Table 1, the reduction in amyloid plaque burden relative to controls suggests that HUC-MSCs may positively impact AD pathogenesis in a transgenic mice model when taken as a whole. Additionally, this decrease in pathology was linked to better sensorimotor and cognitive performance (91-93).

Adipose-derived stem cells

Adipose-derived stem cells (ADSC) diminish Aβ plaques, an AD hallmark characteristic. ADSC therapy results in Aβ deposits decreasing in the brain at a cellular level. Although, some studies illustrated inconclusive causes for decreasing Aβ accumulations. In addition, combining the therapy of ADSC with Melatonin may be due to the microglia activation by the administering of SC, resulting in the Aβ deposits clearance (94, 95).

Based on recent research, activation of microglia can decrease the progression of neurodegenerative diseases such as AD and other dementias (96). On the one hand, microglia have a role in inflammation; on the other hand, they can act as an anti-inflammatory factor (97). Also, some studies suggest that microglial activation in the brain may mediate the Aβ propagation and act as a vehicle via which plaques may migrate to unaffected brain areas (95, 98).

It is crucial to remember that several types of microglia are activated during the development of neurodegenerative illnesses. They can behave in pro-inflammatory and anti-inflammatory ways that are antagonistic to one another. Emerging research intriguingly reveals that stem cell therapy-induced microglial activation favors anti-inflammation rather than inflammation. It is crucial to remember that several types of microglia are activated during the development of neurodegenerative illnesses. They can behave in pro-inflammatory and anti-inflammatory ways that are antagonistic to one another. Emerging research intriguingly reveals that stem cell therapy-induced microglial activation favors anti-inflammation rather than inflammation (99).

The ADSC treatment for microglia activation holds promise for AD management, while more research is required to understand whether this activation lessens or favors ongoing inflammation (100). Treatment with ADSC can cause neuronal survival improvement from the accumulation impacts, which can activate microglial. Besides, it has been shown that the ADSCs administration elevates the neurotrophic factors production, such as brain-derived neurotrophic factor (BDNF), in the brain controls and encourages synapse formation (95, 101, 102). Additionally, as we noted in Table 1, ADSCs have been shown to successfully lower inflammatory factor levels in AD models, including IFN, TNF, IL -1, and IL-2. These neurotrophic and anti-inflammatory effects may help significantly improve AD therapy. Although ADSC

therapy appears promising in treating AD, further studies are required to fully comprehend its workings and potential advantages (103-105).
The Morris Water Maze and Novel Object Recognition tests were predominantly used to examine the learning, memory, and cognitive deficits in the animal models of AD in studies. Nonetheless, a firm and specific conclusion still needs to be made easier due to differences in treatment approaches, AD induction models, and other aspects across the articles under review. Nevertheless, as previously mentioned, the cellular-level mechanisms brought about by treating ADSCs, mainly through microglia activation (106), may be responsible for the observed behavioral improvements. The removal of a plaques and a rise in neurotrophic factors may result from such activation. Numerous reviewed researches show that performance on the Morris water maze test may increase if this clearing occurs in brain regions involved in memory and learning, such as the hippocampus. These results may spur additional investigation to obtain more convincing data to assess the therapeutic potential of ADSCs fully (107).

Human amniotic membrane-MSCs

Significant oxidative stress may have an essential role in the genesis and progression of AD, according to a research growing body (108). Amyloid buildup may be responsible for the increasing of oxidative stress, which leads to mitochondrial dysfunction and lipid peroxidation. C57BL/6JAPP transgenic mice were injected with human placenta amniotic membrane-derived mesenchymal stem cells (HAMMSCs) (109). In the brain, HAMMSCs utilized considerably increased memory and spatial learning and were correlated with decreasing amyloid plaque quantity (110).
Posing lower lipid peroxidation product amounts and higher antioxidative enzyme levels in the cases receiving HAMMSC illustrated a lesser association between Amyloid levels and oxidative stress than in the cases that received phosphate-buffered saline (PBS) (111). As demonstrated, elevated antioxidative enzyme levels and reduced lipid peroxidation product levels. In addition, the HAMMSC-treated group had higher glutathione (GSH) levels and a lower GSH-to-glutathione disulfide ratio than the PBS group. Additionally, malonaldehyde levels and superoxide dismutase activity significantly increased as A levels dropped, but this pattern was not seen in the PBS group (112). These results demonstrate that HAMMSC therapy may improve AD pathology and memory function by reducing oxidative stress (103).

Human placental-MSCs

A study showed that the administration of placenta-derived mesenchymal stem cells (PD-MSCs) in mice significantly decreased cognitive impairments and behavioral alternations by downregulating BACE, APP, and expression of Amyloid (111, 113). Additionally, it was discovered that PD-MSC transplantation reduced the glial cell activation, expression of cyclooxygenase-2, and inducible nitric oxide synthase (114). PD-MSCs have a role in diminishing inflammatory cytokine release while elevating the differentiation of neuronal cells from neuronal progenitor cells as well as preventing neuronal cell death. These outcomes imply that the PD-MSCs neuroprotective properties are mediated by modulation of cytokine expression profiles, hippocampal glial cell activation, neurogenesis, and neuronal death. These data demonstrate a pivotal correlation between MSC-based treatment methods and decreasing CNS damage in AD (115, 116).

Various Extracellular Vesicles of MSC in treatment of AD

Extracellular Vesicles of MSC (MSC-EVs) formed from MSCs are being found as a potential therapeutic intervention for AD treatment (117). These membrane-bound vesicles, formed by MSCs, have many bioactive chemicals (118, 119). These bioactive compounds may affect the MSC-EVs' therapeutic potential, which can modulate cellular processes and immunomodulatory impacts and exert regenerative (120).
Studies have found that MSC-EVs possible to decrease oxidative stress and neuroinflammation, promote neuronal function and survival, and improve synaptic plasticity (121). These processes are all essential aspects of AD pathophysiology, suggesting that MSC-EVs may be a proper therapeutic strategy. Moreover, MSC-EVs promotecognitive function and memory in AD animal models (122).

Several clinical experiments are currently being conducted to assess the MSC-EVs' effectiveness and security in cases with AD. These investigations aim to ascertain whether MSC-EVs can modulate illness, lessen inflammation, and foster neuroprotection. These studies may provide crucial information on the MSC-EVs' therapeutic capacity as a potential AD treatment option (123, 124).

Many biomolecules such as nucleic acids, lipids, and proteins are found in EVs which are synthase by cells and are tiny vesicles (125). They have therapeutic impacts on numerous diseases and act as intercellular messengers (126).
Based on research, BMMSCs and EVs may affect the survival and support the growth of neurons, lessen neuroinflammation, and the immune system (127, 128). For instance, an AD mouse model has shown that BM-MSCs possible to increase cognitive performance and decrease amyloid-beta accumulation (136). Another study illustrated that EVs generated from BMMSCs might promote cognitive performance and induce neurogenesis (129).
Overall, EVs and BMMSCs possess potential therapeutic for AD management (130). Although, more studies are required to understand their action mechanisms and better use them in clinical settings.

Dental pulp stem cells

The Dental pulp stem cells (DPSCs) capabilities for neurological disease therapy have attracted attention recently. Because of their feature to advance into functioning neurons in response to the right inductive signals, DPSCs are considered as MSCs prospective sources for neurodegeneration (131). In addition, DPSCs demonstrated that they have special immunosuppressive and immunomodulatory activities, which lead them to be a potential treatment for CNS injuries and diseases (132).

Also, DPSCs generate neural-related factors that have neuroprotective and nutritional influences and favorable impacts on the immune regulatory response following injury (133, 134). DPSCs diminish immunological responses of Natural killer cells, T and B cells, and Dendritic cells, which have demonstrated tipping in the scales of anti-inflammatory cytokines to inhibit inflammation (132). By blocking the NLRP3 pathways, activating the toll-like receptor 4, and enhancing mitochondrial dysfunction, DPSCs maybe neutralize or reverse neuroinflammation (135). DPSCs can polarize the M2 macrophage phenotype, which is beneficial for response to tissue damage and inflammation (136, 137).

DPSCs are considered possible for CNS illnesses and injuries management because of their excellent features. With an emphasis on their anti-inflammatory and immunomodulatory abilities, this study aimed to summarize recent research on the DPSCs utilized for neurological disorders therapy (133, 138).

Table 1:Summary of studies investigating Alzheimer's disease mice used, experimental models, and key findings.

Author	Experimental Model	Transplantation Method	Results and Conclusion	Reference
Lee G-Y et al.	C57BL/6 mice	Intraperitoneal injection	The study discovered that the mice's scopolamine-induced cognitive abnormalities were alleviated by alpha-pinene treatment. In particular, the therapy enhanced the mice's performance in the Morris water maze tests and passive avoidance, frequently used to gauge an animal model's capacity for learning and memory. The scientists hypothesized that alpha-pinene's advantages for cognitive function might result from its capacity to control cholinergic neurotransmission, lessen oxidative stress, and promote neurogenesis.	(71)
Lee HJ et al.	A double transgenic AD mouse model was utilized for the HUCB-MSC evaluation.	Intraperitoneal injection	In APP/PS1 mice, activation of microglial increases HUCB-MSC therapy. Amyloid deposition declining following HUCB-MSC treatment is associated with switching microglial phenotype from the classic to the form of alternatively activated. Immunomodulation regulates produce of amyloids after HUCB-MSC therapy in APP/PS1 mice.	(93)
Kim K-S et al.	An AD transgenic mouse model was used to assess the AMSC transplantation effect	Stereotaxic (hippocampus)	AD animal model was injected by AMSCs and altered microglial cell properties toward a persistent cytotoxic response rather than an anti-inflammatory response that decreases amyloid β plaques. AMSCs injection increases memory function and decreases AD progression in AD mice.	(103)
Yun H et al.	Double-transgenic mice, APPswe/ PS1d E9, in a C57BL/6 background harbor the Presenilin-1 and APPs we(Swedish mutations K594 N/M595L) with deletion of exon-9(PS1-dE9)under the control of mouse prion protein promoter.	Injected into the tail vein	HUMSCs intravenous infusion enhanced behavioral performance in AD mice. BACE1 downregulation and oxidative stress reduction are correlated with the molecular pathway of HUMSC-mediated advantages impacts.	(115)

AD: Alzheimer's disease, HUCB-MSC: Human umbilical cord blood-derived mesenchymal stem cells, HUMSC: Human umbilical cord-derived stem cell, AMSC: Amniotic membrane stem cell, BACE-1: eta-site amyloid precursor protein cleaving enzyme 1.

CONCLUSION AND FUTURE PERSPECTIVE

The therapeutic potential of MSCs for various neurological disorders, including AD, has garnered considerable interest. The remarkable attributes of MSCs, such as their immunomodulatory and anti-inflammatory activities, regenerative properties, and other advantageous features, position them as promising candidates for AD intervention. Investigations have been conducted into the efficacy and safety of MSCs derived from many sources, such as Wharton's Jelly, adipose tissue, placenta, bone marrow, and UCB. Nonetheless, a more extensive body of clinical research is needed to ascertain the MSC management feasibility and safety of in cases with AD prior to its widespread adoption in clinical practice. In parallel with their application in pulmonary disorders, EVs, particularly exosomes originating from MSCs, may present a safer and more efficacious therapeutic strategy for AD due to their reduced tumorigenicity, immunogenicity, and ease of management compared to their progenitor MSCs. However, a thorough examination of the biogenesis, pharmacokinetics, and biodistribution of MSC-EVs is imperative before they can be integrated as a standard treatment modality.

Furthermore, additional, comprehensive experiments are warranted to develop an optimal protocol for the MSCs preparation and isolation for clinical utilization. The engineering or refinement of MSC-derived EVs has the potential to yield enhanced therapeutic candidates with diminished adverse effects for future clinical applications involving MSC-EVs in AD intervention.

Abbreviations:

AD: Alzheimer's disease, FDA: Food and drug administration, BACE-1: Beta-site amyloid precursor protein cleaving enzyme 1, CDR: Clinical dementia rating, ADCS-ADL: Alzheimer's disease cooperative study-activities of daily living, ADAS-cog: Alzheimer's disease assessment scale-cognitive subscale, SC: Stem cells, BMMSC: Bone Marrow Mesenchymal Stem Cells, iPSC: induced pluripotent stem cell, WJ-MSC: Wharton's Jelly-derived mesenchymal stem cell, ADSC: Adipose-derived stem cells, HAMMSC: Human placenta amniotic membrane-derived mesenchymal stem cell, PBS: Phosphate-buffered saline, GSH: Glutathione, PD-MSC: Placenta-derived mesenchymal stem cell, DPSC: Dental pulp stem cell, AMSC: Amniotic membrane stem cell.

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