Received: 25 March 2022 | Accepted: 18 May 2022

DOI: 10.1002/prp2.977

REVIEW ARTICLE

Adipose tissue-derived stem cells as a potential candidate in treatment of Alzheimer's disease: A systematic review on preclinical studies

Arian Madani Neishaboori[1] | Azadeh Eshraghi[2] | Arezou Tasouji Asl[3] | Marjan Shariatpanahi[4,5] | Mahmoud Yousefifard[1] | Ali Gorji[6,7,8]

[1]Physiology Research Center, Iran University of Medical Sciences, Tehran, Iran

[2]Emergency Medicine Management Research Center, Health Management Research Institute, Iran University of Medical Sciences, Tehran, Iran

[3]School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran

[4]Department of Pharmacology and Toxicology, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran

[5]Neuroscience Research Center (NRC), Iran University of Medical Sciences, Tehran, Iran

[6]Epilepsy Research Center, Neurosurgery Department, Westfälische-Wilhelms-Universität, Münster, Germany

[7]Shefa Neuroscience Research Center, Khatam Alanbia Hospital, Tehran, Iran

[8]Neuroscience Research Center, Mashhad University of Medical Sciences, Tehran, Iran

Correspondence

Marjan Shariatpanahi, Department of Pharmacology and Toxicology, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran.
Email: shariatpanahi.m@iums.ac.ir

Mahmoud Yousefifard, Physiology Research Center, Hemmat Highway, P.O Box: 14665-354, Tehran, Iran.
Email: yousefifard20@gmail.com; yousefifard.m@iums.ac.ir

Funding information

Iran University of Medical Sciences, Grant/Award Number: 22285

Abstract

In recent years, numerous investigations have evaluated the efficacy of adipose tissue-derived stem cells (ADSCs) and their exosome transplantation in managing Alzheimer's disease (AD) in different animal models. However, there are still many contradictions among the studies that hinder reaching a reliable conclusion. Therefore, we aimed to systematically review the existing evidence regarding the efficacy of ADSCs administration in treatment of AD. The systematic search was conducted in the databases of Medline (via PubMed), Embase, Scopus, and Web of Science, in addition to the manual search in Google and Google scholar, to find articles published until March 13, 2021. Preclinical studies were included and two independent reviewers summarized the eligible papers. Ten articles were included in our review. The treatment strategies varied between isolated ADSC, ADSCs exosomes, ADSCs conditioned medium, and combination therapy (ADSCs plus conditioned medium in one study, and ADSCs plus melatonin in another study). Overview of the included articles showed promising results of ADSCs and its conditioned medium/exosome administration in animal models of AD. These studies showed significant learning and memory improvements through ADSCs and their conditioned medium/exosome administration in animal models of AD. In addition, the application of ADSCs reduced the amyloid-beta plaque deposits in the hippocampus and neocortex of these animals. Based on the aforementioned evidence, studies have suggested potential beneficial effects of ADSCs in the treatment of AD, particularly through decreasing the size of Aβ plaques and improvement of cognitive deficits. Further investigations regarding the subject are encouraged to achieve more accurate conclusions.

KEYWORDS

Alzheimer's disease, cell death, cognition, neurodegeneration, stem cells

Arian Madani Neishaboori and Azadeh Eshraghi contributed equally.

1 | INTRODUCTION

Alzheimer's disease (AD) is the seventh most common cause of death in the United States, and its fatality and prevalence are enhancing due to the increase in the elderly population.[1] AD is the most widespread kind of dementia and its symptoms are memory loss and cognitive impairment. It is accompanied by psychological symptoms, such as anhedonia, anxiety, nervousness, delusions, and depression. It certainly disrupts patients' daily activities.[2,3]

The etiology of this nerve-destructive and advancing disease is multifactorial, and both genetics and environment play a role in it. One of the pathophysiological alterations causing this disease involves the extraordinary build-up of intracellular neurofibrillary tangles.[4] Beta-amyloid (Aβ) contains amino acid peptides 36–43 and is a major component of amyloid plaques in the brains of patients with AD. These peptides are derived from Amyloid Protein precursors (APP).[5] This protein is expressed in the cells of the nervous system and is involved in cell attachment, cell contact, and extracellular matrix, and cell skeleton.[6] Aging plaques are made up of strands of protein called amyloid bodies, and some other proteins called apolipoprotein E, synuclein, and alpha-antichymotrypsin.[7] The formation of these plaques seems to be one of the main causes of AD. These plaques cause the connection between the nerve cells to be cut off, and eventually, these nerve cells die and the brain tissue is destroyed. Some important brain chemicals are reduced in patients with AD. These chemical transmitters of the message help transmit signals around the brain. When these substances are reduced in the brain, the signals are not transmitted properly.[8–10] Inflammation of the nervous system can be caused by either damage to the brain tissue itself or induced by peripheral inflammatory processes, which needs appropriate therapeutic strategies to prevent age-related cognitive decline and neurodegenerative diseases.[11] Since a definitive cure for AD has not been found yet, investigations to find a cure for this disease continues.

Stem cell therapy is known as an effective strategy in the treatment of neurological diseases. Stem cells have the ability to differentiate into other cell types and the power of unlimited division and the possibility of using them in the process of cell therapy.[12] Stem cells can suppress neuroinflammation, which plays a key role in the pathogenesis of AD.[13] In this regard, as a potential candidate, stem cells have captured attention. Among different types of stem cells, adipose tissue-derived derived stem cells (ADSCs) are being investigated, due to easy extraction, simple availability, and their immunomodulatory properties.[14,15] Recent progress in using stem cells as treatment candidates has resulted in developing of new therapeutic strategies in the treatment of nervous system diseases. As a motivating factor, ADSCs can be easily separated from Adipose tissue and are easily reproduced in lab conditions. These cells have the ability of distinction to a couple of cell lines. Some studies report that using ADSCs has numerous beneficial effects on some neurological disorders, including AD.[6] Transplanting mesenchymal stem cells, via the intracranial route; in mice models of AD have caused total recovery by releasing brain-derived neurotrophic factor (BDNF) and decreasing Aβ.[16]

In this sense, ADSCs are one of the most popular sources of mesenchymal stem cells, due to their lower potential of inflaming graft rejection responses and tumorigenesis and their less ethical conflictions. Furthermore, they can be administered through the intravenous (IV) route, which is considered a safe, easy, and less complicating route. The therapeutic potential of IV administration of human ADSCs (hADSCs) and their exosomes in nervous system diseases was previously discussed in several disorders, such as Huntington's disease (HD), mouse models of ischemic brain stroke, and spinal cord injuries.[17–20]Although the pathogenesis of AD is rather different from HD and stroke, it has been revealed that IV transplantation of hADSCs in animal models of AD improved memory loss and learning a few months after the application.[21] In recent years, the number of studies investigating the efficacy of ADSCs transplantation in managing AD in animal models has increased.[22,23] However, there are still many contradictions among the studies that hinder reaching a reliable conclusion about the matter. Therefore, in order to reach a reliable conclusion, we aimed to systematically review and present the existing evidence regarding the efficacy of ADSCs administration in the treatment of AD.

2 | MATERIALS AND METHODS

2.1 | Study design

The present article was designed according to the latest version of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[24] As a result, PICO (Problem, Intervention, Comparison, Outcome) in the present study was defined as: P: animal models of AD, I: ADSCs, its conditioned medium or exosome administration, C: comparison with the non-treated AD group, O: any histological or behavioral outcome evaluated in the included studies.

2.2 | Search strategy

The systematic search was conducted in the databases of Medline (via PubMed), Embase, Scopus, and Web of Science, in addition to the manual search in Google and Google scholar, to find articles published until March 13, 2021. The search term in Medline via PubMed is depicted as follows: ((“Alzheimer disease”[mesh] OR “Alzheimer”[TIAB] OR dementia[TIAB]) AND (“Mesenchymal Stem Cells”[Mesh] OR “Adipogenic”[TIAB] OR “Adipogenesis”[TIAB] OR “Adipocytes”[TIAB] OR ((“Stem Cell”[TIAB] OR “Progenitor cell”[TIAB] OR “mother cell”[TIAB]) AND (Adipose[TIAB] OR fat[TIAB])))). The articles achieved through the systematic search were collected, and duplicates were removed using Endnote Software. Finally, the reference lists of the eventually included articles were screened to find additional articles.

2.3 | Selection criteria

After removing duplicates, articles were screened using predefined inclusion and exclusion criteria by two independent reviewers. The inclusion criteria were articles evaluating treatment efficacy of ADSCs or ADSC-related medium and cellular extractions' administration on animal models of AD. Furthermore, the exclusion criteria were lack of a no-treatment AD group (control group), lack of in vivo assessments, remaining duplicate articles, and review articles. After applying the inclusion criteria and removing the excluded studies, the included studies were gathered for the data collection step. Any disagreements were resolved by discussion with a third reviewer.

2.4 | Data collection

Two independent reviewers used a predesigned data sheet based on the PRISMA to extract relevant data from the included articles. The extracted data included the name of the first author, publication year, characteristics of the studied animals (species, strain, and gender), model of AD induction in the animals, interval time between injury and treatment, administered treatment, source of the administered treatment (type of graft), route of the administered treatment, number of the administered cells, the follow-up period, and the behavioral and tissue examinations performed in the studies. Likewise the screening process, any disagreements were resolved by discussion with a third reviewer.

2.5 | Risk of bias assessment

We used SYRCLE's risk of bias tools.[25] This tool evaluates the risk of bias of animal studies in 10 domains of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Two independent reviewers assessed the included papers in detail and rated the signaling questions as low, high, and unclear. Any disagreement was resolved by discussion.

3 | RESULTS

3.1 | Study characteristics

The systematic and manual search in databases resulted in 1134 articles, of which 789 were non-duplicated. Next, the title and abstract screen were performed to eliminate 770 articles, and from the remaining 19 articles, 10 were included in our systematic review[16,22,26–33] (Figure 1). From the included studies, five were performed on rats and five were performed on mice. The experimental model of AD was obtained through Aβ injection in all rat studies, and the five mouse studies used genetically modified mice developing AD at a certain age, in which the time interval between injuries to treatment was accurately indeterminable. The treatment strategies varied between isolated ADSC, ADSCs exosomes, ADSCs conditioned medium, and combination therapy (ADSCs plus conditioned medium in one study, and ADSCs plus melatonin in another study). Type of graft was allograft in three studies and xenograft in seven studies. Behavioral tests varied between Morris Water Maze test, Novel Object Recognition test, Open Field test, Elevated Plus Maze test, Passive Avoidance Learning test, Tail Suspension test, Forced Swim test, and Y maze. Moreover, tissue markers of the Aβ deposits in the brain, including cortex and hippocampus, and neuron survival (or death) were measured among the studies. Eventually, follow-up days varied from 14 to 120 days from the treatment day. Table 1 summarizes the characteristics of the included studies.

3.2 | Effects of ADSC administration in AD animal models

Overall, seven articles evaluated the therapeutic effects of ADSCs in different animal models of AD.[16,22,26,30–33] Although an explicit meta-analysis was not applicable to the included results, an overview of these investigations could help to understand the potential effects and mechanisms of ADSCs administration in experimental models of AD. These studies evaluated the behavioral tests as well as histopathological assessments in AD animal models after application of ADSCs.

Behavioral assessments were performed in five studies. Of these, four investigations performed the Morris Water Maze test to evaluate different cognitive impairment parameters, including the reward system (learning) and the spatial memory[16,22,26,32] after application of ADSCs in animal models of AD. Although one study has reported that the Morris Water Maze did not show any significant improvements after the treatment with ADSCs,[26] another three studies have shown significant learning and memory improvements in the Morris Water Maze test achieved through ADSCs administration.[16,22,32] Moreover, using the Novel Object Recognition test, it has been reported that ADSCs significantly promoted cognitive impairments in AD animal models.[22,26,31] Using the Open Field test, the elevated Plus Maze test, and the passive avoidance learning test, Nasiri et al. have shown limited effects of ADSCs on the improvement of cognitive deficits in a rat model of AD.[26]

The effects of ADSCs on Aβ deposits in different brain regions were evaluated in four studies.[16,22,26,33] As a result of ADSCs treatment, a significant reduction of the number of plaques in the hippocampus was shown in AD animal models in three studies,[16,22,33] while two studies observed a decrease in the number of plaques in the neocortex.[16,22] Ma et al. have reported a significant decrease of the Aβ plaques after the treatment with ADSCs, both in the neocortex and hippocampus, in an animal model of AD.[22] The three mentioned articles used three different methods of treatment of intracranial, intrahippocampal, and intravenous administrations of ADSCs. Nonetheless, Nasiri et al. presented an insignificant decrease in Aβ deposit area in the brain slices of rat models of AD that

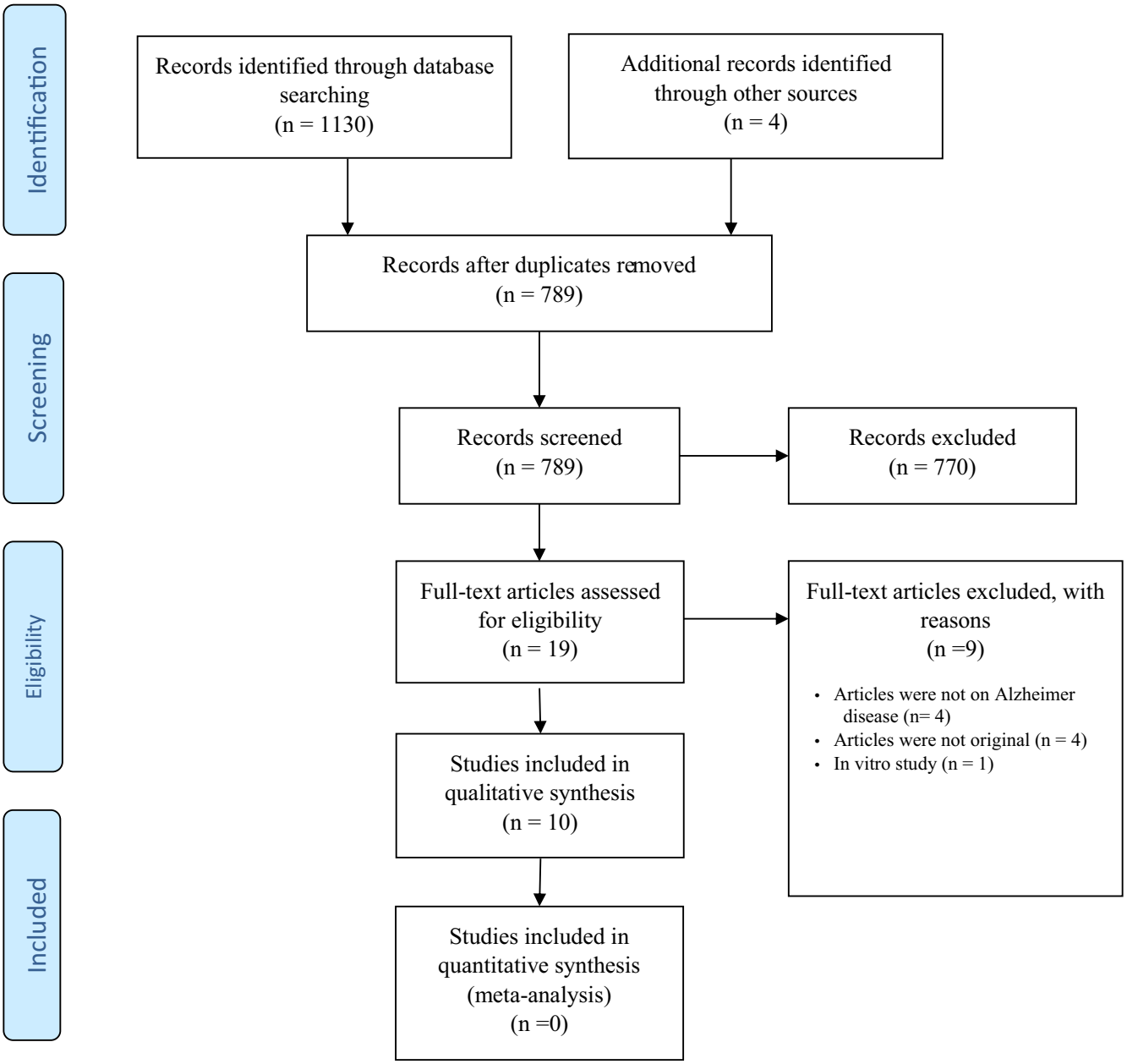

FIGURE 1 PRISMA flow diagram of current systematic review.

receiving ADSCs treatment compared with the animal receiving no treatment.[26] Neuronal death was the other assessment performed in two of the articles evaluated the effect of ADSCs in AD animal models. Both these studies have shown a significant reduction of hippocampal neuronal loss in the ADSCs treatment group compared with the non-treatment control group.[30,32]

3.3 | Effects of exosomes and conditioned media derived from ADSCs in AD animal models

Two studies have evaluated the effect of exosome and conditioned media derived from ADSCs in animal models of AD. Mehrabadi et al. have shown that both learning and memory significantly improved after the application of ADSCs conditioned medium in an AD rat model. The discrimination index in Novel Object Recognition was significantly higher in the conditioned medium-treated group compared with the non-treated animal group, which indicated to an enhanced cognition improvement. Moreover, their study on tissue markers in the hippocampal area revealed a significant increase in neuronal survival rate and a significant decrease in Aβ deposits following ADSCs conditioned medium treatment.[28]

On the other hand, Ma et al. evaluated the effects of ADSCs exosome treatment following the development of AD. They observed that the discrimination index was significantly higher following the treatment with ADSCs exosomes compared with the non-treated animals. Moreover, conditioned medium-treated animals have shown a better performance in the number of arm entries and the

TABLE 1 Characteristics of included studies

Study, year	Gender, strain, species,	Model of injury	Injury to treatment (days)	Treatment	Type of graft	Administration route	Number of cells	Follow up (days)	Behavioral test	Tissue markers
Doshmanziari, 2019[33]	Male, Wistar, Rat	Aβ injection	21	Stem Cell	Xenograft	IV	3.0×10^6	90	NR	CA Aβ deposits
Eftekharzadeh, 2020 [30]	Male, Wistar, Rat	Aβ injection	21	Stem Cell	Xenograft	IV	NR	90	NR	CA neuron death
Kazemiha, 2019[32]	Male, Wistar, Rat	Aβ injection	21	Stem Cell	Xenograft	IV	1.0×10^6	60	MWM	CA neuron death
Kim, 2012[16]	Female, APPswe Tg2576, Mouse	Genetically Modified	NA	Stem Cell	Xenograft	IV, IC	13.0×10^6, 1.0×10^5	96–120	MWM	CA and Cortex Aβ deposits
Ma, 2020[29]	Female, App/PS1, Mouse	Genetically modified	NA	Exosome	Xenograft	IN	NR	14	NOR, Y maze	CA and Cortex Aβ deposits
Ma, 2013[22]	Male, App/PS1, Mouse	Genetically Modified	NA	Stem Cell	Xenograft	ICA	1.0×10^5	25–30	MWM, NOR	CA and Cortex Aβ deposits
Mehrabadi, 2020[28]	Male, Wistar, Rat	Aβ injection	0	Conditioned medium	Allograft	IN	NR	16–20	MWM, NOR	CA neuron survival, CA Aβ deposits
Nasiri, 2019[26]	Male, Wistar, Rat	Aβ injection	7	Stem Cell, Stem Cell + Melatonin	Allograft	IV	1.0×10^6	60–69	OF, EPM, NOR, MWM, PAL	Brain Aβ deposits
Yamazaki, 2015[27]	NR, 5× FAD, Mouse	Genetically modified	NA	Stem Cell + Conditioned medium	Allograft	IV	1.0×10^5	28	TS, FS	NR
Yan, 2014[31]	NR, App/PS1, Mouse	Genetically modified	NA	Stem Cell	Xenograft	ICA	1.0×10^5	28	NOR	NR

Abbreviations: Aβ, Aβ; CA, Hippocampus; EPM, Elevated Plus Maze; FS, Forced Swim Test; IC, Intracerebral; ICA, Intrahippocampal; IN, Intranasal; IP, Intraperitoneal; IV, Intravenous; MWM, Morris Water Maze; NA, Not Applicable; NOR, Novel Object Recognition test; NR, Not Recorded; OF, Open Field test; PAL, Passive Avoidance Learning test; TS, Tail Suspension test.

percentage of behavioral alternations of the Y Maze test. These findings suggest an overall cognition improvement following the treatment with ADSCs. However, the findings of Ma et al. revealed that the treatment with ADSCs had no significant effect on the reduction of the Aβ deposits in the hippocampus and the cortex. They also reported an amelioration in neurological damage of AD in hippocampus, dentate gyrus, and cortex of the animals following exosome treatment.[29]

3.4 | Combination therapies using ADSCs

Only two articles attempted to use ADSCs combination therapy, with *Nasiri* et al. adding melatonin to their stem cell treatment, and Yamazaki et al. applied the ADSCs together with their conditioned medium. The ADSCs plus melatonin treatment has shown outstanding effects, both from tissue and behavioral aspects. They observed that the Aβ deposit area was significantly reduced in rat brains following the ADSCs plus melatonin treatment. Moreover, in their behavioral assessments, their findings showed significant improvements in cognition as well as learning and memory deficits following the treatment in animal models of AD, in the Morris Water Maze, Novel Object Recognition test, and the Passive Avoidance Learning test. However, their Open Filed and Elevated Plus maze tests did not show any significant difference between the animal models of AD receiving no treatment and the models receiving ADSCs plus melatonin treatment.[26]

Yamazaki et al. performed no tissue analysis of Aβ deposits or neuronal loss. Moreover, their behavioral assessments using tail suspension and forced swim test did not depict a significant difference between the mice group receiving no treatment and the animals receiving ADSCs plus conditioned medium treatment. Their findings indicated an overall inefficiency of their treatment method in AD mice models.[27]

3.5 | Risk of bias

There was considerable bias among included studies according to SYRCLE's risk of bias tools (Figure 2). Allocation sequence generation in all included studies was high risk or unclear. In addition, baseline similarities among included animals, allocation concealment, random housing, the blinding status of caregivers/investigators and outcome assessors, and addressing incomplete outcome data were high risk or unclear in all included studies. Moreover, only one study provided adequate data on randomization. There was no evidence of selective reporting in 6 studies and 3 studies were free of other possible biases (Table 2).

4 | DISCUSSION

The present systematic review aimed to evaluate and assess the treatment potential of ADSCs and its derivatives (exosome, conditioned media, and combination therapy) on the resolution of tissue and behavioral impairments in animal models of AD. Overall, the existing evidence in the literature regarding the subject, although scarce, presents us with promising findings. One may conclude

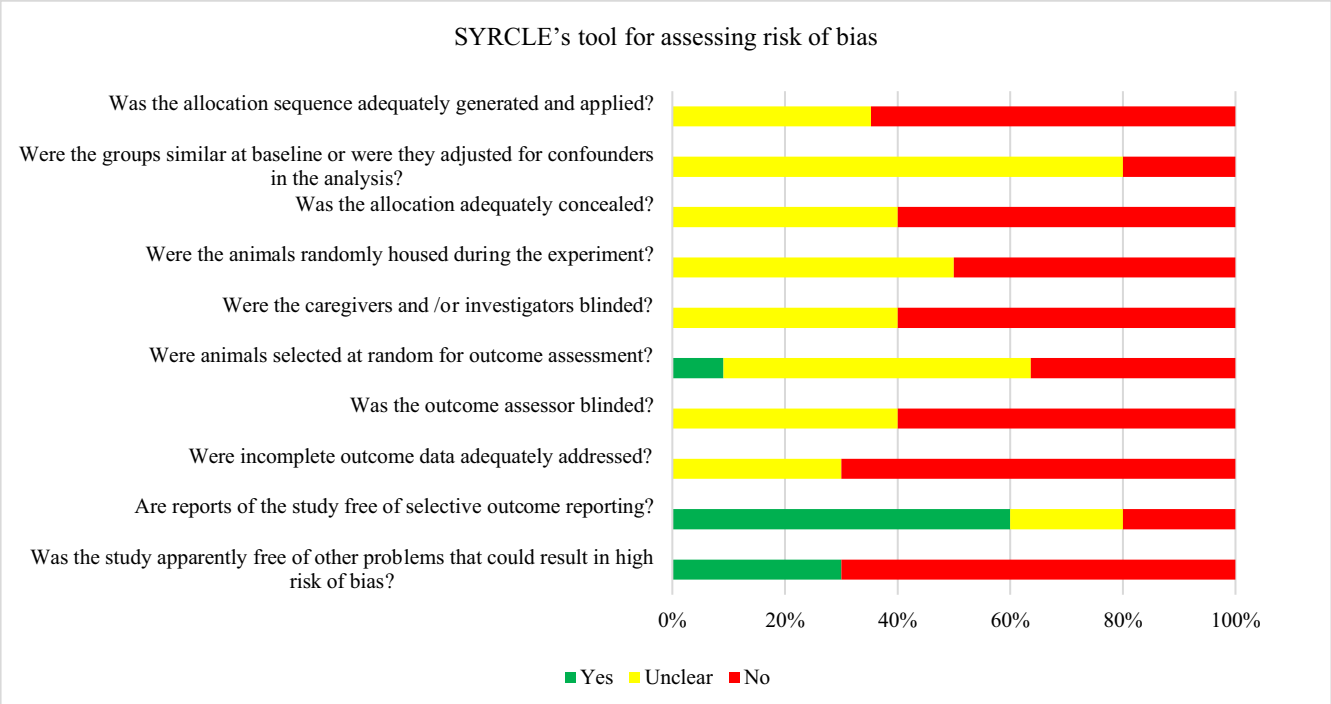

FIGURE 2 Risk of bias assessment of included studies.

TABLE 2 Risk of bias assessment of included papers

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Doshmanziari, 2019[33]	No	Yes	No	Yes	No	No	No	Unclear	Yes	No
Eftekharzadeh, 2020[30]	No	Unclear	Unclear	No	Unclear	Unclear	Unclear	No	Unclear	No
Kazemiha, 2019[32]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes
Kim, 2012[16]	No	No	No	No	No	No	No	No	No	No
Ma, 2020[29]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	No
Ma, 2013[22]	No	Yes	No	Yes	No	No	No	No	Yes	No
Mehrabadi, 2020[28]	Unclear	Yes	No	Unclear	No	Yes	No	No	Yes	Yes
Nasiri, 2019[26]	Unclear	Yes	No	No	No	Unclear	No	No	Yes	Yes
Yamazaki, 2015[27]	No	Unclear	No	Unclear	No	No	No	No	Yes	No
Yan, 2014[31]	No	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear	No	No

Note: Questions according to Hoojimans et al. study[25]: Q1: Sequence generation; Q2: Baseline characteristics; Q3: Allocation concealment; Q4: Random housing; Q5: Caregivers and/or investigators blinding; Q6: Random outcome assessment; Q7: Outcome assessor blinding; Q8: Incomplete outcome data; Q9: Selective outcome reporting; Q10: Other sources of bias. Yes: Low risk; No: High risk.

that further investigations are needed to discuss whether ADSCs are considered as appropriate treatment option in AD, but our results indicate that this treatment method is certainly worth further investigations.

From a cellular level point of view, one could speculate that most of the included articles in our study were consistent with the fact that ADSCs treatment may decrease Aβ deposits in the brain. However, two of the included studies in the present article did show discrepancies, reporting insignificant findings for the decrease in Aβ accumulations, from which Nasir et al. achieved significant results adding a melatonin combination to its ADSCs treatment regimen. The pathophysiology behind may be as a result of microglial activation by the administered stem cells, and subsequently, clearance of Aβ deposits, as suggested by a number of studies.[22,34,35] However, microglia activation, that said by recent articles, was a double-edged sword in the process of AD and other neurodegenerative diseases. In other words, it could play both an inflammatory and an anti-inflammatory role.[36] Accordingly, some studies have presented evidence, stating that microglial activation might propagate Aβ formation in the brain, acting as a carrier through which the plaques could migrate into the unaffected areas of the brain.[37] Nevertheless, studies suggest that many types of microglia were activated at the time of a pathogenesis inside the brain, counteracting to one another, in terms of being proinflammatory and anti-inflammatory.[38] Interestingly, growing evidence suggest that microglial activation as a result of stem cell administration, was more in favor of anti-inflammation, rather than being proinflammatory.[39] As a result, ADSC therapy in AD might be promising with respect to microglial activation, and more evidence is needed to shed light on whether microglial activation following ADSC administration is in favor of the ongoing inflammation or attenuating the inflammation. Moreover, three articles reported a decrease in neuronal loss, which could be as a result of ADSCs treatment enhancing neuronal survival against the toxic effects of Aβ accumulations inside the brain.[40] This again may be attributed to the activation of microglia, as suggested by Vinet et al.[41] In addition, a number of neurotrophic factors have been raised as a result of ADSCs administration and this might be responsible for the promising effects of stem cell therapy in AD models. For instance, the microglial activation through stem cell therapy, could promote the build-up of the well-known BDNF, promoting and modulating synapse formation inside the brain.[42] Furthermore, stem cells, have shown to be effective in lowering inflammatory factors such as IL-1, IL-2, TNF-α, and IFN-γ, when administered in AD models.[43] Overall, these beneficial effects through neurotrophic and anti-inflammatory factors could contribute to large-scale improvements in AD.[44,45]

From a behavioral point of view, learning, memory, and cognitive deficits of the animal models of AD in the included studies, predominantly evaluated by Morris Water Maze and Novel Object Recognition tests, did exhibit improvements. However, due to disparities between the articles in the means of treatment, model of AD induction, etc., a strong and inclusive conclusion is yet to be achieved. Altogether, these behavioral improvements may be attributed to the mentioned cellular level resolves being achieved by ADSCs treatment, especially through the activation of microglia, as stated before. As mentioned, the activation can result in the clearance of Aβ plaques and the increase in neurotrophic factors. Hence, if the Aβ clearance has occurred in areas in the brain dealing with memory and learning, hippocampus, for instance, an improvement will occur in Morris water maze test performance, as observed in a number of the included studies. These findings may be a motivation for future works to be conducted toward

achieving stronger evidence to accurately evaluate the possible ADSCs treatment for AD.

As a limitation, the included articles in our study were almost nonuniform. First, three different treatment routes were used, which may have resulted in differences in the efficacy and safety of the treatment. Second, the AD induction differed, leading to a group of animals being genetically modified to develop AD and another group being injected by the Aβ depositions, which could consequently result in different grades and presentations of the disease. Third, the treatment options of combination therapy and ADSCs exosome therapy were each evaluated in only one study. Collectively, future research should go toward filling these mentioned gaps, for the later scientists to more accurately evaluate and analyze the existing evidence to better achieve a conclusion.

5 | CONCLUSION

The present systematic review aimed to evaluate the existing evidence regarding AD treatment using ADSC. Overall, studies report promising findings regarding the application of ADSCs in the treatment of AD, especially through decreasing the Aβ plaques. As a result, further investigations regarding the subject are encouraged to achieve more accurate conclusions.

AUTHORS' CONTRIBUTIONS

Marjan Shariatpanahi carried out conceptualization, reviewing, and supervision. Mahmoud Yousefifard carried out investigation, writing, and supervision. Azadeh Eshraghi contributed to reviewing and supervision. Arian Madani Neishaboori and Arezou Tasouji Asl carried out investigation, writing, and original draft preparation. Ali Gorji carried out reviewing, visualization, and editing of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENT

The financial assistance of the Iran University of Medical Sciences with grant number 22285 is appreciatively confirmed.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The current review was supported by the Ethics Committee of Iran University of Medical Sciences (Number: IR.IUMS.REC.1399.1447).

DATA AVAILABILITY STATEMENT

All data generated and analyzed in the study are available from the corresponding author upon reasonable request.

ORCID

Marjan Shariatpanahi https://orcid.org/0000-0003-3616-9089

REFERENCES

1. Chan HJ, Roy J, Tipoe GL, Fung M-L, Lim LW. Therapeutic potential of human Stem Cell implantation in Alzheimer's disease. *Int J Mol Sci*. 2021;22(18):10151.
2. As A. 2011 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2011;7(2):208-244.
3. As A. 2010 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2010;6(2):158-194.
4. Graham WV, Bonito-Oliva A, Sakmar TP. Update on Alzheimer's disease therapy and prevention strategies. *Annu Rev Med*. 2017;68:413-430.
5. Meng-Jie L, Zhang L-N, Shang Y-H, Huang H-C, Feng-Xue L. Application progress of induced pluripotent stem cells in Alzheimer's disease. *Med J Chin People's Lib Army*. 2021;46(2):193-199.
6. Joyce N, Annett G, Wirthlin L, Olson S, Bauer G, Nolta JA. Mesenchymal stem cells for the treatment of neurodegenerative disease. *Regen Med*. 2010;5(6):933-946.
7. Patwardhan AG, Belemkar S. An update on Alzheimer's disease: immunotherapeutic agents, stem cell therapy and gene editing. *Life Sci*. 2021;282:119790.
8. George-Hyslop PS. Chapter 98, Molecular genetics of Alzheimer's disease. *Principles of molecular medicine*. Springer. 1998;901-906. https://doi.org/10.1007/978-1-59259-726-0_98
9. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2011;1(1):a006189.
10. Zhang Y-T, He K-J, Zhang J-B, Ma Q-H, Wang F, Liu C-F. Advances in intranasal application of stem cells in the treatment of central nervous system diseases. *Stem Cell Res Ther*. 2021;12(1):1-10.
11. Skok M. Mesenchymal stem cells as a potential therapeutic tool to cure cognitive impairment caused by neuroinflammation. *World J Stem Cells*. 2021;13(8):1072-1083.
12. Si Z, Wang X. Stem cell therapies in Alzheimer's disease: applications for disease modeling. *J Pharmacol Exp Ther*. 2021;377(2):207-217.
13. Qin C, Li Y, Wang K. Functional mechanism of bone marrow-derived Mesenchymal Stem cells in the treatment of animal models with Alzheimer's disease: inhibition of Neuroinflammation. *J Inflamm Res*. 2021;14:4761-4775.
14. Mazini L, Rochette L, Amine M, Malka G. Regenerative capacity of adipose derived stem cells (ADSCs), comparison with mesenchymal stem cells (MSCs). *Int J Mol Sci*. 2019;20(10):2523.
15. de Girolamo L, Lucarelli E, Alessandri G, et al. Mesenchymal stem/stromal cells: a new "cells as drugs" paradigm. Efficacy and critical aspects in cell therapy. *Curr Pharm Des*. 2013;19(13):2459-2473.
16. Kim S, Chang K-A, Park H-G, Ra JC, Kim H-S, Suh Y-H. The preventive and therapeutic effects of intravenous human adipose-derived stem cells in Alzheimer's disease mice. *PloS One*. 2012;7(9):e45757.
17. Lee M, Liu T, Im W, Kim M. Exosomes from adipose-derived stem cells ameliorate phenotype of Huntington's disease in vitro model. *Eur J Neurosci*. 2016;44(4):2114-2119.
18. Sarveazad A, Janzadeh A, Taheripak G, Dameni S, Yousefifard M, Nasirinezhad F. Co-administration of human adipose-derived stem cells and low-level laser to alleviate neuropathic pain after experimental spinal cord injury. *Stem Cell Res Ther*. 2019;10(1):1-15.
19. Sarveazad A, Babahajian A, Bakhtiari M, et al. The combined application of human adipose derived stem cells and Chondroitinase ABC in treatment of a spinal cord injury model. *Neuropeptides*. 2017;61:39-47.
20. Yousefifard M, Shamseddin J, Babahajian A, Sarveazad A. Efficacy of adipose derived stem cells on functional and neurological improvement following ischemic stroke: a systematic review and meta-analysis. *BMC Neurol*. 2020;20(1):1-13.
21. Kim J, Kim D, Kim J, et al. Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived

mesenchymal stem cell reduces amyloid-β plaques. *Cell Death Differ*. 2012;19(4):680-691.
22. Ma T, Gong K, Ao Q, et al. Intracerebral transplantation of adipose-derived mesenchymal stem cells alternatively activates microglia and ameliorates neuropathological deficits in Alzheimer's disease mice. *Cell Transplant*. 2013;22(1_suppl):113-126.
23. Kim K-S, Kim HS, Park J-M, et al. Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model. *Neurobiol Aging*. 2013;34(10):2408-2420.
24. Page MJ, McKenzie JE, Bossuyt PM, et al. Statement: an updated guideline for reporting systematic reviews. *BMJ*. 2020;2021:372.
25. Hooijmans CR, Rovers MM, De Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol*. 2014;14(1):1-9.
26. Nasiri E, Alizadeh A, Roushandeh AM, Gazor R, Hashemi-Firouzi N, Golipoor Z. Melatonin-pretreated adipose-derived mesenchymal stem cells efficeintly improved learning, memory, and cognition in an animal model of Alzheimer's disease. *Metab Brain Dis*. 2019;34(4):1131-1143. doi:10.1007/s11011-019-00421-4
27. Yamazaki H, Jin Y, Tsuchiya A, Kanno T, Nishizaki T. Adipose-derived stem cell-conditioned medium ameliorates antidepression-related behaviors in the mouse model of Alzheimer's disease. *Neurosci Lett*. 2015;609:53-57. doi:10.1016/j.neulet.2015.10.023
28. Mehrabadi S, Motevaseli E, Sadr SS, Moradbeygi K. Hypoxic-conditioned medium from adipose tissue mesenchymal stem cells improved neuroinflammation through alternation of toll like receptor (TLR) 2 and TLR4 expression in model of Alzheimer's disease rats. *Behav Brain Res*. 2020;379:112362. doi:10.1016/j.bbr.2019.112362
29. Ma X, Huang M, Zheng M, et al. ADSCs-derived extracellular vesicles alleviate neuronal damage, promote neurogenesis and rescue memory loss in mice with Alzheimer's disease. *J Control Release*. 2020;327:688-702. doi:10.1016/j.jconrel.2020.09.019
30. Eftekharzadeh M, Simorgh S, Doshmanziari M, Hassanzadeh L, Shariatpanahi M. Human adipose-derived stem cells reduce receptor-interacting protein 1, receptor-interacting protein 3, and mixed lineage kinase domain-like pseudokinase as necroptotic markers in rat model of Alzheimer's disease. *Indian J Pharmacol*. 2020;52(5):392-401.
31. Yan Y, Ma T, Gong K, Ao Q, Zhang X, Gong Y. Adipose-derived mesenchymal stem cell transplantation promotes adult neurogenesis in the brains of Alzheimer's disease mice. *Neural Regen Res*. 2014;9(8):798-805.
32. Kazemiha M, Sarveazad A, Moradi F, et al. Histological and behavioral alterations following hADSCs intravenous Administration in Alzheimer's rat model. *Thrita*. 2019;8(1). https://doi.org/10.5812/thrita.99975
33. Doshmanziari M, Sarveazad A, Moradi F, et al. Evaluation of Aβ deposits in the hippocampus of a rat model of Alzheimer's disease after intravenous injection of human adipose derived Stem cells by Immuno-and Thioflavin S-costaining. *Thrita*. 2018;7(2). https://doi.org/10.5812/thrita.88367
34. Hickman SE, Allison EK, El Khoury J. Microglial dysfunction and defective β-amyloid clearance pathways in aging Alzheimer's disease mice. *J Neurosci*. 2008;28(33):8354-8360.
35. Simard AR, Soulet D, Gowing G, Julien J-P, Rivest S. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. *Neuron*. 2006;49(4):489-502.
36. Qin Q, Teng Z, Liu C, Li Q, Yin Y, Tang Y. TREM2, microglia, and Alzheimer's disease. *Mech Ageing Dev*. 2021;195:111438.
37. d'Errico P, Ziegler-Waldkirch S, Aires V, et al. Microglia contribute to the propagation of Aβ into unaffected brain tissue. *Nat Neurosci*. 2022;25(1):20-25. doi:10.1038/s41593-021-00951-0
38. Chen Y, Colonna M. Two-faced behavior of microglia in Alzheimer's disease. *Nat Neurosci*. 2022;25(1):3-4.
39. Bagheri-Mohammadi S. Microglia in Alzheimer's disease: the role of Stem Cell-microglia interaction in brain homeostasis. *Neurochem Res*. 2021;46(2):141-148. doi:10.1007/s11064-020-03162-4
40. Shin JY, Park HJ, Kim HN, et al. Mesenchymal stem cells enhance autophagy and increase β-amyloid clearance in Alzheimer disease models. *Autophagy*. 2014;10(1):32-44.
41. Vinet J, van Weering HR, Heinrich A, et al. Neuroprotective function for ramified microglia in hippocampal excitotoxicity. *J Neuroinflammation*. 2012;9(1):1-15.
42. Parkhurst CN, Yang G, Ninan I, et al. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell*. 2013;155(7):1596-1609.
43. Wei Y, Xie Z, Bi J, Zhu Z. Anti-inflammatory effects of bone marrow mesenchymal stem cells on mice with Alzheimer's disease. *Exp Ther Med*. 2018;16(6):5015-5020.
44. Zhang Y, Chopp M, Liu XS, et al. Exosomes derived from mesenchymal stromal cells promote axonal growth of cortical neurons. *Mol Neurobiol*. 2017;54(4):2659-2673.
45. Xin H, Li Y, Buller B, et al. Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. *Stem Cells*. 2012;30(7):1556-1564.

How to cite this article: Madani Neishaboori A, Eshraghi A, Tasouji Asl A, Shariatpanahi M, Yousefifard M, Gorji A. Adipose tissue-derived stem cells as a potential candidate in treatment of Alzheimer's disease: A systematic review on preclinical studies. *Pharmacol Res Perspect*. 2022;10:e00977. doi:10.1002/prp2.977