

Unlocking the Potential of Dental Pulp Stem Cells: Neuroprotective and Regenerative Insights for Treating Neurological Diseases

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Abstract

Neurological illnesses impose a significant global health burden, with limited treatment options currently available. Recent advances in regenerative medicine have sparked interest in exploring various stem cell sources for neurological disorder treatment. Dental pulp stem cells (DPSCs) have emerged as a promising option due to their neural crest origin, multilineage differentiation capability, and accessibility through routine dental procedures. This review delves into our current understanding of DPSC function concerning neurological diseases, examining their neuroprotective and regenerative potential. It elucidates how DPSCs can differentiate into neural-like cells and release trophic substances that enhance the survival and functionality of neurons. Furthermore, the review explores the mechanisms underlying DPSCs' neuroprotective effects, shedding light on their immunomodulatory characteristics and ability to regulate inflammatory responses in the central nervous system. The challenges and potential avenues for utilizing DPSCs in neurological disorder treatment are also discussed, emphasizing the importance of large-scale clinical trials, ethical considerations, and well-defined procedures.

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INTRODUCTION

Neurological disorders encompass a broad spectrum, ranging from stroke and Parkinson's disease (PD) to Alzheimer's disease (AD) and spinal cord injuries, presenting significant challenges to modern healthcare. The intricate architecture of brain tissues and the limited regenerative capacity of the central nervous system (CNS) contribute to the dearth of effective treatments. Advances in regenerative medicine have spurred investigations into innovative therapeutic strategies, with a particular focus on stem cells. Dental pulp stem cells (DPSCs), among the diverse types of stem cells, have garnered considerable attention due to their unique qualities and potential applications in neurological conditions. Accessible through routine dental procedures, DPSCs exhibit remarkable regenerative potential, originating from the neural crest during tooth development. Their distinct origin and ability

for multilineage differentiation hold immense promise for the regeneration and repair of brain tissue.

Despite the promising future of DPSCs, unresolved issues and concerns remain before their successful integration into clinical settings. Crucial factors such as large-scale clinical studies, standardized procedures, and ethical considerations are paramount in establishing the safety and efficacy of DPSC-based treatments. This paper seeks to unravel the intricate relationship between neural diseases and DPSCs, offering insights into their therapeutic potential, underlying mechanisms, and the current research landscape in this dynamic and rapidly evolving realm of regenerative medicine.

This research aims to provide a comprehensive overview of the dynamic field concerning DPSC function in neurological diseases. Delving into the intricate mechanisms behind the neuroprotective and regenerative effects of DPSCs, the

exploration includes an examination of their neural crest origin and innate capacity to evolve into neural-like cells.

ROLE OF STEM CELLS IN REGENERATIVE MEDICINE

The fast-developing field of regenerative medicine seeks to replace damaged or diseased tissues and organs with new and creative methods. Applying stem cells is a fundamental aspect of regenerative medicine (Mahla *et al.*, 2016). The ability of stem cells to divide into new stem cells and develop into various cell types is something special. This offers the possibility of replenishing or mending the body's damaged tissues and cells. Because they offer a replenishable supply of cells for tissue engineering or transplantation, stem cells are essential to the field of regenerative medicine. They can be applied to the regeneration of organs or the replacement of damaged cells in cellular therapy. Researchers and medical professionals can create novel treatments using stem cells for a variety of illnesses and ailments, such as diabetes, arthritis, Parkinson's disease, heart disease, and spinal cord injury. Apart from their potential for regeneration, stem cells have also contributed to our comprehension of disease causation and development. Furthermore, because stem cells may be obtained from an individual's own body, there is less chance of immunological problems or rejection when using them in regenerative medicine, which holds enormous potential for personalized treatment. Because stem cells have the ability to replace or repair damaged tissues and organs, they are a crucial part of regenerative medicine. This can lead to novel treatments for a variety of medical diseases and improve the quality of life for patients. Furthermore, by enabling the creation of disease-specific cell lines, stem cells have created new opportunities for medication research (Hoang *et al.*, 2022). Because stem cells may develop into several cell types and can be employed to replace or repair damaged tissues and organs, they are an essential part of regenerative medicine. Because they present a viable remedy for the drawbacks and difficulties associated with conventional medical therapies, stem cells have completely transformed the field of regenerative medicine.

UNDERSTANDING NEUROLOGICAL DISORDERS

Neurological disorders cover a broad range of conditions involving the brain, spinal cord, and nerves. These conditions often have a significant impact on a person's ability to function, which can affect movement, feeling, thinking, behaviour, and other aspects of a person's daily life. Among the common neurological conditions are Parkinson's disease, multiple sclerosis, Alzheimer's disease, epilepsy, stroke, and neuropathy. Neurological disorders cover a wide range of conditions involving the brain, spinal cord, and nerves. Numerous symptoms, including problems with behaviour, movement, sensation, and thinking processes, may arise from them.

The most common cause of dementia cases among older adults is Alzheimer's disease (AD), a progressive dementia. Short-term memory loss, linguistic difficulties, poor judgment, and behavioural disorders are common early symptoms. Intracellular neurofibrillary tangles and extracellular β -amyloid deposits are the most noticeable diseases. Brain shrinkage results from synapse and neuronal loss caused by both illnesses. Only three cholinesterase inhibitors and memantine have been utilized internationally, despite the effects of numerous candidate drugs having been validated in clinical trials (Szeto and Lewis, 2016). Their clinical impact is insufficient, though. They do not address the underlying cause of AD; instead, they are utilized as symptomatic therapy. As one of the emerging treatments for AD, disease-modifying medicines have received attention recently (Cummings *et al.*, 2016). AD pathogenesis may be improved by cell treatment employing SHEDs and DPSCs. NGF, GDNF, BDNF, and other neurotrophic factors are released by DPSCs in the *in vitro* AD models, mitigating amyloid β -induced toxicity (Apel *et al.*, 2009) and guarding against okadaic acid-induced model cells of AD (Wang *et al.*, 2017). Furthermore, because of their paracrine function, transplanting SHEDs into AD mice ameliorates their symptoms in the *in vivo* models of AD (Mita *et al.*, 2015).

A neurodegenerative condition called Parkinson's disease (PD) results in the gradual loss of dopamine neurons in the midbrain. Common symptoms include bradykinesia, stiffness, and resting tremors. Patients may need a wheelchair or become bedridden when their symptoms worsen and make it harder for them to work. Most patients with PD are middle-aged, with 65 years of age or older constituting the majority. Although the exact reason is still unknown, one theory is that dopamine neurons induce the protein α -synuclein to aggregate and accumulate, weakening the surrounding cells in the process. It is possible that using DPSCs will help those with PD. Exosomes released from DPSCs protect midbrain neurons from 6-OHDA-induced apoptosis, and neurotrophic factors like NGF and GDNF released by DPSCs protect midbrain neurons damaged by 6-hydroxydopamine (6-OHDA), a selective dopaminergic toxin (Apel *et al.*, 2009). Furthermore, it has been demonstrated that in a co-culture of dopamine neurons and microglia, DPSCs reduce NO generation, hence acting as protective agents (Gnanasegaran *et al.*, 2017). *In vivo*, in model rats with 6-OHDA-induced degeneration, the paracrine action of neurotrophic factors from SHEDs exhibits neuroprotection against neurodegeneration and recovery of the nigrostriatal dopamine neurons (Fujii *et al.*, 2015).

The neurodegenerative condition known as amyotrophic lateral sclerosis (ALS) progresses over time. It usually starts with a decline in the motor function of the affected limbs, and speaking, eating, and drinking becomes challenging. The patient eventually passes away from paralysis of the breathing muscles. The most popular medications are those for symptoms, including riluzole and edaravone, but their clinical advantages are few. Since there are currently no

proven treatments for ALS, stem cells—including DPSCs and SHEDs—have drawn a lot of attention (Mazzini *et al.*, 2019). Numerous studies have shown that in ALS mouse models, DPCM reduces motor neuron loss and neuromuscular junction fragility (Wang *et al.*, 2019). Promising options for treating ALS include DPSCs and SHED, as they might also have undiscovered miracle benefits.

DENTAL PULP STEM CELLS (DPSCS) IN TREATING NEUROLOGICAL DISORDERS

The term “neurological illnesses” refers to a wide range of disorders affecting the central and peripheral nervous systems. They provide serious challenges to contemporary medicine. Traditional medicines often perform poorly in treating the underlying causes of many illnesses, despite significant advancements in this area. The field of regenerative medicine has emerged as a viable avenue for novel treatment techniques. In this regard, DPSCs have garnered attention due to their potential for treating neurological ailments.

A unique subpopulation of mesenchymal stem cells found in the tooth pulp is known as dental pulp stem cells. Their capacity to develop into a variety of cell types, including neurons, makes them an attractive option for regenerative applications. Non-invasive extraction methods can be employed to obtain DPSCs, which offer a practical solution

to issues brought on by neurological diseases (Lamprey *et al.*, 2022).

DPSCs stand out among the various types of stem cells due to their unique capacity to develop into brain lineages and their accessibility. Tucked away in the dental pulp of teeth, DPSCs are unique among stem cell types in that they provide a less invasive and morally clear source. The purpose of this research is to examine the emerging field of DPSC-based therapeutics designed especially for neurological conditions. According to Luo *et al.* (2018), DPSCs have an amazing ability to differentiate into important nervous system components such as neurons, astrocytes, and oligodendrocytes. DPSCs have a wide range of possible applications for neurological conditions. DPSCs generate a favorable microenvironment for brain repair and regeneration by secreting a wide range of growth factors, cytokines, and extracellular vesicles through paracrine signaling. Furthermore, replacing injured or degraded nervous system cells may be possible thanks to DPSCs’ capacity to develop directly into neural cells.

Because of their special regeneration qualities, dental pulp-derived DPSCs are appealing options for ischemic stroke treatments. DPSCs are promising agents for neuroprotection, angiogenesis, and general tissue repair after an ischemia insult because of their ability to develop into neural cells, release trophic factors, and regulate the inflammatory response (Figure 1) (Nito *et al.*, 2022).

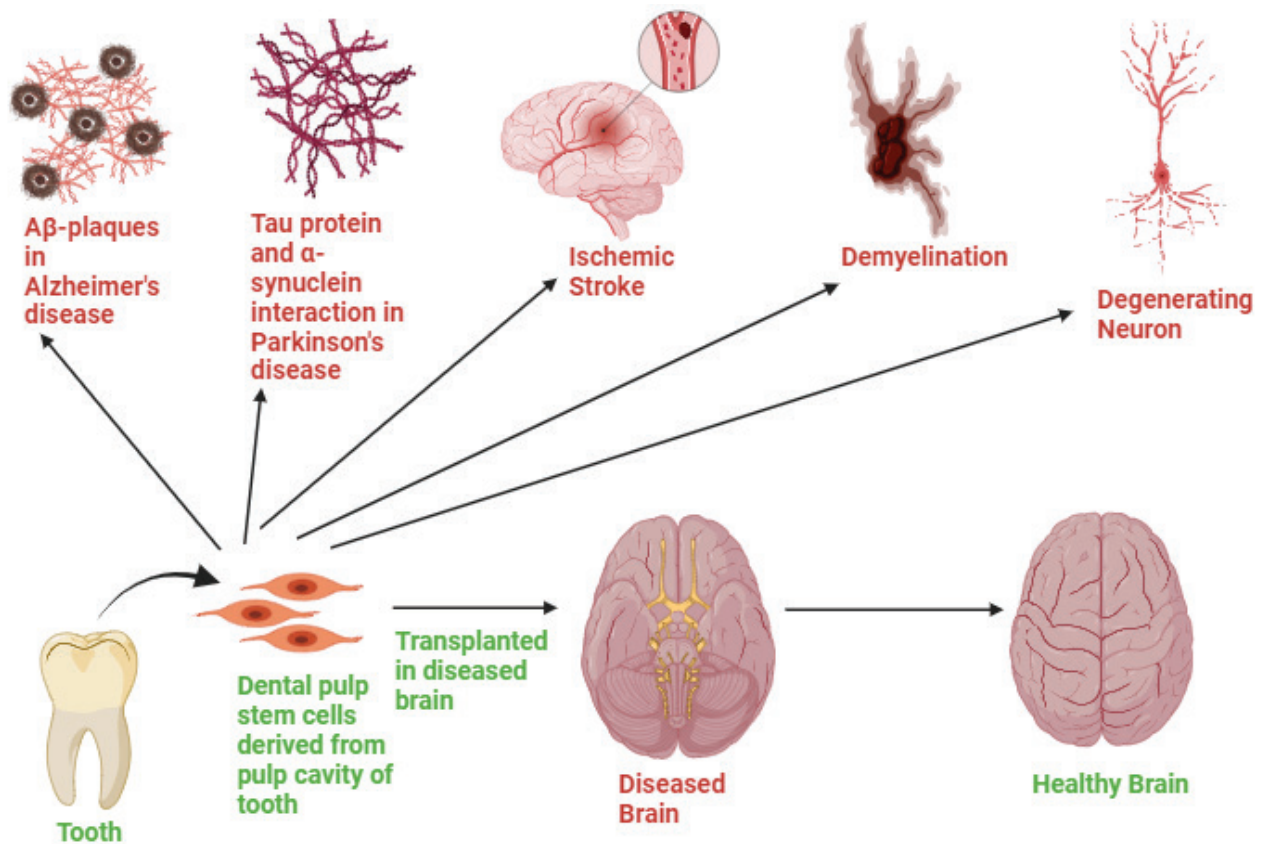


Figure 1: Teeth-derived dental pulp stem cells have been utilised to address many neurodegenerative conditions, including Alzheimer's disease, tau and α-synuclein in Parkinson's disease, ischemic stroke, demyelination, and degenerating neurons.

When exposed to the right neuronal inductive signals *in vitro* and *in vivo*, DPSCs retain the neuronal differentiation capabilities of the cranial neural crest cells from which they arise, enabling them to differentiate towards functionally active neurons. As anticipated, pluripotent embryonic stemness-related markers such as Oct-4, Nanog, and Sox-2 can be expressed by DPSCs. However, it can also spontaneously express both gene and protein forms of early and mature neuronal-specific markers, including nestin, β -III tubulin, and neuronal nuclei (NeuN) (Luo *et al.*, 2018). *In vitro* neural differentiation techniques for DPSCs have been developed more recently. The ability of DPSCs to differentiate into dopaminergic cells and spiral ganglion neurons (SGN) in the right microenvironment is crucial for the clinical research of DPSCs in various neurological illnesses. It was discovered that these differentiated cells displayed neuronal markers and SGN-specific markers, such as Tuj1, GATA3, and NTRK2, following treatment with BDNF, GDNF, NT-3, and SGN-inducing media against DPSC and SHED isolated from non-carious deciduous and permanent teeth (Gonmanee *et al.*, 2018). According to the findings of this *in vitro* investigation, disorders linked to neurosensory loss may benefit from the use of DPSCs in stem cell treatment with 2014, Kanafi *et al.* revealed that when DPSC were cultivated with midbrain cues,

primarily composed of sonic hedgehog (SHH), fibroblast growth factor 8 (FGF8), and basic fibroblast growth factor (bFGF), they displayed differentiation towards functioning dopaminergic neurons. The generated DPSCs released dopamine constitutively and exhibited increased expression of dopaminergic-neuronal markers such as Nurr1, En1, and Pitx3. These experimental results demonstrated that DPSCs maintain a high degree of neuroplastic sensitivity to the neuronal milieu, thereby establishing a novel, accessible, and practical *in vivo* neurogenesis source that may be incorporated into the CNS (Figure 2).

When exposed to a neuroinflammatory milieu, DPSCs significantly control the release of anti-inflammatory cytokines (IL-10, IDO, and COX-2) versus the degree of inflammation in the surrounding tissue. The expressions of BDNF, NGF, GDNF, NT-3, VEGF, and other neurotrophic factors are markedly increased by DPSCs; this may enhance neuronal health and help neurons repair damage (Luo *et al.*, 2018). Further validating the above theoretical perspective revealed that DPSCs not only create larger quantities of hepatocyte growth factor (HGF) and transforming growth factor (TGF) via paracrine processes, but also regulate T cell-related immunological responses (Andrukhov *et al.*, 2019).

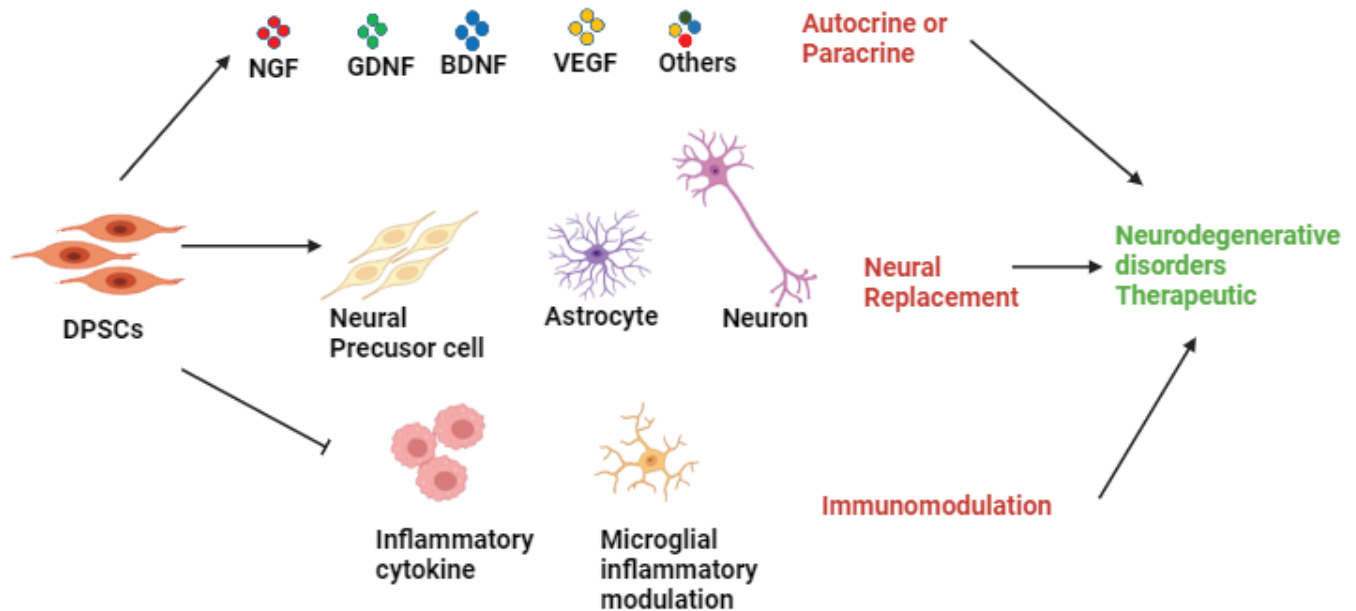


Figure 2: DPSCs secrete a variety of growth factors that can trigger autocrine or paracrine signaling, including NGF, GDNF, BDNF, and VEGF. It generates neurons, astrocytes, and neural precursor cells that replace lost neurons. DPSCs are used to suppress microglial inflammatory regulation and inflammatory cytokine production. All of that is applied therapeutically to the treatment of neurodegenerative diseases. NGF: Nerve Growth Factor; GDNF: Glial Cell Line-Derived Neurotrophic Factor; BDNF: Brain-Derived Neurotrophic Factor; VEGF: Vascular Endothelial Growth Factor

ADVANCEMENTS IN STEM CELL RESEARCH FOR NEURODEGENERATION

Recent advances in stem cell research have brought about paradigm shifts in the never-ending hunt for therapeutic solutions to treat neurodegenerative illnesses. Acknowledging the significant obstacles presented by ailments like ALS, Parkinson's, and Alzheimer's, researchers have embraced a variety of stem cell types and state-of-the-art technology to clarify pathways and create novel treatments. An extensive analysis of current scientific developments in stem cell therapy for neurodegeneration is presented in this publication.

Pluripotent stem cells, exemplified by induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs), serve as flexible platforms for the production of many neural cell lineages. Reprogrammed somatic cells, or iPSCs, offer a customized path across immunogenic hurdles. The foundation of regenerative techniques is the differentiation of PSCs and iPSCs into functioning neurons and glial cells, with a focus on creating scalable and repeatable processes (Romito *et al.*, 2016).

Mesenchymal stem cells (MSCs) are derived from bone marrow, adipose tissue, and tooth pulp. They are known for their potent immunomodulatory and neuroprotective qualities. Because of their ability to support tissue regeneration and anti-inflammatory properties, MSCs are appealing options for treating neurodegenerative diseases. Mechanistic investigations explore the complex signaling cascades that modulate the therapeutic effect of MSCs, opening the door to more specialized and focused uses (Andrukhov *et al.*, 2019).

Endogenous neural stem cells (NSCs) are an inherent source of neuroregeneration that are found within particular niches of the adult brain. Exploring the possibility of using NSCs has been sparked by their capacity to self-renew and specialize into neural lineages. Moreover, exogenous NSCs show potential for promoting neurogenesis and improving functional impairments in preclinical models upon transplantation; hence, a complex understanding of their interactions within the neuronal milieu is necessary (Jin *et al.* 2007).

THERAPEUTIC POTENTIAL OF DPSCS

Dental pulp stem cells have emerged as a promising therapeutic tool in regenerative medicine. Their ability to differentiate into various cell types, such as bone, cartilage, and neural cells, makes them highly versatile for tissue repair and regeneration (Phelps *et al.*, 2018). Furthermore, DPSCs secrete extracellular vesicles that contain a plethora of beneficial factors, including cytokines, growth factors, and microRNAs. These secreted vesicles can interact with target cells and deliver their contents, allowing DPSCs to exert their therapeutic effects. This potential makes DPSCs a valuable resource for treating various diseases and conditions, such as

dental and craniofacial defects, neurodegenerative diseases, and musculoskeletal disorders (Staniowski *et al.*, 2021; Graziano *et al.*, 2008). Additionally, DPSCs can be genetically engineered to enhance their therapeutic benefits, further expanding their potential applications. Overall, DPSCs possess significant therapeutic potential due to their differentiation capabilities and the secretion of beneficial factors through extracellular vesicles. Further research is needed to fully understand the mechanisms and optimize their therapeutic use, but DPSCs hold great promise for advancing regenerative medicine and improving patient outcomes (Madhoun *et al.*, 2021). The therapeutic potential of DPSCs lies in their ability to differentiate into different cell types and secrete extracellular vesicles containing beneficial factors. These vesicles can interact with target cells and deliver their contents, allowing DPSCs to exert their therapeutic effects. Furthermore, DPSCs can be genetically engineered to enhance their therapeutic benefits, making them even more versatile in treating various diseases and conditions. Some of the potential applications of DPSCs include dental and craniofacial defect repair, neurodegenerative disease treatment, and musculoskeletal disorder therapy (Mattei *et al.*, 2021).

CHALLENGES AND OPPORTUNITIES IN STEM CELL THERAPY

A vast array of illnesses and injuries may be treated in a promising way with stem cell therapy. To fully realize the promise of stem cell treatment, however, a number of obstacles and possibilities must be overcome. The development of scalable and affordable manufacturing procedures for stem cell manufacture, as well as addressing ethical concerns with the use of embryonic stem cells, are among the challenges facing stem cell therapy. Potential applications of stem cell treatment include the restoration of lost or damaged tissue and the possibility of curing diseases that are currently incurable. The field has both potential and obstacles with the use of stem cells in therapy. Emerging research, however, indicates that MSC-sEVs (extracellular vesicles generated from mesenchymal stem cells) have comparable or even greater therapeutic efficacies than MSCs for a wide range of illnesses (Shi *et al.*, 2021). These vesicles may be a non-cellular treatment that helps get beyond some of the drawbacks of stem cell-based therapies, namely tumour growth and immunological rejection. When compared to conventional stem cell therapies, the use of MSC-sEVs also has benefits in terms of cost-effectiveness and scalability. All things considered, stem cell therapy has enormous potential to transform the area of regenerative medicine and enhance patient outcomes. The low yield of MSC-exosomes in stem cell treatment is a hurdle as it limits the large-scale manufacture of cell-free medicines.

Dental pulp stem cells have demonstrated significant promise in regenerative medicine and have the potential to completely transform a number of medical specialties.

These multipurpose stem cells can develop into several kinds of cells, including neurons. Scientists want to use DPSCs in the realm of neuromedicine to repair and restore diseased or damaged brain tissue in the future by utilising their regenerative qualities (Yamada *et al.*, 2019). Treatments for neurological conditions like Parkinson's disease, Alzheimer's disease, and spinal cord injuries may advance as a result of this. In addition, DPSCs might be useful in the field of neurovascular medicine, where they could help with vascular regeneration and stroke or traumatic brain injury recovery (Fatima *et al.*, 2017). Furthermore, it has been discovered that DPSCs have neuroprotective qualities, which may add to their potential therapeutic uses in neuromedicine (Yamamoto *et al.*, 2014). To sum up, dental pulp stem cells have shown promise as a tool in neuromedicine, providing treatment options for a range of neurological conditions and traumas. These stem cells can develop into numerous kinds of cells, including neurons. It's possible that DPSCs will be crucial in the creation of novel therapies for neurological illnesses as a result of additional study and discoveries regarding them.

ETHICAL CONSIDERATIONS

Different sources, such as embryos, fetal tissue, and adult tissues, can yield stem cells. Because of ethical issues over the destruction of human embryos, the use of embryonic stem cells has been a particularly difficult subject. The need to gain informed consent and make sure that human tissues are used with respect is emphasized by ethical guidelines (Lo *et al.*, 2009). Participants must be fully informed by researchers about the purpose of the study, any possible dangers, and its advantages. Vulnerable groups, such as those suffering from cognitive impairments, should receive extra consideration to guarantee that their rights are upheld (Gupta *et al.*, 2013). Recent developments in stem cell research sometimes entail genetic engineering for medical benefit. Ethical norms emphasize the need for responsible gene editing procedures and a careful evaluation of any potential long-term effects. It's critical to strike a balance between innovation and morality (Rothschild *et al.*, 2013).

CONCLUSION

DPSCs show promise as a treatment for neurological illnesses. It has been shown that these multipotent stem cells can develop into neural lineages, which aid in neurorepair and regeneration. This creates opportunities for cutting-edge therapies aimed at ailments like spinal cord injury, Parkinson's disease, and stroke. Taking DPSCs from tooth pulp in a non-invasive manner that doesn't hurt the donor makes using them for medicinal purposes morally right. In contrast to other sources of stem cells, this one addresses ethical questions about the use of embryonic or fetal tissues. It is critical to guarantee the effectiveness and safety of DPSC-based treatments. To determine the safety profile of these medicines, comprehend any side effects, and optimize protocols for maximum therapeutic benefit, rigorous preclinical research and clinical

trials are necessary. There are difficulties in transitioning from preclinical results to clinical uses. Obstacles, including enhancing transplantation techniques, guaranteeing correct integration of transplanted cells, and managing possible immunological reactions, must be addressed by researchers. For DPSC-based treatments to be successfully implemented in clinical settings, translational research initiatives are essential. Future DPSC-based neurological therapies might combine stem cell treatments with other therapeutic techniques in combination. Furthermore, individualized medicine strategies that customize care according to unique patient attributes could improve the effectiveness of DPSC-based therapy. As DPSC-based treatments advance, it is critical to take accessibility into account globally. In order to prevent healthcare inequities and promote equitable access to cutting-edge medical interventions, efforts should be taken to guarantee that these cutting-edge therapies are accessible and cheap anywhere in the world.

To sum up, DPSC-based treatments for neurological conditions provide an innovative and morally sound approach to regenerative medicine. Despite obstacles, the creation of safe and efficient remedies is made possible by continued research and dedication to moral behavior. As the area develops, cooperation between scientists, physicians, and regulatory agencies will be crucial to realizing DPSCs' full potential in tackling the intricate problems brought on by neurological illnesses.

CONFLICT OF INTEREST

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REFERENCES

1. Al Madhoun A, Sindhu S, Haddad D, Atari M, Ahmad R, Al-Mulla F. Dental Pulp Stem Cells Derived From Adult Human Third Molar Tooth: A Brief Review. *Front Cell Dev Biol.* 2021;9:717624. Published 2021 Oct 12. doi:10.3389/fcell.2021.717624
2. Andrukhov O, Behm C, Blufstein A, Rausch-Fan X. Immunomodulatory properties of dental tissue-derived mesenchymal stem cells: Implication in disease and tissue regeneration. *World J Stem Cells.* 2019;11(9):604-617. doi:10.4252/wjsc.v11.i9.604
3. Apel C, Forlenza OV, de Paula VJ, *et al.* The neuroprotective effect of dental pulp cells in models of Alzheimer's and Parkinson's disease. *J Neural Transm (Vienna).* 2009;116(1):71-78. doi:10.1007/s00702-008-0135-3
4. Cummings JL, Zhong K, Kinney JW, *et al.* Double-blind, placebo-controlled, proof-of-concept trial of bexarotene in moderate

- Alzheimer's disease. *Alzheimers Res Ther.* 2016;8:4. Published 2016 Jan 29. doi:10.1186/s13195-016-0173-2
5. Fatima N, Khan AA, Vishwakarma SK. Immunophenotypic and Molecular Analysis of Human Dental Pulp Stem Cells Potential for Neurogenic Differentiation. *Contemp Clin Dent.* 2017;8(1):81-89. doi:10.4103/ccd.ccd_998_16
 6. Fujii H, Matsubara K, Sakai K, et al. Mazzini L, Gelati M, Profico DC, et al. Results from Phase I Clinical Trial with Intraspinal Injection of Neural Stem Cells in Amyotrophic Lateral Sclerosis: A Long-Term Outcome. *Stem Cells Transl Med.* 2019;8(9):887-897. doi:10.1002/sctm.18-0154 *Brain Res.* 2015;1613:59-72. doi:10.1016/j.brainres.2015.04.001
 7. Gnanasegaran N, Govindasamy V, Mani V, Abu Kasim NH. Neuroimmunomodulatory properties of DPSCs in an in vitro model of Parkinson's disease. *IUBMB Life.* 2017;69(9):689-699. doi:10.1002/iub.1655
 8. Gonmanee T, Thonabulsombat C, Vongsavan K, Sritanaudomchai H. Differentiation of stem cells from human deciduous and permanent teeth into spiral ganglion neuron-like cells. *Arch Oral Biol.* 2018;88:34-41. doi:10.1016/j.archoralbio.2018.01.011
 9. Graziano A, d'Aquino R, Laino G, Papaccio G. Dental pulp stem cells: a promising tool for bone regeneration [published correction appears in *Stem Cell Rev.* 2008 Spring;4(1):65]. *Stem Cell Rev.* 2008;4(1):21-26. doi:10.1007/s12015-008-9013-5
 10. Gupta UC. Informed consent in clinical research: Revisiting few concepts and areas. *Perspect Clin Res.* 2013;4(1):26-32. doi:10.4103/2229-3485.106373
 11. Hoang DM, Pham PT, Bach TQ, et al. Stem cell-based therapy for human diseases. *Signal Transduct Target Ther.* 2022;7(1):272. Published 2022 Aug 6. doi:10.1038/s41392-022-01134-4
 12. Jin K, Galvan V. Endogenous neural stem cells in the adult brain. *J Neuroimmune Pharmacol.* 2007;2(3):236-242. doi:10.1007/s11481-007-9076-0
 13. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. *Int J Mol Sci.* 2022;23(3):1851. Published 2022 Feb 6. doi:10.3390/ijms23031851
 14. Lo B, Parham L. Ethical issues in stem cell research. *Endocr Rev.* 2009;30(3):204-213. doi:10.1210/er.2008-0031
 15. Luo L, He Y, Wang X, et al. Potential Roles of Dental Pulp Stem Cells in Neural Regeneration and Repair. *Stem Cells Int.* 2018;2018:1731289. Published 2018 May 7. doi:10.1155/2018/1731289
 16. Mahla RS. Stem Cells Applications in Regenerative Medicine and Disease Therapeutics. *Int J Cell Biol.* 2016;2016:6940283. doi:10.1155/2016/6940283
 17. Mattei V, Martellucci S, Pulcini F, Santilli F, Sorice M, Delle Monache S. Regenerative Potential of DPSCs and Revascularization: Direct, Paracrine or Autocrine Effect?. *Stem Cell Rev Rep.* 2021;17(5):1635-1646. doi:10.1007/s12015-021-10162-6
 18. Mita T, Furukawa-Hibi Y, Takeuchi H, et al. Conditioned medium from the stem cells of human dental pulp improves cognitive function in a mouse model of Alzheimer's disease. *Behav Brain Res.* 2015;293:189-197. doi:10.1016/j.bbr.2015.07.043
 19. Nito C, Suda S, Nitahara-Kasahara Y, Okada T, Kimura K. Dental-Pulp Stem Cells as a Therapeutic Strategy for Ischemic Stroke. *Biomedicines.* 2022;10(4):737. Published 2022 Mar 22. doi:10.3390/biomedicines10040737
 20. Romito A, Cobellis G. Pluripotent Stem Cells: Current Understanding and Future Directions. *Stem Cells Int.* 2016;2016:9451492. doi:10.1155/2016/9451492
 21. Rothschild J. Ethical considerations of gene editing and genetic selection. *J Gen Fam Med.* 2020;21(3):37-47. Published 2020 May 29. doi:10.1002/jgf2.321
 22. Shi J, Zhao YC, Niu ZF, et al. Mesenchymal stem cell-derived small extracellular vesicles in the treatment of human diseases: Progress and prospect. *World J Stem Cells.* 2021;13(1):49-63. doi:10.4252/wjsc.v13.i1.49
 23. Staniewski T, Zawadzka-Knefel A, Skośkiewicz-Malinowska K. Therapeutic Potential of Dental Pulp Stem Cells According to Different Transplant Types. *Molecules.* 2021;26(24):7423. Published 2021 Dec 7. doi:10.3390/molecules26247423
 24. Szeto JY, Lewis SJ. Current Treatment Options for Alzheimer's Disease and Parkinson's Disease Dementia. *Curr Neuropharmacol.* 2016;14(4):326-338. doi:10.2174/1570159x14666151208112754
 25. Wang F, Jia Y, Liu J, et al. Dental pulp stem cells promote regeneration of damaged neuron cells on the cellular model of Alzheimer's disease. *Cell Biol Int.* 2017;41(6):639-650. doi:10.1002/cbin.10767
 26. Wang J, Zuzzio K, Walker CL. Systemic Dental Pulp Stem Cell Secretome Therapy in a Mouse Model of Amyotrophic Lateral Sclerosis. *Brain Sci.* 2019;9(7):165. Published 2019 Jul 14. doi:10.3390/brainsci9070165
 27. Yamada Y, Nakamura-Yamada S, Kusano K, Baba S. Clinical Potential and Current Progress of Dental Pulp Stem Cells for Various Systemic Diseases in Regenerative Medicine: A Concise Review. *Int J Mol Sci.* 2019;20(5):1132. Published 2019 Mar 6. doi:10.3390/ijms20051132
 28. Yamamoto A, Sakai K, Matsubara K, Kano F, Ueda M. Multifaceted neuro-regenerative activities of human dental pulp stem cells for functional recovery after spinal cord injury. *Neurosci Res.* 2014;78:16-20. doi:10.1016/j.neures.2013.10.010