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REVIEW

Dental Pulp Stem Cells: From Biological Promise to Translational Relevance, Therapeutic Applications, and System-Level Integration

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KEYWORDS

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ABSTRACT

Stem cells play a crucial role in regenerative medicine, contributing to tissue repair, maintaining homeostasis, and regulating the cellular environment. Among various sources, stem cells derived from human dental pulp are particularly promising due to their accessibility, ethical acceptability, and broad differentiation potential. They can be obtained from permanent and deciduous teeth, including tissues normally discarded, and preserved through cryopreservation, facilitating storage and clinical use. Dental pulp stem cells exhibit multilineage differentiation potential, giving rise to odontogenic, osteogenic, chondrogenic, adipogenic, and neurogenic cell lineages. This enables applications in dental tissue regeneration, nerve repair, blood vessel formation, and restoration of musculoskeletal and pancreatic tissues. Despite more than two decades of intensive research, routine clinical implementation remains limited by biological barriers, methodological heterogeneity, insufficient standardization, regulatory challenges, and incomplete GMP-oriented manufacturing and biobanking frameworks. Unlike previous reviews that primarily summarize the biological properties and regenerative applications of DPSCs, this review integrates biological evidence with translational, manufacturing, regulatory, biobanking, and system-level perspectives in order to identify the major barriers preventing routine clinical implementation. Furthermore, it highlights regenerative veterinary medicine within the One Health framework as a complementary translational platform that may facilitate technology maturation, improve manufacturing and regulatory readiness, and support broader implementation of DPSC-based therapies in human medicine. The major challenge is no longer the biological potential of DPSCs but the coordinated integration of biological, technological, manufacturing, regulatory, and clinical processes required for successful clinical translation.

1. INTRODUCTION

Stem cells are increasingly recognized for their crucial role in regenerative medicine. Within the organism, they remain quiescent until activated, at which point they proliferate to maintain tissue homeostasis and regulate the growth and remodelling of the cellular microenvironment. A key challenge in cell-based therapies is the establishment of stable cell lines, their efficient harvesting, and subsequent transplantation. Since many cells are lost within hours after engraftment, optimizing conditions at the implantation site is crucial for therapeutic efficacy [1]. To enhance the feasibility and cost-effectiveness of such therapies, researchers are exploring accessible sources of stem cells, such as adipose tissue, blood, and other biological materials. Even the observation of reparative processes, rather than complete tissue regeneration, may provide clinically relevant benefits in various types of injury. The mechanisms of stem cell action are diverse and include cellular differentiation, secretion of bioactive molecules, and modulation of immune responses [2]. A major shift in the field is driven by research on stem cells obtained from tissues usually regarded as medical by-products of routine procedures or naturally shed by the body. Particularly promising for future therapeutic strategies are stem cells isolated from human dental pulp, which combine accessibility with considerable regenerative potential [3].

Currently, numerous gaps in knowledge have been identified which, in light of the extensive yet fragmented body of evidence, require a comprehensive synthesis not only of biomedical data but also of organizational, regulatory, and ethical aspects. Although numerous reviews have summarized the biological properties and regenerative potential of DPSCs, comparatively little attention has been paid to the coordinated biological, manufacturing, regulatory, and quality assurance processes required for successful clinical translation. *In vitro* studies are highly promising and demonstrate that dental pulp stem cells (DPSCs)

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possess properties that predispose them to a wide range of regenerative applications, extending beyond oral tissues to include tooth and bone regeneration. Findings from systematic analyses of animal studies indicate a partial translation of these promising results into clinical relevance, while simultaneously highlighting additional challenges associated with DPSC-based research.

Most animal studies (primarily involving rats, mice, chimeric models, minipigs, and dogs) assess transplanted constructs using radiographic and histological methods, describing the regeneration of pulp-like and dentin-like tissues, apical healing, dentin thickening, formation of a dentin bridge, and apical closure. Animal models have been used to evaluate the therapeutic potential of DPSCs in both vital pulp therapy and in mature and immature teeth. Despite encouraging outcomes, a high risk of bias has been reported, particularly in terms of selection, performance, detection, and reporting bias. More favorable outcomes have been associated with hypoxic conditions, the presence of inflammation, and the use of higher-quality biological material derived from younger donors [4]. In canine models, a decrease in the amount of regenerated pulp tissue has been shown to correlate with increasing age [5]. Both in animal studies and in human research, there is a growing emphasis on minimally invasive endodontic strategies, shifting attention away from destructive treatment approaches toward regenerative therapies.

The ongoing transition in translational stem cell research—from *in vitro* studies through *in vivo* animal models—supports the recognition of some findings as relevant at the preclinical stage and is often based on complex approaches involving scaffolds and other biomaterials. However, numerous barriers still limit the clinical implementation of such therapies in humans, including challenges related not only to scientific validation but also to production, scalability, and regulatory and ethical considerations [6].

Research on the regenerative potential of DPSCs clearly illustrates a translational gap, reflecting the divide between basic research and clinical implementation, and the limited availability of fully developed Good Manufacturing Practice (GMP)-compliant products may further delay clinical translation. A review of the literature also reveals a degree of caution among researchers in publishing negative findings, alongside a clear need for standardization and the development of shared databases to prevent duplication of efforts and accelerate scientific progress, as the lack of harmonization contributes to ongoing fragmentation of knowledge. This work compiles key findings on the applications of DPSCs and outlines the major challenges associated with their use in regenerative medicine. Accordingly, this review examines the major barriers limiting clinical implementation, with emphasis on system-level integration of manufacturing, regulatory, and clinical processes. It also considers the potential contribution of regenerative veterinary medicine within the One Health framework. Here, system-level integration refers to the coordinated development of standardized manufacturing, quality control, biomaterials, biobanking, clinical evaluation, and regulatory approval. This integrative perspective distinguishes the present review from previous reports focused primarily on biological characteristics and therapeutic applications.

2. METHODOLOGY

This integrative review summarizes current knowledge on dental pulp stem cells and their applications in regenerative medicine. Studies were identified through a targeted search of peer-reviewed literature in PubMed (as the primary biomedical database) and Google Scholar (used to identify additional literature and recently indexed publications), focusing on articles published in English that report experimental, *in vivo*, or clinical findings related to dental pulp stem cells (DPSCs). The literature search covered studies published from 1918 to June 2026, with a focus on recent evidence from 2023–2026. This review was conducted between 2023 and 2026. The following keywords and their combinations were applied: “dental stem cells” in association with “regenerative medicine,” “translational,” and “animal studies.” Study selection was based on its relevance to DPSC biology, differentiation capacity, regenerative potential, scaffold and growth factor applications, signaling pathways, and translational or clinical implementation. Included studies provided sufficient experimental or clinical data to ensure a robust and evidence-based synthesis. Editorials, conference abstracts, and studies lacking adequate methodological transparency were excluded.

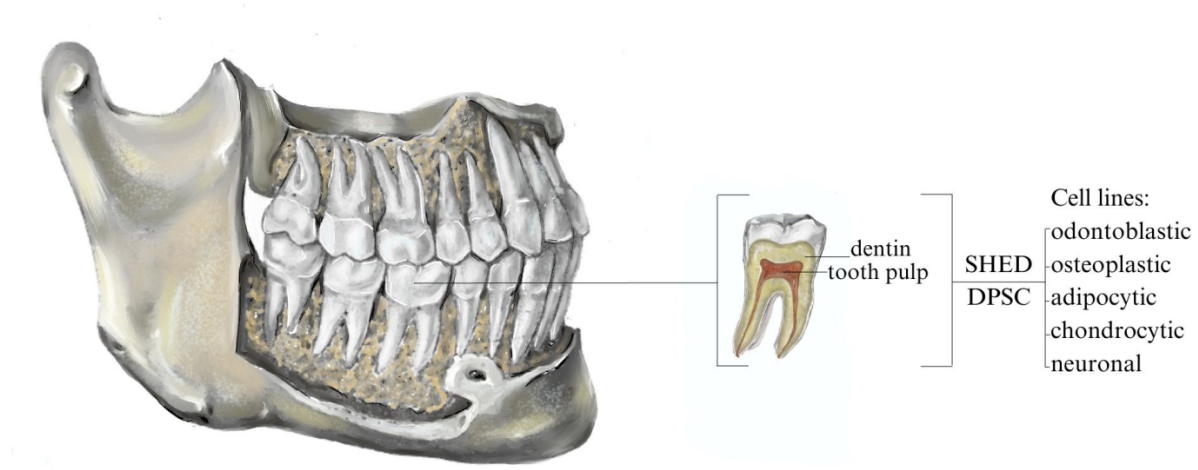
The findings were synthesized narratively to map current research trends and provide an integrative understanding of biological mechanisms and therapeutic applications, rather than a quantitative systematic analysis. To enhance reproducibility, data extraction included the type of study, sample source (human or animal), *in vitro* or *in vivo* experimental conditions, culture methods, laboratory techniques (e.g., enzymatic digestion, cell culture conditions, differentiation assays), and key outcomes. While no new experiments were conducted, all procedures reported in the reviewed studies adhere to established ethical standards for research involving human and animal tissues, including informed consent and institutional ethical approval where applicable. As this study is a literature review without primary data collection, ethical approval was not required.

3. RESULTS

Biological Characteristics of DPSCs and Differentiation Potential

Mesenchymal stem cells from various sources can differentiate into multiple cell types, demonstrate low immunogenicity, and migrate to sites of injury, making them ideal initiators and facilitators of regenerative processes. The most suitable pluripotent stem cells for dental procedures are those derived from dental pulp (DPSCs)[7]. These cells possess the ability to differentiate into odontoblastic, osteoblastic, adipocytic, chondrocytic, and neuronal lineages [8] (Figure 1). HDPSCs are highly valued in tissue engineering, showing promise for the regeneration of dental structures and even the complete restoration of the tooth [9]. With rapid progress in regenerative medicine, numerous stem cell banks specializing in dentistry have been established [10].

Figure 1. The stem cells from exfoliated deciduous teeth (SHED) and dental pulp stem cells (DPSCs), both derived from human teeth, represent source of pluripotent cells. The concept is illustrated based on Henry Gray's "Anatomy of the Human Body" (1918) [11].



Dental pulp stem cells (DPSCs) demonstrate remarkable potential in generating dental pulp and dentin tissue in *in vivo* models, as well as in the development of neuron-like cells [12]. DPSCs exhibit characteristics comparable to bone marrow-derived mesenchymal stromal cells (BM-MSCs), which are widely regarded as the gold standard in stem cell research [13]. They meet the minimal criteria of MSCsdefined by the International Society for Cellular Therapy (ISCT) [14]. *In vitro*, they display a fibroblast-like, spindle-shaped morphology during early expansion and organize into colonies with cells aligned along parallel axes. Certain slower-proliferating cultures adopt a more polygonal and irregular morphology. These colonies are adherent, firmly attaching to the culture substrate. [13]. Under defined culture conditions their multifaceted capabilities extend to applications in neuroregeneration and osteogenesis, addressing defects in the jaw and facial region, including bone fracture repair [15]. DPSCs' angiogenic properties are particularly valuable in aging populations with prevalent neurological disorders such as Alzheimer's disease, Parkinson's disease, dementia, and peripheral neuropathies. Their use in neurodegenerative research promotes directed differentiation and expansion of dental pulp-derived cell lines [16]. Under the influence of osteogenic factors, DPSCs tend to differentiate preferentially into odontoblast-like cells rather than osteoblasts [13].

Isolation, Culture and Experimental Applications

Notably, DPSCs can be obtained from human biological waste, enhancing both accessibility and ethical acceptability [3]. The combination of these advantages has already produced promising results in experimental *in vivo* studies, with mice and rats [17] being the most commonly used models for controlled dental injury. Progress in these studies is expected not only to advance tissue engineering materials but also to drive innovations in biomedical engineering for dentistry. This underscores the importance of refining reproducible laboratory methods, which is a critical step for clinical translation [18]. Ensuring consistent replication of these methods will be key to realizing the full potential of regenerative medicine in dental applications.

Numerous clinical studies and *in vitro* experimental models have investigated DPSCs, highlighting their increasing potential for clinical and commercial applications. Compared to other dental sources, dental pulp offers a patient-friendly method of cell collection, facilitating easier storage and handling. The extraction procedure is carefully designed to minimize trauma to the pulp by reducing drill contact time with dentin and limiting heat generation during the process [19]. Dental pulp is carefully extracted from the tooth chamber and subjected to enzymatic digestion using type I collagenase and dispase. Cells are cultured in Dulbecco's Modified Eagle Medium (DMEM) as well as nutrient mixture Ham's F-12 (DMEM-F12) supplemented with 15% fetal bovine serum (FBS) is added, and the mixture is centrifuged. The resulting cell suspension is seeded onto culture plates and incubated in a CO_2 incubator at 37°C with 5% CO_2. The culture medium is refreshed periodically, with washing using phosphate-buffered saline (PBS). Passaging is performed twice weekly until cells reach confluence. Maximum proliferation is typically achieved with the addition of 20% FBS to the culture medium [20,21]. In the study by Kotova et al., determined that the optimal seeding density per culture well is 1.00×10^4 cells/well. The first passage of the primary culture occurs after 20 ± 1.4 days, with subsequent passages performed every 5–7 days depending on the extent of cell expansion. The proliferative potential of the cells was typically exhausted by the 10th passage [13]. DPSCs can also be isolated via tissue explant outgrowth (DPSC-OG), which allows for the acquisition of a greater number of cells and the isolation of distinct subpopulations; additionally, Kiyokawa et al. developed a novel isolation approach based on scraping (SCIP), similar to DPSC-OG.

During cell culture, the type of medium influences DPSC behavior, with medium supplemented with human serum (HS) supporting proliferation toward adipogenic and osteogenic differentiation, whereas fetal bovine serum (FBS) is effective for chondrogenic differentiation. The culture system must be strictly defined, and the protocol should comply with Good

Manufacturing Practice (GMP) standards; however, in the case of stem cells, this still requires extensive research [22]. It is also important to consider the time frame for using a tooth collected from a patient; when stored at 4°C in PBS, pulp viability can be maintained for up to 5 days [23].

Identifiication of DPSCs involves utilizing epitope markers on their surface, including STRO-1, CD29, CD44, CD73, CD90, CD105, CD146, CD166, CD271 [24], and CD59 [25]. The therapeutic potential of dental pulp stem cells (DPSCs) has been demonstrated in various experimental studies. They can differentiate into Map2- and NF-positive neuronal-like cells as well as mature neurons, contributing to post-stroke functional recovery through non-neural replacement mechanisms. DPSCs have also shown the ability to regenerate the optic nerve in models of corneal blindness, promote vascular endothelial growth, improve cardiac function by increasing vessel formation, and reduce infarct size. Furthermore, these cells exhibit pro-regenerative effects on skeletal muscle, can reverse hyperglycemia in diabetes, and differentiate toward pancreatic cell lineages resembling islet-like cell aggregates, with glucose-dependent release of insulin and C-peptide. In addition, DPSCs contribute to bone formation, highlighting their broad regenerative potential across multiple tissue types [24].

Preclinical and Translational Approaches in Dental Regeneration

In dentistry, DPSCs have been applied to regenerate damaged dentin and pulp, as well as to support pulp revascularization. The underlying mechanisms of dentin regeneration are not yet fully understood, which limits their complete application in tissue engineering. Nevertheless, two methodological approaches have been developed. The first involves the use of growth factors and progenitor cells to promote dentin regeneration within the deep cavity of the tooth. The second approach employs scaffolds on exposed dental pulp, allowing odontoblast-like cells to grow and contribute to tissue restoration [26,27].' These strategies are analogous to *in vivo* therapies, in which proteins such as bone morphogenetic proteins (BMPs) or their corresponding genes are directly applied to exposed dentin. In contrast, *ex vivo* autologous transplantation utilizes recombinant BMPs to promote dentin regeneration [28].

Owing to their unique properties, dental tissues are increasingly preserved in biobanks using cryopreservation or magnetic freezing techniques. Proper handling of teeth is essential, particularly in the context of clinical studies. To definitively establish the regenerative potential of DPSCs, double-blind, randomized clinical trials are required. Additionally, due to the risk of immunological rejection, biobanking procedures must adhere to strictly standardized protocols [24]. Initially, it was thought necessary to isolate, expand, and store dental pulp stem cells individually. However, it is now established that entire teeth can be cryopreserved, significantly reducing the initial preparation costs and labor requirements [29].

The production and biobanking of dental stem cells were analyzed by Yamada I et al., who emphasized that the procedures lacked standardization, highlighting a significant logistical problem due to the involvement of multiple parties. This complicates compliance with regulatory requirements and substantially slows the development of clinical applications. Properly prepared cells can be stored for decades for autologous use [30]. The collected literature confirms the authors' observations regarding the regenerative potential of DPSCs, particularly in the context of dentin–pulp complex formation and the use of biomaterials; however, it also highlights significant methodological limitations and a lack of standardization (Table 1).

Study with key findings	Experimental model	Study aim	Main limitations
Formation of pulp-like tissue and dentin bridge (Asgary et al. 2024)	Animal studies	Pulp–dentin regeneration	High methodological heterogeneity and potential risk of bias
Stronger regenerative capacity in younger donors (Nakashima et al. 2024)	Animal models	Regeneration of pulp–dentin complex	Age-dependent variability
Defined proliferation and culture behavior (Kotova et al. 2021)	In vitro (human DPSCs)	Characterization of cellular morphology and proliferation	Limited long-term expansion
Standardized injury models improve comparability (Yang et al. 2023)	Animal models	Pulp regeneration models	Limited clinical validation
Enhanced regeneration with scaffolds (Alshaibani et al. 2025)	Preclinical (scaffold-based)	Bone regeneration	Methodological heterogeneity
Early clinical signals, limited efficacy proof (Ivanovski et al. 2024)	Clinical trials (mixed)	Clinical translation status	Small cohorts, poor reporting

Lack of standardization in processing (Yamada et al. 2025)	Biobanking/clinical practice	Manufacturing and storage	Regulatory and logistical gaps

Table 1. Experimental and translational evidence base of DPSCs

Microenvironmental Modulation and Scaffold-Enhanced DPSC Regeneration

The neuroectodermal origin of DPSCs from the neural crest has encouraged their application in neurology, leading to significant advancements in the treatment of peripheral nerve injuries. This research, alongside dental applications, provides deeper insights into the mechanisms of neurogenesis using stem cells, gradually reducing the need for invasive surgical procedures. Nonetheless, a limitation of DPSCs is their relatively rapid loss of proliferative capacity and multipotent differentiation potential, highlighting the need for further refinement of isolation and culture techniques [25]. Factors influencing the regenerative potential of stem cells are still being investigated. Stem cells exhibit directional activity in the presence of inflammation, and their functional responses have been assessed by exposing them to elevated levels of cellular stress mediators. In this context, higher concentrations of mediators such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) have been studied in relation to human mesenchymal stem cells (hMSCs) [31]. Several modulatory factors may influence regenerative responses during the preconditioning stage. For instance, probiotics like *Lactobacillus casei* and *Lactobacillus acidophilus*, when added to the culture medium, have been found to enhance the viability of cell lines, improving their condition and intensifying their involvement in osteogenesis. These effects are associated with increased alkaline phosphatase activity and upregulation of genes such as bFGF, EGF-ß, and BMP-2 [32].

The type of scaffold used can also influence stem cell proliferation. Biocompatible and biodegradable scaffolds, such as high molecular weight hyaluronic acid (HMW) biopolymers, have been shown to be effective. While they may not directly enhance proliferation, they are considered safe, as they degrade predictably at the site of administration [33]. Vitamin D3 incorporated into scaffolds composed of chitosan, collagen, and fibrinogen has been shown to significantly enhance angiogenesis and endothelial cell differentiation via the HIF-1/IGF-1/VEGF pathways [34]. Early odontoblastic differentiation is also supported by growth factor-β1 [35]. DPSC differentiation can be further modulated through multiple signaling pathways, including MAPK, PI3K/AKT/mTOR, Notch, and NF-κB. Conversely, impaired Wnt signaling may contribute to the development of adenomatous polyposis coli (APC). Activation of DPSCs can be influenced by β-catenin, elevated extracellular magnesium and calcium levels [25] as well as FBXO32 [36] and compounds such as tideglusib [37]. In addition to differentiation, cell growth is positively affected by ascorbic acid, although the optimal concentration remains undetermined [38]. Semaphorin 4D enhances angiogenesis [39], while low-level laser therapy has been shown to promote proliferation of human dental pulp cells [40]. Conversely, lidocaine, commonly used for pain control in dentistry, negatively impacts osteogenic differentiation [41].

Toward an Integrated Translational Framework for DPSC Implementation

The successful clinical implementation of DPSC-based therapies requires an integrated translational framework founded on system-level integration. While basic research has substantially advanced our understanding of DPSC biology and regenerative mechanisms, effective clinical translation requires consideration of a much broader context. This includes interactions with the tissue microenvironment, immune responses, cellular signaling pathways, and tissue regeneration, as well as GMP-compliant manufacturing, quality control, safety assessment, and regulatory requirements. Consequently, successful implementation depends on the coordinated integration of biomedical research, tissue engineering, manufacturing processes, clinical development, and regulatory frameworks.

One of the major challenges remains the harmonization of research through standardized methodologies and improved reproducibility. Regulatory planning should therefore be incorporated from the earliest stages of product development rather than being addressed only before clinical application [42]. Standardized preclinical models, including genetically modified animal models where appropriate, may improve the reproducibility and comparability of experimental findings; however, they should be developed with subsequent clinical translation in mind [43]. Moreover, the transition from conventional reconstructive procedures to biologically driven regenerative therapies requires standardized criteria for evaluating product quality, efficacy, and safety throughout every stage of development [44]. Despite significant advances in DPSC research, improvements achieved at the cellular level alone are insufficient to ensure successful clinical implementation.

Increasingly, progress in regenerative medicine depends on overcoming translational bottlenecks rather than solely generating additional biological evidence. As emphasized by Aguilera-Cobos et al. [45], the specific characteristics of Advanced Therapy Medicinal Products (ATMPs) should be considered throughout the entire development process, including preclinical research, manufacturing, quality assurance, clinical evaluation, and regulatory planning. Additional challenges include the substantial costs and uncertainty associated with first-in-human clinical studies. Although ATMPs offer considerable potential to address unmet medical needs, their implementation is frequently limited by insufficient translational evidence, difficulties in predicting clinical efficacy, and uncertainties regarding long-term safety. Consequently, establishing a favorable benefit–risk profile remains one of the key prerequisites for the successful clinical implementation of DPSC-based therapies [46]. These translational challenges are summarized in Table 2, which outlines key barriers to clinical implementation of dental pulp stem cell-based therapies.

Barrier	Impact on clinical implementation	Potential future direction
Cell heterogeneity	Variable therapeutic efficacy	Standardized cell characterization and single-cell profiling
Lack of standardized isolation and culture protocols	Poor reproducibility between studies	International GMP-based protocols
Limited cell survival after transplantation	Reduced regenerative efficacy	Optimized scaffolds and preconditioning strategies
Immunological challenges	Risk of graft failure	Immune modulation and personalized approaches
Tumorigenic potential	Safety concerns	Long-term monitoring and quality control
Heterogeneity of animal models	Difficult comparison of outcomes	Harmonized preclinical study design
Regulatory uncertainty	Delayed clinical implementation	International regulatory harmonization
Fragmented biobanking procedures	Variable cell quality	Standardized biobanking guidelines
Limited clinical trials	Insufficient clinical evidence	Large multicenter randomized clinical trials

Table 2. Major barriers limiting clinical translation of DPSCs

Status of DPSCs Clinical Translation

In 2014, only a small number of clinical trials involving dental pulp stem cells had been registered. At that time, La Noce et al. proposed that standardisation should mainly cover general principles of production rather than all stages of development, as clinical evidence was still very limited [47]. By 2022, Song et al. reported a broader range of clinical applications, including autologous transplantation approaches for pulp necrosis and irreversible pulpitis, periapical lesions, and periodontal intrabony defects. Additional indications included periodontitis, post-extraction sockets, cleft lip and palate, degenerative knee disorders, liver cirrhosis, type 1 diabetes, Huntington's disease, as well as aesthetic uses such as wrinkle reduction and treatment of hair loss.

Another emerging approach is the use of conditioned medium derived from dental pulp stem cell cultures (CM) [48].

Ivanovski et al. reported that some studies have progressed to phase III clinical trials, although patient numbers remain limited. While early results often indicate a favourable safety profile, it is still difficult to show clear superiority over standard therapies, which remains a central goal of clinical research. The authors also point to ongoing issues in reporting quality, particularly regarding cell source, dosing, and characterisation. Increasing interest is also directed toward cell-free strategies, especially extracellular vesicle–based therapies [49]. Yamada et al. (2025) assessed current practices in the use of DPSCs and the state of manufacturing and biobanking.

Although chairside micrografting techniques have already been described, standardisation is still lacking. Private dental practitioners appear to play an important role in the clinical use of these regenerative approaches. At the same time, concerns persist about maintaining product quality, particularly in relation to long-term cryopreservation and the uncertainty of long-term outcomes [50]. The current evidence and translational readiness across different therapeutic applications is summarized in Table 3, which which classifies each indication by level of evidence and maturity

Therapeutic application	Biological mechanism	Current evidence	Translational readiness\
Dentin regeneration	Odontoblast differentiation	Strong preclinical evidence	High
Dental pulp regeneration	Cell transplantation and scaffolds	Strong preclinical and early clinical evidence	High

Bone regeneration	Osteogenic differentiation	Strong preclinical evidence	Moderate
Craniofacial reconstruction	Osteogenesis and angiogenesis	Moderate evidence	Moderate
Peripheral nerve regeneration	Neural differentiation and neurotrophic activity	Promising experimental evidence	Low
Neurodegenerative diseases	Neuroprotective and paracrine effects	Preliminary evidence	Low
Cardiac repair	Angiogenesis and paracrine signaling	Animal studies	Low
Pancreatic regeneration	Differentiation into insulin-producing cells	Experimental evidence	Low
Skeletal muscle regeneration	Mesenchymal differentiation	Experimental evidence	Low

Table 3. Therapeutic applications of DPSCs and current level of evidence. Translational readiness based on the current maturity of available evidence presented in the reviewed literature rather than by formal regulatory criteria.. High – supported by extensive preclinical evidence with emerging clinical studies. Moderate – supported mainly by consistent preclinical studies. Low – supported predominantly by experimental or proof-of-concept studies

4. DISCUSSION

Human dental pulp stem cells (DPSCs) represent an accessible and ethically favorable source of pluripotent stem cells with broad regenerative potential. They can be isolated from permanent and deciduous teeth, including tissues normally considered medical waste, and preserved through cryopreservation of entire teeth. DPSCs are capable of differentiating into odontoblastic, osteoblastic, chondrocytic, adipocytic, and neuronal lineages, supporting regeneration of dental pulp and dentin, nerve repair, angiogenesis, as well as musculoskeletal and pancreatic tissue restoration. Their regenerative efficiency can be further enhanced through preconditioning, scaffolds, growth factors, and modulation of key signaling pathways. Due to their neuroectodermal origin, DPSCs hold particular promise for neuroregeneration and the treatment of neurodegenerative disorders. Research on DPSCs extends far beyond dentistry, and the combination of stem cells, biomaterials, and bioactive molecules may ultimately enable complete biological tooth regeneration. Given the high prevalence of tooth loss and endodontic disease, the demand for regenerative treatment strategies is expected to continue increasing [51].

It is already known that such therapies have certain limitations and uncertainties, which depend on the stage of pulp inflammation (advanced infections reduce therapeutic effectiveness), while the overall qualification of the patient for the procedure is equally important. Patient- related factors, including systematic disorders, and may further limittreatment efficacy and therapeutic applicability. Future studies should therefore focus not only on directing cellular differentiation but also on achieving precise morphological adaptation of scaffolds to individual root canal anatomy [52]. Bibliometric analyses indicate that current research is increasingly focused on stem cell biology, biomaterials, and scaffold design [53]. Meerim et al. also suggest that filling the gaps in matching biobanked cells to patient-specific requirements may benefit from artificial intelligence, supported by machine learning. The implementation of DPSCs in clinical practice requires coordinated project management from cell collection and characterization to long-term monitoring of potential side effects [54], which without interdisciplinary collaboration and standardized protocols, such implementation remains difficult to achieve. Although it is already known that DPSCs combined with scaffolds positively influence regeneration in dentistry, for example in alveolar and jawbone regeneration [55], this supports prioritizing research funding in dental, cardiovascular, autoimmune, and bone-related applications [56]. The heterogeneity of methodologies and outcome measurements has also been noted by Sapkal et al., who emphasized the variability of models and assessments, which may create real challenges in synthesizing results. According to the authors, immunological rejection represents the most significant biological barrier, along with sometimes insufficient post-transplant cell survival risk of uncontrolled tumorigenesis.

They also consider the control of spatial control of cell distribution and potential drug delivery functions [57]. Long-term cryopreservation studies further support the clinical potential of DPSCs. Cells stored for 7–8 years ago retain their morphology, differentiation capacity, and the ability to generate functional vascular vessels [58], allowing the preservation of substantial cell resources for both research and clinical applications. These perspectives extend beyond dentistry, as DPSCs are also being explored for other diseases, with an increasing number of studies testing them in costly models, for example in Alzheimer's disease using brain organoids [59].

Research to date has focused on DPSC differentiation, biomaterials and scaffold development, molecular characterization, immunological responses, cell culture protocols, translational studies, and clinical applications. Although DPSCs were first described in 2000,several challenges continue to limit their successful clinical translation. These include immunological rejection, limited cell survival, and risk of uncontrolled proliferation, as well as implantation constraints such as patient health, stage of pulp inflammation, and anatomical variability of root canal structures. Despite this, their potential for further development remains remarkable.

Equally important are organizational and procedural limitations. With the widespread adoption of biobanking, implementing standardized quality control measures across projects is essential to facilitate and accelerate clinical translation in both human and veterinary medicine. Improved characterization of DPSCs has also expanded interest in their applications beyond dentistry, including cardiovascular regeneration. Current research is increasingly exploring combination therapies involving biomaterials, cells, extracellular vesicles, and gene-based therapies. Several important questions remain unanswered. It is still unclear whether regenerated pulp tissue will achieve full functional equivalence with native tissue and whether therapeutic effects will be sustained over time. Long-term safety, complete reinnervation, spatial control of tissue regeneration, and the risk of tumorigenesis also require further investigation. The stability and safety of such therapies in the context of chronic disease management is another critical consideration. Finally, the growing use of biobanking, together with availability of extracted teeth as medical waste, raises important bioethical considerations regarding informed consent, long-term storage, ownership of biological material, and management of patient data.

Most published clinical studies on DPSCs indicate that larger trials, better-designed study groups, and more consistent methods are still needed. These improvements are important to reliably assess how well the therapies work and to meet current regulatory requirements. Similar conclusions have been repeated over the past two decades. Although there has been steady progress in clinical applications of DPSCs, insufficient to overcome key translational barriers. This ongoing pattern suggests that the key challenge is no longer the biological potential of the cells, but rather the difficulty of aligning regulatory rules, production processes, and study designs across different research groups. In other words, the main limitation is systemic rather than scientific. From the point of view of regenerative veterinary medicine, more preclinical and clinical studies in animals with naturally occurring diseases have already provided a stronger basis for using both cell-based and cell-free therapies. If regulatory, financial, and organizational barriers continue to slow down the adoption of these treatments in human medicine, veterinary practice may serve as a useful complementary route within the One Health approach. Companion animals are living longer, and their care allows for longer observation periods, which makes it easier to assess both safety and long-term effects in real clinical conditions. This would not replace human trials but could help reduce translational uncertainty and improve safety and manufacturing strategies.

5. CONCLUSION

Dental pulp stem cells (DPSCs) represent a highly promising source for regenerative medicine, combining accessibility, ethical acceptability, and broad differentiation potential. Their ability to form dental, neural, musculoskeletal, vascular, and pancreatic tissues positions them as versatile tools for tissue repair and functional restoration. The combination of DPSCs with scaffolds, growth factors, and pathway modulation offers potential for personalized regenerative therapies, extending beyond dentistry into neurodegenerative and complex tissue repair applications.

The example of DPSC regenerative potential illustrates a clear translational gap; the lack of harmonized studies leads to fragmented knowledge, highlighting the need to embed these investigations within a strategy of integrated, GMP-oriented translational biobanking.

Considering the persistent translational barriers observed in DPSC research, future efforts should extend beyond repeating similar early-stage clinical studies. Integrating veterinary regenerative medicine may provide an opportunity to refine manufacturing processes, optimize delivery strategies, and evaluate long-term safety under real clinical conditions before broader implementation in human medicine.

Conflict of Interest

The author declares no conflicts of interest in this study.

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Authors Contribution

Conceptualization, Methodology, Formal Analysis, Funding Acquisition, Data Curation, Original Draft Writing, Supervision and Editing, Administration: A.T.

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[1] Gurusamy N, Alsayari A, Rajasingh S, Rajasingh J. Adult Stem Cells for Regenerative Therapy. Prog Mol Biol Transl Sci. 2018;160:1–22.

[2] Wang J, Deng G, Wang S, Li S, Song P, Lin K, Xu X, He Z. Enhancing regenerative medicine: the crucial role of stem cell therapy. Front Neurosci. 2024;18:1–10.

[3] Das M, Sloan AJ. Stem cell sources from human biological waste material: a role for the umbilical cord and dental pulp stem cells for regenerative medicine. Hum Cell. 2023;36:1–13.

[4] Asgary S, Eghbal MJ, Shamszadeh S. Advancements and challenges in stem/progenitor

[5] cell transplantation for dentin-pulp regeneration: a systematic review of animal studies (part I). Am J Stem Cells. 2024;13(3):110-131.

[6] Nakashima M, Iohara K, Zayed M. Pulp regeneration: Current approaches, challenges and novel rejuvenating strategies for an aging population. J Endod; 2020,46(9S):135-142.

[7] Quigley RM, Kearney M, Kennedy OD, Ducan HF. Tissue engineering approaches for dental pulp regeneration: The development of novel bioactive materials using pharmacological epigenetic inhibitors. Bioactive Materials. 2024;40:182-211.

[8] Potdar PD, Jethmalani YD. Human dental pulp stem cells: applications in future regenerative medicine. World J Stem Cells. 2015;7(5):839–851.

[9] Nuti N, Corallo C, Chan BMF, Ferrari M, Gerami-Naini B. Multipotent differentiation of human dental pulp stem cells: a literature review. Stem Cell Rev Rep. 2016;12:511–523.

[10] Liu P, Zhang Y, Chen S, Cai J, Pei D. Application of iPS cells in dental bioengineering and beyond. Stem Cell Rev Rep. 2014;10:663–670.

[11] Liu J, Yu F, Sun Y, Jiang B, Zhang W, Yang J, Xu GT, Liang A, Liu S. Concise reviews: characteristics and potential applications of human dental tissue-derived mesenchymal stem cells. Stem Cells. 2015;33(3):627–638.

[12] Gray H. Anatomy of the Human Body. Lea & Febiger. 1918:200-300.

[13] Gronthos S, Brahim J, Li S, Fisher LW, Cherman N, Boyde A, DenBesten P, Gehron Robey P, Shi S. Stem cell properties of human dental pulp stem cells. J Dent Res. 2022;101(8):531–535.

[14] Kotova AV, Lobov AA, Dombrovskaya JA, Sennikova VY, Ryumina NA, Klausen P, Shavarda AL, Malashicheva AB, Enukashvily NI. Comparative analysis of dental pulp and peridontal stem cells: differences in morphology, functionality, osteogenic differentiation and proteome. Biomedicines. 2021;3, 9(11):1606.

[15] Madhoun AA, 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.

[16] Fujii Y, Hatori A, Chikazu D, Ogasawara T. Application of dental pulp stem cells for bone and neural tissue regeneration in oral and maxillofacial region. Stem Cells Int. 2023;2023:1–11.

[17] Lott K, Collier P, Ringor M, Howard KM, Kingsley K. Administration of epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) to induce neural differentiation of dental pulp stem cell (DPSC) isolates. Biomedicines. 2023;11(2):255.

[18] Xing WB, Wu ST, Wang XX, Li FY, Wang RX, He JH, He Y. Potential of dental pulp stem cells and their products in promoting peripheral nerve regeneration and their future applications. World J Stem Cells. 2023;15(10):960–978.

[19] Yang D, Niedo Solidum JG, Park D. Dental pulp stem cells and current in vivo approaches to study dental pulp stem cells in pulp injury and regeneration. J Bone Metab. 2023;30(3):231–244.

[20] Bakkar M, Liu Y, Fang D, Stegen C, Su X, Ramamoorthi M, Lin LC, Kawasaki T, Makhoul N, Pham H, Sumita Y, Tran SD. A simplified and systematic method to isolate, culture, and characterize multiple types of human dental stem cells from a single tooth. Methods Mol Biol. 2017;1553:191–207.

[21] Eslaminejad MRB, Vahabi S, Shariati M, Nazarian H. In vitro growth and characterization of stem cells from human dental pulp of deciduous versus permanent teeth. J Dent (Tehran). 2010;7(4):185–195.

[22] Emi Inada E, Saitoh I, Terajima M, Kiyokawa Y, Kubota N, Yamaza H, Morohoshi K, Nakamura S, Sato M. Engineered human dental pulp stem cells with promising potential for regenerative medicine. BioTech; 2025, 14(4):88.

[23] Emi Inada E, Saitoh I, Terajima M, Kiyokawa Y, Kubota N, Yamaza H, Morohoshi K, Nakamura S, Sato M. Engineered human dental pulp stem cells with promising potential for regenerative medicine. BioTech; 2025, 14(4):88.

[24] Rodas-Junco B, Villicaña C. Dental pulp stem cells: Current advances in isolation, expansion and preservation. Tissue Eng Regen Med. 2017;14(4):333-347.

[25] Chalisserry EP, Nam SY, Park SH, Anil S. Therapeutic potential of dental stem cells. J Tissue Eng. 2017;8:1–15.

[26] Zhou L, Zhao S, Xing X. Effects of different signaling pathways on odontogenic differentiation of dental pulp stem cells: a review. Front Physiol. 2023;14:1272764. https://doi.org/10.3389/fphys.2023.1272764

[27] Krupińska AM, Skośkiewicz-Malinowska K, Staniowski T. Different approaches to the regeneration of dental tissues in regenerative endodontics. Appl Sci. 2021;11(4):1699.

[28] Jung C, Kim S, Sun T, Cho YB, Song M. Pulp-dentin regeneration: current approaches and challenges. J Tissue Eng. 2019;10:1–16. https://doi.org/10.1177/2041731418819263

[29] Nakashima M, Akamine A. The application of tissue engineering to regeneration of pulp and dentin in endodontics. J Endod. 2005;31(10):711–718.

[30] Gioventù S, Andriolo G, Bonino F, Frasca S, Lazzari L, Montelatici E, Santoro F, Rebulla P. A novel method for banking dental pulp stem cells. Transfus Apher Sci. 2012;47(2):199–206.

[31] Yamada S, Malkmus C, Aasebø E, Mustafa K, Egusa H, Volponi AA. Production and biobanking of dental stem cells for clinical applications in regenerative dentistry: Current practices and future perspectives – A narrative review. J Dent. 2025; 161: 105934.

[32] Mansour A, Mona E, Rugaie A, Asamah, Manhmood, Amer, Khaleel AI, Moneim A, Hafez AM, Sadik E, Abir, Mohammad A. Therapeutic potential of human mesenchymal stem cells engineered with different concentrations of TNF-α and IFN-γ. J Biomater Tissue Eng. 2023;13(5):690–697.

[33] Amini F, Rezvani MB, Bakhtiari R, Ghomsheh ET. Effects of dental pulp stem cell preconditioning on osteogenesis using conditioned media of probiotic bacteria. Avicenna J Med Biotechnol. 2023;15(2):76–83.

[34] Schmidt J, Pavlik V, Suchánek J, Nešporova K, Soukup T, Kapitán M, Pilbauerová N. Low, medium, and high molecular weight hyaluronic acid effects on human dental pulp stem cells in vitro. Int J Biol Macromol. 2023;253:127220.

[35] Dasgupta S, Reddy KP, Datta P, Bauri A. Vitamin D3-incorporated chitosan/collagen/fibrinogen scaffolds promote angiogenesis and endothelial transition via HIF-1/IGF-1/VEGF pathways in dental pulp stem cells. Int J Biol Macromol. 2023;253:127325.

[36] Bai Y, Cheng X, Liu X, Guo Q, Wang Z, Fu Y, He W, Yu Q. Transforming growth factor-β1 promotes early odontoblastic differentiation of dental pulp stem cells via activating AKT, ERK1/2, and p38 MAPK pathways. J Dent Sci. 2023;18(1):87–94.

[37] Xu K, Liu Q, Huang W, Chu Y, Fan W, Liu J, He Y, Huang F. Promotive effect of FBXO32 on the odontoblastic differentiation of human dental pulp stem cells. Int J Mol Sci. 2023;24:7708. https://doi.org/10.3390/ijms24097708

[38] Kornsuthisopon C, Tompkins KA, Osathanon T. Tideglusib enhances odontogenic differentiation in human dental pulp cells in vitro. Int Endod J. 2022;53(3):369–384.

[39] Dietrich A, Fründ HJ, Trojanowicz B, Santos AN, Nguyen AD, Hoang-Vu C, Gerhard CR. Influence of ascorbic acid as a growth and differentiation factor on dental stem cells used in regenerative endodontic therapies. J Clin Med. 2023;12(3):1196. https://doi.org/10.3390/jcm12031196

[40] Turkestani NA, Zhang Z, Nōr JE. Semaphorin 4D induces vasculogenic differentiation of dental pulp stem cells. Dent J. 2023;11(7):160. https://doi.org/10.3390/dj11070160

[41] Karkehabadi H, Zafari J, Khoshbin E, Abbasi R, Esmailnasab S, Doosti-Irani A. Effect of low-level laser therapy on differentiation and proliferation of human dental pulp stem cells: a systematic review. J Lasers Med Sci. 2023;14:e47.

[42] Kim EJ, Yoon JU, Kim CH, Yoon JY, Kim HS, Choi EK. Lidocaine inhibits osteogenic differentiation of human dental pulp stem cells in vitro. J Int Med Res. 2023;51(2):1–13. https://doi.org/10.1177/030006052311521

[43] Smaida R, Hua G, Benkirane-Jessel N, Fioretti F. Three-Dimensional Models of the Dental Pulp: Bridging Fundamental Biology and Regenerative Therapy. International journal of molecular sciences. 2025; 26(22), 10960.

[44] Morita K, Wng J, Okamoto K, Iwata T. The next generation of regenerative dentistry: From tooth development biology to periodontal tissue, dental pulp, and whole tooth reconstruction in the clinical setting. Regenerative Therapy. 2025; 28, 333-344.

[45] Washio A. Regeneration of the dentin-pulp complex in vital pulp therapy: biological basis, biomaterials, and clinical translation. Front. Dent. Med. 2026; 7, 1857656.

[46] Aguilera-Cobos L, Rosario-Lozano MP, Ponce-Polo A, Blasco-Amaro J, Epstein D. Barriers for the evaluation of advanced therapy medicines and their translation to clinical practice: Umbrella review. Health Policy. 2022; 126(12), 1248-1255.

[47] Pizevska M, Kaeda J, Fritsche E, Elazaly H, Reinke P, Amini L. Advanced Therapy Medcinal Products' Translation in Europe: A Developers' Perspective. Front. Med. 2022; 9, 757647.

[48] Marcella La Noce M, Francesca Paino F, Anna Spina A, Pasqualina Naddeo P, Roberta Montella R, Vincenzo Desiderio V, Alfredo De Rosa A, Gianpaolo Papaccio G, Virginia Tirino V, Laino L. Dental pulp stem cells: State of the art and suggestions for a true translation of research into therapy. J Dent. 2014;42(7):761-768.

[49] Song WP, Jin LY, Zhu MD, Wang H, Xia DS. Clinical trials using dental stem cells: 2022 update. World journal of stem cells. 2023;15(3): 31–51.

[50] Ivanovski S, Han P, Peters OA, Sanz M, Bartold PM. The Therapeutic Use of Dental Mesenchymal Stem Cells in Human Clinical Trials. Journal of dental research. 2024;103(12):1173–1184.

[51] Yamanda S, Malkmus C, Aasebø E, Mustafa K, Egusa H, Volponi AA. Production and biobanking of dental stem cells for clinical applications in regenerative dentistry: Current practices and future perspectives—A narrative review. J Dent, 2025, 161: 105934.

[52] Özçınar BM, Özükoç C, Türkmen E, Çakır R. Dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHEDSCs), and periodontal ligament stem cells (PDLSCs) isolation, characterization and the effectiveness of allantoin as bioactive molecule for dental regeneration. J Dent. 2025;154:105604.

[53] Shi RJH, Zhan HL, Yuan CY, Lin KL. Challenges and future directions in pulp regeneration, Europ Cells and Materials. 2025;49:32-34.

[54] Meerim NK, Dzhunushalieva G. Lndscape of tooth regeneration research: a dual-database bibliometric analysis. Tissue Engineering Part B: Reviews. 2025.

[55] Nurbaeva MK, Dzhunushalieva G. Bibliometric analysis of literature on stem cells in regenerative medicine and their clinical applications (2010 to 2024). Precision and Future Medicine. 2024;8(4):137-155.

[56] Alshaibani D, Kamadjaja M, Sitalaksmi R, Ridwan R, Al-Gabri R, Zafar M, Ramalingam S, Alqutaibi A. Regenerative potential of human dental pulp stem cells in scaffold-based alveolar and jaw bone reconstruction: a systematic review. BMC Oral Health. 2025; 25(989).

[57] Devendran A, Anandan Y, Palaniyandi S, Anbazhagan GK. Dental pulp stem cell-based therapy for human diseases. Texila International Journal of Public Health; 2025.

[58] Sapkal R, Shete A, Rajbhoj AN, Patel H, Tamboli A. Drug delivery systems using dental pulp stem cells: a systematic review. International Journal of Environmental Sciences; 2025,11(20):2178-2189.

[59] Yamada S., Holomkova K., Johansen Å, Kadousaraei MJ, Al-Sharabi N, Torelli F, Pagella P, Volponi AA, Egusa H, Fristad I, Mustafa K. Long-Term Biobanked Dental Pulp Stem Cells Retain Angiogenic Potential for Vascularised Tissue Engineering—Laboratory Investigation. International Endodontic Journal. 2025;59(1):105-118.

[60] Wagaskar P, Suryawanshi M, Patil A, Pardeshi V. Therapeutic potential of third molar-derived dental pulp stem cells in Alzheimer's disease: Current evidence and future directions. Ageing Research Reviews. 2026;114:102949.