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Review

Regenerative Applications and Performance of Periodontal Ligament Stem Cells: A Comprehensive Review of In Vivo Studies

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Abstract

Periodontal ligament stem cells (PDLSCs) represent a promising cell source for true periodontal regeneration due to their ability to form bone, cementum, and functional ligament. This review critically synthesised twelve in vivo studies (rats = 5, pigs = 2, dogs = 2, sheep = 2, one human trial) evaluating PDLSC transplantation for periodontal defects. A comprehensive search of PubMed, Web of Science, Embase, and the Cochrane Library (to May 2025) identified 358 records, of which 12 met predefined inclusion criteria. Data extraction encompassed cell source, scaffold, dose, follow-up, and quantitative regenerative outcomes. Nine studies reported cell doses (5×10^5–2×10^7 cells) and six PDLSC regeneration rates (33–100%). After normalisation for host mass, effective delivery ranged from 10^5 to 10^6 cells·kg^{-1}, with optimal outcomes typically above 10^5 cells·kg^{-1}. PDLSC transplantation consistently enhanced alveolar bone, cementum, and periodontal-ligament regeneration compared with scaffold-alone or untreated controls, with the highest outcomes obtained using biocompatible scaffolds such as Hydroxyapatite/Tricalcium Phosphate (HA/TCP), Gelfoam, or amniotic membrane. Both autologous and allogeneic PDLSC achieved equivalent performance and excellent safety, while xenogeneic models confirmed immune tolerance. Despite encouraging results, the evidence remains preliminary—most studies were short-term and small-scale, and only one randomised human trial has been published. Standardisation of cell preparation, scaffold selection, dosing (absolute and mass-normalised), and follow-up is urgently needed. Future research should include Good Manufacturing Practice (GMP)-compliant clinical trials and mechanistic studies on PDLSC differentiation, paracrine signalling, and exosome-mediated effects to consolidate their translational potential for predictable periodontal regeneration.

Keywords: periodontal ligament; stem cells; cell transplantation; periodontitis

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1. Introduction

Periodontitis is a prevalent and progressive inflammatory condition that leads to the destruction of the periodontal apparatus and eventual tooth loss. While conventional treatment methods, such as scaling and root planing, can halt disease progression, they offer limited regenerative capability. Hence, novel biological approaches, including tissue engineering and stem cell-based therapies, are gaining increasing attention for their potential to restore periodontal structures. In addition to its local effects, periodontitis

has been associated with systemic conditions such as diabetes and cardiovascular disease, underscoring the need for therapies that not only control inflammation but also regenerate lost tissues.

It is estimated that 1.1 billion people worldwide are affected by periodontitis, with 50–60% of adults exhibiting at least some level of periodontal disease [1]. Severe periodontitis contributes substantially to disability and disproportionately affects older individuals and those with risk factors such as smoking, diabetes, genetic predisposition, and poor oral hygiene. The periodontium comprises the gingiva, periodontal ligament, root cementum, and alveolar bone [2]. Gingivitis, a reversible inflammation of the gums due to bacterial plaque, is extremely common, affecting more than 90% of people worldwide at some point [3]. If untreated, it may progress to periodontitis, a chronic inflammatory disease characterised by periodontal pocket formation and destruction of tooth-supporting structures [4].

Tissue engineering combines cell biology, materials science, and dentistry to regenerate damaged tissues by creating biologically viable substitutes [5]. It relies on a triad of stem cells, biochemical signals, and scaffolds to support tissue regeneration [6]. Scaffolds must be porous, biocompatible, mechanically stable, and biodegradable; materials range from natural (collagen, hyaluronic acid, silk) to synthetic polylactic-co-glycolic acid (PLGA), polyethylene glycol (PEG), hydroxyapatite (HA), and titanium (Ti) [7–14]. Growth factors such as fibroblast growth factor (FGF), bone morphogenetic protein (BMP), epidermal growth factor (EGF), transforming growth factor-beta (TGF-β), and platelet-derived growth factor (PDGF) promote proliferation and differentiation [15–20]. Optimising the interplay between cells, signals, and scaffolds is essential for successful periodontal regeneration.

Stem cells are characterised by a remarkable ability for self-renewal and differentiation into specialised cell types [21]. Mesenchymal stem cells (MSCs) have been identified in bone marrow and various oral tissues. Several types of dental stem cells have been identified, including those extracted from exfoliated deciduous teeth (SHED) [22], dental follicles (DFSC) [23], apical papilla (SCAP) [24], and dental pulp (DPSC) [25]. Additionally, the extraction of periodontal ligament stem cells (PDLSCs) [26] has proven effective. PDLSCs are known to differentiate into osteoblasts, cementoblasts, adipocytes, and chondrocytes [27]. Two subtypes of PDLSC exist: a-PDLSC (Alveolar socket-derived PDLSC), which exhibit superior regenerative capacity, and r-PDLSC (Root surface-derived PDLSC) [27]. This anatomical and functional differentiation demonstrates that not all PDLSC are equivalent—their location of origin significantly impacts their therapeutic potential, with alveolar socket-derived cells showing enhanced regenerative capabilities for periodontal tissue engineering applications. Studies indicate that PDLSCs from older donors exhibit reduced proliferative and differentiation capacity, whereas cells from younger donors tend to have greater regenerative potential [27].

Although prior reviews have addressed periodontal regeneration using various stem cell sources, they often pooled heterogeneous cell types or focused on single tissues (e.g., bone). A dedicated analysis of PDLSC-mediated regeneration of the entire periodontium is lacking. The present review specifically focuses on PDLSC-driven regeneration of alveolar bone, periodontal ligament, and cementum, aiming to provide insights into factors such as cell source, scaffold type, and translational considerations.

2. Materials and Methods

This integrative review was conducted using a comprehensive search strategy and a narrative synthesis methodology. Some PRISMA elements were incorporated strictly for transparent reporting.

2.1. Research Question

The present integrative review aims to assess whether the transplantation of periodontal ligament stem cells (PDLSCs) can effectively improve the regeneration of periodontal tissues. In order to achieve a focused evaluation, the PICO (Population, Intervention, Comparison, Outcome) approach was adopted. The population under consideration includes both animal and human in vivo models, presenting either naturally occurring or experimentally induced periodontal defects involving loss of alveolar bone and other supporting structures. The intervention involves the transplantation of PDLSC directly into the defect site to induce the formation of the three essential tissues of the periodontium, namely the alveolar bone, the periodontal ligament, and the cementum. The primary outcomes are measured through clinical indicators, including but not limited to probing depth reduction, decreased clinical attachment loss, and bone gain (% regeneration). Furthermore, histological analyses under the microscope are utilised to assess enhancements in tissue organisation, structural regeneration, and the comprehensive integration of regenerated tissues.

2.2. Search Strategy

We used four digital databases: PubMed, Web of Science, Embase, and Cochrane Library. The 2Dsearch platform (https://app.2dsearch.com/ (accessed on 23 October 2025) was used to formulate the search using our keywords. The final search formula used was ("transplantation" OR "periodontal regeneration" OR "stem cell therapy" OR "Periodontitis surgery" OR "Periodontitis therapy") AND ("mouse" OR "in vivo" OR swine OR beagle OR rat OR "human" OR "rabbit" OR "pig") AND ("PDLSC" OR "periodontal ligament stem cell" OR "periodontal ligament stem cells"). Artificial intelligence was also used via the Connected Papers platform (https://www.connectedpapers.com/ (accessed on 23 October 2025)). This allowed us to create a visual tree of related articles, based on the DOI of one of the most frequently cited papers. A manual search was also conducted to include additional relevant studies that may have been missed by the algorithmic search.

2.3. Eligibility Criteria

Inclusion Criteria:

- In vivo studies (animal or human) transplanting PDLSCs alone or compared to other oral cavity-derived stem cells.
- Analyses focused exclusively on PDLSC transplantation effects on periodontal tissues, particularly bone/soft tissue defects mimicking periodontitis.
- Studies using xenografts, autografts, or allografts that assessed regeneration of at least one key periodontal tissue (alveolar bone, periodontal ligament, cementum).
- Articles published in English or French.

Exclusion Criteria:

- Studies combining PDLSC with non-oral stem cells in the same culture.
- Use of gene therapy with PDLSC transplantation.
- Use of PDLSC-derived exosomes.

2.4. Study Selection and Data Extraction

Two independent reviewers screened titles, abstracts, and full texts using predetermined criteria for this integrative synthesis. Discrepancies were resolved by consensus. Data extracted included reference, PDLSC source, host model, culture conditions, scaffold, cell dose, incubation time, study groups, outcomes, attachment loss (AL), probing depth (PD), and percentage of bone regeneration. The data regarding the percentages of bone regeneration were extracted from the articles using tables reporting either the percentage of bone regeneration in millimetres or the percentage of newly formed bone. Regarding

attachment loss and probing depth, these data were extracted from the articles through the tables showing the measurements taken at different time points in the studied groups.

2.5. Risk of Bias Assessment

To assess the quality of the studies and minimise bias, we used the SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) protocol [28] for animal studies and the Cochrane Risk of Bias 2 (RoB 2) tool [29] for human studies. These guidelines provide transparent methods to evaluate the risk of bias and scientific validity. Responses to the risk of bias questions were categorised as YES (low risk), NO (high risk), or UNCLEAR (intermediate risk). The results were plotted using the Robvis tool (https://mcguinlu.shinyapps.io/robvis/ (accessed on 23 October 2025)).

3. Results

3.1. Study Selection

From an initial pool of 358 records, 27 full-text articles were assessed, of which 12 studies fulfilled the eligibility criteria (Figure 1).

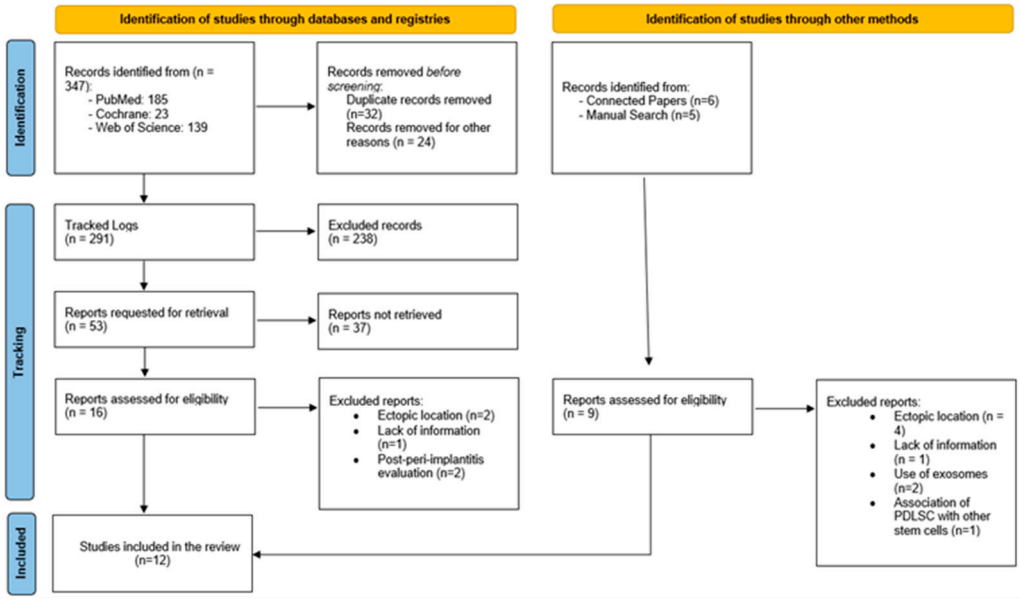

Figure 1. PRISMA flow diagram of study selection.

3.2. Synthesis of Results

Among the twelve included studies ([30–41], Table 1), the majority were conducted in small-animal models (rats, n = 5), complemented by large-animal investigations in pigs (n = 2), dogs (n = 2), and sheep (n = 2); one study was a human clinical trial [41]. Transplantation of periodontal ligament stem cells (PDLSCs) consistently improved periodontal regeneration compared with cell-free or scaffold-only controls. The most frequently employed scaffolds included Gelfoam (a resorbable gelatin sponge; n = 3, [33,36,37]), Hydroxyapatite/Tricalcium Phosphate (HA/TCP) (a bioceramic scaffold; n = 2, [30,32]), and amniotic membrane (a natural collagenous substrate; n = 2, [31,35]), along with single-study materials such as Bio-Oss, Platelet-Rich Fibrin (PRF), Bio-Guide, and Bio-Oss Collagen [38–40]. Follow-up periods ranged from four weeks to twelve months. Across these models, PDLSC therapy enhanced bone formation, cementum deposition, and functional periodontal-ligament fibre re-insertion relative to controls, confirming the reproducibility of its regenerative effects.

Table 1. Characteristics of included studies.

No.	Reference	PDLSC Source	Host Model	Scaffold	Cell Dose	Incubation	Key Findings
1	Liu et al. [30]	Autologous	Miniature pigs	HA/TCP	2×10^7	12 wk	Superior bone regeneration; reduced attachment loss.
2	Iwasaki et al. [31]	Xenogeneic	Rats	Amnion	5×10^5	4 wk	Enhanced bone, cementum, and Sharpey's fibres.
3	Ding et al. [32]	Allogeneic/ Autologous	Pigs	HA/TCP	2×10^6	12 wk	Full periodontal regeneration only in the PDLSC group.
4	Han et al. [33]	Allogeneic	Rats	Gelfoam	1×10^6	28 d (4 wk)	Near-complete bone, cementum and Sharpey's fibres regeneration.
5	Park et al. [34]	Autologous	Beagle dogs	–	6×10^6	8 wk	Best regeneration outcomes in the PDLSC group.
6	Iwasaki et al. [35]	Xenogeneic	Rats	Amnion	–	4 wk	Organised bone and Sharpey's fibres in the PDLSC group.
7	Mrozik et al. [36]	Allogeneic	Sheep	Gelfoam	1×10^7	4 wk	Highest cementum and fibre thickness in the PDLSC group
8	Menicanin et al. [37]	Autologous	Sheep	Gelfoam	2×10^6	6 wk	Complete tissue regeneration in the PDLSC group
9	Qiu et al. [38]	Xenogeneic	Rats	Bio-Guide	–	4 wk	Superior bone, Sharpey's fibre, and cementum in the PDLSC group.
10	Duan et al. [39]	Allogeneic	Rats	PRF or Collagen	–	12–24 d (2–4 wk)	Best bone, Sharpeys fibre, and cementum regeneration with PRF + PDLSC.
11	Nuñez et al. [40]	Allogeneic	Beagle dogs	Bio-Oss Collagen	1.4×10^6	3 mo (12 wk)	Comparable outcomes with the scaffold alone.
12	Chen et al. [41]	Autologous	Humans	Bio-Oss	1×10^7	3–12 mo (12–52 wk)	Greater clinical attachment gain in the PDLSC group.

Notes: HA/TCP = Hydroxyapatite/Tricalcium Phosphate; PRF = Platelet-Rich Fibrin; PDLSC = periodontal ligament stem cell. Autologous = cells from the same individual; Allogeneic = cells from another individual of the same species; Xenogeneic = cells from a different species. wk/d/mo = weeks/days/months. Data extracted as described in Section 2.4.

Quantitative analyses of probing depth (PD) and attachment loss (AL) in pigs [30,32] and dogs [34] demonstrated substantial clinical improvement after PDLSC transplantation (Table 2). In studies by Liu et al. [30] and Park et al. [34], PDLSC-treated sites showed mean PD reductions of approximately 70% and AL gains exceeding 60% versus baseline, outperforming both HA/TCP and untreated controls. Ding et al. [32] observed similar outcomes in swine, with PD and AL reductions greater than 65% for autologous and allogeneic PDLSC groups compared with $\leq$40% in scaffold-only or periodontal-ligament-cell (PDLC) groups. These findings confirm the consistent clinical efficacy of PDLSC across species.

Cell doses ranged from 5×10^5 to 2×10^7 PDLSC per defect (Table 3). After normalisation to host body mass, this corresponded to roughly 10^5–10^6 cells·kg^{-1}, depending on the animal model (rat $\approx$ 0.30 kg; dog $\approx$ 10 kg; sheep $\approx$ 40 kg; pig $\approx$ 35 kg). Low-dose regimens (5×10^5–1×10^6 cells; $\approx 1.7 \times 10^6$–3.3×10^6 cells·kg^{-1}) in rats [31,33] achieved regeneration rates of 33–100% but with high variability. Medium-dose protocols (1.4×10^6–2×10^6 cells; $\approx 4.0 \times 10^4$–5.7×10^4 cells·kg^{-1}) in pigs [32] produced 34–36% regeneration, while high-dose treatments (6×10^6–2×10^7 cells; $\approx 2.5 \times 10^5$–6.0×10^5 cells·kg^{-1}) in dogs [34] and sheep [36] reached 50–95% tissue restoration. A clear dose–response trend emerged, indicating that higher absolute and mass-normalised doses correlate with more complete regeneration. These data suggest a therapeutic threshold near 10^5 cells·kg^{-1}, above which outcomes become consistently favourable.

Table 2. Clinical parameters of probing depth (PD) and attachment loss (AL).

No.	Study	Group	Time (Weeks)	PD (SD, mm)	AL (SD, mm)
1	Liu et al. [30]	PDLSC Autologous	0	10 (0.4)	12.1 (1.8)
2	Liu et al. [30]	PDLSC Autologous	12	2.9 (0.3)	3.3 (0.6)
3	Liu et al. [30]	HA/TCP	0	10.2 (0.4)	12.8 (1.4)
4	Liu et al. [30]	HA/TCP	12	3.6 (0.8)	5.3 (0.3)
5	Liu et al. [30]	Control	0	10 (0.6)	12.4 (1.7)
6	Liu et al. [30]	Control	12	4.7 (0.4)	6.3 (0.5)
7	Ding et al. [32]	Control	0	10 (0.5)	13.4 (1)
8	Ding et al. [32]	Control	12	9 (0.4)	12 (0.8)
9	Ding et al. [32]	HA/TCP	0	10.2 (0.4)	13.8 (1)
10	Ding et al. [32]	HA/TCP	12	10.4 (0.5)	14 (0.7)
11	Ding et al. [32]	PDLSC Autologous	0	10 (0.4)	13.5 (1.8)
12	Ding et al. [32]	PDLSC Autologous	12	2.9 (0.3)	3.3 (0.5)
13	Ding et al. [32]	PDLSC Allogeneic	0	10 (0.4)	12 (1.6)
14	Ding et al. [32]	PDLSC Allogeneic	12	3 (0.3)	3.5 (0.6)
15	Ding et al. [32]	PDLC	0	10 (0.4)	7 (1.5)
16	Ding et al. [32]	PDLC	12	6 (0.3)	4 (0.6)
17	Park et al. [34]	Control	0	5 (0.5)	7.9 (0.9)
18	Park et al. [34]	Control	8	5.2 (0.1)	8.3 (0.7)
19	Park et al. [34]	PDLSC Autologous	0	5.05 (0.58)	7.05 (0.76)
20	Park et al. [34]	PDLSC Autologous	8	2.88 (0.75)	4.03 (0.84)
21	Park et al. [34]	DPSC	0	4.88 (0.53)	6.6 (0.59)
22	Park et al. [34]	DPSC	8	4.54 (0.41)	6.15 (0.58)
23	Park et al. [34]	PAFSC	0	5.04 (0.66)	6.7 (0.8)
24	Park et al. [34]	PAFSC	8	3.85 (0.8)	5 (0.58)

Notes: PD = probing depth, distance from the gingival margin to the base of the periodontal pocket; AL = attachment loss, clinical indicator of periodontal tissue support loss; values expressed as mean ± SD (mm); "0" = baseline, final values correspond to the last follow-up (≥4 weeks); PDLSC Autologous = autologous PDLSC transplantation group; HA/TCP and Control = cell-free comparative groups.

Table 3. Comparative Analysis of PDLSC dose range (non-human studies).

No.	Cell Dose Range	Mass-Normalised Cell Dose Range (Cells·kg^{-1})	Number of Studies	Regeneration Range	Efficacy Rating
1	Low (5×10^5–1×10^6)	1.7×10^6–3.3×10^6 (rats)	2 [31,33]	33–100%	High variability
2	Medium (1.4×10^6–2×10^6)	4.0×10^4–5.7×10^4 (pigs)	1 [32]	34–36%	Low
3	High (6×10^6–2×10^7)	2.5×10^5–6.0×10^5 (dogs and sheep)	3 [34,36]	50–95%	Moderate to high

Notes: Cell dose range = number of PDLSC transplanted per defect; Mass-normalised cell dose range = total number of transplanted cells divided by average host body mass (cells·kg^{-1}); Regeneration range = percentage of periodontal tissue regeneration (bone + ligament + cementum); Efficacy rating = qualitative appraisal of consistency and magnitude of outcomes across studies; only non-human studies explicitly reporting cell dose and regeneration percentage were included; high-dose regimens ($\geq 6 \times 10^6$ cells) showed more consistent results than medium or low doses. Average host weights used for normalisation: rat 0.30 kg; beagle dog 10 kg; miniature pig 35 kg; sheep 40 kg. Dose categories were defined empirically based on distribution: Low ($\leq 1 \times 10^6$), Medium ($1–5 \times 10^6$), High ($\geq 6 \times 10^6$ cells per defect).

Regeneration percentages varied according to both scaffold material and PDLSC origin (Table 4). PDLSC-loaded scaffolds achieved two- to six-fold higher regeneration (33–100%) than their scaffold-only counterparts (3–50%). The autologous PDLSC–HA/TCP construct [30] yielded 80% regeneration compared with 12% in controls, and the allogeneic PDLSC–Gelfoam model [33] achieved complete restoration (100%) versus 50% for Gelfoam alone. PDLSC combined with an amniotic-membrane scaffold [31,35] generated 33–88% regeneration, exceeding amnion-only groups (3–75%), with no immune rejection reported. The highest regeneration percentages corresponded to mass-normalised cell densities within the 5×10^5–10^6 cells·kg^{-1} range, emphasising that both scaffold compatibility and adequate cell loading are critical for optimal outcomes.

Table 4. Regenerative efficacy percentages by PDLSC source and scaffold combination.

No.	Study	Group	Regeneration (%)
1	Liu et al. [30]	PDLSC-HA/TCP Autologous	80
2		HA/TCP	44
3		Control	12
4	Iwasaki et al. [31]	PDLSC-Amnion Xenogeneic	33
5		Control	3
6	Ding et al. [32]	PDLSC-HA/TCP Autologous	36
7		PDLSC-HA/TCP Allogeneic	34
8		HA/TCP	11
9		PDLC	18
10		Control	12
11	Han et al. [33]	PDLSC-Gelfoam Allogeneic	100
12		Gelfoam	50
13	Park et al. [34]	PDLSC Autologous	95
14		PAFSC	78
15		DPSC	67
16		Control	17
17	Iwasaki et al. [35]	PDLSC-Amnion Xenogeneic	88
18		Amnion	75

Notes: Regeneration (%) = mean percentage of total periodontal regeneration reported per study; Amnion = amniotic membrane scaffold; Gelfoam = resorbable gelatin matrix used as carrier for PDLSC; PAFSC = periodontal alveolar follicle stem cell; DPSC = dental pulp stem cell; PDLSC = periodontal ligament stem cell; values express histological and/or radiographic regeneration relative to control; minor inter-study differences reflect animal model and follow-up variability.

When results were stratified by PDLSC source (Table 5), all transplantation types—autologous, allogeneic, and xenogeneic—demonstrated clear superiority over control or scaffold-only groups, with minor quantitative variation across models. Autologous PDLSC approaches yielded the most consistent outcomes, achieving 36–95% tissue regeneration (+24% to +78% versus controls) in studies involving pigs, dogs, sheep, and humans [30,32,34,37,41]. Cell doses in these protocols ranged from 2×10^6 to 2×10^7 cells, corresponding to mass-normalised levels of approximately 5.7×10^4–5.7×10^5 cells·kg^{-1}, and no adverse effects were reported. Allogeneic PDLSC transplantation [32,33,36,39,40] produced comparable regenerative gains (34–100%, +12% to +50% vs. controls) at doses of 2.5×10^5–3.3×10^6 cells·kg^{-1}, confirming the immunomodulatory properties of PDLSC and the absence of rejection. Xenogeneic transplantation in rats [31,35,38] also achieved substantial regeneration (33–88%, +13% to +30%) without immunological reaction, supporting cross-species biocompatibility.

Collectively, these findings demonstrate that regenerative efficacy aligns closely with the mass-normalised dose range identified in Table 3, confirming a therapeutic threshold near 10^5 cells·kg^{-1}, above which regeneration becomes consistent. The comprehensive analysis across Tables 2–5 indicates that PDLSC transplantation enhances periodontal repair in a dose-dependent, scaffold-supported, and source-independent manner. Improvements in clinical parameters—probing depth (PD) and attachment loss (AL)—paralleled histological evidence of new bone, cementum, and periodontal-ligament fibre formation. Regenerative outcomes were maximised when cell delivery exceeded this threshold and when compatible scaffolds such as Hydroxyapatite/Tricalcium Phosphate (HA/TCP), Gelfoam, or amniotic membrane were employed. The most pronounced therapeutic advantages (e.g., Liu et al., 2008 [30], 68%; Park et al., 2011 [34], 78%) occurred with these established

matrices or cell-only approaches, emphasising that scaffold selection and cellular dose act synergistically to determine regenerative success. Both autologous and allogeneic PDLSC sources achieved equivalent performance with excellent safety, underscoring PDLSC transplantation as a clinically translatable, reproducible, and immunologically safe platform for true periodontal regeneration.

Table 5. Comparative analysis of PDLSC sources and therapeutic outcomes.

No.	Cell Source	Number of Studies	Host Models	Mass-Normalised Cell Dose Range (Cells·kg^{-1})	Follow-Up Range	Regeneration Range (%)	Advantage vs. Control	Safety Profile
1	Autologous	5	Pigs, Dogs, Sheep, Humans	5.7×10^4–5.7×10^5	6–52 weeks	36–95	+24% to 78%	No adverse effects reported
2	Allogeneic	5	Rats, Sheep, Dogs	2.5×10^5–3.3×10^6	2–12 weeks	34–100	+12% to 50%	No immunological rejection
3	Xenogeneic	3	Rats only	1.7×10^6–NR	4 weeks	33–88	+13% to 30%	No immune rejection observed

Notes: Autologous, allogeneic and xenogeneic as defined in Table 1; regeneration range (%) = range of periodontal regeneration observed; advantage vs. control = average percentage-point improvement over cell-free groups; safety profile = summary of reported immunological or adverse events; NR = not reported. Data synthesised from in vivo studies quantifying alveolar, ligamentous, and cementum regeneration outcomes. Average host weights used for normalisation: rat 0.30 kg; beagle dog 10 kg; miniature pig 35 kg; sheep 40 kg; human 70 kg.

3.3. Risk of Bias Assessment

A significant discrepancy is evident in the assessment of quality between animal and human studies. Indeed, many reporting parameters in animal studies remain unclear (Figure 2). Furthermore, there is a lack of information on several important aspects of study design, such as randomisation of animal housing, utilisation of independent investigators for allocation, random selection of animals for outcome evaluation, and blinded assessment of results. In contrast, the human study demonstrates minimal risk of bias (see Figure 3), primarily due to the absence of ambiguous reporting.

Our findings (Figure 2) indicate considerable variability in methodological rigour among the animal studies, underscoring the need for more standardised practices. To improve quality and reduce risk of bias, future preclinical studies using PDLSCs for periodontal regeneration should incorporate robust design features such as true randomisation of animals into treatment groups with proper allocation concealment, and blinding of investigators during intervention and outcome assessment. Researchers are strongly encouraged to adhere to established reporting standards like the ARRIVE guidelines by transparently describing key details (e.g., randomisation methods, blinding procedures, sample size rationale, and animal husbandry conditions). Implementing these measures will minimise performance and detection biases and enhance reproducibility. In essence, rigorous experimental design coupled with comprehensive reporting will elevate the internal validity of PDLSC-based periodontal regeneration studies and facilitate more reliable translation of their outcomes to clinical settings.

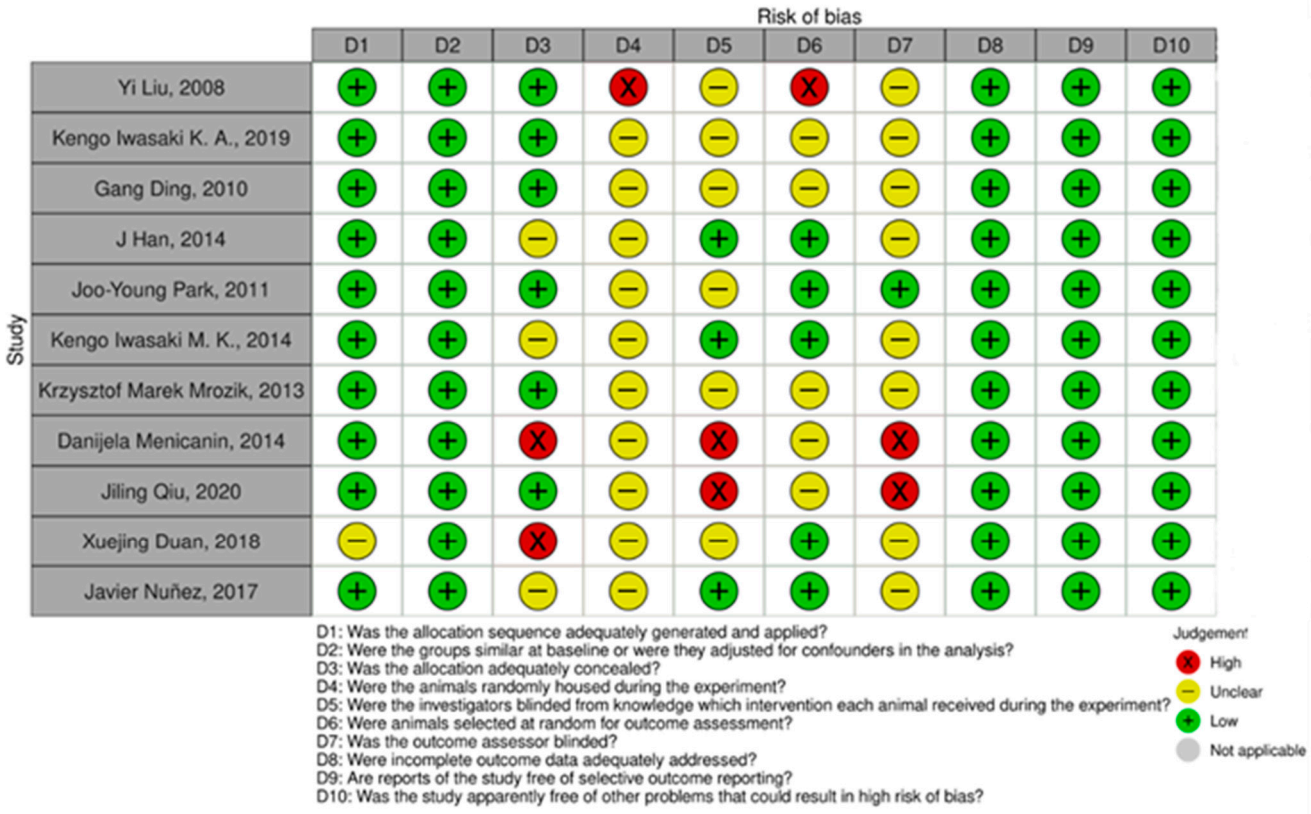

Figure 2. Traffic light plot for risk of bias analysis of the selected animal studies [30–40].

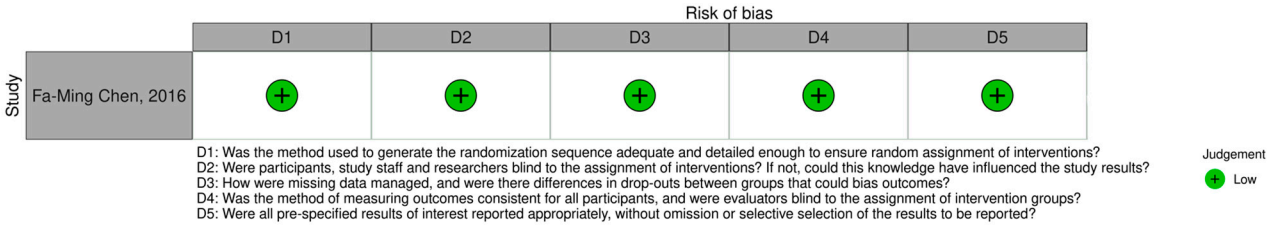

Figure 3. Traffic light plot for risk of bias analysis of a human study [41].

4. Discussion

Previous reviews have addressed regenerative therapies for periodontal defects [27], yet most combined heterogeneous mesenchymal stem cell sources or focused solely on bone regeneration. The present work provides an updated and integrative synthesis centred specifically on periodontal ligament stem cells (PDLSCs), incorporating in vivo evidence from both small- and large-animal models and the first human clinical trial. By merging these findings with a mass-normalised dosing analysis and scaffold performance comparison, this review refines the quantitative and translational understanding of PDLSC-based regeneration.

The included studies collectively confirm that PDLSC transplantation promotes formation of new cementum, periodontal ligament, and alveolar bone compared with scaffold-only or untreated controls. Differences among studies largely reflect variability in cell dose (5×10^5–2×10^7 cells), scaffold composition, defect geometry, and follow-up duration (4–52 weeks). After body-mass normalisation, effective dosing clustered near 10^5 cells·kg^{-1}, above which regeneration outcomes became consistent. This observation complements the Results section and helps to interpret dose–response variability across species.

While rodent models offer proof of concept and mechanistic feasibility, large animals—especially pigs, dogs, and sheep—better replicate human periodontal anatomy and mechanical loading. The human pilot study by Chen et al. [41] further demonstrated safety and clinical attachment gain, though its small sample precludes definitive conclusions. Collectively, these cross-species data demonstrate that PDLSC therapy is feasible, reproducible, and safe, while highlighting the need for standardised protocols that harmonise cell isolation, scaffold design, and outcome metrics.

4.1. Autologous PDLSC Transplantation

Autologous PDLSC transplantation remains the reference strategy for proof-of-concept regeneration. Several studies demonstrated that autologous PDLSC markedly improved periodontal architecture in animal models and humans [30,32,34,37,41].

Liu et al. [30] showed that Hydroxyapatite/Tricalcium Phosphate (HA/TCP) scaffolds loaded with PDLSC achieved substantial bone and ligament formation in miniature pigs and reduced epithelial downgrowth. Park et al. [34] observed that PDLSC transplantation in dogs generated well-organised cementum and ligament fibres, outperforming other oral tissue-derived stem cells. Menicanin et al. [37] reported complete periodontal regeneration in sheep using PDLSC combined with Gelfoam, a resorbable gelatin matrix.

In the human trial by Chen et al. [41], PDLSC therapy led to greater clinical attachment gain and bone fill than Bio-Oss, without adverse effects. Across these studies, cell doses of 2×10^6–2×10^7 cells ($\approx 5.7 \times 10^4$–5.7×10^5 cells·kg^{-1}) yielded consistent results, supporting the importance of dose intensity. Although autologous transplantation avoids immune complications, it remains limited by the need for harvesting, culture expansion, and patient-specific variability.

4.2. Allogeneic PDLSC Transplantation

Allogeneic PDLSC transplantation has shown promising outcomes comparable to autologous grafts, with no evidence of immune rejection [32,33,36,39,40].

Ding et al. [32] demonstrated equivalent bone and ligament regeneration between autologous and allogeneic PDLSC in pigs, highlighting PDLSC's intrinsic immunomodulatory capacity, mediated through secretion of Transforming Growth Factor-β (TGF-β), Hepatocyte Growth Factor (HGF), Prostaglandin E_2 (PGE_2), and Indoleamine 2,3-Dioxygenase (IDO). Han et al. [33] and Mrozik et al. [36] achieved nearly complete regeneration using Gelfoam scaffolds combined with PDLSC. Duan et al. [39] observed synergistic effects when PDLSC were co-delivered with Platelet-Rich Fibrin (PRF), underscoring the contribution of growth-factor release. Nuñez et al. [40] found more limited improvement in supra-alveolar defects, likely due to graft instability and geometry-related factors.

These findings confirm that, when administered at $\approx 2.5 \times 10^5$–3.3×10^6 cells·kg^{-1}, allogeneic PDLSCs provide outcomes comparable to autologous ones, suggesting an attractive "off-the-shelf" alternative for clinical application.

4.3. Xenogeneic PDLSC Transplantation and Conditioned Media

Xenogeneic PDLSC transplantation in rodents [31,35,38] yielded 33–88% regeneration without inflammatory or immune reaction, further confirming PDLSC's immune-privileged behaviour. Iwasaki et al. [31,35] used amniotic-membrane scaffolds and reported well-organised Sharpey's fibres and continuous cementum–bone interfaces. Qiu et al. [38] demonstrated that PDLSC-Conditioned Medium (PDLSC-CM) promoted superior healing compared with gingival MSCs, implying that paracrine- and secretome-mediated mechanisms contribute substantially to PDLSC-driven regeneration.

These data suggest that PDLSC-derived extracellular vesicles or exosomes could form the basis of cell-free therapeutic approaches reproducing much of the regenerative benefit while simplifying regulatory pathways.

4.4. Mechanistic Considerations

Collectively, the evidence indicates two complementary mechanisms underlying PDLSC-induced regeneration: (1) direct differentiation into osteogenic, cementogenic, and fibroblastic lineages within the defect microenvironment, guided by scaffold cues and local growth factors; and (2) paracrine and immunomodulatory signalling, through which PDLSC secrete bioactive molecules such as Bone Morphogenetic Proteins (BMPs), TGF-β, HGF, PGE_2, and IDO, that modulate inflammation, recruit host progenitors, and orchestrate matrix deposition [33,36,39].

The demonstration of regenerative efficacy using PDLSC-CM reinforces the importance of paracrine activity and supports exploration of secretome-based or exosome-mediated therapies. Future work using lineage tracing, single-cell RNA sequencing, and proteomic profiling could clarify the relative contributions of differentiation versus signalling mechanisms.

4.5. Methodological Limitations

This review presents several limitations inherent to the included studies. Firstly, most data were derived from small-scale preclinical animal models, which may not fully replicate the complexity of human periodontitis. The single human study included was preliminary and featured a limited sample size [41]. Secondly, the short follow-up durations ($\leq$12 weeks) restricted the assessment of long-term tissue stability and functional integration [31,34,40]. Thirdly, variation in PDLSC isolation methods, scaffold types, and transplantation protocols contributed to considerable heterogeneity, impeding inter-study comparability [30,31,34]. Furthermore, clinical factors such as donor age, systemic health conditions, and comorbidities, which critically influence regenerative outcomes, were rarely reported or controlled for in preclinical designs [1,3,4,27]. Finally, mechanistic insights into the regenerative process, such as the roles of exosomes and host–graft interactions, remain insufficiently explored [36,39,40].

4.6. Future Directions

Future research should extend the follow-up period beyond 12 weeks to evaluate long-term attachment stability and load-bearing function. Protocol harmonisation, including PDLSC isolation, scaffold fabrication, and quantitative dose reporting, is critical. Comparative trials testing cell sheets, injectable hydrogels, and 3D-bioprinted constructs should be conducted to optimise delivery. Mechanistic studies should focus on PDLSC-derived exosomes, immune modulation, and scaffold–cell interaction. At the same time, human trials that comply with Good Manufacturing Practice (GMP) and are adequately powered and stratified by donor and defect characteristics are needed to confirm the efficacy and safety of the product. Clinical translation will be achieved by defining a reproducible therapeutic window around 10^5 cells·kg^{-1} and integrating scaffold–dose optimisation. Finally, to facilitate reproducibility, future studies should consistently report absolute and mass-normalised cell doses, scaffold properties, and defect dimensions. Larger, standardised large-animal studies are particularly valuable for assessing mechanical integration and scaling up for human application.

5. Conclusions

In preclinical models, Periodontal Ligament Stem Cells (PDLSCs) have shown robust regenerative potential, promoting coordinated formation of new cementum, pe-

riodontal ligament, and alveolar bone. Transplantation of PDLSC—particularly when combined with biocompatible scaffolds such as Hydroxyapatite/Tricalcium Phosphate (HA/TCP), Gelfoam, or amniotic membrane—consistently enhanced periodontal regeneration compared with scaffold-alone controls. Both autologous and allogeneic PDLSC sources demonstrated favourable safety profiles, while xenogeneic models further confirmed immune tolerance.

Quantitative integration of the available data suggests that regenerative outcomes improve markedly when cell delivery exceeds approximately 10^5 cells·kg^{-1}, defining a potential therapeutic threshold for predictable efficacy. Nevertheless, the overall evidence base remains preliminary: most results derive from small-animal studies, follow-up durations rarely extend beyond twelve months, and only a single randomised human trial has been reported. Considerable methodological heterogeneity in cell isolation, dose reporting, scaffold composition, and outcome assessment continues to limit cross-study comparability.

To achieve reliable clinical translation, future research must establish standardised protocols for PDLSC preparation, dosing (absolute and mass-normalised), scaffold selection, and outcome measurement, supported by rigorous risk-of-bias control and long-term follow-up to evaluate functional stability. Well-designed, adequately powered randomised human trials under Good Manufacturing Practice (GMP) conditions are essential to compare autologous and allogeneic sources directly, to define optimal delivery systems, and to validate safety and durability.

Parallel mechanistic investigations should elucidate the relative contributions of PDLSC differentiation, paracrine signalling, and exosome-mediated effects, and determine how donor characteristics influence regenerative performance. Addressing these gaps will enable evidence-based integration of PDLSC therapy into clinical periodontology and move the field closer to achieving predictable, long-term periodontal regeneration.

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Glossary

a-PDLSC	Alveolar socket-derived periodontal ligament stem cell subtype
AL	Attachment loss; clinical measurement of periodontal tissue support
BMP	Bone morphogenetic protein; growth factor promoting osteogenic differentiation
CM	Conditioned medium; culture medium enriched with cell-secreted bioactive factors
Cochrane RoB 2	Cochrane Risk of Bias 2 tool for human randomised studies
DPSC	Dental pulp stem cell
DFSC	Dental follicle stem cell
EGF	Epidermal growth factor; regulator of cell proliferation and wound healing

FGF	Fibroblast growth factor; family of proteins stimulating angiogenesis and tissue repair
GF-CM	Growth factor-conditioned medium
GMSC-CM	Gingival mesenchymal stem cell-conditioned medium
GMP	Good Manufacturing Practice; regulatory standard ensuring product quality and safety
HA/TCP	Hydroxyapatite/tricalcium phosphate; bioceramic scaffold for bone regeneration
HGF	Hepatocyte growth factor; cytokine involved in tissue regeneration and angiogenesis
IDO	Indoleamine 2,3-dioxygenase; enzyme mediating immunomodulatory effects
MEM	Minimum essential medium; basal nutrient medium for cell culture
MSC	Mesenchymal stem cell; multipotent stromal cell capable of differentiating into mesenchymal tissues
PAFSC	Periodontal alveolar follicle stem cell
PD	Probing depth; distance from gingival margin to base of periodontal pocket
PDGF	Platelet-derived growth factor; growth factor stimulating fibroblast and osteoblast activity
PDLC	Periodontal ligament cell (non-stem)
PDLSC	Periodontal ligament stem cell
PEG	Polyethylene glycol; synthetic polymer used in scaffold formulations
PGE_2	Prostaglandin E_2; lipid mediator with anti-inflammatory and immunoregulatory roles
PICO	Population, Intervention, Comparison, Outcome; framework for clinical question design
PLGA	Poly(lactic-co-glycolic acid); biodegradable copolymer used for scaffold fabrication
PRF	Platelet-Rich Fibrin; autologous fibrin matrix enriched in platelets and growth factors
r-PDLSC	Root surface-derived periodontal ligament stem cell subtype
RCT	Randomised controlled trial
RoB 2	Risk of Bias 2; tool for assessing methodological quality of randomised trials
SHED	Stem cells from human exfoliated deciduous teeth
SYRCLE	Systematic Review Centre for Laboratory Animal Experimentation; protocol for assessing bias in animal studies
TGF-β	Transforming growth factor-beta; cytokine promoting tissue repair and cell differentiation

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