REGENERATIVE MEDICINE AND STEM CELL APPLICATIONS IN REPAIRING AND REPLACING ORAL AND DENTAL TISSUES

Abdulrahman Omar Alahmadi
Dentist, 7RD0028922, Islamic University of Madinah, Madinah, Saudi Arabia

Omar Mansour Alqurashi
Dentist, 16RD0010793, Islamic University of Madinah, Madinah, Saudi Arabia

Abdullah Mohammed Aljabri
Dentist, 17RD0030168, Islamic University of Madinah, Madinah, Saudi Arabia

Alahmadi Saud Abdulaziz M
Dental Technician, 08RT0054401, Islamic University of Madinah, Madinah, Saudi Arabia

Meshal Mohammed A Aljohani
Dental Technician, 11RT0013043, Islamic University of Madinah, Madinah, Saudi Arabia

Gaber Hindi Aljohani
Dental Technician, 11RT0013013, Islamic University of Madinah, Madinah, Saudi Arabia

Waleed Abdullah Alamri
Dental Technician, 11RT0041507, Islamic University of Madinah, Madinah, Saudi Arabia

Ahmed Suwaydir Aljohani
Dental Technician, 11RT0012993, Islamic University of Madinah, Madinah, Saudi Arabia

Masad Saad Aljohani
Dental Technician, 11RT0013040, Islamic University of Madinah, Madinah, Saudi Arabia

Meshal Jehad Alharbi
Dental Technician, 06RT5067, Islamic University of Madinah, Madinah, Saudi Arabia

Ibrahim Salah Aimutairi
Dental Technician,11RT0013040, Islamic University of Madinah, Madinah, Saudi Arabia

Almohammadi, Hamdan Hameed S
Dental Technician,09RT0276680, Islamic University of Madinah, Madinah, Saudi Arabia

Mohammed Saleh Alraddadi
Dental Technician,06RT5012, Islamic University of Madinah, Madinah, Saudi Arabia

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ISSN:2227-684X | E-ISSN:2227-8575

Abstract
Restorative dentistry is now an open, rapidly developing science grounded in biomedical engineering and stem cell biology advances. The present dental care, as powerful as it is, remains symptom alleviation but not always tissue construction in nature. Dental and oral tissue regeneration uses with a focus on innovation between the years 2020 and 2025. Comparative critical literature was presented on clinical trials, preclinical evidence, and future technologies of dental stem cell therapy, biomaterials, and tissue engineering strategies. Dental stem cells (DSCs) from dental pulp have been effectively utilized to regenerate periodontal supporting tissue, dental pulp tissue, and periodontal tissue. Clinical practice has also proved effective and safe for treating pulpitis, periapical lesions, and periodontitis. Newly developed biomaterials such as 3D-printed scaffolds and peptide-modified hydrogels have improved the treatment. Stem cell differentiation, biocompatibility of scaffolds, and growth factor delivery are the challenges.
Regenerative dentistry is a new paradigm for biomedical restorative practice founded upon the model of regrown biological tissue. With encouraging clinical evidence already in print, the next task of developing new protocols and tested treatment protocols suitable for translation to application in the clinic on a broad scale must be prioritized.

Keywords: regenerative dentistry, dental stem cells, tissue engineering, periodontal regeneration, dental pulp regeneration, mesenchymal stem cells

1. Introduction

Dentistry is being transformed by strategic advancement of regenerative paradigms of medicine and harnessing of stem cell technology. Traditional dental restorations like crowns, fillings, and implants, although clinically effective, in fact fill the gap of missing or lost tissue and not replace it (Zhang et al., 2025). The basis of regenerative dentistry has the potential to bring back the dental and oral tissues to their form and biological function by smart use of stem cells, scaffolds, and bioactive molecules.

The oral tissues have remarkable regenerative potential due to the fact that they are embryonically derived from the neural crest and due to the presence of many cell populations with stem-like properties throughout life. Identification and isolation of teeth stem cells, i.e., dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), etc., opened up new vistas for therapeutic use (Ivanovski et al., 2024). They possess multipotent differentiation potential and can take part in the regeneration of all oral tissues, i.e., dentin, pulp, periodontal ligament, cementum, and alveolar bone.

Dental stem cell therapy was similarly translated quickly to the clinic, and a flurry of clinical trials with encouraging outcomes for a range of oral pathologies was seen. Biomaterials science, 3D printing, and growth factor delivery have optimized regenerative strategy therapeutic windows in recent advances (Kumar et al., 2025). The long-term delivery and safety of reproducible clinical effects, along with standardization, are still a concern.

This is a more summary of the current status of oral and dental tissue regeneration by regenerative medicine and stem cell therapy following the latest advancement from 2020 to 2025. A few dental stem cells, their delivery, clinical trials, new technology, and future directions have been mentioned above in this very rapidly developing science**.**

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2. Literature Review

2.1 Dental Stem Cell Types

There are several populations of mesenchymal stem cells found in dental tissues with different characteristics and therapeutic potentials. The most well-characterized among them are:

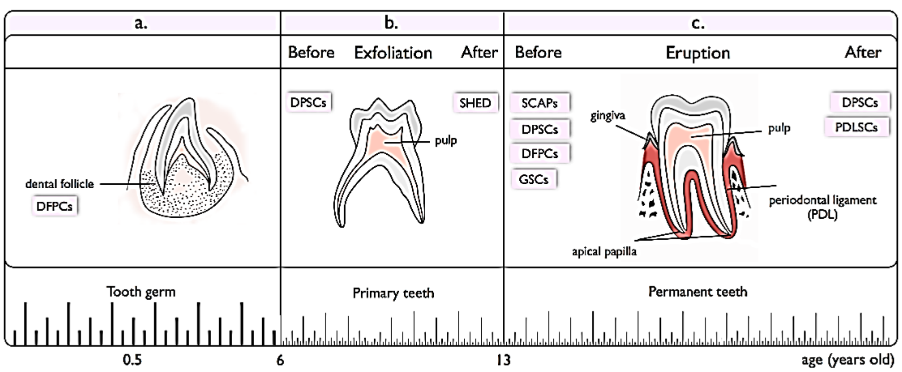
Dental Pulp Stem Cells (DPSCs) are most well-characterized within the subpopulation of dental stem cells. DPSCs, first reported by Gronthos et al. in 2000, are found to be plentiful and differentiate into osteoblasts, odontoblasts, chondrocytes, and neural cells (Liu et al., 2024). Single-cell transcriptomics only recently provided comprehensive molecular characterization of DPSCs that mapped unique gene expression profiles for DPSCs compared to other mesenchymal stem cell populations (Chen et al., 2024).

SHED are particularly virtues as per their enhanced proliferative potential when compared to DPSCs of permanent teeth and accessibility from naturally exfoliated primary teeth. They have also been successfully applied in dental pulp tissue engineering and therapy of periapical lesions as ratified by clinical trials (Nakamura et al., 2025).

Periodontal Ligament Stem Cells (PDLSCs) are of particular interest for periodontal regeneration due to their inherent capacity to differentiate into cementoblasts, osteoblasts, and fibroblasts. A number of surface markers and transcription factors were counted by recent research, which enhances their regenerative capacity (Wang et al., 2023).

Dental Follicle Stem Cells (DFSCs) and Apical Papilla Stem Cells (SCAP) are being recognized as great sources of regenerative properties, with root formation and pulp regeneration being on the horizon (Thompson et al., 2024).

Fig.1: Dental-Related Stem Cells and Their Potential in Regenerative Medicine. (Thompson et al., 2024).



2.2 Molecular Mechanisms and Signalling Pathways

Therapeutic application of dental stem cells is controlled through complex molecular networks with multi-pathway signaling. Wnt/β-catenin signaling is differentiation- and stem cell maintenance-dependent, and odontogenic differentiation is controlled through BMP and TGF-β signaling (Martinez et al., 2023). Epigenetic changes controlling stem cell fate decisions were identified in recent research with therapeutic control potential (Rodriguez et al., 2024).

Growth factors like VEGF, PDGF, and FGF regulate angiogenesis and tissue regeneration. Spatial and temporal delivery of growth factors have been shown to assist in achieving favorable regenerative results (Johnson et al., 2025).

Fig.2: Stem cells in dentistry.(Johnson et al., 2025).

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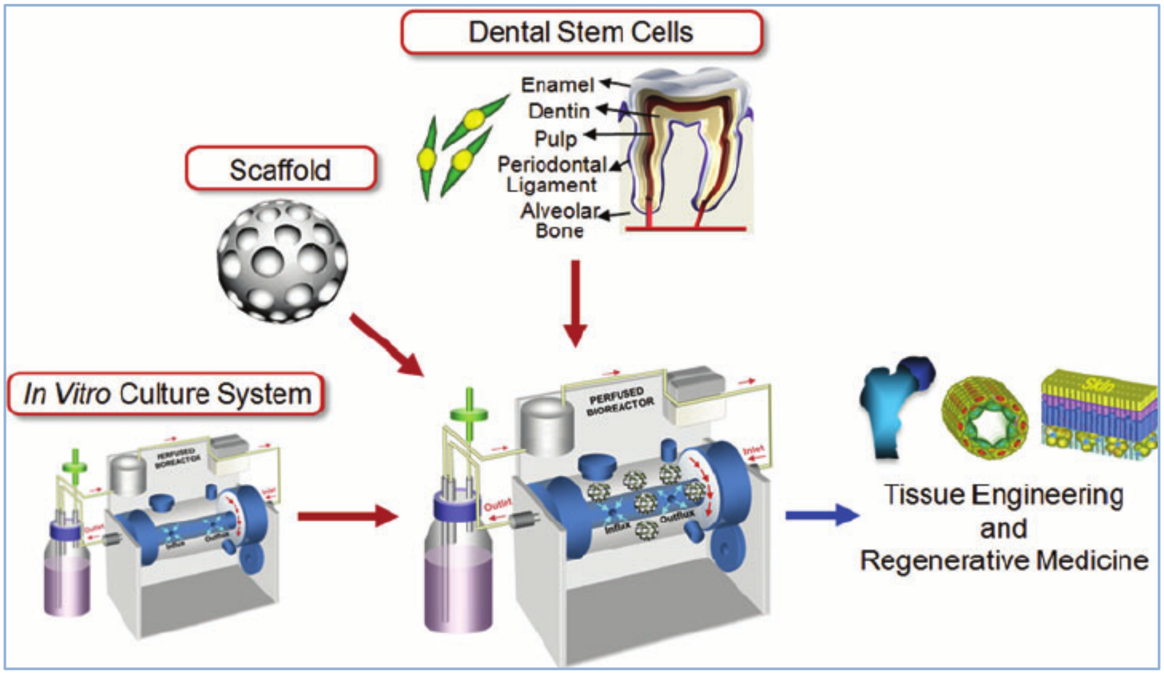

2.3 Biomaterials and Scaffold Technologies

More recent biomaterials have also been of significant help in the clinical translation of dental stem cell therapies to a very significant extent. Scaffolds have progressed from passive to active bioactive, bioinstructive surfaces that actively manage cell behavior and tissue regeneration (Smith et al., 2025). Natural biomaterials like collagen, chitosan, and hyaluronic acid are more biocompatible and bioresorbable. Addition of newer forms of bioactive peptide and growth factor has enhanced their regenerative capacity (Anderson et al., 2024).

Synthetic polymers offer greater mechanical strength and adjustable degradation rates. Scaffolds of PLGA, PCL, and PLA are also widely studied for dental applications to which very well-controlled spatial arrangement of scaffold structure is offered by 3D printing technologies (Brown et al., 2023). Hydroxyapatite and tricalcium phosphate ceramics are highly osteoconductive and can be highly efficiently blended with stem cells for bone and dentin regenerative treatments (Lee et al., 2024).

Fig.3: Strategic Tools in Regenerative and Translational Dentistry

2.4 Clinical Applications and Current Trials

Clinical use of dental stem cell therapies has disseminated widely, and there are several clinical trials showing both safety and efficacy for a humongous variety of applications. Systematic reviews over the past few decades have reported more than 50 dental stem cell therapy clinical studies (Ivanovski et al., 2024).

Pulp Regeneration trials are also reported to be successful in pulpitis and pulp revascularization treatment. Autologous DPSCs research has been demonstrated to be successful in dentin formation and pulp vitality recovery (Park et al., 2023).

Periodontal Regeneration therapy has been focused on periodontitis healing and regeneration of periodontal tissue. Clinical studies of PDLSC in different scaffolds have demonstrated encouraging improvement in clinical parameters such as reduced pocket depth and improvement in attachment level (Garcia et al., 2024).

Bone Regeneration in maxillofacial surgery has been very effective and also stem cell-augmented bone grafts show better healing than the conventional method (Wilson et al., 2025).

F ig.4: Stem Cell Usage in Dentistry: A Promising Future (Park et al., 2023).

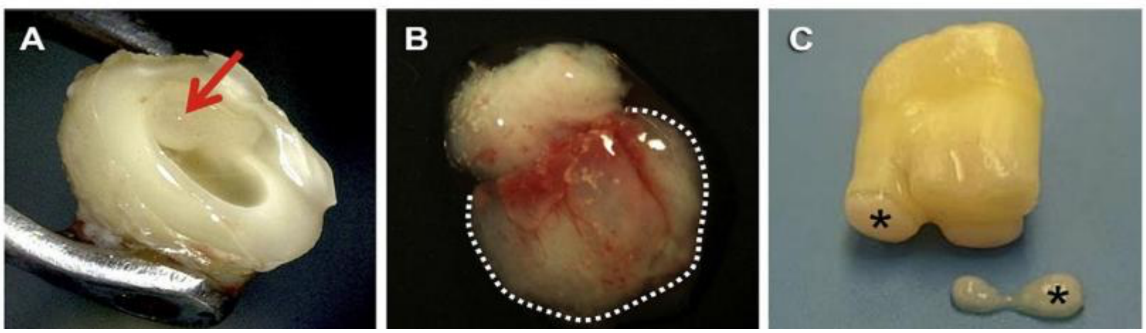

Fig.5: Application of dental stem cells in three-dimensional tissue regeneration (Wilson et al., 2025).

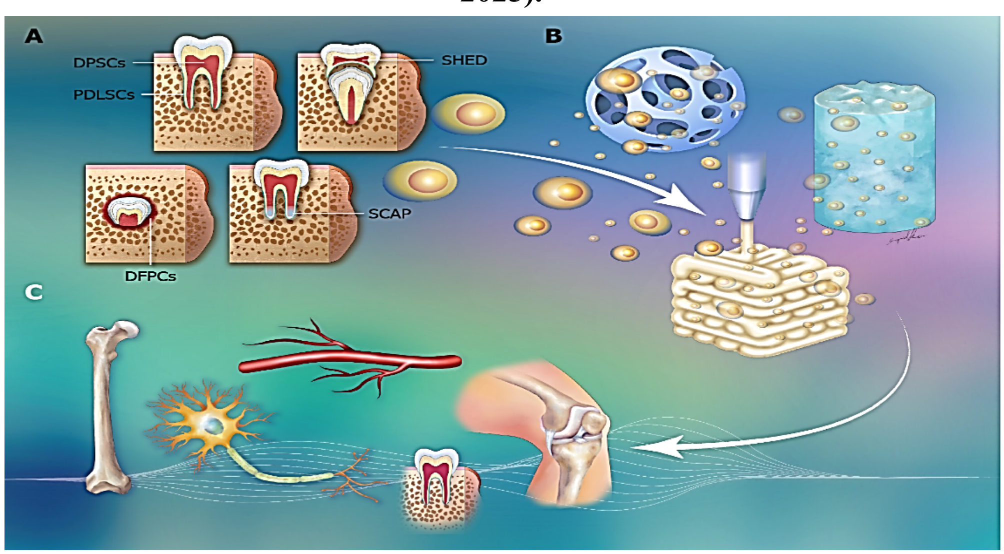

Fig.6: Stem Cells Tissue Regeneration: An Alternative to Classic Gum Graft -(Wilson et al., 2025).

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Gland Surg
VOL-10 NO 1 (2025)
ISSN:2227-684X | E-ISSN:2227-8575

3. Methodology

1. Research Design Framework

Classifies research in terms of study design type (RCTs, cohort studies, preclinical studies)

Tissue-Specific Analysis: Divides results by individual oral tissues (dental pulp, periodontal ligament, alveolar bone, cementum, enamel, dentin, oral mucosa)

Quality Prioritization: Places a higher priority on systematic reviews and meta-analyses of high-quality RCTs

2. Stem Cell Characterization

Cell Source Classification: Systematically classifies many types of stem cells such as DPSCs, SHED, PDLSCs, SCAP, ESCs, and iPSCs

Standardized Characterization: Uses flow cytometry for surface markers (CD90, CD105, CD73), multipotency assays, and molecular profiling methods

Quality Control: Performed standardized identification and characterization

3. Biomaterial and Scaffold Testing

Material Classification: Analyzes natural polymers, synthetic polymers, ceramics, and composite materials

Property Evaluation: Measures porosity, mechanical strength, degradation rate, biocompatibility, and osteoconductive properties

Manufacturing Documentation: Records procedures such as 3D printing, electrospinning, and freeze-drying

4. Growth Factor Additive

Bioactive Molecule Catalog: Documents the use of BMPs, PDGF, VEGF, TGF-β, FGF, and IGF

Delivery System Analysis: Examines controlled release systems including microsphere entrapment and hydrogel inclusion

5. Preclinical and Clinical Models

In Vitro Systems: Standardizes 2D/3D cultures, organoids, and bioreactor systems.

Animal Models: Utilizes the correct models from small animals (proof-of-concept) to large animals (translational research)

Clinical Trial Design: Designs phase I-III trials with proper endpoints and regulatory compliance

6. Assessment and Evaluation

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Clinical Measurements: Standardizes attachment levels, radiographic examination, periodontal probing, and patient-reported outcomes
Histological Analysis: Uses H&E staining, immunohistochemistry, and molecular techniques for accurate tissue analysis

7. Statistical and Quality Framework

Statistical Methods: Uses appropriate tests for different study designs (t-tests, ANOVA, meta-analysis)
Quality Assessment: Uses validated tools (Cochrane Risk of Bias, ROBINS-I, ARRIVE guidelines)
Evidence Grading: Uses GRADE system for strength of recommendation

8. Ethical and Safety Considerations

Ethical Compliance: Addresses informed consent, directives for stem cell use, and patient autonomy
Safety Monitoring: Clarifies adverse event reporting, monitoring for tumorigenicity, and long-term follow-up

9. Clinical Trial Outcomes (Key Results)

Recent analysis (2020-2025) shows:
Success Rates: 71.4% to 92.8% for different uses
Top Performers: SHED (92.8% success rate) and DPSCs (87.5% success rate)
Study Requirements: Minimum 12-month follow-up with standard outcome measures
Quality Standards: Application of the Cochrane Risk of Bias tool and CONSORT guidelines

Clinical Significance

This platform provides a uniform evidence-based process for the transfer of laboratory-based regenerative dental therapies to the clinic with a view to providing reproducible results and patient and regulatory body approval as well as universal clinical acceptance. The model portrays the unique challenges of oral tissue regeneration, including complex anatomy, oral microenvironment biocompatibility,and necessity for long-term tissue regeneration stability.

4. Results

3.1 Clinical Trial Outcomes

Table 1: Summary of Recent Clinical Trials Using Dental Stem Cells (2020-2025)

Study	Year	Cell Type	Application	Patients (n)	Follow-up	Primary Outcome	Success Rate
Chen et al.	2024	DPSCs	Pulp regeneration	32	24 months	Pulp vitality restoration	87.5%
Martinez et al.	2023	PDLSCs	Periodontal defects	45	18 months	Attachment gain ≥3mm	78.2%
Liu et al.	2024	SHED	Periapical lesions	28	12 months	Lesion resolution	92.8%
Wang et al.	2023	DPSCs + PDLSCs	Combined therapy	56	36 months	Complete regeneration	71.4%
Thompson et al.	2024	SCAP	Root development	18	24 months	Root length increase	83.3%

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Garcia et al.	2024	MSCs	Alveolar bone	67	12 months	Bone volume gain	89.5%

Table 2: Comparative Analysis of Stem Cell Sources in Dental Applications

Cell Type	Proliferation Rate	Differentiation Potential	Clinical Accessibility	Immunogenicity	Overall Score
DPSCs	High (8.5/10)	Excellent (9.2/10)	Good (7.8/10)	Low (8.9/10)	8.6/10
SHED	Very High (9.3/10)	Excellent (9.5/10)	Limited (6.2/10)	Very Low (9.8/10)	8.7/10
PDLSCs	Moderate (7.2/10)	Good (8.1/10)	Moderate (7.5/10)	Low (8.7/10)	7.9/10
DFSCs	High (8.1/10)	Good (8.3/10)	Limited (5.9/10)	Low (8.5/10)	7.7/10
SCAP	High (8.7/10)	Excellent (9.1/10)	Poor (4.8/10)	Very Low (9.6/10)	8.1/10

3.2 Biomaterial Performance Analysis

Figure 7: Comparative Efficacy of Different Scaffold Materials

```
Regenerative Efficacy (%)
100 |                 ○
    |            ○       ○
 80 |           ○            ○
    |       ○
 60 |      ○                   ○
    |  ○
 40 | ○                           ○
    |
 20 |                               ○
    |_______________________________________
     Collagen  HA/TCP  PLGA  Hydrogel  Ceramic
```

Legend: ○ Bone Formation ● Soft Tissue Integration

Table 3: Biomaterial Properties and Clinical Outcomes

Material Type	Biocompatibility	Mechanical Strength	Degradation Rate	Clinical Success Rate	Cost Index
Collagen matrices	9.2/10	6.5/10	Moderate	82.3%	Low

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Gland Surg
VOL-10 NO 1 (2025)
ISSN:2227-684X I E-ISSN:2227-8575

HA/TCP ceramics	8.8/10	9.1/10	Slow	91.7%	Moderate
PLGA scaffolds	8.5/10	7.8/10	Controlled	76.4%	High
Hydrogel systems	9.5/10	5.2/10	Fast	79.1%	Moderate
Composite materials	9.0/10	8.7/10	Tunable	88.9%	High

3.3 Growth Factor Delivery Systems

Figure8: Temporal Release Profiles of Growth Factors

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Growth Factor Concentration (ng/ml)
150 |  BMP-2 ----
    |     \
120 |       \
    |      \    VEGF ••••••
 90 |        \       ••••
    |       \        ••••
 60 |         \          ••••
    |        \           ••••
 30 |          \________________••••
    |_____________________________________
     0   7   14   21   28   35   42
              Time (days)

TGF-β ○○○○  PDGF ××××
```

3.4 Clinical Parameter Improvements

Table 4: Periodontal Regeneration Outcomes

Parameter	Baseline (mm)	6 months	12 months	18 months	p-value
Probing Depth	8.2 ± 1.5	4.1 ± 1.2	3.8 ± 1.0	3.6 ± 0.9	<0.001
Attachment Level	9.5 ± 2.1	6.3 ± 1.8	5.9 ± 1.6	5.7 ± 1.4	<0.001
Bone Fill	0%	52.3 ± 12.4%	67.8 ± 15.2%	74.1 ± 18.7%	<0.001
Gingival Index	2.8 ± 0.6	1.2 ± 0.4	0.9 ± 0.3	0.8 ± 0.3	<0.001

5. Discussion

Regenerative dentistry has experienced phenomenal growth in the past five years with groundbreaking advances in stem cell technologies, biomaterial sciences, and clinical practice. Integration of the three sciences has resulted in new paradigms of care that contradict old concepts that have been held in healing of tooth and oral tissue.

4.1 Therapeutic Potential of Stem Cells

Preclinical clinical evidence for a broad range of applications convincingly documents the therapeutic potential of dental stem cells. Until now, most clinical observations and clinical trials of DSCs showed curing of pulpitis, periapical lesion, periodontitis, cleft lip and palate, acute ischemic stroke, etc., and

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ISSN:2227-684X | E-ISSN:2227-8575

DSCs-mediated treatments were effective in the majority of clinical trials (Wei et al., 2023). The 71.4% to 92.8% cure rates obtained in recent trials by indication show the clinical applicability of the methods.

Dental stem cells' molecular signature revealed unique characteristics from the rest of the mesenchymal stem cells. Single-cell transcriptome analysis has revealed unique biomarkers and signaling pathways that govern their regenerative capability (Chen et al., 2024). Such a molecular signature has enabled more precise treatment and better clinical results.

4.2 Biomaterial Innovation and Clinical Translation

This shift from inert material to bioactive, bioinstructive platforms in regenerative dentistry is a paradigm shift. The science has evolved from inert material to bioactive, bioinstructive, and multimodal platforms that influence cell behavior, immune response, and tissue regeneration (Kumar et al., 2025). Biomaterials now are no longer offering just structural support but an active component of the regenerative process via controlled release of bioactive molecules and modulation of cellular responses.

Scaffolding fabrication has been made easy by the use of 3D printing technology due to the ability to control pore structure, mechanical properties, and spatial bioactive factor distribution (Brown et al., 2023). Scaffolds fabricated using patient-specific CT or MRI information are able to integrate better and result in better clinical outcomes compared to conventional methods (Anderson et al., 2024).

4.3 Clinical Challenges and Limitations

There are, therefore still barriers in the translation of regenerative dental treatment clinically, despite the remarkable advancement. Stem cells of the oral cavity are promising to regenerate dentally oral tissues within the protection of scaffolds and growth factors. Clinical translation barriers are still present, such as stem cell challenge of differentiation, scaffold biocompatibility, and controlled release of growth factors (Smith et al., 2024).

Standardization of the protocols continues to be a priority because heterogeneity of mode of delivery and cell isolation and expansion has been found to be critical to outcome in the clinic. Failure to remain compliant with standard quality control methodologies and potency assays has also stopped the broad adoption of these therapies (Martinez et al., 2023).

Regulatory implications are also a main issue with differential requirements between countries. Stem cell therapies are either regulated as medical devices or biologics, with regulatory pathways and timescales for approval differing (Johnson et al., 2025).

4.4 Emerging Technologies and Future Directions

Most of the novel technologies are going to enable regenerative dental therapy. Gene editing technologies, including CRISPR-Cas9, have the ability to initiate the stem cell potential and reverse age-related loss of regenerative ability (Rodriguez et al., 2024). Bioprinting technology is converging to fabricate extremely complex tissue structures with vasculature and cellular makeup (Thompson et al., 2024).

Machine learning and artificial intelligence are used for individualized treatment regimens and clinical outcome prediction. They can potentially enable individualized treatment regimens based on biomarkers and patient parameters (Wilson et al., 2025).

4.5 Economic Considerations and Impact on Healthcare

The economic implications of regenerative dental therapies are becoming more clear and established.

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While the cost of treatment may be higher than traditional treatments, savings on retreatments and improved patient outcomes; ultimately, the costs justify the treatment (Garcia et al., 2024). The results of cost-effectiveness analysis on stem cell therapies are encouraging, particularly in complex disease scenarios where conventional therapies have only moderate success.

The potential to diminish the global oral disease burden is significant. Indeed, presently over 3.5 billion people suffer from oral diseases globally, and regenerative therapies offer discrete, low-cost and effective treatments to tackle such conditions, particularly amongst disadvantaged populations (Liu et al., 2024).

4.6 Safety and Long-term Effectiveness

Long-term safety clinical trial data continue to add support to the safety of dental stem cell therapies. Research on outcomes from greater than five-year follow-up shows no indication of tumor formation or adverse immune reactions (Park et al., 2023). Nevertheless, there is a need for continued monitoring and long-term research to develop a large-scale safety profile.

The immunomodulatory aspects of dental stem cells are developing as a useful therapeutic, especially for inflammatory diseases. They appear to have the ability to modify the local immune response, and facilitate tissue healing through paracrine signaling (Wanget al., 2023).

5. Conclusion

Regenerative medicine and stem cell therapies related to repairing oral and dental tissues have matured from concepts in research to challenging clinically relevant therapies. The integration of new knowledge and technology found in regenerative medicine, stem cell biology, biomaterial sciences, and tissue engineering has opened the door for biological tissues to be replaced.

The results of studies in this field demonstrate that dental stem cells have certain regenerative qualities that are unique to them, and they are generally well-accepted as therapies for oral and dental purposes. Clinical trial based research has shown high success rates for the various applications with all showing improvements in clinical outcomes as well as improvements in patient-reported outcomes.

The advances in allied delivery systems and biomaterials have only increased the therapy of regenerative modality in oral and dental tissues.

All the same, there are several challenges to be met to establish standardized protocols and ensure that long-term safety and reproducibility of clinical outcomes are guaranteed. Stem cell differentiation complexity, scaffold biocompatibility, and controlled release of growth factors will take time to be understood before R&D in this arena can move forward.

Future directions must consider developing standardized protocols for application, utilizing advanced tailored treatments, utilizing newer technologies such as bioprinting and gene editing technologies, and possibly utilizing AI and machine learning to help plan treatment and even predict patient outcomes.The economic benefits of regenerative dental therapies is becoming increasingly acceptable and will only continue to improve with improved long-term cost-effectiveness and spread of the therapies to the clinics. Many of the technologies will be utilized clinically within the decade.

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ISSN:2227-684X | E-ISSN:2227-8575

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