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EXOSOME-BASED THERAPEUTICS IN REGENERATIVE DENTISTRY: A CRITICAL REVIEW OF CURRENT EVIDENCE AND TRANSLATIONAL PERSPECTIVES

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ABSTRACT

Regenerative dentistry has evolved considerably over the past decade with increasing emphasis on biologically driven therapeutic approaches capable of restoring the structural and functional integrity of oral tissues. Among the emerging regenerative strategies, exosome-based therapy has attracted substantial scientific interest because of its ability to mediate tissue repair through cell-free mechanisms. Exosomes are nanosized extracellular vesicles secreted by multiple cell types, particularly mesenchymal stem cells, and contain biologically active molecules including proteins, lipids, messenger RNA, microRNA, cytokines, and growth factors involved in intercellular signaling and tissue remodeling. Recent evidence suggests that exosomes possess substantial regenerative potential in regenerative endodontics, periodontal regeneration, bone tissue engineering, implantology, oral wound healing, oral oncology, and temporomandibular joint repair. Their therapeutic effects are largely attributed to anti-inflammatory, angiogenic, osteogenic, and immunomodulatory properties capable of enhancing cellular proliferation, differentiation, extracellular matrix synthesis, and tissue remodeling. Compared with conventional stem-cell transplantation, exosome-based therapeutics demonstrate several advantages including lower immunogenicity, minimal tumorigenic risk, improved biosafety profile, easier storage, and fewer ethical concerns. Despite promising preclinical findings, several barriers continue to limit routine clinical implementation, including lack of standardized isolation protocols, heterogeneity in exosome composition, difficulties in large-scale manufacturing, limited long-term clinical evidence, and unresolved regulatory concerns. This review critically synthesizes current evidence regarding the biological mechanisms, regenerative applications, translational challenges, and future perspectives associated with exosome-based therapeutics in regenerative dentistry.

Keywords: Exosomes, regenerative dentistry, extracellular vesicles, regenerative endodontics, periodontal regeneration, tissue engineering.

INTRODUCTION

Regenerative dentistry has emerged as one of the most rapidly advancing disciplines in contemporary oral healthcare because of its potential to restore damaged tissues through biologically mediated repair rather than conventional replacement strategies. Traditional restorative procedures and prosthetic rehabilitation have significantly improved clinical outcomes; however, these approaches frequently fail to reproduce the structural complexity and physiological characteristics of native oral tissues. Consequently, increasing scientific attention has shifted toward regenerative strategies integrating stem-cell biology, molecular signaling, biomaterials, and tissue engineering.¹

Among recent advances in regenerative medicine, exosomes have attracted substantial interest because of their ability to regulate intercellular communication and tissue remodeling. Exosomes are extracellular vesicles measuring approximately 30–150 nm in diameter and are secreted through the endosomal pathway by nearly all eukaryotic cells. Initially considered cellular waste products, exosomes are now recognized as biologically active vesicles capable of transporting proteins, lipids, messenger RNA, microRNA, cytokines, and growth factors between cells.² Their molecular cargo influences angiogenesis, osteogenesis, inflammation, cellular proliferation, differentiation, and extracellular matrix remodeling.

Mesenchymal stem-cell-derived exosomes have demonstrated particular relevance in regenerative dentistry because of their anti-inflammatory, angiogenic, osteogenic, and immunomodulatory properties. Current evidence suggests that several therapeutic effects previously attributed to stem-cell transplantation may actually be mediated through extracellular vesicle signaling pathways.³ This observation has shifted scientific focus toward cell-free regenerative strategies capable of overcoming limitations associated with direct stem-cell therapy.

Compared with stem-cell transplantation, exosome-based therapeutics offer several important advantages including lower immunogenicity, reduced tumorigenic risk, easier storage and handling, improved biosafety profile, and fewer ethical concerns.⁴ Within dentistry, exosomes have shown promising applications in regenerative endodontics, periodontal tissue repair, bone regeneration, implantology, oral wound healing, oral cancer diagnostics, and temporomandibular joint regeneration. Nevertheless, despite encouraging experimental findings, routine clinical implementation remains limited because of variability in isolation methods, lack of standardization, limited human clinical trials, and evolving regulatory frameworks.⁵

Therefore, the present review critically evaluates current evidence regarding the biological mechanisms, regenerative applications, translational limitations, and future perspectives associated with exosome-based therapeutics in regenerative dentistry.

METHODOLOGY

A structured literature search was conducted using PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar databases to identify relevant publications investigating exosome-based therapeutics in regenerative dentistry. The search included studies published between January 2013 and March 2026. Keywords and Medical Subject Headings (MeSH) terms included “exosomes,” “extracellular vesicles,” “regenerative dentistry,” “dental stem cells,” “periodontal regeneration,” “regenerative endodontics,” “bone tissue engineering,” “implantology,” “oral wound healing,” and “oral cancer biomarkers.”

The initial electronic search yielded approximately 240 potentially relevant publications. Following removal of duplicate records and preliminary screening of titles and abstracts, nearly 70 articles demonstrating direct relevance to regenerative dental applications of exosomes were selected for full-text evaluation. After detailed assessment for scientific quality, methodological relevance, and applicability to oral healthcare, 26 studies were considered most suitable for qualitative evidence synthesis in the present review, corresponding with the

references included in the manuscript.

The included literature comprised original *in vitro* investigations, animal studies, translational studies, systematic reviews, and high-quality narrative reviews. Particular emphasis was placed on studies evaluating mesenchymal stem-cell-derived exosomes because of their increasing significance in regenerative medicine and oral tissue engineering. Additional manual screening of reference lists from selected articles was also performed to identify potentially relevant publications not retrieved during the primary database search.

Studies unrelated to oral healthcare applications, duplicate publications, conference abstracts without accessible full text, editorials, expert opinions lacking primary evidence, and non-English articles were excluded from the final synthesis. Because of substantial heterogeneity in study design, exosome isolation methods, biomaterial systems, dosage concentrations, and outcome assessment methodologies, quantitative meta-analysis was not considered methodologically appropriate. Therefore, the retrieved evidence was critically synthesized qualitatively with emphasis on regenerative endodontics, periodontal regeneration, bone tissue engineering, implantology, oral wound healing, oral oncology, and translational therapeutic challenges associated with exosome-mediated regenerative therapy.⁶

Biological Basis and Regenerative Mechanisms of Exosomes

Exosomes are membrane-bound extracellular vesicles formed through inward budding of endosomal membranes followed by extracellular release via fusion of multivesicular bodies with the plasma membrane. Their biological activity depends largely on the molecular cargo transported from donor cells to recipient cells.⁷ Mesenchymal stem-cell-derived exosomes are particularly enriched with regenerative signaling molecules capable of modulating angiogenesis, osteogenesis, inflammation, and cellular differentiation.

Exosomes interact with recipient cells through receptor-mediated signaling, membrane fusion, phagocytosis, and endocytosis. Following cellular uptake, exosomal cargo influences intracellular signaling pathways including Wnt/ β -catenin, PI3K/Akt, MAPK, and BMP/Smad pathways involved in tissue regeneration and inflammatory regulation.⁸ Several studies have additionally demonstrated that exosomal microRNAs regulate macrophage polarization and suppress pro-inflammatory cytokines including tumor necrosis factor- α , interleukin-1 β , and interleukin-6, thereby creating regenerative microenvironments favorable for tissue repair.⁹

Angiogenesis represents another major regenerative property of exosomes because newly formed tissues require adequate vascularization for oxygenation and cellular survival. Exosomes enriched with vascular endothelial growth factor and angiogenesis-associated microRNAs have demonstrated the ability to stimulate endothelial-cell proliferation, migration, and capillary formation.¹⁰ These combined osteogenic, angiogenic, and immunomodulatory properties provide the biological basis for increasing interest in exosome-mediated regenerative therapies within dentistry. Major pathways associated with exosome biogenesis, release, uptake, and intracellular signalling involved in regenerative activity are illustrated in Figure 1 and Figure 2.

Applications of Exosomes in Regenerative Dentistry

Regenerative Endodontics

Regenerative endodontics represents one of the most extensively investigated applications of exosome-based therapeutics. Dental pulp stem-cell-derived exosomes have demonstrated the ability to promote odontoblastic differentiation, angiogenesis, extracellular matrix deposition, and pulp-dentin regeneration through activation of signaling pathways associated with mineralization and tissue remodeling.¹¹ Experimental studies have additionally reported suppression of inflammatory mediators within damaged pulp tissues, thereby improving regenerative microenvironments.

Recent investigations have demonstrated that exosomes significantly enhance migration and proliferation of pulp cells while simultaneously stimulating dentin matrix formation.¹² These

findings are particularly important because conventional root canal therapy eliminates infection but fails to restore pulp vitality or sensory function. Exosome-mediated regeneration therefore represents a potential biologically based alternative capable of preserving physiological pulp function. Exosomes have shown promising applications in regenerative endodontics, periodontal regeneration, bone tissue engineering, implantology, oral wound healing, oral oncology, and temporomandibular joint regeneration (Figure 3).

Periodontal Regeneration

Periodontal regeneration has similarly emerged as an important area of investigation because conventional periodontal therapy frequently fails to achieve complete regeneration of periodontal ligament, cementum, and alveolar bone. Exosomes derived from periodontal ligament stem cells and bone marrow mesenchymal stem cells have demonstrated anti-inflammatory and osteogenic properties capable of enhancing collagen synthesis, osteoblast differentiation, and alveolar bone regeneration.¹³

Experimental studies evaluating periodontal defects have demonstrated increased bone volume, improved collagen organization, and reduced inflammatory cytokine expression following exosome administration.¹⁴ Several investigators have additionally reported enhanced expression of RUNX2, alkaline phosphatase, and osteocalcin within regenerated periodontal tissues.¹⁵

Bone Regeneration and Implantology

Bone tissue engineering and implantology represent additional areas where exosome-based therapeutics have shown considerable translational potential. Exosomes stimulate osteogenesis through activation of Wnt/ β -catenin and BMP signaling pathways while simultaneously enhancing angiogenesis necessary for successful bone regeneration and implant osseointegration.¹⁶ Recent investigations evaluating exosome-loaded biomaterials, titanium nanotubes, hydrogels, and collagen scaffolds have reported improved bone formation and accelerated peri-implant healing in experimental models.¹⁷

Peri-implant inflammation remains a major factor contributing to implant failure. Exosomes possess immunomodulatory properties capable of reducing inflammatory responses and enhancing tissue integration around implant surfaces.¹⁸ Surface-functionalized titanium implants loaded with mesenchymal stem-cell-derived exosomes have demonstrated improved osteoblast adhesion and mineralization compared with conventional implant surfaces.

Oral Soft-Tissue Healing

Exosomes have additionally demonstrated promising applications in oral wound healing because of their ability to stimulate fibroblast proliferation, collagen synthesis, angiogenesis, and epithelialization.¹⁹ Such properties may be particularly beneficial following oral surgical procedures, periodontal surgery, traumatic injuries, and mucosal defects. Experimental investigations have reported accelerated healing and reduced scar formation following administration of stem-cell-derived exosomes.²⁰

Temporomandibular Joint Regeneration

Temporomandibular joint disorders frequently involve cartilage degeneration, inflammation, and progressive structural deterioration. Current treatment modalities are primarily symptomatic and often fail to restore damaged cartilage. Exosomes derived from mesenchymal stem cells have demonstrated anti-inflammatory and chondroprotective effects capable of promoting cartilage regeneration and reducing inflammatory destruction within temporomandibular joints.²¹

Oral Oncology and Diagnostic Applications

In recent years, salivary exosomes have emerged as potential biomarkers for oral squamous cell carcinoma because they contain tumor-associated proteins, messenger RNA, and microRNA reflective of molecular alterations associated with carcinogenesis.²² Several studies have demonstrated altered exosomal microRNA expression profiles in patients with oral cancer, thereby suggesting potential applications in early diagnosis, prognostic assessment, and therapeutic monitoring.²³ Representative studies evaluating exosome applications in regenerative dentistry are summarized in Table 1.

Table 1. Representative Studies Evaluating Exosomes in Regenerative Dentistry

Author	Year	Application	Study Design	Principal Findings
Huang et al. ¹¹	2022	Regenerative endodontics	In vitro study	Enhanced odontoblastic differentiation and angiogenesis
Ivica et al. ¹²	2021	Pulp regeneration	Review study	Improved pulp tissue repair and vascularization
Li et al. ¹³	2021	Periodontal regeneration	Experimental study	Enhanced osteogenesis and periodontal ligament repair
Wu et al. ¹⁴	2022	Periodontal inflammation	In vitro/in vivo study	Reduced inflammatory cytokine expression
Hu et al. ¹⁶	2019	Bone regeneration	In vitro osteogenesis model	Increased osteoblast differentiation
Wei et al. ¹⁷	2019	Implantology	Implant surface study	Accelerated osseointegration
Zhang et al. ²¹	2019	TMJ regeneration	Animal study	Reduced cartilage degeneration
Peng et al. ²²	2020	Oral oncology	Molecular study	Potential salivary biomarkers
Zhao et al. ²⁴	2023	Craniofacial regeneration	Review study	Improved scaffold integration
Yin et al. ²⁵	2023	Tissue engineering	Preclinical study	Enhanced extracellular matrix remodeling

The principal advantages and limitations associated with exosome-based therapeutics are summarized in Table 2.

Table 2. Advantages and Limitations of Exosome-Based Therapy

Advantages	Limitations
Lower immunogenicity	Lack of standardization
Reduced tumorigenic risk	Limited clinical trials
Easier storage and handling	Variable isolation techniques
Cell-free therapeutic approach	Short biological half-life
Improved biosafety profile	Difficult large-scale production

Reduced ethical concerns	Regulatory uncertainty
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Common sources of exosomes and their major regenerative applications in dentistry are presented in Table 3.

Table 3. Major Sources of Exosomes Used in Dentistry

Source	Major Application
Dental pulp stem cells	Pulp-dentin regeneration
Periodontal ligament stem cells	Periodontal repair
Bone marrow MSCs	Bone regeneration
Gingival MSCs	Soft-tissue healing
SHED-derived exosomes	Angiogenesis and mineralization
Adipose-derived MSCs	Anti-inflammatory regulation

Major biological mechanisms associated with exosome-mediated regeneration are summarized in Table 4.

Table 4. Biological Mechanisms Associated with Exosome-Mediated Regeneration

Mechanism	Biological Effect
Angiogenesis	Enhanced vascularization
Osteogenesis	Bone formation and mineralization
Immunomodulation	Reduced inflammatory response
Extracellular matrix remodeling	Improved tissue organization
Cellular proliferation	Increased regenerative activity
Macrophage polarization	Tissue-healing microenvironment

Translational Challenges and Future Perspectives

Although exosome-based therapeutics represent a promising advancement in regenerative dentistry, several translational limitations continue to hinder routine clinical implementation. One of the major concerns involves lack of standardized isolation and purification protocols. Variability in centrifugation methods, filtration systems, storage conditions, and characterization techniques contributes to significant heterogeneity among studies and complicates comparison of therapeutic outcomes.²⁴

Large-scale production additionally remains technically challenging because exosome yield

and molecular composition may vary according to donor-cell origin and environmental conditions. Long-term storage stability, pharmacokinetics, biological half-life, and optimal dosage concentrations remain insufficiently understood. Regulatory pathways for exosome-based therapeutics are also still evolving, thereby creating uncertainty regarding commercialization and clinical approval.²⁵

Recent advances in scaffold engineering, hydrogel systems, nanotechnology, and bioactive biomaterials may significantly improve future translational applications. Engineered exosomes with modified cargo and targeted delivery systems are increasingly being investigated to enhance therapeutic specificity and biological stability. Artificial intelligence-assisted molecular profiling may further improve personalized exosome-based regenerative strategies.²⁶ Despite encouraging preclinical evidence, high-quality randomized clinical trials remain essential to establish long-term safety, efficacy, dosage standardization, and clinical predictability before exosome-based therapeutics can become a routine component of clinical dental practice. Engineered exosomes with modified cargo and scaffold-assisted delivery systems are increasingly being investigated to improve therapeutic specificity and biological stability (Figure 4).

CONCLUSION

Exosome-based therapeutics have emerged as one of the most promising cell-free regenerative strategies in contemporary dentistry because of their combined anti-inflammatory, angiogenic, osteogenic, and immunomodulatory properties. Current evidence suggests significant translational potential in regenerative endodontics, periodontal regeneration, bone tissue engineering, implantology, oral wound healing, oral oncology, and temporomandibular joint repair.

Compared with conventional stem-cell transplantation, exosome therapy offers multiple advantages including lower immunogenicity, minimal tumorigenic risk, improved biosafety, easier storage, and reduced ethical concerns. However, substantial limitations related to standardization, manufacturing, storage stability, and limited clinical evidence continue to restrict widespread clinical application.

Future integration of exosome therapy with biomaterials, scaffold engineering, nanotechnology, and precision regenerative medicine may significantly transform regenerative dentistry. Nevertheless, further translational research and large-scale clinical studies remain necessary before exosome-based therapeutics can be routinely integrated into clinical dental care.

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FIGURES

Figure 1. Biogenesis, release, and uptake pathways of exosomes.

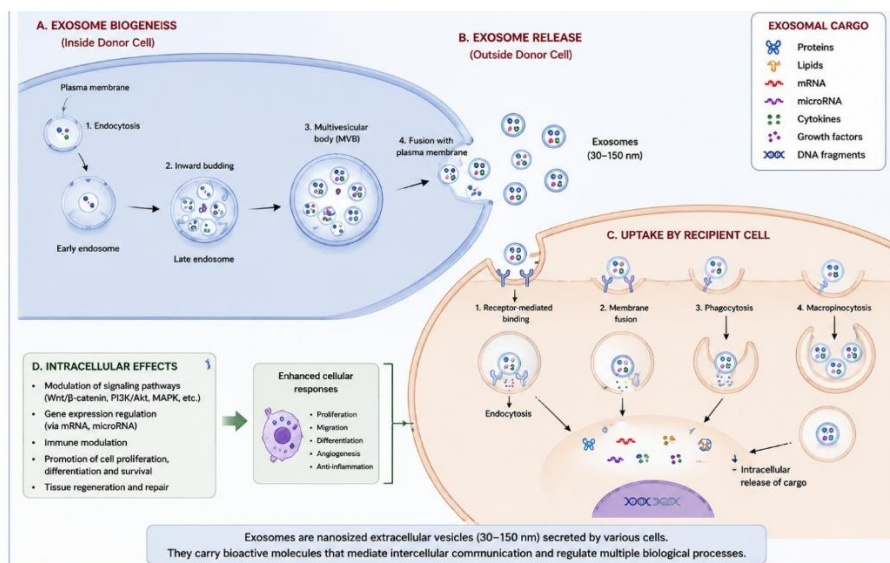


Figure 2. Molecular signalling pathways involved in exosome-mediated regeneration.

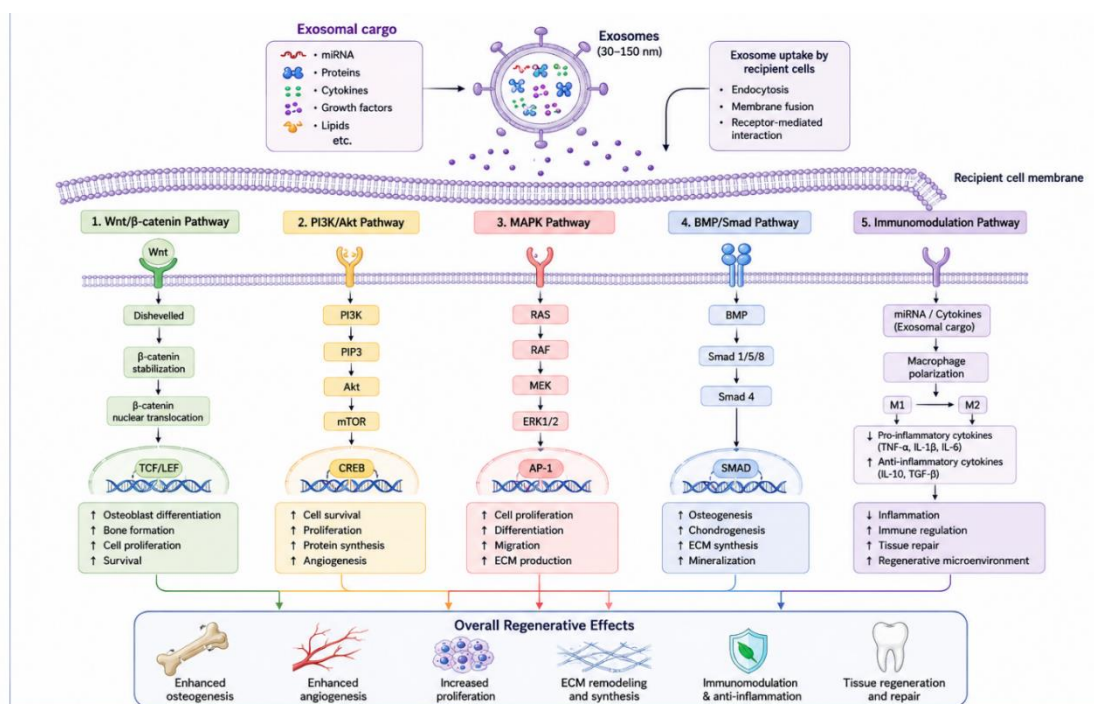


Figure 3. Applications of exosomes in regenerative dentistry.

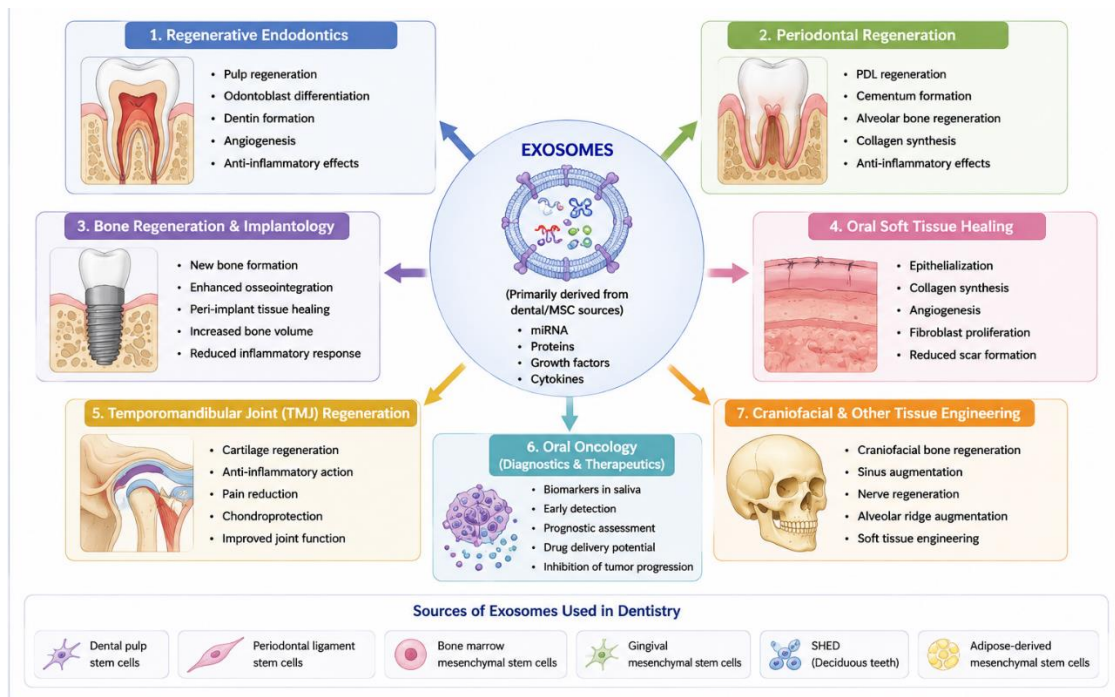


Figure 4. Future translational pathway for clinical integration of exosome-based therapeutics

