ISSN: 2457-0400

Impact Factor: 7.675

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

www.wjahr.com

Volume: 10, Issue: 7

Page N. 01-07

Year: 2026

Review Article

Coden USA: WJAMA3

EXO-SCAFFOLDS: REGENERATING PERIODONTIUM

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Article Received: 16 May 2026 **Article Revised:** 06 June 2026 **Article Published:** 01 July 2026

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India. **DOI:** https://doi.org/10.5281/zenodo.21020460

How to cite this Article: Aishwarya Agale*, Dr. Snehal Kale, Dr. Motilal Jangid, Dr. Roshani Thakur, Dr. Ujjwala Makne, Dr. Dipali Nikam. (2026). Exo-Scaffolds: Regenerating Periodontium. World Journal of Advance Healthcare Research, 10(7), 01–07.

ABSTRACT

The periodontium is a complex, dynamic entity comprising a harmonious union of hard and soft tissues that envelop and stabilize teeth. This intricate relationship between hard and soft tissues enables the periodontal system to effectively absorb and dissipate masticatory forces, thereby ensuring its structural and functional integrity. The regeneration of damaged periodontal tissues, remains a significant hurdle in periodontitis treatment. The ultimate goal of periodontal therapy is to achieve periodontal regeneration. Consequently, there is a pressing need to explore novel therapeutic approaches. Exosomes, which are derived from stem cells, have emerged as a promising adjunct to stem cell therapy, exhibiting comparable therapeutic outcomes. These nanoscale vesicles have demonstrated remarkable potential in modulating immune responses, mitigating inflammation, regulating microbiota, and promoting tissue repair, with particular efficacy in rejuvenating periodontal tissues. Moreover, the integration of exosomes with biomaterial scaffolds in periodontal tissue engineering plays a vital role in the treatment of periodontal defects, from scaffolds that create the microenvironment and deliver signaling molecules.

KEYWORDS: Stem cells, exosome, biomaterial scaffold, tissue engineering.

INTRODUCTION

The periodontium comprises a complex network of mineralized and non-mineralized tissues that play a crucial role in supporting and anchoring the teeth. The dental cementum and alveolar bone—the mineralized structures—interact closely with the gingiva and periodontal ligament, which are soft connective tissues, to absorb and distribute forces generated during chewing. Bartold et al. (2006) emphasized that the functional harmony of these tissues is essential for periodontal health. Disruption in the microbial ecosystem around the periodontium can lead to periodontitis, a chronic inflammatory disease marked by microbial imbalance, or dysbiosis. This dysbiotic state, driven by polymicrobial synergy, induces a harmful immune response, resulting in progressive degradation of the periodontal apparatus and, ultimately, tooth loss.

Lamont et al. (2018) highlighted that excessive activation of the host immune system is a primary driver of osteoclastogenesis, leading to alveolar bone loss.

In recent decades, regenerative techniques such as guided tissue regeneration (GTR), autologous bone grafts, and allografts have shown potential to enhance traditional treatment. Still, they face limitations such as technical complexity, risk of postoperative inflammation, immune rejection, and inconsistent clinical outcomes. Advances in tissue engineering offer promising alternatives for functional restoration of periodontal structures. By integrating principles of cell biology, biomaterials, and biomedical engineering, this field aims to develop biological substitutes that replicate native tissue function.

While stem cell–based scaffolds are widely researched for periodontal regeneration, their clinical use remains limited due to concerns about cell source, harvesting, storage, scalability, and ethical implications. In this context, exosomes, which are nanoscale vesicles secreted by cells during paracrine signaling, have emerged as critical mediators of tissue repair. Loaded with functional proteins, lipids, and nucleic acids, exosomes facilitate targeted intercellular communication and are prized for

their biostability, low immunogenicity, and therapeutic delivery potential. Increasing evidence supports their role as natural nanocarriers capable of modulating immune responses and treating diverse inflammatory, infectious, and autoimmune diseases (Kibria et al., 2018).

EXOSOME BIOGENESIS

Exosomes were initially identified in 1983 during studies on cultured sheep red blood cells (Pan and Johnstone, 1983). These nanosized vesicles, typically 40–150 nanometers in diameter, are now known to originate from a variety of cell types—including those from epithelial, neural, stem cell, and cancer origins—and are found in biological fluids such as saliva, blood plasma, milk, and urine (Johnstone et al., 1987; Kalluri and LeBleu, 2020).

Their production begins within endosomes, where certain biomolecules are packaged into small vesicles that bud inward, forming larger compartments called multivesicular bodies (Hessvik & Llorente, 2018). This process is orchestrated primarily by the ESCRT system, a group of proteins responsible for sorting and enclosing intracellular contents. When this system is not fully active, alternative mechanisms involving membrane-related lipids and proteins, such as ceramide, can substitute to promote vesicle formation.

Transport of these vesicles to the cell surface is regulated by Rab family proteins, while membrane fusion and exosome release are facilitated by SNARE complexes (Bache et al., 2003; Hanson and Cashikar, 2012; Mashouri et al., 2019). Once secreted, exosomes act as carriers for diverse molecules such as RNA, signaling proteins, and bioactive lipids (Mathivanan et al., 2010).

According to van Niel et al. (2006), proteins are the predominant component of exosomes and include both universal and cell-specific markers. These may include antigen-presenting molecules, transmembrane proteins, and structural proteins. Lipid components such as cholesterol, sphingolipids, and phospholipids contribute to both the structural integrity and biological activity of exosomes (Skotland et al., 2019).

EXOSOME EXTRACTION AND IDENTIFICATION

Technique	Principle	Advantages	Limitations	References
Differential ultracentrifugation	Seperates particles based on size and density through sequential spins	Widely used; suitable for large sample volumes; reagent-free	Co-isolation of contaminants; potential damage due to high g-forces	Yu rt al.,2018; Van et al.,2012
Density gradient ultracentrifugation	Separation based on buoyant density using gradient media	Higher purity; preserves vesicle integrity	Labor- intensive; time -consuming	Lin et al., 2022
Ultrafiltration	Uses size selective membranes to retain or exclude particles	No need for labelling; relatively quick	Membrane clogging; expensive; limited scalability	Xu et al., 2017
Size exclusion chromatography	Particles elute at different times based on size using porous gels.	Gentle, lable- free, and preserves vesicle structure	Low resolution when vesicles and contaminants are similar in size	Ing et al., 2014; An et al.,2018
Immunoaffinity capture	Antibodies bind to exosome specific surface proteins (e.g.,CD63, CD81)	High specificity and purity; ideal for targeted isolation	High cost; suitable mainly for small volumes	Sanders et al., 2016
Polymer precipitation	Hydrophilic polymers disrupt hydration shells, promoting precipitation	Fast; inexpensive; gentle on vesicle structure	Low purity; co precipitation of proteins, viruses and other particles	Zeringer et al., 2015; Pin et al., 2017
Microfluidic immunoaffinity chips	Antibody coated microchannels selectively bind exosomes	Rapid; small sample compatibility; easy to integrate	Limited throughout; purity can vary	
Aptamer based isolation	Uses synthetic ssDNA/RNA that bind specific exosomal markers	Cost- effective; low immunogenicity; chemically stable	Still under development; limited commercial availability	Wang et al., 2019a, 2019b

EXOSOMES IN PERIODONTAL TISSUE REPAIR

Exosomes are rich in a variety of bioactive molecules, including proteins, mRNA, microRNA (miRNA), free fatty acids, surface receptors, and cytokines, enabling them to act as mediators of both local and systemic intercellular communication (Meldolesi, 2018). Their functional roles are largely determined by their cellular origin and the specific cargo they carry, such as distinct

proteins and RNA species. Exosomes derived from various cell types contribute differently to physiological and pathological conditions.

Structurally, exosomes express transmembrane proteins such as CD9, CD63, CD81, and CD82, along with heat shock proteins, lipoproteins, and several transport-related proteins. These components aid in both the recognition of exosomes and their targeting capabilities, allowing for selective interaction with recipient cells (Thery et al., 2002).

Implants have emerged as a promising treatment strategy for managing periodontitis, primarily due to their capacity to reduce alveolar bone loss and improve periodontal health.

Shen et al. (2020) demonstrated that dental pulp stem cell-derived exosomes (DPSC-Exos) could shift macrophages from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype, contributing to reduced inflammation and improved healing of alveolar bone and epithelium. These effects were attributed to miR-1246 present in DPSC-Exos.

Adipose-derived stem cell exosomes (ADSC-Exos) have also shown promise as an adjunct to scaling and root planing (SRP). As reported by Mohammed et al. (2018), these exosomes contribute to periodontal regeneration through immunomodulation and anti-inflammatory effects.

Collectively, these studies underscore the importance of pretreatment strategies such as mechanical stimulation to boost the osteogenic capabilities of exosomes, opening new avenues for periodontal regenerative therapy.

THE POSSIBLE MECHANISM OF EXOSOME-MEDIATED PERIODONTAL TISSUE REGENERATION

Immunoregulation and inflammatory regulation of exosome

Periodontitis is a long-standing inflammatory disorder where an overactive immune response plays a central role in activating osteoclasts, leading to the breakdown of alveolar bone. Its progression involves multiple immune cell types, including macrophages, dendritic cells, T and B lymphocytes, and neutrophils.

Recent studies have highlighted the therapeutic potential of exosomes, particularly those derived from mesenchymal stem cells (MSCs), owing to their immune-modulating properties. These extracellular vesicles can influence inflammatory signaling, support immune homeostasis, and foster tissue repair.

An important aspect of immune imbalance in periodontal disease is the disruption of the Th17/Treg ratio. Research shows that exosomes released by periodontal ligament stem cells (PDLSCs) can transfer microRNA-155-5p to CD4+ T cells, altering the expression of SIRT1 and rebalancing Th17 and Treg populations, which may help control inflammation (Zheng et al., 2019).

Further, exosomes from gingival MSCs, when pre-treated with TNF-α, show enhanced expression of CD73 and miR-1260b. These changes promote the shift of macrophages toward an anti-inflammatory (M2) phenotype, contributing to inflammation resolution and protecting alveolar bone (Nakao et al., 2021

In addition to exosomes, conditioned media (CM) from MSCs also demonstrate anti-inflammatory potential. For instance, CM from adipose-derived MSCs (AMSC-CM) reduces the expression of key pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 in activated macrophages, indicating a protective role against bone loss. Similarly, PDLSC-derived CM encourages macrophages to adopt a healing phenotype by decreasing TNF-α levels and increasing markers like IL-10, CD163, and arginase-1 (Liu et al., 2019).

Promotion of endogenous stem cell regeneration and differentiation by exosome

Exosomes contribute to periodontal tissue regeneration by promoting the proliferation of mesenchymal stem cells (MSCs) at defect sites and directing their differentiation toward osteoblastic and odontoblastic lineages. Notably, the conditioned medium from bone marrow-derived MSCs (MSC-CM) has demonstrated strong osteogenic potential, largely due to a combination of bioactive molecules, including insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1), and hepatocyte growth factor (HGF) (Inukai et al., 2013).

Meanwhile, TGF-β1 serves a dual role in bone dynamics, influencing both bone-forming osteoblasts and bone-resorbing osteoclasts to maintain skeletal homeostasis (Janssens et al., 2005). Within periodontal tissues, TGF-β1 has been shown to regulate PDL cell growth, differentiation, and extracellular matrix production, thereby facilitating tissue repair and regeneration (Gao et al., 1998; Tsuyoshi et al., 2004).

Role of exosome in promoting angiogenesis

Angiogenesis is a critical component of tissue repair and regeneration, and several studies have demonstrated a direct association between vascular formation and periodontal bone healing. The conditioned medium derived from bone marrow mesenchymal stem cells (MSC-CM) contains key growth factors such as IGF-1, VEGF, and TGF-β1, which are known to support the migration and proliferation of endogenous stem cells, enhance vascular development, and contribute to early bone formation. In preclinical models, such as rabbits undergoing maxillary sinus augmentation, MSC-CM has been shown to significantly promote bone maturation and regeneration (Katagiri et al., 2015). These findings highlight the therapeutic potential of MSC-CM as a

regenerative strategy for enhancing bone healing in periodontal defects.

Additionally, the osteogenic potential of human gingival mesenchymal stem cells (GMSCs) can be stimulated using conditioned media obtained from both human umbilical vein endothelial cells (HUVECs) and bone marrow-derived MSCs, further supporting the role of paracrine signaling in promoting osteogenic differentiation and bone tissue formation

ADVANTAGE AND LIMITATIONS

Exosomes are gaining recognition as a valuable alternative to traditional stem cell therapy for promoting tissue repair and regeneration. They share many of the therapeutic functions of their parent cells, including regenerative, anti-inflammatory, and immunomodulatory effects. A key advantage of exosomes is their stability—they are enclosed within a protective membrane that prevents enzymatic degradation, allowing for long-term storage. Additionally, they carry a diverse array of bioactive components, such as growth factors, microRNAs (miRNAs), and proteins, which contribute to their therapeutic action.

However, the clinical application of exosomes, particularly in periodontal therapy, faces several challenges. Currently, exosomes are primarily administered through injection, which often leads to rapid clearance by the body and a limited duration of effect. For example, studies have shown that exosomes from B16-BL6 cells are quickly removed from the bloodstream by the liver and then accumulate in the lungs (Takahashi et al., 2013).

In periodontal tissue regeneration, difficulties remain in achieving controlled loading and sustained release of exosomes at the defect site. As a result, overall regenerative outcomes remain inadequate, and the specific exosomal proteins responsible for tissue repair in periodontitis are not yet well understood. Enhancing the retention of exosomes at the site of injury is therefore a critical area for improvement. Additionally, current animal models do not fully replicate the inflammatory bone loss seen in human periodontitis, which complicates the evaluation of exosome-based treatments.

PERIODONTAL TISSUE ENGINEERING

Periodontal tissue engineering primarily encompasses three major components: cell-based therapy, biomaterial scaffold development, and bioactive signaling molecules (Poongodi et al., 2021). Among these, biomaterial scaffolds have gained attention as a valuable tool for regenerative medicine. Designed to replicate the architecture and function of the natural extracellular matrix (ECM), these scaffolds play a critical role in facilitating the repair and regeneration of damaged tissues (Cheng et al., 2019). An effective scaffold in tissue engineering must meet several key criteria, including biocompatibility, biodegradability, adjustable degradation and absorption rates, and a porous three-dimensional architecture to support cellular growth, nutrient diffusion, and metabolic waste removal. Additionally, scaffolds must possess adequate mechanical strength and flexibility, maintain compatibility with the host tissue at the implantation site, and elicit minimal inflammatory or toxic responses (Padial-Molina and Rios, 2014).

Scaffold materials are broadly classified into natural polymers, synthetic polymers, and bioceramics, each with distinct advantages. Natural polymers include a variety of polysaccharides such as alginate, hyaluronic acid, chitosan, and chitin, and protein-based polymers like gelatin, collagen, silk fibroin, fibronectin, and keratin.[26]

In addition to scaffold development, bioactive molecules play a central role in periodontal tissue engineering. Proteins such as platelet-derived growth factor (PDGF), bone morphogenetic proteins (BMPs), basic fibroblast growth factor (bFGF), and concentrated growth factor (CGF) serve as key regulators of cell proliferation, differentiation, gene expression, and tissue remodeling, supporting the functional restoration of periodontal structures

APPLICATION OF EXOSOME COMPOSITE SCAFFOLD IN PERIODONTAL REGENERATION

The integration of exosomes with biomaterial scaffolds has gained considerable attention in periodontal regeneration due to its promising therapeutic results. Since exosomes alone face challenges such as rapid clearance and short bioavailability at the target site, combining them with scaffolds offers a more controlled and localized release. Figure 1 shows an approach where this strategy is applied to treat periodontitis.

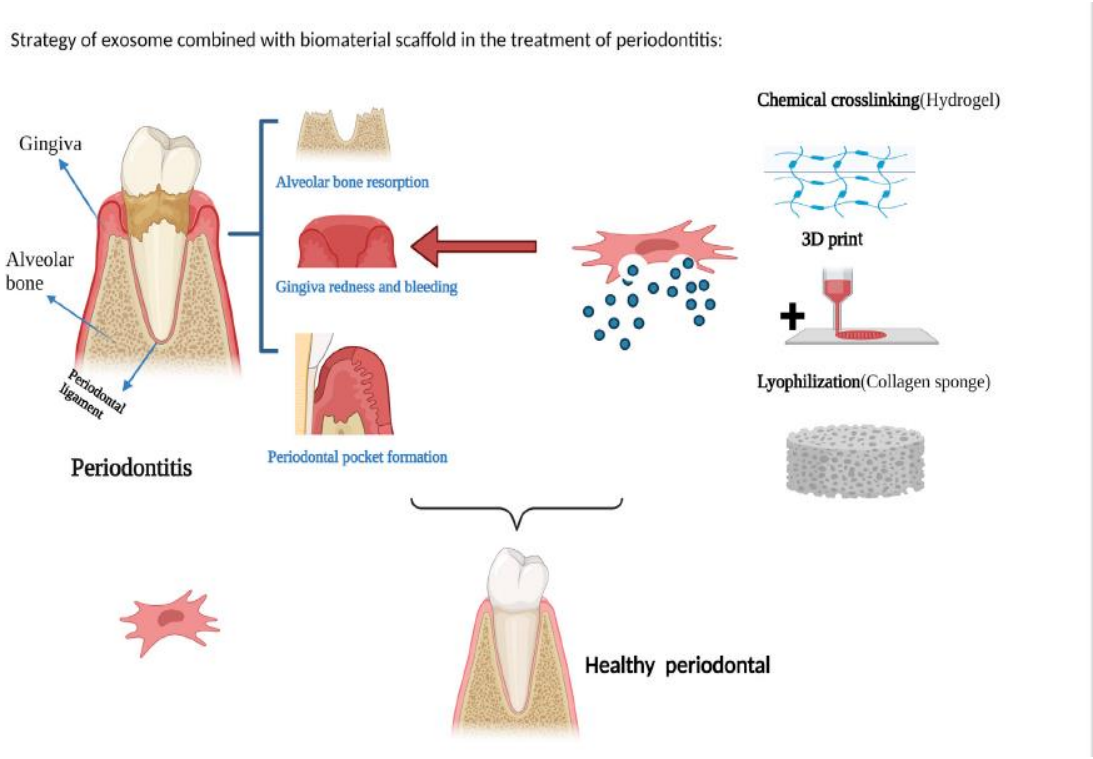
For example, Chew et al. (2019) used a collagen sponge loaded with exosomes derived from human bone marrow mesenchymal stem cells in rats with periodontal defects. This method improved bone and tissue healing without causing adverse effects. Their regenerative action was linked to activation of adenosine receptors and signaling pathways like AKT and ERK, which are involved in cell movement and growth.

Another study by Wang R. et al. (2020) prepared a gelatin-alginate hydrogel cross-linked with calcium chloride and loaded it with periodontal ligament stem cell exosomes. This system supported early-stage bone healing in rats with alveolar defects.

In addition, chitosan hydrogels carrying exosomes from dental pulp stem cells were shown to accelerate bone and gum tissue healing in mice with periodontitis. Inukai et al. (2013) demonstrated that using a collagen sponge with stem cell-conditioned medium in dog models led to improved bone regeneration. Kawai et al. (2015)

confirmed this outcome in rats, observing new tissue formation after four weeks.

These studies consistently highlight that combining exosomes with supportive scaffolds enhances their regenerative potential. This method helps address the practical limitations of exosome therapies—such as uncontrolled release and low retention—bringing us closer to their clinical use in periodontal treatments. However, more clinical research is required to validate their safety and effectiveness in human patients.



CONCLUSION

Stem cells can influence surrounding cells through paracrine signaling, mainly by releasing exosomes and other molecular carriers. These exosomes help regulate cellular behavior in the microenvironment, activate various signaling pathways, and promote the regeneration of damaged tissues. This review highlights the role of exosomes in managing periodontitis, either as independent therapeutic agents or combined with tissue-engineering approaches. Current research shows promising early outcomes and several advantages in repairing periodontal defects, as exosomes are more stable, easier to handle, and more accessible compared to many conventional treatment methods.

However, most available studies are still restricted to animal experiments, and clinical evidence involving human periodontal regeneration remains limited. The mechanisms underlying exosome-based diagnosis and treatment for chronic periodontitis are not yet fully clarified, and varying exosome concentrations can lead to different effects on bone repair and regeneration. To evaluate how exosomes from different cell sources support cementum regeneration, it is essential to understand the functional characteristics of cementum, periodontal ligament, and alveolar bone, as well as the specific pathways through which exosomes enhance regeneration.

Overall, exosome-based strategies—especially when combined with tissue engineering—represent a promising direction for periodontal tissue regeneration, and future research is expected to yield even more impactful results in regenerative medicine.

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