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Review Article

Biomolecules derived from salivary exosomes encapsulated in chitosan for bone regeneration in alveolar osteitis: A systematic review

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Abstract

Alveolar osteitis (dry socket) is a common complication after tooth extraction that delays bone healing and causes significant pain. Conventional treatments are largely palliative and do not actively promote regeneration. Salivary exosomes, rich in bioactive molecules, and chitosan, a biocompatible and biodegradable polymer, might offer a promising combined approach for targeted bone regeneration. The aim of this systematic review was to systematically evaluate the regenerative potential of salivary exosomes encapsulated in chitosan for the treatment of alveolar osteitis. The systematic review was conducted following PRISMA guidelines and the PICO framework. Comprehensive searches were performed across PubMed, ScienceDirect, ProQuest, Cochrane Library, and Google Scholar for English-language articles published between 2021 and 2025. Eligible studies included in vitro, in vivo, and preclinical research assessing chitosan-encapsulated salivary exosomes for bone regeneration. Data were extracted on study design, interventions, outcome measures, and therapeutic effects. From 524 retrieved records, 10 full-text articles were assessed, and two met the eligibility criteria. Both studies demonstrated that chitosan encapsulation improved the stability and delivery efficiency of salivary exosomes. Outcomes included increased osteogenic gene expression (ALP, BMP-2, osteocalcin, RUNX2), enhanced angiogenesis, reduced inflammation, and histological evidence of accelerated bone regeneration compared with conventional treatment. In conclusion, current evidence suggests that salivary exosomes encapsulated in chitosan have strong therapeutic potential for alveolar osteitis by promoting osteogenesis, reducing inflammation, and enhancing bone healing. However, further preclinical validation and controlled human trials are required before clinical translation.

Keywords: Salivary, exosome, chitosan, alveolar osteitis, tooth extraction

Introduction

Alveolar osteitis (AO), or dry socket, is the most common complication after tooth extraction, with a prevalence of 1–5% in routine extractions and up to 30% in surgical third molar extractions. Symptoms typically appear 1–3 days after surgery, including severe pain, a disintegrating blood clot in the socket, and halitosis [1]. Pain may radiate to the ear, temporal, frontal, and maxillary regions, and is often accompanied by low-grade fever, gingival inflammation, grayish pus discharge, exposed alveolar bone, and lymphadenopathy. Several systemic and local risk factors contribute to AO development, such as systemic disease, oral

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contraceptives, smoking, bacterial infection, excessive curettage, use of vasoconstrictors, retained bone fragments, and certain flap designs. If untreated, AO can progress to osteomyelitis, resulting in more severe complications [2,3].

Conventional AO therapy focuses on curettage and debridement to restart the wound healing phase, followed by irrigation with saline, chlorhexidine, or hydrogen peroxide, and application of local medications such as Alvogyl, zinc oxide-eugenol, clove oil, antibiotics, or metronidazole gel [4]. However, these treatments are primarily palliative, and strong antiseptics can suppress granulation tissue formation and contribute to bacterial resistance. The microbiota associated with AO differs from that of uncomplicated healing sockets, being dominated by anaerobic bacteria such as *Prevotella*, *Fusobacterium*, *Parvimonas,* and *Peptostreptococcus*. These bacteria exhibit fibrinolytic activity that destabilizes blood clots [5]. In particular, *Prevotella* produces lipopolysaccharides (LPS), a virulence factor that induces inflammation, interferes with phagocytosis, and promotes alveolar bone resorption [5].

Exosomes are nanosized extracellular vesicles with diverse biomedical applications, including their potential use as vaccine vectors and therapeutic agents against bacterial infection. They exhibit anti-inflammatory, proangiogenic, and immunomodulatory activities, making them valuable in tissue repair. Exosome therapy is a stem cell-based biotechnology that enhances stem cell proliferation, migration, and differentiation, while being efficient, non-immunogenic, low-toxic, and easy to store and distribute [6]. Salivary exosomes provide additional advantages as they can be collected rapidly, simply, and non-invasively. Extracellular vesicles derived from minor salivary glands demonstrate stronger anti-scarring and anti-inflammatory effects compared to adipose-derived exosomes, largely due to matrix metalloproteinases (MMP-1 and MMP-3) that regulate wound contraction, remodeling, and scar reduction [7,8,9]. These properties highlight their potential as biomaterials for AO therapy following tooth extraction [7,8,9].

Combining exosomes with chitosan, a biocompatible and antimicrobial natural polysaccharide, can increase exosome stability and enable controlled release, thereby accelerating granulation tissue formation and angiogenesis. Chitosan also has mucoadhesive properties that allow it to adhere to mucosal tissues, enhancing therapeutic efficacy. Although salivary exosomes have great potential in alveolar wound healing, standardization of their characterization and application methods is still needed for effective clinical application [10,11]. Given these considerations, salivary exosomes encapsulated in chitosan represent a promising therapeutic strategy for AO management, with the potential to accelerate osteoblast proliferation and alveolar bone regeneration. Therefore, the aim of this review was to explore the potential of chitosan-encapsulated salivary exosomes in promoting alveolar bone osteoblast growth after tooth extraction in the context of AO.

Methods

Information sources and search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. A comprehensive literature search was performed across five electronic databases: PubMed, ScienceDirect, Cochrane Library, ProQuest, and Google Scholar. Both free-text terms and controlled vocabulary were applied, including Medical Subject Headings (MeSH) in PubMed and equivalent subject headings in other databases. The search targeted peer-reviewed articles published in English between 2021 and 2025 using the following keyword combination: “salivary” AND “exosome” AND “chitosan” OR “osteitis alveolaris”. Reference organization and citation tracking were managed using Mendeley Reference Manager.

Eligibility criteria

Eligibility criteria were defined using the PICO framework: Population (human subjects, animal models, or cell lines), Intervention (chitosan-encapsulated salivary exosomes), Comparison (salivary exosomes alone, sponge gel), and Outcome (osteoblast regeneration and enhanced oral tissue healing). Eligible study designs included randomized controlled trials, controlled

laboratory experiments, in vivo animal studies, and in vitro cell culture models. Studies were required to address alveolar osteitis, defined either by clinical diagnostic criteria in human studies or by experimentally induced models in preclinical research. Only full-text original research articles published in English between 2021 and 2025 were included. Exclusion criteria included studies unrelated to salivary exosomes, those not addressing bone regeneration or oral wound repair, and all review articles, editorials, or conference abstracts. To prevent duplication, only the most complete or recent report from the same study group was included; complementary findings were integrated without double-counting. Each eligible publication was cross-checked for authorship, year, location, design, sample characteristics, and outcomes to ensure accuracy.

Data extraction

The study selection and data extraction were performed systematically. Titles, abstracts, and full texts were screened using the Rayyan tool to ensure efficient and transparent selection. Two reviewers (S.S. and E.W.B.) independently extracted data using a standardized form to maintain accuracy and minimize bias, while a third reviewer (B.M.B.) verified all entries and resolved disagreements. Extracted data included publication details (first author, year, country), study design (in vitro, in vivo, preclinical), exosome source (saliva, mesenchymal stem cells, others), encapsulation method (type of chitosan, preparation technique, delivery system), and sample characteristics (cell line or species, sample size). Therapeutic outcomes and methodological variables, including treatment duration, administration route, and evaluation intervals, were also collected.

Synthesis method

A narrative synthesis approach was employed to analyze and summarize findings from the included studies. Data were extracted, compared, and organized in alignment with the review objectives, focusing on experimental models, intervention types (salivary exosomes and chitosan encapsulation), therapeutic outcomes, and relevant biomolecular markers. The synthesis aimed to identify consistent patterns, highlight methodological variations, and assess the overall therapeutic potential of the interventions across studies.

Results

Study selection

A systematic search was conducted across five electronic databases using predetermined keywords. The initial search yielded 524 records, comprising 340 from Google Scholar, 177 from ProQuest, and 7 from ScienceDirect, while no relevant articles were retrieved from PubMed or the Cochrane Library. After removing two duplicates and excluding 512 articles based on title and abstract screening, 10 full-text articles were assessed for eligibility. Of these, eight were excluded: two did not address bone regeneration in the oral cavity, and six did not investigate salivary exosomes or chitosan. Ultimately, two studies [13,14] met the predefined inclusion criteria and were included for data extraction and synthesis. Key information, including study design, model system, methodology, type of intervention, and reported outcomes, was systematically extracted and organized into comparative summary tables. The summary of study screening and selection is presented in **Figure 1**.

Characteristics of the studies

The two included studies varied in design, populations, and methodological approaches. Kazanopoulos *et al.* [13] conducted an experimental study in 15 Caucasian adolescent patients, evaluating salivary exosome miRNA analysis as a biomarker for bone remodeling during orthodontic treatment. In contrast, Zhao *et al.* [14] performed experimental and preclinical studies involving patients with alveolar osteitis, human osteoblast cultures, and animal models, focusing on chitosan-based scaffolds combined with bioactive molecules and exosomes. Both studies investigated outcomes related to bone regeneration, but they differed in models, interventions, and endpoints, highlighting the heterogeneity of available evidence.

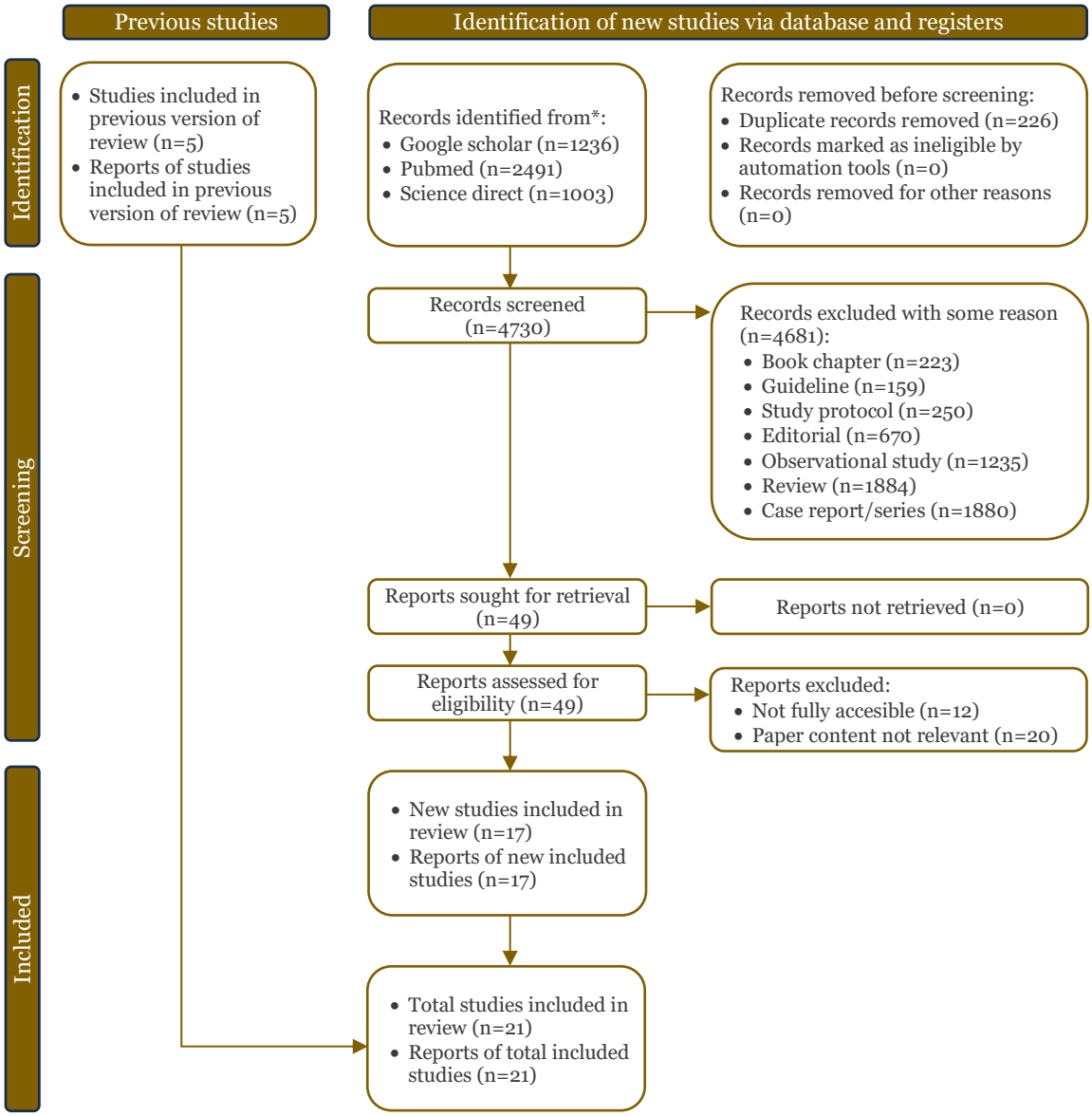

Figure 1 PRISMA flowchart of the study selection.

Effects of salivary exosomes encapsulated in chitosan for bone regeneration in alveolar osteitis

This review identified two studies that examined the regenerative potential of salivary exosomes encapsulated in chitosan. In the first study, Kazanopoulos *et al.* [13] implemented an in vivo experimental model using rodents with surgically induced alveolar bone defects (**Table 1** and **2**). The intervention involved the administration of salivary exosomes encapsulated in chitosan, and the primary outcomes included alkaline phosphatase (ALP) activity, bone regeneration, and bone morphogenetic protein-2 (BMP-2) expression. The results demonstrated that exosome encapsulation significantly promoted bone healing compared with the control groups.

Zhao *et al.* [14] conducted the second investigation using both experimental and preclinical approaches that integrated cell culture and animal models (**Tables 1** and **2**). In this study, chitosan was employed as the encapsulating agent for salivary exosomes. Outcome measures included osteocalcin expression, ALP activity, BMP-2 expression, and histological evaluation of tissue regeneration. The results revealed that salivary exosomes encapsulated in chitosan markedly promoted bone tissue regeneration, thereby supporting the therapeutic potential of this biomolecular strategy for alveolar osteitis.

Table 1. Baseline study characteristics

Author (year)	Study design	Model/system	Methodology	Intervention	Outcome measures	Main findings
Kazanopoulos *et al.* (2025) [13]	Experimental study	Animal model of rats with alveolar osteitis	Experimental (in vivo)	Application of a combination of saliva exosomes and chitosan scaffold	Bone histomorphometry, expression of osteogenic genes (runx2, col1a1, ocn), local inflammation	The combination of exosome-chitosan significantly accelerates bone regeneration compared to the control or single treatment groups
Zhao *et al.* (2022) [14]	Experimental and preclinical studies	Human osteoblast cell culture and initial testing on animal models	Experimental (in vitro) and pre-clinical (in vivo)	Treatment of salivary exosomes on osteoblasts and local application in early bone models	Expression of ALP, RUNX2, TNF-A, IL-6; proliferation, differentiation of osteoblasts	Exosomes increase osteoblast activity and reduce the inflammatory response, showing potential in bone tissue regeneration

Table 2. Articles included in the review and research synthesis

Author (year)	Study design	Sample (P)	Intervention (I)	Comparison (C)	Main outcome (O)
Kazanopoulos *et al.* (2025) [13]	Experimental study	15 Caucasian adolescent patients	The use of salivary exosome miRNA analysis as a non-invasive biomarker to monitor the bone remodeling process during tooth movement	Comparison of salivary miRNA expression before treatment (Day 0) and after 7 days and 40 days of treatment, as well as analysis of changes in miRNA expression during that time	Identification of miRNAs that undergo significant changes during the tooth movement process, particularly the decrease in hsa-miR-4634 expression, and its potential use as a biomarker to monitor bone remodeling
Zhao *et al.* (2022) [14]	Experimental and preclinical studies	Patient with alveolar osteitis	The use of chitosan-based scaffolds combined with nanomaterial, bioactive molecules, and exosomes	Conventional treatment without a specific scaffold	Improving osteogenesis, angiogenesis, and better integration of bone tissue, and enhancing the speed and quality of bone regeneration. This also increases the success rate of healing alveolar osteitis.

Discussion

Bone possesses the intrinsic ability to regenerate; however, the process is generally slow and limited, particularly in the case of large defects that surpass the body's natural healing capacity. Following tooth extraction, periodontal structures, including the alveolar bone, are damaged and may even fracture. It has been reported that alveolar bone healing typically requires 18–20 weeks, culminating in the formation of new vital bone [15]. Conventional treatment strategies, such as bone grafts (autologous, allogeneic, xenogeneic, and synthetic), present several drawbacks, including the risk of infection, graft-versus-host disease (GVHD), and limited donor availability. Artificial bone grafts generated through bone tissue engineering offer an attractive alternative due to their relative ease of preparation and cost-effectiveness. Nevertheless, challenges remain, as insufficient vascularization during early implantation and delayed diffusion of nutrients to the core of the biomaterial may result in cell death and impaired regeneration. Therefore, innovative approaches in bone tissue engineering are urgently needed to optimize bone regeneration and overcome the limitations of conventional therapies.

Research on exosomes derived from MSCs in bone tissue engineering has demonstrated their capacity to interact with biomaterial scaffolds and modulate key processes such as osteoblast differentiation, angiogenesis, and macrophage polarization. The molecular cargo of MSC-derived exosomes contributes to osteoinduction and exhibits strong biocompatibility [16]. These exosomes have also been applied to accelerate fracture healing [17]. Mechanistic studies indicate that exosomal microRNAs (miRNAs) derived from MSCs promote osteoblastic differentiation by regulating specific signaling pathways, including the Wnt pathway [18]. Collectively, these findings suggest that MSC-derived exosomes have the potential to modulate the physiology of multiple target cells, thereby supporting bone tissue regeneration.

Bone regeneration is a complex biological process involving the coordinated activity of multiple cell types, growth factors, and extracellular matrix components to repair or replace damaged tissue. This process encompasses several physiological phases, including inflammation, cell proliferation, osteogenic differentiation, and hard tissue remodeling, and is regulated by molecular signaling pathways such as MAPK, AMPK, and Wnt/β-catenin, which govern osteoblastic differentiation. The function of osteoprogenitor cells plays a pivotal role in bone regeneration. Increasing evidence shows that cells involved in bone remodeling release extracellular vehicles, including exosomes, which modulate proliferation, differentiation, migration, apoptosis, and metabolic cross-talk among bone cells. Bone tissue homeostasis is maintained through dynamic interactions between resident bone cells and microenvironmental cells such as endothelial cells, immune cells, and stromal cells, with exosomes serving as critical mediators of intercellular communication. Dysregulation of these mechanisms, resulting in an imbalance between osteoblast and osteoclast activity, has been implicated in bone-related pathologies, including osteoporosis, arthritis, and osteosarcoma [19].

Hydrogels have been widely employed in biomedical applications as delivery systems for exosomes. Owing to their high-water content, biocompatibility, and ability to mimic the extracellular matrix (ECM), hydrogels have gained considerable attention in tissue engineering. Structurally, hydrogels are polymeric networks capable of retaining water, encapsulating exosomes, enhancing their retention at target sites, and enabling controlled release, thereby improving localized therapeutic effects. Incorporation of exosomes into hydrogel matrices enhances their bioactivity and facilitates the sustained release of bioactive molecules that support tissue regeneration [20]. Beyond improving delivery efficiency, hydrogels integrated with exosomes exhibit superior mechanical strength and biological functionality compared with conventional hydrogels. Exosomes regulate cell behavior within hydrogels, promoting proliferation, migration, and differentiation, which collectively enhance regenerative outcomes and improve the precision of drug delivery systems. Exosomes derived from osteoblasts have been shown to stimulate osteoclast differentiation in vivo, contributing to the removal of damaged tissue [19]. In bone repair, exosomes also promote osteoblast proliferation and differentiation, thereby accelerating bone healing. Taken together, the integration of hydrogels and exosomes offers promising opportunities for the development of advanced biomaterials in bone tissue engineering [21].

Chitosan is a widely utilized polysaccharide in biomedical applications due to its abundance, ease of production, and versatile biological properties. It is the only naturally occurring polycation, with charge density determined by its degree of acetylation and the pH of the surrounding medium. Chitosan can selectively bind metal ions, cholesterol, lipids, and tumor cells, while also exhibiting antifungal activity, tumor inhibition, wound healing acceleration, and immunostimulatory effects [22]. Derived from chitin, chitosan is well recognized for its biocompatibility, biodegradability, non-toxicity, and broad bioactivities, including antioxidant, antitumor, anti-inflammatory, antimicrobial, and immunomodulatory functions. In bone regeneration, chitosan serves as a biomatrix that supports osteoblast differentiation and new bone formation by modulating the osteogenic microenvironment. It plays a crucial role in guiding bone regeneration, enhancing bone density, and promoting fracture healing [23]. Beyond its osteogenic potential, chitosan has been extensively developed as a drug, gene, and biomolecule delivery platform, offering sustained and controlled release. Its administration routes are diverse, including oral, parenteral, topical, buccal, and sublingual delivery. Owing to its strong mucoadhesive properties, chitosan interacts with glycosaminoglycans and proteoglycans of mucosal membranes, making it an effective vehicle for controlled drug delivery systems. Moreover, by modulating tight epithelial junctions, it enhances epithelial permeability, thereby facilitating transepithelial drug transport [17].

The stability of exosomes is a critical determinant of their suitability for clinical applications (**Figure 2**). Nucleases and proteases can degrade vesicular proteins and RNA, thereby diminishing their functionality and stability. These limitations can be addressed by encapsulating exosomes within biomaterials such as hydrogels. Certain hydrogels possess intrinsic properties that regulate cellular processes, including adhesion, proliferation, and differentiation. The integration of exosomes with hydrogels offers multiple advantages for tissue repair and regenerative medicine, as hydrogels provide a biocompatible, biodegradable three-dimensional matrix that supports cell adhesion and proliferation. Moreover, hydrogels enable the gradual release of encapsulated exosomes, sustaining their biological activity and continuously delivering signaling molecules and growth factors that facilitate tissue repair [24].

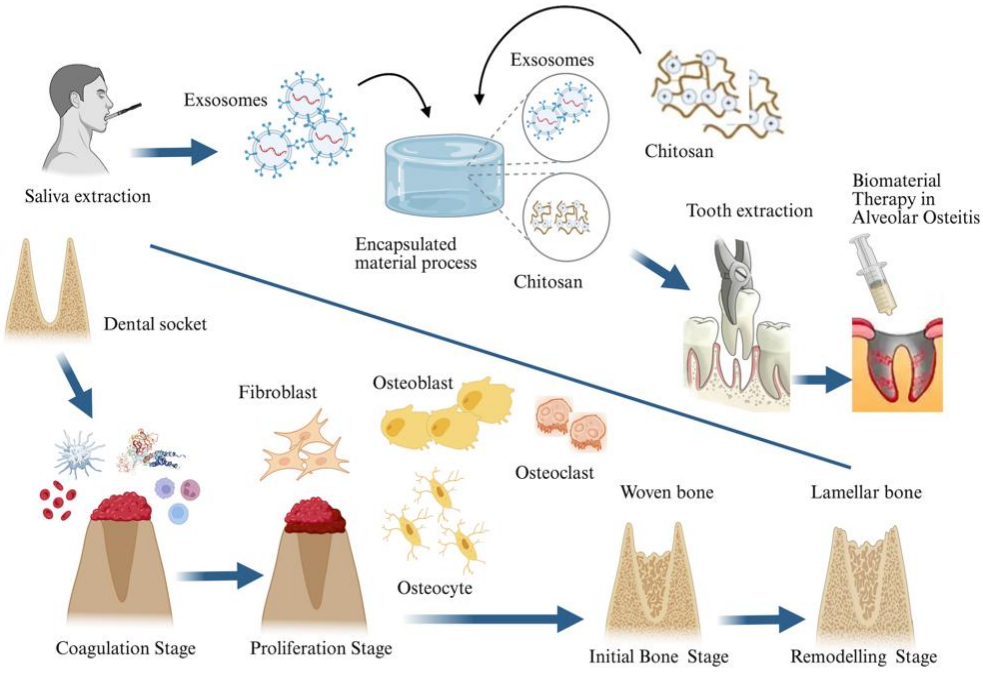

Figure 2. Exosome encapsulation pathway of chitosan in therapeutic biomaterials.

Currently, scientific literature specifically addressing the therapeutic synergy between salivary exosomes and chitosan matrices for alveolar osteitis remains scarce. Nonetheless, evidence from tissue engineering studies indicates that combining exosomes with chitosan-based

biomaterials holds significant promise for bone and periodontal tissue regeneration. For instance, a supramolecular hydrogel composed of NapFFY with SDF-1 and BMP-2 has been shown to effectively promote periodontal bone regeneration and reconstruction in both in vitro and in vivo models. The SDF-1/BMP-2/NapFFY hydrogel has been proposed as a potential alternative to bone transplantation for periodontal defect repair [25]. Similarly, Shen *et al.* [26] demonstrated that in a 10-day in vitro study, exosomes derived from dental pulp stem cells (DPSC-Exo) could be sustainably released from a chitosan scaffold. The DPSC-Exo/chitosan composite enhanced therapeutic efficacy by reducing periodontal inflammation, limiting alveolar bone loss, and decreasing osteoclast numbers compared with PBS, chitosan alone, or DPSC-Exo alone. Furthermore, DPSC-Exo/chitosan promoted periodontal epithelial healing in periodontitis by attenuating inflammation and inducing macrophage polarization from a pro-inflammatory to an anti-inflammatory phenotype.

This regenerative therapy begins with the extraction of saliva, a natural source of exosomes. Exosomes are nanoscale vesicles enriched with biologically active molecules such as microRNAs, proteins, and bioactive lipids, which play critical roles in accelerating tissue repair and modulating immune responses. Following isolation, the exosomes are encapsulated in chitosan, a natural polymer recognized for its biocompatibility, biodegradability, and antibacterial properties. Encapsulation improves exosome stability, prolongs their retention time at the wound site, and enhances penetration into target tissues such as the alveolar bone.

The therapeutic application is particularly relevant in cases of tooth extraction complicated by alveolar osteitis (dry socket). Here, the exosome–chitosan composite biomaterial is delivered directly into the extraction socket to support optimal bone regeneration. The subsequent biological healing process of the alveolar bone occurs in four sequential phases: (1) coagulation, marked by the formation of a blood clot that provides the initial foundation for healing; (2) proliferation, involving the activation and migration of fibroblasts, osteoblasts, osteoclasts, and immune cells, which repair soft tissue and initiate bone formation; (3) initial bone formation, characterized by the development of woven bone, which is structurally immature and disorganized; and (4) remodeling, during which the woven bone is gradually densified and reorganized into lamellar bone, yielding strong and functional tissue.

Although exosomes hold great promise for tissue repair, several limitations hinder their clinical translation. The purification and quantification of exosomes remain challenging, leading to variability in reproducibility and consistency. Moreover, since exosomes derived from different cell types exhibit distinct bioactivities, variability in their sources and characteristics can result in unpredictable therapeutic efficacy. Additional barriers include uneven release rates, difficulties in quantitative assessment, and reduced stability when exosomes are combined with hydrogels for tissue repair [24].

Chitosan-based hydrogels present further challenges. Compared with metal scaffolds, they possess inferior mechanical strength, making them unsuitable for load-bearing applications in large or critical bone defects. Their biodegradability, while advantageous in some contexts, can compromise sustained performance during repair. Furthermore, the clinical preparation and application of chitosan hydrogels often require specialized techniques and equipment, increasing procedural complexity and costs. These issues underscore the need for strategies that carefully balance stability with adequate mechanical support in the clinical deployment of chitosan-based hydrogels [22].

To overcome these limitations, hybrid systems combining natural exosomes with synthetic materials or nanoparticles have been developed to improve stability and drug-loading capacity. However, rigorous testing and validation are essential to confirm their safety, efficacy, and biocompatibility. Ethical and legal considerations also remain critical for the approval and commercialization of exosome-based therapies. Establishing clear regulatory standards and legal frameworks will be vital for widespread adoption. In addition, ethical concerns regarding the sourcing of exosomes—particularly those derived from human tissues—must be addressed to ensure responsible research and clinical application [27].

Conclusion

Salivary exosomes encapsulated in chitosan offer a novel and biologically relevant strategy for enhancing alveolar bone regeneration, particularly in cases complicated by alveolar osteitis. By combining the osteoinductive, immunomodulatory, and angiogenic properties of exosomes with the bioadhesive, biodegradable, and antimicrobial features of chitosan, this therapeutic system provides a targeted and sustained delivery platform that surpasses the efficacy of conventional approaches. Current evidence indicates its ability to upregulate osteogenic gene expression, attenuate inflammation, and accelerate healing. Despite these promising outcomes, significant challenges remain. The reproducible isolation, quantitative characterization, and long-term stability of exosomes, as well as the limited mechanical strength of chitosan scaffolds, continue to hinder clinical translation. Furthermore, ethical, regulatory, and manufacturing considerations must be addressed to ensure safety and scalability. Future research should prioritize rigorous preclinical investigations and controlled human trials to validate efficacy and safety, while also focusing on hybrid biomaterial systems that can overcome the mechanical and stability limitations of chitosan. Establishing standardized protocols for exosome isolation, encapsulation, and clinical-grade production will be critical. With these advancements, exosome–chitosan therapies hold strong potential to emerge as a cost-effective and precise modality for the regeneration of alveolar bone and broader applications in regenerative medicine.

Ethics approval

Not required.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study employed artificial intelligence (AI) tools and methodologies in various capacities to facilitate the systematic literature review. The AI-assisted screening platform Rayyan was employed in the article selection process to manage references, identify duplicates, and facilitate inclusion and exclusion based on eligibility criteria. Furthermore, AI-based language models like ChatGPT and Quillbot were utilized for language refinement, encompassing grammar correction, sentence restructuring, and the enhancement of overall manuscript readability. We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors

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