Journal of Orthopaedic Surgery and Research

SYSTEMATIC REVIEW

Open Access

Therapeutic effect of mesenchymal stem cell-derived exosome therapy for periodontal regeneration: a systematic review and meta-analysis of preclinical trials

Liping Zhou[1,2,3], Wenjia Cai[1,2,3], Yuhan Zhang[1,2,3], Wenjie Zhong[1,2,3], Ping He[4*], Jingsong Ren[4*] and Xiang Gao[1,2,3*]

Abstract

Background To assess the therapeutic effects of mesenchymal stem cell (MSC)-derived exosome therapy on periodontal regeneration and identify treatment factors associated with enhanced periodontal regeneration in recent preclinical studies.

Methods Searches were conducted in PubMed, Cochrane Library, EMBASE, and Web of Science databases until October 10, 2024. A risk of bias (ROB) assessment was performed using the SYRCLE tool. Osteogenic-related parameters were used as the primary outcome measures.

Results In total, 1360 articles were identified, of which 17 preclinical studies were based on MSC-derived exosome therapy, and they demonstrated a beneficial effect on BV/TV (SMD = 13.99; 95% CI = 10.50, 17.48; $p < 0.00001$), CEJ-ABC (SMD = -0.22; 95% CI = -0.31, -0.13; $p < 0.00001$), BMD (SMD = 0.29; 95% CI = 0.14, 0.45; $p = 0.0002$), and Tp.Sp (SMD = -0.08; 95% CI= -0.15, -0.02; $p = 0.02$) compared with the control group. However, no significant differences were observed in Tp.Th (SMD = 0.03; 95% CI = 0.00, 0.07; $p = 0.09$) between the exosome-treated group and control group. Additionally, subgroup analysis indicated that preconditioned exosomes ($p = 0.03$) significantly improved BV/TV. In contrast, there were no significant differences in the enhancement of BV/TV with respect to the application method ($p = 0.29$), application frequency ($p = 0.10$), treatment duration ($p = 0.15$), or source of MSCs ($p = 0.31$).

Conclusions MSC-derived exosomes show great promise for enhancing the quality of periodontal regeneration. However, more standardized and robust trials are needed to reduce heterogeneity and bias across studies and to confirm the therapeutic parameters associated with the enhancement of periodontal regeneration by MSC-derived exosomes.

Registration CRD42024546236.

*Correspondence:
Ping He
582260761@qq.com
Jingsong Ren
1152819817@qq.com
Xiang Gao
xiangg@hospital.cqmu.edu.cn

Full list of author information is available at the end of the article

Keywords Mesenchymal stem cell, Exosomes, Periodontitis, Periodontal regeneration

Introduction

Periodontitis, a chronic infectious disease, is caused by exogenous bacterial invasion and endogenous immune dysregulation [1, 2]. It is primarily characterized by the inflammatory destruction of periodontal supporting tissues, including the periodontal ligaments and alveolar bone, eventually leading to tooth loss [3]. In addition, periodontitis has been linked to 57 systemic diseases, including cardiovascular disease, diabetes, chronic inflammatory bowel disease, and Alzheimer's disease [4]. Therefore, periodontitis imposes a significant burden on the healthcare systems [5]. The therapeutic approach to periodontitis is focused on preventing further disease progression, mitigating clinical symptoms and patient-reported discomfort, promoting potential tissue regeneration, and supporting the long-term preservation of healthy periodontal tissues [6]. Eliminating plaque-retentive factors that contribute to periodontal disease progression is crucial. For instance, root anatomical features such as enamel pearls and palatal grooves can be removed or recontoured to improve plaque control [7]. In addition, current clinical approaches to periodontal treatment primarily include subgingival mechanical debridement of the dental plaque, use of both local and systemic pharmacological therapies, and various periodontal surgical procedures [8–10]. However, despite these efforts, achieving complete and functional periodontal tissue regeneration remains challenging [11].

Mesenchymal stem cells (MSCs) are capable of self-renewal and differentiation into various lineages [12, 13]. Owing to their immunomodulatory and antioxidant properties, MSCs have shown consistent and successful outcomes in the treatment of tissue regeneration [12, 14]. Dental stem cells such as periodontal ligament stem cells (PDLSCs) and dental pulp stem cells (DPSCs), along with a range of non-dental stem cells such as bone marrow mesenchymal stem cells (BMMSCs), have been shown to play important roles in periodontal regeneration [15–19]. However, the major difficulties in stem cell-based therapy for periodontal regeneration include dedifferentiation during MSCs expansion, reduced regenerative potential, post-transplantation immune cell phenotype instability, scarcity of autologous stem cells, and inherent risks associated with allogeneic cell transplantation [20, 21].

Extracellular vesicles (EVs), which originate from cellular membranes and are released into the extracellular space, play crucial roles in intercellular communication [22]. Based on their secretion processes and characteristics, EVs can be classified into exosomes (Exos), derived from endosomes; microvesicles (MVs), originating from the plasma membrane; and apoptotic bodies (ApoEVs) [23, 24]. As an important component of EVs, exosomes consist of bilayer lipids and carry cargo-containing diverse molecules such as amino acids, proteins, and nucleic acids from their parent cells. With diameters ranging from 30 to 150 nm [25], exosomes exhibit therapeutic properties such as promoting cell proliferation, inducing stem cell migration, and reducing inflammation and pain, making them a promising tool for tissue regeneration [26]. Clinical trials have provided additional evidence of their safety and efficacy [27]. Owing to their low immunogenicity, high safety, and multifunctional bioactive properties, a growing body of research has demonstrated that exosomes derived from MSCs play a pivotal role in immunomodulation and hold great potential as alternatives to conventional MSC-based therapies [28–30].

Although numerous studies have highlighted the crucial role of MSC-derived exosomes in periodontal regeneration [28–30], there remains a notable lack of quantitative, systematic, and comprehensive analyses examining the relationship between MSC-derived exosomes and periodontal regeneration. Previous meta-analyses have evaluated their efficacy, but have not thoroughly assessed the specific impact of various factors on periodontal tissue regeneration. In this study, we conducted a meta-analysis and systematic review to comprehensively assess animal models of periodontal regeneration while investigating key variables for optimizing preclinical trial designs to accelerate the translation of MSC-derived exosome therapy into clinical practice.

Materials and methods

This systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and PRISMA 2020 standards [31]. The protocol was officially registered in the PROSPERO database, which is part of the International Prospective Register of Systematic Reviews (CRD42024546236).

Search strategy

We conducted comprehensive searches of PubMed, Web of Science, and EMBASE using the Medical Subject Headings (MeSH) terms 'exosomes' and 'guided tissue regeneration, periodontal' for studies published before October 10, 2024. The complete search strategy is presented in Supplementary Table 1.

Eligibility criteria

The studies included in the meta-analysis met the following criteria: (1) they provided detailed procedures

for establishing periodontitis or periodontal defect models in animals; (2) they comprehensively described the methodologies for isolating and characterizing exosomes from MSCs; (3) the treatment group received either exosomes alone or exosomes with biomaterial assistance, while the control group was administered PBS or alternative dressings; (4) they reported on one or more available outcomes, such as bone volume/total volume (BV/TV), cemento-enamel junction and alveolar bone crest (CEJ-ABC), bone mineral density (BMD), trabecular thickness (Tb.Th), and trabecular separation (Tb.Sp).

Studies excluded from the meta-analysis met the following criteria: (1) articles not published in English; (2) non-randomized controlled trials, such as reviews, commentaries, editorials, case reports, or conference abstracts; (3) exosomes not derived from MSCs; and (4) unavailable or non-extractable data.

Study selection

After removing the duplicates, the remaining references were screened in detail. The initial selection was made by reviewing the titles and abstracts. Subsequently, studies that met the preliminary criteria were subjected to a thorough full-text review based on the pre-established eligibility criteria. Two researchers independently performed study selection, quality evaluation, and data extraction. In cases of disagreement, a third member was involved in the discussion to resolve issues.

Data extraction

Data were extracted from the full text, figures, tables, and supplements of eligible studies and were systematically listed in our pre-designed table by two independen tresearches. The extracted data included study characteristics (authors, publication year), animal model characteristics (sex, age, body weight, modeling method), intervention specifics (MSCs source of exosomes, modification type, concentration, frequency, and route of administration), study design (vehicles, sample size, duration of the follow-up), and outcomes (BV/TV, CEJ-ABC, BMD, Tb.Th, and Tb.Sp). We initially contacted the authors via email to request for missing data (such as sample size and original data) where necessary. When numerical data were unavailable, we used the WebPlotDigitizer online application (https://apps.automeris.io/wpd/) to extract data from the figures.

Quality assessment and risk of bias

The risk of bias was assessed using the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) tool, which is specifically designed for animal studies [32]. This tool evaluates bias across several domains: sequence generation (selection bias), baseline characteristics (selection bias), allocation concealment (selection bias), random housing (performance bias), blinding against personnel (performance bias), random outcome assessment (detection bias), blinding against detection bias (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias.

Statistical analysis

The data were standardized as the standardized mean difference (SMD) and analyzed using the Cochrane Review Manager 5.4. As all outcomes were continuous, effect estimates are presented as SMDs with 95% confidence intervals (CIs). Heterogeneity among eligible studies was assessed using the I^2 statistic. $P < 0.05$ was considered statistically significant. Subgroup analysis and heterogeneity exploration were conducted to explore potential sources of variability. A random-effects model was employed in the meta-analysis, which accounted for the significant heterogeneity due to clinical and methodological differences [33]. Subgroup analyses included factors, such as exosome modification, biomaterial-assisted delivery, exosome source, treatment frequency, and treatment timing.

Results

Search results

Figure 1 presents a flowchart detailing the comprehensive selection process for the eligible studies. A total of 1360 articles were initially identified from PubMed, EMBASE, and Web of Science databases. After removing duplicates, 803 studies were included in the analysis. Ultimately, 17 preclinical studies that met the inclusion criteria and reported the efficacy of MSC-derived exosomes in animal models of periodontal regeneration were included in the meta-analysis.

Study characteristics

The reviewed articles, published between 2019 and 2024, indicated a growing interest in MSC-derived exosomes for periodontal regeneration. The characteristics and application protocols of the exosomes in each selected study are detailed in Tables 1 and 2, respectively. Various animal models were employed, with Sprague Dawley (SD) rats being the most frequently used ($n = 11$), followed by C57BL/6 mice ($n = 4$), Wistar rats ($n = 1$), and Beagles ($n = 1$). In terms of the disease model, nine studies focused on periodontal defects, six on periodontitis, and two on both. Exosomes were sourced from different MSCs, including dental stem cell-derived exosomes in 11 studies and non-dental stem cell-derived exosomes in 6. Among the dental stem cell-derived exosomes were PDLSCs ($n = 6$), DFSCs ($n = 2$), human exfoliated deciduous teeth (SHEDs) ($n = 2$), and apical papilla stem cells (SCAPs) ($n = 1$). For non-dental stem cell-derived exosomes, BMMSCs were the most common ($n = 5$),

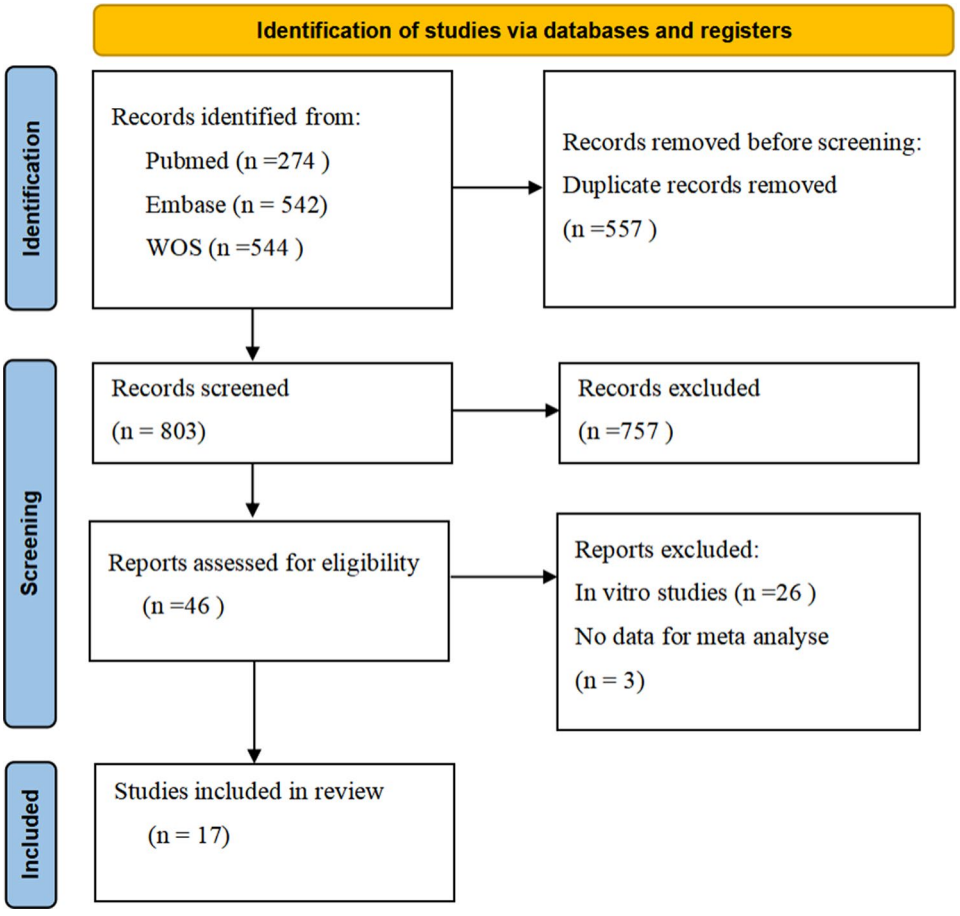

Fig. 1 Flow diagram for the study selection procedure

with one study using umbilical cord mesenchymal stem cells (UCMSCs) ($n = 1$). All 17 studies used local exosomes either through local injection or in combination with biomaterials to promote periodontal regeneration. The frequency of exosome therapy varied, including a single administration, administration every three days, and weekly administration. The sample collection time ranged from 10 days to 8 weeks across trials.

Risk of bias

The overall and individual study results of the SYRCLE bias risk assessment are shown in Supplementary Fig. 1. Generally, the risk of bias in most eligible studies was unclear. Several articles mentioned that the animal groups were assigned randomly; however, detailed descriptions of the randomization procedure and allocation concealment methods were not provided. All the articles indicated that the baseline characteristics of the intervention and control groups were comparable at the beginning of the experiment. Only one trial reported personnel blinding. None of the studies revealed selective reporting or other sources of bias.

Meta-analysis

Seventeen studies were included in this meta-analysis, focusing on five primary outcomes: BV/TV from fourteen studies, CEJ-ABC from five studies, BMD from three studies, Tb.Th from three studies, and Tb.Sp from three studies.

BV/TV

In our meta-analysis, 14 eligible studies reported the BV/TV as an outcome measure. Overall, there was a significant increase in BV/TV with EVs (SMD = 13.99; 95% Cl = 10.50, 17.48; $p < 0.00001$) in comparison to the control group (Fig. 2), although there was relatively high heterogeneity ($I^2 = 97\%$). Among these studies, 11 demonstrated beneficial effects in the exosome group compared to the control group, whereas three showed no significant differences. The symmetry of the funnel plot suggests a low risk of publication bias among the included studies (Supplementary Fig. 2). We further conducted a subgroup analysis to examine the effects of various factors, including pretreatment, application method, injection frequency, treatment duration, and types of mesenchymal cells (Table 3). Notably, studies

Table 1 The main characteristics of all included articles

Study	Year	Species; Gender	Age/Weight	Sample sizes (treatment/ control)	Defects type	Relevant outcomes	Healing time (weeks)
Lai et al.	2023	C57BL/6 male	8 weeks 20–25 g	18mices (3Gs,6/G)	periodontitis	BV/TV、BMD、CEJ-ABC	10d
Wu et al.	2019	SD rats male	8 weeks	40 rats (4Gs,10/G)	periodontal defect 4×2×1.5 mm3	BV/TV	4w
Zhao et al.	2022	SD rats male	250–300 g	9 rats (3Gs,6/G)	periodontal defect 2×1×0.8 mm3	BV/TV	4w
Zhang et al.	2022	C57BL/6 mice male	Two month-old	24 mices (4Gs, 6/G)	periodontitis	BV/TV	14d
Yu et al.	2022	SD rats male	150–180 g	15 rats (3Gs, 5/G)	periodontal defect	BV/TV	6w
Yue et al.	2022	SD rats male	250 to 300 g, 9 to 10 weeks	20rats (2Gs, 10/G)	periodontitis	BV/TV	3 W
Huang et al.	2022	beagle dogs	1-year-old 10 kg	4 beagle dogs (4Gs,2/G)	periodontal defects 2×3×6 mm3	BV/TV、Tb. Sp、PDL	8w
Chew et al.	2019	SD rats male	10 weeks 289 to 413 g	18 rats (3Gs, 12/G)	periodontal defect 2×2×1.5 mm3	BV/TV、Tb.Sp、Tb.Th、Tb.N、PDL	2 W、4 W
Sun et al.	2023	SD rats male	Eight-week-old (250 ± 10 g)	10 rats (2Gs,5/G)	periodontal defect 4×4×1 mm3	BV/TV、Tb.Sp、Tb.Th、Tb.N	6 W
He et al.	2023	Wistar rats male	6 weeks	48 Wistar rats (4Gs,6/G)	periodontal defect 3×1.5×1.5 mm3	BV/TV、BMD	8 W
Ma et al.	2022	SD rats male	12-week-old	72 rats (3Gs,24/G)	periodontal defect 3×2×1 mm3	BV/TV、Tb.Th	2、4、8w
Yu et al.	2020	SD rats male	150–180 g	(4Gs,8/G)	periodontal defect 4×3×2 mm3	BV/TV	3、6w
Lei et al.	2021	SD rats male	10-week-old 103 to 120 g	36rats (*n* = 6、6、6、9、9)	periodontitis periodontal defect 3×1.5×2 mm	BV/TV	4w
Niu et al.	2024	C57BL/6 mice female	6–8 weeks	40 mice (5Gs,8/G)	periodontitis	CEJ-ABC	4w
Xiang et al.	2024	SD rats male	8 weeks, weight: 200–250 g	40 mice (5Gs,8/G)	Periodontitis	CEJ-ABC	4w
Ming et al.	2024	female SD rats	8 week	Twenty-four (4Gs,6/G)	Periodontitis periodontal defect 2.5×1.5 mm	CEJ-ABC、BMD、BV/TV、Tb.N	4w
Yu et al.	2024	C57BL/6 male	8 weeks	Twelve (4Gs,3/G)	Periodontitis	CEJ-ABC、BV/TV	2w、4w

Abbreviations = BV/TV: bone volume/total volume; CEJ-ABC: cementoenamel junction and alveolar bone crest; BMD: bone mineral density; Tb.Th: trabecular thickness; Tb.Th: trabecular separation; Tb.N: trabecular number

utilizing pretreatment as a means of EV modification (SMD = 21.84; 95% Cl = 13.18, 30.50; $p < 0.00001$) showed a significant improvement ($p < 0.00001$) in BV/TV compared to those without pretreatment (SMD = 11.15; 95% CI = 6.80, 15.50; $p < 0.00001$) (Supplementary Fig. 3). Among the six studies that investigated pretreated MSC-derived exosomes, various methods were explored, including gene transfection, 3D culture, cytokine stimulation, and physical stimulation. Nonetheless, no statistically significant differences were observed between the use and non-use of bioactive materials, despite both contributing to improvements in BV/TV ($p = 0.29$) (Supplementary Fig. 4). Subgroup analysis revealed no significant differences in BV/TV with respect to application frequency ($p = 0.10$) (Supplementary Fig. 5), treatment duration ($p = 0.15$) (Supplementary Fig. 6), or MSC type ($p = 0.31$) (Supplementary Fig. 7).

CEJ-ABC

Five articles reported CEJ-ABC with means and SDs. CEJ-ABC is an important indicator of alveolar bone resorption, and its measured distance directly reflects the extent of resorption. The application of MSC-derived exosomes effectively reduced the distance between the CEJ-ABC, as shown by the SMD and its 95% CI (SMD = -0.22; 95% Cl = -0.31, -0.13; $p < 0.00001$). However, heterogeneity testing showed that I^2=98%, indicating a high level of heterogeneity (Fig. 3).

Table 2 Summary of application protocols for the exosomes of all included articles

Study	Source of exosomes	Preconditioning	Exosome concentration	Frequency	Route of administration	Vehicle
Lai et al.	rBMSCs	miR – 26a	50 μg/mL	every three days	injected into the periodontal region	PBS
Wu et al.	SHEDs	/	100 μg	once	implant to the periodontal defect	β-TCP
Zhao et al.	PDLSCs	/	2 μg/μL	once	implant to the periodontal defect	Gel-Alg hydrogel
Zhang et al.	SCAPs	/	5 mg/time	every three days	injected into the periodontal region	PBS
Yu et al.	PDLSCs	3D cultured	1 μg/μL	once	injected into the periodontal region	Matrigel™
Yue et al.	hBMSCs	/	1.5 μg/time	every week	injected into the periodontal region	saline
Huang et al.	DFSCs	LPS	200 μg /time	once a week	injected into the periodontal pocket	hyaluronic acid (HA)
Chew et al.	hMSCs	/	40 mg /time	once	implant to the periodontal defect	collagen sponges
Sun et al.	hUCMSCs	/	1 μg/mL	once	implant to the periodontal defect	3D-printed SF/COL-I/nHA
He et al.	rBMSCs	CTNNB1	300 μg/mL	once	implant to the periodontal defectc	PF127 hydrogel
Ma et al.	DFSCs	/	10 μg/mL	once	implant to the periodontal defect	collagen sponges
Yu et al.	PDLSCs	/	100 μg/100 μL	once	injected in the periodontal defects	microscale magnetically stretched collagen hydrogels
Lei et al.	PDLSCs	/	150ug/ul	once	implant to the periodontal defect	Matrigel、β-TCP
Niu et al.	PDLSCs	FoxO1	2 μg/μL	three times a week	injected in the alveolar bone defects	PBS
Xiang et al.	PDLSCs	Metformin	200 ug/time	Once a week	injected in the alveolar bone defects	PBS
Ming et al.	BMSCs	/	200 μL/time	twice a week	injected in the alveolar bone defects	PCc hydrogel
Yu et al.	SHEDs	Cu^{2+}	20 μL/time	every other day	injected in the alveolar bone defects	(Cu2+) and hyaluronic acid hydrogel

Abbreviations = rBMSCs: rat bone marrow mesenchymal stem cells; SHEDs: stem cells from human exfoliated deciduous teeth; PDLSCs: periodontal ligament stem cells; SCAPs: stem cells from apical papilla; hBMSCs: human bone marrow mesenchymal stem cells; DFSCs: dental follicle stem cells; hMSCs: human mesenchymal stem cells; hUCMSCs: human umbilical cord mesenchymal stem cells; BMMSCs: bone marrow mesenchymal stem cells; LPS: Lipopolysaccharide; PBS: phosphate-buffered saline; β-TCP: β-Tricalcium Phosphate; Gel-Alg: Gelatin-Alginates; SF: silk fibroin

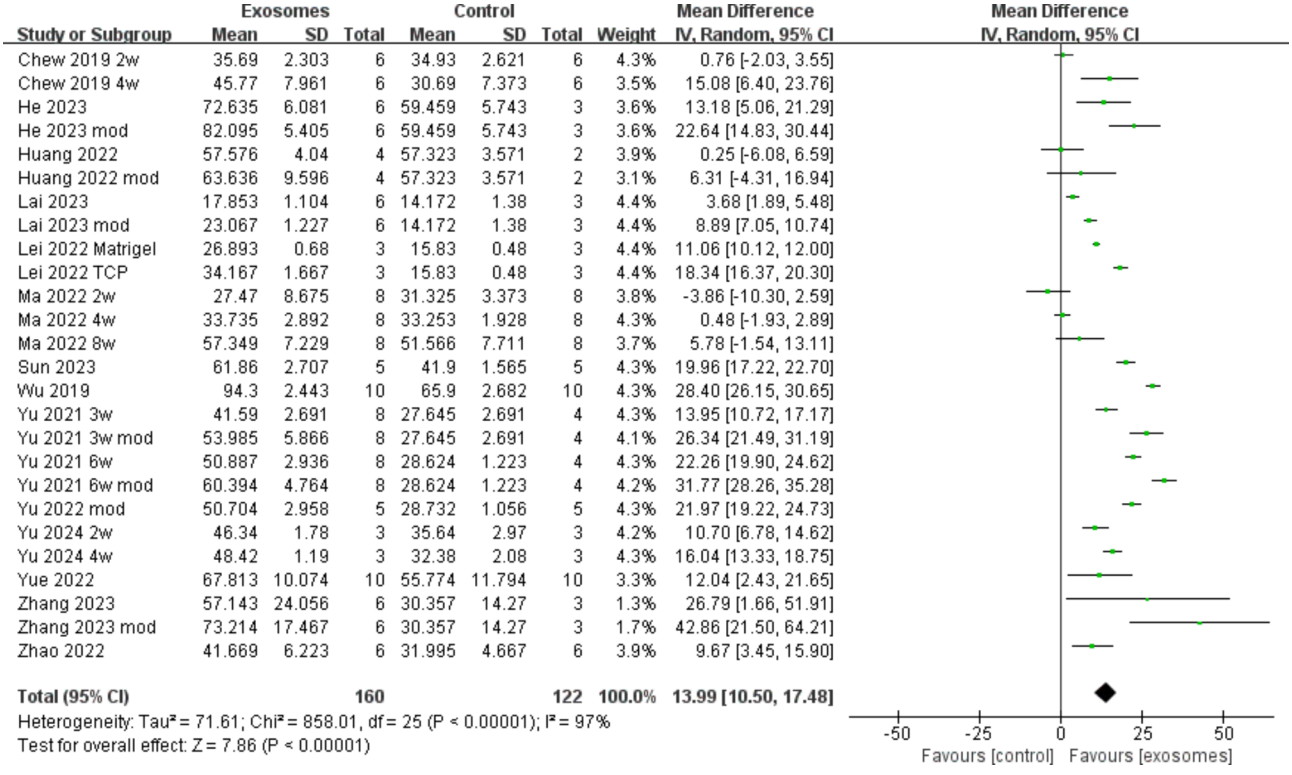

Fig. 2 Forest plot analysis evaluating the effects of MSC-derived exosome therapy on BV/TV compared with controls

Table 3 Subgroup analysis on BV/TV

	Subgroup	*N*	Effect estimate	I^2	P^*	P^{**}
Precondition	Precondition	7	21.84(13.18–30.50)	97%	$p<0.00001$	$P=0.03$
	No precondition	17	11.15(6.80–15.50)	97%	$p<0.00001$	
Application method	Bioactive material delivery	19	14.14(9.86–18.42)	97%	$p<0.00001$	$P=0.29$
	Direct injection	5	10.31(4.73–15.89)	87%	$p<0.00001$	
Treatment duration	More than 4 weeks	16	15.52(11.16–19.88)	97%	$p<0.00001$	$P=0.15$
	Less than 4 weeks	10	10.75(5.92–15.58)	94%	$P<0.00001$	
Application frequency	Single application	17	15.29(10.81–19.76)	98%	$p<0.00001$	$P=0.1$
	Multiple applications	9	10.04(5.66–14.43)	90%	$p<0.00001$	
Types of MSCs	Dental stem cells	18	15.07(10.76–19.38)	97%	$p<0.00001$	$P=0.31$
	Non-dental stem cells	8	11.54(6.18–16.89)	95%	$p<0.00001$	

p* value for heterogeneity within each subgroup. p** value for subgroups difference with meta-regression analysis. MSCs, mesenchymal stem cells

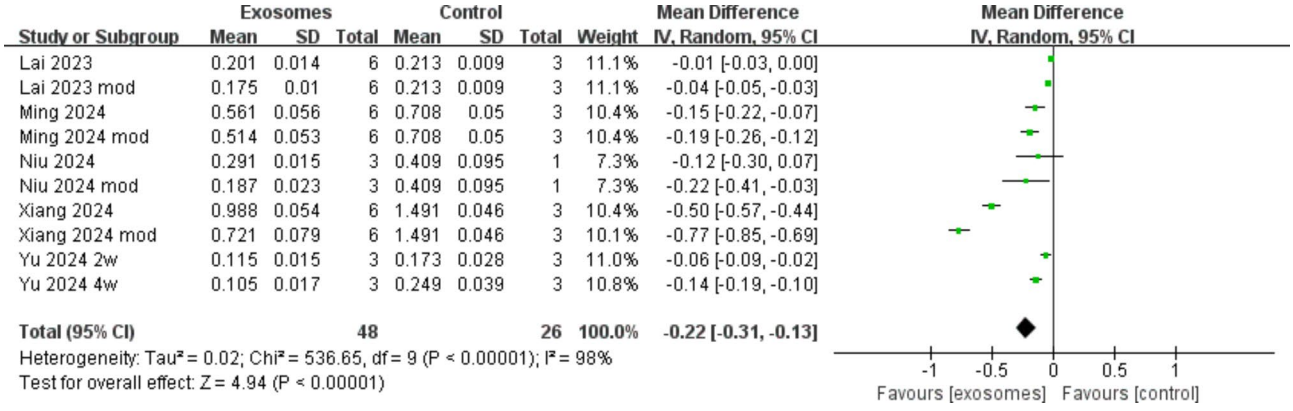

Fig. 3 Forest plot analysis assessing the effects of MSC-derived exosome therapy on CEJ-ABC compared with controls

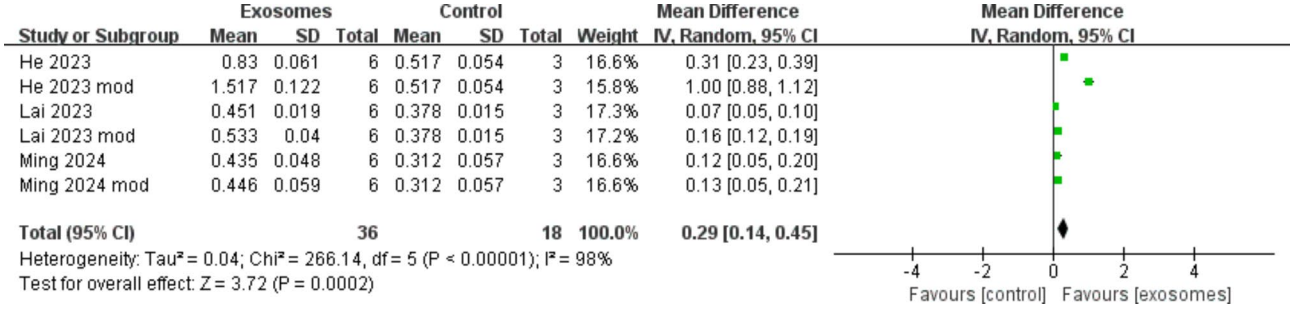

Fig. 4 Forest plot analysis evaluating the effects of MSC-derived exosome therapy on BMD compared with controls

BMD

Three qualified studies were included for the evaluation of BMD. All of these factors showed a statistically significant effect on BMD. Overall analysis showed that MSC-derived exosomes enhanced BMD (SMD = 0.29; 95% CI = 0.14, 0.45; $p = 0.0002$) (Fig. 4).

Tp.Th

Three studies demonstrated an effect on Tp.Th. No significant difference was noted in Tp.Th between the exosome-treated group and the control group (SMD = 0.03; 95% CI = 0.00, 0.07; $p = 0.09$), which may be influenced by the limitations of the available references (Fig. 5).

Tp.Sp

Tb.Sp was also reported in three studies, including five trials. The pooled results showed that in the exosome group, Tp.Sp was significantly lower compared to that in the control group (SMD = -0.08; 95% CI= -0.15, -0.02; $p = 0.02$), indicating that MSC-derived exosomes reduced the average distance between trabeculae. A lower Tp.Sp value indicates denser and closer trabeculae, thereby enhancing the bone microarchitecture (Fig. 6).

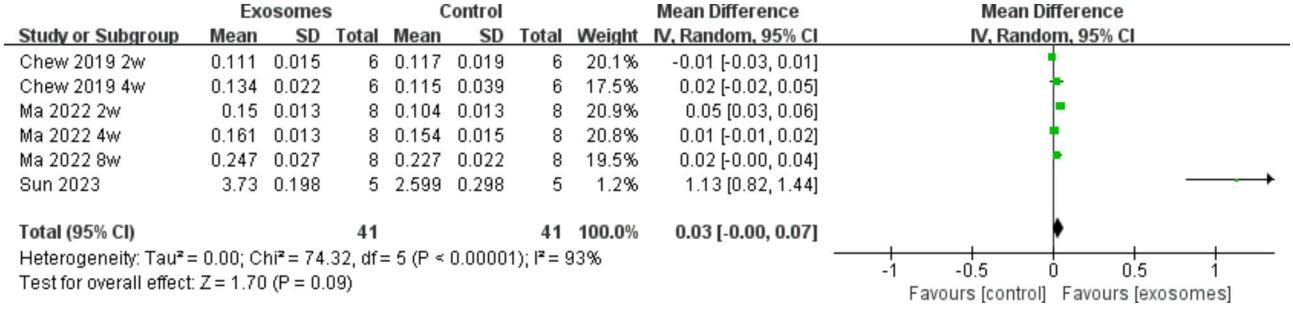

Fig. 5 Forest plot analysis evaluating the effects of MSC-derived exosome therapy on Tp.Th compared with controls

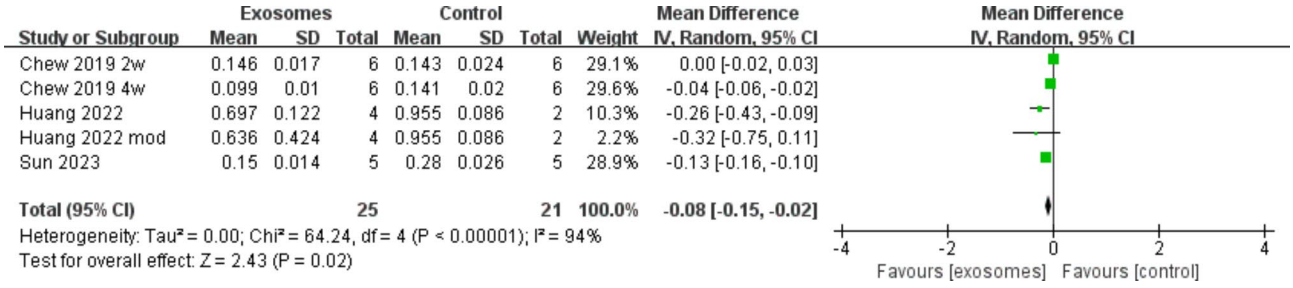

Fig. 6 Forest plot analysis evaluating the effects of MSC-derived exosome therapy on Tp.Sp compared with controls

Discussion

This meta-analysis aimed to examine the therapeutic potential of MSC-derived exosomes in pre-clinical models of periodontitis or periodontal defects based on the osteogenic indicators BV/TV, CEJ-ABC, BMD, Tb. Th, and Tb.Sp. Based on the findings of the 17 eligible studies, MSC-derived exosomes were shown to significantly promote periodontal bone regeneration. However, our conclusions are limited by substantial heterogeneity among the studies. Although we could not identify the specific source of this heterogeneity through subgroup analysis, we observed that differences in modification methods, biological scaffolds, application frequency, treatment duration, and MSCs sources may influence periodontal tissue regeneration. Therefore, our study suggests that MSC-derived exosome-based treatments may be promising for periodontal regeneration and provides valuable insights for the optimization of preclinical study designs.

BV/TV is a key indicator of new bone formation and demonstrated a significant increase in most of the included studies [34]. CEJ-ABC can directly reflect the degree of alveolar bone resorption and has significant clinical value in the diagnosis and treatment of periodontal disease. The use of exosomes significantly reduced the CEJ-ABC distance, thereby promoting periodontal tissue regeneration. BMD, which assesses the mineral content of bone tissue and indicates bone strength and quality, exhibited progress in our study. Moreover, it demonstrated a reduction in Tb.Sp, indicating an enhancement of the trabecular structure in cancellous bone. Although only the effects of pre-treatment with BV/TV revealed significant differences in the subgroup analysis, we still consider that the therapeutic effects of exosome treatment may be influenced by specific factors, leading to variations in different bioactive compounds and their associated signaling pathways. Collectively, these changes indicate improvements in bone health, providing crucial evidence for evaluating the efficacy of MSC-derived exosome therapy in the regeneration of periodontal bone tissue. However, only a limited number of studies have reported other periodontal tissues, such as the reformation of oriented periodontal ligament fibers and newly formed cementum, which are challenging but essential for achieving complete periodontal regeneration [35].

Although subgroup analyses of BV/TV did not reveal a significant difference between dental and non-dental stem cells, exosomes derived from different cell types can exert diverse effects under various physiological and pathological conditions, as well as in different microenvironments where the parental cells reside [25]. Dental stem cells were the most frequently used source of exosomes for periodontal regeneration in our study, likely because of their embryonic-like properties and homology with oral tissue [36–38]. Among the 11 studies on exosomes derived from dental stem cells, six focused on PDLSCs, which are considered the most effective and well-documented stem cell-based therapies for alveolar bone regeneration [39–42]. Moreover, DFSCs located in the dental follicle are closely related to PDLSCs both developmentally and functionally, making them a popular choice for researchers [43]. BMMSCs from non-dental

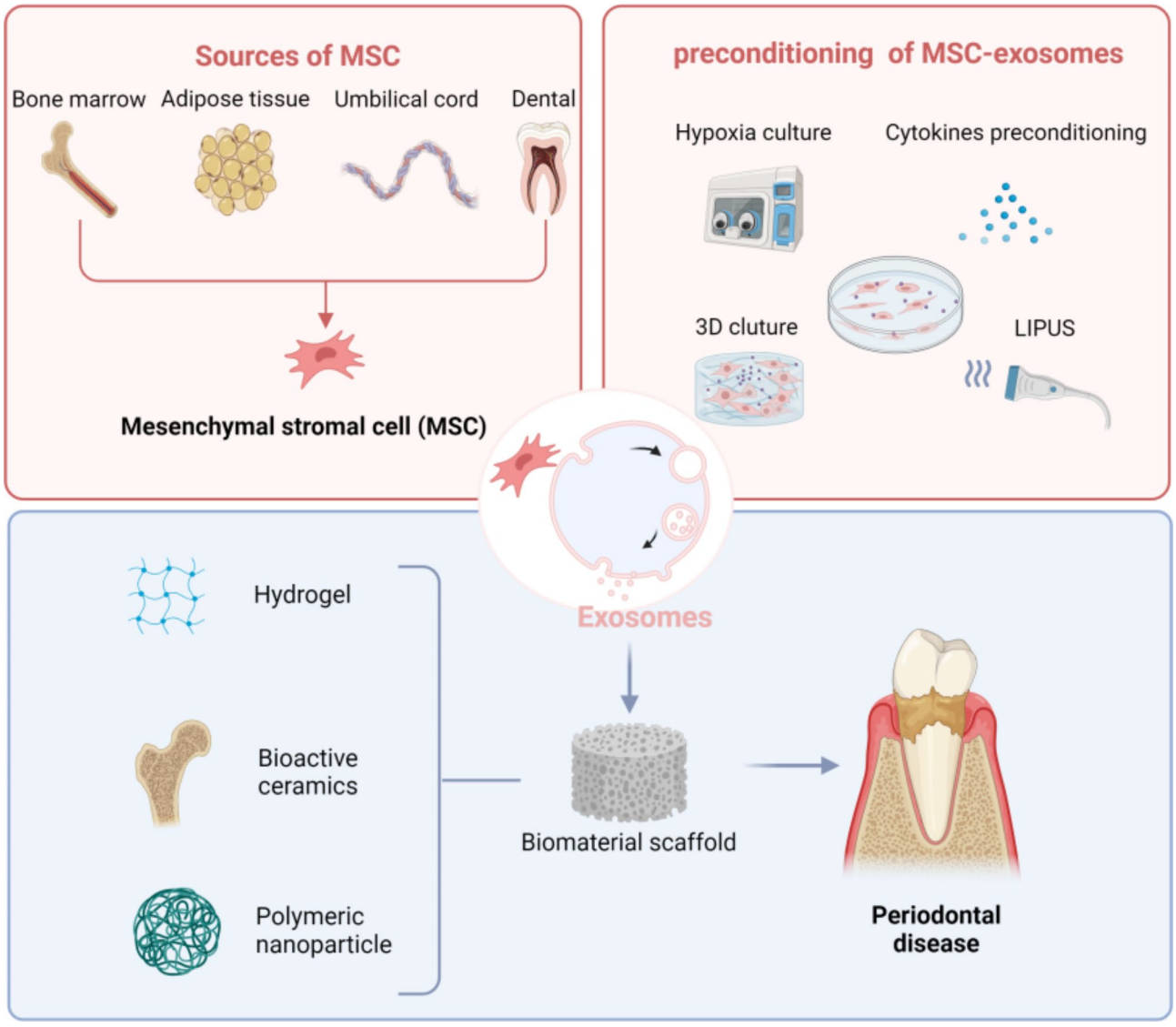

Fig. 7 Various preconditioning methods and administration routes for MSC-sEV

sources are also widely used for periodontal regeneration due to their self-renewal capabilities and the ability to differentiate into osteogenic lineages [44]. Although previous systematic reviews have demonstrated that MSCs can promote bone regeneration, exosomes derived from MSCs offer greater regenerative potential in both quality and quantity, likely because of their ability to carry a more diverse array of biomolecules such as proteins, RNA, and lipids, thereby contributing to improved healing outcomes [45–47]. Therefore, determining the most suitable source of exosomes derived from different stem cells for periodontal regeneration remains a challenge, as research on this topic is currently limited.

Given the advancements and success of exosome research, modified exosomes are attracting more attention than natural exosomes, primarily owing to their enhanced therapeutic efficacy, which can be attributed to higher yields, targeted delivery capabilities, and specialized components [48]. Consistently, our meta-analysis demonstrated that studies involving modified MSC-derived small extracellular vesicles (MSC-sEVs) yielded superior outcomes in terms of BV/TV compared with those using unmodified MSC-sEVs. One of the main strategies for modifying MSC-derived exosomes is the preconditioning of parental cells, including techniques such as 3D or hypoxic culture, exosome engineering, inflammatory preconditioning, and mechanical stimulation (Fig. 7) [49]. This preconditioning modifies the cargo of exosomes, including proteins and nucleotides, thereby enhancing the bioactive effects of MSC-derived exosomes on cell migration, proliferation, anti-inflammatory responses, angiogenesis, and osteogenesis, which

are essential for periodontal regeneration [50–53]. For instance, enhanced angiogenesis may be attributed to the activation of HMGB1/AKT signaling by the 3D culture of MSCs [54] and hypoxia-inducible factor (HIF-1α) [55]. A recent study constructed an engineered CXCR4-overexpressing exosome loaded with miR-126 that efficiently delivered its cargo to macrophages, relieving periodontitis and alleviating alveolar bone loss [56]. Cytokine preconditioning, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and transforming growth factor-β1 (TGF-β1), has been shown to enrich miRNAs in exosomes, including miRNA-299-3p [57], miR-146a [58], miRNA-147b [59] and miRNA-135b [60], which helps reduce inflammation and enhance bone regeneration. Highly expressed proteins in LPS-preconditioned DFSC-sEVs are mainly involved in antioxidant and enzyme regulatory activities [61]. Additionally, low-intensity pulsed ultrasound (LIPUS) presents a feasible and effective approach for mitigating inflammation and preventing bone resorption in the periodontal tissue by increasing the levels of miR-328-5p, miR-487b-3p [51], and miR-935 within exosomes [62]. Therefore, selecting appropriate modification techniques or a combination of multiple loading methods has proven to be effective in increasing the loading potential of exosomes [63]. However, the precise mechanisms underlying exosome modifications aimed at optimizing therapeutic effects remain unclear and require further investigation [64].

Although all the included studies utilized the local application of exosomes in animal models to promote periodontal tissue regeneration, direct injection of exosomes into periodontal defects can lead to rapid release owing to exposure to saliva flow and periodontal pockets, thereby hindering sustained therapeutic effects [65]. Therefore, achieving high loading efficiency and controllable retention stability of exosomes is crucial for accelerating clinical translation applications [66]. Similarly, our meta-analysis confirmed that the combination of MSC-derived exosomes with biomaterial-assisted scaffolds improved bone-healing efficacy compared to studies involving direct exosome injection. Bioactive ceramics, hydrogels, and synthetic polymers are widely used as scaffold materials in exosome delivery systems. Bioactive ceramics, such as hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP), possess a mineral structure similar to that of natural bone, exhibiting excellent osteoconductivity and osteoinductivity [67]. When combined with MSC-derived exosomes, they demonstrated superior alveolar bone formation in rat models of periodontitis compared to other scaffolds [67–69]. Hydrogels such as hyaluronic acid (HA), chitosan (CS), silk fibroin (SF), sodium alginate (ALG), and polyethylene glycol (PEG) are hydrophilic three-dimensional networks [63]formed from naturally derived or synthetic polymers [70]. These hydrogels show promise as scaffolds for exosome carriers because of their advanced biodegradability and biocompatibility [71]. However, rapid in vivo degradation and poor mechanical strength limit their application in tissue regeneration [72]. Environmentally responsive hydrogels and composite scaffolds have been developed to address this issue. For example, temperature-responsive PF127 hydrogels and 3D-printed SF/COL-I/nHA scaffolds have shown excellent potential for promoting the regeneration of alveolar bone in periodontitis [73, 74]. The evolution of exosome delivery methods is advancing toward more intelligent, multifunctional, and sustainable approaches, driving further progress in regenerative medicine.

This meta-analysis has several limitations. First, a large proportion of the included studies was of relatively low quality, as assessed using the SYRCLE risk-of-bias tool, with many studies rated as 'unclear.' Second, although subgroup analyses were performed based on the sources of MSCs, physiological states, and culture conditions of MSCs, the use of scaffolds, treatment frequency, and healing time did not reduce the heterogeneity. Therefore, the credibility of the positive effects of exosomes in periodontal tissue regeneration is limited. Third, animal models of periodontal defects or periodontitis may not fully replicate the pathophysiological changes observed in human periodontitis. Improving the construction of preclinical models is necessary to enhance their clinical relevance. Moreover, outcome measures are limited, primarily focusing on the quality and quantity of periodontal bone, while relatively few studies have addressed the regeneration of other periodontal structures, such as the cementum and periodontal ligament.

Conclusion

Through our systematic review and meta-analysis, we reached the preliminary conclusion that MSC-derived exosomes demonstrated significant efficacy in promoting periodontal regeneration. However, to clarify the optimal source of exosomes, appropriate concentration, and ideal scaffold selection, as well as the frequency and duration of administration, future research should focus on conducting large-scale, high-quality, randomized controlled trials with long-term follow-up. Additionally, the integration of engineered exosomes with tissue engineering strategies aimed at enhancing their circulation time, targeting ability, and drug delivery efficiency in vivo will further expand the potential applications of exosomes in periodontal tissue regeneration, thereby accelerating their clinical translation.

Abbreviations

MSC	Mesenchymal stem cell
MSCs	Mesenchymal stem cells
PDLSCs	Periodontal ligament stem cells
DPSCs	Dental pulp stem cells

BMMSCs	Bone marrow mesenchymal stem cells
DFSCs	Dental follicle stem cells
SHEDs	Human exfoliated deciduous stem cells
SCAPs	Apical papilla stem cells
UCMSCs	Umbilical cord mesenchymal stem cells
EVs	Extracellular vesicles
Exo	Exosomes
MVs	Microvesicles
ApoEVs	Apoptotic bodies
MSC-sEVs	Mesenchymal mesenchymal cell-derived small extracellular vesicles
BV/TV	Bone volume/total volume
CEJ-ABC	Cementoenamel junction and alveolar bone crest
BMD	Bone mineral density
Tb.Th	Trabecular thicknesss
Tb.Sp	Trabecular separation
Tb.N	Trabecular number
CI	Confidence interval
SMD	Standard mean difference
HIF-1α	Hypoxia-inducible factor
TNF-α	Tumor necrosis factor-alpha
IL-1β	Interleukin-1β
TGF-β1	Transforming growth factor-β1
LIPUS	Low-intensity pulsed ultrasound
HA	Hydroxyapatite
β-TCP	β-tricalcium phosphate
CS	Chitosan
SF	Silk fibroin
ALG	Sodium alginate
PEG	Polyethylene glycol

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13018-024-05403-6.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
Conception: L.Z., X.G.; Collected and Analyzed the data: L.Z.,W.C.,Y.Z.; Drafting of the article: L.P, W.C., Y.Z.; Revision of the article: P.H., J.S., W.Z.; Obtaining of funding: X.G.,W.Z.; Final approval of the article: L.Z., X.G.,W.C.,W.Z.,Y.Z.,P.H., J.S.

Funding
The study was supported by Dazhou Municipal Science and Technology Bureau's External Cooperation Projects (22DWHZ0010), the Chongqing Young and Middle-aged Medical High-end Talent Studio (C202308240104), the Chongqing Natural Science Foundation Innovation and Development Joint Fund (CSTB2023NSCQ-LZX0004), the Natural Science Foundation of Chongqing (CSTB2024NSCQ-MSX0434), the Program for Youth Innovation in Future Medicine of Chongqing Medical University (W0055) and Chongqing Outstanding Young Medical Talent (Wenjie Zhong).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]College of Stomatology, Chongqing Medical University, Chongqing 401147 , China
[2]Chongqing Key Laboratory of Oral Diseases , Chongqing 401147, China
[3]Chongqing Municipal Key Laboratory of Oral Biomedical Engineering of Higher Education, Chongqing 401147 , China
[4]Department of Stomatology, Dazhou Central Hospital, Dazhou 635000, China

Received: 5 November 2024 / Accepted: 21 December 2024
Published online: 09 January 2025

References

1. Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol. 2021 2021;21(7):426 – 40. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33510490&query_hl=1 https://doi.org/10.1038/s41577-020-00488-6
2. Meyle J, Chapple I. Molecular aspects of the pathogenesis of periodontitis., Periodontol. 2000. 2015 2015;69(1):7–17. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=26252398&query_hl=1 https://doi.org/10.1111/prd.12104
3. Savage A, Eaton KA, Moles DR, Needleman I. A systematic review of definitions of periodontitis and methods that have been used to identify this disease. J Clin Periodontol. 2009 2009;36(6):458 – 67. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=19508246&query_hl=1 https://doi.org/10.1111/j.1600-051X.2009.01408.x
4. Papageorgiou SN, Hagner M, Nogueira AV, Franke A, Jäger A, Deschner J. Inflammatory bowel disease and oral health: systematic review and a meta-analysis. J Clin Periodontol. 2017 2017;44(4):382 – 93. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=28117909&query_hl=1 https://doi.org/10.1111/jcpe.12698
5. Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J. Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: a call for global action. J Clin Periodontol. 2017. 2017;44(5):456 – 62. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=28419559&query_hl=1 https://doi.org/10.1111/jcpe.12732
6. Graziani F, Karapetsa D, Alonso B, Herrera D, Nonsurgical. and surgical treatment of periodontitis: how many options for one disease? Periodontol 2000. 2017 2017;75(1):152 – 88. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=28758300&query_hl=1 https://doi.org/10.1111/prd.12201
7. Matthews DC, Tabesh M. Detection of localized tooth-related factors that predispose to periodontal infections., Periodontol. 2000. 2004 2004/1/1;34:136 – 50. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14717860&query_hl=1 https://doi.org/10.1046/j.0906-6713.2003.003429.x
8. Chambrone L, Vargas M, Arboleda S, Serna M, Guerrero M, de Sousa J et al. Efficacy of local and systemic antimicrobials in the non-surgical treatment of smokers with chronic periodontitis: a systematic review. J Periodontol. 2016. 2016;87(11):1320-32. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=27498712&query_hl=1 https://doi.org/10.1902/jop.2016.160268
9. Cortellini P, Prato GP, Tonetti MS. The simplified papilla preservation flap. A novel surgical approach for the management of soft tissues in regenerative procedures. Int J Periodontics Restorative Dent. 1999 1999;19(6):589 – 99. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10815597&query_hl=1
10. Krishna R, De Stefano JA. Ultrasonic vs. Hand instrumentation in periodontal therapy: clinical outcomes. Periodontol. 2000. 2016 2016;71(1):113 – 27. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=27045433&query_hl=1 https://doi.org/10.1111/prd.12119
11. Lin NH, Gronthos S, Bartold PM. Stem cells and future periodontal regeneration., Periodontol. 2000. 2009 2009/1/1;51:239 – 51. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Ab

stract&list_uids=19878478&query_hl=1 https://doi.org/10.1111/j.1600-0757.2009.00303.x
12. Brown C, McKee C, Bakshi S, Walker K, Hakman E, Halassy S et al. Mesenchymal stem cells: cell therapy and regeneration potential. J Tissue Eng Regen Med. 2019 2019;13(9):1738-55. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=31216380&query_hl=1 https://doi.org/10.1002/term.2914
13. Plock JA, Schnider JT, Solari MG, Zheng XX, Gorantla VS. Perspectives on the use of mesenchymal stem cells in vascularized composite allotransplantation. Front Immunol. 2013 2013/1/1;4:175. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=23888159&query_hl=1 https://doi.org/10.3389/fimmu.2013.00175
14. Yoshida T, Washio K, Iwata T, Okano T, Ishikawa I. Current status and future development of cell transplantation therapy for periodontal tissue regeneration. Int J Dent. 2012 2012/1/1;2012:307024. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=22315604&query_hl=1 https://doi.org/10.1155/2012/307024
15. Chen FM, Sun HH, Lu H, Yu Q. Stem cell-delivery therapeutics for periodontal tissue regeneration. Biomaterials. 2012 2012;33(27):6320-44. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=22695066&query_hl=1 https://doi.org/10.1016/j.biomaterials.2012.05.048
16. Ding G, Liu Y, Wang W, Wei F, Liu D, Fan Z et al. Allogeneic periodontal ligament stem cell therapy for periodontitis in swine. Stem Cells. 2010 2010;28(10):1829-38. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=20979138&query_hl=1 https://doi.org/10.1002/stem.512
17. Liu J, Ruan J, Weir MD, Ren K, Schneider A, Wang P et al. Periodontal bone-ligament-cementum regeneration via scaffolds and stem cells. Cells. 2019 2019;8(6). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=31167434&query_hl=1 https://doi.org/10.3390/cells8060537
18. Wei X, Guo S, Liu Q, Liu L, Huo F, Wu Y et al. Dental follicle stem cells promote periodontal regeneration through periostin-mediated macrophage infiltration and reprogramming in an inflammatory microenvironment. Int J Mol Sci. 2023. 2023;24(7). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=37047322&query_hl=1 https://doi.org/10.3390/ijms24076353
19. Yang S, Gao J, Chen M, Sun Y, Qiao X, Mao H et al. Let-7a promotes periodontal bone regeneration of bone marrow mesenchymal stem cell aggregates via the fas/fasl-autophagy pathway. J Cell Mol Med. 2023 2023;27(24):4056-68. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=37855249&query_hl=1 https://doi.org/10.1111/jcmm.17988
20. Iwasaki K, Peng Y, Kanda R, Umeda M, Ishikawa I. Stem cell transplantation and cell-free treatment for periodontal regeneration. Int J Mol Sci. 2022 2022;23(3). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=35162935&query_hl=1 https://doi.org/10.3390/ijms23031011
21. Lin H, Chen H, Zhao X, Chen Z, Zhang P, Tian Y et al. Advances in mesenchymal stem cell conditioned medium-mediated periodontal tissue regeneration. J Transl Med. 2021 2021;19(1):456. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=34736500&query_hl=1 https://doi.org/10.1186/s12967-021-03125-5
22. Cheng L, Hill AF. Therapeutically harnessing extracellular vesicles. Nat Rev Drug Discov. 2022 2022;21(5):379 – 99. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=35236964&query_hl=1 https://doi.org/10.1038/s41573-022-00410-w
23. Doyle LM, Wang MZ. Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation and analysis. Cells. 2019 2019;8(7). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=31311206&query_hl=1 https://doi.org/10.3390/cells8070727
24. Zhang X, Zhang H, Gu J, Zhang J, Shi H, Qian H et al. Engineered extracellular vesicles for cancer therapy. Adv Mater. 2021. 2021;33(14):e2005709. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33644908&query_hl=1 https://doi.org/10.1002/adma.202005709
25. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020 2020;367(6478). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=32029601&query_hl=1 https://doi.org/10.1126/science.aau6977
26. Gupta A, Cady C, Fauser AM, Rodriguez HC, Mistovich RJ, Potty A et al. Cell-free stem cell-derived extract formulation for regenerative medicine applications. Int J Mol Sci. 2020. 2020;21(24). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33316880&query_hl=1 https://doi.org/10.3390/ijms21249364
27. Gupta A, Shivaji K, Kadam S, Gupta M, Rodriguez HC, Potty AG et al. Immunomodulatory extracellular vesicles: an alternative to cell therapy for covid-19. Expert Opin Biol Ther. 2021 2021;21(12):1551-60. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33886388&query_hl=1 https://doi.org/10.1080/14712598.2021.1921141
28. Hua S, Bartold PM, Gulati K, Moran CS, Ivanovski S, Han P. Periodontal and dental pulp cell-derived small extracellular vesicles: a review of the current status. Nanomaterials (Basel). 2021 2021;11(7). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=34361246&query_hl=1 https://doi.org/10.3390/nano11071858
29. Riazifar M, Pone EJ, Lötvall J, Zhao W. Stem cell extracellular vesicles: extended messages of regeneration. Annu Rev Pharmacol Toxicol. 2017 2017;57:125 – 54. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=27814025&query_hl=1 https://doi.org/10.1146/annurev-pharmtox-061616-030146
30. Wiklander O, Brennan MÁ, Lötvall J, Breakefield XO, El AS. Advances in therapeutic applications of extracellular vesicles. Sci Transl Med. 2019 2019;11(492). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=31092696&query_hl=1 https://doi.org/10.1126/scitranslmed.aav8521
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The prisma 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021 2021;372:n71. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33782057&query_hl=1 https://doi.org/10.1136/bmj.n71
32. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. Syrcle's risk of bias tool for animal studies. Bmc Med Res Methodol. 2014 2014;14:43. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=24667063&query_hl=1 https://doi.org/10.1186/1471-2288-14-43
33. Naaktgeboren CA, van Enst WA, Ochodo EA, de Groot JA, Hooft L, Leeflang MM et al. Systematic overview finds variation in approaches to investigating and reporting on sources of heterogeneity in systematic reviews of diagnostic studies. J Clin Epidemiol. 2014. 2014;67(11):1200-09. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=25063558&query_hl=1 https://doi.org/10.1016/j.jclinepi.2014.05.018
34. Kazama JJ, Koda R, Yamamoto S, Narita I, Gejyo F, Tokumoto A. Cancellous bone volume is an indicator for trabecular bone connectivity in dialysis patients. Clin J Am Soc Nephrol. 2010 2010;5(2):292 – 98. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=20093344&query_hl=1 https://doi.org/10.2215/CJN.04150609
35. Zhao J, Faure L, Adameyko I, Sharpe PT. Stem cell contributions to cementoblast differentiation in healthy periodontal ligament and periodontitis. Stem Cells. 2021. 2021;39(1):92–102. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33038290&query_hl=1 https://doi.org/10.1002/stem.3288
36. Hu L, Liu Y, Wang S. Stem cell-based tooth and periodontal regeneration. Oral Dis. 2018 2018;24(5):696–705. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=28636235&query_hl=1 https://doi.org/10.1111/odi.12703
37. Liao J, Al SM, Al-Habib M, Tanaka T, Huang GT. Cells isolated from inflamed periapical tissue express mesenchymal stem cell markers and are highly osteogenic. J Endod. 2011 2011;37(9):1217-24. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=21846537&query_hl=1 https://doi.org/10.1016/j.joen.2011.05.022
38. Sonoyama W, Liu Y, Yamaza T, Tuan RS, Wang S, Shi S et al. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: a pilot study. J Endod. 2008 2008;34(2):166 – 71. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18215674&query_hl=1 https://doi.org/10.1016/j.joen.2007.11.021
39. Dan H, Vaquette C, Fisher AG, Hamlet SM, Xiao Y, Hutmacher DW et al. The influence of cellular source on periodontal regeneration using calcium phosphate coated polycaprolactone scaffold supported cell sheets. Biomaterials.

2014. 2014;35(1):113 – 22. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=24120045&query_hl=1 https://doi.org/10.1016/j.biomaterials.2013.09.074
40. Iwata T, Yamato M, Tsuchioka H, Takagi R, Mukobata S, Washio K et al. Periodontal regeneration with multi-layered periodontal ligament-derived cell sheets in a canine model. Biomaterials. 2009 2009;30(14):2716-23. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=19201461&query_hl=1 https://doi.org/10.1016/j.biomaterials.2009.01.032
41. Liu Y, Zheng Y, Ding G, Fang D, Zhang C, Bartold PM et al. Periodontal ligament stem cell-mediated treatment for periodontitis in miniature swine. Stem Cells. 2008. 2008;26(4):1065-73. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18238856&query_hl=1 https://doi.org/10.1634/stemcells.2007-0734
42. Tsumanuma Y, Iwata T, Washio K, Yoshida T, Yamada A, Takagi R et al. Comparison of different tissue-derived stem cell sheets for periodontal regeneration in a canine 1-wall defect model. Biomaterials. 2011. 2011;32(25):5819-25. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=21605900&query_hl=1 https://doi.org/10.1016/j.biomaterials.2011.04.071
43. Zhou T, Pan J, Wu P, Huang R, Du W, Zhou Y et al. Dental follicle cells: roles in development and beyond. Stem Cells Int. 2019 2019/1/1;2019:9159605. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=31636679&query_hl=1 https://doi.org/10.1155/2019/9159605
44. Veronesi F, Giavaresi G, Tschon M, Borsari V, Nicoli AN, Fini M. Clinical use of bone marrow, bone marrow concentrate, and expanded bone marrow mesenchymal stem cells in cartilage disease. Stem Cells Dev. 2013 2013;22(2):181 – 92. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=23030230&query_hl=1 https://doi.org/10.1089/scd.2012.0373
45. Fu J, Wang Y, Jiang Y, Du J, Xu J, Liu Y. Systemic therapy of mscs in bone regeneration: a systematic review and meta-analysis. Stem Cell Res Ther. 2021 2021;12(1):377. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=34215342&query_hl=1 https://doi.org/10.1186/s13287-021-02456-w
46. Li Q, Yang G, Li J, Ding M, Zhou N, Dong H et al. Stem cell therapies for periodontal tissue regeneration: a network meta-analysis of preclinical studies. Stem Cell Res Ther. 2020 2020;11(1):427. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33008471&query_hl=1 https://doi.org/10.1186/s13287-020-01938-7
47. Kirkham AM, Bailey A, Tieu A, Maganti HB, Montroy J, Shorr R et al. Msc-derived extracellular vesicles in preclinical animal models of bone injury: a systematic review and meta-analysis. Stem Cell Rev Rep. 2022. 2022;18(3):1054-66. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=34313927&query_hl=1 https://doi.org/10.1007/s12015-021-10208-9
48. Lai CP, Mardini O, Ericsson M, Prabhakar S, Maguire C, Chen JW et al. Dynamic biodistribution of extracellular vesicles in vivo using a multimodal imaging reporter. Acs Nano. 2014 2014;8(1):483 – 94. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=24383518&query_hl=1 https://doi.org/10.1021/nn404945r
49. Chen S, Sun F, Qian H, Xu W, Jiang J. Preconditioning and engineering strategies for improving the efficacy of mesenchymal stem cell-derived exosomes in cell-free therapy. Stem Cells Int. 2022 2022/1/1;2022:1779346. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=35607400&query_hl=1 https://doi.org/10.1155/2022/1779346
50. Deng DK, Zhang JJ, Gan D, Zou JK, Wu RX, Tian Y et al. Roles of extracellular vesicles in periodontal homeostasis and their therapeutic potential. J Nanobiotechnology. 2022 2022;20(1):545. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=36585740&query_hl=1 https://doi.org/10.1186/s12951-022-01757-3
51. Li X, Zhong Y, Zhou W, Song Y, Li W, Jin Q et al. Low-intensity pulsed ultrasound (lipus) enhances the anti-inflammatory effects of bone marrow mesenchymal stem cells (bmscs)-derived extracellular vesicles. Cell Mol Biol Lett. 2023 2023;28(1):9. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=36717768&query_hl=1 https://doi.org/10.1186/s11658-023-00422-3
52. Xu R, Zhang F, Chai R, Zhou W, Hu M, Liu B et al. Exosomes derived from pro-inflammatory bone marrow-derived mesenchymal stem cells reduce inflammation and myocardial injury via mediating macrophage polarization. J Cell Mol Med. 2019 2019;23(11):7617-31. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=31557396&query_hl=1 https://doi.org/10.1111/jcmm.14635
53. Yu W, Su X, Li M, Wan W, Li A, Zhou H et al. Three-dimensional mechanical microenvironment enhanced osteogenic activity of mesenchymal stem cells-derived exosomes. Chem Eng J. 2021 2021/1/1;417:128040. Available from: https://www.sciencedirect.com/science/article/pii/S1385894720341577 https://doi.org/10.1016/j.cej.2020.128040
54. Gao W, Liang T, He R, Ren J, Yao H, Wang K et al. Exosomes from 3d culture of marrow stem cells enhances endothelial cell proliferation, migration, and angiogenesis via activation of the hmgb1/akt pathway. Stem Cell Res. 2020. 2020;50:102122. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33316600&query_hl=1 https://doi.org/10.1016/j.scr.2020.102122
55. Semenza GL. Targeting hypoxia-inducible factor 1 to stimulate tissue vascularization. J Investig Med. 2016 2016;64(2):361 – 63. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=25955799&query_hl=1 https://doi.org/10.1097/JIM.0000000000000206
56. Luo H, Chen D, Li R, Li R, Teng Y, Cao Y et al. Genetically engineered cxcr4-modified exosomes for delivery of mir-126 mimics to macrophages alleviate periodontitis. J Nanobiotechnology. 2023 2023;21(1):116. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=36991451&query_hl=1 https://doi.org/10.1186/s12951-023-01863-w
57. Zhang S, Jiang L, Hu H, Wang H, Wang X, Jiang J et al. Pretreatment of exosomes derived from hucmscs with tnf-α ameliorates acute liver failure by inhibiting the activation of nlrp3 in macrophage. Life Sci. 2020 2020;246:117401. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=32035931&query_hl=1 https://doi.org/10.1016/j.lfs.2020.117401
58. Liang YC, Wu YP, Li XD, Chen SH, Ye XJ, Xue XY et al. Tnf-α-induced exosomal mir-146a mediates mesenchymal stem cell-dependent suppression of urethral stricture. J Cell Physiol. 2019 2019;234(12):23243-55. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=31144307&query_hl=1 https://doi.org/10.1002/jcp.28891
59. Kim M, Shin DI, Choi BH, Min BH. Exosomes from il-1β-primed mesenchymal stem cells inhibited il-1β- and tnf-α-mediated inflammatory responses in osteoarthritic sw982 cells. Tissue Eng Regen Med. 2021 2021;18(4):525 – 36. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33495946&query_hl=1 https://doi.org/10.1007/s13770-020-00324-x
60. Wang R, Xu B. Tgf-β1-modified msc-derived exosomal mir-135b attenuates cartilage injury via promoting m2 synovial macrophage polarization by targeting mapk6. Cell Tissue Res. 2021. 2021;384(1):113 – 27. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33404840&query_hl=1 https://doi.org/10.1007/s00441-020-03319-1
61. Huang Y, Liu Q, Liu L, Huo F, Guo S, Tian W. Lipopolysaccharide-preconditioned dental follicle stem cells derived small extracellular vesicles treating periodontitis via reactive oxygen species/mitogen-activated protein kinase signaling-mediated antioxidant effect. Int J Nanomedicine. 2022 2022/1/1;17:799–819. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=35228798&query_hl=1 https://doi.org/10.2147/IJN.S350869
62. Zhang T, Chen Z, Zhu M, Jing X, Xu X, Yuan X et al. Extracellular vesicles derived from human dental mesenchymal stem cells stimulated with low-intensity pulsed ultrasound alleviate inflammation-induced bone loss in a mouse model of periodontitis. Genes Dis. 2023. 2023;10(4):1613-25. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=37397561&query_hl=1 https://doi.org/10.1016/j.gendis.2022.06.009
63. Xu M, Yang Q, Sun X, Wang Y. Recent advancements in the loading and modification of therapeutic exosomes. Front Bioeng Biotechnol. 2020 2020/1/1;8:586130. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=33262977&query_hl=1 https://doi.org/10.3389/fbioe.2020.586130
64. Nagelkerke A, Ojansivu M, van der Koog L, Whittaker TE, Cunnane EM, Silva AM et al. Extracellular vesicles for tissue repair and regeneration: evidence, challenges and opportunities. Adv Drug Deliv Rev. 2021 2021/1/1;175:113775.

65. Brennan MÁ, Layrolle P, Mooney DJ. Biomaterials functionalized with msc secreted extracellular vesicles and soluble factors for tissue regeneration. Adv Funct Mater. 2020. 2020;30(37). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=32952493&query_hl=1 https://doi.org/10.1002/adfm.201909125
66. Yan HC, Yu TT, Li J, Qiao YQ, Wang LC, Zhang T et al. The delivery of extracellular vesicles loaded in biomaterial scaffolds for bone regeneration. Front Bioeng Biotechnol. 2020 2020/1/1;8:1015. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=32974327&query_hl=1 https://doi.org/10.3389/fbioe.2020.01015
67. Zhu L, Luo D, Liu Y. Effect of the nano/microscale structure of biomaterial scaffolds on bone regeneration. Int J Oral Sci. 2020 2020;12(1):6. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=32024822&query_hl=1 https://doi.org/10.1038/s41368-020-0073-y
68. Lei F, Li M, Lin T, Zhou H, Wang F, Su X. Treatment of inflammatory bone loss in periodontitis by stem cell-derived exosomes. Acta Biomater. 2022 2022;141:333–43. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=34979326&query_hl=1 https://doi.org/10.1016/j.actbio.2021.12.035
69. Wang X, Chen J, Tian W. Strategies of cell and cell-free therapies for periodontal regeneration: the state of the art. Stem Cell Res Ther. 2022 2022;13(1):536. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=36575471&query_hl=1 https://doi.org/10.1186/s13287-022-03225-z
70. Pishavar E, Luo H, Naserifar M, Hashemi M, Toosi S, Atala A et al. Advanced hydrogels as exosome delivery systems for osteogenic differentiation of mscs: application in bone regeneration. Int J Mol Sci. 2021. 2021;22(12). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=34201385&query_hl=1 https://doi.org/10.3390/ijms22126203
71. Bose S, Sarkar N. Natural medicinal compounds in bone tissue engineering. Trends Biotechnol. 2020;2020(1/1):404–17.
72. Sheikh Z, Qureshi J, Alshahrani AM, Nassar H, Ikeda Y, Glogauer M et al. Collagen based barrier membranes for periodontal guided bone regeneration applications. Odontology. 2017. 2017;105(1):1–12. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=27613193&query_hl=1 https://doi.org/10.1007/s10266-016-0267-0
73. He L, Zhou Q, Zhang H, Zhao N, Liao L. Pf127 hydrogel-based delivery of exosomal ctnnb1 from mesenchymal stem cells induces osteogenic differentiation during the repair of alveolar bone defects. Nanomaterials (Basel). 2023 2023;13(6). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=36985977&query_hl=1 https://doi.org/10.3390/nano13061083
74. Sun X, Mao Y, Liu B, Gu K, Liu H, Du W et al. Mesenchymal stem cell-derived exosomes enhance 3d-printed scaffold functions and promote alveolar bone defect repair by enhancing angiogenesis. J Pers Med. 2023 2023;13(2). Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=36836414&query_hl=1 https://doi.org/10.3390/jpm13020180

Publisher's note