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Extracellular Vesicles and Circulating Nucleic Acids

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The research landscape of extracellular vesicles in periodontitis: a bibliometric analysis from 2015 to 2025

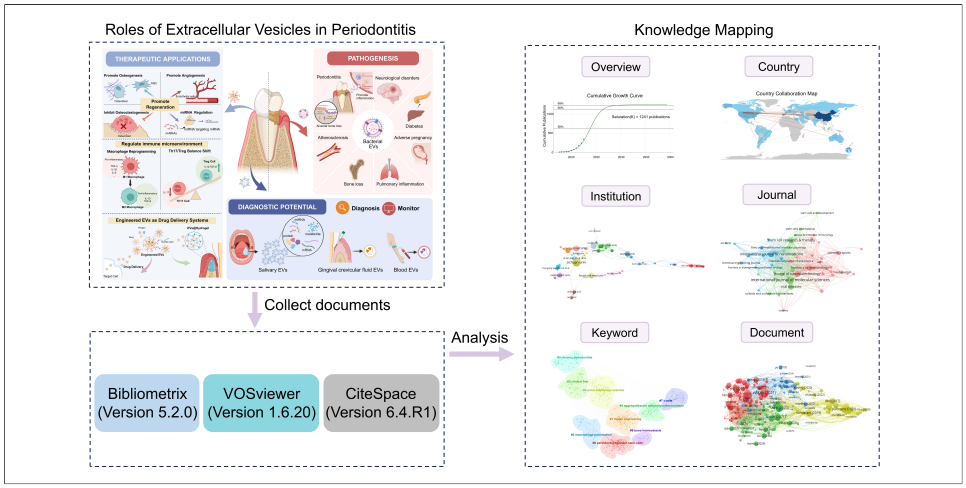
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Extracellular vesicles, periodontitis, bibliometrics, therapeutics, pathogenesis, biomarkers

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Abstract

Aim: Periodontitis is a chronic inflammatory disease that can result in tooth loss in severe cases. Extracellular vesicles (EVs) play multifaceted roles in periodontitis. This study aimed to characterize the research landscape of EVs in periodontitis using a bibliometric approach and to systematically elucidate their functions in this field.

Methods: A comprehensive collection of articles and reviews pertaining to the role of EVs in periodontitis was retrieved from the Web of Science Core Collection, Scopus, and PubMed, spanning 2015 to 2025. Following deduplication and manual screening, bibliometric and visual analyses of publication trends, countries, institutions, journals, keywords, publications, and cited references were conducted using CiteSpace, VOSviewer, and Bibliometrix.

Results: A total of 340 eligible publications from 154 journals and involving 31 countries

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and 427 institutions were included. From 2015 to 2025, the annual publication volume exhibited a marked upward trend, with a logistic growth model predicting a peak in 2027. Co-occurrence networks and citation analyses identified three major research themes: regenerative therapy, pathogenesis, and biomarkers. Furthermore, keyword trend analysis revealed that "immunomodulation" and "drug delivery" are current research hotspots and likely future directions in the field.

Conclusion: This study provides a comprehensive knowledge map of EVs research in periodontitis. The findings indicate that the field is evolving from fundamental mechanistic exploration toward the development of engineered EVs as drug-delivery platforms. By clarifying the diverse roles of EVs in periodontitis, this work offers a conceptual foundation for the development of novel EV-based therapeutic and diagnostic strategies.

INTRODUCTION

Periodontitis, a chronic infectious disease primarily driven by dental plaque biofilms, is hallmarked by the progressive degradation of periodontal supporting structures (gingiva, periodontal ligament, cementum, and alveolar bone). Clinically, it presents with gingival hemorrhage, periodontal pocket formation, and alveolar bone destruction, eventually culminating in tooth hypermobility and exfoliation[1]. A leading cause of tooth loss, periodontitis occurs in 62% of adults, with severe forms accounting for 23.6% of cases[2]. Despite its high prevalence, conventional interventions are predominantly centered on inflammation management, yielding only limited success in periodontal tissue regeneration[3]. Consequently, developing innovative therapies to achieve functional regeneration remains a formidable clinical challenge. Notably, the implications of periodontitis extend far beyond oral health, due to its significant connections to systemic comorbidities, including Alzheimer's disease[4], diabetes mellitus[5], cardiovascular diseases[6], and adverse pregnancy outcomes[7]. Current research seeks to clarify the mechanisms linking periodontitis to the pathogenesis of these systemic disorders.

Extracellular vesicles (EVs) are a population of lipid bilayer vesicles released by virtually all cellular organisms, both eukaryotes and prokaryotes. EVs transfer a wide range of bioactive cargoes, including proteins, lipids, and nucleic acids, to target cells, thus functioning as pivotal mediators of intercellular communication. Through this mechanism, they modulate critical biological processes, such as cellular development, immune responses, and disease progression[8-10]. Accumulating evidence indicates that EVs play multifaceted roles in periodontitis. Specifically, mesenchymal stem cell (MSC)-derived EVs are instrumental in promoting periodontal tissue regeneration[11], whereas immune cell-derived EVs show significant therapeutic potential in modulating the immune microenvironment for inflammatory diseases[12]. Conversely, EVs secreted by periodontal pathogens are recognized as important mediators of alveolar bone destruction and inflammatory progression[13]. Furthermore, these pathogen-derived EVs may contribute to the mechanistic links between periodontitis and systemic comorbidities[14]. Meanwhile, salivary EVs are emerging as highly promising non-invasive diagnostic biomarkers[15]. Research on the roles of EVs in periodontitis has expanded considerably in recent years. A comprehensive overview is needed to consolidate the existing knowledge base, examine the precise roles of EVs in periodontology, and highlight current research directions and translational opportunities.

Bibliometrics applies mathematical and statistical techniques to quantitatively analyze scholarly publications and bibliographic data[16,17]. Bibliometric analysis provides an objective and comprehensive perspective for tracing the evolution of research topics. Systematic analyses of publication output, countries, authors, and institutions can reveal developmental trends, leading research groups, and collaborative networks within a given field. In addition, citation and co-citation analyses, keyword co-occurrence, and clustering analyses can be used to identify seminal publications, intellectual foundations, thematic clusters, and emerging research

frontiers. These approaches offer scholars a comprehensive overview of a research field, facilitate the identification of knowledge gaps, inspire novel research ideas, and help researchers position their potential contributions to the field[18,19]. To date, bibliometric methods have been applied to studies of EVs in cancer[20], cardiovascular diseases[21], osteoarthritis[22], and tissue engineering[23]. However, the research landscape of EVs in periodontitis has not yet been systematically mapped and evaluated from a bibliometric perspective.

Existing reviews have provided valuable syntheses of the biological roles, therapeutic potential, and challenges associated with the clinical translation of EVs in periodontitis[24-27]. These studies have established an important foundation for understanding the diverse functions of EVs in periodontitis. While previous reviews have primarily synthesized the available evidence narratively, the present study uses bibliometric analysis to characterize the research landscape, knowledge structure, and emerging themes in the field of EVs in periodontitis, thereby providing a complementary perspective to conventional literature reviews.

To complement this overview of the literature, the present study analyzes publication trends, leading countries and institutions, core journals, keywords, influential publications, and cited references in the field of EVs and periodontitis. Building on these bibliometric findings, we further discuss current research progress and future directions concerning the therapeutic applications of EVs, their pathogenic roles, and their potential utility as diagnostic biomarkers for periodontitis. Ultimately, this study aims to advance understanding of the diverse roles of EVs in periodontitis and to provide insights that may facilitate the development and clinical translation of function-specific EVs.

Previous studies have shown considerable inconsistency in EV terminology. Although the term "exosome" remains widely used, Minimal Information for Studies of Extracellular Vesicles (MISEV) 2023 guidelines caution that most isolation methods cannot verify an endosomal origin[28]. Therefore, this review follows the MISEV 2023 guidelines and uses "EVs" as an umbrella term unless the available evidence supports assignment to a specific EV subtype. Specific terminology is retained for clearly distinct subtypes, such as apoptotic bodies and outer membrane vesicles (OMVs).

METHODS

Data sources and search strategy

Search terms were expanded using the Medical Subject Headings (MeSH) vocabulary in PubMed according to the study topic, yielding the following search strategy: ("Periodontitis" OR "Periodontal Diseases") AND ("Extracellular Vesicle*" OR "Exovesicle*" OR "Exosome*" OR "Apoptotic Bod*" OR "Microvesicle*"). The publication period ranged from 2015 to 2025, document types were restricted to articles and reviews, and the language was limited to English. To ensure comprehensive literature coverage, parallel searches were conducted across three major databases: Web of Science Core Collection (WOSCC) using the Topic field tag (n = 308), Scopus employing the TITLE-ABS-KEY field (n = 414), and PubMed with restrictions to Title/Abstract (n = 281). All searches were executed on January 18, 2026, to minimize temporal bias. The detailed search strategies are listed in Supplementary Table 1.

Records retrieved from the three databases were harmonized and merged by converting them to the WOSCC format using RStudio and the Bibliometrix package. Duplicate records were removed based on digital object identifier (DOI) matching. For records lacking a DOI, manual deduplication was performed using available bibliographic information. Because WOSCC records generally provided more complete metadata, they were prioritized for retention when duplicate entries were identified. Following data cleaning and deduplication, the final dataset comprised 489 unique publications.

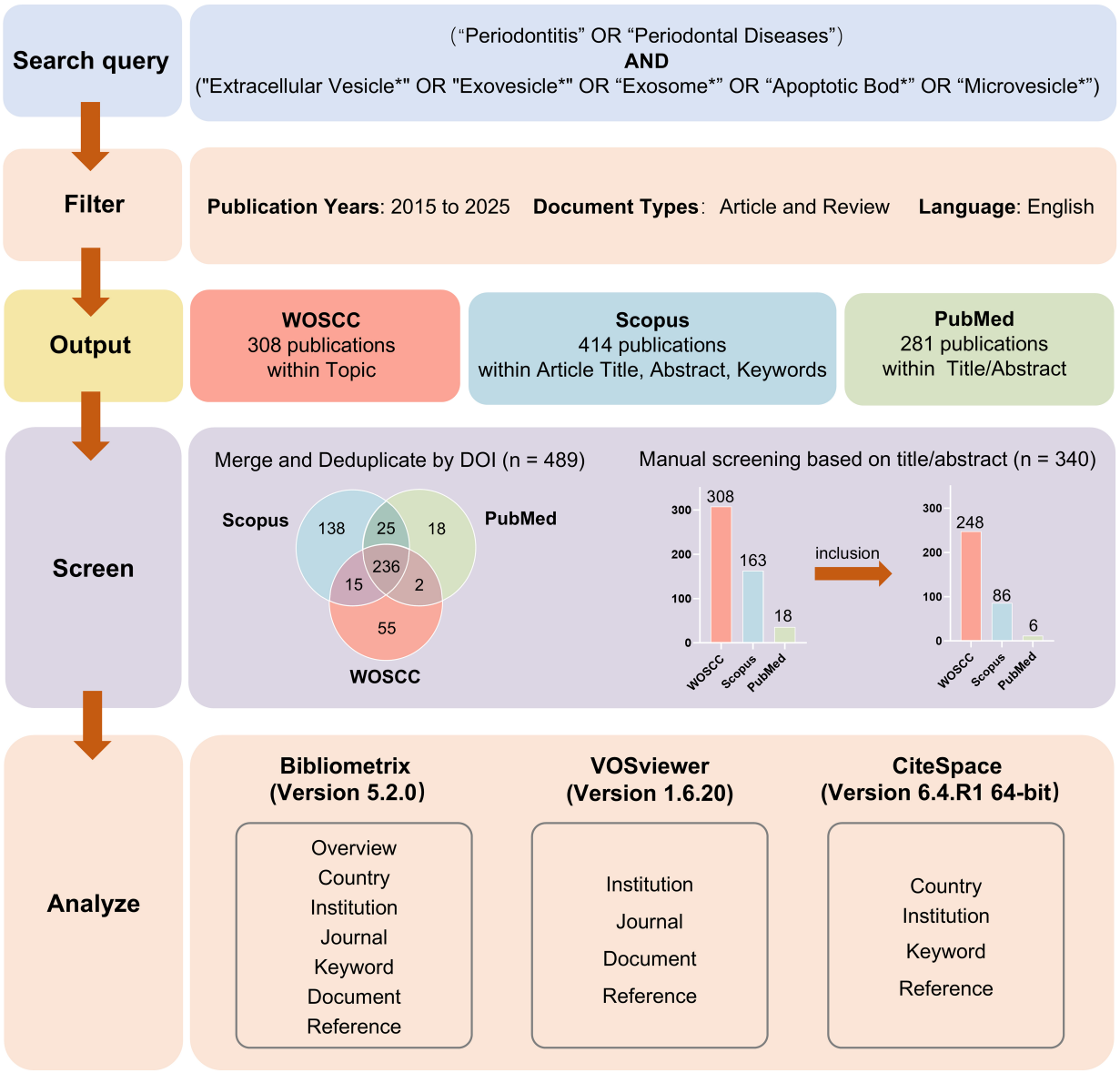


Figure 1. Flowchart of data collection and analysis. A total of 1,003 English articles and reviews published between 2015 and 2025 were retrieved from the WOSCC, Scopus, and PubMed databases according to the search strategy. After merging and deduplicating based on DOI, the collection was reduced to 489 publications. Manual screening of titles and abstracts excluded irrelevant studies, yielding 340 publications for final inclusion. Bibliometric analysis across seven domains was performed using Bibliometrix, CiteSpace, and VOSviewer. DOI: Digital object identifier; WOSCC: Web of Science Core Collection.

Manual screening was carried out to ensure the accuracy of the dataset. Two researchers independently reviewed the titles and abstracts of all retrieved records to assess their eligibility for inclusion. Publications addressing EVs and periodontitis/periodontal disease were included. Records were excluded when the title or abstract clearly indicated that they were unrelated to EVs or periodontitis/periodontal disease. For records whose relevance could not be determined from the title and abstract alone, the full text was retrieved and searched for EV-related and periodontitis-related terms. Records containing terms from both categories were included. Any discrepancies between reviewers were resolved through consultation with a third reviewer. Ultimately, 340 publications were included in the bibliometric analysis [Figure 1].

Data analysis and visualization

To facilitate the analysis using bibliometric software, the formats of the 340 publications were standardized. CiteSpace software was used to convert records from Scopus and PubMed into the WOSCC plain text format. Missing critical metadata fields were manually curated to ensure completeness. Bibliometrix subsequently validated key field quality, confirming all reached "good" or "excellent" ratings. Bibliometrix (v5.2.0), VOSviewer (v1.6.20), and CiteSpace (v6.4.R1) were employed for subsequent bibliometric analysis [Figure 1].

Bibliometrix (v5.2.0) was used to analyze the retrieved collection[29]. General bibliometric information was extracted, and a logistic growth model was used to fit the cumulative publication count over time: $P(t) = K/[1+exp(-b(t-t0))]$, where $P(t)$ represents the predicted cumulative number of publications at time t, and K, b, and $t0$ denote the estimated maximum cumulative number, growth-rate parameter, and inflection point, respectively. The inflection point corresponds to the time at which the rate of publication growth is maximal. Annual publication output was calculated from the first derivative of $P(t)$. Contributions by country were ranked according to corresponding author affiliation, and collaboration networks were visualized using a minimum edge threshold of 1. Institutional and journal rankings were based on publication counts, and the annual publication dynamics of the top 10 entities were plotted in *Microsoft Excel*. Multidimensional collaborations among leading institutions, countries, and authors were visualized using Sankey diagrams. Bradford's law was applied to identify core journals, and their h-indexes were analyzed. Trend topics were identified through term frequency analysis following data cleaning. Citation analysis was performed on documents and references from 2015 to 2025. To further identify emerging research hotspots, documents between 2023 and 2025 underwent additional citation analysis. Documents were ranked according to normalized total citations, and the top 10 were visualized using ggplot2 (v4.0.0).

VOSviewer (v1.6.20) was used for bibliometric analysis and visualization of the retrieved collection[30]. Node sizes were proportional to their assigned weights. An institutional co-authorship network was constructed, with node weights proportional to document counts. Institutions were filtered using a minimum threshold of one publication per institution. Two journal citation networks were generated, with node weights proportional to document counts and citation frequencies, respectively. Journals were filtered using minimum thresholds of two publications and five citations per journal. Document bibliographic coupling was subsequently analyzed. Node weights were scaled according to citation frequencies for the 2015-2025 corpus and normalized citation counts for the 2023-2025 corpus. Both corpora were subjected to a minimum citation threshold of five citations per document. A reference co-citation network was also constructed, with node weights proportional to citation frequencies. The minimum citation threshold was set at five citations per reference.

CiteSpace (v6.4.R1) was also used to analyze and visualize the retrieved collections[31]. The time span was set from 2015 to 2025, with a time slice of one year. Collaboration networks of countries and institutions were constructed separately, and the betweenness centrality of each network node was calculated. Betweenness centrality was defined by the number of shortest paths passing through a given node. Nodes with a betweenness centrality > 0.1 were considered central nodes. A keyword co-occurrence network was constructed, and node labels were displayed for keywords with a frequency greater than 20 after synonym merging. Node size was proportional to keyword frequency, while nodes surrounded by a purple outer ring represented central nodes. Keyword clustering analysis was performed, and a timeline visualization was generated. Clustering performance was evaluated using the modularity Q value and the mean silhouette score (S value). It is generally accepted that $Q > 0.3$ indicates significant community structure, whereas S reflects cluster homogeneity, with $S > 0.5$ indicating acceptable clustering quality and $S > 0.7$ indicating high reliability[32,33]. Furthermore, burst detection analysis was conducted to identify references exhibiting the strongest citation bursts.



Figure 2. Analysis of all publications. (A) Main information about the collection; (B) and (C) life cycle of scientific production using a logistic growth model. (B) Annual publications curve: blue dots, observed annual publications from the collection; red dashed vertical line, peak year (Tm); (C) cumulative growth curve: green dots, observed cumulative publications; horizontal dashed lines, saturation thresholds. All analyses were performed using Bibliometrix v5.2.0. K: Maximum saturation capacity; R2: coefficient of determination; Tm: peak year.

RESULTS

Overview

A total of 340 documents regarding EVs in periodontitis were retrieved between 2015 and 2025 [Figure 2A]. A logistic growth model implemented in Bibliometrix was used to characterize the research life cycle of the field. Such models provide insights into the developmental stage of a research topic, forecast upcoming trajectories, and project the timeline for the research domain to plateau. The model yielded a coefficient of determination (R^2) of 0.97, indicating an excellent agreement between the observed and fitted publication data [Figure 2B]. The estimated maximum saturation capacity (K) was 1,241 publications [Figure 2C]. The ratio of cumulative publications to the K value indicates the developmental stage of the field. As of the last observation year (2025), the cumulative number of publications had reached 340, accounting for 27.4% of K. This indicates that the field is in a rapid growth phase (defined as 10%-50% of saturation) and remains a highly active research direction. The inflection point, corresponding to the maximum publication growth rate (50% of K), is projected to occur in 2027, with an estimated 134 publications. Thereafter, the growth rate is predicted to decline as the research topic approaches maturation. The time interval between the emergence of the field (10% of K) and near-saturation (90% of K) is estimated to be 10.2 years.

Country

Geographical analysis identified 31 contributing countries based on corresponding author affiliations. The top 10 countries ranked by the number of publications (11 due to tied rankings) are shown in Supplementary Figure 1A and Table 1. China ranked first with 210 publications, accounting for 61.8% of the total collection. However, its average citation rate was relatively low at 24.8 citations per article. The USA ranked second with

Table 1. Top 10 most productive countries ranked by their number of publications (including 11 countries due to tied rankings)

Ranking	Country	Count	Percentage	Centrality	Total citations	Average article citations
1	China	210	61.8%	0.34	5,206	24.8
2	USA	22	6.5%	0.77	1,538	69.9
3	Korea	16	4.7%	0.00	808	50.5
4	Australia	13	3.8%	0.34	556	42.8
5	Iran	11	3.2%	0.14	127	11.5
6	Japan	10	2.9%	0.00	549	54.9
7	Chile	7	2.1%	0.06	107	15.3
8	Egypt	4	1.2%	0.00	186	46.5
9	Germany	4	1.2%	0.16	24	6
10	India	4	1.2%	0.05	15	3.8
11	Malaysia	4	1.2%	0.00	75	18.8

22 publications (6.5%) but achieved the highest average citation rate, with 69.9 citations per article. These findings indicate that while China is the most productive country in this field, its modest average citation rate suggests a need to increase its research impact. Alternatively, the low average citation rate may partly result from the recent increase in publication output, as newer articles have had less time to accumulate citations. The collaboration map [Supplementary Figure 1B] illustrates a centralized international network dominated by several core countries. High-frequency collaboration pairs include China-USA, China-Japan, USA-Australia, and USA-Japan. CiteSpace analysis identified the USA (Centrality, C = 0.77), China (C = 0.34), Australia (C = 0.34), Germany (C = 0.16), and Iran (C = 0.14) as the five central nodes in the collaboration network [Table 1]. Notably, the USA exhibited the highest centrality, highlighting its prominent bridging and hub role within the international collaboration network, while China and Australia also demonstrated substantial network connectivity.

Institution

The institutional affiliation analysis identified core research forces and potential collaborative targets. A closely-knit collaboration network dominated by Chinese universities, with limited international interaction, was identified among 427 total contributing institutions [Supplementary Figure 2A]. Table 2 presents the top 10 institutions, nine of which are based in China. Sichuan University ranks first with 109 articles (32.1% of the total) and, with a centrality of 0.15, constitutes a critical hub in the institutional collaboration network. Air Force Medical University ranks second with 51 articles (15.0%), followed by Wuhan University (11.2%). Supplementary Figure 2B shows that most of the top 10 entities entered this field between 2019 and 2021 with a stable output. Sichuan University entered this research field in 2019 and subsequently showed a steady increase in publication output. Notably, Seoul National University, the only non-Chinese institution among the top 10 contributors, maintained publication activity from 2020 to 2023 but produced no publications during 2024 and 2025. Furthermore, Supplementary Figure 2C highlights the dominant position of China, with outgoing publication flows substantially exceeding those of other nations. Sichuan University ranks first in publication output among Chinese institutions. Scholars including Tian Weidong, Guo Shujuan, Liu Qian, and Huo Fangjun are highly productive researchers affiliated with Sichuan University.

Journal

Identifying the journals that most frequently publish research in this field assists scholars in selecting appropriate publication venues. The 340 publications were distributed across 154 journals [Figure 2A]. Table 3 presents the top-ranking journals (12 journals due to tied rankings). The *International Journal of Molecular Sciences* [impact factor (IF) = 4.9, h-index = 12] ranked first, with 23 publications. Other prominent journals

Table 2. Top 10 most productive institutions ranked by their number of publications

Ranking	Institution	Count	Percentage	Centrality	Country
1	Sichuan University	109	32.1%	0.15	China
2	Air Force Medical University	51	15.0%	0.01	China
3	Wuhan University	38	11.2%	0.01	China
4	Qingdao University	29	8.5%	0.02	China
5	Sun Yat-sen University	26	7.6%	0.06	China
6	Xi'an Jiao Tong University	26	7.6%	0.08	China
7	Shanghai Jiao Tong University	23	6.8%	0.01	China
8	Seoul National University	22	6.5%	0	Korea
9	Capital Medical University	21	6.2%	0.04	China
10	Jilin University	21	6.2%	0.01	China

Table 3. Top 10 most productive journals ranked by the number of publications (including 12 journals due to tied rankings)

Ranking	Journal	Count	H-index	Total citations	JCR	IF (2024)
1	*International Journal of Molecular Sciences*	23	12	571	Q1	4.9
2	*International Journal of Nanomedicine*	14	9	289	Q1	6.5
3	*Stem Cell Research & Therapy*	14	8	617	Q1	7.3
4	*Frontiers in Immunology*	13	8	630	Q1	5.9
5	*Journal of Nanobiotechnology*	13	8	323	Q1	12.6
6	*Oral Diseases*	12	6	150	Q1	2.9
7	*Journal of Periodontal Research*	8	7	154	Q1	3.4
8	*Journal of Clinical Periodontology*	6	3	126	Q1	6.8
9	*Scientific Reports*	6	4	92	Q1	3.9
10	*Advanced Science*	5	4	173	Q1	14.1
11	*BMC Oral Health*	5	3	33	Q1	3.1
12	*Frontiers in Cellular and Infection Microbiology*	5	3	262	Q2	4.8

IF: Impact factor; JCR: Journal Citation Reports.

in the molecular/nanomedicine area include the *International Journal of Nanomedicine* (14 publications) and the *Journal of Nanobiotechnology* (13 publications). Four stomatology journals were represented, notably the *Journal of Clinical Periodontology*, a widely recognized journal in periodontology. Immunology and stem cell biology are represented by *Stem Cell Research & Therapy* (14 publications) and *Frontiers in Immunology* (13 publications). This distribution across multiple disciplines indicates that EVs research in periodontitis closely integrates traditional dentistry with immunology, materials science, and nanomedicine. Remarkably, 11 of the top 12 journals are classified as Journal Citation Reports (JCR) Q1, including high-IF journals such as the *Journal of Nanobiotechnology* (IF = 12.6) and *Advanced Science* (IF = 14.1). These findings indicate that research on EVs in periodontitis is being disseminated through influential journals across several disciplines.

In citation networks, the *International Journal of Molecular Sciences* leads in number of publications [Supplementary Figure 3A], while *Frontiers in Immunology* leads in the total number of citations [Supplementary Figure 3B]. Regarding annual trends [Supplementary Figure 3C], the *International Journal of Molecular Sciences* has published steadily since 2016, whereas most other top journals began publishing around 2022.

Table 4. 154 journals were classified into 3 zones by Bradford's law

Zone	Count of Journal	Count of Publications	Percentage
1 (core)	10	114	33.53%
2	39	114	33.53%
3	105	112	32.94%
Total	154	340	100.0%

Bradford's law of scattering, one of the three major laws in bibliometrics, describes the distribution of publications across journals within a given research field. When journals are ranked in descending order based on the quantity of publications within a specific field, they can be categorized into three distinct areas: a core area, a related area, and an unrelated area, with each area containing equal numbers of articles[34,35]. The 154 journals found in this study were divided into three zones according to Bradford's law, resulting in the identification of 10 core journals [Supplementary Figure 3D and Table 4].

Keywords

The keyword co-occurrence network generated by CiteSpace comprised 305 nodes, displaying labels with frequency > 20 [Figure 3A]. "Extracellular vesicles", "mesenchymal stem cells", and "periodontitis" emerged as core keywords. Nodes with high betweenness centrality included "differentiation", "cells", "activation", and "expression", acting as pivotal structural bridges within the network. Spatially, the upper region links to pathogenic mechanisms ("outer membrane vesicles", "*Porphyromonas gingivalis*", and "inflammation"), whereas the lower region focuses on their regenerative and therapeutic roles ("regeneration", "angiogenesis", and "osteogenic differentiation"). A clustering analysis grouped keywords into 10 clusters [Figure 3B]. This clustering structure showed high robustness (modularity $Q = 0.4858 > 0.3$) and excellent homogeneity (weighted mean silhouette $S = 0.7716 > 0.7$). The major clusters were primarily associated with two research themes: therapeutics (#0 tissue engineering and #9 engineered exosomes), and pathogenesis (#2 outer membrane vesicles, #3 *Porphyromonas gingivalis*, #7 alveolar bone loss, and #8 microbiota dysbiosis).

Figure 3C and D show an evolutionary trajectory over the past decade. Initially, research on EVs in periodontitis focused on pathogenic mechanisms (Clusters #2, #3, #7 and #8), characterized by "outer membrane vesicles", "*Aggregatibacter actinomycetemcomitans*", and "gram-positive bacteria." Notably, themes in Clusters #2 and #3 have recently resurged. Subsequently, the focus shifted to bone regeneration-oriented therapies utilizing MSC-EVs (Cluster #0), evidenced by "regeneration", "osteogenesis", and "angiogenesis." Recently, the research frontier has pivoted toward "drug delivery" and "immunomodulation". Engineered EVs for drug delivery represent an emerging but still scarce area (Cluster #9). Meanwhile, immunomodulation (Cluster #4) has become a focal point, emphasizing macrophage polarization and the use of macrophage-derived EVs as therapeutics. Significantly, trend topics highlight a growing clinical interest in EVs as diagnostic biomarkers [Figure 3D].

Documents and references

Figure 4A displays the top 10 cited publications in the field between 2015 and 2025, highlighting the therapeutic and pathogenic roles of EVs in periodontitis. Early studies demonstrated that human mesenchymal stem cell-derived EVs (MSC-EVs) promote periodontal tissue and alveolar bone regeneration[36]. MSC-EVs retain the immunomodulatory properties of their parent cells[37] and have been implicated in modulating macrophage polarization toward the M1 or M2 phenotype[38]. EVs from dental pulp stem cells (DPSCs)[39] or tumor necrosis factor-alpha (TNF-α)-preconditioned gingival mesenchymal stem cells (GMSCs)[40] can facilitate M2 macrophage polarization, thereby supporting tissue repair. In addition, adipose tissue-derived EVs have entered clinical trials for periodontal pocket treatment[41]. Beyond

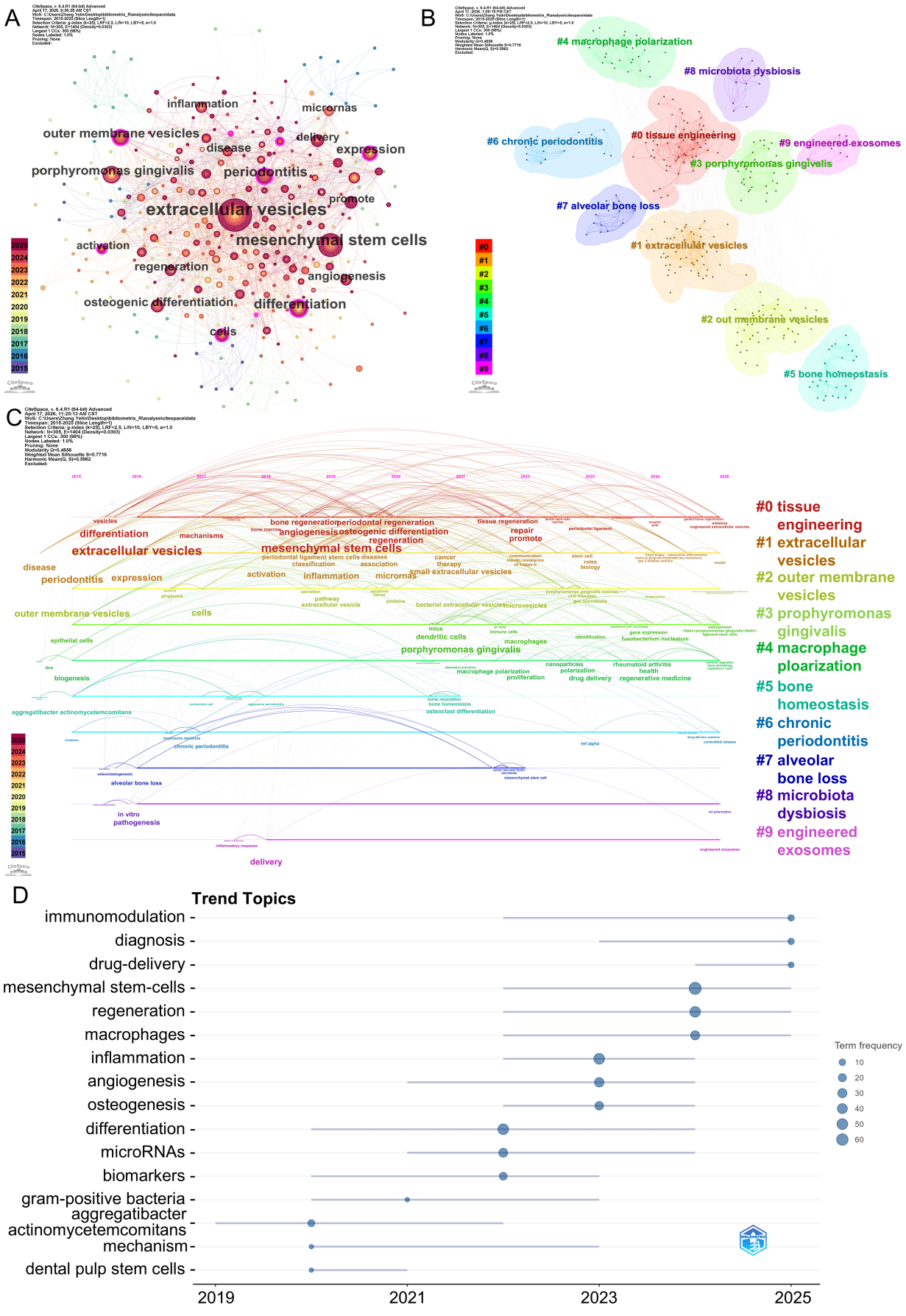


Figure 3. Bibliometric profiling of keywords. (A) Keyword co-occurrence network; (B) Keyword cluster mapping; (C) Timeline view of keyword clusters; (D) Temporal evolution of topic trends. Analyses were performed using CiteSpace v6.4.R1 (A-C) and Bibliometrix v5.2.0 (D).

mammalian sources, plant-derived EVs (e.g., those isolated from ginger) show therapeutic potential through inhibition of *Porphyromonas gingivalis (P. gingivalis)* pathogenicity[42]. In contrast, bacterial OMVs are pathogenic[43]. *P. gingivalis* OMVs trigger periodontitis by inducing a metabolic shift toward glycolysis in macrophages[44]. *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans)* OMVs can cross the blood-brain barrier and induce TNF-α production, suggesting a pathophysiological link to Alzheimer's disease[45]. Further details of these highly cited publications are provided in Supplementary Table 2.

To overcome time-lag bias, articles from 2023-2025 were ranked by normalized total citations [Figure 4B]. Among the top 10, one review highlighted salivary EVs as periodontal biomarkers[46]. One study investigated the effects of bone marrow mesenchymal stem cell (BMSC) derived EVs on alveolar bone metabolism under inflammatory conditions[47]. The remaining studies focused on therapeutic applications. Sources of therapeutic EVs have expanded beyond MSCs[37,41], with EVs derived from Schwann cells[48] and M2 macrophages[49,50] demonstrating their capacity to enhance bone regeneration. In addition, EVs are increasingly being explored as drug delivery systems[51]. For example, melatonin-loaded M2 macrophage-derived EVs have been shown to reduce endoplasmic reticulum stress and the unfolded protein response, thereby restoring the osteogenic and cementogenic differentiation capacity of inflamed periodontal ligament cells[50]. Additionally, the optimization of hydrogels as EV carriers remains an active area of research[52,53]. Collectively, these advancements further drive the clinical application of EV treatments. A detailed summary of the ten publications is presented in Supplementary Table 3.

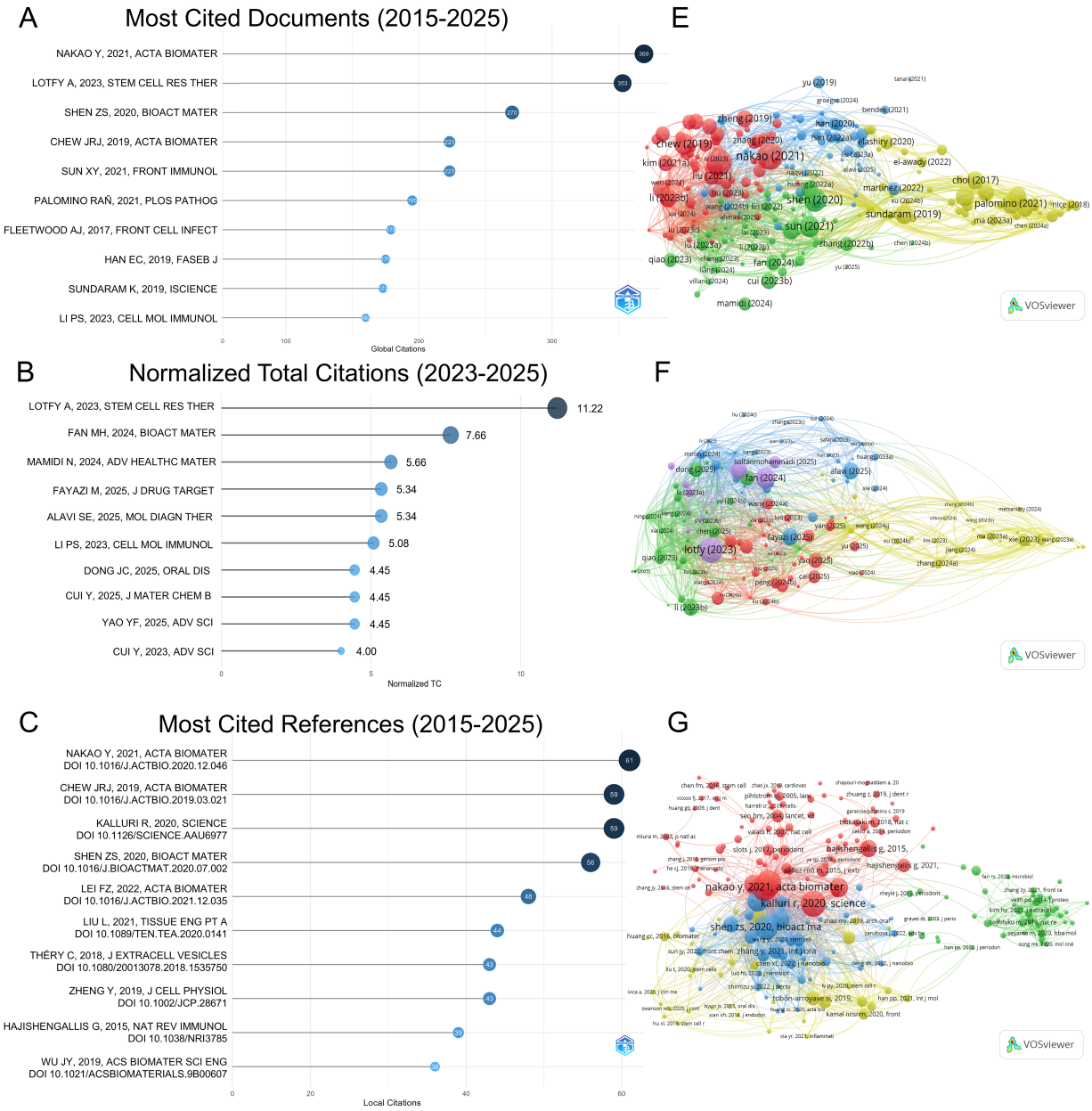
A total of 20,159 cited references were identified, constituting the knowledge base of this research field [Figure 2A]. Figure 4C and D display the 10 most cited and the 10 top references with the strongest citation bursts. Notably, the study by Nakao *et al.* ranked first among both the most cited documents [Figure 4A] and the most cited references [Figure 4C][40]. The highly cited references can be categorized into three themes. The first encompasses disease background and theoretical consensus, including the immunopathogenesis of periodontitis[54,55], EV biogenesis[9,10], MISEV guidelines[56], and the role of periodontal ligament stem cells (PDLSCs) in tissue engineering[57]. The second theme involves disease mechanisms, with studies demonstrating how EVs derived from periodontal pathogens and stressed host cells contribute to disease progression[58,59]. The third theme focuses on therapeutic applications, highlighting the potential and effectiveness of MSC-EVs from diverse sources[36,39,40,60-65]. Figure 4E-G shows citation-weighted VOSviewer clustering networks for documents in the time periods 2015-2025 and 2023-2025 and cited references. These networks further illustrate the central position of the highly cited publications and references identified in Figure 4A-C within the knowledge structure of the field.

DISCUSSION

General information

This study analyzed 340 articles on EVs in periodontitis published between 2015 and 2025. The life cycle analysis of scientific production indicated that this research area is currently in a growth phase. According to the logistic growth model, the field is projected to peak in 2027 and to take approximately 10.2 years from emergence to near-saturation. These findings suggest research on EVs in periodontitis remains an active area of investigation. This rapid growth can be attributed to several factors. First, the increasing clinical and social demand for regenerative periodontal therapies has accelerated the translational exploration of EVs. Second, advances in EV isolation, characterization, and detection technologies have improved feasibility and reproducibility, thereby reducing technical barriers. Furthermore, integrating EV research with bioengineering has broadened the scope of potential applications.

China has become the leading contributor to research in this field, driven largely by institutions such as Sichuan University, Air Force Medical University, and Wuhan University. As China's top institutions for stomatology research, they represent key nodes within the current research network. Despite its substantial



D Top 10 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2015 - 2025
Théry C, 2018, J EXTRACELL VESICLES, DOI 10.1080/20013078.2018.1535750 [56]	2018	**8.05**	2020	2023	
Mohammed E, 2018, BIOMOLECULES, DOI 10.3390/biom8040167 [63]	2018	**6.37**	2020	2023	
Chew JRJ, 2019, ACTA BIOMATER, DOI 10.1016/j.actbio.2019.03.021 [36]	2019	**5.78**	2020	2022	
Wu JY, 2019, ACS BIOMATER SCI ENG, DOI 10.1021/acsbiomaterials.9b00607 [61]	2019	**4.61**	2022	2023	
van Niel G, 2018, NAT REV MOL CELL BIO, DOI 10.1038/nrm.2017.125 [9]	2018	**4.57**	2022	2023	
Zhao MY, 2019, ARCH ORAL BIOL, DOI 10.1016/j.archoralbio.2019.06.002 [58]	2019	**3.86**	2020	2022	
Tomokiyo A, 2019, STEM CELLS DEV, DOI 10.1089/scd.2019.0031 [57]	2019	**3.81**	2022	2023	
Pivoraite U, 2015, INFLAMMATION, DOI 10.1007/s10753-015-0173-6 [64]	2015	**3.73**	2019	2020	
Pan WY, 2019, INT J ORAL SCI, DOI 10.1038/s41368-019-0064-z [55]	2019	**3.43**	2022	2023	
Zhang ZY, 2021, FRONT CELL INFECT MI, DOI 10.3389/fcimb.2020.585917 [59]	2021	**2.97**	2023	2025	

Figure 4. Bibliometric profiling of documents and references. (A) The top 10 most cited documents (2015-2025); (B) The top 10 documents with normalized total citations (2023-2025); (C) The top 10 most cited references; (D) The top 10 references with the strongest citation bursts, ranked by burst strength; (E) Bibliographic coupling network of documents (2015-2025), weighted by citations; (F) Bibliographic coupling network of documents (2023-2025), weighted by normalized citations; (G) Co-citation network visualization of cited references, weighted by citations. Analyses were performed using Bibliometrix v5.2.0 (A-C), CiteSpace v6.4.R1 (D), and VOSviewer v1.6.20 (E-G). DOI: Digital object identifier; TC: total citations.

publication output, China exhibited a lower average citation rate than countries such as the USA, Japan, and Korea. This difference may partly reflect the recent increase in publication volume, as newer articles have had less time to accumulate citations. Nevertheless, this suggests potential to further increase the impact and visibility of research outputs from China while strengthening international collaborations.

Journal analysis provides insights into patterns of knowledge dissemination within a research field. Identifying core journals may help researchers select appropriate venues for publication. The *International Journal of Molecular Sciences* was the most productive journal in this field. Furthermore, journals identified as core journals according to Bradford's Law are all classified as JCR Q1. Several of these journals, such as the *Journal of Nanobiotechnology* and *Advanced Science,* have IFs exceeding 10, indicating that research on EVs in periodontitis is being published in widely recognized, high-impact multidisciplinary journals. In addition, the concentration of publications in a relatively small number of core journals may facilitate literature retrieval and help researchers remain informed of emerging developments in the field.

Analysis of highly cited publications and references provides insight into the intellectual foundation of this research field [Figure 4], where keyword analysis facilitates the identification of major research themes and emerging trends [Figure 3]. To support a systematic interpretation of the bibliometric findings, the following discussion integrates the knowledge base and research themes identified in the analysis with evidence from the broader literature. In addition to highly cited studies and references with strong citation bursts, relevant studies from the wider body of literature are included to contextualize and complement the bibliometric results. Collectively, this synthesis reveals that EVs play three distinct roles in periodontitis: serving as potential therapeutic agents for periodontal regeneration, acting as mediators in the pathogenesis of periodontitis and its associated comorbidities, and functioning as diagnostic biomarkers with potential clinical utility [Figure 5]. The subsequent sections will elaborate on these three roles.

Therapeutic applications of EVs in periodontitis

Promoting periodontal bone regeneration

Periodontal tissue regeneration is the primary goal in the treatment of periodontitis, and the functional restoration of damaged alveolar bone remains a major clinical challenge. Therapeutic strategies employing EVs to facilitate periodontal bone repair encompass multiple pathways, including restoration of the osteogenic differentiation potential of MSCs, suppression of osteoclastogenesis, and stimulation of angiogenesis within the defect site.

EVs promote periodontal bone regeneration primarily by stimulating the osteogenic differentiation of MSCs[66]. PDLSCs are resident MSCs within periodontal tissues that possess self-renewal and multipotent differentiation capabilities. PDLSCs are regarded as a critical cell source for periodontal regeneration owing to their capacity for osteogenic differentiation[57]. EVs derived from a variety of cell types have been reported to enhance the replicative activity, migration, and osteogenic differentiation capabilities of PDLSCs. Cell sources include BMSCs[60], DPSCs[67], dental follicle cells (DFCs)[68], and stem cells from human exfoliated deciduous teeth (SHED)[69]. In addition to mammalian sources, plant-derived EVs have also demonstrated the capacity to promote the osteogenic differentiation of PDLSCs. For instance, EV-like particles derived from the leaves of *Paris polyphylla var. yunnanensis* were shown to be efficiently internalized by PDLSCs, upregulating the expression of alkaline phosphatase (ALP), Runt-related transcription factor 2 (RUNX2), and osteopontin (OPN), thereby enhancing their osteogenic differentiation[70]. Additionally, the mechanisms by which EVs promote bone regeneration may also involve the activation of endogenous BMSCs at the bone defect site. For instance, following cellular uptake, SHED-EVs can stimulate the migration and differentiation of BMSCs. In an *in vivo* study, the EV-treated group exhibited upregulated collagen type 1 (COL1) expression in the defect area, accompanied by enhanced alveolar bone repair. This outcome might

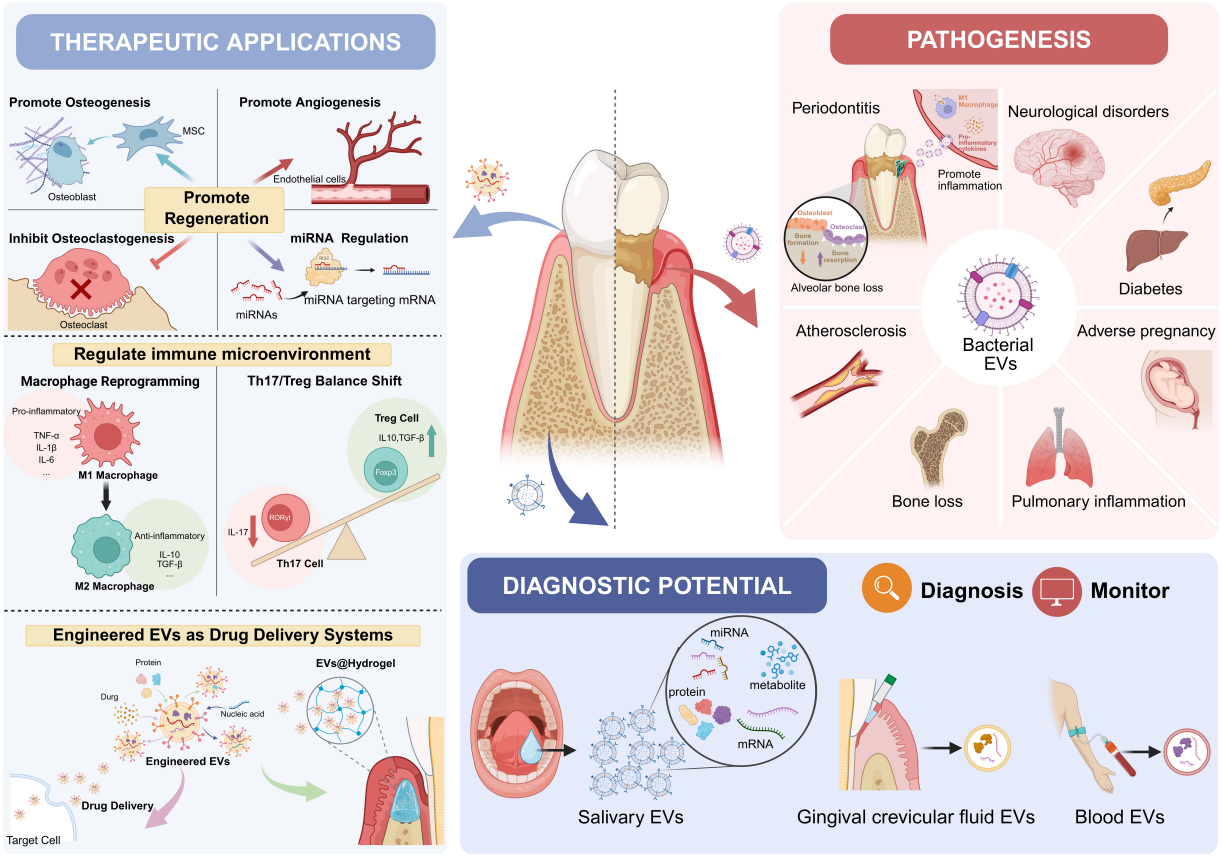


Figure 5. Roles of EVs in periodontitis. EVs play three core roles in periodontitis. Regarding therapeutic applications, EVs promote periodontal bone regeneration, modulate the immune microenvironment, and serve as drug delivery systems. In terms of pathogenesis, bacterial EVs not only contribute to periodontal tissue destruction but are also associated with various systemic diseases. Regarding diagnostic potential, EVs serve as promising diagnostic biomarkers. [Created in BioRender. Yixing, Z. (2026) https://BioRender.com/d17m8vx]. EVs: Extracellular vesicles; IL: interleukin; miRNA: microRNA; mRNA: messenger RNA; MSC: mesenchymal stem cell; TGF-β: transforming growth factor beta; Th17: T helper 17; TNF-α: tumor necrosis factor-alpha; Treg: regulatory T cell.

be associated with the ability of SHED-EVs to recruit endogenous cells and facilitate the migration of BMSCs toward the bone defect region[61].

Alveolar bone healing is inhibited in inflammatory microenvironments due to disruption of the osteogenic-osteoclastic balance caused by periodontitis[71]. Therefore, suppressing osteoclastogenesis while promoting osteoblast differentiation to restore this homeostatic balance is pivotal for periodontal bone regeneration. It has been reported that MSC-derived apoptotic bodies inhibit osteoclast differentiation *via* miR-223-3p, thereby alleviating alveolar bone destruction[72]. Similarly, BMSC-derived apoptotic bodies can suppress osteoclast formation by downregulating TNF-α secretion from pro-inflammatory macrophages[73]. DFC-EVs regulate the osteoprotegerin (OPG)/receptor activator of nuclear factor κB (RANK)/RANK ligand (RANKL) signaling pathway, thereby inhibiting osteoclast formation and promoting periodontal tissue regeneration[74].

Osteogenesis is intricately coupled with angiogenesis. The vascular system provides nutritional support to bones, thereby facilitating osteogenesis and ensuring the structural integrity of bone tissue[75]. Consequently, angiogenesis plays a crucial role in EVs-mediated periodontal bone regeneration. Research indicates that Schwann cell-derived EVs regulate angiogenesis in periodontal bone defect models, thereby accelerating periodontal bone regeneration[48]. Similarly, SHED-EVs have been shown to mediate both angiogenesis and osteogenesis *via* the AMP-activated protein kinase (AMPK) signaling pathway[61].

As vital components of EVs, microRNAs (miRNAs) mediate regulation of gene expression at the post-transcriptional level and serve as one of the primary effector molecules in the mechanisms promoting periodontal tissue regeneration[76]. For instance, SHED-EV-derived miR-92a-3p ameliorates periodontitis progression by inactivating the Krüppel-like transcription factor 4 (KLF4)/ phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway. Silencing miR-92a-3p reverses the pro-proliferative and osteogenic effects of SHED-EVs on PDLSCs[77]. These investigations into miRNA functions also lay the foundation for subsequently enhancing EV efficacy through bioengineering approaches. Although considerable research has focused on the therapeutic potential of miRNAs, their ability to simultaneously regulate numerous target genes by incomplete complementary pairing leads to the complexity and unpredictability of their biological functions. This broad regulatory capacity may also induce off-target effects, or even produce results contrary to the intended outcomes. Therefore, these issues must be carefully addressed before EV-miRNA-based therapeutic strategies can be genuinely implemented in clinical practice.

Modulating the immune microenvironment

The initiation and progression of periodontitis involve a complex immune microenvironment characterized by interactions among multiple immune cell populations. Notably, these immune cells serve not only as therapeutic targets modulated by EVs but also as important sources of EVs that contribute to periodontal regeneration[25].

Macrophages are a key component of the innate immune system. While they contribute to immune protection, excessive accumulation and overactivation can lead to periodontal tissue destruction[38]. Macrophages exhibit considerable heterogeneity and plasticity. Changes in the local microenvironment can activate distinct signaling pathways, driving macrophages toward specific phenotypes. The two best characterized phenotypes are M1 and M2[78]. M1 macrophages, also known as classically activated macrophages, predominantly rely on the inducible nitric oxide synthase (iNOS) pathway[79] and are typically induced by Toll-like receptor (TLR) ligands and interferon gamma (IFN-γ). Polarization toward the M1 phenotype is primarily driven by the activation of the signal transducer and activator of transcription 1 (STAT1) signaling pathway[80]. Characterized by the robust secretion of pro-inflammatory mediators, including TNF-α, interleukin (IL)-6, IL-1β, and C-C motif chemokine ligand 2 (CCL2)[81], M1 macrophages function in the phagocytosis and clearance of microorganisms. They also present antigens to trigger adaptive immunity, ultimately promoting T helper 1 (Th1) responses[82]. In contrast, M2 macrophages represent the alternatively activated phenotype driven by the arginase pathway[79]. M2 polarization is promoted by IL-4, IL-13, and IL-10 through the activation of STAT3/STAT6 signaling pathways. M2 macrophages exert immunosuppressive effects, displaying reduced antigen-presenting capacity while secreting cytokines that promote T helper 2 (Th2) responses and facilitate tissue repair[82]. Furthermore, these cells express high levels of markers such as cluster of differentiation (CD) 209, CD206, C-C chemokine receptors (CCRs), and IL-10[81].

Notably, the M1/M2 macrophage ratio increases significantly during the progression of inflammation. Moreover, these phenotypes can interconvert under specific microenvironmental conditions. Therefore, inducing the timely transition of macrophage phenotypes represents an important mechanism by which EVs modulate the periodontal immune microenvironment. EVs derived from GMSCs[40,83], human umbilical cord-derived MSCs[84] , and DPSCs[39] have all been shown to ameliorate the periodontal inflammatory microenvironment by facilitating macrophage polarization toward the M2 phenotype. Although inflammatory macrophage-derived EVs[85]and apoptotic bodies[86] exacerbate bone loss in periodontitis, M2 macrophage-derived EVs (M2-EVs) can modulate the functional states of other immune cells to facilitate periodontal tissue repair. For instance, M2-EVs can promote bone regeneration within an inflammatory environment by reprogramming immature neutrophils into a reparative terminal state known as Anxa1^{hi}

neutrophils[49]. Additionally, M2-EVs inhibit osteoclast differentiation through multiple mechanisms, such as the delivery of miR-1227-5p to target the osteoclast-associated receptor (OSCAR)[87], transferring CYLD lysine 63 deubiquitinase to suppress STAT3 signaling[88], and regulating the pyruvate kinase M2 (PKM2)/hypoxia-inducible factor-1α (HIF-1α) signaling axis[89].

T cell-mediated adaptive immunity is crucial within the periodontal inflammatory microenvironment. Clinical studies have demonstrated an upregulation of T helper 17 (Th17) cells and a downregulation of regulatory T (Treg) cells in the peripheral blood of patients with periodontitis[90], indicating a disruption of the Th17/Treg homeostasis. This Th17/Treg imbalance affects alveolar bone resorption. Th17 cells can exert pro-inflammatory effects by secreting IL-17. Moreover, RANKL expressed on their surface can bind to RANK, leading to the differentiation and activation of osteoclasts. Therefore, Th17 cells are considered potentially destructive factors in periodontitis[91]. Treg cells play an important role in immune self-tolerance, preventing excessive damage from the immune system[92]. Forkhead box protein 3 (Foxp3), the marker transcription factor of Treg cells, can inhibit osteoclast formation through the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and CD80/86 pathway[93,94]. CTLA-4, which is preferentially expressed by Tregs, is an anti-osteoclastogenic molecule that can directly bind to osteoclast precursors, preventing their differentiation into mature osteoclasts[95]. Studies have shown that the presence of Treg cells can reduce the severity of periodontitis[93]. Accordingly, restoring the Th17/Treg cell balance in periodontitis represents a promising strategy for preventing alveolar bone loss. BMSC-EVs[90] and PDLSC-EVs[65] have been shown to reduce the Th17/Treg ratio through miRNA transfer, thereby ameliorating the inflammatory microenvironment. Similarly, beyond acting merely as therapeutic targets, EVs secreted by T cells can actively modulate the immune microenvironment. Treg cells possess tissue-repair promoting capabilities, and Treg-derived EVs can suppress the activation of effector $CD4^+$ T cells through the delivery of the immunomodulatory molecule CD73, thereby limiting pathological inflammation and alleviating periodontitis[96].

Engineered EVs as drug delivery systems

EVs are considered ideal candidates for drug delivery systems due to their distinct biological properties. These properties include the capacity to cross diverse biological barriers, the capacity to transport multifunctional cargoes (e.g., proteins, nucleic acids, and lipids), and their low toxicity and immunogenicity[97]. Engineered EVs, generated by modifying and manipulating natural EVs using bioengineering techniques, exhibit enhanced cargo-loading capacity, targeting precision, and prolonged circulation half-life, thereby improving their therapeutic efficacy and translational potential[98]. Currently, the engineering of EVs primarily focuses on two aspects: cargo loading and surface modification.

Strategies for encapsulating therapeutic cargo into EVs can be broadly categorized into endogenous (active loading) and exogenous (passive loading) approaches[99]. Endogenous loading involves introducing therapeutic agents into parent cells through transfection or co-incubation, allowing their subsequent incorporation into EVs during biogenesis. In contrast, exogenous loading employs physical techniques such as sonication, freeze-thaw cycles, electroporation, and extrusion to directly introduce cargo into isolated EVs[100]. Given the important regulatory roles of nucleic acid therapeutics in treating periodontitis, multiple studies have engineered EVs to deliver specific miRNAs (e.g., miR-26a[101], miR-23b[102], and miR-423-5p[103]) or transcription factors such as Forkhead box O1 (FoxO1)[104] to enhance their therapeutic efficacy. Furthermore, conventional anti-inflammatory and immunosuppressive drugs, including aspirin[105], metformin[106], and methotrexate[107], have been encapsulated into EVs to treat periodontitis by remodeling the immune microenvironment and promoting osteogenic differentiation. Beyond functional cargo loading, precise targeted delivery is equally crucial. Surface modification of EVs can be achieved by fusing targeting peptides or antibodies with EV membrane proteins, typically facilitated by transfecting parent cells using

viral or non-viral vectors[108]. For instance, Yang *et al.* modified the EV surface with anti-CD80 antibodies, enabling targeted delivery to $CD80^+$ macrophages. This strategy allowed the efficient delivery of methotrexate encapsulated within the EVs, precisely promoting the polarization of macrophages toward an anti-inflammatory phenotype[109]. Similarly, Luo *et al.* utilized a lentiviral vector system to display C-X-C motif chemokine receptor 4 (CXCR4) on the EV surface, significantly enhancing homing to M1 macrophages. These engineered EVs were subsequently employed to deliver miR-126, promoting the repolarization of M1 macrophages toward an anti-inflammatory phenotype. *In vivo*, local administration of these EVs effectively attenuated pathological alveolar bone resorption and osteoclastogenesis[110].

Although inflammatory microenvironment modulation supports periodontal regeneration, anti-inflammatory therapy alone is insufficient to restore alveolar bone. Effective strategies should also enhance the osteogenic capacity of MSCs and osteoblasts or improve targeting of EVs to these cells. Osteogenic preconditioning of parental cells can generate EVs with enhanced pro-osteogenic activity[111]. For example, SHED-EVs produced after osteogenic induction promoted PDLSCs' osteogenesis through bone morphogenetic protein (BMP)/Smad and Wnt/β-catenin signaling[112]. Likewise, EVs derived from osteogenically preconditioned DPSCs were enriched in osteogenesis-related proteins and enhanced the osteogenic differentiation of BMSCs[113]. In addition, surface engineering can improve targeting of EVs to MSCs or osteoblasts. EVs modified with BMSCs target aptamers exhibited greater accumulation in bone tissue[114], whereas EVs functionalized with bone-targeting peptides were more readily internalized by osteoblasts[115]. Although these approaches have shown bone targeting efficacy in osteoporosis models, they remain unvalidated in periodontitis. EVs can also serve as a delivery system for osteogenic therapeutic cargoes. For instance, DFC-EVs loaded with the osteogenic miRNA miR-423-5p were readily internalized by PDLSCs, significantly promoted their osteogenic differentiation, and enhanced periodontal tissue regeneration in a periodontal defect model[103].

Prolonging the local retention and enabling the sustained release of EVs at periodontal defect sites are beneficial for periodontal bone regeneration. Consequently, hydrogels have emerged as promising delivery platforms for EVs. Characterized by their unique three-dimensional architecture, hydrogels are highly hydrophilic polymer networks capable of rapidly absorbing and retaining large amounts of fluid without dissolving[116]. The combination of EVs with hydrogels can effectively enhance the structural stability of EVs during the therapeutic transport process and facilitate sustained release *in vivo*[99]. EVs can be integrated into hydrogels through physical adsorption, which involves immersing the hydrogel in an EV suspension to allow binding through non-covalent interactions. Alternatively, integration can be achieved through chemical methods, including covalent crosslinking, self-assembling peptide crosslinking, and surface functionalization[52]. Multifunctional hydrogel systems have been investigated for periodontal bone regeneration. Peng *et al.* developed a multifunctional DNA-based hydrogel termed Agevgel. Through physical self-assembly, this system incorporates antibacterial silver nanoclusters and immunomodulatory M2-EVs. Agevgel not only prolonged the local retention time and enabled the sustained release of M2-EVs *in vivo*, but also significantly accelerated the healing rate of defective alveolar bone[117]. Ming *et al.* designed an oxygen-releasing thermosensitive hydrogel loaded with calcium peroxide nanoparticles and BMSC-EVs. Exhibiting excellent biocompatibility, this delivery system effectively inhibited anaerobic bacterial growth and promoted the regeneration of periodontal defects[118]. These multifunctional hydrogel systems endow EV-based delivery platforms with synergistic therapeutic efficacy, offering a promising translational strategy for comprehensive periodontal tissue regeneration in complex infected microenvironments.

Role of EVs in the pathogenesis of periodontitis

Localized periodontal destruction mediated by bacterial EVs

Periodontitis is a bacteria-induced chronic inflammatory disease. Periodontal pathogens proliferate abundantly within the gingival crevice, where their secreted virulence factors and parasitic behaviors trigger robust immune responses in gingival tissues. Microbial dysbiosis and hyperactive immune responses disrupt the homeostasis of alveolar bone, breaking the dynamic balance between osteoclasts and osteoblasts, ultimately leading to bone resorption[119,120].

Bacterial extracellular vesicles (BEVs) are important mediators in the pathogenic mechanisms of periodontal pathogens. BEVs are spherical nanostructures enclosed by a bacterial lipid bilayer, with diameters ranging from approximately 20 to 400 nm[121]. They mediate bidirectional communication both within bacterial communities and between bacteria and host cells, representing a key mechanism through which bacteria regulate physiological and pathological processes[43]. OMVs are a specific subset of BEVs derived from Gram-negative bacteria. Their cargo is highly dependent on growth conditions and can encompass proteins, nucleic acids, and diverse virulence factors[121]. OMVs are key mediators of the pathogenicity of Gram-negative bacteria. The lipid bilayer of OMVs protects bacterial virulence factors from degradation and facilitates their delivery into host cells[122]. OMVs also contribute to bacterial adhesion. For instance, the adhesion of *A. actinomycetemcomitans* to epithelial cells and tooth surfaces is mediated by surface-associated components such as fimbriae and microvesicles[123]. Furthermore, OMVs actively participate in biofilm establishment, host invasion, and immune regulation[124].

P. gingivalis, a member of the "red complex" pathogens, is considered a keystone pathogen in periodontitis[125]. Nevertheless, periodontitis is not driven by *P. gingivalis* alone, but arises from the complex interplay between a dysbiotic polymicrobial community and dysregulated host immune-inflammatory responses[126]. OMVs from *P. gingivalis,* one of the most extensively studied periodontal pathogens, have also received considerable attention. *P. gingivalis* OMVs contain gingipains, lipopolysaccharides (LPS), and nucleic acids (DNA and RNA) originating from the pathogen[127]. These OMVs exhibit a stronger invasive capacity than intact *P. gingivalis* cells[128] and are instrumental in both the onset and the rapid clinical deterioration of periodontal infections. *P. gingivalis* OMVs can activate complex signaling pathways in human gingival epithelial cells to trigger the release of inflammatory mediators and disrupt the epithelial barrier function, thereby compromising the critical defensive line of periodontal tissues against microbial invasion[24,129]. Additionally, *P. gingivalis* OMVs actively modulate the periodontal immune microenvironment. They promote a pro-inflammatory state by stimulating the release of inflammatory mediators (e.g., IL-6, IFN-β, TNF-α, IL-12p70) and nitric oxide, as well as by activating inflammasomes and inducing pyroptotic cell death in macrophages[44].

Periodontal pathogen-derived BEVs can disrupt the osteogenic-osteoclastic balance in periodontal tissues through multiple pathways, ultimately exacerbating alveolar bone loss. For instance, *P. gingivalis* OMVs can impair vascular endothelial cell-mediated osteogenesis by activating the cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING)/TANK-binding kinase 1 (TBK1) signaling pathway[130]. They can also directly induce osteoclastogenesis through the activation of TLR2[131]. Similarly, *Fusobacterium nucleatum* (*F. nucleatum*) OMVs have been shown to activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome and impair the mineralization capacity of PDLSCs through the nuclear factor kappa light-chain enhancer of activated B cells (NF-κB) p65 signaling pathway[132]. *F. nucleatum* OMVs can also promote macrophage polarization toward the pro-inflammatory M1 phenotype and increase osteoclast numbers, thereby exacerbating periodontal tissue destruction[133]. Furthermore, BEVs secreted by the Gram-positive anaerobe *Filifactor alocis (F. alocis)* have been reported to simultaneously suppress the osteogenic differentiation of BMSCs and upregulate their RANKL/OPG ratio through a TLR2-dependent mechanism[134]

. Consequently, periodontal pathogen-derived BEVs disrupt bone metabolic homeostasis. Interventions targeting these vesicles may represent a promising therapeutic strategy for addressing alveolar bone loss in periodontitis.

Given the pivotal roles of the oral microbiota and their BEVs in maintaining oral health and influencing disease progression, the development of vaccines targeting specific periodontal pathogens has attracted considerable interest. OMVs play critical roles in both antigenicity and mucosal immune activation. Notably, the LPS and anionic-LPS-modified proteins contained within *P. gingivalis* OMVs harbor immunodominant epitopes that elicit *P. gingivalis*-specific antibody responses in murine models[135]. Nakao *et al.* developed a *P. gingivalis* OMV-based vaccine adjuvanted with the synthetic double-stranded RNA analog polyriboinosinic polyribocytidylic acid [Poly(I:C)]. Following intranasal administration, this vaccine elicited high levels of *P. gingivalis*-specific IgA in nasal washes and saliva, as well as IgG and IgA in serum[136,137]. A bivalent periodontal vaccine formulated with *P. gingivalis* and *A. actinomycetemcomitans* OMVs effectively decreased the quantities of both bacteria within the oral cavity of mice when administered intranasally[138]. A trivalent vaccine comprising OMVs from *P. gingivalis, Treponema denticola* (*Td*), and an *Escherichia coli* derivative (EcNΔflhD) has been developed. In canine models, this vaccine was administered using a heterologous intranasal priming and subcutaneous booster (IN-prime/SC-boost) regimen, which elicited robust mucosal immune responses[139]. Nevertheless, further studies are required to fully evaluate the therapeutic potential and translational feasibility of OMV-based vaccine platforms.

Bacterial EVs as pivotal mediators in periodontitis and related systemic diseases

BEVs derived from periodontal pathogens not only exert local destructive effects on periodontal tissues but can also enter the systemic circulation and affect distant organs and tissues. Consequently, BEVs are considered an important mechanistic link between periodontal disease and systemic conditions[24,27,140].

Periodontitis has been established as a significant risk factor for cardiovascular disease. Translocation of periodontal pathogens into the bloodstream is facilitated when periodontal tissues are compromised by inflammation or ulceration. Notably, *P. gingivalis* has been detected within atherosclerotic plaques[141]. Researchers have increasingly focused on the relationship between periodontal pathogen BEVs and cardiovascular disease. Studies indicate that *P. gingivalis* OMVs possess potent platelet-aggregating activity, which plays a critical role in the formation of atherosclerotic plaques[142]. Furthermore, *P. gingivalis* OMVs may play an important role in vascular damage; they increase vascular permeability by promoting stress fiber formation and inducing the lysosome/endosome-mediated degradation of vascular endothelial-cadherin[143]. These OMVs also significantly enhance endothelial permeability in a gingipain-dependent manner[144]. Owing to their LPS content, *P. gingivalis* OMVs can promote foam cell formation, a key pathological feature of cardiovascular disease[145]. Furthermore, *P. gingivalis* OMVs induce the calcification of vascular smooth muscle cells by activating the extracellular signal-regulated kinase 1/2 (ERK1/2)/RUNX2 signaling pathway, a hallmark event of atherosclerosis[146].

BEVs constitute a potential pathogenic pathway for periodontitis-associated neurological disorders. *A. actinomycetemcomitans* OMVs can cross the blood-brain barrier to deliver extracellular RNA (exRNA) into the brain, thereby increasing brain TNF-α expression[45]. These OMVs are internalized by meningeal macrophages and transfer exRNA to microglia, which subsequently promote IL-6 production through the NF-κB pathway to trigger neuroinflammation[147]. Additionally, these OMVs can induce the production of pro-inflammatory cytokines (TNF-α and IL-6) in the brain by activating TLR4 and TLR8 signaling pathways through myeloid differentiation primary response 88 (MyD88). *A. actinomycetemcomitans* OMVs can also migrate to the trigeminal ganglion by retrograde axonal transport along maxillofacial nerves, similarly upregulating pro-inflammatory cytokines[148]. Moreover, *P. gingivalis* OMVs can migrate to the brain through

the trigeminal nerve and induce cognitive impairment. This effect is thought to be mediated by the suppression of brain-derived neurotrophic factor (BDNF) expression in neurons, coupled with increased TNF-α production by macrophages[149].

A bidirectional relationship exists between periodontitis and diabetes. Periodontitis-associated inflammation and infection can contribute to insulin resistance and pancreatic β-cell dysfunction. Conversely, a hyperglycemic state facilitates the proliferation of oral bacteria and increases susceptibility to periodontitis[14,150]. EVs have emerged as potential mediators linking the pathophysiology of these two diseases. Studies have shown that plasma EVs from rats with periodontitis impair glucose tolerance and insulin sensitivity in diabetic models while suppressing insulin-mediated signaling pathways in the liver[151]. Similarly, circulating EVs from periodontitis patients significantly inhibit glucose uptake and insulin signaling in HepG2 cells, thereby promoting the development of insulin resistance[151]. Further investigations specifically targeting pathogen-derived BEVs revealed that *P. gingivalis* OMVs can enter the systemic circulation and deliver gingipains to hepatocytes. This process suppresses the AKT/glycogen synthase kinase-3 beta (GSK-3β) signaling pathway and impairs hepatic glycogen synthesis, ultimately exacerbating hyperglycemia[152].

BEVs are closely associated with adverse pregnancy outcomes. *P. gingivalis* OMVs have been shown to localize within trophoblasts[153], highlighting their potential pathogenic role in this condition. Evidence from *in vitro* models demonstrates that *P. gingivalis* OMVs disrupt the contribution of trophoblasts to vascular transformation. Furthermore, by activating neutrophils, these OMVs impair the immunomodulatory capacity of trophoblasts required to maintain immune homeostasis[154]. *P. gingivalis* OMVs also alter trophoblast metabolism, thereby reducing the migration and invasion capabilities of these cells. *In vivo* murine models further confirm that *P. gingivalis* OMVs restrict placental and fetal weight gain, and this effect is accompanied by downregulated expression of glucose transporters in the placenta[155].

BEVs are also implicated in the pathological processes of other systemic diseases. For instance, *P. gingivalis* OMVs can induce caspase-3 activation and poly (ADP-ribose) polymerase (PARP) cleavage, leading to lung epithelial cell apoptosis. This interference alters the normal distribution of tight junction components, thereby compromising the integrity of the lung epithelial barrier and contributing to the pathogenesis of respiratory diseases[156]. Furthermore, upon intraperitoneal administration, *F. alocis* BEVs accumulate in long bones and induce osteoclastogenesis through TLR2, resulting in systemic bone loss *in vivo*[157].

Endogenous EVs in local periodontal destruction and systemic disease-associated periodontitis progression

Beyond BEVs, endogenous EVs derived from host cells also contribute to periodontitis progression. Resident cells within the inflammatory periodontal microenvironment release EVs with proinflammatory and tissue-destructive properties. For example, EVs derived from LPS-preconditioned PDLSCs, which mimic a chronic inflammatory microenvironment, exacerbate alveolar bone loss in experimental periodontitis by activating the NLRP3 inflammasome and promoting macrophage M1 polarization[158]. Similarly, EVs secreted by LPS-stimulated periodontal ligament fibroblasts induce inflammatory responses while impairing the osteogenic activity of osteoblasts[58]. Aberrant angiogenesis is another hallmark of periodontitis. Under inflammatory conditions, PDLSC-EVs promote angiogenesis in human umbilical vein endothelial cells (HUVECs)[159]. In addition, periodontitis is associated with the expansion of Gli1+ cells. EVs released by inflammatory Gli1+ cells recruit and activate neutrophils, thereby contributing to periodontal tissue destruction[160]. Collectively, pathogenic EVs released by local periodontal cells and their downstream signaling pathways may represent promising therapeutic targets for periodontitis.

Given the bidirectional relationship between periodontitis and systemic disorders, EVs derived from distant organs may also contribute to periodontal inflammation and bone loss. For instance, EVs derived from metabolically impaired livers are elevated in type 2 diabetes mellitus and preferentially accumulate in periodontal tissues, where they induce pyroptosis in periodontal ligament cells and exacerbate alveolar bone resorption[161]. In diabetic conditions, EVs released by bone marrow-derived macrophages impair autophagy in gingival epithelial cells, thereby exacerbating periodontitis[162]. Moreover, exposure to high-glucose concentrations increases miR-124-3p levels in osteocyte-derived EVs, resulting in impaired osteogenic function through the regulation of galectin-3. This mechanism may contribute to dysregulated alveolar bone remodeling in diabetes[163]. Periodontitis is also often more severe in postmenopausal women. Under estrogen-deficient conditions, EVs released by proinflammatory macrophages in visceral adipose tissue can prime quiescent macrophages toward a proinflammatory phenotype following exposure to periodontal pathogens, thereby sustaining chronic inflammation[164]. These findings highlight endogenous EVs originating from periodontal tissues and distant organs, including the liver, bone marrow, and adipose tissue, as important pathogenic mediators linking systemic disorders to periodontitis.

Diagnostic potential of biofluid EVs as clinical biomarkers

As a biofluid that directly interacts with the oral microenvironment and can be collected non-invasively, saliva has considerable potential as a diagnostic medium for periodontitis and for monitoring disease progression[165]. Compared with whole saliva, which may contain contaminants such as food debris and microorganisms, salivary EVs can be separated from contaminants during the isolation process. Moreover, the lipid bilayer of salivary EVs protects their cargo from enzymatic degradation, including by salivary enzymes such as amylase[15]. Consequently, salivary EVs may serve as more sensitive and specific biomarkers for oral diseases.

Current research identifies distinct salivary EV signatures in periodontitis, including mRNA, proteins, metabolites, microRNA, and other molecular cargoes. Salivary EVs from periodontitis patients show reduced levels of the bone turnover marker osterix (OSX) alongside increased expression of the pro-inflammatory cytokine TNF-α[166]. Furthermore, programmed death-ligand 1 (PD-L1) expression correlates positively with severity of inflammation[167]. EVs-related tetraspanins CD9/CD81 show significant downregulation in salivary EVs of patients with periodontitis[168]. Notably, specific miRNAs enriched in salivary EVs (hsa-miR-140-5p, hsa-miR-146a-5p, and hsa-miR-628-5p) are markedly upregulated in periodontitis[169]. Metabolomic analysis revealed distinct alterations in salivary EVs from children with localized aggressive periodontitis, including in acetylcholine, creatinine, L-pipecolic acid, and N-acetylneuraminate levels[170]. Longitudinal studies further demonstrate the capacity of EVs to dynamically reflect therapeutic responses. Wang *et al*. investigated salivary EVs in patients with periodontitis who exhibited clinical improvement following non-surgical periodontal therapy. Their findings revealed a reduction in specific EV subpopulations ($CD63^+/CD24^+/CD142^+$), a downregulation of pro-inflammatory cytokines (IL-6, IL-2), and an upregulation of the anti-inflammatory cytokine IL-10[171]. Collectively, these findings highlight the potential of salivary EVs as a promising liquid biopsy tool for the diagnosis and monitoring of periodontitis.

Gingival crevicular fluid (GCF) is another common oral biofluid. Although GCF collection is more technically demanding than saliva, its site-specific nature allows it to more accurately reflect local periodontal activity[172]. Patients with periodontitis exhibit significantly higher total concentrations of GCF-EVs, which are positively correlated with clinical measures of periodontal disease severity. Notably, no significant difference in EV concentration was observed in concurrently collected saliva samples[173]. Furthermore, pregnant women with gestational diabetes mellitus and periodontitis show significantly elevated concentrations of GCF-EVs, with EV cargo enriched in proteins associated with immune responses and glucose and insulin signaling pathways[174]. In summary, GCF-EVs represent promising diagnostic biomarkers for periodontitis, although the current evidence base remains limited.

Oral disease-associated EVs can enter the systemic circulation and may therefore serve as blood-based diagnostic biomarkers for periodontitis[172]. Patients with chronic periodontitis exhibit more than twofold differential expression of 33 miRNAs in plasma-derived EVs[175]. Another study identified miR-1304-3p, miR-200c-3p, C/D box small nucleolar RNA (SNORD) 57, and SNORD1771 from plasma-derived EVs as potential biomarkers for periodontitis[176]. However, because circulating EVs are distant from the primary sites of many oral diseases, they are susceptible to systemic confounding factors. Moreover, disease-related signals may be diluted within the bloodstream, potentially reducing their diagnostic sensitivity[172]. For example, in pregnant women with gestational diabetes mellitus and periodontitis, EV concentration and biomarker profiles were altered in GCF, whereas no significant differences were detected in plasma EVs[174].

Limitations

This study has several limitations. First, with regard to data sources and retrieval, despite integrating WOSCC, Scopus, and PubMed to maximize literature coverage, relevant studies indexed exclusively in other databases (e.g., Google Scholar and Dimensions) may have been overlooked. Moreover, only English-language publications were included, which may have excluded high-quality studies published in other languages and consequently underestimated the contributions of certain countries or regions. Only articles and reviews were considered, whereas other document types, such as conference proceedings, were excluded despite their potential to capture emerging research trends.

Second, regarding indicators and methodology, bibliometric indicators primarily reflect research productivity, visibility, and scholarly influence rather than methodological quality, scientific rigor, or clinical relevance of individual studies. Therefore, they cannot directly assess the substantive quality of specific publications. Citation-based indicators are also subject to temporal bias, as recently published studies may be underrepresented due to their limited time for citation accumulation. In addition, citation counts do not differentiate between supportive and critical citations. Furthermore, the identified research hotspots and evolutionary trends are inherently descriptive and retrospective. While they provide insights into publication patterns and the intellectual structure of the field during a defined period, they do not support causal inferences regarding the drivers of scientific development.

Future studies should incorporate additional databases, broader language coverage, and complementary methodologies, such as systematic reviews, content analyses, and expert evaluations, to provide a more comprehensive and robust understanding of this research field.

Future perspectives

Building on the evolutionary trends identified in the bibliometric analysis, future research should prioritize the translational development of EV-based therapeutic and diagnostic strategies while further elucidating the roles of EVs in the pathogenesis of periodontitis and its associated comorbidities.

In line with current research priorities in immunomodulation and targeted drug delivery, MSC-EVs from diverse tissue sources have demonstrated the capacity to attenuate periodontitis-associated inflammation and promote periodontal tissue repair and regeneration. However, their therapeutic efficacy may vary according to cellular origin. Therefore, systematic comparative studies are needed for the rational selection and optimal clinical translation of MSC-EVs. Initial evidence indicates source-dependent differences. Ma *et al*. compared uptake by PDLSCs of EVs derived from DFCs, adipose-derived MSCs, BMSCs, and umbilical cord MSCs, and found that DFC-EVs were internalized most rapidly and reached uptake saturation earliest[103]. Zheng *et al*. reported that SHEDs produced more EVs than DPSCs, while SHED-EVs more effectively promoted PDLSC proliferation, migration, and osteogenic differentiation[69]. Similarly, GMSC-EVs exhibited greater immunomodulatory activity than BMSC-EVs *in vitro*[177]. Nevertheless, current comparative evidence is

largely limited to *in vitro* studies and is insufficient to establish the superiority of any single MSC-EV source for periodontal regeneration. Future systematic, head-to-head studies using standardized EV isolation, characterization, and quality-control procedures, as well as harmonized disease models and outcome measures, are required to define the relative advantages, limitations, and optimal clinical applications of MSC-EVs from different sources. Such studies may facilitate the development of source-specific EV therapies for periodontal inflammation control and tissue regeneration.

In studies of the pathogenic roles of EVs, *P. gingivalis* and OMVs have remained prominent research hotspots. Notably, the cluster #8 "microbiota dysbiosis" emerged during the early development of this research field but received relatively limited attention in subsequent studies. Given that periodontitis is not driven by a single microorganism but arises from the interplay among dysbiotic polymicrobial biofilms, host immune-inflammatory responses, and environmental factors[126], further investigation into polymicrobial BEV interactions is warranted. Consequently, although studies focusing on *P. gingivalis* and its OMVs have provided important insights into specific virulence factors and molecular mechanisms, they cannot fully recapitulate the interspecies interactions and BEV-mediated communication networks that characterize human periodontitis. Future research should therefore progress from single-species BEV models toward multispecies-derived BEVs and, ultimately, BEVs isolated from patient-derived subgingival microbiota. Such approaches may provide a more comprehensive understanding of how polymicrobial BEV networks contribute to periodontal inflammation, alveolar bone loss, and the development of periodontitis-associated systemic diseases.

Research on EVs as clinical biomarkers is attracting increasing attention. Saliva is readily accessible and amenable to repeated, non-invasive sampling, facilitating broad implementation and large-scale longitudinal cohort studies. Consequently, salivary EVs have been investigated extensively in the context of periodontitis. However, salivary EVs are susceptible to dilution effects and interference from the oral microbiota, which may limit their ability to accurately localize periodontal lesions when used in isolation. Future diagnostic strategies should therefore move beyond single-analyte assays toward integrated multiparametric and multi-omics approaches, enabling comprehensive monitoring of disease dynamics, therapeutic response, and prognosis. Among the currently available sample types, GCF is collected closest to periodontal lesions. Consequently, GCF-EVs may provide greater site specificity and diagnostic sensitivity. However, systematic characterization of GCF-EVs, including proteomic profiling, remains in its early stages. Although blood collection is more invasive than saliva and GCF sampling, plasma-derived EVs may better reflect long-term systemic alterations and could be particularly valuable for detecting systemic disorders associated with periodontitis. Future studies should capitalize on the complementary strengths of these biofluids to establish integrated EV-based biomarker platforms. Nevertheless, substantial efforts are still required before EVs can be translated into routine clinical biomarkers for periodontitis.

In addition to these emerging research topics, the clinical translation of EV-related findings requires careful consideration of the limitations of currently available experimental models. Substantial differences exist between animal models and humans with respect to oral microbial composition and abundance, periodontal anatomy, and immune responses. Non-human primates more closely resemble humans in periodontal tissue structure and disease phenotypes[178], but their high cost limits widespread use. In contrast, rodents, particularly mice, harbor oral microbiota that differ markedly from those of humans[179], and experimental periodontitis typically requires ligature placement and/or inoculation with human periodontal pathogens[180]. Therefore, EV-related mechanisms identified in animal models should be extrapolated to human periodontitis with caution. Their translational relevance requires further validation in human-derived samples and experimental systems with greater physiological relevance to human disease.

Conclusion

This study provides a comprehensive bibliometric analysis of research on EVs in periodontitis from 2015 to 2025, revealing a rapidly expanding field with substantial scientific influence, led primarily by China and several of its major research institutions. Current research hotspots are centered on immunomodulation and targeted therapeutic delivery. Collectively, the available evidence highlights multifaceted roles of EVs in periodontitis. From a therapeutic perspective, EVs promote periodontal tissue regeneration and modulate the immune microenvironment, while engineered EVs offer a versatile platform for targeted cargo delivery. In contrast, pathogenic EVs contribute to disease progression by amplifying inflammatory responses and disrupting bone homeostasis, thereby driving periodontal tissue destruction and potentially linking periodontitis to systemic comorbidities. Furthermore, although biofluid-derived EVs show considerable potential as diagnostic biomarkers, rigorous validation and the establishment of standardized multi-biomarker panels are still required to facilitate their clinical translation. Future research should focus on standardized comparisons of EVs from different cellular sources, clinically relevant polymicrobial pathogenic models, and prospective validation of EV-based diagnostic and therapeutic strategies.

DECLARATIONS

Authors' contributions

Contributed to the study conception and design: Zhang Y (Yelin Zhang), Wang S, Wang L, Pu Z, Yang R, Zhang Y (Yang Zhang), Li Z, Ma L, Yang H
Performed data collection: Yang R, Zhang Y (Yang Zhang), Li Z
Performed data analysis and visualization: Zhang Y (Yelin Zhang), Wang S, Wang L, Pu Z
Wrote the first draft of the manuscript: Zhang Y (Yelin Zhang)
Reviewed and revised the manuscript: Ma L, Yang H
Oversaw funding acquisition: Yang H
All authors read and approved the final manuscript.

Availability of data and materials

The data collected and analyzed in this article were retrieved from the WOSCC, Scopus, and PubMed databases, and all data extraction procedures were conducted properly.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool Gemini (version 3.1, released 2026-02-19) was used solely for language editing and grammar checking. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable. This study was based on bibliometric analysis of published literature and did not involve human participants or animal experiments.

Consent for publication

Not applicable.

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Supplementary Materials

Supplementary Materials

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