

Supplementary Materials

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

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Supplementary Figure 1. Contribution and collaboration among countries.

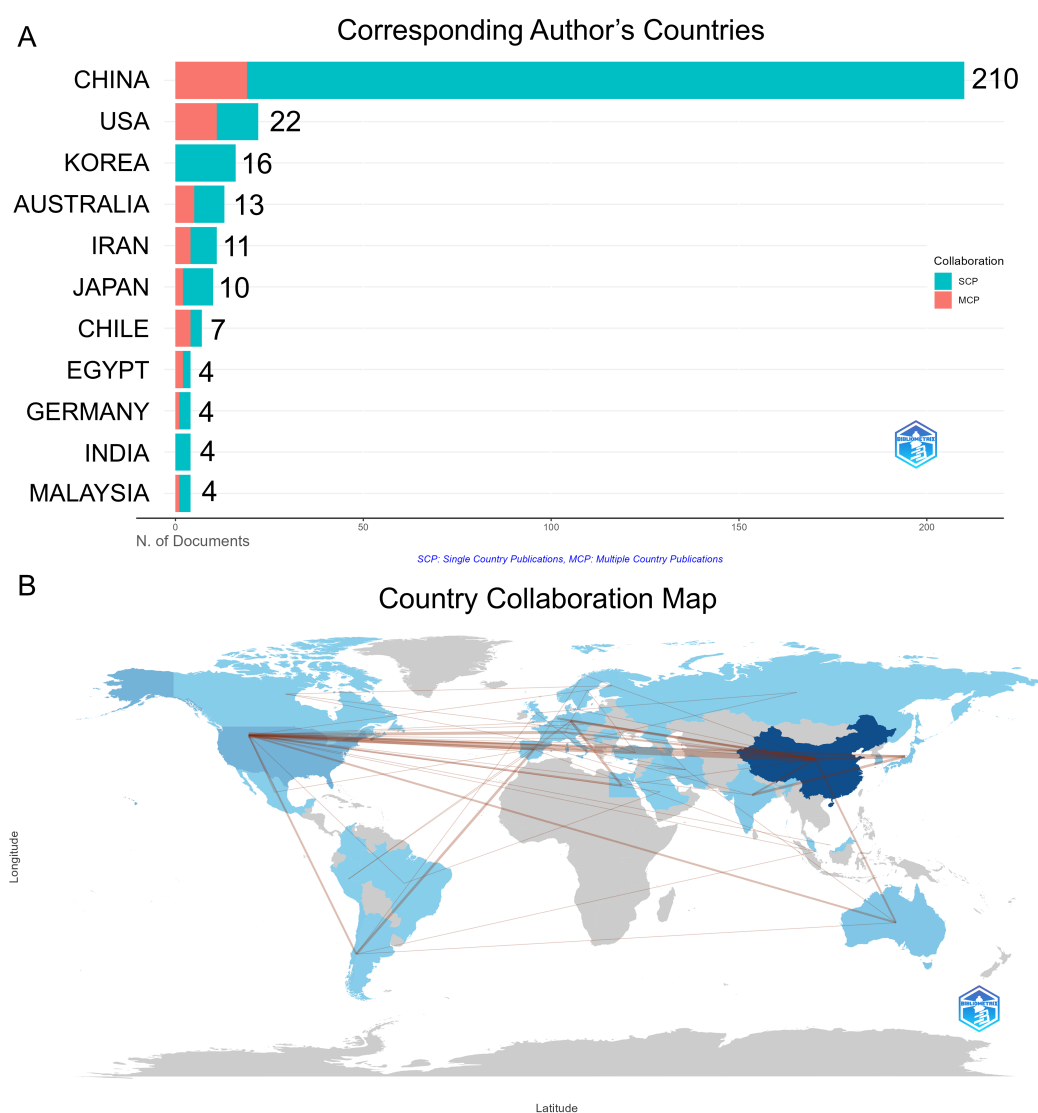
Supplementary Figure 2. Contribution and collaboration among institutions.

Supplementary Figure 3. Bibliometric profiling of journals.

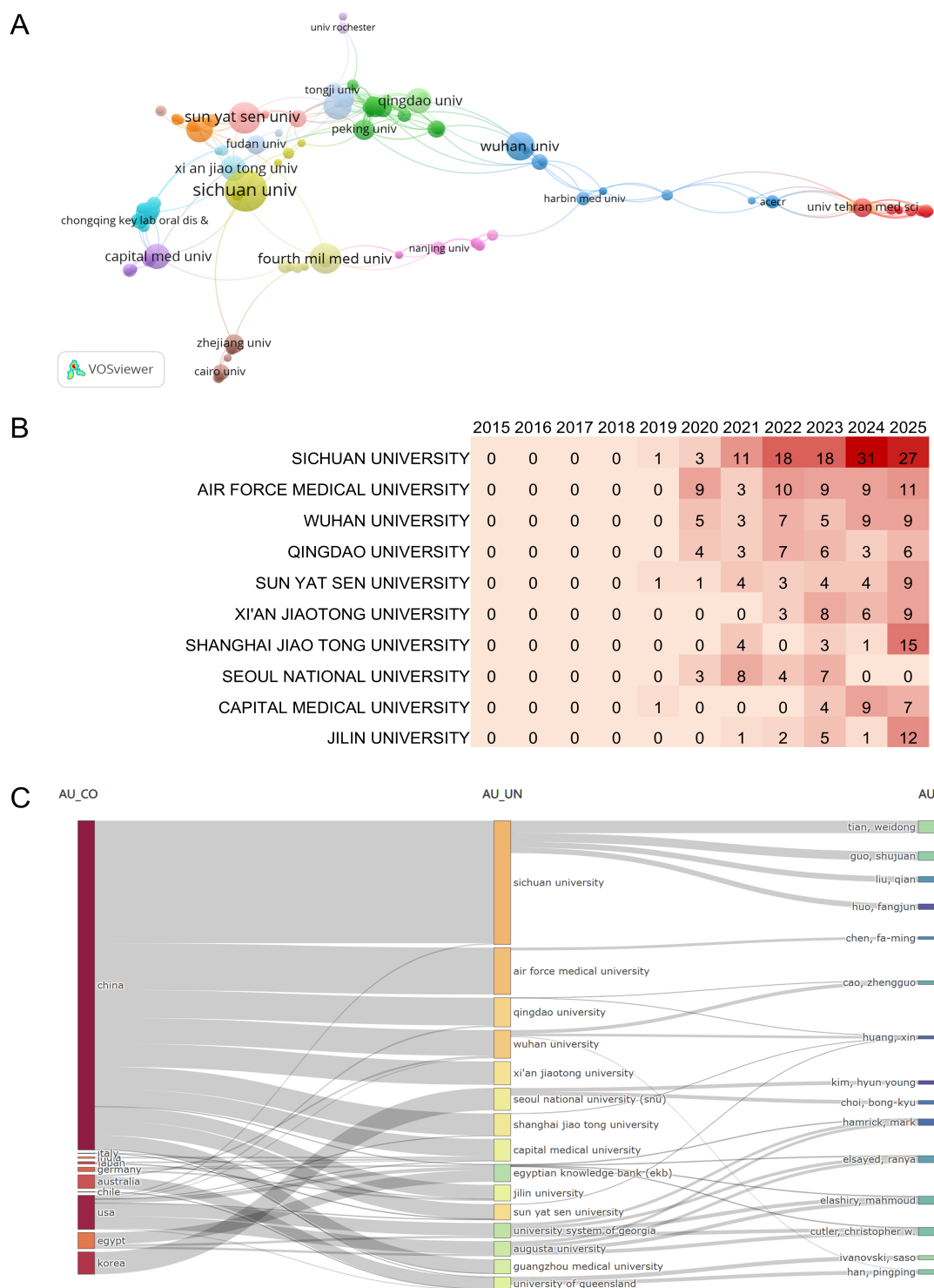
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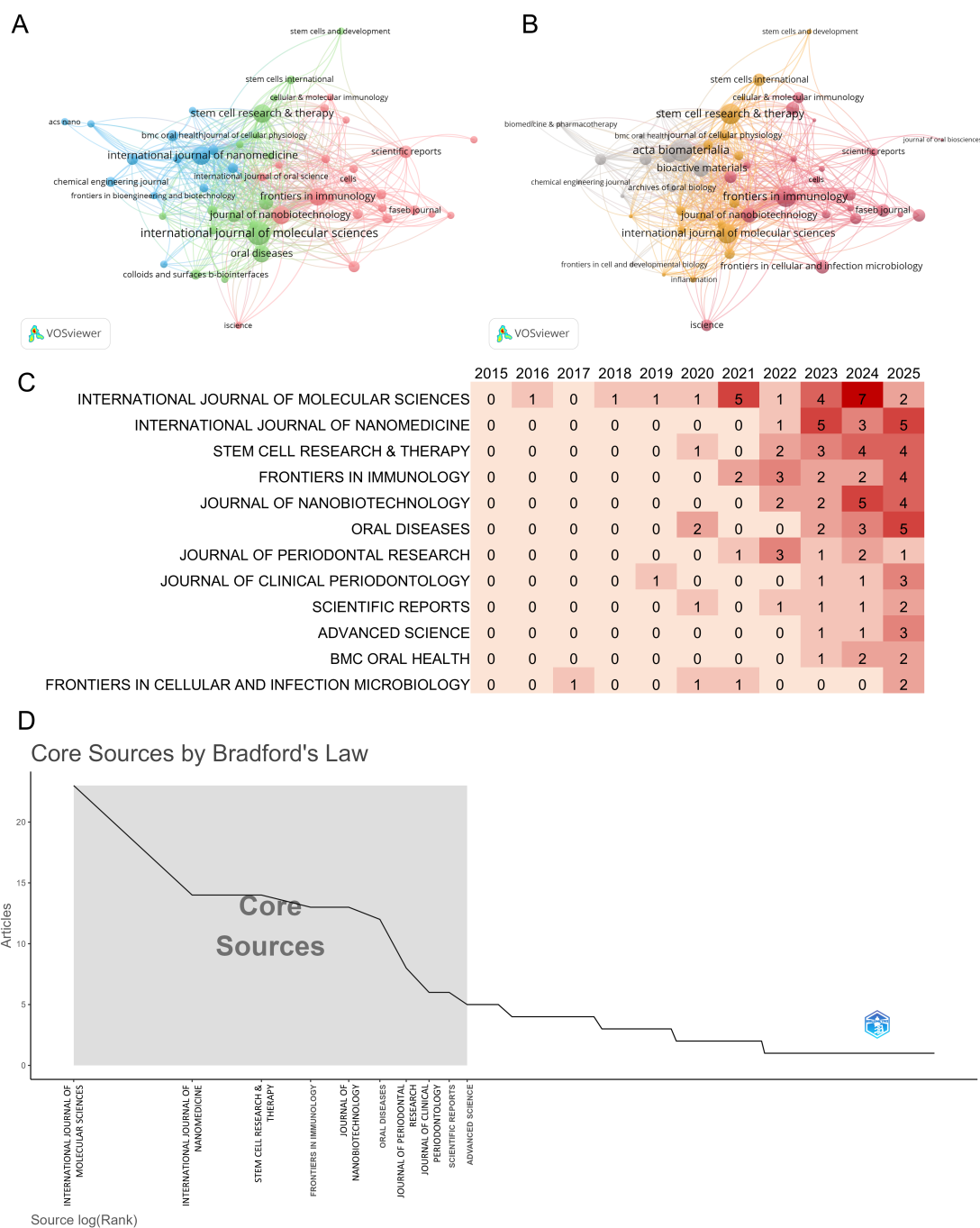
Supplementary Table 3. Content summary of the top 10 documents with normalized total citations (2023-2025).



Supplementary Figure 1. Contribution and collaboration among countries. (A) The top 10 most productive countries; (B) Country collaboration world map (min edges = 1). All analyses were performed using Bibliometrix v5.2.0.



Supplementary Figure 2. Contribution and collaboration among institutions. (A) Institutional co-authorship network weighted by publications; (B) Annual publication dynamics of the top 10 productive institutions; (C) Sankey diagram of the top 15 institutions, countries, and authors. Analyses were performed using VOSviewer v1.6.20 (A) and Bibliometrix v5.2.0 (B and C).



Supplementary Figure 3. Bibliometric profiling of journals. (A) Journal citation network weighted by publications; (B) Journal citation network weighted by citations; (C) Annual publication dynamics of the top 10 journals; (D) Journals classified into core and non-core sources according to Bradford's law. Analyses were performed using VOSviewer v1.6.20 (A and B) and Bibliometrix v5.2.0 (C and D).

Supplementary Table 1. Detailed search strategies for the three databases

Item	Web of Science Core Collection	Scopus	PubMed
Database	Science Citation Index Expanded (SCI-EXPANDED)	Scopus	PubMed
Search field	Topic (TS)	Article title, Abstract, Keywords (TITLE-ABS-KEY)	Title/Abstract
Search query	TS = ("Periodontitis" OR "Periodontal Diseases") AND TS = ("Extracellular Vesicle*" OR "Exovesicle*" OR "Exosome*" OR "Apoptotic Bod*" OR "Microvesicle*")	TITLE-ABS-KEY ("Periodontitis" OR "Periodontal Diseases") AND TITLE-ABS-KEY ("Extracellular Vesicle*" OR "Exovesicle*" OR "Exosome*" OR "Apoptotic Bod*" OR "Microvesicle*")	("Periodontitis"[Title/Abstract] OR "Periodontal Diseases"[Title/Abstract]) AND ("Extracellular Vesicle*" [Title/Abstract] OR "Exovesicle*" [Title/Abstract] OR "Exosome*" [Title/Abstract] OR "Apoptotic Bod*" [Title/Abstract] OR "Microvesicle*" [Title/Abstract])
Timespan	2015-2025	2015-2025	2015-2025
Document types	Article; Review	Article; Review	Exclude preprints; article/review selected in screening
Language	English	English	English
Search date	January 18, 2026	January 18, 2026	January 18, 2026
Records retrieved	n = 308	n = 414	n = 281
Export format	Plain text file full record and cited references	CSV complete metadata	PubMed; NBIB

Supplementary Table 2. Content summary of the top 10 most cited documents (2015-2025)

Reference (Articles)	Source/type of EVs*	Key components	Experimental model	Main effects	Mechanism/Pathway
Nakao <i>et al.</i> 2021, <i>Acta Biomater.</i> [40]	Exosomes derived from TNF- α preconditioned gingival MSCs	CD73, miR-1260b upregulated	Ligature-induced periodontitis in mice (<i>in vivo</i>) + periodontal ligament cells, macrophages (<i>in vitro</i>)	Induced M2 macrophage polarization; reduced alveolar bone resorption and TRAP-positive osteoclasts	CD73 mediates M2 macrophage polarization; EV- derived miR-1260b targets Wnt5a-mediated RANKL pathway and inhibits osteoclastogenesis
Shen <i>et al.</i> 2020, <i>Bioact Mater.</i> [39]	DPSC-exosomes incorporated into chitosan hydrogel	miR-1246	Ligature-induced periodontitis in mice (<i>in vivo</i>) + macrophages (<i>in vitro</i>)	Accelerated alveolar bone regeneration and periodontal epithelial healing; suppressed periodontal inflammation	miR-1246 in DPSC- exosomes facilitates macrophages polarization from a pro- inflammatory phenotype to an anti- inflammatory phenotype.
Chew <i>et al.</i> 2019, <i>Acta Biomater.</i> [36]	Human MSC- exosomes	CD73/ecto-5'- nucleotidase (NT5E)	Periodontal defect model in rat (<i>in vivo</i>) + periodontal ligament cells (<i>in vitro</i>)	Promoted bone and periodontal ligament regeneration; enhanced periodontal ligament cell migration and proliferation	CD73-mediated adenosine receptor activation and downstream pro-survival AKT and ERK signaling

Fleetwood <i>et al.</i> 2017, <i>Front Cell Infect Microbiol.</i> [44]	<i>Porphyromonas gingivalis</i> OMVs	Not identified (gingipains proposed)	Macrophages (<i>in vitro</i>)	Induced robust secretion of TNF α , IL-6, IL-12p70, IL-10, IFN β , NO; induced macrophage glycolysis, inflammasome activation, and pyroptosis	Metabolic reprogramming; caspase-1 activation and IL-1 β /IL-18 secretion
Han <i>et al.</i> 2019, <i>FASEB J.</i> [45]	<i>Aggregatibacter actinomycetemcomitans</i> OMVs	Bacterial extracellular RNAs (exRNAs)	Human macrophage- like U937 cells (<i>in vitro</i>) + intracardiac injection in mice (<i>in vivo</i>)	Promoted TNF- α production; crossed the blood-brain barrier and increased brain TNF- α	TLR8/NF- κ B signaling; exRNAs loaded into host RNA-induced silencing complex to regulate host genes expression
Sundaram <i>et al.</i> 2019, <i>iScience.</i> [42]	Ginger exosome-like nanoparticles (GELNs)	Phosphatidic acid (PA), plant miRNAs	<i>P. gingivalis</i> (<i>in vitro</i>) + oral inoculation with <i>P. gingivalis</i> in mice (<i>in vivo</i>)	Selectively taken up by <i>P. gingivalis</i> ; inhibited its pathogenicity; alleviated <i>P. gingivalis</i> -induced bone loss	PA unsaturation governs uptake specificity; PA and miRNAs target multiple virulence factors and inhibit <i>P. gingivalis</i> attachment

Reference (Reviews)	Review topic/focus
Lotfy <i>et al.</i> 2023, <i>Stem Cell Res Ther.</i> [41]	MSC-derived exosomes in clinical trials, including immunomodulation, regenerative medicine, gene delivery; sources, isolation, characterization, dosage, routes of administration; challenges and future directions. Notably, a clinical trial is investigating adipose tissue-derived exosomes as a therapeutic approach for periodontitis.
Sun <i>et al.</i> 2021, <i>Front Immunol.</i> [38]	Macrophage polarization in periodontitis, including characteristics, functions, and molecular signaling of M1/M2 phenotypes in tissue destruction and repair. Notably, exosomes are discussed in the section on immunoregulatory treatment of periodontitis associated with macrophage polarization.
Ñahui Palomino <i>et al.</i> 2021, <i>PLoS Pathog.</i> [43]	Bacterial EVs as a common language of microbiota-host communication, including the discovery, isolation, biogenesis of Bacterial EVs, and their health-promoting and pathogenic roles. Notably, there have been several reports that EVs from an oral pathogen act as immunomodulators.
Li <i>et al.</i> 2023, <i>Cell Mol Immunol.</i> [37]	Immunomodulatory properties and therapeutic applications of MSCs and dental stem cells, including their main therapeutic uses, mechanisms, extrinsic inflammatory cues, and intrinsic metabolic circuitries. Notably, the role of EVs in periodontitis are discussed in the section on immunoregulatory pathways.

*EVs, extracellular vesicles. The umbrella term “EVs” is used throughout the main text in accordance with the MISEV2023 guidelines [28], whereas the Supplementary Tables 2 and 3 retain the vesicle-subtype terminology (e.g., “exosomes”) used in the original studies.

Supplementary Table 3. Content summary of the top 10 documents with normalized total citations (2023-2025)

Reference (Articles)	Source/type of EVs*	Key components	Experimental model	Main effects	Mechanism/Pathway
Dong <i>et al.</i> 2025, <i>Oral Dis.</i> [47]	Exosomes derived from <i>P. gingivalis</i> LPS-stimulated BMSCs (BMExo- LPS)	miR-151-3p downregulated	BMSCs and RAW264.7 (<i>in vitro</i>)	LPS inhibited BMSC proliferation and osteogenesis; BMExo-LPS promoted osteoclastogenesis, by increased TRAP+ and osteoclast genes/proteins expression	loss of exosomal miR-151- 3p derepresses PAFAH1B1 to enhance osteoclast differentiation
Cui <i>et al.</i> 2025, <i>J Mater Chem B.</i> [48]	Schwann cell- derived exosomes (SC-EXOs); GelMA hydrogel delivery	EVs cargo not identified	Human periodontal ligament cells (hPDLCs), vascular endothelial cells (<i>in vitro</i>); periodontal bone defects in rats (<i>in vivo</i>)	Enhanced osteogenic differentiation of hPDLCs; stimulated angiogenesis in endothelial cells; accelerated periodontal bone regeneration	Not investigated

Yao et al. 2025, <i>Adv Sci.</i> [49]	M2 macrophage- derived EVs (M2- EVs)	EVs cargo not identified	Neutrophils (<i>in vitro</i>); ligature- induced periodontitis in mice (<i>in vivo</i>); scRNA-seq	Alleviated alveolar bone loss; reprogrammed immature neutrophils into a reparative Anxa1 ^{hi} subpopulation with osteogenic/angiogenic capacity	Disrupted neutrophil maturation trajectory; Acvr11/Fpr2 drove the differentiation of Anxa1 ^{hi} neutrophils; Anxa1 ^{hi} neutrophils secrete OSM
Cui et al. 2023, <i>Adv Sci.</i> [50]	Engineered M2 macrophage-derived exosomes load with melatonin (Mel@M2-exos); GelMA hydrogel delivery	Melatonin (loaded cargo)	LPS-inflamed hPDLs and macrophages (<i>in vitro</i>); ligature- induced periodontitis in rats (<i>in vivo</i>)	Promoted timely M1 to M2 macrophage reprogramming; enhanced osteogenic and cementogenic differentiation of inflammatory hPDLs; accelerated periodontal bone regeneration in rats	Immune reprogramming; reduced excessive endoplasmic reticulum stress and unfolded protein response; decreased apoptosis (Caspase-3↓, Bcl-2↑)

Reference (Reviews)	Review topic/focus
Lotfy <i>et al.</i> 2023, <i>Stem Cell Res Ther.</i> [41]	Detailed information is provided in Table S2.
Fan <i>et al.</i> 2024, <i>Bioact Mater.</i> [52]	Hydrogel-exosome systems for tissue engineering, including application in skin, bone (including periodontitis), cartilage, nerve, and tendon; exosomes biogenesis, sources, isolation, and engineering; and hydrogel encapsulation and release strategies.
Mamidi <i>et al.</i> 2024, <i>Adv Healthc Mater.</i> [53]	Multifaceted hydrogel scaffolds for biomedical applications, including tissue engineering, drug delivery, bone tissue engineering, dental applications, and biosensors, as well as environmental remediation.
Fayazi <i>et al.</i> 2025, <i>J Drug Target.</i> [51]	Drug delivery systems for periodontitis, highlighting EVs and other nanocarriers, including liposomes, polymeric, dendrimeric, mesoporous silica, and metallic nanoparticles, as well as therapeutic approaches involving antibiotics, herbal agents, nanozymes, and photothermal therapy, with emphasis on their mechanisms, advantages, and limitations.

Alavi <i>et al.</i> 2025, <i>Mol Diagn Ther.</i> [46]	Salivary biomarkers for periodontal disease, including proinflammatory cytokines (IL-1 β , IL-6, and TNF- α), enzymatic markers (MMP-8 and MMP-9), microbial DNA/RNA, oxidative stress markers, and exosomes/miRNAs; technological advances in salivary diagnostics, such as biosensors, lab-on-a-chip, and AI.
Li <i>et al.</i> 2023, <i>Cell Mol Immunol.</i> [37]	Detailed information is provided in Table S2

*EVs, extracellular vesicles. The umbrella term “EVs” is used throughout the main text in accordance with the MISEV2023 guidelines [\[28\]](#), whereas the Supplementary Tables 2 and 3 retain the vesicle-subtype terminology (e.g., “exosomes”) used in the original studies.