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Nanomaterials: innovative approaches for addressing key objectives in periodontitis treatment

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Periodontitis is a chronic inflammatory disease primarily caused by dental plaque, which is a significant global public health concern due to its high prevalence and severe impact on oral, and even systemic diseases. The current therapeutic plan focuses on three objectives: pathogenic bacteria inhibition, inflammation control, and osteogenic differentiation induction. Existing treatments still have plenty of drawbacks, thus, there is a pressing need for novel methods to achieve more effective treatment effects. Nanomaterials, as emerging materials, have been proven to exert their inherent biological properties or serve as stable drug delivery platforms, which may offer innovative solutions in periodontitis treatment. Nanomaterials utilized in periodontitis treatment fall into two categories, organic and inorganic nanomaterials. Organic nanomaterials are known for their biocompatibility and their potential to promote tissue regeneration and cell functions, including natural and synthetic polymers. Inorganic nanomaterials, such as metal, oxides, and mesoporous silica nanoparticles, exhibit unique physicochemical properties that make them suitable as antibacterial agents and drug delivery platforms. The inorganic nanosurface provides terrain induction for cell migration and osteogenic regeneration at defect sites by introducing different surface morphologies. Inorganic nanomaterials also play a role in antibacterial photodynamic therapy (aPDT) for eliminating pathogenic bacteria in the oral cavity. In this review, we will introduce multiple forms and applications of nanomaterials in periodontitis treatment and focus on their roles in addressing the key therapeutic objectives, to emphasize their promising future in achieving more effective and patient-friendly approaches toward periodontal tissue regeneration and overall health.

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1 Introduction

Periodontitis is a chronic multifactorial inflammatory disease primarily induced by dental plaque, and it is characterized by progressive destruction of the dental tissue.[1] It ranks as the most prevalent oral disease and is a significant public health concern.[2,3] Periodontitis can lead to gingival inflammation, clinical attachment loss, and alveolar bone loss,[4] making it the primary trigger of tooth loss and severely decreasing patients' quality of life. Nonetheless, epidemiological studies reveal a strong association between periodontitis and many systemic diseases including cardiovascular diseases,[5] type II diabetes,[6] rheumatoid arthritis,[7] Alzheimer's disease,[8] and cancer.[9,10] Furthermore, the release of inflammatory agents can create a conducive environment for bacteria to enter the bloodstream, thus leading to odontogenic bacteremia, triggering severe complications.[11] Consequently, the treatment of periodontitis holds promise for improving the management of systemic diseases, highlighting the therapeutic potential of addressing periodontitis.

Nevertheless, treating periodontitis presents substantial medical and socio-economic challenges. Common treatment methods include non-surgical approaches such as scaling and root planning, surgical interventions like periodontal flap surgery, and adjunctive therapies involving local medications and systemic antibiotic. It's important to note that neither non-surgical nor extensive surgical techniques can completely eradicate periodontal microorganisms.[12] Achieving satisfactory therapeutic results often requires combining multiple approaches. However, challenges such as significant patient discomfort, extended treatment durations, and uncertain efficacy cannot be disregarded. In summary, there remains

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a pressing need for ideal methods to treat periodontitis and achieve predictable periodontal tissue regeneration.

Nanomaterials are undergoing significant advancements in the field of medicine. Nanomaterials fall into two categories: organic nanomaterials and inorganic nanomaterials, all with considerable biological application potential. Possessing promising properties, nanomaterials offer potential applications across various dental therapeutic modalities, including local drug delivery, restorative materials, bone grafts, and implant surface modifications.[13] The clinical utilization of nanomaterials in periodontitis treatment involves harnessing their inherent biological properties for therapy, employing them as drug delivery platforms, and combined with novel therapeutic technologies.

Organic nanomaterials encompass nature and synthetic polymers. They represent a prominent topic in biomedical research due to their excellent biocompatibility and their potential to promote cell adhesion, proliferation, cell-to-cell interactions, cell migration, and tissue regeneration.[14] Inorganic nanomaterials encompass metal, oxides, and structured compounds like mesoporous silica nanoparticles. Inorganic nanomaterials exhibit exceptional physicochemical properties that offer valuable functionalities and hold significant promise in biomedicine.[15] Currently, the application of inorganic nanomaterials in dental therapy centers on their roles as antibacterial agents[16] and reliable drug delivery platforms.[17] Meanwhile, by introducing different surface morphologies, inorganic nanosurface provides terrain induction for cell migration and osteogenic regeneration at defect sites. Additionally, they can serve as sensitizers or targeting moieties in antibacterial photodynamic therapy (aPDT), which is an effective approach for eliminating pathogenic bacteria in the oral cavity.[18] In this review, we will provide insights into the diverse applications of classic nanomaterial structures in the context of periodontitis treatment and update the primary treatment scenarios they engage in (Fig. 1 and Table 1).

2 Pathogenesis and nanomaterials' therapeutic strategies for periodontitis

To develop an accurate treatment plan, a comprehensive understanding of periodontitis pathogenesis is essential. Periodontitis, an inflammatory disease primarily induced by bacteria, is initiated by predominant pathogens like *Porphyromonas gingivalis*. These pathogens activate the host's defense mechanisms, leading to tissue destruction through the release of mediators that stimulate connective tissue breakdown, particularly affecting alveolar bone and periodontal connective tissue.[74,75] As a result, the three key treatment objectives for periodontitis encompass inhibiting pathogenic bacteria, controlling inflammation, and promoting osteogenic differentiation, ultimately facilitating periodontal tissue regeneration and functional recovery (Fig. 2).

The first objective is to utilize antimicrobial properties. The primary cause of periodontitis is plaque biofilm, a complex community of various bacteria, such as *P. gingivalis*. While antibiotics have traditionally been used to combat pathogens, their overuse can lead to antibiotic resistance, making these drugs less effective and potentially causing various side effects. In contrast, nanomaterials offer a promising alternative. Due to their small size, high surface energy, and charge density, nanomaterials can easily penetrate pathogen cells, effectively eradicating them. To be specific, the high surface energy of nanomaterials increased reactivity and interaction with biological membranes, enhancing their antimicrobial efficacy, and the positively charged nanoparticles interact electrostatically with the negatively charged bacterial cell wall, disrupting the cell membrane's permeability.[76]

The second objective aims to regulate inflammatory mediators and immune responses in the context of periodontitis. The interplay between pathogenic microorganisms and the immune system initiates a host defense response, which significantly contributes to periodontal tissue damage. This defense response exhibits a dual nature: on one hand, immune cells, particularly macrophages, serve as crucial guardians of tissue homeostasis and effective defenders against microbial invasion. Conversely, uncontrolled escalation and hyperactivation of these host defense mechanisms can trigger an inflammatory cascade. This inflammatory environment, characterized by the excessive production of proinflammatory mediators, ultimately leads to tissue damage. Therefore, mitigating an exaggerated immune response and suppressing inflammation represent fundamental objectives in periodontitis therapeutics. Recent scientific efforts to alleviate inflammation associated with periodontitis have predominantly focused on modulating macrophage and neutrophil polarization.[77] Additionally, targeted interventions have been aimed at inhibiting inflammation by manipulating key signal transduction pathways, notably, p38 MAPK,[30] NF-κB,[47] and reactive oxygen species (ROS) scavenging.[78]

The third objective is tissue regeneration. The bacterial toxins produced by pathogenic microorganisms within the biofilm, along with the exacerbated host immune response, ultimately lead to defects in periodontal tissues and bone loss. This cascade of events can result in various periodontal dysfunctions, such as tooth movement, displacement, and even tooth loss.[79] Therefore, the primary objective of periodontal treatment, and the ultimate goal, is to restore the structures and functions of periodontal tissues. Nanomaterials, owing to their exceptional biocompatibility and diverse biological capabilities, can serve as agents to induce osteogenic differentiation through various pathways and mechanisms. For instance, they can modulate pathways like Wnt/β-catenin signaling and the ERK/AMPK pathway to regulate cell migration, adhesion, and osteogenic differentiation of periodontal cells and stem cells. Ultimately, this facilitates periodontal tissue regeneration and bone repair, aligning with the therapeutic objectives of periodontal treatment.

3 Nanomaterials in periodontitis treatment application

In periodontitis treatment, different forms of nanomaterials have been explored and applied, showing promising

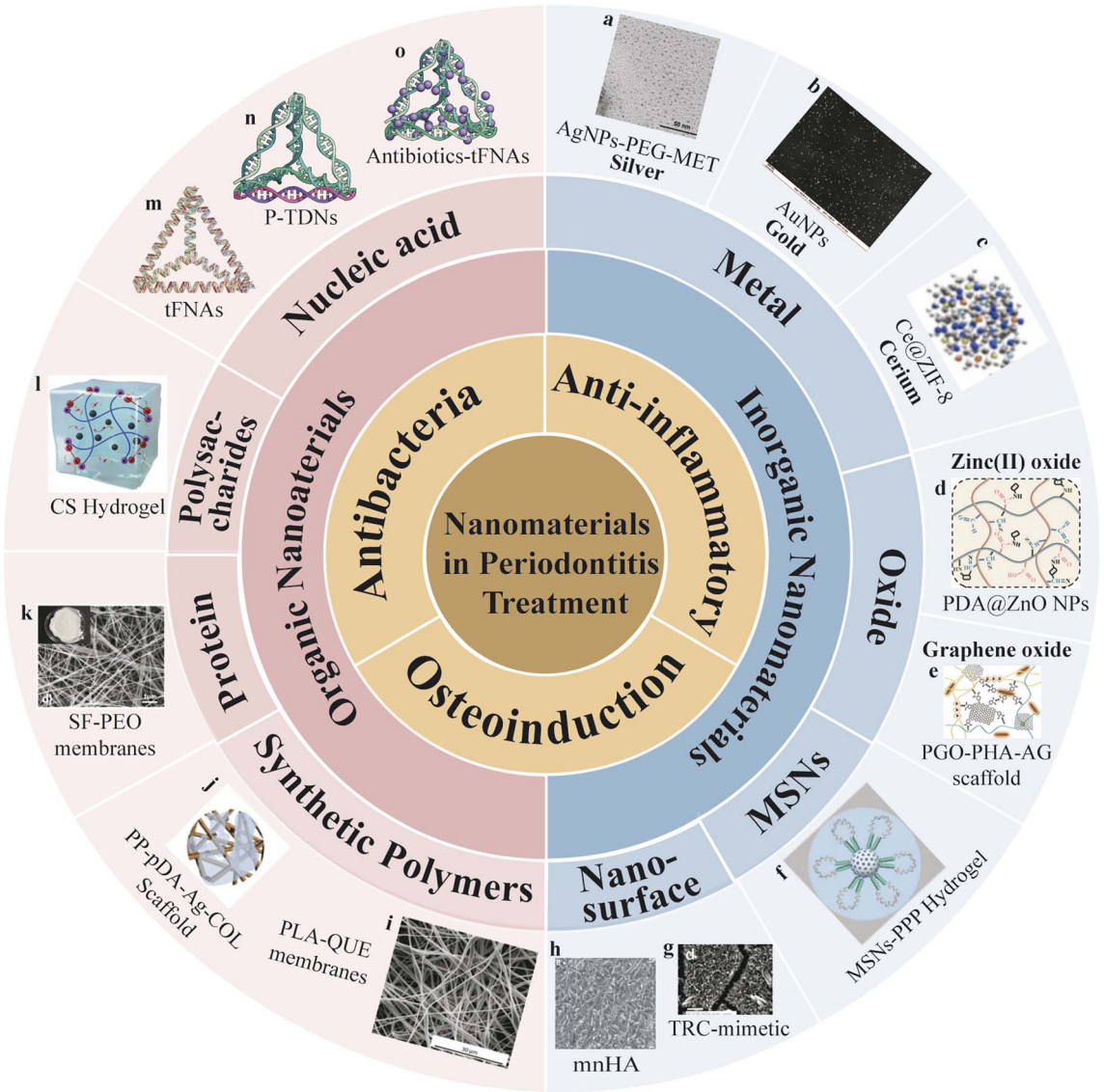

Fig. 1 Nanomaterials in periodontitis treatment (a) figure of silver surface attached with metronidazole molecules *via* a polyethylene glycol (PEG) linker (AgNPs-PEG-MET). Adapted under the terms of the CC-BY Creative Commons Attribution 3.0 Unported license from ref. 19. Copyright 2023, Dove Medical Press Limited. (b) Figure of gold nanoparticles (AuNPs). Adapted with permission from ref. 20. Copyright 2023, Elsevier. (c) Figure of Ce-doped ZIF-8 nanoparticles (ZIF-8: Ce NPs). Adapted with permission from ref. 21. Copyright 2023, ACS. (d) Figure of PDA coated ZnO NPs (PDA@ZnO NPs). Adapted with permission from ref. 22. Copyright 2023, Wiley. (e) Figure of a polydopamine-mediated graphene oxide (PGO) and hydroxyapatite nanoparticle (PHA)-incorporated conductive alginate/gelatin (AG) scaffold (PGO-PHA-AG scaffold). Adapted under the terms of the CC BY-NC-ND license from ref. 23. Copyright 2022, KeAi Publishing. (f) Figure of MSN-incorporated PPP hydrogel. Adapted under the terms of the CC BY-NC-ND license 4.0 from ref. 24. Copyright 2022, KeAi Publishing. (g) Figure of tooth root cementum (TRC)-mimetic. Adapted under the terms of the CC BY-NC-ND license 4.0 from ref. 25. Copyright 2022, American Chemical Society. (h) Figure of hydroxyapatite (HA) bioceramics with micro-nano-hybrid surface (mmHA). Adapted under the terms of the CC-BY Creative Commons Attribution 3.0 Unported license from ref. 26. Copyright 2015, Dove Medical Press Limited. (i) Figure of electrospun polylactic acid nanofibers loaded with Quercetin (PLA-QUE) membranes. Adapted under the terms of the CC BY-NC-ND license from ref. 27. Copyright 2022, MDPI. (j) Figure of silver-modified/collagen-coated electrospun PLGA/PCL scaffold (PP-pDA-Ag-COL scaffolds). Adapted with permission from ref. 28. Copyright 2019, ACS. (k) Figure of silk fibroin/poly(ethylene oxide) (SF/PEO) membranes. Adapted with permission from ref. 29. Copyright 2019, Elsevier. (l) Figure of Chitosan (CS) hydrogel. Adapted under the terms of the CC BY-NC-ND license 4.0 from ref. 30. Copyright 2020, KeAi Publishing. (m) Figure of tFNAs. (n) Figure of tFNAs loaded with PNAs (P-TDNs). (o) Figure of antibotics-tFNAs.

therapeutic outcomes. Their therapy approach usually has multiple therapeutic effects addressing three major aspects: antibacterial activity, anti-inflammatory capability, and tissue regeneration facilitation. This multifaceted approach is crucial for periodontitis treatment and holds promise for offering innovative therapeutic strategies. Hence, as the commonly utilized treatment methods still hold their defects, several emerging therapeutic technologies employ nanomaterials aiming to achieve better healing efficiency, such as aPDT, tissue engineering, and drug delivery. In this section, we will delve

Table 1 Different forms of nanomaterials employed in periodontitis treatment

Nanomaterials	Structure		Research mode	Therapeutic effect in periodontitis treatment	Mechanism	References
Tetrahedral framework nucleic acid	Monomer		*In vitro*/vivo	Anti-inflammatory, osteogenic differentiation induction	MAPK/ERK pathway inhibited	31
	Conjugate[a]	t-GL13K	*In vitro*	Antibacterial	Bacterial uptake of AMPs increased Susceptibility to the protease-rich extracellular environment	31
		P-TDNs	*In vitro*	Antibacterial	Bacterial uptake of asPNA increased → asPNA target ftsZ gene → bacterial growth inhibited	32
		stFNA–miR	*In vitro*/vivo	Osteogenic differentiation induction	Bacterial uptake of miR increased → expression of HDAC5 downgraded, osteogenic differentiation upgraded	
		ASOs-tFNAs	*In vitro*	Antibacterial	Bacterial uptake of ASOs increased → EPS synthesis and biofilm thickness decreased, expression of gtfBCD, gbpB, ftf downgraded	33
		tFNAs-Ery	*In vitro*	Antibacterial	Bacterial uptake of Ery increased → drug resistance inhibited	34
		tFNAs-ampicillin	*In vitro*	Antibacterial	Bacterial uptake of ampicillin increased → bacterial cell wall synthesis-related genes downgraded, antibiotic sensibility-related genes upgraded	35
Chitosan	CSnp (chitosan nanoparticle)		*In vitro*	Anti-inflammatory	Regulate paracrine signaling → macrophages polarization and PdLF migration increased	36
	Chitosan hydrogel		*In vitro*/vivo	Anti-inflammatory	NF-κB and p38 MAPK signaling inhibited Exosome-mediated transfer of miR-1246 increased	30
Hyaluronic acid	MBGN-MNCl/MHA gels[b]		*In vitro*	Anti-inflammatory, antibacterial, osteogenic differentiation induction	Irregular periodontal defects fitting Expression of bone-related genes increased	37

Table 1 (*Contd.*)

Nanomaterials	Structure	Research mode	Therapeutic effect in periodontitis treatment	Mechanism	References
				High load and sustained release of antibacterial MNCl	
	ROS-responsive HA@CUR NPs[c]	*In vitro*/vivo	ROS-responsive Anti-inflammatory, antibacterial, osteogenic differentiation induction	Release and maintain CUR in response to ROS Enhance cellular uptake at inflammation sites	38
Silk fibroin	TA/SF nanofibrous membranes[d]	*In vitro*	Osteogenic differentiation induction	*In situ* formation of HAp → osteogenic differentiation upgraded Induce a conformational change in SF molecules from random coils to β-sheets Cell proliferation promoted	39
	SF/GN membranes[e]	*In vitro*	Antibacterial, tissue regeneration	Prolonged release of vancomycin High cell compatibility Promote attachment, spreading, and proliferation of periodontal ligament cells	40
Synthetic polymers	A 3D aligned nanofibrous scaffold	*In vitro*/vivo	Osteogenic differentiation induction	Guide-oriented arrangement and elongation of cells	41
	Tri-Layered nanocomposite hydrogel scaffold with growth factors	*In vitro*/vivo	Osteogenic differentiation induction	Cementogenic, fibrogenic, and osteogenic differentiation of hDFCs increased	42
	A three-layered graded membrane nanostructure	*In vitro*	Osteogenic differentiation induction	Adjust the bioresorption behavior for optimal osteogenesis in different sites for defect repairs	43
	PDA coating of nanofibrous scaffolds	*In vitro*/vivo	Osteogenic differentiation induction	Hydroxyapatite mineralization increased PDLSCs osteogenic differentiation increased	44
	CTP-SA doped with Cu_2O and TiO_2@PDA nanoparticles[f]	*In vitro*/vivo	Antibacterial, osteogenic differentiation induction	TiO_2@PDA: generate ROS under blue light irradiation Cu_2O nanoparticles: antibacterial effect Cu^2: proliferation and osteogenic differentiation of BMSCs increased	45

Table 1 (*Contd.*)

Nanomaterials	Structure	Research mode	Therapeutic effect in periodontitis treatment	Mechanism	References
Silver nanoparticles	Monomer	*In vitro*	Antibacterial	Disrupt ATP molecules → direct damage to the cell membrane	16
	Chitosan-fucoidan complex-coated AgNPs	*In vitro*	Antibacterial	Biocompatibility, drug encapsulation, and cellular uptake increased	46
	Conjugate AgNPs-CHL, AgNPs-PEG-MET[g]	*In vitro*	Antibacterial, anti-inflammatory	Proinflammatory cytokines downgraded Levels of metalloproteinases MMP3 and MMP8 downgraded	19
Gold	$Au_{25}Sv_9$[h]	*In vitro*/vivo	Anti-inflammatory	NF-κB pathway inhibited	47
	AuNPs	*In vitro*	Anti-inflammatory	Macrophage: M1 → M2	48
		In vitro/vivo	Osteogenic differentiation induction	Wnt/β-catenin pathway, ERK/AMPK pathway and autophagy pathway upgraded	49–51
Cerium	ZIF-8: Ce NPs[i]	*In vitro*	Anti-inflammatory	SOD and CAT enzyme mimic activity → ROS scavenging Pro-inflammatory mediators downgraded NF-κB signaling pathway inhibited Macrophage: M1 → M2	52
	Quercetin-loaded ZIF-8: Ce NPs	*In vitro*	Anti-inflammatory	Anti-inflammation efficiency inceased	53
	CeO_2 NPs	*In vitro*/vivo	Anti-inflammatory and antibacterial	MAPK-NF-κB pathway inhibited Nrf2-HO-1 pathway upgraded	54
Graphene oxide	Monomer	*In vitro*	Antibacterial	*P. gingivalis* inhibited Bacterial cell membranes' structural integrity inhibited	55
	GO-AMOX[j]	*In vitro*	Antibacterial	Enzyme hydrolysis → controlled AMOX release	56
	GQDs-Cur[k]	*In vitro*	Antibacterial	Periodontal pathogens inhibited Biofilm-related genes downgraded	57
Zinc(II) oxide	Mino-ZnO@Alb[l]	*In vitro*	Antibacterial	Increase the encapsulation efficiency and loading capacity of minocycline	58

Table 1 (*Contd.*)

Nanomaterials	Structure	Research mode	Therapeutic effect in periodontitis treatment	Mechanism	References
				Targeted drug release in acidic environments typical of infection sites Demonstrates a broad antimicrobial spectrum	
	ZnO gel	*In vivo*	Antibacterial	Significant improvement in periodontal health outcomes after 1 month with PDT compared to SRP alone	59
Mesoporous silica nanoparticles	MSNs-antibiotics	*In vitro*	Antibacterial	Stable release of carried antibiotics	60–62
	MSN-Baicalin (BA)	*In vitro*	Anti-inflammatory	Cellular internalization increased by endocytosis and thiol-mediated mechanisms → immuno-inflammatory responses downgraded	63
	MSN-resveratrol (RSV)	*In vitro*/vivo	Anti-inflammatory	SIRT1/AMPK pathway upgraded NF-κB pathway inhibited Macrophage: M1 → M2	64
Composite of multiple materials	PP-pDA-Ag-COL[m]	*In vitro*/vivo	Antibacterial, osteogenic differentiation induction	Nanofibrous scaffold: MC3T3 cell adhesion and osteogenic differentiation increased AgNPs: antibacterial effect	28
	Composite PVA/CS films incorporating AgNPs[n]	*In vitro*	Antibacterial	*S. aureus* inhibited	65
	PEKK coated with/in an AgNP-in-epoxy lining	*In vitro*	Antibacterial	*P. gingivalis* inhibited	66
	SF-GO nano-configurations	*In vitro*	Osteogenic differentiation induction	Cell proliferation and osteo/cementoblast differentiation, cementum physiological synthesis increased	67
	P-GO scaffolds[o]	*In vitro*	Osteogenic differentiation induction	Osteogenic differentiation, cell proliferation, calcium deposition increased	68
	SF/CS/rGO blended membranes[p]	*In vitro*	Osteogenic differentiation	Bone regeneration increased	69
	PG-Cu@MSNs scaffold[q]	*In vitro*/vivo	Antibacterial, osteogenic differentiation induction	Osteogenesis and antibacterial effects increased	70
	Ag@QHMS[r]	*In vitro*	Antibacterial, osteogenic differentiation induction	Sustained Ag^{+} release → stable antibacterial effects	71

Table 1 (*Contd.*)

Nanomaterials	Structure	Research mode	Therapeutic effect in periodontitis treatment	Mechanism	References
	BPNSs (Black phosphorus nanosheets)	*In vivo*	Antibacterial, anti-inflammatory	Osteogenic differentiation of BMSCs increased Rapid electron transport → ROS consumption capabilities Antibacterial and anti-inflammatory capabilities → protect cells from oxidative stress and accompanying inflammatory reactions induced by aPDT	72
	CeO_2@Ce6[s]	*In vitro*/vivo	Antibacterial, anti-inflammatory	SOD and CAT enzyme mimic activity → ROS scavenging	18
Inorganic nanosurface	Titanium surfaces with microgrooves and nanopores	*In vitro*	Osteogenic differentiation induction	Actin cytoskeleton polymerization increased ERK and p38 MAPK pathways upgraded Nuclear translocation and transcriptional activity increased → TAZ activation increased	73
	Titanium surfaces mimicking TRC	*In vivo*	Osteogenic differentiation induction	Regulates periodontal ligament cells and coordinates phosphate metabolism	25
	Hybrid nanorod and microrod (mnHA) surfaces	*In vitro*	Osteogenic differentiation induction	Wnt pathway upgraded	26

[a] t-GL13K: tFNAs loaded with GL13K; P-TDNs: tFNAs loaded with asPNA; stFNA-miR: tFNAs loaded with miRNA; ASOs-tFNAs: tFNAs loaded with ASOs; tFNAs-Ery: tFNAs loaded with erythromycin; tFNAs-ampicillin: tFNAs loaded with ampicillin. [b] Methacrylic anhydride modified HA with minocycline hydrochloride-loaded mesoporous bioactive glass nanoparticles. [c] HA-based nano-loading system designed to encapsulate curcumin into nanoparticles. [d] Tannic acid modified electrospun silk fibroin nanofibrous membranes. [e] Silk fibroin nanofibrous membranes containing gelatin nanospheres. [f] Sodium alginate hydrogel composites doped with Cu_2O nanoparticles and PDA-coated titanium dioxide nanoparticles. [g] AgNPs loaded with chlorhexidine and metronidazole. [h] Peptide-coated gold cluster. [i] Ce-doped ZIF-8 nanoparticles. [j] Amoxicillin linked to GO using a peptide linker. [k] Graphene quantum dots coupled with curcumin. [l] Zinc oxide nanoparticles incorporated into an albumin-based carrier. [m] Silver-modified/collagen-coated electrospun PLGA/PCL scaffold. [n] AgNPs incorporated into a composite film synthesized from poly(vinyl alcohol) cross-linked with oxidized chitosan. [o] PCL scaffolds coated with GO. [p] Chitosan/silk fibroin membranes incorporating reduced graphene oxide. [q] Copper-loaded MSNs integrated into a PLGA/gelatin fiber matrix. [r] Quaternary ammonium salts-modified core–shell MSNs containing Ag nanoparticles. [s] CeO_2 coupled with chlorin e6.

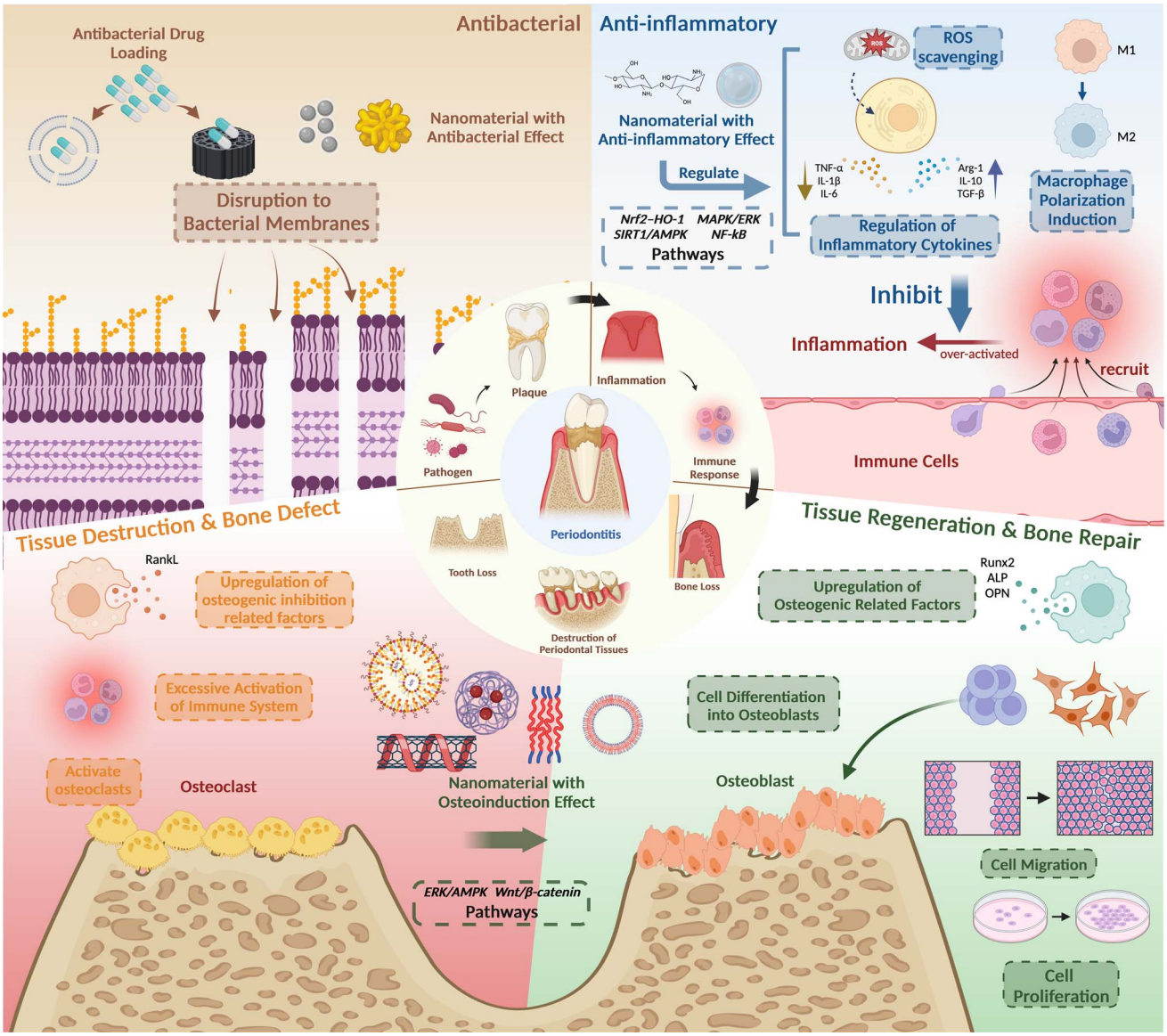

Fig. 2 The pathological mechanism and treatment strategies of periodontitis. Created with https://BioRender.com/.

into the latest advancements in the design strategies of nanomaterial in periodontitis treatment including organic nanomaterials, inorganic nanomaterials and nanosurface, summarize their applications across *in vitro* and *in vivo* studies, and introduce their combination with emerging therapeutic technologies.

3.1 Organic nanomaterials

3.1.1 Nucleic acid-tetrahedral framework nucleic acids (tFNAs). Tetrahedral framework nucleic acids, commonly referred to as tetrahedral DNA nanostructures (TDN),[80] have emerged as a distinctive nanoscale architecture garnering significant interest in biomedical investigations. tFNAs comprise four preassembled single-stranded DNA (ssDNA) molecules, each containing three complementary sequence blocks adhering to the Watson–Crick base pairing principles. This arrangement yields a stable tetrahedral framework composed of interconnected DNA helical triangles, and also offers mechanical flexibility at every vertex.

Remarkably, tFNAs have been found to be biologically active despite DNA's polyanionic nature. Their spatial configuration enables easy traversal of cellular plasma membranes, enhancing the effective delivery of nucleic acids with negative or neutral charge.[81] tFNAs also show remarkable structural stability within living cells, lasting up to 48 hours,[82] while also demonstrating exceptional biocompatibility.[83] Moreover, research indicates that relatively high concentrations of tFNAs can stimulate cell proliferation, differentiation, and migration.[84] Additionally, tFNAs offer programmability and unique modification sites, facilitating the incorporation of small molecules and nucleic acids, thereby serving as a versatile drug delivery platform.[85]

Zhou *et al.* present compelling evidence on tFNAs' anti-inflammatory and osteogenic differentiation-inducing properties in periodontitis treatment (Fig. 3). Their research demonstrates that tFNAs protect periodontal ligament stem cells (PDLSCs) from inflammation by suppressing the MAPK/ERK signaling pathway phosphorylation. *In vivo* experiments on mice's periodontium show reduced inflammatory cell infiltration and pro-inflammatory factor release in the tFNAs-treated group, highlighting their anti-inflammatory efficacy. Moreover, assessments of osteogenic markers in PDLSCs treated with

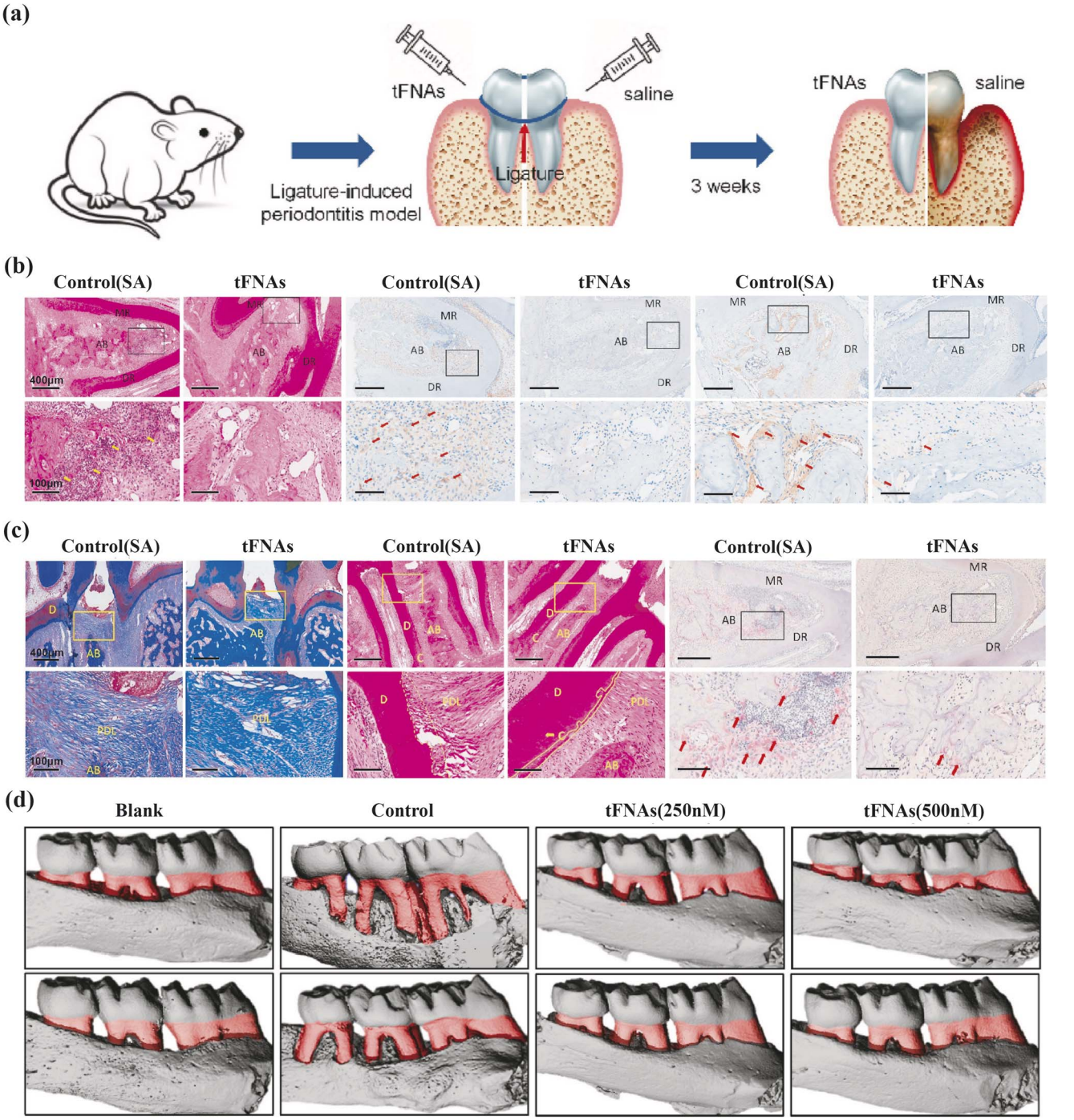

Fig. 3 The protective effect of tFNAs on periodontium under inflammatory conditions. (a) Schematic diagram of the rat periodontitis experiment. (b) H&E staining (yellow arrow: inflammatory cells), the immunohistochemical results of IL-1β/IL-6 (red arrow) at 5× and 20× magnifcation. (c) Masson staining, H&E staining (yellow solid line: cementum, yellow dotted line: cementum absorbed by inflammation), TRAP staining (red arrow: osteoclasts) at 5× and 20× magnification. (d) The micro-CT 3D reconstruction images of left maxillary alveolar bone (red part: the exposure of root). MR/DR = mesial root/distal root; AB = alveolar ridge; D = dentin; C = cementum; PDL = periodontal ligament. Adapted under the terms of the CC BY-NC-ND license 4.0 from ref. 80. Copyright 2020, Elsevier.

tFNAs under inflammatory conditions show promising results. Mice with periodontitis receiving tFNAs injections in the gingival sulcus exhibit denser periodontal ligaments, increased collagen fiber density, intact cementum and Sharpey fibers, decreased osteoclast populations, and reduced bone resorption compared to control groups. Collectively, these findings underscore the therapeutic potential of tFNAs in bone regeneration.[80]

Additionally, findings from other researchers support tFNAs' ability to utilize their unique biological properties, including modulating periodontitis-related pathways and acting as drug delivery vectors, to provide therapeutic benefits. These studies offer additional validation of tFNAs' potential in periodontitis treatment, providing a complementary perspective on their therapeutic utility.

Effective antibacterial activity is crucial in combating periodontitis, which is primarily triggered by bacterial biofilm formation. In antimicrobial therapy, tFNAs serve as versatile drug delivery vehicles. Liu discussed the structure of t-GL13K, where tFNAs are used to deliver GL13K peptides.[31] These peptides (antimicrobial peptide, AMPs) are antimicrobial agents that interact with microbial membranes through electrostatic and hydrophobic forces, causing irreversible membrane damage and cytoplasmic leakage.[86] By increasing bacterial uptake and membrane interactions, t-GL13K showed improved effectiveness against *Escherichia coli*.[87] Additionally, t-GL13K remained effective against *P. gingivalis* due to reduced susceptibility to extracellular protease-rich environments. Beyond traditional peptides, nucleic acids can be easily integrated with tFNAs using base pairing principles. Zhang and colleagues created the P-TDNs vector system, which incorporates antisense peptide nucleic acids (asPNA) into tFNAs. These synthetic DNA analogs target the *ftsZ* gene in bacteria, leading to a dose-dependent decrease in *ftsZ* expression and bacterial growth inhibition, demonstrating potential for asPNA delivery.[32] MicroRNAs have also been linked with tFNAs, with Zhang and team designing antisense oligonucleotide sequences (ASOs) targeting conserved regions of the VicK protein-binding site, using tFNAs as the delivery method (ASOs-tFNAs) (Fig. 4). This strategy significantly reduced EPS production and biofilm thickness, facilitating the treatment of chronic biofilm-related infections that are resistant to standard treatments.[33]

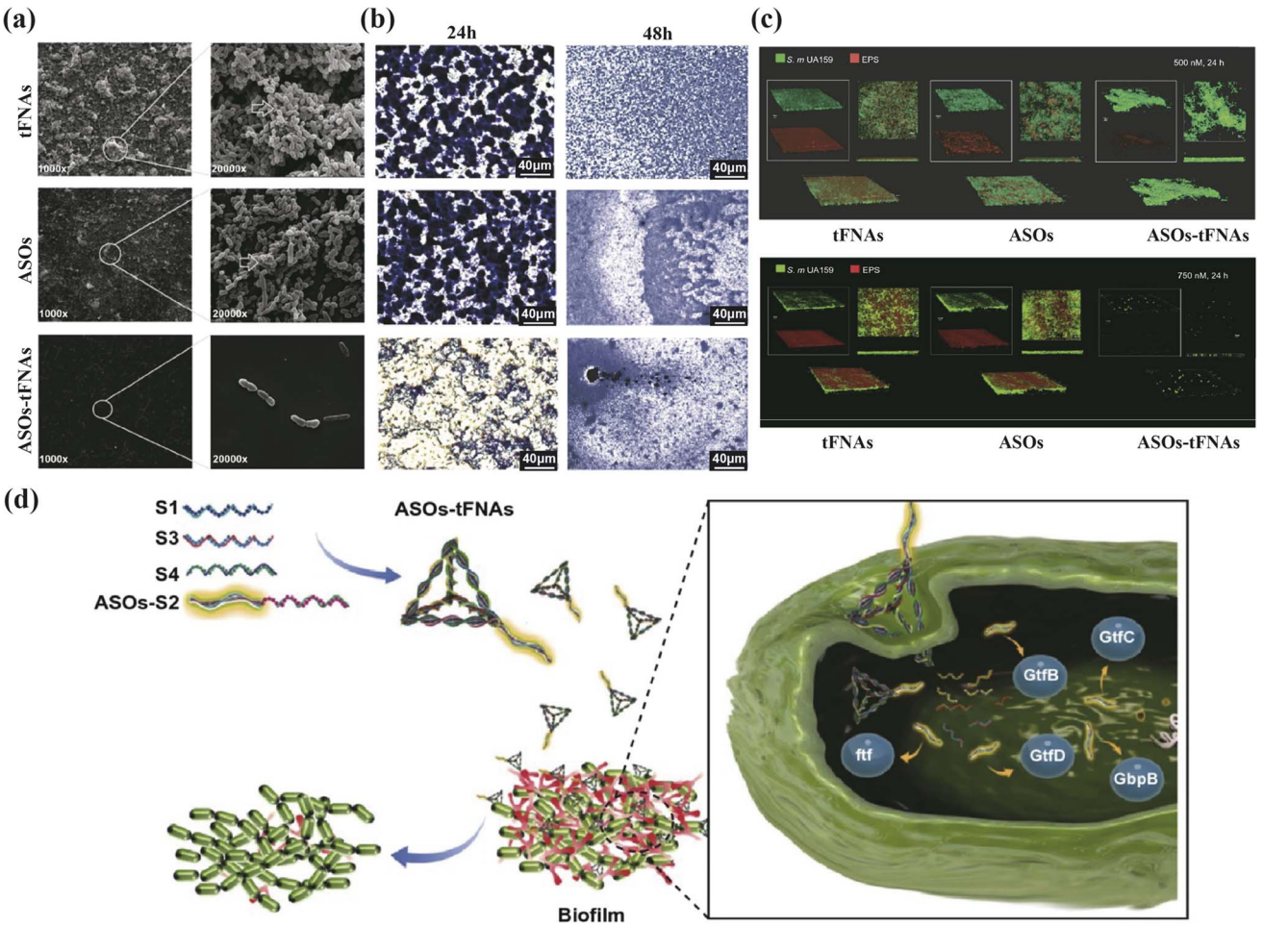

Fig. 4 Multi-targeted ASOs-tFNAs for inhibiting biofilm formation and virulence. (a) SEM images of the structure of biofilms (24 h), (b) crystal violet staining of *S. mutans* cells (24 h, 48 h), (c) dual-label imaging and 3D visualization of EPS (red) and bacteria (green) in *S. mutans* biofilms, after treated with tFNAs, ASOs, or ASOs-tFNA. (d) Schematic diagram of the mechanism of ASOtFNAs delivery system. Adapted under the terms of the CC BY-NC-ND license 4.0 from ref. 33. Copyright 2020, Springer.

Furthermore, tFNAs have been crucial in delivering small-molecules like erythromycin and methicillin, with research showing enhanced bacterial uptake and improved antibacterial activity, thereby addressing bacterial resistance challenges.[34,35]

Furthermore, tFNAs have exhibited the capacity to induce osteogenic differentiation in stem cells *via* the Wnt/β-catenin and Notch pathways, offering novel methods for tissue regeneration in periodontitis treatment. Shao *et al.* observed upregulated expression of key proteins in the Wnt pathway in adipose-derived stem cells (ADSCs) treated with tFNAs, promoting ADSC osteogenic differentiation.[88] Zhou *et al.* demonstrated tFNAs' stimulation of the Notch pathway in dental pulp stem cells (DPSCs), enhancing osteogenic differentiation through increased expression of crucial Notch pathway factors.[89] Alkaline phosphatase staining and calcium deposition assays further corroborated these findings. In addition to the osteogenic effect of the tFNAs itself, it can also carry microRNAs targeting osteogenic genes to transport them into cells, stabilizing the microRNA structure[90] and increasing its endocytosis rate, while also exerting better therapeutic effects. Li's study involved the loading of miR-2861 onto tFNAs (stFNA-miR), which targets histone deacetylase 5 (HDAC5) to upgrade runt-related transcription factor 2 (Runx2) protein expression.[91] This research investigated the impact of stFNA-miR on bone regeneration and drug toxicity in both *in vitro* and *in vivo* models. Statistical analysis confirmed the successful transportation of stFNA-miR into bone marrow-derived mesenchymal stem cells (BMSCs) and its release upon RNase H cleavage. Furthermore, the anticipated regulation of proteins was observed. *In vivo* experiments demonstrated promising outcomes for bone regeneration within the defect area.[92]

In conclusion, tFNAs represent a versatile and promising platform for drug delivery and therapeutic applications, showcasing exceptional biocompatibility, stability, cellular uptake capabilities, and diverse biological function. Their potential to transport a range of bioactive molecules into target cells positions them as valuable tools in advancing biomedical research and innovative therapies, such as in periodontitis treatment.

3.1.2 Natural polymers. Polymers constitute a large portion of organic nanomaterials, which can be categorized into natural polymers and synthetic polymers based on their sources. Generally speaking, organic nanomaterials exhibit excellent biocompatibility, making them widely applicable in tissue engineering. However, different sources endow them with distinct advantages: natural polymers are characterized by lower biotoxicity, better degradability, and some unique biological functions; whereas synthetic polymers benefit from their high processability, lower manufacturing costs, and convenient preparation methods. In this section, we will introduce the various subcategories and specific applications of natural polymers, and the application of synthetic polymers will be discussed in Section 3.1.3.

3.1.2.1 Polysaccharides—chitosan and hyaluronic acid

3.1.2.1.1 Chitosan (CS). Chitosan, primarily sourced from crustacean exoskeletons, is a naturally derived biomaterial renowned for its attributes including biodegradability, biocompatibility, non-toxicity, hydrophilicity, and intrinsic antibacterial and antifungal properties.[93]

As a naturally derived biomaterial, CS possesses distinctive anti-inflammatory characteristics, capable of modulating various cytokines based on factors such as structure, deacetylation degree, relative molecular mass, and dosage.[94] In the study conducted by Hebatullah, engineered bioactive chitosan-based nanoparticles (CSnp) were investigated for their potential to upregulate proteins with antioxidant and immunoregulatory properties, promoting the polarization of macrophages into the M2 phenotype and PdLF migration *via* paracrine signaling.[36] However, further research is warranted to comprehensively assess the capacity of CSnp to enhance periapical tissue healing *in vivo*.

In most scenarios, CS is usually used as a drug-loading platform. Through chemical modifications, CS can acquire elasticity, flexibility, and induce minimal inflammatory responses owing to its β-(1,4) glycosidic bonds, rendering it an exceptional platform for drug delivery.[95] Chitosan-based materials aiming periodontitis treatment comes in various terms including scaffolds,[96] films,[97] *etc.*, however, the chitosan hydrogel has become a current research hotspot for its easily-modified mechanical properties[98] and its ability to fit in different shapes and sizes of tissue defects by simply inject the pre-gel solution.[99] For instance, Shen *et al.* fabricated DPSC-Exo-incorporated CS (DPSC-Exo/CS) and then proved its abilities to facilitate macrophages to convert to an anti-inflammatory phenotype, cut down epithelial lesion and speed up the alveolar bone coalescence in periodontitis mice.[30] More research is underway to leverage the unique drug-carrying biological characteristics of CS.

3.1.2.1.2 Hyaluronic acid (HA). HA is a glycosaminoglycan and a natural component of the extracellular matrix,[100] known for its high water retention, absorbency, and excellent biocompatibility. Biologically, HA exhibits significant anti-inflammatory properties by inhibiting the production of pro-inflammatory mediators,[101] and it also possesses antimicrobial properties that inhibit the growth and adhesion of various microorganisms.[102] Clinical randomized studies have shown that using HA as an adjunct to standard non-surgical periodontal therapy improves the antioxidant status in the oral cavity of periodontitis patients, reduces gingival inflammation, and increases periodontal attachment.[103]

However, HA's clinical efficacy is limited by its sensitivity to free radicals and susceptibility to degradation by hyaluronidase.[104,105] To enhance its resistance to degradation and mechanical strength, a series of chemical modifications are necessary. Hu *et al.* addressed these limitations by modifying HA with methacrylic anhydride (MHA), achieving cross-linking under UV irradiation.[37] This modification not only compensates for HA's instability and weak mechanical strength but also provides an injectable drug delivery approach, facilitating localized drug delivery to periodontal lesions. Despite laboratory evidence of HA's antimicrobial capability, systematic reviews of clinical trials indicate that HA as an adjunct to non-surgical mechanical treatment of periodontitis does not provide

additional benefits in reducing the prevalence of *P. gingivalis* in subgingival biofilms.[106] To further enhance the antibacterial and tissue regeneration capabilities of MHA gels, Hu *et al.* introduced minocycline hydrochloride (MNCl) loaded spherical mesoporous bioactive glass nanoparticles (MBGNs) to prepare MBGN-MNCl/MHA gels for treating irregular periodontal defects caused by periodontitis. Research data showed that MHA gels have good morphological adaptability, healing within the defect area after 30 seconds of UV irradiation, and exhibit excellent anti-inflammatory effects with low cytotoxicity. MBGNs (120 nm) have outstanding osteogenic properties, significantly promoting the expression of ALP, Runx2, OPN, and bone-related genes in MC3T3-E1 cells. Additionally, they can achieve a high load of 120 mg g^{-1} of antibacterial MNCl with sustained release, effectively inhibiting the proliferation of *Streptococcus mutans*. Hu *et al.*'s experimental results provide valuable insights for further chemical modifications of HA, enhancing its clinical utility in periodontal therapy.

Beyond leveraging HA's inherent biological functions, HA can also serve as a tool for targeted drug delivery in periodontitis treatment by specifically binding to various receptors, such as CD44, and facilitating endocytosis.[107] Chen *et al.* developed an HA-based nano-loading system designed to encapsulate curcumin (CUR) into nanoparticles (NPs), targeting macrophages, fibroblasts, and epithelial cells with high CD44 expression, thereby achieving targeted delivery of CUR.[38] Since excessive ROS produced during periodontitis can cause DNA damage, protein denaturation, and periodontal tissue damage, the researchers further modified HA using the pinacol ester of 4-hydroxybenzeneboronic acid (PBAP) to create an HA-PBAP ROS-responsive smart nano-loading system. This modification enabled HA@CUR NPs to release the drug in response to ROS, enhancing cellular uptake at inflammation sites and maintaining drug release at the lesion. The research demonstrated that HA@CUR NPs exhibit high antibacterial, anti-inflammatory, ROS scavenging, and immunomodulatory capabilities. Moreover, HA's ability to achieve long-term retention in the oral cavity ensures prolonged treatment for periodontitis, thereby benefiting patient compliance. As a novel multifunctional nanocarrier, HA@CUR NPs offer a promising reference for clinical applications in treating periodontitis.

3.1.2.2 Protein-silk fibroin (SF). Silk fibroin, a high-purity protein extracted from silk, boasts a rich amino acid composition with over 20 constituents, including glycine, alanine, and serine.[108] This natural polymer offers exceptional mechanical attributes, encompassing biocompatibility, permeability to oxygen and water, degradability, and inducing minimal inflammatory responses.[29] In terms of fabrication versatility, SF lends itself to flexible processing, enabling the production of nanoparticles,[109] nanofibers,[29] and scaffold[14] in periodontitis therapy.

Silk fibroin has long been recognized as a strong candidate for guided tissue regeneration (GTR) membranes due to its excellent mechanical properties. However, the regeneration process of SF solution can disrupt the protein conformation and the parallel fiber structure of natural SF fibers, which limits their application in GTR treatments.[110] Furthermore, SF-based membranes traditionally exhibit limited bone repair capabilities.[111] To address these limitations, Zheng *et al.* developed a straightforward method for the direct modification of electrospun SF nanofibrous membranes, enhancing both their mechanical properties and osteogenic functions.[39] Tannic acid (TA), with its rich phenolic hydroxyl moieties, provides abundant chelate sites for Ca^{2+} ions, thereby accelerating the *in situ* formation of hydroxyapatite (HAp) on the SF nanofibrous membranes. Additionally, TA induces a conformational change in SF molecules from random coils to β-sheets. The results indicated that the TA modification improved the hydrophilicity and mechanical performance of the SF membranes. Further experiment evaluated SF-based nanofibrous membranes for cell growth, proliferation, and osteogenic differentiation. The ST film-MI7d group showed higher OD values on day 5, indicating better osteoblast proliferation due to its porous structure and HAp content. Flow cytometry revealed low necrosis and apoptosis, confirming no adverse effects on cell viability. The living rate of MC3T3 cells was high across all groups, demonstrating good cytocompatibility. The ST film-MI7d group had lower ALP activity on day 7 but the highest on day 14, indicating positive effects on osteogenic differentiation. This group also showed the highest ECM mineralization and calcium deposition, suggesting that HAp formation on the film enhances osteogenesis by regulating protein synthesis and promoting bone mineral generation. Due to the simplicity and efficiency of the method, TA-mediated SF fiber modification holds significant potential for future applications.

In addition to their role in tissue regeneration and repair, enhancing the antibacterial activity of SF fiber-based biomaterials is crucial for achieving comprehensive treatment effects for periodontitis. Song *et al.* addressed this by developing novel silk fibroin nanofibrous membranes containing gelatin nanospheres (SF/GN membranes).[40] Utilizing core–shell electrospinning technology, they incorporated substantial amounts of positively charged gelatin type A nanospheres (GANs) and negatively charged gelatin type B nanospheres (GBNs) loaded with positively charged vancomycin into the silk fibroin nanofibers. By adjusting the weight ratio between the nanospheres at the nanoscale using single-nozzle electrospinning, they achieved a prolonged release of vancomycin (up to 14 days). The experiment demonstrated that SF nanofibrous membranes with GBNs sustained vancomycin release for over 14 days, while those without GBNs stopped after 2 days. The presence of GBNs prolonged the release due to attractive interactions with vancomycin. Antibacterial tests showed that vancomycin-loaded membranes inhibited *S. aureus*, with larger inhibition zones for higher vancomycin loading. Membranes with vancomycin-loaded GBNs maintained antibacterial effects after the initial burst release, indicating enhanced sustained release and efficacy. Furthermore, they also found that SF/GN membranes exhibited excellent cytocompatibility and supported cell viability and proliferation. Live/dead assays and DNA content tests confirmed high cell viability and proliferation on membranes containing GBNs, compared to those without. SEM images showed enhanced cell attachment and spreading on GBN-containing membranes. These results underscored the

beneficial role of SF/GN membranes (loaded with GBNs) in promoting cell adhesion and growth by exposing cell recognition sites upon membrane dissolution.

3.1.3 Synthetic polymers. Synthetic polymers are widely used nanomaterials in periodontitis research due to their excellent spinnability and thermal stability,[112] which made them easy to prepare into diverse forms, including nanoparticles,[113] nanospheres, nanofibrous, and scaffold.[41] Polycaprolactone (PCL) is a biodegradable polymer with availability, low price, and suitability for modification, and more importantly, it has a long degradation time that coincides with tissue healing, making PCL a popular material in tissue engineering.[114] Polylactic acid (PLA) was extracted from plants in the first case and can now be prepared easily by chemical methods. During its degradation, PLA only generates CO_2 and H_2O, which makes it highly environmentally friendly.[115] Polylactic acid-*co*-glycolic acid (PLGA) has a long history since the 1970s, due to its excellent biocompatibility and biodegradability,[116] used in different senses, including biodegradable sutures, drug delivery, and tissue engineering.

3.1.4 Organic nanomaterial applied in tissue engineering in periodontitis treatment. In recent years, diverse strategies have been explored to address severe bone defects through bone tissue engineering therapy. These approaches encompass biomimetic scaffolds, which mimic the microarchitecture of native bone tissue to facilitate tissue formation and cell differentiation;[117] stem cell engineering therapy, involving the use of various stem cells from dental tissue to regenerate periodontal structures;[118] and guided bone regeneration (GBR) therapy, which employs barrier membranes to isolate fibroblasts in surrounding soft tissues, enabling the proliferation of osteoblasts to achieve tissue regeneration and repair of bone defects.[119] Organic nanomaterials have also emerged as a vital resource in tissue engineering due to their biocompatibility and multiple biological capabilities.

In practice, biomimetic scaffolds and stem cell engineering therapy often share common design principles and are frequently combined to enhance therapeutic outcomes. For instance, Zhang *et al.* integrated PCL-PEG (PCE) nanofibers into porous chitosan (CS) to create a 3D aligned layer-by-layer nanofibrous scaffold. They assessed its potential for topographic guidance and periodontium regeneration by introducing the 3D scaffold into an *in vitro* rBMSCs model and a rat periodontal defect model. In this scaffold, PEG improved water wettability and degradation of PCL, while CS enhanced material adhesion and provided anti-inflammatory properties. Their findings indicated that the nanoscale arrangement of scaffolds offered cues for cell alignment, promoting the alignment of adhered cells in the same direction. Furthermore, the scaffold directed the osteoblastic differentiation of MSCs, consistent with results in the rat model.[41] To further enhance hard tissue regeneration, Sowmya *et al.* introduced rhCEMP1, rhFGF2, and PRP-derived growth factors into a three-layer nanocomposite hydrogel scaffold containing nBGC and chitin-PLGA polymeric blend. They evaluated cementogenic, fibrogenic, and osteogenic differentiation of hDFCs on the scaffold and in rabbit periodontal defect models. Positive results were observed in groups with growth factors.[42] As stem cells, including BMSCs, DFCs, and PDLSCs, possess robust osteogenic differentiation abilities, numerous studies are exploring the use of stem cells as a crucial component in periodontal regeneration.[48,120] Consequently, the potential combination of stem cells and scaffolds holds promise for advancing tissue engineering in periodontitis treatment.

In the realm of guided bone regeneration therapy, membrane forms are widely accepted. Polymer membranes, in particular, have emerged as promising materials that overcome limitations associated with non-resorbable and weak membranes. These materials offer absorbability, high strength, and ease of use. Liao *et al.* employed nano HA/collagen/PLA (nHAC/PLA) as a barrier membrane to create osteoblast/complex constructs and nano carbonated hydroxyapatite/collagen (nCHAC) complexes as bioactive components. These materials effectively induced the differentiation of undifferentiated cells at the recipient site of the graft into osteoblasts and promotion of new bone formation.[43] Hasani-Sadrabadi *et al.* developed a PDA-coated PCL (PDA-PCL) membrane modified with functional proteins, including cytokines, growth factors, and extracellular proteins, to precisely control the chemical characteristics of the matrix based on physical patterns, thereby facilitating periodontal tissue regeneration.[44] Beyond traditional membrane forms, novel structures such as injectable sodium alginate hydrogel composites (CTP-SA) have also been investigated. These composites avoid the need for precise membrane tailoring before implantation. Xu *et al.* reported a CTP-SA doped with Cu_2O nanoparticles and PDA-coated titanium dioxide (TiO_2@PDA) nanoparticles. Under blue light irradiation, TiO_2@PDA generated ROS, exhibiting antibacterial properties and oxidizing Cu^+ in Cu_2O nanoparticles to Cu^{2+}, promoting osteogenesis. This technique allows CTP-SA to transform between antibacterial and osteogenic modes, offering a novel GTR strategy in terms of form and treatment cycle.[45]

3.2 Inorganic nanomaterials—metal, oxide, silica and inorganic nanosurface

Inorganic nanomaterials, encompassing metals, oxides, and silicates, play a pivotal role in the development of advanced periodontitis treatment strategies. Their synthesis and processing are relatively straightforward, allowing these materials to be reduced to nanoscale dimensions through physical and chemical methods. In this nanosized form, they can be effectively incorporated into various periodontitis treatment modalities. Moreover, introducing diverse surface morphologies through inorganic nanosurface modification provides terrain induction for cell migration and osteogenic regeneration at defect sites. These tailored surface features can guide cellular behavior, promoting more effective tissue integration and enhancing the regenerative processes essential for healing and repair. Notably, due to their distinctive physical properties, inorganic materials such as metals are particularly useful in aPDT, where they synergistically enhance the antibacterial effects of aPDT. This section explores the different subcategories of inorganic nanomaterials employed in periodontitis treatment, and the application of aPDT will be discussed in Section 3.2.5.

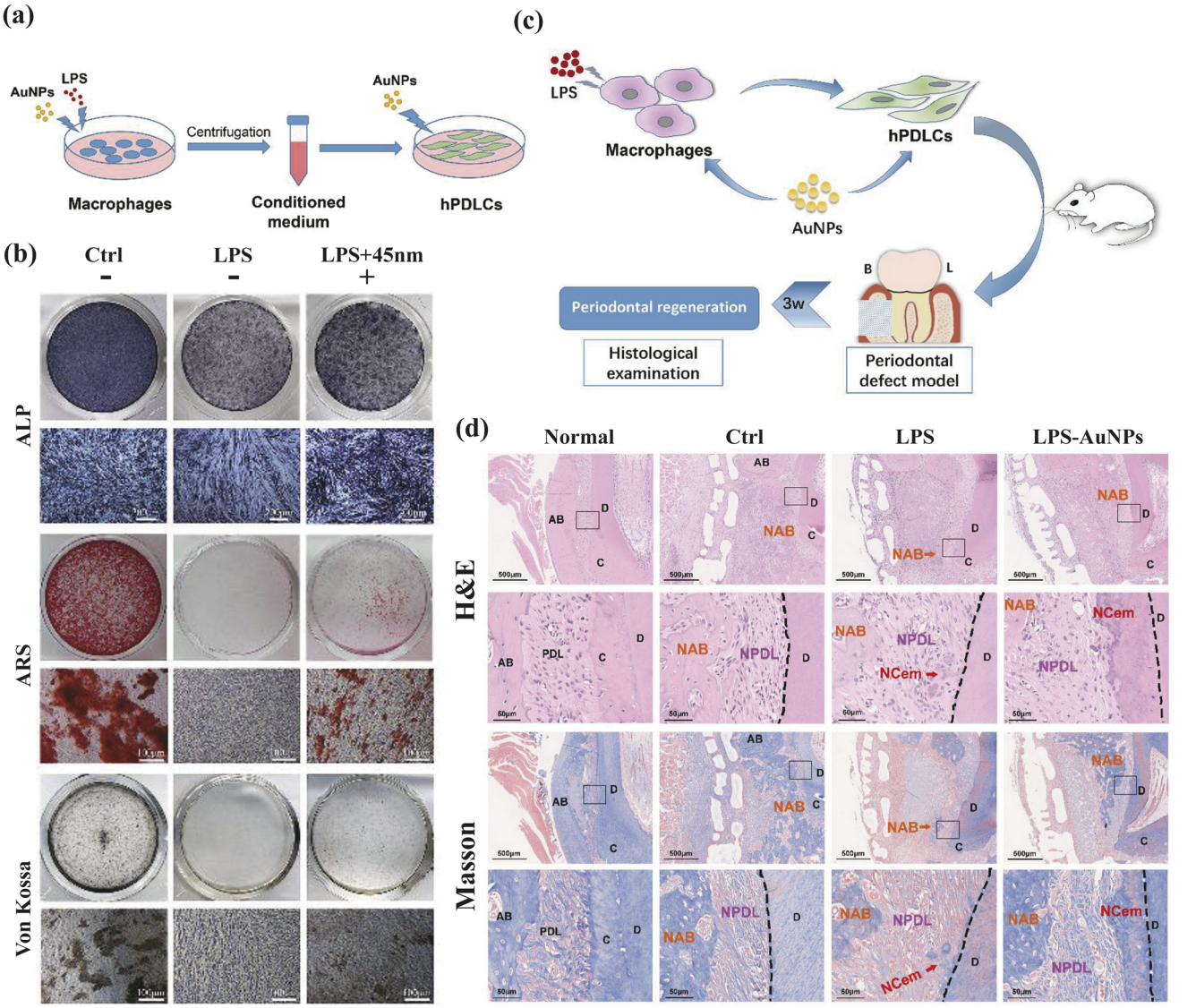

Fig. 5 AuNPs modulate the crosstalk between macrophages and periodontal ligament cells for periodontitis treatment. (a and b) AuNPs promote osteogenic and cementogenic differentiation of hPDLCs in LPS-induced inflammatory conditions. (A) Schematic diagram. (b) ALP staining (day 7); ARS and Von Kossa staining (day 21). (c and d) The macrophage-hPDLCs coculture system modulated by AuNPs showed better periodontal regeneration potential in a rat periodontal defect model. (c) Schematic diagram. (B = buccal side, L = lingual side). (d) H&E and Masson staining (3 weeks). Adapted under the terms of the CC BY-NC-ND license 4.0 from ref. 48. Copyright 2019, Elsevier.

3.2.1 Metal

3.2.1.1 Silver nanoparticles (AgNPs). AgNPs, characterized by their unique physicochemical properties,[121] enhanced antibacterial activities,[122] and excellent drug loading capabilities,[123] demonstrated promise in dental therapy. In much of the research, AgNPs are typically synthesized using the chemical deoxidization method, where Ag^+ ions in $AgNO_3$ are chemically reduced to Ag^0 atoms using $NaBH_4$.[124] However, concerns about the cost and toxicity associated with this chemical deoxidization method have been raised. To adopt a greener synthesis approach, researchers have turned to various natural products, leading to the production of diverse biosynthesized AgNPs, including those synthesized from plant extracts[121] and by endophytic fungi *Fusarium semitectum*.[125]

AgNPs exhibit a broad-spectrum antibacterial effect, including drug-resistant strains. This effect is attributed to the release of Ag^+ ions, which disrupt ATP molecules and cause direct damage to the cell membrane.[16] Importantly, AgNPs have a low potential to induce antibacterial resistance.[126] Due to their potent antibacterial activity, AgNPs are employed either independently or integrated into other nanostructures for early-stage antibacterial treatment of periodontitis.

In scenarios where AgNPs are applied separately for antibacterial therapy to enhance their biocompatibility, biodegradability, and cellular uptake, Venkatesan *et al.* developed chitosan-fucoidan complex-coated AgNPs. This approach aimed to leverage better drug encapsulation and cellular absorption abilities of chitosan-fucoidan polyelectrolytes/nanoparticles.[46] However, the primary application of AgNPs is to serve as novel

antibacterial agents within various nanomaterials, such as guided tissue regeneration and guided bone regeneration (GBR) scaffolds. Qian *et al.*, for instance, introduced a novel silver-modified/collagen-coated electrospun PLGA/PCL scaffold (PP-pDA-Ag-COL) impregnated with AgNPs to impart antibacterial properties. In their study, the scaffolds can release silver ions out of AgNPs in a controlled speed, thus significantly inhibited the growth of *S. mutans* and *Staphylococcus aureus*, promoting both bacterial inhibition and the proliferation and differentiation of MC3T3 cells.[28] Similarly, Constantin *et al.* incorporated AgNPs into a composite film synthesized from poly(vinyl alcohol) (PVA) cross-linked with oxidized chitosan (OxCS), demonstrating significant antimicrobial activity against *S. aureus*.[65] Additionally, Lee *et al.* employed an epoxy lining to incorporate AgNPs onto the Polyetheretherketone (PEKK) surface and evaluated their antibacterial activity against *P. gingivalis* using the disc diffusion method. Their results indicated that 0.5% Ag-PEKK and Ag-PEEK exhibited diffusive properties that suppressed the growth of *P. gingivalis*.[66] In summary, AgNPs' exceptional antibacterial properties position them as promising nanomaterials for the antibacterial treatment of periodontitis.

In addition to their remarkable antibacterial properties mentioned earlier, AgNPs can also serve as an effective drug delivery platform. By co-administering them with an antibacterial agent, it becomes possible to synergistically harness the antibacterial effects of both AgNPs and the medication, thereby significantly enhancing antibacterial treatment efficacy. Steckiewicz *et al.* conducted experiments in which they combined AgNPs with chlorhexidine (AgNPs-CHL) and metronidazole (AgNPs-PEG-MET) and assessed their antibacterial and anti-inflammatory properties *in vitro*. The results demonstrated their successful downgrading in the production of proinflammatory cytokines like IL-1β, and the inhibition of tissue degradation by cutting down the production of metalloproteinases MMP3 and MMP8.[19]

3.2.1.2 Gold. Gold nanostructures have gained prominence in biomedicine for their potential in treating diverse diseases.[48] Unlike some metal nanoparticles that can induce oxidative stress and toxicity, gold nanostructures have exhibited favorable biocompatibility and cellular internalization, characterized by vesicular accumulation reminiscent of autophagosomes,[127] possibly through a ROS-associated mechanism.[128]

In the context of inflammation control, gold nanostructures have demonstrated significant regulatory effects on relevant signaling pathways. Yuan *et al.* investigated a peptide-coated gold cluster ($Au_{25}Sv_9$) in an inflammatory osteoclast model and inflammation-induced bone destruction mice model.[47] Their findings indicate that $Au_{25}Sv_9$ dose-dependently suppressed the secretion and transcriptional regulation of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, while suppressing NF-κB activation. These results underscore the anti-inflammatory potential of the gold cluster *in vitro* and *in vivo*. Ni *et al.* synthesized gold nanoparticles (AuNPs) to examine their effects on macrophages of varying sizes (Fig. 5).[48] Notably, AuNPs, particularly those with a diameter of 45 nm, promoted M2-related factors expression, such as Arg-1, IL-10, and TGF-β, while downregulating CD86, a surface marker associated with the M1 phenotype. This effect suggests the anti-inflammatory capability of AuNPs by promoting the transition of macrophages from M1 phenotype to M2 phenotype.

Beyond their anti-inflammatory properties, gold nanostructures have gained recognition for their remarkable bone regeneration capabilities. Zhang's study revealed that the osteogenic differentiation function of AuNPs is size-dependent, inhibitory at 5 nm, and promotive at 45 nm.[127] This differentiation was confirmed by the expression of osteogenic genes, that Alkaline Phosphatase (ALP) and Collagen Type I (COL1) were produced earlier than Osteopontin (OPN), Osteocalcin (OCN), conforming to the biological behavior of osteogenic differentiation.[49] Zhang's team delved into the underlying mechanisms, demonstrating that 45 nm AuNPs activate the Wnt/β-catenin pathway, effectively enhancing hPDLSC proliferation,[50] and promoting hPDLSC differentiation into osteoblasts through the ERK/AMPK pathway.[51] Moreover, TEM images of AuNPs-treated PDLPs revealed an increase in autophagic vesicles, prompting an investigation into the autophagy pathway. In the 13 and 45 nm AuNPs treatment groups, heightened mRNA expression of LC3 and Beclin1, along with an increase in LC3-II, suggested autophagosome formation. Inhibition experiments at different autophagy stages reversed the AuNPs-induced osteogenesis, highlighting the link between autophagy and osteogenesis.[127] Lastly, Zhang's team combined AuNPs with PDLSC sheets, harnessing the osteogenic induction ability of AuNPs alongside the accessibility and multipotency of PDLSC sheets, offering a novel strategy for treating bone defects.[129]

3.2.1.3 Cerium. In the field of biomedical research, nanomaterials incorporating cerium (Ce) have garnered significant attention due to their distinctive properties, notably the presence of abundant oxygen vacancies and the capability for transformation between Ce(III) and Ce(IV) ions. These unique characteristics position Ce-based nanomaterials as promising candidates for addressing oxidative stress-related ailments.[130] Li *et al.* demonstrated the anti-oxidative potential of Ce-doped ZIF-8 nanoparticles (ZIF-8: Ce NPs) in periodontitis treatment, confirming their safety. These Ce-endowed ZIF-8 NPs exhibited superoxide dismutase (SOD) and catalase (CAT) enzyme mimic capability, facilitating ROS elimination, and thereby exerting multiple biological effects. These effects encompass protection against oxidative stress-induced cell damage through Zn^{2+} activity, modulation of pro-inflammatory mediators, and suppression of the NF-κB pathway, along with the induction of macrophage transition from the M1 to M2 phenotype.[52] To further enhance the coordinated regulation of host immunity, researchers introduced the antioxidant drug quercetin onto nano-octahedral ceria, resulting in improved inflammation mitigation efficiency.[53] Moreover, cerium oxide nanoparticles (CeO_2 NPs) have demonstrated SOD and CAT mimetic activities, along with oxidase-like properties.[131] Leveraging these distinctive attributes, CeO_2 NPs have been applied in the treatment of periodontitis. Research has revealed that CeO_2 NPs possess anti-inflammatory and antioxidant capabilities by suppressing the MAPK-NF-κB signaling pathway and upgrading the Nrf2-HO-1 pathway. These actions were accompanied by the

regulation of associated protein expression in RAW 264.7 cell inflammation model induced by LPS, as well as a cut down in inflammation observed in a periodontitis rat model.[54]

3.2.2 Oxide

3.2.2.1 Graphene oxide (GO). Graphene is a two-dimensional sheet of sp^2-hybridized carbon, recognized as the thinnest and strongest element known.[132] It is celebrated for its exceptional biocompatibility in the field of biomedicine. Furthermore, graphene exhibits potential antibacterial and tissue regenerative properties, rendering it a promising candidate for dental treatments, particularly in the context of periodontal disease.[55,133] Due to its capacity for facile functionalization through various functional groups, multiple derivatives of graphene have been developed to attain specific properties suited to diverse applications. In dentistry, the primary focus has been on graphene, graphene oxide, graphene quantum dots (GQDs), and reduced graphene oxide (rGO) due to their remarkable antibacterial and tissue regenerative capabilities.

GO, in particular, stands out for its superior chemical stability and water solubility.[134] Additionally, it maintains an atomic structure even thinner than graphene itself.[135] He *et al.* produced GO nanosheets from natural graphite using a modified Hummers' method and assessed their antibacterial activity against *P. gingivalis* at varying concentrations. The results demonstrated a reduction in bacterial cell activity with increasing GO concentration, along with structural integrity loss in the cell membrane and cell wall, as confirmed by TEM images, thus highlighting its potent antimicrobial activity.[55] To combine the antimicrobial properties of GO with its potential as a drug carrier, Trusek *et al.* attached amoxicillin (AMOX) to GO using a peptide linker (Leu-Leu-Gly). They dispersed this composite within a hydrogel containing the enzyme responsible for AMOX release from GO, resulting in the formation of GO-AMOX Alginate Capsules. This capsule exhibited excellent physical stability and showed no cytotoxicity. With the use of bromelain (BROM) as the enzyme, the capsule effectively released AMOX, holding significant medical potential.[56]

Furthermore, numerous studies have reported optimal cell adhesion and proliferation on plastic or glass plates coated with GO, garnering substantial interest in the field of tissue engineering.[136] Vera-Sánchez *et al.* developed SF-GO nanoconfigurations as scaffold supports for human periodontal ligament stem cells (hPDLSCs). SF exhibited excellent compatibility with film-format GO, promoting cell proliferation and favoring osteo/cementoblast differentiation, particularly by stimulating cementum physiological synthesis.[67] Park *et al.* fabricated P-GO scaffolds and assessed their impact on the adhesion, proliferation, as well as osteogenic differentiation of PDLSCs. GO was used as an osteogenic-inducing coating material to enhance the capacity of PCL scaffolds, the experimental group exhibited increased cell proliferation, greater presence of cytoskeletal elements and nuclei on the GO-coated scaffold surface, and a 60% increase in calcium deposition, underscoring its remarkable bioactivity and osteogenic differentiation potential.[68]

In addition to GO, other common nanomaterials used in the treatment of periodontitis include rGO and GQDs. Jabbari *et al.* fabricated chitosan/silk fibroin (CS/SF) membranes incorporating rGO as promising candidates for guided bone regeneration in bone tissue engineering.[69] Moreover, GQDs coupled with curcumin (Cur) were found to enhance aPDT by suppressing periodontal pathogens in both planktonic and biofilm forms and downregulating the expression pattern of biofilm-related genes, as demonstrated by Pourhajibagher *et al.*[57]

3.2.2.2 Zinc(II) oxide (ZnO NPs). Metal oxide nanoparticles, especially when in nano-size, exhibit inherent properties including antibacterial efficacy and compatibility with human cells.[137] These nanoparticles offer versatile and tunable shapes, achievable through various synthesis methods by modulating reaction conditions.[138,139]

ZnO nanoparticles are particularly renowned for their shape controllability, biocompatibility, and antimicrobial prowess. Recent investigations have predominantly concentrated on the integration of ZnO NPs into nanofibers,[140] membrane,[141] and scaffolds to confer antibacterial attributes. For instance, Mou *et al.* addressed the limitations of conventional minocycline treatments by developing a novel nanohydrogel, Mino-ZnO@Alb, which incorporates ZnO NPs into an albumin-based carrier.[58] This formulation aims to optimize drug delivery through several innovative features. Firstly, ZnO NPs enhance the stability of the albumin nanoparticles (Alb NPs) and increase the encapsulation efficiency (EE) and loading capacity (LD) of minocycline. This is achieved through coordination bonding between ZnO and both albumin and the drug molecules, thereby improving drug retention and controlled release characteristics under physiological conditions. According to their experimental results, the Mino-ZnO@Alb nanohydrogel exhibits pH-responsiveness, enabling targeted drug release in acidic environments typical of infection sites. This feature enhances therapeutic efficacy while minimizing systemic side effects. The nanohydrogel also demonstrates a broad antimicrobial spectrum due to the combined effects of minocycline and ZnO NPs, making it suitable for combating infections caused by various pathogens. Furthermore, the formulation's biocompatibility and biodegradability ensure minimal cytotoxicity and potential for tissue repair, which are critical for applications in periodontal treatments and other localized therapies. By reducing the dosage of minocycline required for effective treatment, the nanohydrogel aims to enhance patient compliance and reduce the risk of systemic toxicity associated with conventional minocycline formulations.

Moreover, the application of ZnO NPs in aPDT has advanced to clinical research, as detailed in Section 3.2.5.

3.2.3 Mesoporous silica nanoparticles (MSNs). Mesoporous silica nanoparticles represent sponge-like bulk materials characterized by an open porous structure, facilitating the straightforward loading of therapeutics within the silica matrix.[142] MSNs are acclaimed as promising drug carriers due to their robust physicochemical properties, exceptional biocompatibility, and minimal cytotoxicity,[143] these attributes enable the mitigation of systemic toxicity and address challenges related to low drug solubility. MSNs not only enable effective co-delivery of diverse drug types, including antibiotics,[60,61] BMP-2,[144] and curcumin,[145] but also hold the potential to enhance

therapeutic efficacy. Their utility extends to combating antibiotic resistance and enabling sustained drug release by responding to subtle stimuli within the cellular milieu.[24]

In the context of antibacterial therapy, MSNs have been harnessed for the transport of antibiotics such as meropenem,[61] tetracycline,[60] and vancomycin,[62] all exhibit antibacterial effects against the corresponding pathogenic bacteria by carrying antibiotics. Furthermore, MSNs have been explored for the management of host inflammatory responses triggered by subgingival tooth biofilms. Baicalin (BA), a natural flavonoid with potent anti-inflammatory properties but limited solubility and bioavailability, has been effectively harnessed.[143] Li *et al.* engineered a red-emissive MSNs-based nanosystem with CPD capping to precisely control the release of baicalin in response to glutathione. This system utilizes endocytosis and thiol-mediated mechanisms for cellular internalization, offering precise modulation of immuno-inflammatory responses.[63] Also, resveratrol (RSV) has great potential in the therapy of diabetes periodontitis due to its effective antioxidant and anti-inflammatory properties, so it has become a heated topic to overcome its poor water solubility, fast decomposition, and short serum half-life.[146] By grafting RSV onto MSNs (MSN-RSV), the bioavailability of RSV was enhanced, regulating macrophage polarization through the activation of the SIRT1/AMPK pathway and suppression of the NF-κB pathway. Additionally, MSN-RSV displayed the ability to modulate glucose metabolism, ameliorate insulin resistance (IR), and control glucose homeostasis.[64]

Furthermore, the synergy of MSNs with other drug delivery systems can yield combined effects. For instance, Lian *et al.* integrated copper-loaded MSNs (Cu@MSNs) into a PLGA/gelatin fiber matrix, creating a composite PG-Cu@MSNs fibrous scaffold for guided bone regeneration. This scaffold exhibits dual functionality, promoting both osteogenesis and antibacterial effects.[70] MSNs can also serve as carriers for other nanomaterials, such as AgNPs, to construct composite nanostructures. Quaternary ammonium salts (QAS)-modified core–shell MSNs containing Ag nanoparticles (Ag@QHMS) demonstrate sustained Ag^+ release, leading to effective and stable concentration-dependent antibacterial effects and enhancing osteogenic differentiation of BMSCs.[71]

3.2.4 Inorganic nanosurface. Nanosurface modification of biomaterials entails altering surfaces at the nanoscale to introduce specific topographies that enhance the biological functions of these materials.[147] Surface modification achieves through diverse treatments like sandblasting, large-grit, and acid-etched (SLA) techniques,[73] however, research indicates that nanoscale features foster more favorable interactions between the materials and the host's biological responses.[148] These nanosurfaces offer a significantly increased surface area and can be meticulously designed with precise sizes and shapes, resulting in improved biocompatibility and more robust biological reactions. Recent attention has focused on surfaces with micro/nanoscale topographies, demonstrating enhanced osteogenic differentiation compared to conventionally treated surfaces,[149] mostly focusing on titanium and bioceramics surfaces.

Hu *et al.* successfully engineered titanium surfaces featuring hierarchical topographies comprising microgrooves and nanopores using a combination of selective laser melting (SLM) and alkali heat treatment (AHT). This innovative approach induced differentiation of PDLSCs by promoting actin cytoskeleton polymerization and activating the ERK and p38 MAPK signaling pathways. This, in turn, facilitated TAZ activation through nuclear translocation and increased transcriptional activity.[73] Conversely, Yamada *et al.* adopted a biomimetic approach, seeking to replicate the morphology and physicochemical properties of living tissues.[25,150] They crafted titanium surfaces mimicking tooth root cementum (TRC), creating a specialized topographical and mechanical microenvironment that regulates periodontal ligament cells and coordinates phosphate metabolism, ultimately inducing endogenous periodontium regeneration. In the realm of bioceramics, Mao's team prepared hybrid nanorod and microrod (mnHA) surfaces on hydroxyapatite bioceramics. These surfaces were found to possess the capacity to induce osteogenic and cementogenic differentiation of hPDLSCs through the Wnt pathway.[26]

3.2.5 Inorganic nanomaterial applied in antibacterial photodynamic therapy in periodontitis treatment. Antimicrobial photodynamic therapy finds its roots in Photodynamic therapy (PDT), originally devised for cancer treatment, wherein abnormal cell growth is targeted and eliminated through necrosis or apoptosis.[151] When applied to combat bacterial, fungal, or viral infections, this approach is referred to as aPDT.

The mechanism underlying aPDT consists of two pivotal components: a non-toxic light-absorbing dye (photosensitizer or PS) and visible light of an appropriate wavelength. In this process, the PS is activated by light, instigating a phototoxic reaction that generates ROS. These ROS, in turn, inflict damage on biomolecules and cellular structures through oxidation, culminating in the demise of microorganisms.[152] Nevertheless, the accumulation of ROS post-aPDT can elevate oxidative stress in periodontal tissues, initiating adverse endogenous immune responses, and ultimately leading to cell death and tissue degradation.[153] Consequently, managing the dual effects of ROS in aPDT has emerged as a critical challenge.

Li *et al.* addressed this challenge by combining Black phosphorus nanosheets (BPNSs) with ICG/aPDT, harnessing the potent ROS elimination capability and low cytotoxicity of BPNSs to safeguard periodontal structures.[72] BPNSs, characterized by a two-dimensional folded bilayer structure along the *Z*-axis, facilitate rapid electron transport. Their elemental state promotes swift oxidation reactions, forming P–O bonds, which confer these nanomaterials with robust ROS consumption capabilities.[154] Consequently, their research revealed that despite exerting antibacterial and anti-inflammatory capabilities, BPNSs also protect healthy cells from oxidative stress and accompanying inflammatory reactions induced by aPDT.

As previously discussed, CeO_2 NPs possess the ability to combat chronic inflammation and oxidative stress.[131] Hence, Sun *et al.* coupled CeO_2 with the highly efficient red-light-excited photosensitizer Chlorin e6 (Ce6) through silane encapsulation, harnessing the SOD and CAT functions of CeO_2 nanoparticles within the aPDT system. This innovative approach mitigated the issue of local ROS accumulation.[18] Results demonstrated that CeO_2@Ce6 NPs exhibited

formidable sterilization and anti-inflammatory capabilities, validated through both *in vitro* and *in vivo* experiments.

Mathew *et al.* synthesized a nano ZnO gel containing ZnO NPs *via* a bio-hydrothermal method to minimize potential risks or hazards.[59] Previous studies indicated its biocompatibility with no toxicity against red blood cells and mouse fibroblast cell lines, contrasting with moderate toxicity of conventional ZnO powder *in vitro*.[155] This bio-synthesis approach suggests reduced ecological toxicity when compared to chemically synthesized ZnO. This study evaluated the efficacy of photodynamic therapy (PDT) using bio-hydrothermally synthesized nano ZnO gel combined with visible light as an adjunct to scaling and root planing (SRP) for treating periodontitis. Results showed significant improvement in periodontal health outcomes after 1 month with PDT compared to SRP alone. By 3 months, all adjunctive therapies, including PDT, demonstrated similar clinical parameter improvements and reduction in *P. gingivalis* levels, indicating sustained benefits in periodontal treatment. These findings underscore the potential of using nano ZnO gel and visible light PDT as adjunctive therapies for periodontitis, suggesting further validation through longitudinal studies with larger samples and extended follow-up to confirm efficacy and safety in clinical practice.

In summary, nanomaterials can play an important role in aPDT therapy with their unique structural, physical, or chemical properties.

4 Conclusions and perspectives

Periodontitis is a disease with complex pathogenesis, along with the bacterial and biological factor diversity of the human oral cavity. Therefore, the difficulty of the current treatment is to accurately target various biological mechanisms in the pathogenesis process and maximize the biological effects. This review briefly describes several typical nanostructures for periodontitis treatment and introduces their application scenarios, including direct therapeutic effects, drug loading, and combination with emerging treatment technologies. In summary, as a novel technology, nanomaterials are a valid therapeutic modality that is feasible in periodontitis treatment. However, it should be noted that the current technology still has limitations, such as manufacturing difficulties, high costs, limited efficacy, and especially the scarcity of clinical studies, which reveals that *in vivo* investigations are urgently needed. Hence, we hope that more in-depth research can be carried out in the academic community in the future to realize the market application of nanomaterials in periodontitis treatment.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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