Nano Research

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Review Article

# Emerging applications of bioactive peptides and proteins in the treatment of periodontitis

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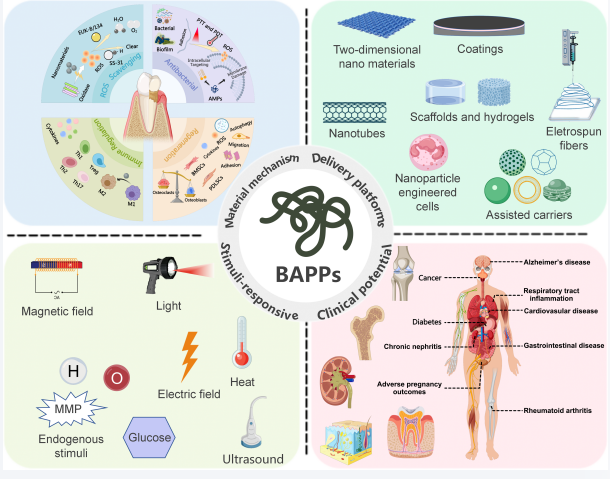
**Cite this article:** *Nano Research*, **2026**, *19*, 94908547. https://doi.org/10.26599/NR.2026.94908547

**ABSTRACT:** Driven by oral pathogenic microorganisms, periodontitis is a chronic inflammatory disease, leading to progressive destruction of periodontal supporting tissues. Conventional therapies can alleviate symptoms, but are limited in their ability to eradicate pathogens, regenerate functional tissues, and prevent antibiotic resistance. Recent years have seen bioactive peptides and proteins (BAPPs) emerge as promising candidates for periodontitis treatment, owing to their multifunctional nature, excellent specificity, high biocompatibility, and favorable biodegradability. However, the enzymatic degradation of BAPPs leads to their short half-life *in vivo*. Therefore, rationally designed delivery strategies are indispensable to enhance the stability of BAPPs and improve targeting efficacy. This review summarizes the therapeutic mechanisms of BAPPs in periodontitis, including their antibacterial, immunomodulatory, antioxidant, and tissue-regenerating activities. It further explores advanced delivery strategies, such as nanoparticles, scaffold- or hydrogel-based platforms, and stimuli-responsive systems activated by pH, reactive oxygen species (ROS), enzymes, light, or magnetic fields, to achieve the precise spatiotemporal control of BAPPs delivery. Additionally, the discussion further encompasses the clinical translational potential of BAPPs, alongside extant barriers and future outlook, thereby paving the way for more effective and safe periodontitis treatment strategies.




**KEYWORDS:** periodontitis, bioactive peptides and proteins, antibacterial, immune regulation, antioxidant, periodontal tissue regeneration

## 1 Introduction

Periodontitis is a chronic inflammatory disease triggered by dental plaque biofilms, leading to progressive destruction of periodontal supporting tissues, including the gingiva, periodontal ligament, and alveolar bone [1]. It's a highly prevalent global oral disease affecting over 1.1 billion people and increasing in prevalence, adversely impacts oral health, quality of life, and is linked to systemic conditions [2]. Beyond the impairment of masticatory function and oral health, this disease has been strongly related to systemic disorders like cardiovascular diseases [3], diabetes [4], and Alzheimer's disease [5]. Periodontitis involves complex interactions among microbial infection, host immunity, and tissue destruction. Pathogens like *Porphyromonas gingivalis* (Pg) and *Actinobacillus actinomycetemcomitans* (Aa) in dental plaque sustain chronic inflammation by releasing virulence factors and activating immune responses [6]. This leads to elevated pro-inflammatory cytokines including interleukin-1$\beta$ (IL-1$\beta$) and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) as well as enhanced activity of matrix metalloproteinases (MMPs), driving connective tissue degradation and alveolar bone resorption [7]. Conventional periodontal therapies, such as

**Received:** December 22, 2025; **Revised:** February 6, 2026
**Accepted:** February 6, 2026

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mechanical debridement, antibiotics, and surgery, are limited by incomplete biofilm removal, antibiotic resistance risks, and poor regenerative outcomes, necessitating the development of novel strategies [8].

Insights from the evolving fields of molecular biology and biomaterials science have illuminated the unique advantages and therapeutic potential of bioactive peptides and proteins (BAPPs) for periodontitis treatment. BAPPs are functional biomolecules composed of specific amino acid sequences, characterized by their high specificity, low molecular weight, strong targeting capability, excellent biocompatibility, and favorable biodegradability [9]. In the treatment of periodontitis, BAPPs exert therapeutic effects through multiple mechanisms, as depicted in Fig. 1. Some peptides exert direct antimicrobial activity by disrupting bacterial membrane integrity to eliminate periodontal pathogens. BAPPs also demonstrate immunomodulatory functions by influencing macrophage polarization, thereby attenuating excessive inflammatory responses. Additionally, some BAPPs play a role in managing oxidative stress, reducing inflammatory damage, and promoting tissue protection. Furthermore, select peptides such as amelogenin and fibroblast growth factor (FGF) facilitate periodontal regeneration by enhancing the proliferation and differentiation of periodontal ligament stem cells (PDLSCs), leading to the reconstruction of alveolar bone and periodontal ligament structures [10]. Compared with conventional antibiotics, BAPPs exhibit multiple therapeutic advantages. Notably, their antimicrobial mechanisms are less likely to induce bacterial resistance. BAPPs can also simultaneously target multiple therapeutic pathways while demonstrating superior tissue compatibility. These properties enable BAPPs to promote tissue repair through inflammatory microenvironment modulation [11]. However, key challenges persist including instability and activity loss during enzymatic degradation or loading; suboptimal delivery systems with poor biocompatibility; clinical translation barriers including non-standardized production, limited large-animal data, high-dose side effects, and personalized therapy costs; and incomplete mechanistic understanding of multi-factor and microenvironmental interactions [9, 12, 13]. It is imperative to shift the focus to novel stabilization methods, responsive codelivery platforms, artificial intelligence (AI)-driven peptide and carrier design, large-scale clinical validation, and deepened mechanistic studies [9]. These are the key elements required to enable precise, clinically viable BAPP therapies.

The unique oral environment leads to rapid drug clearance due to salivary washout [12]. The periodontal pocket microenvironment characterized by proteolytic enzymes, low pH, and high oxidative stress may further compromise BAPP stability [13], resulting in quick degradation and low bioavailability. Another critical challenge lies in achieving targeted BAPP accumulation and controlled release at inflammatory sites. To address these limitations, researchers have developed various innovative structural optimization strategies and delivery systems. Biomaterial-based delivery platforms including hydrogels, nanoparticles, and microspheres can protect BAPPs from degradation through physical encapsulation or chemical conjugation while prolonging their therapeutic duration [9]. Particularly, the emerging stimuli-

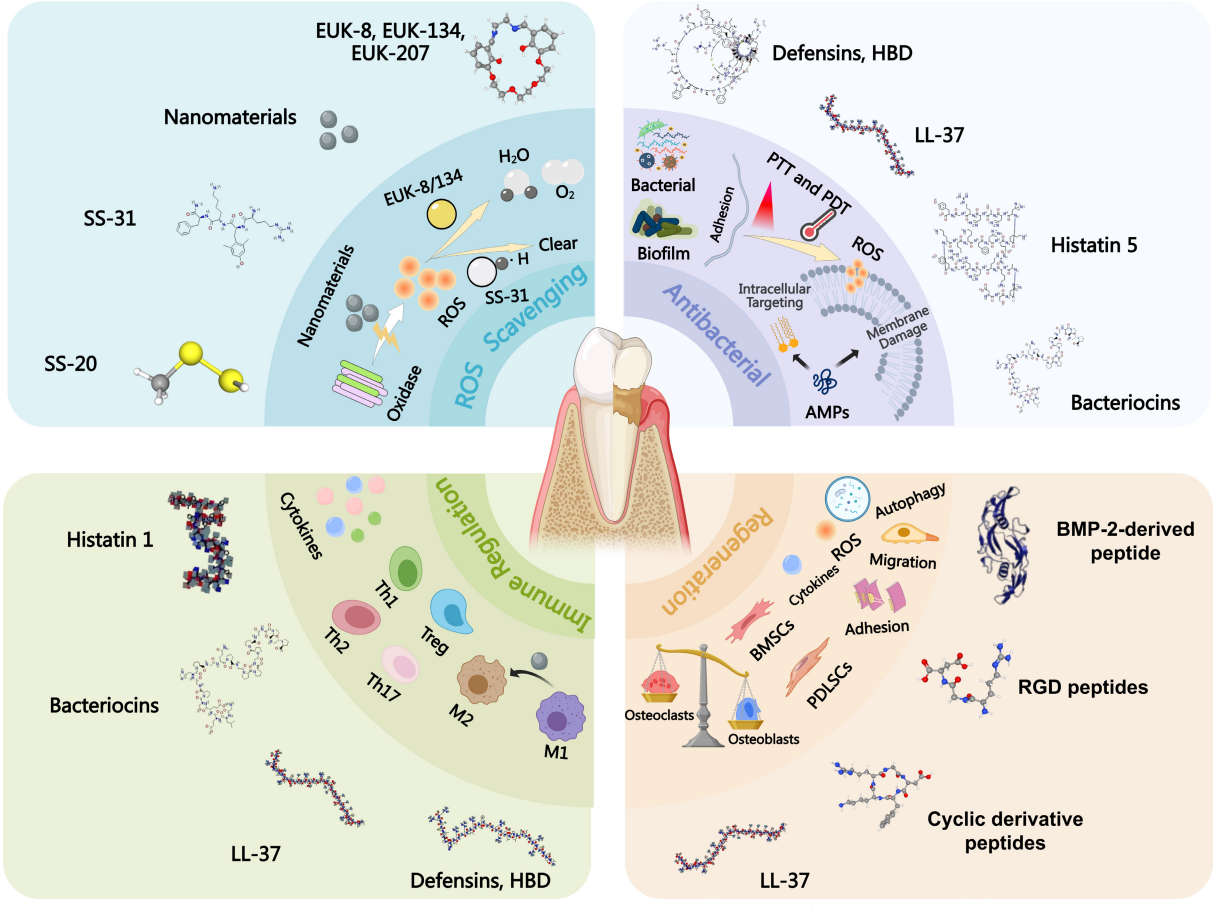


**Figure 1** Schematic of BAPPs with antibacterial, tissue regeneration, immune regulation, and ROS scavenging functions.

responsive delivery systems in recent years enable intelligent release of BAPPs based on periodontitis pathological features such as localized pH reduction, upregulation of specific enzymes, and high oxidative stress [14]. For instance, pH-sensitive hydrogels undergo swelling in the acidic environment of inflamed sites to release encapsulated antimicrobial peptides (AMPs), while MMP-responsive nanoparticles dissociate in response to highly expressed MMPs at inflammatory sites, thereby releasing therapeutic proteins [15, 16]. Beyond delivery system optimization, significant progress has also been made in combinatorial BAPP strategies. Researchers have found that sequential administration of functionally distinct BAPPs can better mimic natural tissue repair processes [17]. A representative example involves initial application of AMPs to control infection, followed by growth factors to promote tissue regeneration. This temporally controlled therapeutic strategy has demonstrated superior efficacy compared to monotherapy in animal models [18]. Furthermore, the combination of BAPPs with other therapeutic modalities like mechanical debridement, antibiotic administration, photodynamic therapy and stem cell therapy, have demonstrated synergistic effects [19]. These innovative treatment strategies provide novel approaches for the comprehensive management of periodontitis.

In summary, BAPPs offer new opportunities and possibilities for periodontitis treatment. Through the elucidation of their mechanisms, optimization of delivery strategies, and resolution of key challenges in clinical translation, BAPPs are poised to become an important next-generation therapeutic approach for periodontitis. This review aligns BAPP multifunctionality with stage-specific periodontal pathogenesis and explores integrated delivery strategies for targeted therapy, summarizing advances in mechanisms, delivery, and translation to guide the development of precise treatments that improve patient outcomes.

## 2 Periodontitis: Pathogenesis and systemic disease associations

Figures 2 and 3 illustrate the etiology, pathogenesis, and associations with systemic diseases of periodontitis, respectively. The pathogenesis of the disease originates from oral bacterial colonization and biofilm formation that triggers a host immune response, leading to excessive reactive oxygen species (ROS) production. These ROS damage the periodontium through various pathways and are implicated in the development of systemic diseases. BAPPs can selectively target distinct pathological aspects of periodontitis.

### 2.1 Oral pathogens: The initiating factor of periodontitis

The pathological progression of periodontitis originates from dysbiosis of the oral microbiome, primarily driven by the formation and development of dental plaque biofilms. These structurally complex microbial communities are characterized by the predominance of keystone pathogens, such as Pg, *Fusobacterium nucleatum* (Fn), *Treponema denticola* (Td), and *Prevotella intermedia* (Pi), which play pivotal roles in disease pathogenesis. These pathogens form specific symbiotic relationships known as the "red complex" and "orange complex", whose presence exhibits a strong link to the development and advancement of periodontal disease [20]. Biofilm formation constitutes a highly organized, dynamic process. Initially, pioneer species such as *Streptococcus* and *Actinomyces* adhere to the tooth surface via saliva-derived protein films (acquired pellicle) [1, 21]. Following successful colonization, these bacteria proliferate and secrete diverse extracellular polymeric substances (EPS), including polysaccharides, proteins, lipids, and extracellular DNA (eDNA), collectively establishing the three-dimensional structural matrix of the biofilm. This extracellular matrix not only provides structural support for microbial

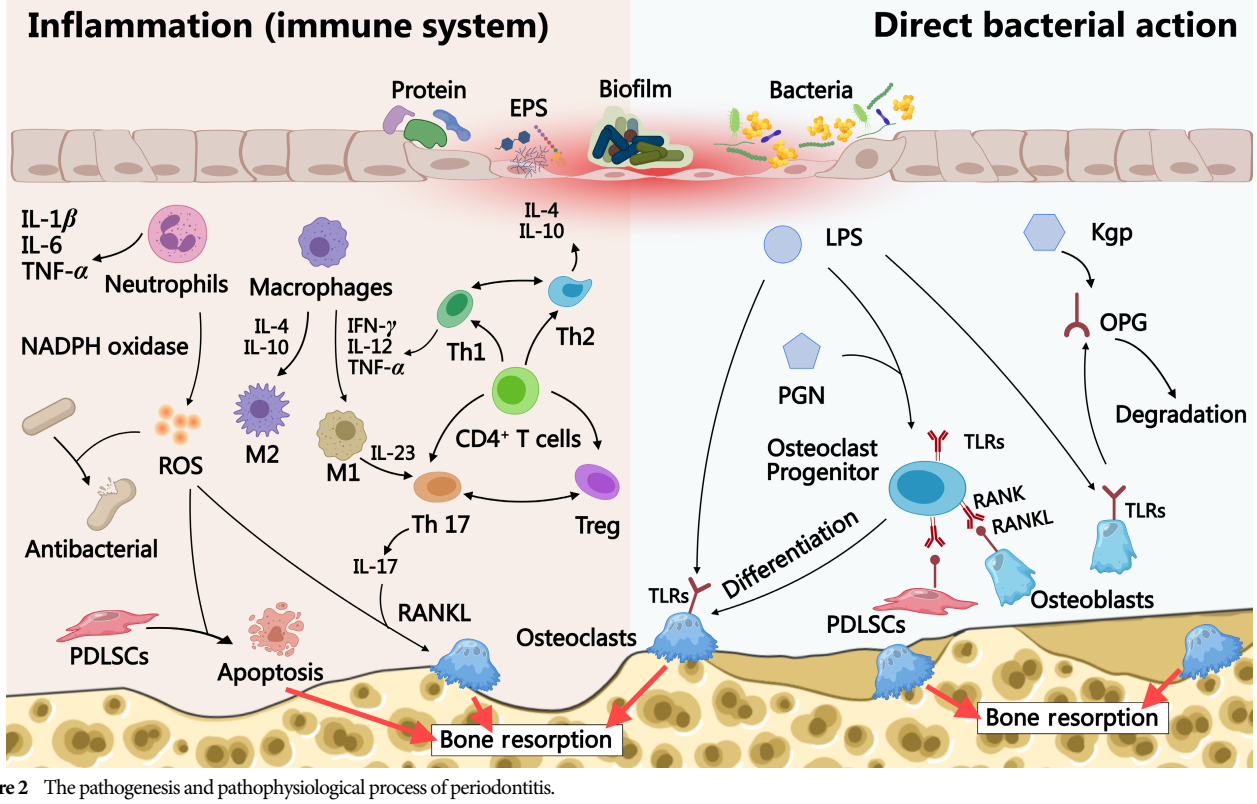


**Figure 2** The pathogenesis and pathophysiological process of periodontitis.

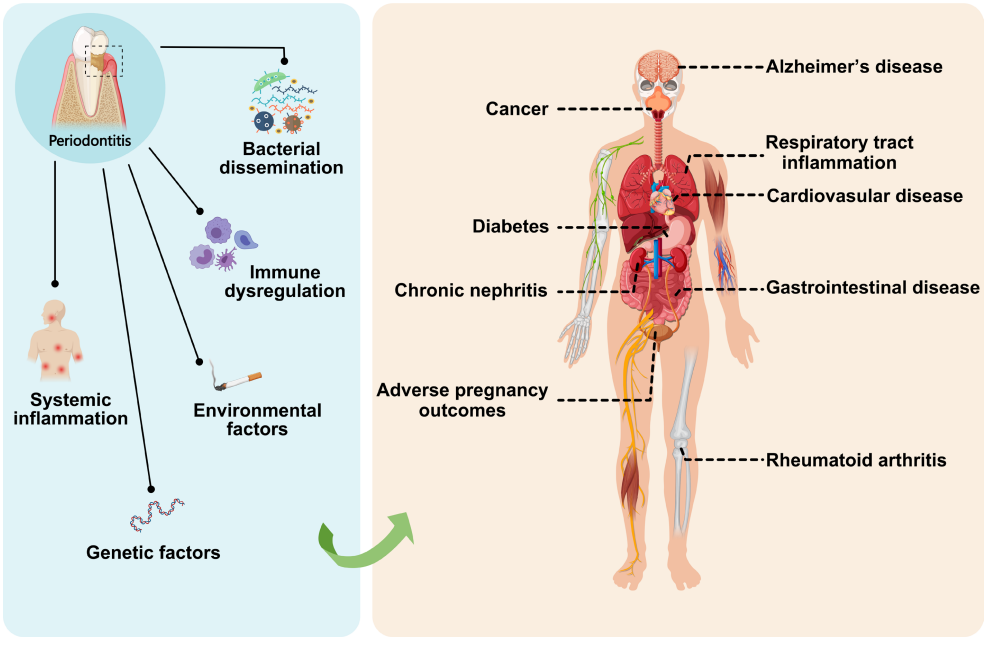


**Figure 3** The relationship between periodontitis and systemic diseases.

communities, but more critically, establishes a protective barrier that enables bacteria to evade host immune defenses and resist antimicrobial agents [21]. Through bacterial fermentation, the biofilm develops an acidic microenvironment around pH 4.5–5.5 that selectively promotes pathogen proliferation and enhances virulence [22]. Concurrently, a steep oxygen gradient forms in the biofilm, with aerobic conditions at the surface to strict anaerobiosis in deeper layers, creating distinct ecological niches for bacteria with varying metabolic requirements. Most notably, biofilm bacteria employ quorum sensing systems for intercellular communication, coordinating gene expression and collective behaviors to significantly enhance their adaptability and pathogenicity [21]. Among numerous periodontal pathogens, Pg has attracted wide research attention due to its unique pathogenic mechanisms, which has developed disproportionate virulence despite its low abundance [23]. Through multiple virulence factors including gingipains, fimbriae, lipopolysaccharide (LPS), and outer membrane vesicles, Pg orchestrates sophisticated manipulation of host immune responses by inhibiting the complement system activation, impairing phagocytic function and modulating signaling via Toll-like receptors (TLRs). These immunomodulatory effects collectively compromise host defense mechanisms while enhancing bacterial survival [24, 25]. Notably, such immune subversion not only facilitates Pg persistence but also disrupts oral microbial homeostasis. This creates an ecological niche that favors the proliferation of secondary pathogens, ultimately driving periodontal tissue destruction.

## 2.2 Immune-inflammatory response: The core mechanism of tissue destruction

The pathogenesis of periodontitis fundamentally represents an over activated host immune response. When bacterial pathogens and their virulence factors breach the epithelial barrier, they trigger a complex cascade of immune-inflammatory reactions that, while aimed at pathogen clearance, paradoxically contribute to periodontal tissue destruction [26]. During the early inflammatory phase (24–48 h), neutrophils rapidly infiltrate the inflammatory site as first-line defenders. These phagocytes recognize bacterial pathogen-associated molecular patterns (PAMPs), particularly LPS and lipoproteins, through surface TLRs [27]. Activated neutrophils generate excessive ROS and release various proteolytic enzymes for bacterial killing. However, when this response becomes dysregulated or prolonged, the neutrophil-derived cytotoxic substances damage not only pathogens but also surrounding healthy tissues [28]. Notably, activated neutrophils secrete multiple proinflammatory cytokines including IL-1$\beta$, TNF-$\alpha$, and interleukin-8 (IL-8). These mediators function bidirectionally through recruiting additional immune cells to the lesion site and amplifying local inflammation through downstream signaling pathways like NF-$\kappa$B and MAPK [26]. As inflammation progresses (3–7 days), macrophages emerge as key mediators in the periodontal microenvironment. Under periodontitis micro-conditions, macrophages predominantly polarize into the pro-inflammatory M1 phenotype, secreting substantial quantities of IL-12, IL-23, and TNF-$\alpha$ [29]. These cytokines play a dual role, not only sustaining and amplifying local inflammation but also modulating subsequent adaptive immunity. Of particular significance, periodontal pathogens such as Pg can actively subvert macrophage polarization by inhibiting their transition to anti-inflammatory M2 phenotype, thereby promoting chronic inflammatory states [30]. Accumulating evidence confirms that macrophages play pivotal roles during chronic stages of periodontitis, especially in maintaining persistent inflammatory milieu. During later disease stages (1–2 weeks post-initiation), the adaptive immune system assumes predominant control of the inflammatory response. T lymphocytes play pivotal roles in periodontal immunity, with functionally distinct subsets exhibiting markedly different effects [31]. Recent research has focused on the Th17 cell subset, which secretes interleukin-17 (IL-17). This potent proinflammatory cytokine recruits and activates neutrophils, stimulates fibroblasts and epithelial cells to produce inflammatory mediators, and directly promotes osteoclastogenesis and bone resorption. This multifaceted activity exacerbates local

inflammation while accelerating alveolar bone destruction [32]. Clinical studies demonstrate significantly elevated Th17 cell proportions in chronic periodontitis lesions, suggesting that their pathological hyperactivation may be a key driver of disease progression [33].

The pathological activation of osteoclasts constitutes the central mechanism of bone destruction in periodontitis. Osteoclast precursor differentiation into mature bone-resorbing cells is tightly regulated by the RANKL/RANK/OPG signaling axis [34]. Under physiological conditions, osteoprotegerin (OPG) competitively binds receptor activator of nuclear factor-κB ligand (RANKL), thereby inhibiting osteoclastogenesis. However, the inflammatory milieu of periodontitis markedly disrupts this equilibrium through proinflammatory cytokines-mediated RANKL overexpression, which not only causes suppression of OPG production but also elevates the RANKL/OPG ratio. This dysregulation drives excessive osteoclast activation and directly mediates progressive alveolar bone loss [35]. Furthermore, the inflammatory environment impairs osteoblast function, creating a "double-hit" mechanism that exacerbates skeletal metabolic imbalance [36, 37].

Recent studies have further elucidated the pivotal roles of diverse immune cells in periodontitis pathogenesis. As professional antigen-presenting cells, dendritic cells orchestrate T-cell activation through antigen presentation, critically determining the immune response polarization toward either pro-osteoclastic Th17 or bone-protective regulatory T cell (Treg) differentiation [31]. Natural killer (NK) and natural killer T (NKT) cells modulate inflammatory and immune responses via cytokine secretion and dynamic interactions with dendritic cells [38]. While B cell-derived antibodies contribute to pathogen clearance, they may simultaneously participate in autoimmune reactions through molecular mimicry mechanisms [39]. These findings collectively demonstrate that the immunopathology of periodontitis involves a more sophisticated cellular network than previously recognized, characterized by intricate cross-talk among multiple immune cell populations.

### 2.3 Oxidative stress: The amplifier of tissue damage

ROS exhibit a dual-edged role in the pathogenesis of periodontitis: serving as crucial weapons in host defense while simultaneously acting as key mediators of tissue damage. The imbalance between ROS generation and scavenging, known as oxidative stress, significantly amplifies periodontal tissue destruction during disease progression [40]. In the context of periodontitis, virulence factors such as LPS from pathogens like Pg are key activators of immune cells, notably neutrophils and macrophages. These activated phagocytes initiate a "respiratory burst" via the NADPH oxidase (NOX2) and myeloperoxidase (MPO) systems, generating substantial ROS for antimicrobial defense [41]. Under physiological conditions, these reactive molecules primarily target invading pathogens. However, in chronic inflammatory states like periodontitis, sustained and uncontrolled ROS production overwhelms the tissue's antioxidant capacity, resulting in oxidative stress-mediated tissue injury [42].

Oxidative stress mediates periodontal tissue damage through multiple pathological mechanisms. Excessive ROS accumulation primarily induces direct cellular membrane damage via lipid peroxidation, resulting in membrane disruption and functional impairment. Furthermore, apoptosis, particularly in fibroblasts and PDLSCs, is triggered via the ROS-induced oxidation of key cellular components. This oxidative damage results in the denaturation of proteins and breaks in DNA strands. This form of cell death, which is programmed, markedly hastens the degradation of the periodontal ligament. Concurrently, byproducts like malondialdehyde (MDA), an indicator of lipid peroxidation, perpetuate a self-reinforcing cycle of oxidative stress that intensifies tissue breakdown [40–42].

ROS further exacerbates periodontal tissue destruction through osteoclast-mediated bone resorption and dysregulated cellular processes. Experimental evidence demonstrates that ROS enhance RANKL-induced osteoclast differentiation and potentiate the bone-resorbing activity of mature osteoclasts [43]. Clinically, elevated ROS levels in periodontal pockets of periodontitis patients show strong correlation with increased osteoclast activity, representing a pivotal mechanism of alveolar bone loss [44]. Moreover, ROS activate pro-inflammatory signaling pathways including NF-κB and MAPK, creating a feed-forward loop that amplifies local inflammation and accelerates tissue breakdown [45]. ROS-dependent autophagy dysregulation exacerbates periodontitis. Chronic ROS accumulation can overactivate autophagy, shifting it from homeostasis to a driver of cell death and tissue destruction [46].

Therefore, ROS act as a central driver of periodontitis progression, inflicting direct cellular damage while also amplifying inflammation and tissue breakdown through osteoclast activation, heightened inflammatory responses, and autophagy modulation. In a healthy state, a tightly regulated antioxidant defense system preserves intracellular redox balance by promptly eliminating excess ROS. However, in chronic periodontitis, sustained inflammatory reactions hinder the performance of the antioxidant defense system, rendering it incapable of effectively neutralizing excessive ROS, thereby causing the rise in oxidative impairment [28]. A marked decline in antioxidant enzyme activity has been documented at the site of the periodontal pocket in patients, indicating an inadequate defense against persistent oxidative stress that worsens tissue destruction [47].

### 2.4 Periodontal-systemic interplay: Far-reaching consequences

Periodontitis is significantly associated with other systemic disorders, such as cardiovascular diseases, diabetes, respiratory diseases, and rheumatoid arthritis as shown in Fig. 3 [48]. The systemic interactions among periodontitis and other systemic disorders could be mediated by the following three pathways. Firstly, translocation of periodontal pathogens and their virulence factors like LPS into circulation during daily activities or dental treatments may cause transient bacteremia and subsequent damages to remote organs and systemic inflammation [48–51]. Secondly, pro-inflammatory cytokines such as TNF-α released from periodontal lesions may increase the levels of C-reactive protein in the circulation and induce insulin resistance [52, 53]. Periodontal pathogens can also stimulate the activation of signaling pathways such as PI3K/Akt/mTOR and increase the activities of glycolysis and lipogenesis in liver, which may contribute to hyperlipidemia and atherosclerosis [3]. Finally, the ROS produced in periodontal lesions may cause oxidative damages to other organs, especially accelerating the progression of chronic kidney disease and damaging the functions of endothelial cells [54]. Clinical findings that periodontal therapy could improve the functions of endothelial cells and decrease systemic inflammation also supported the close relationship between oral health and overall health [48].

## 3 Traditional therapeutics: Applications and limitations

### 3.1 Clinical applications of conventional therapies

Current clinical management of periodontitis primarily relies on mechanical debridement, pharmacological therapy, and surgical intervention. As a cornerstone treatment, mechanical debridement including supragingival scaling and subgingival root planing physically removes dental plaque and calculus to eliminate local irritants [55]. Comprehensive meta-analyses demonstrate that standardized mechanical therapy can achieve an average reduction of 1.0–1.5 mm in probing depth and approximately 0.5 mm of clinical attachment gain [56]. Adjunctive pharmacological treatments predominantly involve locally delivered antimicrobial agents like 0.12% chlorhexidine gluconate and systemic antibiotics such as amoxicillin-metronidazole combination, which can significantly enhance therapeutic outcomes in selected cases [57]. For moderate-to-severe periodontitis, various surgical procedures including flap surgery and guided tissue regeneration are employed to eliminate periodontal pockets and promote tissue regeneration [55].

### 3.2 Limitations of current treatments

Although current therapeutic modalities have demonstrated certain clinical efficacy, several critical limitations remain unresolved. Mechanical debridement is significantly compromised by the complex anatomy of periodontal pockets, with markedly reduced efficacy in deep pockets (> 5 mm) and furcation areas, where residual biofilm often leads to disease recurrence [58]. Antibiotic therapy faces growing challenges of antimicrobial resistance, with global surveillance data indicating a 30%–50% increase in resistance rates among periodontal pathogens to commonly used antibiotics over the past decade [57]. Furthermore, existing treatments show limited capacity to promote functional periodontal tissue regeneration, with newly formed tissues frequently failing to reconstruct the integrated cementum-periodontal ligament-alveolar bone complex [59]. Another fundamental limitation lies in the inability of current therapies to effectively modulate excessive host immune responses, a core mechanism of tissue destruction [26, 27].

### 3.3 Unmet clinical needs

Several critical unmet needs persist in current periodontal therapy including the development of targeted antimicrobial strategies capable of complete biofilm eradication without host tissue damage, the urgent requirement for integrated treatment modalities that simultaneously address multiple pathological processes including anti-microbial, anti-inflammatory, and pro-regenerative, alongside the establishment of personalized decision-making systems to optimize clinical outcomes [60]. These unmet clinical needs create significant opportunities for novel therapeutic agents like BAPPs. Notably, the systemic health benefits of existing treatments remain controversial, with some studies demonstrating limited effects of mechanical therapy alone on systemic inflammatory markers [9, 13], suggesting the potential necessity for combined interventions targeting both local and systemic impacts.

## 4 Emerging therapeutics: BAPPs and their regulatory targets

As outlined in Table 1, BAPPs have in recent years presented a promising therapeutic approach for periodontitis, leveraging their

**Table 1** The relative advantages and limitations of BAPPs

| Category | Core function | Advantages | Limitations | Representative peptide | Clinical readiness | Ref. |
|---|---|---|---|---|---|---|
| Antimicrobial peptides | Direct sterilization;<br>Biofilm disruption;<br>Moderate immunomodulation | Broad antibacterial spectrum;<br>Low drug resistance induction;<br>Anti-inflammatory activity | Enzyme susceptibility;<br>Potential local stimulation;<br>Hydrophilic-hydrophobic imbalance | LL-37 | Moderate (partially in Phase II clinical trials) | [18, 63] |
| Immunomodulatory peptides | Macrophage polarization regulation;<br>T cell balance modulation;<br>Excessive inflammation inhibition | Precise immunomodulation;<br>Synergistic tissue repair;<br>High biocompatibility | Complex mechanism;<br>Microenvironment sensitivity;<br>Synergistic factor dependence;<br>Challenging release precision | MLIF | Limited (primarily preclinical) | [68] |
| Growth factor derived-peptides | Cellular proliferation;<br>Angiogenesis;<br>Tissue regeneration | Strong targeting and clear function;<br>High repair efficiency;<br>Good translational foundation;<br>Multi-platform adaptability | Enzyme susceptibility;<br>Risk of ectopic tissue formation;<br>High production cost | BMP2-derived peptide | High (clinically approved or in Phase II/III trials, with partial FDA approval) | [78, 79] |
| Antioxidant peptides | ROS scavenging;<br>Oxidative stress inhibition;<br>Cytoprotection | Oxidative damage alleviation;<br>Improved repair microenvironment;<br>Endogenous origin with high safety;<br>Synergistic potential with other BAPPs | pH susceptibility;<br>Poor stability;<br>Low efficacy as monotherapy | SS-31 | Limited (primarily preclinical) | [65] |
| Cell adhesion/ recruitment peptides | Enhanced cell adhesion;<br>Stem cell recruitment | Enhanced cell colonization;<br>Improved biocompatibility;<br>Simple and modifiable structure | Limited functionality;<br>Cellular aggregation risk;<br>Cell-type dependent recruitment | RGD peptide | Limited (primarily preclinical) | [80] |

multifunctionality, high specificity, and excellent biocompatibility. As shown in Fig. 4, BAPPs can modulate key processes in the periodontal microenvironment, including antimicrobial activity, immune regulation, ROS homeostasis, and tissue regeneration. Furthermore, their therapeutic efficacy is greatly improved by the participation of sophisticated delivery systems, offering novel strategies for periodontitis treatment.

### 4.1 The origin, design, and preparation process of BAPPs

BAPPs are a class of functional amino acid sequence molecules (typically no more than 50 amino acids) with diverse sources, varied design approaches, and well-established synthesis technologies.

BAPPs can be derived from both natural and artificial sources. Naturally occurring BAPPs primarily come from enzymatic hydrolysis or fermentation of food proteins (e.g., milk, soy, fish, shellfish), as well as endogenous peptides like hormones and antimicrobial peptides [9]. Artificial design involves rationally modifying or creating peptides based on known structures to enhance their activity, stability, and safety [15].

The design of BAPPs centers on modifying natural templates or utilizing computer-aided de novo design to enhance peptide activity, selectivity, and stability [9]. By employing bioinformatics databases and in silico enzymatic hydrolysis tools, researchers can predict potential bioactive peptide sequences in proteins based on the structure-activity relationship (SAR) of BAPPs. Computational analyses of properties like hydrophobicity and charge distribution, combined with molecular docking against targets (e.g., angiotensin-converting enzyme (ACE)), enable the rational screening and optimization of functional peptides.

Peptide synthesis is categorized into biosynthesis and chemical synthesis. Biosynthesis, involving enzymatic hydrolysis and microbial fermentation, uses proteases like pepsin or microbial activity to produce bioactive peptide mixtures. These methods are cost-effective and scalable, making them suitable for large-scale production and industrial applications. Chemical synthesis, particularly solid-phase peptide synthesis, enables precise production of designed peptides including modified sequences. It is straightforward to operate and suitable for developing high-purity, well-defined short- to medium-chain peptides. Recombinant DNA technology further supports the generation of larger bioactive molecules [9, 15, 17]. To improve stability and bioavailability, strategies like carrier conjugation and nano-encapsulation are employed for controlled release.

The preparation process of BAPPs typically involves extraction, purification, and identification. Common extraction methods include chemical extraction and salt precipitation, while purification relies on membrane separation, chromatographic techniques, and electrophoresis [15]. Identification is achieved primarily through mass spectrometry (MS) and nuclear magnetic resonance (NMR), which determine molecular weight, sequence, and structural features [18]. Additionally, peptide self-assembly into functional nanostructures is governed by non-covalent interactions such as electrostatic forces, hydrogen bonding, π-π stacking, and hydrophobic effects [9, 17].

### 4.2 BAPPs as direct antimicrobial agents

BAPPs, particularly AMPs, exhibit potent antibacterial functions through direct microbial killing or biofilm disruption. For instance, defensins like human β-defensin 1 (HBD1) and its derived short peptide Pep-B (ACPIFTKIQGTCYRG) bind to bacterial LPS via electrostatic interactions, compromising membrane integrity to inhibit pathogen proliferation while reducing proinflammatory cytokine release. These peptides demonstrate broad-spectrum activity against key periodontal pathogens like Pg [61]. The AMP LL-37 (LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES) not only exhibits direct bactericidal effects but also disrupts bacterial membranes and inhibits biofilm formation, effectively reducing pathogenic load in periodontal pockets [18]. By targeting microbial-specific structures, these peptides minimize antibiotic resistance

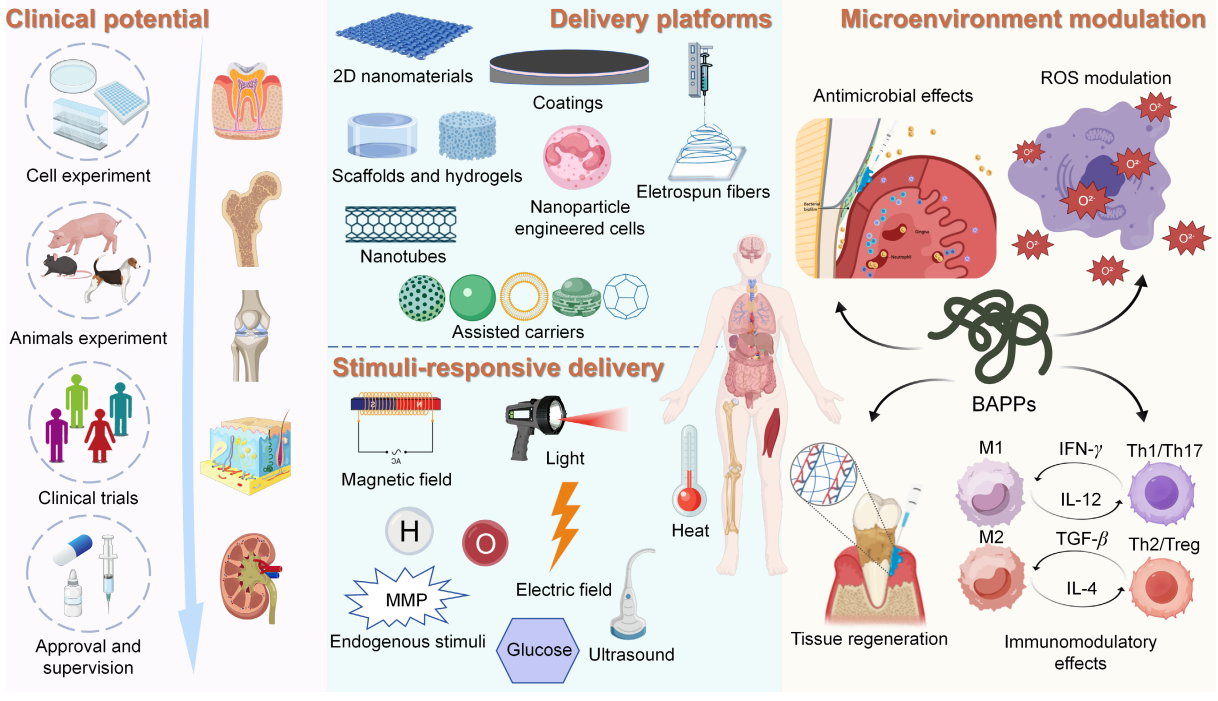


**Figure 4** Summary of BAPPs, including their clinical potential, delivery platforms, stimuli-responsive delivery, and microenvironment modulation.

risks, offering novel therapeutic strategies for periodontitis management.

#### 4.2.1 *Antimicrobial mechanisms*

Membrane adhesion: The antimicrobial efficacy of BAPPs primarily relies on their interactions with bacterial cell membranes through two fundamental mechanisms including electrostatic attraction between positively charged antimicrobial peptides like defensins and the negatively charged bacterial surface [62], and hydrogen bond formation. Representative examples include HBD1 and its derivative Pep-B (ACPIFTKIQGTCYRG), which directly bind LPS to neutralize bacterial surface charge while concurrently suppressing inflammatory responses, thereby potentiating antibacterial effects [63]. Furthermore, specific antimicrobial peptides such as the monocyte locomotion inhibitory factor (MLIF, Met-Gln-Cys-Asn-Ser) utilize functional motifs like Gln-Cys-Asn to interact with bacterial adhesion molecules, inducing membrane integrity disruption through targeted molecular interactions [64].

Cell membrane damage: BAPPs can directly disrupt bacterial cell membranes through multiple mechanisms. Cationic antimicrobial peptides like HBD1 bind to negatively charged bacterial membranes via electrostatic interactions, leading to membrane depolarization and increased permeability, ultimately resulting in leakage of cellular contents and bacterial death [63]. Furthermore, certain peptides can inhibit ion channels on bacterial membranes, further compromising membrane stability. Excessive accumulation of ROS also serves as a crucial antimicrobial mechanism of BAPPs. For instance, antioxidant peptides like SS-31 (D-Arg-Dmt-Lys-Phe-$NH_2$) indirectly suppress bacterial oxidative stress defense systems by scavenging ROS [65].

Intracellular components disruption: BAPPs can also be internalized into bacterial cells to disrupt critical metabolic pathways. For example, certain antimicrobial peptides can bind to bacterial DNA or RNA, inhibiting replication and transcription processes [18, 61]. Additionally, some BAPPs such as MLIF-related peptides may suppress the immune signaling pathways, reducing the generation of bacterial virulence factors and thereby attenuating pathogenicity [64].

Biofilm inhibition and disruption: BAPPs can suppress biofilm formation by interfering with bacterial quorum sensing (QS) systems and adhesion molecule expression. For example, HBD1 has been shown to downregulate toll-like receptor 2 (TLR-2) and TLR-4 expression, thereby reducing bacterial aggregation and extracellular polymeric substance (EPS) production [63]. Furthermore, certain peptides indirectly diminish bacterial colonization in inflammatory microenvironments by blocking neutrophil migration. Regarding established biofilms, some BAPPs can promote biofilm dispersion and clearance through membrane structure disruption and QS signal inhibition [66].

#### 4.2.2 *Representative BAPPs for antimicrobial applications*

BAPPs with antimicrobial properties can be classified into naturally-derived and synthetic categories. Naturally-occurring antimicrobial peptides include both animal- and plant-derived variants. Animal-derived peptides such as defensins and antimicrobial peptide-RP1 exhibit broad-spectrum antibacterial activity. For instance, antimicrobial peptide-RP1 (AMRLTYNKPCLYGT) demonstrates potent free radical scavenging capacity and bacterial growth inhibition [67]. MLIF indirectly mitigates bacterial infections by suppressing monocyte migration and inflammatory responses [68]. Plant-derived antimicrobial peptides like the corn gluten hydrolysate CSQAPLA display remarkable antioxidant and antimicrobial activities [69], functioning through dual mechanisms of ROS scavenging and bacterial membrane function inhibition. Regarding synthetic peptides, SS-31 exemplifies a mitochondria-targeting peptide that modulates oxidative stress balance to enhance host defense against bacterial pathogens [65]. Another synthetic peptide, Pep-B, exerts its antibacterial effects by inhibiting NF-$\kappa$B and MAPK signaling pathways, thereby reducing pro-inflammatory cytokine release during bacterial infection [63].

### 4.3 BAPPs as immunomodulators

The progression of periodontitis is closely associated with excessive activation of host immune responses. BAPPs can modulate immune cell functions to rebalance the inflammatory microenvironment. MLIF reduces pro-inflammatory cytokine expression including IL-1$\beta$ and TNF-$\alpha$ by inhibiting monocyte migration and M1 macrophage polarization, thereby alleviating periodontal inflammation [64]. Transforming growth factor-$\beta$ (TGF-$\beta$) and IL-4 promote M2 macrophage polarization, which suppresses excessive inflammation while enhancing tissue repair [18]. Additionally, programmed cell death protein 5 (PDCD5) mitigates immunopathological damage in periodontitis by inhibiting histone deacetylase 3 (HDAC3) to reduce pro-fibrotic factor expression, consequently ameliorating periodontal fibrosis [70, 71].

#### 4.3.1 *Immunomodulatory mechanisms*

Macrophage polarization reprogramming: Macrophages serve as pivotal effector cells in the immune response during periodontitis, with their functional diversity manifested through distinct polarization phenotypes of M1 and M2. M1 macrophages, stimulated by pro-inflammatory signals such as interferon-$\gamma$ (IFN-$\gamma$) or LPS, exacerbate periodontal tissue destruction through the secretion of inflammatory mediators including IL-1$\beta$, TNF-$\alpha$, and ROS. On the contrary, M2 macrophages stimulated by IL-4 or IL-10 exhibit anti-inflammatory properties that promote tissue repair, secreting regenerative factors like vascular endothelial growth factor (VEGF) and TGF-$\beta$ [18]. Research demonstrates that MLIF can reduce monocyte migration by inhibiting the VLA-4/VCAM-1 pathway, while progranulin (PGRN) and its derived peptide ATSTTRIN suppress M1 polarization through NF-$\kappa$B pathway blockade [64]. Additionally, the short peptide Pep-B, derived from HBD1, significantly downregulates IL-6 and TNF-$\alpha$ expression by inhibiting TLR-2/4 signaling [63]. These findings collectively indicate that modulating macrophage polarization through BAPPs represents a novel approach for alleviating periodontal inflammation.

Modulation of T cell subset homeostasis: $CD4^+$ T cells and their differentiated subsets (Th1, Th2, and Th17) play crucial roles in maintaining immune homeostasis during periodontitis. Th1 cells promote bone resorption through the secretion of IFN-$\gamma$ and IL-12, whereas Th2 cells suppress osteoclast activity via IL-4 and IL-10 production [31–33]. Vasoactive intestinal peptide (VIP) can restore Th1/Th2 balance via the dual action of inhibiting T-bet (a Th1-specific transcription factor) and promoting GATA-3 (a Th2 marker) [72]. The IL-17 produced by Th17 cells significantly enhances RANKL expression, thereby accelerating alveolar bone loss. In contrast, regulatory T cells (Tregs) mitigate excessive inflammatory responses through the secretion of IL-10 and TGF-$\beta$.

Mechanistically, TGF-$\beta$ and IL-2 promote Treg differentiation by inducing Foxp3 expression via the Smad3/Stat5 signaling pathway [31]. These findings suggest that BAPPs targeting T cell subsets like VIP and TGF-$\beta$ represent promising therapeutic candidates for periodontitis management.

Targeting key inflammatory pathways: The NF-$\kappa$B and MAPK pathways serve as central hubs for inflammatory signaling in periodontitis. Stimulation by LPS via TLR4 activates the I$\kappa$B kinase (IKK) complex, leading to I$\kappa$B degradation and NF-$\kappa$B nuclear translocation. This process ultimately induces the transcription of pro-inflammatory mediators [31]. The APETx2 peptide specifically inhibits acid-sensing ion channel 3 (ASIC-3), thereby blocking downstream NF-$\kappa$B and p38 MAPK signaling and reducing IL-1$\beta$ production [73, 74]. Furthermore, MLIF-related peptides suppress macrophage inflammatory protein (MIP-1$\alpha$) and IL-8 secretion by inhibiting the MAPK pathway [64]. These findings demonstrate that BAPPs can achieve precise immunomodulation through multi-target intervention in inflammatory signaling networks.

#### *4.3.2 Representative BAPPs for immunomodulatory applications*

Immunomodulatory BAPPs can be categorized into four functional classes, including M1 inhibition, M2 induction, Th1/Th2 balance regulation, and NF-$\kappa$B suppression. Pep-B, a synthetic peptide derived from HBD1, demonstrates potent anti-inflammatory effects by electrostatically binding to and inhibiting both NF-$\kappa$B and MAPK pathways, leading to significant reductions in IL-6 and TNF-α levels [63]. MLIF, a pentameric oligopeptide, contains a functional tripeptide domain Gln-Cys-Asn that simultaneously inhibits monocyte migration and promotes Th2 polarization [64]. BAPPs originating from IL-4/IL-10 directly induce M2 macrophage differentiation, with preclinical studies confirming their efficacy in reducing bone resorption in periodontitis models.

### 4.4 BAPPs as ROS scavengers

Excessive ROS in periodontitis induce oxidative stress that exacerbates tissue damage. BAPPs, particularly antioxidant peptides (AOPs), can effectively scavenge ROS and restore redox homeostasis. For instance, carnosine (the endogenous $\beta$-alanyl-L-histidine) neutralizes free radicals via its histidine residues, reducing oxidative damage in gingival tissues [40]. Peptide SS-31 specifically targets mitochondria to suppress ROS generation, thereby protecting PDLSCs from oxidative stress-induced apoptosis [75]. These BAPPs maintain periodontal redox homeostasis by regulating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and mitochondrial electron transport chain function. Notably, certain BAPPs, such as ankyrin-B (ANKB) and parathyroid hormone (PTH), modulate autophagy and cell senescence by inhibiting peroxidation, offering therapeutic potential for bone and neurodegenerative diseases [14, 15].

#### *4.4.1 ROS scavenging mechanisms*

Direct ROS scavenging by antioxidant peptides: AOPs, a class of natural or synthetic molecules with remarkable free radical-scavenging capacity, can directly neutralize ROS to mitigate oxidative damage in periodontal tissues. Carnosine can effectively eliminates superoxide anions ($O_2^-$) and hydroxyl radicals (·OH) through hydrogen atom donation from its histidine residue [40]. Furthermore, some plant-derived antioxidant peptides demonstrate dose-dependent scavenging effects on radicals like 2,2-diphenyl-1-picrylhydrazyl (DPPH), significantly reducing ROS levels in periodontitis microenvironments [76].

Suppression of ROS generation pathways: BAPPs can effectively block ROS production by inhibiting key enzymatic activities, particularly those of NADPH oxidase (NOX). The synthetic peptide SS-31 targets the mitochondrial inner membrane to prevent electron leakage from the electron transport chain, thereby reducing ROS generation [65]. Additionally, C-peptide suppresses high glucose (HG)-activated NOX and restores mitochondrial function, leading to further decreases in ROS levels [77].

Modulation of redox homeostasis: BAPPs can enhance cellular antioxidant capacity by activating endogenous defense systems, particularly the Nrf2/HO-1 pathway. For example, some AOPs effectively suppress LPS-induced glutamate release and ROS production, thereby protecting cells from oxidative damage.

#### *4.4.2 Representative BAPPs for ROS modulation*

Therapeutic BAPPs for ROS scavenging in periodontitis can be categorized into four classes consist of endogenous peptides like carnosine, synthetic peptides including SS-31 and PTH 1-34, natural oligopeptides such as MLIF, and recombinant proteins like platelet-derived growth factor (PDGF). These bioactive agents function through diverse yet complementary mechanisms, whereby carnosine directly neutralizes ROS, SS-31 suppresses ROS generation at its source, MLIF modulates immune responses, while PDGF-BB and PTH 1-34 promote tissue regeneration. Through targeting critical pathways such as NOX/PI3K-Akt, NF-$\kappa$B/MAPK, and mTOR signaling, these BAPPs provide multifaceted therapeutic strategies against periodontitis.

### 4.5 BAPPs for periodontal tissue regeneration

BAPPs drive periodontal tissue regeneration by enhancing the proliferation, differentiation, and extracellular matrix synthesis of PDLSCs. Specifically, PDGF-BB and insulin-like growth factor-1 (IGF-1) activate PI3K/Akt and Erk1/2 pathways to stimulate osteogenic differentiation [78]. Bone morphogenetic protein-2 (BMP-2) and its mimetic peptide (P24, EKKEEQQEKKKKE EKREKRK) induce alveolar bone regeneration through Smad and Wnt signaling cascades [79]. Moreover, fibronectin-derived RGD peptides promote periodontal reattachment by enhancing cell adhesion via integrin receptors [80]. The synergistic actions of these BAPPs facilitate the reconstruction of functional periodontal complex structures.

#### *4.5.1 Tissue regeneration mechanisms*

Promotion of cell adhesion and migration: BAPPs significantly enhance periodontal tissue regeneration by mimicking the structural and functional properties of the extracellular matrix (ECM). For instance, peptides containing the RGD sequence (arginine–glycine–aspartate) can specifically bind to integrin receptors, thereby improving the adhesion and migration capabilities of PDLSCs and bone marrow mesenchymal stem cells (BMSCs), which establishes a foundation for tissue regeneration. Furthermore, the PHSRN peptide derived from fibronectin (FN) synergizes with RGD to further activate the $\alpha5\beta1$ integrin receptor, promoting cell spreading and ECM deposition [80].

Regulation of stem cell differentiation: BAPPs regulate the osteogenic and cementogenic differentiation of PDLSCs by activating key signaling pathways. BMP-2 and its mimetic peptides P24 promote osteogenic differentiation via the Smad and Wnt

pathways, upregulating the expression of runt-related transcription factor 2 (RUNX2) and osteocalcin (OCN) [79]. PDGF-BB activates the PI3K-Akt and Ras-Erk1/2 pathways, enhancing PDLSC proliferation and angiogenesis while suppressing inflammatory responses [78]. Additionally, osteogenic growth peptide (OGP) augments the osteogenic potential of mesenchymal stem cells (MSCs) through the HO-1-eNOS and RhoA/ROCK signaling cascades [81].

Anti-inflammatory effects: The inflammatory microenvironment in periodontitis presents a major obstacle to tissue regeneration. BAPPs can promote M2 macrophage polarization through IL-4 and IL-10 induction, thereby reducing the secretion of pro-inflammatory cytokine like TNF-$\alpha$ and IL-6, modulating immune responses, and facilitating tissue repair [18, 63, 64].

#### *4.5.2 Representative BAPPs in periodontal regeneration*

Among the BAPPs currently approved for clinical applications in periodontal tissue regeneration, PDGF-BB and BMP-2 represent the most prominent examples [78, 79]. PDGF-BB, one of the few FDA-approved BAPPs for periodontal bone defect repair, has demonstrated clinical efficacy comparable to autografts when combined with $\beta$-tricalcium phosphate ($\beta$-TCP), significantly improving clinical attachment level (CAL) and bone fill percentage in clinical trials. While materials above exhibit remarkable osteogenic potential, their high-dose application may lead to adverse effects including ectopic bone formation and inflammation, prompting recent research to focus on its mimetic peptides to mitigate side effects while achieving controlled release [82]. Several promising candidates are currently under preclinical investigation, including fibroblast growth factor-2 (FGF-2), stromal cell-derived factor-1 (SDF-1), and antimicrobial peptides like LL-37. FGF-2 promotes PDLSCs proliferation and angiogenesis, with animal studies demonstrating enhanced alveolar bone regeneration, though delivery system optimization remains crucial to prevent rapid degradation [83]. SDF-1 facilitates endogenous MSC recruitment to injury sites via C-X-C chemokine receptor type 4 (CXCR4) receptor activation, with its combination with E7 peptide showing improved cell homing efficiency [84]. AMPs demonstrate dual functionality of antibacterial properties and regenerative capacity, effectively reducing pathogen load while accelerating epithelial healing in diabetic periodontitis models [85].

## 5 Design optimization and delivery strategies for BAPPs

The unique oral cavity environment coupled with the inherent instability and rapid degradation of BAPPs often results in inadequate bioavailability when administered locally in their native form. Consequently, rational design and optimization of either their molecular structures or delivery systems become paramount to ensure effective local concentrations, targeted accumulation, and controlled release. Figure 5 and Table 2 illustrate the key design optimization and delivery strategies for BAPPs.

### 5.1 Structural optimization of delivery systems

The delivery efficiency of BAPPs is intrinsically linked to the

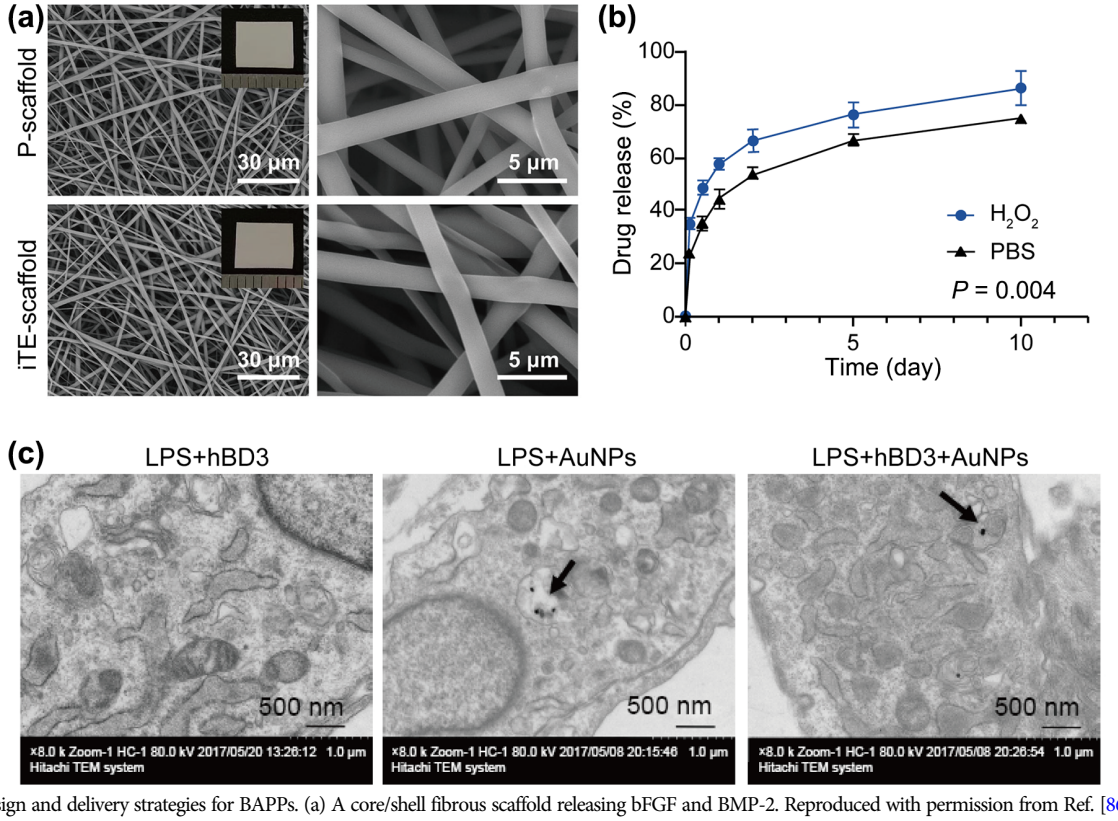


**Figure 5** Design and delivery strategies for BAPPs. (a) A core/shell fibrous scaffold releasing bFGF and BMP-2. Reproduced with permission from Ref. [86], © Ding, T. et al. (b) An injectable ROS-responsive hydrogel was developed for sustained calcitonin gene-related peptide (CGRP) delivery in the presence of $H_2O_2$. Reproduced with permission from Ref. [14], © Zhan, C. et al. Advanced Science published by Wiley-VCH GmbH 2025. (c) AuNPs enhanced the cellular uptake efficiency of hBD3 in inflammatory microenvironments. Reproduced with permission from Ref. [87], © Zhou, J. et al. This work is published and licensed by Dove Medical Press Limited 2018.

**Table 2** Comparison of different delivery strategies of BAPPs

| Delivery strategy | Representative type | Advantages | Limitations | Load/release mechanism | Ref. |
|---|---|---|---|---|---|
| Hydrogel | HA, GelMA | ECM-mimetic structure;<br>Tunable pore size;<br>Appropriate degradation rate;<br>Excellent cytocompatibility;<br>Broad compatibility with BAPPs | Limited mechanical strength;<br>Poor release-degradation match;<br>Pronounced initial burst release | Directly mixing into matrix;<br>Physically or chemically combining;<br>Incorporating stimuli-responsive release | [94] |
| Scaffolds | PCL, TCP Electrospun fibers | High specific surface area;<br>Controllable core-shell design;<br>Tunable porosity regulation<br>Robust structural support;<br>Microenvironment simulation;<br>Facilitated cell co-culture | Potential inhibition of BAPPs activity;<br>Poor controllability of degradation rate;<br>Poor hydrophilicity and cell adhesion | Direct blending encapsulation;<br>Core-shell loading by coaxial/emulsion;<br>Adsorption after surface modification | [86] |
| Surface coating | PDA, MPN | Substance surface modification;<br>Material functionalization;<br>Simple and easy to spread;<br>Sustained BAPPs release | Limited load-bearing capacity;<br>Internal environment-sensitive stability;<br>Unsuitable for large defects | Physical adsorption or covalent grafting;<br>Releasing through coating degradation;<br>Releasing through stimulus response | [99] |
| Nanomaterials | Nanoparticles | Controllable size;<br>Targeted delivery;<br>Enhanced cellular delivery;<br>Enzymatic resistance;<br>Prolonged half-life | Poor biocompatibility of some carriers;<br>Complex large-scale production process;<br>Potential slight immune response | Surface adsorption or pore embedding;<br>Covalent anchoring or co-precipitation;<br>Carrier degradation or stimuli response | [90] |
| | Nanotubes | Surface adsorption;<br>Internal packaging | | Internal packaging;<br>Surface modification;<br>Carrier degradation or stimuli response | [100] |
| | 2D-nanomaterials | Large specific surface area;<br>Easy functionalization | | Physical interactions;<br>Stimulus response | [101] |
| Endogenous stimulus response | ROS, pH, glucose, enzymes | Release on-demand | Dependent on stimulation conditions;<br>Complex design;<br>Difficulty on stimulus parameter control | Sensitive chemical bonds or pH-triggered degradation | [97] |
| Exogenous stimulus response | Ultrasound, light, magnetic/electric field | Non-invasive;<br>Precise regulation;<br>Releasing on time or in dose | | Ultrasound-triggered destruction;<br>Photothermal phase-transition release;<br>Field-induced carrier deformation | [98] |

physicochemical properties of their carrier systems. Precise modulation of structural parameters in delivery systems enables protection, controlled release, and targeted delivery of BAPPs. Core-shell architectures represent one of the most promising designs, where the core encapsulates therapeutic BAPPs while the shell provides protection and functional modification [12]. Studies demonstrate that gelatin-polycaprolactone core-shell nanoparticles delivering amelogenin significantly enhance stability in gingival crevicular fluid, extending half-life to 3.5-fold that of free proteins. Three-dimensional porous scaffolds, owing to their high surface area and biomimetic structure, serve as ideal carriers for periodontal regeneration [12, 14]. Fibronectin-functionalized mesoporous silica scaffolds combined with FGF-2 markedly promote PDLSC migration and differentiation, achieving 40% higher cementum regeneration rates in animal models [86].

### 5.2 Microenvironment-responsive delivery strategies

The unique pathological microenvironment of periodontitis lesions provides natural triggering conditions for designing smart delivery systems. pH-responsive systems leverage the acidic environment (pH 5.5–6.5) at inflammatory sites for targeted release. Polyethylene glycol hydrogels containing acetal bonds remain stable at physiological pH but undergo rapid degradation in the acidic periodontal pocket environment, enabling on-demand release of LL-37 [87–89]. ROS-responsive systems are designed to exploit elevated ROS levels in lesions, where thioether-containing nanoparticles undergo structural rearrangement upon ROS exposure, simultaneously releasing encapsulated superoxide dismutase mimetics and scavenging excess ROS [14]. Recent advancements have developed dual-responsive systems, such as pH/MMP-responsive nanocarriers that concurrently respond to acidic conditions and matrix metalloproteinase overexpression for more precise drug release regulation [15, 16].

### 5.3 Surface functionalization strategies

Surface functionalization can significantly enhance the targeting capability and biocompatibility of delivery systems [9]. Antibody conjugation represents the most straightforward targeting strategy. For example, Pg-specific IgG-modified liposomes achieve 8 to 10-fold higher local drug concentrations through pathogen-specific binding [90]. Cell membrane coating technology leverages natural membrane structures for both immune evasion and lesion targeting. Macrophage membrane-coated nanoparticles demonstrate intrinsic inflammatory tropism, showing over 75% targeting efficiency in periodontitis models [91]. Furthermore, bioinspired adhesive molecules like dopamine can prolong intraoral retention. For instance, dopamine-modified chitosan microspheres exhibit 6–8 h of gingival adhesion, significantly surpassing unmodified counterparts (1–2 h) [92, 93].

### 5.4 Temporally controlled release systems

Periodontal tissue repair requires coordinated interventions across distinct healing phases. To address this, researchers have developed delivery systems with sequential release capabilities [94]. Bilayer

microspheres can release antimicrobial peptides (80% within 24 h) from the outer layer for infection control, followed by sustained amelogenin release (over 14 days) from the inner core to promote tissue regeneration, thereby mimicking the natural healing cascade [95]. More advanced triple-phase systems demonstrate programmed release in the sequence of antimicrobial agents for infection eradication, anti-inflammatory factors for immune modulation, and growth factors for tissue regeneration, achieving 60% higher periodontal regeneration efficiency in large animal models [96]. These temporally controlled systems provide novel strategies for complex periodontal regeneration by precisely recapitulating the natural healing chronology [97, 98].

## 6 Combination strategies of BAPPs and other therapeutic modalities

### 6.1 Combinatorial applications of diverse BAPPs

Although BAPPs have shown considerable potential in tissue regeneration and periodontal immunomodulation, single-function BAPPs often exhibit inherent limitations in clinical applications. Rational design and combinatorial administration of functionally distinct BAPPs can synergistically address multiple pathological aspects of periodontitis, thereby promoting comprehensive tissue repair and immune homeostasis.

#### *6.1.1 Antibacterial-immunomodulatory synergism*

Periodontopathic bacteria serve as the primary key etiologic agent in the initiation and progression of periodontitis, whose pathogenesis is closely associated with excessive inflammatory responses. Combining antibacterial and immunomodulatory strategies may represent an effective therapeutic approach. Taking antimicrobial peptide LL-37 and immunomodulatory peptide IL-4 as examples [18, 63], the former directly eliminates pathogens by disrupting bacterial membranes and inhibiting biofilm formation, while the latter modulates the host response by promoting M2 macrophage polarization and reducing levels of pro-inflammatory cytokines, including TNF-$\alpha$ and IL-1$\beta$ [82]. Their combination demonstrates synergistic effects. On the one hand, IL-4 enhances macrophage phagocytic activity, cooperating with antimicrobial peptides to clear pathogens, on the other hand, immunomodulatory peptides accelerate inflammation resolution after bacterial suppression, thereby preventing tissue damage caused by excessive immune responses.

#### *6.1.2 Antioxidant-regenerative synergism*

The combination of antioxidant peptides and regenerative BAPPs can simultaneously mitigate oxidative stress and enhance tissue regeneration. The mitochondrial-targeted antioxidant peptide SS-31 can effectively scavenge excess ROS, reducing oxidative damage to osteoblasts [65], while regenerative factors like BMP-2 and FGF-2 are able to promote osteogenic differentiation and angiogenesis, respectively [79, 83]. The cooperative mechanisms are demonstrated by SS-31's ability to alleviate ROS-induced cytotoxicity in stem cells and fibroblasts while optimizing the regenerative microenvironment through localized antioxidant protection, thereby potentiating BMP-2/FGF-2 efficacy [99]. Furthermore, SS-31-mediated reduction of oxidative stress creates favorable conditions that significantly enhance BMP-2-driven osteogenesis and FGF-2-induced vascularization, ultimately leading to accelerated tissue repair through synergistic regenerative effects.

#### *6.1.3 Antibacterial-regenerative synergism*

The synergistic application of antimicrobial BAPPs and regenerative BAPPs enables concurrent infection control and periodontal tissue regeneration while preventing pathogen-mediated destruction of newly formed tissues. Taking AMPs and VEGF as representative examples, AMPs disrupt the "infection-ischemia" vicious cycle through pathogen elimination, which establishes favorable conditions for VEGF to subsequently promote angiogenesis following infection control [100]. This enhanced vascularization provides critical oxygen and nutrient supply for tissue repair, while the improved local blood circulation prevents hypoxic fibrosis, ultimately reducing scar formation and optimizing healing quality [102, 103].

#### *6.1.4 Immunomodulatory-regenerative synergism*

The combined use of immunomodulatory and regenerative BAPPs enables simultaneous regulation of the immune microenvironment and direct stimulation of cellular proliferation to promote tissue regeneration. The synergistic effects are exemplified by VIP, which suppresses Th1/Th17 cell responses and upregulates anti-inflammatory cytokines like IL-10, cooperating with OGP that directly stimulates osteoblast proliferation [72]. The synergistic mechanism operates through immune-osteogenic coupling, where VIP counteracts inflammation-induced osteogenesis suppression alongside OGP-mediated bone deposition enhancement [104]. Particularly in aggressive periodontitis with significant bone loss, this dual-targeted strategy simultaneously addresses inflammatory control and bone regeneration, resulting in clinically predictable reparative outcomes.

### 6.2 Combination of BAPPs with other therapies

Characterized primarily by chronic inflammation, periodontitis drives the progressive breakdown of periodontal tissues, ultimately leading to their destruction. While conventional treatments such as mechanical debridement (scaling and root planing (SRP)) and antibiotics can control infection [105, 106], they face significant limitations including high risks of antibiotic resistance and inadequate tissue regeneration capacity. For example, traditional agents like minocycline gel provide rapid, reliable infection control but lack regenerative function and may induce resistance. In contrast, BAPPs offer multifunctional activity, including antimicrobial, anti-inflammatory, antioxidant, immunomodulatory, and regenerative effects, suitable for complex tissue repair scenarios with infection. However, their clinical translation is limited by stability, cost, and early-stage evidence. Consequently, a synergistic strategy that integrates existing treatment modalities with BAPPs may facilitate integrated therapeutic outcomes.

The combined application of BAPPs, such as AMPs, BMPs, and PDGF, with SRP enhances bacterial clearance, attenuates inflammation, as well as promotes PDLSC proliferation and osteogenic differentiation, leading to improved clinical attachment levels and accelerated bone regeneration [107, 108]. In antimicrobial applications, BAPPs synergize with antibiotics by disrupting biofilm architecture and improving drug permeability, thereby reducing dosage requirements and minimizing resistance development, as exemplified by the LL-37/doxycycline combination, which shows superior efficacy against periodontal pathogens along with reduced pocket depth and inflammatory

cytokines clinically. Furthermore, BAPPs enhance photodynamic therapy (PDT) through mechanisms like photosensitizer targeting and synergistic biofilm eradication, simultaneously reducing bacterial load and supporting tissue repair. In regenerative therapy, BAPPs such as BMP-2 and FGF-2 synergize with stem cells to enhance osteogenesis and angiogenesis, while peptides like SDF-1 and LL-37 facilitate stem cell recruitment and modulate the inflammatory microenvironment, respectively. Additionally, BAPPs can be integrated into biomaterial systems, such as chitosan scaffolds, for sustained and targeted delivery, thereby optimizing therapeutic outcomes in periodontal regeneration.

## 7 Advantages and improvements

Periodontitis presents significant therapeutic challenges including incomplete pathogen eradication, limited tissue regeneration capacity, and antibiotic resistance issues. In this context, BAPPs have emerged as a breakthrough therapeutic strategy due to their unique capacity for multi-mechanistic microenvironment modulation. Globally, over 80 BAPPs have been approved with more than 150 in clinical development and 400–600 in preclinical research. The market is projected to reach $400 billion by 2026. BAPPs exhibit higher biocompatibility, biodegradability, and design flexibility compared to other nanomaterials. They enable targeted microenvironment modulation and support diverse biofunctions [9]. Table 3 presents a comparative analysis of BAPPs and various emerging non-peptide strategies, outlining their respective advantages and disadvantages. Derived from natural or artificial sources, BAPPs circumvent the potential toxicity and accumulation risks associated with metallic nanoparticles [66, 87] and are easier to standardize and scale up compared to cell-based carriers [92]. Although immune cell-derived nanomaterials possess inherent targeting capability, their payload capacity is limited. In contrast, BAPPs allow easy chemical modification of surfaces and structures for integrated drug loading and controlled release.

However, challenges including short half-life, enzymatic degradation, high production cost, and limited barrier penetration restricted the application of BAPPs. Current solutions involve nanocarrier encapsulation, stimulus-responsive systems, and structural modifications to enhance stability and controllability. Hydrogel- and scaffold-based delivery systems can prolong material half-life through sustained release mechanisms, maintaining effective local BAPP concentrations, while stimuli-responsive systems enable precise drug release triggered by endogenous microenvironmental cues or exogenous stimuli including pH, enzymes, and ROS. Nanoparticle-incorporated systems further improve targeting specificity, biocompatibility, and stability, with functionalized modifications enhancing penetration capability into periodontal pockets.

Currently, the clinical translation of BAPPs demonstrates a distinct tiered progression. Novel BAPPs and intelligent delivery systems are primarily at the preclinical stage, while validated combinations have advanced to large animal trials. Candidates in clinical stages often utilize established carriers such as injectable hydrogels, whereas approved agents typically depend on simpler platforms including collagen sponges. There are several critical challenges remain for clinical translation. The proteolytic susceptibility of natural BAPPs demands innovative stabilization strategies including structural modifications such as cyclization and D-amino acid substitution, as well as protective approaches like nano-encapsulation. Developing multifactorial delivery systems with precise spatiotemporal control represents another critical challenge, particularly for achieving coordinated regulation of inflammatory responses, antimicrobial activity, and osteogenic processes during periodontal repair. Furthermore, overcoming manufacturing scalability hurdles and establishing cost-effective production protocols remain essential for clinical translation.

Future research should focus on establishing multi-mechanism synergistic therapeutic systems by developing integrated platforms combining BAPPs with nanomaterials and biophysical stimulation such as ultrasound and electric fields to achieve temporally controlled antimicrobial, anti-inflammatory and regenerative effects. A representative example would be bilayer hydrogels co-loaded with antimicrobial peptides like LL-37 and osteogenic peptides derived from BMP-2 that can sequentially release payloads in response to bacterial enzymes and the acidic microenvironment of bone defects respectively. Equally important is the advancement

**Table 3** Analysis of BAPPs and other non-peptide strategies

| Strategy | Representative type | Advantages | Limitations | Clinical readiness | Ref. |
|---|---|---|---|---|---|
| BAPPs | AMPs/AOPs | Diverse functions;<br>Precise targeting;<br>High biocompatibility;<br>Low resistance risk;<br>Mature synthesis | Suboptimal stability and short half-life | Limited (primarily preclinical) | [36, 82] |
| Small molecule drugs | Chlorhexidine | Simple, low-cost synthesis;<br>High-compliance oral route;<br>Mature, versatile delivery | Poor targeting with side effects;<br>Resistance risk;<br>Limited, non-synergistic effect | High (mature clinical transformation) | [109, 110] |
| Antibody therapy | Monoclonal antibody | Specific and precise targeting;<br>High stability, long half-life | Significant immunogenicity;<br>High cost and lengthy production;<br>Poor tissue penetration;<br>Limited functions | Moderate (partial clinical approval) | [111, 112] |
| Exosomes | Stem cell-derived exosomes | Natural, multifunctional carrier;<br>High loading capacity;<br>Multi-component synergy;<br>Low immunogenicity;<br>High biosafety | Low manufacturability;<br>Complex separation & purification;<br>High batch-to-batch variability;<br>Stringent storage needs;<br>Difficulties in large-scale production | Limited (primarily preclinical) | [113] |
| RNA therapy | siRNA, miRNA | Multi-gene regulation;<br>Precise, high-efficacy targeting;<br>Potent therapeutic outcomes;<br>High design flexibility | Poor stability;<br>Low delivery efficiency;<br>Potential off-target effects;<br>Unverified long-term biological safety | Limited (restricted clinical evidence) | [114, 115] |

of precision delivery technologies, including targeted modification approaches using functionalized nanoparticles to enhance BAPP accumulation in periodontal tissues, or employing exogenous stem cells as carriers to improve homing efficiency. For clinical translation acceleration, priority should be given to short peptides containing 5–50 amino acids due to their synthetic simplicity, cost-effectiveness and superior stability, while establishing standardized evaluation systems encompassing production protocols of good manufacturing practice (GMP) and multicenter clinical trials. The development of personalized treatment strategies represents another critical direction, where customized BAPP combinations such as antioxidant peptide-loaded microspheres for patients with high ROS levels could be designed based on individual microbiomic profiles and inflammatory biomarker characteristics.

## 8 Conclusions and prospects

BAPPs address key periodontitis treatment challenges by providing multifaceted therapeutic effects. Their efficacy is enhanced via advanced delivery systems enabling precise, sustained, and targeted release. We review the recent advances of BAPPs and their delivery platforms in periodontitis. However, their clinical translation continues to face challenges including inadequate stability, limited delivery control, immunogenicity, high manufacturing costs, and individual microenvironmental heterogeneity. Future efforts should focus on the development of intelligent multi-factor delivery systems, dynamic regulatory strategies and AI driven biomanufacturing. Moreover, the limitations of this review lie primarily in the preclinical nature and model heterogeneity of the cited evidence, along with the absence of direct clinical data on BAPP safety and efficacy in humans. Therefore, while continued efforts are needed to develop more advanced platforms and integrated therapies, their ultimate clinical evaluation will be essential to address the insufficiency referred in this review for future translational validation and clinical exploration.

## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Acknowledgements

This paper was supported by various funding sources, including the Basic Public Welfare Research Project of Zhejiang Province (No. LGF22H140007) and the Research and development project of Stomatology Hospital Affiliated to Zhejiang University School of Medicine (No. RD2022JCXK01).

## Declaration of competing interest

The authors declare no conflict of interest.

## Author contribution statement

J. F. S.: Conceptualization, data curation, formal analysis, investigation, visualization, validation, writing – original draft. Q. H. L.: Conceptualization, data curation, formal analysis, writing – original draft. L. J. Y.: Investigation, validation, visualization. Y. M.: Supervision, writing – review & editing. P. D.: Conceptualization, supervision, writing – review & editing. Q. M. C.: Conceptualization, supervision, writing – review & editing. P. S.: Funding acquisition, resources, supervision, writing – review & editing.

## Informed consent

Not applicable.

## Ethics statement

Not applicable.

## Use of AI statement

None.

## References

[1] Belibasakis, G. N.; Belstrøm, D.; Eick, S.; Gursoy, U. K.; Johansson, A.; Könönen, E. Periodontal microbiology and microbial etiology of periodontal diseases: Historical concepts and contemporary perspectives. *Periodontol. 2000*, in press, DOI: 10.1111/prd.12473.

[2] Trindade, D.; Carvalho, R.; Machado, V.; Chambrone, L.; Mendes, J. J.; Botelho, J. Prevalence of periodontitis in dentate people between 2011 and 2020: A systematic review and meta-analysis of epidemiological studies. *J. Clin. Periodontol.* **2023**, *50*, 604–626.

[3] Sanz, M.; Marco del Castillo, A.; Jepsen, S.; Gonzalez-Juanatey, J. R.; D'Aiuto, F.; Bouchard, P.; Chapple, I.; Dietrich, T.; Gotsman, I.; Graziani, F. et al. Periodontitis and cardiovascular diseases: Consensus report. *J. Clin. Periodontol.* **2020**, *47*, 268–288.

[4] Marruganti, C.; Suvan, J. E.; D'Aiuto, F. Periodontitis and metabolic diseases (diabetes and obesity): Tackling multimorbidity. *Periodontol. 2000*, in press, DOI: 10.1111/prd.12536.

[5] Sansores-España, D.; Carrillo-Avila, A.; Melgar-Rodriguez, S.; Díaz-Zuñiga, J.; Martínez-Aguilar, V. Periodontitis and Alzheimer´s disease. *Med. Oral Patol. Oral Cir. Buccal.* **2021**, *26*, e43–e48.

[6] Jakubovics, N. S.; Goodman, S. D.; Mashburn-Warren, L.; Stafford, G. P.; Cieplik, F. The dental plaque biofilm matrix. *Periodontol. 2000* **2021**, *86*, 32–56.

[7] Hajishengallis, G.; Chavakis, T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. *Nat. Rev. Immunol.* **2021**, *21*, 426–440.

[8] Elashiry, M.; Morandini, A. C.; Cornelius Timothius, C. J.; Ghaly, M.; Cutler, C. W. Selective antimicrobial therapies for periodontitis: Win the "battle and the war". *Int. J. Mol. Sci.* **2021**, *22*, 6459.

[9] Hao, Z. W.; Zhang, Z. Y.; Wang, Z. P.; Wang, Y.; Chen, J. Y.; Chen, T. H.; Shi, G.; Li, H. K.; Wang, J. W.; Dong, M. C. et al. Bioactive peptides and proteins for tissue repair: Microenvironment modulation, rational delivery, and clinical potential. *Military Med. Res.* **2024**, *11*, 75.

[10] Nagayasu-Tanaka, T.; Anzai, J.; Takedachi, M.; Kitamura, M.; Harada, T.; Murakami, S. Effects of combined application of fibroblast growth factor (FGF)-2 and carbonate appetite for tissue regeneration in a beagle dog model of one-wall periodontal defect. *Regen. Ther.* **2023**, *23*, 84–93.

[11] Ma, J. P.; Zhang, L.; Lei, B. Multifunctional MXene-based bioactive materials for integrated regeneration therapy. *ACS Nano* **2023**, *17*, 19526–19549.

[12] Rambhia, K. J.; Sun, H. L.; Feng, K.; Kannan, R.; Doleyres, Y.; Holzwarth, J. M.; Doepker, M.; Franceschi, R. T.; Ma, P. X. Nanofibrous 3D scaffolds capable of individually controlled BMP and FGF release for the regulation of bone regeneration. *Acta Biomater.* **2024**, *190*, 50–63.

[13] Xu, Z. Y.; Wang, Y.; Li, S. S.; Li, Y. H.; Chang, L. L.; Yao, Y.; Peng, Q. Advances of functional nanomaterials as either therapeutic

agents or delivery systems in the treatment of periodontitis. *Biomater. Adv.* **2025**, *175*, 214326.

[14] Zhan, C. N.; Dai, Q. Y.; Ren, J. H.; Jin, L. J.; Wang, W. P.; Ye, Z.; Tsoi, J. K. H.; Lin, Y. F. CGRP-loaded ROS-responsive hydrogel restores neuro-angiogenic signaling to promote bone regeneration in diabetes-associated periodontitis. *Adv. Sci.* **2025**, *12*, e06438.

[15] Fan, D. Y.; Xie, R. Y.; Liu, X. H.; Li, H. H.; Luo, Z. H.; Li, Y. B.; Chen, F.; Zeng, W. B. A peptide-based pH-sensitive antibacterial hydrogel for healing drug-resistant biofilm-infected diabetic wounds. *J. Mater. Chem. B* **2024**, *12*, 5525–5534.

[16] Son, J.; Parveen, S.; MacPherson, D.; Marciano, Y.; Huang, R. H.; Ulijn, R. V. MMP-responsive nanomaterials. *Biomater. Sci.* **2023**, *11*, 6457–6479.

[17] Fraser, D.; Benoit, D. Dual peptide-functionalized hydrogels differentially control periodontal cell function and promote tissue regeneration. *Biomater. Adv.* **2022**, *141*, 213093.

[18] Li, C. C.; Du, L. W.; Xiao, Y. Y.; Fan, L.; Li, Q. L.; Cao, C. Y. Multi-active phlorotannins boost antimicrobial peptide LL-37 to promote periodontal tissue regeneration in diabetic periodontitis. *Mater. Today Bio* **2025**, *31*, 101535.

[19] Fischer, N. G.; de Souza Araújo, I. J.; Daghrery, A.; Yu, B. Q.; Dal-Fabbro, R.; dos Reis-Prado, A. H.; Silikas, N.; Rosa, V.; Aparicio, C.; Watts, D. C. et al. Guidance on biomaterials for periodontal tissue regeneration: Fabrication methods, materials and biological considerations. *Dent. Mater.* **2025**, *41*, 283–305.

[20] Wu, J.; Guo, Z. X.; Wang, L.; Shen, Y.; Li, X.; Zhang, Z. W.; Han, X.; Zhang, J. L.; Cai, K. Z.; Tang, C. B. *Porphyromonas gingivalis* induces Zbp1-mediated macrophages PANoptosis in periodonitis pathophysiology. *Exp. Mol. Med.* **2025**, *57*, 964–978.

[21] He, J. L.; Liu, Y. F.; Xu, H. Z.; Wei, X. L.; Chen, M. H. Insights into the variations in microbial community structure during the development of periodontitis and its pathogenesis. *Clin. Oral Invest.* **2024**, *28*, 675.

[22] Sha, Z. M.; Wu, Y. J.; Zheng, Y.; Yang, K.; Gong, X. Y.; Xuan, L.; Li, X.; Chen, X. P. Advances in pH-responsive drug delivery systems for periodontitis treatment. *Drug Deliv.* **2025**, *32*, 2522109.

[23] Blasco-Baque, V.; Garidou, L.; Pomié, C.; Escoula, Q.; Loubieres, P.; Le Gall-David, S.; Lemaitre, M.; Nicolas, S.; Klopp, P.; Waget, A. et al. Periodontitis induced by *Porphyromonas gingivalis* drives periodontal microbiota dysbiosis and insulin resistance via an impaired adaptive immune response. *Gut* **2017**, *66*, 872–885.

[24] Liu, G. Q.; Xue, J. L.; Zhou, X.; Gui, M. X.; Xia, R. D.; Zhang, Y. S.; Cai, Y. H.; Li, S. H.; Shi, S. T.; Mao, X. L. et al. The paradigm shifts of periodontal regeneration strategy: From reparative manipulation to developmental engineering. *Bioact. Mater.* **2025**, *49*, 418–436.

[25] Pandi, K.; Angabo, S.; Gnanasekaran, J.; Makkawi, H.; Eli-Berchoer, L.; Glaser, F.; Nussbaum, G. *Porphyromonas gingivalis* induction of TLR2 association with Vinculin enables PI3K activation and immune evasion. *PLoS Pathog.* **2023**, *19*, e1011284.

[26] Hajishengallis, G. Periodontitis: From microbial immune subversion to systemic inflammation. *Nat. Rev. Immunol.* **2015**, *15*, 30–44.

[27] Sansores-España, L. D.; Melgar-Rodríguez, S.; Vernal, R.; Carrillo-Ávila, B. A.; Martínez-Aguilar, V. M.; Díaz-Zúñiga, J. Neutrophil N1 and N2 subsets and their possible association with periodontitis: A scoping review. *Int. J. Mol. Sci.* **2022**, *23*, 12068.

[28] Ando, Y.; Tsukasaki, M.; Huynh, N. C. N.; Zang, S. Z.; Yan, M. L.; Muro, R.; Nakamura, K.; Komagamine, M.; Komatsu, N.; Okamoto, K. et al. The neutrophil-osteogenic cell axis promotes bone destruction in periodontitis. *Int. J. Oral Sci.* **2024**, *16*, 18.

[29] Sun, X. Y.; Gao, J. K.; Meng, X.; Lu, X. X.; Zhang, L.; Chen, R. Polarized macrophages in periodontitis: Characteristics, function, and molecular signaling. *Front. Immunol.* **2021**, *12*, 763334.

[30] Gan, Z. Q.; Xiao, Z. C.; Zhang, Z.; Li, Y.; Liu, C.; Chen, X.; Liu, Y. B.; Wu, D. L.; Liu, C. F.; Shuai, X. T. et al. Stiffness-tuned and ROS-sensitive hydrogel incorporating complement C5a receptor antagonist modulates antibacterial activity of macrophages for periodontitis treatment. *Bioact. Mater.* **2023**, *25*, 347–359.

[31] González-Osuna, L.; Sierra-Cristancho, A.; Cafferata, E. A.; Melgar-Rodríguez, S.; Rojas, C.; Carvajal, P.; Cortez, C.; Vernal, R. Senescent $CD4^+CD28^-$ T lymphocytes as a potential driver of Th17/Treg imbalance and alveolar bone resorption during periodontitis. *Int. J. Mol. Sci.* **2022**, *23*, 2543.

[32] Neurath, N.; Kesting, M. Cytokines in gingivitis and periodontitis: From pathogenesis to therapeutic targets. *Front. Immunol.* **2024**, *15*, 1435054.

[33] Huang, N.; Dong, H.; Luo, Y. Q.; Shao, B. Th17 cells in periodontitis and its regulation by A20. *Front. Immunol.* **2021**, *12*, 742925.

[34] Araújo, A. A.; Souza, T. O.; Moura, L. M.; Brito, G. A. C.; Aragão, K. S.; Araújo, L. S.; Medeiros, C. A. Z.; Alves, M. S. C. F.; Araújo, R. F. Jr. Effect of telmisartan on levels of IL-1, TNF-α, down-regulated COX-2, MMP-2, MMP-9 and RANKL/RANK in an experimental periodontitis model. *J. Clin. Periodontol.* **2013**, *40*, 1104–1111.

[35] Kittaka, M.; Yoshimoto, T.; Levitan, M. E.; Urata, R.; Choi, R. B.; Teno, Y.; Xie, Y. X.; Kitase, Y.; Prideaux, M.; Dallas, S. L. et al. Osteocyte RANKL drives bone resorption in mouse ligature-induced periodontitis. *J. Bone Miner. Res.* **2023**, *38*, 1521–1540.

[36] Chen, T. H.; Wang, Y.; Hao, Z. W.; Hu, Y. K.; Li, J. F. Parathyroid hormone and its related peptides in bone metabolism. *Biochem. Pharmacol.* **2021**, *192*, 114669.

[37] Yan, J. Y.; Yang, T.; Ma, S. Y.; Li, D. F.; Hu, C.; Tan, J. L. Macrophage-derived mitochondria-rich extracellular vesicles aggravate bone loss in periodontitis by disrupting the mitochondrial dynamics of BMSCs. *J. Nanobiotechnol.* **2025**, *23*, 208.

[38] Lee, H.; Joo, J. Y.; Song, J. M.; Kim, H. J.; Kim, Y. H.; Park, H. R. Immunological link between periodontitis and type 2 diabetes deciphered by single-cell RNA analysis. *Clin. Transl. Med.* **2023**, *13*, e1503.

[39] Chen, Y.; Wang, H.; Yang, Q. D.; Zhao, W. H.; Chen, Y. Y.; Ni, Q. Q.; Li, W. L.; Shi, J. L.; Zhang, W.; Li, L. et al. Single-cell RNA landscape of the osteoimmunology microenvironment in periodontitis. *Theranostics* **2022**, *12*, 1074–1096.

[40] Sczepanik, F. S. C.; Grossi, M. L.; Casati, M.; Goldberg, M.; Glogauer, M.; Fine, N.; Tenenbaum, H. C. Periodontitis is an inflammatory disease of oxidative stress: We should treat it that way. *Periodontol. 2000* **2020**, 45–68.

[41] Huang, X. F.; Xie, M. R.; Wang, Y. X.; Lu, X. F.; Mei, F.; Zhang, K. W.; Yang, X. L.; Chen, G. J.; Yin, Y.; Feng, G. X. et al. *Porphyromonas gingivalis* aggravates atherosclerotic plaque instability by promoting lipid-laden macrophage necroptosis. *Sig. Transduct. Target. Ther.* **2025**, *10*, 171.

[42] Xin, L. J.; Zhou, F. Y.; Zhang, C. W.; Zhong, W. J.; Xu, S. H.; Jing, X.; Wang, D.; Wang, S.; Chen, T.; Song, J. L. Four-Octyl itaconate ameliorates periodontal destruction via Nrf2-dependent antioxidant system. *Int. J. Oral Sci.* **2022**, *14*, 27.

[43] Jang, J. S.; Hong, S. J.; Mo, S. Z.; Kim, M. K.; Kim, Y. G.; Lee, Y.; Kim, H. H. PINK1 restrains periodontitis-induced bone loss by preventing osteoclast mitophagy impairment. *Redox Biol.* **2024**, *69*, 103023.

[44] Weng, Y. T.; Wang, H. C.; Li, L.; Feng, Y. H. Z.; Xu, S. Y.; Wang, Z. L. Trem2 mediated Syk-dependent ROS amplification is essential for osteoclastogenesis in periodontitis microenvironment. *Redox Biol.* **2021**, *40*, 101849.

[45] Tian, Y. J.; Li, Y.; Liu, J. L.; Lin, Y.; Jiao, J.; Chen, B.; Wang, W. M.; Wu, S. L.; Li, C. Y. Photothermal therapy with regulated Nrf2/NF-κB signaling pathway for treating bacteria-induced periodontitis. *Bioact. Mater.* **2022**, *9*, 428–445.

[46] Xu, X. Y.; Wang, J.; Xia, Y. L.; Yin, Y.; Zhu, T. X.; Chen, F. M.;

Hai, C. X. Autophagy, a double-edged sword for oral tissue regeneration. *J. Adv. Res.* **2024**, *59*, 141–159.
[47] Xin, X. R.; Xiang, X. C.; Xin, Y.; Li, Q.; Ma, H. N.; Liu, X. C.; Hou, Y. B.; Yu, W. X. Global trends in research on oxidative stress associated with periodontitis from 1987 to 2022: A bibliometric analysis. *Front. Immunol.* **2022**, *13*, 979675.
[48] Villoria, G. E. M.; Fischer, R. G.; Tinoco, E. M. B.; Meyle, J.; Loos, B. G. Periodontal disease: A systemic condition. *Periodontol. 2000* **2024**, *96*, 7–19.
[49] Pink, C.; Holtfreter, B.; Völzke, H.; Nauck, M.; Dörr, M.; Kocher, T. Periodontitis and systemic inflammation as independent and interacting risk factors for mortality: Evidence from a prospective cohort study. *BMC Med.* **2023**, *21*, 430.
[50] Jungbauer, G.; Stähli, A.; Zhu, X. L.; Auber Alberi, L.; Sculean, A.; Eick, S. Periodontal microorganisms and Alzheimer disease-A causative relationship? *Periodontol. 2000* **2022**, *89*, 59–82.
[51] Robledo-Montaña, J.; Díaz-García, C.; Martínez, M.; Ambrosio, N.; Montero, E.; Marín, M. J.; Virto, L.; Muñoz-López, M.; Herrera, D.; Sanz, M. et al. Microglial morphological/inflammatory phenotypes and endocannabinoid signaling in a preclinical model of periodontitis and depression. *J. Neuroinflammation* **2024**, *21*, 219.
[52] Hajishengallis, G. Interconnection of periodontal disease and comorbidities: Evidence, mechanisms, and implications. *Periodontol. 2000* **2022**, *89*, 9–18.
[53] Koziel, J.; Potempa, J. Pros and cons of causative association between periodontitis and rheumatoid arthritis. *Periodontol. 2000* **2022**, *89*, 83–98.
[54] Chapple, I. L. C.; Hirschfeld, J.; Cockwell, P.; Dietrich, T.; Sharma, P. Interplay between periodontitis and chronic kidney disease. *Nat. Rev. Nephrol.* **2025**, *21*, 226–240.
[55] Sanz, M.; Herrera, D.; Kebschull, M.; Chapple, I.; Jepsen, S.; Berglundh, T.; Sculean, A.; Tonetti, M. S.; EFP Workshop Participants and Methodological Consultants. Treatment of stage I-III periodontitis-The EFP S3 level clinical practice guideline. *J. Clin. Periodontol.* **2020**, *47*, 4–60.
[56] Lin, Z. K.; Strauss, F. J.; Lang, N. P.; Sculean, A.; Salvi, G. E.; Stähli, A. Efficacy of laser monotherapy or non-surgical mechanical instrumentation in the management of untreated periodontitis patients. *A systematic review and meta-analysis. Clin. Oral Invest.* **2021**, *25*, 375–391.
[57] Teughels, W.; Feres, M.; Oud, V.; Martín, C.; Matesanz, P.; Herrera, D. Adjunctive effect of systemic antimicrobials in periodontitis therapy: A systematic review and meta-analysis. *J. Clin. Periodontol.* **2020**, *47 Suppl 22*, 257–281.
[58] Bosshardt, D. D. The periodontal pocket: Pathogenesis, histopathology and consequences. *Periodontol. 2000* **2018**, *76*, 43–50.
[59] Sculean, A.; Nikolidakis, D.; Nikou, G.; Ivanovic, A.; Chapple, I. L. C.; Stavropoulos, A. Biomaterials for promoting periodontal regeneration in human intrabony defects: A systematic review. *Periodontol. 2000* **2015**, *68*, 182–216.
[60] Slots, J. Periodontitis: Facts, fallacies and the future. *Periodontol. 2000* **2017**, *75*, 7–23.
[61] Batoni, G.; Maisetta, G.; Esin, S. Therapeutic potential of antimicrobial peptides in polymicrobial biofilm-associated infections. *Int. J. Mol. Sci.* **2021**, *22*, 482.
[62] Fu, J.; Zong, X.; Jin, M. L.; Min, J. X.; Wang, F. D.; Wang, Y. Z. Mechanisms and regulation of defensins in host defense. *Sig. Transduct. Target. Ther.* **2023**, *8*, 300.
[63] Tanabe, G.; Mori, T.; Araki, M.; Kataoka, H.; Into, T. Role of LL-37 in oral bacterial DNA accumulation in dental plaque. *J. Dent. Res.* **2024**, *103*, 177–186.
[64] Zhang, X.; Song, M. Y.; Wang, H. B.; Zhang, Q.; Liu, Z. Y.; Deng, J. Y. Application of a modified multifunctional short peptide in the treatment of periodontitis. *Sci. Rep.* **2024**, *14*, 22855.
[65] Ye, P.; Liu, H.; Qin, Y.; Li, Z. Y.; Huang, Z. W.; Bu, X. W.; Peng, Q.; Duan, N.; Wang, W. M.; Wang, X. SS-31 mitigates oxidative stress and restores mitochondrial function in cigarette smoke-damaged oral epithelial cells via PINK1-mediated mitophagy. *Chem. Biol. Interact.* **2024**, *400*, 111166.
[66] Mahmoud, M. Y.; Steinbach-Rankins, J. M.; Demuth, D. R. Functional assessment of peptide-modified PLGA nanoparticles against oral biofilms in a murine model of periodontitis. *J. Controlled Release* **2019**, *297*, 3–13.
[67] Li, Y. X.; Yang, P.; Meng, R.; Xu, S. T.; Zhou, L. L.; Qian, K.; Wang, P. Z.; Cheng, Y. L.; Sheng, D. Y.; Xu, M. J. et al. Multidimensional autophagy nano-regulator boosts Alzheimer's disease treatment by improving both extra/intraneuronal homeostasis. *Acta Pharm. Sin. B* **2024**, *14*, 1380–1399.
[68] Godina-Gonzalez, S.; Furuzawa-Carballeda, J.; Utrera-Barillas, D.; Alcocer-Varela, J.; Teran, L. M.; Vazquez-del Mercado, M.; Leal, Y. A.; Alvarado-Cabrero, I.; Velazquez, J. R. Amebic monocyte locomotion inhibitory factor peptide ameliorates inflammation in CIA mouse model by downregulation of cell adhesion, inflammation/chemotaxis, and matrix metalloproteinases genes. *Inflamm. Res.* **2010**, *59*, 1041–1051.
[69] Wang, X.; Fu, J.; Bhullar, K. S.; Chen, B. J.; Liu, H. R.; Zhang, Y.; Wang, C. F.; Liu, C. X.; Su, D.; Ma, X. et al. Identification, *in silico* selection, and mechanistic investigation of antioxidant peptides from corn gluten meal hydrolysate. *Food Chem.* **2024**, *446*, 138777.
[70] Wang, K.; Zhang, X. W.; Wang, Y. F.; Jin, G. W.; Li, M. Y.; Zhang, S. S.; Hao, J.; Jin, R.; Huang, X. J.; Wu, H. N. et al. PDCD5 regulates iNKT cell terminal maturation and iNKT1 fate decision. *Cell. Mol. Immunol.* **2019**, *16*, 746–756.
[71] Weng, L.; Ye, J. J.; Yang, F. H.; Jia, S.; Leng, M. H.; Jia, B.; Xu, C. L.; Zhao, Y.; Liu, R. X.; Xiong, Y. F. et al. TGF-β1/SMAD3 regulates programmed cell death 5 that suppresses cardiac fibrosis post-myocardial infarction by inhibiting HDAC3. *Circ. Res.* **2023**, *133*, 237–251.
[72] Villanueva-Romero, R.; Gutiérrez-Cañas, I.; Carrión, M.; Pérez-García, S.; Seoane, I. V.; Martínez, C.; Gomariz, R. P.; Juarranz, Y. The anti-inflammatory mediator, vasoactive intestinal peptide, modulates the differentiation and function of Th subsets in rheumatoid arthritis. *J. Immunol. Res.* **2018**, *2018*, 6043710.
[73] Izumi, M.; Ikeuchi, M.; Ji, Q. H.; Tani, T. Local ASIC3 modulates pain and disease progression in a rat model of osteoarthritis. *J. Biomed. Sci.* **2012**, *19*, 77.
[74] Bian, J.; Cai, F.; Chen, H.; Tang, Z. Z.; Xi, K.; Tang, J. C.; Wu, L.; Xu, Y. C.; Deng, L. F.; Gu, Y. et al. Modulation of local overactive inflammation via injectable hydrogel microspheres. *Nano Lett.* **2021**, *21*, 2690–2698.
[75] Meng, L. L.; Wen, W. J. Mitochondrial dysfunction in diabetic periodontitis: Mechanisms and therapeutic potential. *J. Inflamm. Res.* **2025**, *18*, 115–126.
[76] Lu, X. Y.; Xu, Z. X.; Shu, F.; Wang, Y. D.; Han, Y. H.; Yang, X. R.; Shi, P. L.; Fan, C. Q.; Wang, L. L.; Yu, F. et al. Reactive oxygen species responsive multifunctional fusion extracellular nanovesicles: Prospective treatments for acute heart transplant rejection. *Adv. Mater.* **2024**, *36*, 2406758.
[77] Ramzy, A.; Thompson, D. M.; Ward-Hartstonge, K. A.; Ivison, S.; Cook, L.; Garcia, R. V.; Loyal, J.; Kim, P. T. W.; Warnock, G. L.; Levings, M. K. et al. Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes. *Cell Stem Cell* **2021**, *28*, 2047–2061.e5.
[78] Galarraga-Vinueza, M. E.; Barootchi, S.; Nevins, M. L.; Nevins, M.; Miron, R. J.; Tavelli, L. Twenty-five years of recombinant human

growth factors rhPDGF-BB and rhBMP-2 in oral hard and soft tissue regeneration. *Periodontol. 2000* **2024**, *94*, 483–509.

[79] Wang, W. X.; Zhang, G. R.; Wang, Y. Y.; Ran, J. C.; Chen, L.; Wei, Z.; Zou, H. H.; Cai, Y.; Han, W. An injectable and thermosensitive hydrogel with nano-aided NIR-II phototherapeutic and chemical effects for periodontal antibacteria and bone regeneration. *J. Nanobiotechnol.* **2023**, *21*, 367.

[80] Huang, C. C.; Kang, M. Y.; Shirazi, S.; Lu, Y.; Cooper, L. F.; Gajendrareddy, P.; Ravindran, S. 3D Encapsulation and tethering of functionally engineered extracellular vesicles to hydrogels. *Acta Biomater.* **2021**, *126*, 199–210.

[81] Li, R. Y.; Li, W. F.; Teng, Y. S.; Li, R. Z.; Kong, S. Y.; Chen, X.; Luo, H. T.; Chen, D. Y.; Guo, Y. Q.; Qing, Y. Q. et al. Ameliorating macrophage pyroptosis via ANXA1/NLRP3/Caspase-1/GSDMD pathway: Ac2-26/OGP-loaded intelligent hydrogel enhances bone healing in diabetic periodontitis. *Biofabrication* **2025**, *17*, 025001.

[82] Hao, Z. W.; Chen, R. X.; Chai, C.; Wang, Y.; Chen, T. H.; Li, H. K.; Hu, Y. K.; Feng, Q. Y.; Li, J. F. Antimicrobial peptides for bone tissue engineering: Diversity, effects and applications. *Front. Bioeng. Biotechnol.* **2022**, *10*, 1030162.

[83] Tsuboi, R.; Kitagawa, H.; Imazato, S. FGF-2 release and bonding/physical properties of 4-META/MMA-based adhesive resins incorporating small FGF-2-loaded polymer particles. *Dent. Mater.* **2020**, *36*, 1586–1594.

[84] Li, Q. H.; Li, C.; Yan, J.; Zhang, C. L.; Jiang, Y.; Hu, X. T.; Han, L. W.; Li, L.; Wang, P.; Zhao, L. Z. et al. Evenly distributed microporous structure and E7 peptide functionalization synergistically accelerate osteogenesis and angiogenesis in engineered periosteum. *Adv. Sci.* **2025**, *12*, 2406084.

[85] Herman, A.; Herman, A. P. Antimicrobial peptides for diabetic wound healing: Preclinical and clinical studies. *Adv. Wound Care* **2025**, *14*, 619–634.

[86] Ding, T.; Kang, W. Y.; Li, J. H.; Yu, L.; Ge, S. H. An *in situ* tissue engineering scaffold with growth factors combining angiogenesis and osteoimmunomodulatory functions for advanced periodontal bone regeneration. *J. Nanobiotechnol.* **2021**, *19*, 247.

[87] Zhou, J.; Zhang, Y. H.; Li, L. J.; Fu, H. M.; Yang, W. R.; Yan, F. H. Human β-defensin 3-combined gold nanoparticles for enhancement of osteogenic differentiation of human periodontal ligament cells in inflammatory microenvironments. *Int. J. Nanomedicine* **2018**, *13*, 555–567.

[88] Supanchart, C.; Thawanaphong, S.; Makeudom, A.; Bolscher, J. G.; Nazmi, K.; Kornak, U.; Krisanaprakornkit, S. The antimicrobial peptide, LL-37, inhibits *in vitro* osteoclastogenesis. *J. Dent. Res.* **2012**, *91*, 1071–1077.

[89] Lin, S. H.; Xu, Z. Q.; Liu, Y. L.; Yang, G. Z.; Qi, X. Y.; Huang, Y. J.; Zhou, M. L.; Jiang, X. Q. Engineered macrophage membrane-camouflaged nanodecoys reshape the infectious microenvironment for efficient periodontitis treatment. *ACS Nano* **2025**, *19*, 15345–15362.

[90] Jiang, Y. N.; Pan, X. M.; Yao, M. Y.; Han, L.; Zhang, X.; Jia, Z. R.; Weng, J.; Chen, W. X.; Fang, L. M.; Wang, X. L. et al. Bioinspired adhesive and tumor microenvironment responsive nanoMOFs assembled 3D-printed scaffold for anti-tumor therapy and bone regeneration. *Nano Today* **2021**, *39*, 101182.

[91] Song, R.; Wan, Z.; Yuan, X. J.; Wang, N.; Gao, Y. K.; Zhang, L. X.; Ren, H. H.; Jin, Y.; Liu, X. Y.; Sang, J. Y. et al. Macrophage membrane functionalized composite microspheres promote bone regeneration in periodontitis via manipulating inflammation reversing-osteogenesis coupling. *Mater. Today Bio* **2025**, *32*, 101789.

[92] Juriga, D.; Kalman, E. E.; Toth, K.; Barczikai, D.; Szöllősi, D.; Földes, A.; Varga, G.; Zrinyi, M.; Jedlovszky-Hajdu, A.; Nagy, K. S. Analysis of three-dimensional cell migration in dopamine-modified poly(aspartic acid)-based hydrogels. *Gels* **2022**, *8*, 65.

[93] Zhang, J.; Wang, M.; Hu, L. W.; Zhang, Q.; Chen, E. N.; Wang, Z. C.; Shi, Y. D.; Tan, L.; Xiao, S. M. A universal coating strategy for inhibiting the growth of bacteria on materials surfaces. *Front. Chem.* **2022**, *10*, 1043353.

[94] Deng, Y. H.; Sun, A. X.; Overholt, K. J.; Yu, G. Z.; Fritch, M. R.; Alexander, P. G.; Shen, H.; Tuan, R. S.; Lin, H. Enhancing chondrogenesis and mechanical strength retention in physiologically relevant hydrogels with incorporation of hyaluronic acid and direct loading of TGF-β. *Acta Biomater.* **2019**, *83*, 167–176.

[95] Jin, S.; Yang, R. L.; Hu, C.; Xiao, S. Q.; Zuo, Y.; Man, Y.; Li, Y. B.; Li, J. D. Plant-derived polyphenol and LL-37 peptide-modified nanofibrous scaffolds for promotion of antibacterial activity, anti-inflammation, and type-H vascularized bone regeneration. *ACS Appl. Mater. Interfaces* **2023**, *15*, 7804–7820.

[96] Zhu, Y. J.; Xiu, Z. L.; Jiang, X. X.; Zhang, H. F.; Li, X. F.; Feng, Y. R.; Li, B. J.; Cai, R.; Li, C. H.; Tao, G. Injectable hydrogels with ROS-triggered drug release enable the co-delivery of antibacterial agent and anti-inflammatory nanoparticle for periodontitis treatment. *J. Nanobiotechnol.* **2025**, *23*, 205.

[97] Zhao, Y. Z.; Huang, L. T.; Lin, G. L.; Tong, M. Q.; Xie, Y. L.; Pan, H. X.; Shangguan, J. X.; Yao, Q.; Xu, S. H.; Xu, H. L. Skin-adaptive film dressing with smart-release of growth factors accelerated diabetic wound healing. *Int. J. Biol. Macromol.* **2022**, *222*, 2729–2743.

[98] Huang, W. C.; Lin, C. C.; Chiu, T. W.; Chen, S. Y. 3D gradient and linearly aligned magnetic microcapsules in nerve guidance conduits with remotely spatiotemporally controlled release to enhance peripheral nerve repair. *ACS Appl. Mater. Interfaces* **2022**, *14*, 46188–46200.

[99] Huang, B. L.; Wu, Z. H.; Ding, S.; Yuan, Y.; Liu, C. S. Localization and promotion of recombinant human bone morphogenetic protein-2 bioactivity on extracellular matrix mimetic chondroitin sulfate-functionalized calcium phosphate cement scaffolds. *Acta Biomater.* **2018**, *71*, 184–199.

[100] Abdulmalik, S.; Gallo, J.; Nip, J.; Katebifar, S.; Arul, M.; Lebaschi, A.; Munch, L. N.; Bartly, J. M.; Choudhary, S.; Kalajzic, I. et al. Nanofiber matrix formulations for the delivery of Exendin-4 for tendon regeneration: *In vitro* and *in vivo* assessment. *Bioact. Mater.* **2023**, *25*, 42–60.

[101] Shen, H.; Lin, H.; Sun, A. X.; Song, S. J.; Wang, B.; Yang, Y. H.; Dai, J. W.; Tuan, R. S. Acceleration of chondrogenic differentiation of human mesenchymal stem cells by sustained growth factor release in 3D graphene oxide incorporated hydrogels. *Acta Biomater.* **2020**, *105*, 44–55.

[102] Comune, M.; Rai, A.; Chereddy, K. K.; Pinto, S.; Aday, S.; Ferreira, A. F.; Zonari, A.; Blersch, J.; Cunha, R.; Rodrigues, R. et al. Antimicrobial peptide-gold nanoscale therapeutic formulation with high skin regenerative potential. *J. Controlled Release* **2017**, *262*, 58–71.

[103] Chereddy, K. K.; Her, C. H.; Comune, M.; Moia, C.; Lopes, A.; Porporato, P. E.; Vanacker, J.; Lam, M. C.; Steinstraesser, L.; Sonveaux, P. et al. PLGA nanoparticles loaded with host defense peptide LL37 promote wound healing. *J. Controlled Release* **2014**, *194*, 138–147.

[104] Ma, S. Q.; Xu, S. D.; Li, M. T.; Du, Y. Q.; Tian, G. J.; Deng, J. Y.; Zhang, W. Y.; Wei, P. F.; Zhao, B.; Zhang, X. S. et al. A bone targeting nanoparticle loaded OGP to restore bone homeostasis for osteoporosis therapy. *Adv. Healthcare Mater.* **2023**, *12*, 2300560.

[105] Hashim, N. T.; Babiker, R.; Chaitanya, N. C. S. K.; Mohammed, R.; Priya, S. P.; Padmanabhan, V.; Ahmed, A.; Dasnadi, S. P.; Islam, M. S.; Gismalla, B. G. et al. New insights in natural bioactive compounds for periodontal disease: Advanced molecular mechanisms and therapeutic potential. *Molecules* **2025**, *30*, 807.

[106] Chen, Y. G.; Lu, F. M.; Zhang, Z. C.; Li, X.; Zhang, R. X.; Zheng, T. Y. Ferroptosis and macrophage efferocytosis in periodontitis:

Biological insights and therapeutic advances. *Virulence* **2025**, *16*, 2573660.

[107] Asparuhova, M. B.; Caballé-Serrano, J.; Buser, D.; Chappuis, V. Bone-conditioned medium contributes to initiation and progression of osteogenesis by exhibiting synergistic TGF-β1/BMP-2 activity. *Int. J. Oral Sci.* **2018**, *10*, 20.

[108] Ma, Q. L.; Jiang, N.; Liang, S.; Chen, F. L.; Fang, L.; Wang, X.; Wang, J. J.; Chen, L. H. Functionalization of a clustered $TiO_2$ nanotubular surface with platelet derived growth factor-BB covalent modification enhances osteogenic differentiation of bone marrow mesenchymal stem cells. *Biomaterials* **2020**, *230*, 119650.

[109] Wu, M. H.; Liu, H. F.; Li, D.; Zhu, Y. F.; Wu, P.; Chen, Z.; Chen, F. X.; Chen, Y.; Deng, Z. M.; Cai, L. Smart-responsive multifunctional therapeutic system for improved regenerative microenvironment and accelerated bone regeneration via mild photothermal therapy. *Adv. Sci.* **2024**, *11*, 2304641.

[110] Liu, X. F.; Li, L. L.; Gaihre, B.; Park, S.; Li, Y.; Terzic, A.; Elder, B. D.; Lu, L. C. Scaffold-free spheroids with two-dimensional heteronano-layers (2DHNL) enabling stem cell and osteogenic factor codelivery for bone repair. *ACS Nano* **2022**, *16*, 2741–2755.

[111] Bonini, S.; Lambiase, A.; Rama, P.; Sinigaglia, F.; Allegretti, M.; Chao, W.; Mantelli, F.; REPARO Study Group. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology* **2018**, *125*, 1332–1343.

[112] Pflugfelder, S. C.; Massaro-Giordano, M.; Perez, V. L.; Hamrah, P.; Deng, S. X.; Espandar, L.; Foster, C. S.; Affeldt, J.; Seedor, J. A.; Afshari, N. A. et al. Topical recombinant human nerve growth factor (cenegermin) for neurotrophic keratopathy: A multicenter randomized vehicle-controlled pivotal trial. *Ophthalmology* **2020**, *127*, 14–26.

[113] Ju, Y. K.; Hu, Y.; Yang, P.; Xie, X. Y.; Fang, B. R. Extracellular vesicle-loaded hydrogels for tissue repair and regeneration. *Mater. Today Bio* **2023**, *18*, 100522.

[114] Han, Y. F.; Wu, Y.; Wang, F. X.; Li, G. F.; Wang, J.; Wu, X.; Deng, A. F.; Ren, X. X.; Wang, X. H.; Gao, J. et al. Heterogeneous DNA hydrogel loaded with Apt02 modified tetrahedral framework nucleic acid accelerated critical-size bone defect repair. *Bioact. Mater.* **2024**, *35*, 1–16.

[115] Owusu-Akyaw, A.; Krishnamoorthy, K.; Goldsmith, L. T.; Morelli, S. S. The role of mesenchymal-epithelial transition in endometrial function. *Hum. Reprod. Update* **2019**, *25*, 114–133.