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# Current Progress in Nanomaterials for Diabetic Periodontitis Therapy

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## Abstract

Diabetic periodontitis (DP) presents a complicated therapeutic challenge driven by microbial dysbiosis, immune dysregulation, and impaired tissue repair. Conventional treatments often fail to achieve predictable regeneration in this high-risk scenario due to the unique hyperglycemic and pro-inflammatory microenvironment. This review examines the paradigm shift in therapies offered by fast developing nanotechnology, moving beyond simple pathogen control toward integrated strategies. In this review, we identify different functional nanomaterial classes, including potent antibiofilm agents, immunomodulators designed to reprogram macrophage phenotypes and scavenge reactive oxygen species, and "smart" carriers enabling enzyme-responsive delivery. Furthermore, the role of nanocomposite scaffolds in facilitating alveolar bone regeneration is also highlighted. Beyond therapeutic mechanisms, we rigorously evaluate translational barriers, including biocompatibility, manufacturing consistency, and regulatory requirements. A critical emphasis is placed on the current scarcity of clinical data specifically derived from DP cohorts. The review concludes by forecasting the development of multifunctional, theranostic nanoplatforms that seamlessly integrate into clinical workflows, addressing the specific metabolic and inflammatory demands of DP to ensure safety and unlock their full therapeutic potential.

## Keywords

Diabetic Periodontitis, Nanotechnology, Immunomodulation, Tissue Regeneration

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# 1. Introduction

## 1.1. Disease Burden and Clinical Gaps

Periodontitis is a chronic inflammatory disease initiated by dysbiotic dental plaque biofilms, leading to the progressive destruction of the tooth-supporting apparatus, including the periodontal ligament and alveolar bone [1]. As a major global public health concern, it not only represents a leading cause of tooth loss in adults but also imposes a substantial medical and socioeconomic burden [2]. The complexity of periodontitis escalates significantly when it coexists with systemic conditions, most notably diabetes mellitus. The bidirectional relationship between periodontitis and diabetes has been well-established, where each condition adversely influences the other. On one hand, diabetes exacerbates periodontal destruction by fostering a hyperinflammatory state, impairing host immune responses, and altering bone metabolism [3]. On the other hand, the chronic inflammation stemming from periodontitis can worsen insulin resistance and complicate glycemic control, creating a vicious cycle that makes treatment particularly challenging [4].

Current clinical management for periodontitis, whether in diabetic or non-diabetic patients, is primarily centered on mechanical debridement, such as scaling and root planing (SRP), often supplemented with adjunctive antimicrobial agents [5]. While these conventional therapies are effective in reducing the microbial load and temporarily alleviating inflammation, their efficacy is often limited and transient, especially in the context of diabetic periodontitis [6]. Several critical gaps persist. First, mechanical instruments are hard to completely eradicate pathogenic biofilms located in deep periodontal pockets, furcation areas, or dentinal tubules, leading to frequent disease recurrence [7]. Second, the systemic or local application of antibiotics faces challenges like inadequate concentration at the target site, the development of bacterial resistance, and potential systemic side effects [8]. Most importantly, these conventional approaches primarily target the microbial trigger but fail to adequately address the dysregulated host immune response and cleanse the established pro-inflammatory microenvironment, which are particularly pronounced in diabetic patients [5] [8]. Consequently, they fall short in promoting predictable and functional regeneration of the tissues destroyed by the disease, a fundamental goal of definitive periodontal therapy. Therefore, there is a pressing need for innovative therapeutic strategies that can simultaneously eliminate deep-seated pathogens, modulate the aberrant inflammatory cascade, and facilitate robust tissue regeneration, thereby breaking the pathological loop in diabetic periodontitis.

## 1.2. Pathophysiology and Clinical Definition of Diabetic Periodontitis

In this review, diabetic periodontitis (DP) is operationally defined as periodontitis occurring in patients with a confirmed diagnosis of either Type 1 or Type 2 diabetes mellitus (T1D or T2D). The severity and progression of DP are heavily in-

fluenced by the patient's glycemic control status, often measured by HbA1c levels; therefore, interpreting therapeutic outcomes requires considering this metabolic baseline [9].

The bidirectional synergy between diabetes and periodontitis is driven by a distinct pathophysiological map. Chronic hyperglycemia accelerates the accumulation of advanced glycation end-products (AGEs), which bind to their receptors (RAGE) on periodontal tissues. The AGE-RAGE axis triggers profound oxidative stress and sustains a hyperinflammatory state [10]. Furthermore, diabetes compromises local microcirculation via impaired angiogenesis and alters bone turnover by uncoupling osteoblast and osteoclast activities, leading to accelerated alveolar bone loss [11]. Conventional therapies often fail to address these specific metabolic drivers. Thus, ideal nanomaterials for DP must be explicitly designed to target these drivers—such as utilizing nanozymes to scavenge hyperglycemia-induced ROS, pro-angiogenic nanoparticles to restore microcirculation, and osteoinductive scaffolds to rebalance bone remodeling under diabetic conditions [12].

### 1.3. The Promise of Nanomaterials

In recent years, the rapid advancement of nanotechnology has introduced a new paradigm for addressing the limitations of conventional periodontal therapies [13]. Nanomaterials, typically defined as materials with at least one dimension in the nanoscale (1 - 100 nm), possess unique physicochemical properties that are not present in their bulk counterparts. These properties, including a high surface-area-to-volume ratio, quantum effects, and tunable surface chemistry, make them exceptionally promising for biomedical applications, particularly in the complex milieu of the oral cavity [14]. Therapeutic nanoparticles (NPs) are being engineered to tackle the multifaceted pathology of periodontitis through several key advantages.

Firstly, many nanoparticles, especially inorganic ones like silver (AgNPs), zinc oxide (ZnO), and iron oxide ($Fe_xO_y$ NPs), exhibit potent, broad-spectrum antimicrobial activity [15]-[17]. Their therapeutic mechanisms often involve physical disruption of bacterial membranes and generation of extracellular reactive oxygen species (ROS), which are less likely to induce the resistance commonly seen with conventional antibiotics. Secondly, nanomaterials can be designed to actively modulate the host immune response. For instance, cerium oxide ($CeO_2$) and polydopamine (PDA) nanoparticles can act as powerful antioxidants to scavenge excessive intracellular ROS, thereby mitigating oxidative stress-driven inflammation amplified by the AGE-RAGE axis in diabetic environments [18]. Specifically-designed nanoparticles can influence macrophage polarization, shifting them from a pro-inflammatory M1 phenotype to a pro-reparative M2 phenotype, which is crucial for resolving inflammation and initiating tissue repair [19]. Thirdly, nanoparticles can serve as exceptional platforms for targeted drug delivery [20]. By functionalizing their surfaces or encapsulating therapeutic agents, they can deliver drugs specifically to the periodontal pocket, enhancing local bioavailability while

minimizing systemic exposure and side effects [21]. Finally, a significant advantage of nanomaterials is their potential to promote tissue regeneration. They can act as scaffolds that provide a structural template for cell attachment and growth, or as bioactive agents that stimulate osteogenic differentiation of periodontal ligament stem cells (PDLSCs) and facilitate alveolar bone regeneration [22]. Crucially for DP, these smart scaffolds can be tailored to release pro-angiogenic factors to reverse diabetes-induced microvascular impairment and rebalance the dysregulated osteoblast/osteoclast coupling to rescue altered bone turnover. For example, gold nanoparticles (AuNPs) and magnesium oxide (MgO) nanoparticles have demonstrated direct osteoinductive capabilities [23] [24]. The integration of these multifunctional properties into a single platform offers a holistic approach to treating periodontitis, addressing its microbial, inflammatory, and tissue-destructive components simultaneously.

### 1.4. Scope of This Review

Given the burgeoning research in this field, this review aims to provide a comprehensive overview of the application of nanomaterials in the treatment of periodontitis, with a particular focus on the unique challenges presented by diabetes. Instead of classifying nanomaterials by their chemical composition, this review is structured around their primary therapeutic functions and applications to better highlight their potential roles in a comprehensive clinical strategy. The subsequent sections will systematically explore the use of nanomaterials for: 1) Antibacterial and anti-biofilm strategies, detailing how nanoparticles are employed to eradicate pathogenic biofilms more effectively than conventional methods; 2) Immunomodulation and anti-inflammatory control, focusing on nanomaterials designed to rebalance the dysregulated host response and resolve chronic inflammation fueled by diabetic oxidative stress; 3) Targeted and controlled-release delivery systems, discussing the engineering of smart nanocarriers for precise drug delivery to the periodontal niche; and 4) Tissue regeneration and functional restoration, examining the role of nanomaterials as scaffolds and bioactive cues to promote the regeneration of lost bone and soft tissues by overcoming diabetes-associated healing impairments. Finally, we will address the critical aspects of biocompatibility, safety, and translational pathways, discussing the current challenges and future perspectives for translating these promising nanotechnologies from the laboratory bench to clinical practice. By organizing the discussion around these functional pillars, we aim to provide a clear and application-oriented perspective on how nanotechnology is poised to revolutionize the management of diabetic periodontitis.

## 2. Classification of Periodontal Nanomaterials

The therapeutic potential of nanomaterials in periodontitis is not merely a consequence of their nanoscale dimensions but is deeply rooted in a sophisticated and highly tunable design space. This space encompasses the fundamental choice of

material, the precise engineering of its physical and chemical properties, and the formulation of its delivery format to navigate the complex periodontal pocket microenvironment. Effectively harnessing these elements allows for the creation of tailored interventions that can address the multifaceted challenges of diabetic periodontitis, moving beyond the limitations of conventional therapies. This section will explore the taxonomy of nanomaterials, the key design levers that govern their function, and the diverse delivery formats that translate these engineered particles into clinically relevant applications.

### 2.1. Taxonomy: Inorganic, Organic, and Nanocomposites

The vast sorts of nanomaterials employed in periodontal research can be broadly classified into three major families: inorganic, organic, and nanocomposites, each offering a unique set of properties suited to different therapeutic strategies (**Figure 1**) [25].

Inorganic nanomaterials, including metals, metal oxides, and structured compounds like mesoporous silica nanoparticles (MSNs), form a cornerstone of this field. They exhibit exceptional and inherent physicochemical properties that make them powerful agents for both direct therapy and drug delivery [26]. Metallic nanoparticles such as those based on silver (AgNPs) and gold (AuNPs) are renowned for their potent, broad-spectrum antimicrobial activity, which arises from mechanisms like ion release and reactive oxygen species (ROS) generation, offering an alternative to traditional antibiotics [15] [23]. Metal oxides, such as zinc oxide (ZnO) and cerium oxide ($CeO_2$), can also function as enzyme mimics, or "nanozymes," that modulate the oxidative and inflammatory environment of the periodontal pocket [16] [18]. A distinct advantage of many inorganic materials is their high surface area-to-volume ratio, which provides a high density of active sites for catalytic reactions and cellular interactions [27]. MSNs, with their tunable pore sizes and high porosity, are exemplary drug delivery platforms, capable of hosting and providing sustained release of antibiotics, anti-inflammatory agents, or growth factors within the periodontal pocket [28] [29].

Organic nanomaterials, which include natural and synthetic polymers as well as nucleic acid constructs, are primarily lauded for their excellent biocompatibility and their capacity to interact favorably with biological systems [30]. Polymers like chitosan, poly (lactic-co-glycolic acid) (PLGA), and hyaluronic acid (HA) are frequently used to create nanoparticles, hydrogels, and scaffolds. Their biodegradability can be tuned, and their surfaces are readily modified to enhance cell adhesion, guide cell migration, and promote tissue regeneration [31] [32]. Chitosan, for instance, possesses intrinsic antibacterial properties and mucoadhesive characteristics, making it an excellent candidate for local drug delivery systems [33]. A more recent and sophisticated class of organic constructs involves nucleic acid nanotechnology, such as tetrahedral framework nucleic acids (tFNAs). These three-dimensional DNA nanostructures exhibit remarkable structural stability, biocompatibility, and the ability to traverse cell membranes. They can act as plat-

forms for delivering therapeutic peptides or gene-silencing agents, and have even been shown to directly stimulate osteogenic differentiation pathways, such as the Wnt/$\beta$-catenin and Notch pathways, offering a novel approach to tissue regeneration [34].

Bridging these two categories are nanocomposites, which synergistically combine the strengths of different materials to achieve functionalities that a single component cannot. By embedding inorganic nanoparticles within an organic polymer matrix, for example, researchers can create scaffolds or membranes that possess both the mechanical resilience and biocompatibility of the polymer and the potent antibacterial or osteogenic activity of the inorganic phase. A common example is the incorporation of nano-hydroxyapatite (nHA) into a collagen or PLGA scaffold, creating a biomimetic composite that provides structural support while actively promoting new bone formation [31]. Similarly, loading MSNs into a chitosan hydrogel results in a system that offers injectability for filling irregular defects, sustained drug release from the silica pores, and the inherent beneficial properties of the hydrogel matrix [28]. These composite systems represent a powerful strategy for developing multifunctional platforms that can simultaneously combat infection, control inflammation, and orchestrate tissue repair.

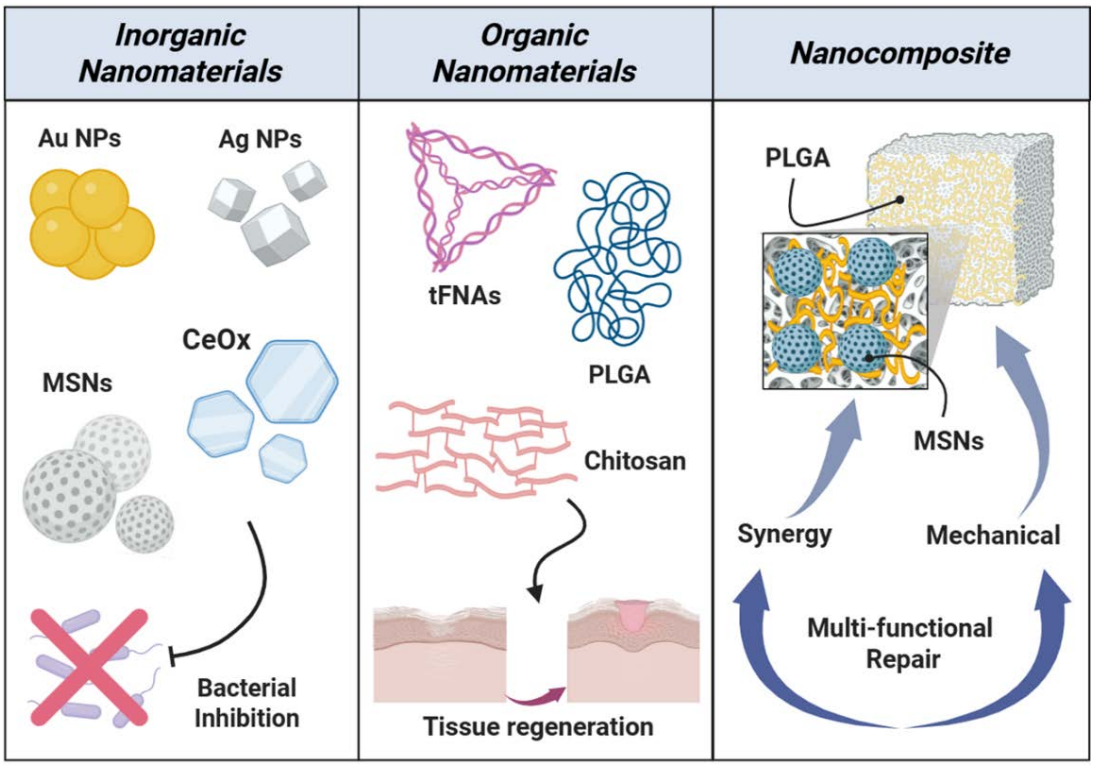


**Figure 1.** Overview of material-based nanotherapeutic categories. The diagram illustrates the functional dichotomy between Inorganic Nanomaterials (focused on bacterial inhibition; e.g., Ag NPs, MSNs) and Organic Nanomaterials (focused on tissue regeneration; e.g., PLGA, Chitosan). It further highlights the development of Nanocomposites that integrate organic matrices with inorganic fillers to achieve enhanced mechanical properties and multi-functional repair via synergistic mechanisms. This schematic diagram was created using BioRender (https://www.biorender.com/).

### 2.2. Rational Design and Environmental Responsiveness

The therapeutic efficacy of a nanomaterial is contingent upon the precise modulation of its key design parameters, principally its physical morphology, surface chemistry, and environmental responsiveness [35]. Fundamentally, size and shape are primary determinants of biological activity. These attributes dictate the nanoparticle's surface-to-volume ratio and the number of available active sites. Smaller particles, for instance, often exhibit enhanced antimicrobial activity [36], while specific morphologies like nanorods may present superior catalytic or osteogenic potential [37] [38]. Surface engineering is central to functional customization. Modifying the surface with polymers such as chitosan can improve adhesion and retention within the gingival sulcus [39], whereas functionalized coatings can facilitate penetration through biofilm barriers. A more sophisticated strategy imparts "on-demand" capabilities, enabling nanomaterials to release their payload only when triggered by pathological cues like the acidic pH or high matrix metalloproteinase (MMP) levels found in periodontal pockets [40]. This spatiotemporally precise approach minimizes off-target effects and represents a significant advancement toward precision medicine for periodontitis.

### 2.3. Nanomaterial Delivery Systems and Theranostic Platforms

The clinical translation of engineered nanomaterials is critically dependent on their formulation into effective delivery systems, which are essential for ensuring stability and sustained release within the periodontal pocket. Injectable hydrogels, often composed of polymers like chitosan or hyaluronic acid, represent a highly adaptable format. These systems can be loaded with therapeutic nanoparticles and administered as a liquid, undergoing in situ gelation to conform precisely to irregular defect topographies, thereby serving as both a drug depot and a temporary regenerative scaffold [41] [42]. Alternatively, for guided tissue or bone regeneration (GTR/GBR), nanomaterials are integrated into solid-state formats such as membranes, films, or electrospun fibers [43]. These structures act as bioactive barriers, preventing epithelial downgrowth while delivering osteoinductive agents like nano-hydroxyapatite (nHA) or magnesium oxide (MgO) to actively promote bone formation [44]. At the forefront of innovation are multimodal theranostic platforms, which merge therapy with diagnostics. For instance, superparamagnetic iron oxide nanoparticles (SPIONs) can enable magnetic resonance imaging (MRI) for lesion visualization while also functioning as photothermal agents for bacterial eradication [45]. Such integrated systems, which may include quantum dots for real-time tracking, promise to personalize periodontal treatment by enabling non-invasive monitoring of drug delivery and therapeutic response.

## 3. Antibacterial and Antibiofilm Applications

Controlling the pathogenic microbial communities within the periodontal pocket is a cornerstone of periodontitis therapy. Nanomaterials offer a paradigm shift from conventional antibiotics, providing multi-pronged attacks against bacteria

and their resilient biofilm structures. This section details the direct antibacterial actions of various nanomaterials, explores advanced antibiofilm strategies often augmented by external stimuli, and discusses the critical safety considerations inherent to their design.

### 3.1. Direct Antibacterial Nanomaterials

Certain nanomaterials possess intrinsic bactericidal or bacteriostatic properties, offering a direct therapeutic approach without relying on traditional antibiotics [46]. Among these, silver nanoparticles (AgNPs) are particularly potent, primarily through the sustained release of $Ag^+$ ions, which disrupt bacterial membranes and vital enzymatic functions [47]. Their effectiveness is profoundly influenced by key physical parameters; smaller sizes and positive surface charges enhance interaction with and penetration of negatively charged bacterial walls, boosting antimicrobial activity. Moreover, particle morphology is crucial, as non-spherical shapes with more reactive facets can exhibit superior bactericidal effects [48]. While generally less potent in direct killing, gold nanoparticles (AuNPs) disrupt bacterial metabolic pathways and are highly versatile [23]. Their exceptional photothermal conversion efficiency makes them ideal for near-infrared (NIR) light-mediated ablation of bacteria, and they serve as stable platforms for conjugating other therapeutic agents, thereby synergistically enhancing treatment efficacy [49].

### 3.2. Antibiofilm Strategies and PDT/PTT-Assisted Therapies

Eradicating the mature, deeply-seated biofilm in the subgingival pocket presents a formidable challenge that mechanical debridement alone often fails to meet. Nanotechnology-enabled strategies, particularly those assisted by external energy sources, offer innovative solutions to dismantle these complex structures. Photodynamic therapy (PDT) and photothermal therapy (PTT) are at the forefront of these advancements. In PDT, a photosensitizer-loaded nanoparticle is delivered to the biofilm and activated by light of a specific wavelength, producing cytotoxic ROS that kill embedded bacteria [50]. PTT, as mentioned with AuNPs, uses light-absorbing nanoparticles to generate lethal heat upon irradiation [51]. The advantages of these therapies are significant: they are minimally invasive, highly localized, and their physical mechanisms of action are less likely to induce microbial resistance compared to chemical agents. AgNPs, for instance, can enhance PDT by leveraging their plasmonic properties to amplify the light-harvesting capability of nearby photosensitizers, leading to greater ROS production and improved therapeutic outcomes [52].

To rigorously evaluate the antibiofilm efficacy of these nanotherapeutics, several concise criteria must be met. Effective nanomaterials should demonstrate deep biofilm penetration, robust disruption of the extracellular polymeric substance (EPS) matrix, and a significant reduction in viable bacterial counts within mature, multi-species biofilms [53]. Furthermore, traditional static in vitro models often fail to capture the dynamic fluid flow and complex host-microbe interactions of

the oral cavity. Therefore, moving forward, efficacy must be validated in advanced model systems that best approximate the periodontal pocket environment, such as dynamic flow-cell biofilm models, microfluidic platforms, or in vivo diabetic animal models.

## 4. Immune and Inflammation Modulation

Beyond their direct antimicrobial and antioxidant activities, nanomaterials offer sophisticated strategies for modulating the host immune response, which is a critical determinant of tissue destruction and healing in periodontitis. The dysregulated inflammatory cascade, characterized by a persistent pro-inflammatory state, presents a key therapeutic target. Advanced nano-therapeutics are increasingly designed not just to eliminate pathogens but to actively reprogram the inflammatory microenvironment, fostering a shift from destructive inflammation toward a state conducive to resolution and repair.

### 4.1. Nanomodulation of Macrophage Phenotypes

Modulating macrophage polarization is a key strategy in nano-immunotherapy for periodontitis, where a pro-inflammatory M1 phenotype drives tissue destruction through cytokines like TNF-$\alpha$ and IL-1$\beta$. Nanosystems aim to shift this balance toward an anti-inflammatory M2 phenotype, which promotes resolution and repair via mediators such as IL-10 [54] [55]. This transition can be achieved through the intrinsic properties of nanomaterials or delivered biological cargoes. For instance, specific nanoparticles have been shown to facilitate M2 polarization and suppress M1 markers, reducing inflammatory responses and osteoclast activity [56]. Similarly, nano-based delivery systems can transport immunomodulatory agents, such as stem cell-derived exosomes, to guide macrophage differentiation toward a regenerative M2 state [57]. By engineering nanomaterials that precisely interact with immune signaling pathways, it is possible to control the local cytokine environment, creating conditions conducive to periodontal tissue healing [58].

### 4.2. Multifunctional Nanozymes

Nanozymes, as nanomaterials possessing intrinsic enzyme-like activities, represent a particularly versatile class of immunomodulators, offering a broad spectrum of antibacterial, anti-inflammatory, and pro-regenerative effects. These artificial enzymes mimic natural counterparts such as superoxide dismutase (SOD), catalase (CAT), and peroxidase (POD), enabling the sustained and efficient neutralization of excessive reactive oxygen species (ROS) that exacerbate inflammation and tissue damage. For instance, metal-phenolic networks, specifically copper tannic acid (CuTA) nanosheets, integrated into a hydrogel platform, have demonstrated microenvironment-responsive release triggered by elevated matrix metalloproteinase (MMP) levels in inflamed periodontal tissues [56]. The liberated CuTA nanozyme not only exhibits direct antibacterial and antiplaque properties against various pathogens, including P. gingivalis and S. aureus, but also

engages in cascaded SOD- and CAT-like activities to effectively scavenge multiple ROS types. Crucially, this system modulates macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype via the Nrf2/NF-κB pathway, thereby diminishing pro-inflammatory cytokines and fostering osteogenesis. Similarly, copper nanodots can be engineered for triple enzymatic activities, capable of neutralizing free radicals, eliminating bacteria, and penetrating deeply into gingival tissues when formulated in an ionic liquid gel [59]. These examples underscore nanozymes' capacity to serve as integrated therapeutic systems, addressing multiple facets of periodontitis pathophysiology in a coordinated and sophisticated manner.

### 4.3. Modulation of Neutrophil and T-Cell Responses

While macrophage polarization is a primary focus, the host-response in DP involves a broader spectrum of immune cells that nanomaterials can target. In the diabetic microenvironment, neutrophil dysfunction is prominent, characterized by impaired chemotaxis and exaggerated release of destructive reactive oxygen species and matrix metalloproteinases [60]. Nanoparticles engineered with antioxidant properties can mitigate this neutrophil-mediated collateral tissue damage. Additionally, DP is marked by an imbalance in adaptive immunity, specifically an elevated Th17 to Treg cell ratio [61]. Emerging research suggests that specifically functionalized nanomaterials, such as those co-delivering immunomodulatory cytokines or utilizing tolerogenic dendritic cell-targeting ligands, can help restore the Th17/Treg balance. By addressing these broader cellular dysfunctions, nanotherapeutics offer a more comprehensive resolution of DP-associated inflammation [62].

## 5. Nanocarrier Systems for Periodontal Therapy

The intricate and dynamic environment of the periodontal pocket presents a significant hurdle for effective therapeutic intervention. To overcome challenges such as rapid clearance by the gingival crevicular fluid and nonspecific drug distribution, advanced nanomaterials are being engineered with sophisticated targeting and on-demand release capabilities. These systems aim to enhance drug retention at the site of inflammation, increase local bioavailability, and orchestrate payload release in direct response to pathological cues, thereby maximizing therapeutic efficacy while minimizing off-target effects.

### 5.1. Localized Retention and Enzyme-Responsive Release

Achieving prolonged therapeutic agent residence within the periodontal pocket is paramount for effective local drug delivery. This is frequently accomplished through mucoadhesive biomaterials, which enhance contact and retention time within the pocket [21]. Furthermore, negatively charged nanomaterials can be retained at inflamed sites via electrostatic adsorption, ensuring concentrated therapeutic delivery where needed [63]. Critically, "smart" delivery systems leverage

the unique enzymatic environment of periodontitis; for instance, hydrogels responsive to elevated matrix metalloproteinase (MMP) levels can degrade to release encapsulated therapeutic agents precisely at the site of active tissue destruction [64]. This strategy ensures controlled, on-demand drug liberation, thereby minimizing premature leakage and off-target effects.

### 5.2. Receptor-Mediated Precision Targeting

To further refine therapeutic delivery, nanomaterials can be functionalized with specific motifs that target receptors overexpressed on inflamed tissues or immune cells. This approach directs drug carriers to specific cell populations, ensuring potent immunomodulatory or antimicrobial agents are delivered with enhanced precision. The integration of such targeting ligands with stimuli-responsive platforms, where targeted nanoparticles are released from a scaffold in response to local cues, creates a hierarchical delivery system. This cascade amplifies the effective dose at the action site while substantially reducing systemic exposure and potential side effects.

## 6. Biocompatibility and Clinical Translation

The journey of nanotherapeutic agents from laboratory concepts to clinical realities in periodontology is paved with critical considerations regarding their safety, manufacturing consistency, and translational viability. While the preclinical potential is immense, advancing these innovative therapies requires a rigorous evaluation of their long-term biological impact, the feasibility of scalable production, and a clear pathway through regulatory and clinical validation. Ethical and practical economic factors further shape their ultimate integration into standard dental care (Figure 2).

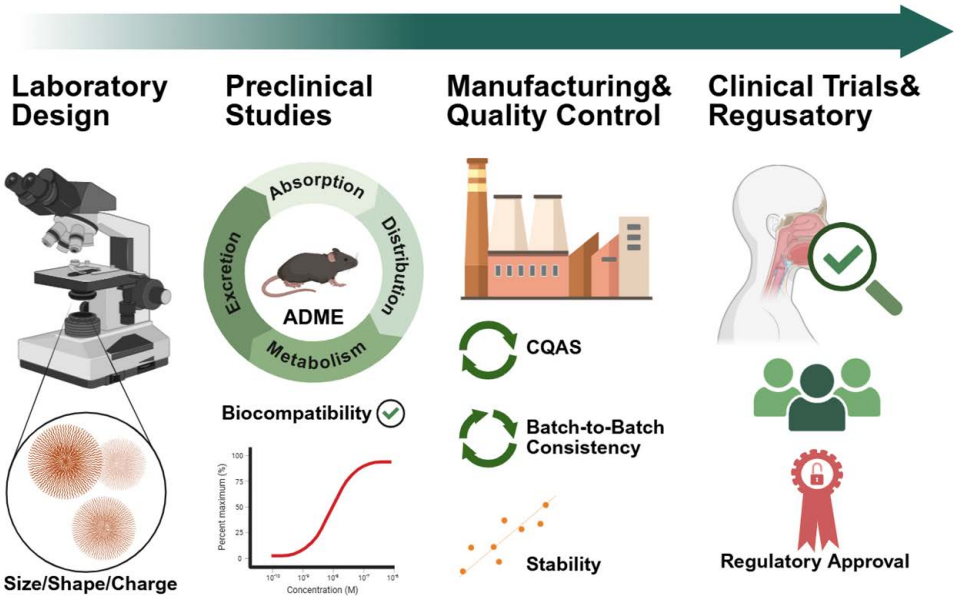


Figure 2. Key validation checkpoints in the translational pathway of novel therapeutic agents.

Successful translation requires navigating four distinct stages: 1) Rational design based on physicochemical parameters (size/shape/charge); 2) Preclinical validation of pharmacokinetics (ADME) and biocompatibility; 3) Standardization of manufacturing processes to maintain stability and batch consistency via CQAs; and 4) Clinical evaluation culminating in regulatory approval. Each step represents a critical filter for safety and efficacy.

### 6.1. Biocompatibility and Long-Term Safety Assessment

The successful clinical translation of nanotherapeutics fundamentally relies on their biocompatibility and long-term safety, which are intricately linked to their physicochemical properties like size, shape, and surface charge [65]. While smaller metal nanoparticles can enhance therapeutic effects, they may also increase toxicity risks, necessitating strategies such as PEGylation to reduce immunogenicity and prolong circulation [66]. A critical safety concern for metal-based nanoparticles involves the dissolution and release of metal ions, which contribute to both therapeutic action and potential host toxicity [67]. Thus, comprehensive toxicokinetic studies (ADME) are indispensable, evaluating the biodistribution, metabolism, and clearance of these materials, alongside the biocompatibility of their degradation products to ensure their kinetics align with tissue regeneration timelines without adverse reactions.

### 6.2. Manufacturing Consistency and Quality Control

Transitioning nanotherapeutics from laboratory research to large-scale, GMP-compliant production presents a significant hurdle, demanding rigorous batch-to-batch consistency for a reliable clinical product. Critical Quality Attributes (CQAs), encompassing particle size distribution, surface chemistry, zeta potential, drug loading efficiency, and release profiles, must be meticulously defined and controlled, as even minor deviations can profoundly alter a nanoparticle's bioavailability, efficacy, and safety [68]. Furthermore, maintaining the stability of nanoformulations during storage and transport is crucial, as aggregation or degradation can lead to loss of function and new safety risks. The development of robust analytical methods for monitoring these CQAs throughout the product lifecycle is non-negotiable for regulatory approval, despite the inherent complexity and cost associated with such characterization and scale-up processes.

### 6.3. Evidence Level: Preclinical Mechanisms vs. Clinical Endpoints

A critical gap in current periodontal nanomedicine is the disparity between mechanistic in vitro claims and demonstrated in vivo or clinical efficacy, particularly for the DP cohort. Most current evidence is confined to preclinical stages [69]. In vitro studies primarily report mechanistic outcomes, such as bacterial membrane disruption, ROS scavenging efficiency, and osteogenic gene expression. While animal studies provide higher-level evidence of reduced inflammatory infiltrate and preliminary radiographic bone changes, they often lack standardized metabolic

monitoring.

To bridge the translational gap, future early-phase clinical trials must clearly define and report standardized clinical endpoints. Efficacy should be evaluated using standard periodontal parameters, including probing depth (PD) reduction, clinical attachment level (CAL) gain, and bleeding on probing (BOP). Crucially, for DP patients, these local outcomes must be correlated with systemic glycemic to fully validate the bidirectional therapeutic benefit of these multifunctional nanoplatforms.

### 6.4. Regulatory Pathways and Clinical Validation

The clinical evidence supporting nanotherapeutics in periodontitis largely remains in the preclinical phase, predominantly relying on in vitro and animal models. Direct extrapolation to the complex human oral environment often proves challenging, highlighting an urgent need for well-designed early-phase clinical trials to bridge this translational gap. A significant obstacle is the current lack of harmonized and standardized methods for nanoparticle characterization and risk assessment, which complicates regulatory evaluation [70]. To facilitate progress, establishing standardized clinical endpoints is crucial; these should prioritize safety and tolerability, while also incorporating established markers of periodontal inflammation and radiographic assessment of alveolar bone regeneration as key indicators of regenerative efficacy. Such standardization is essential for meaningful data comparison and to satisfy the robust data requirements of regulatory bodies for novel therapies.

## 7. Outlook and Conclusions

The exploration of nanotechnology in periodontal therapy reveals a promising frontier poised to transcend conventional treatments. The journey from bench to bedside, however, hinges on addressing multifaceted challenges, from fundamental biocompatibility to clinical integration. A paramount objective is multifunctional integration, envisioning intelligent nanoplatforms that concurrently execute antibacterial, immunomodulatory, regenerative, and diagnostic functions. This holistic approach, targeting the interconnected pathological processes, is steering towards personalized, monitorable pathways that move beyond one-size-fits-all solutions. The development of nanobiosensors for rapid diagnostics and trackable nanoparticles for non-invasive monitoring could enable adaptive regimens tailored to individual patient needs. For widespread adoption, these advanced strategies must seamlessly fuse with established clinical workflows, such as being delivered via injectable hydrogels or smart mouthwashes post-scaling and root planing (SRP). Crucially, the validation of these nanotherapeutics must be prioritized within the diabetic periodontitis (DP) population. The unique hyperglycemic and pro-inflammatory microenvironment in DP presents a formidable challenge, and data from standard models cannot be directly extrapolated. There is a significant data gap and an urgent need for dedicated research in relevant DP

models to address this high-risk group. Successfully navigating the complexities of DP will not only meet a critical clinical need but also robustly validate the transformative potential of nanotechnology to redefine the future of periodontal care and functional tissue restoration.

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## Statement

All authors have approved the final version of this manuscript.

## Data Availability Statement

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

## Conflicts of Interest

The authors declare no conflict of interest.

## References

[1] Sanz, M., Marco del Castillo, A., Jepsen, S., Gonzalez-Juanatey, J.R., D'Aiuto, F., Bouchard, P., *et al.* (2020) Periodontitis and Cardiovascular Diseases: Consensus Report. *Journal of Clinical Periodontology*, **47**, 268-288. https://doi.org/10.1111/jcpe.13189

[2] Sanz, M., Herrera, D., Kebschull, M., Chapple, I., Jepsen, S., Berglundh, T., *et al.* (2020) Treatment of Stage I–III Periodontitis—The EFP S3 Level Clinical Practice Guideline. *Journal of Clinical Periodontology*, **47**, 4-60. https://doi.org/10.1111/jcpe.13290

[3] Preshaw, P.M., Alba, A.L., Herrera, D., Jepsen, S., Konstantinidis, A., Makrilakis, K., *et al.* (2012) Periodontitis and Diabetes: A Two-Way Relationship. *Diabetologia*, **55**, 21-31. https://doi.org/10.1007/s00125-011-2342-y

[4] Buranasin, P., Kominato, H., Mizutani, K., Mikami, R., Saito, N., Takeda, K., *et al.* (2023) Influence of Reactive Oxygen Species on Wound Healing and Tissue Regeneration in Periodontal and Peri-Implant Tissues in Diabetic Patients. *Antioxidants*, **12**, Article 1787. https://doi.org/10.3390/antiox12091787

[5] Cobb, C.M. and Sottosanti, J.S. (2021) A Re-Evaluation of Scaling and Root Planning. *Journal of Periodontology*, **92**, 1370-1378. https://doi.org/10.1002/jper.20-0839

[6] Simpson, T.C., Clarkson, J.E., Worthington, H.V., MacDonald, L., Weldon, J.C., Needleman, I., *et al.* (2022) Treatment of Periodontitis for Glycaemic Control in People with Diabetes Mellitus. *Cochrane Database of Systematic Reviews*, **2022**, CD004714. https://doi.org/10.1002/14651858.cd004714.pub4

[7] Asare, E.O., Mun, E.A., Marsili, E. and Paunov, V.N. (2022) Nanotechnologies for Control of Pathogenic Microbial Biofilms. *Journal of Materials Chemistry B*, **10**, 5129-5153. https://doi.org/10.1039/d2tb00233g

[8] Baran, A., Kwiatkowska, A. and Potocki, L. (2023) Antibiotics and Bacterial Re-

sistance—A Short Story of an Endless Arms Race. *International Journal of Molecular Sciences*, **24**, Article 5777. https://doi.org/10.3390/ijms24065777

[9] Vigersky, R.A. and McMahon, C. (2019) The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. *Diabetes Technology & Therapeutics*, **21**, 81-85. https://doi.org/10.1089/dia.2018.0310

[10] Sohn, Y., Jeong, H.J. and Park, J. (2025) The Link between Hyperinsulinemia and Periodontitis in Diabetics. *Journal of Dental Research*, **105**, 294-301. https://doi.org/10.1177/00220345251366952

[11] Ding, F., Zhang, W., Liu, T., Rong, X., Cui, Y., Meng, L., *et al.* (2025) MK-4 Ameliorates Diabetic Osteoporosis in Angiogenesis-Dependent Bone Formation by Promoting Mitophagy in Endothelial Cells. *Drug Design, Development and Therapy*, **19**, 2173-2188. https://doi.org/10.2147/dddt.s503930

[12] Zou, X., Fan, X., Xu, P., Yu, X., Luo, C., Kang, Z., *et al.* (2026) Selenium-Albumin Corona Rinse Ameliorates Diabetic Periodontitis by Inhibiting Inflammation, Anti-Bacterial and Improving Osteogenesis via Activating TrxR1/ROS/$\beta$-Catenin Anti-Oxidation Cascade. *Biomaterials*, **328**, Article 123835. https://doi.org/10.1016/j.biomaterials.2025.123835

[13] Farokhzad, O.C. and Langer, R. (2009) Impact of Nanotechnology on Drug Delivery. *ACS Nano*, **3**, 16-20. https://doi.org/10.1021/nn900002m

[14] Nsairat, H., Lafi, Z., Al-Sulaibi, M., Gharaibeh, L. and Alshaer, W. (2023) Impact of Nanotechnology on the Oral Delivery of Phyto-Bioactive Compounds. *Food Chemistry*, **424**, Article 136438. https://doi.org/10.1016/j.foodchem.2023.136438

[15] Yu, Y., Zhou, Z., Huang, G., Cheng, H., Han, L., Zhao, S., *et al.* (2022) Purifying Water with Silver Nanoparticles (AgNPs)-Incorporated Membranes: Recent Advancements and Critical Challenges. *Water Research*, **222**, Article 118901. https://doi.org/10.1016/j.watres.2022.118901

[16] Brasiunas, B., Popov, A., Lisyte, V., Kausaite-Minkstimiene, A. and Ramanaviciene, A. (2024) ZnO Nanostructures: A Promising Frontier in Immunosensor Development. *Biosensors and Bioelectronics*, **246**, Article 115848. https://doi.org/10.1016/j.bios.2023.115848

[17] Zandieh, M. and Liu, J. (2021) Nanozyme Catalytic Turnover and Self-Limited Reactions. *ACS Nano*, **15**, 15645-15655. https://doi.org/10.1021/acsnano.1c07520

[18] Zhang, M., Zhu, R., Deng, B., Huang, Y. and Ren, H. (2025) Z-Scheme $CeO_2$@PDA/BiOBr Heterojunction with PDA Electronic Transfer Medium for Photocatalytic Elimination of Methylene Blue and Tetracycline. *Journal of Molecular Structure*, **1334**, Article 141925. https://doi.org/10.1016/j.molstruc.2025.141925

[19] Lu, Q., Kou, D., Lou, S., Ashrafizadeh, M., Aref, A.R., Canadas, I., *et al.* (2024) Nanoparticles in Tumor Microenvironment Remodeling and Cancer Immunotherapy. *Journal of Hematology & Oncology*, **17**, Article No. 16. https://doi.org/10.1186/s13045-024-01535-8

[20] Mitchell, M.J., Billingsley, M.M., Haley, R.M., Wechsler, M.E., Peppas, N.A. and Langer, R. (2021) Engineering Precision Nanoparticles for Drug Delivery. *Nature Reviews Drug Discovery*, **20**, 101-124. https://doi.org/10.1038/s41573-020-0090-8

[21] Joshi, D., Garg, T., Goyal, A.K. and Rath, G. (2016) Advanced Drug Delivery Approaches against Periodontitis. *Drug Delivery*, **23**, 363-377. https://doi.org/10.3109/10717544.2014.935531

[22] Lauritano, D., Limongelli, L., Moreo, G., Favia, G. and Carinci, F. (2020) Nanomaterials for Periodontal Tissue Engineering: Chitosan-Based Scaffolds. A Systematic Review. *Nanomaterials*, **10**, Article 605.

https://doi.org/10.3390/nano10040605

[23] Li, W., Cao, Z., Liu, R., Liu, L., Li, H., Li, X., *et al.* (2019) AuNPs as an Important Inorganic Nanoparticle Applied in Drug Carrier Systems. *Artificial Cells, Nanomedicine, and Biotechnology*, **47**, 4222-4233. https://doi.org/10.1080/21691401.2019.1687501

[24] Singh, J.P., Singh, V., Sharma, A., Pandey, G., Chae, K.H. and Lee, S. (2020) Approaches to Synthesize MgO Nanostructures for Diverse Applications. *Heliyon*, **6**, e04882. https://doi.org/10.1016/j.heliyon.2020.e04882

[25] Zong, C., Bronckaers, A., Willems, G., He, H. and Cadenas de Llano-Pérula, M. (2023) Nanomaterials for Periodontal Tissue Regeneration: Progress, Challenges and Future Perspectives. *Journal of Functional Biomaterials*, **14**, 290. https://doi.org/10.3390/jfb14060290

[26] Fang, L., Zhou, H., Cheng, L., Wang, Y., Liu, F. and Wang, S. (2023) The Application of Mesoporous Silica Nanoparticles as a Drug Delivery Vehicle in Oral Disease Treatment. *Frontiers in Cellular and Infection Microbiology*, **13**, Article 1124411. https://doi.org/10.3389/fcimb.2023.1124411

[27] Boles, M.A., Ling, D., Hyeon, T. and Talapin, D.V. (2016) The Surface Science of Nanocrystals. *Nature Materials*, **15**, 141-153. https://doi.org/10.1038/nmat4526

[28] Xu, B., Li, S., Shi, R. and Liu, H. (2023) Multifunctional Mesoporous Silica Nanoparticles for Biomedical Applications. *Signal Transduction and Targeted Therapy*, **8**, Article No. 435. https://doi.org/10.1038/s41392-023-01654-7

[29] Jafari, S., Derakhshankhah, H., Alaei, L., Fattahi, A., Varnamkhasti, B.S. and Saboury, A.A. (2019) Mesoporous Silica Nanoparticles for Therapeutic/Diagnostic Applications. *Biomedicine & Pharmacotherapy*, **109**, 1100-1111. https://doi.org/10.1016/j.biopha.2018.10.167

[30] Zhang, Y., Fang, F., Li, L. and Zhang, J. (2020) Self-Assembled Organic Nanomaterials for Drug Delivery, Bioimaging, and Cancer Therapy. *ACS Biomaterials Science & Engineering*, **6**, 4816-4833. https://doi.org/10.1021/acsbiomaterials.0c00883

[31] Grigoraş, C.G., Simion, A.I. and Drob, C. (2024) Hydrogels Based on Chitosan and Nanoparticles and Their Suitability for Dyes Adsorption from Aqueous Media: Assessment of the Last-Decade Progresses. *Gels*, **10**, Article 211. https://doi.org/10.3390/gels10030211

[32] Dinakar, Y.H., Rajana, N., Kumari, N.U., Jain, V. and Mehra, N.K. (2023) Recent Advances of Multifunctional PLGA Nanocarriers in the Management of Triple-Negative Breast Cancer. *AAPS PharmSciTech*, **24**, Article No. 258. https://doi.org/10.1208/s12249-023-02712-7

[33] Ardean, C., Davidescu, C.M., Nemeş, N.S., Negrea, A., Ciopec, M., Duteanu, N., *et al.* (2021) Factors Influencing the Antibacterial Activity of Chitosan and Chitosan Modified by Functionalization. *International Journal of Molecular Sciences*, **22**, Article 7449. https://doi.org/10.3390/ijms22147449

[34] Zhou, J., Tang, C., Song, X., Wang, Y., Lin, B., Lin, M., *et al.* (2025) Tetrahedral Framework Nucleic Acids Ameliorate Cholestatic Liver Disease by Activating Wnt/$\beta$-Catenin Signaling and Promoting ERK1/2 Phosphorylation. *Regenerative Biomaterials*, **12**, rbaf017. https://doi.org/10.1093/rb/rbaf017

[35] Du, B. and Tung, C.H. (2020) Enzyme-assisted Photodynamic Therapy Based on Nanomaterials. *ACS Biomaterials Science & Engineering*, **6**, 2506-2517. https://doi.org/10.1021/acsbiomaterials.9b00968

[36] Sayed, F.A., Eissa, N.G., Shen, Y., Hunstad, D.A., Wooley, K.L. and Elsabahy, M.

(2022) Morphologic Design of Nanostructures for Enhanced Antimicrobial Activity. *Journal of Nanobiotechnology*, **20**, Article No. 536. https://doi.org/10.1186/s12951-022-01733-x

[37] Laurenti, M. and Cauda, V. (2017) ZnO Nanostructures for Tissue Engineering Applications. *Nanomaterials*, **7**, Article 374. https://doi.org/10.3390/nano7110374

[38] Chawla, V., Bundel, P. and Singh, Y. (2025) ALP-Mimetic Cyclic Peptide Nanotubes: A Multifunctional Strategy for Osteogenesis and Bone Regeneration. *Biomacromolecules*, **26**, 1686-1700. https://doi.org/10.1021/acs.biomac.4c01484

[39] Yoon, S.W., Kim, M.J., Paeng, K.W., Yu, K.A., *et al.* (2020) Efficacy of Local Minocycline Agents in Treating Peri-Implantitis: An Experimental *in Vivo* Study in Beagle Dogs. *Pharmaceutics*, **12**, Article 1016. https://doi.org/10.3390/pharmaceutics12111016

[40] Wang, T., He, Z., Yuan, C., Deng, Z., Li, F., Chen, X., *et al.* (2022) MMP-Responsive Transformation Nanomaterials with IAP Antagonist to Boost Immune Checkpoint Therapy. *Journal of Controlled Release*, **343**, 765-776. https://doi.org/10.1016/j.jconrel.2022.02.018

[41] Mo, C., Zhang, W., Zhu, K., Du, Y., Huang, W., Wu, Y., *et al.* (2024) Advances in Injectable Hydrogels Based on Diverse Gelation Methods for Biomedical Imaging. *Small Methods*, **8**, e2400076. https://doi.org/10.1002/smtd.202400076

[42] Thambi, T., Li, Y. and Lee, D.S. (2017) Injectable Hydrogels for Sustained Release of Therapeutic Agents. *Journal of Controlled Release*, **267**, 57-66. https://doi.org/10.1016/j.jconrel.2017.08.006

[43] Bottino, M.C., Thomas, V., Schmidt, G., Vohra, Y.K., Chu, T.G., Kowolik, M.J., *et al.* (2012) Recent Advances in the Development of GTR/GBR Membranes for Periodontal Regeneration—A Materials Perspective. *Dental Materials*, **28**, 703-721. https://doi.org/10.1016/j.dental.2012.04.022

[44] Chai, X., Lin, J., Xu, C., Sun, D. and Liu, H.H. (2024) Engineering Triphasic Nanocomposite Coatings on Pretreated Mg Substrates for Biomedical Applications. *ACS Applied Materials & Interfaces*, **16**, 54716-54730. https://doi.org/10.1021/acsami.4c13811

[45] Avasthi, A., Caro, C., Pozo-Torres, E., Leal, M.P. and García-Martín, M.L. (2020) Magnetic Nanoparticles as MRI Contrast Agents. *Topics in Current Chemistry*, **378**, Article No. 40. https://doi.org/10.1007/s41061-020-00302-w

[46] Ndayishimiye, J., Kumeria, T., Popat, A., Falconer, J.R. and Blaskovich, M.A.T. (2022) Nanomaterials: The New Antimicrobial Magic Bullet. *ACS Infectious Diseases*, **8**, 693-712. https://doi.org/10.1021/acsinfecdis.1c00660

[47] Hussain, M.A., Nijabat, A., Rehman, M.M.u., Qurashi, R., Siddiqui, M.H., Alamri, S., *et al.* (2024) Management of Tomato Bacterial Canker Disease by the Green Fabricated Silver Nanoparticles. *BMC Plant Biology*, **24**, Article No. 597. https://doi.org/10.1186/s12870-024-05238-7

[48] Xiong, Q., Fang, Q., Xu, K., Liu, G., Sang, M., Xu, Y., *et al.* (2021) Near-Infrared Light-Responsive Photothermal *A*-$Fe_2O_3$@Au/PDA Core/shell Nanostructure with On-Off Controllable Anti-Bacterial Effects. *Dalton Transactions*, **50**, 14235-14243. https://doi.org/10.1039/d1dt02251b

[49] Ye, Y., Zheng, Q., Wang, Z., Wang, S., Lu, Z., Chu, Q., *et al.* (2024) Metal-Phenolic Nanoparticles Enhance Low Temperature Photothermal Therapy for Bacterial Biofilm in Superficial Infections. *Journal of Nanobiotechnology*, **22**, Article No. 713. https://doi.org/10.1186/s12951-024-02985-5

[50] Gu, Y., You, Y., Yang, Y., Liu, X., Yang, L., Li, Y., *et al.* (2024) Multifunctional

EGCG@ZIF-8 Nanoplatform with Photodynamic Therapy/Chemodynamic Therapy Antibacterial Properties Promotes Infected Wound Healing. *ACS Applied Materials & Interfaces*, **16**, 50238-50250. https://doi.org/10.1021/acsami.4c08169

[51] Kim, H., Chung, K., Lee, S., Kim, D.H. and Lee, H. (2016) Near-Infrared Light-Responsive Nanomaterials for Cancer Theranostics. *WIREs Nanomedicine and Nanobiotechnology*, **8**, 23-45. https://doi.org/10.1002/wnan.1347

[52] Zhao, J., Gao, N., Xu, J., Zhu, X., Ling, G. and Zhang, P. (2023) Novel Strategies in Melanoma Treatment Using Silver Nanoparticles. *Cancer Letters*, **561**, Article 216148. https://doi.org/10.1016/j.canlet.2023.216148

[53] Ali, A.A., Al Bostami, R.D. and Al-Othman, A. (2024) Nanogel-Based Composites for Bacterial Antibiofilm Activity: Advances, Challenges, and Prospects. *RSC Advances*, **14**, 10546-10559. https://doi.org/10.1039/d4ra00410h

[54] Gong, J., Ye, C., Ran, J., Xiong, X., Fang, X., Zhou, X., *et al.* (2023) Polydopamine-Mediated Immunomodulatory Patch for Diabetic Periodontal Tissue Regeneration Assisted by Metformin-ZIF System. *ACS Nano*, **17**, 16573-16586. https://doi.org/10.1021/acsnano.3c02407

[55] Qiao, D., Cheng, S., Song, S., Zhang, W., Chen, B., Yan, F., *et al.* (2024) Polarized M2 Macrophages Induced by Glycosylated Nano-Hydroxyapatites Activate Bone Regeneration in Periodontitis Therapy. *Journal of Clinical Periodontology*, **51**, 1054-1065. https://doi.org/10.1111/jcpe.13999

[56] Xu, Y., Luo, Y., Weng, Z., Xu, H., Zhang, W., Li, Q., *et al.* (2023) Microenvironment-responsive Metal-Phenolic Nanozyme Release Platform with Antibacterial, ROS Scavenging, and Osteogenesis for Periodontitis. *ACS Nano*, **17**, 18732-18746. https://doi.org/10.1021/acsnano.3c01940

[57] Tao, Y., Liu, T., Jing, F., Tan, X., Zhao, X., Bernaerts, K.V., *et al.* (2025) Adipose-derived Stem-Cell-Derived Exosomes Encapsulated Patch for Modulating Inflammation and Promoting Tissue Regeneration. *ACS Nano*, **19**, 21271-21289. https://doi.org/10.1021/acsnano.4c16058

[58] Xiu, Z., Zhu, Y., Li, X., Jiang, X., Feng, Y., He, L., *et al.* (2025) A Multifunctional Injectable Microsphere with Enhanced Near-Infrared Photo-Antibacterial, ROS Scavenging, and Anti-Inflammatory Properties for Periodontitis Treatment. *Theranostics*, **15**, 3750-3780. https://doi.org/10.7150/thno.107793

[59] Gao, Y., Zhang, W., Xue, R., Shu, Y. and Wang, J. (2023) An Ionic Gel Incorporating Copper Nanodots with Antibacterial and Antioxidant Dual Functions for Deep Tissue Penetration Treatment of Periodontitis in Rats. *Biomaterials Science*, **11**, 3547-3560. https://doi.org/10.1039/d3bm00309d

[60] Clayton, S.M., Shafikhani, S.H. and Soulika, A.M. (2024) Macrophage and Neutrophil Dysfunction in Diabetic Wounds. *Advances in Wound Care*, **13**, 463-484. https://doi.org/10.1089/wound.2023.0149

[61] Harrandah, A.M. (2025) The Oral-Gut-Systemic Axis: Emerging Insights into Periodontitis, Microbiota Dysbiosis, and Systemic Disease Interplay. *Diagnostics*, **15**, Article 2784. https://doi.org/10.3390/diagnostics15212784

[62] Metcalfe, S.M. (2011) LIF in the Regulation of T-Cell Fate and as a Potential Therapeutic. *Genes & Immunity*, **12**, 157-168. https://doi.org/10.1038/gene.2011.9

[63] López-Estévez, A.M., Portela, M.G., Piñeiro-Alonso, L., Castillo-González, R., Sancho-Temiño, L., Gómez-Lado, N., *et al.* (2026) Nanoassemblies for Oral Protein Delivery—The Case of Monoclonals for Inflammatory Bowel Disease. *Journal of Controlled Release*, **389**, Article 114455. https://doi.org/10.1016/j.jconrel.2025.114455

[64] Meng, H., Su, J., Shen, Q., Hu, W., Li, P., Guo, K., *et al.* (2025) A Smart MMP-9-

Responsive Hydrogel Releasing M2 Macrophage-Derived Exosomes for Diabetic Wound Healing. *Advanced Healthcare Materials*, **14**, e2404966. https://doi.org/10.1002/adhm.202404966

[65] Haidar, L.L., Bilek, M. and Akhavan, B. (2024) Surface Bio-Engineered Polymeric Nanoparticles. *Small*, **20**, Article 2310876. https://doi.org/10.1002/smll.202310876

[66] Patsula, V., Tulinska, J., Trachtová, Š., Kuricova, M., Liskova, A., Španová, A., *et al.* (2019) Toxicity Evaluation of Monodisperse Pegylated Magnetic Nanoparticles for Nanomedicine. *Nanotoxicology*, **13**, 510-526. https://doi.org/10.1080/17435390.2018.1555624

[67] Jiang, H., Li, L., Li, Z. and Chu, X. (2024) Metal-Based Nanoparticles in Antibacterial Application in Biomedical Field: Current Development and Potential Mechanisms. *Biomedical Microdevices*, **26**, Article No. 12. https://doi.org/10.1007/s10544-023-00686-8

[68] Osouli-Bostanabad, K., Puliga, S., Serrano, D.R., Bucchi, A., Halbert, G. and Lalatsa, A. (2022) Microfluidic Manufacture of Lipid-Based Nanomedicines. *Pharmaceutics*, **14**, Article 1940. https://doi.org/10.3390/pharmaceutics14091940

[69] Chen, H., Zhang, Y., Yu, T., Song, G., Xu, T., Xin, T., *et al.* (2022) Nano-Based Drug Delivery Systems for Periodontal Tissue Regeneration. *Pharmaceutics*, **14**, Article 2250. https://doi.org/10.3390/pharmaceutics14102250

[70] Lin, P.C., Lin, S., Wang, P.C. and Sridhar, R. (2014) Techniques for Physicochemical Characterization of Nanomaterials. *Biotechnology Advances*, **32**, 711-726. https://doi.org/10.1016/j.biotechadv.2013.11.006