

Research Progress of Inorganic Nanomaterials in the Treatment of Periodontitis

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Abstract: Periodontitis is a chronic inflammatory disease characterized by the progressive destruction of periodontal tissues. Conventional oral pharmacotherapy has limitations, including gastrointestinal adverse reactions, allergic responses, low local drug concentration in periodontal pockets, and the risk of inducing drug-resistant bacteria. In recent years, nanomaterials have provided novel strategies for periodontitis treatment owing to their unique physicochemical properties and high loading capacity. This review summarizes recent research progress on inorganic nanomaterials for periodontitis treatment. By analyzing the physicochemical properties, mechanisms of action, and in vitro and in vivo performance of various inorganic nanomaterials, this article highlights their substantial potential to enhance therapeutic efficacy and promote bone tissue regeneration. Concurrently, this review identifies current challenges, including concerns regarding biosafety and complex fabrication processes, and discusses future research directions, thereby providing a theoretical foundation and novel insights for precision periodontitis therapy.

Keywords: Periodontitis, Nanostructures, Antimicrobial, Clinical translation

1. Introduction

Periodontitis is a chronic infectious disease characterized by the progressive destruction of the supporting tissues surrounding the teeth. Over the past three decades, both the incidence and prevalence of periodontal diseases in China have shown a continuous upward trend ^[1]. The clinical manifestations of periodontitis include gingival inflammation and bleeding, formation of periodontal pockets, alveolar bone resorption, as well as tooth loosening and migration. Without therapeutic intervention, it ultimately leads to tooth loss, severely impacting masticatory function and potentially contributing to other systemic diseases such as diabetes mellitus, coronary artery disease, and rheumatoid arthritis ^[2]. Treatment approaches for periodontitis are generally categorized into surgical and pharmacological therapies. Surgical instruments often face difficulty accessing the root, furcation, and basal areas of periodontal pockets, limiting the achievement of optimal therapeutic outcomes. Traditional oral pharmacotherapy, used as an adjunctive treatment, presents several limitations in clinical application, including gastrointestinal adverse reactions, allergic responses, and low local drug concentration within periodontal pockets that may lead to the development of drug-resistant bacteria ^[3,4].

Nanomaterials, defined as materials possessing structural units with at least one dimension in the range of 1~100 nm, are noted for their designability. By virtue of their capacity to improve drug bioavailability, modulate drug absorption kinetics, enable sustained and/or controlled release, prevent drug aggregation, and facilitate targeted delivery ^[5], these materials present new and more effective therapeutic modalities for periodontitis. Specifically, inorganic nanomaterials have been extensively utilized in research concerning periodontitis treatment, attributed to their strong antibacterial properties, superior osteoinductive potential, high chemical stability, and comparatively well-established fabrication techniques. Consequently, a thorough exploration of the application of inorganic nanomaterials in periodontitis management is of considerable theoretical and practical significance, contributing to the development of more efficient and safer therapeutic regimens and the enhancement of patient outcomes. This topic has become a key research focus, and this paper reviews the advancements in this dynamic field.

2. Inorganic Nanomaterials in Periodontitis Therapy

The primary inorganic nanomaterials applied in the treatment of periodontitis include metal and metal oxide nanomaterials, ceramic nanomaterials, and carbon-based nanomaterials (Figure 1). By leveraging their unique physicochemical properties and biological functions, these three classes of materials address the complex pathological processes of periodontitis from different perspectives, tackling issues such as bacterial infection, inflammatory response, and tissue destruction.

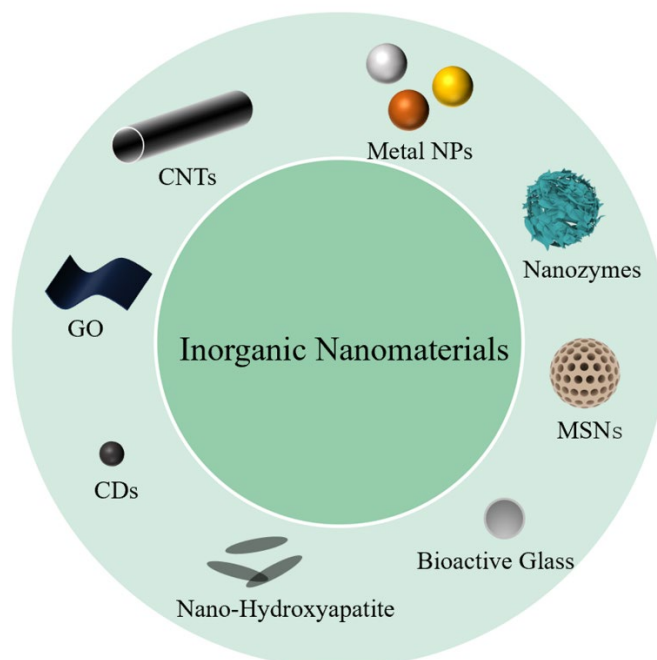


Figure 1: Common inorganic nanomaterials used for the treatment of periodontitis.

2.1 Metal and Metal Oxide Nanomaterials

Metal and metal oxide nanomaterials encompass a range of metal sources, including silver (Ag), copper (Cu), magnesium (Mg), zinc (Zn), titanium (Ti), iron (Fe), gold (Au), and cerium (Ce). Some of these materials possess intrinsic antibacterial properties. Through the release of metal ions, they can effectively penetrate the cells of oral pathogenic bacteria and disrupt bacterial physiological functions via multiple mechanisms. For instance, silver nanoparticles (AgNPs) can release silver ions that bind to bacterial DNA, interfering with replication; react with sulfur-containing groups in proteins, leading to their inactivation; and potentially induce the production of reactive oxygen species (ROS), causing oxidative damage, all of which contribute to their antibacterial effect [6]. Zinc ions (Zn^{2+}) can specifically bind to negatively charged phospholipid groups on the bacterial cell membrane, disrupting its structure. Concurrently, zinc ions can enter the cell to inhibit the activity of bacterial DNA helicase, interfere with nucleic acid replication, and suppress respiratory functions. This synergistic action of metabolic inhibition and structural disruption ultimately achieves the antibacterial effect [7].

Another category consists of nanozymes, which are materials with enzyme-mimicking catalytic activities. They achieve sustainable biological effects through catalytic cycles. Based on their catalytic functions, nanozymes used in periodontitis treatment can generally be classified into pro-oxidant nanozymes and antioxidant nanozymes. Recently, Li et al. [8] constructed a cascade nanozyme with both of these functionalities through a dual-metal (copper-cerium) doping strategy. Under near-infrared (NIR) light irradiation, this copper-cerium bimetallic nanozyme acts as a photosensitizer, generating ROS via photodynamic effects and rapidly increasing temperature through photothermal effects. In vitro experiments demonstrated an inhibition rate of up to $98.69 \pm 0.23\%$ against *Porphyromonas gingivalis*, a major periodontal pathogen. In the absence of light, the nanozyme leverages the valence state changes of cerium to exhibit peroxidase-like activity, effectively scavenging excess ROS in inflamed tissues and thereby alleviating oxidative stress-induced damage to periodontal ligament cells. In vivo experiments further confirmed that this material not only significantly reduces inflammatory infiltration in periodontal tissues but also exerts anti-inflammatory and antioxidant effects by upregulating the Nrf2/HO-1 signaling

pathway, effectively inhibiting alveolar bone resorption.

2.2 Ceramic Nanomaterials

Ceramic nanomaterials primarily include bioactive glass, hydroxyapatite, and silica. Among these, bioactive glass nanomaterials are mainly composed of elements such as silicon, calcium, and phosphorus. On one hand, they possess excellent bioactivity and osteoconductivity, enabling them to directly participate in the mineralization process of new bone and cementum, thereby promoting the functional reconstruction of periodontal tissues^[9,10]. For instance, in MC3T3-E1 osteoblast precursor cells treated with mesoporous bioactive glass nanoparticles (MBGNs), the mRNA expression levels of key osteogenic regulators were significantly upregulated: Runt-related transcription factor 2 (Runx2) increased by approximately 440%, osteopontin (OPN) and the osteoblast transcription factor Osterix both increased by about 300%, and the early osteogenic marker alkaline phosphatase (ALP) increased by roughly 230%. This synergistic upregulation at the gene transcription level establishes a molecular foundation for subsequent extracellular matrix synthesis and mineralization, demonstrating the potent osteoinductive activity of MBGNs^[10]. On the other hand, certain bioactive glasses can release specific ions, such as silver ions (Ag^+) and Zn^{2+} , to help inhibit the growth of periodontal pathogens, thereby aiding in the control of periodontal inflammation^[11]. Nano-hydroxyapatite, with a chemical composition highly similar to the inorganic mineral component of human bone tissue, is well-suited for periodontal bone tissue repair and facilitates tissue recovery following periodontitis treatment.

Silica nanoparticles include both solid silica nanoparticles and mesoporous silica nanoparticles (MSNs). Their core advantage lies in their superior drug delivery capabilities. Silica nanoparticles, particularly mesoporous silica, have become a more favorable choice for drug loading due to their tunable morphology, pore structure, and porosity, as well as their excellent biocompatibility and ease of functionalization^[12]. For example, Li et al.^[13] constructed a mesoporous silica nanoparticle-tetracycline (MSN-TC) delivery system, which demonstrated favorable drug loading capacity and sustained release characteristics. The system achieved a drug loading rate of 25.17%, with in vitro release lasting up to 72 hours. This system not only exhibited significant antibacterial activity against *Porphyromonas gingivalis*, with a minimum inhibitory concentration (MIC) of 100 $\mu\text{g/mL}$, but also markedly alleviated bacteria-induced calvarial bone destruction, restoring bone microstructural parameters to near-normal levels.

2.3 Carbon-Based Nanomaterials

Among carbon-based nanomaterials, carbon dots (CDs), a type of zero-dimensional nanomaterial with a size of less than 10 nm, have demonstrated promising application prospects in the medical field due to their low toxicity, modifiable surface, and excellent optical properties^[14]. Xin et al.^[15] reported that melatonin-derived carbon dots not only exhibit good water solubility and biocompatibility but also retain the inherent antioxidant and anti-inflammatory properties of melatonin. Specifically, they significantly inhibit alveolar bone resorption, reduce osteoclast activation, and scavenge ROS, thereby effectively alleviating inflammatory responses in periodontal tissues.

In addition to carbon dots, graphene oxide (GO) is characterized by its oxygen-rich structure, which enables it to anchor various metal nanoparticles and bioactive molecules, thereby enhancing its multifunctionality. Studies have shown that graphene oxide alone can stimulate the self-renewal and osteogenic differentiation of stem cells^[16]. Furthermore, it can serve as a nanofiller; leveraging its excellent mechanical properties, it is often used as a reinforcing component in nanofibrous membranes to improve drug loading capacity and sustained release efficacy for periodontitis treatment^[17].

Carbon nanotubes (CNTs) are cylindrical structures composed of rolled graphene sheets. They are widely utilized due to their exceptional tensile strength, light weight, unique electronic structure, as well as chemical and thermal stability^[18]. Suo et al.^[19] successfully fabricated a carbon nanotube/chitosan/sodium alginate composite scaffold via solution blending combined with three-dimensional printing technology, systematically evaluating the effects of different carbon nanotube concentrations on scaffold performance. The study found that the incorporation of carbon nanotubes effectively enhanced the mechanical properties of the material. The composite scaffold exhibited good biocompatibility and promoted the adhesion and proliferation of human periodontal ligament cells. When the carbon nanotube concentration exceeded 0.5%, the composite scaffold showed significantly enhanced antibacterial activity against *Porphyromonas gingivalis*. This three-dimensionally printed composite scaffold, which combines suitable mechanical properties, favorable cytocompatibility, and certain antibacterial activity, provides a new material option for periodontal tissue regeneration.

Despite the favorable antibacterial properties exhibited by metal nanoparticles, their cytotoxicity and long-term biosafety still require in-depth investigation. Nasiri et al. [20] reported that silver nanoparticles exhibit dose-dependent cytotoxicity towards human periodontal ligament fibroblasts at high concentrations. Moreover, much of the research on metal nanoparticles has been conducted *in vitro*, lacking sufficient *in vivo* experiments and clinical data to support their long-term safety. Current preparation techniques for inorganic nanomaterials also have limitations. Certain related technologies require urgent development, and process details need further optimization. For instance, the chemical reduction method for synthesizing silver nanoparticles relies heavily on reagents such as sodium borohydride, which presents disadvantages including toxicity, high cost, and susceptibility to introducing impurities. These issues may result in poor biocompatibility and unstable performance, restricting the application of this technology in the biomedical field. Although the hydrothermal method can produce well-crystallized nanocrystals such as zinc oxide, the reaction process occurs within an autoclave, making real-time monitoring difficult and leading to poor reproducibility and reliability of the process [21]. When preparing bioactive glass via the sol-gel method, the structures formed through acid/base-catalyzed routes are fragile and prone to fracturing, requiring prolonged curing times [22]. In recent years, inorganic nanomaterials have undergone continuous optimization in terms of long-term stability and suitability for large-scale production. Chen et al. [23] developed ultra-small molybdenum-based nanodots as highly efficient antioxidants. By employing a simple process of reducing phosphomolybdic acid with tannic acid, they circumvented the complexities associated with traditional preparation methods while achieving excellent biosafety. *In vitro* experiments demonstrated low toxicity to gingival fibroblasts, and animal studies showed no obvious organ damage, overcoming the challenges of high-concentration toxicity and accumulation risks associated with conventional metal nanoparticles. These nanodots ameliorate the pathological state of periodontitis through the combined effects of antioxidant, anti-inflammatory, and anti-apoptotic activities, addressing the limitation of traditional inorganic nanomaterials that often rely on a single therapeutic mechanism.

In summary, inorganic nanomaterials represent one of the earliest and most extensively studied material categories in the treatment of periodontitis. Their core advantages lie in strong antibacterial activity, excellent osteoinductivity, high chemical stability, and relatively mature preparation processes. However, their limitations, including insufficient biosafety, defects in preparation techniques, and a narrow therapeutic mechanism, have emerged as key factors restricting clinical translation. These limitations manifest as cytotoxicity induced by high concentrations of metal ions, high costs and poor reproducibility associated with fabrication processes, and the restriction to either single antibacterial or osteoregenerative functions. Subsequent optimization efforts, building upon the resolution of safety concerns and the innovation of preparation techniques, have focused on promoting functional diversity and synergy. This approach aims to better align inorganic nanomaterials with the comprehensive therapeutic requirements of periodontitis treatment while preserving their inherent advantages.

3. Challenges in the Clinical Translation of Nanomaterials

Although nanomaterials have demonstrated remarkable application prospects in the field of periodontitis treatment, their translation from laboratory research to clinical practice still faces numerous complex challenges. These challenges pertain not only to the physicochemical properties of the materials themselves but also encompass multiple aspects such as biosafety evaluation, feasibility of technical implementation, and cost and quality control.

Biosafety and long-term toxicity assessment represent core issues in the clinical translation of nanomaterials. Metal nanoparticles, such as silver nanoparticles, exhibit significant antibacterial efficacy; however, their accumulation within periodontal tissues may induce cytotoxicity or immune responses. Furthermore, studies have found that the catalytic activity of nanozymes in the complex oral environment may disrupt the normal redox balance [24,25]. Therefore, if nanomaterials are to be applied in clinical practice, systematic long-term animal experiments and preclinical studies are still required to evaluate their safety.

The regulation of nanomaterial stability and the efficiency of targeted delivery are also important factors affecting clinical translation. Although intelligently responsive nanomaterials developed in recent years have provided new directions for targeted delivery, their stability in the complex oral environment still requires improvement. Xu et al. [26] found that physiological fluctuations in pH may lead to premature drug release, while excessive reliance on specific stimulus signals may compromise the reliability of drug delivery systems. In addition, the limited tissue penetration capability of nanomaterials makes it difficult for them to breach the biofilm barrier and penetrate deep infection sites within periodontal

pockets, a challenge that significantly reduces the targeted delivery capacity of nanomedicines [27]. In recent years, microneedle technology, as an efficient delivery vehicle for nanomedicines, has demonstrated significant advantages in periodontitis treatment. Studies have shown that loading functional nanomaterials into microneedle systems not only enables drug delivery through the gingival barrier to reach deep periodontal pockets [28] but also allows for precise drug release and multiple therapeutic functions by incorporating intelligent response characteristics [29]. In the future, optimizing the synergistic design of microneedle materials and nanocarriers is expected to further advance the precision of periodontitis treatment.

The preparation of nanomaterials at the laboratory research stage typically relies on precision instruments and complex processes, such as surface functionalization modification and precise particle size regulation. These methods face significant difficulties when scaled up for industrial production, and the high cost of preparing high-quality nanomaterials remains prohibitive, severely limiting their widespread application in clinical practice.

Differences between preclinical models and human physiological characteristics may also lead to translational failure. Current research is largely based on periodontitis models in rodents, whose periodontal anatomical structures and immune responses differ from those of humans [30]. Such discrepancies may result in nanomaterials exhibiting different effects in animal model experiments compared to actual human applications.

4. Conclusion

Inorganic nanomaterials, owing to their unique antibacterial properties, osteoinductive capabilities, and advantages in drug delivery, have demonstrated broad application prospects in the treatment of periodontitis. However, the application of nanomaterials still faces multifaceted challenges related to safety, targeting efficiency, large-scale production, and economic viability. In the future, the development of multifunctional nanomaterials and research on clinical translation will represent important directions in this field. It is believed that with continuous advancements in research, nanomaterials will play an increasingly significant role in periodontitis treatment, bringing improved therapeutic outcomes for patients.

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