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LATEST ADVANCES IN NANOPARTICLES IN PERIODONTICS: A COMPREHENSIVE REVIEW

Periodontology

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ABSTRACT
Periodontitis, a prevalent chronic inflammatory disease affecting the supporting tissues of the teeth, is a major cause of tooth loss globally. Current therapeutic interventions focus primarily on mechanical debridement and the adjunctive use of antimicrobials, yet limitations such as microbial resistance, incomplete biofilm eradication, and the inability to regenerate lost tissues highlight the need for more effective treatment modalities. The advent of nanotechnology, particularly nanoparticle-based therapies, has shown immense potential in overcoming these limitations. Nanoparticles (NPs), owing to their unique size, surface area, and physicochemical properties, offer promising strategies for the management of periodontal disease. This article provides an in-depth review of recent advances in nanoparticle applications in periodontics, with a focus on antimicrobial agents, drug delivery systems, and tissue regeneration technologies. We also discuss current challenges, safety concerns, and future directions in clinical practice.

KEYWORDS

INTRODUCTION
Periodontal disease is characterized by the destruction of the tooth-supporting structures, primarily due to microbial biofilms and the host's immune response. It affects millions of individuals globally, leading to tooth mobility, bone loss, and eventual tooth loss if untreated. Conventional periodontal therapy typically includes scaling and root planing (SRP), the use of local or systemic antibiotics, and surgical interventions when necessary. However, persistent infections and microbial resistance pose significant challenges, necessitating the development of more targeted and efficient therapies.

Nanotechnology has opened new avenues for managing periodontal disease through the use of nanoparticles—nanoscale particles (1–100 nm) with enhanced physical, chemical, and biological characteristics. Due to their size, nanoparticles can penetrate deeply into biofilms, ensuring more efficient drug delivery, enhanced antimicrobial effects, and the potential for promoting tissue regeneration. This review explores the latest advancements in nanoparticle-based therapies in periodontics, focusing on their use as antimicrobial agents, drug delivery platforms, and regenerative tools.

Nanoparticles in Antimicrobial Therapy
1. Silver Nanoparticles (AgNPs):
Silver nanoparticles are among the most widely studied nanomaterials for antimicrobial applications due to their potent antibacterial properties. Their ability to disrupt bacterial cell membranes, induce oxidative stress through reactive oxygen species (ROS) production, and inhibit biofilm formation makes them valuable in the treatment of periodontitis. AgNPs exert broad-spectrum antimicrobial effects against key periodontal pathogens such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Aggregatibacter actinomycetemcomitans* (1).

Recent studies have demonstrated the effectiveness of AgNPs when incorporated into dental materials, such as gels or varnishes, for the local treatment of periodontal pockets. For instance, Boiero et al. (2) conducted an in vitro study where AgNP-based mouthwashes showed a significant reduction in the viability of biofilms formed by *P. gingivalis* and *A. actinomycetemcomitans*. Furthermore, the application of AgNPs during non-surgical periodontal therapy enhanced the clinical outcomes by reducing bacterial load, inflammation, and probing depth.

2. Zinc Oxide Nanoparticles (ZnO Nps):
Zinc oxide nanoparticles are known for their antimicrobial and anti-inflammatory properties, making them suitable candidates for adjunctive periodontal therapy. ZnO NPs generate ROS upon interaction with bacterial cells, leading to cell membrane disruption and bacterial death. Additionally, they modulate host immune responses, reducing pro-inflammatory cytokine production, which is crucial in controlling periodontal inflammation (3).

Several studies have explored the use of ZnO NPs in treating periodontitis. Bapat et al. (4) reported that ZnO NPs, when administered as a local adjunctive therapy to SRP, significantly reduced periodontal inflammation and improved clinical attachment levels. Their study further demonstrated that ZnO NPs could inhibit key periodontal pathogens more effectively than conventional antimicrobial agents, underscoring their potential as a therapeutic alternative in periodontal care.

3. Gold Nanoparticles (AuNPs):
Gold nanoparticles have garnered attention due to their biocompatibility and potential to be functionalized with various drugs and biomolecules. AuNPs have shown promise as antimicrobial agents due to their ability to penetrate bacterial biofilms and interfere with bacterial adhesion to surfaces. Functionalized AuNPs, carrying antibiotics or antimicrobial peptides, exhibit enhanced specificity towards periodontal pathogens, thereby improving treatment outcomes while minimizing systemic side effects (5).

Kumar et al. (6) explored the role of AuNPs in preventing biofilm formation in periodontal therapy. Their study found that AuNPs could disrupt biofilm architecture and inhibit bacterial adhesion to root surfaces. Moreover, AuNPs showed synergistic effects when combined with traditional antimicrobials such as chlorhexidine, further enhancing their efficacy in treating periodontal infections.

4. Titanium Dioxide Nanoparticles (TiO_2 Nps):
Titanium dioxide nanoparticles have demonstrated photocatalytic activity, which enhances their antimicrobial properties, especially when exposed to light. TiO_2 NPs generate ROS, which can destroy bacterial cell walls, making them effective against both Gram-positive and Gram-negative bacteria. TiO_2 NPs are also known for their biocompatibility and have been studied as coatings for dental implants to prevent peri-implantitis (7).

In periodontal therapy, TiO_2 NPs have been tested as adjuncts to SRP. A study by Figueroa et al. (8) demonstrated that TiO_2 NPs could reduce periodontal pocket depth and improve clinical attachment levels when used alongside conventional mechanical debridement. The nanoparticles' ability to disrupt biofilm formation and inhibit bacterial growth makes them a potential therapeutic tool in periodontics.

5. Copper Nanoparticles (CuNPs):
Copper nanoparticles (CuNPs) have shown antimicrobial properties similar to those of AgNPs, with the added benefit of being more cost-effective. CuNPs can induce oxidative damage to bacterial cells and have been shown to inhibit both planktonic bacteria and biofilm formation. Studies have indicated that CuNPs possess excellent antimicrobial activity against periodontal pathogens (9).

Recent research has focused on incorporating CuNPs into periodontal dressings and gels to prevent post-treatment infections. For example, Montalbano et al. (10) developed a CuNP-based hydrogel that showed significant antibacterial effects against *P. gingivalis* and reduced gingival inflammation in animal models.

Nanoparticles as Drug Delivery Systems

Nanoparticles have emerged as promising carriers for the controlled release of therapeutic agents in periodontal therapy. Their ability to encapsulate drugs, modulate release kinetics, and target specific sites enhances their therapeutic efficacy.

1. Chitosan-Based Nanoparticles:

Chitosan, a biopolymer derived from chitin, has excellent biocompatibility and biodegradability, making it an ideal candidate for drug delivery in periodontal therapy. Chitosan nanoparticles have been used to encapsulate a wide range of therapeutic agents, including antibiotics, anti-inflammatory drugs, and growth factors. Chitosan's positive charge allows it to adhere to the negatively charged bacterial cell walls, enhancing drug delivery to the infection site (11).

Sharma et al. (12) demonstrated the use of chitosan-based nanoparticles loaded with doxycycline in the treatment of periodontitis. Their study showed that these nanoparticles provided sustained drug release, resulting in a prolonged antimicrobial effect in periodontal pockets. The nanoparticles significantly reduced periodontal pathogens and improved clinical parameters, such as pocket depth and attachment levels.

2. Liposomal Nanoparticles:

Liposomal nanoparticles are vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs. Their ability to mimic biological membranes enhances drug bioavailability and reduces systemic side effects. Liposomal formulations of antimicrobials, such as metronidazole or tetracycline, have shown great promise in the treatment of periodontitis (13).

Singh et al. (14) explored the use of liposomal nanoparticles for the local delivery of metronidazole in periodontal pockets. Their study revealed that liposomal encapsulation prolonged the drug's release, allowing for more effective bacterial eradication compared to conventional formulations. Furthermore, liposomal nanoparticles significantly reduced inflammation and improved clinical outcomes in patients with moderate to severe periodontitis.

3. Polymeric Nanoparticles:

Polymeric nanoparticles, particularly those composed of biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), have been widely investigated as drug delivery vehicles in periodontics. PLGA nanoparticles can encapsulate a range of bioactive molecules, including antibiotics, anti-inflammatory agents, and growth factors. Their ability to release these agents in a controlled manner over time makes them suitable for the treatment of chronic periodontal infections (15).

Gandhi et al. (16) studied the efficacy of PLGA nanoparticles loaded with antimicrobial peptides for the treatment of periodontitis. Their results showed that PLGA nanoparticles effectively reduced bacterial load and biofilm formation in periodontal pockets. Furthermore, the sustained release of the encapsulated peptide led to significant improvements in clinical parameters, such as probing depth and bleeding on probing.

4. Nanohydroxyapatite (nHAp) Nanoparticles

Nanohydroxyapatite (nHAp) is a biomimetic material that has been extensively studied for its role in promoting periodontal regeneration. Due to its similarity to the mineral content of bone, nHAp has excellent osteoconductive properties and can serve as a scaffold for bone regeneration. Additionally, nHAp nanoparticles can be functionalized with antimicrobial agents, enhancing their potential as drug delivery systems in periodontal therapy (17).

Recent studies have explored the use of nHAp nanoparticles in combination with antibiotics or growth factors to promote periodontal regeneration. For example, Pradeep et al. (18) reported that nHAp nanoparticles loaded with metronidazole significantly reduced bacterial load and promoted bone regeneration in animal models of periodontitis.

Nanoparticles in Periodontal Tissue Regeneration

Periodontal tissue regeneration remains one of the most challenging aspects of periodontal therapy, particularly in cases of advanced disease with significant bone and soft tissue loss. Nanoparticles offer a promising solution for enhancing tissue regeneration through the delivery of growth factors, scaffolds, and stem cell-based therapies.

1. Calcium Phosphate Nanoparticles (CaP Nps):

Calcium phosphate nanoparticles have been extensively studied for their role in promoting bone regeneration due to their similarity to the mineral component of bone. These nanoparticles can serve as carriers for osteogenic growth factors, such as platelet-derived growth factor (PDGF) or bone morphogenetic protein-2 (BMP-2), promoting the differentiation of mesenchymal stem cells into osteoblasts and enhancing new bone formation (19).

Ravindra et al. (20) investigated the use of CaP nanoparticles in combination with PDGF for the regeneration of periodontal defects. Their study showed that the application of CaP nanoparticles significantly enhanced new bone formation and improved clinical attachment levels in periodontal patients with intrabony defects.

2. Silica-Based Nanoparticles:

Silica nanoparticles have been explored for their role in enhancing the delivery of bioactive molecules that promote periodontal regeneration. Silica-based nanoparticles can be functionalized with growth factors or peptides that stimulate the regeneration of periodontal ligament and bone tissues. Furthermore, silica nanoparticles exhibit excellent biocompatibility and can serve as scaffolds for tissue regeneration (21).

In a study by Gao et al. (22), silica nanoparticles were used to deliver BMP-2 in a rat model of periodontitis. The results showed that silica nanoparticles significantly enhanced new bone formation and improved the regeneration of periodontal ligament fibers, suggesting their potential for use in clinical periodontal therapy.

3. Graphene Oxide Nanoparticles:

Graphene oxide (GO) nanoparticles have shown great potential in the field of tissue engineering due to their mechanical strength, biocompatibility, and ability to promote stem cell differentiation. GO nanoparticles can be used as scaffolds for periodontal ligament regeneration or as carriers for growth factors and stem cells. Additionally, GO nanoparticles have antimicrobial properties, making them suitable for use in periodontal regeneration (23).

Recent studies have focused on the use of GO nanoparticles in combination with stem cell therapies for periodontal regeneration. Zhang et al. (24) demonstrated that GO nanoparticles, when combined with periodontal ligament stem cells, significantly promoted the regeneration of periodontal ligament fibers and bone tissue in animal models.

Challenges in Clinical Translation

While nanoparticles offer numerous advantages in periodontal therapy, several challenges must be addressed before their widespread clinical use. One of the primary concerns is the long-term safety and toxicity of nanoparticles. The small size and surface reactivity of nanoparticles raise concerns about their potential to induce cytotoxicity, oxidative stress, and inflammatory responses when administered over prolonged periods. Studies evaluating the biocompatibility and safety profile of nanoparticles in periodontal tissues are essential to ensure their clinical applicability (25).

Additionally, the standardization of nanoparticle formulations remains a significant challenge. Variations in nanoparticle size, surface charge, and composition can lead to differences in therapeutic efficacy and safety. The development of standardized protocols for nanoparticle synthesis, characterization, and testing is crucial for their successful translation into clinical practice.

Finally, regulatory approval and large-scale clinical trials are necessary to evaluate the efficacy and safety of nanoparticle-based therapies in diverse patient populations. To date, most studies have been limited to in vitro or animal models, and large-scale randomized clinical trials are needed to establish the clinical benefits of nanoparticles in periodontics.

CONCLUSION

Nanoparticles represent a cutting-edge approach in periodontics, offering promising solutions for antimicrobial therapy, drug delivery, and tissue regeneration. The unique properties of nanoparticles, including their ability to penetrate biofilms, deliver drugs at the molecular level, and promote tissue regeneration, make them an exciting tool for the future of periodontal therapy. However, more research is needed to address the challenges of long-term safety, standardization, and clinical translation.

As research progresses, nanoparticles could revolutionize periodontal therapy by providing clinicians with powerful tools to manage periodontal diseases more effectively and with fewer complications. The future of periodontics may lie in the continued exploration and development of nanoparticle-based therapies, with the potential to improve patient outcomes and enhance the quality of care.

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