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Nanoparticle Based Antimicrobial Photodynamic Therapy In Periodontics

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Abstract:
The increasing focus on antimicrobial photodynamic therapy (aPDT) highlights its potential to combat drug-resistant microorganisms by utilizing photosensitizers (PSs) and light to produce reactive oxygen species (ROS) for microbial cell death. Despite its promise, clinical applications face limitations such as poor water solubility, low target specificity, and photobleaching. To overcome these challenges, nanotechnology has emerged as a solution, offering nanoparticles that either carry PSs or act as PSs themselves. These nanoparticles enhance therapy effectiveness by improving PS stability, targeting, and delivery, especially against biofilm-related infections. Additionally, various types of nanoparticles such as liposomes, polymeric nanoparticles, mesoporous silica, gold and silver nanoparticles have been explored for their antibacterial properties and drug delivery capabilities. Research shows promise in treating oral infections, periodontitis, and peri-implantitis, though further clinical studies are needed to fully harness the potential of aPDT combined with nanotechnology.
Key Word: *photodynamic therapy; nanoparticles; periodontitis; peri-implantitis; gingivitis; oral infections.*

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I. Introduction

Periodontitis stands among one of the most common oral health conditions globally and is considered as a leading cause for teeth loss among adults. Chronic periodontitis, though often accompanied by persistent inflammation, has significant implications on overall general health in addition to the compromises on the function of the oral chewing system. Conventional approaches to managing periodontitis typically involve basic treatments like plaque control and mechanical periodontal therapies, along with surgical interventions and antibiotics. However, incomplete plaque removal can lead to recurrent inflammation, which often results in unsuccessful treatment. Additionally, the overuse of antibiotics has contributed to the growing issue of bacterial resistance, rendering antibiotic treatments less effective. Recently, antimicrobial photodynamic therapy (aPDT) has garnered considerable attention for treating oral infections, as it offers consistency in results and minimal side effects [(1).]

The recent focus on the aPDT (antimicrobial photodynamic therapy) research highlights its potential as a promising method for addressing drug-resistant microorganisms. This approach leverages non-toxic photosensitizers (PSs) and harmless light specific wavelengths for generating reactive oxygen species (ROS), which further lead to microbial cell death. Several limitations have impeded the clinical use of PSs, like issues with poor water solubility, uncontrollable drug release, poor target selectivity and low extinction coefficients. Additionally, photobleaching can result in unintended side effects and damage to health tissues[(2)]. A systematic review can examine the effectiveness of aPDT as an adjunct to surgical and non-surgical treatments, focusing on both clinical and patient related outcomes in periodontitis and peri-implantitis patients. The findings suggest that aPDT can offer comparable improvements in clinical attachment level (CAL) and probing depth (PD) when compared against traditional periodontal treatment for both the conditions[(3)]. To address these challenges, researchers have developed novel nanomaterials designed to either serve as carriers for PSs or function as PSs themselves. These advancements aim to enhance the effectiveness and safety of the treatment[(2)].

Nanotechnology involves manipulation of materials at the scale of 1 to 100 nanometers. Over recent decades, it has significantly advanced biomedicine and dentistry, by enhancing the mechanical and physical properties of materials, and introducing innovative nano-based diagnostic techniques and drug delivery systems[(4)]. Nanoparticles offer advantages over traditional materials due to their improved stiffness, transparency, resistance to heat, abrasion, and solvents, as well as their enhanced toughness and overall performance. In biomedicine, nanoparticles have made significant strides as drug delivery systems, also known as nanocarriers. Developing advanced drug delivery systems that can target specific sites with precise therapeutic doses is essential for progress in clinical medicine[(5)]. Nanotechnology, especially through the use of nanoparticles, has led to significant advancements in medicine, particularly for many periodontal diseases.

Various metallic ions and biodegradable polymers with antimicrobial activity had been utilized to create these nanoparticles. The shape, size, surface characteristics and internal properties if these nanoparticles play a crucial role in managing biofilm infections. Nanoparticles can infiltrate cell organelles and affect biostructures by interacting with nucleic acids and membrane-embedded proteins. Their small size provides a distinct advantage in drug delivery compared to other methods[4].

II. Photosensitiser And Nanoparticles

Photosensitisers (PSs) are essential elements in PDT, as they induce the generation of ROS upon absorption of specific lights. Almost all the PSs are small molecules and they commonly suffer from various problems in the PDT environment, like low solubility and poor stability. Recently, many reports on the nanomedicine-based PDT have been documented. They showed that various nanomaterials can serve either as the PSs carrier or as the direct PSs, thus enhancing the efficacy of PDT[1].

Innovative designs have been created in form of nanoparticles (NPs) are either loaded with or encapsulated around photosensitizers (PS) to serve as delivery vehicles, or where the NPs themselves function as photosensitizers. These nanoparticles are produced using methods such as bottom-up, top-down or molecular self-assembly techniques[6].

The encapsulation of photosensitizers in biodegradable and biocompatible nanoparticles, including liposomes, micelles, polylactic-glycolic acid, solid lipid nanoparticles, and cyclodextrins, has been employed to enhance their anticancer or antimicrobial effectiveness as drug delivery vehicles[7].

Encapsulating photosensitizers (PS) in nanoparticles enhances photodynamic therapy (PDT) efficacy by offering several benefits:

1. Increased concentrations of PS for generating reactive oxygen species (ROS), which lowers the likelihood of multidrug resistance by preventing the target cell from expelling the PS.
2. Improved selective delivery of PS through either passive or active targeting mechanisms.
3. Utilization of hydrophobic or poorly water-soluble PS.
4. Prevention of PS dimerization, which can lead to PS inactivation when it is in a free state[8].

Nanoparticles are recently being used in aPDT to enhance the effectiveness of the treatment. Four types of nanoparticles to PS interactions have been reported.

1- PS embedded in polymeric nanoparticles
2- PS bound to the surface of nanoparticles
3- PS alongside nanoparticles
4- Nanoparticles as the PS
5- This classification distinguishes between active NP (functioning as photosenstizer) and passive NP (other categories). Active NP can further be divided into biodegradable (PLA, PLGA, liposomes) and non-biodegradable types (gold, silica)[9].

III. Commonly Used Nanoparticles In Pdt

Liposomes

Liposomes were the first nanoparticles systems to be used in clinical settings. They are biodegradable, biocompatible and non-toxic. These are prepared by self-assembled spherical structure with multiple concentric lipid bilayers, having the ability to adhere to microbial cell walls[10].

Gold and Silver Nanoparticles

Gold and silver are among the most commonly utilized metals for nanoparticles in medical applications. These nanoparticles typically range in size from 1 to 100 nanometers. Silver nanoparticles, in particular, are known for their potent antibacterial properties. Their large surface area and high reactivity allow for extensive modifications and functionalization, enhancing their targeting capabilities and bioavailability[11].

Metal oxide nanoparticles

Iron oxide and zinc oxide are among the most frequently used metal oxide nanoparticles. These NPO can be coated with gold or silica particles. These are employed as drug delivery system due to their high loading capacity and ability for controlled release. Research has demonstrated that zinc nanoparticles possess antibacterial properties and have been effectively utilized in photodynamic applications[12].

Mesoporous silica Nanoparticles (MSNs)

Silica nanoparticles have been widely investigated and are known for their strong mechanical properties, relatively inert chemical composition, and low cytotoxicity. Mesoporous silica nanoparticles (MSNs), which range in size from 2 to 50 nanometers, are highly versatile. Theyoffer advantages such as ease of drug encapsulation, stability, adjustable volume and pore size, with a large surface area. Additionally, MSNs are

recognized for their ability to downregulate pro-inflammatory mediators, thereby influencing the immune response[13].

Chitosan nanoparticles

Chitosan is a non-toxic, naturally occurring biopolymer. Chitosan nanoparticles can be produced using methods such as ion-gelation, precipitation with tripolyphosphate, or crosslinking with glutaraldehyde. The properties of these nanoparticles are influenced by the molecular weight of the chitosan[14].

Polymeric Nanoparticles

These nanoparticles are characterized by high solubility, ease of preparation, stability, and biodegradability, as well as biocompatibility. They are recognized for their extended blood circulation time, ability to modulate biodistribution and enhanced solubility. The commonly used materials include PVA (poly-vinyl alcohol), PLGA (poly-lactic-co-glycolic acid) and PLA(poly-lactic acid)[15].

Titanium oxide (TiO2)

Lately, there is a growing interest in TiO2 due to its excellent stability in physical environment and biocompatibility, along with its low toxicity. When exposed to ultraviolet light (UV) light, it produces reactive oxygen species (ROS) that have strong bactericidal effects, demonstrating significant antimicrobial activity[16].

Quantum Dots (QDs)

Quantin dots (QDs) are imaging probes that exhibit high quantum yields, size tunable fluorescent emission and excellent stability. They are targeted to specific pathological areas and are water soluble. Additionally, they have the potential to function as PS on their own[17].

Fullerenes

Fullerenes, particularly C60, represent the third stable form of carbon and are utilized as NP in various drug delivery systems. They possess photodynamic activity and can function as photosensitizers themselves. Fullerenes strongly absorb UV light and moderately absorb visible light, making them effective as photosensitizers. Due to their structure, they exhibit high triplet yield and extended triplet excited state, leading to the generation of reactive oxygen species (ROS) upon photoactivation, indicating their potential as photosensitizers[18].

Anionic surfactant dioctyl sodium sulfosuccinate (aerosol OT, AOT) AOTAlginate nanoparticles.
AOT are non-toxic and have shown to increase the ROS yield of photosensitisers[19].

IV. Nanoparticles Targeting Oral Infections.

Over the past decade, the combination of antimicrobial photodynamic therapy (aPDT) with nanotechnology has garnered significant interest from the scientific community for its potential to positively impact various oral infections caused by microorganisms. With increasing microbial resistance to antimicrobial medications, aPDT is an emerging promising alternative, showing good effectiveness against a range of microbes relevant to dental and medical fields. However, the effectiveness of aPDT on biofilm have been limited due to the hydrophobic nature of many photosensitisers (PSs). To enhance the antimicrobial efficacy of this therapy, nanotechnology has developed innovative systems to effectively deliver hydrophobic PSs to targeted microorganisms[20].

For antimicrobial applications, various strategies combining antimicrobial photodynamic therapy (aPDT) with nanoparticles have been explored. One strategy involves using nanoparticles to enhance the photoinactivation kinetics of microorganisms, while another approach focuses on optimizing the binding and absorption of photosensitizers (PSs) by microorganisms[21].

A key challenge is developing a photosensitizer (PS) that selectively targets microorganisms without affecting surrounding healthy tissues, which can be addressed through nanotechnology-based functionalization. Furthermore, research has indicated that adding cationic charges to the PS can enhance its effectiveness against both Gram-positive and Gram-negative bacteria[22].

When using photosensitizes in dental applications, they may cause discoloration of teeth, gums and prostheses. To address this issue, nanotechnology can be employed to encapsulate photosensitizers within nanoparticles, providing physical protection and preventing pigmentation of the treated areas. Antimicrobial photodynamic therapy (aPDT) has gained significant attention in recent research, with numerous in vitro and in vivo studies exploring its efficacy against various pathogens of medical and dental relevance. Despite this progress, clinical studies investigating the integration of aPDT with nanotechnology for managing oral diseases caused by microorganisms remain limited[23].

V. Periodontitis And Peri Implantitis

MB-loaded PLGA nanoparticles have shown significant activity against biofilms on patients with chronic periodontitis. After 5 minutes if red light irradiation(100 mW/cm²), the bacterial activity was reduced by 60% in the planktonic phase and 48% in the biofilm phase[24].

Clinical Indocyanine Green -loaded nanospheres coated with chitosan (ICG-Nano/c) were used to target Porphyromonas gingivalis. The positively charged ICG-Nano/c adhered effectively to the surface of this Gram-negative bacterium, resulting in a reduction in bacterial viability by 2 log10 (96.71%) to 4 log10 (99.99%)[25]. Notably, using the intermittent irradiation along with air cooling, enhanced the therapeutic penetration, while it reduced the thermal tissue damage as well[26].

Multifunctional nanoparticles, were engineered to activate antimicrobial photodynamic therapy (aPDT) against pathogens associated with periodontitis. These nanoparticles were stable, biocompatible, and non-cytotoxic. The NP-based aPDT effectively reduced biofilms of three single-species periodontitis by nearly 4-5 times after 3 minutes of irradiation with 630nm light (100 $mW \cdot cm^{-2}$)[27].

P.gingivalis was notably prevalent in deeper pockets, deeper than 4mm. Thus, an important consideration for aPDT targeting periodontitis is ensuring that the light source can penetrate deeply, deep enough to reach the bottom of the periodontal pocket. The aPDT using upconversion nanoparticles coated with titanium dioxide (UCNPs@TiO2) reduced the colony forming units (CFU) of three single species biofilms by nearly 4 times. After 5 minutes of irradiation at 2.5 W/cm^2, the planktonic bacteria were effectively eliminated by 2mm at the 4^{th} hour. This UCNPs@TiO2-mediated aPDT shows significant promise towards the effective management of periodontitis.

Peri-implantitis is an inflammatory response affecting the tissues around an osseointegrated implant, causing teeth loss and loss of surrounding bone. While various factors can contribute to implant failure, substantial evidence indicates that anaerobic plaque bacteria have a harmful impact on peri-implant tissue health. Similar to periodontitis, plaque acts as the primary trigger for peri-implantitis[20].

While there have been limited reports on nanomaterial-based antimicrobial photodynamic therapy (aPDT) for peri-implantitis, nanosurface layers have shown promise in preventing infections. Various nanocoating on the implant surface, including TiO2, silver, hydroxyapatite (HA) were applied using techniques such as anodization, silver plating and sintering. The two layered silver HA nanocoating effectively prevented microbial growth in the surrounding media and reduced the biofilms of the implant surfaces by 97.5%. This innovative nanocoating demonstrated a lesser rate of infection, improved osseointegration along with accelerated bone healing[28].

An in vivo study conducted by Laura Marise de Freitas et al. demonstrated that Methylene Blue-loaded PLGA nanoparticles (MB-NP) achieved a 25% greater bacterial killing effect compared to free Methylene Blue. The study found that MB-NP-mediated photodynamic therapy (PDT) exhibited superior efficacy against human dental plaque bacteria. While Methylene Blue on its own lacks effective photochemical properties, encapsulation in PLGA enhances its phototoxicity upon release. Consequently, MB-NP has potential for reducing bacterial counts in patients with periodontitis as an adjunct to scaling and root planing. Additionally, similar in vitro studies have explored the use of nanoparticle-based PDT[29].

Additionally, these nanoparticles exhibited higher photothermal conversion efficiency compared to free ICG[30]. Marina Usacheva et al. conducted an in vitro study using AOT-alginate nanoparticles encapsulating Toluidine Blue (TB). they found that the combination of naturally occurring polysaccharide sodium alginate with AOT significantly enhanced the retention of water-soluble molecules within the cells and increased cellular accumulation, leading to better therapeutic efficiency of PS. The study demonstrated that encapsulating the dye in alginate nanoparticles improved its stability and allowed it to remain in bacterial biofilms for a longer duration[19].

Another in vitro study by Nagahara et al. investigated Chitosan-encapsulated ICG nanoparticles (ICG-Nano/c). The results demonstrated that chitosan-loaded nanoparticles were more effective at disrupting biofilm microorganisms compared to free ICG[31]. M. Li et al. conducted an in vitro study using core-shell nanostructures of upconversion nanoparticles and TiO2 (UCNPs@TiO2). Their research demonstrated that UCNPs@TiO2 achieved a greater reduction in biofilm-associated organisms compared to the control, highlighting the inhibitory effects of UCNPs@TiO2 on periodontitis-related pathogens[20]. Furthermore, Ribeiro, A. P. D conducted an in vitro study comparing cationic and anionic nanoemulsions encapsulated in liposome nanoemulsions (ClAlPc) with free ClAlPc. The study, which involved methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-susceptible Staphylococcus aureus (MSSA biofilm cultures, found that the cationic NE-ClAlPc effectively killed resistant strains of S.aureus through photodynamic action. In an in-vivo study conducted by De Moraes, lipid nanoemulsions contains ClAlPc were used to assess the VEGF levels in the normal gingival tissues following PDT. They observed an increase in the VEGF levels in the gingival tissues after PDT, suggesting an enhanced osteoblastic activity and bone regeneration[33].

VI. Conclusion

In conclusion, antimicrobial photodynamic therapy (aPDT) represents a promising alternative for addressing drug-resistant microorganisms, particularly in the context of oral infections, periodontitis, and peri-implantitis. The integration of nanotechnology into aPDT has significantly enhanced its therapeutic potential by improving the stability, targeting, and delivery of photosensitizers (PSs). Various nanoparticles, such as liposomes, metal nanoparticles, and polymeric nanoparticles, have shown considerable antibacterial efficacy and improved drug delivery. However, despite these advancements, further clinical studies are necessary to optimize these nanotechnology-based systems and fully realize the potential of aPDT for widespread medical and dental applications.

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