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Nanoparticles Enhanced Photodynamic Therapy in the Treatment of Periodontitis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Periodontitis is a bacterial-induced inflammatory disease of alveolar bone and soft tissues eventually leading to the loss of the tooth. Elimination of the infectious agent is the ultimate goal of periodontal therapy, either by mechanical debridement, non-surgical therapy, minimally invasive or noninvasive procedures, or surgical therapy. Recent advances in treatment and technology have led to the discovery of different options, of which photodynamic therapy (PDT) is being used as an aid to conventional periodontal therapy. It helps in overcoming microbial resistance to antimicrobials. However, studies have documented that, PDT shows not much of a difference in the clinic-microbiological parameters. Hence, nanoparticles are encapsulated with Photosensitizers which enhance the stability and penetrability of diseased cells and microorganisms and are used as a novel technique. This review article, is a discussion on PDT in the treatment of periodontitis, with an emphasis on nanoparticles, which can be used in enhancing the effect of photosensitizers (PS) and improving the PDT activity, also various studies based on nanoparticles used in PDT in treating periodontitis are discussed in this review.

Keywords: Lasers; nanoparticles; periodontitis; photodynamic therapy.

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1. INTRODUCTION

Periodontitis is a bacteria-induced inflammatory disease of the periodontium and alveolar bone eventually leading to tooth loss. Over the years, mechanical debridement i.e., scaling and root planing (SRP), has been the gold standard of periodontal therapy [1]. However, it is tough to eliminate the periodontopathogens from the deeper sites, which can be attributable to the anatomical complexity of tooth roots, which predisposes the development of bacterial niches both chemically and mechanically [2]. Moreover, few patients are at risk due to systemic illness, hereditary factors, and smoking, accompanied by chronic periodontal diseases. Hence various treatment methods adjuvant to SRP including, chemotherapy and surgery are being used as a part of periodontal therapy [2,3].

Due to the ability of bacterial pathogens to breed in oral biofilms and the poor availability of the antimicrobial agent, at the site of action, the pathogens often persist in the periodontal pocket area, thus escaping host immunity and usual antimicrobial drugs [4]. In this case, the use of antibiotics systemically is limited, as the drug's minimal inhibitory concentration (MIC) is hard to achieve in gingival crevicular fluid (GCF) and is scarce in oral biofilms. Moreover, bacterial resistance is a limiting factor [4]. Surgery is not always indicated in patients with periodontitis, owing to their medical condition. All the above drawbacks have led to the discovery of various alternatives, one of which is photodynamic therapy (PDT) [4]. However, there are many disadvantages with the conventional PDT, like the reduced depth of penetration or uptake by the bacterial cells, among few. Hence, nanoparticles have been devised as new technological advancement and are being researched. This review article gives insight into how nanoparticles are advantageous and can be employed over conventional PDT photosensitizers. Thus giving a scope of future research in this field.

2. PDT IN PERIODONTITIS

PDT is a non-invasive therapy discovered accidentally in the early 20th century, which was then applied to treat neoplasms and various skin infections and to eliminate microbes by photoactivation in the medical field. The principle of PDT is that when a photoactivable substance i.e, a photosensitizer (PS) when in contact with the target cells and exposed to a source of light of a suitable wavelength gets excited and produces reactive oxygen species (ROS) by transferring its energy to the oxygen molecule [5]. Thus, ROS and singlet oxygen ($^1O_2$) produced are cytotoxic and are known to oxidize the target cells' macromolecules, leading to cell death or apoptosis [6]. It was first introduced as a treatment of choice for neoplasms. Photodynamic therapy has emerged as an alternative to antimicrobial regimens and mechanical debridement in eliminating dental plaque species as a result of the pioneering work of Professor Michael Wilson and colleagues at the Eastman Dental Institute, University College London, UK. In recent years, many studies have reported that PDT is efficient in eliminating the periodontal pathogens in periodontal and peri-implant diseases and thus it is being used as an adjunct to phase 1 periodontal therapy [7].

Z Malik (1990) said that anionic and neutral photosensitizers efficiently kill gram-positive bacteria and induce growth inhibition or killing by PDT.

The three important components in a PDT are photosensitizer, reactive oxygen species, and a suitable light source. All three components have not been known to have any noxious effects on the host tissue or cells apart from the targeted or diseased cell or tissue, compared to other chemotherapeutic drugs. The advantages of this therapy are its minimally invasive approach, innocuous, and can be administered multiple times without cumulative toxicity [6].

Braun A, Dehn C et al (2008) assessed the effect of adjunctive antimicrobial photodynamic therapy (aPDT) in chronic periodontitis and concluded that in such patients the clinical outcome of conventional subgingival debridement can be improved by adjunctive aPDT [8].

Despite its rapidly growing applications and widespread use, it has yet to be incorporated as a treatment of choice in treating periodontal diseases, because of certain limitations like poor solubility of PS in water, hydrophobicity, lack of an ideal PS, challenges in formulating PS, incomplete uptake of PS by oral biofilms, selecting the right light wavelength for an effective treatment outcome is necessary. Moreover, planning and monitoring the treatment response is difficult [8]. Nanoparticles application in PDT has been a major step ahead in solving some of the challenges associated with traditional PDT. In this review, we will discuss

various nanoparticle-based PDT in periodontal therapy.

3. PRINCIPLE OF PHOTODYNAMIC THERAPY

Professor Herman von Tappeiner in 1904 used the phrase “photodynamic action” to describe interactions between specific chemical substances, oxygen, and light. Another German physician, Friedrich Meyer-Betz, introduced the term “photodynamic therapy”. At first, PDT was applied to treat neoplasms in medicine [9].

Now, PDT is employed in treating infections i.e, antibacterial PDT. Thus very well can be employed in treating periodontal infections. It is known that the bactericidal effect of PDT is by the destruction of the cytoplasmic membrane, which is the main mechanism of PDT in bacterial destruction. The ROS that is generated during photodynamic therapy is cytotoxic species, responsible for the inhibition of plasma membrane enzyme or DNA destruction of bacteria, or inactivation of the transport system of the membrane [9]. The cytotoxic effect is induced neither by photosensitizer nor by the light source individually, however, few black-pigmented bacteroides (e.g. *Prevotella* and *Porphyromonas spp.*) can be killed by light at a wavelength of 660 nm. This is related to inner porphyrins (photoactivable substances) that are synthesized by bacteria themselves [10]. Classically, in PDT, the PS is administered to the target cells and the light source is exposed in the area where the drug is localized. Consequently, ROS (Singlet oxygen and free radicals) are generated, which is the characteristic effect of the PS, where, after exposure to the light source of a specific wavelength, it absorbs the light and goes into an excited singlet state. On absorption, the PS can emit heat, gleam (fluorescence), and might undergo intersystem crossing leading to an excited triplet state, characterized by a longer duration (microseconds) compared to the singlet state (nanoseconds). This gives enough time for the incidence of phosphorescence, where the PS is returned to the basal state, or for the photochemical reactions (Type1 or Type 2) to occur. In Type 1 reaction, the cytotoxic species, such as lipid-derived radicals, hydroxyl radicals, and superoxide are generated, when the electron transfer reactions from the triplet state molecule with the involvement of a substrate interact with the oxygen [10]. In Type II reaction, the energy transfers from the triplet state PS molecule to the molecular oxygen at the ground state to create singlet oxygen at the excited state which causes cytotoxicity because of the ability of the excited singlet oxygen to oxidize several biological molecules such as lipids nucleic acids and proteins [11].

In type 1 reaction the PS transfers energy directly to molecular oxygen in the triplet state, resulting in free radicals’ generation and oxidation of intracellular structures leading to cell death. Whereas, in type 2 reaction, the electrons are transferred from PS to molecular oxygen, leading to singlet oxygen production [12]. The type 1 and type 2 reaction percentage depend on the PS used. The basis of antimicrobial PDT is expected to be the Type 2 reaction [11,12].

The efficiency of singlet oxygen generated is influenced by multiple factors like the chemical structure of the PS used, the intensity of light, the wavelength of light, and the concentration of oxygen. However, improving the photosensitizers and light sources is given much attention [13]. Fig.1 illustrates the principle of PDT.

The ideal properties of a Photosensitizer include: [11,12]

1. Should have high affinity towards the microorganisms.
2. A broad-spectrum activity.
3. Low binding affinity towards host cells to avoid the risk of photo-destruction of host tissues.
4. There should be a low propensity towards resistant bacterial strains.
5. There should be minimal risk of mutagenic processes.
6. Chemical toxicity should be low.

The limitations of first-generation photosensitizers (porphyrins) in clinical application include prolonged photosensitivity, low light penetration depth, low clearance rate, and poor selectivity. Hence second-generation photosensitizers were developed to resolve these issues. These include the porphyrinoid derivatives (phthalocyanine, chlorine) and nonporphyrinoid derivatives like chalcogen-containing dyes (Methylene blue MB), and derivatives of hypocrellin, squaraine, and boron-dipyrromethene [1]. Gram-positive microorganisms are generally susceptible to photoactivation, whereas gram-negative bacteria often show resistance to it if the outer membrane permeability is not modified. This is related to the limitation encountered by the PS to penetrate the bacterial cell. Literature has documented that photosensitizers like

porphyrins, phthalocyanines, and phenothiazines (e.g., methylene blue and toluidine blue O) in antimicrobial PDT, penetrate the cell membrane of gram-positive and gram-negative bacteria. This is because the positive charge of the photosensitizer promotes the binding to the gram-negative bacterial membrane and leads to localized damage and increased permeability [12].

4. LIMITATIONS IN THE CURRENT PDT

Over the years, PDT emerged as an effective choice for treating periodontitis. However, several studies have reported the inefficacy of the PDT, in completely disrupting the biofilms. This is mainly due to the limitations of currently available photosensitizers. It is mainly attributed to the reduced susceptibility to antimicrobial PDT, which is related to the different phenotypes expressed by the microorganism growing in the oral biofilm. The bacterial cells are capable of expelling the photosensitizer via multidrug resistance pumps [8]. It has been shown that phenothiazine-based photosensitizers, including methylene blue and toluidine blue O, are substrates of multidrug resistance pumps in bacteria. The bacteria growing in the biofilm may be in a starved or slow growth state [14-16].

Fontana et al., in their study, reported the reduced penetration of MB into the biofilm and its retention in the outer layers of biofilm clusters resulted in the decreased susceptibility by confocal scanning laser microscopy susceptibility of biofilms [13]. O'Neill et al. have reported similar findings [17], where they studied the efficacy of toluidine blue-mediated PDT.

Water channels carry transporting solutes into and out of the depths of a biofilm, but they do not ensure access to the interior of the cell clusters [11] which can range in diameter from 20 to 600 μm [13]. With the growing importance of PDT in the treatment of periodontitis, new drug delivery systems and targeting approaches are being investigated to address the current PDT's shortcomings [18].

Substances that target biofilm matrix or non-growing bacteria (persistent cells) within biofilms have recently received attention. Bacteriophages and naturally occurring or synthetic antimicrobial peptides that act against bacteria without causing resistance have been reported previously. Light-only therapy, antibody-photosensitizer, bacteriophage-photosensitizer conjugates, and nanoparticles have all gained rising attention [18,19]. The nanoparticles were introduced in PDT with the primary intention to increase the effectiveness of the therapy by increasing the penetration of PS and reducing multidrug-resistant pumps [20].

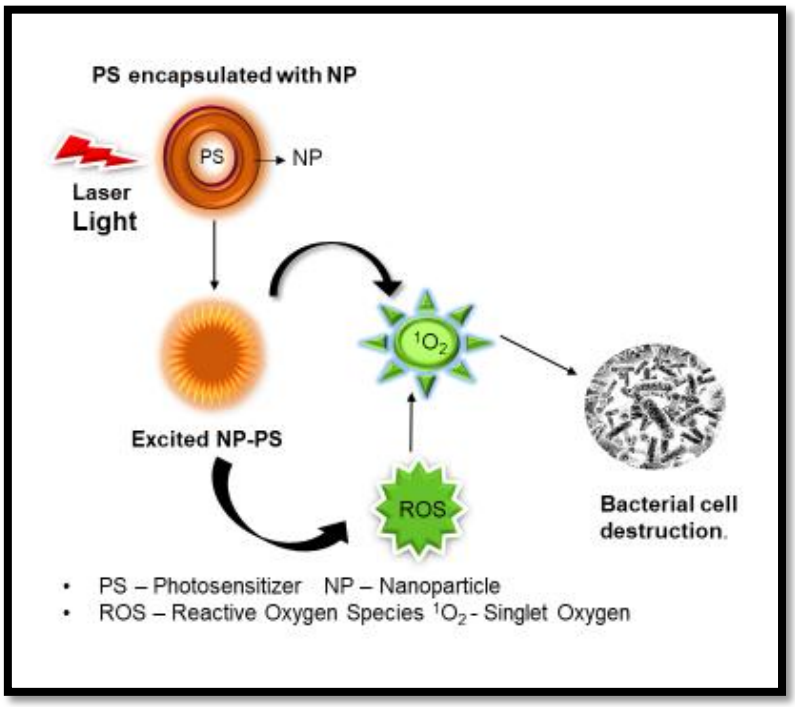

Fig. 1. The mechanism of PDT

5. NANOPARTICLES IN PDT

Nanotechnology is the engineering of materials on a scale of 1-100 nm. It has transformed the fields of biomedicine, and dentistry by improving, the physical and mechanical properties of materials, and introducing new nano delivery systems and diagnostic modalities over the last few decades [20].

Nanoparticles are superior to conventional materials, because of enhanced stiffness, transparency, resistance to heat, abrasion, solvent, and toughness and exhibit better performance. In the field of biomedicine, nanoparticles have achieved immense progress as drug delivery systems, or nanocarriers. It is crucial to develop newer drug delivery systems with therapeutic dosages at specific sites in the field of medicine in clinical sciences [21]. Thus, nanotechnology, particularly nanoparticles, has achieved breakthrough strategies in medicine, especially in periodontal diseases.

Various biodegradable polymers, metallic ions with antibacterial properties, have been employed for the development of nanoparticles. The size of nanoparticles is advantageous property, in drug delivery over other counterparts [20].

New precise designs were developed, where nanoparticles (NP) were loaded or encapsulated with PS to act as a vehicle or, the NP acts as PS itself. Nanoparticles are produced through top-down, bottom-up, or molecular self-assembly approaches [22]. The size, shape, surface, chemical and interior properties of the resulting NPs are important to consider in the control of biofilm infection. Nanoparticles penetrate ell organelles by altering the functions of the biostructures via being in contact with the nucleic acids and proteins embedded in membranes [20].

6. ADVANTAGES OF NANOPARTICLES [20-23]

1. Enhanced stability, and solubility i.e., dissolution in an aqueous medium and controlled release.
2. Enhanced bioavailability and reduced clearance by increased transportation across the cell membrane.
3. Enhanced drug loading capacity due to increased surface area per unit mass and high surface reactivity.
4. Enhanced tissue tolerance attributable to size simulation, and biomimicking natural tissue.

Encapsulating photosensitizers in a suitable drug carrier, such as nanoparticles, is a potential approach for enhancing photosensitizer efficacy, which includes increased photosensitizer accumulation in target cells and inhibition of the target cell's ability to pump out photosensitizers. The photodynamic activity of the PS is enhanced by incorporating the photosensitizer in nanoparticles and preventing its inactivation by plasma reductases, thus protecting its photodynamic activity. Various studies have shown promising results for better drug degradation and availability at the site of action owing to the above-mentioned advantages of nanoparticle systems [20,23].

Nanoparticles used in PDT can be broadly divided into two classes by Chatterjee et al. [19] active participants and passive carriers in PS excitation. The active participants are further subdivided based on the mechanism of activation into (a) Photosensitizer (b) Self-illuminating (c) Upconverting. Passive carriers are further classified depending on material composition into (a) biodegradable polymer-based nanoparticles and (b) non-polymer-based nanoparticles, e.g., ceramic and metallic nanoparticles.

The Photosensitizers can either be covalently bound to the nanoparticle or embedded in the nanoparticle or encapsulated by the nanoparticle or the nanoparticle can itself act as a photosensitizer [23].

Nanoparticle-based PDT has been well explored in the field of cancer therapy. Some nanoparticles like gold nanoparticles, silica, metal oxides, polymer-based nanoparticles, and up conversions have been used in PDT. Quantum dots and fullerenes belong to another group of nanostructures and act as PS. However, in the field of antimicrobial PDT, it is gaining recent attention, and thus based on the literature the nanoparticles used in PDT against biofilm elimination have been listed in Table 1.

Table 1. Commonly used nanoparticles in PDT

Nanoparticles	Description
Liposomes [24]	Liposomes are the first clinically used nanoparticle systems. It is non-toxic, biodegradable, and biocompatible. They are produced by self-closed spherical nanostructures with one or more concentric lipid bilayers and adhere to the bacterial cell wall.
Gold and Silver Nanoparticles [25]	Gold/Silver is one of the most used metals for nanoparticles in medicine. Gold/Silver nanoparticles are 1-100nm in size. Silver is one of the strongest antibacterial nanoparticles. The surface area and high reactivity enable further modifications and functionalization, thus improving its target potential and bioavailability.
Metal oxide nanoparticles [26]	The most commonly used metal oxide nanoparticles are Iron oxide, Zinc oxides. They might be coated with silica or gold particles. They are used as drug delivery systems because of their properties like controlled release and high loading capacity. Studies have reported that zinc nanoparticles have been shown to have antibacterial properties and have been successfully used in a photodynamic property.
Mesoporous silica Nanoparticles (MSNs) [27]	Nanoparticles of silica have been extensively studied and have been considered to have robust mechanical properties, relatively inert chemical composition, and non-cytotoxic. MSNs are of size - 2-50 nm and proved to be versatile with attractive features like ease of encapsulation of drugs, stability, tunable pore size, and volume and large surface area, also, MSNs are known to downregulate pro-inflammatory mediators, hence playing a role in the immune response.
Chitosan nanoparticles [28]	Chitosan is a naturally occurring, non-toxic biopolymer. Chitosan nanoparticles are made either by ion-gelation method, precipitation with tripolyphosphate, or crosslinking using glutaraldehyde. Its properties depend on its molecular weight. It is known to be the safest carrier for drug delivery systems because of its biodegradability and biocompatible properties.
Polymeric Nanoparticles [29]	These nanoparticles have high solubility, and ease of preparation, are stable, increased availability, and are biodegradable and biocompatible. These have been known for prolonged blood circulation time, modulating biodistribution, and increased solubility. Most commonly used are PLGA (Poly-lactic (co-glycolic) acid) PVA (Poly-Vinyl Alcohol), PLG (Poly-lactic Acid)
Titanium oxide (TiO2) [30]	Recently gained interest due to its good biocompatibility, high stability in the physiological environment, and low toxicity. Upon ultraviolet (UV) exposure, it generates ROS that exerts potent bactericidal properties, thus exhibiting antimicrobial activity.
Quantum Dots (QDs) [31,32]	They are nanoparticulate imaging probes with high quantum yields, high photostability, and fluorescent emission properties that can be tunable by size can be targeted to specific pathological areas and is made water-soluble. They have the potential to be a photosensitizer in themselves.

Nanoparticles	Description
Fullerenes [33]	Fullerenes are the third stable isotope of (C60), used as nanoparticles in various drug delivery systems. It has photodynamic activity and is used as a photosensitizer in itself. It absorbs UV light strongly, whereas moderately absorbs visible light. Hence it is used as a photosensitizer. Because of the structure, fullerene molecules have a high triplet yield, extended triplet-excited state, and generate ROS after photoactivation. This indicates that they can act as PS.
Anionic surfactant dioctyl sodium sulfosuccinate (aerosol OT, AOT) AOT-Alginate nanoparticles [34].	AOT-alginate nanoparticles are non-toxic and have been reported to improve the ROS yield of photosensitizers.

Table 2. *In-vitro* and in-vivo studies on nanoparticle-based PDT in treating periodontitis

Author	Study Design	Context	Nanoparticle used	Results
Laura Marise de Freitas et al. [35]	*In vivo*	MB-NP-mediated PDT exhibited a 25% greater killing effect compared with free MB. It exhibits a superior photodynamic effect on human dental plaque bacteria. Methylene blue lacks the photochemical properties initially, and when encapsulated in PLGA it regains its phototoxicity when released by PLGA.	Methylene blue-loaded PLGA nanoparticles (MB-NP)	MB-loaded nanoparticles have been reported to be efficacious when compared to free MB in the improvement of clinical parameters and in reducing the bacterial count in treating periodontitis as an adjunct to SRP.
Vanja Klepac-Ceraj et al. [36]	*In vitro*	Photosensitizer shows time-dependent release, when encapsulated by nanoparticles, and shows phototoxicity resulting in photodynamic nano-agent.	Cationic methylene blue PLGA nanoparticles	Cationic MB-loaded nanoparticles were shown to be more efficacious when compared to anionic and free MB.
Enyu Shi et al. [37]	*In vitro*	Some cationic polymers have a high bacterial cell penetration activity, which is manifested primarily by adsorption onto negatively charged bacterial surfaces and even interaction with gram-negative bacteria's inner membranes. Polycationic molecular brushes are a new variant of branched cationic polymer defined as dense layers of cationic polymer chains grafted onto a molecule.	Self-assembled nanoparticles containing Indocyanine green (ICG) and polycationic brush (sPDMA@ICG NPS).	The efficacy of ICG delivery into the bacterial cells is increased by sPDMA@ICG NPs, thus exhibiting synergistic PTT and PDT performance. Also, the photothermal conversion efficiency is high and stronger compared to free ICG.

Author	Study Design	Context	Nanoparticle used	Results
Marina Usacheva et al. [34]	*In vitro*	Anionic surfactant dioctyl sodium sulfosuccinate (aerosol OT, AOT) and a naturally occurring polysaccharide sodium alginate, significantly improve the retention of water-soluble molecules in cells and the cellular accumulation, resulting in boosted therapeutic efficacy of PS.	AOT-alginate nanoparticles encapsulating Toluidine blue (TB)	The dye's stability is increased by encapsulating it in alginate nanoparticles, which could help it stay in bacterial biofilms longer.
Nagahara et al. [38]	*In vitro*	Indocyanine green, encapsulated nanoparticles penetrate the bacterial cell wall and can improve the effect of ICG significantly.	Chitosan encapsulated ICG nanoparticles (ICG-Nano/c).	ICG-loaded chitosan nanoparticles are more efficacious in disrupting the biofilm microorganisms than free ICG.
M. Li et al. [39]	*In vitro*	Investigated the inhibitory effects of UCNPs TiO2 on periodontitis-related pathogens	Core-shell nanostructure of up-conversion nanoparticles and TiO2 (UCNPs@TiO2)	UCNPs@TiO2 were able to achieve a greater reduction of organisms in the biofilm compared to the control.
Ribeiro, A. P. D [40]	*In vitro*	Cationic and Anionic Nanoemulsion ClAlPc has been studied compared to free ClAlPc.	ClAlPc encapsulated in liposome nanoemulsions	The effect of ClAlPc encapsulated in nanoemulsion was assessed on MRSA and MSSA biofilm cultures and found that cationic NE-ClAlPc was able to kill resistant strains of S.areus photo-dynamically.
De Moraes [41]	*In vivo*	Evaluation of VEGF levels in normal gingival tissues after PDT application mediated by ClAlPc loaded in a lipid nanoemulsion.	Lipid nanoemulsion containing ClAlPc	This study reported that there was an increase in VEGF levels in gingival tissue post PDT thus promoting bone regeneration through osteoblastic activity.

ICG-Nano/c - ClAlPc - Chloro-aluminium phthalocyanine VEGF – Vascular Endothelial Growth factor

PDT is shown to be effective against oral biofilms, in treating periodontitis, and peri-implantitis as an adjunct to SRP. Nanoparticles-based antimicrobial PDT with recent attention has been conducted in vitro and in vivo for treating periodontitis and peri-implantitis. Studies have shown that nanoparticles-based PDT has a better impact in eliminating periodontal pathogens in treating periodontitis than photosensitizer alone. Table 2 shows the list of studies where various nanoparticles with PS have been used as an adjunct in the treatment of periodontitis.

7. CONCLUSION AND FUTURE PERSPECTIVE

Antimicrobial photodynamic therapy is a non-invasive approach used as an adjunct to SRP in the treatment of periodontitis. However, some challenges need to be addressed. The nanotechnology revolution is known to have a significant impact on PDT and is expected to continue to have an impact on the field. This novel approach is proving to be efficacious over the conventional PDT, in terms of better availability, increased depth of penetration, solubility, stability, and increased uptake of the photosensitizer by the microorganisms in biofilm. Various biodegradable polymer-based nanoparticles (PLGA, Chitosan), when bound covalently to the PS, have been shown to improve the efficacy of PS by increasing its solubility and stability and thus showing the capability of inactivating the microorganisms photodynamically, especially against the gram-negative microorganisms. Also, studies have suggested that cationic nanoparticle drug delivery has better efficacy than the anionic counterparts. Antimicrobial photodynamic therapy effectively eliminates the infectious microorganisms without much harm to the adjacent tissue cells and eliminates multi-drug resistance pumps, thus reducing the use of antibiotics and not resulting in antibiotic resistance. However, there is not enough evidence, that nanoparticles-based PDT is being employed to treat periodontitis in-vivo, and it is a very interesting field to be explored. Hence this field can fetch many opportunities for employing nanoparticles in the field of PDT in treating periodontitis. The combination of nanoparticles and drug delivery systems in photodynamic therapy can be a future trend in the treatment of periodontitis. Also, one should keep in mind the important issue is to interpret the nanotoxicity of the nanoparticles, where there is no sufficient evidence.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist

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