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REVIEW

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The potential of plant-based nanoparticles (PBNPs) for managing dental and orofacial infections within the antimicrobial resistance (AMR) crisis

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ABSTRACT

The emergence of antimicrobial resistance (AMR) has significantly compromised the management of dental and orofacial infections, including periodontitis, peri-implantitis, dental caries, and oral candidiasis. The overuse of antibiotics in dental practice has contributed to the rise of multidrug-resistant pathogens, necessitating alternative antimicrobial strategies. Plant-derived nanoparticles, synthesized using medicinal plant extracts rich in bioactive compounds such as flavonoids, terpenoids, and phenolic acids, have demonstrated promising antimicrobial activity and biocompatibility. Green synthesis methods allow the fabrication of metal nanoparticles without hazardous reagents, improving their safety and ecological profile. These nanoparticles exert antimicrobial effects through multiple mechanisms, including disruption of microbial biofilms, induction of reactive oxygen species (ROS), interference with DNA replication, and compromise of microbial membrane integrity. Their broad-spectrum activity has been validated in preclinical studies targeting oral pathogens such as *Streptococcus mutans*, *Porphyromonas gingivalis*, and *Candida albicans*. Applications in dentistry include their incorporation into periodontal gels, implant coatings, and anticariogenic agents. In vitro studies on oral cell lines and limited in vivo models report minimal cytotoxic effects, supporting their potential for clinical use. However, the lack of standardized synthesis protocols, formulation stability data, and long-term toxicity assessments pose barriers to translation. Regulatory pathways for herbal nanotherapeutics remain underdeveloped, and well-designed randomized clinical trials are required to evaluate safety, efficacy, and pharmacokinetic behavior in humans. Future efforts should focus on optimizing nanoparticle formulation for dental applications, conducting comparative studies with existing antimicrobials, and developing delivery systems tailored to intraoral use. Plant-based nanoparticles represent a potential adjunct or alternative to conventional antimicrobial agents in dental care, offering a strategy to manage infections without exacerbating resistance. Their successful clinical integration will depend on addressing current limitations through collaborative translational research and regulatory support.

KEYWORDS

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Introduction

Antimicrobial resistance (AMR) represents a significant threat to global health, undermining the efficacy of antimicrobial agents in treating infections across medical and dental fields. Within dentistry, the rise of AMR has compromised the management of common orofacial infections such as periodontitis, dental caries, peri-implantitis, and oral candidiasis. These conditions, often polymicrobial in nature, require antimicrobial therapy for resolution. However, increasing resistance among oral pathogens has made many first-line antibiotics ineffective, thus developing the exploration of alternative antimicrobial strategies [1].

Historically, antibiotics have played a central role in dentistry; used for both prophylaxis and treatment of oral and systemic infections. Since the development of penicillin, dental practitioners have relied on empirical antibiotic prescriptions, particularly in acute dental pain, swelling, and surgical interventions. Over the past two decades, the routine and sometimes unwanted prescription of broad-spectrum antibiotics has led to the emergence of resistant strains among oral microbiota. This misuse, coupled with limited awareness of resistance development in dental microbes, has significantly contributed to the global AMR crisis [2,3].

Dental practitioners account for nearly 10% of the total outpatient antibiotic prescriptions globally, with considerable geographical variation. Inappropriate prescribing is widespread, often driven by unexperienced diagnostic treatments, patient demand, or preventive assumptions. Resistant oral pathogens such as *Streptococcus mutans*, *Enterococcus faecalis*, and *Porphyromonas gingivalis* are increasingly identified in clinical failures of endodontic and periodontal therapies. In addition, fungal pathogens like *Candida albicans* show decreasing sensitivity to conventional antifungal agents in cases of oral candidiasis [4].

In the United States, approximately 14% of antibiotic prescriptions issued by general dentists are considered inappropriate. In European settings such as Croatia, audits between 2015 and 2019 revealed that less than 50% of

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prescriptions followed recommended medications. A surveillance study in Germany analyzing 300 isolates from dental infections reported high resistance rates to clindamycin and erythromycin among Streptococcus and Staphylococcus species. Globally, bacterial AMR contributed to 4.95 million deaths in 2019, with 1.27 million directly attributable to resistant infections. If unaddressed, projections estimate up to 10 million AMR-related deaths annually by 2050 [5].

The ongoing AMR crisis is accelerated by several limitations within current dental antimicrobial strategies. These include over-dependence on empirical therapy, lack of rapid diagnostic tools, inconsistent adherence to prescribing guidelines, and insufficient development of new antimicrobial agents. Additionally, standard antibiotics fail to disrupt biofilms effectively, which are common in oral infections. With limited new drugs development technology and increasing resistance to antimicrobial agents, dental practitioners face limited therapeutic options [5,6].

Given the urgent need for sustainable and effective alternatives, this review aims to explore the potential of PBNPs as antimicrobial agents in dentistry. The objective is to evaluate the synthesis methods, mechanisms of action, application in dental conditions, biocompatibility, and translational challenges associated with PBNPs. This review emphasizes their potential to reduce antibiotic dependency in dental care and contribute to AMR mitigation efforts [7].

The AMR Crisis in Dental Health

Antimicrobial resistance presents a challenge in dental and oral healthcare, particularly in the management of persistent and recurrent infections such as periodontitis, peri-implantitis, endodontic infections, and oral candidiasis. These conditions are often polymicrobial, characterized by complex biofilms that reduce antibiotic penetration and allow microbial communities to survive even after conventional therapy [8].

Recent investigations in oral microbiology have demonstrated that biofilm-associated bacteria exhibit up to 1000-fold greater resistance to antibiotics than their planktonic counterparts. In the context of endodontic infections, *Enterococcus faecalis* is frequently isolated from failed treatments and shows resistance to ampicillin and clindamycin in several regional studies. In a cohort analysis from Germany, *Staphylococcus aureus* and *Streptococcus anginosus* showed increased resistance to erythromycin and tetracycline, complicating the management of acute odontogenic abscesses [9].

In India, isolates from periodontal pockets have shown high resistance rates to metronidazole and doxycycline drugs frequently prescribed in empirical periodontal therapy. Similarly, oral isolates of *Candida albicans* in diabetic and immunocompromised patients have demonstrated reduced susceptibility to fluconazole and itraconazole in Southeast Asian populations, posing additional therapeutic challenges [10].

These developments underscore a growing clinical burden like prolonged treatment durations, increased risk of systemic distribution, delayed surgical recovery, and unwanted treatment costs. Furthermore, the limited availability of rapid and precise antimicrobial susceptibility testing in routine dental practice results in empirical prescribing remaining as the practice, increasing the risk of antimicrobial resistance [11]. Given these limitations, research in adjunctive and alternative antimicrobial therapies has grown. One such approach is the integration of nanotechnology-based solutions, particularly plant-derived nanoparticles (PBNPs). Unlike traditional antimicrobials, PBNPs have demonstrated unique efficacy against biofilm-forming oral pathogens, including multidrug-resistant strains. In periodontal models, biosynthesized silver nanoparticles from *Azadirachta indica* and zinc oxide nanoparticles from Curcuma longa have shown significant inhibition of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* at sub-MIC levels, with minimal toxicity to gingival fibroblasts [12].

While the evidence remains largely preclinical, these findings suggest that PBNPs may offer an effective adjunct to standard care. Their capacity to disrupt microbial communication (quorum sensing), generate reactive oxygen species, and prevent extracellular matrix formation positions them as strategic tools in combating biofilm-dominated dental infections. However, for these agents to be effectively integrated into dental protocols, more targeted research including comparative trials with existing antimicrobials and evaluations of clinical endpoints is required [13].

Synthesis of Plant-Based Nanoparticles

One of the defining features of PBNPs is their synthesis from naturally occurring compounds found in medicinal plants. These nanoparticles can be engineered to have specific antimicrobial properties by using various synthesis methods, many of which incorporate phytochemicals with innate antimicrobial capabilities [Figure 1] [14].

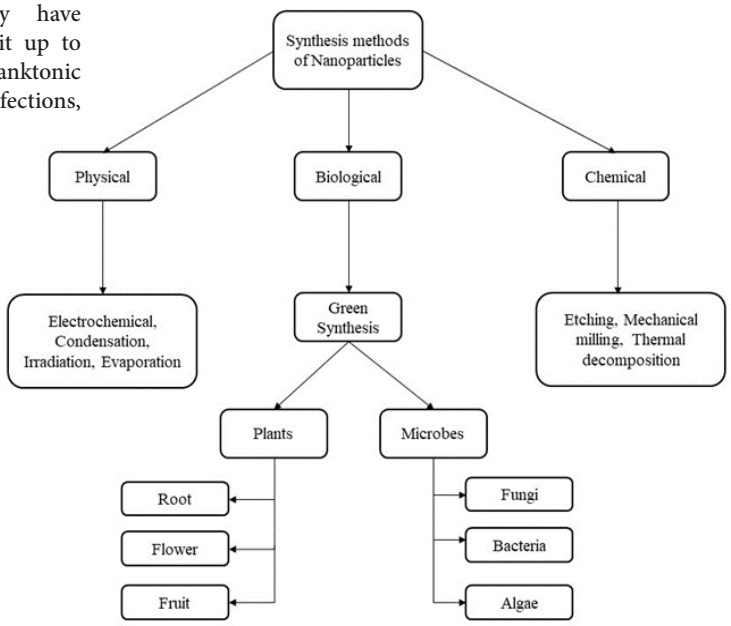

Figure 1. Different synthesis methods of nanoparticles.

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PBNPs are primarily synthesized using medicinal plant extracts that are rich in bioactive compounds like flavonoids, alkaloids, phenolics, and terpenoids, which act as natural reducing and stabilizing agents. Below are the main methods used in synthesizing PBNPs:

Green synthesis with aqueous extracts

In green synthesis, plant extracts are combined with metal ions to reduce and stabilize nanoparticles. For example, gold, silver, and zinc oxide nanoparticles can be synthesized by mixing a plant extract (e.g., neem or green tea) with a metal salt solution. Phytochemicals in the extract reduce the metal ions, forming nanoparticles in an eco-friendly process that avoids harsh chemicals [Table 1] [12].

Microwave-assisted synthesis

Microwave-assisted synthesis is a rapid method where plant extracts and metal ions are exposed to microwave irradiation, accelerating nanoparticle formation. This technique reduces reaction time and produces nanoparticles with controlled sizes and uniform morphology, which is critical for their efficacy in antimicrobial applications [13].

Ultrasound-assisted synthesis

In ultrasound-assisted synthesis, ultrasonic waves break down plant materials, enhancing the release of phytochemicals that aid in reducing metal ions to nanoparticles. This technique can yield smaller and more homogeneously distributed nanoparticles, which are more effective in infiltrating bacterial biofilms [13].

Biosynthesis with plant-derived polymers

Plant-derived polymers like pectin, cellulose, or alginate can serve as stabilizing agents in PBNP synthesis. These biopolymers not only stabilize the nanoparticles but also confer additional biocompatibility, making them safer for therapeutic applications in dental care [14].

These methods provide a foundation for creating PBNPs with unique properties that can target microbial pathogens in dental environments.

Mechanisms of Action of PBNPs

The antimicrobial action of PBNPs is multifaceted, leveraging both the intrinsic antimicrobial properties of the plant extracts and the physical properties of nanoparticles. Some primary mechanisms by which PBNPs exert their antimicrobial effects are as follows:

1. Disruption of biofilm formation

Biofilms present a formidable barrier against conventional antibiotics in dental infections. PBNPs, particularly those synthesized from plants like *Azadirachta indica* (neem) or *Ocimum sanctum* (holy basil), are effective in disrupting biofilm architecture. The nanoparticles penetrate the extracellular matrix, destabilizing biofilm structure and rendering bacteria more susceptible to treatment [15].

2. Production of reactive oxygen species (ROS)

PBNPs, especially those containing metals like silver or copper, can induce oxidative stress in microbial cells by generating reactive oxygen species (ROS). This oxidative damage targets bacterial cell walls, proteins, and DNA, leading to cell death. ROS production is especially effective against anaerobic bacteria implicated in periodontitis [16].

3. Damage to microbial DNA

Some PBNPs directly interact with microbial DNA, causing breaks in the DNA strands or interfering with replication. For example, zinc oxide nanoparticles synthesized from turmeric extracts have demonstrated DNA-damaging effects on *Streptococcus mutans*, a primary pathogen in dental caries [17].

4. Disruption of cell membrane integrity

The phytochemicals in PBNPs interact with microbial cell membranes, altering membrane permeability. This disruption leads to leakage of cellular contents and, ultimately, cell death. Silver PBNPs, for instance, are known to interact with bacterial cell membranes, causing structural damage [18].

Applications of PBNPs in Dental Care

The unique properties of PBNPs make them versatile agents for treating a range of dental infections. Their efficacy against

Table 1. Plant, method, metal, and size range in comparative synthesis methods of PBNPs.

Plant Source	Synthesis Method	Metal Used	Size Range (nm)
Azadirachta indica (Neem)	Aqueous leaf extract	Ag	10–50
Camellia sinensis (Green Tea)	Aqueous leaf extract	Ag	15–40
Magnolia kobus (Magnolia)	Aqueous leaf extract	Ag	15–500
Mikania micrantha (Mile-a-minute)	Aqueous leaf extract	CuO	15
Dillenia indica (Elephant Apple)	Aqueous leaf extract	CuO	15
Sansevieria trifasciata (Snake Plant)	Aqueous leaf extract	$ZnFe_2O_4$	5–20
Acacia nilotica (Gum Arabic Tree)	Aqueous leaf extract	Ag	~5.7
Epipremnum aureum (Devil's Ivy)	Aqueous leaf extract	ZnO	29
Citrullus colocynthis (Bitter Apple)	Aqueous leaf extract	Cu	~17
Aegle marmelos (Bael)	Aqueous leaf extract	FeO	~18.8

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bacterial and fungal pathogens has been extensively studied, indicating their potential in various therapeutic applications in dentistry.

1. Treatment of periodontitis

Periodontitis, a chronic inflammatory condition affecting the periodontal ligaments and bone, is often exacerbated by biofilm-forming bacteria. PBNPs derived from neem and green tea have shown significant promise in reducing biofilm formation in periodontal pockets. These nanoparticles not only inhibit bacterial growth but also reduce inflammation in gingival tissues, promoting periodontal healing [19].

2. Management of peri-implantitis

Peri-implantitis, an infection surrounding dental implants, poses a significant challenge due to its resistance to conventional therapies. PBNPs with antimicrobial and anti-inflammatory properties can be applied as coatings on implants to prevent biofilm formation. Silver and zinc oxide PBNPs derived from medicinal plants like turmeric have demonstrated substantial antimicrobial action against peri-implant pathogens [18,19].

3. Prevention and treatment of dental caries

Dental caries, primarily caused by *Streptococcus mutans*, can be effectively managed using PBNPs synthesized from plants such as clove or cinnamon, known for their antimicrobial properties. These nanoparticles not only inhibit bacterial growth but also prevent the formation of acidogenic biofilms, reducing the incidence of dental caries [20].

4. Treatment of oral candidiasis

Oral candidiasis, often caused by *Candida albicans*, is a common fungal infection in immunocompromised patients. PBNPs synthesized from plants like tea tree oil or garlic have shown antifungal properties, disrupting the fungal cell membrane and inhibiting biofilm formation. These nanoparticles offer an alternative to antifungal medications, especially in cases where C. albicans has developed resistance [21].

Limitations and Future Potential

PBNPs have gained significant attention as emerging antimicrobial agents in dental medicine. Derived from phytochemicals such as flavonoids, phenolics, and terpenoids, these nanoparticles are synthesized through green chemistry approaches that avoid toxic reagents. This synthesis strategy enhances their biological compatibility and positions them as safer alternatives to chemically derived nanoparticles [22].

Several in vitro studies support the biocompatibility of PBNPs. For instance, silver nanoparticles synthesized using Azadirachta indica have demonstrated minimal cytotoxicity on human gingival fibroblasts and keratinocytes, while also exhibiting broad-spectrum antimicrobial properties. Similarly, zinc oxide nanoparticles derived from *Camellia sinensis* and *Syzygium aromaticum* have shown effective inhibition of pathogenic oral biofilms with low toxicity to host tissues. These preclinical findings are reinforced by animal studies reporting minimal inflammatory response and favorable tissue integration. Mechanistically, PBNPs are known to induce limited oxidative stress compared to chemically synthesized analogs, and may modulate cytokine expression to reduce inflammatory signaling.

Despite encouraging data, significant limitations hinder the clinical integration of PBNPs. A primary concern is the variability in plant extract composition, which is influenced by seasonal, geographical, and extraction-related factors. This inconsistency leads to heterogeneity in nanoparticle size, morphology, and surface charge all critical parameters affecting biological behavior. Moreover, the absence of standardized synthesis and characterization protocols complicates comparative evaluation across studies and impairs reproducibility [23].

The current body of clinical evidence is sparse. While in vitro and in vivo animal studies form the foundation of our understanding, well-designed human trials assessing efficacy, toxicity thresholds, and therapeutic endpoints are lacking. As of 2024, few registered clinical trials have investigated the use of biosynthesized nanoparticles in dental materials, and none have completed large-scale efficacy assessments. Regulatory pathways remain underdeveloped for herbal nanotherapeutics, with no harmonized global framework addressing critical elements such as permissible exposure limits, long-term toxicological profiling, or manufacturing controls. Without alignment with ISO standards or clear FDA/EMA guidance, widespread adoption of PBNPs in dentistry remains limited [24].

Moreover, the potential applications of PBNPs in oral healthcare are extensive. Silver and zinc-based PBNPs have been incorporated into dental adhesives, composites, and sealants to prevent secondary caries and inhibit microbial colonization. In periodontal therapy, nanoparticle-loaded gels derived from *Curcuma longa* and *Ocimum sanctum* have demonstrated antimicrobial and anti-inflammatory effects against *P. gingivalis* and *A. actinomycetemcomitans*. PBNPs also show promise in endodontics as adjunctive irrigants or intracanal medicaments, improving disinfection outcomes in resistant root canal infections. Additionally, in implantology, PBNP coatings on titanium surfaces have enhanced osseointegration and reduced peri-implant biofilm formation in preclinical models [25] [Table 2].

In preventive care, certain PBNPs have demonstrated remineralization potential when incorporated into toothpaste or varnishes, suggesting future applications in early caries management. It is important to note that while calcium phosphate-based particles have shown such effects, only those synthesized via documented plant-based methods qualify as PBNPs in this context. To realize the full potential of PBNPs, collaborative research efforts are essential across nanotechnology, pharmacognosy, and clinical dentistry. Future investigations should prioritize formulation stability, pharmacokinetics, delivery mechanisms suited for the oral cavity, and the development of scalable, GMP-compliant production systems. Addressing these translational gaps will be critical in positioning PBNPs as viable, sustainable tools in modern dental therapeutics.

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Table 2. Plant, method, metal, and size range in comparative synthesis methods of PBNPs.

PBNP Type	Plant Source	Metal	Test Model	Observed Toxicity/Biocompatibility	Future Applications
Silver nanoparticles (AgNPs)	*Salacia chinensis*	Ag	Human periodontal fibroblasts, erythrocytes, MG-63 osteoblasts	High biocompatibility; enhanced osteoinductive potential; no significant cytotoxicity	Coatings for implants, periodontal regeneration scaffolds
Silver nanoparticles (AgNPs)	*Mangifera indica*	Ag	GIC composite tested against *S. aureus*, *E. coli*	Improved mechanical strength of GIC; protective antibacterial effect	Dental restorative materials, antimicrobial sealants
Gold nanoparticles (AuNPs)	*Anogeissus latifolia*	Au	Human fibroblasts, erythrocytes, MG-63 cells	Enhanced cell viability; high biocompatibility	Drug delivery in periodontics, wound healing gels
Zinc oxide nanoparticles (ZnONPs)	*Anogeissus latifolia*	ZnO	In vitro osteogenic activity assays	Osteogenic potential; no notable cytotoxicity	Bone graft enhancers, endodontic irritants
Silver nanoparticles (AgNPs)	White pepper oleoresin	Ag	Antimicrobial assays	Effective antimicrobial action; specific cytotoxicity not reported	Herbal mouth rinses, localized drug carriers
Silver nanoparticles (AgNPs)	*Olea europaea*	Ag	Antimicrobial assays	Significant antimicrobial efficacy; limited biocompatibility data	Periodontal dressing agents, subgingival irrigation
Zinc oxide nanoparticles (ZnONPs)	Clove and cinnamon extracts	ZnO	Antimicrobial assays	Strong antimicrobial properties; cytotoxicity not detailed	Toothpaste additives, enamel remineralization agents

Conclusions

The rise of antimicrobial resistance in dental health calls for innovative solutions, and PBNPs offer a compelling alternative to traditional antimicrobial agents. Synthesized from medicinal plant extracts, PBNPs possess unique mechanisms that disrupt biofilms, produce oxidative stress, damage microbial DNA, and compromise cell membranes. These properties make them effective against a range of dental infections, including periodontitis, peri-implantitis, dental caries, and oral candidiasis. Moreover, PBNPs demonstrate promising safety and biocompatibility profiles, positioning them as a viable option for future antimicrobial therapies in dentistry. The continued research and development of PBNPs could pave the way for a new era in dental infection management, where plant-based, eco-friendly, and effective antimicrobial agents take center stage in combating the global AMR crisis in dentistry.

Disclosure statement

No potential conflict of interest was reported by the author.

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