

Phytochemical-Based Nanotherapeutics in Oral Healthcare: Current Evidence, Challenges and Future Perspectives

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Abstract

Phytochemicals have attracted vast interest in oral healthcare because of their antimicrobial, antibiofilm, anti-inflammatory and antioxidant properties. Compounds such as curcumin, resveratrol, quercetin, epigallocatechin-3-gallate, berberine and propolis-derived constituents have been investigated for their high potential in management of several dental problems. However, many phytochemicals have poor aqueous solubility, limited stability and low bioavailability, which restrict their therapeutic application. Nanotechnology offers a means of improving these limitations through nanoparticles, liposomes, nano emulsions, nanostructured lipid carriers, nanogels and mucoadhesive systems which may improve stability, local retention, controlled release and delivery to diseased tissues. This review summarizes important phytochemicals, relevant nanocarrier systems, current oral-health applications, clinical evidence, major limitations and future research priorities.

Keywords: Microbiome; Nanotechnology; Nanoparticles; Oral Healthcare; Phytochemicals

Introduction

The oral cavity is a complex microbial and biological environment in which biofilms, host response and tissue factors contribute to oral health issues such as dental caries, periodontitis and endodontic infections. Conventional treatment remains essential, but the increasing antimicrobial resistance and biofilm persistence has made the researchers look for alternative and adjunctive approaches.

Plant-derived phytochemicals possess several biological properties such as antimicrobial, antibiofilm, antioxidant and anti-inflammatory activity. Curcumin, resveratrol, quercetin, Epigallocatechin gallate (EGCG) and propolis are among such phytochemicals. However, biological activity of these does not always prove successful clinically because these phytochemicals have poor solubility, instability and limited bioavailability [1].

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Nanotechnology provides an opportunity to address some of these pharmaceutical limitations. Nano formulations have the potential to improve dispersion, protect active compounds from degradation, provide controlled release and facilitate local delivery. In dentistry, nanoparticles have been evaluated in caries prevention, periodontal therapy, endodontics, oral mucosal drug delivery and oral cancer management. The combination of phytochemicals and nanotechnology therefore represents an important interdisciplinary area connecting pharmaceutical formulation with clinical dentistry [2].

Why phytochemical-based nanotherapeutics?

The therapeutic potential of phytochemicals may be attributed to their following abilities:

- 1. **Antimicrobial and antibiofilm activity:** Phytochemicals interfere with bacterial growth, adhesion, biofilm formation, virulence factors and microbial metabolism. For example, Epigallocatechin-3-gallate (EGCG), is effective against *Streptococcus mutans*, including inhibition of acid production and extracellular polysaccharide-related mechanisms [3].
- 2. **Anti-inflammatory and antioxidant activity:** Curcumin, resveratrol and quercetin possess the ability to modulate inflammatory and oxidative pathways which lead to periodontal tissue destruction [4].

Nanocarriers relevant to oral healthcare

Different nanocarriers may be selected according to the phytochemical and intended clinical application:

- 1. **Polymeric nanoparticles:** Polymeric nanoparticles such as Chitosan and PLGA can provide controlled release and protection of unstable compounds [5].
- 2. **Liposomes:** Liposomes can incorporate hydrophilic as well as lipophilic compounds and may facilitate localized delivery [6].
- 3. **Nano emulsions:** Nano emulsions can improve the dispersion of poorly water-soluble phytochemicals and may be suitable for topical oral formulations [7].
- 4. **Solid lipid nanoparticles and nanostructured lipid carriers:** These can improve the solubility, stability, encapsulation and controlled release of lipophilic phytochemicals [8].
- 5. **Mucoadhesive systems:** These can prolong contact with oral mucosa and may be useful when prolonged local exposure is required [9].

Major phytochemicals of interest

Table 1 summarizes the major phytochemicals of interest in oral healthcare, highlighting their principal biological properties, potential oral applications, and the rationale for incorporating them into nanocarrier-based delivery systems.

Phytochemical	Major properties	Potential oral application	Nano formulation rationale
Curcumin	Antimicrobial, anti-inflammatory, antioxidant	Periodontitis, caries, oral mucosal disorders	Improve solubility and stability
Resveratrol	Antioxidant, anti-inflammatory	Periodontitis, inflammatory disorders	Improve bioavailability and local delivery
Quercetin	Antioxidant, anti-inflammatory, antibiofilm	Periodontitis, oral infections	Controlled/local release

EGCG	Antibacterial, antioxidant, antibiofilm	Caries, periodontal and endodontic infections	Improve stability and sustained action
Propolis	Antimicrobial, anti-inflammatory, antioxidant	Periodontitis, caries, oral mucosal conditions	Standardized controlled delivery
Berberine	Antimicrobial, anti-inflammatory, antioxidant	Caries, periodontal and endodontic diseases	Improve bioavailability
Other flavonoids	Antimicrobial and antioxidant	Biofilm and endodontic applications	Localized delivery

Table 1: Important phytochemicals and potential oral applications.

Curcumin: Curcumin possesses antimicrobial, antioxidant and anti-inflammatory properties. Systematic reviews have reported promising anticaries activity, including effects on *S. mutans* growth, acid production and biofilm-related mechanisms. Curcumin has poor aqueous solubility and limited bioavailability, so, nano-formulations such as polymeric nanoparticles, liposomes, micelles and lipid-based systems can help improve its efficacy [10].

Resveratrol: Resveratrol, in some studies has demonstrated anti-inflammatory, antioxidant and bone-protective effects in periodontal models. Nano- and liposome-based formulations may improve its pharmacological performance, making delivery technology an important area for future investigation [11].

Quercetin: Quercetin has antimicrobial, antioxidant and anti-inflammatory properties and has been investigated in relation to periodontal disease and other oral conditions. Drug-delivery approaches are of particular interest because of its limited bioavailability [12].

EGCG: EGCG, the major catechin in green tea, has demonstrated activity against oral microorganisms and has been investigated in caries, periodontal and endodontic applications [13].

Propolis: Use of propolis been investigated in mouthwashes, toothpastes, gels and local periodontal delivery systems and has been found to be effective [14].

Potential oral healthcare applications

- Dental caries:** Phytochemical nanotherapeutics when used with Curcumin and EGCG have shown to interfere with bacterial adhesion, biofilm development and acid production, thereby helping in prevention of dental caries [15].
- Periodontal disease:** Nanoparticle-based periodontal delivery has shown promising antimicrobial and inflammatory effects as high local concentrations of antibacterial agents may be achieved without requiring high systemic doses [16].
- Endodontic infections:** Nanoparticles such as Flavonoids have been investigated as irrigant adjuncts and intracanal medicaments [17].
- Oral mucosal disorders:** Mucoadhesive nanoparticles can increase residence time at the mucosal surface and may improve localized delivery. This approach has applications in oral mucositis and other localized mucosal conditions [18].
- Oral cancer:** Phytochemical nanotherapeutics are also being explored for oral squamous cell carcinoma. Curcumin and other phytochemicals have demonstrated promising preclinical activity, while nano formulations may address poor solubility and bioavailability [19].

Current strength and limitations of evidence

The available evidence for phytochemical-based nanotherapeutics in oral healthcare is encouraging [20]. However, it should be taken into consideration that most studies have been conducted using *in-vitro* and preclinical models. Also the differences in formulations, concentrations, study models and outcome measures also make direct comparison difficult.

Table 2 summarizes the current level of evidence for selected phytochemicals, ranging from laboratory and preclinical investigations to available clinical studies. It also provides an overall assessment of their present therapeutic potential and highlights the need for further clinical validation.

Phytochemical	Laboratory evidence	Animal/preclinical evidence	Clinical evidence	Overall assessment
Curcumin	Strong	Moderate	Limited/mixed	Promising but needs better clinical validation
Resveratrol	Strong	Moderate	Limited	Potential adjunct
Quercetin	Moderate	Emerging	Very limited	Early-stage
EGCG	Moderate-strong	Emerging	Limited	Promising antibiofilm candidate
Propolis	Strong	Moderate	Emerging	One of the more clinically developed natural products
Berberine	Emerging	Emerging	Very limited	Requires further validation

Table 2: Current level of evidence for selected phytochemical nanotherapeutics.

Challenges and research gaps

Despite the promising therapeutic potential of phytochemical-based nanotherapeutics, several challenges need to be addressed before their wider clinical application. These include:

- Standardization of phytochemicals:** The composition and biological activity of plant-derived products may vary with plant species, geographical origin, cultivation conditions, extraction methods and processing. This variability can affect reproducibility and comparison between studies.
- Standardization and characterization of nano formulations:** Variations in nanoparticle preparation can significantly influence their biological performance.
- Development of clinically relevant oral models:** Many studies rely on planktonic microorganisms or single-species biofilms, which do not fully represent the complex oral environment. Future investigations should incorporate multispecies biofilms, dentin models, saliva-containing systems and relevant oral tissue models to provide more clinically meaningful evidence.
- Consideration of the oral microbiome:** The objective of antimicrobial therapy should not be limited to eliminating individual pathogens. Broad antimicrobial activity may also affect beneficial microorganisms within the oral microbiome. Future research should therefore evaluate the effects of phytochemical nanotherapeutics on microbial diversity and overall microbiome balance, in addition to their activity against specific pathogens.
- Clinical translation:** Majority of the studies are lab based and clinical studies are relatively limited. Future research should progress systematically from laboratory models to well-designed clinical trials, with special attention to efficacy, biocompatibility and long-term safety.

Future Perspectives

The future of phytochemical-based nanotherapeutics lies in development of targeted, controlled and responsive delivery systems. Development of pH-responsive nanoparticles may provide improved local retention and controlled release of phytochemicals at specific sites of oral disease. The combination of different phytochemicals or phytochemicals with antimicrobial agents can also be explored for enhanced therapeutic effects.

Future studies must also utilize multispecies biofilm models and microbiome-based evaluation to better simulate the oral environment. Use of nanostructured lipid carriers must also be explored as they can integrate pharmaceutical formulation expertise with the biological activity of plant-derived compounds, providing a potential platform for the development of novel oral therapeutics.

Conclusion

Phytochemical-based nanotherapeutics represent a promising intersection between natural-product pharmacology, pharmaceutical technology and oral healthcare. Curcumin, resveratrol, quercetin, EGCG and propolis have demonstrated encouraging antimicrobial, antibiofilm, antioxidant and anti-inflammatory properties. Nanotechnology may overcome important limitations associated with these compounds by improving stability, solubility, local retention and controlled release.

The greatest opportunity now lies in moving from promising laboratory observations to standardized, clinically relevant formulations. Interdisciplinary collaboration between dental and pharmaceutical researchers can play an important role in this transition.

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