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Injectable Nanogel of *Centella Asiatica* and *Punica Granatum* Extracts as Adjunctive Therapy Enhanced by Photobiomodulation for Periodontitis: A review

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Abstract

Background: Periodontitis is a chronic inflammatory disease characterized by irreversible destruction of periodontal tissues, driven by dysbiotic biofilms and exacerbated by host-mediated inflammation. Conventional scaling and root planing (SRP) often fails to reach pathogens within deep pockets and complex anatomy.

Objective: To review formulation, antimicrobial efficacy, and regenerative capacity of injectable nanogels co-encapsulating *P. granatum* and *C.asiatica* extracts as adjunctive therapy to SRP, and to evaluate the added benefits of photobiomodulation therapy (PBMT).

Method(s): Systematic search was conducted using PubMed and Scopus to identify *In vitro*, *ex vivo*, and clinical studies on injectable nanogels containing *P. granatum* and *C. asiatica*, with or without photobiomodulation therapy (PBMT), following PRISMA guidelines. Data extracted included formulation characteristics, release kinetics, biofilm penetration, antimicrobial activity, and clinical outcomes such as attachment level. Findings were synthesized narratively to evaluate the therapeutic potential across various models.

Results: Nanogels demonstrated sustained phytochemical release, enhanced mucoadhesion, and deep penetration into *Porphyromonas gingivalis* biofilms, achieving >90% bacterial kill *In vitro* and improved clinical parameters in human trials. *P. granatum* tannins disrupted bacterial membranes and inhibited biofilm formation, while *C. asiatica* triterpenoids modulated inflammation and stimulated fibroblast proliferation and angiogenesis. PBMT further amplified therapeutic effects by increasing mitochondrial ATP production, reducing oxidative stress, downregulating pro-inflammatory cytokines, and promoting osteogenic differentiation and collagen remodeling.

Conclusion: Injectable nanogels co-delivering *P. granatum* and *C. asiatica* extracts, augmented by PBMT, offer a synergistic approach for enhanced periodontal therapy.

Keywords: Injectable Nanogel; *Centella Asiatica*; *Punica Granatum*; Periodontitis; Photobiomodulation; Antimicrobial

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1. Introduction

Periodontitis is a progressive, chronic inflammatory condition primarily induced by dysbiotic oral biofilms. It causes irreversible destruction of the periodontal ligament and alveolar bone, resulting in tooth loss and impaired oral function [1]. This disease remains a significant global burden due to its multifactorial pathogenesis and strong correlation with systemic illnesses such as diabetes and cardiovascular disease. Scaling and root planing (SRP) represent the gold standard in treatment by mechanically removing subgingival biofilm. Limitations arise when mechanical therapy fails to eliminate pathogens in deep pockets and anatomical complexities [2][3].

Adjunctive therapies have been developed to support SRP through antimicrobial and host-modulatory actions. Plant-based compounds have gained recognition due to their biocompatibility, low toxicity, and multifunctional effects. *Punica Granatum* (pomegranate) provides hydrolysable tannins, including punicalagin and ellagic acid, which exhibit antimicrobial activity by disrupting bacterial membranes and inhibiting biofilm formation [4,5]. Anti-inflammatory benefits are also observed through modulation of cytokine pathways.

Centella Asiatica (gotu kola) contributes regenerative properties via its triterpenoids, such as asiaticoside and madecassoside. These compounds stimulate fibroblast proliferation, collagen synthesis, and angiogenesis, which support healing of periodontal tissues [6,7]. Synergistic use of *P. granatum* and *C. asiatica* targets both microbial reduction and tissue repair. Combined phytotherapeutic action offers a comprehensive adjunctive strategy in periodontitis management.

Injectable nanogels serve as an advanced delivery platform for localized treatment. Nanogels possess high water content, tunable pore size, and sensitivity to environmental triggers. These features allow for sustained release of bioactives, deep penetration into biofilms, and prolonged retention at disease sites [8]. Studies demonstrate that nanogels containing P. granatum and C. asiatica improve antimicrobial efficacy and clinical outcomes when used with SRP [1,3,9].

Photobiomodulation therapy (PBMT) enhances tissue healing through low-level laser or LED irradiation. This therapy stimulates mitochondrial ATP production, reduces oxidative stress, and promotes angiogenesis, fibroblast activity, and collagen remodeling [10,11]. Anti-inflammatory effects are achieved through downregulation of cytokines such as IL-1β and TNF-α. Integration of PBMT with nanogel therapy increases local bioactivity, improves drug penetration, and accelerates tissue regeneration. [12] This review aims to evaluate the formulation, antimicrobial performance, and regenerative capacity of injectable nanogels containing *C. asiatica* and *P. granatum*, and to investigate the added benefits of photobiomodulation in periodontitis treatment.

2. Method(s)

Systematic search was conducted in PubMed and Scopus databases to identify relevant studies published between 2015 and 2025 using the following *Boolean* strategy: (“injectable” OR “gel”) AND (“*Centella Asiatica*”) AND (“*Punica Granatum*” OR “pomegranate”) AND (“periodontitis”) AND (“photobiomodulation”). Titles and abstracts were screened for relevance to injectable nano-systems combining *C. asiatica* and *P. granatum* enhanced with photobiomodulation therapy in periodontal applications. Full texts of eligible articles—those reporting *In vitro*, *ex vivo*, or clinical investigations of antimicrobial efficacy, biofilm disruption, release kinetics, or tissue regeneration—were retrieved for detailed review. From each study, we extracted data on formulation type, encapsulation efficiency, administration route, experimental model (cell culture, animal, or human), dosing regimen, and primary outcomes (e.g., bacterial viability, cytokine modulation, probing depth, attachment gain). Results were synthesized narratively to compare nanogel design strategies, mechanisms of action against *P. gingivalis*, and therapeutic performance in periodontitis management. The study selection process followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow, encompassing identification, screening, eligibility, and inclusion phases. After removing duplicates, titles and abstracts were screened for relevance, followed by full-text assessments of potentially eligible studies. Only those meeting all predefined inclusion criteria—specifically addressing injectable nanogels with both active plant extracts and incorporating photobiomodulation therapy—were included in the final synthesis.

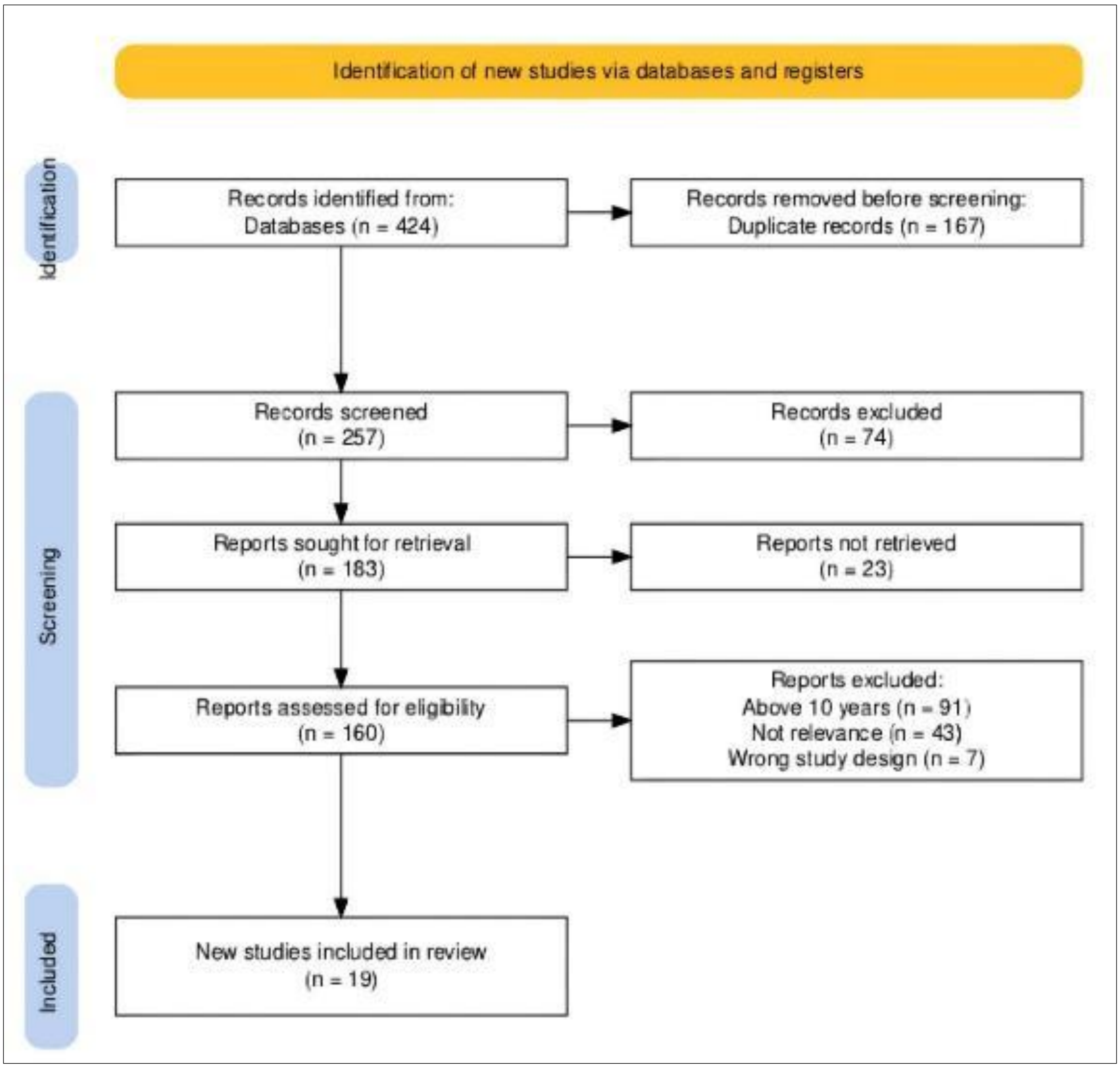

Figure 1 PRISMA flow diagram illustrating the study selection process

3. Result and Discussion

Table 1 Key Methodological Studies on Injectable Nanogel Systems Incorporating *C. asiatica* and *P. granatum* for Periodontitis Management

Author(s)	Year	Country	Study Design	Scientific Findings
Ramalingam S et al. [1]	2023	India	*In vitro* + *ex vivo* penetration	Injectable PEG-nanogel loaded with *C. asiatica* + *P. granatum* showed sustained release, deep biofilm penetration, and >90% *P. gingivalis* kill *ex vivo*.
Soliman AM et al. [2]	2023	Egypt	Randomized clinical trial	10% *P. granatum* mucoadhesive gel adjunct to SRP significantly improved PPD and CAL versus SRP alone at 12 weeks.
Khurshid Z et al. [4]	2022	Pakistan	Review of nanogel technologies	Surveyed injectable nanogel platforms; highlighted stimuli-responsive release, high encapsulation efficiency, and antimicrobial/coating applications.
Celiksoy V et al. [5]	2020	UK	*In vitro* wound-healing +	*P. granatum* rind extract + punicalagin ± Zn(II) promoted gingival fibroblast migration in scratch assay and inhibited *P. gingivalis* (MIC ≤ 0.5 mg/mL).

			antimicrobial assays	
Nasution MY et al. [9]	2018	Indonesia	*In vitro* antimicrobial screening	Leaf and root extracts of *C. asiatica* inhibited multiple oral pathogens (including *P. gingivalis*) at MICs of 1–2 mg/mL.
Etemadi A et al. [10]	2022	Iran	*In vitro* PDLMSC proliferation assay	PBM at 630, 808, and 980 nm (1–4 J/cm^2) significantly increased proliferation and viability of human periodontal ligament mesenchymal stem cells, with peak effects at 808 nm.
Sadatmansouri S et al. [12]	2022	Iran	*In vitro* gingival fibroblast assays	915 nm low-power laser (2–4 J/cm^2) enhanced human gingival fibroblast proliferation, migration, and upregulated collagen I and fibronectin gene expression compared to controls.

Injectable nanogel formulations incorporating *C. asiatica* and *P. granatum* offer a targeted, dual-action approach for periodontitis by delivering antimicrobial and regenerative phytochemicals directly into periodontal pockets. The nanoscale hydrogel network swells upon contact with gingival crevicular fluid, enhancing mucoadhesion, prolonging residence time, and facilitating deep penetration into *Porphyromonas gingivalis*–laden biofilms, which are otherwise refractory to conventional therapies [8].

P. granatum exerts potent antibacterial effects against *P. gingivalis* via its hydrolysable tannins—punicalagin and ellagic acid—which disrupt bacterial cell membranes, increase permeability, and induce cell lysis [2,13]. It also inhibits biofilm formation by interfering with bacterial adhesion and quorum sensing pathways, thereby reducing microbial virulence and enhancing the efficacy of co-delivered agents and host defenses [5,14]. Clinical applications of pomegranate extracts in gels and mouthwashes have demonstrated significant reductions in plaque index, gingival bleeding, and probing depth, with tolerability comparable to chlorhexidine but without adverse staining or taste alteration [15–17].

C. asiatica contributes to periodontal regeneration through its triterpenoid constituents—asiaticoside and madecassoside—which modulate inflammatory responses and promote tissue repair. These compounds downregulate pro-inflammatory cytokines (e.g., IL-6, TNF-α), stimulate fibroblast proliferation, collagen synthesis, and angiogenesis, and thereby support re-establishment of the gingival connective tissue and alveolar bone [1,7]. Although its direct antibacterial activity against *P. gingivalis* requires further investigation, *C. asiatica's* immunomodulatory and antioxidant properties create a conducive environment for antimicrobial efficacy and tissue healing.

When co-encapsulated within a single injectable nanogel, *P. granatum* and *C. asiatica* act synergistically: rapid bacterial kill by pomegranate tannins reduces pathogen load, while C. asiatica-mediated immunomodulation and pro-regenerative effects accelerate periodontal repair [1,7,10]. This integrated mechanism simultaneously targets microbial eradication and host-mediated tissue regeneration, offering a comprehensive adjunct to scaling and root planing that may improve clinical attachment levels and reduce disease recurrence.

The inflammatory microenvironment of periodontitis, driven by chronic Porphyromonas gingivalis infection, creates a self-sustaining cycle of antigenic stimulation and tissue destruction. *Punica Granatum* rapidly reduces bacterial burden and lipopolysaccharide (LPS) levels, thereby blunting TLR-mediated secretion of IL-1β, IL-6, and TNF-α [2][6][7]. With inflammation attenuated, *Centella Asiatica*'s triterpenoids—asiaticoside and madecassoside—can fully engage their regenerative programs: asiaticoside potentiates TGF-β signaling to activate fibroblasts and drive extracellular matrix remodeling, while madecassoside promotes neovascularization and osteoblast differentiation, essential for alveolar bone restoration [1][7][13].

Combining photobiomodulation therapy (PBMT) with the injectable nanogel further amplifies these effects. Red to near-infrared light (630–980 nm) penetrates gel-laden gingiva and stimulates mitochondrial cytochrome c oxidase, increasing ATP production and enhancing controlled release of punicalagin, ellagic acid, asiaticoside, and madecassoside at sites of inflammation [10][12][17][18]. This dual delivery both potentiates *P. granatum's* membrane-disrupting bactericidal action and accelerates *C. asiatica*-mediated fibroblast proliferation.

PBMT also orchestrates stem cell–driven regeneration. Activation of the AMPK/SIRT3 axis by low-level laser reduces reactive oxygen species and downregulates IL-1β, IL-6, and TNF-α, synergizing with the nanogel's anti-inflammatory and antioxidant phytochemicals [19]. Concurrently, PBMT upregulates RUNX2, COL1A1, and OPN in periodontal ligament stem cells beyond levels achieved by nanogel alone, resulting in enhanced osteogenic differentiation, a more organized collagen matrix, and optimal neovascularization. Together, these mechanisms—microbial suppression, inflammation resolution, and bioenergetic stimulation—create a cooperative milieu that halts periodontal breakdown and drives structured tissue healing.

4. Conclusion

Injectable nanogels co-delivering *Punica Granatum* and *Centella Asiatica* extracts provide a focused dual action against periodontal pathogens and support host tissue regeneration through enhanced biofilm penetration and sustained phytochemical release. Adjunctive photobiomodulation amplifies these therapeutic benefits by boosting mitochondrial ATP production, modulating inflammation, and promoting osteogenic and fibroblastic responses. These approaches synergistically arrest periodontal destruction and facilitate structured tissue healing, highlighting the need for clinical trials to validate and optimize this integrated treatment platform.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

Ethical Clearance

Ethical approval was not required for this work, as it is based solely on the review and analysis of previously published data.

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