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Characterization and application of in Situ curcumin/ZNP hydrogels for periodontitis treatment

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Abstract: Periodontitis, a chronic inflammatory disease impacting the tissues supporting teeth, demands innovative therapeutic strategies. While scaling and root planning (SRP) remain the gold standard, adjunctive treatments are needed to address bacterial persistence and bone resorption. This study explored an in situ curcumin/zinc oxide nanoparticle (Cur/ZNP) hydrogel designed to enhance antibacterial action, reduce inflammation, and promote bone health. Methods included in vitro antibacterial and cytotoxicity evaluations, as well as in vivo testing using a rat periodontitis model. Hydrogels were applied to periodontal pockets, and outcomes such as bacterial growth inhibition, transcriptional responses in gingival tissues, and alveolar bone preservation were assessed. Key markers, osteocalcin (OCN) and osteoprotegerin (OPG), were analyzed to gauge bone metabolism. Results demonstrated that the Cur/ZNP hydrogel exhibited synergistic antibacterial effects against Porphyromonas gingivalis, superior biocompatibility, and robust modulation of immune responses compared to individual Cur or ZNP hydrogels. Alveolar bone loss was significantly mitigated, with enhanced OCN and OPG expression indicating improved bone preservation. Cur/ZNP hydrogels represent a promising advancement in periodontitis management, offering enhanced bacterial inhibition, immune modulation, and bone health support. Future studies should optimize formulation stability and explore broader antimicrobial effects to realize clinical potential.

Keywords: *Curcumin, Hydrogel, Periodontitis.*

1. Introduction

Periodontitis, a leading cause of tooth loss globally, is a multifactorial disease characterized by the progressive destruction of the supporting structures of the teeth, including the gingiva, periodontal ligament, and alveolar bone. The primary etiological factor is the presence of bacterial biofilms, which induce an inflammatory response that exacerbates tissue degradation [1]. Traditional treatments like scaling and root planing (SRP) focus on mechanical debridement to remove subgingival plaque and calculus, creating an environment conducive to periodontal healing [2, 3]. However, SRP often leaves residual bacterial toxins in deeper pockets and irregular root surfaces, limiting its overall effectiveness and necessitating supplementary therapeutic strategies [3-5].

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The use of antibiotics, either systemically or locally, has been a common adjunct to SRP. While antibiotics can enhance bacterial clearance, their overuse has raised significant concerns regarding antimicrobial resistance and adverse drug reactions. This underscores the urgent need for novel, biocompatible alternatives to complement mechanical therapy and target the microbial and inflammatory components of periodontitis more effectively.

Curcumin, a natural polyphenolic compound derived from turmeric, has demonstrated potent antimicrobial, anti-inflammatory, and antioxidant properties, making it a promising candidate for periodontal therapy, enhancing the bond strength of implants/ crowns, filling materials and anti-cariogenic [6-12]. However, its clinical application is constrained by poor water solubility, rapid degradation, and limited bioavailability [6, 13-17]. To overcome these limitations, zinc oxide nanoparticles (ZNPs) have emerged as an effective delivery system. ZNPs not only improve curcumin's stability and bioavailability but also exhibit intrinsic antimicrobial and osteogenic properties, enhancing their therapeutic potential [1, 17-23].

This study focuses on the development and characterization of an in situ curcumin/ZNP hydrogel. By combining the complementary benefits of curcumin and ZNPs, this hydrogel aims to provide a localized, sustained-release therapy for periodontitis. The research evaluates the hydrogel's antibacterial activity, biocompatibility, and impact on bone preservation through in vitro and in vivo analyses, offering insights into its potential as a transformative approach in periodontal treatment.

2. Materials and Methods

The study was conducted on the ethical approval from the Institutional Review Board Committee of Riyadh Elm University, Riyadh, Saudi Arabia.

2.1. Hydrogel Preparation

Methylcellulose served as the hydrogel base, with curcumin and ZNPs incorporated at optimized concentrations. The injectability, stability, and release kinetics of the hydrogels were evaluated to ensure effective drug delivery.

2.2. In Vitro Testing

Antibacterial efficacy was assessed against P. gingivalis through growth inhibition assays. Cytotoxicity was evaluated using human oral keratinocyte (HOK-1) cells to confirm biocompatibility.

2.3. Animal Study Design

Experimental periodontitis was induced in Sprague-Dawley rats using silk ligatures and P. gingivalis inoculation. Rats were treated with Cur hydrogel, ZNP hydrogel, or Cur/ZNP hydrogel for four weeks. Sham and untreated groups served as controls.

2.4. Outcome Measures

Gene Expression: RNA sequencing analyzed immune modulation in gingival tissues. Protein Levels: OCN and OPG levels were measured via immunohistochemistry and ELISA.

3. Results

3.1. Hydrogel Properties

The Cur/ZNP hydrogel displayed a porous, stable structure with efficient drug release, achieving sustained delivery over one week.

3.2. Antibacterial Effects

Cur/ZNP hydrogels exhibited superior inhibition of P. gingivalis growth compared to individual components, demonstrating a concentration-dependent response.

3.3. Biocompatibility

Cytotoxicity assays confirmed the hydrogel's safety, with no adverse effects observed in HOK-1 cells.

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3.4. In Vivo Outcomes

Bone Loss Mitigation: Cur/ZNP hydrogel significantly reduced alveolar bone resorption (figure 1), supported by shorter CEJ-ABC distances and increased BV/TV and Tb.Th values as shown in figure 2 a and b.

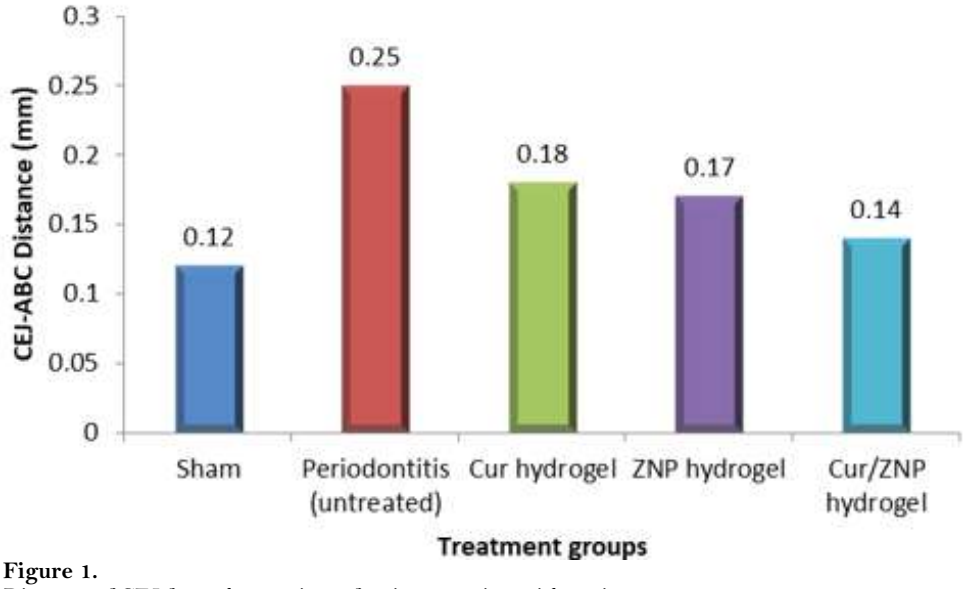

Figure 1.
Distance of CEJ from three points after intervention with various treatment groups.

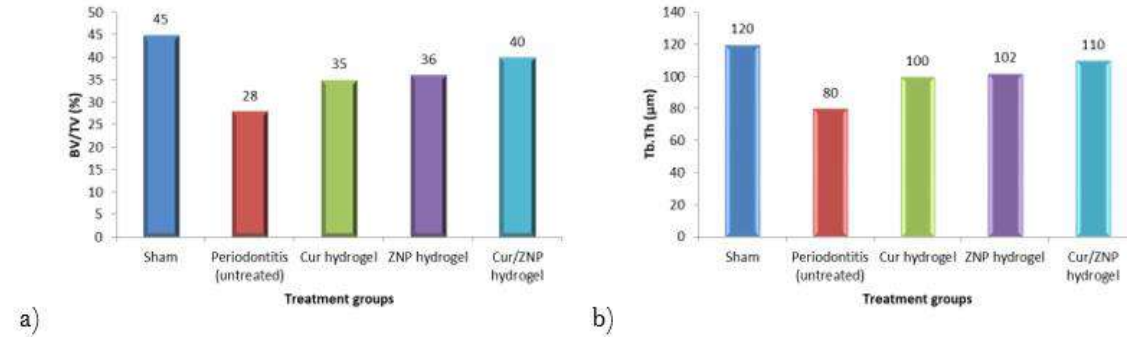

Figure 2.
(a) Displaying the efficacy of various treatment groups on BV/TV levels (volume of mineralized bone; (b) length of Tb.Th.

- Immune Modulation: Transcriptional analysis highlighted enhanced immune regulation and reduced expression of pro-inflammatory markers.
- Bone Metabolism: Elevated OCN and OPG levels indicated improved osteogenesis and reduced bone resorption as shown in Figure 3 a and b.

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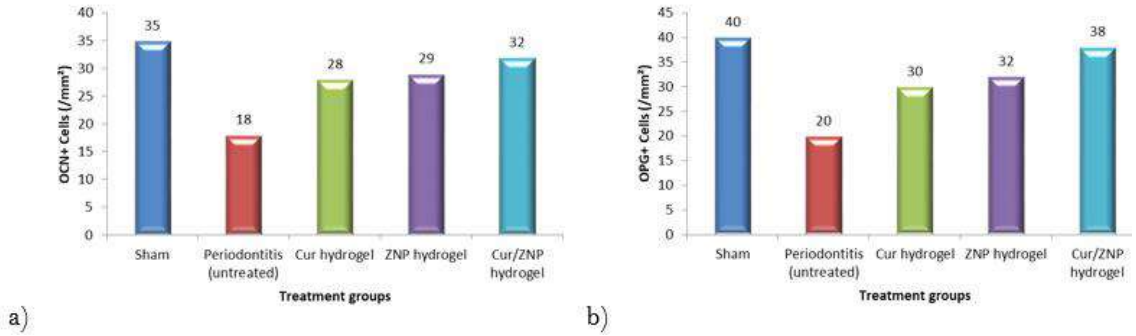

Figure 3.
(a) the number of OCN cells in on treatment with various treatment groups; (b) level of OPG cells in bony matrix on intervention of various therapies.

4. Discussion

The Cur/ZNP hydrogel demonstrates a promising combination of antimicrobial, anti-inflammatory, and osteoprotective properties [3, 24, 25]. By combining curcumin's well-established anti-inflammatory and antibacterial effects with the osteogenic potential of zinc oxide nanoparticles, the hydrogel addresses critical challenges in periodontitis management [2, 26, 27]. Compared to SRP alone or individual hydrogel components, this formulation offers enhanced bacterial inhibition, immune modulation, and bone health outcomes [28, 29]. The inclusion of ZNPs amplifies curcumin's bioavailability and therapeutic action, particularly in reducing alveolar bone resorption, as evidenced by shorter CEJ-ABC distances and increased BV/TV and Tb.Th metrics. Additionally, the immune modulation observed in transcriptional analyses highlights the hydrogel's potential in addressing the inflammatory component of periodontitis, a key driver of disease progression.

The significant upregulation of osteocalcin (OCN) and osteoprotegerin (OPG) levels further underscores the formulation's ability to promote bone regeneration [4, 25, 30, 31]. These outcomes are pivotal for long-term periodontal stability, as bone loss is a hallmark of advanced periodontitis. Importantly, the Cur/ZNP hydrogel demonstrated superior biocompatibility, ensuring its suitability for clinical application without adverse effects on surrounding tissues [32-36].

While these findings are encouraging, challenges remain. Optimizing the formulation's stability and enhancing its shelf-life are crucial for widespread adoption. Moreover, the hydrogel's efficacy should be validated in more complex microbial environments and clinical settings to ensure robustness across diverse patient populations [5, 37]. Future research could explore potential synergistic effects with other biomaterials or adjunctive therapies to further enhance therapeutic outcomes. Finally, long-term studies examining patient-centered outcomes, such as attachment level gain and quality of life improvements, will be critical for translating these promising results into routine clinical practice.

5. Conclusion

Cur/ZNP hydrogels represent a significant advancement in periodontitis treatment, offering a multi-faceted approach to managing bacterial infection and preserving alveolar bone. These findings support their potential for clinical application in periodontal therapy.

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