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Review article

Biological potential of nano-curcumins in dental and maxillofacial infections and inflammation: A systematic review

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Abstract

Objective: Periodontitis is a prevalent oral infection with increasing global incidence. This study investigated the biological potential and therapeutic benefits of nano-curcumins (Nano-CURs) for preventing and managing dental and maxillofacial infections and their associated inflammatory complications.

Materials and methods: This systematic review followed PRISMA guidelines and included preclinical and clinical studies retrieved from PubMed/MEDLINE, Web of Science, Scopus, Embase, and the Cochrane Library before August 18, 2025.

Results: In 23 included studies, Nano-CURs mainly comprised periodontitis, gingivitis, ligature-induced periodontitis, lipopolysaccharide-induced periodontal disease, and peri-implantitis. CUR-based nanocarriers improve solubility, bioavailability, and the controlled release of the drug. These nanocarriers demonstrate potent antibacterial and antibiofilm activity against key periodontal and peri-implant pathogens. It also attenuates inflammatory signaling, decreases cytokine production and oxidative stress, and possesses favorable biocompatibility.

Conclusion: Evidence derived predominantly from preclinical studies indicates that Nano-CURs are well tolerated and may effectively inhibit dental and maxillofacial infections and associated inflammation.

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Introduction

Oral and maxillofacial infections are common causes of hospitalization, increasing the length of hospital stay and causing chronic systemic disorders in affected individuals (El Chaar 2025; Eshghpour et al. 2024; Lixandru et al. 2024). These infections can still pose significant risks for fatal complications, particularly in patients with suppressed immune systems and systemic diseases (Bali et al. 2015; Lixandru et al. 2024). Other complications of dental and oral infections include systemic inflammatory response syndrome due to sepsis, pulmonary obstruction, osteomyelitis, necrotizing fasciitis, endocarditis, and thrombotic disorders in various body parts (Bali et al. 2015; Jevon et al. 2020; Li et al. 2000). Periodontal pathogens and subsequent immune-inflammatory responses after microbial biofilm buildup may cause an increase in inflammatory factors and the inflammation and tissue damage occur as a result of increased levels of inflammatory cytokines and mediators, including Interleukin-1 beta (IL-1β), IL-6, IL-17A, Chemokine (C-C motif) ligand 5 (CCL5), Cyclooxygenase-2 (COX-2), Monocyte Chemoattractant Protein-1 (MCP-1), Inducible Nitric Oxide Synthase (iNOS), and Tumor Necrosis Factor-alpha (TNF-α) (Chen et al. 2024).

Oral and maxillofacial infections are typically polymicrobial, involving aerobic and anaerobic bacteria. Key pathogens include *Streptococcus* species, especially the viridans group streptococci, major contributors to odontogenic and deep-space infections. Anaerobic bacteria are also important, particularly *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Porphyromonas gingivalis* (associated with periodontal and peri-implant infections), and *Escherichia coli* species, which play roles in abscess formation and tissue destruction and may be acquired as postoperative infections (Akram et al. 2022; Kamiński et al. 2022; Wang et al. 2022). Analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) are applied to decrease inflammation and pain, and antibiotics such as amoxicillin, tetracycline, gentamicin, ampicillin, and penicillin VK are used for this condition. However, these antibiotics face a significant challenge, such as microbial resistance (Akram et al. 2022; Raeisi et al. 2025). Therefore, it is necessary to find new therapeutic strategies. Phytochemicals are noted for their minimal side effects compared to conventional pharmaceuticals and their significant role in mitigating inflammation, antibacterial effect, and neutralizing free radicals (Amini et al. 2026; Ansari et al. 2025; Darvishi et al. 2025; Lalehgani et al. 2025; Mardani-Nafchi et al. 2025; Nikfarjam et al. 2026). Curcumin (CUR) is an orange-yellow phenolic compound with anti-inflammatory and antioxidant properties used in traditional and modern clinical applications. This polyphenolic compound, extracted from the rhizome of *Curcuma longa* L., has been used against various diseases and as a food coloring agent (Beigi et al. 2025; El-Saadony et al. 2022; Ghahfarrokhi et al. 2023; Raeisi et al. 2025; Tian et al. 2025). This polyphenolic compound has a molecular weight of 368.4 g/mol and a molecular formula of $C_{21}H_{20}O_6$ (Guru et al. 2020). Curcuminoids constitute a class of phenolic compounds derived from diferuloylmethane, encompassing CUR, demethoxycurcumin, bis-demethoxycurcumin, and cyclic CUR. Among these constituents, CUR represents the predominant fraction, whereas cyclic CUR is present in comparatively smaller amounts (Guru et al. 2020; Priyadarsini 2014). Nevertheless, despite its advantageous biological attributes, the clinical application of CUR is substantially limited by its inherently low bioavailability, with only a small fraction of the administered dose reaching the systemic circulation. This pharmacokinetic limitation is primarily attributable to poor aqueous solubility, inadequate gastrointestinal absorption, rapid metabolism, limited tissue penetration, and rapid systemic elimination (Bučević Popović et al. 2024; Tabanelli et al. 2021). So, these factors prevent the achievement of therapeutic plasma concentrations necessary for clinical efficacy.

Studies have shown that nanocarriers can improve the therapeutic efficacy, bioavailability, and targeted delivery of drugs, making them far more effective and biocompatible for therapeutic and clinical use (Maghsoudinia et al. 2022; Samani et al. 2023; Samani et al. 2025).

This systematic review examines the biological efficacy and potential benefits of Nano-CUR in preventing and managing dental and maxillofacial infections, as well as its role in addressing infection-related inflammatory complications.

Materials and Methods

Review guideline

This systematic review followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework.

Eligibility criteria (Inclusion and exclusion criteria)

The research question was formulated according to the PICO (Population, Intervention, Comparison, and Outcomes) framework model, as outlined in Table 1.

We included all clinical and preclinical studies that investigated Nano-CUR for maxillofacial infections and inflammatory conditions. Moreover, in accordance with the eligibility criteria, we excluded certain publication types, including all review and editorial articles. Additionally, case reports, conference abstracts or posters, unpublished study protocols, studies that do not contain original data, abstract publications, letters to the editor, and articles published in non-English languages were excluded from the analysis.

Table 1. PICO framework applied in this review

Element	**Description**
Population	Preclinical models (using cell lines, pathogens, and animal studies) and human subjects with dental or maxillofacial infections and inflammatory conditions, including periodontitis, gingival fibroblasts, oral mucositis, osteomyelitis, and maxillofacial inflammation.
Intervention	Nano-formulated CUR, such as NP, nanomicelles, nanocapsules, liposomal CUR, or other nanocarrier-based CUR systems, is used for oral infections and inflammation.
Comparison	Placebo, CUR alone, standard therapeutic interventions, or no treatment.
Outcomes	Biological outcomes include anti-inflammatory, antimicrobial, and healing-acceleration mechanisms, as well as the advantage of using CUR in a nanoformulation.

CUR, Curcumin; NP, Nanoparticle

Data sources and literature search strategy

An extensive electronic search was conducted on August 18, 2025, across major databases, including PubMed/MEDLINE, Web of Science, Scopus, Embase, and the Cochrane Library, to retrieve relevant studies. The search strategy integrated Medical Subject Headings (MeSH) terminology with commonly used free-text keywords identified from prior studies. To enhance sensitivity and ensure the inclusion of all pertinent articles, a comprehensive set of search terms were employed (Supplementary 1).

We conducted thorough database searches for this systematic review and examined relevant primary studies and previously published review articles. The search strategy was refined and screened iteratively to ensure that all eligible articles were included. To effectively manage references and eliminate duplicates, all retrieved records were imported into

EndNote version 21.0.1 (Thomson Reuters, July 25, 2023).

Screening process and full-text assessment

Two reviewers independently screened the titles/abstracts of all identified records based on our predefined inclusion and exclusion criteria. They then obtained full-text versions of potentially relevant studies and rigorously examined them to confirm eligibility, with exclusion reasons clearly recorded at this stage. Discrepancies between reviewers were resolved through discussion, and in cases where agreement was not achieved, a third reviewer was involved to make the final determination.

Quality assessment

Various risk-of-bias assessment tools were applied to assess the methodological quality of the included publications, depending on the study design. The SYRCLE Risk of Bias (RoB) tool was specifically employed for animal studies, as it is designed for preclinical research and evaluates potential biases across several domains. These items are discussed in the findings section. Each category was categorized as “yes” (low risk), “no” (high risk), or “unclear” when the available data did not allow for a definitive judgment (Hooijmans et al. 2014).

For *in vitro* studies, the QUIN (Quality Assessment Tool for In Vitro Studies) was applied, assigning scores of 2 for adequately reported parameters, 1 for inadequately described parameters, and 0 for unreported parameters (Min et al. 2024; Sheth et al. 2024).

In randomized controlled trials (RCTs), risk of bias was appraised using the Cochrane Risk of Bias 2 (RoB 2) framework, which systematically evaluates potential bias in five key domains (Sterne et al. 2019).

We employed the Robvis visualization package to depict risk of bias assessments visually. Furthermore, a Traffic Light Plot was produced to offer a study-specific overview, highlighting the risk of bias across all domains for each RCT and experimental study (McGuinness and Higgins 2021).

Data extraction process and synthesis

In this stage, two reviewers independently performed data extraction using standardized tables to register key study information, including author, publication year, type of study design, study’s sample (population/animals/cells/pathogens), Nano-CUR intervention details (Type of Nano formulation, dosage, and time), quality assessment and reported outcomes related to mechanisms of action and advantages associated with nanocarriers administration. The extracted data were qualitatively synthesized, emphasizing the main therapeutic properties and underlying biological mechanisms of Nano-CUR in periodontitis.

Results

Search results and characteristics of included studies

As illustrated in the PRISMA flowchart in Figure 1, 23 records were finally included after the screening (Abd-Elmonsif et al. 2025; Afrasiabi et al. 2023; Atila et al. 2024; Bossiela et al. 2023; Chen et al. 2024; Ekambaram et al. 2021; Guru et al. 2020; Hr et al. 2023; Khamooshi et al. 2022; Liu et al. 2024; Maleki Dizaj et al. 2022; Malekzadeh et al. 2021; Negahdari et al. 2021; Perez-Pacheco et al. 2023; Pérez-Pacheco et al. 2021; Pourhajibagher et al. 2021; Shahmoradi et al. 2023; Shirmohammadi et al. 2023; Tonon et al. 2022; Xiu et al. 2025; Xu et al. 2023; Zakria et al. 2024; Zambrano et al. 2018). Overall, this study included 4 clinical trial articles (Guru et al. 2020; Malekzadeh et al. 2021; Pérez-Pacheco et al. 2021; Zakria et al. 2024) and 19 other articles were conducted *in vivo* and *in vitro* (12 *in vitro* studies and 7 *in vivo* studies) (Abd-Elmonsif et al. 2025; Afrasiabi et al. 2023; Atila et al.

2024; Bossiela et al. 2023; Chen et al. 2024; Ekambaram et al. 2021; Hr et al. 2023; Khamooshi et al. 2022; Liu et al. 2024; Maleki Dizaj et al. 2022; Negahdari et al. 2021; Perez-Pacheco et al. 2023; Pourhajibagher et al. 2021; Shahmoradi et al. 2023; Shirmohammadi et al. 2023; Tonon et al. 2022; Xiu et al. 2025; Xu et al. 2023; Zambrano et al. 2018). The initial electronic search yielded 361 titles and abstracts. After removing duplicates, the total was reduced by 68 articles. Four studies were excluded as they focused solely on the benefits of CUR incorporated into a Nano-carrier system (including formulation, physicochemical properties, and delivery studies) (Chakraborty and Ramamurthy 2024; Chauhan et al. 2018; Murgia et al. 2019; Zhang et al. 2023). Additionally, two articles were excluded as irrelevant to the study's objectives (Hamza 2022; Sahebalam et al. 2023), and one study was excluded because it did not specifically involve CUR, instead examining turmeric and curry leaf oil (Sindi et al. 2023). These studies examined the antimicrobial, anti-inflammatory, and antioxidant properties, as well as the therapeutic effects of Nano-CUR on bone and gingival tissues. Some studies also investigated the side effects and cytotoxicity of the CUR nanodelivery system, as shown in Table 2.

Risk of bias assessment

Risk of bias evaluation was performed using SYRCLE’s risk of bias tool for in vivo studies, with judgments classified as low, high, or unclear risk (Figure 2A). The results were visualized through a traffic light plot, where green represented low risk of bias, red indicated high risk, and yellow reflected unclear or insufficiently reported information. In addition, the risk of bias in RCTs was presented in Figure 2B using both a traffic light plot.

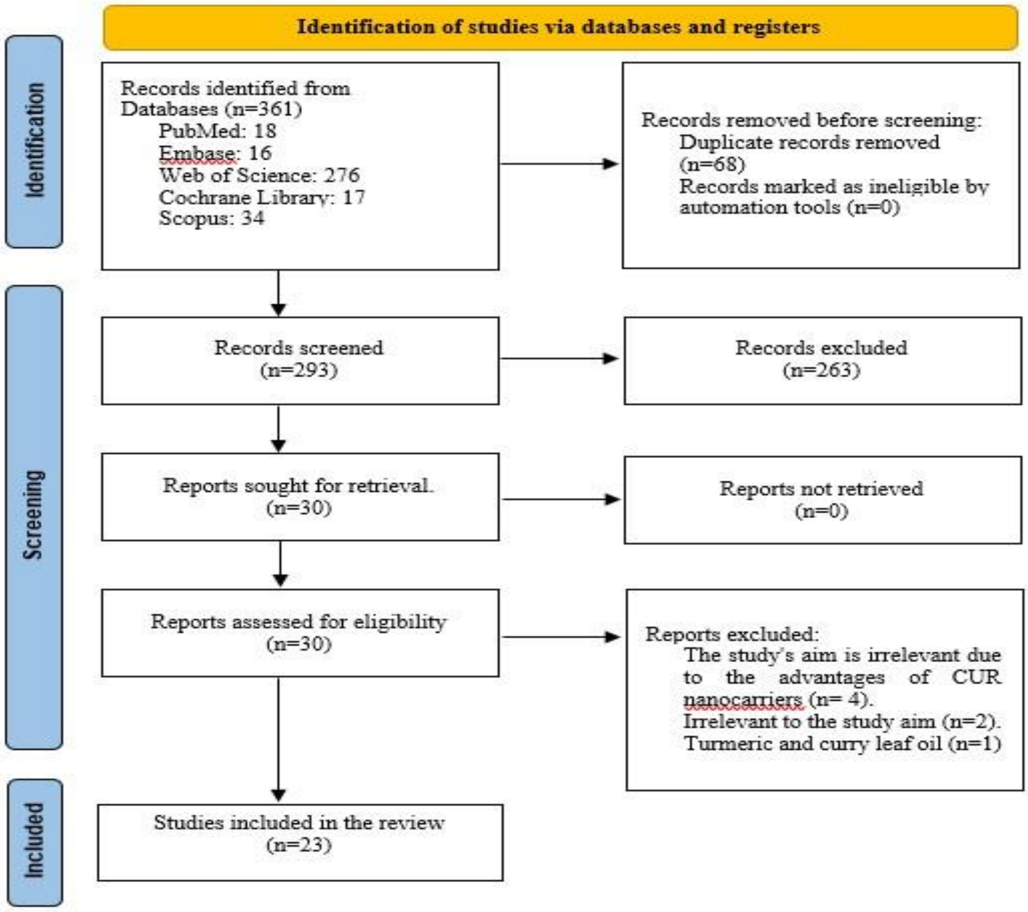

Figure 1. Diagram of the study selection process for the systematic review

Table 2. Summary of CUR-Nano studies characteristics

Reference	**Study design**	**Samples**	**Intervention details (CUR-Nano carrier, dosage, duration)**	**Main associated mechanisms and advantages of CUR-nanocarriers**
(Guru et al. 2020)	Randomized clinical trial	45 patients with mild-to-moderate chronic periodontitis.	Scaling and root planing, plus 2% CUR nanogel (chairside-prepared, Pluronic F127-based), were applied. The gel was applied subgingivally once, and patients were followed at baseline, 21, and 45 days.	Significant reduction in PI, GI, PPD, and CAL in all groups, with CUR nanogel comparable to chlorhexidine. It reduced *Tannerella forsythia*, *Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans*.
(Malekzadeh et al. 2021)	Randomized clinical trial	50 patients with generalized plaque-induced gingivitis and mild periodontitis	Nano-CUR soft gel capsules (80 mg) were administered once daily for 4 weeks. Clinical parameters were measured at baseline, day 7, 14, and 28.	Significant reduction in PBI and MGI compared to placebo at 14 and 28 days, reflecting anti-inflammatory and antioxidant effects. No substantial changes in PI. Improved systemic bioavailability of CUR (overcoming poor solubility and stability issues of free CUR). Reduced in gingival inflammation without local staining.
(Pérez-Pacheco et al. 2021)	Randomized clinical trial	20 patients with generalized periodontitis	CUR-NPs (PGLA/PLA) 0.05 mg/mL applied topically and evaluated at 1, 3, and 6 months.	Improved anti-inflammatory effects (reduced IL-6 and TNF-α) inhibited pathogens such as *A. actinomycetemcomitans* while promoting beneficial microbes, such as Veillonella Parvula, counts. It also enhanced clinical parameters (PPD, CAL GR, and BOP). There are no additive benefits to nonsurgical periodontal treatment.
(Zakria et al. 2024)	Randomized clinical trial	22 patients with stage II grade B periodontitis	Nano-CUR gel 2% applied subgingivally and assessed at 0, 3, and 6 months.	Anti-inflammatory effect via IL-6 reduction in gingival crevicular fluid, improved periodontal tissue regeneration, and clinical outcomes of periodontitis.
(Abd-Elmonsif et al. 2025)	*In vivo*	42 mature male albino rats	Mesenchymal exosomes and Nano-CUR 200 µg Nano-CUR loaded on 200 µg Bone Marrow-Derived Mesenchymal Stem Cells-derived exosomes, injected intraperiodontally once, and the studied groups were analyzed at 2 and 4 weeks.	Anti-inflammatory via reduced IL-1β, enhanced collagen formation in periodontal ligament, cementum, alveolar bone, and improved tissue regeneration and periodontal repair. It improved bioavailability and targeted delivery of CUR.
(Perez-Pacheco et al. 2023)	*In vivo*	24 adult male Holtzman rats	CUR-loaded PLA/PLGA NPs (0.05 mg/mL) were applied on days 0, 3, 5, 7, 9, and 11 after ligature removal and evaluated at 7 and 14 days.	Improved bone volume fraction (µCT), increased collagen content and extracellular matrix density, osteocyte density, Runx2 expression (osteogenic transcription factor), Arg1, Itgam, and Arg1/Inos ratio (indicates a shift toward an M2 macrophage) gene expression.
(Zambrano et al. 2018)	*In vivo* and *ex vivo*	16 Holtzman rats; *in vivo* model of LPS-induced periodontal disease; *ex vivo* analysis of gingival tissues.	CUR-loaded PLGA NP (0.05 mg/mL CUR) or empty NP were injected locally into the gingival tissues; 3 µL per injection; administered twice weekly for 28 days.	CUR-NPs inhibited inflammatory bone resorption, reduced osteoclast numbers, attenuated neutrophil and mononuclear cell infiltration, decreased fibroblastic cell proliferation, and suppressed p38 MAPK and NF-κB signaling.
(Xu et al. 2023)	*In vivo* and *in vitro*	*In vitro*: Bone marrow-derived macrophages (BMDMs), mouse fibroblasts (mGFs); *In vivo*: 24 C57BL/6 male mice, LIP model	NP-embedded functional hydrogel at 50 µg CUR per 20 µL hydrogel dosage injected into the gingival sulcus once per week for 2 weeks; *in vitro* release studied up to 10 days	Decreased Il-1β, IL-6, IL-17a, Ccl5, COX-2, MCP-1, iNOS, TNF-α. It also increased CAT, GPX1, GSH metabolism and decreased ROS. CUR-NPs increased CD206+ macrophages, reduced neutrophils, and T and B cells in the gingiva and cervical lymph nodes.

Table 2. Continued

(Chen et al. 2024)	*In vivo* and *in vitro*	*In vitro*: (RAW264.7 macrophages, HGFs, Caco-2 cells, *P. gingivalis*) 3 per experimental condition *In vivo*: (12 Sprague-Dawley rat periodontitis model) experiments.	Hyaluronic acid–4-(hydroxymethyl) phenylboronic acid pinacol ester conjugates (ROS-responsive) encapsulating CUR; dosages varied across assays (10 µg/mL in cell assays, 20-40 µg/mL antibacterial assays, repeated subgingival injections in rats every other day for 4 weeks)	Neutralize H_2O_2, enhanced ROS scavenging, improved HO-1, SOD, CAT gene expression, improved uptake via CD44 targeting, reduced TNF-α, IL-1β, IL-6, COX-2, MMP-8 and improved IL-10. It also modulated macrophage polarization (Improved M2, reduced M1) and revealed antibacterial activity against *P. gingivalis*. Moreover, it increases the solubility and stability of CUR, enables ROS-triggered controlled release, and sustains a therapeutic effect.
(Liu et al. 2024)	*In vivo* and *in vitro*	*In vitro*: *P. gingivalis* ATCC 33277; Human oral keratinocyte-1 (HOK-1) cells performed in triplicate. *In vivo*: 25 male Sprague–Dawley rats	CUR/ zinc oxide hydrogel NPs at 1–3 mg/mL; in rats, 200 µL of 2 mg/mL hydrogel was injected into the periodontal pocket once a week for 1 month	Antibacterial activity against *P. gingivalis*, inhibition of EPS production, modulation of bone resorption signaling, downregulation of Ceacam1 expression, and promotion of osteocalcin and osteoprotegerin expression. It also indicated good biocompatibility and sustained therapeutic effect.
(Xiu et al. 2025)	*In vivo* and *in vitro*	*In vitro*: Human periodontal ligament stem cells and RAW264.7 cells were used, and for antibacterial tests, *S. aureus*, *E. coli*, and *P. gingivalis* were used in ≥3 biological replicates. *In vivo*: 36 rat periodontitis model	Encapsulated iron-CUR-NPs composed of 10 mg CUR + 20 mg FeCl3·6H2O in Polyvinylpyrrolidone solution; 20 mg microspheres with 500 µL bacterial suspension, ± 808 nm NIR 1 W/cm^2, 5 min, 2 h incubation; Microsphere extracts for 48 h ± LPS (100 ng/mL) or IL-4 (20 ng/mL).	They effectively scavenged ROS and protected cells from oxidative stress. They activated the Nrf2/HO-1/NQO-1 antioxidant pathway and inhibited the NLRP3 inflammasome. They also promoted macrophage M2 polarization, inhibited the M1 phenotype, reduced TNF-α and IL-1, IL-1β, and upregulated Arg-1 and IL-10. CUR-NPs demonstrated strong adhesion and retention on teeth and gingival tissues, enabling localized delivery and prolonged therapeutic effects. The nanocarriers provided controlled release of CUR and minocycline. They also demonstrated excellent biocompatibility with periodontal ligament cells and immune cells.
(Ekambaram et al. 2021)	*In vitro*	3 scaffold groups using Vero cell lines	CUR-loaded SPEEK+NH_2–ZrO_2 nanofibrous scaffold fabricated by electrospinning. CUR incorporated at 5 mg with SPEEK polymer and aminated zirconia NP. Antibacterial activity tested by agar well diffusion at 50–500 µg/ml.	CUR-NPs exhibited potent antibacterial activity (larger inhibition zones than gentamicin) and were effective against *Streptococcus oralis*. Scaffolds were cytocompatible, uniform in morphology, well-structured, and sustained drug incorporation. They also showed synergistic antibacterial action and improved cellular proliferation and adhesion.
(Negahdari et al. 2021)	*In vitro*	27 implants were used and *Staphylococcus aureus*, *Escherichia coli*, and *Enterococcus faecalis* were cultured in brain heart infusion.	CUR nanocrystals (~95 nm, spherical) were prepared as a solution (60 mg/ml) and applied in 10 µl to the implant's internal cavity. The implants were then submerged in bacterial suspensions for 24 h.	Nano-CUR reduced bacterial CFUs compared with water, achieving>99% inhibition across all strains. Higher torque enhanced antibacterial effect against pathogens.

Table 2. Continued

(Pourhajibagher et al. 2021)	*In vitro*	5 specimens per group were assessed, and *Streptococcus mutans* (ATCC 35668) was used.	Nano-CUR-ABBL discs containing CUR-NP at 0.5%, 1%, 2%, and 5% (w/w), activated by LED (435±20 nm, 5 min), tested over 0, 15, 30, 60 days	CUR-NP embedded in ABBL showed sustained antibacterial and anti-biofilm activity with increasing aging time.
(Khamooshi et al. 2022)	*In vitro*	48 acrylic discs were assessed, and standard strains of *S. mutans* (ATCC 35668), *Streptococcus. sanguinis* (ATCC 10556), *Lactobacillus acidophilus* (ATCC 314), and *Candida albicans* (ATCC 14053) were used.	CUR-NPs were synthesized via ionic gelation (CUR+ sodium tripolyphosphate). Incorporated into acrylic discs at 0.5%, 1%, and 2% (w/w) and antimicrobial evaluation at 1, 3, and 7 days.	CFUs were reduced compared to the control, especially at 2% concentration. Biofilm formation was inhibited at all concentrations. However, the direct agar DAD did not indicate any growth inhibition zones.
(Maleki Dizaj et al. 2022)	*In vitro*	15 patients with dental implant failure (gingival crevicular samples), *P. gingivalis* isolates.	CUR nanocrystals prepared by solvent antisolvent precipitation + spray drying. Characterized by DLS. Tested at concentrations 50, 25, 12.5, 6.25, 3.12 µg/mL.	Antibacterial activity against *P. gingivalis* was observed, with growth inhibition at a MIC of 6.25 µg/mL. Bactericidal activity was observed at an MBC of 12.5 µg/mL, and inhibition zones increased in a dose-dependent manner, with 50 µg/mL as the most effective concentration.
(Tonon et al. 2022)	*In vitro*	4 biofilm models were used. ATCC strains: *P. gingivalis* (W83), *Fusobacterium nucleatum* (25586), *S. oralis* (35037); multispecies biofilms on 24-well plates and titanium discs; Human periodontal ligament fibroblasts for cytotoxicity	Depending on the assay, CUR-loaded poly-ε-caprolactone NPs were tested at 0.25–500 µg/mL and applied for 24–120 h.	Photoactivated CUR-NPs enhanced antibacterial effects. Moreover, MIC/MBC values showed dose- and light-dependent bacterial inhibition. Biofilm reduction is more effective on *S. oralis* and partially on *P. gingivalis* on titanium. NPs improve CUR stability and homogeneity and can serve as an adjunctive therapy for peri-implantitis.
Afrasiabi, 2023, (Afrasiabi et al. 2023)	*In vitro*	Human gingival fibroblasts seeded at 10,000 cells and *A. actinomycetemcomitans* (ATCC 700685, JP2 clone); HGFs; RBCs for hemocompatibility.	Nanoliposomes loaded with CUR (83.4% EE) and DOX (47.2% EE) were studied over 12 h, and release was also studied.	Additive antimicrobial effect of Nanoliposomes-CUR+DOX+LED (84.2% bacterial reduction). It demonstrated a strong anti-biofilm effect (82.7% reduction with LED), a significant decrease in bacterial metabolic activity (75%), and sustained drug release.
(Bossiela et al. 2023)	*In vitro*	Periodontal ligament fibroblast cells isolated from 2 healthy children and periodontitis patients.	Nano-CUR was prepared in-house; fibroblasts were treated with different concentrations of Nano-CUR (10, 3, 1.5, 0.7, and 0.3 mmol/mL) at 24, 48, and 72 h.	Increased cell viability and proliferation in a concentration and time-dependent manner, reduced the number of apoptotic cells, and enhanced *FGF* gene expression in treated fibroblasts. Fibroblast proliferation was improved compared to untreated controls.
(Hr et al. 2023)	*In vitro*	3 disk diffusion assays *T. forsythia* (Tf ATCC 43037), *P. gingivalis* (Pg ATCC 33277), *Prevotella intermedia* (Pi ATCC 25611), *A. actinomycetemcomitans* (Aa ATCC 43718)	Pure Nano-CUR used and MIC range tested at 100, 50, 25, 12.5, 6.25, 3.12, 1.6, 0.8, 0.4, and 0.2 µg/mL and incubated at 48–72 h (MIC); 18–24 h (disk diffusion)	All formulations inhibited the growth of pathogenic organisms at higher concentrations, but MIC values varied by pathogen and formulation. Moreover, inhibition zones decreased with lower concentrations, and all were less effective than moxifloxacin. Nanocarriers improved sustained antimicrobial activity and CUR delivery.
(Atila et al. 2024; Shahmoradi et al. 2023)	*In vitro*	All experiments were conducted in triplicate. *P. gingivalis* ATCC33277 strain (anaerobic culture)	Dendrosomal CUR; MIC 4–256 µg/mL, for 30–150 s (10.6–63.6 J/cm²). Sublethal dendrosoaml CUR doses (½–¼ MIC) combined with laser applied for 30–150 s	Inhibited *P. gingivalis* growth (MIC ≥4 µg/mL), combination (antimicrobial photodynamic therapy with 2–4 µg/mL dendrosomal CUR + 30 s irradiation) completely eradicated *P. gingivalis*.

Table 2. Continued

(Chen et al. 2024; Shirmohammadi et al. 2023)	*In vitro*	Clinically isolated *P. gingivalis* from a patient with chronic periodontal disease and dental pulp stem cells performed in triplicate.	Mesoporous silica NPs loaded with CUR (6.25, 12.5, 25, 50 µg/m) were applied for 48 h for bacterial culture and 72 h for the cytotoxicity assay.	Antimicrobial activity against *P. gingivalis* (dose-dependent), sustained CUR release from mesoporous NPs, improved bioavailability of CUR, high drug-loading (68%), and nanosize enhances cellular interactions.
(Atila et al. 2024; Liu et al. 2024)	*In vitro*	Human dental pulp stem cells, HGFs, *Escherichia. Coli* DSM 787, *Staphylococcus. aureus* DSM 683 was used in a triplicate/quadruplet design.	Injectable Liposome-Loaded Hydrogel Formulations with CUR. The samples were assessed for 14 days. α-tocopherol-loaded liposomes groups tested 1–12 µL/100 µL (0.6 mg/mL stock). Hydrogels + CUR tested up to 12 µL/100 µL for 7–21 days.	Lip/CUR were toxic at high doses, but Lip/CUR + α-Tocopherol eliminated toxicity. Hydrogels delay release, enhancing viability at higher doses. The composition improved odontogenic differentiation, wound healing, antioxidant protection (especially with chitosan hydrogels), and cell viability. They revealed antimicrobial potency. Hydrogels with Lip/Cur+Toc showed strain-dependent inhibition. Nanosized vesicles, high encapsulation, biocompatibility, sustained release, higher stability, water uptake, and improved solubility of hydrophobic drugs.

CUR-NP, Curcumin nanoparticles; LPS, Lipopolysaccharides; PLGA, Poly(lactic-co-glycolic acid); MAPK, Mitogen-activated protein kinase; TNF-α, Tumor Necrosis Factor-alpha; IL-1β, Interleukin-1 beta; NF-κB, Nuclear factor-κB; ROS, Reactive Oxygen Species; PI, Plaque Index; GI, Gingival index; PPD, Probing pocket depth; CAL, Clinical attachment level; PBI, Papillary bleeding index; MGI, Modified gingival index; CFU, Colony forming unit; CFU, Colony forming unit; NR, Not reported; BOP, Bleeding on probing; GR, Gingival recession; ABBL, Activa BioActive Base/Liner; LED, Light emitting diod; CFUs, Colony-forming units; DAD, Diffusion assay; DLS, Dynamic light scattering; MIC, Minimum inhibitory concentration; MBC, Minimum bactericidal concentration; DOX, Doxycycline; PVC, Polyvinyl chloride; LIP, Ligature-induced periodontitis; COX-2, Cyclooxygenase-2; MCP-1, Monocyte Chemoattractant Protein-1; iNOS, Inducible Nitric Oxide Synthase; TNF-α, Tumor Necrosis Factor-alpha; CAT, Catalase; GPX1, Glutathione Peroxidase 1; GSH, Glutathione; Lip, Liposomes; HGFs, Human gingival fibroblasts; MMP-8, Matrix Metalloproteinase-8; SOD, Superoxide Dismutase; NLRP3, NLR family pyrin domain containing 3.

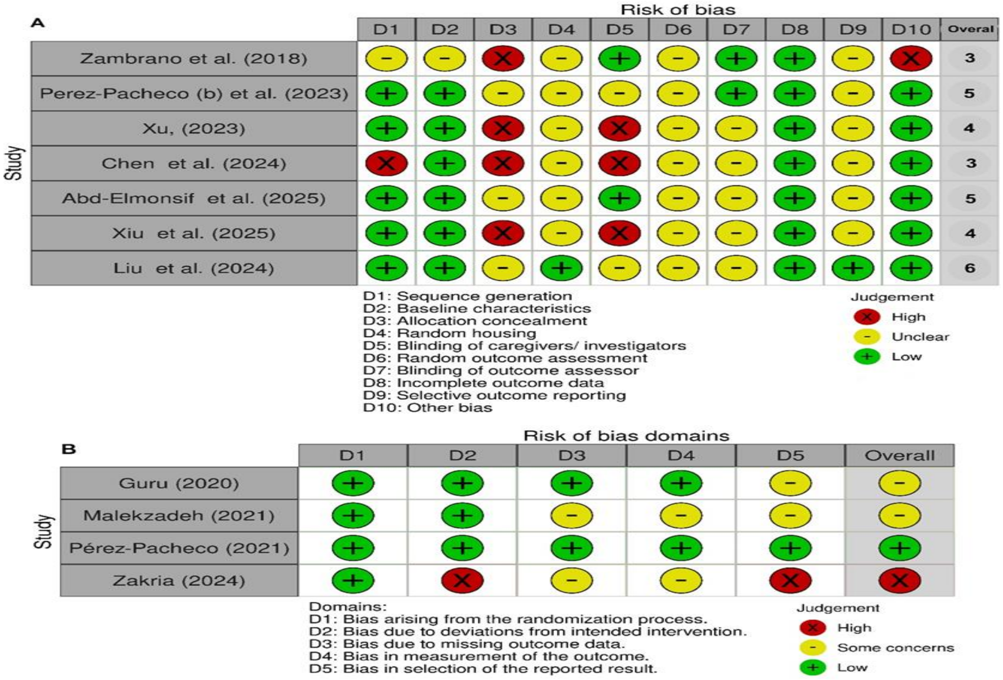

Figure 2. The summary traffic light plot for animal (Figure 2A) and clinical (Figure 2B) studies

In vitro studies (QUIN tool)

Furthermore, the QUIN tool results for each study were tabulated in Table 3. Twelve *in vitro* studies were assessed with the QUIN tool, yielding scores ranging from 11/24 (46%) to 16/24 (66.7%). Eleven were classified as medium risk of bias, and one (Ekambaram et al. 2021) was rated high risk. None of the studies reached the low-risk threshold of more than 70%.

Studies performed most consistently in domains covering stated aims, methodological description, outcome measurement, and presentation of results. In contrast, sample size calculation, randomization, operator details, blinding, and outcome assessor information were frequently not specified or inadequately reported shortcomings that may undermine reproducibility and heighten the risk of measurement and observer bias.

Table 3. The results of the QUIN tool for *in vitro* studies

Studies	1. Clearly stated aims/objectives	2. Explanation of sample size calculation	3. Explanation of sampling technique	4. Details of the comparison group	5. Explanation of methodology	6. Operator details	7. Randomization	8. Method of measurement of outcome	9. Outcome assessor details	10. Blinding	11. Statistical analysis	12. Presentation of results	Overall score	Risk of bias
Ekambaram et al. (2021)	2	0	1	1	2	0	0	2	0	0	1	2	11 (46 %)	High
Negahdari et al. (2021)	2	0	1	2	2	0	0	1	0	0	2	2	12 (50 %)	Average
Pourhajibagher et al. (2021)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.2 %)	Average
Khamooshi et al. (2022)	2	1	1	2	2	0	0	2	0	0	2	2	14 (58.3 %)	Average
Maleki Dizaj et al. (2022)	2	2	2	2	2	0	0	2	0	0	2	2	16 (66.7 %)	Average
Tonon et al. (2022)	2	1	2	2	2	0	0	2	0	0	2	2	15 (62.5%)	Average
Afrasiabi et al. (2023)	2	0	2	2	2	0	0	2	0	0	2	2	14 (58.3 %)	Average
Bossiela et al. (2023)	2	0	2	2	2	0	0	2	0	0	2	2	14 (58.3 %)	Average
Hr et al. (2023)	2	0	1	2	2	0	0	2	0	0	1	2	12 (50%)	Average
Shahmoradi et al. (2023)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.2 %)	Average
Shirmohammadi et al. (2023)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.2 %)	Average
Atila et al. (2024)	2	0	1	2	2	0	0	2	0	0	2	2	13 (54.2 %)	Average

Criteria are scored as follows: Adequately specified = 2; Inadequately specified = 1; Not specified = 0. The final score is interpreted as follows: a score above 70% indicates a low risk of bias; a score between 50% and 70% reflects an average risk of bias; and a score below 50% signifies a high risk of bias. This assessment is based on the QUIN tool formula: Final score = Total score * (100) / (2 * number of applicable criteria).

In vivo studies (SYRCLE tool)

Across the six included studies, the overall methodological quality was variable. Liu et al. (Liu et al. 2024) (score: 6), Pérez-Pacheco et al. (Perez-Pacheco et al. 2023), and Abd-Elmonsif et al. (Abd-Elmonsif et al. 2025) achieved a higher proportion of low-risk domains (score: 5), indicating better reporting and study design. Baseline comparability (Domain 2) and incomplete outcome data (Domain 8) were consistently rated as low risk, reflecting adequate group equivalence and minimal attrition bias. Domains pertaining to random housing (Domain 4), random outcome assessment (Domain 6), and selective reporting (Domain 9) were frequently judged as unclear, owing to insufficient methodological detail. The greatest concerns arose in allocation concealment (Domain 3) and blinding of caregivers and investigators (Domain 5), where high-risk ratings were most common, raising the possibility of selection and performance bias. While preclinical findings were broadly positive, these limitations warrant measured interpretation (Figure 2A).

Randomized clinical trials (RoB 2 tool)

Additionally, among the four RCTs evaluated, only Pérez-Pacheco et al. (Pérez-Pacheco et al. 2021) had a low overall risk of bias reflecting sound methodology across all domains, whereas Guru et al. (Guru et al. 2020) and Malekzadeh et al. (Malekzadeh et al. 2021) raised some concerns primarily around deviations from intended interventions and incomplete reporting. While Zakria et al. (Zakria et al. 2024) was rated high risk owing to deficiencies in randomization, missing outcome data, and outcome measurement. These results highlight variability in methodological quality across the included RCTs, with selective reporting and incomplete outcome data being the most common sources of bias (Figure 2B).

Discussion

This systematic review aims to evaluate and synthesize the available evidence from preclinical and clinical studies on the therapeutic and biological potential of nano-CUR formulations for the management of dental and maxillofacial infections and inflammatory diseases, with a focus on their anti-inflammatory, antimicrobial, antioxidant, healing, and tissue-regenerative properties, as discussed below.

Periodontal disease primarily stems from oral microbial infections that trigger gingival inflammation. If left untreated, this inflammation can affect the entire periodontium and lead to periodontal disease (Bartold and Van Dyke 2013). Gingivitis is a reversible condition marked by inflammation confined to the gums. In contrast, periodontitis is an irreversible state marked by alveolar bone loss, tooth mobility, and the potential for tooth loss. Chronic periodontitis results in delayed wound healing and significant damage to the gingiva, periodontal ligament, and alveolar bone (Cho et al. 2021; Engeland et al. 2014). These complications can disrupt the treatment process and sometimes lead to treatment failure (Engeland et al. 2014). CUR exhibits substantial anti-inflammatory properties by inhibiting pro-inflammatory cytokines and mediators, such as TNF-α, matrix metalloproteinases (MMPs), IL-1, IL-4, IL-6, prostaglandin E2 (PGE2), signal transducer and activator of transcription 1 (STAT1), procalcitonin (PCT), and COX-2, while simultaneously promoting the expression of anti-inflammatory cytokines like IL-4 and IL-10. Furthermore, CUR has been demonstrated to suppress crucial transcription factors involved in the inflammatory response, including NF-κB (Muhammad Ridho et al. 2024). Its administration is also associated with decreased levels of periodontitis-related biomarkers, such as C-reactive protein (CRP), alkaline phosphatase (ALP), and procalcitonin (PCT) (Muhammad Ridho et al. 2024). Periodontal inflammation is marked by progressive gingival inflammation, irreversible tissue damage, and alveolar bone loss. Inflammatory cells, including neutrophils and macrophages, can activate the nuclear factor-κB (NF-κB) signaling pathway, leading to the production of inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, IL-8, and tumor necrosis factor-α (TNF-α), which contribute to progressive tissue destruction (Zhang et al. 2025). Xiu et al. demonstrated that encapsulated iron-CUR-nanaoparticles (NPs), composed of 10 mg CUR and 20 mg $FeCl_3 \cdot 6H_2O$ in a polyvinylpyrrolidone solution, exhibited anti-inflammatory and immunomodulatory effects. Iron-CUR-NPs inhibited NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, which reduced caspase-1, promoted M2 macrophage polarization while suppressing the M1 phenotype, reduced TNF-α and IL-1β expression, and upregulated Arg-1 and IL-10 levels (Xiu et al. 2025). Zambrano et al. employed an *in vivo* model of lipopolysaccharides (LPS)-induced periodontal disease in Holtzman rats with *ex vivo* analysis of gingival tissues, where local injections of CUR-loaded PLGA or poly(lactic-co-glycolic acid) NPs (0.05 mg/mL, 3 µL per site, twice weekly for 28 days) significantly inhibited inflammatory bone resorption, reduced osteoclast numbers, attenuated neutrophil and mononuclear cell infiltration, decreased fibroblast proliferation, and suppressed p38 MAPK and NF-κB signaling pathways (Zambrano et al. 2018). Another study investigated the effects of a NP-embedded functional hydrogel containing CUR (50 µg per 20 µL dose) applied in vitro to bone marrow-derived macrophages (BMDMs) and mouse gingival fibroblasts (mGFs), and in vivo to a C57BL/6 male mouse ligature-induced periodontitis (LIP) model via gingival sulcus injection once weekly for two weeks; the hydrogel exhibited sustained release over 10 days and significantly reduced the expression of pro-inflammatory mediators such as IL-6, IL-17A, IL-1β, CCL5, COX-2, TNF-α, MCP-1, and iNOS (Xu et al. 2023). Chen et al. developed reactive oxygen species (ROS)–responsive hyaluronic acid-4-(hydroxymethyl) phenylboronic acid pinacol ester conjugates encapsulating CUR and evaluated their effects both *in vitro* using RAW264.7 macrophages, human gingival fibroblasts (HGFs), Caco-2 cells, and *P. gingivalis*, and in vivo in a Sprague-Dawley rat periodontitis model. The formulations enhanced cellular uptake through CD44-mediated targeting, exhibited antibacterial activity against *P. gingivalis*, modulated macrophage polarization by promoting the M2 phenotype while suppressing M1, and reduced TNF-α, IL-1β, IL-6, COX-2, and MMP-8 levels while increasing IL-10 expression (Chen et al. 2024). Other clinical and *in vivo* studies have shown that Nano-CURs can help limit inflammation in tissues and cells by inhibiting inflammatory cytokines such as IL-6, TNF-α, and IL-1β (Abd-Elmonsif et al. 2025; Pérez-Pacheco et al. 2021; Zakria et al. 2024). Among studies involving human participants, initial clinical evidence suggests possible reductions in gingival inflammation and improvements in periodontal indices. However, the limited number of available trials precludes definitive conclusions regarding clinical efficacy at this stage. Xu et al. conducted a study on an NP-embedded functional hydrogel infused with CUR (50 µg per 20 µL), examining its effects both *in vitro* (using bone marrow-derived macrophages and mouse gingival fibroblasts) and *in vivo* (in C57BL/6 mice via a LIP model). The results showed that weekly injections into the gingival sulcus over 2 weeks increased $CD206^+$ macrophages and reduced infiltration of neutrophils, T cells, and B cells in gingival tissues and cervical lymph nodes (Xu et al. 2023).

The microenvironment characterized by oxidative stress can severely damage periodontal tissues and is a precursor to inflammation and progression of periodontitis. This situation poses a significant obstacle to effective periodontal therapy (Sczepanik et al. 2020). Periodontal pathogenic bacteria trigger host defense responses, leading to neutrophil accumulation in gingival tissues and primary ROS sources during phagocytosis (Miralda and Uriarte 2021). Patients with periodontitis exhibit elevated levels of malondialdehyde (MDA), hydrogen peroxide (H_2O_2), mitochondrial dysfunction, adenosine triphosphate (ATP) reduction synthesis, oxidative DNA damage, reduced activity of antioxidants such as superoxide dismutase (SOD) and catalase (CAT), and altered total antioxidant capacity (TAC) and other oxidative stress biomarkers (Patil et al. 2024; Shang et al. 2023). Xiu et al. reported that treatment with iron-CUR-NPs containing 10 mg CUR effectively scavenged ROS, protected cells from oxidative stress, and activated the Nrf2/HO-1/NQO-1 antioxidant signaling pathway (Xiu et al. 2025). Chen et al. comprehensively evaluated ROS-responsive hyaluronic acid-4-(hydroxymethyl)phenylboronic acid pinacol ester conjugates encapsulating CUR. This study encompassed *in vitro* and *in vivo* analyses utilizing RAW264.7 macrophages, human gingival fibroblasts (HGFs), Caco-2 cells, and the periodontal pathogen, *P. gingivalis*. The findings revealed that the treatment effectively neutralized H_2O_2, enhanced ROS scavenging capabilities, and significantly upregulated the expression of critical antioxidant genes, including heme oxygenase-1 (HO-1), SOD, and CAT (Chen et al. 2024). NP-embedded CUR hydrogel *in vitro* and *in vivo*; weekly gingival sulcus injections for 2 weeks increased antioxidant activity, including CAT, glutathione peroxidase 1 (GPX1), and glutathione (GSH) metabolism, while ROS levels were sustained in vitro for up to 10 days (Xu et al. 2023). Another study showed that injectable liposome-loaded hydrogel formulations containing CUR demonstrated antioxidant effects and enhanced periodontal tissue regeneration and wound healing, particularly when combined with chitosan or tocopherol (Atila et al. 2024). These antioxidant effects are predominantly substantiated by laboratory and animal studies, while direct validation in clinical periodontal contexts remains limited.

CUR displays diverse antibacterial mechanisms that target various structural and functional aspects of Gram-negative and Gram-positive bacterial cells (Dai et al. 2020). It enhances the activity of ATPase inhibitors and compromises bacterial membrane stability by enhancing permeability, resulting in the efflux of vital intracellular constituents and culminating in cellular rupture (lysis) (Mun et al. 2014). CUR exerts antibacterial activity through a multifactorial mechanism targeting essential bacterial processes and structures. It disrupts quorum-sensing pathways, thereby suppressing the synthesis of virulence factors and inhibiting biofilm formation, both of which are critical for bacterial communication and persistence (Di Salle et al. 2021). Additionally, CUR interferes with bacterial cell division by inhibiting the polymerization of FtsZ, an essential component of the cytokinetic ring required for septum formation. It also induces oxidative stress in bacterial cells by increasing ROS production and accumulation, causing oxidative damage to proteins, lipids, and nucleic acids. CUR demonstrates photosensitizing properties, significantly increasing its bactericidal efficacy against bacteria under blue-light irradiation via photoactivated ROS production. Furthermore, it perturbs bacterial cell metabolism by disrupting enzymatic activities involved in energy production and biosynthesis (Dai et al. 2022).

CUR has also been shown to have irreversible detrimental effects on dental plaque by inducing bacterial apoptosis, likely by enhancing bacterial cell membrane permeability. By effectively hindering the formation of plaque biofilms, CUR demonstrates its potential as a prophylactic agent to prevent periodontal diseases (Li 2024). In our study, CUR-NPs demonstrate significant antibacterial activity against various microorganisms, including oral and systemic pathogens. Notable examples include *P. gingivalis* (ATCC 33277, W83), *Tannerella forsythia*

(ATCC 43037), *Aggregatibacter actinomycetemcomitans* (ATCC 700685, JP2 clone), *Fusobacterium nucleatum* (ATCC 25586), *Prevotella intermedia* (ATCC 25611), *Streptococcus mutans* (ATCC 35668), *Streptococcus sanguinis* (ATCC 10556), *Streptococcus oralis* (ATCC 35037), *Lactobacillus acidophilus* (ATCC 314), *Enterococcus faecalis*, *Staphylococcus aureus* (DSM 683), *E. coli* (DSM 787), and *Candida albicans* (ATCC 14053) (Afrasiabi et al. 2023; Atila et al. 2024; Chen et al. 2024; Ekambaram et al. 2021; Guru et al. 2020; Hr et al. 2023; Khamooshi et al. 2022; Liu et al. 2024; Maleki Dizaj et al. 2022; Negahdari et al. 2021; Pérez-Pacheco et al. 2021; Pourhajibagher et al. 2021; Shahmoradi et al. 2023; Shirmohammadi et al. 2023; Tonon et al. 2022; Xiu et al. 2025). The antimicrobial effects observed include inhibition zones that exceed those of gentamicin administration (Ekambaram et al. 2021).

The majority of antibacterial evidence discussed in this review is derived from *in vitro* investigations that assess planktonic bacteria or biofilm models, and clinical corroboration remains limited. Guru et al. conducted an RCT in patients with mild-to-moderate chronic periodontitis, in which scaling and root planing were supplemented with a single subgingival application of 2% CUR nanogel, with follow-up at baseline, 21, and 45 days, demonstrating that CUR nanogel exhibited antibacterial effects comparable to chlorhexidine by significantly reducing *Tannerella forsythia*, *Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans* (Guru et al. 2020). Additionally, Nano-CUR has demonstrated significant antibacterial activity against periodontitis-associated bacteria. All formulations inhibited pathogen growth at higher concentrations, with minimum inhibitory concentrations (MICs) varying by pathogen and formulation. However, inhibition zones diminished at lower concentrations, and overall efficacy was inferior to that of moxifloxacin (Hr et al. 2023).

Tonon reported that CUR-loaded poly-ε-caprolactone NPs, tested at concentrations ranging from 0.25 to 500 µg/mL and applied over 24 to 120 hours depending on the specific assay, exhibited enhanced antibacterial effects upon photoactivation. The MIC and minimum bactericidal concentration (MBC) values indicated that bacterial inhibition was both dose- and light-dependent. Notably, these NPs were particularly effective in reducing biofilm formation against *S. oralis* and showed partial effectiveness against *P. gingivalis* on titanium surfaces (Tonon et al. 2022). Nanoformulated CUR can inhibit bacterial growth and biofilm formation, achieving over 99% inhibition rates across various strains (Negahdari et al. 2021). Additionally, photoactivated CUR-loaded poly-ε-caprolactone NPs significantly enhance bacterial eradication and biofilm reduction in (*S. oralis* and partially on *P. gingivalis*), particularly on titanium surfaces (Tonon et al. 2022). Furthermore, combinations of nanoliposome-CUR with doxycycline (DOX) and light irradiation yield synergistic antimicrobial effects, resulting in up to 84% reduction in bacteria and 82% reduction in biofilms (Afrasiabi et al. 2023). Another study evaluated *Streptococcus mutans* using Nano-CUR-ABBL discs containing 0.5%, 1%, 2%, and 5% (w/w) CUR-NPs activated by LED, demonstrating that CUR-NP-embedded ABBL exhibited sustained antibacterial and anti-biofilm activity that persisted and increased over aging (Pourhajibagher et al. 2021).

Chronic periodontitis and its accompanying inflammatory processes can significantly affect various histological features of the dental pulp (Kostenkova et al. 2025). These changes may include disruption or loss of continuity in the odontoblastic layer, disruption of the gingival epithelial tissue, inflammatory cell infiltration within the pulp, disordered fiber arrangement, loss of alveolar bone and pulp tissue, fibrosis, calcification, and necrosis to a lesser extent. Such histopathological alterations indicate that periodontal inflammation may extend its effects beyond the supporting tissues, compromising the dental pulp's structural and functional integrity (Vaziri et al. 2023; Xiu et al. 2025). According to Xiu et al. study, *in vitro* and *in vivo* evaluations of the effects of iron-CUR-NPs, formulated from 10 mg of CUR and 20 mg of $FeCl_3 \cdot 6H_2O$ in a polyvinylpyrrolidone solution, showed that the treatment exhibited strong adhesion and retention on the tooth and gingival surfaces, increased alignment of fibers, restoration of epithelial tissue structure, arranged and make compact collagen fibers, improved in alveolar bone height. Moreover, it enhanced osteogenic activity by interacting with associated proteins such as Runx2 and osteocalcin (OCN) (Xiu et al. 2025). Another study reported that CUR-loaded PLGA NP (0.05 mg/mL CUR) reduced the number of osteoclasts and decreased fibroblastic cell proliferation after 28 days of treatment (Zambrano et al. 2018).

According to Pérez-Pacheco, adult male Holtzman rats were treated with CUR-loaded PLA/PLGA NPs at a dose of 0.05 mg/mL. The NPs were administered on days 0, 3, 5, 7, 9, and 11 after ligature removal, with evaluations conducted at 7 and 14 days post-treatment. The results revealed significant improvements in bone regeneration parameters, including an increased bone volume fraction observed via micro-computed tomography (µCT), enhanced collagen deposition and extracellular matrix density, a higher osteocyte density, and upregulated expression of the osteogenic transcription factor Runx2. These findings indicate a pronounced osteogenic and reparative effect from the CUR-loaded NP treatment (Perez-Pacheco et al. 2023). CUR-loaded zinc NPs (Cur/ZNPs) significantly reduced alveolar bone resorption and increased OCN and osteoprotegerin (OPG) expression levels. The Cur/ZNPs also demonstrated a notable osteoprotective effect, as indicated by a decreased distance between the cemento-enamel junction and the alveolar bone crest (CEJ-ABC), alongside an elevated bone volume fraction (BV/TV). However, no statistically significant differences in OCN and OPG expression were observed between the CUR hydrogel and the Cur/ZNP hydrogel groups in periodontal tissues, suggesting that both formulations yield comparable osteogenic regulatory outcomes (Liu et al. 2024). In the study by Abd-Elmonsif et al., mature male albino rats were used to assess the therapeutic efficacy of mesenchymal exosomes in combination with Nano-CUR. This study incorporated 200 µg of Nano-CUR into 200 µg of bone marrow-derived mesenchymal stem cell (BMSC)-derived exosomes. The composite formulation was administered as a single intraperiodontal injection, and the experimental groups were evaluated at 2 and 4 weeks post-treatment. The results demonstrated that this combined therapy significantly enhanced collagen formation within the periodontal ligament, cementum, and alveolar bone, ultimately leading to improved tissue regeneration and overall periodontal repair (Abd-Elmonsif et al. 2025). In another study, periodontal ligament fibroblast cells were isolated from both healthy pediatric donors and patients diagnosed with periodontitis to evaluate the biological effects of Nano-CUR. The fibroblast cultures were treated with varying concentrations of Nano-CUR (10, 3, 1.5, 0.7, and 0.3 mmol/mL) over 24, 48, and 72 hours. The results showed that Nano-CUR treatment significantly enhanced cell viability and proliferation in a concentration and time-dependent manner while reducing apoptotic cells. Furthermore, Nano-CUR treatment upregulated the expression of fibroblast growth factor (FGF) genes. It promoted fibroblast proliferation compared with untreated controls, suggesting its potential role in supporting periodontal tissue regeneration (Bossiela et al. 2023).

A clinical study evaluating 50 patients with generalized plaque-induced gingivitis and mild periodontitis was conducted. The findings demonstrated that treatment with the tested formulation significantly reduced both the Papillary Bleeding Index (PBI) and the Modified Gingival Index (MGI) compared with the placebo group at both the 14-day and 28-day time points. These results indicate marked improvements in gingival inflammation and overall periodontal health (Malekzadeh et al. 2021). Moreover, a randomized clinical trial was conducted on patients with mild-to-moderate chronic periodontitis to evaluate the adjunctive efficacy of a 2% CUR nanogel formulation. The results indicated a significant reduction in the Plaque Index (PI), Gingival Index (GI), Probing Pocket Depth (PPD), and Clinical Attachment Level (CAL) across all treatment groups. Notably, the CUR nanogel demonstrated therapeutic outcomes comparable to those of chlorhexidine, underscoring its potential as an effective and biocompatible adjunct in periodontal therapy (Guru et al. 2020).

Figure 3 illustrates the mechanistic pathways by which Nano-CUR combats infections and reduces inflammation.

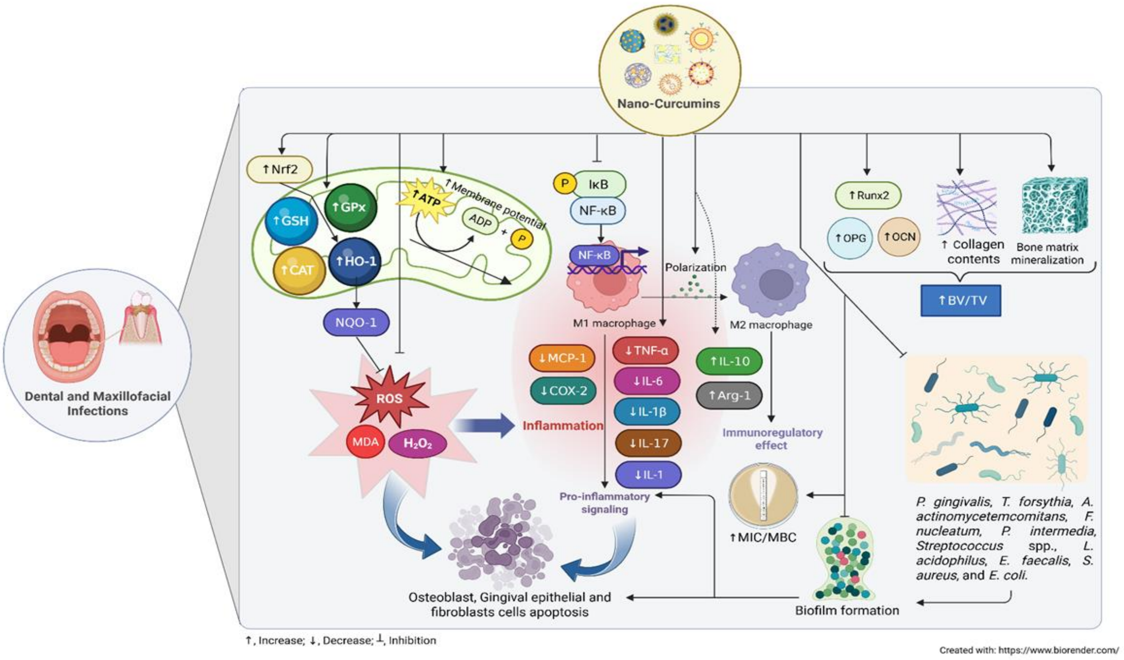

Figure 3. Mechanistic pathways of Nano-CUR in modulating infection and inflammatory responses. CUR-NPs demonstrate a wide range of therapeutic effects, including anti-inflammatory, antioxidant, antibacterial, and tissue-regenerative properties. Their anti-inflammatory activity is primarily due to the suppression of p38 MAPK and NF-κB signaling pathways, along with reductions in pro-inflammatory cytokines such as IL-1β, IL-1, IL-6, IL-17a, TNF-α, COX-2, and MCP-1. Additionally, CUR-NPs promote macrophage polarization towards an M2 phenotype, as evidenced by increased Arg-1 expression and IL-10 upregulation. These NPs reduce neutrophil and mononuclear cell infiltration, inhibit fibroblast proliferation, and enhance periodontal tissue regeneration, as indicated by improved collagen formation, increased alveolar bone density, and elevated levels of osteogenic markers such as Runx2, osteocalcin, and osteoprotegerin. Furthermore, their antioxidant mechanisms involve activation of the Nrf2/HO-1/NQO1 pathway, resulting in enhanced activities of CAT, SOD, and GPX1 and overall ROS scavenging, which alleviates oxidative stress in gingival tissues. The antibacterial properties of CUR-NPs are robust and broad-spectrum, showing dose-dependent inhibition of key periodontal pathogens.

The primary curcuminoid constituents found in turmeric include demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), and the more recently identified cyclocurcumin (CC) (Sandur et al. 2007; Shegokar 2018). Each compound contributes unique structural and biological characteristics to the overall curcuminoid profile. The composition typically features CUR as the predominant component in commercially available CUR preparations, accounting for approximately 77% of the total curcuminoid content. This is followed by demethoxycurcumin at around 17%, with bisdemethoxycurcumin making up the remaining portion (Shegokar 2018). To address the instability at alkaline pH, poor aqueous solubility, rapid metabolism, and low bioavailability of CUR, NPs are used (Hegde et al. 2023). In this study, CUR was applied by various nanocarriers, including polymeric NPs, nanogels/hydrogels, nanofibers/scaffolds, nanocrystals, solid nanocomposites/discs, liposomes/nanoliposomes, mesoporous NPs, exosome-based NPs, metal-based NPs, and ROS-responsive/hyaluronic acid-conjugated NPs (Figure 4).

NPs enhance CUR's solubility, stability, and dispersibility (Bertoncini-Silva et al. 2024; Malekzadeh et al. 2021; Zhang et al. 2023; Zheng and McClements 2020). They improve mucosal adhesion and penetration, prevent aggregation, and ensure uniform drug distribution within electrospun nanofibers, thereby increasing the dissolution rate. Smaller NP sizes contribute to a more uniform distribution, improved redispersion of nanocrystals, and homogeneous CUR distribution. These enhancements lead to better mucosal deposition, sustained *in vitro* release, higher tensile strength, greater stability, and improved compatibility in the treatment of periodontal disease (Chakraborty and Ramamurthy 2024; Tonon et al. 2022; Zhang et al. 2023). Moreover, Nano-CUR systems demonstrated high encapsulation efficiency, improved solubility of hydrophobic drugs such as CUR, and prolonged release profiles, thereby minimizing toxicity at higher doses. When incorporated into chitosan hydrogels, they provided biocompatibility, tunable porosity, and localized delivery. These features enhanced the healing process and produced synergistic antimicrobial effects, highlighting their potential for regenerative and infection-control applications (Atila et al. 2024).

Furthermore, it enables targeted treatment of specific areas in the oral cavity, providing a more precise therapeutic approach (Zhang et al. 2025). In a study, CUR-nanocarriers exhibited several therapeutic advantages that address the inherent limitations of free CUR. By encapsulating CUR within hyaluronic acid (HA)-based NPs, its solubility and stability were significantly enhanced. Moreover, the ROS-responsive PBAP linker enabled controlled drug release specifically in oxidative microenvironments. The inclusion of hyaluronic acid facilitated targeted uptake via CD44 receptors, ensuring superior intracellular delivery within inflamed periodontal tissues. These nanocarriers scavenged ROS more effectively than free CUR, bolstered antioxidant defenses, and promoted stronger anti-inflammatory and antibacterial responses. Furthermore, they demonstrated excellent biocompatibility, characterized by low cytotoxicity and minimal hemolysis, and sustained a therapeutic effect in a rat periodontitis model (Chen et al. 2024).

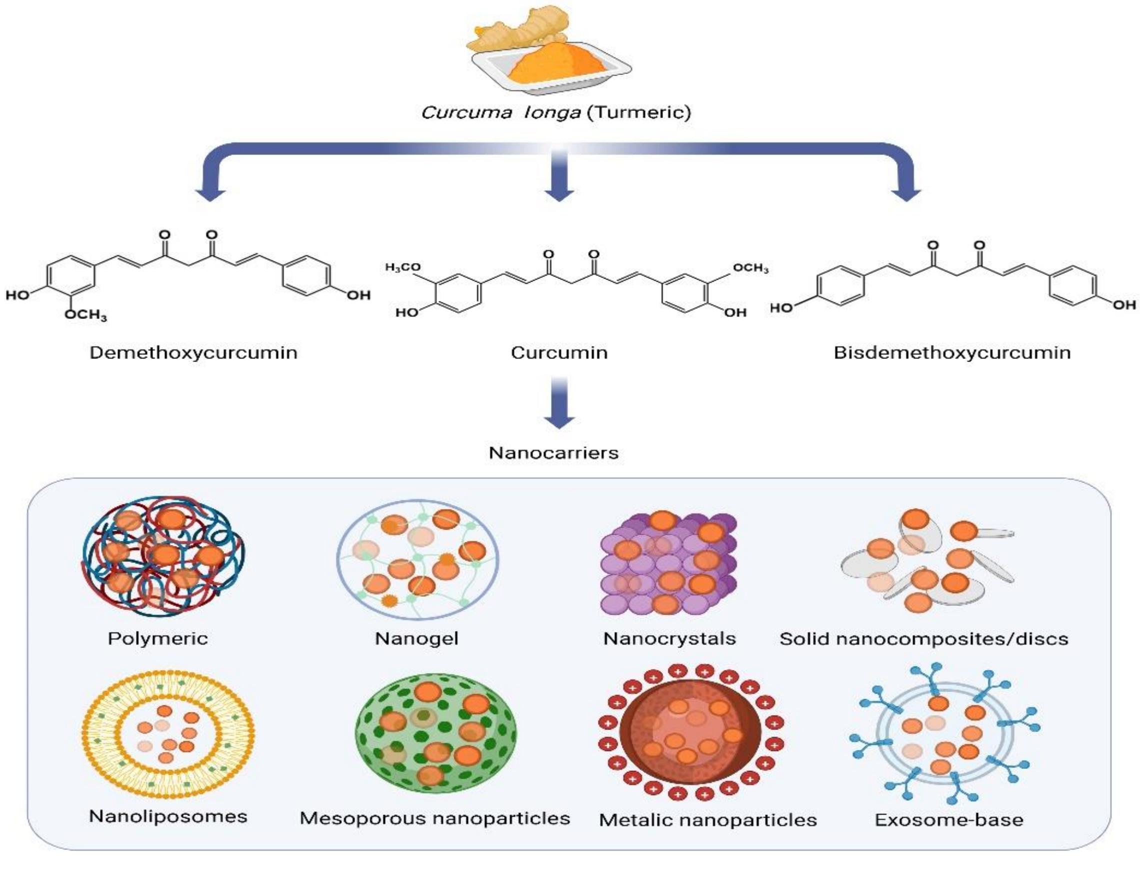

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Figure 4. The molecular structures of the principal curcuminoids present in turmeric and the most critical nanocarriers of CUR

Higher Nano-CUR concentrations in pulpal pastes increased their solubility, allowing selection based on patient age and desired duration of paste dissolution. Clinically, faster-dissolving pastes may suit younger patients, while more stable ones are preferable for more prolonged use (Sahebalam et al. 2023). Chauhan et al. conducted a study that involved both *in vitro* and *ex vivo* evaluations. An *in vitro* film system using gelatin-based films was developed, and *ex vivo* goat mucosa was used for bioadhesion testing. CUR-loaded crosslinked gelatin films were prepared via solvent casting/evaporation, containing 2 mg CUR per 5 mm × 4 mm film, with gelatin concentrations ranging from 2.58-5.41% w/v. Biodegradation of the films was assessed in phosphate buffer at 37°C for up to 90 days. The results demonstrated that CUR was entrapped in an amorphous form within uniform films. The optimized films exhibited high crosslinking, significant swelling, excellent folding endurance, and a neutral surface pH. Sustained CUR release was observed for up to 7 days. The matrix density and crosslinker concentration modulated swelling and biodegradation, and the nanoformulation provided enhanced CUR solubility, controlled release, and improved stability compared to free CUR (Chauhan et al. 2018). CUR-loaded nanostructured lipid carriers (CUR-NLCs) were prepared with lipid mixtures and Tween 20, achieving complete CUR solubilization (2.5% w/w), nanoscale size (~120 nm), high entrapment efficiency (100%), and good stability (ZP -33 to -37 mV). These NLCs were incorporated into metronidazole-loaded mucoadhesive sponges and freeze-dried into highly porous buccal tablets. The results showed that the CUR-NLCs enhanced CUR solubility and stability at acidic pH, forming small, stable spherical

NPs with high encapsulation efficiency, and no free CUR was detected. Colloidal stability was maintained by electrostatic repulsion and Tween 20 steric hindrance. When incorporated into mucoadhesive buccal tablets, the system enabled controlled, localized drug release, prolonged mucosal retention, rapid hydration and sustained swelling, and adequate protection of CUR, allowing synergistic delivery of both hydrophilic (MTR) and hydrophobic (CUR) drugs (Murgia et al. 2019).

On the other hand, these CUR nanocarrier systems vary considerably across parameters such as particle size distribution, surface charge, degradation kinetics, drug loading efficiency, release profiles, and tissue interaction dynamics, rendering direct pharmacokinetic and enabling targeted delivery to defined tissues, cells, and intracellular compartments between them difficult to draw (Alshawwa et al. 2022; Xu et al. 2025).

None of the included RCTs reporting complications from different doses of CUR loaded with NPs reported any specific side effects, and all patients tolerated the treatment with Nano-CURs (Malekzadeh et al. 2021; Pérez-Pacheco et al. 2021; Zakria et al. 2024). Laboratory studies also noted that the synthesized CUR-NPs showed high cytocompatibility and non-cytotoxicity, making them an effective biomaterial for periodontal regeneration (Afrasiabi et al. 2023; Bossiela et al. 2023; Chen et al. 2024; Ekambaram et al. 2021; Liu et al. 2024; Shirmohammadi et al. 2023; Tonon et al. 2022). Moreover, one study reported no significant decrease in cell survival after exposure to the NPs compared with cells cultured without any materials. As a result, the synthesized CUR-NPs demonstrated non-cytotoxic properties toward dental pulp stem cells (Shirmohammadi et al. 2023). However, a study showed that CUR-loaded liposomes exhibited cytotoxic effects on hDPSCs and hGFs at higher concentrations (≥12 μL/100 μL, stock 0.6 mg/mL), reducing cell viability. However, when α-Tocopherol was co-encapsulated with CUR, the toxicity was significantly diminished. α-Tocopherol served as a stabilizer and antioxidant, effectively reducing oxidative stress while facilitating a delayed, sustained release from the liposomal bilayer and hydrogel matrices. This dual action prevented a burst release of CUR and minimized dose-dependent toxicity, thereby preserving the viability and differentiation capacity of stem cells. This effect was particularly pronounced when delivery occurred through chitosan hydrogels, further enhancing biocompatibility and slowing release (Atila et al. 2024). However, some studies reported rare side effects primarily involving dermatological reactions such as pruritus or localized indurated edema, particularly following topical administration of turmeric. Additionally, under certain high-dose *in vitro* conditions, CUR has been associated with potential cytotoxicity and genotoxic effects, including DNA damage (Gupta et al. 2013). However, short-term safety outcomes appear favorable; data regarding long-term safety in humans, standardized dosing regimens, and post-treatment monitoring remain inadequate.

Although these potentials of CUR NPs in prevention and relieving dental and maxillofacial infections and associated inflammatory complications, a significant proportion of the existing evidence originates from *in vitro* and animal research. Although these studies offer valuable mechanistic insights and proof-of-concept findings, their applicability to routine clinical practice is inherently constrained. Consequently, the subsequent findings should be evaluated in accordance with the hierarchy of evidence, explicitly distinguishing between preclinical data and results established in human clinical investigations.

The limitations of the present study include the small number of clinical trials, which restricted the ability to evaluate different doses of Nano-CUR and their side effects. Heterogeneity in bias assessment across *in vivo* and RCT studies, and the medium overall quality of the *in vitro* studies, were other limitations. Additionally, the absence of histological examination, including assessment of osteogenesis and wound-healing properties, posed another challenge in this study. The existing evidence is further constrained by the considerable heterogeneity among nano-CUR formulations. Each platform has a distinct physicochemical profile and biological behavior, with meaningful differences in stability, release kinetics, and tissue interactions that complicate cross-study comparisons.

The results of the included laboratory and clinical studies showed that CUR-NPs are promising in preventing dental and maxillofacial infections and inflammatory complications. The studies also reported no significant side effects or cytotoxicity in patients or treated cells. The studies further indicated generally favorable short-term safety outcomes, with no significant adverse effects or cytotoxicity identified in patients or treated cells. However, long-term safety profiles have not been adequately elucidated. CUR-NPs offer a range of therapeutic advantages for periodontal and peri-implant diseases through their improved bioavailability, sustained release, and targeted delivery. They effectively inhibit key periodontitis pathogens, reduce biofilm formation, and exhibit potent antibacterial activity.

These NP formulations improve mucosal adhesion, penetration, and deposition, effectively preventing aggregation and ensuring uniform drug distribution. As a result, they enhance dissolution, redispersion, and therapeutic efficacy. Additionally, their high encapsulation efficiency and compatibility with hydrogels or nanostructured carriers enable localized, tunable delivery, enhance drug targeting and prolonged therapeutic effects, and minimize toxicity.

Nevertheless, definitive conclusions regarding clinical efficacy cannot yet be drawn. Large, methodologically rigorous RCTs employing standardized interventions, extended follow-up periods, and clinically meaningful outcome measures are necessary prior to recommending routine clinical application.

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Conflicts of interest

The authors had no competing interests.

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Authors' Contributions

Study conception and design: RFT; data collection: SHS and UC; analysis and interpretation of results: SHS and RFT; draft manuscript: CMTS. All authors reviewed the results and approved the final version of the manuscript.

Abbreviations

CUR = Curcumin
IL-1β = Interleukin-1 beta
CCL5 = Chemokine (C-C motif) ligand 5
COX-2 = Cyclooxygenase-2
MCP-1 = Monocyte Chemoattractant Protein-1
iNOS = Inducible Nitric Oxide Synthase
TNF-α = Tumor Necrosis Factor-alpha
NSAIDs = Nonsteroidal anti-inflammatory drugs
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
MeSH = Medical Subject Headings
QUIN = Quality Assessment Tool for In Vitro Studies
RCTs = Randomized controlled trials
RoB 2 = Risk of Bias 2
NP = Nanoparticles
LPS = Lipopolysaccharides

PLGA = Poly(lactic-co-glycolic acid)
MAPK = Mitogen-activated protein kinase
NF-κB = Nuclear factor-κB
ROS = Reactive Oxygen Species
PI = Plaque Index
GI = Gingival Index
PPD = Probing Pocket Depth
CAL = Clinical Attachment Level
PBI = Papillary Bleeding Index
MGI = Modified Gingival Index
CFU = Colony Forming Unit
NR = Not Reported
BOP = Bleeding on Probing
GR = Gingival Recession
ABBL = Activa BioActive Base/Liner
LED = Light Emitting Diode
DLS = Dynamic Light Scattering
MIC = Minimum Inhibitory Concentration
MBC = Minimum Bactericidal Concentration
DOX = Doxycycline
PVC = Polyvinyl Chloride
LIP = Ligature-Induced Periodontitis
CAT = Catalase
GPX1 = Glutathione Peroxidase 1
GSH = Glutathione
Lip = Liposomes
HGFs = Human Gingival Fibroblasts
MMP-8 = Matrix Metalloproteinase-8
SOD = Superoxide Dismutase

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