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Chemically Modified Curcumin as a Host Modulation Therapy in Periodontitis: An Overview

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ABSTRACT

Chemically modified curcumin (CMC) represents a novel host-modulating approach for managing periodontitis, designed to overcome the poor bioavailability and instability of natural curcumin. Among its analogues, CMC2.24, a triketonic zinc-binding derivative, exhibits potent anti-inflammatory, antioxidant, and anti-collagenolytic effects. Preclinical studies demonstrate that CMC2.24 effectively suppresses NF-κB and MMP activity, reduces pro-inflammatory cytokines, and preserves alveolar bone in ligature- and diabetes-induced periodontitis models, with minimal cytotoxicity. Various formulations, including nanoparticles, gels, and collagen scaffolds, enhance local delivery and therapeutic retention. Although no human trials are yet available, the robust preclinical evidence positions CMC derivatives as promising, safe, and biocompatible adjuncts to conventional periodontal therapy. Future research should focus on standardized formulations, long-term safety, and well-controlled clinical trials to confirm translational efficacy.

Keywords: Chemically modified curcumin, CMC2.24, Curcumin Analogues, Periodontitis, Host Modulation, MMP Inhibition, NF-κB, Local Delivery

INTRODUCTION

Periodontitis is a long-standing inflammatory condition initiated by polymicrobial biofilms, leading to progressive breakdown of the supporting structures of teeth and contributing substantially to tooth loss globally. The disease's pathogenesis reflects a dysregulated host response to subgingival biofilms, where excessive proteolytic activity and unresolved inflammation lead to connective tissue degradation and alveolar bone resorption. Contemporary periodontal therapy therefore combines infection control (mechanical debridement) with increasing interest in host-modulation strategies that target the inflammatory and collagenolytic components of tissue breakdown.[1]

Curcumin, a polyphenolic compound derived from Curcuma longa, has attracted substantial attention as a potential adjunct in periodontal therapy because of its anti-inflammatory, antioxidant, and antimicrobial properties shown in preclinical and clinical studies. Clinical trials and meta-analyses evaluating locally delivered curcumin formulations (gels/ointments) as adjuncts to scaling and

root planning report improvements in clinical parameters (probing depth, clinical attachment) and reductions in inflammatory markers, although heterogeneity in formulations, doses and follow-up intervals limit firm conclusions. Despite its biological activity, the therapeutic application of native curcumin is limited by unfavorable pharmacokinetic characteristics, including low water solubility, rapid metabolic conversion, and insufficient bioavailability at target sites, thereby reducing its clinical effectiveness when used systemically or in short-acting topical formulations.[2]

To address these limitations, targeted medicinal-chemistry strategies have led to the development of chemically modified curcumin analogues intended to improve molecular stability, tissue bioavailability, and biological efficacy, while preserving the beneficial properties of the parent compound. Among these, CMC2.24 has emerged as the most extensively studied lead compound. Preclinical work shows that CMC2.24 possesses superior anti-inflammatory and anti-collagenolytic activity compared with parent curcumin: it inhibits NF-κB and p38 MAPK signaling, reduces pro-inflammatory cytokine production, attenuates matrix metalloproteinase (MMP) activation, and, critically, provides greater protection against alveolar bone loss in experimental periodontitis models. These mechanistic and efficacy data come from complementary in vitro assays and several animal models, including LPS-induced and diabetes-associated periodontitis.[3]

Comparative studies further suggest that CMC2.24 and related analogues act through partially distinct mechanisms from natural curcumin and are dose-responsive for key outcomes such as MMP inhibition and bone-sparing effects, supporting their candidacy as host-modulating therapeutics for periodontal disease.[4] Reviews of CMC derivatives and recent formulation studies highlight multiple promising delivery strategies (systemic short-term dosing and local sustained-release systems) but also emphasize that clinical data specifically on chemically modified curcumins remain sparse relative to the literature on natural curcumin formulations.[5]

Given this background, chemically modified curcumins—particularly CMC2.24—represent a compelling translational avenue for host modulation in periodontitis: they combine rational chemical design with demonstrated preclinical efficacy across molecular, cellular and whole-organism endpoints. Nevertheless, critical knowledge gaps remain (optimal dosing and route, long-term safety, standardized local-delivery platforms, and well-designed clinical trials) and must be addressed to move CMCs from bench to bedside. This review synthesizes the chemistry, mechanisms, preclinical evidence and formulation approaches for chemically modified curcumins in periodontal therapy and outlines the translational steps needed for clinical implementation. [6]

CURCUMIN: CHEMISTRY, PHARMACOLOGY, AND RATIONALE

Curcumin, a bright yellow polyphenolic compound, is the principal bioactive constituent of Curcuma longa (turmeric), a plant widely used in traditional medicine and culinary practices. Chemically, curcumin is known as diferuloylmethane and has the molecular formula $C_{21}H_{20}O_6$. Structurally, it consists of two aromatic rings containing o-methoxy and phenolic hydroxyl groups linked by a seven-carbon chain with conjugated double bonds and a β-diketone moiety. This unique structure is responsible for its antioxidant and metal-chelating properties.

Pharmacologically, curcumin exhibits a broad spectrum of biological activities, including anti-inflammatory, antioxidant, antimicrobial, anticancer, and wound-healing effects. Its anti-inflammatory action primarily occurs through downregulation of NF-κB, COX-2, and pro-inflammatory cytokines such as TNF-α and IL-6. Its antioxidant potential arises from its ability

to scavenge reactive oxygen species and enhance endogenous antioxidant enzymes like superoxide dismutase and catalase.[7]

In dentistry and periodontology, curcumin has been explored for its capacity to reduce inflammation, promote wound healing, and inhibit microbial growth in periodontal pockets. However, to maximize its therapeutic value, the rationale for further molecular enhancement stems from the need to improve its stability, bioavailability, and retention in periodontal tissues—leading to the development of chemically modified curcumin (CMC) derivatives.

CURCUMIN AND ITS LIMITATIONS

Despite its promising pharmacological profile, the clinical utility of curcumin is significantly constrained by poor bioavailability resulting from low gastrointestinal absorption, rapid metabolism, and quick systemic elimination. It is poorly soluble in water and unstable at alkaline pH, which limits its effectiveness in maintaining therapeutic concentrations under physiological conditions.

To overcome these drawbacks, researchers have developed chemically modified curcumin (CMC) derivatives, aiming to enhance curcumin's stability, solubility, tissue penetration, and sustained activity in inflammatory environments such as periodontal pockets.

The β-diketone moiety of native curcumin, prone to hydrolytic and oxidative degradation, is chemically altered or removed in mono-carbonyl curcumin (MCC) derivatives. Such modifications improve stability and prevent rapid metabolic reduction. Among these, CMC2.24, a prototype triketonic zinc-binding curcumin derivative, exhibits potent inhibition of matrix metalloproteinases (MMP-2, MMP-9, and MMP-13)—enzymes responsible for collagen degradation and alveolar bone loss.

By removing the central methylene group and introducing electron-withdrawing substituents, CMC2.24 enhances metal ion (Zn^{2+}) chelation, enabling it to function as both an antioxidant and selective MMP inhibitor. Preclinical studies in ligature-induced periodontitis models have demonstrated that CMC2.24 significantly reduces inflammatory cell infiltration, osteoclast activity, and bone resorption, without cytotoxic effects on gingival fibroblasts.

Moreover, curcumin analogues modified via PEGylation or nanoparticle conjugation further enhance solubility and local retention, allowing effective delivery through gels or chips for periodontal applications. These delivery systems sustain drug release, promote fibroblast attachment, and improve soft-tissue healing—making chemically modified curcumin derivatives a rational and evidence-based innovation for transforming natural curcumin into a stable, bioavailable, and targeted adjunct in periodontal therapy.

MECHANISM OF ACTION OF CHEMICALLY MODIFIED CURCUMIN IN PERIODONTITIS

Chemically modified curcumin (CMC) derivatives exert their therapeutic effects in periodontitis through multifactorial mechanisms targeting the key molecular pathways involved in inflammation, oxidative stress, and tissue degradation. The most studied derivative, CMC2.24, demonstrates enhanced anti-inflammatory and anti-collagenolytic activity compared to native curcumin, primarily due to improved chemical stability and metal-ion binding affinity.

1. Inhibition of Matrix Metalloproteinases (MMPs)

Excessive activity of MMPs, particularly MMP-8, MMP-9, and MMP-13, contributes to collagen breakdown and alveolar bone loss in periodontitis. CMC2.24 functions as a triketonic compound with strong affinity for zinc ions, enabling interaction with the catalytic domains of matrix metalloproteinases and thereby reducing their collagenolytic activity, leading to enzyme inhibition without affecting physiological collagen turnover (Golub et

al., 2018). In a rat model of ligature-induced periodontitis, oral administration of CMC2.24 significantly reduced MMP-9 and MMP-13 expression and prevented alveolar bone resorption.[8]

2. Suppression of Pro-inflammatory Cytokines

CMC derivatives downregulate key pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6 by blocking the NF-κB signaling pathway, a central regulator of periodontal inflammation. In a study by Gupta et al. (2020), CMC2.24 treatment led to a marked decrease in NF-κB activation and COX-2 expression in gingival tissues, indicating potent immunomodulatory effects.[9]

3. Antioxidant and Redox-Modulating Effects

CMC analogs maintain and enhance curcumin's inherent antioxidant property by stabilizing phenolic groups and preventing oxidative degradation. This results in decreased lipid peroxidation, reactive oxygen species (ROS), and nitric oxide levels in periodontal tissues, thereby limiting oxidative damage to fibroblasts and osteoblasts. [9,10]

4. Modulation of Bone Metabolism

CMC2.24 has been shown to regulate bone homeostasis by inhibiting RANKL-induced osteoclastogenesis and promoting osteoblast differentiation.8 demonstrated a significant reduction in TRAP-positive osteoclasts in CMC2.24-treated animals, suggesting potential for alveolar bone preservation.

5. Promotion of Soft Tissue Healing

Due to improved solubility and bioavailability, CMC-based formulations maintain higher concentrations within periodontal pockets, enhancing fibroblast proliferation and collagen deposition. This property supports wound healing and early tissue attachment following surgical therapy. [7,9,11]

Collectively, these mechanisms position CMC derivatives, particularly CMC2.24, as promising adjuncts in periodontal therapy by combining anti-inflammatory, antioxidant, and bone-protective effects within a single molecular framework.

PRECLINICAL AND CLINICAL EVIDENCES OF CMC IN PERIODONTAL THERAPY

Evidence to date is preclinical only: multiple rat models (ligature-induced, LPS/AGEs, diabetic), one large-animal study (beagle/dog), and dose-response studies.[6]

The compound most consistently studied is CMC2.24 (a triketonic, Zn^{2+}-binding chemically modified curcumin). Across studies it reduces MMP activity, inflammatory cytokines (IL-1β, TNF-α), oxidative markers, gingival inflammation, and alveolar bone loss compared with placebo or native curcumin.[4]

Effective doses reported vary by species and study: common rat doses ≈ 30 mg/kg (many rodent studies), but dose-response work has shown significant effects at lower doses (reports of efficacy even at ~1 mg/kg/day in some settings); dog studies used ~10 mg/kg oral for short durations.[12] Toxicity/weight-loss was generally not reported at tested doses.[13]

Extensive preclinical research has demonstrated the therapeutic potential of chemically modified curcumin (CMC), particularly CMC2.24, in managing periodontal inflammation and tissue destruction. Most studies employ ligature- or LPS-induced periodontitis models in rats, where systemic administration of CMC2.24 (1–30 mg/kg) significantly reduced MMP activity (MMP-8, MMP-9, MMP-13), pro-inflammatory cytokines (IL-1β, TNF-α), and oxidative stress markers, resulting in reduced alveolar bone loss and improved histologic healing (Golub et al., 2018; de Almeida Brandão et al., 2019). Even at low doses (1 mg/kg), CMC2.24 preserved bone architecture and inhibited collagenolytic enzymes, indicating strong potency.

In diabetic-associated periodontitis models, CMC2.24 enhanced resolution pathways by increasing resolvin E1 and suppressing NF-κB activation.3 Comparative studies

revealed that, unlike native curcumin, CMC2.24 maintained anti-inflammatory effects while achieving measurable bone preservation.[4]

A translational beagle-dog study confirmed these findings, where oral CMC2.24 (10 mg/kg) decreased pocket depth, gingival inflammation, and active MMP-9 without adverse effects (Deng et al., 2020). Systematic reviews further affirm consistent anti-inflammatory and anti-bone-resorptive outcomes across all animal models.[14]

Although no human clinical trials have yet been published, the robust preclinical data indicate that CMC derivatives, especially CMC2.24, could serve as promising adjuncts to conventional periodontal therapy, offering stable, bioavailable, and targeted inhibition of destructive host responses.

Author & Year	**Model / Species**	**Compound & Dose**	**Route / Duration**	**Control / Comparator**	**Main Findings / Outcomes**
Golub LM et al., 2018[8]	Ligature-induced periodontitis, rats	CMC2.24 (30 mg/kg)	Oral, daily for 10–14 days	Placebo & native curcumin	↓ MMP-2, MMP-9, MMP-13; ↓ IL-1β & TNF-α; ↓ bone loss; improved histology
Wang HH et al., 2019[9]	Ligature-induced periodontitis, rats	CMC2.24 (dose not specified)	Oral, 2 weeks	Untreated & curcumin groups	↓ Bone resorption; ↓ systemic inflammation (CRP, IL-6); ↑ antioxidant capacity
de Almeida Brandão D et al., 2019[13]	Ligature-induced periodontitis, rats	CMC2.24 (1–30 mg/kg, dose–response)	Oral, 15 days	Vehicle-treated control	Dose-dependent ↓ bone loss; ↓ MMP-9 & TNF-α even at low doses
Curylofo-Zotti FA et al., 2018[4]	LPS-induced periodontitis, rats	CMC2.24 (30 mg/kg) vs curcumin	Oral, 10 days	Natural curcumin & saline	Only CMC2.24 ↓ bone resorption vs curcumin
Elburki MS et al., 2017[3]	Diabetes-associated periodontitis, rats	CMC2.24 (~30 mg/kg)	Systemic, 4 weeks	Vehicle & untreated diabetic	↓ NF-κB; ↑ resolvin E1; ↓ cytokines & MMP-9; improved bone parameters
Deng J et al., 2020[12]	Naturally occurring periodontitis, beagle dogs	CMC2.24 (10 mg/kg)	Oral, 4 weeks	Placebo	↓ Gingival inflammation, pocket depth, MMP-9; less bone loss; well tolerated
Dhaifullah E et al., 2021[14]	Systematic review (7 preclinical studies)	–	–	–	Consistent anti-inflammatory & bone-protective results; no human trials
Wendorff-Tobolla LM et al., 2023[16]	Systematic review/meta-analysis	–	–	–	Confirmed CMC2.24 efficacy; need for clinical trials

FORMULATION, DELIVERY STRATEGIES, SAFETY, AND FUTURE DIRECTIONS OF CHEMICALLY MODIFIED CURCUMIN (CMC) IN PERIODONTAL THERAPY;

Chemically modified curcumin (CMC) has been developed to overcome curcumin's inherent limitations of poor solubility, rapid metabolism, and low bioavailability[11]. Among its derivatives, CMC 2.24—a triketonic analog—has shown potent anti-inflammatory and host-modulatory effects in periodontal models.[3,4]

For formulation and delivery, CMC has been incorporated into biodegradable gels, liposomes, nanoparticles, and collagen scaffolds, enabling localized and sustained drug release in periodontal pockets.[11] Chitosan and PLGA nanoparticle-based systems enhance mucosal adhesion, prolong intra-pocket residence time, and improve penetration into gingival and periodontal tissues. [4.] In rat models, topical or systemic administration of CMC 2.24 significantly reduced alveolar bone resorption, MMP-9 activity, and inflammatory cytokine expression, outperforming native curcumin [3,15]

Regarding safety and toxicity, in-vitro studies confirm that CMC exhibits minimal cytotoxicity to gingival fibroblasts and periodontal ligament cells at therapeutic concentrations.[4] Animal studies reported no systemic toxicity or organ damage following repeated topical or oral administration.[3] The localized mode of delivery ensures low systemic exposure and rapid metabolism, enhancing its safety profile.[15]

Future directions include optimizing standardized CMC formulations with reproducible release kinetics and exploring stimuli-responsive nanocarriers (e.g., pH- or enzyme-sensitive systems) for site-specific release in diseased pockets. Combining CMC with growth factors, probiotics, or regenerative biomaterials could further enhance tissue healing. However, challenges remain in maintaining chemical stability, ensuring uniform drug loading, and conducting well-controlled human clinical trials to confirm long-term efficacy and safety.[16]

CONCLUSION

Chemically modified curcumin (CMC) represents a structurally optimized derivative of natural curcumin, developed to enhance its anti-inflammatory and antioxidant performance in periodontal disease management. useful for treating periodontal diseases. By modifying the structure of curcumin, researchers have created forms like CMC 2.24 that are more stable, more soluble, and more effective in reaching periodontal tissues. Studies in animals models have shown that CMC helps reduce bone loss, inflammation, and tissue destruction, while also promoting healing.

The main advantages of CMC are its better stability, local delivery potential, and minimal toxicity compared to regular curcumin. When used in gels, nanoparticles, or collagen scaffolds, it provides slow and sustained release, making it suitable for periodontal pockets. CMC also appears safe, showing no significant harm to cells or organs in available studies.

However, there are still important shortcomings. Most evidence comes from animal studies, and clinical data in humans are limited. There is also no standard formulation or dosage, and differences in drug release, stability, and absorption remain challenges. Large, long-term clinical trials are needed to confirm its benefits and safety in real patients.

In summary, CMC represents a promising and biocompatible adjunct for periodontal therapy that combines the natural benefits of curcumin with improved pharmacological properties. With further refinement and human testing, it could become a reliable, safe, and eco-friendly therapeutic option for managing periodontal inflammation and promoting tissue regeneration.

Declaration by Authors

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