



The role of curcumin in periodontal therapy: An update

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ABSTRACT

Background: Periodontal diseases, including gingivitis and periodontitis, present a significant global health burden, particularly affecting adults and especially the aging population. The etiology involves complex interactions between microbial colonization and host immune-inflammatory responses, leading to tissue destruction and bone resorption. Current conventional treatments, primarily focused on mechanical debridement and antimicrobial agents, often have limitations and challenges, including antibiotic resistance and limited tissue regenerative potential. Curcumin, a polyphenolic compound derived from the *Curcuma longa* plant, has emerged as a promising adjunctive therapeutic agent owing to its remarkable pharmacological properties. Extensive preclinical research has revealed the potential anti-inflammatory, antioxidant, antimicrobial, and immunomodulatory effects of curcumin. These attributes make it a compelling candidate for addressing various aspects of periodontal pathogenesis. Furthermore, curcumin's capacity to *in vitro* inhibit various periodontopathogens such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* demonstrates its potential as a natural antimicrobial agent. Its adjunctive use in local drug delivery systems, such as gels or nanoparticles, holds promise for targeted delivery and sustained release within periodontal pockets, enhancing its therapeutic potential. However, challenges related to its bioavailability, stability, and dosage standardization need to be addressed for successful clinical outcomes.

Key words: periodontal diseases; curcumin; bioactive compounds, inflammatory response, microbial dysbiosis

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Curcumin is a polyphenol found in turmeric (*Curcuma longa*), with several health benefits owing to the antioxidant, anti-inflammatory, and antimicrobial properties, making it a compelling candidate for addressing various aspects of periodontal pathogenesis.

INTRODUCTION

Periodontal diseases are a spectrum of inflammatory conditions that damage the supporting structures of the teeth including the gingiva, bone, and periodontal ligament. Periodontal diseases are the most common chronic oral diseases affecting millions of people worldwide, with poor oral hygiene and plaque accumulation as primary etiological factors. Without prompt treatment, periodontal infections can have significant effects on the periodontium, eventually leading to tooth loss. The treatment protocol traditionally focuses on non-surgical interventions such as scaling, and root planning combined with the administration of appropriate antimicrobial agents to combat the pathogenic bacteria [1-3].

Curcumin, a natural extract from *Curcuma longa* roots, is considered as a functional food element offering potential benefits in the treatment of periodontal diseases. Multiple studies have suggested that curcumin possesses anti-inflammatory and antioxidant properties, which can help reduce inflammation and oxidative stress, two key factors in the development and progression of periodontal diseases. Additionally, curcumin has demonstrated antimicrobial effects, making it an attractive adjunct therapeutic modality in periodontal infections. Local administration of curcumin-containing nanomaterials has also been found to prevent bone resorption and

inflammation associated with experimental periodontal disease. These properties make curcumin an appealing candidate for a variety of periodontal applications [4-6]. Its safety and anti-inflammatory properties make it highly attractive. Thus, it is imperative to review the current state of its use within the context of periodontal diseases. This article aims to provide a comprehensive update on the applications, mechanisms, clinical efficacy, safety, and prospects of curcumin in periodontal therapy.

Curcumin: An overview: Curcumin (Curc; diferuloylmethane) is the yellow key ingredient of the natural spice turmeric. It is a polyphenolic derived lipophilic bioactive compound extracted from roots of *Curcuma longa*. Turmeric (*Curcuma longa* L.) is the popular household name for the spice well-known for its deep orange yellow colour, extensively used as a flavouring agent in many Asian and Middle Eastern cuisines. Its original flowering plant belongs to the ginger family, Zingiberaceae, native to India and Southeast Asia. The active constituents of turmeric include the three curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (turmerone, atlantone, and zingiberone), sugars, proteins, and resins. Oral administration of curcumin is absorbed by the body as an active metabolite from tetrahydrocurcumin, which

is converted by an enzyme found in the intestinal epithelium called reductase [7-8].

The use of turmeric and its active compound, curcumin, can be traced back thousands of years in traditional Indian and Chinese medicine systems. In India, curcumin has been a fundamental component of Ayurvedic medicine for over 4,000 years and was used to treat various conditions, including gastrointestinal disorders, respiratory diseases, and skin conditions. It has also been used in traditional Chinese medicine for centuries, mainly for its anti-inflammatory and analgesic properties, among other proposed health benefits. Curcumin has also been historically recognized as an antimicrobial agent. In recent years, curcumin has gained considerable attention for its role as a dietary supplement with potential applications in various fields, including pharmaceuticals and nutraceuticals [9-10].

Extensive research and clinical trials have indicated that curcumin possesses significant therapeutic potential, encompassing its pharmacological actions as an antibacterial, anti-mutagenic, and antioxidant. A large body of investigation has also provided important insights into the anti-inflammation effects of curcumin as well as its anti-aging and neuroprotective effects [11-13]. It has been established that curcumin is a highly pleiotropic molecule capable of modulating key inflammatory pathways, including inhibition of NF- κ B and COX-2 expression. As such, it was generally suggested that curcumin is useful as a viable therapeutic option in many chronic diseases such as inflammatory bowel disease, arthritis, pancreatitis, and chronic anterior uveitis [14-15]. Additionally, its capacity to mitigate oxidative stress and control the release of pro-inflammatory mediators showcased promise for cardiovascular diseases in particular, as evidenced by its benefits in improving endothelial function, reducing atherosclerotic plaque formation, and regulating lipid metabolism [16].

Studies exploring curcumin's impact on oncogenesis have revealed its potential in targeting multiple signalling pathways involved in the initiation, development, and growth of tumour cells. These anticarcinogenesis effects are predominantly mediated through its negative regulation of various transcription factors, growth factors, protein kinases, and other oncogenes [17-18]. Additionally, it demonstrated therapeutic efficacy in controlling the proliferation of cancer cells by arresting them at different phases of the cell cycle and inducing apoptosis [18]. Preclinical investigations highlighted its ability to hinder the growth of various cancer cell lines, suggesting a potential role as adjunct therapy for various malignancies. Promising findings have been reported in breast, colon, and prostate cancer stem cells in culture [19-20]. Clinical trials continue to be conducted to establish its safety and efficacy as a complementary approach to conventional cancer treatment of some malignancies and determine its *in vivo* molecular targets.

Further applications extend to metabolic disorders, where curcumin demonstrated potential in addressing obesity, hypertension, and insulin resistance, suggesting a positive impact on reducing the risk of diabetes and associated cardiovascular complications [21]. Studies also suggested hepatoprotective effects against toxin-induced liver damage and non-alcoholic fatty liver disease [22]. Curcumin's therapeutic potential also included neurodegenerative diseases, with a particular focus on Alzheimer's disease. Some research suggested that curcumin may help prevent the buildup of beta-amyloid plaques in the brain, a hallmark of Alzheimer's pathology [23].

The safety and bioavailability of curcumin have been subjects of extensive research. While generally regarded as safe and well-tolerated in humans when consumed as a part of the regular diet, its low bioavailability, primarily due to poor solubility and

rapid metabolism, has presented a challenge in utilizing its therapeutic advantages. Various strategies have been explored to enhance curcumin's bioavailability, including the use of adjuvants, nanoparticle formulations, and structural analogs, aiming at improving its stability in human systems. At moderate doses, curcumin is generally safe with limited adverse effects however, some reports have indicated that high doses may lead to gastrointestinal disturbances, and it may interact with certain medications due to its influence on drug-metabolizing enzymes [24-25]. The

complex interplay between curcumin's safety profile, absorption and metabolism patterns, and its potential health benefits remains an area of active research.

Curcumin and periodontal therapy: Gingivitis, the mild form of periodontal diseases (Table 1), affects about 80% of adults globally. Gingivitis is initiated by infections caused by periodontal pathogens present in the oral biofilms leading to prolonged inflammatory reactions in the gingival tissue [26].

Table 1: Classification of periodontal diseases.

Staging a Periodontitis Patient		Initial Periodontitis	Moderate	Severe with potential for tooth loos	Advanced with potential for dentition loos
Periodontitis stage		Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL at site of greatest loss	I to 2 mm	3 to 4 mm	≥ 5mm	≥ 5mm
	Radiographic bone loss	Coronal third (<15%)	Coronal third (15% to 33%)	Extending to mid-third of root and beyond	Extending to mid-third of root and beyond
	Tooth loss	No tooth loss due to periodontitis		Tooth loss due to periodontitis of ≤ 4 teeth	Tooth loss due to periodontitis of ≥ 5 teeth
Complexity	Local	Maximum probing depth ≤ 4mm	Maximum probing depth ≤ 5mm	In addition to stage II complexity: Probing depth ≥ 6 mm Vertical bone loss ≥ 3mm Furcation involvement Class II or III Moderate ridge defect	In addition to stage III complexity: Need for complex rehabilitation due to: Masticatory dysfunction Secondary occlusal trauma (tooth mobility degree ≥ 2) Severe ridge defect Bite collapse, drifting, flaring less than 20 remaining teeth (10 opposing pairs)
		Mostly horizontal bone loss	Mostly horizontal bone loss		

Without proper treatment, the gingival tissues retract, followed by alveolar bone resorption and possible tooth loss (periodontitis) due to the chronic inflammation induced by inflammatory mediators, such as interleukins (ILs), matrix metalloproteinases (MMPs), and prostaglandin E2 (PGE2). Furthermore, the accumulation of reactive oxygen species produced

by immune cells causes aggravation of the periodontal tissues' damage and bone loss [27]. Major pathogens identified as etiological factors for periodontitis include anaerobic bacteria such as Porphyromonas gingivalis, Prevotella intermedia, and Aggregatibacter actinomycetemcomitans. Eliminating microbial irritation through the mechanical removal of the

subgingival plaque halts the progression of the disease and might prevent its recurrence. The use of certain systemic agents to counteract the inflammatory and osteoclastic activity impacting the periodontal tissues might also be an effective approach [28].

Oral microbial biofilms are composed largely of organisms with inflammatory potential, and they also play an important role in preventing expansion of pathogenic organisms. Changes in the local environment such as plaque accumulation, smoking, or certain metabolic diseases, alter the oral cavity's ecosystem, resulting in dysbiosis, which forms the etiologic basis for all oral diseases. While this dysbiotic interaction between the host tissues and the bacteria in the biofilm is responsible for the inflammatory periodontal tissue destruction, genetic susceptibility also plays an important role in the process. The genetic makeup of the host as well as gene variants in different populations affect the microbial colonization rate and composition of the biofilms, which in turn, influence the susceptibility to the disease and the progression rate [29-30].

Various studies have been conducted to evaluate the efficacy of curcumin administration as a novel therapeutic approach for the treatment of chronic periodontitis. In one of the earliest studies, curcumin effectively reduced inflammation and connective tissue breakdown in the experimental periodontitis animal model. This effect was explained, at least in part, by the inhibition of inflammatory mediators including IL-6 and PGE₂, as well as modulation of NF- κ B activation. Curcumin treatment also resulted in a significant reduction of the inflammatory infiltrate, increasing collagen content and fibroblastic cell numbers. The authors however, reported that although natural curcumin was effective in suppressing inflammatory response based on these findings, it had no effect on alveolar bone loss in the same experimental model [31]. In a similar model of ligature-induced periodontitis in rats, both curcumin and piperine had

positive effects on tissue repair, including increased TGF- β levels, improved collagen repair, reduced cellularity, and decreased NF- κ B activation in periodontal tissues. Curcumin also significantly enhanced early bone repair in the experimental group. The authors thus suggested that curcumin and piperine individually hold promise for the treatment of periodontal disease by promoting tissue repair [32].

A study by Nasra et al., [33] aimed at developing an injectable, in-situ gel containing curcumin for the treatment of periodontal pockets and assessing its clinical efficacy. Various gel formulations were created and tested for their physical properties. The chosen formulation (with 30% thermosensitive polymer and 1% pH-sensitive and mucoadhesive polymer), maintained curcumin stability, allowed easy application into the periodontal pockets through a needle, and a controlled drug release for prolonged duration. Clinical evaluation of the treated group proved that this stabilized formulation of 2% curcumin in situ gel was an effective adjunct to the conventional treatment in patients with chronic periodontitis and helped improving clinical signs in terms of reduction of probing depth and bleeding index. In another study using 1% curcumin gel along with conventional treatment, significant improvements in clinical parameters and reductions in the count of periodontopathic bacteria (*Porphyromonas gingivalis*, *Prevotella intermedia*, and *Fusobacterium nucleatum*) were reported after 6 months when compared with control sites receiving the conventional treatment only [34].

Nandini et al., [35] compared the effectiveness of the 1% curcumin solution with chlorhexidine solution in a cohort of periodontitis patients. After 45 days of receiving both interventions, their results showed that 1% curcumin solution was as effective as a 0.2% chlorhexidine mouthwash. In a similar clinical study, periodontitis patients who underwent scaling and root planning, followed by curcumin mouthwash (20%) for 21 days, displayed significantly greater improvement of

gingival inflammation than those who underwent only scaling and root planning with no significant difference in plaque indices [36].

A study by Shahzad et al., [37] reported an inhibitory effect of curcumin on the planktonic growth of *A. actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis*. Moreover, curcumin suppressed *Porphyromonas gingivalis* homotypic and *Porphyromonas gingivalis*-*S. gordonii* biofilm formations. A study by Bomdyal et al., [38] further confirmed that curcumin powder at high concentration (100 µg/ml) hindered the growth of *Porphyromonas gingivalis* and *Prevotella intermedia* in vitro. The effect of curcumin on *Streptococcus mutans* on tooth surfaces and extracellular matrix proteins was also investigated in another study. The results showed that curcumin, at a concentration of 128 µg/ml, completely inhibited *Streptococcus mutans* attachment to human teeth [39].

Although natural curcumin's prospective therapeutic applications are theoretically promising based on these in vitro findings and clinical observations, its short plasma half-life, low bioavailability, and poor gastrointestinal absorption rate following oral administration are variables that restrict its usefulness [24]. Structural alteration had thus been suggested to the compound in an effort to create synthetic analogues that might improve its pharmacological characteristics. The biphenolic compound's structure was modified by adding different side chains at the carbon position, which resulted in the creation of brand-new polyenolic zinc-binding inhibitors. Two chemically modified curcumin-2.5 and -2.24 (4-phenylaminocarbonyl curcumin) were endorsed as a potential pharmacological strategy for managing patients with chronic inflammatory periodontal diseases [40-41].

These chemically modified curcumin compounds had been extensively examined in vitro, in cell and tissue culture systems, and in vivo across a spectrum of

animal species, including rats, rabbits, and dogs. Curcumin, in its chemically modified triketonic form, was reportedly a more potent anti-inflammatory modulator when compared to its diketonic natural version. In animal studies involving experimentally induced periodontitis, only chemically modified curcumin significantly reduced alveolar bone resorption, even though both products appeared to limit the inflammatory process [42-43]. Curcumin-2.24 was more effective in suppressing the inflammatory mediators IL-1, IL-6, PGE2, and MMP-9 secretion from human monocytes in culture [44]. In addition, curcumin-2.24 treatment in vitro was associated with decreased activation/phosphorylation of NF-κB light-chain-enhancer of activated B cells, which regulates transcription of a number of gene products associated with inflammatory diseases [45]. In a study utilizing an animal model of severe periodontitis and poorly controlled diabetes, curcumin-2.24 prevented alveolar bone loss and suppressed both pro- and active MMP-2 and MMP-9 in the gingival tissues [46]. Based on these anticollagenolytic effect and potent MMPs inhibitory activity, together with the structural modifications that enhanced their bioavailability, the chemically modified curcumin compounds have been proposed as a potentially effective therapeutic modality for periodontitis.

Conclusion and future directions: In recent years, the consideration of natural compounds and functional foods for the management of periodontal diseases has gained significant attention within the field of dental research and oral health. Among these natural compounds, curcumin, especially in the chemically modified form, has shown great promise for its potential application in periodontal disease management. The multifaceted pharmacological properties including its anti-inflammatory, antioxidant, and antimicrobial effects, make it a promising

candidate for the development of novel treatment strategies in periodontal health. Current research endeavors are aimed at elucidating the mechanisms underlying curcumin's efficacy in periodontal diseases, with a focus on its impact on the inflammatory response, periodontal tissue regeneration, and microbial dysbiosis. As the field continues to evolve, the prospects of curcumin are promising.

Ongoing investigations target optimizing curcumin's delivery systems and formulations to enhance its bioavailability and efficacy as an adjunctive aid for clinical applications. Personalized approaches considering genetic factors and host response variations may provide a tailored therapeutic strategy for individuals suffering from periodontal diseases. Standardization of extraction methods and quality control measures are imperative to ensure consistency and reliability in curcumin-based products. Furthermore, the development of evidence-based guidelines for its clinical usage, including the determination of optimal dosages and treatment duration require more investigations. To enhance its utilization, future research in this area is expected to also focus on exploring the synergistic effects of curcumin with conventional periodontal therapies and medications as well as establishing its safety profile and long-term effects harnessing the full potential in periodontal disease management.

Abbreviations: COX-2: cyclooxygenase-2, NF-κB: Nuclear factor kappaB, ILs: interleukins, MMPs: matrix metalloproteinases, PGE2: prostaglandin E2, TGF-β: transforming growth factor- β.

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