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Current Evidence on the Use of Curcumin in Modern Periodontology- A Narrative Review

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Abstract

Curcumin, the main bioactive ingredient in turmeric, has been used to treat multiple diseases and conditions due to its numerous health benefits and therapeutic effects. The properties of natural and chemically modified curcumin (CMC) have been extensively investigated, with strong evidence on its anti-inflammatory, anti-microbial (antibacterial, antiviral, antifungal properties), antioxidant, anti-angiogenic, anti-carcinogenic, antispasmodic, hepato-protective, and wound healing properties. The aim of this review aims to present an overview of the use of curcumin in periodontal therapy and the biological mechanisms behind its properties. Findings from in vitro studies suggest that curcumin can promote osteogenesis, down regulate proteases, promote wound healing, and suppress periodontal bacteria. Results from animal studies suggest the potential of curcumin to reduce periodontal inflammation and alveolar bone loss. Topical application of curcumin has been evaluated in clinical studies as an adjunct to periodontal therapy in the form of gel, mouthwash, irrigation solution, adhesive strip, sponge, and chip. The benefits of the topical use of curcumin have been compared to those of chlorhexidine and have been widely confirmed in pre-clinical studies. The majority of clinical studies report superior clinical and microbiological results when curcumin is used in combination with mechanical therapy. Nonetheless, there is a lack of randomized clinical trials with long-term follow-up and adequate sample size. The low toxicity, limited side effects, availability, low cost, and a full spectrum of beneficial biological properties are among the main advantages of curcumin. Despite the major health benefits associated with the use of curcumin, more studies are warranted to further investigate its effectiveness in the management of periodontal disease.

Keywords

Introduction

The roots of the plant Curcuma longa, which belongs to the ginger family, is the source of a colorful spice, widely known as turmeric. With its distinctive taste, turmeric has long been used in culinary, particularly in South-eastern Asia cuisine, in the cosmetic and fabric dye industry. Curcumin is the main bioactive ingredient in turmeric and it has been associated with a variety of health benefits and therapeutic effects [1].

The therapeutic use of turmeric in traditional medicine dates back to ancient times, with its origins in the Indian Vedic tradition [1]. Historically, turmeric has been used in the treatment of multiple diseases and conditions, however, the first scientific report on its anti-bacterial properties was only published in 1949 [2]. The first scientific study on the use of curcumin in Dentistry was published in 1994. The authors reported the beneficial effects of dietary turmeric in oral carcinogenesis in hamsters [3].

The properties of curcumin have been extensively investigated, with strong evidence on its antibacterial, anti-inflammatory, anti-oxidant, anti-tumor, and anti-angiogenic effects. Natural curcumin is poorly absorbed in the gastrointestinal tract, which reduces its bioavailability. Due to the wide range of biological effects, safety, and lack of significant adverse effects of curcumin, there has been increasing interest in the production of synthetic analogs to improve the pharmacological characteristics of the natural compound [4].

The potential of curcumin as a therapeutic agent to help restore oral health is vast [5]. More recent studies suggest that chemically modified curcumin (CMC) has host-modulating properties, while curcumin-based gel and mouthwashes have the potential to reduce plaque, gingival inflammation, and pocket depth [6]. This narrative review aims to present an overview of the use of curcumin in periodontal therapy and the biological mechanisms behind its properties. The clinical relevance of this review lies in the need for evidence-based natural approaches to oral diseases and conditions and the potential benefits associated with this compound.

New trends- Growing Demand for Natural Products

There is a growing demand for a more integrative health approach, one that considers all factors that influence health and disease, such as genetic and environmental risk factors, lifestyle, diet, and

emotional wellbeing. Integral and functional medicines are two modalities that have expanded significantly, with similar trends observed for holistic, biological, and functional dentistry. The main difference between these emerging trends and traditional medicine and dentistry is that healthcare professionals treat the patient as a whole, as opposed to treating the disease and its symptoms [6,7].

In line with more holistic approaches, there has also been increased interest in decreasing the chemical body burden, which can originate from the environment (air, water, soil, food, etc.), medications, and personal care products, among other sources [8]. Herbal and natural products play an important role in these integrative approaches, with turmeric having potent medicinal effects as a supplement and therapeutic agent for numerous diseases and conditions [5]. While herbal products are increasingly popular, their use should be based on scientific evidence. In this review, the scientific foundation for the use of curcumin in periodontology will be discussed.

Therapeutic Use of Curcumin in Medicine

A recent bibliometric analysis of the literature on curcumin found over 18,000 publications on the topic, including clinical and experimental research, in vitro studies, meta-analyses, and reviews, from which half were published after 2014. The majority of studies evaluated curcumin use in relation to cancer, inflammatory conditions, and oxidative stress. The overwhelming number of studies on this natural compound points to its promising therapeutic properties [9].

Several beneficial biological activities have been associated with curcumin, including anti-inflammatory, anti-microbial (antibacterial, antiviral, antifungal properties), antioxidant, anti-angiogenic, anti-carcinogenic, antispasmodic, hepato-protective, and wound healing properties. It affects multiple signaling molecules and cellular activities. Therefore, it has been investigated for the treatment of a variety of inflammatory conditions and tumors, through in vitro, experimental, and clinical studies (Table 1). In dentistry, curcumin has been evaluated for the treatment of oral mucosal lesions, oral cancer, and periodontal disease [10-17,5].

Respiratory system [11]	Asthma, respiratory allergy, fibrosis, bronchitis, acute lung injury
Joints [10]	Rheumatoid arthritis, osteoarthritis
Digestive system [12]	Inflammatory bowel disease, pancreatitis, Helicobacter pyloric gastric inflammation, ulcerative colitis, reflux esophagitis
Neurological system [13]	Alzheimer disease, Parkinson's disease, multiple sclerosis
Metabolic conditions [10]	Diabetes, metabolic syndrome
Hepatic conditions [14]	Non-alcoholic steatohepatitis, alcoholic liver disease, hepatic fibrosis, liver injury, cirrhosis, hepatotoxicit
Cardiovascular system [15]	Heart failure, cardiac hypertrophy, aortic aneurism, atherosclerosis, cardiomyopathy, myocardial infarction, stroke

Cancer [16]	Breast cancer, lung cancer, skin cancer, hematological cancers, digestive system cancers, prostate cancer, brain tumors, head and neck cancer
Skin conditions [17]	psoriasis, atopic dermatitis, iatrogenic dermatitis, wound healing, skin aging

Table 1: Medical conditions that can potentially benefit from the therapeutic use of curcumin.

Curcumin Characteristics

Turmeric has three main curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Also known as diferuloylmethane, curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) corresponds to 1-6% of turmeric components, being the pigment that gives its characteristic orange/yellow color [1]. In commercial turmeric powder, the average curcumin concentration is 3.1% by weight [18]. Curcumin is a polyphenol with low solubility in water, being poorly absorbed and quickly eliminated by the gastrointestinal tract in its natural state [19]. It can be found in the form of turmeric, curcuminoids, or curcumin [20].

Delivery: Agents that increase the bioavailability and bio-efficacy of curcumin have been used as delivery systems, which include micelles, microgels, liposomes, phospholipids, emulsions, lipid carriers, and biopolymer nanoparticles. Most delivery agents act by decreasing the degradation of curcumin in the gastrointestinal tract [20]. Piperine, the main active ingredient in black pepper, has also been found to increase the availability of curcumin by 2000%. Chemical modifications of curcumin have been explored as another way to enhance its bioavailability. Vehicles such as corn oil, cellulose, and carboxymethyl have been suggested to improve curcumin availability [21].

Metabolism: Curcumin's metabolism happens primarily in the liver and intestines, being further metabolized by the intestinal microbiome. After oral intake, it undergoes multiple reduction reactions, reaching peak concentration in the body after 1-2 hours [22].

Safety profile: The US Food and Drug Administration (FDA) considers curcuminoids generally safe for humans. Safety has been confirmed through numerous clinical trials, which report general good tolerance and lack of toxicity, even at high doses (4000 mg/day and above) [23]. The European Food and Safety Authority (EFSA) has suggested the acceptable daily intake (ADI) value to be and 3 mg/kg body weight for curcumin [24].

Side effects: Despite curcumin's minimal toxicity, mild side effects such as headache, diarrhea, rash, allergy, and yellow stool have been reported in a dose-escalation study. In total, 30% of the included healthy volunteers who were administered 1 to 12 g in a single oral dose presented one of those side effects [25].

Synthetic analogs: Different CMC compounds have been formulated to change its diketone form into triketone form, improving the chemical properties such as zinc-binding, bioavailability, and therapeutic effects. Some analogs include difluorinated-curcumin (CDF), dimethoxycurcumin, compound 23, GO-

Y039, CMC 2.24, and EF24. Pre-clinical studies suggest stronger inhibition of matrix metalloproteinases (MMPs) for CMC, as compared to its natural form [26].

Therapeutic Use of Curcumin in Periodontology

In Vitro Studies

Multiple in vitro studies have reported the anti-inflammatory activity of curcumin and CMC. Studies on human periodontal ligament stem cells (hPDLSCs) exposed to curcumin report increased osteogenic cell differentiation and improved balance between MMPs and their tissue inhibitors [27,28]. Exposure of human gingival fibroblasts to curcumin enhanced wound healing when compared to CHX exposure [29]. Gingival tissues from periodontitis patients presented comparable MMP-9 decrease when exposed to curcumin or doxycycline [30]. The antimicrobial capacity of curcumin has also been reported in studies on periodontal bacteria, including *Porphyromonas gingivalis* (Pg), *Aggregatibacter actynomycentencomitans* (Aa), and *Fusobacterium nucleatum* (Fn). Even with concentration as low as 12 µg/ml, curcumin was able to decrease bacterial metabolic activity, adhesion and biofilm formation in vitro when used alone or as part of photodynamic therapy (PDT) [31-37]. In human gingival fibroblasts and macrophages exposed to Pg LPS, curcumin reduced inflammatory cytokines and cyclooxygenase-2 (COX-2) expression [34-36,38]. Hu et al. [39,40] have suggested the Nuclear factor-κB (NF-κB) pathway as another potential mechanism through which curcumin can affect the initial steps of periodontitis development [40].

Animal Studies

Results from numerous experimental periodontitis studies confirm the findings from in vitro studies and suggest beneficial effects for natural curcumin and CMC in the reduction of inflammation and alveolar bone loss (Table 2). The effects of curcumin on the alveolar bone is affected by the dose, vehicle, and animal model used in the study [41-57]. Some studies suggest that CMC is superior to the natural version in the prevention of alveolar bone loss [52,57-61].

Authors	Year	Animal Model	Mode of Administration	Results
Ghavimi et al. [61]	2020	Dog	Curcumin and aspirin membrane	Curcumin and aspirin membrane increased osteogenic potential, can be beneficial to GBR
Ay et al. [45]	2020	Rat	Oral gavage (30 mg/kg/day) for 15 days	Curcumin decreased IL-1β and IL-6 mRNA expression in gingival tissues
Wang et al. [57]	2019	Rat	Oral gavage (30 mg/kg/day) for 14 days	CMC 2.24 decreased alveolar bone loss by 80%-90%, curcumin did not inhibit alveolar bone loss
Deng et al. [46]	2020	Dog	Oral CMC2.24 capsule daily for 3 months	CMC 2.24 improved clinical parameters, inflammation and alveolar bone loss compared to placebo, besides reducing MMP-9, MMP-2 n gingival tissue, and GCF IL-1β
Pimentel et al. [51]	2020	Rat	Oral gavage for 30 days	In diabetic rats, natural curcumin and insulin reduced alveolar bone loss and positively modulated immune-inflammatory mediators

Guimaraes-Stabili et al. [52]	2019	Rat	Oral gavage for 15 days	Curcumin increased early bone repair; Curcumin + piperine improved collagen repair, and decreased activation of NF-κB in gingival tissues
Brandao et al. [52]	2018	Rat	Oral gavage 0 , 1, 3, 10, and 30 mg/kg/day for 28 days	Low doses of CMC2.24 (1 mg/kg/day) significantly reduced alveolar bone resorption
Akpinar et al. [41]	2017	Rat	Gastric gavage 75 and 150 mg/kg/day	Systemic curcumin reduced alveolar bone loss in experimental periodontitis
Xiao et al. [43]	2018	Rat	Oral gavage every 2 days	Curcumin reduced gingival inflammation and alveolar bone loss, and modulated collagen fibers.
Zambrano et al. [48]	2018	Rat	Curcumin-loaded nanoparticles injection	Curcumin inhibited bone resorption, decreased osteoclast and the inflammatory infiltrate
Curylofo-Zotti et al. [58]	2018	Rat	Oral intubation curcumin or CMC2.24 30 and 100 mg/kg/day for 15 days	CMC2.24 reduced alveolar bone resorption in LPS-induced periodontitis
Theodoro et al. [49]	2017	Rat	Curcumin solution +/- LED for 30 days	PDT using curcumin and LED effectively treated induced periodontitis
Elburki et al. [53]	2017	Rat	Oral gavage CMC 2.24	CMC 2.24 reduced gingival inflammatory cytokines and MMPs, alveolar bone loss, activation of p65 (NF-κB) and p38 MAPK
Elburki et al. [54]	2017	Rat	Oral gavage CMC 2.25	In rats with diabetes and periodontitis, CMC 2.24 reduced inflammation, hyperglycemia and connective tissue destruction
Bakir et al. [59]	2020	Rat	Oral gavage (30 mg/kg/d) for 15 days	Curcumin presented positive host modulation properties and decreased alveolar bone loss in experimental periodontitis
Correa et al. [51]	2020	Rat	Oral gavage 100 mg/kg/day curcumin for 30 days	Curcumin combined or not with resveratrol decreases alveolar bone loss in experimental periodontitis
Hosadurga et al. [60]	2014	Rat	Topical application 2% gel every second day for 6 days	Curcumin improved inflammation and inhibited 43% of edema
Elburki et al. [26]	2014	Rat	Oral intubation with CMC 2.24 for 2 weeks	CMC 2.24 decrease inflammation and alveolar bone loss in experimental periodontitis
Hu et al. [40]	2013	Rat	CMC 2.5 oral gavage 1 mL suspension 100 mg/kg	In diabetic rats, CMC reduced local and systemic inflammation and prevented tissue destruction
Zhou et al. [44]	2013	Rat	Oral gavage (100 mg/kg/day) for 30 days	Curcumin reduced ligature-induced periodontitis alveolar bone loss via suppression of RANKL/RANK/OPG
Guimaraes et al. [55]	2011	Rat	Gastric gavage 30 and 100 mg/kg/day for 15 days	Curcumin did not prevent alveolar bone loss in ligature-induced periodontitis
Guimaraes et al. [47]	2019	Rat	Oral gavage 30 and 100 mg/kg/day for 15 days	Curcumin reduced the inflammatory infiltrate and elevated collagen content in LPS-induced periodontitis

Mau et al. [56]	2016	Rat	Gastric gavage 30 and 100 mg/kg/day for 14 days	Curcumin inhibited inflammatory marker production and osteoclastogenesis, decreasing alveolar bone loss.

Table 2: Experimental studies on the use of curcumin in periodontology.
GBR: Guided Bone Regeneration; PDT: Photodynamic Therapy, CMC: Chemically Modified Curcumin.

In the study from Elburki et al. [54], oral administration of CMC 2.24 led to lower gingival levels of MMP and inflammatory cytokines, and reduced activation of NF-κB and p38 MAPK. In diabetic rats with periodontitis, CMC 2.24 reduced hyperglycemia, inflammation, and connective tissue destruction [54]. In a recent systematic review and meta-analysis on the use of curcumin in experimental periodontitis, Borges et al. [21] reported that oral administration of 30mg/kg/day of CMC for at least 15 days was able to reduce periodontal bone loss. When natural curcumin was used, the 30mg/kg/day dose did not affect bone loss while the 100mg/kg/day dose led to less bone destruction, as compared to the control group [21].

The mechanisms behind the anti-inflammatory effects of curcumin and CMC in experimental periodontitis includes decreased expression of MMPs, inflammatory cytokines, such as TNF-α, IL-6 and IL-1β mRNA in gingival tissues, and osteoclastogenesis markers, such as RANK and RANKL [44,56,59].

While most experimental studies on periodontitis and curcumin used oral or gastric gavage, Hosadurga et al. [60] investigated the topical application of curcumin gel in experimental periodontitis in rats in comparison to placebo. Gingival inflammation and edema were significantly lower in the test group [60]. More recently, the use of a collagen curcumin membrane infused with aspirin and curcumin was tested on bone defects in dogs. In defects where the test membrane was used, there was an increase in osteogenesis when compared to defects covered with a commercial membrane. The authors suggested that the antimicrobial and anti-inflammatory properties of curcumin can improve the results of guided bone regeneration procedures [61].

Clinical Studies-Topical Curcumin

Topical application of curcumin has been evaluated as an adjunct to periodontal therapy for gingivitis and chronic periodontitis in the form of gel, mouthwash, irrigation solution, adhesive strip, sponge, and chip (Table 3). Curcumin gel has been the most studied delivery method in clinical periodontal studies [62-84].

Authors	Year	Sample	Diagnosis	Mode of Administration	Groups	Duration	Parameters	Results
Guimaraes et al. [55]	2011	n=100	Gingivitis	Mouthwash, 2x/day	A - CHX	21 days	PI, GI, bacterial count	Comparable GI and bacterial count; PI

					B - curcumin			better for CHX
Mali et al. [73]	2012	n=60	Gingivitis	Mouthwash, 2x/day	A - CHX B - curcumin	21 days	PI, GI, bacterial count	Comparable for all parameters
Muglikar et al. [74]	2013	n=30	Gingivitis	Mouthwash, 2x/day	1 - SRP + CHX 2 - SRP + curcumin 3- SRP	21 days	PI, GI	Comparable for all parameters
Chatterjee et al. [72]	2017	n=50	Gingivitis	Mouthwash, 2x/day	A - curcumin B - placebo C- CHX	28 days	PI, GI, BOP	Comparable for all parameters
Arunachalam et al. [75]	2017	n=30	Gingivitis	Mouthwash, 2x/day	I - saline II - CHX III - curcumin	28 days	PI, GI, salivary ROM	Comparable reduction in PI, GI; ROM reduction higher in curcumin group
Singh et al. [82]	2015	n=40	Gingivitis	Gel, 2x/day	A - CHX B - curcumin	21 days	PI, GI and SBI	Better clinical outcomes in curcumin group.
Kandwal et al. [63]	2015	n=60	Gingivitis	Gel, 2x/day	A - curcumin B - CHX	21 days	PI, GI	Comparable for all parameters
Pulikkotil et al. [64]	2015	n=40	Gingivitis	Gel, 2x/day	I - CHX + metronidazole II - CHX III - curcumin and CHX	29 days	PI, GI, BOP, PD, IL-1β and CCL28 in GCF	Comparable for most parameters. Higher levels of IL-1β and CCL28 in CHX group

Jaswal et al. [68]	2014	n=100	Gingivitis	Gel	1-arm study oral daily gel	21 days	PBI	Curcumin was effective at reducing gingival inflammation
Kaur et al. [84]	2017	n=60	Gingivitis	Capsules 350mg/day	I - SRP + curcumin II - SRP	21 days	PI, GI, PPD	Better clinical results in the curcumin group
Malekzadeh et al. [83]	2020	n=48	Gingivititis and periodontitis	Capsules 80mg 1x/day	A - Nano curcumin B - placebo	28 days	MGI, PBI, PI	PBI, MGI higher in placebo group; PI comparable
Guru et al. [30]	2017	n=45	Chronic periodontitis	Gel	1 - SRP 2 - SRP + nano curcumin 3- SRP + CHX	45 days	BOP, PPD, CAL, bacterial count	Comparable results for curcumin and CHX, which were better than SRP alone.
Siddharth et al. [67]	2020	n=25	Chronic periodontitis	Gel	Test - SRP + curcumin Control - - SRP + CHX	3 months	SBI, PPD, relative AL, bacterial count	Curcumin group presented better results for SBI, PPD, relative AL, and CFUs than CHX group

Meghana et al. [69]	2020	n=20	Chronic periodontitis, flap surgery	Gel	A - curcumin gel postop B - Coe pak	7 days	Tissue response, early wound healing, pain	Comparable results for most outcomes. Curcumin group used less analgesics after surgery
Anusha et al. [76]	2019	n=10	Chronic periodontitis	Gel	Test - SRP + curcumin Control - SRP	28 days	PI, GI, PPD, CAL	Reduction in PI and PPD greater in test group
Kaur et al. [84]	2019	n=30	Chronic periodontitis	Gel	Test - SRP + curcumin Control - SRP + CHX	6 months	PI, GI, PPD, CAL, salivary IL-1β	No differences between groups
Guru et al. [30]	2017	n=25	Chronic periodontitis	Gel	1) SRP + curcumin 2) SRP + ornidazole	30 days	PI, PPD, CAL	Superior results for curcumin group
Pulido et al. [10]	2016	n=30	Chronic periodontitis	Gel	Test - SRP + curcumin Control - SRP	45 days	PI, GI, SBI, PPD	Higher reduction in clinical parameters observed in curcumin group
Singh et al. [62]	2015	n=30	Chronic periodontitis	Gel	1) SRP + curcumin 2) SRP + CHX	30 days	PPD, CAL, CFU	Superior results for curcumin group

Shahzad et al. [38]	2015	n=30	Chronic periodontitis	Gel	I - SRP II - SRP + gel	28 days	PI, GI, PPD, CAL, bacterial count	The test group presented a more pronounced improvement in clinical and bacterial parameters
Kandwal et al. [63]	2015	n=30	Chronic periodontitis	Gel	Test - SRP + curcumin + periodontal pack Control - SRP + periodontal pack	45 days	PI, GI, PPD, CAL	No significant differences between groups
Elburki et al. [26]	2014	n=25	Chronic periodontitis	Gel	Test - SRP + gel Control - SRP	6 months	PI, BI, PPD, CAL, microbiological count	Lower microbiological count for periodontal bacteria was observed for curcumin group.
Jaswal et al. [68]	2014	n=15	Chronic periodontitis	Gel	I - SRP + CHX II - SRP + curcumin III - SRP	45 days	PI, GI, PPD, CAL	Curcumin and CHX presented comparable clinical improvement
Behal et al. [65]	2011	n=30	Chronic periodontitis	Gel	Test - SRP + curcumin Control - SRP	46 days	PI, GI, SBI, PPD, RAL, trypsin-like activity	Greater improvement was observed for the test group

Sreedhar et al. [70]	2015	n=15	Chronic periodontitis	Gel	Quadrant 1: SRP Quadrant 2: SRP + curcumin gel application for 5 min Quadrant 3: SRP + curcumin gel application for 5 min + PDT day Quadrant 4: SRP + curcumin gel + PDT day 0, 7, 21	21 days	BOP, PPD, CAL, SBI, bacterial culture	Quadrants 3 and 4 tended to have better results for all parameters.
Mohammad CA. [71]	2020	n=90	Chronic periodontitis	Gel	A - SRP + curcumin gel + Coe pak B - SRP + Coe pak		PI, GI, BOP, PPD, CAL, serum levels of zinc, copper, magnesium, IL-1β, and TNF-α	Curcumin gel led to higher reduction of IL-1β, TNF-α, copper, and clinical parameters and increase of zinc and magnesium
Ivanaga et al. [79]	2019	n=25	Chronic periodontitis and diabetes	Irrigation solution	1) SRP 2) SRP + curcumin irrigation	6 months	PDD, BOP, CAL, GR, PI	SRP + PDT using curcumin and LED irradiation led to higher CAL gain in residual

					3) SRP + LED 4) SRP + irrigation + LED			pockets in diabetic patients
Gottumukkala et al. [77]	2013	n=23	Chronic periodontitis	Irrigation solution	I - SRP + CHX II - SRP + curcumin III - SRP	6 months	Redness, PI, PPD, microbiological parameters	Modest benefit of curcumin irrigation when compared to CHX
Guimaraes et al. [47]	2019	n=60	Chronic periodontitis	Irrigation solution	I - SRP + CHX II - SRP + curcumin III - SRP	2 months	PI, GI, PPD, microbiological parameters	CHX showed highest improvement in clinical outcomes. No differences for microbiological parameters
Perez-Pacheco et al. [78]	2020	n=20	Chronic periodontitis	Irrigation solution	I - SRP + nanoparticles 50 µg curcumin II - SRP + empty nanoparticles	180 days	BOP, PPD, CAL, GCF IL-1α, IL-6, TNFα, and IL-10, bacterial count	Comparable results, no benefits for curcumin group
Anusha et al. [76]	2019	n=45	Chronic periodontitis and RA	Mouthwash	A - SRP + CHX	6 weeks	PI, CAL, PPD, RA disease activity	Highest PI and RA parameters seen in curcumin group; highest

					B - SRP + curcumin/essential oils B - SRP			reduction PPD and CAL seen in CHX group.
Anil et al. [80]	2019	n=15	Moderate or advanced periodontitis requiring surgery	Strip	Test - curcumin mucoadhesive film Control - placebo mucoadhesive film	7 days	Healing, pain	Significantly lesser pain in curcumin group, more analgesics consumed in control group
Mau et al. [56]	2016	n=20	Chronic periodontitis	Strip	I - SRP II - SRP + curcumin strip	21 days	GCF SOD	Lower levels of SOD detected in curcumin treated sites
Gottumukkala et al. [81]	2014	n=60	Chronic periodontitis	Collagen sponge	I - SRP + CHX chip II - SRP + curcumin in collagen	6 months	PI, GI, PPD, CAL, bacterial count	CHX presented superior results for all parameters
Singh et al. [82]	2018	n=40	Chronic periodontitis	Chip	A - SRP + CHX chip B - SRP + curcumin chip C - SRP	3 months	PI, GI, PPD, RAL	Comparable results for CHX and curcumin chip, which were superior to control group

Table 3: Clinical studies on the use of curcumin in periodontology.

PI: Plaque Index; GI: Gingival Index; PPD: Pocket Probing Depth; CAL: Clinical Attachment Level; RAL: Relative Attachment Level; GCF: Gingival Crevicular Fluid; GR: Gingival Recession; BOP: Bleeding On Probing; SBI: Sulcus Bleeding Index; SOD: Superoxide Dismutase; ROM: Reactive Oxygen Metabolites; RA: Rheumatoid Arthritis; CHX:

Chlorhexidine; PDT: Photodynamic Therapy.

Gel: In studies comparing the application of curcumin gel to CHX gel in gingivitis patients (applied twice a day for 21 days), curcumin was at least as effective as CHX in improving plaque index, gingiva index, and bleeding on probing. Pulikkotil & Nath [62,63] assigned sixty volunteers with healthy gingiva to one of three groups: curcumin gel, CHX gel, or CHX/metronidazole (MTZ) gel. Participants did not perform any oral hygiene apart from the oral application of the gel twice a day for 10 minutes for the duration of the study (29 days). The curcumin group presented the lowest increase in GCF (IL-1β and chemokine ligand 28- CCL28), while the clinical variables were similar for all three groups. The authors concluded that the anti-inflammatory effect of curcumin gel was comparable to CHX-MTZ gel and superior to CHX gel [64].

The first study to investigate the use of sub-gingival curcumin gel as an adjunct to periodontitis treatment was published in 2011. Through a split-mouth design, control sites were subjected to Scaling and Root Planning (SRP) and 2% turmeric gel, while control sites were subjected to SRP alone [65]. Both groups exhibited improved outcomes for clinical parameters and trypsin-like enzyme activity, but greater reductions were observed in sites treated with curcumin gel. For pocket depth, test sites presented a 1.1 mm higher average reduction than control sites. Since then, numerous studies have further investigated the use of curcumin gel in periodontitis patients and the majority provides evidence of better clinical and microbiological outcomes when compared to placebo or SRP alone (Table 3) [65]. For the studies that provide a comparison between curcumin and CHX gel, curcumin gel performed equally or better than CHX [66-68].

Recently, the postoperative application of curcumin gel was compared to periodontal dressing application after flap surgery in twenty patients. Early wound healing and tissue response were similar in both groups, however, the curcumin group reported less use of analgesics after surgery [69]. Using a split-mouth design, Sreedar et al. [70] compared four groups: SRP, SRP + Curcumin gel, SRP + gel + PDT at day 0, SRP + gel + PDT at days 0, 7 and 21. Quadrants that were subjected to curcumin gel and photoactivation presented superior clinical results than SRP alone or combined with curcumin gel [70].

Muhammad (2020) [71] reported higher reduction of serum IL-1β, and TNF-α and increased serum levels of zinc and magnesium when SRP was combined with curcumin gel in chronic periodontitis patients [71].

Mouthwash: In a randomized controlled trial of patients with moderate to severe gingivitis, one session of professional prophylaxis followed by twice-daily curcumin mouthwash use presented comparable results to CHX mouthwash for gingival and plaque index, when used for 14 and 28 days. These findings were supported by additional studies by additional gingivitis studies [72]. In addition to beneficial clinical results, Arunachalam et al. (2018) [75] also reported lower levels of salivary reactive oxygen metabolites (ROM) after use of curcumin oral rinse in gingivitis, which was not observed for CHX oral rinse [74,75].

In chronic periodontitis patients with rheumatoid arthritis, the effect of SRP alone or combined with CHX or curcumin/essential oils mouthwash was investigated. While the CHX group presented a higher

reduction in PPD and CAL, only the curcumin group had improvement in markers of rheumatoid arthritis [76].

Irrigation solution: The use of 1% curcumin solution as an irrigation solution for periodontal pockets in combination with SRP has been reported in the literature. Gottummukkala et al. (2013) [77] compared SRP alone, SRP combined with CHX solution or curcumin solution in the treatment of chronic periodontitis. Subgingival irrigation took place at baseline and at follow-up after 7, 14, and 21 days. Clinical parameters showed a slight benefit of curcumin in relation to CHX after 3 months, however, after 6 months, greater pocket depth reduction was observed in the CHX group. There were no differences in the BANA microbiological test results during the study. The authors concluded that, due to the lower toxicity and fewer side effects, irrigation with a curcumin solution can be an adequate substitute for CHX solution. In the study from Perez-Pacheco et al. (2020) [77] nano curcumin particles were used as an irrigation solution during SRP for the treatment of periodontitis. When compared to a placebo, the curcumin group did not present any clinical nor microbiological benefit. In type 2 diabetic patients with residual periodontal pockets, the combination of SRP and PDT using curcumin and LED irradiation showed the most positive results when compared to SRP alone, combined with curcumin irrigation or LED irradiation after 3 months [78,79].

Strip: Postoperative use of a mucoadhesive curcumin strip was evaluated after periodontal surgery in 15 patients. In each patient, control sites received a placebo strip and test sites received the curcumin strip. Healing was uneventful for all areas. After 7 days, significantly lesser pain was reported for sites that received the strip [80].

Sponge: A collagen sponge was tested for local drug delivery of curcumin in sites with pocket depth of 5 mm or more in sixty chronic periodontitis patients subjected to SRP. Control sites received CHX chips, and clinical and microbiological parameters were evaluated after 3 and 6 months. Greater results were observed for the CHX group, which can indicate the inefficacy of this delivery method for curcumin [81].

Chip: Local drug delivery using CHX or curcumin chip was compared to SRP alone in forty chronic periodontitis patients using a split-mouth design. After 3 months, CHX and curcumin sites exhibited superior clinical results, measured as plaque index, gingival index, pocket depth, and relative attachment level, with no differences between CHX and curcumin treatment [82].

Clinical Studies- Systemic Curcumin

Malekzadeh et al. (2020) [83] studied the effect of 80 mg curcumin capsules once a day or placebo on forty-eight patients who suffered from gingivitis or mild periodontitis. After 28 days, there was a statistically significant difference in papillary bleeding index (PBI), and modified gingival index (MGI), with better outcomes observed in the test group. After 4 weeks, all patients were subjected to SRP. In the absence of SRP, systemic curcumin presented positive effects of gingival bleeding and inflammation [83].

The effect of systemic curcumin as an adjunct to periodontal treatment in gingivitis patients was investigated by Kaur et al. [84] Sixty patients were enrolled and as randomly assigned to receive SRP or SRP combined with 350 mg of an antioxidant mixture containing curcumin, lycopene and piperine. Gingival clinical parameters were evaluated after 3 weeks and reduction in plaque index, gingival index and pocket depth were marginally higher in the test group, suggesting that adjuvant systemic antioxidants can help reduce gingival inflammation [84].

Anti-Inflammatory and Anti-Microbial Properties of Curcumin

In periodontology, the most relevant biologic activities of curcumin are related to its anti-inflammatory and antimicrobial properties. Multiple molecular mechanisms have been described to explain curcumin's anti-inflammatory actions, including:

- **Nuclear Factor Kappa (NF-κB):** this protein plays a crucial role in the cellular and molecular signaling that takes place during several chronic inflammatory diseases, including periodontitis, rheumatoid arthritis, inflammatory bowel disease, and asthma. In in vitro experiments, exposure of cells to cytokines, microbial pathogens, or their products induces activation of NF-κB, which is suppressed by curcumin [85,86].
- **Cyclooxygenase-2 (COX-2):** this enzyme catalyzes the formation of prostaglandins, which are important mediators in the inflammatory response. Prostaglandins have been implicated in the pathogenesis of periodontitis and alveolar bone resorption. Curcumin has been demonstrated to inhibit COX-2 expression in vitro [87].
- **Inducible nitric oxide synthase (iNOS):** This enzyme is key for the production of nitric oxide and is regulated by NF-κB. Nitric oxide is an important signaling molecule that participates in the pathogenesis of inflammation in the lungs, joints, intestines, and gingiva [88]. Curcumin can promote degradation of iNOS and inhibit its synthesis [89].
- **Vascular endothelial cell surface adhesion molecules:** including E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion molecule-1 (VCAM-1). Expression of these adhesion proteins in the endothelium is mediatedby pro-inflammatory cytokines and NF-κB, resulting in the extravasation of leukocytes from the blood vessels into the tissues [90]. Curcumin down regulates expression of vascular adhesion proteins by inhibiting NF-κB [91].
- **Cytokines:** Curcumin has been demonstrated to regulate the expression of multiple pro-inflammatory cytokines, such as IL-1β, IL-2, IL-5, IL-6, IL-8, IL-12, IL-18, and TNF-α. Those molecules are crucial components of the tissue destruction process in periodontal disease [92].
- **AP-1 transcription factor:** curcumin has been shown to inhibit this protein, which regulates a variety of cellular responses through gene expression, such as proliferation and apoptosis. Regulation of AP-1 indirectly affects the production of iNOS, cytokines, and matrix metalloproteinases (MMPs) [85].
- **MMPs:** these endopeptidases degrade extracellular and membrane components, including collagen, and mediate periodontal destruction. MMP-1, 3, 9, 14, and 13 secretion can be inhibited by curcumin [92].

- **Anti-oxidant:** curcumin is a potent scavenger for free radical compounds, including reactive oxygen species. It also inhibits the generation of free radicals and lipid peroxidation. These actions contribute to the reduction of oxidative stress [93].
- **Cytoprotective proteins:** the potential of curcumin to stimulate the expression of cytoprotective proteins, such as catalase, glutathiones, and superoxide dismutase, which indirectly decrease oxidative stress [93].

The anti-microbial activity of curcumin has been attributed to its effect reducing microbial cell division, inhibition of virulence factors, damage to the microbial membrane, prevention of microbial adhesion to host cells, and consequent reduction in biofilm formation [94]. Also, as a photosensitizer, when subjected to light irradiation, the resulting photo toxicity prevents microbial growth. A few in vitro studies evaluated PDT with curcumin and reported moderate to strong antimicrobial activity against *Aa*, *Pg*, and *Fn* [32,33,37,95]. However, evidence on the clinical benefits of curcumin PDT as an adjunct to periodontal treatment is scarce [79,96].

Take-Home Message

Findings from in vitro studies suggest that curcumin has the ability to promote osteogenesis, downregulate proteases, promote wound healing, and suppress periodontal bacteria. Findings from animal studies suggest the enormous potential of curcumin and its derivatives to contribute to mechanical periodontal treatment, as experimental inflammation and alveolar bone loss show remarkable reduction after curcumin treatment.

Despite the high number of clinical studies on the use of curcumin in periodontology, there are several missing points before curcumin can become part of the traditional treatment approach. The low toxicity, limited side effects, availability, low cost, and a full spectrum of beneficial biological properties are among the main advantages of curcumin. Results from most clinical trials suggest that the benefits of curcumin and CMC are at least comparable to CHX, but with fewer side effects and higher patient acceptance. In gingivitis, the use of mouthwash seems to provide the most efficient delivery of curcumin, whereas in periodontitis, the use of curcumin gel has been the most studied form. Currently, adjunctive PDT with curcumin does not seem to provide additional benefits to SRP, however, it can be beneficial in the treatment of smokers and patients who have systemic disease. Additional studies are warranted to shed light on substantivity, formulations, delivery, and doses. Curcumin analogs seem to present superior outcomes due to increased bioavailability and potency. For wound healing, the use of curcumin strips and gel shows good potential and should be further explored. Although still in its infancy, the use of membranes containing curcumin can open new possibilities for tissue regeneration in the future.

The anti-plaque, antioxidant and anti-inflammatory properties of curcumin are remarkable, however, the lack of robust scientific studies with larger samples and longer follow-ups currently hinders its clinical application. While the majority of pre-clinical and clinical studies on periodontal disease have investigated the topical application of curcumin, its potential to improve the host response when used

as a nutritional supplement should not be ignored despite.

Conclusion

Curcumin, an ancient natural remedy and spice, has been extensively studied for its wide spectrum of health benefits, mainly related to the anti-microbial, anti-inflammatory, anti-oxidant, and anti-cancer properties. In periodontology, the benefits of curcumin topical use have been compared to those of chlorhexidine due to its potential to combat plaque, modulate the host response, decrease periodontal inflammation, and alveolar bone loss. Those properties have been widely confirmed in pre-clinical studies. The majority of clinical studies on the adjunctive use of curcumin in periodontal disease report superior clinical and microbiological results when compared to mechanical therapy alone. Nonetheless, there is a lack of randomized clinical trials with long-term follow-up and adequate sample size. Despite the major health benefits associated with systemic supplementation with curcumin, more studies are warranted in order to investigate its effectiveness in the management of periodontal disease. Lastly, curcumin analogs have improved the chemical structure of this polyphenol to improve its biological activity; however, its clinical application requires further scientific investigation.

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