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Curcumin for the management of periodontal diseases: a review

Abstract:

Periodontal disease is one of the most common cause of tooth loss among adults. Research shows that inflammation is one of the crucial components in the initiation and progression of periodontitis. Various herbal medicines have recently been receiving attention for the management of periodontitis owing to their general safety and multitude of pharmacological actions. Curcumin, a bioactive polyphenol extracted from *Curcuma longa*, possesses antioxidant, antimicrobial, antiinflammatory, analgesic and anticarcinogenic properties. Several studies have assessed the usefulness of curcumin against periodontal diseases and the results have shown equivalent or even higher efficacy compared to the regularly used drugs for the management of periodontitis such as chlorhexidine. Herein, we review the experimental and clinical findings on the anti-periodontitis effects of curcumin and the pharmacological mechanisms underlying these effects.

Keywords: Inflammation; Gingivitis; Herbal medicine; Curcumin; Periodontitis; Herbal mouthwash

Introduction

Poor oral/dental health causes significant pain and suffering and therefore affects general health (1). Loss of teeth due to periodontitis often causes discomfort and endangers the esthetics and function. Studies have revealed a possible link between systemic health problems and periodontitis (2, 3). More than one-half in adults are affected by periodontal diseases (4-8). There is a recent worldwide increase in the use of medicinal plants in the management of various conditions including periodontal diseases due to their efficacy and favorable side effect profile (9).

Literature search

In this review, we searched manuscripts with the following keywords: antioxidant capacity, anti-inflammatory, gingivitis, herbal medicine, curcumin, periodontitis, herbal mouthwashes, alternative medicine. The search databases include Google Scholar, PubMed, Web of Science, Scopus from 1990 - 2019 using the EndNote software.

Periodontal disease

Periodontal disease is a set of inflammatory conditions affecting the gingiva and the supporting structures of the periodontium(10, 11). Periodontal diseases are classified into gingival diseases and periodontitis (12). The gingival disease is usually being characterized by inflammatory dental plaque accumulation in the gingival tissues. The clinical presentation of the gingival disease includes areas of swelling, redness and bleeding. Periodontal ligament and alveolar bone are not affected (13, 14). Gingivitis means inflammation of the gingiva which can lead to

periodontitis (15, 16). Periodontitis is an condition where there is periodontal tissue inflammation resulting in alveolar bone destruction (13, 17).

The clinical signs of periodontitis include changes in the gingival tissue morphology, gingival overgrowth is one of the modifications that occurs in chronic periodontitis may be detectable clinically. Polymorphonuclear leukocytes and monocytes pass through the subepithelial connective tissue through the junctional epithelium and into the gingival sulcus (18). Bleeding upon probing and periodontal pocket formation that lead to tooth loss if untreated (19). The periodontal pocket facilitates bacterial colonization and subgingival plaque formation (13, 17) (**Figure 1**).

Various non-surgical interventions such as application of numerous antimicrobials and chemotherapeutic agents including chlorhexidine, triclosan, cetylpyridinium chloride have been tried for the management of periodontal diseases. Some cases will need surgical management. Since the etiology of periodontitis is multifactorial and complex etiologies management of periodontitis can be challenging (20) (21).

Herbal medicine strategy

Herbal medicines were used to manage various conditions since time immemorial (22). Since natural medicines have potentially fewer side effects and lower costs than synthetic drugs, the use of phytopharmaceuticals has become widespread worldwide. Natural remedies have been shown to have antioxidant, antiseptic and anti-inflammatory effects (21, 23) which can be potentially beneficial in preventing and treating periodontal diseases.

Curcumin

Curcumin (diferuloylmethane) is a natural compound obtained from *Curcuma longa* (24, 25). Besides to its extensive culinary use, curcumin has been used for centuries for its medicinal properties to manage various conditions (26-28) (29, 30). Curcumin has been shown to have antioxidant (31, 32), antimicrobial (33), anti-inflammatory (34-37), analgesic (38), antimicrobial (33) and anticarcinogenic and chemosensitizing properties (39-42). Curcumin can be safely consumed up to 8g per day (43). Various formulations of curcumin are available including oral and topical formulations (44, 45). We have performed a comprehensive review of literature on the usefulness of curcumin in periodontitis.

Effect of curcumin on experimental models of periodontitis

One study aimed to assess the effect of resveratrol and curcumin on the progression of experimental periodontitis in rats. Intergroup comparisons showed higher bone-loss in the placebo group compared to the active treatment groups (46). Gu et al (47), evaluated the effect of orally administration of 4-methoxycarbonylcurcumin (CMC 2.5) for 3 weeks in Streptozotocin (STZ) induced periodontal disease. The results showed that CMC 2.5 reduced inflammatory markers including Matrix metallopeptidase 9 (MMP-9), Matrix metallopeptidase 13 (MMP-13) and Interleukin 1 beta (IL-1β). Daily intragastric administration of curcumin inhibits the expression of Interleukin 6 (IL-6), tumor necrosis factor alpha (TNF‑α), Prostaglandin E2 (PGE2), cyclooxygenase-2 (COX-2) in the gingival tissues in ligature-induced periodontal disease in the rat. There was also a significant reduction of inflammatory cell infiltrate and increased collagen content and fibroblastic cell numbers in the curcumin-treated animals (48). Daily curcumin administration to rats inhibited the inflammatory markers in the gingival tissues

(49). Besides, curcumin treatment resulted in a significant increase in collagen and fibroblasts. Curcumin (5–30 μmol/L) dose-dependently inhibited COX-2 mRNA and protein synthesis in *P. gingivalis* LPS -stimulated human gingival fibroblasts (HGFs) (50).

Mau et al(51), showed that curcumin reduced receptor activator of nuclear factor-κB ligand (RANKL)-induced osteoclast differentiation and the expression of osteoclastic specific genes in a dose-dependent manner. Curcumin reduced tartrate-resistant acid phosphatase (TRAP)-positive and polymorphonuclear cells infiltration and alveolar bone destruction in ligature-induced experimental periodontitis model. Local administration of nanocurcumin reduced inflammatory bone resorption of hemi-maxillae in a lipopolysaccharides (LPS)-induced model of periodontal disease (52).

Administration of curcumin significantly reduced bone resorption in mandibles and RANKL, receptor activator of nuclear factor-κB (RANK) and osteoprotegerin (OPG) in mandibles in rat ligature-inducted periodontitis. It also reduced the inflammatory cytokine expression levels in gingival tissues of the experimental periodontitis animals (53). Application of 2% curcumin gel lead to statistically significant reduction in the probing pocket depth (PPD) and gingival index (GI). GI was determined and recorded at 4 gingival sites per tooth according to the following criteria: (0) normal gingiva, (1) mild gingivitis without bleeding on probing, (2) moderate gingivitis with bleeding on probing, and (3) severe gingivitis with ulceration and spontaneous bleeding. The sum of the scores from the four areas of each tooth was divided by 4 to derive the GI for that tooth. The average GI value obtained after calculating individual GI (54).

There was no significant difference in the morphometric analysis at mesiobuccal, midbuccal, distobuccal, mesiopalatal, midpalatal, and distopalatal site following administration of curcumin gel in an experimental periodontitis model of rat (55). Systemic administration of curcumin and piperine increased Transforming growth factor beta (TGF-β) levels, reduced Nuclear factor-κB (NF-κB) activation and reduced cellular infiltrate, associated with enhanced collagen content and accelerated soft tissue repair in ligature-induced periodontitis. Although, only curcumin increased early bone repair in ligature-induced periodontitis (56).

Effects of curcumin on periodontal diseases in clinical studies

In a randomized study the efficacy of curcumin was compared to chlorhexidine in the management of chronic periodontitis. There was a greater reduction of clinical attachment level (CAL) and PPD after curcumin than chlorhexidine after 30 days (57). In another randomized clinical study (split-mouth design) administration of curcumin gel (10 mg *curcuma longa* extract/gram) significantly decreased plaque index (PI), GI, probing depth (PD) and clinical attachment loss after 45 days (58). In a single-blind, randomized study, PI, GI and saliva collection for ROM (whole oxidant capacity of saliva) in three groups (control (saline), curcumin mouth rinse and chlorhexidine mouth rinse groups) were performed. The curcumin group showed a significant reduction in ROM contents after 4 weeks (59). In patients with chronic periodontitis application of curcumin gel (1 mg/ml) along with scaling and root planing lead to reduction in the number of periopathogens. There was also an improvement in various clinical parameters including PPD, CAL, PI and bleeding index (BI) after 6 months compared to the control group which received only scaling and root planing (60). In a double-blinded randomized

study, the efficacy of curcumin and chlorhexidine mouth rinses on PI, GI and sulcus bleeding index (SBI) in gingivitis patients was evaluated. There was a clinically significant reduction in all parameters in curcumin and chlorhexidine groups (61). In another pilot randomized study, the efficacy of 1% curcumin solution as an adjunct to thorough scaling and root planing in patients with chronic periodontitis was evaluated. There was a significant improvement in BOP, redness, plaque index and PPD in the curcumin group after one month compared to chlorhexidine gluconate and a positive control (saline) group. The microbiological analysis showed significant reduction in the number of BANA positive sites in the curcumin group after 1 month and by the end of study period (62). Application of curcumin collagen sponge or chlorhexidine (CHX) chips (Periocol-CG) for chronic periodontitis leads to a significant reduction in PI and GI scores at the end of the 6-month study period. There was also a significant improvement in the microbiological parameters, PPD and CAL levels in both groups (63).

Another study investigated the effect of curcumin and doxcycline in the inhibition of Matrix metallopeptidase 9 (MMP-9) activity in gingival tissue samples from chronic periodontitis patients. Curcumin demonstrated 61.01% reduction in the MMP-9 activity at 1500 µg/ml concentration and doxycycline demonstrated 59.58% decrease in the MMP-9 activity at 300 µg/ml concentration (64). One study evaluated the efficacy of subgingival application of 0.2% chlorhexidine gel and 2% curcumin gel as an adjunct to scaling and root planing in the management of mild to moderate periodontal pockets. Both agents had an impact on mild to moderate periodontal pockets, but the curcumin gel was more efficient than the chlorhexidine gel (65). The effects of curcumin and chlorhexidine mouth-washes was assessed in three groups

(patients who underwent scaling and root planing followed by the use of curcumin mouthwash, patients underwent scaling and root planing followed by the use of chlorhexidine mouthwash, patients underwent only scaling and root planing). When compared to the scaling and root planing group there was a significant improvement in clinical parameters in the other groups (66). A randomized single-blinded (split-mouth) study was conducted to assess the effect of curcumin as an adjunct to scaling and root planing in patients with chronic periodontitis The results showed a decrease in the CAL, probing depth, PI, GI, and microbiologic parameters (Porphyromonas gingivalis, Tanerella forsythia, and Treponema denticola) after curcumin gel application (67). *In-situ* gel formulations of curcumin containing 2% curcumin significantly reduced the PD, BI, and to a lesser extent of PI after one-month treatment in patients with chronic periodontitis (68). A randomized, double-blinded, parallel study compared the IL-1β and CCL28 levels after application of curcumin extract, chlorhexidine and chlorhexidine-metronidazole and metronidazole in an experimental gingivitis human model. The increase of IL-1β and CCL28 in the curcumin and chlorhexidine-metronidazole groups was significantly less than that of the chlorhexidine alone group (69). In a single-blind, randomized study, the periodontitis patients received scaling and root planing after which test either curcumin gel (*C. longa* extract-10 mg) or ornidazole were injected. Administration of curcumin gel significantly reduced PD, PI and clinical attachment loss than ornidazole group after 1 month in these patients with chronic periodontitis (70).

Potential mechanisms for the anti-periodontitis effects

The hallmark of periodontal disease is inflammation and bone loss (71). Bone remodeling maintains the integrity of the skeleton by formation of bone via osteoblasts and removal of mineralized bone by osteoclasts. The RANKL and its OPG receptor play an important role in the bone remodeling regulation (72). RANKL and OPG have an imperative role in the healing of destructive periodontal disease (73, 74). RANKL is expressed by osteoblasts, fibroblasts, chondrocytes, activated T cells and B cells stromal cells as well as other mesenchymal cells (75, 76). Curcumin suppresses the RANKL/RANK/OPG expression thereby inhibiting the inflammatory response and bone loss during experimental periodontitis (53). The NF-kB activation increases the expression of various inflammatory cytokines and chemokines involved in the pathogenesis of various inflammatory diseases (77). NF-kB was activated when oral epithelial cells were exposed to *Porphyromonas gingivalis* and *Fusobacterium nucleatum* which are periodontopathogens that induced apoptosis of monocytes and neutrophils (78-80).

The two main signaling pathways activated downstream of toll like receptor 4 (TLR4) are p38 MAPK and NF-kB. They are considered as the 'general indicators of inflammatory activity' (81). TLRs recognize and respond to various types of microbial challenges. Activation of TLR4 enhances the activation of mitogen-activated protein kinases and the translocation of nuclear NF-κB (82). Bacterial infection elicits an inflammatory response that will eventually exacerbate bone destruction (83). The RANK ligand-induced osteoclastogenesis is mediated by NF-κB. NF-κB pathway inhibition results in inhibition of osteoclast formation as well as bone resorptive activity (84).

There is a close relationship between reactive oxygen species (ROS) and periodontitis (85-89). ROS have been implicated in inducing oxidative damage to pathogens (90, 91). However, overproduction of ROS can result in oxidative damage which is strongly associated with periodontal destruction (17, 92).

The dental plaque harbors several pathogens which stimulate the release a number of inflammatory cytokines including TNF-α and interleukins. These cytokines attract polymorphonuclear cells (PMNs) to the infection site. In response to this bacterial challenge, PMN secretes a variety of proteolytic enzymes and an increase in O_2 production (93). ROS can aggravate inflammatory injury through NF-κB (94, 95) and induce apoptosis through c-Jun N-terminal kinase (JNK) activation (96). A reduction in ROS levels has shown to reduce bone loss (97).

The biological mechanisms of curcumin-mediated effects involve regulation of several molecular targets, including protein kinases, cytokines, growth factors, transcription factors and other enzymes such as cyclooxygenase-2. Curcumin inhibits the NF-κB activation pathway, reduces the synthesis of COX-2 (50), and inhibits the signaling of TLR4 (98) Curcumin inhibits the expression of inflammatory cytokines (99-102). This evidence suggests that curcumin potentially ameliorates the initial stages of periodontitis (50). Curcumin promotes healing of wound by migration of fibroblasts (103, 104).

Advances in the formulations of curcumin

Curcumin can be used in various formulations including soaps, cosmetics, capsules, ointments, energy drinks and capsules (44). The therapeutic use of curcumin is limited due to its rapid

metabolism and low solubility resulting in poor bioavailability (105).(106-108). Various formulations such as micelles, nanoparticles, liposomal vesicles, phospholipid complexes, nano-emulsions and polymers are being tried to improve the efficiency of curcumin delivery (109). Synthesis of curcumin derivative with a carbonyl substituent at the C-4 position increases its anti-inflammatory therapeutic properties due to the presence of an additional electron-withdrawing group. 4-methoxycarbonylcurcumin has a methoxycarbonyl group at C4 which improves its solubility, acidity as well as greater albumin and zinc-binding capacities. This modification potentiates the MMP-inhibitory effects of 4-methoxycarbonylcurcumin compared to curcumin (110, 111). (47). Zambrano et al. (52) found that nanoparticles synthesized from polylatic acid and co-glycolic acid increased the half-life of curcumin by 15-fold in rats (112). These nanoparticle formulations allow for chemical modifications that may increase its absorption (113). In patients with chronic periodontitis i*n-situ* gel-forming formulations will form strong gels after application at the delivery site thereby increasing the duration of contact of active formulation in the site (68, 114). Encapsulated curcumin in nanoparticles, enhanced the water solubility of curcumin. Conversely, free curcumin exhibited a better photodynamic property than curcumin -nanoparticle(115).

Conclusion

Periodontal disease remission/control is characterized by a significant inflammation reduction, some improvement in other clinical parameters, and a stabilization of disease progression. Ideally, restoration to periodontal stability should be considered a major therapeutic goal and can be achieved by controlling inflammation and infection, decreasing predisposing factors, and

controlling modifying factors. Curcumin is an effective and safe alternative to several common medications and has a multitude of therapeutic benefits in various diseases. Curcumin can counterbalance periodontal inflammation, oxidative stress and dental destruction. There is growing evidence that curcumin show equivalent or even higher efficacy compared with the regularly used medications for the management of periodontitis such as chlorhexidine. Curcumin analogs have also been investigated in the management of periodontitis. Therefore, the development of chemically modified curcumin analogs with improved anti-inflammatory and anti-periodontitis effects is an ongoing attempt that could lead to the introduction of novel anti-periodontitis drug candidates in the future.

Conflict of interest: None.

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Figure legend

Figure 1. Pathogenesis of periodontitis.

Tables

Table 1. The effectiveness of curcumin for the management of gingivitis – clinical studies.

Table 2. Experimental model's studies showing the impact of curcumin on periodontitis.