The Potential Role of Curcumin in Periodontal Therapy: A Review of the Literature

Rania Livada[1], Jacob Shiloah[1], David A. Tipton[2] and Mustafa Kh. Dabbous[2,3]

[1]Department of Periodontology, [2]Department of Bioscience Research, [3]Department of Microbiology, Immunology, and Biochemistry, College of Medicine, University of Tennessee Health Science Center, Memphis TN 38163 USA

Abstract

Periodontitis is a chronic inflammatory disease in the oral cavity caused by bacterial biofilm attached to tooth surfaces. The periodontal pathogenic microorganisms trigger the disease process; however, the destruction of the periodontium is mostly caused by the host's immune response to the bacterial insults.

The main thrust of periodontal therapy has been centered traditionally on reducing the microbial load by mechanical and antimicrobial means. This approach has been reported to be effective for the majority of patients and sites. However, modulating the host response by anti-inflammatory agents could provide another viable pathway to managing poorly responding periodontal patients. The overall objective of this paper is to review current data pertinent to curcumin and its dual anti-inflammatory and antimicrobial properties and to explore its potential in managing patients with periodontal diseases. Curcumin has a wide biological spectrum that could provide clinicians with an alternative anti-inflammatory and antimicrobial agent for managing a variety of maladies including periodontal diseases. However, large-scale longitudinal randomized clinical trials are needed to prove efficacy and effectiveness of curcumin in managing periodontitis. Furthermore, its structure requires modification in order to improve its bioavailability and its clinical effectiveness. Further research aiming at improving its delivery and formulation will enhance its dual potential as an important anti-inflammatory and anti-microbial agent in periodontology.

Key words: Periodontal therapy, curcumin, host modulation therapy

Introduction

Periodontitis is a chronic inflammatory disease that is characterized by destruction of the connective tissue and the alveolar bone around teeth, eventually leading to tooth loss. In the United States adult population, periodontitis has been reported to affect 64.7 million individuals, or 48% of the adult population (Eke *et al.*, 2015).

The microbial biofilm is the primary etiological factor in the initiation and progression of periodontal diseases (Haffajee and Socransky, 1994). While the biofilm may contain hundreds of diverse bacterial species, current data suggest that only a small number of Gram-negative, anaerobic or capnophilic bacterial species are implicated in the pathogenesis of periodontal diseases. Since the late 1990s, *Porphyromonas gingivalis*, *Tannerella forsythia,* and *Treponema denticola* ("the red-complex"), have been recognized as important periodontal pathogens (Socransky *et al.*, 1998). Other putative pathogens include *Fusobacterium nucleatum, Prevotella intermedia, Cambylobacter rectus* and *Eubacterium nodatum*. Recent studies have identified other microorganisms that may play a role in the pathogenesis of periodontitis such as *Herpes simplex* virus (HSV), *Epstein-Barr* virus (EBV) and *Cytomegalovirus* (CMV; Slots, 2010). While microorganisms are capable of triggering the disease process, the destruction of the periodontium is mostly caused by the host's immune response. This includes production of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), proteases that result in connective tissue destruction [matrix metalloproteinases (MMPs)], and prostanoids (*e.g.,* prostaglandin E_2, or PGE_2), which promote alveolar bone resorption (Page, 1998).

Correspondence to: Rania Livada, College of Dentistry, University of Tennessee Health Science Center, 875 Union Ave, Memphis TN, 38163 USA. Phone: +1 901-448-6242; Fax no: +1 901 – 448 -6751; E-mail: rlivada@uthsc.edu

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Current management of periodontal diseases centers primarily on non-specific reduction of the microbial load attached to the teeth and restoring gingival health through non-surgical and surgical periodontal procedures. A thorough scaling and root planing alone or combined with local or systemic administration of antibiotics has been shown to be effective for the majority of patients and sites (Slots and Jorgensen, 2002). However, the response to periodontal therapy is not universal, especially among tobacco smokers, poorly controlled diabetics, and patients with aggressive forms of periodontal disease (Tonetti *et al*., 2011). Indiscriminate use of antibiotics in these patients could lead to bacterial resistance or side effects (Bidault *et al*., 2007). Modulating the host response by an array of anti-inflammatory agents could provide a viable alternative to these patients (Palombo, 2011; Shiloah *et al*., 2014).

The overall objective of this paper is to review current data pertinent to curcumin and its potential as an antimicrobial and a host response modulator in periodontal therapy.

Turmeric/curcumin

The use of turmeric for health reasons and preservation of food has been described in traditional Chinese and Indian medicine since the 7th century AD. Turmeric was mentioned in the writings of Marco Polo following his historic journey to China and India in 1280 AD, and it was first introduced to Europe in the 13th century AD by Arab traders. The Portuguese explorer Vasco de Gama visited the Indian subcontinent during the 15th century and brought turmeric and other spices of the Orient to the West (Aggarwal *et al*., 2007).

Turmeric is derived from the plant *Curcuma longa*, an herbaceous perennial plant that belongs to the *Zingiberaceous* family. Turmeric contains a wide variety of phytochemicals, including curcumin, demethoxycurcumin, bisdemethoxycurcumin, zingiberene, curcumenol, curcumol, eugenol, tetrahydrocurcumin, triethylcurcumin, turmerin, turmerones, and turmeronols (Chattopadhyay *et al*., 2004). Curcumin composes approximately 2-5% of the herb, gives the yellow color to turmeric, and is considered responsible for most of the therapeutic effects. Curcumin was first discovered in the early 19th century by Vogel and Pelletier (1815) who isolated a "yellow colouring substance" from turmeric. However, its chemical structure was not identified as diferuloylmethane until almost 100 years later (Milobedzka *et al*., 1910). Most currently available commercial preparations of curcumin contain approximately 77% diferuloylmethane, 18% demethoxycurcumin, and 5% bisdemethoxycurcumin.

The absorption, distribution, metabolism, and excretion of curcumin have been extensively reported in rodents (Ireson *et al*., 2002) and humans (Vareed *et al*., 2008). Curcumin undergoes a rapid and efficient metabolism that severely curtails the availability of the parent compound. When administered orally, curcumin is converted through the liver and intestinal metabolism into curcumin glucuronide and curcumin sulfonate (Ravindranath and Chandrasekhara, 1980). However, when administered systemically or intraperitoneally, it is metabolized into tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol (Ravindranath and Chandrasekhara, 1981). Additionally, curcumin is poorly absorbed from the gastrointestinal tract after oral intake and is mostly excreted unchanged with the feces. The small portion that is absorbed is completely eliminated by biliary and renal excretion, and is not stored in any organ. Moreover, the levels of parent curcumin in blood plasma, bile, and urine are extremely low even after high doses. Thus, any effects on peripheral tissues must be considered to be mediated by the degradation products or the metabolites of curcumin. In order to enhance the bioavailability of curcumin, it is combined with other spices such as piperine, a component of black pepper. This compound has been shown to increase the bioavailability of curcumin by as much as 154% through suppression of its glucuronidation that occurs primarily in the liver and in the intestine (Shoba *et al*., 1998).

Curcumin possesses a wide range of biologic activities and targets many molecules and receptors. Its anti-bacterial activity was first reported in by Schraufstatter and Bernt (1949). Since then, it has been shown to have anti-inflammatory, anti-oxidant (Zbarsky *et al*., 2005), anticancer (Mehta *et al*., 1997; Li *et al*., 2004; Song *et al*., 2005; LoTempio *et al*., 2005), chemopreventive (Surh, 2003), antiplatelet, wound healing (Sidhu *et al*.,1998), anti-diabetic (Srinivasan, 1972; Seo *et al*., 2008) and cholesterol-lowering properties (Patil and Srinivasan, 1971), among many others. It has long been used for treatment of a wide range of inflammatory diseases such as arthritis (Liacini *et al*., 2002), pancreatitis (Masamune *et al*., 2006), asthma (Abidi *et al*., 2014), chronic obstructive pulmonary disease (Biswas and Rahman, 2008), inflammatory bowel disease (Holt *et al*., 2005), and colitis (Salh *et al*., 2003). It has also been successfully employed in managing various autoimmune diseases including scleroderma (Tourkina *et al*., 2004), psoriasis (Bosman, 1994), and multiple sclerosis (Natarajan and Bright, 2002). Its potential as an adjunct in managing periodontitis has been reported only recently. (Gottumukkala *et al*., 2013; Muglikar *et al*., 2013; Bhatia *et al*., 2014; Anitha *et al*., 2015)

Mechanism of anti-inflammatory actions of curcumin

The potent anti-inflammatory actions of curcumin are attributed to several mechanisms and to its multiple molecular targets. First, it suppresses the activation of the transcription factor NF-κB, which is a key signaling molecule in the elaboration of the inflammatory response (Singh and Aggarwal, 1995; Giuliani *et al*., 2001) as well as in cell proliferation, oncogenesis and cell transformation (Luque and Gelinas, 1997). NF-κB activation is reported in many chronic inflammatory diseases including rheumatoid arthritis (Handel *et al*., 1995), inflammatory bowel disease, asthma (Hart *et al*., 1998),

pancreatitis, oral lichen planus, and *Helicobacter pylori*-induced gastritis (Foryst-Ludwig and Naumann, 2000). Stimulation of cells with various inflammatory agents (e.g., TNF-α, IL-1β, and LPS from Gram-negative periodontal pathogens) leads to activation and transcription of NF-ϰB (Baldwin, 1996). Curcumin has been shown to suppress this activation process (Pendurthi *et al.*, 1997; Surh *et al.*, 2001). Chronic periodontitis is also associated with NF-ϰB activation, suggesting the potential of inhibitors of NF-ϰB by agents such as curcumin in managing it (Ambili *et al.*, 2005)

Secondly, curcumin downregulates the expression of cyclo-oxygenase-2 (COX-2), an enzyme that catalyzes the synthesis of prostaglandins (PGs) and is linked to most forms of inflammation, including periodontitis. Curcumin significantly inhibits LPS-induced COX-2 expression, contributing to a decreased synthesis of PGE_2, which is a potent stimulator of bone resorption and a key player in periodontal disease (Hong *et al.*, 2004). Another molecular target of curcumin is inducible nitric oxide synthase (iNOS), a strong pro-inflammatory molecule that is regulated by NF-ϰB. Several agonists, such as pro-inflammatory cytokines (IL-1β, TNF-α) and bacterial lipopolysaccharides, increase iNOS expression, indicating that it may also play a role in bone inflammation. Nitric oxide (NO) and PGs may react synergistically in promoting inflammation (Surh *et al.*, 2001). Several *in vitro* and *in vivo* studies reported evidence for interplay between COX-2 and iNOS expression and activities (Salvemini *et al.*, 1993; Tetsuka *et al.*, 1996). Curcumin inhibits synthesis of iNOS protein (Brouet and Ohshima, 1995), and promotes its direct degradation (Ben *et al.*, 2011).

Additionally, curcumin downregulates the expression of various vascular endothelial cell surface adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and E-selectin. These molecules are important in inflammation because of their ability to facilitate leukocyte extravasation from the vasculature into the tissues. These cell adhesion proteins are not normally present on the endothelial cell surface but are induced by various pro-inflammatory cytokines such as IL-1β and TNF-α (Mantovani *et al.*, 1992; Mantovani *et al.*, 1997). Curcumin downregulates the levels of cell adhesion molecules via its inhibition of NF-ϰB and subsequent inhibition of the cytokines that stimulate their expression. Curcumin has also been shown to have inhibitory effects on an array of cytokines such as IL-1β (Cho *et al.*, 2007), IL-2 (Ranjan *et al.*, 2004), IL-5 (Kobayashi *et al.*, 1997), IL-6 and IL-8 (Cohen *et al.*, 2009), IL-12 (Fahey *et al.*, 2007), IL-18 (Hidaka *et al.*, 2002), and TNF-β (Aggarwal, 2003). These cytokines are significant components of the inflammatory process, especially in periodontitis. Moreover, curcumin inhibits the expression of the transcription factor AP-1, which is a crucial regulator in various distinct biological functions. By inhibiting the AP-1 pathway, curcumin inhibits the expression of cytokines, iNOS, and several MMPs. MMPs are a large family of endopeptidases that play a central role in the breakdown of extracellular matrix and basement membrane components. Specifically, it has been demonstrated that curcumin inhibits secretion of MMP-1 -3, -9, 14 (Kim *et al.*, 2005) and 13 (Yang *et al.*, 2013). Lastly, curcumin is a very potent antioxidant (Dinkova-Kostova and Talalay, 2008), a property that might contribute to its anti-inflammatory action. Curcumin is able to scavenge superoxide anion (O_2^-), hydroxyl radicals (OH), H_2O_2, singlet oxygen, nitric oxide and others (Sreejayan and Rao, 1997). In addition, it acts indirectly by inducing the expression of cytoprotective proteins such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx), among others (Panchal *et al.*, 2008).

Antimicrobial actions of curcumin

Curcumin has been reported to possess antibacterial (Schraufstatter and Bernt, 1949; Bhavani and Sreenivasa, 1979) and antifungal properties (Apisariyakul *et al.*, 1995). Its activity ranges from bacteriostatic (Shahi *et al.*, 2000) to bactericidal for several pathogenic Gram-positive bacteria (Negi *et al.*, 1999) such as *Staphylococcus aureus*, as well as Gram-negative bacteria, including *Pseudomonas aeruginosa* (Packiavathy *et al.*, 2014), *Klebsiella pneumoniae* (Magesh *et al.*, 2013), as well as different fungal species (*Candida albicans* and *Paracoccidioides brasiliensis;* Martins *et al.*, 2009).

With regard to oral bacteria, curcumin exhibited a high level of antibacterial activity against *Streptococcus mutans* and *Streptococcus pyogenes* (Najah and Neama, 2015). These bacteria are highly pathogenic and play an important role in the development of dental caries. Additionally, curcumin was shown to have antibacterial activity against most of the common bacteria associated with pulpitis, such as *Lactobacillus casei* and *Actinomyces viscosus,* as well as against periodontal pathogens (*P. intermedia* and *P. gingivalis*; Praveenkumar *et al.*, 2013). Curcumin inhibited the growth of *P. gingivalis, P. intermedia, F. nucleatum,* and *T. denticola* in a dose-dependent manner (Izui *et al.*, 2016).

Several mechanisms of actions have been reported concerning the antibacterial properties of curcumin. It has been suggested that curcumin inhibits bacterial cell division (Rai *et al.*, 2008). Tyagi *et al.* (2015) showed that curcumin can induce bacterial membrane permeabilization, leading to permanent damage and cellular death in both Gram-positive and Gram-negative bacteria. Furthermore, curcumin inhibits *S. mutans* biofilm formation by suppressing sortase A which is an enzyme responsible for the bacterial attachment (Hu *et al.*, 2013a) to human tooth surfaces and extra-cellular matrix proteins (Song *et al.*, 2012). Moreover, several reports have demonstrated that curcumin has synergistic antibacterial effects with important antibiotics such as cefixime, vancomycin and tetracycline against *S. aureus* (Moghaddam *et al.*, 2009) and *P. aeruginosa* by negatively affecting their virulence, quorum sensing, and biofilm initiation (Rudrappa and Bais, 2008).

The utilization of curcumin in periodontics

In vitro studies

Lipopolysaccharide derived from *P. gingivalis* is a major inflammatory stimulus and trigger of the host's immune response. It induces macrophages and monocytes to produce pro-inflammatory cytokines (IL-1β and TNF-α; Baqui *et al*., 1998), which can lead to inflammatory cascades resulting in periodontal tissue destruction. Studies have shown that curcumin can inhibit *P. gingivalis* LPS-induced expression of IL-1β and TNF-α in a dose-dependent manner (Chen *et al*., 2008). LPS can also stimulate COX-2 release from human monocytes (Hofer *et al*., 2004), human gingival fibroblasts (Ara *et al*., 2008) and osteoblasts (Kwak *et al*., 2008), as well as the production of PGE_2, which participates in inflammation. Hu *et al.* (2013b) have reported on curcumin's ability to attenuate *P. gingivalis* LPS-induced COX-2 synthesis via suppression of the NF-κB pathway in human gingival fibroblasts, suggesting that curcumin may delay the disease process of periodontitis in its initial stages. Additionally, curcumin appears to possess inhibitory action on the planktonic growth of several periodontal pathogens, including *Aggregatibacter actinomycetemcomitans, F. nucleatum* and *P. gingivalis*, as reported by Shahzad *et al.* (2015). Curcumin significantly reduced the metabolic activity of multiple bacterial species in the biofilm, including periodontal pathogens.

Animal studies

Several animal studies have confirmed results obtained from *in vitro* studies. In ligature-induced experimental periodontitis in rats, curcumin effectively controls the expression of TNF-α, IL-6 and PGE_2 by modulating NF-κB activation. Curcumin was administered to 60 Holtzman rats by the intragastric route daily in two dosages (30 and 100 mg/kg) for 15 days. Animals in the control group had ligature wires but had only the corn oil vehicle and served as negative controls. Bone resorption was assessed by micro-computed tomography, and the inflammatory status was evaluated by stereometric analysis. The test group treated with curcumin had a marked reduction of the inflammatory cell infiltrate with concomitant repair by stimulating fibroblast proliferation and collagen production. Curcumin failed to prevent alveolar bone resorption at either concentration, but its potent anti-inflammatory effect suggests that it may have a therapeutic potential in managing periodontal diseases (Guimarães et al, 2011). This suggestion contradicts a subsequent report by Zhou *et al*., (2013) that demonstrated a decrease in alveolar bone resorption following curcumin administration in rats. Additionally, pro-inflammatory cytokines (TNF-α and IL-6) and osteoclastogenesis-related molecules (RANKL and RANK) were suppressed in the curcumin group compared to the control and vehicle group. In a subsequent study, Mau *et al.* (2016) reported that curcumin diminished RANKL-induced osteoclast differentiation and expression of osteoclastic genes along with the number of osteoclasts. In this report, experimental periodontitis was induced in Sprague-Dawley rats by injection of *P. gingivalis* LPS rather than by ligature wires and curcumin was administered to the test group for 14 days intragastrically. Curcumin was shown to ameliorate alveolar bone resorption through inhibition of major inflammatory markers and osteoclastogenesis.

A recent short-term (4 week) study by Hosadurga *et al.* (2014) used a 2% curcumin gel applied topically to the gingiva with a tuberculin syringe in Wistar albino rats with experimentally induced periodontitis. Curcumin was applied every other day for 6 days in the test group. Periodontal measurements were taken pre-operatively and at the end of the 4-week observation period. Reduction of gingival inflammation and edema was noted in the test group at the end of the study that was statistically significant compared to the control group. Additionally, reduction in pocket depths and bone loss was noted that did not reach statistical significance. The authors attributed their results to the anti-inflammatory properties of the curcumin gel and pointed to its potential use in periodontal therapy.

Clinical studies

Curcumin given in conjunction with scaling and root planing has positive synergistic effects on the treatment outcomes of periodontitis and has been employed in several forms such as solution, gel, mouthwash and sponge. Bhatia *et al.* (2014) treated 25 patients with chronic periodontitis with periodontal pockets of at least 5 mm in depth. The test group received scaling and root planing along with intrapocket application of a gel containing 1% curcumin at baseline and at 1-, 3-, and 6-month intervals. The control group received scaling and root planing alone. At the end of the observation period, there were significant improvements in the clinical parameters of periodontitis, including reduction in pocket depth and bleeding, and gain in clinical attachment levels in both groups but with more pronounced improvement in the test group. In regard to the microbiological parameters, curcumin significantly reduced the levels of *P. gingivalis, P. intermedia, F. nucleatum* and *Capnocytophaga sp*. at the end of the six-month observation period (Bhatia *et al*., 2014). In a clinical trial of 30 patients comparing 1% curcumin gel and 0.1% chlorhexidine gel application following scaling and root planing, significant improvement in the clinical parameters as well as reduction of the colony forming units was reported in both groups. However, more significant reduction was noted in the curcumin group and the authors recommended its use over chlorhexidine, especially because of its minimal side effects (Anitha e*t al*., 2015).

A clinical trial of a curcumin-containing mouthwash (20% solution) was prescribed for 30 patients with chronic gingivitis, following scaling and root planing. Significant reduction of gingival inflammation was reported in the test group compared to the control group at the end of the 21-day observation period. However, no significant difference in microbial plaque indices was noted, pointing to curcumin's anti-inflammatory properties alone (Muglikar *et al.*, 2013).

In another study, subgingival irrigation with a 1% curcumin solution following scaling and root planing was utilized in 23 patients with chronic periodontitis and pockets of 5 mm in depth. Pocket irrigation was repeated 3 times over 21 days. The control group was irrigated with 0.2% chlorhexidine. At the end of the 6-month observation period, both groups showed improvement in the clinical and microbiological parameters but with no statistically significant differences detected between the groups (Gottumukkala *et al.*, 2013). In contrast, in a subsequent study, the same author compared chlorhexidine chip with a resorbable sponge containing curcumin placed subgingivally as adjuncts to scaling and root planing. In this study of 60 patients, clinical and microbiological parameters were improved in both groups but more significantly in the chlorhexidine group (Gottumukkala *et al.*, 2014).

Safety and adverse effects

Curcumin has been consumed for centuries as a dietary spice at levels up to 100 mg/day (Shishodia *et al.*, 2005). Despite its long history of use, it should not be assumed that this natural product is innocuous if taken without consideration of the patient's past medical history and current medications. Animal studies did not reveal significant toxicity related to curcumin. High doses of 5 g/kg administered orally to rats failed to demonstrate any toxicity (Wahlstrom and Blennow, 1978). Additionally, systematic preclinical safety studies conducted by the US National Cancer Institute did not report any adverse effects in rats, dogs and monkeys of curcumin doses of up to 3.5 g/kg administered up to 3 months in duration (National Cancer Institute, 1996).

A Phase I clinical trial demonstrated the safety of curcumin in humans: doses as high as 8 g/day administered for 3 months did not elicit any adverse effects (Cheng *et al.*, 2001). In similar safety studies, a daily oral dose of 1.2–2.1 g of curcumin in patients with rheumatoid arthritis (Deodhar *et al.*, 1980) and a daily dose of 3.6 g for up to 4 months in patients with advanced colorectal cancer were reported to be safe and well tolerated by patients and did not lead to any measurable toxic effects (Sharma *et al.*, 2014). The most common adverse effects of curcumin are mild diarrhea or nausea. A single oral dose of curcumin ranging from 500 to 12,000 mg was given in 24 patients; seven of these subjects reported adverse effects including diarrhea, headache, rash, and yellowish stool (Lao *et al.*, 2006).

Limitations and recommendations

While animal studies and limited clinical trials have shown promising results, there are still limitations and precautions that must be addressed prior to a wide clinical use of curcumin in patients with periodontitis. Like other natural polyphenols, curcumin is poorly soluble in water and must be solubilized in ethanol or dimethyl sulfoxide (DMSO). Additionally, it appears that curcumin has low systemic bioavailability following oral dosing due to first pass effect and to some degree intestinal metabolism of the molecule, thus limiting its therapeutic applications (Garcea *et al.*, 2005). Furthermore, it is absorbed poorly in the gastrointestinal tract and metabolizes rapidly (Anand *et al.*, 2007).

Further research aimed at improving curcumin formulations and delivery systems are needed. Structural curcumin analogs have been recently developed in order to optimize its therapeutic effects by increasing potency, slowing metabolism, and increasing absorption (Basnet and Skalko-Basnet, 2011). Other promising approaches to increase its bioavailability include the use of nanoparticles (Tiyaboonchai *et al.*, 2007), liposomes (Li *et al.*, 2005), micelles (Suresh and Srinivasan, 2007) and phospholipid complexes (Liu *et al.*, 2006) for delivery.

Taking into consideration the vast number and multitude of curcumin actions and properties, several warnings and precautions should be given to all medical professionals and patients. Curcumin should not be taken by pregnant women due to its ability to induce menstruation, and contraction of the uterus that may lead to miscarriage (Ernst, 2002). Curcumin may increase the risk of bleeding due to its antiplatelet properties, as it was shown to inhibit the cyclooxygenase pathway by blocking the GPIIb/IIIa receptor. Additionally, it causes an increase in prostacyclin activity, an inhibitor of aggregation (Srivastava *et al.,* 1985), therefore it is not recommended for patients on anticoagulant drugs or those with pre-existing bleeding disorders (Kim *et al.*, 2012). Curcumin may also increase bleeding during surgery and post-operatively, and should not be consumed for at least two weeks prior to an elective surgery. While curcumin increases bile secretion and flow, and induces gallbladder contraction, thus preventing formation of gallstones (Rasyid *et al.*, 2002), it is an ineffective treatment for removal of gallstones, as it may exacerbate the problem by flushing fragments of gallstones through the bile duct and blocking it. Furthermore, allergic reactions to curcumin such as rash or urticaria have been reported (Liddle *et al.*, 2006), and patients with allergies to plants in the ginger family or curcuma genus are most susceptible to these side effects. Patients who are allergic to yellow food coloring, which is often derived from turmeric, should also avoid curcumin.

Lastly, potential drug interactions of curcumin with some anticoagulant and antiplatelet medications (camptothecin, celiprolol, cyclophosphamide, doxorubicin, mechlorethamine, midazolam and others) have been reported, as they are all metabolized by the CYP3A4 enzyme in the liver.

Conclusion

Curcumin has a wide biological spectrum of activity that could provide clinicians with an alternative anti-inflammatory and antimicrobial agent for managing a variety of maladies, including periodontal diseases. However, large-scale longitudinal randomized clinical trials are needed to prove efficacy and effectiveness of curcumin in managing periodontitis. Furthermore, its structure requires modification to improve its bioavailability and its clinical effectiveness. Further research aiming at improving its delivery and formulation will enhance its dual potential as an important anti-inflammatory and anti-microbial agent in periodontology.

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