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Curcumin A Therapeutic Approach In Periodontal Disease: A Review

KEYWORDS: Curcumin, Inflammation, Periodontal disease, Therapy

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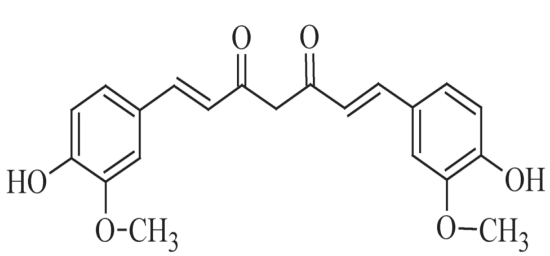
ABSTRACT *Periodontitis is a bacterial initiated but host modulated chronic infection that leads to destruction of the connective tissue supporting the teeth. Immune and Inflammatory response directed against specific bacteria and its products become responsible for the local periodontal, tissue loss in susceptible persons. Non – surgical therapy has been the main stay of periodontal disease management with mechanical removal of plaque being the predominant method. However some individuals non responsive with only mechanical therapy benefit from supplementation with antimicrobial therapy. The use of adjunctive antimicrobial therapy has been plagued by problems of microbial resistance of local and gut flora. This has led to renewed interest in the discovery of novel anti-infective natural compounds derived from plants. Turmeric, a rhizome of curcumalonga, is an herb known for its medicinal properties and is a more acceptable option for a common man. Here we review the anti-inflammatory properties of curcumin and its various forms in modulatory host response as a potential therapy in periodontal disease.*

Introduction

One of the most common diseases affecting human race is periodontal disease. American Academy of Periodontology (2000) defined Chronic Periodontitis as, "inflammation of the gingiva extending into the adjacent attachment apparatus. The disease is characterized by loss of clinical attachment due to destruction of the periodontal ligament and loss of the adjacent supporting bone". Severe peridontitis that can lead to tooth loss affects 10-15% of the global population [1]. Progressive Connective tissue less initiated by the interaction with microorganisms and enhanced by the host inflammatory factors can best describe the destruction seen in periodontitis [2]. Many studies have explored the use of systemic agents to counteract the inflammatory and Osteoclastic, activity occurring in periodontal tissues [3]. Therapies for management of bacterial induced host inflammatory destructive diseases are being explored. The curcumin (1,7-Bis) (4-hydroxyl 3 methoxy phenyl)-1,6–heptadiene-3,5–Dione) is the active ingredient in the herbal remedy and dietary spice turmeric (Curcuma longa Linn). Curcumin action in suppressing the activity of Toll like receptos (TLRS) has initiated great interest in identifying and expanding its therapeutic potential in limiting the destruction in periodontitis [4].

Figure 1: Chemical structure of Curcumin



Chemistry of Curcumin

The structure was first identified in 1910 by J. Milobedzka, Stanislaw Kostanecki and Wiktor Lampe. Curcumin includes several functional groups. The aromatic ring systems, which are polyphenols are connected by two-α, α-unsaturated carbonyl groups. The diketones form stable enols or are easily deprotonated and form enolates, while the-α,α- unsaturated carbonyl is a good Michael acceptor and undergoes nucleophilic addition [5].

Historical use

The origin of the plant Curcuma longa L, which belongs to Zingiberaceae family in India. The rhizomes of turmeric are used in Asian Cookery, Medicine, Cosmetics and fabric dying for more than 2000 years [6].

As part of the ancient Indian medical system, Ayurveda, a poultice of turmeric paste is used to treat common eye infections, and to dress wound, treat bites, burns, acne and various skin diseases [7]. In food and perfumes and as a natural yellow colouring agent as well as an approved food additive to flavor various types of curries and mustards [8]. Recent emphasis on the use of natural and complementary medicines in Western medicine has drawn the attention of the scientific community to this ancient remedy. Research has revealed that curcumin has surprisingly wide range of beneficial properties, including anti–inflammatory, antioxidant, chemo-preventive and chemotherapeutic activity. These activities have been demonstrated both cultured cells and in animal models and have paved the way for ongoing human clinical trials [9]. Curcuma longa is an ingredient in Indian functional foods but the amount required for disease management, i.e. a minimum of 8 g., pose problems particularly because of taste [10]. It has also been documented that soluble curcumin as compare to crude extract of turmeric shows better results for management of various health parameters with enhanced antioxidant activity as well as effective cytoprotective and a potential chemotherapeutic agent for treatment of human leukemia [11].

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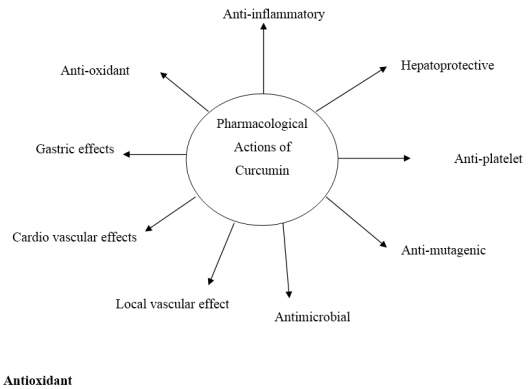
Pharmacological actions
Figure-2: Pharmacological Actions



Antioxidant

Antioxidant
Curcumin protect against free radical damage because it is a strong antioxidant [12]. Water and fat soluble extracts of turmeric and its curcumin component exhibit strong antioxidant activity comparable to that of Vitamins C and E [13]. An *in-vitro* study measuring the effect of curcumin on endothelial heme oxygenase-1, an inducible stress protein, was conducted utilizing bovine aortic endothelial cells. Incubation (for 18 hours) with curcumin resulted in enhanced cellular resistance to oxidative damage [14].

Anti-inflammatory
It reduces inflammation by lowering histamine levels and possibly by increasing the production of natural cortisone by the adrenal glands [15]. Its anti inflammatory properties may be attributed to its ability to inhibit both biosynthesis of inflammatory prostaglandins from arachidonic acid and neutrophil function during inflammatory states [16].

Hepatoprotective
It protects the liver from a number of toxic compounds such as Carbon tetrachloride (CCl_4), galactosamine, acetaminophin, and Aspergillus aflatoxin. Turmeric's hepatoprotectic effect is mainly a result of its antioxidant properties as well as its ability to decrease the formation of pro-inflammatory cytokines sodium curcuminate, a salt of curcumin, also exerts cholerectic effects by increasing biliary excretion of bile salts, cholesterol and bilirubin as well as by increasing bile solubility, therefore possibly preventing and treating cholelithiasis. Curcumin has Cholerectic activity that increases bile output and solubility, which may be helpful in treating gallstones [17-21].

Anti-platelet
It has been shown to prevent platelets from clumping together, which in turn improves circulation [22]. Inhibition of platelet aggregation by curcumin constituents is thought to be via potentiation of prostacyclin synthesis and inhibition of thromboxane synthesis.

Anti-mutagenic
Curcumin is anti-mutagenic as it potentially helps to prevent new cancers that are caused by chemotherapy or radiation therapy used to treat existing cancers. It effectively inhibits metastasis of melanoma (skin cancer) cells and may be especially useful in deactivating the carcinogens in cigarette smoke and chewing tobacco [23]. The anti carcinogenic effects of turmeric and curcumin are due to direct antioxidant and free radical scavenging effects and their ability to indirectly increase glutathione levels, thereby aiding in hepatic detoxification of mutagens and carcinogens and in inhibiting nitrosamine formation [24].

Antimicrobial
Turmeric extract and the essential oil of curcuma longa inhibit the growth of a variety of bacteria, parasites and pathogenic fungi. Improvements in lesions were observed in the dermatophyte and fungi–infected guinea pigs, as at 7 days post turmeric application, the lesions disappeared [25]. Curcumin has also been found to have moderate activity against *Plasmodium falciparum* and Leishmania major [26].

Cardiovascular effects
Turmeric's protective effects on the cardiovascular system include, lowering cholesterol and triglyceride levels, decreasing susceptibility of low density lipoprotein to lipid peroxidation and inhibiting platelet aggregation [27]. These effects have been noted even with low doses of turmeric. A study of 18 atherosclerotic rabbits administered low–dose (1.6 – 3.2 mg/kg body weight, daily) turmeric extract demonstrated decreased susceptibility of LDL to lipid peroxidation in addition to lower plasma cholesterol and triglyceride levels. Higher dose did not decrease lipid peroxidation of LDL, but cholesterol and triglyceride levels decrease were noted, although a lesser degree than with lower dose. Turmeric extracts effects on cholesterol levels may be due to decreased cholesterol uptake in the intestines and increase conversion of cholesterol to bile acids in the liver [28].

Local effects
Fresh juice from rhizome or a paste prepared from turmeric or decoction is often used as a local application as well as internally in the treatment of leprosy, snake bites, and vomiting associated with pregnancy [28].

Gastric effects
Curcumin has a significant role in the cases of gastric ulcers. An open, phase II trial was performed on 25 patients with endoscopically diagnosed gastric ulcer. Participants were provided 600 mg powdered turmeric, five times daily. After 4 weeks, ulcers had completely healed in 48% patients. The success rate increased over time, with 76% being ulcer free after 12 weeks of treatment. No significant adverse reactions or blood abnormalities were noted [29].

Mechanism of curcumin in modulating periodontal inflammation
The main target of curcumin is NFαB whose modulation following TLR4 activation by LPS could be the main mechanism involved in affecting periodontal disease [30]. Some pathogens like *P. gingivalis* evade TLR4 and activated TLR2 for their protection. Curcumin can inhibit the activity of TLR2, 4 and 9 and would be potent to prevent excess connective tissue loss in periodontitis initiated by various pathogens [31].

Curcumin has shown to suppress or inhibits cytokines such as TNF-α, IL-1, -2, -6, -8, -12, mitogen activated protein kinase (MAPK), and c-Jun N terminal kinase (JNK). It also has shown to down regulate enzymes like the inducible nitric oxide synthase (iNOS), COX-2, and lipxygenase (LOX) [32]. It inhibits NF-kB activation, matrix metalloproteinate (MMP-1, -9, -13) secretion, COX-2 expression and anti apoptotic protein such as Bcl2 and activates Caspase -3, NFkB and Phosphatidy inositol 3-kinase (PI3K / Akt) activation induced by IL-1α is suppressed by curcumin [33]. The

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expression of intercellular adhesion molecular (ICAM-1) Vascular cell adhesion molecule-1(VCAM–1), IL-6, -8, and monocyte chemotactic protein -1 (MCP –1) induced by TNF - α is inhibites by curcumin [34]. Curcumin has been shown to decrease the expression COX-2, 5-LOX, macrophage protein, and chemokine receptor type 4 (CXCR -4) [35]. Curcumin was also found to decrease gene expression of mitochondrial DNA (mt DNA), nuclear respiratory factor (NRF1), and mitochondrial transcription factor A (Tfam) [36]. Thus, curcumin suppresses inflammation through multiple pathways.

therapeutic uses in periodontal disease

Topical application

Applying a paste made from 1 tsp of turmeric with ½ tsp of salt and ½ tsp of mustard oil provides relief from gingivitis and peridontitis. It is recommended to rub the teeth and gums with this paste twice daily [37].

Mouthwash

In a study by Waghmare et al about 100 subjects were randomly selected Both gingival index and plaque index with recorded at 0, 14, and 21 days. It was concluded that chlorhexidine gluconate as well as turmeric mouthwash can be effectively used as an adjunct to mechanical plaque control methods in prevention of plaque and gingivitis. Turmeric mouthwash prepared by dissolving 10mg of curcumin extract in 100ml of distilled water and 0.005% of flavouring agent peppermint oil with pH adjusted to 4 is found to be effective as most widely used chlorhexidine mouthwash. Though chlorhexidine gluconate has been found to be more effective when antiplaque property was considred. The effect of turmeric observed may be because of its anti – inflammatory action, reduction in total microbial count was observed in both the groups [38].

Local drug delivery system

In a study conducted by Behal et al, 30 subjects with chronic localized or generalized periodontitis with pocket depth of 5-7 mm were enrolled in a split–mouth study design. Control sites received scaling and Root planning (SRP) alone, while experimental sites received SRP plus 2% whole turmeric gel. Both groups demonstrated statistically significant reduction in plaque index, gingival index, sulcus bleeding index, probing pocket depth and gain in relative attachment loss. There was a significant reduction in trypsin – like enzyme activity of "red complex" micro organisms. Greater reduction was observed in all parameters in the experimental group in comparison to those in the control group. Thus, the local drug delivery system containing 2% whole turmeric gel can be used as an adjunct to scaling and root planning [39].

Subgingival irrigant

In a study conducted by Suhag et al., Periodontal sites were treated on day 0 (base line) by a single episode of scaling and root planning. Subsequently selected sites were irrigated (triple irrigation regimen) with either saline (0.9%), Chlorhexidine (0.2%) curcumin (1%) or served as non irrigated control sites on day 0 (base line) immediately following instrumentation. Triple irrigation regimen was repeated for the next 5 consecutive days and on days 15 and 21. Clinical parameters recorded were probing pocket depth (PPD), bleeding on probing (BOP) and redness for 200 sites in 20 patients with chronic peridontitis. The results indicated that the irrigated sites had significant improvement in all parameters as compared with the non irrigated sites on days 2, 3, 4 and 5. The curcumin group showed significant reduction in BOP (100%) and redness (96%) when compared with the chlorhexidine group and saline group on day 5. However, the difference between groups was not significant at the next recall visits. Mean PPD reduction was significantly greater for the curcumin group than all other group on all post – treatment days. Thus, 1% curcumin solution can cause better resolution of inflammatory signs than chlorhexidine and saline irrigation as a subgingival irrigan [40].

Surgical Wound Healing

Habiboallah et al. performed a study to compare the effects of Curcuma longa – ghee formulation and hyaluronic acid on gingival wound healing following surgery in beagle dogs. A significant difference in the inflammatory and repair parameters of the healing process as regards to cases treated with curcuma longa was observed. The results suggested a positive potential therapeutic effect on surgical wound healing particularly improvement of periodontal treatment consequences after surgery [41].

Adverse effects

Generally considered safe, but may cause gastric irritation, stomach upset, nausea, diarrhea, allergic skin reactions, and anti-thrombosis activity interfering with blood – clot formation.

Future challenges

One of the major concerns with developing curcumin for clinical efficacy is its low oral bio availability that can be attributed to its poor absorption, high rate of metabolism in the intestines, and rapid elimination from the body. Also, little information is available to determine its safety in higher doses. Nanotechnology based novel strategies are being aggressively explored worldwide to enhance curcumins bioavailability and reduce perceived toxicity [42].

Conclusion

Turmeric is considered a safe, non toxic and effective alternative for many conventional drugs due to its distinguished therapeutic properties and multiple effects on various systems of the body. The influence of curcumin on TLRs and hence in inactivation of NFαB could be the common link which could justify the use of curcumin in managing periodontal infection and destruction. Further research is required to determine the optimal dosage, bio availability and bio – efficacy of curcumin based drugs.

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