Use of Curcumin in Periodontal Inflammation

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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 mainstay of periodontal 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. The identification of modified tetracycline made a paradigm shift in host modulation wherein the inflammatory pathway of host connective tissue destruction was altered without affecting the microbial profile. Systemic and locally delivered curcumin shows potential for having similar anti-inflammatory properties. Here we review the anti-inflammatory properties of curcumin and its various forms in modulatory host response as a potential therapy in periodontal diseases.

TLRs by periodontal pathogens. Of the 10 TLRs identified, TLRs 2 and 4 appears important in periodontitis [18,19] TLR4 is of interest as it is activated by LPS. Activation of TLR4 leads to further activation of mitogen-activated protein kinases and nuclear translocation of nuclear factor-kappa B (NF-κB) [19]. *P. gingivalis* though a gram negative organism evades the activation of TLR4 designed to detect LPS. It is however sensed and detected by TLR2. *P. gingivalis* manipulates the protective TLR2 to cause undermining of the protective host response [20]. This was seen in TLR2 deficient mice which were immune to infection of periodontium by *P. gingivalis* [21]. TLR2 inhibition leads to inactivation of NF-κB leading to protection of *P. gingivalis* and also preventing periodontal loss. NF-κB activation has been shown to be important for the release and expression of inflammatory cytokines involved in periodontal inflammation and destruction [22,23] NF-κB in epithelial cells gets activated when incubated in presence of *F.nucleatum* and *P.gingivalis* [24] Suppression of NF-κB in gingival fibroblasts lead to reduction in levels of IL-6, 8, MCP1 [25].

Curcumin and Periodontal Disease

Although bacteria are essential for periodontal disease; most of the damage is caused by inflammatory mediators and free radicals [26,27]

Neuropathic pain	TNF-a, NF-κB, IL-1b, VEGF, NO
Obesity	Wnt/β-catenin, Adipose, TNF-a, MCP-1, IL-6
Periodontitis	NF-κB pathway, MAPK pathways
Psoriasis	NF-κB, STAT3TNF-a, LAP1, LAP2, Bcl-xL, keratinocytes proliferation
Renal ischemia	TCL4, Hsp-70, TNF-a, NF-κB, MAPK, PS6, neutrophil infiltration, inflammatory chemokine, superoxide dismutase
Scleroderma	TGIF, TGF-b/Smad2, NF-κB, AP-1STAT, MAPkinase

Table 1: Mechanism of action of curcumin in various condition

Mechanism of curcumin in modulating periodontal inflammation

The main target of curcumin is NF-κB whose modulation following TLR4 activation by LPS could be the main mechanism involved in affecting periodontal disease [44]. Some pathogens like *P gingivalis* evade TLR4 and activate 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 [45].

Curcumin has shown to suppress or inhibit 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 downregulate enzymes like the inducible nitric oxide synthase (iNOS), COX-2, and lipoxygenase (LOX) [46]. It inhibits NF-κB activation, matrix metalloproteinase .

(MMP-1, -9, and -13) secretion, COX-2 expression, and anti-apoptotic protein such as Bcl2 and activates Bax and caspase-3. NF-κB and phosphatidylinositol 3-kinase (PI3K/Akt) activation induced by IL-1β is suppressed by curcumin [47]. The expression of intercellular adhesion molecule-1(ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), IL-6, -8, and monocyte chemotactic protein-1 (MCP-1) induced by TNF –α is inhibited by curcumin [48]. Curcumin has been shown to decrease the expression COX-2, 5-LOX, macrophage inflammatory protein-1a (MIP-1a), adhesion molecules, C-reactive protein, and chemokine receptor type 4 (CXCR-4) [49]. Curcumin was also found to decrease gene expression of mitochondrial DNA (mtDNA), nuclear respiratory factor 1 (NRF1), and mitochondrial transcription factor A (Tfam) [50]. Thus, curcumin suppresses inflammation through multiple pathways.

Advances in Curcumin to be a Therapy for Periodontal Disease

Curcumin has major limitations of poor solubility, lack of systemic bioavailability and rapid metabolic disposition [51]. This limits the use of orally administered curcumin for any systemic effects. Chemically modified curcumin (CMC) with a carbonyl substituent at the C-4 position showed improved solubility, better serum albumin binding activity and greater aciditity, enhanced zinc binding characteristic and leading to MMP inhibition [52,53] CMC demonstrated better inhibition of MMPs and proinflammatory is inhi" " Ņ kтарl' SILdĮMLdžþ

could be the common link which could justify the use of curcumin in managing periodontal infection and destruction. The development of chemically modified curcumin and the later development into nano formulation augur well to the use in periodontal condition. Recent advances in drug delivery systems brings back hope in developing smart local and systemic forms of nano curcumin to combat either independently or as an adjuvant the periodontal disease. The host

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