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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.

Keywords: Curcumin, Host modulation therapy, Inflammation, Periodontal disease, Therapy

Introduction

One of the most common diseases affecting human race is periodontal disease. 47% of US adults have been identified to have this disease [1]. Severe periodontitis that can lead to tooth loss affects 10-15% of the global population [2]. Progressive connective tissue loss initiated by the interaction with microorganisms and enhanced by the host inflammatory factors can best describe the destruction seen in periodontitis [3]. The complex interplay between pathogenic microorganisms and host immune systems determine the establishment of periodontal disease. Major pathogens identified include Porphymonas gingivalis, Prevetella intermedia, Aggregatibacter actinomycetemcomitans from among the more than 300 species constituting the dental biofilm [4]. Several inflammatory mediators like interleukin (IL)-1β, IL-6, Tumour necrosis factor (TNF)-α, Interferon, prostaglandin (PGE2) released by host immune cells like neutrophils and macrophages orchestrate the destruction of periodontal tissues [5,6].

Reducing the quantity of dental biofilm has been the main stay of periodontal therapy towards plaque induced diseases. Scaling, root planing and meticulous oral hygiene techniques aim at reducing the pathogenic bacterial levels to proportions manageable by the host innate immune system [7,8]. However with the host factor taking precedence as being more important in pathogenesis of periodontitis, therapeutic focus has shifted in modulating the host systems [9,10]. Many studies have explored the use of systemic agents to counteract the inflammatory and osteoclastic activity occurring in periodontal tissues [11]. Therapies for management of bacterial induced host inflammatory destructive diseases are being explored. Turmeric has been used for medicinal purpose for the treatment of many diseases. Turmeric (also known as *Curcuma longa*) is a member of the ginger family, Zingaberaceae. This yellow spice contains the polyphenol curcumin in its rhizome [12]. Curcumin action in suppressing the activity of Toll like receptors (TLRs) has initiated great interest in identifying and expanding its therapeutic potential in limiting or halting the destruction in periodontitis. Additional anti-microbial property can come in useful in bacterial induced periodontitis [12]. This review tries to explore the evidence on curcumin as a therapy for periodontal disease and the future of curcumin in periodontal management.

Important Characteristics of Periodontal Inflammation

Innate immunity is the first line of defence to counteract bacterial assault and support the host. It is inherited and phylogenetically on the older side [13]. It was considered to act in a non-specific role to activate the specific acquired immunity orchestrated by B and T lymphocytes [14]. Thereafter it was assumed that this non-specific immunity goes into its siesta. Discovery of the pattern-recognition receptors has brought in some respect for the innate immune response. These receptors respond in a specific manner to distinct microbial structure like Lipopolysaccharide (LPS) or lipoteichoic acid [15]. Innate immune mechanism has now been recognized to interplay between bacterial ingress and the need for adaptive immunity to respond. It has been observed that to succeed, the pathogens should be able to affect and disable the innate immunity including complement and TLR family of pattern recognition receptors [16,17].

Toll like receptors are a family of pattern recognition receptors which act as mediators of innate immunity and inflammation. They are able to affect the subsequent adaptive immune responses. TLRs are present in first line phagocytes, eg. neutrophils, macrophages, and respond to distinct types of microbial structures. However, the destruction seen in periodontitis is attributed to the over activation of

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] Prospective studies including clinical trials indicate that controlling inflammation remains a principal strategy for preventing and managing periodontal disease. Similarly, evidence from humans and animal models demonstrate that anti-inflammatory agents or host modulatory agents used as adjunct can improve periodontal status [28-30].

Previous evidence shows that curcumin effectively inhibited cytokine gene expression at both the mRNA and the protein level and produced a dose-dependent inhibition of the activation of nuclear factor-κB in the gingival tissues [31] The same authors demonstrated in an experimental periodontitis model induced in rats, that curcumin effectively inhibited cytokine gene expression at mRNA and protein levels, but NF-κB was inhibited only with the lower dose of curcumin, whereas p38 MAPK activation was not affected [32] Curcumin produced a significant reduction on the inflammatory infiltrate and increased collagen content and fibroblastic cell numbers [32] Elburki et al. [33] demonstrated that chemically modified curcumin prevented alveolar bone loss and lowered production of IL-1β and matrix metalloproteinase (MMPs) in rats. Similar results were seen by Gu et al. [34]. Curcumin inhibited activator protein 1 (AP-1) and prevented the receptor antagonist of nuclear factor kappa B ligand (RANKL) production induced by *P. gingivalis* infection [35]. Curcumin dose-dependently inhibited TNF-α and IL-1β gene expression and protein synthesis in cells stimulated with *P. gingivalis* [36]. In an in vitro and in vivo study comparatively evaluated the adjunctive efficacy of turmeric, curcumin, and traditional nonsurgical methods for treating periodontal pockets. At 24 hours, the in vitro release pattern showed that 70% of turmeric was released compared to 78% for curcumin chips. At 72 hours, these levels had increased to 78% of turmeric and 80% of curcumin. By the end of 80 hours, 100% of drug release had taken place [37]. In a study conducted by Behal et al. [38] proposed that local drug delivery system containing 2% whole turmeric gel can be used as an adjunct to scaling and root planing as it significantly reduced trypsin-like enzyme activity of "red complex" microorganisms. Gottumukkala et al. [39] failed to show any significant improvements in clinical and microbial parameters after use of indigenous curcumin based collagen when compared against CHX chips. Waghmare et al. [40] 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. Muglikar et al. [41] evaluated curcumin mouthwash among patients with chronic gingivitis and showed anti-inflammatory effects. In a study conducted by Suhag et al. [42] and Gottumukkala et al. [43] demonstrated that 1% curcumin solution can cause better resolution of inflammatory signs and improvement in microbial parameters than chlorhexidine and saline irrigation as a subgingival irrigant (Table 1).

Systemic condition	Action of curcumin
Allergy, asthma and bronchitis	NF-κB pathway, MAPK pathways, histamine release
AIDS	HIV long-terminal repeats, HIV-1 protease and integrase, p300/CREB-binding, protein specific acetyltransferase
Arthritis	COX, Lipoxygenase, NF-κBSTAT3, MMP-1, MMP-3, MMP13, mRNAs
Cancer	PPAR-γ, NF-κB, AP-1, MAPkinasese, Akt, MTORC1
Cardiovascular diseases	Caspase pathway, TNF-a, NF-KB, Bcl2, IL-6, MCP-1
Cerebral edema	Aquaporin-4 expressions, IL-1b
Diabetes	PPAR-γ
Diabetic encephalopathy	iNOS
Diabetic Nephropathy	Post transitional modifications of histones H3
Diabetic retinopathy	Aggregation and insolubilization of lensprotein
Hepatic fibrogenesis	PPARγ
Inflammatory bowel disease	Lipid peroxidation, neutrophil infiltration
Neurodegenerative disease	Antioxidant, and LRRK2, mRNA

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 cytokines including MMP 9, 13, TNFα, IL1β, MCP1, IL6, PGE2 compared to free curcumin. CMC significantly suppressed the activation of NF-κB by LPS which in turn could be the explanation for the reduced levels of pro-inflammatory cytokines.

Nano formulation of curcumin makes it amenable to be delivered in an aqueous solution greatly enhancing the bioavailability. Nanocurcumin (Nc) also was found to target and inhibit the activation of NF-κB as in conventional curcumin which in turn lead to inhibition of the expression of IL-6, IL-8, TNF-α in a dose dependent manner [54] Nc has been found to affect the activated NF-κB similar to free curcumin as shown on pancreatic cancer cell lines. The DNA binding ability of NF-κB is dampened by Nc. Nc also shows ability in inhibiting pro inflammatory cytokines including IL-6, 8, and TNF-α.

Nc has shown compatibility with various nanocarriers including some smart ones. As with any inflammatory condition, there is a presence of oxidative stress due to excess production of free radicals like .OH, ONOO- and reduction of local pH which leads to cellular destruction; as an extension of inflammation. ROS/RNS can be the result of the overspill of intracellular production in activated macrophages [54]. These events also occur in periodontal inflammation. Carriers which can deliver active pharmacological agents in centres of inflammation will be gaining importance in such chronic destructive conditions like periodontitis. These carriers can release agents to areas under oxidative stress. A new system of smart nano carriers has been developed to deliver nanoparticle active agent in areas of oxidative stress. Pu et al. [54] developed curcumin nano particles (NPs) and delivered it to the area specific with high oxidative stress by a pH responsive NPs made of N-palmitoyl chitosan (NPCS) to deliver curcumin. These dual responsive nanoparticles for oxidative stress and reduced pH released its payload of encapsulated curcumin in an inflammatory milieu.

Further research should be concentrated on formulation of nano curcumin specific for periodontitis. A recent study nano-curcumin particles in a chitosan film displayed potential for the treatment of periodontal disease [53]. So the effects brought about by the treatment regimen using curcumin can have a synergistic effect of anti-inflammatory and antioxidant properties could be used in the treatment of periodontal disease. The safety of curcumin and its various forms has been studied with positive results. It has been observed that very high doses of curcumin of upto 400 mg/kg and longer duration of upto 8 weeks did not cause any adverse effects in rats but lead to reduction in the TNF–α and IL-6 levels in rats [54]. With newer formulation, lower doses can achieve the same efficacy of that of conventional curcumin.

Conclusion

There is definitely an overlap in the mechanism of periodontal inflammation and destruction and the effects caused by curcumin. The influence of curcumin on TLRs and hence the inactivation of NF-κB

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 mechanism of tissue destruction can be modulated and manipulated to help in the recovery of periodontal tissues. Pharmaceutical giants should get interested in coming together with academics and clinicians to help develop simple to use effective formulations targeted to halt periodontal inflammation and destruction due to periodontitis.

References

1. Papapanou PN (2012) The prevalence of periodontitis in the US: forget what you were told. J Dent Res 91: 907-908.
2. Armitage GC (2004) Periodontal diagnoses and classification of periodontal diseases. Periodontol 2000 34: 9-21.
3. Preshaw PM, Seymour RA, Heasman PA (2004) Current concepts in periodontal pathogenesis. Dent Update 31: 570-572, 574-8.
4. Teles R, Teles F, Frias-Lopez J, Paster B, Haffajee A (2013) Lessons learned and unlearned in periodontal microbiology. Periodontol 2000 62: 95-162.
5. Benakanakere M, Kinane DF (2012) Innate cellular responses to the periodontal biofilm. Front Oral Biol 15: 41-55.
6. Gorr SU (2012) Antimicrobial peptides in periodontal innate defense. Front Oral Biol 15: 84-98.
7. Heitz-Mayfield LJ (2009) Systemic antibiotics in periodontal therapy. Aust Dent J 54 Suppl 1: S96-101.
8. Leszczy Å, Ska A, Buczko P, Buczko W, Pietruska M (2011) Periodontal pharmacotherapy - an updated review. Adv Med Sci 56: 123-131.
9. Salvi GE, Lang NP (2005) Host response modulation in the management of periodontal diseases. J Clin Periodontol 32 Suppl 6: 108-129.
10. Kirkwood KL, Cirelli JA, Rogers JE, Giannobile WV (2007) Novel host response therapeutic approaches to treat periodontal diseases. Periodontol 2000 43: 294-315.
11. Gokhale SR, Padhye AM (2013) Future prospects of systemic host modulatory agents in periodontal therapy. Br Dent J 214: 467-471.
12. Nagpal M, Sood S (2013) Role of curcumin in systemic and oral health: An overview. J Nat Sci Biol Med 4: 3-7.
13. Janeway CA (2002) Jr. Medzhitov R. Innate immune recognition. Annu Rev Immunol 20: 197–216.
14. Fearon DT (1997) Seeking wisdom in innate immunity. Nature 388: 323-324.
15. Medzhitov R (2007) Recognition of microorganisms and activation of the immune response. Nature 449: 819-826.
16. Lambris JD, Ricklin D, Geisbrecht BV (2008) Complement evasion by human pathogens. Nat Rev Microbiol 6: 132-142.
17. Roy CR, Mocarski ES (2007) Pathogen subversion of cell-intrinsic innate immunity. Nat Immunol 8: 1179-1187.
18. Krauss JL, Potempa J, Lambris JD, Hajishengallis G (2010) Complementary Tolls in the periodontium: how periodontal bacteria modify complement and Toll-like receptor responses to prevail in the host. Periodontol 2000 52: 141-162.
19. Nussbaum G, Ben-Adi S, Genzler T, Sela M, Rosen G (2009) Involvement of Toll-like receptors 2 and 4 in the innate immune response to Treponema denticola and its outer sheath components. Infect Immun 77: 3939-3947.
20. Hajishengallis G, Tapping RI, Harokopakis E, Nishiyama SI, Ratti P, et al. (2006) Differential interactions of fimbriae and lipopolysaccharide from Porphyromonas gingivalis with the Toll-like receptor 2-centred pattern recognition apparatus. Cell Microbiol 8: 1557–1570.
21. Burns E, Bachrach G, Shapira L, Nussbaum G (2006) Cutting Edge: TLR2 is required for the innate response to Porphyromonas gingivalis: activation leads to bacterial persistence and TLR2 deficiency attenuates induced alveolar bone resorption. J Immunol 177: 8296-8300.
22. DiDonato JA, Hayakawa M, Rothwarf DM, Zandi E, Karin M (1997) A cytokine-responsive IkappaB kinase that activates the transcription factor NF-kappaB. Nature 388: 548-554.
23. Mercurio F, Zhu H, Murray BW, Shevchenko A, Bennett BL, et al. (1997) IKK-1 and IKK-2: cytokine-activated IkappaB kinases essential for NF-kappaB activation. Science 278: 860-866.
24. Milward MR, Chapple IL, Wright HJ, Millard JL, Matthews JB, et al. (2007) Differential activation of NF-kappaB and gene expression in oral epithelial cells by periodontal pathogens. Clin Exp Immunol 148: 307-324.
25. Nakajima Y, Furuichi Y, Biswas KK, Hashiguchi T, Kawahara K, et al. (2006) Endocannabinoid, anandamide in gingival tissue regulates the periodontal inflammation through NF-kappaB pathway inhibition. FEBS Lett 580: 613-619.
26. Graves DT (1999) The potential role of chemokines and inflammatory cytokines in periodontal disease progression. Clin Infect Dis 28: 482-490.
27. Lang NP, Adler R, Joss A, Nyman S (1990) Absence of bleeding on probing. An indicator of periodontal stability. J Clin Periodontol 17: 714-721.
28. Axelsson P, Lindhe J (1981) Effect of controlled oral hygiene procedures on caries and periodontal disease in adults. Results after 6 years. J Clin Periodontol 8: 239-248.
29. Paquette DW, Simpson DM, Friden P, Braman V, Williams RC (2002) Safety and clinical effects of topical histatin gels in humans with experimental gingivitis. J Clin Periodontol 29: 1051-1058.
30. Paquette DW, Waters GS, Stefanidou VL, Lawrence HP, Friden PM, et al. (1997) Inhibition of experimental gingivitis in beagle dogs with topical salivary histatins. J Clin Periodontol 24: 216-222.
31. Guimarães MR, Coimbra LS, de Aquino SG, Spolidorio LC, Kirkwood KL, et al. (2011) Potent anti-inflammatory effects of systemically administered curcumin modulate periodontal disease in vivo. J Periodontal Res 46: 269-279.
32. Elburki MS, Rossa C, Guimaraes MR, Goodenough M, Lee HM, et al. (2014) A novel chemically modified curcumin reduces severity of experimental periodontal disease in rats: initial observations. Mediators Inflamm.
33. Gu Y, Lee HM, Napolitano N, Clemens M, Zhang Y, et al. (2013) 4-methoxycarbonyl curcumin: a unique inhibitor of both inflammatory mediators and periodontal inflammation. Mediators Inflamm 2013: 329740.
34. Okahashi N, Inaba H, Nakagawa I, Yamamura T, Kuboniwa M, et al. (2004) Porphyromonas gingivalis induces receptor activator of NF-kappaB ligand expression in osteoblasts through the activator protein 1 pathway. Infect Immun 72: 1706-1714.
35. Chen D, Nie M, Fan MW, Bian Z (2008) Anti-inflammatory activity of curcumin in macrophages stimulated by lipopolysaccharides from Porphyromonas gingivalis. Pharmacology 82: 264-269.
36. Kudva P, Tabasum ST, Gupta S (2012) Comparative evaluation of the efficacy of turmeric and curcumin as a local drug delivery system: a clinicomicrobiological study. Gen Dent 60: e283-287.
37. Behal R, Mali AM, Gilda SS, Paradkar AR (2011) Evaluation of local drug-delivery system containing 2% whole turmeric gel used as an adjunct to scaling and root planing in chronic periodontitis: A clinical and microbiological study. J Indian Soc Periodontol 15: 35-38.
38. Gottumukkala SN, Sudarshan S, Mantena SR (2014) Comparative evaluation of the efficacy of two controlled release devices: Chlorhexidine chips and indigenous curcumin based collagen as local drug delivery systems. Contemp Clin Dent 5: 175-181.
39. Waghmare PF, Chaudhari AU, Karhadkar VM, Jamkhande AS (2011) Comparative evaluation of turmeric and chlorhexidine gluconate mouthwash in prevention of plaque formation and gingivitis: a clinical and microbiological study. J Contemp Dent Pract 12: 221-224.

40. Muglikar S, Patil KC, Shivswami S, Hegde R (2013) Efficacy of curcumin in the treatment of chronic gingivitis: a pilot study. Oral Health Prev Dent 11: 81-86.
41. Suhag A, Dixit J, Dhan P (2007) Role of curcumin as a subgingival irrigant: A pilot study. PERIO: Periodontal Pract Today 2: 115-21
42. Gottumukkala SN, Koneru S, Mannem S, Mandalapu N (2013) Effectiveness of sub gingival irrigation of an indigenous 1% curcumin solution on clinical and microbiological parameters in chronic periodontitis patients: A pilot randomized clinical trial. Contemp Clin Dent 4: 186-191.
43. Tu CT, Han B, Yao QY, Zhang YA, Liu HC, et al. (2012) Curcumin attenuates Concanavalin A-induced liver injury in mice by inhibition of Toll-like receptor (TLR) 2, TLR4 and TLR9 expression. Int Immunopharmacol 12: 151-157.
44. Goel A, Kunnumakkara AB, Aggarwal BB (2008) Curcumin as "Curecumin": from kitchen to clinic. Biochem Pharmacol 75: 787-809.
45. Buhrmann C, Mobasheri A, Busch F, Aldinger C, Stahlmann R, et al. (2011) Curcumin modulates nuclear factor kappaB (NF-kappaB)-mediated inflammation in human tenocytes in vitro: role of the phosphatidylinositol 3-kinase/Akt pathway. J Biol Chem 286: 28556-28566.
46. Kim KH, Lee EN, Park JK, Lee JR, Kim JH, (2012) Curcumin attenuates TNF-a-induced expression of intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and proinflammatory cytokines in human endometriotic stromal cells. Phytother Res 26: 1037-1047.
47. Jurenka JS (2009) Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Altern Med Rev 14: 141-153.
48. Kuo JJ, Chang HH, Tsai TH, Lee TY (2012) Positive effect of curcumin on inflammation and mitochondrial dysfunction in obese mice with liver steatosis. Int J Mol Med 30: 673-679.
49. Begum AN, Jones MR, Lim GP, Morihara T, Kim P, (2008) Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. J Pharmacol Exp Ther. 326: 196-208.
50. Zhang Y, Golub LM, Johnson F, Wishnia A (2012) pKa, zinc- and serum albumin-binding of curcumin and two novel biologically-active chemically-modified curcumins. Curr Med Chem 19: 4367-4375.
51. Zhang Y, Gu Y, Lee HM, Hambardjieva E, Vranková K, et al. (2012) Design, synthesis and biological activity of new polyenolic inhibitors of matrix metalloproteinases: a focus on chemically-modified curcumins. Curr Med Chem 19: 4348-4358.
52. Pu HL, Chiang WL, Maiti B, Liao ZX, Ho YC, et al. (2014) Nanoparticles with dual responses to oxidative stress and reduced ph for drug release and anti-inflammatory applications. ACS Nano 8: 1213-1221.
53. Mazzarino L, Borsali R, Lemos-Senna E (2014) Mucoadhesive Films Containing Chitosan-Coated Nanoparticles: A New Strategy for Buccal Curcumin Release. J Pharm Sci 103: 3764-3771.
54. Fu Y, Zheng S, Lin J, Ryerse J, Chen A (2008) Curcumin protects the rat liver from CCl4-caused injury and fibrogenesis by attenuating oxidative stress and suppressing inflammation. Mol Pharmacol 73: 399-409.