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REVIEW ARTICALE

# BIO-CHEMICAL PROPERTIES OF CURCUMIN AND CURCUMIN ANALOGUE-2 AND CURCUMIN ANALOGUE-2 IN THE TREATMENT OF PERIODONTAL DISEASE·A NARRATIVE REVIEW

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**Abstract**

Periodontitis is an inflammatory disease which affects both soft and hard tissues. Many treatment options have been employed to treat periodontitis out of which scaling and root planing are the standard procedures to initially reduce inflammation and improve tissue conditions. Although, scaling and root planing can reduce the inflammation, other agents or adjuncts should be used which can decrease the inflammation systemically or locally in an effective manner without side effects of using antibiotics. One of the traditional herbs used in Chinese and Indian ayurveda is Curcumin. Curcumin is known for its anti-inflammatory antioxidant and anti-microbial effect. As Curcumin is less stable with less bio-availabilty, there is need for formulation of Curcumin analogues which are long lasting, highly stable and also have high bioavailability. Curcumin analogue -2 is known to have high anti-inflammatory, anti-microbial and antioxidant effect which can combat with periodonto-pathogenic bacteria and the inflammation due to periodontal supporting tissues. Therefore, this review focuses on bio-chemical properties of Curcumin and its formulated Curcumin analogue -2 and mechanism of Curcumin analogue -2 in the treatment of periodontitis.

***Keywords:*** Curcumin, Curcumin analogue-2, Periodontitis

## INTRODUCTION

Periodontitis is a chronic inflammatory disease which is primarily caused by the by anaerobic gram negative bacteria such as red complex microorganism Porphyromonas gingivalis, Prevotella intermedia, Tanerella forsythia and others in the microbial plaque[1] that results in breakdown of periodontal connective tissue and further leading to bone loss. The host inflammatory reaction as a response to bacterial attack is mediated by release of inflammatory mediators such as interleukin-1 (IL-1),

IL-6 as well as tumor necrosis factors, prostagalndins-2, anti-collagenases like Matrix metalloproteinases.[2] Addressing the removal of etiological factors, results in elimination of the disease or arrest the progression of the disease. The conventional approach, scaling and root planing sometimes fall short in achieving the goals of periodontal therapy either because of presence of tissue penetrative bacteria or because of exaggerated host inflammatory response. This lead to emergence of local drug delivery agents which penetrates deeply in to the tissues at low concentrations and also reduces the need of the systemic antibiotics and its potential adverse effects like developing antibiotic resistance. There are many local drug delivery agents in the treatment of periodontitis which are mostly antibiotics and there are few natural herbs which have proven their efficacy in the treatment of periodontitis. One of such potential agents is the curcumin. For centuries, its been used as a culinary spice, food preservative, and as a natural yellow food colouring substance. Traditional medicinal systems like Indian Ayurveda and Chinese herbs have relied heavily on turmeric (golden spice) which is a bioactive polyphenol extract that has anti-inflammatory[3], anti-oxidant[4], wound healing[5] anti-microbial and analgesic properties. Throughout the history, it has been used primarily as an herbal remedy for a range of liver, gastrointestinal, and pulmonary conditions. It is also used as a cosmetic agent for skin care in Asia, Europe, and America.[6] According to epidemiological research, people who regularly consume turmeric may be able to reduce their risk of developing cancer by 10–50%.[7] It has also been used as a treatment for enhancing delayed healing and has demonstrated a number of additional therapeutic effects in both in vitro and in vivo model systems.

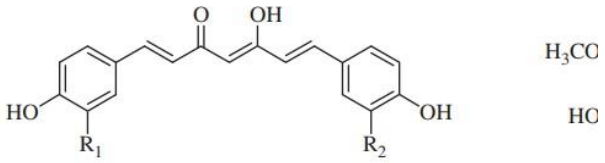
This coloring compound (curcumin 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-hepta diene-3,5-dione; 2), a natural dietary ingredient which is derived from the perennial herb Curcuma longa L[8] was first isolated in 1815, first crystallized in 1870, and Lampe et al. clarified its chemical structure in 1910.[9] Though it possess wide range of medicinal properties, Curcumin is unstable with less bioavailability[10] and weakly soluble in water, but it dissolves readily in organic solvents like ethanol, methanol, acetone, and dimethyl sulfoxide.[11] Clinical application is still limited due to its poor absorption and requires high doses for its therapeutical actions. Due to these reasons, synthesis of novel Chemically Modified Curcumins (CMC's) with improved zinc binding have been discovered and are replacing the use of original curcumin in clinical studies.[12] These Chemically Modified Curcumins or analogs have well defined chemical composition and enhanced pharmacological properties with low toxicity and potential inhibitory activity for Matrix metallo proteinases (MMP's) and cytokines.

Therefore, Curcumin analogs with high stability and more bio-availabilty have been discovered to act as a therapeutic potential against periodontal disease. This review focuses mainly on Curcumin and it's analogues.

**Structure of Curcumin**

Curcumin has many functional groups and is a simple symmetrical β-diketone. It is (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6- heptadiene-3,5-dione. Two α, β-unsaturated carbonyl groups link the two aromatic rings that contain phenolic groups. According to Nelson and Pandey, the chemical formula of curcumin is $C_{21}H_{20}O_6$, and the molecular weight is 368.38 g/mole.[13,14]

In acidic and neutral pH, curcumin is not soluble in water. In the solid phase and in acidic solutions, these carbonyl groups produce a diketone moiety that occurs in keto-enolic tautomeric forms, where an energetically more stable enol-form is present. In mild alkaline conditions, curcumin readily deprotonatesto produce the enolate moiety. Curcumin's quick metabolism is thought to be facilitated by these simple tautomeric reactions.[15] Curcumin though is naturally available and advantageous; it also has few disadvantages such as instability, enolization, fast metabolism and poor bioavailability. These factors are few reasons why curcumin is less likely to be used in medical field and this led to the development of curcuminoids or curcumin analogues with enhanced properties and better bioavailability. This can be achieved by modifying the methylene group and b-diketone moiety in the structure of curcumin. Elimination of alpha hydrogen molecules can prevent enolization of curcumin.[16]




1.Curcumin (Cur-A): $R_1=R_2=OCH_3$
2.Demethoxycurcumin (Cur-B) : $R_1=H$ ,$R_2=OCH_3$
3.Bisdemethoxycurcumin (Cur-C): $R_1=R_2=H$

**Figure1**. Structure of curcumin

**Curcumin analogues**

Ohtsu et al. through his various experiments has synthesized a number of Curcumin analogues. Curcumin analogs are synthetically prepared by changing a molecule in the structure of curcumin. They are characterized as pleiotropic agents.[17]

They have only one target and have both anti-inflammatory and anti-proliferative properties. Analogues of Curcumin inhibit a wide range of proteins, enzymes, and molecular targets linked to inflammation and proliferation. Better anti-proliferative and anti-inflammatory properties are obtained by combining a number of Curcumin analogues with functional groups.[14]

**Synthesis of curcumin analogue-2**

Curcumin analogues are generally synthesized by certain reactions such as aldol condensation, or simple condensation or azide-alkyne cyclo addition. In aldol condensation, sodium hydroxide is used as catalyst and ethanol is used as solvent. Halogenated Curcumin analogues are synthesized using condensation process whereas triazoled curcumin analogues from aromatic aldehydes are synthesized using azide –alkyne cyclo addition.

According to Mazumder et al in 1997[18] and Roughley & whiting in 1973[19], Curcumin and its analogues (1–7) were synthesized by condensation of 2,4-pentanedione with two equivalents of substituted benzaldehyde based on the available methods.

The usual procedure was to dissolve 2,4-pentanedione (1.0 g, 0.01 mol) and boron oxide (0.49 g, 0.007 mol) in 10 ml of EtOAc, stir for 0.5 hours at 40 °C, then add the corresponding benzaldehyde (0.02 mol) and tributyl borate (4.6 g, 0.02 mol) and stir for another 0.5 hours. After that, n-butylamine (1 ml) was added drop wise over the course of 30 minutes in 10 ml of EtOAc. To finish the reaction, the mixture was left to stand overnight at 40 C after being stirred for an additional four hours. After hydrolyzing the mixture with HCl (0.4 N, 15 ml), the aqueous layer was extracted three times using EtOAc. [20,21]

After being cleaned with water, the combined organic layers were dried on top of Na2SO4. Pure 1–4 and 7 were obtained by recrystallizing the leftover paste from EtOH and purifying it using column chromatography (silica gel, cyclohexane–EtOAc) after the solvent was removed under low pressure.[22]

**Curcumin analog 2 in Periodontitis**

Curcumin analogs have more stability and high bioavailability. The production of many inflammatory mediators that contribute to the pathophysiology of several inflammatory illnesses depends on NF-κB activation. It makes host modification treatments for chronic inflammatory diseases a top target for this pathway. Activated fibroblasts, monocytes, and macrophages release pro-inflammatory cytokines such IL-1β and TNF-α, which are important in the pathophysiology of periodontitis. The direct degradation of connective tissues in chronic inflammatory illnesses is mostly caused by catabolic enzymes like MMPs, which are produced in response to the release of these cytokines. Prostaglandins and leukotrienes are examples of lipid mediators of inflammation that are produced when IL-1β and TNF-α activate other inflammatory mediators like cycloxygenase-2 and 5-lipoxygenase.[2,10]

Curcumin analogue-2 has found to reduce the excessive levels of IL-1β to B normal levels. It has also been associated with marked inhibition of both p38 MAPK and NF-κB signaling. This inhibition of p38 MAPK and NF-κB signaling reduces the synthesis of pro-inflammatory cytokines, such as IL-6, TNF-α, and prostaglandin E2 and causing reduction in periodontal inflammation. These actions eventually reduce pocket depth and help in gaining attachment.

It also significantly lowers the inflammation caused by cellular infiltration. It lowers the quantity of TRAP-positive multinucleated cells (osteoclasts) and bone resorption[10] there by mediating the inflammatory response of periodontitis.

**Differences between Curcumin and Curcumin analogue-2**

The below table helps us to differentiate curcumin and curcumin analogs

**Table1.Difference between Curcumin and Curcumin analogues-2**

| Characteristic | Curcumin | Curcumin analogue -2 |
|---|---|---|
| Bioavailability | Less | High |
| Solubility | High | Low |
| Stability | Low | High |
| Toxicity | High | Low |
| Inhibitory effect to MMPS | Low | High |
| Dosage required to act on humans and animals | High | Low |
| Fat metabolism | High | Low |
| Enolization | Present | Absent |

Since pro MMPs can be activated by proteases like trypsin and other substances like Reactive Oxygen Species, curcumin analog -22 inhibitions of these factors may offer, at least partially, extra mechanisms for minimizing tissue breakdown.

Since Curcumin analogues have better advantages than curcumin, there is need for utilization of Curcumin analogues in management of periodontitis and other medical fields.[23]

## CONCLUSION

Several modern Curcumin analogues provide improved absorption, increased potency, slowed metabolism, and delayed elimination to help with poor bioavailability. Multifunctional nano-platforms, including liposomes, NPs, nano-carriers and nano-arrays, micelles, 3D printing, and other intriguing new formulations, offer improved curcumin targeting, resistance to the metabolic process, and longer circulation times to increase therapeutic efficacy.

Improving the solubility and stability and bio-availability in Curcumin analogues can help in improving the therapeutic applications of Curcumin. Advanced researches and formulations can help in utilizing Curcumin analogues in medicinal fields.

## DECLARATIONS

***Conflicts of interest and financial disclosures***

No conflict of interest and there was no external source of funding for the research in question.

***Ethical approval***

Study was approved by Institutional Research Review Board

***Source of funding***

The work was not funded.

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