

Cure from the rhizomes: the medicine behind the Indian saffron *Curcumin*

**Sujatha S.*, Priyadharshini R., Shwetha V., Yashoda Devi B. K.,
Pavan Kumar T., Rizwana Azmi**

Department of Oral Medicine
and Radiology, Faculty of
Dental Sciences, Ramaiah
University of Applied Sciences,
Bangalore, Karnataka, India

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***Correspondence to:**

Dr. Sujatha S.,
Email: s_sujathajanardhan@yahoo.com

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ABSTRACT

Indian system of medicine has always focused on cure from the nature. Plant products from the Indian household have been used as medicine to cure myriad of ailments since ancestral times. Curcumin is a polyphenol, an active ingredient found in turmeric. In Southeast Asia, turmeric has been used as a coloring, flavoring and as a therapeutic agent. The use of turmeric to treat ailments dates back to the times of Charaka and Shushruta. It has been widely used as an antiseptic for cuts, burns, and bruises, and as an antibacterial agent. Modern medicine has begun to understand its importance in recent times. Unfortunately its poor solubility, limited absorption and enhanced metabolism limits its bioavailability for its extended therapeutic use. Integration of nanotechnology in drug design and development has led the way to development of nanocurcumin with improved pharmacological properties. A precise understanding of effective dose, safety, and mechanism of action is required for the rational use of turmeric in the treatment of human diseases. This review focuses on the molecular actions of curcumin and its possibility to be used as a therapeutic agent in conditions affecting oral mucosa.

Keywords: Curcumin, Indian medicine, Oral Lesions, Turmeric

INTRODUCTION

The conventional Indian Medicinal systems like Ayurveda, Siddha and Unani employ a large number of medicinal plants for treatment of various diseases. Since the time of Charaka and Shushruta, plants per se as well as compounds extracted from plants have been the central dogma of Indian medicine. Herbs like Tulsi, Turmeric, Aloe Vera, Neem, Garlic, Fenu Greek, Sanjeevini, Eucalyptus, Cinnamon, Ajwain etc., have been used to treat medical conditions like skin diseases, acne, lacerations, burns and common cold.¹ The World Health

Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. India, being the largest producer of medicinal herbs is called as botanical garden of the world.²

Turmeric is the most common and important ingredient in the Indian cuisine. It is regarded as an auspicious herb in religious rituals and Indian women apply it on skin as a cosmetic agent. It has been used for its coloring, flavouring and medicinal properties. Preparations of turmeric with slaked lime have been used as topical medication for fresh wounds and bruises and as counterirritants for insect bites.

Turmeric paste is used to facilitate scabbing in chicken pox and small pox, in the treatment of arthritis, asthma, flatulence, dyspepsia and oral cancer. Mixed in milk it is indicated as an expectorant and as a paste with neem is used for its antiseptic and anti-inflammatory properties. It is considered to exert a gastroprotective effect by increasing mucin production.^{1,3}

Turmeric is a member of the ginger family (Zingiberaceae) and has been extensively utilized in traditional Indian and Chinese medicine. Curcuma species contain turmerin, essential oils (such as turmerones, atlantones and zingiberene) and curcuminoids. The active ingredient found in this rhizome is the polyphenol curcumin. The yellow pigmented fraction of turmeric contains curcuminoids which makes up to 5% of the chemical composition of turmeric. It includes curcumin, demethoxy curcumin and bisdemethoxycurcumin. Chemically, Curcumin is (7-bis(4-hydroxy 3-methoxy phenyl)-1,6-heptadiene-3,5-dione), a polyphenol that constitutes 2-8% of turmeric preparations.⁵

THE BIOLOGY BEHIND

Curcumin exhibits analgesic, antibacterial, anti-inflammatory, anti-tumor, anti-allergic, anti-oxidant, antiseptic, antispasmodic, astringent, carminative, anti-depressive, cholagogue, cholorectic, digestive, diuretic, anti fungal, anti viral, hepatoprotective, thrombo-suppressive, anti- arthritic, anti-tussive properties, anti-diabetic, lipid lowering, anti- infectious and anti clastogenic properties. Curcumin exhibits low oral bioavailability. Orally administered curcumin undergoes rapid first-pass metabolism and some degree of intestinal metabolism and excreted in the bile and urine as conjugates of glucuronides and sulfates. Curcumin undergoes transformation during absorption via the intestine and is possibly subjected to entero-hepatic recirculation. However, the bioavailability of curcumin can be increased by piperine which is an alkaloid in pepper, potentially by inhibition of xenobiotic glucuronidation. Serum curcumin concentrations were found to attain peak plasma level 1-2 h after oral intake and gradually decline within 12 hrs.⁴

The anti inflammatory action of curcumin is attributed to its inhibitory action on cellular uptake of arachidonic acid, phospholipases A₂, C, and D, cyclo-oxygenases, lipoxygenases, Platelet-activating factor (PAF), Adenosine Diphosphate (ADP), arachidonic acid (AA), epinephrine, collagen mediated platelet aggregation and thromboxane A₂ formation. Curcumin also down regulates the production of collagenases, hyaluronidase and elastase from activated macrophages, which also contributes to its anti-inflammatory action.⁵

Curcumin mediated release of reactive oxygen species (ROS) involves a number of pathways and enzymes including release of cytochrome c from mitochondria, caspase-3 activation, and poly-(ADPribose) polymerase

(PARP) cleavage, release of apoptosis inducing factor (AIF) and endonuclease G (EndoG), induction of chromatin condensation and DNA fragmentation as well depletion of glutathione (GSH).⁶ These molecular effects makes curcumin a radiosensitising agent for tumor cells at the same time offers radioprotective action for normal cells.

Curcumin interferes with all three stages of tumorigenesis: initiation, promotion and progression. Curcumin inhibits number of cytokines and Signal Transducers and Activator of Transcription (STAT), including NF- κ B, MAPK, cytokines, TNF- α as well as TNF- α induced IL-1 β , IL-6 and IL-8. Curcumin reduces the invasion and metastasis of cancer cells by inhibiting MMP-2 and MMP-9. Curcumin induces apoptosis and cytotoxicity through activation of caspase-3, promotes the expression of Bax, cytochrome c, and p53, and inhibits the expression of anti apoptotic factors Bcl-2 and Bcl-XL.⁶ Apart from its chemoprotective effect, it also exhibits chemosensitizing and radiosensitizing as well as chemoprotective and radioprotective effects.⁶

The antioxidant property of curcumin is similar to Vitamin C and E, Butylated hydroxyanisole (BHA) and Butylated hydroxytoluene (BHT). It scavenges hydrogen peroxide, super oxide radical and nitric oxide and inhibits nitric oxide synthase activity in macrophages. The antioxidant activity of curcumin is mediated through upregulation of hemeoxygenase-1, glutathione peroxidase, superoxide dismutase, catalase, modulatory subunit of gamma-glutamyl-cysteine ligase, and NAD(P)H:quinone oxidoreductase 1.⁵

FORMULATIONS

Curcumin is available in the market as capsules of 250mg, 300mg, 400mg, 450mg, 500mg, and 750mgs, and gel with or without volatile oils of tumeric rhizome. Nano formulations of curcumin including curcumin bound to chitosan, poly lactic-co-glycolic acid (PLGA) nanocurcumin, curcumin bound to fibroin polypeptide, polymeric curcumin nanoparticles, liposomal formulations, nanoemulsion of curcumin and derivatives of curcumin have also been patented.

Although the pharmacological properties of curcumin are very promising, its poor water solubility, poor absorption, rapid degradation and elimination limits its therapeutic use. To achieve therapeutic dose level, administration of 12-20g per day is required, dose at which adverse effects are perceived. These limitations can be overcome by nanocurcumin formulations. Formulation of nanocurcumin by encapsulation of curcumin within nanocarrier systems like liposomes, biodegradable microspheres, chitosan, and silk microspheres improves its pharmacological action by enhanced solubilization, improved bioavailability and controlled drug release. However, the relative safety of curcumin and its

nanoformulations, tissue specificity, stability are yet to be addressed.⁷

CLINICAL APPLICATIONS

Oral mucositis

Erythema, mucositis, ulcerations, dryness, bleeding are disruptive consequences of radiotherapy and chemotherapy. The efficacy of curcumin in alleviating these symptoms has been studied. Inhibition of NFκB, arachidonic acid metabolism and lipid peroxidation by curcumin relieves inflammation and reduces ulceration and erythema. It was also observed that topical turmeric application is valuable in preventing and delaying the onset of mucositis. Oral curcumin is also known to reduce the severity of radiation induced dermatitis and desquamation.^{8,9}

Periodontitis

Local application of turmeric extract (2% whole turmeric gel) to deep periodontal pocket showed significant reduction in pocket depth and pathogenic organisms causing periodontitis, the red complex bacteria.¹⁰ It was also noted to be potent in eliminating the local irritants, reducing gingival inflammation and pocket depth. 0.1% turmeric mouth wash has been a successful adjunct to mechanical plaque control in reducing microbial population and gingival inflammation.¹¹

Oral potentially malignant disorders

The management of leukoplakia, erythroplakia, oral lichen planus (OLP) and submucous fibrosis has been debatable varying from conservative clinical follow up to complete surgical excision of the lesion. The anti carcinogenic properties of curcumin can be utilised in effectively managing these conditions. Various topical and systemic formulations of curcumin have been explored in this aspect. Topical application of 5% curcumin paste thrice daily for four weeks gave a considerable reduction in size of the lesion than symptoms when compared to 0.1% triamcinolone acetonide paste for the treatment of OLP.¹²

Curcumin (standardized extract of turmeric, containing at least 95% curcuminoids) at a dose of 6000 mg/day for a period of two weeks showed significant reduction in signs and symptoms of OLP.¹³ Treatment of oral leukoplakia with oral curcumin (3.6 g/day) for a period of six months, demonstrated considerable and consistent clinical response without any adverse effects.¹⁴ Systemic curcumin is also effective in relieving burning sensation in patients with submucous fibrosis (SMF).^{15,16}

Oral administration of curcumin was associated with an increase in vitamins C and E levels and a decrease in MDA and 8-hydroxydeoxyguanosine (8-OHdG) contents in the serum and saliva of patients with precancerous lesions.¹⁷

Carcinogenesis

Topical curcumin as low as 3-10 μmol has shown to impede carcinogenesis. A tissue target concentration of 100-nmol/g tissue range was found in gastrointestinal mucosa following dietary dose of 0.2%, which equates to approximately 300 mg/kg per day. Only trace amounts of curcumin and its metabolites have been demonstrated in plasma. Oral curcumin administration has seen to hamper carcinoma of colon, skin, stomach, liver, lung, duodenum, soft palate, breasts as well as metastases in animal models. It reduces adduct formation by benzo(a)pyrene or by aflatoxin B1. The chemopreventive action of curcumin is said to be mediated through induction of cytochrome-c release, Bid cleavage, activation of caspase-3 and caspase-9, downregulation of Bcl-2, BclX2, COX-2, 5-LOX, iNOS, TNF, IL-6, IL-8, IL-12, and fibroblast growth factor-2, xanthine oxidase, scavenging reactive oxygen/superoxide, inhibition of CYP1A1, suppression of NF-κB, STAT3, Egr-1, AP-1, and PPAR-γ and activation of β-catenin.⁴ NF κB activation in head and neck squamous cell carcinoma suppresses apoptosis, induces proliferation, mediates inflammation, angiogenesis, tumor metastasis and confers radioresistive and chemoresistive properties to tumor cells. The difference in size, membrane structure and protein composition are responsible for differential uptake of curcumin by normal and malignant cells.¹⁸

Candidiasis

There is inconclusive evidence with respect to antifungal activity of curcumin. Among candidal species, *Candida albicans* has shown to be more susceptible to curcumin including species resistant to conventional antifungal agents (Minimum Inhibitory Concentration (MIC): 64mg/dl). Photoactivation of curcumin has shown antifungal properties against candidal species at doses that are not harmful to the host.¹⁹ The photodynamic action of curcumin was found to be maximum at 5, 10 and 20μM and complete fungicidal activity was observed at 20μM, 37.5J/cm² of LED light. In a study by Dovigo LN et al, complete inactivation of the yeast was observed at 20μM and the minimum energy required for this outcome was 5.28 J cm².¹⁹ Curcumin inhibited adhesion of candida to buccal epithelial cells (at concentration > 256mg/dl) and is shown to decrease candidal biofilm formation and metabolic activity of candida.²⁰ In the absence of irradiation with blue light, a higher concentration of curcumin is required to achieve the fungicidal effect. This curcumin mediated phototoxicity is said to be mediated through the production of ROS. In animal models, 20, 40 and 80μM of curcumin produced significant reduction in number of yeasts and hyphae in the keratin layer with no adverse effects on normal mucosa.¹⁹

ADVERSE EFFECTS

Although curcumin is a regular component in daily cuisine, there is a possibility of adverse reaction pertaining to increased dose in pharmacological preparations.

Toxicity has not been observed even in doses as high as 8000mg/day.⁶ Dryness of mouth and throat, nausea, gastric irritation and diarrhea has been reported. Increased serum alkaline phosphatase and lactate dehydrogenase level has been reported in susceptible individuals. The symptoms are dose related and resolved with discontinuation of the medication.¹³ Supplemental doses of turmeric (2g/day) have been reported to increase the risk of renal stone. The commercially available forms having Curcumin C3 contain 0.025% of soluble oxalate compared to natural turmeric that has 90% of soluble oxalate. The daily dietary intake of turmeric (1-2g/day) contains 22-99mg of oxalate. However, the risk of increased oxalate load leading to a risk of renal stone formation is seen only in susceptible individuals.

CONCLUSION

With the increase in evidence of the medicinal properties behind traditional Indian life style, food habits and customs, the treatment protocols and regimens are observing a shift towards noninvasive herbal remedies. Turmeric being the exotic crop of India has been used to treat myriad of diseases and ailments since ancient times. Though its use as a main stream drug for treating ailments is debatable, its use as an adjuvant can be of immense benefit to the patient. Currently its anti-tumor, radioprotective and radio sensitising properties have drawn considerable attention for its use in treatment of oral potentially malignant disorders and cancer.

Although curcumin is acknowledged as Generally Recognized as Safe (GRAS) molecule by the FDA, its poor bioavailability and water solubility as well as its rapid metabolism and clearance from the body, limits its druggability. Nano formulations of curcumin improves its therapeutic efficacy by maintaining sustained delivery of curcumin and improving its bioavailability by protecting it from degradation.

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