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Review Article

Dentistry Section

Curcumin – Pharmacological Actions And its Role in Oral Submucous Fibrosis: A Review

ABHIJEET ALOK[1], INDRA DEO SINGH[2], SHIVANI SINGH[3], MALLIKA KISHORE[4], PRAKASH CHANDRA JHA[5]

ABSTRACT

Turmeric has been in use for thousands of years as a dye, flavouring and a medicinal herb. Ancient Indian medicine has touted turmeric as an herb with the ability to provide glow and lustre to the skin as well as vigour and vitality to the entire body. Since curcumin has antimicrobial, antioxidant, astringents and other useful properties, it is quite useful in dentistry also. Curcumin, the most active polyphenolic constituent, is the active ingredient in the traditional herbal remedy and dietary spice turmeric. In gel form it is a component in local drugs delivery system. The objective of this article is to review the pharmacological action of turmeric and its use in treating oral submucous fibrosis.

Keywords: Antioxidant, Fibrinolytic property, Herbal medicine, Nanoparticles, Turmeric

INTRODUCTION

Medicinal herbs have been used as treatment modalities since ages in many parts of the world and have been variedly used throughout human history. The most common natural product from such herbs used for medicinal purposes is polyphenols since it has the most anti-oxidant effect.

Curcumin (diferuloylmethane) is a polyphenol compound isolated from ground rhizomes of the plant (*Curcuma longa*) L. (Zingiberaceae) found in South Asia [1]. Curcumin is naturally occurring yellow pigment of turmeric having wide spectrum of biological action [2]. Curcumin has been used extensively in ayurvedic medicine for centuries, as it is nontoxic and has a variety of therapeutic properties including antioxidant, analgesic, anti-inflammatory, antiseptic activity, anticarcinogenic activity, chemopreventive, chemotherapeutic activity, anti-tumour, antiviral, antibacterial, antifungal properties and antiplatelet acticvity [3,4].

Curcumin exhibits a big promise as a therapeutic agents due to its properties and is currently in human trials for a variety of conditions like multiple myeloma, pancreatic cancer, colon cancer, mastitis myelodysplastic syndromes, psoriasis, alzheimer's disease, diabetic nephropathy, periodontal disease, oral cancers, recurrent apthous stomatitis, pre cancerous lesion and conditions etc [5].

PHARMACOLOGICAL PROPERTIES OF CURCUMIN

Curcumin (1,7-bis (hydroxyl-3-methoxyphenyl) -1,6-heptadiene-3,5-dione), is the most important active polyphenolic ingredient responsible for the biological activity of turmeric [6]. It was first isolated from the drug in 1815, but its structure was not elucidated until 1913. Curcumin is insoluble in water, but soluble in ethanol and acetone. The naturally occurring ratios of curcuminoids in curcumin are about 5% bisdemethoxycurcumin, 15% demethoxycurcumin, and 80% curcumin [7]. The various components of the turmeric have their medical importance [Table/Fig-1].

Various pharmacological actions of curcumin have been studied by various researchers worldwide. Curcumin has the ability to suppress the acute and chronic inflammation. It reduces inflammation by lowering histamine levels and by possibly increasing the production of natural cortisone by adrenal glands [8]. Additionally, *in vitro* studies of curcumin showed anti-inflammatory action on human vascular cells. The mechanism of action by which curcumin shows anti-inflammatory effect is by attenuating inflammatory response of TNF-α stimulated human endothelial cells by interfering with NF-κB. Furthermore, curcumin is also capable of preventing platelet-derived growth factor (PDGF) [9].

Several studies have shown that curcumin has a strong capability for scavenging superoxide radicals, hydrogen peroxide and nitricoxide (NO) from activated macrophages, reducing iron complex and inhibiting lipid peroxidation. It has been shown to scavenge various reactive oxygen species produced by macrophages (including superoxide anions, hydrogen peroxide and nitrite radicals) both *in vitro* as well as *invivo* [10]. These actions may be the major mechanism by which curcumin exhibits its antioxidant activities.

Curcumin potentially helps to prevent the new cancers that are caused by chemotherapy or radiation. More recently curcumin has been found to possess anti-cancer activities via its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumour igenesis and

Curcumin	Anti-HIV, Anti-EBV, Antiadenoma – carcinogenic, Antiaflatoxin, Antiatherosclerotic, Antiaggregant, Antiangiogenic, Antiarachidonate, Antiviral, Antioxidant, Anticancer, Antiedemic, Anti-ischemic, Apoptotic, Antiinflammatory, Antileukemic, Antileukotrene, Antilymphomic, Antimelanomic, Antimetastatic, Antimutagenic, Antinitrososaminic, Antitumour agent, Antiperoxidant, Antiprostaglandin, Antisarcomic, Metal chelator, Antithromboxane, Cox-2inhibitor, Fibrinolytic, Hepatoprotective, Immunostimulant, Ornithine decarboxylase inhibitor, Protease inhibitor, Protein kinase inhibitor.
Bis-desmethoxycurcumin	Antiangiogenic, Antiiflammatory, Cytotoxic, Anticancer
Desmethoxy Curcumin	Antiangiogenic, Antiinflammatory, Anticancer
Tetrahydro Curcumin	Antioxidant, Antiinflammatory
Alpha Curcumene	Antitumour, Antiinflammatory
Ar- turmerone	Anti-inflammatory, Antitumour, Cox-2 inhibitor, Choleretic, Hepatotonic
Curcumol	Anticancer, Antitumour(cervix), Anti-sarcomic
Curdione	Anti-leukopenic, Antisarcomic, Antitumour, Anti X-radiation
DehydroCurdione	Analgesic, Antiarthritic, Antiedemic, Antiinflammatory, Antioxidant, Antipyretic, Calcium channel blocker.
Zingiberene	Antirhinoviral, Antiulcer, Carminative

[Table/Fig-1]: Components and their medicinal importance

metastasis [11]. In various studies, anti tumour-promoting effects of curcumin were studied and proved. In these studies it was proved that curcumin showed antitumour-promoting effects due to the induction of apoptosis in human leukemia cells [12]. Investigations have shown specific inhibitory effect of cyclooxygenase (cox) - 2 by dietary curcumin in human colon cancer cells and human breast carcinoma cells [13,14]. In addition, curcumin affects a variety of growth factor receptors and cell adhesion molecules involved in tumour growth, angiogenesis and metastasis.

Oxidative stress may contribute to several aspects of HIV disease. A role for plant derived metabolites having synergistic antioxidant activity may protect patients from viral replication and oxidative stress induced cell death. The potential efficacy of antioxidants (turmeric, water-soluble extract turmerin and lipid soluble curcumin) as anti-HIV drugs was examined. When Tm was combined with 3'azido3'deoxythmidine (AZT) (5μM), combination inhibited infection by 37% and increased cell numbers by 30%; whereas Tm (80 ng/ml) inhibited infection by 26% and increased cell number by 60%. In the proliferation assay, lymphocytes from HIV-infected patients showed better inhibition of mitogen responsiveness to Tm (800 ng/ml) when compared to AZT at 5 μM or Tm at 80 ng/ml. Turmerin inhibited HIV-infected T-cell proliferation and, in combination with AZT, decreased T-cell infection and increased cell viability. These data suggest that effective anti-HIV therapy may be possible using lower, less toxic doses of AZT in the presence of turmerin [15].

Curcumin has got antimicrobial action. Curcumin inhibits the growth of various bacterias like *Streptococci*, *Staphylococci, Lactobacillus* etc and also prevents *Helicobacter pylori* strains *in vitro* [16]. The inhibitory effects of curcumin on the cariogenic property of *Streptococcus mutans* is observed at concentrations of 0.5 to 4 mg/ml. It is also effective against *Enterococcus faecalis*, and will serve to be useful as root canal medicaments in endodontics [17]. It also acts as antifungal agent as it is active against *Aspergillus flavus*, *A.parasiticus*, *Fusarium moniliforme*, *Penicillium digitatum* [16]. It has anti protozoan activity against *E.histolytica*, *Leishmania*, *Plasmodium falciparum*.

Curcumin has diverse therapeutic effects, one of them is antihyperalgesic effect. In a study it was seen that the vanilloid moiety of curcumin is important for activation of the transient receptor potential vanilloid 1 (TRPV1), which plays an important role in nociception. The vanilloid moiety of curcumin is considered important for activation of the transient receptor potential vanilloid 1 (TRPV1), which plays an important role in nociception. Further, the results emphasize that curcumin blocks TRPV1 activation by capsaicin in a competitive manner and thereby inhibits TRPV1-mediated pain hypersensitivity [18].

Curcumin is considered to be of low toxicity in man and animals. In a study conducted, 25 volunteers were included in phase one clinical trial. These 25 volunteers were administered up to 8000 mg of curcumin per day for 3 months and no apparent toxic sign was noticed. Five other clinical trials in which humans were given 1125-2500 mg curcumin per day confirmed the apparent safety of the substance [19]. There are no reports of adverse effects of either curcumin or its analogues except for rare cases of contact dermatitis, one of which occurred as an occupational illness of a miller working in a spice shop.

CURCUMIN ROLE IN ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis (OSMF) is a potentially malignant condition with characteristic features of stiffness of mucosa and restricted mouth opening. The fibrosis leads to stiffness of oral mucosa and deeper tissues with progressive limitation in opening of the mouth and protrusion of the tongue, thus causing difficulty in eating, swallowing and phonation [20].

A wide range of treatment modalities have been proprosed for OSMF, but none have been proved to be curative, so the search for effective treatment modality still continues. Plants have been a major source of medicine since the time immemorial. Various studies have been conducted worldwide to show the therapeutic effect of curcumin on OSMF.

Agarwal N et al., conducted a study to check the efficacy of turmeric in 30 OSMF patients. An improvement in mouth opening and burning sensation was noticed. It was hypothesized that curcumin exerts anti-inflammatory activity by inhibiting a number of different molecules that participates in the process of inflammation. They also exhibit fibrinolytic property due to its ability to inhibit lipid peroxidation and check cellular proliferation, thereby reducing the rate of collagen synthesis [21].

Another study conducted by Deepa DA et al., to evaluate the efficacy of curcumin and turmeric dispensed in two forms namely curcumin capsules and turmeric oil in 48 patients with OSMF. Statistically significant improvement was observed in the clinical signs and symptoms of patients treated with curcumin and turmeric oil. It showed anti-inflammatory action and fibrinolytic properties [22].

Yadav M et al., conducted a study for comparison of curcumin with intralesional steroid injections in osmf patients. Improvement of burning sensation, interincisal distance and tongue protrusion was evaluated on a weekly basis and it was found that there was marked improvement in burning sensation, intreincisal distance and tongue protrusion [23].

Balwant Rai conducted a study to know the possible mechanism of action for curcumin in pre-cancerous lesions and condition based on serum and salivary markers of oxidative stress. It was found that curcumin mediates its anti pre-cancer activities by increasing levels of vitamins C and E and preventing lipid peroxidation and DNA damage. This could be due to curcumin-induced production of vitamins C and E and preventive DNA damage by decreasing the oxidation stress. This suggests that the anti-precancerous effects of curcumin are mediated through pro-oxidant and anti-oxidant pathways [24].

Zhang SS et al., showed in their study that curcumin inhibits proliferation, disrupts the cell cycle, induces apoptosis, and decreases the expression levels of type I and III collagen; confirming its potential therapeutic value in OSMF patient [25].

Another study showed that use of curcumin in osmf significantly reduce connective tissue growth factor which is associated with the onset and progression of OSMF [26].

Various studies have been conducted over a period of time showing the efficacy of curcumin in treating the osmf patients. Constant use of curcumin showed marked improvement in osmf patients due to its pharmacological activities.

FUTURE PROSPECTS OF CURCUMIN

Few studies have been conducted worldwide to use curcumin as conjugated nano particles. Curcumin conjugated silver nan oparticles show anti-bacterial activity and can successfully determine nucleic acid (DNA and RNA) in the concentration range 100-1000ng/mL [26]. These curcumin conjugated nano particles can be used as anti cancer agent also.

CONCLUSION

Turmeric is a popular spice used in Indian curry. Curcumin is an active ingredient of turmeric. Curcumin is actively used in ayurvedic medicine to cure various diseases. Curcumin due to its properties should be used in patients with OSMF as application of it is beneficial and inexpensive too. The use of curcumin should be frequent and must be prescribed by clinicians. But still further researches are required to check for bio-efficacy of curcumin in various other diseases.

REFERENCES

[1] Borra SK, et al. Effect of Curcumin Against Oxidation of Biomolecules by Hydroxyl Radicals. *J Clin Diagn Res*. 2014;8(10):CC01-05.
[2] Chattopadhyay I, Biswas K, Bandhopadhyay U, Banerjee R. Tumeric and curcumin:Biological actions and medicinal applications. *Current science*. 2004;87:44-53.
[3] Sandur SK, et al. Role of pro-oxidants and antioxidants in the anti-inflammatory and apoptotic effects of curcumin (diferuloylmethane). *Free Radic Biol Med*. 2007;43(4); 568-80.
[4] Prakash P, Misra A, Surin WR, Jain M, Bhatta RS, Pal R, et al. Anti-platelet effects of Curcuma oil in experimental models of myocardial ischemia-reperfusion and thrombosis. *Thromb Res*. 2010;127:111-18.
[5] Afshariani R, Farhadi P, Ghaffarpasand F, Roozbeh J. Effectiveness of Topical curcumin for treatment of mastitis in breastfeeding women: a randomized, double-blind, placebo-controlled clinical trial. *Oman Medical Journal*. 2014;29(5):330-34.
[6] Nagpal M, Sood S. Role of curcumin in systemic and oral health: An overview. *J Nat SciBiol Med*. 2013;4:3-7.
[7] Ireson C, Orr S, Jones DJL, et al. Characterization of metabolites of the chemopreventative agent curcumin in rat and human hepatocytes and in rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. *Cancer Research*. 2001;61:1058-64.
[8] Baum L, Ng A. Curcumin interaction with copper and iron suggests one possible mechanism of action in alzheimer's disease animal models. *J Alzheimers Dis.* 2004;6(4):367-77.
[9] Kim YS, Ahn Y, Hong MH, Joo SY, Kim KH, Sohn IS, et al. Curcumin attenuates inflammatory responses of TNF-alpha-stimulated human endothelial cells. *J Cardiovasc Pharmacol*. 2007;50(1):41-49.
[10] Joe B, Vijaykumar M, Lokesh BR. Biological properties of curcumin–cellular and molecular mechanisms of action. *Crit Rev Food Sci Nut.* 2004,44(2):97-111.
[11] LoTempio MM, Veena MS, Steele HL, Ramamurthy B, Ramalingam TS, Cohen AN, et al. Curcumin suppresses growth of head and neck squamous cell carcinoma. *Clin Cancer Res*. 2005;11(19 pt 1):6994-7002.
[12] Kuo ML, Huang TS, Lin JK. Curcumin, an antioxidant and antitumour promoter, induces apoptosis in human leukemia cells. *Biochim Biophys Acta*. 1996;1317(2):95-100.
[13] Goel A, Boland CR, Chauhan DP. Specific inhibition of cyclooxygenase –2(COX-2) expression by dietary curcumin in HT 29 human colon cancer cells. *Cancer Lett.* 2001;172(2):111-18.
[14] Shao ZM, Shen ZZ, Liu CH, Sartippour MR, Go VL, Hever D, et al. Curcumin exerts multiple suppressive effects on human breast carcinoma cells. *Int J Cancer.* 2002;98(2):234-40.
[15] Cohly HHP, Asad S, Das SK, Angel MF, Rao M. Effect of Antioxidant (Turmeric, Turmerin and Curcumin) on Human Immunodeficiency Virus. *Int J Mol Sci.* 2003;4(2):22-33.
[16] Moghadamtousi SZ, Kadir HA, Hassandarvish P, Tajik H, Abubakar S, Zandi K. A review on antibacterial, antiviral, and antifungal activity of curcumin. *Biomed Res Int*. 2014;2014:186864.
[17] Neelakantan P, Subbarao C, Sharma S, Subbarao CV, Garcia-Godoy F, Gutmann JL. Effectiveness of curcumin against *Enterococcus faecalis* biofilm. *Acta Odontologica Scandinavica.* 2013;71(6):1453-7.
[18] Yeon KY, Kim SA, Kim YH, Lee MK, Ahn DK, Kim HJ, et al. Curcumin produces an antihyperalgesic effect via antagonism of TRPV1. *J Dent Res*. 2010;89(2):170-74.
[19] Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of turmeric (Curcuma longa). *J Altern Complement Med*. 2003;9(1):161-68.
[20] Dyavanagoudar SN. Oral submucous fibrosis: review on etiopathogenesis. *J Cancer Sci Ther*. 2009;1:72-77.
[21] Agarwal N, et al. Evaluation of efficacy of turmeric in management of oral submucous fibrosis. *J Indian Acad Oral Med Radiol.* 2014;26(3):260-63.
[22] Deepa DA, Balan A, Sreelatha KT. Comparative study of the Efficacy of curcumin and turmeric oil as chemopreventive agents in oral submucous fibrosis: a clinical and histopathological evaluation. *J Indian Acad Oral Med Radiol*. 2010;22(2):88-92.
[23] Yadav M, et al. Comparison of curcumin with intralesional steroid injections in oral submucous fibrosis -a randomized, open-label interventional study. *J Oral Biol Craniofac Res*. 2014;4(3):169-73.
[24] Rai B, Kaur J, Jacobs R, Singh J. Possible action mechanism for curcumin in pre- cancerous lesions based on serum and salivary markers of oxidative stress. *J Oral Sci*. 2010;52(2):251-56.
[25] Zhang SS, et al. Antifibrotic Effect of Curcumin in TGF-β1-Induced Myofibroblasts from Human Oral Mucosa. *Asian Pacific J Cancer Prev*. 2012;13(1):289-94.
[26] El Khoury E, Abiad M, Kassaify ZG, Patra D. Green synthesis of curcumin conjugated nanosilver for the applications in nucleic acid sensing and anti-bacterial activity. *Colloids Surf B Biointerfaces*. 2015;7(127C):274-80.

PARTICULARS OF CONTRIBUTORS:
1. Senior Lecturer, Department of Oral Medicine and Radiology, Sarjug Dental College and Hospital, Darbhanga, Bihar, India.
2. Associate Professor and Head, Department of Psychiatry, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India.
3. Post Graduate Student, Department of Public Health Dentistry, Institute of Dental Sciences, Bareilly, U.P, India.
4. Senior Consultant, Yashoda Hospital, Ghaziabad, U.P, India.
5. Senior Lecturer, Department of Oral Medicine and Radiology, Rama Dental College Hospital and Research Centre, Kanpur, U.P, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Abhijeet Alok,
Senior Lecturer, Department of Oral Medicine and Radiology, Sarjug Dental College and Hospital,
Hospital Road, Laheriasarai, Darbhanga-846003, Bihar, India.
E-mail : drabhijeet786@gmail.com

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