

# CURCUMIN IN MEDICINE: BOON OR BANE

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**Abstract:** In the recent past curcumin has gained a lot of excitement because of its potential as prophylactic and therapeutic agent in various diseases. The aim of this review was to assess the role of curcumin in the treatment of oral potentially malignant disorders. Turmeric is composed of a group of three curcuminoids: curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins and resins. Curcumin is a polyphenol that is contained in the rhizomes of *Curcuma longa* Linn. The active components are thought to be the curcuminoids, primarily curcumin, which is commonly available worldwide. Curcumin possesses anti-oxidant, anti-inflammatory, and pro-apoptotic activities. Curcumin is a promising therapeutic agent. This article explores the mechanism of curcumin and its role in potentially malignant disorders.

**Keywords:** Curcumin, antioxidant, potentially malignant disorders

## Introduction

As the rate of development of potentially malignant disorders (PMD) into oral carcinoma are enlarging and it was seen that oral carcinoma accounts for 3% among all of malignancies worldwide. So, there should be early detection of the oral PMD, but there is diagnostic delay in the recognition of manifestation of oral PMD which is caused by the lack of awareness among the general population and health-care professionals. The World Health Organization defines PMD as a lesion/condition which has a risk of transforming into malignancy either at initial or later diagnosis and most commonly occurring PMDs are Leukoplakia, erythroplakia, Lichen planus (LP), and oral submucous fibrosis (OSMF) as they are more likely to transform into malignancies.<sup>1</sup> Various treatment modalities have blossomed in the recent past for the treatment of PMD viz. antioxidants, carotenoids, vitamin A, conventional surgery, laser ablation or cryosurgery. Plants derived antioxidants have been a major source of medicine since ages in many part of the world. Turmeric has a number of medicinal properties. Curcumin, a diferuloylmethane, is a yellow substance which is extracted from the root of the plant *Curcuma longa* and a commonly used food additive as well as a spice and a coloring agent. It is also considered as a medicinal herb in India and China where as in recent manners, it's been said that Curcumin has chemo preventive effect against cancers.<sup>2</sup>

They exhibit antineoplastic, antiproliferative, and antimutagenic activities by subduing initiation, progression, and metastasis and interrupting cell cycle by disrupting mitotic structures and inducing apoptosis. It also helps in reduction of inflammation along with its antimicrobial and a chemo-radio sensitizing properties. Even it enhances the process of wound healing apart from its antineoplastic properties. Curcumin is available in oral, intravenous, subcutaneous, and topical application in the form of gel, ointments, and nasal spray.<sup>1</sup>

## Curcumin Chemistry

The yellow color of turmeric is exclusively due to presence of polyphenolic curcuminoids along with presence of alcoholic extract namely Curcumin i.e. curcumin I or diferuloylmethane, demethoxycurcumin which is curcumin II and bisdemethoxycurcumin, known as curcumin III. Among the curcuminoids, curcumin is the main and biologically targeted phytochemical and the curcumin originates from *C. longa* with molecular weight of 368.38, a melting point of 179–183 °C, and chemical formula of  $C_{21}H_{20}O_6$ . Under the various physiological conditions, it exist in both as an enol and a bis-keto form.<sup>3,4</sup> The commercially available curcumin is a mixture of curcumin (approx. 77%), demethoxycurcumin (approx. 18%) and bisdemethoxy-curcumin (approx. 5%) rather than pure Curcumin.

## Pharmacokinetics

Animal studies have demonstrated that curcumin remains unchanged when passes through gastrointestinal with oral dosage of 40-85 percent. Most of the absorbed flavonoid being metabolized in the intestinal mucosa and liver. Curcumin which is often formulated with bromelain for increased absorption and enhanced anti-inflammatory effect has low rate of absorption.<sup>5</sup>

## Mechanism of curcumin

### a) Antioxidant activity of curcumin

Oxidative stress and oxidative damage comes under the pathophysiology of many chronic inflammatory and degenerative disorders such as cancer. The reactive oxygen species (ROS) particularly  $O_2^-$  and  $OH^\cdot$  are having special role in the development of cancer. Hence in order to prevent from the oxidative damage of DNA, lipid or protein the effects of these free radicals can be diluted by the anti-oxidant mechanism. Curcumin inhibited ROS generation in rat peritoneal macrophages at the concentration of 10  $\mu$ M. It showed similar effects in red blood cells. Curcumin has also been shown to scavenge  $O_2^-$  and  $OH^\cdot$  radicals.<sup>6</sup>

In contrary, a few reports showing curcumin as pro-oxidant indicated that the pro-oxidant and anti-oxidant effects of curcumin are dependent on dose and the chemical environment (e.g., availability of free  $Cu^{2+}$  ions). Another free radical, nitrous oxide (NO), also plays important roles as an oxidant, inflammatory- and immune-modulator. Preclinical studies have suggested that curcumin may inhibit induction of macrophage nitrous oxide synthase (NOS) activity at concentrations of 1–20  $\mu$ M. In mice, oral administration of an aqueous alkaline solution of curcumin, notably at a tiny dose of 92 ng/g-BW strongly inhibited murine hepatic

lipopolysaccharide-induced peak inducible NOS (iNOS) gene expression. As inhibition of iNOS activity may represent a mechanism of intervention during carcinogenesis, apparent activity of curcumin at low concentrations would have considerable implications for cancer chemoprevention. Cellular stress induced an Endothelial heme oxygenase-1 (HO-1) protein. Its main action is the degradation of heme to the anti-oxidant biliverdin and the vasoactive molecule carbon monoxide (CO).<sup>4,6</sup>

#### **Anti-inflammatory effects by inhibition of arachidonic acid pathways:**

The arachidonic acid metabolism consists of two well-described pathways, the cyclooxygenase (COX) and the lipoxygenase (LOX) pathways. The key enzyme which converts arachidonic acid to prostaglandins and thromboxanes in the COX pathway is cyclooxygenase. There are two COX isozymes viz. COX-1 and COX-2. An essential isoform i.e. COX-1 is generally expressed in most of the tissues and gastrointestinal ulcers or impairment of renal blood flow type of adverse effects occurred due to its inhibition. Though the inflammation due to cytokines and intracellular signals induces the COX-2; still normal tissues through the hormones of ovulation and pregnancy, growth factors, oncogenes, and tumour promoters, also produces the same COX-2 which is primarily expressed only in brain and spinal cord tissue. COX-2 over expression has been implicated in the carcinogenesis of many tumours such as in colon, rectum, breast, head and neck, lung, pancreas, stomach, and prostate.<sup>4</sup>

Curcumin has ability to inhibit induction of COX-2 gene expression in oral and colon epithelial cells. Curcumin showed a strong inhibition of chemically induced PGE<sub>2</sub> production in colon cells at a concentration of 20 µM. In a study in human colon carcinoma cell lines carried by Lev-Ari et al., incubation of HT29 cells and SW480 cells with different concentrations of curcumin, resulted in inhibition of PGE<sub>2</sub> synthesis, down regulation of COX-2 protein levels, and increased apoptosis of those cells that constitutively express COX-2 protein.<sup>6</sup>

One of the implicated mechanisms for COX-2 down regulation is inhibition of the activity of the IκB Kinase (IKK) signalling complex responsible for phosphorylation of inhibitor of NF-κB (IκB) and subsequently the activation of the transcription factor NF-κB. This finding was also supported by the fact that commonly used anti-inflammatory drugs such as aspirin and salicylates, which inhibit the activity of IκB kinase-β, have also been linked to a decreased incidence of colorectal cancer. Apart from the well known roles of COX-2, later studies suggest that the COX-1 isozyme also plays role in inflammation and carcinogenesis; indeed the balance between the metabolic products of COX-1 and COX-2 catalysis appears important in physiologic function and response to inflammation.<sup>4</sup>

Curcumin and some of its analogues do arrive to inhibit COX-1 transcription. Such inhibition is significant, as it has been linked to a potential influence on the local spread of malignancy and the communication between malignant cells and their neighbouring stromal cells. Numerous studies have indicated that the transcription factor, NF-κB plays important role to induce inflammation and is constitutively active in patients with cancer. The role of NF-κB in suppression of apoptosis, tumour growth, invasion, angiogenesis, and metastasis, via variety of downstream effectors, is well documented.<sup>4</sup> Therefore, an agent that can target NF-κB is of great interest for the treatment of pancreatic cancer. From a philosophical standpoint, as cancer and most chronic diseases have a multifactor aetiology, natural diet-derived agents such as curcumin that act at multiple cellular levels may stand a better chance of improving the prevention or management of these diseases than agents that affect a single cellular target. A pleiotropic activity in the cell is provided by ability of curcumin to inhibit multiple levels of the NF-κB, AP-1, and JNK signaling pathways.<sup>4</sup>

#### **Anticarcinogenic Effects:**

Curcumin's capacity to inhibit the process of carcinogenesis at three stages i.e. tumor promotion, angiogenesis, and tumor growth is nicely reviewed through the study done by Akram M et al. It's been popularly said through many of the studies in both invitro and invivo that; curcumin are capable of suppressing the activity of several common mutagens and carcinogens in a variety of cell types. Direct antioxidant and free-radical scavenging effects is providing anticarcinogenic effects of turmeric and curcumin along with their ability to increase glutathione levels indirectly, thereby aiding in hepatic detoxification of mutagens and carcinogens, and inhibiting nitrosamine formation.<sup>5</sup>

Curcumin's induction of apoptosis in cancer cells by a variety of mechanisms as described above, as well as its inhibition of DNA topoisomerase II at micromolar concentrations, hints at its potential for chemotherapeutic activity in the treatment of cancer. Published anecdotes of curcumin's activity as a topical treatment for cancer can be found, most notably Kuttan's<sup>7</sup> report of turmeric as a topical treatment for oral cancers and leukoplakia. This research group reported a reduction in the size of the lesions in 10% of the 62 patients treated, but there was no control group, no assessment of anti-inflammatory activity and no chemical analysis of the preparation applied.<sup>4</sup>

#### **Role of curcumin in potentially malignant disorders**

Curcumin possesses several pharmacological properties, including anti-inflammatory, antimicrobial, antiviral, antifungal, antioxidant, chemo-sensitizing, radio-sensitizing, and wound healing activities. It is known to suppress tumor initiation, promotion and metastasis in experimental models, and it can also act as an anti-proliferative agent by interrupting the cell cycle, disrupting mitotic spindle structures, and inducing apoptosis and micro-nucleation. In spite of reported minor adverse effects, large doses of up to 12,000 mg per day of curcumin were found to be well tolerated in humans. Therefore, based on the safety and toxicity profile, in several clinical trials the targeted doses for curcumin can be recommended in between 4,000–8,000 mg to obtain the maximum therapeutic effects. It seems that curcumin is a pluripotent pharmacological agent and may be the new hope for reducing incidence of cancer and precancer.<sup>8</sup>

It was noted that the markers in saliva, serum and vitamin level increased, whereas (malondialdehyde) MDA and (8-hydroxy-2'-deoxyguanosine) 8-OHd levels decreased simultaneously in patients suffering from leukoplakia, oral submucous fibrosis and lichen planus. Through the results of study conducted by Rai et al. study, it can be assumed that curcumin has anticancer properties by

increasing the levels of vitamins C and E along with suppression of the peroxidation of lipids, and prevention of DNA damage. Even few of authors explained that there was reduction in the size of the lesions among those patients who all received the topical turmeric/ curcumin in treatment of oral cancers and leukoplakia.<sup>8</sup>

Even the efficacy of Curcumin was evaluated in one of the prospective study where Curcumin was given to those patients who were having precancerous lesions i.e. leukoplakia, oral sub-mucous fibrosis (OSMF), and lichen planus (LP). Pain control and resolution of the lesion were the main clinical criteria which were used for assessing changes in oral leukoplakia and LP. Evaluation of pain was done on visual analogue scale (VAS) and for healing, changes in lesion size included ulcer size from baseline, while in OSMF, change in mouth opening was considered. Along with this, collection of serum and salivary samples was done. Curcumin improved the clinical symptoms and reduced the lesion size in all patients, which was suggestive of anti-precancerous effect through antioxidant pathways.<sup>9</sup>

A phase I clinical study performed in Taiwan also investigated the potential anti-carcinogenesis activity of curcumin in patients with pre-invasive malignant or high risk premalignant conditions i.e. resected cancer of the bladder, Bowen disease of the skin, uterine cervical intraepithelial neoplasia, intestinal metaplasia of the stomach, or oral leukoplakia. Curcumin were given to those patients in the dosages of 1,000 to 8,000 mg (500 mg of synthetic curcumin per capsule, 99% purity) daily for three months and histological improvements of the premalignant lesions was seen among many of the patients with oral leukoplakia.<sup>2</sup>

### Curcumin limitations and approaches

As we all know every coin has two ends. In the same way Curcumin also suffers from few of the limitations. As due to low solubility, rapid metabolism, and low bioavailability; limited therapeutic success was seen in cell culture systems. Henceforth the applicability of various novel drug delivery systems like micelles, liposomal vesicles, nanoparticles, nanoemulsions, phospholipid complexes and polymeric implants in order to enhance the bioavailability of curcumin and to make it more worthy for therapeutic prevention or risk reduction at the precancerous stage has been under investigation in the last two decades.<sup>4</sup>

Even the nanotechnology based different drug delivery systems such as polymeric nano particles, solid lipid nanoparticles (SLN), liquid crystal systems, precursor systems for liquid crystals, liposomes, and micro emulsions are also taken into the consideration in order to improve a formulation's most desirable properties and for ensured activity to make a bright future.<sup>4</sup>

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