LITERATURE REVIEW ON TURMERIC/CURCUMIN AND THEIR DIFFERENT BIOLOGICAL ACTIVITIES

Turmeric was described as *Curcuma longa* by Linnaeus and its taxonomic position as follows:

Class	Liliopsida
Subclass	Commenlinids
Order	Zingiberales
Family	Zingiberaceae
Genus	*Curcuma*
Species	*Curcuma longa*



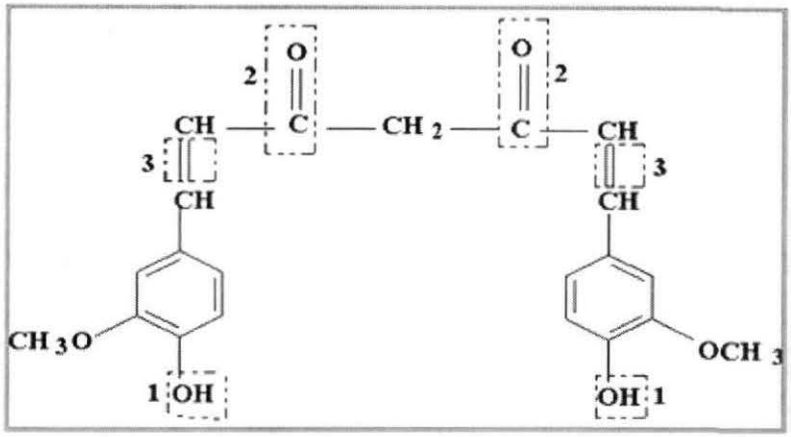
DISTRIBUTION: Cultivated throughout Asia including India, China and tropical countries.

DESCRIPTION: A rhizomatous perennial herb that measures up to 60-90 cm in height with short stem and tuft of erect leaves. Its rhizome is cylindrical, ovate, orange coloured often short branched. The flowers are pale yellow in spikes concealed by the sheathing petioles and with green flowering plates.

CHEMICAL COMPOSITION:

The important constituent of *Curcuma longa* L. is **curcumin** a diferuloylmethane (3-4%), responsible for the yellow colour. Curcumin was first isolated in 1815

and its chemical structure was determined by Roughley and Whiting in 1973. Curcumin has a melting point at 176- 177^{0}C and forms red brown salt with alkali. It is soluble in ethanol, alkali, ketone, acetic acid and chloroform. The main chain in the curcumin molecule is the aliphatic chain, unsaturated and aryl group can be substituted.



Chemical structure of curcumin

[1.Parahydroxyl groups, 2. Keto groups, 3.Double bonds]

Curcumin comprises of curcumin I (94%), curcumin II (6%) and curcumin III (0.3%). Demethoxy and bisdemethoxy derivatives of curcumin have also been isolated.

Turmeric also contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%). The abundant starch is largely gelatinized. A complex acidic arabinogalactan, ukonan A, is also present. It also contains 2-7% essential oil, comprising mainly bisabolane, guaiane, and germacrane sesquiterpenes: turmerone, ar-turmerone, zingiberene, curlone, etc.; the high content of bisabolane derivatives distinguishes turmeric from other Curcuma species (Tomoda. et. al., 1990).

BIOLOGICAL PROPERTIES OF *CURCUMA LONGA* L.

ANTI-INFLAMMATORY

In traditional medicine, turmeric has been used as a potent anti-inflammatory agent and there are many papers relating the activity of compounds extracted from *C. longa* L. being potent inhibitors of inflammation. Curcumin was effective against carrageenin-induced oedema in rats (Ghatak & Basu, 1972; Srivastava & Srimal , 1985; Brouet & Ohshima, 1995) and mice (Srimal & Dhawan, 1973). Mukhophadhyay *et al.* (1982) demonstrated the anti-inflammatory activity of curcumin and other semi-synthetic analogues (sodium curcuminate, diacetyl curcumin, triethyl curcumin and tetrahydro curcumin) in carrageenin-induced rat paw edema and cotton pellet granuloma models of inflammation in rats. Arora *et. al* (1971) investigated the anti-inflammatory activity in different fractions of the petroleum ether extract of the rhizomes of turmeric (fractions A and B) in animal models and found effective in reducing granuloma growth and no toxic effects were observed. Anti-inflammatory and anti-arthritic actions of volatile oil of *C. longa* L. were also observed by Chandra and Gupta (1972).

Curcumin, in case of atopic asthmatics in response to house dust mites, inhibited Dermatophagoides farinea (D*f*)-induced lymphocyte proliferation and production of IL-2, IL-5, GM-CSF, and IL-4 in a concentration-dependent manner (Kobayashi, et.al., 1997) .Curcumin also inhibited experimental allergic encephalomyelitis (EAE) in association with a decrease in IL-12 production from macrophage/microglial cells and differentiation of neural Ag-specific Th1 cells (Natarajan & Bright, 2001). Patients with 'definite' rheumatoid arthritis were studied to compare the anti-rheumatic activity of curcumin and showed significant improvement

in morning stiffness, walking time and joint swelling, following two weeks of curcumin or phenylbutazone therapy (Deodhar 1980).

The anti-inflammatory role of curcumin was also mediated through downregulation of cyclooxygenase-2 and inducible nitric oxide synthetase through suppression of NF-κB activation (Surh. et.al., 2001). Curcumin also enhances wound-healing in diabetic rats and mice and in H_2O_2 - induced damage in human keratinocytes and fibroblasts (Phan *et. al,* 2001).

ANTI-TUMOR/ ANTI-CARCINOGENIC

The anti-tumor and antiproliferative effect of curcumin, against a variety of transformed and nontransformed cell types were investigated. Curcumin, a diferuloyl methane, the major pigment in turmeric inhibits proliferation of a wide variety of transformed cells such as HeLa cells, (Huang *et. al.*, 1997), Jurkat cells (Piwocka, Jaruga, Skierski, Gradzka and Sikora, 2001), prostrate cancer cells (Mukhopadhyay *et. al.*, 2001), MCF-7 cells (Henry et. al., 1998), AK-5 tumor cells (Khar., Ali., Pardhasaradhi., Begum and Anjum. 1999) and many others. Several studies in recent years have also shown the inhibitory effect of turmeric and curcumin in different experimental tumorigenic models (Huang., M.T, 1994) and it has been found to be a potent inhibitor of the initiation and promotion of chemical carcinogen (12-O tetradecanoyl-phorbol-13 acetate (TPA), 1,2-dimethylhydrazine dihydrochloride (DMH), 20-methylcholanthrene, dimethyl benathracene (DMBA), benzo[a]pyrene, 7,12-dimethylbenz [a] anthracene etc.) induced tumor formation in animals (Huang, Smart, Wong and Conney, 1988; Kim et. al., 1988; Soudamini & Kuttan 1989; Deshpande, Ingle and Maru. 1997, 1998).

The effect of turmeric and curcumin were also observed in different experimental tumorigenic models. The modulating effects of turmeric (T), ethanolic turmeric extract (ETE) and curcumin-free aqueous turmeric extract (CFATE) on the initiation or post-initiation phases of DMBA-induced mammary tumorigenesis were investigated in female Sprague-Dawley rats. Dietary administration of 1% T / 0.05% ETE resulted in significant suppression of DMBA-induced mammary tumorigenesis as seen by reduction in tumor multiplicity, tumor burden and tumor incidence (Deshpande.,Ingle and Maru. 1998). The effects of curcumin in oral cancers were assessed in experimental tumorigenesis using Syrian golden hamster cheek pouch model. Cheek pouches were painted with the carcinogen dimethyl benathracene (DMBA) and were fed with curcumin through diet. At the end of 14 weeks, animals given curcumin showed lower percentage of microscopic tumors as compared to controls (Krishnaswamy et al., 1998). Effects of curcumin and its derivative, tetrahydrocurcumin (THC), on development of putative, preneoplastic aberrant crypt foci (ACF) in colons of mice initiated with 1,2-dimethylhydrazine dihydrochloride (DMH) was also judged and were found to have potential chemopreventive activity against colon carcinogenesis (Kim et.al., 1998). The effect of curcumin, chlorogenic acid, caffeic acid and ferulic acid on tumor promotion in mouse skin by 12-O-tetradecanoyl-13-acetate was also studied by Huang et al. (1988), and observed that all these compounds inhibited the epidermal ornithine decarboxylase (ODC) and epidermal DNA synthesis, being curcumin the most efficient. The anticarcinogen potential of turmeric exract and curcumin was also substantiated by the reduction in tumour formation induced by subcutaneous injection of 20-methylcholanthrene (Soudamini & Kuttan.1989).

Oral treatment with T or ETE or CFATE did not show any toxicity as judged by body weights, liver weights or liver/body weight ratios (Deshpande.,Ingle and Maru. 1998). Chemopreventive

action of dietary curcumin on 7,12-dimethylbenz[a]anthracene (DMBA)-initiated and 12-O tetradecanoyl-phorbol-13 acetate (TPA) promoted skin tumor formation in male swiss ablino mice was investigated where the dietary administration of curcumin significantly inhibited the number of tumors per mouse and the tumor volume (Limtrakul, Lipigorngoson, Namwong, Apisariyakul and Dunn. 1997). Pretreatment of rats with 1% turmeric through the diet resulted in a significant decrease in induction of B(a)P-induced CYP 1A1 and 1A2 and phenobarbitone (PB)-induced CYP 2B1 in liver, lung and stomach, although the extent of the decrease was different. These results suggest that turmeric/curcumin(s) are likely to inhibit activation of carcinogens metabolized by CYP 450 isozymes, namely, CYP 1A1, 1A2 and 2B1. Topical application of low doses of curcumin inhibited 12-*O*-tetradecanoylphorbol-13-acetate -induced tumor promotion (Huang *et.al.*, 1988).

ANTI-MUATGENIC

The anti-mutagenic effects of turmeric on the levels of benzo [a] pyrene induced DNA adducts in the livers of rats were studied, where turmeric at levels of 0.1-0.5% in the diet decreased DNA adducts and mutagen load (Mukundan, Chacko, Annapurna and Krishnaswamy, 1993). Curcumin was also to inhibit the mutagenesis induced by aflatoxin B_1 (AFB_1). Dietary administration of curcumin to rats significantly reduced the number of gamma-glutamyl transpeptidase-positive foci induced by AFB_1 which is considered as the precursor of hepatocellular neoplasm (Kapoor & Priyadarsini. 2001).

Curcumin as well as its two natural analogues i.e demethoxy curcumin (dmC) and bisdemethoxycurcumin (bdmC) were found to be highly effective in suppressing genotoxicity of cooked food mutagens in a dose-dependent manner, in both the frame shift (TA98) as well as

base pair mutation sensitive (TA 100) strains of *S. typhimurium*. However, bdmC appeared to be a relatively less active antimutagen compared to C and dmC .These analogues were also found to be potent inhibitors of S9-mediated mutagenicity of hetorocyclic amines (Shishu, Singla and Kaur. 2002:).

ANTI-OXIDANT

Natural phenolic antioxidants from medicinal or edible plants have recently received much attention as promising agents for reducing the deleterious effects of oxidative stress-induced diseases. Curcumin present in turmeric is an active phenolic compound and scavenge hydroxyl and superoxide anions (Ruby., Kuttan., Babu., Rajasekharan and. Kuttan. 1995). Its antioxidant property, has further been shown by its capacity to inhibit lipid peroxidation in mouse red blood cells (Toda et.al., 1998), in rat liver (Reddy and Lokesh, 1994). The effect of retinol deficiency and curcumin/turmeric on lipid peroxidation and fatty acid profile was studied in liver, kidney, spleen and brain microsomes of rats. Feeding 0.1% curcumin or turmeric for three weeks in diet to retinol deficient rats reduced the lipid peroxidation respectively to 12.5 or 22.6%, in liver, 23.7 or 24.1% in kidney, 14.4 or 18.0% in spleen and 16.0 or 31.4% in brain. 18. The inhibitory effects of curcumin and tetrahydrocurcumin (THC), one of the major metabolites of curcumin were also examined on the lipid peroxidation of erythrocyte membrane ghosts induced by tertbutyl-hydroperoxide. THC showed a greater inhibitory effect than curcumin (Song *et.al.*,2001). Studies showed that curcumin is a good scavenger of hydroxyl radical at high concentrations but at low concentrations activated the Fenton system to generate an increased amount of hydroxyl radical. Curcumin was also studied for superoxide scavenging activity and was found to be a potent scavenger. Curcumin was able to reduce ferric ions to promote the

Fenton type reaction to generate a hydroxyl radical in the presence of hydrogen peroxide ((Kunchandy & Rao, 1980). Curcumin inhibited induction of iNOS in macrophages activated with lipopolysacharides and IFN-γ (Brouet & Ohshima.1995) and was able to protect hemoglobin from nitrite-induced oxidation to methemoglobin (Umakrishnan & Rao, 1995). Curcumin was also able to reduce the amount of nitrite formed by the reaction between oxygen and nitric oxide generated from sodium nitroprusside (Sreejayan and Rao, 1997).

Curcumin (CUR) also prevented the glutathione loss occurring in dexamethasone-treated thymocytes by enhacing intracellular glutathione content in treated cells. Results showed that CUR treatment elevated the concentrations of glutathione and non-protein sulfhydryl groups, thus preventing their decrease in apoptotic thymocytes (Jaruga, *et.al.,* 1998) .Protective effects of curcumin (U1), tetrahydrocrcumin (THU1), against ferric nitrilotriacetate (Fe-NTA)-induced oxidative renal damage were also studied in male ddY mice, which showed suppression of oxidative stress-induced renal damage by dietary U1 and THU1. The *in vivo* antioxidant effects of THU1 were greater than those of U1 probably because THU1 may be more easily absorbed than U1 from the gastrointestinal tract and also had some advantages as a food additive because it is colorless. (Okada, *et. al,* 2001). Curcumin is able to repair most of the oxidized amino acid, with a great efficiency. In addition, cucumin also reacts with thiol radicals, indicating curcumin can be a powerful antioxidant to repair both oxidative and reductive damage caused to proteins by radiation (Kapoor & Priyadarshini.2001).

ANTI-BACTERIAL

Curcumin showed antibacterial property by inhibiting growth of *Streptococcus aureus* and *Staphylococcus albus* (Chopra et. al., 1941). Bhavani Shankar and Murthy (1979) investigated

the activity of turmeric fractions against intestinal bacteria such as *Lactobacillus.* Curcumin also inhibited the growth of H. pylori cagA+ strains *in vitro* (Mahady ,Pendland., Yun and Lu. 2002).

ANTI-VIRAL

The anti-viral effects of curcumin were determined on purified human immunodeficiency virus type 1 (HIV-1) integrase, where curcumin showed inhibition of an integrase deletion mutant containing only amino acids 50-21 probably by interacting with the integrase catalytic core (Mazumder, Raghaban, Weinstein, Kohn and Pommer. 1995). Curcumin also acted as an efficient inhibitor of Epstein-Barr virus (EBV) key activator Bam H fragment z left frame 1 (BZLF1) protein transcription in Raji DR-LUC cells. EBV inducers such as 12-0- tetradecanoylphorbol-13-acetate, sodium butyrate and transforming growth factor-beta increase the level of BZLF1 m-RNA at 12-48 hr treatment in these cells, which was effectively blocked by curcumin (Hergenhahn *et. al*, 2002). Curcumin was also capable of downregulating HPV18 transcription (Prustry and Das, 2005).

ANTI-PROTOZOAN

The ethanolic extract of the rhizomes was found to have anti- *Enatamoeba histolytica* activity. Curcumin was also found to have anti-*Leishmania* activity *in vitro* (Koide et. al., *2002).* Anti-*Plasmodium falciparum* and anti- *L. major* effects of curcumin have also been reported (Rasmussen et. al., 2000)

ANTI-VENOM

Ar-tumerone, isolated from *C. longa,* was found to neutralize both haemorrhagic activity of *Bothrops* venom and 70% lethal effect of *Crotalus* venom in mice (Araujo & Leon 2001