

# Curcumin: a natural yellow pigment with great potential

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It is a wonder that a natural yellow pigment which has been consuming in India since the second millennium BC in both medicine and food (*Remember the hallmark yellow in the signature seasonings and fragrant dish of Indian subcontinent often called 'Curry'!*) has become one of the most cited natural molecule in terms of its capacity to deliver a multitude of health guarding effects as studied and established by modern scientific community around the globe. The pigment 'curcumin' (the spice "cumin" contains no curcumin, despite the similar name!) is isolated from the rhizomes of a plant called turmeric (*Curcuma longa L.*, Zingiberaceae family) native to south India and now cultivating in various south east asian countries.

Aerobic organisms during the process of conversion of oxygen into energy generate various free radicals as byproducts, which are unstable but capable of independent existence. An uncontrolled production of these species in the cell or the so-called oxidative stress may result in tissue damage and aging. The ultimate effect of free radical-mediated reactions in biological systems is nothing but dreadful diseases like cancer, cardiovascular diseases, neurodegenerative diseases, various respiratory diseases, renal diseases, eye diseases etc. Modern interest on turmeric started in 1970's when researchers found that the herb may possess anti-inflammatory and antioxidant properties. For example, it was demonstrated that curcumin can protect (52 percent) hemoglobin from nitrate-induced oxidation to methemoglobin at 400  $\mu\text{M}$  concentration. Some of the well studied potential effects of curcumin, as an antioxidant, is described below to substantiate its role in future medicine and/or as a dietary supplement capable of providing an array of health-promoting/maintaining benefits. Though a clear statement like "Indians are more healthy than the other nationals because of extensive turmeric consumption" may be of a very high claim, observational and epidemiological studies have already confirmed that people who consume diets rich in turmeric have lower rates of breast, prostate, lung and colon cancers (1). It has been estimated that the average daily intake of turmeric in the Indian diet is about 2- 2.5g, which equates to about 60-100 mg of curcumin per day. Systematic preclinical animal studies funded NCI did not discover any adverse effects, when doses up to 3.5 g/kg body weight was administered for 3 months.

Though the absorption, metabolism and tissue distribution of curcumin has mainly been studied in rodents, a comprehensive pharmacokinetic data in humans have yet to come. Studies have found that curcumin exhibits very low oral bioavailability and may undergo intestinal metabolism and excretion in the bile. However, several observations in human volunteers and patients have shown that curcumin may possess systemic biological activity even at low oral doses. In a small study performed in Taiwan, a single oral dose of 20 mg of curcumin was appeared to be sufficient to induce

contraction of the gall bladder as assessed by ultrasound scanning, compared to amyllum placebo.

The major metabolic pathway and the degradation products of curcumin *in vivo* as reported in many studies are depicted in Figure 1 (2).

## ROLE OF CURCUMIN IN CANCER

Although a few human clinical trials have been completed to date, hundreds of peer-reviewed scientific papers have been published in the recent past about its remarkable ability to halt or prevent many chronic disease states including cancer. NCI has taken many serious efforts to encourage and support research on curcumin to develop it as a preventive agent and/or drug for cancer. The rationale behind this effort is the well-tracked chemopreventive mechanisms, the validated biological activity in preclinical studies and its proven safety to humans. The mechanisms responsible for apoptosis (programmed cell death) by curcumin were found to be very complex involving the inhibition of a variety of cell signaling pathway genes like Akt, NF- $\kappa\text{B}$ , AP-1 or JNK, up-regulation of some cell growth arrest genes and DNA damage inducible genes like GADD and down-regulation of the expression of survival genes *egr-1*, *c-myc*, *Bcl-xl* and *IAP* or abnormal tumor suppressor genes such as *p53* (3). It strongly inhibits DNA and RNA synthesis and increases mitochondrial membrane permeability; a very significant property in the apoptosis of proliferating cells. It can also prevent proliferation by cell cycle arrest in the G2/M phase in a variety of malignant tumors. G2/M arrest renders cells more susceptible to the cytotoxic effects of radiation, suggesting that curcumin may find significance as a radiosensitizer (4). In short, curcumin is an example of a natural dietary agent capable of acting at multi levels in cellular pathway for the prevention or treatment of diseases with multifactorial etiologies such as cancer.

The ability to inhibit COX-2 gene overexpression, which is implicated in the carcinogenesis of many different tumors, has suggested a plausible role of curcumin to protect children against leukemia (5). Curcumin was shown to induce apoptosis among leukemia B lymphoma cells and inhibits the multiplication of leukemia cells in laboratory studies. It has been shown to possess potent antiproliferative and proapoptotic effects in melanoma cells and neuroblastoma cell lines by suppressing the I $\kappa\text{B}$  kinase and NF- $\kappa\text{B}$  activity. The efficacy of curcumin to offer a dose- and time-dependent decrease in cell viability, cell cycle arrest and induction of apoptosis is encouraging to the development of a natural drug with known NF- $\kappa\text{B}$  inhibitory activity and little toxicity in humans, unlike the existing inhibitors.

Various studies have reported that curcumin inhibits Angiogenesis, the formation of new blood vessels from the host vasculature to feed the growing tumor in non-malignant and malignant cells, and reduces the number and size of existing tumors and decreases the incidence of new tumor formation (6). It can also affect proteins related to cell-cell adhesion and inhibits the production of cytokines relevant in tumor growth. Earlier research conducted at the University of Texas, M.D. Anderson Cancer Center has shown that curcumin can help to prevent tumor formation and the spread of breast cancer tumor cells to the lungs in mice (7).

Curcumin can also inhibit Cytochrome P450, a phase I metabolizing isoenzyme which is required for toxic chemicals such as heterocyclic amines to induce DNA adduct formation leading to carcinogenesis, and on the other hand to activate phase II metabolizing enzymes generally regarded as favorable detoxifiers, implies its strong promise as a possible safe and non toxic chemopreventive and/or treatment agent for colon, skin, stomach, liver, lung, duodenum, soft palate and breasts cancers (8).

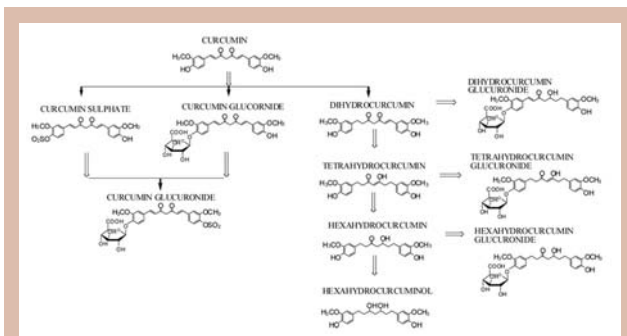


Figure 1. Degradation products of curcumin *in vivo*

Another area of research where curcumin may find wonderful application is in the development of dietary strategies to prevent the stimulated growth of breast tumors by environmental estrogens (9). In this context, sufficient data has already been presented to establish curcumin and isoflavonoids as the most potent inhibitors (95 percent) against the growth of human breast tumor cells which turns out to be an example how effective the combinations of phytochemicals in preventing or treatment against the growth of breast tumors induced by environmental estrogens.

Furthermore, curcumin can enhance cancer cells' sensitivity to certain drugs commonly used to combat cancer and can potentially improve the effectiveness of radiation treatment (4). For example, IFN-Gamma chemotherapy was found to be effective against non-small cell lung cancer, which was relatively insensitive in the absence of curcumin. Another study reported that curcumin could protect animals from the tumor-producing effects of deadly gamma radiation and it protects against damaging ultraviolet light, which is known to play a role in the development of skin cancer.

## ROLE OF CURCUMIN IN CARDIOVASCULAR DISEASES

Curcumin's remarkable ability in maintaining and/or improving the cardiovascular health is a subject of recent research over the globe and several encouraging results against a variety of conditions that model human heart disease have been published in peer-reviewed medical journals. It was reported that curcumin could protect rats from oxidative stress injury known as ischemia/reperfusion, following an experimentally induced stroke (10).

Oxidation of low-density lipoproteins (LDL) is implied to play a vital role in Atherosclerosis, deposition of cholesterol and lipids on arterial walls to form damaging plaques to block the blood flow. In this regard, many *in vivo* animal studies have clearly shown curcumin's ability as an antioxidant to prevent the free radical mediated oxidation of cellular and subcellular membranes that are associated with atherosclerosis. Moreover, it helps to lower total cholesterol levels and increase high density lipoproteins (HDL) level. In a small study conducted on human volunteers researchers reported a highly significant (29 percent) increase in HDL among subjects who consumed 500 mg of curcumin per day for seven days (11). Subjects also experienced 11 percent decrease in total serum cholesterol and 33 percent decrease in serum lipid peroxides. It is actually a more effective anti-clotting agent than the ulcer-inducing stomach irritating aspirin.

In addition to cholesterol, excess levels of homocysteine are generally regarded as an independent risk factor for cardiovascular disease. Researchers suggest that elevated cholesterol alone may not cause heart disease; however it is quite possible to have a cardiac arrest even with normal cholesterol levels; but with elevated homocysteine levels. Curcumin has been found to prevent the dysfunction of the endothelial cells, caused by the elevated homocysteine and may provide a role in the treatment of patients with high homocysteine (12). Similarly, curcumin was also shown to completely inhibit the effect of dangerous marker protein called C-reactive protein, on endothelial cells (13).

## ROLE OF CURCUMIN IN INFLAMMATORY DISEASES

Inflammation is generally regarded as a source of many health challenges. The anti-inflammatory action of curcumin includes lowering histamine levels and increasing the production of natural cortisone by adrenal glands. It inhibits release of the pro-inflammatory cytokine TNF- $\alpha$  and the gene that makes inflammatory COX-2 enzymes. In an impressive study conducted at Cornell University, New York, a dose-dependent treatment of the cells exposed to two known tumor promoters *viz.* bile acids and phorbol esters with curcumin suppressed COX-2 protein induction and genetic COX-2 expression (as measured by mRNA), and effectively inhibited the production of inflammatory-causing prostaglandin E2 indicating its plausible role in chronic inflammatory events such as Crohn's disease and ulcerative colitis (14). Investigations have also been carried out recently to check the anti-inflammatory actions of curcumin and its synthetic analogues in various models (15). Sodium curcumin, triethyl curcumin and tetrahydrocurcumin were found to be good anti-inflammatory agents than hydrocortisone acetate in an experimental inflammation model

induced by carrageenin and formalin in albino rats. Furthermore, it was reported that the gavage administration of 200 mg of curcumin suppresses diethyl nitrosamine-induced inflammation and hyperplasia in rats, indicating its inhibitory action towards the inflammation-factor lipoygenase.

Yet another breakthrough in curcumin research happened to be its capacity to prevent the aggregation of amyloid proteins to amyloid oligomers and fibrils and hence to reduce the formation amyloid plaques *in vivo*, which is characterised as the fundamental reason for Alzheimer's disease. *In vivo* studies further established curcumin's capacity to cross the blood-brain barrier and bound plaques when injected peripherally into aged Tg mice. When fed to aged Tg2576 transgenic mice expressing amyloid precursor proteins with advanced amyloid accumulation, curcumin got binded to plaques and reduced amyloid levels and plaque burden (16). These data supports the rationale for curcumin use in clinical trials for preventing or treating AD. Curcumin has also shown promise in the pathogenesis of Experimental Allergic Encephalomyelitis by blocking IL-12 signaling in T cells and suggested a role in the treatment of multiple sclerosis and other Th1 cell-mediated inflammatory diseases (17). Among arthritis patients, it significantly improved morning stiffness, walking time, joint swelling etc when a daily dosage of 1200 mg of curcumin for two weeks was given.

In a diabetes mellitus rat model study, administration of curcumin was found to offer a reduction of the blood sugar, Hb and glycosylated Hb levels significantly (18). In the case of cataract, the rats treated with naphthalene to induce cataract and kept on a diet supplemented with only 0.005 percent (w/w) curcumin were found to have significantly less opacification of lenses as compared to controls (19). Being an efficient singlet oxygen quencher at physiological or pharmacological concentration, it may be useful pharmacologic agent diseases such as erythropoietic protoporphyria, pellagra and cataractogenesis. Curcumin can also chelate toxic metals like cadmium and lead, and potentially reduce their neurotoxicity and tissue damage. More interestingly, a possibility has also been reported as inhibitors of HIV-1 and HIV-2 proteases against AIDS (20).

In summary, curcumin can be considered as a magic molecule in terms of its nontoxicity and biological activity including the prevention and treatment of a variety of dreadful diseases like cancer, cardiovascular, neurodegenerative and many other inflammatory diseases. No serious adverse effects have been reported due to the consumption of curcumin so far. Though many human trials are needed before we can know with any certainty how best curcumin can develop as a drug, to supplement one's diet regularly with curcumin would seem to be of no-brainer as it is consumed safely by millions of people literally for millennia. But one thing is certain: most doctors especially from west are not aware of the potential benefits of this fascinating herb.

## REFERENCES AND NOTES

- 1) C. H. Hsu.; A. L. Cheng. *Adv. Exp. Med. Biol.* 595, 471-480, (2007).
- 2) C. Ireson, S. Orr et al., *Cancer Research*, 61, pp. 1058-1064 (2001).
- 3) B. B. Aggarwal, A. Kumar et al., *Anticancer Res.*, 23(1A), p. 363, (2003).
- 4) M. Li, Z. Zhang et al., *Cancer Res.*, 67(5), p. 1988 (2007).
- 5) S. Anuchapreeda, P. Thanarattanakorn et al., *Arch Pharm Res.*, 29(10), p. 866 (2006).
- 6) S. M. Sagar, D. Yance et al., *Curr Oncol.*, 13(1), p. 14 (2006).
- 7) B. B. Aggarwal, S. Shishodia et al., *Clin Cancer Res.*, 11(20), p. 7490 (2005).
- 8) S. Singh, A. Khar, *Anticancer Agents Med Chem.*, 6(3), p. 259 (2006).
- 9) S. P. Verma, B. R. Goldin, *Environ Health Perspect.*, 106(12), p. 807 (1998).
- 10) J. Jiang, W. Wang et al., *Eur J Pharmacol.*, 561(1-3), p. 54 (2007).
- 11) K. B. Soni, R. Kuttan, *Indian J Physiol Pharmacol.*, 36(4), p. 273 (1992).
- 12) G. Ramaswami, H. Chai et al., *J Vasc Surg.*, 40(6), p. 1216 (2004).
- 13) V. Jefremov, M. Zilmer et al., *Ann N Y Acad Sci.*, 1095, p. 449 (2007).
- 14) F. Zhang, N. K. Altorki *Carcinogenesis*, 20(3), p. 445 (1999).
- 15) A. Mukhopadhyay, N. Basu et al., *Agents Actions.*, 12(4), p. 508 (1982).
- 16) F. Yang, G. P. Lim, *J Biol Chem.*, 280(7), p. 5892 (2005).
- 17) C. Natarajan, J. J. Bright, *J Immunol.*, 168(12), p. 6506 (2002).
- 18) M. Kuroda, Y. Mimaki, *Biol Pharm Bull.*, 28(5), p. 937 (2005).
- 19) U. Pandya, M. K. Saini, *Toxicol Lett.*, 115(3), p. 195 (2000).
- 20) A. J. Vlietinck, T. De Bruyne, *Planta Med.*, 64(2), p. 97 (1998).