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CURCUMIN: PROPERTIES AND MEDICINAL APPLIATION

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ABSTRACT

Turmeric, derived from the plant *Curcuma longa*, is a gold-colored spice commonly used in the Indian subcontinent, not only for health care but also for the preservation of food and as a yellow dye for textiles. Curcumin, which gives the yellow color to turmeric, was first isolated almost two centuries ago, and its structure as diferuloylmethane was determined in 1910. Since the time of Ayurveda (1900 bc) numerous therapeutic activities have been assigned to turmeric for a wide variety of diseases and conditions, including those of the skin, pulmonary, and gastrointestinal systems, aches, pains, wounds, sprains, and liver disorders. Extensive research within the last half century has proven that most of these activities, once associated with turmeric, are due to curcumin. These include its anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant, anti-fertility, anti-diabetic, anti-bacterial, anti-fungal, anti-protozoal, anti-viral, anti-fibrotic, anti-venom, anti-ulcer, hypotensive and hypocholesteremic activities. Its anti-cancer effect is mainly mediated through induction of apoptosis. Its anti-inflammatory, anti-cancer and anti-oxidant roles may be clinically exploited to control rheumatism, carcinogenesis and oxidative stress-related pathogenesis. Thus, curcumin has the potential for the development of modern medicine for the treatment of various diseases.

Key words : Curcumin, diferuloylmethane, medicinal properties.

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INTRODUCTION

Turmeric (*Curcuma longa*) is extensively used as a spice, food preservative and coloring material in India, China and South East Asia[1]. Curcumin also has its application in the textile and pharmaceutical industry [1]. It is considered as auspicious and is a part of Hindu rituals. It is used extensively in Ayurveda, Unani and Siddha systems of medicine as a home remedy for various diseases[2,3] such as biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis[4]. A paste of powdered turmeric with slaked lime is used for treatment of sprains and swelling caused by the injury, applied locally over the affected area. Turmeric powder is also used orally for the treatment of sore throat[2]. It is an aromatic stimulant, cooling agent, carminative in cases of diarrhea, intermittent fever.

The powder is an official reagent in British pharmacopoeia for testing alkalinity[5]. Tincture of curcumin is included in Indian Pharmaceutical Codex 1953. For the last few decades, extensive work has been done to establish the biological activities and pharmacological actions of turmeric and its extracts. Curcumin (diferuloylmethane), the main yellow bioactive component of turmeric has been shown to have a wide spectrum of biological actions. These include its anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant, anti-fertility, anti-diabetic, anti-bacterial, anti-fungal, anti-protozoal, anti-viral, anti-fibrotic, anti-venom, anti-ulcer, hypotensive and hypocholesteremic activities. Its anti-cancer effect is mainly mediated through induction of apoptosis. Its anti-inflammatory, anti-cancer and anti-oxidant roles may be clinically exploited to control rheumatism, carcinogenesis and oxidative stress-related pathogenesis. Clinically, curcumin has already been used to reduce post-operative inflammation. Safety evaluation studies indicate that both turmeric and curcumin are well tolerated at a very high dose without any toxic effects. Thus curcumin have the potential for the development of modern medicine for the treatment of various diseases.

Taxonomic position of the turmeric described by Linnaeus is as follows

Class : Lilipsida
Subclass : Commelinds
Order : Zingiberales
Family : Zingeberaceae
Genus : *Curcuma*
Species : *Curcuma longa*

CHEMICAL COMPOSITION[6-8]:

Turmeric contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%). The essential oil (5.8%) obtained from steam distillation of rhizomes contains α-phellandrene (1%) sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberine (25%) and sesquiterpines (53%). Curcuminioids (2-5%) oleoresins derived from ethanolic extraction are responsible for yellow colour. Curcuminioids mainly comprise of curcumin I (Freuloyl methane-77%) curcumin II (Demethoxy curcumin; 17%) curcumin III (Bis Demethoxy curcumin; 3%), cyclo curcuminoid. Another water soluble 5-κDa peptide and turmerin was isolated from turmeric and found to be efficient antioxidant/DNA protectent / antimutagen properties. Extensive research has been carried on curcumin as it is safe up to 8 gm/day.

CHARACTERISTIC OF CURCUMIN:

Physiochemical properties:

Curcumin was first isolated in 1815[9] and the chemical structure was determined by Roughley and Whiting in 1973[10]. It is soluble in ethanol, acetone, chloroform, dimethyl formamide, dimethyl sulfoxide. Its melting point is 176-177^{0}C. t forms reddish brown salt with alkali. Curcumin is a bis α,β, unsaturated β- diketone. Curcumin exhibits keto-enol tautomeric forms. In neutral and acidic condition curcumin exhibits bis keto form. In acidic condition curcumin acts as a powerful hydrogen donor[11]. In basic pH above 8 enolate form of the curcumin predominates and acts as a powerful electron donor a mechanism more typical for antioxidants[11].

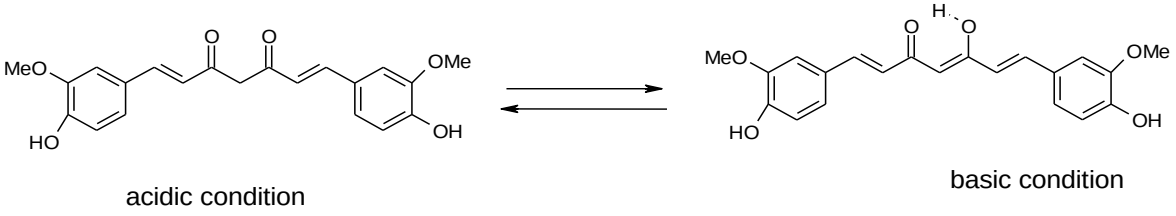

Figure 1: Curcumin in acidic and basic conditions.

Degradation of curcumin in basic pH has been reported by Wang et al (1997)[12]. The degradation kinetics of curcumin under various pH conditions and the stability of curcumin in physiological matrices have been demonstrated.(Figure 1) Curcumin was found to undergo degradation up to 90% in serum free 0.1 M phosphate buffer of pH 7.2 at 37^0 C. The decomposition of curcumin was pH dependent and occurs faster under neutral and basic pH condition. Curcumin showed more stability in cell culture medium containing 10% fetal calf serum and also in human blood; less than 20% curcumin decomposed with in 1 hr and about 50% of curcumin was remained after

8 hr. The major degradation product were found to be trans 6(4'- hydroxyl-3' methoxy phenyl) 2, 4, dioxo 5 hexenal and vanillin ferulic acid ferloylmethane were identified as minor degradation products. Further the stability of curcumin can be improved by lowering the pH or by the addition of glutathione, N-acetyl-L cysteine, ascorbic acid and rat liver microsomes. Vanillin, the degraded product of curcumin, a naturally occurring flavoring agent has antimutagenic properties in bacterial and in mammalian cells and vanillin is also a powerful scavenger of superoxide and hydroxyl radical[12].

Pharmacokinetic properties:

Curcumin is reported to have poor bioavailability though it is lipophilic in nature. About 75% of dose was excreted unchanged when given orally a dose of 1 g/kg to the rats. Negligible amount of curcumin appeared in the urine [13]. Another study conducted on rats showed that on oral administration of the [^{3}H] curcumin led to about 89% of radioactivity being excreted in feces and 6% in the urine. The i.p administration of curcumin showed that 73% of radioactivity was found in feces and 11% was in bile [14]. These studies show that curcumin poorly absorbed from the gut coupled with high degree of metabolism of curcumin in rat liver[14] and humans[15]. An i.v administration of curcumin resulted in the excretion of dose more than 50% through bile, suggesting that the curcumin follows entero hepatic circulation after biotransformation [16].

Studies also reveal that curcumin undergoes o-conjugation to curcumin glucuronide and curcumin sulfate and bioreduction to tetrahydro curcumin, hexahydro curcumin and hexahydro curcuminol in rats and humans [17]. Furthermore, the same study showed that in human intestinal fractions, conjugation of curcumin with activated sulfuric and glucoronic acid was much more abundant whereas conjugation in human hepatic fractions was much less extensive than in rat tissue. The degradation pattern is shown below [17](Figure 2).

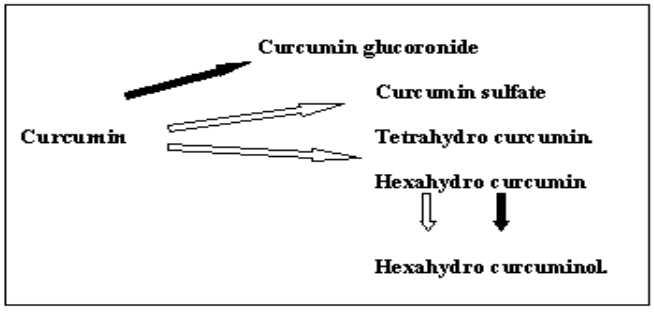

Figure 2: Schematic representation of metabolism of curcumin in intestinal hepatic cytosol (open arrow) and microsomes (closed arrow).

Tetrahydro curcumin, a metabolite was found to be more potent than curcumin in the carregeenin-induced rat paw edema test for anti-inflammatory activity [18] and less potent than curcumin as an inhibitor of phorbol 12 myristate 13 acetate induced tumor promotion in mouse skin[18]. Further studies on metabolites, curcumin sulfate, curcumin glucuronide, tetrahydro curcumin, hexahydro curcumin and hexahydro curcuminol showed lesser potency as their metabolic progenitor curcumin [18]. It can be concluded that curcumin metabolism in intestine generates metabolites devoid of biological activities towards cancer chemoprevention and less potent then their metabolic precursor.

USES OF CURCUMIN

The use of turmeric for health purposes is nothing new. As a folklore medicine, its use has been documented in both Indian and Chinese cultures. The long list of uses include anti-septic, analgesic, anti-inflammatory, anti-oxidant, anti-malarial, insectrepellant, and other activities associated to turmeric[19–27]. Perhaps one of the most often prescribed uses is for wound-healing[28]. This activity is well known to people from the Indian subcontinent. Modern research has provided considerable evidence, and the mechanism by which turmeric/curcumin could accelerate wound-healing has been described[29–36]. It is now well recognized that most chronic diseases are the result of disregulated inflammation[37,38]. Turmeric has been traditionally described as an anti-inflammatory agent. Recent scientific evidence has indeed demonstrated that turmeric, and curcumin in particular, exhibits potent anti-inflammatory activities as determined by a wide variety of systems[39–49]. Therefore, it is not too surprising that turmeric displays activities against a variety of diseases. Because curcumin also exhibits potent anti-oxidant activity, whether the anti-inflammatory activity of curcumin is mediated through its anti-oxidant mechanism is not clear. Since most well-characterized antioxidants do not exhibit anti-inflammatory activity, it is unlikely that the anti-inflammatory activity of curcumin is due to its anti-oxidant activity.

Anti-tumor activity of curcumin

Curcumin is proved its anticancer properties in various cell lines [50-55], animal models [56-62] and also in humans[63]. The exact mechanism of action of curcumin is not yet explored. Curcumin is proposed to suppress number of key elements in cell signal transduction pathways relevant to growth the differentiation and malignant transformation. Among cell signaling events inhibited by the curcumin are protein kinase[64], c-Jun/AP-1 activation [65] (c2), prostaglandin biosynthesis [66-68], glutathione S-transferase P1-1 (GSTP1-1) [69-70], down regulation of Bcl-XL and IAP, release

of cytochrome C and inhibition of Akt [71], up regulation of capsase 8, capsase 3 and capsase 9 [72], inducing tumor necrosis factor- related apoptosis-inducing ligand (TRAIL) [73] , epithelial growth factor receptor (GFTR)[74-75] and inhibition of nuclear factor kB (NFkB) by activation of IkBα[76-77] are few of them.

Curcumin also has been reported show different helpful activities including anti-coagulant activiy[78], anti-fertility[79], anti-diabetic[80], anti-microbial[81], anti-fungal[82], anti-protozoal[83-84] and anti-viral[85]. Curcumin can also be used for treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease.

Anti -inflammatory activity of curcumin

Inflammatory Bowel Disease (IBD) refers to a group of diseases that principally affect the small and large intestines and is characterized by chronic inflammation of unknown etiology. The two major and relatively well-defined clinical entities are ulcerative colitis and Crohn's disease. Ulcerative colitis is confined to the colon and is characterized by a chronic but superficial inflammatory process that always involves the distal portion and extends in a continuous fashion for a variable length proximally. Crohn's disease can affect both the small and the large intestine. Inflammation is focal but can affect all layers of the bowel wall and can be associated with several transluminal complications including abscesses and fistulae [86]

Anti-diabetic effect

Curcumin prevents galactose-induced cataract formation at very low doses[87]. Both turmeric and curcumin decrease blood sugar level in alloxan-induced diabetes in rat[88]. Curcumin also decreases advanced glycation end productsinduced complications in diabetes mellitus[89].

Anti-fertility activity

Petroleum ether and aqueous extracts of turmeric rhizomes show 100% anti-fertility effect in rats when fed orally[90]. Implantation is completely inhibited by these extracts[91]. Curcumin inhibits 5*a*-reductase, which converts testosterone to 5*a*-dihydrotestosterone, thereby inhibiting the growth of flank organs in hamster[92]. Curcumin also inhibits human sperm motility and has the potential for the development of a novel intravaginal contraceptive[93].

Anti-microbial activity of curcumin

Curcumin have antibacterial activity. Both curcumin and the oil fraction suppress growth of several bacteria like *Streptococcus*, *Staphylococcus*, *Lactobacillus*,etc.[94]. The aqueous extract of turmeric rhizomes has antibacterial effects[95]. Curcumin also prevents growth of *Helicobacter pylori* CagA+ strains *in vitro*[96].

Ether and chloroform extracts and oil of *C. longa* have antifungal effects[97-99]. Crude ethanol extract also possesses anti-fungal activity[100]. Turmeric oil is also active against *Aspergillus flavus, A. parasiticus*, *Fusarium moniliforme* and *Penicillium digitatum*[101].

Curcumin has been proved for anti-protozoal activity. The ethanol extract of the rhizomes has anti-*Entamoeba histolytica* activity. Curcumin has anti-*Leishmania* activity *in vitro*[102]. Several synthetic derivatives of curcumin have anti-*L. amazonensis* effect[103]. Anti-*Plasmodium falciparum* and anti-*L. major* effects of curcumin have also been reported[104].

Curcumin has been shown to have anti-viral activity[105]. It acts 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[106]. 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 h after treatment in these cells, which is effectively blocked by curcumin[106]. Most importantly, curcumin also shows anti-HIV (human immunodeficiency virus) activity by inhibiting the HIV-1 integrase needed for viral replication[107-108]. It also inhibits UV lightinduced HIV gene expression[109]. Thus curcumin and its analogues may have the potential for novel drug development against HIV.

Anti-venom effect

Ar-turmerone, isolated from *C. longa*, neutralizes both haemorrhagic activity of *Bothrops* venom and 70% lethal effect of *Crotalus* venom in mice. It acts as an enzymatic inhibitor of venom enzymes with proteolytic activities[110].

Anti-coagulant activity

Curcumin shows anticoagulant activity by inhibiting collagen and adrenaline-induced platelet aggregation *in vitro* as well as *in vivo* in rat thoracic aorta[111].

CLINICAL STUDIES AND MEDICINAL APPLICATIONS OF CURCUMIN

Although various studies have been carried out with turmeric extracts and some of its ingredients in several animal models[112-114]. Only a few clinical studies are reported so far. In patients undergoing surgery, oral application of curcumin reduces post-operative inflammation[115]. Recently, curcumin has been formulated as slow-release biodegradable microspheres for the treatment of inflammation in arthritic rats. It is evident from the study that curcuminbiodegradable microspheres could be successfully employed for therapeutic management of inflammation[116].

SAFETY EVALUATION WITH CURCUMIN

Curcumin was given to Wistar rats, guinea pigs and monkeys of both sexes at a dose of 300 mg/kg body wt. No pathological, behavioural abnormalities or lethality was observed[114]. No adverse effects were observed on both growth and the level of erythrocytes, leucocytes, blood constituents such as haemoglobin, total serum protein, alkaline phosphatase, etc.[117]. Human clinical trials also indicate that curcumin has no toxicity when administered at doses of 1–8 g/day[118] and 10 g/day[118].

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