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REVIEW ARTICLE

Curcumin: A Potential Bioactive Agent

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ABSTRACT

Curcumin (diferuloylmethane), the main yellow bioactive component of turmeric has shown a wide spectrum of biological actions. Clinically, curcumin has already been used to reduce post-operative inflammation. Safety evaluation studies indicate that curcumin is well tolerated at a very high dose without any toxic effects. Moreover, curcumin have the potential for the development of modern medicine for the treatment of various diseases. This review paper serves to highlight the extensive work done to establish the biological and pharmacological actions, safety and stability aspects along with the structure and possible modifications in curcumin to enhance its bioeffectiveness.

Keywords: Curcumin, anticancer, bioavailability, anti-inflammation, antiviral

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INTRODUCTION

Curcumin is the active ingredient in the herbal remedy and dietary spice turmeric (Curcuma longa Linn). Curcumin was identified to be responsible for most of the biological effects of turmeric [1].This vibrant yellow spice, derived from the rhizome of the plant, has a long history of use in traditional medicines of China and India [2]. Use of curcumin as a folk remedy continues today. As part of the ancient Indian medical system, ayurveda, a poultice of turmeric paste is used to treat common eye infections, and to dress wounds, treat bites, burns, acne and various skin diseases [3]. In Northern India, women are given a tonic of fresh turmeric paste with powder of dried ginger roots and honey in a glass of hot milk to drink twice daily after childbirth. A poultice of turmeric is also applied to the perineum to aid in the healing of any lacerations in the birth canal [4]. Powdered turmeric is taken with boiled milk to cure cough and related respiratory ailments [3] and roasted turmeric is an ingredient used as an antidysenteric for children [3]. This ancient remedy is also used to treat dental diseases, digestive disorders such as dyspepsia and acidity, indigestion, flatulence, ulcers, as well to alleviate the hallucinatory effects of hashish and other psychotropic drugs [5]. In food and manufacturing, curcumin is currently used in perfumes and as a natural yellow coloring agent, as well as an approved food additive to flavor various types of curries and mustards [5-6]. Recent emphasis on the use of natural and complementary medicines in Western medicine has drawn the attention of the scientific community to this ancient remedy.

CHEMICAL COMPOSITION OF TURMERIC

Turmeric contains a number of phytoconstituents namely protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%). The essential oil (5.8%) obtained by steam distillation of rhizomes has *α*-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%) [7]. Curcumin (diferuloylmethane) (3–4%) is responsible for the yellow colour, and comprises curcumin I (94%), curcumin II (6%) and curcumin III (0.3%) [8]. Demethoxy and bisdemethoxy derivatives of curcumin have also been isolated. Curcumin was isolated in 1815 and its chemical structure was determined by Roughly and Whiting [9] in 1973. It has a melting point at 176–177°C; forms a reddish-brown salt with alkali and is soluble in ethanol, alkali, ketone, acetic acid and chloroform.

PHARMACOLOGICAL ACTION OF CURCUMIN

Effect on cardiovascular system (CVS)

Curcumin protects from damage caused by myocardial infarction [10] by decreasing the severity of pathological changes. Curcumin improves Ca^{2+} transport from the cardiac muscle sarcoplasmic reticulum, thereby raising the possibility of pharmacological interventions to correct the defective Ca^{2+} homeostasis in the cardiac muscle [11]. Curcumin has significant hypocholesteremic effect in hypercholesteremic rats [12]. Oral administration of curcumin

significantly decreases the lipid peroxides (33%), increased HDL cholesterol (29%), decreased total serum cholesterol (11-12%) [13].

Effect on gastrointestinal system (GI)

Stomach: Turmeric powder has beneficial effect on the stomach. It increases mucin secretion in rabbits and may thus act as gastroprotectant against irritants [14]. Controversy exists regarding antiulcer activity of curcumin. Both antiulcer [15] and ulcerogenic [16-17] effects of curcumin have been reported but detailed study is still required. Curcumin has been shown to protect the stomach from ulcerogenic effects of phenylbutazone in guinea pigs at 50 mg/kg dose [18-19]. It also protects from 5-hydroxytryptamine-induced ulceration at 20 mg/kg dose [18-19]. However, small concentration of 0.5% curcumin failed to protect against histamine-induced ulcers [20].

Intestine: Curcumin has some pharmacological effects on the intestine also. Antispasmodic activity of sodium curcuminate was observed in isolated guinea pig ileum [21]. Anti-flatulent activity was also observed in both *in vivo* and *in vitro* experiments in rats [22]. Curcumin also enhances intestinal lipase, sucrase and maltase activity [23].

Liver: Curcumin and its analogues have protective activity in cultured rat hepatocytes against carbon tetrachloride (CCl_4), D-galactosamine, peroxide and ionophore-induced toxicity [24]. Curcumin also protects against diethyl nitrosamine and 2-acetylaminofluorine-induced altered hepatic foci development [25]. Increased level of bile was reported in dogs by both curcumin [26].

Pancreas: Curcumin increases the activity of pancreatic lipase, amylase, trypsin and chymotrypsin [27]. A synthetic derivative of *p*-tolylmethylcarbinol (an ingredient of *C*. *longa*) 1-phenyl-1-hydroxy-*n*-pentane increases bicarbonate levels as well as plasma secretion [28].

Effect on nervous system

Curcumin and its complex with manganese offer protective action against vascular dementia by exerting antioxidant activity [29-30]. Curcumin also reduces oxidized proteins in amyloid pathology in Alzheimer transgenic mice [31]. It also decreases lipid peroxidation in rat liver microsomes, erythrocyte membranes and brain homogenates [32].

BIOLOGICAL ACTION OF CURCUMIN

Turmeric plant extract (curcumin and other derivatives) have anti-inflammatory, anti-arthritic, antioxidant, anti-microbial, anti-leishmanial, hepato protective, anti-cancer, anti-ulcer and anti diabetic activity.

Anti-inflammatory agents

The water extracts of *C. longa* along with volatile oil, petroleum ether and alcohol shows anti-inflammatory effects [33]. The natural analogues of curcumin, i.e. FHM and BHM, are also potent anti-inflammatory agents. Curcumin is effective against carrageen induced oedema in rats [33] and mice [34]. Curcumin offers anti-inflammatory effect through inhibition of NF*k*B activation [35]. Curcumin has also been shown to reduce the TNF-*a*-induced expression of the tissue factor gene in bovine aortic-endothelial cells by repressing activation of both AP-1 and NF*k*B. The anti-inflammatory role of curcumin is also mediated through down regulation of cyclooxygenase-2 and inducible nitric oxide synthetase through suppression of NF*k*B activation [36].

Anti-cancer activity

Anti-cancer activity of curcuma is by inhibiting tumour cell proliferation, induction of analysis, inhibition of transformation of normal cells to tumour cells and inhibition of invasion of metastasis. A number of animal studies have shown that curcumin has a dose-dependent chemopreventive effect in colon, duodenal, stomach, esophageal and oral carcinogenesis [37]. Colon carcinoma is prevented by curcumin through arrest of cell-cycle progression independent of inhibition of prostaglandin synthesis [38]. Curcumin was an effective cytotoxic agent against the mouse bladder tumor line MBT-2 and the UMUC human bladder tumor cell line, and effectively inhibited implantation and growth of bladder tumor cells in C3H mice [39]. Curcumin inhibits cancer development in rat stomach initiated by Nmethyl- N-nitro-N-nitrosoguanisine (MNNG) [40] and reduces the incidence and/or multiplicity of esophageal tumors and preneoplastic lesions in rats with N-nitrosomethylbenzylamine-induced esophageal carcinogenesis [41].

Anti-coagulant activity

By inhibiting collagen and adrenaline-induced platelet aggregation Curcumin shows anticoagulant activity both *in vitro* as well as *in vivo* in rat thoracic aorta [42].

Anti-fibrotic effect

Curcumin suppresses bleomycin-induced pulmonary fibrosis in rats [43]. It also suppresses bleomycin-induced alveolar macrophage-production of TNF-*a*, superoxide and nitric oxide. Thus curcumin acts as a potent anti-fibrotic agent. Oral administration of curcumin at 300 mg/kg dose inhibits bleomycin-induced pulmonary fibrosis by increase in total cell counts and biomarkers of inflammatory responses.

Anti-mutagenic activity

Curcumin has shown the reduction in the number of aberrant cells in cyclophosphamide-induced chromosomal aberration with the dose of 100 and 200 mg/kg body wt in Wistar rats [44]. Curcumin exerts both pro- mutagenic and anti-mutagenic effects. Curcumin has also been shown to be non-protective against hexavalent chromium-induced DNA strand break. In fact, the total effect of chromium and curcumin is additive in causing DNA breaks in human lymphocytes and gastric mucosal cells [45].

Anti-fertility activity

100% anti-fertility effect has been observed with aqueous extracts of turmeric rhizomes in rats on oral administration [46]. Curcumin inhibits 5*a*-reductase, which converts testosterone to 5*a*-dihydrotestosterone, thereby inhibiting the growth of flank organs in hamster [47]. Ability of curcumin to inhibit human sperm motility has developed the potential for its application in the development of novel intra-vaginal contraceptive [48].

Anti-bacterial activity

Growth of several bacteria like *Streptococcus*, *Staphylococcus and Lactobacillus* [22] could be suppressed by curcumin. The aqueous extract of turmeric rhizomes has reported the antibacterial effects [49]. *In vitro* growth of *Helicobacter pylori* can also be prevented by the use of curcumin [50].

Anti-diabetic effect

Curcumin decreases advanced glycation end products induced complications in diabetes mellitus [51]. At very low doses, curcumin prevents galactose-induced cataract formation [52]. Curcumin decrease blood sugar level in alloxan-induced diabetes in rat [53]. Curcumin also reduces oxidative stress in diabetic induced rats having increased NADPH/NADP ratio as well as increased activity of oxidative enzymes [54].

Anti-protozoan activity

In vitro curcumin has anti-*Leishmania* activity [55]. Several synthetic derivatives of curcumin have anti- *Leishmania*. *amazonensis* effect [56]. Anti-*Plasmodium falciparum* and anti-*Leishmania major* effects of curcumin have also been reported [57].

Anti-viral effect

Curcumin 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 [58]. 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 [58]. Therefore, curcumin has been shown to have antiviral activity. More importantly, curcumin also shows anti-HIV (human immunodeficiency virus) activity by inhibiting the HIV-1 integrase needed for viral replication [59-60]. It also inhibits UV light-induced HIV gene expression [61]. Thus curcumin and its analogues may have the potential for novel drug development against HIV.

BIOAVAILABILITY ASPECTS OF CURCUMIN

Curcumin has got poor bioavailability but is remarkably well tolerated and does not appear to be toxic to animals [62] or humans [63] even at high doses. Curcumin has also been measured in human tissue, i.e. in the liver and portal blood of 12 patients undergoing resection of hepatic metastases of colorectal cancer. They administer dose of 450 – 3600 mg curcumin daily for 1 week prior to surgery [64]. Low nano-molar levels of curcumin and its metabolites, curcumin glucuronide and curcumin sulfate, were detected in portal serum of all 3 patients who received 3600 mg of curcumin. Metabolic reduction products of curcumin (hexahydrocurcumin and hexahydrocurcuminol) were found in the liver of 1 patient. Therefore, the researchers concluded that the bioavailability of curcumin is poor in tissues remote from the gastrointestinal tract, including the liver.

An independent dose-escalation study on 15 patients with advanced colorectal cancer was conducted in the United Kingdom [65]. Patients consumed a single daily dose of 440 – 2200 mg curcuma extract, equivalent to 36 –180 mg curcumin, for up to 4 months. The treatment was well tolerated and there was no dose-limiting toxicity. Lao et al. studies also gave a similar result in healthy human volunteers consuming a single dose of curcumin ranging from 500 to 12,000 mg [66]. No dose-limiting toxicities were observed, and low levels of curcumin were only detected in the serum receiving the highest doses of curcumin (10,000 or 12,000 mg/day). Interestingly, curcumin was only detected in 2 of these 6 patients, perhaps indicating the existence of genetic modifiers of curcumin metabolism.

STABILITY ASPECTS OF CURCUMIN

The stability of curcumin toward chemical degradation by alkali has been investigated by several laboratories with varying results, possibly due to differences in the media used [67-70]. Tonnesen et al. [68] identified degradation products including ferulic acid and feruloylmethane, and studied kinetics of degradation in a MeOH/aqueous buffer medium (1:9), with phosphate buffer (pH 6 – 9) or carbonate buffer (pH 9 – 10). The rate behavior was complex showing several peaks and valleys in the 7 – 10 pH regimes, showing second order rate kinetics in curcumin. Wang et al. [69] found that curcumin decomposed 90% within 30 min in 0.1 M phosphate buffer at pH 7.2 at 378C, and tentatively identified the decomposition product trans-6-(4_-hydroxy-3_-methoxyphenyl)-2,4-dioxo-5-hexenal, from which they identified vanillin as a final product along with ferulic acid and feruloylmethane.

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STRUCTURAL ASPECTS OF CURCUMIN

Curcumin is a lipophilic molecule and rapidly permeates cell membranes [71]. Curcumin was found to affect the structure and function of cellular membranes and mimic typical events occurring during apoptosis; however, the cellular response to curcumin contrasted with typical apoptotic cell death because loss of membrane integrity was immediate, partly reversible, and cells could recover in a relatively short time [71]. To overcome its limited water solubility, a number of new approaches have been explored to deliver curcumin effectively, such as liposome encapsulation [72-73]. Arezzini et al. [74] has sought to improve solubility by modifying the structure by covalent linking of a sugar to curcumin and have studied its potential as an agent for treatment of iron-overload disease. Metal ion complexation of curcumin, those with the cations $[VO]^{2+}$ [75,76], Mn^{2+} [77,78], $Fe^{2+/3+}$ [79-82] and Cu^{2+} [83-85] have findings of particular biological interest.

CONCLUSION

On the basis of various literatures survey, curcumin was considered to be an effective bioactive agent. The low water solubility and poor bioavailability of curcumin can be overcome by various structural modifications. Stability aspect shows better effect and less toxicity offering better pharmacodynamic characteristics. A lot of work has been done and a lot to do in this field.

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