Turmeric and curcumin: Biological actions and medicinal applications

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Turmeric (*Curcuma longa*) is extensively used as a spice, food preservative and colouring material in India, China and South East Asia. It has been used in traditional medicine as a household remedy for various diseases, including biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis. 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, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, antifertility, antidiabetic, antibacterial, antifungal, antiprotozoal, antiviral, antifibrotic, antivenom, antiulcer, hypotensive and hypocholesteremic activities. Its anticancer effect is mainly mediated through induction of apoptosis. Its antiinflammatory, anticancer and antioxidant 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, both turmeric and curcumin have the potential for the development of modern medicine for the treatment of various diseases.

INDIA has a rich history of using plants for medicinal purposes. Turmeric (*Curcuma longa* L.) is a medicinal plant extensively used in Ayurveda, Unani and Siddha medicine as home remedy for various diseases[1,2]. *C. longa* L., botanically related to ginger (Zingiberaceae family), is a perennial plant having a short stem with large oblong leaves and bears ovate, pyriform or oblong rhizomes, which are often branched and brownish-yellow in colour. Turmeric is used as a food additive (spice), preservative and colouring agent in Asian countries, including China and South East Asia. It is also considered as auspicious and is a part of religious rituals. In old Hindu medicine, it is extensively used for the treatment of sprains and swelling caused by injury[1]. In recent times, traditional Indian medicine uses turmeric powder for the treatment of biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis[3]. In China, *C. longa* is used for diseases associated with abdominal pains[4]. The colouring principle of turmeric is the main component of this plant and is responsible for the antiinflammatory property.

Turmeric was described as *C. longa* by Linnaeus and its taxonomic position is as follows:

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

The wild turmeric is called *C. aromatica* and the domestic species is called *C. longa*.

Chemical composition of turmeric

Turmeric contains 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%)[5]. Curcumin (diferuloylmethane) (3–4%) is responsible for the yellow colour, and comprises curcumin I (94%), curcumin II (6%) and curcumin III (0.3%)[6]. Demethoxy and bisdemethoxy derivatives of curcumin have also been isolated[7] (Figure 1). Curcumin was first isolated[8] in 1815 and its chemical structure was determined by Roughley 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.

Biological activity of turmeric and its compounds

Turmeric powder, curcumin and its derivatives and many other extracts from the rhizomes were found to be bioactive (Table 1). The structures of some of these compounds[4] are presented in Figure 1. Turmeric powder has healing effect on both aseptic and septic wounds in rats and rab-

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bits[10]. It also shows adjuvant chemoprotection in experimental forestomach and oral cancer models of Swiss mice and Syrian golden hamsters[11]. Curcumin also increases mucin secretion in rabbits[12]. Curcumin, the ethanol extract of the rhizomes, sodium curcuminate, [feruloyl-(4-hydroxycinnamoyl)-methane] (FHM) and [bis-(4-hydroxycinnamoyl)-methane] (BHM) and their derivatives, have high antiinflammatory activity against carrageenin-induced rat paw oedema[13,14]. Curcumin is also effective in formalin-induced arthritis[13]. Curcumin reduces intestinal gas formation[15] and carbon tetrachloride and D-galactosamine-induced glutamate oxaloacetate transaminase and glutamate pyruvate transaminase levels[16,17]. It also increases bile secretion in anaesthetized dogs [18] and rats[19], and elevates the activity of pancreatic lipase, amylase, trypsin and chymotrypsin[20]. Curcumin protects isoproterenol-induced myocardial infarction in rats[21]. Curcumin, FHM and BHM also have anticoagulant activity[22,23]. Curcumin and an ether-extract of *C. longa* have hypolipemic action in rats[24] and lower cholesterol, fatty acids and triglycerides in alcohol-induced toxicity[25]. Curcumin is also reported to have antibacterial[15], antiamoebic[26] and antiHIV[27] activities. Curcumin also shows antioxidant activity[28–31]. It also shows antitumour[32–34] and anticarcinogenic[35–38] activities. The volatile oil of *C. longa* shows antiinflammatory[39], antibacterial[40,41] and antifungal[41] activities. The petroleum ether extract of *C. longa* is reported to have antiinflammatory activity[42]. Petroleum ether and aqueous extracts have 100% antifertility effects in rats[43]. Fifty per cent ethanolic extract of *C. longa* shows hypolipemic action[44] in rats. Ethanolic extract also possesses antitumour activity[45]. Alcoholic extract and sodium curcuminate can also offer antibacterial activity[15,18]. The crude ether and chloroform extracts of *C. longa* stem are also reported to have antifungal effects[46]. A *C. longa* fraction containing ar-turmerone has potent antivenom activity[47].

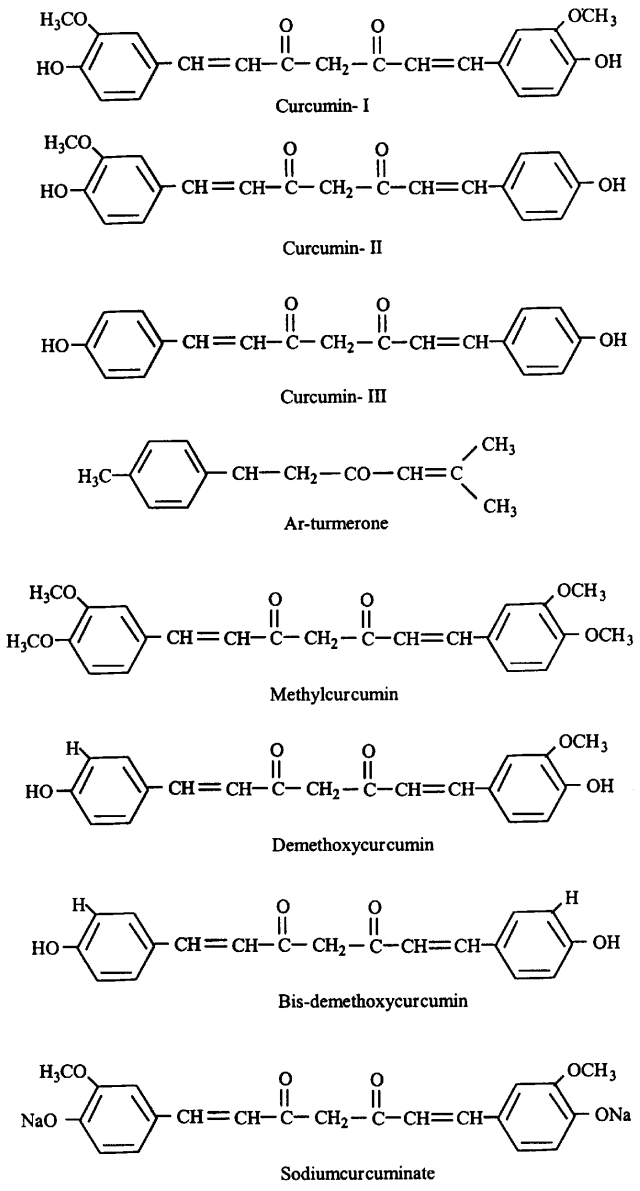

Figure 1. Structure of natural curcuminoids.

Pharmacological action of turmeric and its extract

Several pharmacological activities and medicinal applications of turmeric are known[1,2,4]. Although curcumin has been isolated in the 19th century, extracts of the rhizomes of *C. longa* have been in use from the Vedic ages[1,48]. Some of the medicinal applications[3] of turmeric are mentioned in Table 2.

Pharmacological action of curcumin

Effect on gastrointestinal system

Stomach: Turmeric powder has beneficial effect on the stomach. It increases mucin secretion in rabbits and may thus act as gastroprotectant against irritants[12]. However, controversy exists regarding antiulcer activity of curcumin. Both antiulcer[49] and ulcerogenic[50,51] effects of curcumin have been reported but detailed studies are still lacking. Curcumin has been shown to protect the stomach from ulcerogenic effects of phenylbutazone in guinea pigs at 50 mg/kg dose[52,53]. It also protects from 5-hydroxytryptamine- induced ulceration at 20 mg/kg dose[52,53]. However, when 0.5% curcumin was used, it failed to protect against histamine-induced ulcers[54]. In fact, at higher doses of 50 mg/kg and 100 mg/kg, it produces ulcers in rats[51]. Though the mechanism is not yet clear, an increase in the gastric acid and/or pepsin secretion and reduction in mucin content have been implicated in the induction of gastric ulcer[55]. Recent studies in our laboratory indicate that curcumin can block indomethacin, ethanol and stress-induced gastric ulcer and can also prevent pylorus-ligation-induced acid secre-

tion in rats. The antiulcer effect is mediated by scavenging of reactive oxygen species by curcumin (unpublished observation).

Intestine: Curcumin has some good effects on the intestine also. Antispasmodic activity of sodium curcuminate was observed in isolated guinea pig ileum[14]. Antiflatulent activity was also observed in both *in vivo* and *in vitro* experiments in rats[15]. Curcumin also enhances intestinal lipase, sucrase and maltase activity[56].

Liver: Curcumin and its analogues have protective activity in cultured rat hepatocytes against carbon tetrachloride, D-galactosamine, peroxide and ionophore-induced toxicity[17,30,57]. Curcumin also protects against diethylnitrosamine and 2-acetylaminofluorine-induced altered hepatic foci development[58]. Increased bile production was reported in dogs by both curcumin and essential oil of *C. longa*[19,59].

Pancreas: 1-phenyl-1-hydroxy-*n*-pentane, a synthetic derivative of *p*-tolylmethylcarbinol (an ingredient of *C. longa*) increases plasma secretion and bicarbonate levels[60]. Curcumin also increases the activity of pancreatic lipase, amylase, trypsin and chymotrypsin[20].

Table 1. Biological activity of turmeric and its compounds

Compound/extract	Biological activity	Reference
Turmeric powder	Wound-healing	10
Ethanol extract	Antiinflammatory	71
	Hypolipemic	44
	Antitumour	45
	Antiprotozoan	26
Petroleum ether extract	Antiinflammatory	71
	Antifertility	43
Alcoholic extract	Antibacterial	15
Crude ether extract	Antifungal	46
Chloroform extract	Antifungal	46
Aqueous extract	Antifertility	43
Volatile oil	Antiinflammatory	39
	Antibacterial	15
	Antifungal	41
Curcumin	Antibacterial	40
	Antiprotozoan	15
	Antiviral	27
	Hypolipemic	24
	Hypoglycemic	110
	Anticoagulant	23
	Antioxidant	77,79
	Antitumour	97,98
	Anticarcinogenic	91
Ar-turmerone	Antivenom	47
Methylcurcumin	Antiprotozoan	123
Demethoxycurcumin	Antioxidant	29
Bisdemethoxycurcumin	Antioxidant	29
Sodium curcuminate	Antiinflammatory, antibacterial	18

Table 2. Medicinal properties of turmeric

Turmeric finds medicinal applications in	Anaemia, atherosclerosis, diabetes, oedema, haemorrhoids, hepatitis, hysteria, indigestion, inflammation, skin disease, urinary disease, wound and bruise healing, psoriasis, anorexia, cough, liver disorders, rheumatism, sinusitis

Effect on cardiovascular system

Curcumin decreases the severity of pathological changes and thus protects from damage caused by myocardial infarction[21]. Curcumin improves Ca^{2+}-transport and its slippage from the cardiac muscle sarcoplasmic reticulum, thereby raising the possibility of pharmacological interventions to correct the defective Ca^{2+} homeostasis in the cardiac muscle[61]. Curcumin has significant hypocholesteremic effect in hypercholesteremic rats[62].

Effect on nervous system

Curcumin and manganese complex of curcumin offer protective action against vascular dementia by exerting antioxidant activity[63,64].

Effect on lipid metabolism

Curcumin reduces low density lipoprotein and very low density lipoprotein significantly in plasma and total cholesterol level in liver alongwith an increase of α-tocopherol level in rat plasma, suggesting *in vivo* interaction between curcumin and α-tocopherol that may increase the bioavailability of vitamin E and decrease cholesterol levels[65]. Curcumin binds with egg and soy-phosphatidylcholine, which in turn binds divalent metal ions to offer antioxidant activity[66]. The increase in fatty acid content after ethanol-induced liver damage is significantly decreased by curcumin treatment and arachidonic acid level is increased[67].

Anti-inflammatory activity

Curcumin is effective against carrageenin-induced oedema in rats[13,14,68,69] and mice[70]. The natural analogues of curcumin, viz. FHM and BHM, are also potent antiinflammatory agents[14]. The volatile oil[39] and also the petroleum ether, alcohol and water extracts of *C. longa* show antiinflammatory effects[71]. The antirheumatic activity of curcumin has also been established in patients who showed significant improvement of symptoms after administration of curcumin[72]. That curcumin stimulates stress-induced expression of stress proteins and may act in a way similar

to indomethacin and salicylate, has recently been reported[73]. Curcumin offers antiinflammatory effect through inhibition of NFκB activation[74]. Curcumin has also been shown to reduce the TNF-α-induced expression of the tissue factor gene in bovine aortic-endothelial cells by repressing activation of both AP-1 and NFκB[75]. The antiinflammatory role of curcumin is also mediated through downregulation of cyclooxygenase-2 and inducible nitric oxide synthetase through suppression of NFκB activation[34]. Curcumin also enhances wound-healing in diabetic rats and mice[76], and in H_2O_2-induced damage in human keratinocytes and fibroblasts[31].

Antioxidant effect

The antioxidant activity of curcumin was reported[77] as early as 1975. It acts as a scavenger of oxygen free radicals[6,78]. It can protect haemoglobin from oxidation[29]. *In vitro*, curcumin can significantly inhibit the generation of reactive oxygen species (ROS) like superoxide anions, H_2O_2 and nitrite radical generation by activated macrophages, which play an important role in inflammation[79]. Curcumin also lowers the production of ROS *in vivo*[79]. Its derivatives, demethoxycurcumin and bis-demethoxycurcumin also have antioxidant effect[29,30]. Curcumin exerts powerful inhibitory effect against H_2O_2-induced damage in human keratinocytes and fibroblasts[31] and in NG 108-15 cells[80]. Curcumin reduces oxidized proteins in amyloid pathology in Alzheimer transgenic mice[81]. It also decreases lipid peroxidation in rat liver microsomes, erythrocyte membranes and brain homogenates[28]. This is brought about by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase[82]. Recently, we have observed that curcumin prevents oxidative damage during indomethacin-induced gastric lesion not only by blocking inactivation of gastric peroxidase, but also by direct scavenging of H_2O_2 and $^{\bullet}OH$ (unpublished observation). Since ROS have been implicated in the development of various pathological conditions[83–85], curcumin has the potential to control these diseases through its potent antioxidant activity.

Contradictory to the above-mentioned antioxidant effect, curcumin has pro-oxidant activity. Kelly *et al.*[86] reported that curcumin not only failed to prevent single-strand DNA breaks by H_2O_2, but also caused DNA damage. As this damage was prevented by antioxidant α-tocopherol, the pro-oxidant role of curcumin has been proved. Curcumin also causes oxidative damage of rat hepatocytes by oxidizing glutathione and of human erythrocyte by oxidizing oxyhaemoglobin, thereby causing haemolysis[87]. The pro-oxidant activity appears to be mediated through generation of phenoxyl radical of curcumin by peroxidase–H_2O_2 system, which cooxidizes cellular glutathione or NADH, accompanied by O_2 uptake to form ROS[87].

The antioxidant mechanism of curcumin is attributed to its unique conjugated structure, which includes two methoxylated phenols and an enol form of β-diketone; the structure shows typical radical-trapping ability as a chain-breaking antioxidant (Figure 1)[88,89]. Generally, the nonenzymatic antioxidant process of the phenolic material is thought to be mediated through the following two stages:

$$S\text{-}OO^{\circ} + AH \rightarrow SOOH + A^{\circ},$$

$$A^{\bullet} + X^{\bullet} \rightarrow \text{Nonradical materials},$$

where *S* is the substance oxidized, AH is the phenolic antioxidant, $A^{\bullet}$ is the antioxidant radical and $X^{\bullet}$ is another radical species or the same species[90] as $A^{\bullet}$. $A^{\bullet}$ and $X^{\bullet}$ dimerize to form the non-radical product. Masuda *et al.*[89] further studied the antioxidant mechanism of curcumin using linoleate as an oxidizable polyunsaturated lipid and proposed that the mechanism involves oxidative coupling reaction at the 3′position of the curcumin with the lipid and a subsequent intramolecular Diels–Alder reaction.

Anticarcinogenic effect – induction of apoptosis

Curcumin acts as a potent anticarcinogenic compound. Among various mechanisms, induction of apoptosis plays an important role in its anticarcinogenic effect. It induces apoptosis and inhibits cell-cycle progression, both of which are instrumental in preventing cancerous cell growth in rat aortic smooth muscle cells[91]. The antiproliferative effect is mediated partly through inhibition of protein tyrosine kinase and c-myc mRNA expression and the apoptotic effect may partly be mediated through inhibition of protein tyrosine kinase, protein kinase C, c-myc mRNA expression and bcl-2 mRNA expression[91]. Curcumin induces apoptotic cell death by DNA-damage in human cancer cell lines, TK-10, MCF-7 and UACC-62 by acting as topoisomerase II poison[92.] Recently, curcumin has been shown to cause apoptosis in mouse neuro 2a cells by impairing the ubiquitin–proteasome system through the mitochondrial pathway[93]. Curcumin causes rapid decrease in mitochondrial membrane potential and release of cytochrome *c* to activate caspase 9 and caspase 3 for apoptotic cell death[93]. Recently, an interesting observation was made regarding curcumin-induced apoptosis in human colon cancer cell and role of heat shock proteins (hsp) thereon[94]. In this study, SW480 cells were transfected with hsp 70 cDNA in either the sense or antisense orientation and stable clones were selected and tested for their sensitivity to curcumin. Curcumin was found to be ineffective to cause apoptosis in cells having hsp 70, while cells harbouring antisense hsp 70 were highly sensitive to apoptosis by curcumin as measured by nuclear condensation, mitochondrial transmembrane potential, release of cytochrome *c*, activation of caspase 3 and caspase 9 and other parameters for apoptosis[94]. Expression of glutathione S-transferase P1-1 (GSTP1-1) is correlated to carcinogenesis and curcumin has been shown to induce apoptosis in K562 leukaemia cells by inhibiting the expression of GSTP1-1 at transcription level[95]. The mechanism of cur-

cumin-induced apoptosis has also been studied in Caki cells, where curcumin causes apoptosis through down-regulation of Bcl-XL and IAP, release of cytochrome *c* and inhibition of Akt, which are markedly blocked by *N*-acetylcysteine, indicating a role of ROS in curcumin-induced cell death[96]. In LNCaP prostrate cancer cells, curcumin induces apoptosis by enhancing tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)[97]. The combined treatment of the cell with curcumin and TRAIL induces DNA fragmentation, cleavage of procaspase 3, 8 and 9, truncation of Bid and release of cytochrome *c* from mitochondria, indicating involvement of both external receptor-mediated and internal chemical-induced apoptosis in these cells[97]. In colorectal carcinoma cell line, curcumin delays apoptosis along with the arrest of cell cycle at G_1 phase[98]. Curcumin also reduces *P53* gene expression, which is accompanied with the induction of HSP-70 gene through initial depletion[98] of intracellular Ca^{2+}. Curcumin also produces nonselective inhibition of proliferation in several leukaemia, nontransformed haematopoietic progenitor cells and fibroblast cell lines[99]. That curcumin induces apoptosis and large-scale DNA fragmentation has also been observed in $V\gamma9V\delta2^+$ T cells through inhibition of isopentenyl pyrophosphate-induced NFκB activation, proliferation and chemokine production[100]. Curcumin induces apoptosis in human leukaemia HL-60 cells, which is blocked by some antioxidants[35]. Colon carcinoma is also prevented by curcumin through arrest of cell-cycle progression independent of inhibition of prostaglandin synthesis[101]. Curcumin suppresses human breast carcinoma through multiple pathways. Its antiproliferative effect is estrogen-dependent in ER (estrogen receptor)-positive MCF-7 cells and estrogen-independent in ER-negative MDA-MB-231 cells[37]. Curcumin also downregulates matrix metalloproteinase (MMP)-2 and upregulates tissue inhibitor of metalloproteinase (TIMP)-1, two common effector molecules involved in cell invasion[37]. It also induces apoptosis through P53-dependent Bax induction in human breast cancer cells[38]. However, curcumin affects different cell lines differently. Whereas leukaemia, breast, colon, hepatocellular and ovarian carcinoma cells undergo apoptosis in the presence of curcumin, lung, prostate, kidney, cervix and CNS malignancies and melanoma cells show resistance to cytotoxic effect of curcumin[102].

Curcumin also suppresses tumour growth through various pathways. Nitric oxide (NO) and its derivatives play a major role in tumour promotion. Curcumin inhibits iNOS and COX-2 production[69] by suppression of NFκB activation[34]. Curcumin also increases NO production in NK cells after prolonged treatment, culminating in a stronger tumouricidal effect[33]. Curcumin also induces apoptosis in AK-5 tumour cells through upregulation[103] of caspase-3. Reports also exist indicating that curcumin blocks dexamethasone-induced apoptosis of rat thymocytes[104,105]. Recently, in Jurkat cells, curcumin has been shown to prevent glutathione depletion, thus protecting cells from caspase-3 activation and oligonucleosomal DNA fragmentation[106]. Curcumin also inhibits proliferation of rat thymocytes[104]. These strongly imply that cell growth and cell death share a common pathway at some point and that curcumin affects a common step, presumably involving modulation of AP-1 transcription factor[104,106].

Pro/antimutagenic activity

Curcumin exerts both pro- and antimutagenic effects. At 100 and 200 mg/kg body wt doses, curcumin has been shown to reduce the number of aberrant cells in cyclophosphamide-induced chromosomal aberration in Wistar rats[107]. Turmeric also prevents mutation in urethane (a powerful mutagen) models[108]. Contradictory reports also exist. Curcumin and turmeric enhance γ-radiation-induced chromosome aberration in Chinese hamster ovary[109]. 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[110].

Anticoagulant activity

Curcumin shows anticoagulant activity by inhibiting collagen and adrenaline-induced platelet aggregation *in vitro* as well as *in vivo* in rat thoracic aorta[23].

Antifertility activity

Petroleum ether and aqueous extracts of turmeric rhizomes show 100% antifertility effect in rats when fed orally[43]. Implantation is completely inhibited by these extracts[111]. Curcumin inhibits 5α-reductase, which converts testosterone to 5α-dihydrotestosterone, thereby inhibiting the growth of flank organs in hamster[112]. Curcumin also inhibits human sperm motility and has the potential for the development of a novel intravaginal contraceptive[113].

Antidiabetic effect

Curcumin prevents galactose-induced cataract formation at very low doses[114]. Both turmeric and curcumin decrease blood sugar level in alloxan-induced diabetes in rat[115]. Curcumin also decreases advanced glycation end products-induced complications in diabetes mellitus[116].

Antibacterial activity

Both curcumin and the oil fraction suppress growth of several bacteria like *Streptococcus*, *Staphylococcus*, *Lactobacillus*, etc.[15]. The aqueous extract of turmeric rhizomes

has antibacterial effects[117]. Curcumin also prevents growth of *Helicobacter pylori* CagA$^+$ strains *in vitro*[118].

Antifungal effect

Ether and chloroform extracts and oil of *C. longa* have antifungal effects[41,46,119]. Crude ethanol extract also possesses antifungal activity[120]. Turmeric oil is also active against *Aspergillus flavus*, *A. parasiticus*, *Fusarium moniliforme* and *Penicillium digitatum*[121].

Antiprotozoan activity

The ethanol extract of the rhizomes has anti-*Entamoeba histolytica* activity. Curcumin has anti-*Leishmania* activity *in vitro*[122]. Several synthetic derivatives of curcumin have anti-*L. amazonensis* effect[123]. Anti-*Plasmodium falciparum* and anti-*L. major* effects of curcumin have also been reported[124].

Antiviral effect

Curcumin has been shown to have antiviral activity[4]. 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[125]. 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[125]. Most importantly, curcumin also shows anti-HIV (human immunodeficiency virus) activity by inhibiting the HIV-1 integrase needed for viral replication[27,126]. It also inhibits UV light-induced HIV gene expression[127]. Thus curcumin and its analogues may have the potential for novel drug development against HIV.

Antifibrotic effect

Curcumin suppresses bleomycin-induced pulmonary fibrosis in rats[128]. Oral administration of curcumin at 300 mg/kg dose inhibits bleomycin-induced increase in total cell counts and biomarkers of inflammatory responses. It also suppresses bleomycin-induced alveolar macrophage-production of TNF-α, superoxide and nitric oxide. Thus curcumin acts as a potent antiinflammatory and antifibrotic agent.

Antivenom effect

Ar-turmerone, isolated from *C. longa*, neutralizes both haemorrhagic activity of *Bothrops* venom and 70% lethal effect of *Crotalus* venom in mice[4]. It acts as an enzymatic inhibitor of venom enzymes with proteolytic activities[47].

Pharmacokinetic studies on curcumin

Curcumin, when given orally or intraperitoneally to rats, is mostly egested in the faeces and only a little in the urine[129,130]. Only traces of curcumin are found in the blood from the heart, liver and kidney. Curcumin, when added to isolated hepatocytes, is quickly metabolized and the major biliary metabolites are glucuronides of tetrahydrocurcumin and hexahydrocurcumin[131,132]. Curcumin, after metabolism in the liver, is mainly excreted through bile.

Clinical studies and medicinal applications of turmeric and curcumin

Although various studies have been carried out with turmeric extracts and some of its ingredients in several animal models[1,4,133], only a few clinical studies are reported so far.

Turmeric

Powdered rhizome is used to treat wounds, bruises, inflamed joints and sprains[134] in Nepal. In current traditional Indian medicine, it is used for the treatment of biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis[48]. Data are also available showing that the powder, when applied as capsules to patients with respiratory disease, gives relief from symptoms like dyspnoea, cough and sputum[135]. A short clinical trial in 18 patients with definite rheumatoid arthritis showed significant improvement in morning stiffness and joint swelling after two weeks of therapy with oral doses of 120 mg/day[53]. Application of the powder in combination with other plant products is also reported for purification of blood and for menstrual and abdominal problems[136].

Curcumin

In patients undergoing surgery, oral application of curcumin reduces post-operative inflammation[137]. Recently, curcumin has been formulated as slow-release biodegradable microspheres for the treatment of inflammation in arthritic rats[138]. It is evident from the study that curcumin-biodegradable microspheres could be successfully employed for therapeutic management of inflammation[138].

Safety evaluation with turmeric and curcumin

Detailed studies have been reported on the safety evaluation of the rhizomes of *C. longa* and its alcohol extract, curcumin[132,139]. The major findings are presented below.

Turmeric

The average intake of turmeric by Asians varies from 0.5 to 1.5 g/day/person, which produces no toxic symptoms[2].

Male and female Wistar rats, guinea pigs and monkeys were fed with turmeric at much higher doses (2.5 g/kg body wt) than normally consumed by humans. No changes were observed in the appearance and weight of kidney, liver and heart[132]. Also, no pathological or behavioural abnormalities were noticed and no mortality was observed.

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[133]. 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.[139]. Human clinical trials also indicate that curcumin has no toxicity when administered at doses of 1–8 g/day[140] and 10 g/day[141].

Future prospects

Turmeric has been used in ayurvedic medicine since ancient times, with various biological applications. Although some work has been done on the possible medicinal applications, no studies for drug-development have been carried out as yet. Although the crude extract has numerous medicinal applications, clinical applications can be made only after extensive research on its bioactivity, mechanism of action, pharmacotherapeutics and toxicity studies. However, as curcumin is now available in pure form, which shows a wide spectrum of biological activities, it would be easier to develop new drugs from this compound after extensive studies on its mechanism of action and pharmacological effects. Recent years have seen an increased enthusiasm in treating various diseases with natural products. Curcumin is a non-toxic, highly promising natural antioxidant compound having a wide spectrum of biological functions. It is expected that curcumin may find application as a novel drug in the near future to control various diseases, including inflammatory disorders, carcinogenesis and oxidative stress-induced pathogenesis.

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Received 8 January 2004; revised accepted 31 March 2004