

## Some Biological Properties of Curcumin: A Review

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Curcumin (diferuloyl methane), a small-molecular weight compound isolated from the roots of *Curcuma longa* L. (family Zingiberaceae), has been used traditionally for centuries in Asia for medicinal, culinary and other purposes. A large number of *in vitro* and *in vivo* studies in both animals and man have indicated that curcumin has strong antioxidant, anti-carcinogenic, anti-inflammatory, anti-angiogenic, antispasmodic, antimicrobial, anti-parasitic and other activities. The mechanisms of some of these actions have recently been intensively investigated. Curcumin inhibits the promotion/ progression stage of carcinogenesis by induction of apoptosis and the arrest of cancer cells in the S, G2/M cell cycle phase. The compound inhibits the activity of growth factor receptors. The anti-inflammatory properties of curcumin are mediated through their effects on cytokines, lipid mediators, eicosanoids and proteolytic enzymes. Curcumin scavenges the superoxide radical, hydrogen peroxide and nitric oxide, and inhibits lipid peroxidation. These actions may be the basis for many of its pharmacological and therapeutic properties.

Curcumin is a nutraceutical of low toxicity, which has been used successfully in a number of medical conditions that include cataracts, cystic fibrosis, and prostate and colon cancers.

**Keywords:** curcumin, *Curcuma longa*, anti-oxidant, anti-inflammatory, anti-cancer.

Curcumin (diferuloyl methane), the natural yellow pigment in the roots of turmeric, is a polyphenolic compound that is isolated from the rhizomes of *Curcuma longa* L. and related species (family Zingiberaceae). It represents about 4% of the dry weight of the drug. For centuries, turmeric has been used in several Asian countries as a culinary spice in curry to give it its characteristic flavour and colour [1]. In addition turmeric has been added to food in order to preserve its freshness and nutritive value, improve palatability, aesthetic appeal and to prolong the shelf life of perishable food items. Turmeric has also found a place as an important folk medicinal

plant with reputed therapeutic effects against various illnesses and conditions that include inflammation and infection. It is used also as a tonic and "blood purifier", as a topical cream, in bath soaps, and also to treat cuts, wounds, bruises and sprains.

In Western countries, turmeric is approved as a food additive, and is also used as a coloring agent in items as diverse as pharmaceuticals, yellow mustards and cosmetics, as well as in dyes for hair and fur [2]. The importance of turmeric as a therapeutically useful substance was strengthened with the discovery that it is very rich in phenolics (referred to as

curcuminoids). These compounds are known now to be strong anti-oxidants.

Several recent reviews have dealt with specific properties of curcumin and curcuminoids [for example, 3-9]. In the present work, the aim was to up-date the published literature on these important compounds, with special emphasis on their most important pharmacological properties, possible therapeutic uses, and novel bioactivities.

### Chemical Properties of Curcumin

Curcumin [1, 7-bis (hydroxyl-3-methoxyphenyl)-1,6-heptadiene-3, 5-dione] ( $C_{21}H_{20}O_6$ ), is the most important active ingredient responsible for the biological activity of turmeric (Figure 1). It was first isolated from the drug in 1815, but its structure was not elucidated until 1913. Curcumin is insoluble in water, but soluble in ethanol and acetone. The naturally occurring ratios of curcuminoids in curcumin are about 5% bisdemethoxycurcumin, 15% demethoxycurcumin, and 80% curcumin [10].

Curcumin is relatively unstable in phosphate buffer at pH 7.4, and the stability is strongly improved by either lowering the pH, or by adding glutathione, *N*-acetyl cysteine, ascorbic acid or rat liver microsomes [11]. Chemical synthesis of curcumin analogues has resulted in compounds with stronger anti-oxidant and cancer chemoprotective activities [12].

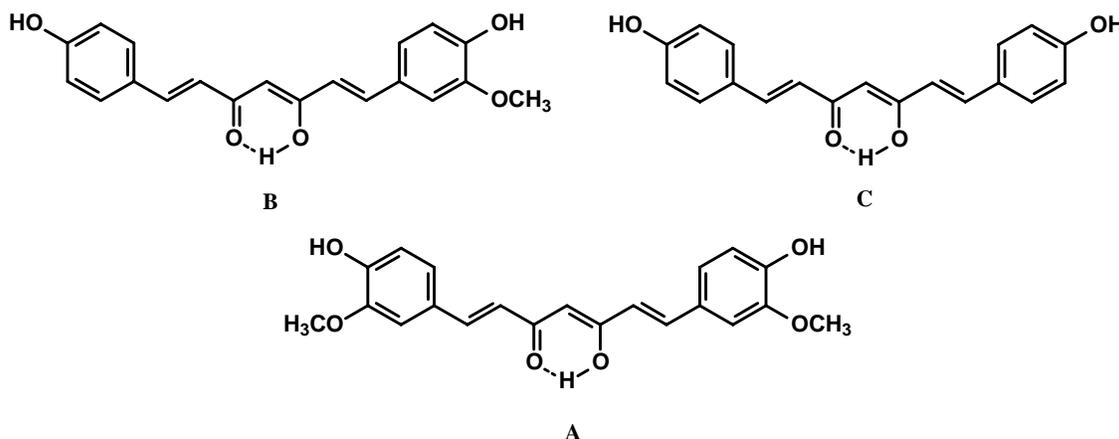
As a regulatory prerequisite for the registration of curcumin as a potential therapeutic agent in human medicine, a reliable method for measuring its concentration in plasma and/or urine is required. Several methods for measuring curcumin in biological fluids have been published, but more

recently HPLC and isocratic liquid chromatographic (ILC) methods were developed [13, 14]. These methods were claimed by the authors to be reproducible, accurate, sensitive and specific. The assays only required minimal amounts of fluid (about 0.2 mL) and were able to detect concentrations of curcumin down to 2.5 ng/mL. However, this is higher than that expected to be present in body fluids of humans either consuming or being treated with the substance. Heath et al [15] have also published an HPLC method for the quantitation of tetrahydrocurcumin in plasma and urine.

### Pharmacological Properties of Curcumin

**Kinetics:** It has been reported [16] that, in rats, about 75% of orally administered curcumin is excreted in faeces, and only traces in urine. When curcumin (up to 5  $\mu\text{g/mL}$ ) was added *in vitro* to either hepatocyte or microsomal suspensions, it disappeared within 30 minutes. It was inferred that curcumin was metabolized rapidly in the blood after intravenous administration.

Following ingestion of curcumin in mice, it is biotransformed first into dihydrocurcumin and tetrahydrocurcumin. Subsequently, these metabolites are converted to monoglucuronide conjugates [17-19]. Intraperitoneal (i.p.) injection of curcumin (0.1g/kg) resulted in a concentration in the plasma of 2.25  $\mu\text{g/mL}$  within the first 15 minutes [19]. One hour after the i.p. injection, the concentrations of curcumin in the intestines, spleen, liver, and kidneys were 177.0, 26.1, 26.9, and 7.5  $\mu\text{g/g}$ , respectively. Only traces (4.1  $\mu\text{g/g}$ ) were found in the brain at 1 hour. In the plasma, curcumin, tetrahydrocurcumin and two conjugates of curcumin were detected by HPLC.



**Figure 1:** Chemical structures of (A) curcumin, (B) demethoxycurcumin and (C) bisdemethoxycurcumin.

A study of the biotransformation of curcumin by human and rat hepatocytes found that hexahydrocurcumin and hexahydrocurcuminol were the major metabolites of curcumin, and that none of these metabolites was biologically active in inhibiting PGE<sub>2</sub> [10]. It was suggested that the availability of curcumin was greatest in the colon, as the gastrointestinal tract seems to be exposed more prominently to unmetabolized curcumin than any other tissues [10]. This suggestion is in line with the clinical observation of the salutary action of curcumin as a colorectal cancer chemopreventative agent. More recently, Wang et al [20] studied the *in vitro* degradation of curcumin and reported that more than 20% of it decomposes within 1 hour, and that after 8 hours of incubation, 50% is still intact. The major degradation products included *trans*-6-(4-hydroxy-3-methoxyphenyl)-2,4-dioxo-5-hexenal. Minor degradation products included vanillin, ferulic acid and feruloyl methane. Curcumin binds with serum albumin through hydrophobic interactions [21], and therefore may be transported to appropriate target cells, where it exhibits its pharmacological effects. It has also been demonstrated that curcumin readily penetrates into the cytoplasm and is able to accumulate in membranous structures, such as plasma membranes, endoplasmic reticulum, and the nuclear envelope [22].

The *in vivo* bioavailability of curcumin following ingestion was considered low by Ammon and Wahl [3], but others estimated that it was 65% [23]. Interestingly, this bioavailability can be enhanced in humans and rats by concomitant ingestion of piperine (a component of pepper) [24]. In patients with cancer, curcumin and its metabolites were detected in hepatic tissue and portal blood [25] and in the colorectum [26] following oral administration of curcumin at doses of 450 – 3600 mg daily for 7 days. The authors concluded that a daily dose of 3.6 g curcumin achieves pharmacologically efficacious levels in the colorectum, with negligible distribution of the compound outside the gut, while the curcumin doses required for the provision of hepatic levels sufficient to exert pharmacological activity are probably not feasible in humans.

Little was known about the metabolic fate of curcumin and its natural congeners. However, in a recent study conducted with precision-cut liver slices from male and female Sprague-Dawley rats, five reductive, but no oxidative metabolites of curcumin and its demethoxy and bisdemethoxy analogues were

observed and identified by HPLC and GC-MS analysis. The major reductive metabolites were the hexahydrocurcuminoids in both male and female rat liver slices, whereas male rats formed more octahydro- than tetrahydro- metabolites and female rats more tetrahydro- than octahydrocurcuminoids. Tetrahydro-, hexahydro- and octahydro-metabolites were predominantly present as glucuronides, but a significant proportion of sulphate conjugates was also observed. The lack of formation of oxidative metabolites of curcumin and the ready generation of reductive metabolites were confirmed using rat liver microsomes and cytosol, respectively. Results of enzymatic hydrolysis studies conducted under various conditions revealed that curcumin and demethoxycurcumin are chemically less stable than bisdemethoxycurcumin, whereas the reductive metabolites of all three curcuminoids are stable. In view of the chemical instability of the parent curcuminoids, it was proposed that their major phase I metabolites, the stable hexahydro products, should be used as biomarkers for exposure in clinical studies [27].

**Effect on isolated tissue preparations:** It has been reported that curcuminoids (including curcumin) relax isolated rat uterus and guinea pig ileum by receptor-dependent and independent mechanisms, and they reduce the force of contraction induced by oxytocin [28]. They also relax isolated rat aorta [29].

**Anti-oxidant actions:** Several studies have shown that curcumin has a strong capability for scavenging superoxide radicals, hydrogen peroxide and nitric oxide (NO) from activated macrophages [9, 30], reducing iron complex and inhibiting lipid peroxidation [31]. These actions may be the major mechanism by which curcumin exhibits its pharmacological / therapeutic activities [32, 33].

Unnikrishnan and Rao [34] investigated the anti-oxidant actions of curcumin and its derivatives demethoxycurcumin, bisdemethoxycurcumin and diacetylcurcumin, and found that these substances can protect haemoglobin (Hb) from oxidation at a concentration as low as 0.08 mM, except diacetylcurcumin, which has little effect on the inhibition of nitrite induced oxidation of Hb. It has also been shown that curcumin inhibits the NO synthase activity of macrophages [35]. Bonte et al [36] have also shown that curcumin, through its anti-oxidant activity, protects human keratinocytes from xanthine oxidase injury. Reddy and Lokesh [37] have

shown that oral administration of curcumin (30 mg/kg) to rats for 10 days reduces the iron-induced hepatic damage by lowering lipid peroxidation. Lipid peroxidation and oxidative stress induced by nicotine have also been ameliorated by curcumin treatment [38].

Curcumin has been shown to protect renal cells and neural glial cells from oxidative stress [39]. Additionally, curcumin is also known to enhance the activities of other anti-oxidants, such as super oxide dismutase (SOD), catalase, and glutathione peroxidase [40]. Feeding curcumin at a level of 0.1% for three weeks diminished the degree of lipid peroxidation in tissues of retinol-deficient rats [41]. Curcumin also protects against oxidative stress in endothelial cells by induction of haem oxygenase-1 [42]. Through its anti-oxidant actions, curcumin can protect tissues from the effects of oxidative stress induced by radiation (REF), metals [43], and severe injury to skeletal muscles [44].

**Anti-inflammatory actions:** Using several animal models of acute and chronic inflammation, several authors have demonstrated an anti-inflammatory action of curcumin approximately equal to that of the reference drug phenylbutazone in acute inflammation, but only half as active in chronic inflammation (see earlier reviews on curcumin). The probable mechanisms of this action have been the subject of recent intensive investigations, and it has been concluded that curcumin modulates many inflammatory mediators, both *in vitro* and *in vivo*, through complex reactions on cytokines, lipid mediators and proteolytic enzymes (reviewed by Joe and Lokesh [9]). Curcumin can inhibit leukotriene formation in rat peritoneal polymorphonuclear neutrophils, and it was more effective than hydrocortisone in this respect [9]. Huang *et al* [45] showed that curcumin inhibits proliferation of blood mononuclear cells and vascular smooth muscle cells. These authors suggested that curcumin could be used clinically in transplant atherosclerosis.

It has been shown that curcumin inhibits IL-1 $\beta$ -stimulated gene expression of a neutrophil chemotactic peptide, interleukin-8 (IL-8) and inhibits lipopolysaccharide-induced production of IL-1 and TNF $\alpha$  by a human monocyte protein macrophage cell line [46, 47] In addition, curcumin has been shown to inhibit the proinflammatory I Th1 cytokine profile [48], and NF-kappaB activation pathway [49, 50].

In rats, curcumin protected against the renal interstitial inflammation and fibrosis elicited by urethral occlusion. Inhibition of the NF-kappaB-dependant pathway is, at least in part, involved in the mechanisms, but AP-1 inhibition is unlikely to be involved in the beneficial effects of curcumin [51].

Curcumin inhibits the cellular uptake of arachidonic acid (AA), which is an important pro-inflammatory eicosanoid [52]. It has also been shown by many workers (for example, [53]) that curcumin inhibits cyclo-oxygenases (COX) and lipo-oxygenases (LO) and several phospholipases involved in the release of AA from membranes. Curcumin has been shown to inhibit several matrix metalloproteinases (MMPs) and collagen synthesis [54, 55] and to lower the release of many proteolytic enzymes, such as elastase, collagenase and hyaluronidase from activated macrophages [56]. Curcumin also inhibits the upregulation of MMPs, possibly because of its inhibitory potential on protein kinase C [54].

**Anticarcinogenic actions:** The anticarcinogenic activity of curcumin (and/or its analogues) was the subject of detailed investigations in several laboratories [for example, 25, 42, 50, 57-61]. Carcinogenesis is a process that consists of three separate but interrelated stages, initiation, promotion and progression. Oxidative and inflammatory tissue damage plays an important role in the promotion of cancer [6]. Being a potent anti-inflammatory and anti-oxidant agent, curcumin may prevent cancer by suppressing tumour promotion. It also inhibits growth and induces apoptosis in a range of different cell types, for example human bladder cancer cells [127], and arrests cancer cells in the S, G2/M cell cycle phase [62]. It is active in a number of different signalling pathways; some of these have recently been summarized [6, 9, 60]. These pathways include inhibiting signalling through NF- $\kappa$ B (that regulates expression of many genes, including that of COX-2, the enzyme responsible for inflammation and malignant transformation) and reduction of the expression of COX-2 [50], and this is the basis for testing curcumin for the prevention of colon cancer [63]. Curcumin also interacts with many cell regulatory proteins, such as the mitogen-activated protein (MAP) cascade. It directly inhibits v-Src, which leads to a decrease in phosphorylation of Shc, cortactin and focal adhesion kinase (FAK). Additionally, curcumin inhibits the activity of FAK directly. This causes loss of Src-mediated cell mobility, and thus could have important implications

for invasion and metastasis [64]. In addition to its other properties, the strongly inhibitory actions of curcumin on several cytochrome P-450s, phenol sulphotransferase, and glutathione S-transferases may be a factor in its anticarcinogenic action [11, 65]. Angiogenesis (formation of new blood vessels from a pre-existing vascular network) is a critical mechanism in a number of diseases that include cancer and atherosclerosis. Curcumin has an anti-angiogenic action that is mediated, at the molecular level, by inhibition of vascular endothelial growth factor (VEGF), angiopoietins (Ang 1 and Ang 2), and inhibition of fibroblast growth factors (bFGF)-induced angiogenesis (reviewed by Dulak [66]).

Bone inflammation and cancer are diseases that increase bone resorption. Curcumin is known to stimulate cell apoptosis and to inhibit bone resorption. Therefore, its use has been advocated in cases of bone inflammation and cancer [67].

Most of the data supporting the anti-tumour activity of curcumin were obtained *in vitro*. Curcumin is being clinically evaluated as a chemoprotective agent for major cancer targets that include prostate, colon, and lung (reviewed by Manson et al [60]). More epidemiological and clinical trials involving large numbers should lend support to the obtained *in vivo* and *in vitro* results.

### Therapeutic properties of curcumin

Several experimental animal studies and human clinical trials have been conducted, and the following is a brief survey of some of the most recent ones.

**Anti-viral actions:** Several *in vivo* and *in vitro* studies have indicated that curcumin possesses moderate to high inhibitory activity on certain viruses that include human simple-virus-2 [68] and type I HIV [69]. Curcumin was shown to be effective in inhibiting P24 antigen production in cells either acutely or chronically infected with HIV-1 [70], and also inhibiting the enzymic reactions associated with HIK 1 integrase, but not other viral (HIV-1 reverse transcriptase) and cellular (RNA polymerase II) nucleic acid processing enzymes [71, 72]. Curcumin was ineffective in inhibiting HIV-1 multiplication in acutely infected MT-4 cells [72]. It was shown that two curcumin analogues, dicaffeolymethan and rosmarinic acid have more potent antiviral activity than curcumin [73].

**Effect on immunity:** Curcumin has been shown to modulate immunity. The immunosuppressive activity of cyclosporine is potentiated by curcumin in rat heterotropic cardiac transplant models [74]. Mucosal CD4(+) T and B cells increase in animals treated with curcumin, suggesting that it modulates lymphocyte-mediated immune functions [75]. More recently, Gao et al [76] studied the effect of curcumin on mitogen/antigen induced proliferation of splenic lymphocytes, induction of cytotoxic T lymphocytes, lymphokine activated killer cells, and the production of cytokines by T lymphocytes and macrophages. It was found that curcumin irreversibly impaired the production of these immune functions. It was proposed that the compound might have inhibited these immune functions by inhibiting NF- $\kappa$ B target genes involved in the induction of these immune responses.

**Effect on colitis:** Several recent publications have demonstrated some beneficial effects of curcumin in experimental colitis and suggest that it may, therefore, be useful in the treatment of inflammatory bowel disease (IBD) in humans. The basis of this therapeutic effect was suggested to be a decrease in lipid peroxidation, reduction in the degree of both neutrophil infiltration and lipid peroxidation in the inflamed colon, as well as a decreased serine protease activity. Curcumin also reduced the levels of nitric oxide (NO) and  $O_2^-$  associated with the favourable expression of Th 1 and Th 2 cytokines and inducible NO synthase [77]. Salh et al [78] also found a beneficial effect for curcumin in experimental colitis and proposed that the mechanism of this action is correlated with the inhibition of the activation of NF- $\kappa$ B and the reduction in the activity of p38 MAPK.

**Effect on cystic fibrosis (CF):** CF, the most common hereditary disease in the white population, is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It has been reported that curcumin can correct the mutational defects of CF in mice, probably through the inhibition of sarco (endo) plasmic reticulum  $Ca^{+2}$ -ATPase [79]. Subsequently, this promising finding was verified by a number of workers (reviewed by Mall and Kunzelmann [80]). A few reports confirmed this result in animals, but others could not reproduce it in human and other animal models.

**Effect on wound healing:** It has been reported that curcumin improves cutaneous wound healing in

normal and diabetic rats by enhancing granulation tissue formation, biosynthesis of extracellular matrix proteins, and TGF-B1, and by faster re-epithelization and increased collagenization of wounds [81]. More recently, a beneficial effect was reported of curcumin in radiation-impaired healing of excisional wounds in mice [82]. The ability of curcumin to enhance wound healing was utilized by making curcumin-incorporated collagen films [83].

**Anti-diabetic action:** Babu and Srinivasan [84] found that inclusion of curcumin in the diet of streptozotocin-diabetic rats (0.5% in the diet for 8 weeks) did not alter the glucose excretion or fasting blood glucose concentration, although it improved the metabolic status of these rats. On the other hand, it was reported that administration of either curcumin or turmeric to alloxan-diabetic rats resulted in significant reduction in blood sugar, haemoglobin and glycosated haemoglobin levels [85]. Curcumin also ameliorated the oxidative stress encountered by the diabetic rats. This was evidenced by lower concentrations of thiobarbituric acid reactive substances (TBARS) and enhanced activity of the anti-oxidant enzyme, glutathione peroxidase. The enzyme sorbitol dehydrogenase, which catalyzes the conversion of sorbitol to fructose, was also lowered. The above actions were more pronounced with curcumin than with turmeric. Nishiyama et al [86] confirmed the antidiabetic action of curcumin in mice, and proposed a molecular mechanism for this action that involves peroxisome proliferator-activated receptor (PPAR)- $\gamma$  activation, and that the main components in turmeric (curcuminoids and sesquiterpenoids) act to reduce hyperglycaemia in either an additive or synergistic fashion.

**Antibacterial and anti-fungal actions:** Kim et al [87] reported on the action of curcumin and materials derived from *C. longa* rhizomes against several plant pathogenic fungi *in vivo*. The responses varied with the tested pathogen. Fungicidal action comparable to that of the fungicidal agent chlorothalonil was observed with curcumin. More recently, Mishra et al [88] tested various synthesized curcumin bioconjugates viz. 4,4'-di-*O*-glycinoyl-curcumin, 4,4'-di-*O*-D-alaninoyl-curcumin, 4,4'-di-*O*-(glycinoyl-di-*N*-piperoyl)-curcumin, 4,4'-di-*O*-piperoyl curcumin, curcumin-4,4'-di-*O*- $\beta$ -D-glucopyranoside and 4,4'-di-*O*-acetylcurcumin, along with piperoyl glycine, *in vitro* against different bacteria and fungi. The 4,4'-di-*O*-(glycinoyl-di-*N*-piperoyl)-curcumin and 4,4'-di-*O*-acetylcurcumin

were found to be more effective than Cefepime, a commercially available antibacterial drug, at the same concentration. The 4,4'-di-*O*-(glycinoyl-di-*N*-piperoyl)-curcumin and 4,4'-di-*O*-piperoyl curcumin had antifungal activity *in vitro* almost comparable with fluconazole, the most popular antifungal drug. These bioconjugates synthesized from curcumin were found to be more potent than curcumin itself against many common strains of bacteria, as well as fungi. The enhanced activity of these bioconjugates in comparison with curcumin may be due to either improved cellular uptake or reduced metabolism of these bioconjugates, resulting in the building up of a sufficient concentration inside the infected cells. This report suggests that suitably designed curcumin bioconjugates have the potential to become useful antibacterial/antifungal drugs.

**Anti-parasitic action:** Significant *in vitro* inhibitory efficacy of both curcumin and an ethanolic extract of *C. longa* against *Plasmodium falciparum*, *Leishmania major*, *Coccidia* and *Trypanosoma* species have been reported [89-91]. The leishmanicidal effect of curcumin has also been confirmed *in vitro* [92]. More recently, curcumin was shown to be of benefit in the therapy of malaria [93]. The compound inhibited chloroquine-resistant *Plasmodium falciparum* growth in culture in a dose dependent manner with an IC<sub>50</sub> of approximately 5  $\mu$ M. In addition, oral administration of curcumin to mice infected with the malaria parasite (*Plasmodium berghei*) reduced blood parasitaemia by 80-90% and significantly enhanced the survival of the mice. Several components in turmeric (including curcumin, demethoxycurcumin, bisdemethoxycurcumin and cyclocurcumin) have been shown to have nematocidal activity [94] when they are given as a mixture, but not when they are given independently, suggesting either an additive or synergistic activity.

**Effect on Alzheimer's disease:** Because of the anti-inflammatory and anti-oxidant actions of curcumin, it was tested against Alzheimer's disease [95]. An alternative mechanism of these effects is metal chelation, which may reduce amyloid aggregation or oxidative neurotoxicity. Metals can induce A $\beta$  aggregation and toxicity, and are concentrated in Alzheimer's diseased brain. The chelators desferrioxamine and clioquinol have exhibited anti-Alzheimer's disease effects. For a fuller discussion of the use of phytochemicals (including curcumin) in Alzheimer's disease see the review of Calabrese et al [96].

**Prevention of tissues against oxidative damage:**

Curcumin and tetrahydrocurcumin have been shown to possess hepatoprotective activity against several hepatic diseases and toxic substances. Experimental hepatotoxicity, induced by carbon tetrachloride [97], ethanol [98], and erythromycin estolate [99], was ameliorated by either curcumin or tetrahydrocurcumin. Reddy and Lokesh [37] have shown that oral administration of curcumin (30 mg/kg) to rats for 10 days reduces the iron-induced hepatic damage by lowering lipid peroxidation. The basis of the hepatoprotective action was suggested to be the anti-oxidant action of curcumin. It has also been shown that curcumin inhibits NF-kappa B activation and reduces the severity of experimental steatohepatitis in mice [100].

Curcumin and tetrahydrocurcumin have been shown to have nephroprotective actions against several renal diseases and toxins. Nephrotoxicities were induced in rats by high doses of cisplatin [101], adriamycin [102, 103], and gentamicin [104]. These drugs are known to generate free radicals in renal tissues. Curcumin, given at various oral and parenteral doses, either prevented or ameliorated the biochemical, physiological or histopathological signs of nephrotoxicity. The basis of the nephroprotection was postulated to be through the anti-oxidant action of curcumin.

Curcumin has been reported to protect rats with pulmonary toxicity induced by either amiodarone [105] or the herbicide paraquat [106]. At high doses, these substances are known to generate free radicals in the pulmonary tissues. The free radical scavenging activity of curcumin was suggested as the basis of the protection.

It has been reported that, in rats, curcumin is effective in preventing lead-induced neurotoxicity [107], focal cerebral ischemia [108], and naphthalene-induced ocular toxicity in rats [109]. Again, the anti-oxidant action of curcumin was the main mechanism proposed for this protection.

**Miscellaneous actions:** It has been reported that curcumin has the potential of being utilized as a vaginal contraceptive and for HIV prevention. Within 30 minutes of incubation with curcumin (30 g/mL), the motility of human sperms was inhibited by about 20% without significant effect on sperm viability [110]. Higher concentrations of curcumin induced total loss of motility.

Diabetes, ageing and lack of adequate consumption of antioxidants are among the most important risk factors in the genesis of cataracts (opacity of the eye). As curcumin has been shown to be a substance with strong anti-oxidant, anti-hyperglycaemic and anti-ageing properties, its activity against the onset and maturation of cataract induced by 4-hydroxy-trans-nonenal [111], galactose [112], and selenium [113] was investigated in rats. It has been found that inclusion of curcumin in the diet at a concentration of 0.002% (but not at levels of 0.01% or higher) was effective in mitigating the cataracts.

Protection from chronic diseases of aging involves antioxidant activities, mitochondrial stabilizing functions, metal chelating activities, inhibition of apoptosis of vital cells, and induction of cancer cell apoptosis. Miquel et al [114] and Ferrari [115] reported that curcumin may have anti-aging properties, probably because of the fact that it has all the above mentioned properties.

Curcumin in the diet of rats (0.5%) increased the activities of pancreatic lipase, amylase, trypsin and chymotrypsin [9]. Curcumin has also been reported to be useful against acute pancreatitis [116]. Using ultrasonography, curcumin (20 mg/person) has been shown to contract the gall bladder in healthy humans [117], and it has been proposed that this effect is in line with the reduced rate of gall stone formation in response to a lithogenic diet that was seen in curcumin-fed mice [9]. A pilot study has shown that *C. longa* (and Neem) may be useful in scabies in man. Turmeric was used as a paste for the treatment of scabies in 814 Indian villagers. In 97% of cases a cure was obtained within 3 to 15 days of treatment. This was reported to be a very cheap, easily available, effective and acceptable mode of treatment for affected people in poor countries. No toxic or adverse reaction was observed [118]. These preliminary results need to be verified in controlled clinical trials, using an acceptable reference drug (s).

**Interactions of curcumin with drugs and food**

**additives:** In rats and man, curcumin inhibits phenol sulphotransferase, several cytochrome P 450s (for example, P 450 1A1/1A2 and to a lesser extent 2B1 and 2B2) and glutathione S-transferase [11, 65, 119]. As a result, enzyme metabolism of xenobiotics taken concomitantly with curcumin would be expected to be lower. As was mentioned earlier, the oral bioavailability of curcumin can be enhanced by concomitant ingestion of piperine (a

component of pepper) in humans and rats [24]. The basis of this interaction has not been elucidated. It was recently shown that curcumin exhibits a synergistic action with 5-fluorouracil in inhibiting the growth of AGS human gastric carcinoma cells *in vitro* [118]. Curcumin has been shown to potentiate the immunosuppressant action of cyclosporine [72].

**Toxicological properties of curcumin:** Curcumin is considered to be of low toxicity in man and animals [23]. In a phase 1 clinical trial with 25 volunteers, administration of up to 8000 mg of curcumin per day for 3 months induced no apparent toxic sign. Five other clinical trials in which humans were given 1125–2500 mg curcumin per day confirmed the apparent safety of the substance [8]. It is estimated that adults in India ingest 80–200 mg of curcumin daily [23]. There are no reports of adverse effects of either curcumin or its analogues except for rare cases of contact dermatitis [121-123], one of which occurred as an occupational illness of a miller working in a spice shop. Many Indian women apply turmeric to their skin in an effort to minimize unwanted hair growth, but few experience dermatitis. Of 62 patients completing an 18-month study of the topical use of curcumin to treat skin and mucous membrane cancers, only one reported an adverse effect of scalp itching [124].

An investigation of the colorants that may be present in the transferable picture tattoos used by children showed that curcumin was one of the eleven colorants that could be identified. However, on the

basis of the results obtained, the risk of an allergic reaction from the colorant seemed to be limited [125]

Oral administration of curcumin to rats at doses up to 5 g/kg caused no overt signs of toxicity [23]. The American Herbal Association classifies turmeric as a menstrual stimulant, and some sources recommend avoiding curcumin in pregnancy. Its use is not recommended during breast-feeding, as effects on breast-feeding infants are unknown [2]. Turmeric may have an antiplatelet activity [126], and its concurrent use with anticoagulants may lead to an additive effect. Although there are no reports of this in humans, its use should be avoided in patients with bleeding disorders and bile duct obstruction and should only be used under the supervision of a physician in patients with gallstones.

### Conclusions

Curcumin is a nutraceutical substance with many pharmacological activities, some of which have been experimentally and clinically utilized in both man and animals. Notable among these are the antioxidant, anti-inflammatory and anti-carcinogenic properties, all three of which seem to be interrelated. It is encouraging that curcumin is of low toxicity. Despite a plethora of phytochemical, pharmacological, biochemical and toxicological data on curcumin, large well-designed clinical trials and epidemiological data are warranted to substantiate its usefulness in the treatment and/or prevention of cancer, rheumatoid arthritis and other conditions of human patients.

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