

CURCUMIN: THE SPICE FOR LIFE

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ABSTRACT

Curcumin is the product obtained by solvent extraction of turmeric i.e., the ground rhizomes of *Curcuma longa* L. (*Curcuma domestica* Valetton) and purification of the extract by crystallization. Extensive research within the last half a century has proven that most of these activities, associated with turmeric are due to curcumin. Curcumin has been shown to exhibit anti-oxidant, anti-inflammatory, antiviral, anti bacterial, anti fungal and anti cancer activities and thus has a potential against various malignant diseases, diabetes, allergies, arthritis, Alzheimer's disease and other chronic diseases. These effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases and other enzymes. Curcumin is remarkably non-toxic and exhibits limited bioavailability. The purpose of this review is to provide a brief summary of the current knowledge of the effects of curcumin. Curcumin exhibits great promise as a therapeutic agent, and is currently in human clinical trials for a variety of conditions. Since multi targeted therapy is more effective than the mono targeted therapy, curcumin has promising scope in the future research.

Key words: Curcumin, turmeric, anti-inflammation, anti oxidant, cancer, bacterial.

INTRODUCTION

For several thousands of years, cultures from around the world have used naturally occurring dietary components which have been discovered to be biologically active. These plant-derived chemicals have generated considerable interest recently for their potential to combat human disease such as cancer, inflammation, and atherosclerosis. Curcumin is a chemical of the polyphenol family derived from the rhizome *Curcuma*

longa L. The dried, ground product of this root is the common spice known as turmeric. Turmeric contains three different analogues of curcumin i.e. diferuloylmethane, also called curcumin, demethoxycurcumin and bisdemethoxycurcumin. Whether all three analogues exhibit equal activity is not clear. While in most systems curcumin was found to be most potent^{1, 2} in some systems bisdemethoxycurcumin were found to exhibit higher activity.^{3,4}

Most commercial turmeric preparations consist of ~2-8% active curcumin. The popularity of turmeric has increased in the U.S. with the Food and Agriculture Organization of the United Nations estimating that approximately 2400 metric tons of turmeric is imported annually for consumer use. In concordance with this increase in use, curcumin has stimulated an increase in research with several hundred research studies over the past 10-20 years examining its role in the treatment and prevention of cancer, cardiovascular disease, and inflammation etc.

Pharmacokinetics

Pharmacokinetic studies in animals have demonstrated that 40-85 percent of an oral dose of curcumin passes through the gastrointestinal tract unchanged, with most of the absorbed flavonoid being metabolized in the intestinal mucosa and liver.^{5,6} Due to its low rate of absorption, curcumin is often formulated with bromelain for increased absorption and enhanced anti-inflammatory effect.

Curcumin Pharmacological Actions

Antioxidant Effects

Water- and fat-soluble extracts of turmeric and its curcumin component exhibit strong antioxidant activity, comparable to vitamins C and E.⁷ Curcumin was shown to be eight times more potent than vitamin E in lipid peroxidation, and three times more powerful than vitamin C in neutralizing free radicals.^{10,11} A study of ischemia in the feline heart demonstrated that curcumin pretreatment decreased ischemia-induced changes in the heart.⁸ An *in vitro* study measuring the effect of curcumin on endothelial heme oxygenase-1, an inducible stress protein, was conducted utilizing bovine aortic endothelial cells. Incubation (18 hours) with curcumin resulted in enhanced cellular resistance to oxidative damage.⁹

The antioxidant activity of curcumin could be mediated through antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Curcumin has been

shown to serve as a Michael acceptor, reacting with glutathione and thioredoxin.

Anti-inflammatory Effects

Curcumin works to inhibit the inflammatory activity and synthesis of the enzymes implicated in inflammation, such as, cyclooxygenase-2 and 5-lipoxygenase. Its anti-inflammatory action may also be attributed to inhibition of pro-inflammatory leukotrienes, prostaglandins and arachidonic acid, as well as to its neutrophil function during inflammatory states. Curcumin has been found to inhibit NF- κ B-dependent gene transcription¹², and the induction of COX-2 and iNOS in cell culture and animal studies.^{13, 14}

Hepatoprotective Effects

Curcumin has been found to have hepatoprotective characteristics. Animal studies have demonstrated its hepatoprotective effects from a variety of hepatotoxic insults, including carbon tetrachloride (CCl₄),^{15, 16} galactosamine,¹⁷ acetaminophen (paracetamol),¹⁸ and Aspergillus aflatoxin.¹⁹ Curcumin's hepatoprotective effect is mainly a result of its antioxidant properties, as well as its ability to decrease the formation of proinflammatory cytokines. In rats with CCl₄-induced acute and subacute liver injury, curcumin administration significantly decreased liver injury in test animals compared to controls.¹⁶

Anticarcinogenic Effects

To explain the anticarcinogenic effects of curcumin on different tumors, a wide variety of mechanisms have been implicated, including inhibition of ROI, suppression of inflammation, downregulation of ODC, inhibition of cell proliferation, inhibition of cytochrome P450 isoenzymes, induction of GSH, suppression of certain oncogenes (e.g., cHa-ras, c-jun, and c-fos), inhibition of transcription factors NF- κ B and AP-1, suppression of COX2, inhibition of cell-cycle-related proteins (PCNA, cyclin E, p34 cdc2), inhibition of chromosomal damage, inhibition of oxidation of DNA bases, inhibition of

malondialdehyde (MDA) DNA adduct formation, inhibition of tumor implantation, inhibition of protein tyrosine kinase and protein kinase C activity, inhibition of biotransformation of carcinogens, and induction of glutathione S-transferase (GST) activity etc.^{20,21,22,23}

Animal studies involving rats and mice, as well as in vitro studies utilizing human cell lines, have demonstrated curcumin's ability to inhibit carcinogenesis at three stages: tumor promotion, angiogenesis, and tumor growth.²⁴ Curcumin is capable of suppressing the activity of several common mutagens and carcinogens in a variety of cell types in both in vitro and in vivo studies. The anticarcinogenic effects of curcumin are due to direct antioxidant and free-radical scavenging effects, as well as their ability to indirectly increase glutathione levels, thereby aiding in hepatic detoxification of mutagens and carcinogens, and inhibiting nitrosamine formation.²⁵

Antimicrobial Effects

Turmeric extract and the essential oil of *Curcuma longa* inhibit the growth of a variety of bacteria, parasites, and pathogenic fungi.

Anti bacterial effect

Both curcumin and the oil fraction suppress growth of several bacteria like *Streptococcus*, *Staphylococcus*, *Lactobacillus*, etc.²⁶ The aqueous extract of turmeric rhizomes has antibacterial effects.²⁷ Curcumin also prevents growth of *Helicobacter pylori* CagA⁺ strains in vitro.²⁸

Antiviral 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.²⁹ EBV inducers such as 12-O-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.²⁹ Most importantly, curcumin also shows anti-HIV (human

immunodeficiency virus) activity by inhibiting the HIV-1 integrase needed for viral replication^{30, 31}. It also inhibits UV light induced HIV gene expression.³² Thus curcumin and its analogues may have the potential for novel drug development against HIV.

Antiprotozoan activity

The ethanol extract of the rhizomes has anti-*Entamoeba histolytica* activity. Curcumin has anti-*Leishmania* activity in vitro.³³ Several synthetic derivatives of curcumin have anti-*L. amazonensis* effect.³⁴ Anti-*Plasmodium falciparum* and anti-*L. major* effects of curcumin have also been reported.³⁵

Antifungal effect

Ether and chloroform extracts and oil of *C. longa* have antifungal effects.^{36, 37, 38} Crude ethanol extract also possesses antifungal activity.³⁹ Turmeric oil is also active against *Aspergillus flavus*, *A. parasiticus*, *Fusarium moniliforme* and *Penicillium digitatum*.⁴⁰

Cardiovascular Effects and its effects on lipid metabolism

Curcumin decreases the severity of pathological changes and thus protects from damage caused by myocardial infarction.⁴¹ Curcumin improves Ca²⁺-transport and its slippage from the cardiac muscle sarcoplasmic reticulum, thereby raising the possibility of pharmacological interventions to correct the defective Ca²⁺ homeostasis in the cardiac muscle.⁴² Curcumin has significant hypocholesteremic effect in hypercholesteremic rats.⁴³

Its protective effects on the cardiovascular system include lowering cholesterol and triglyceride levels, decreasing susceptibility of low density lipoprotein (LDL) to lipid peroxidation,⁴⁴ and inhibiting platelet aggregation.⁴⁵ These effects have been noted even with low doses.⁴⁴ Turmeric extract's effect on cholesterol levels may be due to decreased cholesterol uptake in the intestines and increased conversion of cholesterol to bile acids in the liver.⁴⁶

Gastrointestinal Effects

It increases mucin secretion in rabbits and may thus act as gastro protectant against irritants.⁴⁷ both antiulcer⁴⁸ and ulcerogenic⁴⁹,⁵⁰ effects of curcumin have been reported but detailed studies are still lacking. It also protects from 5-hydroxytryptamine- induced ulceration at 20 mg/kg dose.^{51, 52} In fact, at higher doses of 50 mg/ kg and 100 mg/kg, it produces ulcers in rats.⁵⁰ It also enhances intestinal lipase, sucrase and maltase activity.⁵³ Curcumin and its analogues have protective activity in cultured rat hepatocytes against carbon tetrachloride, D-galactosamine, peroxide and ionophore-induced toxicity.^{54, 55, 56} It also increases the activity of pancreatic lipase, amylase, trypsin and chymotrypsin.⁵⁷

Antidiabetic Effect

Curcumin prevents galactose-induced cataract formation at very low doses.⁵⁸ Both turmeric and curcumin decrease blood sugar level in alloxan-induced diabetes in rat.⁵⁹ Curcumin also decreases advanced glycation end products induced complications in diabetes mellitus.⁶⁰

Antifertility Effect

Curcumin inhibits 5 α -reductase, which converts testosterone to 5 α -dihydrotestosterone, thereby inhibiting the growth of flank organs in hamster.⁶¹ Curcumin also inhibits human sperm motility and has the potential for the development of a novel intravaginal contraceptive.⁶²

Anticoagulant Effect

Curcumin shows anticoagulant activity by inhibiting collagen and adrenaline-induced platelet aggregation *in vitro* as well as *in vivo* in rat thoracic aorta.⁶³

Effect on Alzheimer's disease

In *in vitro* studies, curcumin has been reported to inhibit amyloid- β -protein (A β) aggregation, and A β -induced inflammation, as well as the activities of β -secretase and

acetylcholinesterase. In *in vivo* studies, oral administration of curcumin has resulted in the inhibition of A β deposition, A β oligomerization, and tau phosphorylation in the brains of AD animal models, and improvements in behavioral impairment in animal models. These findings suggest that curcumin might be one of the most promising compounds for the development of AD therapies.⁶⁵ Aging baby boomers are becoming increasingly aware of the risk of Alzheimer's disease, first in their parents and eventually in their own generation. Curcumin may offer some hope as a treatment for this devastating disease.

Antifibrotic Effect

Curcumin suppresses bleomycin-induced pulmonary fibrosis in rats. 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.

Antifertility Effect

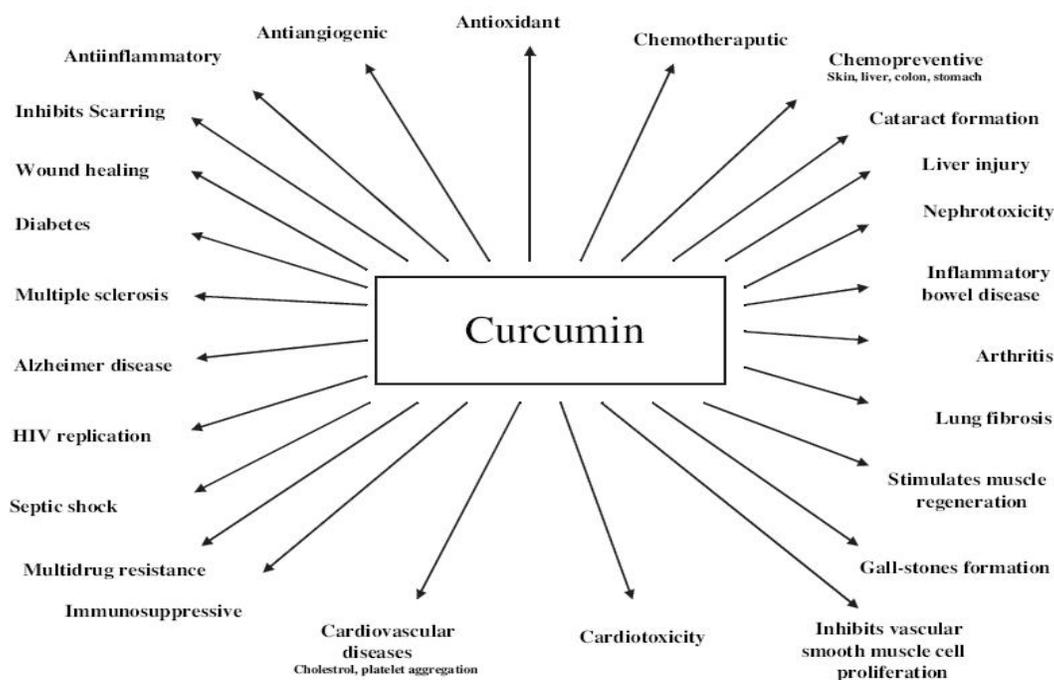
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Other Benefits of Curcumin

In scientific studies, Curcumin has shown promise for:

- Treatment for Indigestion and upper abdominal pain due to functional disorders of the biliary system.
- Treatment for cataracts.
- As a contraceptive.
- Possible treatment for Multiple Sclerosis.
- Arthritis treatment

Curcumin Pharmacological Actions



Side Effects and Toxicity

No significant toxicity has been reported following either acute or chronic administration of turmeric extracts at standard doses. At very high doses (100 mg/kg body weight), curcumin may be ulcerogenic in animals, as evidenced by one rat study.⁶⁴

Bioavailability

Several trials with unformulated curcumin show extensive glucuronidation and sulfation and typically undetectable levels of free curcumin.^{66,67} Phase I clinical trials have shown that curcumin is safe even at high doses (12 g/day) in humans but exhibit poor bioavailability (very low serum levels of free curcumin). Major reasons contributing to the low plasma and tissue levels of curcumin appear to be due to poor absorption, rapid metabolism, and rapid systemic elimination.

Solubility

Curcumin is an oil soluble pigment, practically insoluble in water at acidic and

neutral pH, soluble in alkali. It is soluble in organic solvents such as acetone, ethanol, DMSO and di methyl formamide. The solubility of curcumin in these solvents is approximately 1mg/ml and in acetone is atleast 20mg/ml.

CONCLUSION

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 and showing multiple effects. Extensive scientific research over the past decade has shown the ability of this compound to modulate multiple cellular targets and hence possesses preventive and therapeutic value against a wide variety of diseases. Curcumin has a diverse range of molecular targets like transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis. Despite its demonstrated efficacy and safety, limited

curcumin bioavailability and ulcerative colitis continues to be highlighted as a major concern. Changing of route and medium of curcumin administration, blocking of metabolic pathways by concomitant administration with other agents, developing novel delivery systems and structural modifications are the main strategies now being explored in attempts to improve the bioavailability of curcumin and avoiding acid degradation of the drug due to stomach acids. Enhanced bioavailability of curcumin and avoidance of stomach acid degradation in the near future is likely to bring this promising natural product to the forefront of therapeutic agents for treatment of human disease. Yet, novel delivery strategies offer significant promise and are worthy of further exploration in attempts to enhance the bioavailability and to prevent the stomach acid degradation at high doses. 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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