

Curcumin: Getting Back to the Roots

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ABSTRACT: The use of turmeric, derived from the root of the plant *Curcuma longa*, for treatment of different inflammatory diseases has been described in Ayurveda and in traditional Chinese medicine for thousands of years. The active component of turmeric responsible for this activity, curcumin, was identified almost two centuries ago. Modern science has revealed that curcumin mediates its effects by modulation of several important molecular targets, including transcription factors (e.g., NF- κ B, AP-1, Egr-1, β -catenin, and PPAR- γ), enzymes (e.g., COX2, 5-LOX, iNOS, and hemeoxygenase-1), cell cycle proteins (e.g., cyclin D1 and p21), cytokines (e.g., TNF, IL-1, IL-6, and chemokines), receptors (e.g., EGFR and HER2), and cell surface adhesion molecules. Because it can modulate the expression of these targets, curcumin is now being used to treat cancer, arthritis, diabetes, Crohn's disease, cardiovascular diseases, osteoporosis, Alzheimer's disease, psoriasis, and other pathologies. Interestingly, 6-gingerol, a natural analog of curcumin derived from the root of ginger (*Zingiber officinalis*), exhibits a biologic activity profile similar to that of curcumin. The efficacy, pharmacologic safety, and cost effectiveness of curcuminoids prompt us to "get back to our roots."

KEYWORDS: curcumin; antioxidant; anti-tumor; curcumin analogs

INTRODUCTION

The turmeric (*Curcuma longa*) plant, a perennial herb belonging to the ginger family, is cultivated extensively in south and southeast tropical Asia. The rhizome of this plant is also referred to as the "root" and is the most useful part of the plant for culinary and medicinal purposes. The most active component of turmeric is curcumin, which makes up 2–5% of the spice. The characteristic yellow color of turmeric is due to the curcuminoids, first isolated by Vogel in 1842. Curcumin is an orange-yellow crystalline powder practically insoluble in water. The structure of curcumin (C₂₁H₂₀O₆) was first described in 1910 by Lampe and Milobedeska and shown to be diferuloylmethane.¹

Turmeric is used as a dietary spice, coloring agent in foods and textiles, and a treatment for a wide variety of ailments. It is widely used in traditional Indian medicine to cure biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis. Turmeric paste in slaked lime is a popular home remedy

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for the treatment of inflammation and wounds. For centuries, curcumin has been consumed as a dietary spice at doses up to 100 mg/day. Recent phase I clinical trials indicate that human beings can tolerate a dose as high as 8 g/day with no side effects.² The focus of this review is to describe the effect of curcumin in various diseases.

DISEASE TARGETS OF CURCUMIN

Ancient texts of Indian medicine describe the use of curcumin for a wide variety of inflammatory diseases including sprains and swellings caused by injury, wound healing, and abdominal problems.³ Texts on traditional medicine in China describe the uses of curcumin for the treatment of diseases that are associated with abdominal pain. There are over 1,500 citations in Medline relating to the biologic effect of curcumin. Perhaps most of the activities associated with curcumin are based on its ability to suppress inflammation. Curcumin has been shown to be effective in acute as well as chronic models of inflammation.

Antiinflammatory and Antioxidant Properties. Several studies have shown that curcumin is a potent antioxidant (FIG. 1). In fact, curcumin has been found to be at least 10 times more active as an antioxidant than even vitamin E.⁴ Curcumin prevents the oxidation of hemoglobin and inhibits lipid peroxidation (for references see Ref. 1). 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 1.⁵ Reaction of curcumin with these agents reduces intracellular GSH in

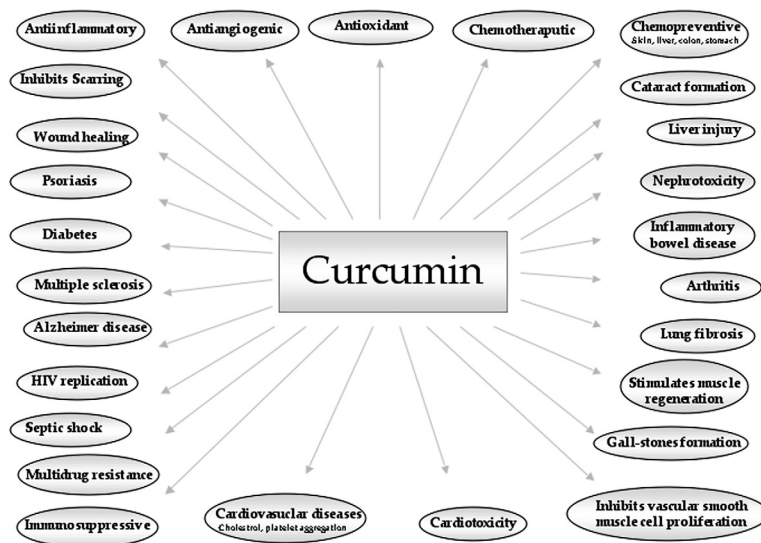


FIGURE 1. Disease targets of curcumin.

the cells. The suppression of lipid peroxidation by curcumin could lead to suppression of inflammation.

Anticancer Properties. The anticancer potential of curcumin in various systems was recently reviewed.¹ Curcumin has been shown to block transformation, tumor initiation, tumor promotion, invasion, angiogenesis, and metastasis. *In vivo*, curcumin suppresses carcinogenesis of the skin, forestomach, colon, and liver in mice. Curcumin also suppresses mammary carcinogenesis. Curcumin has been shown to inhibit the proliferation of a wide variety of tumor cells, including B-cell and T-cell leukemia, colon carcinoma, epidermoid carcinoma, and various breast carcinoma cells.

Cardioprotective Effects. Curcumin has been effective against atherosclerosis and myocardial infarction.⁶ The proliferation of peripheral blood mononuclear cells (PBMCs) and vascular smooth muscle cells (VSMCs), which are hallmarks of atherosclerosis, is inhibited by curcumin. Curcumin prevents the oxidation of low-density lipoproteins (LDLs), inhibits platelet aggregation, and reduces the incidence of myocardial infarction.

Skin Diseases. Curcumin has been shown to be effective against different skin diseases including skin carcinogenesis, psoriasis,⁷ scleroderma,⁸ and dermatitis. Numerous reports suggest that curcumin accelerates wound healing. In addition, curcumin also prevents the formation of scars and plays a role in muscle regeneration following trauma.⁶

Diabetes. In type II diabetes, administration of curcumin reduced the blood sugar, hemoglobin, and glycosylated hemoglobin levels significantly in an alloxan-induced diabetic rat model. Diabetic rats maintained on a curcumin diet for 8 weeks excreted less albumin, urea, creatinine, and inorganic phosphorus. Dietary curcumin also partially reversed the abnormalities in plasma albumin, urea, creatine, and inorganic phosphorus in diabetic animals.⁶

Rheumatoid Arthritis. Curcumin has also been shown to possess antirheumatic and antiarthritic effects, most likely through the downregulation of COX2, tumor necrosis factor (TNF), and other inflammatory cytokines.⁶

Multiple Sclerosis. Multiple sclerosis is characterized by the destruction of oligodendrocytes and myelin sheath in the CNS. Curcumin inhibits experimental allergic encephalomyelitis by blocking interleukin (IL)-12 signaling in T cells, suggesting it would be effective in the treatment of multiple sclerosis.⁶

Alzheimer's Disease. Curcumin can suppress oxidative damage, inflammation, cognitive deficits, and amyloid accumulation in Alzheimer's disease.⁹

Inflammatory Bowel Disease. Ukil *et al.*¹⁰ recently investigated the protective effects of curcumin on inflammatory bowel disease induced in a mouse model. Pretreatment of mice with curcumin for 10 days significantly ameliorated the appearance of diarrhea and the disruption of the colonic architecture.

Cystic Fibrosis. Cystic fibrosis, the most common lethal hereditary disease in the white population, is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene. In a recent report, Egan *et al.*¹¹ demonstrated that curcumin corrected the cystic fibrosis defects in DeltaF508 CF mice.

Others. Curcumin was found to be a potent and selective inhibitor of human immunodeficiency virus (HIV-1) long-terminal repeat-directed gene expression, which governs the transcription of type 1 HIV-1 provirus. It has also been shown to prevent cataractogenesis in an *in vitro* rat model. Treatment with curcumin also pre-

vented experimental alcoholic liver disease. Curcumin has a protective effect on cyclophosphamide-induced early lung injury. Nephrotoxicity, a problem observed in patients who are administered chemotherapeutic agents, can be prevented with curcumin.⁶

MOLECULAR TARGETS OF CURCUMIN

Various studies have shown that curcumin modulates numerous targets (FIG. 2). These include the growth factors, growth factor receptors, transcription factors, cytokines, enzymes, and genes regulating apoptosis.

Cytokines and Growth Factors. Numerous growth factors have been implicated in the growth and promotion of tumors. Curcumin has been shown to downregulate the expression of several cytokines including TNF, IL-6, IL-8, IL-12, and fibroblast growth factor-2.⁶

Receptors. Curcumin has been shown to downregulate both epithelial growth factor receptor (EGFR) and HER2/neu receptors. It also modulates androgen receptors.⁶

Transcription Factors. Curcumin may also operate through suppression of various transcription factors including NF- κ B, STAT3, Egr-1, AP-1, PPAR- γ , and beta catenin activation.⁶ These transcription factors play an essential role in various diseases. The constitutively active form of NF- κ B has been reported in a wide variety of cancers. NF- κ B is required for the expression of genes involved in cell proliferation, cell invasion, metastasis, angiogenesis, and resistance to chemotherapy. Bharti *et al.*¹² demonstrated that curcumin inhibited IL-6-induced STAT3 phosphorylation

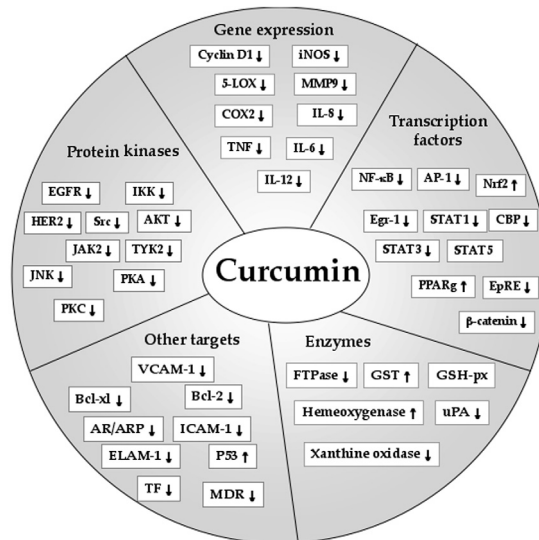


FIGURE 2. Molecular targets of curcumin.

and consequent STAT3 nuclear translocation. Activation of PPAR- γ inhibits the proliferation of nonadipocytes. Xu *et al.*¹³ demonstrated that curcumin dramatically induced the gene expression of PPAR- γ and activated PPAR- γ . AP-1, another transcription factor that has been closely linked with proliferation and transformation of tumor cells, has been shown to be suppressed by curcumin. Studies also suggest that curcumin has a potential therapeutic effect on prostate cancer cells through downregulation of AR and AR-related cofactors.⁶

Proinflammatory Enzymes. Curcumin has been shown to suppress the expression of COX2, 5-LOX, and iNOS, most likely through the downregulation of NF- κ B activation.⁶

Protein Kinases. Curcumin suppresses a number of protein kinases including mitogen-activated protein kinases, JNK, PKA, PKC, src tyrosine kinase, phosphotyrosine kinase, I κ B α kinase, JAK kinase, and the growth factor receptor protein tyrosine kinases.⁶

Cell Cycle. Curcumin modulates cell-cycle-related gene expression. Specifically, curcumin induced G0/G1 and/or G2/M phase cell cycle arrest, upregulated CDKs, p21WAF1/CIP1, p27KIP1, and p53, and slightly downregulated cyclin B1 and cdc2. We found that curcumin can indeed downregulate cyclin D1 expression¹⁴⁻¹⁶ at the transcriptional and posttranscriptional levels.

Adhesion Molecules. Curcumin inhibits inflammation by blocking the adhesion of monocytes to endothelial cells by inhibiting the activation of the cell adhesion molecules ICAM-1, VCAM-1, and ELAM-1.⁶

Antiapoptotic Proteins. Curcumin induces apoptosis by inducing cytochrome *c* release, Bid cleavage, and caspase 9 and 3 activation and by downregulating the antiapoptotic proteins Bcl-2 and Bcl_{xL}.¹

Multidrug Resistance. Multidrug resistance is associated with decreased drug accumulation in tumor cells due to increased drug efflux. Curcumin downregulates drug resistance by inhibiting the expression of the *mdr* gene, which is responsible for this phenomenon.⁶

LESSONS LEARNED FROM SYNTHETIC ANALOGS OF CURCUMIN

To elucidate which portion of the molecule is critical for the activity, a large number of structural analogs of curcumin have been synthesized (FIG. 3A). Some analogs are more active than native curcumin, whereas others are less active¹⁷⁻³² (TABLE 1). It was found that the phenolic analogs were more active than the nonphenolic analogs.³³ The highest antioxidant activity was obtained when the phenolic group was sterically hindered by the introduction of two methyl groups at the ortho position. The phenolic group is essential for free radical scavenging activity, and the presence of the methoxy group further increases the activity.³⁴ Curcumin shows both antioxidant and pro-oxidant effects. Ahsan *et al.*³⁵ have shown that both of these effects are determined by the same structural moieties of the curcuminoids.

Dinkova-Kostova and Talalay³⁰ showed that the presence of hydroxyl groups at the ortho-position on the aromatic rings and the beta-diketone functionality were required for high potency in inducing Phase 2 detoxification enzymes. Curcumin is a noncompetitive inhibitor of rat liver microsomal delta 5 desaturase and delta 6 desaturase. Kawashima *et al.*³⁶ have shown that only half the structure is essential

TABLE 1. Relative potency of curcumin and its synthetic analogs

Effects	References
Analogs more potent than curcumin	
THC: lipid peroxidation under aqueous condition by pulse radiolysis technique	17
HC: preventing nitrite-induced oxidation of haemoglobin	18
NaC: carrageenin-induced rat hind paw edema	19
HMBME: inhibition of prostate cancer	20
BJC005, CHC011, and CHC007: formation of Fos-/Jun- DNA complex	21
Tocopheryl curcumin: inhibiting Tat transactivation of HIV-LTR	22
4,4'-DAC : histamine blocking activity	23
Copper chelates of 2-hydroxynaphthyl curcumin: antitumor activity	24
Hydrazinocurcumin: BAECs proliferation	25
o-hydroxy substituted analog: inhibiting alcohol and PUFA induced oxidative stress	26
Di-O-glycinoyl curcumin and 2'-deoxy-2'-curcuminyll uridine: antiviral activity	27
Pyrazole and isoxazole analogs: Cox-2 inhibitory activity	28
1,7-bis-(2-hydroxy-4-methoxyphenyl)-1,6-heptadiene-3,5-dione): AL activity	29
Salicylcurcuminoid: antioxidant	
Analogs less potent than curcumin	
THC: lipid peroxidation under aerated condition by pulse radiolysis technique	17
THC: TPA-induced mouse ear edema and skin carcinogenesis	30
Analogs as potent as curcumin	
5-hydroxy-1,7-diphenyl-1,4,6-heptatriene-3-one: Scavenge hydroxyl radicals	31
Manganese complexes of curcumin and diacetylcurcumin: Scavenge hydroxyl radicals	32

ABBREVIATIONS: THC, tetrahydrocurcumin; NaC, sodium curcumin; HMBME, 4-hydroxy-3-methoxybenzoic acid methyl ester; DAC, diacetylcurcumin; BAEC, bovine aortic endothelial cells; PUFA, thermally oxidized sunflower oil; Cox-2, cyclooxygenase-2; AL, anti-leishmanial.

for desaturase inhibition. A 3-hydroxy group of the aromatic ring is essential for the inhibition, and a free carboxyl group at the end opposite the aromatic ring interferes with the inhibitory effect.

Simon *et al.*³⁷ found that the presence of the diketone moiety in the curcumin molecule seems to be essential for its ability to inhibit the proliferation of MCF-7 human breast tumor cells. The aromatic enone and dienone analogs of curcumin were demonstrated to have potent antiangiogenic properties in an *in vitro* SVR assay.³⁸

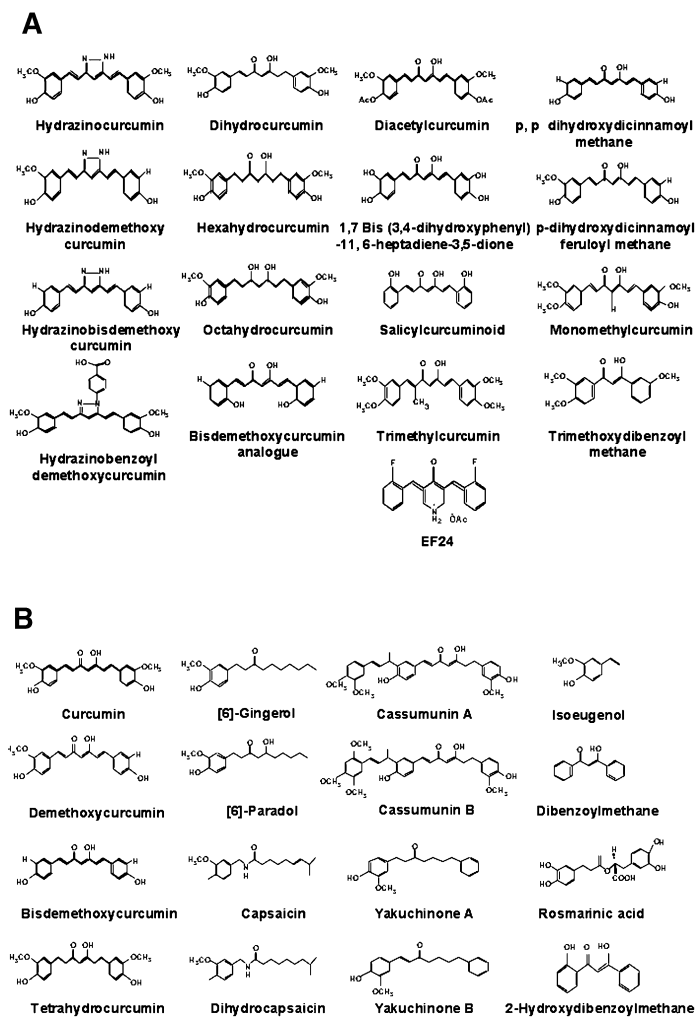


FIGURE 3. Structure of various analogs of curcumin. Hydrazinocurcumin,²⁵ hydrazinodemethoxycurcumin,²⁵ hydrazinobisdemethoxycurcumin,²⁵ hydrazinobenzoyl-demethoxycurcumin,²⁵ dihydrocurcumin,⁵⁰ hexahydrocurcumin,⁵¹ octahydrocurcumin,⁵¹ bisdemethoxycurcumin,⁵² diacetylcurcumin,⁵¹ salicylcurcuminoid,³⁰ monomethylcurcumin,⁵³ trimethylcurcumin,⁵³ and 7-bis(3,4-dihydroxyphenyl)11,6-heptadiene-3,5-dione.⁵³

TABLE 2. Sources and site of action of natural analogs of curcumin^a

Analogs	Source	Target	Ref.
6-Gingerol	Ginger (<i>Zingiber officinale</i> Roscoe)	TNF, NF- κ B, AP-1, COX2, ODC, iNOS, p38MAPK, antifungal	39
8-Gingerol	Ginger (<i>Zingiber officinale</i> Roscoe)		39
6-Paradol	Ginger (<i>Zingiber officinale</i> Roscoe)	Caspase activation	40
Shogaol	Ginger (<i>Zingiber officinale</i> Roscoe)	<i>Helicobacter pylori</i>	41
Cassumunin A&B	Ginger (<i>Zingiber cassumunar</i>)	Antioxidant	42
Diarylheptanoids	Ginger (<i>Zingiber spp.</i>)	PGE2 and LT	43
Dibenzoylmethane	Licorice (<i>Glycyrrhiza echinata</i>)	COX2, LOX, HIF, VEGF	43
Galanals A&B	Zingiber (<i>Zingiber mioga</i> Roscoe)	Caspase 3, bcl2	44
Garcinol	Kokum (<i>Garcinia indica</i>)	NF- κ B, COX-2, iNOS, HAT	45
Isoeugenol	Cloves (<i>Eugenia caryophyllus</i>)	NF- κ B, antioxidant β -amyloid	46
Yakuchinone A&B	Galanga (<i>Alpinia officinarum</i>)	PG synthetase, COX2, iNOS, NF- κ B, insecticidal, adhesion molecules, TNF, AP-1, 5-HETE	47

^aFor structure of these analogs, see FIGURE 3.

NATURAL ANALOGS OF CURCUMIN

Natural curcumin contains three major curcuminoids, namely, curcumin, demethoxycurcumin, and bisdemethoxycurcumin (FIG. 3B). Several analogs of curcumin have been identified from other plant sources. These include 6- and 8-gingerol, 6-paradol, cassumunin, galanals, diarylheptanoids, yakuchinones, isoeugenol, and dibenzoylmethane. Like curcumin, gingerol, paradol, cassumunin, shogaol, and diarylheptanoids are also derived from the roots of the plant (TABLE 2).³⁹⁻⁴⁷ Although most of these analogs exhibit activities very similar to those of curcumin, whether they are more potent or less potent than curcumin has not been established. Yakuchinones⁴⁸ have been shown to be more potent inhibitors of 5-HETE production than curcumin. Synthetic cassumunins also show stronger protective activity than curcumin against oxidative cell death induced by hydrogen peroxide.⁴² Garcinol is more potent than curcumin in inhibiting tumor cells.⁴⁵ The anticancer potential of galanals, however, is comparable to that of curcumin.⁴⁴ Curcumin has been shown to be more cytotoxic than isoeugenol, bis-eugenol, and eugenol.⁴⁹

CONCLUSION

The medicinal properties of curcumin and its analogs have been known to mankind for ages. Modern science has now provided a scientific basis to the numerous reports of the medicinal effects of these most inexpensive, yet pharmacologically safe, polyphenols. Extensive research in the last few years has indicated that most diseases are caused by the dysregulation of multiple signaling pathways, thus casting doubt on how effective monotherapy against single targets will prove to be. Curcumin and its analogs have been found to attack multiple targets, which provides the basis for their effectiveness in so many different diseases. Although most of the NSAIDS are now either withdrawn or survive with black box warnings, curcumin is one that is not known to show any adverse effects, even at doses as high as 8 g a day. Thus, a trip back to our “roots” to explore the “roots” of *Curcuma longa* as a source for better treatments will certainly prove productive. As Hippocrates said almost 25 centuries ago, “let food be thy medicine and medicine be thy food.”

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