CURCUMIN: THE INDIAN SOLID GOLD

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Abstract: Turmeric, derived from the plant *Curcuma longa*, is a gold-colored spice commonly used in the Indian subcontinent, not only for health care but also for the preservation of food and as a yellow dye for textiles. Curcumin, which gives the yellow color to turmeric, was first isolated almost two centuries ago, and its structure as diferuloylmethane was determined in 1910. Since the time of Ayurveda (1900 BC) numerous therapeutic activities have been assigned to turmeric for a wide variety of diseases and conditions, including those of the skin, pulmonary, and gastrointestinal systems, aches, pains, wounds, sprains, and liver disorders. Extensive research within the last half century has proven that most of these activities, once associated with turmeric, are due to curcumin. Curcumin has been shown to exhibit antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities and thus has a potential against various malignant diseases, diabetes, allergies, arthritis, Alzheimer's disease, and other chronic illnesses. These effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. Curcumin exhibits activities similar to recently discovered tumor necrosis factor blockers (e.g., HUMIRA, REMICADE, and ENBREL), a vascular endothelial cell growth factor blocker (e.g., AVASTIN), human epidermal growth factor receptor blockers (e.g., ERBITUX, ERLOTINIB, and GEFTINIB), and a HER2 blocker (e.g., HERCEPTIN). Considering the recent scientific bandwagon that multitargeted therapy is better than monotargeted therapy for most diseases, curcumin can be considered an ideal *"Spice for Life"*.

1. INTRODUCTION

The questions of whether medicines discovered today are safer, more efficacious, and more affordable than generic medicines (whose patents have expired) or medicines that are centuries old could be answered "no" for most of the modern medicines. If so, then it is logical to revisit and revive these age-old medicines for the welfare of mankind. Curcumin is one such medicine. Its history goes back over 5000 years, to the heyday of Ayurveda (which means the science of long life). Turmeric derived from the rhizome of the plant *Curcuma longa* has

been used by the people of the Indian subcontinent for centuries with no known side effects, not only as a component of food but also to treat a wide variety of ailments.

Turmeric is a spice of golden color that is used in cooking in the Indian subcontinent. Because of its color and taste, turmeric was named "Indian saffron" in Europe. Today, India is the primary exporter of turmeric (known as haldi in India). Although its ability to preserve food through its antioxidant mechanism, to give color to food, and to add taste to the food is well known, its health-promoting effects are less well recognized or appreciated. It was once considered a cure for jaundice, an appetite suppressant, and a digestive. In Indian and Chinese medicines, turmeric was used as an anti-inflammatory agents to treat gas, colic, toothaches, chest pains, and menstrual difficulties. This spice was also used to help with stomach and liver problems, to heal wounds and lighten scars, and as a cosmetic.

Turmeric was mentioned in the writings of Marco Polo concerning his 1280 journey to China and India and it was first introduced to Europe in the 13th century by Arab traders. Although Vasco de Gama (a Portugeese sailor) during 15th century, after his visit to India, truly introduced spices to the West, it was during the rule of British in India that turmeric was combined with various other spices and renamed "curry powder," as it is called in the West. What is there in turmeric that has therapeutic potential, how does this substance mediates its effects, with what types of receptor does it interact, and for what type of diseases is it effective? All of these questions will be addressed in this review.

2. COMPOSITION OF TURMERIC

Turmeric contains a wide variety of phytochemicals, including curcumin, demethoxycurcumin, bisdemethoxycurcumin, zingiberene, curcumenol, curcumol, eugenol, tetrahydrocurcumin, triethylcurcumin, turmerin, turmerones, and turmeronols.[1] Curcumin, demethoxycurcumin, and bisdemethoxycurcumin have also been isolated from *Curcuma mangga*,[2] *Curcuma zedoaria*,[3] *Costus speciosus*,[4] *Curcuma xanthorrhiza*,[4] *Curcuma aromatica*,[5] *Curcuma phaeocaulis*,[5] *Etlingera elatior*,[6] and *Zingiber cassumunar*[7] (Figure 1; see Table 1). Curcumin is the phytochemical that gives a yellow color to turmeric and is now recognized as being responsible for most of the therapeutic effects. It is estimated that 2–5% of turmeric is curcumin. Curcumin was first isolated from turmeric in 1815, and the structure was delineated in 1910 as diferuloylmethane. Most currently available preparations of curcumin contain approximately 77% diferuloylmethane, 18% demethoxycurcumin, and 5% bisdemethoxycurcumin. Curcumin is hydrophobic in nature and frequently soluble in dimethylsulfoxide, acetone, ethanol, and oils. It has an absorption maxima around 420 nm. When exposed to acidic conditions, the color of turmeric/curcumin turns from yellow to deep red, the form in which it is used routinely for various religious ceremonies.

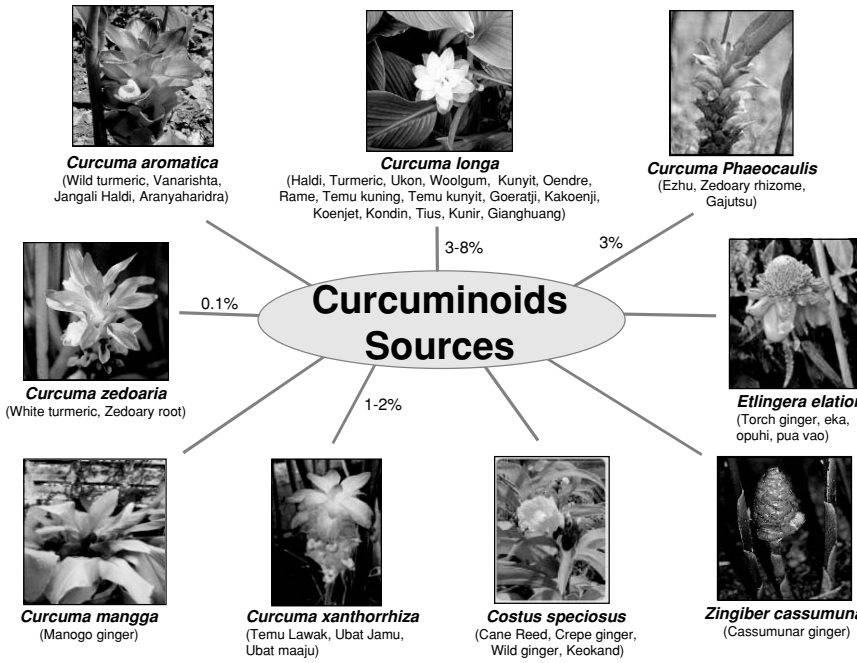

Figure 1. Sources of curcuminoids. (See also Plate 1 in the Color Plate Section.)

3. CURCUMIN ANALOGUES

As indicated earlier, turmeric contains three different analogues of curcumin (i.e., diferuloylmethane, also called curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Figure 2). Whether all three analogues exhibit equal activity is not clear. Although in most systems curcumin was found to be most potent,[8,9] in some systems bisdemethoxycurcumin was found to exhibit higher activity.[3,10] There are also suggestions that the mixture of all three is more potent than either one alone.[11,12]

When administered orally, curcumin is metabolized into curcumin glucuronide and curcumin sulfonate.[13] However, when administered systemically or intraperitoneally, it is metabolized into tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol. Tetrahydrocurcumin has been shown to be active in some systems[14–18] and not in others.[13,19] Whether other metabolites of curcumin exhibit biological activity is not known.

4. USES OF CURCUMIN

The use of turmeric for health purposes is nothing new. As a folklore medicine, its use has been documented in both Indian and Chinese cultures. The long list of uses

Table 1. List of various species of curcuma.

C. aeruginosa	*C. coriacea*	*C. meraukensis*	*C. rubricaulis*
C. albicoma	*C. decipiens*	*C. montana*	*C. rubrobracteata*
C. albiflora	*C. domestica*	*C. musacea*	*C. sessilis*
C. alismatifolia	*C. ecalcarata*	*C. mutabilis*	*C. sichuanensis*
C. amada	*C. ecomata*	*C.neilgherrensis*	*C. singularis*
C. amarissima	*C. elata*	*C. nilamburensis*	*C. soloensis*
C. americana	*C. erubescens*	*C. ochrorhiza*	*C. sparganifolia*
C. angustifolia	*C. euchroma*	*C. officinalis*	*C. speciosa*
C. aromatica*	*C. exigua*	*C. oligantha*	*C. spicata*
C. attenuata	*C. ferruginea*	*C. ornata*	*C. stenochila*
C. aurantiaca	*C. flaviflora*	*C. pallida*	*C. strobilifera*
C. australasica	*C. glans*	*C. parviflora*	*C. sulcata*
C. bakeriana	*C. glaucophylla*	*C. parvula*	*C. sumatrana*
C. bicolor	*C. gracillima*	*C. peethapushpa*	*C. sylvatica*
C. brog	*C. grahamiana*	*C. petiolata*	*C. sylvestris*
C. burttii	*C. grandiflora*	***C. phaeocaulis****	*C. thalakaveriensis*
C. caesia	*C. haritha*	*C. pierreana*	*C. thorelii*
C. cannanorensis	*C. harmandii*	*C. plicata*	*C. trichosantha*
C. caulina	*C. heyneana*	*C. porphyrotaenia*	*C. vamana*
C. careyana	*C. inodora*	*C. prakasha*	*C. vellanikkarensis*
C. ceratotheca	*C. latiflora*	*C. pseudomontana*	*C. viridiflora*
C. chuanezhu	*C. latifolia*	*C. purpurascens*	*C. wenchowensis*
C. chuanhuangjiang	*C. leucorhiza*	*C. purpurea*	*C. wenyujin*
C. chuanyujin	*C. leucorrhiza*	*C. raktakanta*	***C. xanthorrhiza****
C. cochinchinensis	*C. loerzingii*	*C. ranadei*	*C. yunnanensis*
C. codonantha	***C. longa****	*C. reclinata*	*C. zanthorrhiza*
C. coerulea	*C. longiflora*	*C. rhabdota*	***C. zedoaria****
C. colorata	*C. longispica*	*C. rhomba*	*C. zerumbet*
C. comosa*	*C. lutea*	*C. roscoeana*	
C. cordata	*C. malabarica*	*C. rotunda*	
C. cordifolia	***C. mangga****	*C. rubescens*	

Note: Curcuma is indicated by C.
*Curcuminoids have been isolated from the plant indicated in bold.
Source: Modified from http://en.wikipedia.org/wiki/Curcuma.

include antiseptic, analgesic, anti-inflammatory, antioxidant, antimalarial, insect-repellant, and other activities associated to turmeric.[4,20–27] (Figure 3). Perhaps one of the most often prescribed uses is for wound-healing.[28] This activity is well known to people from the Indian subcontinent. Modern research has provided considerable evidence, and the mechanism by which turmeric/curcumin could accelerate wound-healing has been described.[29–36]

It is now well recognized that most chronic diseases are the result of dis-regulated inflammation,[37,38] Turmeric has been traditionally described as an anti-inflammatory agent. Recent scientific evidence has indeed demonstrated that turmeric, and curcumin in particular, exhibits potent anti-inflammatory activities as determined by a wide variety of systems.[39–49] Therefore, it is not too surprising that turmeric displays activities against a variety of diseases. Because curcumin also exhibits potent antioxidant activity, whether the anti-inflammatory activity of curcumin is mediated through its antioxidant mechanism is not clear. Since most

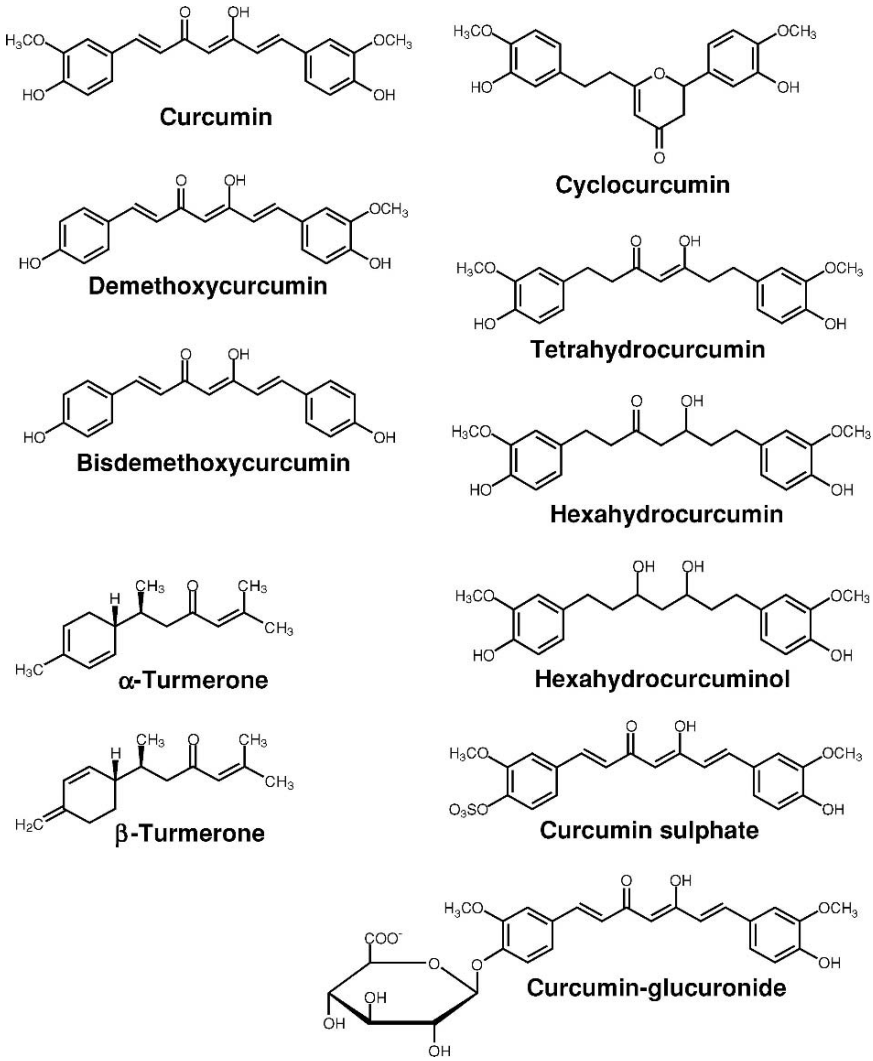

Figure 2. Chemical structures of curcumin and its analogues.

well-characterized antioxidants do not exhibit anti-inflammatory activity, it is unlikely that the anti-inflammatory activity of curcumin is due to its antioxidant activity.

5. MOLECULAR TARGETS OF TURMERIC/CURCUMIN

Most molecular targets established in modern biology were discovered within the last three decades. The effect of curcumin on most of these targets has

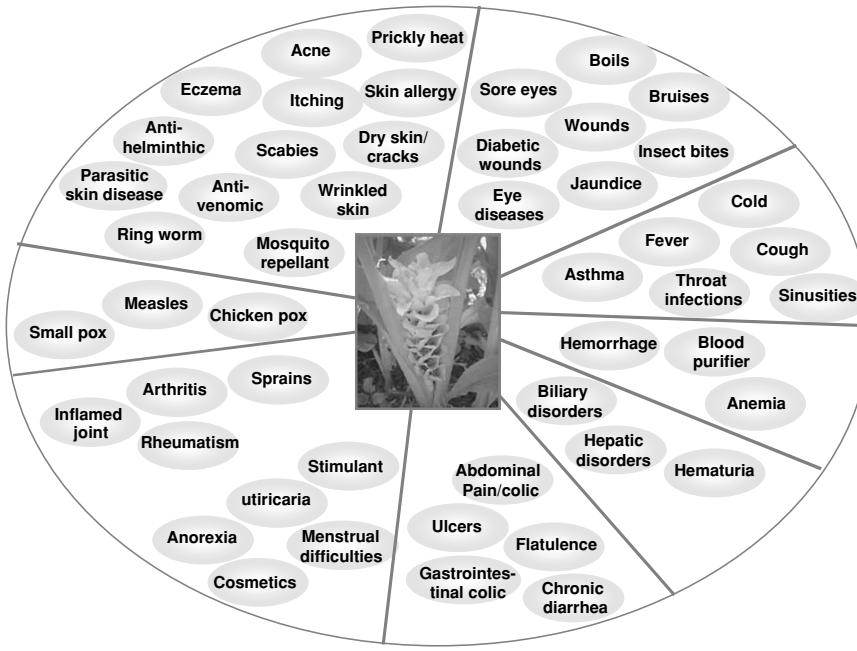

Figure 3. Traditional uses of curcmin. (See also Plate 2 in the Color Plate Section.)

been examined[10,12,45,50–201] (Figure 4). The results have revealed that curcumin can modulate several different transcription factors,[50–96,113,114] cytokines,[45,97–112] growth factors,[202–215] kinases,[115–128] and other enzymes.[91,129–159] Although most diseases are caused by dysregulated inflammation, to find a safe and efficacious anti-inflammatory agent is a real challenge in modern medicine. Steroids are perhaps the best known anti-inflammatory agents. However, there are numerous side effects associated with them. In addition to steroids, numerous nonsteroidal antiinflamatory drugs (NSAIDs) have been discovered within the last century, and these include salicylates, ibuprofen, sulindac, phenylbutazone, naproxen, diclofenac, indomethacin, and coxibs.[216] Experience over the years has indicated that most of these NSAIDs are associated with a constellation of side effects. Perhaps the best example is the cardiovascular system-related side effects recently identified with most coxibs.[217–219] Although the intake of such anti-inflammatory agents can be justified for chronic conditions, they are not appropriate as chemopreventive agents under normal conditions, because that purpose requires long periods of time. Thus, there is a great need for safer and efficacious anti-inflammatory agents.

Numerous lines of evidence suggest that curcumin is a potent anti-inflammatory agent (see Figure 5). First, curcumin suppresses the activation of the transcription factor NF–κB, which regulates the expression of pro-inflammatory gene products.[50–81] Second, curcumin downregulates the expression of COX-2, an

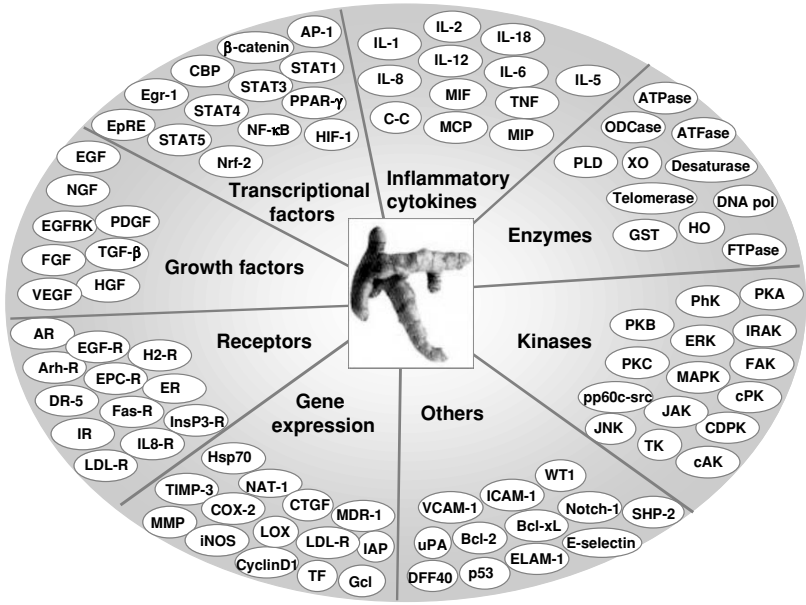

Figure 4. Molecular targets of curcumin. Abbreviations used: NF-κB, nuclear factor-κB; AP-1, activating protein-1; STAT, signal transducers and activators of transcription; Nrf-2, nuclear factor erythroid 2-related factor; Egr-1, early growth response gene-1; PPARγ, peroxisome preoliferator-activated receptor-γ; CBP, CREB-binding protein; EpRE, electrophile response element; CTGF, connective tissue growth factor; EGF, epidermal growth factor; EGFRK, EGF receptor-kinase; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; NGF, nerve growth factor; PDGF, platelet-derived growth factor; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor; AR, androgen receptor; Arh-R, aryl hydrocarbon receptor; DR-5, death receptor-5; EGF-R, EGF-receptor; EPC-R, endothelial protein C-receptor; ER-α, estrogen receptor-α; Fas-R, Fas receptor; H2-R, histamine (2)-receptor; InsP3-R, inositol 1,4,5-triphosphate receptor; IR, integrin receptor; IL-8-R, interleukin-8-receptor; LDL-R, low-density lipoprotein-receptor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase-3; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; LOX, lipoxygenase; Gcl, glutamate-cysteine ligase; NAT, arylamine *N*-acetyltransferases; IAP, inhibitory apoptosis protein; HSP-70, heat shock protein 70; MDR, multidrug resistance; TNF-α, tumor necrosis factor-α; IL, interleukin; MCP, monocyte chemoattractant protein; MIF, migration inhibition protein; MIP, macrophage inflammatory protein; cAK, autophosphorylation-activated protein kinase; CDPK, Ca^{2+}-dependent protein kinase; cPK, protamine kinase; ERK, extracellular receptor kinase; FAK, focal adhesion kinase; IARK, IL-1 receptor-associated kinase; JAK, janus kinase; JNK, c-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; PhK, phosphorylase kinase; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; pp60c-src, a nonreceptor protein tyrosine kinase c-Src, cellular src kinase; TK, protein tyrosine kinase; FPTase, farnesyl protein transferase; GST, gluthathione-*S*-transferase; HO, hemeoxygenase; ICAM-1, intracellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; ELAM-1, endothelial leukocyte adhesion molecule-1; Bcl-2, B-cell lymphoma protein 2; SHP-2, Src homology 2 domain-containing tyrosine phosphatase 2, uPA, urokinase-type plasminogen activator, DFF40; DNA fragmentation factor, 40-kd subunit. (See also Plate 3 in the Color Plate Section.)

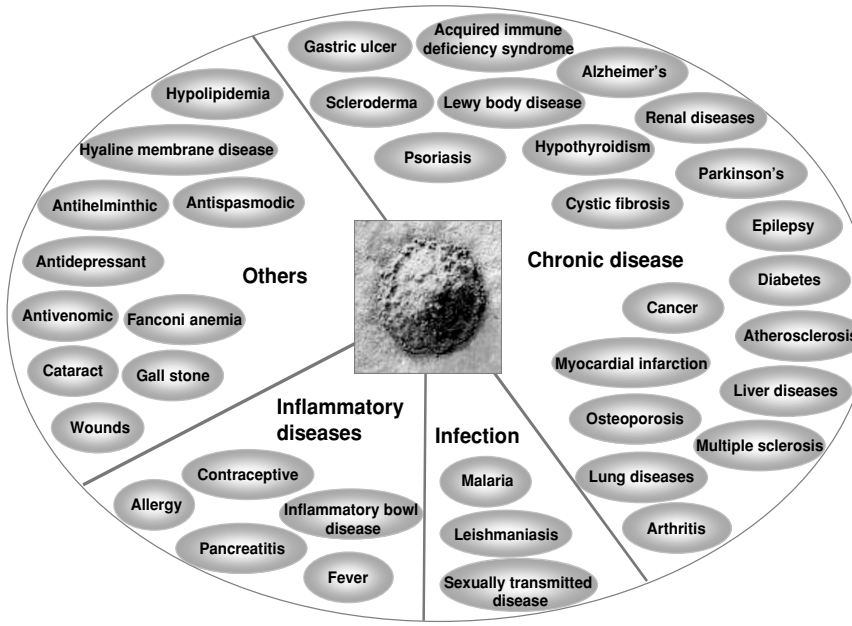

Figure 5. Potential uses of curcumin based on modern technology. (See also Plate 4 in the Color Plate Section.)

enzyme linked with most types of inflammations.[75,177–181,183] Third, curcumin inhibits the expression of another pro-inflammatory enzyme, 5-LOX.[177,182–184] Additionally, curcumin has been shown to bind to the active site of 5-LOX and inhibit its activity[183] Fourth, curcumin downregulates the expression of various cell surface adhesion molecules that have been linked with inflammation.[220–222] Fifth, curcumin downregulates the expression of various inflammatory cytokines, including TNF, IL-1, IL-6, IL-8, and chemokines.[45,97–112] Sixth, curcumin has been shown to inhibit the action of TNF, one of the most pro-inflammatory cytokines.[97–100] Seventh, curcumin is a potent antioxidant, which might contribute to its anti-inflammatory action.[16,19,31,159,223–279] All of this recent evidence confirms the anti-inflammatory action of curcumin, known for thousands of years. Its pharmacological safety combined with its anti-inflammatory action, makes it an ideal agent to explore for preventive and therapeutic situations.

Whereas pro-oxidants are considerd mediators of numerous diseases, antioxidants are generally believed to delay or halt the disease. However, this paradigm is not always valid, as most cytokines mediate their effects through pro-oxidant mechanisms. Reactive oxygen species (ROS) also play an important role in cell-mediated cytotoxicity (CMC) of the immune system. Numerous reports indicate that curcumin could mediate both pro-oxidant and antioxidant roles. First, curcumin could induce the expression of ROS,[8,280–282] which plays an important role in the antiproliferative effects of this molecule.[283] Second, curcumin binds

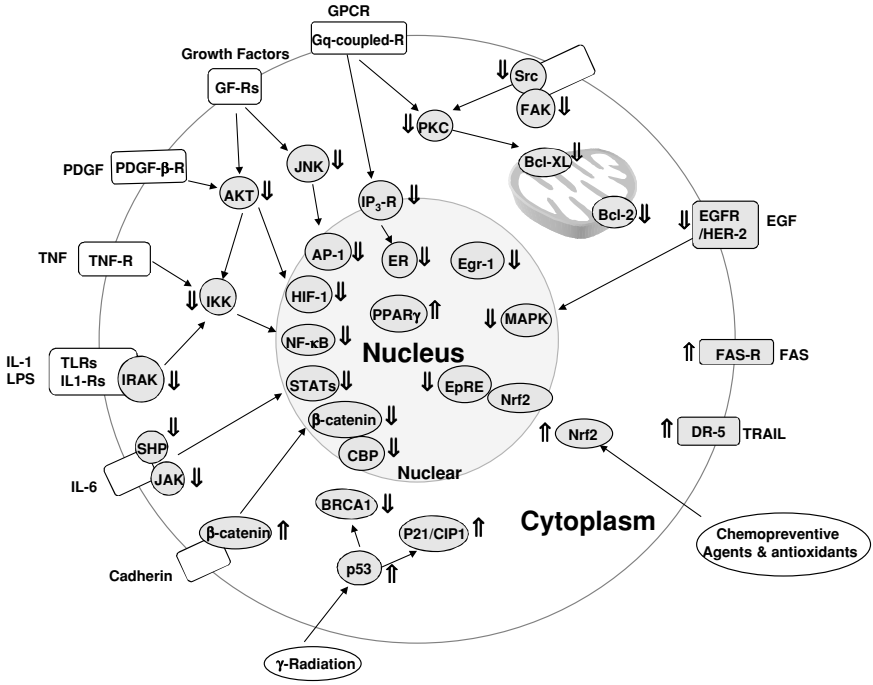

Figure 6. Signaling pathway modulated by curcumin. Intermediates upregulated by curcumin are indicated as ⇑ and those downregulated by curcumin are indicated as ⇓.

thioredoxin reductase (TR) and converts this enzyme to NADPH oxidase, thus leading to the production of ROS.[284] Because TR is overexpressed in tumor cells,[285–287] curcumin kills tumor cells through this mechanism. Third, curcumin suppresses lipid peroxidation.[224,226–228,232,234,238,252,256,264,265,268,288,289] Fourth, curcumin increases the expression of intracellular glutathione.[139,140,142,143,146,290–294] Fifth, curcumin could also play an antioxidant role through its ability to bind iron.[229] All of these reports combined suggest the ability of curcumin to modulate the redox status of the cells. That curcumin can modulate the cellular action of various growth factors and cytokines has also been demonstrated (Figure 6). First, curcumin has been shown to downregulate the effect of epidermal growth factor (EGF) through downregulation of expression and activity of EGF receptors (EGFR).[203,210–212] Second, curcumin has been shown to downregulate the activity of human EGFR-2 (called HER2/neu),[127] a growth factor receptor closely linked with cancer of the breast, lung, kidney, and prostate. Third, curcumin suppresses the action of interleukin (IL)-6 through the downregulation of STAT3 activation.[296] Fourth, curcumin modulates the action of TNF, a growth factor for tumor cells.[297] Fifth, curcumin negatively regulates the action of IL-2,[298] a growth factor for T cells. Thus, curcumin can affect the action of a wide variety of growth factors.[202–215]

Angiogenesis is a process of vascularization of the tissue, which is critical for the growth of solid tumors. Numerous molecules have been linked with angiogenesis. These include vascular endothelial growth factor (VEGF), COX-2, fibroblast growth factor (FGF), and TNF. Evidence suggests that curcumin could suppress angiogenesis.[113,205,208,299–303] Curcumin includes its ability to downregulate the expression of VEGF.[208] Likewise, it downregulates FGF-mediated angiogenesis.[205] Curcumin was found to negatively regulate the expression of COX-2[74,177–181] and suppresses both the expression and action of TNF.[97–100]

6. CURCUMIN RECEPTORS

Receptors are cellular proteins to which a molecule binds, leading to secondary cellular responses. Whether there are any authentic receptors for curcumin is not known. However, numerous molecules to which curcumin binds have been identified. These include serum albumin,[304,305,306] 5-LOX,[183,307] xanthine oxidase,[159] thioredoxin reductase,[284] iron,[295] COX-2,[308] IKK,[309] *p*-glycoprotein,[310,311] GST,[291] PKA,[115] PKC.[115] cPK,[115] PhK,[115] autophosphorylation-activated protein kinase,[115] pp60c-src tyrosine kinase,[115] Ca^{2+}-dependent protein kinase (CDPK),[116] Ca^{2+}-ATPase of sarcoplasmic reticulum,[131] aryl hydrocarbon receptor,[186] rat river cytochrome p450s,[291] Topo II isomerase,[312] inositol 1,4,5-triphosphate receptor,[313] and glutathione.[143]

7. DISEASE TARGETS OF CURCUMIN

Extensive research within the last half a decade has revealed that curcumin has potential against a wide variety of diseases, both malignant and nonmalignant (see Figure 5). The potential of curcumin, however, has not been systematically examined through the modern multicenter, randomized, double-blind, placebo-controlled clinical trials.[314–335] Its potential in humans is indicated either through preclinical studies, some pilot studies in humans, anecdotal studies in patients, or epidemiological studies. Curcumin has been shown to exhibit activity against numerous inflammatory diseases, including pancreatitis,[100,214,261,336,337] arthritis,[105,338–341] inflammatory bowel disease (IBD),[332] colitis,[342–344] gastrititis,[345,346] allergy,[99,347,348] and fever,[349,350] possibly through the downregulation of inflammatory markers, as indicated earlier. The effect of curcumin against various autoimmune diseases has also been demonstrated; they include scleroderma,[351] psoriasis,[352]multiple sclerosis,[111,353] and diabetes.[354–362] Again, these effects of curcumin are through the regulation of pro-inflammatory signaling.

Although once thought to be distinct, the molecular targets for both the prevention and therapy of cancer are now considered the same,[363,364]. Numerous lines of evidence suggest the potential of curcumin against various types of cancer[11,56,76,83,95,145,153,155,273,283,298,309,365–462] (see Table 2). First,

Table 2. Chemopreventive and anticancer effects of curcumin.

Skin
External cancerous lesion[405]
Human basal cell carcinoma[469]
Human melanoma[412–414]
Human epidermal carcinoma[415]
Prevention from
7,12-dimethylbenz[a]anthracene[11,406]
Prevention from azoxymethanol[407]
Prevention from benz[a]pyrene and
12-O-tetradecanoylphorbol-13-acetate[408]
Prevention from 12-O-tetradecanoylphorbol-13-acetate[153,155,409]
Prevention from
12-O-tetradecanoylphorbol-13-acetate- and
7,12-dimethylbenz[a]anthracene[410]

Oral
Prevention from
methyl-(acetoxymethyl)-nitrosamine[416]
Prevention from 4-nitroquinoline 1-oxide[417]
Prevention from
7,12-dimethylbenz[a]anthracene[418–420]

Esophageal
Prevention from
N-nitrosomethylbenzylamine[421]

Forestomach
Prevention from benzo[a]pyrene[406,422,423]
Prevention from
N-methyl-N'-nitro-N-nitrosoguanidine[424]

Intestine
Prevention from Min/+ mouse
(a model of familial adenomatous polyposis)[425,426]

Colon
Colon adeno carcinoma[95,435–440]
Prevention from azoxymethane[427–433]
Prevention from 1,2-dimethylhydrazine dihydrochrolide[434]

Mammary gland
Prevention from 7,12-dimethylbenz[a]anthracene[11,427,441–443]
Prevention from diethylstilbestrol[444]
Prevention from radiation[365,455]

Liver
Human hepatoblastoma[371,462]
Prevention from diethylnitrosamine[366,367,369]
Prevention from N-nitrosodiethylamine and phenobarbital[370]

Prostate
Prevention from 3,2'-dimethyl-4-aminobiphenol (DMAB) and 2-amino-1-methylimidazo[4,5-b]pyridine (PhIP)[372]

Blood and Bone Marrow
Human leukemia[145,273,373–379]
T-lymphocyte[298,380,381]
Rat thymocytes[382]
Rat histhymocytoma[283]
B-cell lymphoma[56,383,384]
B-cell non-Hodgkin's lymphoma[385,386]
Burkitt's lymphoma[387]
Human multiple myeloma[83,309,388]
Primary effusion lymphoma[389]

Brain
Neuroblastoma[390,391]
Ehrlich's ascites carcinoma[456,480]
Astrocytoma[393]

Breast
Breast carcinoma [394–399]

Gatrointestinal
Gastric signet ring carcinoma[400]

Head and Neck
Head and neck squamous cell carcinoma[76,200,401]

Lung
Human lung[402,447]

Pancreas
Pancreatic carcinoma[403]

Ovarian
Human ovarian[404]

curcumin has been shown to suppress the proliferation of a wide variety of tumor cells through the downregulation of antiapoptotic gene products, activation of caspases, and induction of tumor suppressor genes such as $p53$.[95,145,283,298,313,351,373–384,389–393,396,397,399–403,411,412,415,435–440,463–499]

Second, curcumin has also been to shown to suppress the invasion of tumors through the downregulation of matrix metalloproteinases (MMPs) and cell surface adhesion molecules[134,208,220,301,302,340,346,500–507] Third, curcumin suppresses the angiogenesis of tumors through the suppression of angiogeneic cytokines.[508–512] Fourth, the anti-inflammatory effects of curcumin contribute to its antitumor activity as well.[39–49]

Curcumin has also been shown to play a role in diabetes mellitus type II, in which the patient develops a resistance to insulin.[354,356,359–361,513] Both NF–κB and TNF have been linked with the induction of resistance to insulin. Because curcumin can downregulate the activation of NF–κB and downregulate TNF expression and TNF signaling,[97–100] it can be exploited in diabetic patients. Several animal studies have demonstrated that curcumin can overcome insulin resistance.[514,515]

That curcumin prevents myocardial infarction and other cardiovascular diseases has also been demonstrated.[202,516–524] The effects of curcumin in cardiovascular diseases are linked to its ability to (1) inhibit platelet aggregation,[215,525–529] (2) inhibit inflammatory response,[90,202,530–532] (3) lower LDL and elevate HDL,[533–538] (4) inhibit fibrinogen synthesis,[539] and (5) inhibit oxidation of LDL.[288,531,540–542] All of these activities contribute to the cardiovascular effects of curcumin. Because curcumin can suppress amyloid-induced inflammation, curcumin has also been linked to the suppression of Alzheimer's disease.[150,297,327,543–554]

8. CONCLUSION

The above description and various other chapters in this volume prove that curcumin has enormous potential for a variety of diseases. There are, however, still several unanswered questions. First, phase I clinical trials have indicated that as high as 12 g of curcumin per day for over 3 months is well tolerated in humans.[334] What the optimum dose of curcumin is for the treatment of a given disease is not clear. Serum levels of curcumin tend to be low,[334] which might be responsible for its pharmacological safety, These data have led to the notion that curcumin has low bioavailability. Second, the tissue concentration of curcumin and how it compares to what is seen in cell culture conditions are not known. There are studies, however, that suggest that agents such as piperine (a component of black pepper) can enhance the bioavailability of curcumin through suppression of its glucuronidation occurring primarily in the liver and in the intestine.[317] Third, whether there are components of turmeric other than curcumin that have beneficial effects either alone or in combination with curcumin needs to be determined. For instance, numerous activities have been assigned to turmeric oil.[307,555–559] Fourth, what effect do other spices have on the pharmacology and the biology of curcumin needs to be determined. Fifth, structural analogues of curcumin that are more bioavailable and efficacious are needed. However, this

might compromise the safety of curcumin. Sixth, well-controlled large clinical trials are required to determine the potential of curcumin both in the prevention and therapy of a disease. All of these studies should further add to the usefulness of curcumin. Overall, the biological safety, combined with its cost and efficacy, and thousands of years of experimentation justify calling curcumin "Indian Solid Gold."

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ABBREVIATIONS USED

EGF, epidermal growth factor; EGFR, EGF receptor; NF-κB, nuclear factor-κB; TNF, tumor necrosis factor; AP-1, activating protein-1; JNK, c-jun N-terminal kinase; MMP, matrix metalloprotease; COX-2, cyclooxygenase 2; iNOS, inducible nitric oxide synthase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TGF-β1, transforming growth factor beta 1; IL, interleukin; STAT, signal transducers and activators of transcription; proteins, low molecular weight proteins; NSAIDs, nonsteroidal anti-inflammatory drugs; amyloid precursor; GST, gluthathione-S–transferase; LOX, lipooxygenase; ROS, reactive oxygen species; VEGF, vascularendothelial growth factor; FGF, fibroblast growth factor; IKK, IκB kinase; PKC, protein kinase C; PKA, protein kinase A.

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