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## Commentary

# Curcumin as “Curecumin”: From kitchen to clinic

Ajay Goel<sup>a</sup>, Ajaikumar B. Kunnumakkara<sup>b</sup>, Bharat B. Aggarwal<sup>b,\*</sup>

<sup>a</sup> Gastrointestinal Cancer Research Laboratory, Department of Internal Medicine, Charles A. Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX, United States

<sup>b</sup> Cytokine Research Laboratory, Departments of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, United States

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### ABSTRACT

Although turmeric (*Curcuma longa*; an Indian spice) has been described in Ayurveda, as a treatment for inflammatory diseases and is referred by different names in different cultures, the active principle called curcumin or diferuloylmethane, a yellow pigment present in turmeric (curry powder) has been shown to exhibit numerous activities. Extensive research over the last half century has revealed several important functions of curcumin. It binds to a variety of proteins and inhibits the activity of various kinases. By modulating the activation of various transcription factors, curcumin regulates the expression of inflammatory enzymes, cytokines, adhesion molecules, and cell survival proteins. Curcumin also down-regulates cyclin D1, cyclin E and MDM2; and upregulates p21, p27, and p53. Various preclinical cell culture and animal studies suggest that curcumin has potential as an antiproliferative, anti-invasive, and antiangiogenic agent; as a mediator of chemoresistance and radioresistance; as a chemopreventive agent; and as a therapeutic agent in wound healing, diabetes, Alzheimer disease, Parkinson disease, cardiovascular disease, pulmonary disease, and arthritis. Pilot phase I clinical trials have shown curcumin to be safe even when consumed at a daily dose of 12 g for 3 months. Other clinical trials suggest a potential therapeutic role for curcumin in diseases such as familial adenomatous polyposis, inflammatory bowel disease, ulcerative colitis, colon cancer, pancreatic cancer, hypercholesterolemia, atherosclerosis, pancreatitis, psoriasis, chronic anterior uveitis and arthritis. Thus, curcumin, a spice once relegated to the kitchen shelf, has moved into the clinic and may prove to be “Curecumin”.

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## 1. Introduction

Natural plant products have been used throughout human history for various purposes. Having coevolved with life, these natural products are billions of years old. Tens of thousands of them are produced as secondary metabolites by the higher plants as a natural defense against disease and infection.

Medicines derived from plants have played a pivotal role in the health care of many cultures, both ancient and modern [1–5]. The Indian system of holistic medicine known as Ayurveda uses mainly plant-based drugs or formulations to treat various ailments including cancer. Of the approximately 877 small-molecule drugs introduced worldwide between 1981 and 2002, most (61%) can be traced back to their origins in natural

\* Corresponding author. Tel.: +1 713 792 3503.

E-mail address: [aggarwal@mdanderson.org](mailto:aggarwal@mdanderson.org) (B.B. Aggarwal).  
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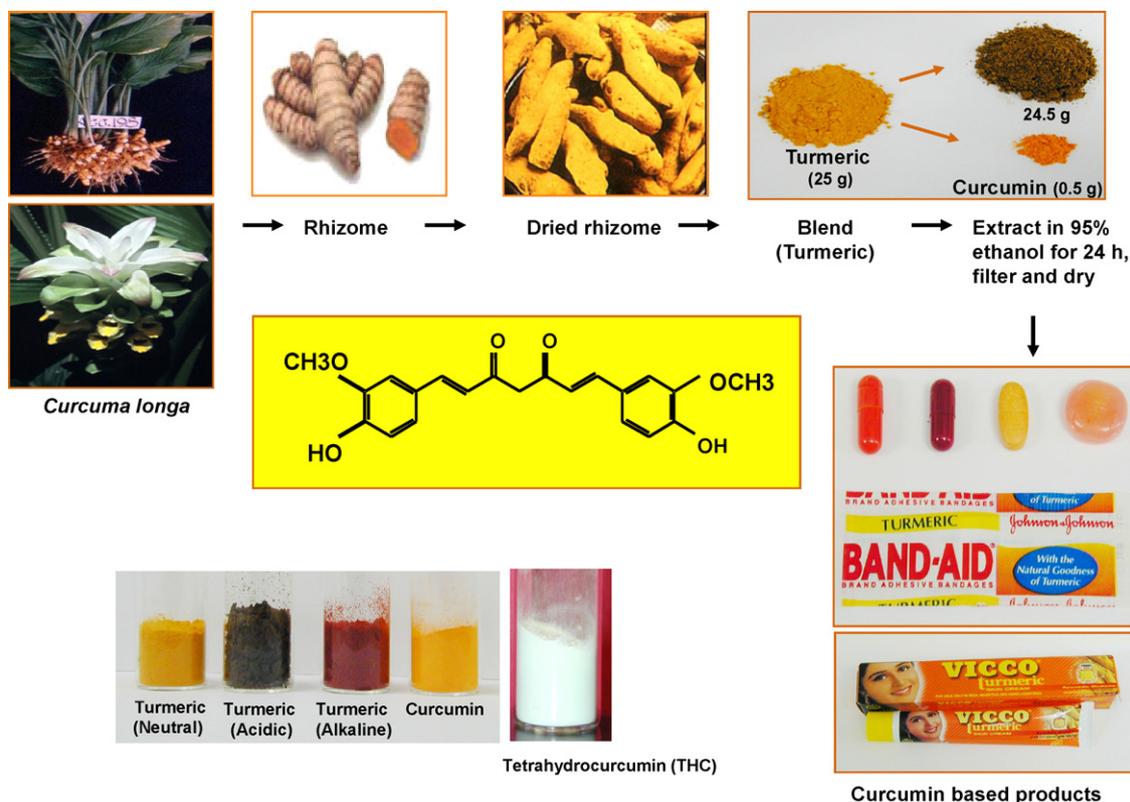
products [1]. This is not surprising since plant-based drugs may be more suitable – at least in biochemical terms – for medicinal human use than the many exotic synthetic drugs produced through combinatorial chemistry. Nonetheless, modern medicine has neither held in very high esteem nor encouraged the medicinal use of natural products.

Over the last two decades, however, successful attempts to better understand molecular mechanisms of action of some natural products have kindled interest in their therapeutic use in modern medical settings. Remarkably, most of the natural products experimentally evaluated so far have been found to be nontoxic or to have effective doses far below their toxic doses. The role of natural products in human healthcare cannot be underestimated. An estimated 80% of individuals in developing countries depend primarily on natural products to meet their healthcare needs [6]. Recent surveys suggest that one in three Americans uses medicinal natural products daily and that possibly one in two cancer patients (i.e., up to 50% of patients treated in cancer centers) uses them as well. The current review is limited to curcumin, a natural product in use for thousands of years

Curcumin (diferuloylmethane), a polyphenol, is an active principle of the perennial herb *Curcuma longa* (commonly

known as turmeric) (Fig. 1). The yellow-pigmented fraction of turmeric contains curcuminoids, which are chemically related to its principal ingredient, curcumin. The major curcuminoids present in turmeric are demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin III), and the recently identified cyclocurcumin [7]. The major components of commercial curcumin are curcumin I (~77%), curcumin II (~17%), and curcumin III (~3%). The curcuminoid complex is also referred to as Indian saffron, yellow ginger, yellow root, *kacha haldi*, ukon, or natural yellow 3. Curcuminoids are present in 3–5% of turmeric. Though principally cultivated in India, Southeast Asia, China, and other Asian and tropical countries and regions, turmeric is also common in other parts of the world and is recognized by different names in different languages worldwide (Table 1). [8]

Curcumin was first isolated in 1815, obtained in crystalline form in 1870 [9,10], and ultimately identified as 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E) or diferuloylmethane. In 1910, the feruloylmethane skeleton of curcumin was confirmed and synthesized by Lampe [11]. Curcumin is a yellow-orange powder that is insoluble in water and ether but soluble in ethanol, dimethylsulfoxide, and acetone. Curcumin has a melting point of 183 °C, a molecular



**Fig. 1** – Isolation, extraction, and structure of curcumin. Curcumin capsules, pills, lozenges, band-aid and cream commonly sold in the market are shown. The change in color of turmeric at acidic and alkaline pH is also shown. Tetrahydrocurcumin (THC), a major metabolite of curcumin, exhibits whitish color. Alkaline turmeric (red color) is also referred as “Kumkum”. The traditional Kumkum, or Kungumam as it is called in Tamil Nadu (India), is made from dried turmeric. The turmeric is dried and powdered with a bit of slaked lime, which turns the rich yellow powder into red color. The kungumam (also called Bindi, Bindu, Tilak or Sandoor) is an auspicious symbol. When a girl or a married woman visits a house, it is a sign of respect (in case of an elderly lady) or blessings (in case of a young girl) to offer kumkum to them when they leave. Kumkum is also widely used for worshipping the Hindu goddesses, especially Shakti and Lakshmi. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

**Table 1 – Various names of turmeric/curcumin in different languages**

Language	Name
Arabic	Kurkum, Uqdah safra
Armenian	Toormerik, Turmerig
Assamese	Halodhi
Bengali	Halud
Bulgarian	Kurkuma
Burmese	Hsanwen, Sanwin, Sanae, Nanwin
Catalan	Cúrcuma
Chinese	Yu chin, Yu jin, Wohng geung, Geung wohng, Wat gam, Huang jiang, Jiang huang, Yu jin, Yu jin xiang gen
Croatian	Indijski šafran, Kurkuma
Czech	Kurkuma, Indický Šafrán, Žlutý kořen, Žlutý závor
Dhivehi	Reen'dhoo
Danish	Gurkemeje
Dutch	Geelwortel, Kurkuma Tarmeriek, Koenjit, Koenir
English	Indian saffron
Esperanto	Kurkumo
Estonian	Harilik kurkuma, Kurkum, Pikk kollajuur, Lõhnnav kollajuur, Harilik kurkuma, Kurkum, Pikk kollajuur, Lõhnnav kollajuur Zardchubeh
Farsi	Kurkuma, Keltajuuri
Finnish	Kurkuma, Safran des Indes, Terre-mérite, Souchet des Indes
Galician	Cúrcuma
German	Curcuma, Kurkuma, Indischer Safran, Gelbwurz
Greek	Kitrinoriza, Kourkoumi, Kourkoumas
Gujarati	Halad, Haldar
Hebrew	Kurkum
Hindi	Haldi
Hungarian	Kurkuma, Sárga gyömbérgyökér
Icelandic	Túrmerik
Indonesian	Kunyit, Kunir; Daun kunyit
Italian	Curcuma
Japanese	Ukon, Tamerikku
Kannada	Arishina, Arisina
Khmer	Romiet, Lomiet, Lamiet
Korean	Kang-hwang, Keolkuma Kolkuma, Sim-hwang, Teomerik, Tomerik, Tumerik, Ulgum, Ulgumun
Laotian	Khi min khun, Khmin khun
Latvian	Kurkuma
Lithuanian	Ciberžole, Kurkuma, Dažine, ciberžole
Malay	Kunyit basah
Malayalam	Manjal
Marathi	Halad
Nepali	Haldi, Hardi, Besar
Norwegian	Gurkemeie
Pahlavi	Zard-choobag
Pashto	Zarchoba
Polish	Kurkuma, Ostryz' dlugi, Szafran indyjski
Portuguese	Açafrão da Índia, Curcuma
Punjabi	Haldi
Romanian	Curcuma
Russian	Koren, kurkumy, Kurkuma

**Table 1 (Continued)**

Language	Name
Sanskrit	Ameshta, bahula, bhadra, dhirgharaja, gandaplashika, gauri, gharshani, haldi, haridra, harita, hemaragi, hemaragini, hrivilasini, jayanti, jwarantika, kanchani, kaveri, krimighana, kshamada, kshapa, lakshmi, mangalaprada, mangalya, mehagni, nisha, nishakhya, nishawa, pavitra, pinga, pinja, pita, patavaluka, pitika, rabhangavasa, ranjani, ratrimanika, shifa, shiva, shobhana, shyama, soughagouhaya, suvarna, suvarnavarna, tamasini, umavara, vauragi, varavarnini, varnadatri, varnini, vishagni, yamini, yohitapriya, yuvati
Singhalese	Kaha
Slovak	Kurkuma
Slovenian	Kurkuma
Spanish	Cúrcuma, Azafrán arabe
Swahili	Manjano
Swedish	Gurkmeja
Tagalog	Dilaw
Tamil	Manjal
Telugu	Haridra, Pasupu
Thai	Kha min chan, Kha min; Wanchakmadluk
Tibetan	Gaser, Sga ser
Turkish	Hint safrani, Sari boya, Zerdeçal, Safran kökü, Zerdali, Zerdeçöp, Zerdecube
Ukrainian	Kurkuma
Urdu	Haldi, Zard chub
Vietnamese	Bot nghe, Cu nghe, Nghe, Uat kim, Khuong hoang
Yiddish	Kurkume

Modified from Ravindran et al. [8].

formula of  $C_{21}H_{20}O_6$ , and a molecular weight of 368.37 g/mol. Spectrophotometrically, the maximum absorption ( $\lambda_{max}$ ) of curcumin in methanol occurs at 430 nm and in acetone at 415–420 nm [12]. A 1% solution of curcumin contains 1650 absorbance units. Curcumin appears brilliant yellow hue at pH 2.5–7 and red at pH > 7. Curcumin exists in enolic and  $\beta$ -diketonic forms. The fact that curcumin in solution exists primarily in its enolic form [13] has an important bearing on the radical-scavenging ability of curcumin.

The stability of curcumin in aqueous media improves at high pH (>11.7) [14,15]. Although quite soluble in organic solvents such as DMSO, ethanol, methanol, or acetone, it is poorly soluble in aqueous solvents [16]. Curcumin is stable at acidic pH but unstable at neutral and basic pH, under which conditions it is degraded to ferulic acid and feruloylmethane [15–17]. Most curcumin (>90%) is rapidly degraded within 30 min of placement in phosphate buffer systems of pH 7.2 [15,17]. The ability of antioxidants such as ascorbic acid, N-acetylcysteine (NAC), and glutathione to prevent this degradation suggests that an oxidative mechanism is at work. Degradation of curcumin is extremely slow at pH 1–6 [15], as normally encountered in the stomach. In contrast, one of curcumin's major metabolites (tetrahydrocurcumin, or THC) is quite stable at neutral or basic pH [18] and still possesses antioxidant activities [19–21]. Curcumin is soluble in 0.1 M sodium hydroxide, although it remains stable for only 1–2 h. In comparison, curcumin is more stable in cell culture medium containing 10% fetal calf serum and in human blood, <20% of

**Table 2 – A list of molecular targets of curcumin**

Transcriptional factors
Activating protein-1↓
β-Catenin↓
CREB-binding protein↓
Early growth response gene-1↓
Electrophile response element↑
Hypoxia inducible factor-1↓
Notch-1↓
Nuclear factor-kappa B↓
Nuclear factor 2-related factor↑
Peroxisome proliferator-activated receptor-gamma↓
Signal transducers and activators of transcription-1↓
Signal transducers and activators of transcription-3↓
Signal transducers and activators of transcription-4↓
Signal transducers and activators of transcription-5↓
Wilms' tumor gene 1↓
Inflammatory cytokines
Interleukin-1↓
Interleukin-2↓
Interleukin-5↓
Interleukin-6↓
Interleukin-8↓
Interleukin-12↓
Interleukin-18↓
Monocyte chemoattractant protein↓
Migration inhibition protein↓
Macrophage inflammatory protein↓
Tumor necrosis factor alpha↓
Enzymes
Arylamine N-acetyltransferases-1↓
ATFase↓
ATPase↓
Cyclooxygenase-2↓
Desaturase↓
DNA polymerase↓
Farnesyl protein transferase↓
Gluthathione-S-transferase↓
Glutamyl cysteine ligase
Hemeoxygenase-1↑
Inducible nitric oxide synthase↓
Lipoxygenase↓
Matrix metalloproteinase↓
NAD(P)H:quinone oxidoreductase↓
Ornithine decarboxylase↓
Phospholipase D↓
Src homology 2 domain-containing tyrosine phosphatase 2↓
Telomerase↓
Tissue inhibitor of metalloproteinase-3↓
Glutamate-cysteine ligase↑
Kinases
Autophosphorylation-activated protein kinase↓
Ca <sup>2+</sup> -dependent protein kinase↓
EGF receptor-kinase↓
Extracellular receptor kinase↓
Focal adhesion kinase↓
IL-1 receptor-associated kinase↓
Janus kinase↓
c-jun N-terminal kinase↑
Mitogen-activated protein kinase↓
Phosphorylase kinase↓
Protamine kinase↓
Protein kinase A↓
Protein kinase B↓
Protein kinase C↓
pp60c-src tyrosine kinase↓

**Table 2 (Continued)**

Protein tyrosine kinase↓
Growth factors
Connective tissue growth factor↓
Epidermal growth factor↓
Fibroblast growth factor↓
Hepatocyte growth factor↓
Nerve growth factor↓
Platelet derived growth factor↓
Tissue factor↓
Transforming growth factor-β1↓
Vascular endothelial growth factor↓
Receptors
Androgen receptor↓
Aryl hydrocarbon receptor↓
Chemokine (C-X-C motif) receptor 4↓
Death receptor-5↑
EGF-receptor↓
Endothelial protein C-receptor↑
Estrogen receptor-alpha↓
Fas receptor↑
Histamine (2)-receptor↓
Human epidermal growth factor receptor-2↓
Interleukin 8-receptor↓
Inositol 1,4,5-triphosphate receptor↓
Integrin receptor↓
Low density lipoprotein-receptor↑
Adhesion molecules
Endothelial leukocyte adhesion molecule-1↓
Intracellular adhesion molecule-1↓
Vascular cell adhesion molecule-1↓
Antiapoptotic proteins
B-cell lymphoma protein 2↓
Bcl-xL↓
Inhibitory apoptosis protein-1 ↓
Others
Cyclin D1↓
DNA fragmentation factor 40-kd subunit↑
Heat-shock protein 70↑
Multi-drug resistance protein↓
Urokinase-type plasminogen activator↓
P <sup>53</sup> ↑

For more information, see Ref. [43,44,195].

curcumin being degraded within 1 h and approximately 50% by 8 h [15]. *trans*-6-(4'-Hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal is a major degradation product; vanillin, ferulic acid, feruloylmethane are minor degradation products. The amount of vanillin increases with incubation time. In addition, curcumin appears to be stabilized by forming complexes with cyclodextrin [22].

## 2. Traditional uses of curcumin

Traditionally, turmeric has been put to use as a foodstuff, cosmetic, and medicine. As a spice, it is used to provide curry with its distinctive yellow color and flavor. It is used as a coloring agent in cheese, butter, and other foods [23,24]. In folk medicine, turmeric and natural curcuminoids have been applied as therapeutic preparations over the centuries in different parts of the world. In Ayurvedic medicine, curcumin

is a well-documented treatment for various respiratory conditions (e.g., asthma, bronchial hyperactivity, and allergy) as well as for liver disorders, anorexia, rheumatism, diabetic wounds, runny nose, cough, and sinusitis [25]. In traditional Chinese medicine, it is used to treat diseases associated with abdominal pain [26]. In ancient Hindu medicine, it was used to treat sprains and swelling [25]. Throughout the Orient, it has traditionally been used to good therapeutic effect, particularly as an anti-inflammatory [12], and many of its therapeutic effects have been confirmed by modern scientific research. Such effects include antioxidant [27], anti-inflammatory [24,28,29], anticarcinogenic and antimicrobial [30–32], hepatoprotective [32], thrombosuppressive [33], cardiovascular (i.e., as protection against myocardial infarction) [29,34,35], hypoglycemic [36–38], and antiarthritic (i.e., as protection against rheumatoid arthritis) [39]. The most compelling and key rationale for the continuing traditional therapeutic use of curcumin is its extremely good safety profile. To date, no studies in either animals [40,41] or humans [42] have discovered any toxicity associated with the use of curcumin, and it is clear that curcumin is not toxic even at very high doses.

### 3. Molecular targets of curcumin

Accumulating evidence suggests that curcumin has a diverse range of molecular targets, which supports the notion that curcumin influences numerous biochemical and molecular cascades (Table 2). Among its molecular targets are transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis.

#### 3.1. Curcumin interacts with numerous targets

Curcumin is apparently a highly pleiotropic molecule that interacts physically with its numerous targets (Table 3). It binds to and inhibits the activity of enzymes, growth factor receptors, metals, albumin, and other molecules. It binds to proteins such as P-glycoprotein [68,69], multidrug resistance proteins 1 and 2 (MRP1 and MRP2) [59], glutathione [59], protein kinase C, ATPase [52,53], ErbB2 [61], and alpha1-acid glycoprotein (AGP) [50]. By directly binding small  $\beta$ -amyloid species, curcumin blocks aggregation and fibril formation in vitro and in vivo [51]. Curcumin irreversibly binds CD13/aminopeptidase N (APN) and inhibits tumor invasion and angiogenesis [55]. Curcumin has also been shown to inhibit the activity of lipoxygenase by binding lipoxygenase itself [65] or binding to phosphatidylcholine (PC) micelles and thereby inhibiting lipoxygenase 1 [74].

#### 3.2. Curcumin inhibits activation of transcription factors

Curcumin is a potent inhibitor of the activation of various transcription factors including nuclear factor- $\kappa$ B (NF- $\kappa$ B), activated protein-1 (AP-1), signal transducer and activator of transcription (STAT) proteins, peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), and  $\beta$ -catenin [44]. These transcription factors regulate the expression of genes that contribute to

**Table 3 – Ligands that physically interact with curcumin**

Albumin	[45–49]
Alfa-acid glycoprotein	[50]
Amyloid protein	[51]
ATPase	[52,53]
Autophosphorylation-activated protein kinase (AK)	[54]
CD13/aminopeptidase N	[55]
DNA polymerase-Y	[56]
Focal adhesion kinase	[57]
Glutathione	[58]
GST-P1	[60]
HER2	[61]
Human alpha1-acid glycoprotein (AGP)	[50]
Iron, Cu <sup>2+</sup> , Zn <sup>2+</sup>	[62,63]
Lipoxygenase	[64,65]
Microtubulin	[66]
MRP 1 and 2	[59]
Nucleic acid	[67]
P-glycoprotein	[68–70]
Phosphorylase kinase (PhK),	[54]
Protein kinase A (PkA),	[54]
Protein kinase C (PkC),	[54]
Protamine kinase (cPK),	[54]
pp60c-src tyrosine kinase	[54,57]
Thioredoxin reductase	[71]
Topoisomerase II	[72]
Ubiquitin isopeptidase	[73]

tumorigenesis, inflammation, cell survival, cell proliferation, invasion, and angiogenesis.

#### 3.3. Curcumin downregulates the activity of multiple kinases

A variety of tyrosine kinases are activated by mutations that contribute to the malignant transformation, growth, and metastasis of human cancers. Accordingly, protein kinases involved in key growth signaling cascades are good candidate targets for novel chemopreventive approaches to treat many human cancers. For example, most human cancers over-express epidermal growth factor receptor (EGFR) and HER2/neu, which ultimately stimulates the proliferation of cancer cells [75]. Cellular experiments in vitro have shown that short-term treatment with curcumin inhibits EGFR kinase activity and EGF-induced tyrosine phosphorylation of EGFR in A431 cells and depletes cells of Her2/neu protein. Similar to geldanamycin, curcumin is extremely potent at degrading intracellular HER2 and disrupting its tyrosine kinase activity [76]. Additionally, as recently shown in our laboratory, curcumin may downregulate bcl-2 expression, thereby contributing to antiproliferative activity. Curcumin has also been shown to induce apoptosis in acute T cell leukemias by inhibiting the phosphatidylinositol 3 kinase/AKT pathway and to induce G2/M arrest and nonapoptotic autophagic cell death in malignant glioma cells by abrogating Akt and Erk signaling pathways [77].

Curcumin's effects are also apparently mediated through its inhibition of various other serine/threonine protein kinases. As we have previously shown, curcumin completely inhibits the activity of several protein kinases including phosphorylase kinase, protein kinase C (PKC), protamine kinase (cPK), autophosphorylation-activated protein kinase (AK), pp60c-src

tyrosine kinase. Other investigators have shown similar suppression of phorbol-12-myristate-13-acetate (PMA)-induced activation of cellular PKC by curcumin [43,44].

Most inflammatory stimuli typically activate 1 of 3 independent MAPK pathways leading to activation of the p44/42 MAPK (also called ERK1/ERK2), JNK, or p38 MAPK pathway, respectively. Curcumin can apparently inhibit all of these pathways directly or indirectly, thus providing evidence of its potent anti-inflammatory and anticarcinogenic effects [43,44].

### 3.4. Curcumin inhibits expression of growth and metastases promoting genes

Overexpression of oncogenes promotes tumor cell growth and provides an ideal platform on which to design chemopreventive regimens. Cyclooxygenase-2 (COX-2) is associated with a wide variety of cancers including cancers of the colon, lung and breast. Because of the importance of COX-2 inhibition in human carcinogenesis, much research in the past decade has been focused on the development of specific COX-2 inhibitors [78]. Several studies have shown that curcumin downregulates the expression of COX-2 protein in different tumor cell lines, most likely through the downregulation of NF- $\kappa$ B activation that is required for COX-2 activation. There is also evidence in the literature that curcumin-induced suppression of cell proliferation results in decreased cyclin D1 expression and CDK4-mediated retinoblastoma protein phosphorylation. As shown in hepatocellular cancer cells, curcumin appears to alter the metastatic potential of tumor cells by inhibiting the activity of matrix metalloproteinase-9 (MMP-9) and MMP-2 [79]. In experiments with ex vivo cultured BALB/c mouse peritoneal macrophages, curcumin reduced the production of iNOS mRNA in a concentration-dependent manner. Finally, curcumin appears to be able to exert anti-inflammatory and growth-inhibitory effects on cancer cells by inhibiting the expression of interleukin 1 $\beta$  (IL-1 $\beta$ ), interleukin 6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) on the one hand and cyclin E on the other [80,81].

### 3.5. Curcumin inhibits expression of multiple genes/pathways involved in apoptosis, cell invasion, and adhesion

Curcumin also operates through regulating the activities of additional molecular targets that control cell adhesion, apoptosis, and invasion. In this regard, curcumin has been shown to be an extremely potent inhibitor of TNF- $\alpha$ -induced expression of intracellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin in human umbilical vein endothelial cells. By apparently inhibiting the induction of steady-state transcription levels of ICAM-1, VCAM-1 and E-selectin, curcumin may be interfering detrimentally with the TNF- $\alpha$ -induced signaling event at an early stage. Additionally, curcumin has been shown to mediate its anticancer, chemosensitive, and radiosensitive effects via activation of p53 and simultaneous downregulation of MDM2 oncogene expression via the PI3K/mTOR/ETS2 pathway in human prostate cancer (PC3) and colon cancer (HT-29) cell lines [82,83] and to induce apoptosis and nuclear translocation and activation of p53 in human neuroblastoma cells [84].

### 3.6. Curcumin regulates activities of several enzymes that mediate tumor growth

In addition to directly regulating the expression of candidate genes, curcumin also appears to effectively regulate the activities of enzymes that control tumor growth and proliferation. Curcumin blocks fibrosis in anti-Thy1 glomerulonephritis through its upregulation of hemoxygenase-1 (HO-1) gene expression, suggesting that it has antifibrotic effects in glomerular disease [85]. Similarly, curcumin can reportedly induce HO-1 expression through the generation of reactive oxygen species, p38 activation, and phosphatase inhibition [86].

Curcumin can also apparently suppress tumor cell growth through its effects on Ras protein pathways. Ras proteins, in order to extend their biological activity, must be isoprenylated at a conserved cysteine residue near the carboxyl terminus (Cys-186 in mammalian Ras p21 proteins). Previous studies have indicated that an intermediate in the mevalonate pathway, most likely farnesyl pyrophosphate, donates this isoprenyl group and that inhibitors of the mevalonate pathway might be able to block the transforming effects of Ras oncogenes expression. Indeed, in one study evaluating such a role for curcumin, curcumin derivatives strongly inhibited FPTase activity, thereby suggesting another potential mechanism by which curcumin might suppress cellular growth [43,44].

In another investigation, curcumin remarkably inhibited the activity of xanthine oxidase (XO) in vitro in PMA-treated NIH3T3 cells. Induction of XO activity is considered a major cause of PMA-mediated tumor promotion, and curcumin's marked ability to inhibit PMA-induced increases in such activity appears to lie in its direct inactivation of the XO protein [43,44].

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## 4. Preclinical studies of curcumin

### 4.1. Curcumin is a potent chemopreventive agent

Numerous studies in rodent models argue for curcumin's chemopreventive potential in cancer (Table 4). Curcumin can reportedly suppress the tumorigenic activity of a wide variety of carcinogens in cancers of the colon, duodenum, esophagus, forestomach, stomach, liver, breast, leukemia, oral cavity, and prostate. In studies in mice, curcumin was able to inhibit 7,12-dimethylbenz[a]anthracene (DMBA)-initiated and 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted skin tumor formation [31,120,126]. Curcumin has also shown an ability to inhibit the mammary tumor-initiating activity of DMBA [110] and the in vivo formation of mammary DMBA-DNA adducts in female rats [111] and to exert chemopreventive activity when administered during the promotion/progression stage of colon carcinogenesis [91]. Meanwhile, one group has studied not only curcumin's chemopreventive effects but also its effects on the initiation or post-initiation phase of N-nitrosomethylbenzylamine (NMBA)-induced esophageal carcinogenesis in male F344 rats [100]. Using a slightly different approach, another group investigated curcumin's ability to prevent tumors in C57BL/6J-Min/+ (Min/+) mice that bear a germline mutation in the APC gene and spontaneously

**Table 4 – Curcumin exhibits chemopreventive effects against various cancers**

Cancer	Carcinogen	Animal	Dose	Reference
<b>Gastrointestinal cancers</b>				
Aberrant crypt foci (ACF)	Azoxymethane	Rat	2000 ppm	[87]
Colon cancer	Azoxymethane	Mice	0.5–0.2% (w/w)	[88]
Colon cancer	DMH	Mice	0.5%	[89]
Colon cancer	Azoxymethane	Rat	2000 ppm	[90]
Colon cancer	Azoxymethane	Rat	0.2 or 0.6% (w/w)	[91]
Colon cancer	PhIP	Apc (min) mice	2000 ppm	[92]
Colon cancer	Azoxymethane	Rat	1 or 2% (w/w)	[93]
Colon cancer	Azoxymethane	Rat	0.6% (w/w)	[94]
Colon cancer	1,2-Dimethylhydrazine	Rat	0.6%	[95]
Colitis	TNBS	Mice	0.5–5%, diet	[96]
Colitis	DNB	Mice	0.25%; diet	[97]
Colitis	TNBS	Mice	50 mg/kg	[98]
Ulcerative colitis	DNCB	Rat	25–100 mg/kg	[99]
Duodenal tumor	MNNG	Mice	0.5–2.0% (w/w)	[88]
Esophageal cancer	NMBA	Rat	500 ppm	[100]
FAD	Azoxymethane	Mice	2%	[101]
FAP	–	Min/+ mice	0.1, 0.2 or 0.5% (w/w)	[102]
Forestomach neoplasia	B[a]P	Mice		[103]
Forestomach cancer	B[a]P	Mice	2% (w/w)	[104]
Forestomach neoplasia	B[a]P	Mice		[105]
Stomach cancer	MNNG	Rat	0.05% (w/w)	[106]
<b>Liver cancers</b>				
Hepatic hyperplasia	Diethylnitrosamine	Rat	200 or 600 mg/kg	[107]
Liver cancer	Diethylnitrosamine	Mice	0.2% (w/w)	[107]
<b>Lung cancers</b>				
Lung cancer	B[a]P and NNK	A/J mice	2000 ppm	[108]
<b>Blood cancers</b>				
Lymphoma/leukemia	DMBA	Sencar mice	2% (w/w)	[109]
<b>Breast cancers</b>				
Mammary tumor	DMBA	Rat	0.8–1.6% (w/w)	[93]
Mammary tumor	DMBA	Rat	50–200 mg/kg	[110]
Mammary tumor	DMBA	Rat	1% (w/w)	[111]
Mammary tumor	DMBA	Sencar mice	2% (w/w)	[109]
Mammary tumor	Gamma radiation	Rat		[112]
Mammary tumor	Gamma radiation	Rat	1% (w/w)	[113]
Mammary tumor	DMBA	Rats		[114]
Mammary tumor	DMBA	Sencar mice		[115]
Mammary tumor	Gamma radiation	Rat		[113]
<b>Oral cancers</b>				
Oral cancer	MNA	Hamster		[116]
Oral cancer	NQO	Rat	500 ppm	[117]
<b>Prostate cancers</b>				
Prostate cancer	DMAB and PhIP	Rat	15–500 ppm	[118]
<b>Skin cancers</b>				
Dermatitis	TPA + UV-A	Mice		[119]
Skin tumor	TPA	Mice		[120]
Skin tumor	DMBA	Mice		[103]
Skin tumors	TPA	Mice	10 and 30 $\mu$ mol	[121]
Skin tumor	TPA	Mice		[122]
Skin tumor	TPA	Mice	1, 10, 100 or 3000 nmol	[123]
Skin tumor		Mice		[124]
Skin tumor	DMBA	Mice		[105]
Skin tumor	B[a]P and DMBA	Mice		[101]
<b>Other cancers</b>				
Multi-organ cancer	DHPN, EHEN	Rat	1% (w/w)	[125]

*Abbreviations:* FAP, familial adenomatous polyposis; ACF, aberrant crypt foci; FAD, focal areas of dysplasia; B[a]P, benzo[a]pyrene; DMBA, 7,12-dimethylbenz[a]anthracene; TPA, 12-O-tetradecanoylphorbol-13-acetate; NNK, 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone; NQO, 4-nitroquinoline-1-oxidase; DMAB, 3,2'-dimethyl-4-aminobiphenol; PhIP, 2-amino-1-methylimidazo[4,5-b]pyridine; DHPN, 2,2'-dihydroxy-di-n-propylnitrosamine; EHEN, N-ethyl-N-hydroxyethylnitrosamine.

develop numerous intestinal adenomas by 15 weeks of age [127]. The data obtained in that study were corroborated by a later study of the effects of curcumin on apoptosis and tumorigenesis in male *apc* (*min*) mice treated with the human dietary carcinogen 2-amino 1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) [92].

At least one study has examined curcumin's preventive effect on the development of adenomas in the intestinal tract of C57BL/6J-*Min*/+ mice, a model of human familial adenomatous polyposis (FAP) [102]. Another group reported that, during the initiation phases of azoxymethane-induced colonic carcinogenesis, azoxymethane inhibits the expression of colonic COX-1 expression without affecting that of COX-2 [128]. However, they also found that simultaneous treatment with dietary curcumin may increase COX-2 expression to compensate for the azoxymethane-induced reduction of COX-1 expression.

In another recent study, the effects of curcumin administered at a daily dose of 100 mg/kg were investigated in an animal (Wistar rat) model of *N*-nitrosodiethylamine (DENA)-initiated and phenobarbital (PB)-induced hepatocarcinogenesis [129]. In a recent follow-up study, the investigators in that study have substantiated this finding by reporting that 100 mg/kg curcumin daily prevented the reduction of defensive hepatic glutathione antioxidant activity, decreased lipid peroxidation, and minimized the histological alterations induced by DENA/PB [130]. In another study, investigators found that the administration of curcumin and a synthetic analog to nicotine-treated Wistar rats over a period of 22 weeks enhanced biochemical marker enzyme and lipid profiles [131]. In a study in rodents, curcumin was able to inhibit the development of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG)-induced stomach cancer [106], an effect that may be mediated in part by an ability to suppress the proliferation of *Helicobacter pylori* (the major pathogen in human gastric cancer) [132].

#### 4.2. Curcumin inhibits proliferation of tumor cells in vitro

Curcumin has the ability to inhibit the proliferation of an extremely wide array of cancer cell types in vitro. This includes cells from cancers of the bladder, breast, lung, pancreas, prostate, cervix, head and neck, ovary, kidney, and brain; and osteosarcoma, leukemia and melanoma [12].

#### 4.3. Curcumin exhibits antitumor activity in animals

Besides the extensive in vitro demonstrations of curcumin's antiproliferative effects, numerous other studies have evaluated its efficacy in various animal models in vivo (Table 5). The first animal studies of curcumin's antitumor effects – performed with ascitic lymphoma cells in mice – were reported in 1985 by Kuttan et al. [133]. More recently, others have studied the antitumoral and inhibitory effects of curcumin on melanoma cells [141] and melanoma lung metastasis in mice [147].

Other studies in vivo have investigated the effects of curcumin on tumor angiogenesis and the biomarkers COX-2 and VEGF in hepatocellular carcinoma cells implanted in nude mice [148]. One group demonstrated that systemic administration of curcumin for 6 consecutive days to rats bearing the highly cachectic Yoshida AH-130 ascites hepatoma significantly inhibited tumor growth [149]. Meanwhile, others have shown that curcumin can suppress the growth of head and neck carcinoma [140], modulate the growth of prostate cancer in rodents [145], and inhibit the growth of human pancreatic cancer in nude mice, in part by suppressing angiogenesis and inducing apoptosis as reported recently [143].

More recent studies have evaluated curcumin's chemosensitizing and radiosensitizing effects. Our group [135] evaluated the chemosensitizing effect of curcumin in combination with paclitaxel on breast cancer metastases to the lung. Others examined the effects of curcumin on human breast

**Table 5 – A list of studies describing antitumor effects of curcumin in animals**

Tumor	Route	Dose	Model	Reference
Ascites <sup>2</sup>	i.p.	50 mg/kg	Ascites	[133]
Ascites	i.p.	50 mg/kg	Ascites	[134]
Breast <sup>1</sup>	Diet	2% (w/w)	Orthotopic	[135]
Breast <sup>1</sup>	Diet	1% (w/w)	Orthotopic	[136]
Colon <sup>2</sup>	i.v.	40 mg/kg	Xenograft	[137]
Gastric cancer	Oral	50–200 mg/kg	Xenograft	[138]
Glioblastoma	i.t.	10 mg/kg	Orthotopic	[77]
HCC <sup>3</sup>		100–200 mg/kg	Orthotopic	[139]
Hepatoma	Oral	50–200 mg/kg	Xenograft	[138]
HNSCC <sup>4</sup>	Sub cute	50–250 μmol/L	Xenograft	[140]
Leukemia	Oral	50–200 mg/kg	Xenograft	[138]
Melanoma	i.p.	25 mg/kg	Xenograft	[141]
Ovarian	i.p.	500 mg/kg	Orthotopic	[142]
Pancreas <sup>2</sup>	i.v.	40 mg/kg	Xenograft	[143]
Pancreas	Gavage	1 gm/kg	Orthotopic	[144]
Prostate	Diet	2% (w/w)	Xenograft	[145]
Prostate	Gavage	5 mg/kg	Xenograft	[146]
Prostate	Gavage	5 mg/day	Xenograft	[82]

1, Lung metastases; 2, liposomal curcumin; 3, intrahepatic metastasis; i.p., intraperitoneal; i.t., intratumoral; i.v., intravenous; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma.

cancer (MDA-MB-231) cells in an immunodeficient mouse model of metastasis [136] and observed that the number of lung metastases significantly decreased after intercardiac injection of curcumin, a clear demonstration of curcumin's promise for dietary chemoprevention of metastases [136].

In our laboratory, we have recently investigated curcumin's effects alone and in combination against several cancers. We have found that (a) the combination of curcumin and gemcitabine inhibits pancreatic cancer growth in nude mice by inhibiting NF- $\kappa$ B regulated gene expression, cell proliferation, and angiogenesis [144]; (b) the combination of curcumin and docetaxel is effective against human ovarian cancer in nude mice [142]; (c) curcumin can suppress the growth of human glioblastoma in rodents [77]; and (d) curcumin sensitizes colon cancers in nude mice to oxaliplatin [137]. In addition, other recent studies have shown that curcumin sensitizes prostate cancers to chemotherapeutics and radiation by downregulating expression of the MDM2 oncogene [82]. Together, these *in vivo* animal studies clearly suggest curcumin's anticancer potential when administered either alone or in combination with currently employed chemotherapeutic agents or radiation.

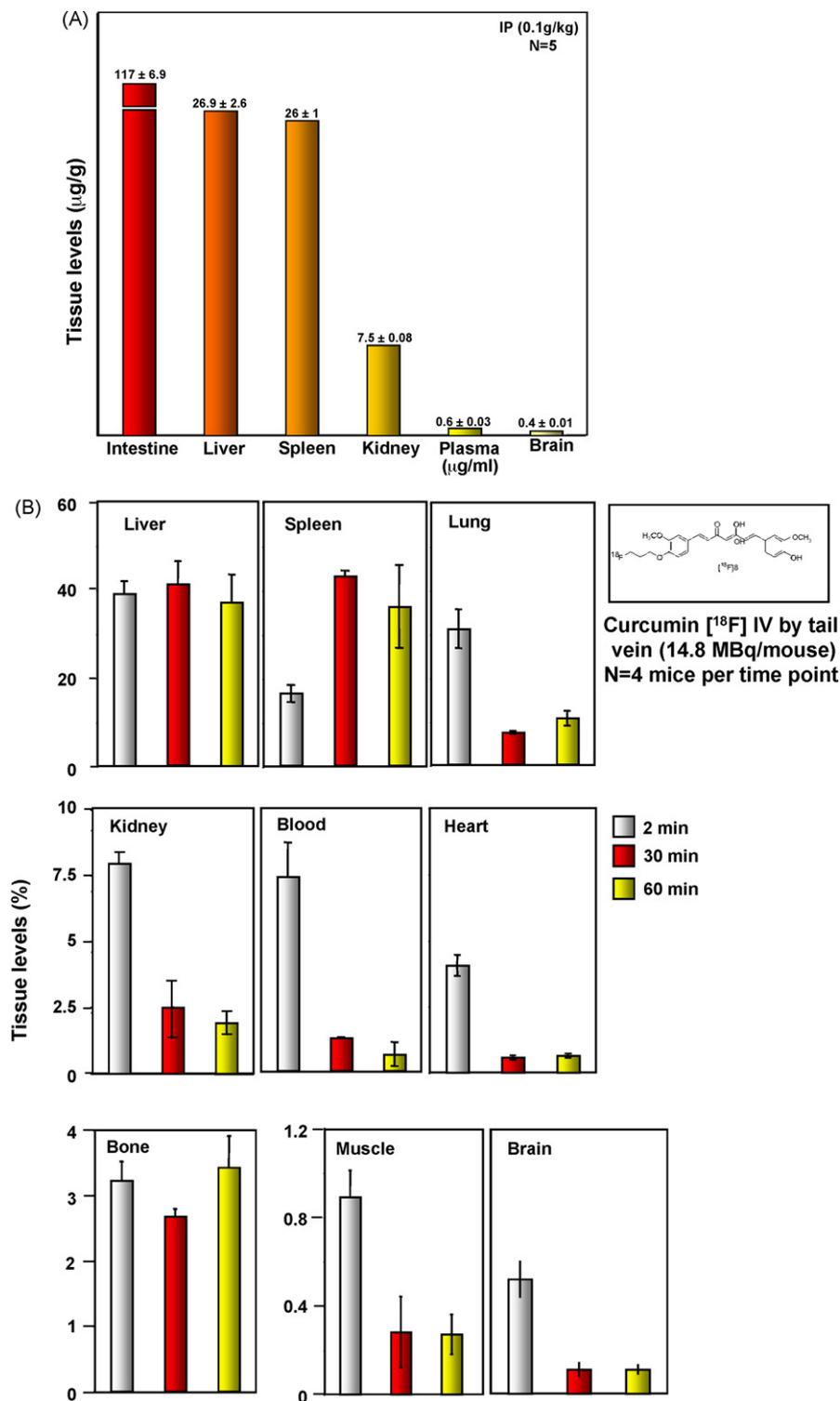
## 5. Pharmacokinetic and pharmacodynamic studies of curcumin in animals and humans

The pharmacokinetics and pharmacodynamics of curcumin have been widely investigated. Perhaps the first study to examine the uptake, distribution, and excretion of curcumin was conducted in 1978 by Wahlstrom and Blennow in Sprague-Dawley rats [150]. When administered orally at a dose of 1 g/kg, approximately 75% of the ingested curcumin was excreted in the feces and only negligible amounts in the urine. As indicated by blood plasma levels and biliary excretion, curcumin was poorly absorbed from the gut. No apparent toxic effects were seen after doses of up to 5 g/kg. When intravenously injected, curcumin was actively transported into the bile. Most of the drug was metabolized, however, again suggesting poor absorption and rapid metabolism. Later, Holder et al. [151] administered deuterium- and tritium-labeled curcumin orally and intraperitoneally to rats and, like Wahlstrom and Blennow, found that most of it was excreted in the feces. When they administered curcumin intravenously and intraperitoneally to cannulated rats, the curcumin was excreted in the bile. The major biliary metabolites were glucuronides of tetrahydrocurcumin (THC) and hexahydrocurcumin (HHC); the minor biliary metabolite was dihydroferulic acid accompanied by traces of ferulic acid. In another study in which 400 mg curcumin was administered orally to rats, most of the administered curcumin (40%) was excreted unchanged in the feces, none in the urine (although curcumin glucuronide and sulfates were detected there), and none in heart blood (although traces were found in portal blood, liver, and kidney) [152]. Thirty minutes after administration, 90% of the curcumin had appeared in the stomach and small intestine; by 24 h, only 1% remained there [152]. In another study by the same investigators, tritium-labeled curcumin administered at doses of 400, 80, and 10 mg was later detectable in the blood, liver, and kidney. At all three

doses, the labeled curcumin was eliminated mainly through the feces and negligibly through the urine. At the two lowest doses (80 and 10 mg), most of the labeled curcumin was excreted within 72 h; conversely, at 400 mg, considerable amounts of labeled curcumin were still present in the tissues of interest 12 days after administration. The percentage of curcumin absorbed (60–66% of the given dose) remained constant regardless of the dose administered [153], indicating that increasing the dose of curcumin did not necessarily result in higher absorption.

In 1999, Pan et al. [18] investigated the pharmacokinetics of curcumin in mice. They found that, within the first 15 min after intraperitoneal (*i.p.*) administration of curcumin (0.1 g/kg), plasma curcumin levels had already reached 2.25  $\mu$ g/mL (Fig. 2). One hour after administration, curcumin levels in the intestines, spleen, liver, and kidneys had reached 177.04, 26.06, 26.90, and 7.51  $\mu$ g/g, respectively, but only trace levels (0.41  $\mu$ g/g) in the brain. In comparison, after oral administration of 1 g/kg curcumin, serum plasma levels peaked at 0.5  $\mu$ M. Pan et al. also found curcumin-glucuronoside, dihydrocurcumin-glucuronoside, THC-glucuronoside, and THC to be the major metabolites of curcumin *in vivo*. Together, these results agree with those of Ireson et al. [154,155], who examined curcumin metabolites in both rats and humans. As several groups have shown, the liver appears to be the major organ responsible for metabolism of curcumin [150,156,157]. Examining rat liver tissue slices for the presence of curcumin metabolites, Hoehle and coworkers observed several reductive metabolites including THC, HHC, and octahydrocurcumin (OHC) and noted a predominance of OHC in males versus THC in females. They also identified both glucuronide and sulfate conjugates of THC, HHC, and OHC. This suggests that curcumin undergoes extensive reduction, most likely via alcohol dehydrogenase, before conjugation. In a Min/+ mouse model of FAP, Perkins et al. [102] examined the pharmacokinetics of curcumin administered either in the diet or in  $^{14}$ C-labeled form as a single intraperitoneal dose. Though detected in only trace amounts in the plasma, curcumin was detected at levels ranging from 39 to 240 nmol/g in the small intestinal mucosa. The radiolabeled curcumin disappeared rapidly from tissues and plasma within 2–8 h after dosing. On the basis of their findings, Perkins et al. concluded that a daily dose of 1.6 g of curcumin is required for efficacy in humans. More recently, in a study examining the tissue distribution of radiolabeled fluoropropyl-substituted curcumin mice, Ryu et al. found that curcumin was bound to  $\beta$ -amyloid plaques in the brain, thereby suggesting its possible use for brain imaging (Fig. 2) [158].

Pharmacokinetic studies in humans have generally produced similar data though not always. In contrast to the case in rodents, oral dosing of curcumin at 4–8 g in one study resulted in peak plasma levels of 0.41–1.75  $\mu$ M [159]. In a small study of 15 patients given oral curcumin (36–180 mg) daily for up to 4 months, metabolites were not detected in the blood or urine but were detected in the feces [160]. In another study, Garcea et al. [161] examined the pharmacologically active levels of curcumin in patients with colorectal cancer who ingested curcumin at daily doses of 3600, 1800, or 450 mg for 7 days. By measuring curcumin's effects on the colorectal levels



**Fig. 2** – Plasma and tissue distribution of curcumin administered via intraperitoneal (i.p.) and systemic routes. (A) Curcumin (0.1 g/kg) was administered (i.p.) to mice (N = 5), sacrificed 1 h later and concentration of curcumin in various tissues was analysed by HPLC. The data is replotted from [18]. (B) ICR mice were injected with [<sup>18</sup>F] labeled curcumin in 0.2 mL of 10% ethanol-saline via tail vein. The mice were sacrificed at the indicated times (2, 30, 60, and 120 min). Samples of blood, heart, lung, liver, spleen, kidney, muscle, brain, and bone were removed, weighed, and counted. Data are expressed as the percent injected dose per gram of tissue (% ID/g). The data is replotted from [158].

of DNA adduct 3-(2-deoxy- $\beta$ -di-erythro-pentafuranosyl)-pyr[1,2- $\alpha$ ]-purin-10(3H)one M(1)G and COX-2 protein, they showed that curcumin was taken up by both normal and malignant colorectal tissues and that it decreased M(1)G but not COX2 levels.

As most of these studies indicate, curcumin has poor bioavailability, and several groups have investigated ways to enhance it. Piperine has been shown to significantly enhance curcumin's bioavailability in studies involving both rats and healthy human volunteers. In brief, Shoba et al. [162] combined curcumin with piperine, a known inhibitor of hepatic and intestinal glucuronidation, and examined the resulting serum levels of curcumin. In the rat studies, administration of curcumin alone at a dose of 2 g/kg, resulted in moderate serum concentrations over 4 h. In contrast, concomitant administration with piperine 20 mg/kg increased for a short period the serum concentration of curcumin, significantly increased the time to maximum concentration while significantly decreasing elimination half-life and clearance, and increased bioavailability by 154%. In humans, on the other hand, administration of curcumin alone resulted in undetectable or trace amounts in the serum, whereas concomitant administration with piperine 20 mg/kg produced much higher concentrations and increased bioavailability by an astonishing 2000%. In another study in rats, other investigators found that a formulation of curcumin phosphatidylcholine given orally enhanced curcumin's bioavailability five-fold in plasma and in liver; but levels were lower in gastrointestinal mucosa [163]. Meanwhile, other attempts to increase the bioavailability of curcumin have been made, including the use of liposomal curcumin [143], nanoparticles of curcumin [164], and synthetic analogues of curcumin [165].

Whether curcumin metabolites are as active as curcumin itself is not clear. Although most studies indicate that curcumin glucuronides and THC are less active than curcumin [154,166], others suggest otherwise [20,21,89,167–172]. The differences in results so far are most likely due to the assays employed. For example, the phenolic glucuronides of curcumin and its natural congeners, but not the parent compounds, have been shown to inhibit the assembly of microtubule proteins under cell-free conditions, implying that the glucuronides are chemically reactive [167].

## 6. Clinical studies of curcumin

In response to the growing mass of *in vitro* and *in vivo* evidence for curcumin's chemopreventive and therapeutic efficacy, a number of clinical trials over the past two and a half decades have addressed the pharmacokinetics, safety, and efficacy of curcumin in humans (Table 6). Although these trials have concerned numerous inflammatory diseases including cancer, our focus in the sections to come will be on those dealing with cancers.

### 6.1. Curcumin is extremely safe and well tolerated

The potential use of curcumin in chemopreventive or therapeutic settings has raised the obvious issues of toxicity and tolerance. At least three different phase I clinical trials

indicate that curcumin is well tolerated when taken at doses as high as 12 g/day [159,162] (Table 6). These results were recently confirmed in an elegant dose-escalation trial to determine curcumin's maximum tolerated dose and safety [193]. In that trial, a standardized powder extract of uniformly milled curcumin (C3 Complex™, Sabinsa Corporation), was administered to 24 healthy volunteers at single doses ranging from 500 to 12,000 mg. Remarkably, only minimal, non-dose-related toxicity was seen and then only in seven subjects (30%). No curcumin was detected in the serum of subjects administered 500, 1000, 2000, 4000, 6000 or 8000 mg and only low levels in two subjects administered 10,000 or 12,000 mg.

### 6.2. Curcumin has anti-inflammatory and antirheumatic activity

Rheumatoid arthritis is a frequent complication in the elderly, and most treatments aim at reducing the temporary symptoms attributable to the underlying inflammatory activity [194]. The need for new treatment approaches has led to the recent introduction of potent disease-modifying antirheumatic drugs (DMARDs), whose clinical benefits are unfortunately offset by their high cost and frequently undesirable side effects. Curcumin has been considered as an alternative.

In the first clinical trial of curcumin's efficacy as an antirheumatic, investigators compared its antirheumatic potential with that of phenylbutazone in a short-term, double-blind, crossover study involving 18 relatively young patients (age range, 22–48 years) [39]. Each subject received a daily dose of either curcumin (1200 mg) or phenylbutazone (300 mg) for 2 weeks. At the dose used, curcumin was well tolerated, had no side effects, and exerted an antirheumatic activity comparable to that of phenylbutazone.

Meanwhile, in a study of curcumin's anti-inflammatory properties, Satoskar et al. [173] evaluated curcumin's effects on spermatic cord edema and tenderness in 46 men between 15 and 68 years old who had just undergone surgical repair of an inguinal hernia and/or hydrocele. After surgery, subjects were randomly assigned to receive curcumin (400 mg), phenylbutazone (100 mg), or placebo (250 mg lactose) three times a day on postoperative days 1–5. As in a previous study by Deodhar et al. [39], curcumin was deemed quite safe and, along with phenylbutazone, elicited much better anti-inflammatory responses than placebo did [173].

### 6.3. Curcumin has potential as palliative therapy for cancerous skin lesions

External sebaceous neoplasms (e.g., actinic keratosis, superficial basal cell carcinoma, and external genital warts) have traditionally been treated topically with corticosteroid creams. In a study by Kuttan et al. [174], curcumin's efficacy when applied as either an ethanol extract of turmeric or as an ointment to external cancerous skin lesions was evaluated in 62 patients. Regardless of the application, curcumin provided remarkable symptomatic relief that was in many cases relatively durable (lasting several months) and in all cases (except for a single adverse reaction in one subject) extremely safe. Its effects included less itching in almost all cases,

**Table 6 – A list of clinical trials with curcumin in patients with different diseases**

Disease	Dose/frequency	Patients	End point modulation	Reference
<b>Safety trials</b>				
Phase 1	2000 mg/day <sup>1</sup>	10	Piperine enhanced bioavailability by 2000%	[162]
Phase-I	500–12,000 mg/day × 90 days	25	Histologic improvement of precancerous lesions <sup>4</sup>	[159]
Phase 1	500–12,000 mg/day	24	Safe, well-tolerated even at 12 g/day	[42]
<b>Efficacy trials</b>				
Rheumatoid arthritis	1200 mg/day × 14 days	18	Improved symptoms	[39]
Postoperative inflammation	400 mg; 3×/day × 5 days	46	Decrease in inflammation	[173]
External cancerous lesions	1% ointment × several months	62	Reduction in smell in 90% patients, reduction of itching in all cases, dry lesions in 70% patients reduction in lesion size and pain in 10% patients	[174]
Cardiovascular	500 mg/day × 7 days	10	Decreased serum lipid peroxidase (33%), increased HDL cholesterol (29%), decreased total serum cholesterol (12%)	[175]
Atherosclerosis	10 mg; 2×/day × 28 days	12	Lowered LDL and apoB, increased HDL and ApoA	[176]
HIV	625 mg; 4×/day × 56 days	40	Well tolerated	[177]
Gall bladder function	20 mg, single dose (2 h)	12	Decreased gall bladder volume by 29%	[178]
Gall bladder function	20–80 mg, single dose (2 h)	12	Decreased gall bladder volume by 72%	[179]
Chronic anterior uveitis	375 mg; 3×/day × 84 days	32	Eighty-six percent decrease in chronic anterior uveitis	[180]
Idiopathic Inflammatory Orbital Pseudotumors	375 mg; 3×/day × 180–660 days	8	Four patients recovered completely One patient showed decrease in swelling, no recurrence	[181]
Psoriasis	1% curcumin gel	40	Decreased PhK <sup>2</sup> , TRR <sup>3</sup> , parakeratosis, and density of epidermal CD8+ T cells	[182]
Colorectal cancer	36–180 mg/day × 120 days	15	Lowered GST	[160]
Colorectal cancer	450–3600 mg/day × 120 days	15	Lowered inducible serum PGE2 levels	[183]
Irritable bowel syndrome	72–144 mg/day × 56 days	207	Reduced symptoms	[184]
Liver metastasis of CRC	450–3600 mg/day × 7 day	12	Low bioavailability	[156]
Colorectal cancer	450–3600 mg/day × 7 days	12	Decreased M1G DNA adducts	[161]
Cadaveric renal transplantation	480 mg; ×1–2/day × 30 days	43	Improved renal function, reduced neurotoxicity	[185]
Tropical pancreatitis	500 mg/day × 42 days	20	Reduction in the erythrocyte MDA levels Increased erythrocyte GSH levels	[186]
Ulcerative proctitis	550 mg; × 2–3/day × 60 days	5	Improved symptoms	[187]
Crohn's disease	360 mg; ×3/day × 30 days; ×4 for 60 days	5	Improved symptoms	[187]
Ulcerative colitis	2000 mg/day × 180 days	89	Low recurrence; improved symptoms	[188]
Familial adenomatous polyposis	480 mg; ×3/day × 180 days	5	Decrease in the number of polyps was 60.4% Decrease in the size of polyps was 50.9%	[189]
Improves cognitive function	–	1010	Better MMSE score <sup>5</sup>	[190]
Prostatic intraepithelial neoplasia (PIN) <sup>1</sup>	–	24	–	[191]
<i>Helicobacter pylori</i> infection <sup>2</sup>	300 mg/day × 7 days	25	Significant improvement of dyspeptic symptoms	[192]

Note: 1, + piperine 20 mg/kg; 2, PhK: phosphorylase kinase; 3, TRR: keratinocyte transferrin receptor; 4, histologic improvement of precancerous lesions was seen in one out of two patients with recently resected bladder cancer, two out of seven patients of oral leucoplakia, one out of six patients of intestinal metaplasia of the stomach, one out of four patients with CIN and two out of six patients with Bowen's disease; 5, MMSE: Mini-Mental State Examination Score; 1, Zyflamend, a polyherbal preparation containing curcumin was used; PIN: prostatic intraepithelial neoplasia.

reduced lesion odor in 90%, dry lesions in 70%, and smaller lesion size and pain mitigation in 10%.

#### 6.4. Curcumin lowers serum cholesterol and lipid peroxide levels in healthy individuals

While investigating the mechanisms of curcumin's chemopreventive effects, in another study, Kuttan and coworkers

[175] monitored curcumin's effect on serum cholesterol and lipid peroxide levels in 10 healthy volunteers. Daily administration of curcumin (500 mg) for 7 days led to a significant 33% decrease in serum lipid peroxides, a 29% increase in serum HDL cholesterol, and a nearly 12% decrease in total serum cholesterol. Together, these striking findings suggest a potential chemopreventive role for curcumin in arterial diseases [175]. In concordant with these findings are

results of another study in which curcumin (10 mg) administered twice a day for 28 days lowered serum LDL and increased serum HDL levels in patients with atherosclerosis [176].

#### 6.5. Curcumin may prevent gallstone formation

Curcumin has been evaluated for its ability to induce gall bladder emptying and thus reduce gallstone formation, a potential risk factor for gall bladder cancer. Agents that can induce the gall bladder to contract and empty itself (e.g., erythromycin, fatty meals, and amino acids) have been shown to reduce gallstone formation. In a randomized, double-blind, crossover study involving 12 healthy volunteers [178], 20 mg curcumin produced a positive cholekinetic effect that led to 29% contraction of the gall bladder. A subsequent study indicated that doses of 40 and 80 mg curcumin produced 50% and 72% contraction of the gall bladder volume, respectively. Together, these results suggest that curcumin can effectively induce the gall bladder to empty and thereby reduce the risk of gallstone formation and ultimately gall bladder cancer.

#### 6.6. Curcumin is effective in patients with chronic anterior uveitis and idiopathic inflammatory orbital pseudotumors

Curcumin's anti-inflammatory effect has also been evaluated in two rare inflammatory diseases—chronic anterior uveitis (CAU) and idiopathic inflammatory orbital pseudotumors (IIOTs). In a study by Lal et al. [180] involving patients with CAU, curcumin was administered orally at a dose of 375 mg three times a day for 12 weeks. Patients were segregated into two groups: 18 patients who received curcumin alone and 14 patients who, in addition to CAU, had a strong reaction to a PPD tuberculosis test and so received antitubercular treatment in addition to curcumin. Patients in both groups began showing improvement after 2 weeks of treatment, although those in the combination therapy group had a better response rate of 86%. Moreover, at 3 years of follow-up, the recurrence rate was much lower in the combination therapy group than in the group treated with curcumin only (36% versus 55%). Although approximately one in five patients in each treatment group lost their vision in the follow-up period because of various complications of the primary disease (e.g., vitritis, macular edema, central venous block, cataract formation, and glaucomatous optic nerve damage), none reported any side effects of the curcumin therapy. In fact, in terms of safety and efficacy, curcumin compared favorably with the only current standard treatment for CAU (i.e., corticosteroid therapy).

Encouraged by this clinical study, Lal et al. [181] proceeded to evaluate curcumin as treatment for IIOT and found it to be both safe and effective. In that relatively small study, eight patients took curcumin orally at a dose of 375 mg three times a day for 6–22 months and were followed up every 3 months for 2 years. Although only five patients completed the study, four of them recovered completely and the fifth experienced a complete resolution of tumor-related swelling despite some residual limits on range of motion. Just as encouraging was the lack of any recurrence or side effects.

#### 6.7. Curcumin beneficially affects psoriasis

Curcumin has also been shown to have beneficial effects on psoriasis, another proinflammatory and potentially arthritis-inducing skin disease. In one particular study, Heng et al. [182] evaluated curcumin's antipsoriatic effects indirectly by measuring its influence on phosphorylase kinase activity. (Curcumin is a potent selective inhibitor of phosphorylase kinase, increased levels of which are considered by some to be a surrogate marker of psoriatic disease.) Phosphorylase kinase activity was assayed in four groups of 10 patients each: (i) those with active untreated psoriasis; (ii) those with resolving psoriasis treated with calcipotriol, a vitamin D3 analogue and an indirect inhibitor of phosphorylase kinase; (iii) those with resolving psoriasis treated with curcumin; and (iv) normal nonpsoriatic subjects. Phosphorylase kinase activity was highest in the patients with active untreated psoriasis, lower in the calcipotriol-treated group, even lower in the curcumin-treated group, and lowest in normal subjects. Interestingly, the decreased phosphorylase kinase activity in calcipotriol and curcumin-treated patients was associated with corresponding decreases in the expression of keratinocyte transferrin receptor (TRR), severity of parakeratosis, and density of epidermal CD8+ T cells.

#### 6.8. Curcumin safely exerts chemopreventive effects against multiple human cancers

Apparently, curcumin can also safely exert chemopreventive effects on premalignant lesions. In a prospective phase I dose-escalation study, Cheng et al. [159] examined the safety, efficacy, and pharmacokinetics of curcumin in 25 patients with a variety of high-risk. Precancerous lesions (i.e., recently resected urinary bladder cancer ( $n = 2$ ), arsenic Bowen's disease of the skin ( $n = 6$ ), uterine cervical intraepithelial neoplasm [CIN] ( $n = 4$ ), oral leukoplakia ( $n = 7$ ), and intestinal metaplasia of the stomach ( $n = 6$ )). Curcumin was administered to the first three patients at a starting dose of 500 mg/day for 3 months and, if no grade 2 or higher toxicities were observed, was increased to 1000, 2000, 4000, 8000, and finally 12,000 mg/day. Curcumin was not toxic at doses of 8000 mg/day or lower, reaching peak serum concentrations at 1–2 h ( $0.51 \pm 0.11 \mu\text{M}$  at 4000 mg,  $0.63 \pm 0.06 \mu\text{M}$  at 6000 mg, and  $1.77 \pm 1.87 \mu\text{M}$  at 8000 mg) and being gradually eliminated (principally through nonurinary routes) within 12 h. Although frank malignancies occurred despite curcumin treatment in one patient each with CIN and oral leukoplakia, a remarkable number of patients (i.e., one patient with recently resected bladder cancer, two with oral leukoplakia, one with intestinal metaplasia of the stomach, one with CIN, and two with Bowen's disease) showed histologic improvement of their precancerous lesions.

#### 6.9. Curcumin modulates biomarkers of colorectal cancer

Curcumin can also apparently modulate biomarkers of colorectal cancer. In a pilot dose-escalation study in 15 patients with drug-resistant advanced colorectal cancer, Sharma et al. [160] assessed the pharmacodynamics and pharmacokinetics of a novel encapsulated turmeric extract administered at

doses ranging from 440 to 2200 mg/day for up to 4 months. (Depending on the dose, each capsule contained 36–180 mg of curcumin.) The compound's effects were measured in terms of its effects on two surrogate biomarkers (i.e., glutathione-S-transferase [GST] activity and DNA adducts formed between M(1)G and malondialdehyde) in blood cells. The compound was deemed safe and effective after the investigators observed no dose-limiting toxicity and a significant (59%) decrease in GST activity at the lowest dose (440 mg) but none at higher doses and clinically effective, and radiologically stable disease in 33% (5/15) of patients after 2–4 months of treatment.

In a subsequent dose-escalation study in a similar population, Sharma et al. [183] further explored the pharmacology of curcumin administered in capsules at daily doses ranging from 0.45 to 3.6 g daily for up to 4 months. This time, the compound's effects on leukocytes were measured in terms of three potential biomarkers: GST activity, deoxyguanosine adduct M(1)G levels, and PGE<sub>2</sub> production *ex vivo*. In a comparison of inducible PGE<sub>2</sub> production immediately before and 1 h after dosing on days 1 and 29, the highest dose (3.6 g) elicited significant decreases (62% and 57%, respectively). Consequently, the investigators chose the 3.6 g dose for further evaluation in a phase II trial in cancers outside the gastrointestinal tract.

In a subsequent and similar study, the same investigators asked whether pharmacologically active levels of curcumin could be achieved in the colorectum of colorectal cancer patients [161]. Encapsulated curcumin was administered orally at three different daily doses (3600, 1800, or 450 mg) for 7 days. Its biodistribution was then assayed by comparing curcumin levels in biopsied specimens of normal and malignant colorectal tissue obtained at diagnosis and 6–7 h after the last curcumin dose, measuring the levels of M(1)G and COX-2 protein in blood samples obtained 1 h after the last curcumin dose, and quantitating blood levels of curcumin and its metabolites by high-performance liquid chromatography and UV spectrophotometry or mass spectrometry. At the highest dose (3600 mg), the concentrations of curcumin differed between normal and malignant tissues ( $12.7 \pm 5.7$  versus  $7.7 \pm 1.8$  nmol/g). However, both normal and malignant tissues from patients so treated contained curcumin sulfate and curcumin glucuronide, and their peripheral circulation contained trace amounts of curcumin. Furthermore, the DNA adduct M(1)G was 2.5 times more abundant in cancerous tissues than in normal tissues. At the highest dose (3600 mg), curcumin lowered M<sub>1</sub>G levels (from  $4.8 \pm 2.9$  to  $2.0 \pm 1.8$  adducts per  $10^7$  nucleotides) but not COX-2 protein levels in cancerous tissues. Together, these results suggested that curcumin orally administered at a dose of 3600 mg could reach pharmacologically efficacious levels in the colorectum while at the same time being negligibly distributed outside the gut [161].

### 6.10. Curcumin helps reduce symptoms of irritable bowel syndrome

There is evidence that curcumin may help relieve symptoms of the extremely common gastric disorder known as irritable bowel syndrome (IBS). This chronic condition is characterized by abdominal pain, alterations in bowel habits and stool

frequency, and poor quality of life and appears to be causally associated with antibiotic use and inflammatory infection. In a partially blinded, randomized, pilot study in which 207 healthy adults were randomly assigned to receive either one or two tablets of a standardized turmeric extract daily for 8 weeks, IBS symptoms improved significantly after treatment [184].

In a study by another group of investigators, oral curcumin was administered in daily doses ranging from 450 to 3600 mg to 12 patients about to undergo surgery for hepatic metastases of colorectal cancer to determine whether enough of the curcumin would reach normal and malignant human liver tissue in concentrations sufficient to elicit pharmacologic activity [156]. The compound's resulting poor bioavailability (as indicated by low nanomolar levels of the parent compound and its glucuronide and sulfate conjugates in the peripheral or portal circulation) led the investigators to conclude that achieving pharmacologically effective concentrations of curcumin in the liver is not feasible.

### 6.11. Curcumin improves early renal graft function

Curcumin has also been shown to beneficially influence early kidney graft function, presumably due to its known ability to induce the activity of the antioxidant hemoxygenase-1. In a randomized, placebo-controlled trial, a combination of curcumin 480 mg and quercetin 20 mg was administered orally in capsule form to cadaveric kidney transplant recipients for 1 month, starting immediately after transplantation. The trial's 43 subjects were randomly assigned to placebo (control), low-dose (one capsule + one placebo), or high dose (two capsule) regimens [185]. Graft function was assessed in terms of delayed graft function (i.e., the need for dialysis in the first week after transplantation) and slowed graft function (i.e., serum creatinine  $>2.5$  mg/dL by post-transplantation day 10). The investigators consequently observed much better early graft function in treated patients than in controls (71% [low-dose] versus 93% [high-dose] versus 43% [controls]), no delayed graft function in any treated patients but delayed function in 14% (2/14) of controls, and significantly lower serum creatinine levels in treated patients after 2 and 30 days of treatment. They also noted significantly higher levels of urinary HO-1 in the two active treatment groups. Interestingly, however, when compared with both the low-dose and control regimens, only the high-dose regimen appeared to lower the incidence of acute graft rejection at 6 months posttransplantation (0% versus 14.3%) and reduce the incidence of tremors (13% versus 46%).

### 6.12. Curcumin improves clinical outcome in patients with tropical pancreatitis

Curcumin appears to improve the clinical outcomes of patients suffering from chronic pancreatitis, an intensely painful inflammatory condition induced by oxidative stress, by reversing lipid peroxidation. As shown in a randomized, placebo-controlled pilot study involving 20 patients with tropical pancreatitis, an oral combination of curcumin 500 mg and piperine 5 mg provided effective pain relief and beneficially modulated a pair of markers of oxidative stress

(i.e., significantly reduced malonyldialdehyde levels and increased glutathione levels in erythrocytes) [186].

### **6.13. Curcumin is therapeutic in patients with inflammatory bowel disease**

Curcumin also appears to have beneficial therapeutic effects on inflammatory bowel disease. Marked by chronic inflammation of the colon and encompassing both ulcerative colitis and Crohn's disease, inflammatory bowel disease is a frequent complication of and risk factor for colorectal cancer in humans. In a preliminary open-label study based on its preclinically established anti-inflammatory and antioxidant properties, curcumin was administered to a small population of patients with previously treated ulcerative proctitis ( $n = 5$ ) or Crohn's disease ( $n = 5$ ) [187]. The five patients with ulcerative proctitis, who had been previously treated with 5-aminosalicylic acid (5ASA) compounds and (in four cases) corticosteroids, received curcumin orally at a dose of 550 mg twice daily for 1 month and then three times daily for another month. The five patients with Crohn's disease received curcumin orally at a dose of 360 mg (one capsule) three times daily for 1 month and then 360 mg (four capsules) four times daily for another 2 months. By study's end, all five cases of ulcerative proctitis had significantly improved to the point that two patients stopped taking 5ASAs and two others (including one who stopped taking prednisone) reduced their 5ASA dosages. This improvement was documented in terms of a return to normal limits of the inflammatory indices of sedimentation rate and C-reactive protein (CRP) level. Meanwhile, although only four of five Crohn's disease patients completed the study, those four also experienced marked clinical improvement after curcumin treatment, as evidenced by reductions in several indices including Crohn's disease activity index (CDAI) scores, sedimentation rate (i.e., a mean reduction of 10 mm/h, and CRP (i.e., a mean reduction of 0.1 mg/dL). Moreover, these four patients continued to show significant symptomatic improvement (i.e., more formed stools, less frequent bowel movements, and less abdominal pain and cramping) at monthly follow-up visits. In light of these extremely encouraging findings, the investigators concluded that double-blind placebo-controlled follow-up studies were warranted.

In a subsequent randomized, double-blind, placebo-controlled multicenter trial [188], Hanai et al. demonstrated curcumin's ability to safely and effectively prevent the relapse of quiescent ulcerative colitis when delivered as maintenance therapy. The 89 patients enrolled in the trial were randomly assigned to a 6-month regimen of either placebo ( $n = 44$ ) or curcumin 1000 mg after breakfast and 1000 mg after dinner ( $n = 45$ ) in combination with sulfasalazine or mesalamine. After 6 months of treatment, the relapse rate among evaluable patients ( $n = 82$ ) was significantly higher in the placebo group (20.5% [8/39]) than in the curcumin-treated group (4.7% [2/43]). Curcumin also appeared to suppress disease-associated morbidity, as assessed in terms of clinical activity index (CAI) and endoscopic index (EI) scores. After an additional 6-month follow-up period, during which patients in both groups took sulfasalazine or mesalamine, another 8 curcumin-

treated patients and another 6 placebo-treated patients experienced a disease relapse.

### **6.14. Curcumin reduces polyp numbers in patients with familial adenomatous polyposis**

Curcumin also appears to safely exert beneficial effects in patients with FAP, an autosomal-dominant disorder characterized by the formation of hundreds of colorectal adenomas and eventually the development of colorectal cancer. Typically, the growth of the adenomatous polyps is controlled in part by treatment with nonsteroidal anti-inflammatory drugs and COX-2 inhibitors, despite the considerable side effects. Therefore, in a very small clinical trial, Cruz-Correa et al. [189] evaluated curcumin's ability to induce adenoma regression in previously colectomized patients with FAP. In all five cases, combination treatment with curcumin 480 mg and quercetin 20 mg orally three times a day for a mean duration of 6 months significantly decreased mean polyp number and size by 60.4% and 50.9%, respectively, without producing any noticeable toxic side effects.

### **6.15. Curcumin may improve cognitive function in the elderly**

Despite preclinical evidence of curcumin's ability to bind  $\beta$ -amyloids and thereby reduce plaque burdens [51], there has been little, if any, supporting epidemiologic evidence of this. However, in a recent large, population-based study of 1010 elderly nondemented Asians, those who consumed curry "occasionally" and "often or very often" scored significantly better on the Mini-Mental State Examination (MMSE), a established measure of cognitive function, than did those who "never or rarely" consumed curry [190]. At the least, this finding warrants further investigation of curcumin's cognitive effects.

### **6.16. Curcumin may beneficially influence several cancer precursor conditions**

In addition to the published studies reviewed above, several other trials have been investigating curcumin's therapeutic and chemopreventive potential in certain cancer precursor conditions. One of them, a small 18-month study involving 24 human subjects and still in progress, is investigating curcumin's effect on prostatic intraepithelial neoplasia (PIN), a precursor of prostate cancer, when given in combination with a herbal product called zyflamend [191]. Another study, recently reported, found curcumin to exert beneficial effects in patients with *H. pylori* infection, a precursor of gastric cancer [192].

### **6.17. Curcumin has potential in advanced pancreatic cancer**

Curcumin has also been examined as a single-agent in patients with advanced pancreatic cancer [196]. A dose of 8 g curcumin per day was administered for 2 months. The results of this study showed that curcumin is well tolerated and a sign of biological activity found in most patients.

**Table 7 – A list of ongoing clinical trials with curcumin in patients with different diseases**

Disease	Study type/design	Patients #	Start date	Trial site
Colon cancer	Phase-I, randomized	24	Completed	University of Michigan, Ann Arbor, USA
Colorectal cancer, ACF <sup>1</sup>	Phase-I, randomized <sup>2</sup>	–	Suspended	Rockefeller University Hospital, New York, USA
Colon cancer	Phase-III, randomized	100	March 2006	Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel
Colorectal cancer, ACF <sup>1</sup>	Phase-II, non-randomized	48	September 2006	University of Illinois, Chicago, USA
FAP	Phase-II, randomized <sup>4</sup>	68	July 2005	University of Pennsylvania, Philadelphia, USA
FAP	Phase-II, non-randomized	–	November 2005	Johns Hopkins University, Baltimore, USA
Aberrant crypt foci	Prevention, randomized <sup>5</sup>	60	April 2004	Cancer Institute of New Jersey, New Brunswick, USA
Pancreatic cancer	Phase-II, non-randomized <sup>6</sup>	45	July 2004	Rambam Medcial Center, Haifa, Israel
Pancreatic cancer	Phase-II, non-randomized	50	November 2004	M.D. Anderson Cancer Center, Houston, USA
Pharmacokinetics	Treatment, non-randomized	6	August 2005	Massachusetts General Hospital, Boston, USA
Myelodysplastic syndrome	Phase II	30		University Massachusetts, Worcester, USA (Raza A.)
Alzheimer's disease	Phase-II, randomized	33	July 2003	University of California Los Angeles, Los Angeles, USA
Alzheimer's disease	Phase-I and II, randomized <sup>7</sup>	30	Completed	Chinese University of Hong Kong, Shatin, Hong Kong
Multiple myeloma	Randomized <sup>8</sup>	30	November 2004	M.D. Anderson Cancer Center, Houston, USA
Myelodysplastic syndrome	Phase-I and II, non-randomized <sup>9</sup>	50	December 2006	Hadassah Medical Organization, Jerusalem, Israel
Psoriasis	Phase-II, non-randomized <sup>10</sup>	–	October 2005	University of Pennsylvania, Philadelphia, USA
Epilepsy	Phase 1	?	?	AIIMS, Delhi, India (Gupta Y.K.)
Advanced HNSCC	Phase II (1–8 g/day; 56 days)	40	?	Himalyan Institute of Medical Sciences, India (Saini S.)
HNSCC	Phase II/III DBRPC (3.6 g/day, bid)	300	?	AIIMS, Delhi, India (Bahadur S./Ranju R./Rath G.K./Julka P.K.)
Cervical cancer (Stage Iib, IiIb)	Phase II/III DBRPC (2 g/day, bid, 1 year)	100	?	AIIMS, Delhi, India (Singh N./Jain S.K./Rath G.K./Julka P.K.)
Oral premalignant lesions	Phase II/III DBRPC (4 g/day, bid × 28 days)	90	?	Tata Memorial Cancer Center, India (D'Cruz A.)
Oral premalignant lesions	Phase II/III DBRPC (3.6 g/day, bid)	96	November 2006	Amrita Institute, Kochi, India (Kuriakose M.A.)
Oral leukoplakia	Phase II (curcumin gel, 3×/day, 6 month)	100	?	Regional Cancer Center, India (Ramadas K., Pillai M.R.)
Gall bladder cancer	Phase II (2–8 g/day)	60	?	BHU, India (Shukla V.K.)
Pancreatic cancer	Phase II (8 g/day)	40	August 2007	Kyoto University, Japan (Kanai M., Guha S.)
PSC	Phase I (8 g/day)	20	August 2007	Amsterdam Medical Center (Krishnadath K., Guha S.)
Ulcerative colitis	Phase I (8 g/day)	20	August 2007	Amsterdam Medical Center (Krishnadath K., Guha S.)
Barretts Metaplasia	Phase I (8 g/day)	20	August 2007	Amsterdam Medical Center (Krishnadath K., Guha S.)
MGUS	Phase 1 (3.4 g/day)			St. George Hospital, Sydney (Terrance Diamond)

ACF, aberrant crypt foci; DBRPC, double-blind randomized placebo-controlled; clinical trials were performed with curcumin in combination with 2. quercetin<sup>2</sup>, sulindac; 2, celecoxib; 3, 4, curcuminoids; 5, NSAIDs; 6, gemcitabine; 6, ginkgo extract; 7, bioperine; 8, coenzyme Q10; 10, curcuminoids C3 complex; 11, gemcitabine + S-1; PSC: Primary Sclerosing Cholangitis. Website: [www.clinicaltrial.gov](http://www.clinicaltrial.gov).

## 7. Ongoing clinical trials of curcumin

Enthusiasm for further studies of curcumin's chemopreventive and therapeutic effects continues to grow. Three trials of curcumin have recently concluded, although their results

have yet to be published. At least 12 active clinical trials of curcumin are ongoing in the United States, Israel, and Hong Kong (Table 7). Curcumin is being used alone in most of these trials and in combination with quercetin or sulindac in one. Meanwhile, chemoprevention trials of curcumin in hepato-

cellular carcinoma, gastric cancer, and colon cancer are ongoing in Japan. Here in the United States, several randomized and nonrandomized phase I/II trials ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)) are investigating curcumin's effects on a range of human malignancies (e.g., colorectal cancer, aberrant crypt foci, FAP, pancreatic cancer, multiple myeloma, Alzheimer's disease, myelodysplastic syndrome, and psoriasis) when given alone or in conjunction with other natural substances or nonsteroidal anti-inflammatory drugs (NSAIDs).

Five ongoing phase I/II trials are studying curcumin's preventive and therapeutic effects on colorectal cancers in patients with FAP and ACF. Two-phase II trials are interrogating the effects of curcumin in advanced pancreatic cancers. An Israeli trial is investigating the combined effects of curcumin and gemcitabine in patients with chemotherapy-naïve, locally advanced or metastatic adenocarcinomas of the pancreas, while an exploratory clinical trial in the United States is testing the efficacy of curcumin alone in patients with unresectable or metastatic pancreatic cancers.

Two double-blind, placebo-controlled phase II trials are evaluating the efficacy, safety, and tolerability of two doses of curcumin C3 complex versus placebo in patients with mild to moderate Alzheimer's disease. An Israeli clinical trial is investigating the clinical efficacy of curcumin alone or in combination with coenzyme Q10 in patients with myelodysplastic syndrome (MDS). At M.D. Anderson Cancer Center, a pilot trial of curcumin alone or in combination with bioprine (a black pepper extract) is underway in patients with asymptomatic multiple myeloma.

## 8. Adverse effects of curcumin

Though curcumin is demonstrably bioactive and nontoxic, there are rare anecdotal reports of its deleterious side effects under certain conditions. Frank et al. [197] reported that copper-bound curcumin loses its ability to inhibit liver and kidney tumors in Cinnamon rats. Others have noted that curcumin can exhibit some blood-thinning properties such as suppression of platelet aggregation, although it remains to be established whether curcumin interacts in any way with blood-thinning drugs. Although several published studies suggest that curcumin may beneficially induce apoptosis in part through its induction of p53 expression [198], at least two other studies suggest that curcumin may instead have a deleterious, antiapoptotic effect by downregulating p53 [199,200]. Similarly, although dozens of studies indicate that curcumin potentiates the effect of chemotherapeutic agents, at least one study done in mice suggests that a curcumin-supplemented diet may inhibit the antiproliferative effects of cyclophosphamide on breast cancer growth (the investigators in that study, however, monitored tumor growth for only 3 days) [201]. There have also been reports of curcumin-induced allergic contact dermatitis [202,203] and urticaria in humans.

## 9. Conclusions

Extensive research over the last half century has made clear that most chronic illnesses can only be cured by multi-

targeted, as opposed to mono-targeted, therapy [204–206] and that promiscuous targeting of a disease cell's multiple bypass mechanisms is a therapeutic virtue [207]. Consequently, agents that can modulate multiple cellular targets are now attractive objects of research. As this review has shown, curcumin is one such agent and has the potential to treat a variety of diseases. More extensive, well-controlled clinical trials are now needed to fully evaluate its potential in terms of optimal dose, route of administration, and disease targets and potential interactions with other drugs. In light of the long and established experience with curcumin as a foodstuff and as a natural medicine in humans, its low cost, its proven chemopreventive and therapeutic potential, and its pharmacological safety, curcumin is moving rapidly from the kitchen shelf toward the clinic.

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