available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Curcumin as "*Curecumin*": From kitchen to clinic

Ajay Goel [a], *Ajaikumar B. Kunnumakkara* [b], *Bharat B. Aggarwal* [b,*]

[a] *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*
[b] *Cytokine Research Laboratory, Departments of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, United States*

ARTICLE INFO

Keywords:
Anticancer
Natural products
Curcumin

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, hypercholesteremia, 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".

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 (B.B. Aggarwal).
0006-2952/$ – see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.bcp.2007.08.016

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

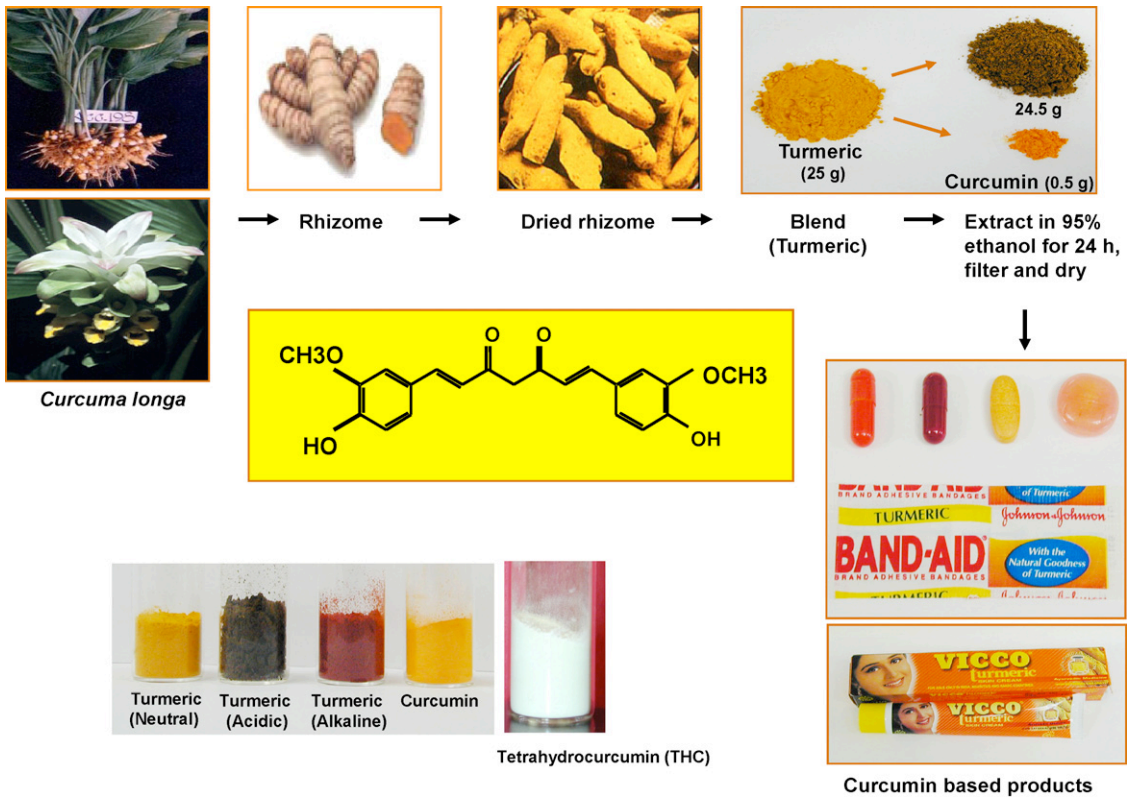

Fig. 1 – Isolation, extraction, and structure of curcumin. Curcumin capsules, pills, lozenges, band-aid and cream commonly sold in the market are shown. The change in color of turmeric at acidic and alkaline pH is also shown. Tetrahydrocurcumin (THC), a major metabolite of curcumin, exhibits whitish 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 zázvor
Dhivehi	Reen'dhoo
Danish	Gurkemeje
Dutch	Geelwortel, Kurkuma Tarmeriek, Koenjit, Koenir
English	Indian saffron
Esperanto	Kurkumo
Estonian	Harilik kurkuma, Kurkum, Pikk kollajuur, Lõhnav kollajuur, Harilik kurkuma, Kurkum, Pikk kollajuur, Lõhnav kollajuur
Farsi	Zardchubeh
Finnish	Kurkuma, Keltajuuri
French	Curcuma, 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 khün
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, Ostryż długi, Szafran indyjski
Portuguese	Açafrão da Índia, Curcuma
Punjabi	Haldi
Romanian	Curcuma˘
Russian	Koren, kurkumy, Kurkuma
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 safranı, Sarı 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 (λ_{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 β-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 preoliferator-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^{2+}-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↓
- Prorein kinase C↓
- pp60c-src tyrosine kinase↓
- 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^{53}↑

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 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 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 β-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-κB (NF-κB), activated protein-1 (AP-1), signal transducer and activator of transcription (STAT) proteins, peroxisome proliferator-activated receptor-γ (PPAR-γ), and β-catenin [44]. These transcription factors regulate the expression of genes that contribute to tumorigenesis, inflammation, cell survival, cell proliferation, invasion, and angiogenesis.

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^{2+}, Zn^{2+}	[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]

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 overexpress 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. Cyclooxygense-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-κB 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 1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α) 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-α-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-α-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].

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
Gastrointestinal cancers				
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]
Liver cancers				
Hepatic hyperplasia	Diethylnitrosamine	Rat	200 or 600 mg/kg	[107]
Liver cancer	Diethylnitrosamine	Mice	0.2% (w/w)	[107]
Lung cancers				
Lung cancer	B[a]P and NNK	A/J mice	2000 ppm	[108]
Blood cancers				
Lymphoma/leukemia	DMBA	Sencar mice	2% (w/w)	[109]
Breast cancers				
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]
Oral cancers				
Oral cancer	MNA	Hamster		[116]
Oral cancer	NQO	Rat	500 ppm	[117]
Prostate cancers				
Prostate cancer	DMAB and PhIP	Rat	15–500 ppm	[118]
Skin cancers				
Dermatitis	TPA + UV-A	Mice		[119]
Skin tumor	TPA	Mice		[120]
Skin tumor	DMBA	Mice		[103]
Skin tumors	TPA	Mice	10 and 30 μmol	[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]
Other cancers				
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]nthracene; TPA, 12-O-tetradecanoylphorbol-13-acetate; NNK, 4-(methyl-nitrosamino)-I-(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[2]	i.p.	50 mg/kg	Ascites	[133]
Ascites	i.p.	50 mg/kg	Ascites	[134]
Breast[1]	Diet	2% (w/w)	Orthotopic	[135]
Breast[1]	Diet	1% (w/w)	Orthotopic	[136]
Colon[2]	i.v.	40 mg/kg	Xenograft	[137]
Gastric cancer	Oral	50–200 mg/kg	Xenograft	[138]
Gliobalstoma	i.t.	10 mg/kg	Orthotopic	[77]
HCC[3]		100–200 mg/kg	Orthotopic	[139]
Hepatoma	Oral	50–200 mg/kg	Xenograft	[138]
HNSCC[4]	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[2]	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-κB 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 μg/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 μg/g, respectively, but only trace levels (0.41 μg/g) in the brain. In comparison, after oral administration of 1 g/kg curcumin, serum plasma levels peaked at 0.5 μM. 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 radiolabled 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 β-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 μM [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

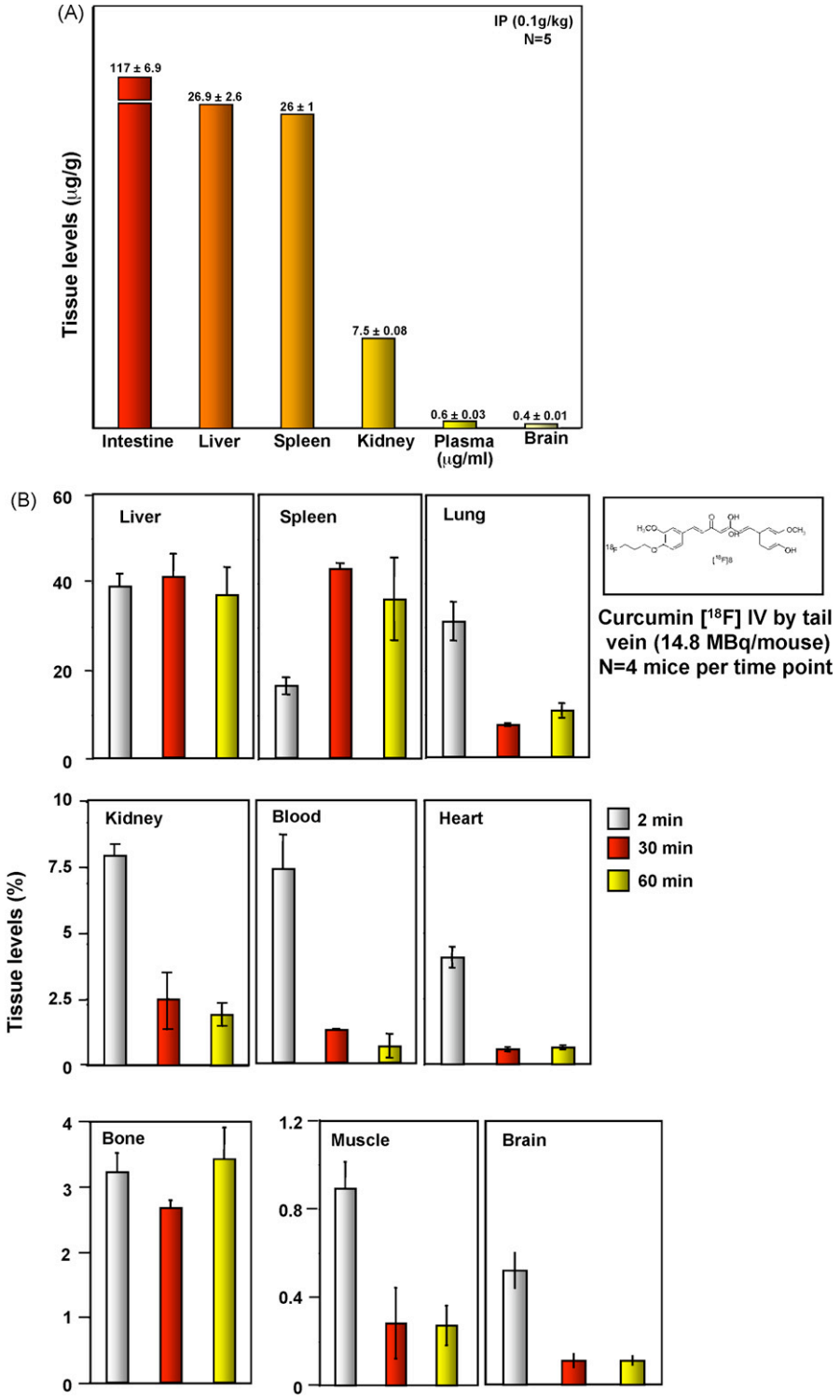

Fig. 2 – Plasma and tissue distribution of curcumin administered via intraperitoneal (i.p.) and systemic routes. (A) Curcumin (0.1 g/kg) was administered (i.p.) to mice ($N = 5$), sacrificed 1 h later and concentration of curcumin in various tissues was analysed by HPLC. The data is replotted from [18]. (B) ICR mice were injected with [^{18}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-β-di-erythro-pentafuranosyl)-pyr[1,2-α]-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
Safety trials				
Phase 1	2000 mg/day[1]	10	Piperine enhanced bioavailability by 2000%	[162]
Phase-I	500–12,000 mg/day × 90 days	25	Histologic improvement of precancerous lesions[4]	[159]
Phase 1	500–12,000 mg/day	24	Safe, well-tolerated even at 12 g/day	[42]
Efficacy trials				
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[2], TRR[3], 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[5]	[190]
Prostatic intraepithelial neoplasia (PIN)[1]		24		[191]
Helicobacter pylori infection[2]	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 ± 0.11 μM at 4000 mg, 0.63 ± 0.06 μM at 6000 mg, and 1.77 ± 1.87 μM 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_2 production ex vivo. In a comparison of inducible PGE_2 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 ± 5.7 versus 7.7 ± 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_1G levels (from 4.8 ± 2.9 to 2.0 ± 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-aminosalicyclic 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 β-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[1]	Phase-I, randomized[2]	–	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[1]	Phase-II, non-randomized	48	September 2006	University of Illinois, Chicago, USA
FAP	Phase-II, randomized[4]	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[5]	60	April 2004	Cancer Institute of New Jersey, New Brunswick, USA
Pancreatic cancer	Phase-II, non-randomized[6]	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[7]	30	Completed	Chinese University of Hong Kong, Shatin, Hong Kong
Multiple myeloma	Randomized[8]	30	November 2004	M.D. Anderson Cancer Center, Houston, USA
Myelodysplastic syndrome	Phase-I and II, non-randomized[9]	50	December 2006	Hadassah Medical Organization, Jerusalem, Israel
Psoriasis	Phase-II, non-randomized[10]	–	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, abrerrant crypt foci; DBRPC, double-blind randomized placebo-controlled; clinical trials were performed with curcumin in combination with 2. quercetin[2], sulindac; 2, celecoxoib; 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.

7. Ongoing clinical trials of curcumin

Enthusiasm for further studies of curcumin's chemopreventive and therapeutic effects continues to grow. Three trials of curcumiun 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.Clinical-Trials.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.

Acknowledgements

We would like to thank Jude Richard, ELS, for carefully editing the manuscript and providing valuable comments. Dr. Aggarwal is the Ransom Horne, Jr, Professor of Cancer Research. This work was supported by grants from the Clayton Foundation for Research and from cancer center support grant 5P30 CA016672-32 from National Institute of Health.

REFERENCES

[1] Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981–2002. J Nat Prod 2003;66:1022–37.
[2] Butler MS. The role of natural product chemistry in drug discovery. J Nat Prod 2004;67:2141–53.
[3] Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. Life Sci 2005;78:431–41.
[4] Gurib-Fakim A. Medicinal plants: traditions of yesterday and drugs of tomorrow. Mol Aspects Med 2006;27:1–93.
[5] Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. J Nat Prod 2007;70:461–77.
[6] Mukherjee PK, Wahile A. Integrated approaches towards drug development from Ayurveda and other Indian system of medicines. J Ethnopharmacol 2006;103:25–35.
[7] Kiuchi F, Goto Y, Sugimoto N, Akao N, Kondo K, Tsuda Y. Nematocidal activity of turmeric: synergistic action of curcuminoids. Chem Pharm Bull (Tokyo) 1993;41:1640–3.
[8] Ravindran PN. Turmeric—the golden spice of life. Turmeric: The genus *Curcuma*. Taylor and Francis Group; 2006. p. 1–14.
[9] Aggarwal BB, Surh YJ, Shishodia S. The molecular targets and therapeutic uses of curcumin in health and disease. Adv Exp Med Biol 2007;595. Springer publication.
[10] Daybe FV. Uber Curcumin. den Farbstoff der Curcumawurzzel Ber 1870;3:609.
[11] Lampe V. Milobedzka. J Ver Dtsch Chem Ges 1913;46:2235.
[12] Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res 2003;23:363–98.
[13] Shen L, Ji HF. Theoretical study on physicochemical properties of curcumin. Spectrochim Acta A Mol Biomol Spectrosc 2007;67:619–23.

[14] Bernabe-Pineda M, Ramirez-Silva MT, Romero-Romo M, Gonzalez-Vergara E, Rojas-Hernandez A. Determination of acidity constants of curcumin in aqueous solution and apparent rate constant of its decomposition. Spectrochim Acta A Mol Biomol Spectrosc 2004;60:1091–7.
[15] Wang YJ, Pan MH, Cheng AL, Lin LI, Ho YS, Hsieh CY, et al. Stability of curcumin in buffer solutions and characterization of its degradation products. J Pharm Biomed Anal 1997;15:1867–76.
[16] Tonnesen HH, Karlsen J. Studies on curcumin and curcuminoids. VI. Kinetics of curcumin degradation in aqueous solution. Z Lebensm Unters Forsch 1985;180: 402–4.
[17] Oetari S, Sudibyo M, Commandeur JN, Samhoedi R, Vermeulen NP. Effects of curcumin on cytochrome P450 and glutathione-S-transferase activities in rat liver. Biochem Pharmacol 1996;51:39–45.
[18] Pan MH, Huang TM, Lin JK. Biotransformation of curcumin through reduction and glucuronidation in mice. Drug Metab Dispos 1999;27:486–94.
[19] Somparn P, Phisalaphong C, Nakornchai S, Unchern S, Morales NP. Comparative antioxidant activities of curcumin and its demethoxy and hydrogenated derivatives. Biol Pharm Bull 2007;30:74–8.
[20] Pari L, Murugan P. Tetrahydrocurcumin prevents brain lipid peroxidation in streptozotocin-induced diabetic rats. J Med Food 2007;10:323–9.
[21] Murugan P, Pari L. Antioxidant effect of tetrahydrocurcumin in streptozotocin–nicotinamide induced diabetic rats. Life Sci 2006;79:1720–8.
[22] Tomren MA, Masson M, Loftsson T, Tonnesen HH. Studies on curcumin and curcuminoids XXXI. Symmetric and asymmetric curcuminoids: stability, activity and complexation with cyclodextrin. Int J Pharm 2007;338:27–34.
[23] Govindarajan VS. Turmeric–chemistry, technology, and quality. Crit Rev Food Sci Nutr 1980;12:199–301.
[24] Ammon HP, Wahl MA. Pharmacology of *Curcuma longa*. Planta Med 1991;57:1–7.
[25] Araujo CC, Leon LL. Biological activities of *Curcuma longa* L.. Mem Inst Oswaldo Cruz 2001;96:723–8.
[26] Aggarwal BB, Takada Y, Oommen OV. From chemoprevention to chemotherapy: common targets and common goals. Expert Opin Investig Drugs 2004;13:1327–38.
[27] Sreejayan, Rao MN. Nitric oxide scavenging by curcuminoids. J Pharm Pharmacol 1997;49:105–7.
[28] Brouet I, Ohshima H. Curcumin, an anti-tumour promoter and anti-inflammatory agent, inhibits induction of nitric oxide synthase in activated macrophages. Biochem Biophys Res Commun 1995;206:533–40.
[29] Dikshit M, Rastogi L, Shukla R, Srimal RC. Prevention of ischaemia-induced biochemical changes by curcumin & quinidine in the cat heart. Indian J Med Res 1995;101:31–5.
[30] Rao CV, Rivenson A, Simi B, Reddy BS. Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. Cancer Res 1995;55:259–66.
[31] Limtrakul P, Lipigorngoson S, Namwong O, Apisariyakul A, Dunn FW. Inhibitory effect of dietary curcumin on skin carcinogenesis in mice. Cancer Lett 1997;116:197–203.
[32] Kiso Y, Suzuki Y, Watanabe N, Oshima Y, Hikino H. Antihepatotoxic principles of *Curcuma longa* rhizomes. Planta Med 1983;49:185–7.
[33] Srivastava R, Dikshit M, Srimal RC, Dhawan BN. Anti-thrombotic effect of curcumin. Thromb Res 1985;40:413–7.
[34] Nirmala C, Puvanakrishnan R. Protective role of curcumin against isoproterenol induced myocardial infarction in rats. Mol Cell Biochem 1996;159:85–93.
[35] Venkatesan N. Curcumin attenuation of acute adriamycin myocardial toxicity in rats. Br J Pharmacol 1998;124:425–7.
[36] Srinivasan M. Effect of curcumin on blood sugar as seen in a diabetic subject. Indian J Med Sci 1972;26:269–70.
[37] Babu PS, Srinivasan K. Influence of dietary curcumin and cholesterol on the progression of experimentally induced diabetes in albino rat. Mol Cell Biochem 1995;152:13–21.
[38] Arun N, Nalini N. Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. Plant Foods Hum Nutr 2002;57:41–52.
[39] Deodhar SD, Sethi R, Srimal RC. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). Indian J Med Res 1980;71:632–4.
[40] Shankar TN, Shantha NV, Ramesh HP, Murthy IA, Murthy VS. Toxicity studies on turmeric (*Curcuma longa*): acute toxicity studies in rats, guineapigs & monkeys. Indian J Exp Biol 1980;18:73–5.
[41] Qureshi S, Shah AH, Ageel AM. Toxicity studies on *Alpinia galanga* and *Curcuma longa*. Planta Med 1992;58:124–7.
[42] Lao CD, Ruffin MTt, Normolle D, Heath DD, Murray SI, Bailey JM, et al. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med 2006;6:10.
[43] Aggarwal BB, Bhatt ID, Ichikawa H, Ahn KS, Sethi G, Sandur SK, et al. Curcumin–boiological and medicinal properties. Turmeric: the genus *Curcuma*. Taylor and Francis Group; 2006. p. 297–368.
[44] Shishodia S, Singh T, Chaturvedi MM. Modulation of transcription factors by curcumin. Adv Exp Med Biol 2007;595:127–48.
[45] Pulla Reddy AC, Sudharshan E, Appu Rao AG, Lokesh BR. Interaction of curcumin with human serum albumin–a spectroscopic study. Lipids 1999;34:1025–9.
[46] Zsila F, Bikadi Z, Simonyi M. Unique, pH-dependent biphasic band shape of the visible circular dichroism of curcumin–serum albumin complex. Biochem Biophys Res Commun 2003;301:776–82.
[47] Barik A, Priyadarsini KI, Mohan H. Photophysical studies on binding of curcumin to bovine serum albumins. Photochem Photobiol 2003;77:597–603.
[48] Wang F, Yang J, Wu X, Liu S. Study of the interaction of proteins with curcumin and SDS and its analytical application. Spectrochim Acta A Mol Biomol Spectrosc 2005;61:2650–6.
[49] Kunwar A, Barik A, Pandey R, Priyadarsini KI. Transport of liposomal and albumin loaded curcumin to living cells: an absorption and fluorescence spectroscopic study. Biochim Biophys Acta 2006;1760:1513–20.
[50] Zsila F, Bikadi Z, Simonyi M. Induced circular dichroism spectra reveal binding of the antiinflammatory curcumin to human alpha1-acid glycoprotein. Bioorg Med Chem 2004;12:3239–45.
[51] Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, et al. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 2005;280:5892–901.
[52] Logan-Smith MJ, Lockyer PJ, East JM, Lee AG. Curcumin, a molecule that inhibits the Ca^{2+}-ATPase of sarcoplasmic reticulum but increases the rate of accumulation of Ca^{2+}. J Biol Chem 2001;276:46905–11.
[53] Bilmen JG, Khan SZ, Javed MH, Michelangeli F. Inhibition of the SERCA Ca^{2+} pumps by curcumin. Curcumin putatively stabilizes the interaction between the nucleotide-binding and phosphorylation domains in the absence of ATP. Eur J Biochem 2001;268:6318–27.
[54] Reddy S, Aggarwal BB. Curcumin is a non-competitive and selective inhibitor of phosphorylase kinase. FEBS Lett 1994;341:19–22.
[55] Shim JS, Kim JH, Cho HY, Yum YN, Kim SH, Park HJ, et al. Irreversible inhibition of CD13/aminopeptidase N by the

antiangiogenic agent curcumin. Chem Biol 2003;10:695–704.
[56] Takeuchi T, Ishidoh T, Iijima H, Kuriyama I, Shimazaki N, Koiwai O, et al. Structural relationship of curcumin derivatives binding to the BRCT domain of human DNA polymerase lambda. Genes Cells 2006;11:223–35.
[57] Leu TH, Su SL, Chuang YC, Maa MC. Direct inhibitory effect of curcumin on Src and focal adhesion kinase activity. Biochem Pharmacol 2003;66:2323–31.
[58] Awasthi S, Pandya U, Singhal SS, Lin JT, Thiviyanathan V, Seifert Jr WE, et al. Curcumin–glutathione interactions and the role of human glutathione-S-transferase P1-1. Chem Biol Interact 2000;128:19–38.
[59] Wortelboer HM, Usta M, van der Velde AE, Boersma MG, Spenkelink B, van Zanden JJ, et al. Interplay between MRP inhibition and metabolism of MRP inhibitors: the case of curcumin. Chem Res Toxicol 2003;16:1642–51.
[60] Iersel ML, Ploemen JP, Struik I, van Amersfoort C, Keyzer AE, Schefferlie JG, et al. Inhibition of glutathione-S-transferase activity in human melanoma cells by alpha,beta-unsaturated carbonyl derivatives. Effects of acrolein, cinnamaldehyde, citral, crotonaldehyde, curcumin, ethacrynic acid, and *trans*-2-hexenal. Chem Biol Interact 1996;102:117–32.
[61] Jung Y, Xu W, Kim H, Ha N, Neckers L. Curcumin-induced degradation of ErbB2: a role for the E3 ubiquitin ligase CHIP and the Michael reaction acceptor activity of curcumin. Biochim Biophys Acta 2007;1773:383–90.
[62] Baum L, Ng A. Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. J Alzheimers Dis 2004;6:367–77. discussion 443–9.
[63] Ishihara M, Sakagami H. Re-evaluation of cytotoxicity and iron chelation activity of three beta-diketones by semiempirical molecular orbital method. In Vivo 2005;19:119–23.
[64] Jankun J, Aleem AM, Malgorzewicz S, Szkudlarek M, Zavodszky MI, Dewitt DL, et al. Synthetic curcuminoids modulate the arachidonic acid metabolism of human platelet 12-lipoxygenase and reduce sprout formation of human endothelial cells. Mol Cancer Ther 2006;5:1371–82.
[65] Skrzypczak-Jankun E, Zhou K, McCabe NP, Selman SH, Jankun J. Structure of curcumin in complex with lipoxygenase and its significance in cancer. Int J Mol Med 2003;12:17–24.
[66] Gupta KK, Bharne SS, Rathinasamy K, Naik NR, Panda D. Dietary antioxidant curcumin inhibits microtubule assembly through tubulin binding. FEBS J 2006;273:5320–32.
[67] Zsila F, Bikadi Z, Simonyi M. Circular dichroism spectroscopic studies reveal pH dependent binding of curcumin in the minor groove of natural and synthetic nucleic acids. Org Biomol Chem 2004;2:2902–10.
[68] Romiti N, Tongiani R, Cervelli F, Chieli E. Effects of curcumin on P-glycoprotein in primary cultures of rat hepatocytes. Life Sci 1998;62:2349–58.
[69] Anuchapreeda S, Leechanachai P, Smith MM, Ambudkar SV, Limtrakul PN. Modulation of P-glycoprotein expression and function by curcumin in multidrug-resistant human KB cells. Biochem Pharmacol 2002;64:573–82.
[70] Chearwae W, Anuchapreeda S, Nandigama K, Ambudkar SV, Limtrakul P. Biochemical mechanism of modulation of human P-glycoprotein (ABCB1) by curcumin I, II, and III purified from Turmeric powder. Biochem Pharmacol 2004;68:2043–52.
[71] Fang J, Lu J, Holmgren A. Thioredoxin reductase is irreversibly modified by curcumin: a novel molecular mechanism for its anticancer activity. J Biol Chem 2005;280:25284–90.
[72] Martin-Cordero C, Lopez-Lazaro M, Galvez M, Ayuso MJ. Curcumin as a DNA topoisomerase II poison. J Enzyme Inhib Med Chem 2003;18:505–9.
[73] Mullally JE, Fitzpatrick FA. Pharmacophore model for novel inhibitors of ubiquitin isopeptidases that induce p53-independent cell death. Mol Pharmacol 2002;62:351–8.
[74] Began G, Sudharshan E, Appu Rao AG. Inhibition of lipoxygenase 1 by phosphatidylcholine micelles-bound curcumin. Lipids 1998;33:1223–8.
[75] Lengyel E, Sawada K, Salgia R. Tyrosine kinase mutations in human cancer. Curr Mol Med 2007;7:77–84.
[76] Tikhomirov O, Carpenter G. Identification of ErbB-2 kinase domain motifs required for geldanamycin-induced degradation. Cancer Res 2003;63:39–43.
[77] Aoki H, Takada Y, Kondo S, Sawaya R, Aggarwal BB, Kondo Y. Evidence that curcumin suppresses the growth of malignant gliomas in vitro and in vivo through induction of autophagy: role of Akt and ERK signaling pathways. Mol Pharmacol 2007;72(1):29–39.
[78] Grosser T. The pharmacology of selective inhibition of COX-2. Thromb Haemost 2006;96:393–400.
[79] Mitra A, Chakrabarti J, Banerji A, Chatterjee A, Das BR. Curcumin, a potential inhibitor of MMP-2 in human laryngeal squamous carcinoma cells HEp2. J Environ Pathol Toxicol Oncol 2006;25:679–90.
[80] Cho JW, Lee KS, Kim CW. Curcumin attenuates the expression of IL-1beta, IL-6, and TNF-alpha as well as cyclin E in TNF-alpha-treated HaCaT cells; NF-kappaB and MAPKs as potential upstream targets. Int J Mol Med 2007;19:469–74.
[81] Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IkappaBalpha kinase and Akt activation. Mol Pharmacol 2006;69:195–206.
[82] Li M, Zhang Z, Hill DL, Wang H, Zhang R. Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway. Cancer Res 2007;67:1988–96.
[83] Song G, Mao YB, Cai QF, Yao LM, Ouyang GL, Bao SD. Curcumin induces human HT-29 colon adenocarcinoma cell apoptosis by activating p53 and regulating apoptosis-related protein expression. Braz J Med Biol Res 2005;38:1791–8.
[84] Liontas A, Yeger H. Curcumin and resveratrol induce apoptosis and nuclear translocation and activation of p53 in human neuroblastoma. Anticancer Res 2004;24:987–98.
[85] Gaedeke J, Noble NA, Border WA. Curcumin blocks fibrosis in anti-Thy 1 glomerulonephritis through up-regulation of heme oxygenase 1. Kidney Int 2005;68:2042–9.
[86] McNally SJ, Harrison EM, Ross JA, Garden OJ, Wigmore SJ. Curcumin induces heme oxygenase 1 through generation of reactive oxygen species, p38 activation and phosphatase inhibition. Int J Mol Med 2007;19:165–72.
[87] Rao CV, Simi B, Reddy BS. Inhibition by dietary curcumin of azoxymethane-induced ornithine decarboxylase, tyrosine protein kinase, arachidonic acid metabolism and aberrant crypt foci formation in the rat colon. Carcinogenesis 1993;14:2219–25.
[88] Huang MT, Lou YR, Ma W, Newmark HL, Reuhl KR, Conney AH. Inhibitory effects of dietary curcumin on forestomach, duodenal, and colon carcinogenesis in mice. Cancer Res 1994;54:5841–7.
[89] Kim JM, Araki S, Kim DJ, Park CB, Takasuka N, Baba-Toriyama H, et al. Chemopreventive effects of carotenoids

and curcumins on mouse colon carcinogenesis after 1,2-dimethylhydrazine initiation. Carcinogenesis 1998;19:81–5.
[90] Rao CV, Rivenson A, Simi B, Reddy BS. Chemoprevention of colon cancer by dietary curcumin. Ann N Y Acad Sci 1995;768:201–4.
[91] Kawamori T, Lubet R, Steele VE, Kelloff GJ, Kaskey RB, Rao CV, et al. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. Cancer Res 1999;59:597–601.
[92] Collett GP, Robson CN, Mathers JC, Campbell FC. Curcumin modifies Apc(min) apoptosis resistance and inhibits 2-amino 1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) induced tumour formation in Apc(min) mice. Carcinogenesis 2001;22:821–5.
[93] Pereira MA, Grubbs CJ, Barnes LH, Li H, Olson GR, Eto I, et al. Effects of the phytochemicals, curcumin and quercetin, upon azoxymethane-induced colon cancer and 7,12-dimethylbenz[a]anthracene-induced mammary cancer in rats. Carcinogenesis 1996;17:1305–11.
[94] Kwon Y, Malik M, Magnuson BA. Inhibition of colonic aberrant crypt foci by curcumin in rats is affected by age. Nutr Cancer 2004;48:37–43.
[95] Shpitz B, Giladi N, Sagiv E, Lev-Ari S, Liberman E, Kazanov D, et al. Celecoxib and curcumin additively inhibit the growth of colorectal cancer in a rat model. Digestion 2006;74:140–4.
[96] Sugimoto K, Hanai H, Tozawa K, Aoshi T, Uchijima M, Nagata T, et al. Curcumin prevents and ameliorates trinitrobenzene sulfonic acid-induced colitis in mice. Gastroenterology 2002;123:1912–22.
[97] Salh B, Assi K, Templeman V, Parhar K, Owen D, Gomez-Munoz A, et al. Curcumin attenuates DNB-induced murine colitis. Am J Physiol Gastrointest Liver Physiol 2003;285:G235–43.
[98] Ukil A, Maity S, Karmakar S, Datta N, Vedasiromoni JR, Das PK. Curcumin, the major component of food flavour turmeric, reduces mucosal injury in trinitrobenzene sulphonic acid-induced colitis. Br J Pharmacol 2003;139:209–18.
[99] Venkataranganna MV, Rafiq M, Gopumadhavan S, Peer G, Babu UV, Mitra SK. NCB-02 (standardized Curcumin preparation) protects dinitrochlorobenzene-induced colitis through down-regulation of NFkappa-B and iNOS. World J Gastroenterol 2007;13:1103–7.
[100] Ushida J, Sugie S, Kawabata K, Pham QV, Tanaka T, Fujii K, et al. Chemopreventive effect of curcumin on *N*-nitrosomethylbenzylamine-induced esophageal carcinogenesis in rats. Jpn J Cancer Res 2000;91:893–8.
[101] Huang MT, Deschner EE, Newmark HL, Wang ZY, Ferraro TA, Conney AH. Effect of dietary curcumin and ascorbyl palmitate on azoxymethanol-induced colonic epithelial cell proliferation and focal areas of dysplasia. Cancer Lett 1992;64:117–21.
[102] Perkins S, Verschoyle RD, Hill K, Parveen I, Threadgill MD, Sharma RA, et al. Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis. Cancer Epidemiol Biomarkers Prev 2002;11:535–40.
[103] Azuine MA, Bhide SV. Chemopreventive effect of turmeric against stomach and skin tumors induced by chemical carcinogens in Swiss mice. Nutr Cancer 1992;17:77–83.
[104] Singh SV, Hu X, Srivastava SK, Singh M, Xia H, Orchard JL, et al. Mechanism of inhibition of benzo[a]pyrene-induced forestomach cancer in mice by dietary curcumin. Carcinogenesis 1998;19:1357–60.
[105] Nagabhushan M, Bhide SV. Curcumin as an inhibitor of cancer. J Am Coll Nutr 1992;11:192–8.
[106] Ikezaki S, Nishikawa A, Furukawa F, Kudo K, Nakamura H, Tamura K, et al. Chemopreventive effects of curcumin on glandular stomach carcinogenesis induced by *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine and sodium chloride in rats. Anticancer Res 2001;21:3407–11.
[107] Chuang SE, Cheng AL, Lin JK, Kuo ML. Inhibition by curcumin of diethylnitrosamine-induced hepatic hyperplasia, inflammation, cellular gene products and cell-cycle-related proteins in rats. Food Chem Toxicol 2000;38:991–5.
[108] Hecht SS, Kenney PM, Wang M, Trushin N, Agarwal S, Rao AV, et al. Evaluation of butylated hydroxyanisole, myo-inositol, curcumin, esculetin, resveratrol and lycopene as inhibitors of benzo[a]pyrene plus 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in A/J mice. Cancer Lett 1999;137:123–30.
[109] Huang MT, Lou YR, Xie JG, Ma W, Lu YP, Yen P, et al. Effect of dietary curcumin and dibenzoylmethane on formation of 7,12-dimethylbenz[a]anthracene-induced mammary tumors and lymphomas/leukemias in Sencar mice. Carcinogenesis 1998;19:1697–700.
[110] Singletary K, MacDonald C, Wallig M, Fisher C. Inhibition of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumorigenesis and DMBA-DNA adduct formation by curcumin. Cancer Lett 1996;103:137–41.
[111] Deshpande SS, Ingle AD, Maru GB. Chemopreventive efficacy of curcumin-free aqueous turmeric extract in 7,12-dimethylbenz[a]anthracene-induced rat mammary tumorigenesis. Cancer Lett 1998;123:35–40.
[112] Inano H, Onoda M, Inafuku N, Kubota M, Kamada Y, Osawa T, et al. Chemoprevention by curcumin during the promotion stage of tumorigenesis of mammary gland in rats irradiated with gamma-rays. Carcinogenesis 1999;20:1011–8.
[113] Inano H, Onoda M. Radioprotective action of curcumin extracted from *Curcuma longa* LINN: inhibitory effect on formation of urinary 8-hydroxy-2′-deoxyguanosine, tumorigenesis, but not mortality, induced by gamma-ray irradiation. Int J Radiat Oncol Biol Phys 2002;53:735–43.
[114] Lin CC, Ho CT, Huang MT. Mechanistic studies on the inhibitory action of dietary dibenzoylmethane, a beta-diketone analogue of curcumin, on 7,12-dimethylbenz[a]anthracene-induced mammary tumorigenesis. Proc Natl Sci Counc Repub China B 2001;25:158–65.
[115] Lin CC, Lu YP, Lou YR, Ho CT, Newmark HH, MacDonald C, et al. Inhibition by dietary dibenzoylmethane of mammary gland proliferation, formation of DMBA-DNA adducts in mammary glands, and mammary tumorigenesis in Sencar mice. Cancer Lett 2001;168:125–32.
[116] Azuine MA, Bhide SV. Protective single/combined treatment with betel leaf and turmeric against methyl (acetoxymethyl) nitrosamine-induced hamster oral carcinogenesis. Int J Cancer 1992;51:412–5.
[117] Tanaka T, Makita H, Ohnishi M, Hirose Y, Wang A, Mori H, et al. Chemoprevention of 4-nitroquinoline 1-oxide-induced oral carcinogenesis by dietary curcumin and hesperidin: comparison with the protective effect of beta-carotene. Cancer Res 1994;54:4653–9.
[118] Imaida K, Tamano S, Kato K, Ikeda Y, Asamoto M, Takahashi S, et al. Lack of chemopreventive effects of lycopene and curcumin on experimental rat prostate carcinogenesis. Carcinogenesis 2001;22:467–72.
[119] Ishizaki C, Oguro T, Yoshida T, Wen CQ, Sueki H, Iijima M. Enhancing effect of ultraviolet A on ornithine decarboxylase induction and dermatitis evoked by 12-o-tetradecanoylphorbol-13-acetate and its inhibition by curcumin in mouse skin. Dermatology 1996;193:311–7.

[120] Huang MT, Smart RC, Wong CQ, Conney AH. Inhibitory effect of curcumin, chlorogenic acid, caffeic acid, and ferulic acid on tumor promotion in mouse skin by 12-*O*-tetradecanoylphorbol-13-acetate. Cancer Res 1988;48:5941–6.
[121] Lu YP, Chang RL, Huang MT, Conney AH. Inhibitory effect of curcumin on 12-O-tetradecanoylphorbol-13-acetate-induced increase in ornithine decarboxylase mRNA in mouse epidermis. Carcinogenesis 1993;14:293–7.
[122] Huang MT, Ma W, Lu YP, Chang RL, Fisher C, Manchand PS, et al. Effects of curcumin, demethoxycurcumin, bisdemethoxycurcumin and tetrahydrocurcumin on 12-*O*-tetradecanoylphorbol-13-acetate-induced tumor promotion. Carcinogenesis 1995;16:2493–7.
[123] Huang MT, Ma W, Yen P, Xie JG, Han J, Frenkel K, et al. Inhibitory effects of topical application of low doses of curcumin on 12-O-tetradecanoylphorbol-13-acetate-induced tumor promotion and oxidized DNA bases in mouse epidermis. Carcinogenesis 1997;18:83–8.
[124] Soudamini KK, Kuttan R. Inhibition of chemical carcinogenesis by curcumin. J Ethnopharmacol 1989;27:227–33.
[125] Takaba K, Hirose M, Yoshida Y, Kimura J, Ito N, Shirai T. Effects of *n*-tritriacontane-16,18-dione, curcumin, chlorphyllin, dihydroguaiaretic acid, tannic acid and phytic acid on the initiation stage in a rat multi-organ carcinogenesis model. Cancer Lett 1997;113:39–46.
[126] Huang MT, Lysz T, Ferraro T, Abidi TF, Laskin JD, Conney AH. Inhibitory effects of curcumin on in vitro lipoxygenase and cyclooxygenase activities in mouse epidermis. Cancer Res 1991;51:813–9.
[127] Mahmoud NN, Carothers AM, Grunberger D, Bilinski RT, Churchill MR, Martucci C, et al. Plant phenolics decrease intestinal tumors in an animal model of familial adenomatous polyposis. Carcinogenesis 2000;21:921–7.
[128] Kwon Y, Magnuson BA. Effect of azoxymethane and curcumin on transcriptional levels of cyclooxygenase-1 and -2 during initiation of colon carcinogenesis. Scand J Gastroenterol 2007;42:72–80.
[129] Sreepriya M, Bali G. Chemopreventive effects of embelin and curcumin against N-nitrosodiethylamine/phenobarbital-induced hepatocarcinogenesis in Wistar rats. Fitoterapia 2005;76:549–55.
[130] Sreepriya M, Bali G. Effects of administration of Embelin and Curcumin on lipid peroxidation, hepatic glutathione antioxidant defense and hematopoietic system during *N*-nitrosodiethylamine/phenobarbital-induced hepatocarcinogenesis in Wistar rats. Mol Cell Biochem 2006;284:49–55.
[131] Kalpana C, Rajasekharan KN, Menon VP. Modulatory effects of curcumin and curcumin analog on circulatory lipid profiles during nicotine-induced toxicity in Wistar rats. J Med Food 2005;8:246–50.
[132] Mahady GB, Pendland SL, Yun G, Lu ZZ. Turmeric (*Curcuma longa*) and curcumin inhibit the growth of *Helicobacter pylori*, a group 1 carcinogen. Anticancer Res 2002;22:4179–81.
[133] Kuttan R, Bhanumathy P, Nirmala K, George MC. Potential anticancer activity of turmeric (*Curcuma longa*). Cancer Lett 1985;29:197–202.
[134] Ruby AJ, Kuttan G, Babu KD, Rajasekharan KN, Kuttan R. Anti-tumour and antioxidant activity of natural curcuminoids. Cancer Lett 1995;94:79–83.
[135] Aggarwal BB, Shishodia S, Takada Y, Banerjee S, Newman RA, Bueso-Ramos CE, et al. Curcumin suppresses the paclitaxel-induced nuclear factor-kappaB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice. Clin Cancer Res 2005;11:7490–8.
[136] Bachmeier B, Nerlich AG, Iancu CM, Cilli M, Schleicher E, Vene R, et al. The chemopreventive polyphenol curcumin prevents hematogenous breast cancer metastases in immunodeficient mice. Cell Physiol Biochem 2007;19:137–52.
[137] Li L, Ahmed B, Mehta K, Kurzrock R. Liposomal curcumin with and without oxaliplatin: effects on cell growth, apoptosis, and angiogenesis in colorectal cancer. Mol Cancer Ther 2007;6:1276–82.
[138] Cui SX, Qu XJ, Xie YY, Zhou L, Nakata M, Makuuchi M, et al. Curcumin inhibits telomerase activity in human cancer cell lines. Int J Mol Med 2006;18:227–31.
[139] Ohashi Y, Tsuchiya Y, Koizumi K, Sakurai H, Saiki I. Prevention of intrahepatic metastasis by curcumin in an orthotopic implantation model. Oncology 2003;65:250–8.
[140] LoTempio MM, Veena MS, Steele HL, Ramamurthy B, Ramalingam TS, Cohen AN, et al. Curcumin suppresses growth of head and neck squamous cell carcinoma. Clin Cancer Res 2005;11:6994–7002.
[141] Odot J, Albert P, Carlier A, Tarpin M, Devy J, Madoulet C. In vitro and in vivo anti-tumoral effect of curcumin against melanoma cells. Int J Cancer 2004;111:381–7.
[142] Lin YG, Kunnumakkara AB, Nair A, Merritt WM, Han LY, Armaiz-Pena GN, et al. Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor—{kappa}B pathway. Clin Cancer Res 2007;13:3423–30.
[143] Li L, Braiteh FS, Kurzrock R. Liposome-encapsulated curcumin: in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis. Cancer 2005;104:1322–31.
[144] Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB. Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappaB-regulated gene products. Cancer Res 2007;67:3853–61.
[145] Dorai T, Cao YC, Dorai B, Buttyan R, Katz AE. Therapeutic potential of curcumin in human prostate cancer. III. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo. Prostate 2001;47:293–303.
[146] Hong JH, Ahn KS, Bae E, Jeon SS, Choi HY. The effects of curcumin on the invasiveness of prostate cancer in vitro and in vivo. Prostate Cancer Prostatic Dis 2006;9:147–52.
[147] Menon LG, Kuttan R, Kuttan G. Inhibition of lung metastasis in mice induced by B16F10 melanoma cells by polyphenolic compounds. Cancer Lett 1995;95:221–5.
[148] Yoysungnoen P, Wirachwong P, Bhattarakosol P, Niimi H, Patumraj S. Effects of curcumin on tumor angiogenesis and biomarkers, COX-2 and VEGF, in hepatocellular carcinoma cell-implanted nude mice. Clin Hemorheol Microcirc 2006;34:109–15.
[149] Busquets S, Carbo N, Almendro V, Quiles MT, Lopez-Soriano FJ, Argiles JM. Curcumin, a natural product present in turmeric, decreases tumor growth but does not behave as an anticachectic compound in a rat model. Cancer Lett 2001;167:33–8.
[150] Wahlstrom B, Blennow G. A study on the fate of curcumin in the rat. Acta Pharmacol Toxicol (Copenh) 1978;43:86–92.
[151] Holder GM, Plummer JL, Ryan AJ. The metabolism and excretion of curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) in the rat. Xenobiotica 1978;8:761–8.
[152] Ravindranath V, Chandrasekhara N. Absorption and tissue distribution of curcumin in rats. Toxicology 1980;16:259–65.

[153] Ravindranath V, Chandrasekhara N. Metabolism of curcumin–studies with [3H]curcumin. Toxicology 1981;22:337–44.
[154] Ireson C, Orr S, Jones DJ, Verschoyle R, Lim CK, Luo JL, et al. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. Cancer Res 2001;61:1058–64.
[155] Ireson CR, Jones DJ, Orr S, Coughtrie MW, Boocock DJ, Williams ML, et al. Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiol Biomarkers Prev 2002;11: 105–11.
[156] Garcea G, Jones DJ, Singh R, Dennison AR, Farmer PB, Sharma RA, et al. Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration. Br J Cancer 2004;90:1011–5.
[157] Hoehle SI, Pfeiffer E, Solyom AM, Metzler M. Metabolism of curcuminoids in tissue slices and subcellular fractions from rat liver. J Agric Food Chem 2006;54:756–64.
[158] Ryu EK, Choe YS, Lee KH, Choi Y, Kim BT. Curcumin and dehydrozingerone derivatives: synthesis, radiolabeling, and evaluation for beta-amyloid plaque imaging. J Med Chem 2006;49:6111–9.
[159] Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS, et al. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 2001;21:2895–900.
[160] Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM, et al. Pharmacodynamic and pharmacokinetic study of oral *Curcuma* extract in patients with colorectal cancer. Clin Cancer Res 2001;7:1894–900.
[161] Garcea G, Berry DP, Jones DJ, Singh R, Dennison AR, Farmer PB, et al. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. Cancer Epidemiol Biomarkers Prev 2005;14:120–5.
[162] Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 1998;64:353–6.
[163] Marczylo TH, Verschoyle RD, Cooke DN, Morazzoni P, Steward WP, Gescher AJ. Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine. Cancer Chemother Pharmacol 2007;60:171–7.
[164] Bisht S, Feldmann G, Soni S, Ravi R, Karikar C, Maitra A. Polymeric nanoparticle-encapsulated curcumin (''nanocurcumin''): a novel strategy for human cancer therapy. J Nanobiotechnol 2007;5:3.
[165] Sun A, Shoji M, Lu YJ, Liotta DC, Snyder JP. Synthesis of EF24-tripeptide chloromethyl ketone: a novel curcumin-related anticancer drug delivery system. J Med Chem 2006;49:3153–8.
[166] Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, et al. Curcumin, demethoxycurcumin, bisdemothoxycurcumin, tetrahydrocurcumin, and turmerones differentially regulate anti-inflammatory and antiproliferative responses through a ROS-independent mechanism. Carcinogenesis 2007;28(8):1765–73.
[167] Pfeiffer E, Hoehle SI, Walch SG, Riess A, Solyom AM, Metzler M. Curcuminoids form reactive glucuronides in vitro. J Agric Food Chem 2007;55:538–44.
[168] Sugiyama Y, Kawakishi S, Osawa T. Involvement of the beta-diketone moiety in the antioxidative mechanism of tetrahydrocurcumin. Biochem Pharmacol 1996;52: 519–25.
[169] Okada K, Wangpoengtrakul C, Tanaka T, Toyokuni S, Uchida K, Osawa T. Curcumin and especially tetrahydrocurcumin ameliorate oxidative stress-induced renal injury in mice. J Nutr 2001;131:2090–5.
[170] Naito M, Wu X, Nomura H, Kodama M, Kato Y, Osawa T. The protective effects of tetrahydrocurcumin on oxidative stress in cholesterol-fed rabbits. J Atheroscler Thromb 2002;9:243–50.
[171] Pari L, Amali DR. Protective role of tetrahydrocurcumin (THC) an active principle of turmeric on chloroquine induced hepatotoxicity in rats. J Pharm Pharm Sci 2005;8:115–23.
[172] Murugan P, Pari L. Effect of tetrahydrocurcumin on plasma antioxidants in streptozotocin–nicotinamide experimental diabetes. J Basic Clin Physiol Pharmacol 2006;17:231–44.
[173] Satoskar RR, Shah SJ, Shenoy SG. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. Int J Clin Pharmacol Ther Toxicol 1986;24:651–4.
[174] Kuttan R, Sudheeran PC, Josph CD. Turmeric and curcumin as topical agents in cancer therapy. Tumori 1987;73:29–31.
[175] Soni KB, Kuttan R. Effect of oral curcumin administration on serum peroxides and cholesterol levels in human volunteers. Indian J Physiol Pharmacol 1992;36:273–5.
[176] Ramirez Bosca A, Soler A, Carrion-Gutierrez MA, Pamies Mira D, Pardo Zapata J, Diaz-Alperi J, et al. An hydroalcoholic extract of *Curcuma longa* lowers the abnormally high values of human-plasma fibrinogen. Mech Ageing Dev 2000;114:207–10.
[177] James JS. Curcumin: clinical trial finds no antiviral effect. AIDS Treat News 1996;1–2.
[178] Rasyid A, Lelo A. The effect of curcumin and placebo on human gall-bladder function: an ultrasound study. Aliment Pharmacol Ther 1999;13:245–9.
[179] Rasyid A, Rahman AR, Jaalam K, Lelo A. Effect of different curcumin dosages on human gall bladder. Asia Pac J Clin Nutr 2002;11:314–8.
[180] Lal B, Kapoor AK, Asthana OP, Agrawal PK, Prasad R, Kumar P, et al. Efficacy of curcumin in the management of chronic anterior uveitis. Phytother Res 1999;13:318–22.
[181] Lal B, Kapoor AK, Agrawal PK, Asthana OP, Srimal RC. Role of curcumin in idiopathic inflammatory orbital pseudotumours. Phytother Res 2000;14:443–7.
[182] Heng MC, Song MK, Harker J, Heng MK. Drug-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. Br J Dermatol 2000;143:937–49.
[183] Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res 2004;10:6847–54.
[184] Bundy R, Walker AF, Middleton RW, Booth J. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: a pilot study. J Altern Complement Med 2004;10:1015–8.
[185] Shoskes D, Lapierre C, Cruz-Correa M, Muruve N, Rosario R, Fromkin B, et al. Beneficial effects of the bioflavonoids curcumin and quercetin on early function in cadaveric renal transplantation: a randomized placebo controlled trial. Transplantation 2005;80:1556–9.
[186] Durgaprasad S, Pai CG, Vasanthkumar, Alvres JF, Namitha S. A pilot study of the antioxidant effect of curcumin in tropical pancreatitis. Indian J Med Res 2005;122:315–8.
[187] Holt PR, Katz S, Kirshoff R. Curcumin therapy in inflammatory bowel disease: a pilot study. Dig Dis Sci 2005;50:2191–3.

[188] Hanai H, Iida T, Takeuchi K, Watanabe F, Maruyama Y, Andoh A, et al. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol 2006;4:1502–6.
[189] Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD, et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clin Gastroenterol Hepatol 2006;4:1035–8.
[190] Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH. Curry consumption and cognitive function in the elderly. Am J Epidemiol 2006;164:898–906.
[191] Rafailov S, Cammack S, Stone BA, Katz AE. The role of zyflamend, an herbal anti-inflammatory, as a potential chemopreventive agent against prostate cancer: a case report. Integr Cancer Ther 2007;6:74–6.
[192] Di Mario F, Cavallaro LG, Nouvenne A, Stefani N, Cavestro GM, Iori V, et al. A curcumin-based 1-week triple therapy for eradication of *Helicobacter pylori* infection: something to learn from failure? Helicobacter 2007;12:238–43.
[193] Lao CD, Demierre MF, Sondak VK. Targeting events in melanoma carcinogenesis for the prevention of melanoma. Expert Rev Anticancer Ther 2006;6:1559–68.
[194] Kobelt G. Health economic issues in rheumatoid arthritis. Scand J Rheumatol 2006;35:415–25.
[195] Chen YC, Tsai SH, Shen SC, Lin JK, Lee WR. Alternative activation of extracellular signal-regulated protein kinases in curcumin and arsenite-induced HSP70 gene expression in human colorectal carcinoma cells. Eur J Cell Biol 2001;80:213–21.
[196] Dhillon N, Aggarwal BB, Li L, Chiao P, Sarkar F, Wolff RA, et al. Phase II trial of curcumin (diferuloyl methane), an NF-κB inhibitor, in patients with advanced pancreatic cancer. J Clin Oncol 2006;24:14151.
[197] Frank N, Knauft J, Amelung F, Nair J, Wesch H, Bartsch H. No prevention of liver and kidney tumors in Long-Evans Cinnamon rats by dietary curcumin, but inhibition at other sites and of metastases. Mutat Res 2003;523–524:127–35.
[198] Aggarwal BB, Banerjee S, Bharadwaj U, Sung B, Shishodia S, Sethi G. Curcumin induces the degradation of cyclin E expression through ubiquitin-dependent pathway and up-regulates cyclin-dependent kinase inhibitors p21 and p27 in multiple human tumor cell lines. Biochem Pharmacol 2007;73:1024–32.
[199] Moos PJ, Edes K, Mullally JE, Fitzpatrick FA. Curcumin impairs tumor suppressor p53 function in colon cancer cells. Carcinogenesis 2004;25:1611–7.
[200] Tsvetkov P, Asher G, Reiss V, Shaul Y, Sachs L, Lotem J. Inhibition of NAD(P)H:quinone oxidoreductase 1 activity and induction of p53 degradation by the natural phenolic compound curcumin. Proc Natl Acad Sci USA 2005;102:5535–40.
[201] Somasundaram S, Edmund NA, Moore DT, Small GW, Shi YY, Orlowski RZ. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. Cancer Res 2002;62:3868–75.
[202] Hata M, Sasaki E, Ota M, Fujimoto K, Yajima J, Shichida T, et al. Allergic contact dermatitis from curcumin (turmeric). Contact Dermat 1997;36:107–8.
[203] Swierczynska MK, Krecisz B. Occupational skin changes in persons working in contact with food spices. Med Pr 1998;49:187–90.
[204] Keith CT, Borisy AA, Stockwell BR. Multicomponent therapeutics for networked systems. Nat Rev Drug Discov 2005;4:71–8.
[205] Sams-Dodd F. Target-based drug discovery: is something wrong? Drug Discov Today 2005;10:139–47.
[206] Morphy R, Kay C, Rankovic Z. From magic bullets to designed multiple ligands. Drug Discov Today 2004;9: 641–51.
[207] Mencher SK, Wang LG. Promiscuous drugs compared to selective drugs (promiscuity can be a virtue). BMC Clin Pharmacol 2005;5:3.