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Review

Multi-targeted therapy by curcumin: how spicy is it?

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Although traditional medicines have been used for thousands of years, for most such medicines neither the active component nor their molecular targets have been very well identified. Curcumin, a yellow component of turmeric or curry powder, however, is an exception. Although inhibitors of cyclooxygenase-2, HER2, tumor necrosis factor, EGFR, Bcr-abl, proteosome, and vascular endothelial cell growth factor have been approved for human use by the United States Food and Drug Administration (FDA), curcumin as a single agent can down-regulate all these targets. Curcumin can also activate apoptosis, down-regulate cell survival gene products, and up-regulate p53, p21, and p27. Although curcumin is poorly absorbed after ingestion, multiple studies have suggested that even low levels of physiologically achievable concentrations of curcumin may be sufficient for its chemopreventive and chemotherapeutic activity. Thus, curcumin regulates multiple targets (multitargeted therapy), which is needed for treatment of most diseases, and it is inexpensive and has been found to be safe in human clinical trials. The present article reviews the key molecular mechanisms of curcumin action and compares this to some of the single-targeted therapies currently available for human cancer.

Keywords: Cancer / Curcumin / Cyclooxygenases / Multi-targeted therapy / Tumor necrosis factor

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1 Introduction

How often are we told, "this or that compound is not specific" (in terms of its target)? That a given disease or illness is caused by dysregulation of multiple molecular targets raises the question of whether we are looking for specific disease targets or specific molecular targets as therapeutics. One of the ironies of the modern system of medicine is that, although current clinical therapeutic regimens ordinarily use a combination of drugs that target multiple pathways, most synthetic drug discovery efforts are focused on identification of single biological targets. This paradigm is fast changing, however, and drugs that target multiple pathways are becoming common. It is now becoming increasingly apparent that the underlying molecular bases for most common human diseases are far more complex and frequently involve both genetic as well as environmental factors [1 – 3]. If such is the case, it argues against the usefulness of current drug discovery approaches that are centered on single-target or single-drug approaches. It would seem that even though such an approach is of a limited benefit in some specific cases, it is highly likely that such a specific drug will often be inadequate to regulate the various molecular targets that must be affected for a drug to show its best efficacy.

Highlighting these limitations of the current drug-discovery approach, in the past decade we have had very limited success with the development of new effective drugs for various human ailments, in spite of increasing levels of investments made by the pharmaceutical industry [4]. As inadequate as it may seem now, the rationale for single-target-based drug discovery paradigm was perfectly legitimate until recently, since it allowed an increased screening ability and an overall productivity for drug design [5, 6]. However, with the completion of the human genome project and with our advancing knowledge about the function of individual genes and the different signaling pathways they regulate, it has become imperative to adopt a multi-target-based drug

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Abbreviations: **COX**, cyclooxygenase; **EGF**, epidermal growth factor; **FAP**, familial adenomatous polyposis; **NSAID**, nonsteroidal anti-inflammatory drugs; **TNF-α,** tumor necrosis factor α; **VEGF**, vascular endothelial growth factor

development paradigm for the treatment of complex human diseases [7]. Even though several single-target-based drugs have been developed in the past few years for the management of various human cancers, only recently has it become clear that several of these drugs have multiple side effects limiting their usefulness. In addition, the treatment costs associated with such drugs are beyond the reach of a large segment of the population, even in most developed nations in the world. Therefore, there is a clear need for the identification of safe, less expensive, and multi-targeted therapeutic regimens. One of the candidate approaches would be to exploit natural compounds (or "nutraceuticals") that have traditionally been used for centuries in various parts of the world to treat different ailments.

The current review explores the use of curcumin as one of the natural compounds known to interact with multiple targets and which has been used for centuries to treat a large number of disease situations [8]. We will here focus on the effects of curcumin on the selected molecular targets that have been exploited for anti-cancer therapeutic drug development.

Curcumin was first isolated in 1815. The first modern citation on the subject appeared in the Pub Med database in 1959, with only 3 citations appearing up to 1970 and 70 until 1990. By 2007, there were 1979 citations, illustrating the extent of the growing interest in this molecule. Turmeric, from which curcumin is derived, was first cited in 1950 by Chaudhuri *et al.* as "Turmeric, haldi or haridra, in eye disease," in an article published in *Antiseptic* [9].

2 Bioavailability of curcumin

Some of the issues that are often considered central to the efficacy and usefulness of adopting a regimen are its absorption, metabolism, and eventual bioavailability in the target organs within the body. It is perhaps not always possible to have the detailed understanding of the pharmacokinetics, pharmacodynamics, biodistribution, and metabolism of most compounds in the early stages of their development. However, due to the immense interest in curcumin over the past decade, enough data have been accumulated on these parameters from both animal studies and from several studies performed on human subjects.

Wahlstrom and Blennow in 1978 [10] performed the first study where they orally administered 1 g/kg curcumin to rats and determined that as much as 75% of curcumin was excreted in the feces, with negligible amounts appearing in the urine. Measurements of blood plasma levels and biliary excretion showed that 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 bile. The major part of the drug was metabolized, however, thus suggesting poor absorption and rapid metabolism. Because curcumin at even very high doses was found to be safe, subsequent studies attempted using higher amounts of curcumin, hoping to get around its poor absorption issues, but the percentage of curcumin absorbed remained constant (60 – 66% of the given dose), regardless of the dose administered [11, 12], suggesting that administration of more curcumin does not result in higher absorption. Pan *et al.* [13] investigated the pharmacokinetic properties of intraperitoneal injections of curcumin in mice, and it was observed that 1 h after administration, the levels of curcumin in the intestines, spleen, liver, and kidneys were 177.04, 26.06, 26.90, and 7.51 μg/g, respectively. Oral dosing of 1 g/kg curcumin resulted in a peak serum plasma concentration of 0.5 μM. The liver was found to be the major organ responsible for metabolism of curcumin [10, 14, 15]. Perkins and coworkers [16] examined the pharmacokinetics of curcumin in the Min/+ mouse model of familial adenomatous polyposis (FAP) using either dietary curcumin or a single dose of labeled curcumin. Traces of curcumin were detected in the plasma. Its concentration in the small intestinal mucosa was between 39 and 240 nmol/g of tissue. It was suggested that a daily dose of 1.6 g of curcumin is required for efficacy in humans. In contrast to findings in rodents, neither curcumin nor its metabolites were found in blood or urine when 15 patients received oral dosing between 36 and 180 mg of curcumin daily for up to 4 months, but curcumin was recovered from feces [17].

Many of these studies indicated that curcumin has a poor bioavailability once ingested. In an attempt to enhance bioavailability, Shoba *et al.* [18] combined curcumin with piperine, a known inhibitor of hepatic and intestinal glucuronidation, and examined the serum levels of curcumin in rats and healthy human volunteers. When curcumin was given alone to rats, at a dose of 2 g, moderate serum concentrations were achieved over a period of 4 h. Simultaneous administration of piperine (20 mg) resulted in a significant increase in the serum curcumin concentrations, while elimination half-life and the bioavailability of curcumin was increased by 154%. On the other hand, serum levels in humans were either undetectable or very low after a dose of 2 g/kg curcumin alone. Concomitant administration of piperine 20 mg/kg produced much higher concentrations, and the increase in bioavailability was 2000%. Thus, piperine enhances the serum concentration and the extent of absorption and bioavailability of curcumin in both rats and humans.

It is unclear whether curcumin metabolites are as active as curcumin itself, since most studies indicate that curcumin glucuronides are less active than curcumin [19, 20] whereas other studies suggest that they may be more active than curcumin [21 – 26].

The average daily intake of turmeric in the diet in India is approximately 2 – 2.5 g for a 60-kg individual. This roughly corresponds to an intake of 60 – 100 mg of curcumin daily [27]. Assuming that curcumin-associated dietary habits

partly are responsible for the lower cancer incidence in the Indian population, the bioavailability of such low concentrations of curcumin should not be a concern in a chemopreventive or chemotherapeutic setting using curcumin.

3 Animal studies

Curcumin is notable for the diversity of its biological activities in preclinical models of tumorigenesis at a very wide range of physiologically attainable doses. Emerging evidence suggests that curcumin may have not only chemopreventive but also therapeutic effects. In addition to the extensive *in vitro* experiments performed to evaluate the efficacy of curcumin in various cancer cell lines, a large number of animal studies have now been completed supporting and highlighting the potential role of curcumin as a chemopreventive and therapeutic compound.

Anticancer activity of curcumin was first demonstrated in a model of Dalton's lymphoma cells grown as ascites, in which curcumin inhibited the cell growth in Chinese hamster ovary (CHO) cells at a concentration of 0.4 mg/mL and curcumin was able to reduce the development of animal tumors [28]. Huang *et al.* [29] showed growth-inhibitory effects of topical curcumin treatment on the tumor promotion in mouse skin. Similar effects of curcumin were subsequently noted in other animal studies in which skin tumors were induced by chemical carcinogens [30 – 33]. Odot *et al*. [34] studied the anti-tumoral effect of curcumin against melanoma cells *in vivo*. Menon *et al*. [35] reported curcumin-induced inhibition of B16F10 melanoma lung metastasis in mice.

In several reports, curcumin has been shown to prevent cancer in the colon, skin, stomach, liver, lung, duodenum, soft palate, and breast of rodents following oral administration. The effects of dietary curcumin on colon carcinogenesis in particular have been demonstrated in both chemical and genetic animal models [36, 37]. Curcumin has been shown to be protective in inhibiting tumorigenesis both in the initiation phase of chemical models [38] as well as in genetic models of multiple intestinal neoplasia that permit the study of inhibition of the promotion phase of carcinogenesis [16, 39, 40].

The effects of curcumin on tumor angiogenesis and the biomarkers cyclooxygenase (COX)-2, and vascular endothelial growth factor (VEGF) were investigated in hepatocellular carcinoma cells implanted in nude mice [41]. Busquets *et al*. [42] demonstrated that systemic administration of curcumin for 6 consecutive days to rats bearing the highly cachectic ascites hepatoma resulted in significant inhibition of tumor growth. Another study showed that curcumin suppresses the growth of head and neck carcinoma [43]. Multiple studies have shown that curcumin can modulate the growth of prostate cancer in rodents [44, 45]. In another study, curcumin inhibited the growth of human pancreatic cancer in nude mice, in part through the suppression of angiogenesis and induction of apoptosis [46]. Singletary *et al*. [47, 48] showed protective effects of curcumin on chemical-induced breast cancer in rats.

Our laboratory recently investigated the effect of curcumin in combination with paclitaxel as a chemosensitizer of breast cancer metastases to the lung [49]. More recently, Bachmeier *et al.* [50] examined the effects of curcumin on the human breast cancer cell line MDA-MB-231 in a mouse metastasis model. The investigators observed that curcumin significantly decreased the number of lung metastases in immunodeficient mice after intercardiac injection of cancer cells implying that dietary chemoprevention of metastases holds promise with curcumin treatment [50].

Sivalingam *et al.* [51] evaluated the effect of curcumin in indomethacin-induced small intestinal damage in rats and found that curcumin was very effective in reducing the nonsteroidal anti-inflammatory drugs (NSAID)-induced small intestinal damage. Jiang *et al.* [52] determined whether curcumin prevents cerebral ischemia/reperfusion injury in rats. The authors reported that a single injection of curcumin (1 and 2 mg/kg, i.v.) 30 min after focal cerebral ischemia/reperfusion in rats significantly diminished infarct volume, improved neurological deficit, decreased mortality, and reduced the water content of the brain [52]. Similarly, in another recent study, curcumin significantly inhibited heavy metal-induced neurotoxicity in rats [53].

Shpitz *et al*. [54] recently investigated the chemopreventive effects of celecoxib and curcumin alone and in combination using the 1,2-dimethylhydrazine (DMH) rat model and concluded that curcumin augments the growth inhibitory effect of celecoxib. Our group also recently demonstrated the combined effect of curcumin and gemcitabine against pancreatic cancer. We found that curcumin in combination with gemcitabine inhibited pancreatic cancer growth in nude mice through the inhibition of NF-κB-regulated gene expression, cell proliferation, and angiogenesis [55]. We have also shown the efficacy of curcumin combined with docetaxel against human ovarian cancer in nude mice [56]. The ability of curcumin to suppress the growth of human glioblastoma in rodent models was also recently shown by our group [57]. Studies also showed that curcumin sensitizes oxaliplatin to inhibit colon cancer growth in nude mice [58]. Recent studies showed that curcumin acts as a chemosensitizer as well as a radiosensitizer for prostate cancer by downregulating the MDM2 oncogene [59]. Collectively, these studies clearly indicate that curcumin is a promising anticancer agent, either alone or in combination with currently employed chemotherapeutic agents or radiation.

4 Regulation of molecular targets by curcumin

Curcumin has been shown to regulate the expression and activity of a wide variety of molecules that play central roles

in various diseases. Below is a description of some of these targets.

4.1 Tumor necrosis factor

Tumor necrosis factor α (TNF-α) belongs to the TNF superfamily of pro-inflammatory cytokines and is an important mediator for inflammatory tissue damage and has other immune-regulatory functions [60]. Given the importance of TNF-α in inflammation-mediated human diseases, the past years have witnessed an increasing interest in the development of TNF-α antagonists as effective therapies for rheumatoid arthritis, inflammatory bowel disease, and various human cancers. There is convincing evidence that under specific conditions TNF-α is a tumor promoter, and several trials have investigated the role of TNF-α antagonists in cancer. Since the initial cloning of the TNF-α gene, multiple studies that have attempted TNF-α therapy have shown little promise due to minimal tumor-specific response and side effects associated with such treatments [61].

Curcumin treatment has profound effects on modulation of TNF-induced signaling and has been consistently shown to inhibit the expression of TNF-α [62–64]. Curcumin has been shown to inhibit LPS or phorbol 12-myristate-13 acetate (PMA)-induced TNF-α in dendritic cells, macrophages, monocytes, alveolar macrophages, and endothelial and bone marrow cells [65–67]. Similar observations were made in rats, in which curcumin treatment attenuated TNF-α in sodium taurocholate-induced acute pancreatitis [68].

Our group was the first to report that curcumin can suppress the TNF signaling pathway [69]. In our more recent study, we showed that curcumin completely blocks TNF-induced NF-κB activation through inhibition of phosphorylation of NF-κB that leads to suppression of cell survival and proliferation [70]. In another study, curcumin was examined for its efficacy in TNF-α-induced NF-κB activation in human breast cancer MCF-7 cells; that study found, in agreement with our study, that curcumin significantly blocked the TNF-α-induced NF-κB activation and inhibited the proteasomal activity of MCF-7 cells [71].

A recent study investigated the effect of curcumin treatment on the expression of proinflammatory cytokines and cyclin E in TNF-α-treated HaCaT cells [72]. Curcumin inhibited the expression of TNF-α-induced IL1β, IL6, and TNF-α in these cells. In addition, curcumin inhibited the activation of MAPK (JNK, p38 MAPK, and ERK) and NF-κB in TNF-α-treated HaCaT cells [72]. In another study, curcumin treatment blocked the expression of TNF-α mRNA in a rat model of hemorrhage and resuscitation [73]. Studies by Siddiqui *et al.* [74] on rats with sepsis found that curcumin treatment both before and after the onset of sepsis could reduce tissue injury, reduce mortality, and decrease TNF-α expression. The analysis of molecular pathways indicated that curcumin restores PPAR-γ expression in the liver of rats with sepsis within 20 h. Similar results were obtained in endotoxin-treated cultured RAW 264.7 cells, in which curcumin suppressed endotoxin-induced TNF-α expression and markedly elevated PPAR-γ expression [74].

Studies performed in cultured HT29 intestinal epithelial cells stimulated with TNF-α and IL1ß showed that curcumin could block the binding of Shiga-like toxins (Stx) to intestinal epithelial cells by inhibiting Gb3 synthase (GalT6) mRNA expression [67]. In another set of experiments, three major active principles isolated from the crude methanol extract of the rhizomes of *Curcuma zedoaria* [1,7-bis (4-hydroxyphenyl)-1,4,6-heptatrien-3-one, procurcumenol, and epiprocurcumenol] were reported to suppress the production of TNF-α in LPS-stimulated macrophages [75]. These studies suggest that the anti-inflammatory activity of curcumin could well be correlated with its ability to inhibit inflammatory cytokines at the protein level as well as the mRNA level.

4.2 Cyclooxygenase-2

COX are the key enzymes that catalyze the conversion of arachidonic acid to prostaglandins and thromboxanes [76]. COX consist of two different isoforms, COX-1 and COX-2. COX-1 is a constitutive isoform present in most human tissues [77, 78]. It is believed that COX-1 inhibition results in serious side effects such as peptic ulceration or impairment of renal blood flow. On the other hand, COX-2 is constitutively expressed only in brain and spinal cord tissues but was shown to be inducible in cells that were genetically transformed with the oncogene v-*src* or treated with phorbol esters [79, 80]. COX-2 can also be induced by a variety of growth factors and proinflammatory cytokines under a number of pathophysiological conditions [78]. COX-2 overexpression has been implicated in the cancers of the colon, rectum, breast, head and neck, lung, pancreas, stomach and prostate [81, 82].

COX-2 inhibition became an issue in drug-development due to reports that showed that patients treated with aspirin or other NSAID demonstrated a 40–50% reduced mortality risk from colorectal cancer [83–85]. These observations became the basis for the development of COX-2-specific inhibitors (or Coxibs), which were subsequently shown to reduce the incidence of intestinal polyps in patients with FAP and prevent the recurrence of colorectal adenomas and cancers, as well as regulate angiogenesis [86–88]. However, recent concerns over the toxicity of systemic selective COX-2 inhibition and the risks for cardiovascular and renal toxicity have dampened the enthusiasm for the use of Coxibs and have cast serious doubts on COX-2 inhibition as a safe and effective chemoprevention strategy [89–92].

Huang and his coworkers [93] showed for the first time that curcumin could inhibit *in vitro* lipoxygenase (LPO) and COX activities in mouse epidermis. Ireson *et al* [19] showed that curcumin at a concentration of 20 μM successfully inhibited chemically induced PGE_2 production in

colon cancer cells. Similarly, in another study, curcumin inhibited HT-29 colon cancer-cell growth in a concentration- and time-dependent manner, as well as inhibited the mRNA and protein expression of COX-2 but not COX-1 [94]. Analogous observations were made in a more recent study in which curcumin treatment inhibited COX-2 protein activity and expression but increased the incidence of apoptotic cell death in a dose-dependent manner [95]. Although the precise mechanisms behind such effects are still unclear, it is believed that this effect may be mediated via inhibition of the IKK-signaling complex, which is responsible for the phosphorylation of IκB [96].

In an *in vitro* model of osteoarthritis, curcumin treatment down-regulated COX-2 and MMP-9 [97]. Similar results were obtained in chondrocytes stimulated with TNF-α. Curcumin also reversed the IL1β-induced down-regulation of collagen type II and β1-integrin receptor expression [98]. In another study, curcumin significantly decreased COX-2, EGFR, and p-Erk1/2 expressions in a dose-dependent manner in p34 and PC-14 lung and pancreatic cancer cells [99].

In a recent animal model study of experimental colitis, curcumin treatment (50 – 100 mg/kg per day) significantly attenuated the overall colonic nitrite levels, down-regulated COX-2 and iNOS expression, and reduced the activation of p38 MAPK [100]. In support of these observations, another independent study showed that curcumin improved overall survival rate and histological alterations, reduced the expression of COX-2 and inflammatory cytokines, and increased the PGE_2 levels in a rat model of experimental colitis [101].

4.3 Human epidermal growth factor receptor (EGFR1/HER1) and HER2/neu receptor signaling

The epidermal growth factor receptor (EGFR1or HER1) and HER2 belong to the HER family of receptors. Both EGFR1 and HER2 are expressed in a variety of nonmalignant tissues as well as in a variety of human cancers including those of the colorectum, stomach, head and neck, breast, and lung [102 – 104]. Both EGFR and HER2 play an important role in cancer development and progression that includes regulation of cell proliferation, apoptosis, angiogenesis, and metastasis [102]. Increased EGFR and HER2 expression correlates with poor response to chemotherapy, increased disease progression, and poor survival [105]. The precise mechanisms responsible for tumorigenic activity arising from these receptors in different types of cancer are not fully understood. However, the crucial role that EGFR1 and HER2 play in human cancers has led to an extensive search for selective inhibitors of their signaling pathway. A large body of preclinical studies and clinical trials thus far has suggested that targeting these receptors may be beneficial for cancer therapy. Although a variety of different approaches are currently being used to target these receptors, the most promising strategies in clinical development include use of monoclonal antibodies or small molecule inhibitors that prevent ligand binding or blocking tyrosine kinase enzymatic activity. Several blocking mAb against the EGFR1 have been developed, including Erbitux (cetuximab) and the tyrosine kinase inhibitors (TKI) gefitinib and erlotinib. Erbitux is a HER1/EGFR-targeted mAb that is currently in clinical development, whereas the HER2-specific trastuzumab (Herceptin) was among the first such agents that was approved and licensed. Phase I trial results in patients with advanced breast and ovarian cancers have shown HER2 down-regulation, increased apoptosis, and reduced proliferation [106]. In spite of the fact that anti-EGFR/HER1 and anti-HER2 therapeutic molecules have shown some benefit in phase I and II clinical studies for cancer management, the treatment costs with these agents are exorbitant, and treatment is associated with some adverse effects [107]. It has been shown that inhibiting EGFR causes skin and gastrointestinal abnormalities including diarrhea, nausea, and vomiting [107]. There is evidence that anti-EGFR therapy does not associate with any appreciable degree of myelosuppression, as would be anticipated from such agents [108 – 111].

It was reported that short-term treatment of cells with curcumin inhibited EGF-induced tyrosine phosphorylation of EGFR in A431 cells [112, 113] and depleted cells of HER2/neu protein [114]. However, unlike glendamycin, curcumin was reported to be a much more potent inhibitor of intracellular HER2 and to have efficacy in reducing tyrosine kinase activity [115]. Curcumin also interrupts platelet-derived growth factor receptor (PDGF) and EGF signaling by inhibiting tyrosine phosphorylation of PDGF-betaR and EGFR in hepatic stellate cells [116]. Cells treated with curcumin showed reduced levels of phosphorylated phosphatidylinositol-3 kinase (PI-3K/AKT), extracellular signal-regulated kinase (ERK), and the Jun N-terminal kinase (JNK) [116]. Curcumin treatment of P34 lung cancer cells and PC-14 pancreatic cancer cells decreased COX-2, EGFR, and p-Erk1/2 expressions in a dose-dependent manner [99].

Curcumin treatment of the human colon cancer-cell lines HT-29 and Caco2 inhibited EGFR-mediated cell growth , and it was suggested that such reduced EGFR activity was a consequence of trans-activation of the early growth factor-1 (Egr-1) gene [117]. Another study proposed that curcumin may also activate PPAR-γ, and this may serve as yet another alternative explanation for the molecular mechanism that forms the basis of EGFR down-regulation [118].

4.4 Vascular endothelial growth factor

VEGF is principally known to be an active mediator of angiogenesis [119 – 121]. VEGF expression is frequently elevated in several human cancers [122, 123]. Increased VEGF expression correlates with enhanced microvessel

density and metastatic spread in some tumors. Owing to the key role of VEGF in tumor angiogenesis, VEGF has emerged as one of the most promising therapeutic target for cancer therapy. In terms of designing anti-VEGF therapy, the common approaches usually involve either targeting VEGF directly or its cell surface receptors indirectly. Receptor-targeted molecules primarily utilize monoclonal antibodies, and direct mediators of VEGF activity are commonly composed of receptor tyrosine kinase inhibitors. A disadvantage of receptor-targeted approaches is that the VEGF receptors (VEGF receptors 1 and 2) lack specificity and may bind to other members of the VEGF superfamily that regulate other regulatory functions [124, 125]. Therefore, the best-studied and most advanced approach to VEGF inhibition is the development of the humanized mAb bevacizumab (Avastin), which is the only anti-angiogenic agent approved by the FDA for the treatment of cancer. In a large randomized controlled trial [126], the addition of bevacizumab to standard chemotherapy for patients with previously untreated metastatic colorectal cancer increased median survival by 30%.

Modulation of pathological angiogenesis by curcumin is one of its key activities. The first evidence for such effects was observed when curcumin effectively inhibited endothelial cell proliferation in a dose-dependent manner [127]. Curcumin and its derivatives demonstrated significant inhibition of basic fibroblast growth factor (b-FGF)-mediated corneal neovascularization in mice [127]. In subsequent studies, curcumin effectively decreased the formation of ascites fluid in mice following intraperitoneal injection and reduced the number of EAT cells and human umbilical vein endothelial cells (HUVEC) *in vitro* [128]. Such effects of curcumin are attributed to its ability to induce apoptosis in these cells. *In vitro* studies clearly indicated a time-dependent response of curcumin in VEGF inhibition and angiopoietin 1 and 2 gene expression in EAT cells, VEGF and angiopoietin 1 gene expression in NIH3T3 cells, and KDR gene expression in HUVEC [128]. Similarly, curcumin inhibited the transcript levels of VEGF and b-FGF in estrogen receptor-negative MDA-MB-231 breast-cancer cells [129].

4.5 Proteasome

The proteasome is a large enzyme complex with multiple catalytic-binding sites and is responsible for the degradation of several intracellular proteins [130, 131]. The ubiquitin-proteasome pathway causes degradation of numerous intracellular proteins that mediate cellular transcription; stress responses, cell cycle regulation, and various cellular DNA repair mechanisms [132]. The proteasome degradation capacity for tumor-suppressor and proapoptotic protein targets is known to be dysregulated in many human malignancies and thus provides the optimal rationale for its selection for cancer therapy. Recent preclinical studies have indicated that proteasome inhibition decreases proliferation, induces apoptosis, enhances the activity of chemotherapy and radiation, and reverses chemoresistance in a variety of hematologic and solid malignancy models *in vitro* and *in vivo* [93 – 97].

Bortezomib is the first proteasome inhibitor investigated in clinical trials. Two Phase II trials have shown that treatment with bortezomib, alone or in combination with dexamethasone, showed survival benefits in patients with recurrent and/or refractory multiple myeloma [133, 134]. Bortezomib has also shown some benefit in preclinical studies of a variety of solid tumors, such as non-small lung cancer and cancers of the breast, gastric, colon, and pancreas. However, a growing understanding on the mechanisms of action of proteasome inhibitors has led to their incorporation into combination regimens with both standard chemotherapeutics and novel agents. Taken together, these studies demonstrate the power of rational drug design and development to provide novel effective therapies for patients with hematological and solid malignancies.

Interest in curcumin's role as a proteasome inhibitor were initiated when it was reported that curcumin-induced apoptosis is mediated through the impairment of the ubiquitin-proteasome system (UPS) in the mouse neuro 2a cells [135]. In this study, curcumin treatment resulted in a dose-dependent decrease in proteasome activity and an increase in ubiquitinated proteins [135]. In their follow-up studies, these authors demonstrated that curcumin disrupts UPS function by directly inhibiting the enzyme activity of the proteasome's 20S core catalytic component [136, 137]. Similar to other proteasome inhibitors, curcumin exposure induced neurite outgrowth and the stress response, as was evident from the induction of various cytosolic and endoplasmic reticulum chaperones as well as induction of the transcription factor CHOP/GADD153. The direct inhibition of proteasome activity also caused an increase in the half-life of IκB-alpha that ultimately led to the down-regulation of NF-κB activation [136].

In more recent studies, curcumin-induced down-regulation of cyclin E was reversed by the proteasome inhibitors lactacystin and N-acetyl-L-leucyl-L-leucyl-L-norleucinal, suggesting the role of ubiquitin-dependent proteasomal pathway [138]. In this study, curcumin enhanced the expression of tumor cyclin-dependent kinase (CDK) inhibitors p21 and p27 as well as tumor-suppressor protein p53 but suppressed the expression of retinoblastoma (Rb) protein, suggesting that proteasome-mediated down-regulation of cyclin E and up-regulation of CDK inhibitors may contribute to the antiproliferative effects of curcumin against various tumors [138].

4.6 BCR-ABL

The BCR-ABL oncogene codes for a chimeric BCR-ABL protein that has constitutively activated ABL tyrosine kin-

ase activity and has been suggested to be the underlying cause of chronic myeloid leukemia (CML) [139, 140]. BCR-ABL activates multiple signal transduction pathways, including Ras-Raf-mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI-3K), STAT-5/Janus kinase, and Myc oncogenes. Increased BCR-ABL activity has been shown to result in uncontrolled cell proliferation and reduced apoptosis, thus allowing the malignant expansion of pluripotent stem cells in the bone marrow [141].

Imatinib mesylate (Gleevac) is an oral, small-molecule tyrosine kinase inhibitor (TKI) that has been developed as a specific BCR-ABL-inhibitor [142]. Imatinib has also been shown to inhibit other signaling proteins, including PDGF receptor (PDGFR) and c-Kit [143]. Imatinib acts by binding to the inactive form of BCR-ABL and thereafter limiting its ability to switch to an active form, and thus eventually resulting in blocking the associated signal transduction pathway [143].

The efficacy of imatinib was demonstrated in a phase III clinical trial at a dose of 400 mg daily to patients with newly diagnosed CML. Imatinib significantly improved the hematologic and major cytogenetic response of these patients after 19 months of treatment [144]. Although not clinically significant, imatinib therapy has been associated with few adverse events, including symptoms of superficial edema, nausea, muscle cramps, and rashes. However, more recently, imatinib was reported to be associated with cardiotoxicity and congestive heart failure [145].

There is evidence now to suggest that curcumin also regulates BCR-ABL activity. K562 cells or HL-60 cells treated with curcumin showed both concentration- and time-dependent growth inhibition, as well as down-regulation of p210bcr/abl, MEK-1, and c-JUN proteins [146]. It was suggested that such effects of curcumin in down-regulating p210bcr/abl might ultimately lead to retardation of the Ras signal transduction pathway in human cancers and thus provide an attractive target for prevention of neoplasia. A mechanistic explanation for these findings was provided in a subsequent study in which it was shown that down-regulation of p210(bcr/abl) by curcumin involves dissociation of the binding of p210(bcr/abl) with Hsp90/p23 complex [147].

4.7 Topoisomerase

Topoisomerases are essential enzymes required for DNA metabolism, in which they act to adjust DNA supercoiling, which is a key requirement in the cellular processes of transcription and replication. Their enzymatic mechanism creates transient nicks or breaks in the double-stranded DNA, allowing DNA to be converted between topological isomers. Humans possess two types of topoisomerase enzymes, type I and type II topoisomerases, and both have been identified as clinically important targets for cancer chemotherapy [148]. Camptothecin derivatives interact with topoisomerase-I, whereas actinomycin D and anthracycline derivatives interact with topoisomerase-II [149]. Still, the camptothecins are by far the most promising antitumor agents due to their ability to regulate cellular functions such as DNA replication, transcription and recombination [150]. Camptothecin induced topoisomerase cleavage complexes can be readily converted into replication double strand breaks causing DNA damage and inhibition of DNA synthesis [151]. At least two mechanisms that result in DNA synthesis inhibition following topoisomerase inhibition include direct block of replication forks that have collided with the topoisomerase cleavage complexes, and secondly indirect replication arrest by S-phase checkpoint activation [152]. Because of the pharmacological interest of camptothecins in cancer chemotherapy, novel camptothecin analogues have been developed in the last three decades for clinical evaluation against several human cancers. Despite some promise shown by these compounds, a major limitation to the clinical efficacy of camptothecin-containing therapies is the drug resistance associated with these agents [150]. Efforts are currently underway to better understand the mechanisms of cell resistance to camptothecins and accordingly devise approaches to overcome specific mechanisms, either by chemical modifications or by combination with modulating agents.

Curcumin has been shown to be an inhibitor of topoisomerase enzyme, and these effects were first appreciated when curcumin and its analogues were reported to have topoisomerase I and II enzyme inhibition activity at low concentrations [153]. Similar effects were observed when the effects of curcumin on the human cancer cell lines TK-10, MCF-7, and UACC-62 were assessed using the IC50 dose levels [154]. It was demonstrated that 50 μM curcumin inhibited topoisomerase II, and such effects were comparable to those of the antineoplastic agent etoposide [154]. These results suggested that DNA damage induced by topoisomerase II poisoning is a possible mechanism by which curcumin initiates apoptosis and increased the evidence suggesting its possible use in cancer therapy.

4.8 Tubulin

Microtubules are essential components of the cell cytoskeleton and are critical for the appropriate segregation of organelles during cell division. Drugs that interfere with microtubule function lead to failure of alignment of the daughter chromosomes, and these cells fail to pass through various cell cycle checkpoints and ultimately succumb to apoptotic death [155]. Improvements in anti-tumor activity using anti-tubulin therapy may be achieved by selectively increasing the delivery of these drugs to the tumor cells, using either immuno-conjugates or novel delivery systems. The majority of the currently approved drugs bind to β-tubulin; however, the newer compounds are targeted to bind α-tubulin [156]. Tubulin-binding drugs can be classi-

fied according to the site on tubulin these drugs bind to. Most of these agents target the taxane-binding site and include the taxanes, the epothilones, discodermolide, eleutherobin, and launilamide. The other two sites currently targeted therapeutically are the vinca binding site, by agents including dolastatins, maytansinoid immunoconjugates, vinflunine and halichondrin B analogues, and the colchicine-binding site, by combretastatin A4 and its analogues. Drugs that bind to the colchicine domain have been reported to show promise as vascular-targeting agents [157]. With the advent of such drugs, some improvements in tumor response rates have been seen, but randomized trials need to be completed before the safety and efficacy of specific novel tubulin-binding agents can be established.

Curcumin-induced G2/M arrest in MCF-7 breast-cancer cells is due to the assembly of aberrant, monopolar mitotic spindles that are impaired in their ability to segregate chromosomes [158]. The production of cells with extensive micronucleation after curcumin treatment suggests that some of curcumin's effects are due to its ability to disrupt normal mitosis and promote genetic instability [158]. In support of this, analyses of the gene expression profiles of curcumin treated HT-29 and Caco-2 colon-cancer cells revealed that curcumin down-regulates expression of metallothionein genes, tubulin genes, p53, and several other genes involved in colon carcinogenesis [159]. A more recent study showed that curcumin also induces significant depolymerization of interphase microtubules, disrupts microtubule assembly *in vitro*, reduces GTPase activity, and induces tubulin aggregation in HeLa and MCF-7 cells [160].

4.9 Apoptosis inducer

Apoptosis is an essential process for cell selection and survival, and resistance to apoptosis can promote malignant transformation of otherwise normal eukaryotic cells. Proteins that regulate apoptosis are thus integral to the development of human cancers [161]. A delicate balance between pro- and antiapoptotic mechanisms determines whether a cell death signal can activate the execution of the apoptotic cell death program. In this regard, the family of inhibitor of apoptosis (IAP) proteins has been recently identified and is categorized as a novel category of apoptosis-regulatory proteins [162, 163]. IAP are considered a class of caspase inhibitors that selectively bind and inhibit caspases-3, -7, and -9, and novel therapeutic drugs that target IAP have theoretically the required potential for the treatment of human cancers [164]. The discovery of caspase inhibitors has revealed the existence of alternative backup cell death programs for apoptosis. The broad-spectrum caspase inhibitor zVAD-fmk modulates the three major types of cell death including apoptotic cell death, necrotic cell death, and autophagic cell death [165].

Curcumin modulates apoptotic cell machinery through activation of caspases-3 and -8 but not caspase-9 in melanoma cells [166]. Curcumin also induces Fas receptor aggregation in a FasL-independent manner, and expression of dominant negative FADD significantly inhibited curcumin-induced cell death [166]. Curcumin prevents UV irradiation-induced and photosensitization-related apoptotic changes, including c-Jun N-terminal kinase (JNK) activation, loss of mitochondrial membrane potential (MMP), mitochondrial release of cytochrome C, caspase-3 activation, and cleavage/activation of PAK2 in human epidermoid carcinoma A431 cells [167, 168].

The role of the NF-κB signaling pathway in curcumin-mediated apoptosis has been clearly elucidated in multiple studies in head and neck squamous cell carcinoma (HNSCC) (169], mantle cell lymphoma [170], lung cancer [171], melanoma cells [172], cardiomyocytes [173, 174], liver cancer [175], and T-cell lymphoma [176]. Similar observations were made in animal model systems in which curcumin was found to have both proapoptotic and anti-angiogenic effects, suggesting its usefulness as a promising chemotherapeutic agent [177]. Additional mechanisms of curcumin-mediated apoptotic effects were observed in T-cell acute lymphoblastic leukemia malignant cells in which curcumin suppressed constitutively activated targets of PI3′-kinase (AKT, FOXO and GSK3), leading to the inhibition of proliferation and induction of caspase-dependent apoptosis [178]. Most recent studies have indicated that curcumin is an effective therapeutic agent for suppression of anti-apoptotic factors and activation of calpain and caspase proteolytic cascades for apoptosis in human malignant glioblastoma cells [179, 180].

P53 protein plays an important role in mediating apoptosis through transcriptional activation of pro-apoptotic proteins usually categorized into two groups including the death-receptor pathway and the mitochondrial apoptotic pathway [181]. Caspases are the key proteins that modulate the apoptotic response and among these, caspase-3 is a key executioner of apoptosis, which in turn is activated by caspase-9. Multiple studies have shown that curcumin down-regulates both pro-caspase-9 and pro-caspase-3 expression in a time-dependent manner in colon cancer cells [166, 182, 183]. In addition, it has been shown that curcumin up-regulated the serine phosphorylation of p53 in a time- and concentration-dependent manner [183, 184].

Collectively, all these studies suggest that curcumin mediates its effects through a wide variety of growth regulatory mechanisms in tumor cells, and thus curcumin has a legitimate potential to be used a multi-targeted drug of choice in the management of human cancers and various other diseases.

5 Studies of curcumin in human subjects

The past decade has witnessed an increased interest in validating and reconfirming the *in vitro* and *in vivo* evidence

for the chemopreventive potential of curcumin in human subjects. The initial studies were primarily focused on determining the safety profile of curcumin, while more-recent studies are exploiting the potential chemotherapeutic role of curcumin in treating various human cancers. The data obtained thus far have surpassed the expectations of most investigators, and it is probably just a matter of time before we can clearly appreciate the true potential of curcumin as a "magic bullet" for the management of various human diseases. This Section will briefly list various important studies performed in human subjects to support the role of curcumin as a "multi-targeted" therapeutic drug of choice in the coming years.

Several studies over the years have investigated the pharmacokinetics, toxicity, and tolerance for curcumin in humans. Based on multiple studies and different phase I clinical trials, it has been shown that curcumin when taken as high as 12 g/day is well tolerated [18, 185, 186]. In this context, even the most recent trial, which investigated a dose-escalation regimen to determine the maximum tolerated dose and safety of a single dose of standardized powder extract, reported no serious side effects and concluded that curcumin is well tolerated even at high doses up to 8000 mg [185].

The first study of the clinical efficacy of curcumin was a short-term, double blind, crossover study in 18 patients (22 to 48 years old) with rheumatoid arthritis [187]. In this study, 1200 mg curcumin/day was administered for a total of 2 weeks, and it was concluded that curcumin was well tolerated, had no side effects, and showed anti-rheumatic activity comparable to that of phenylbutazone. Similar anti-inflammatory effects of curcumin were noticed in another study with 46 male patients having inguinal hernia and/or hydrocoele treated with either 400 mg of curcumin or placebo or phenylbutazone [188]. Similar to the results of the previous study, curcumin was found to be quite safe, and phenylbutazone and curcumin produced a better anti-inflammatory response than did placebo. Anti-inflammatory effects of curcumin were reinforced in two other clinical studies involving the rare inflammatory diseases of chronic anterior uveitis and idiopathic inflammatory orbital pseudotumors [189, 190]. In both of these trials, the efficacy of curcumin and recurrences following treatment were comparable to those for corticosteroid therapy, which is at present considered the only available standard treatment for this disease.

In light of multiple animal studies showing protective effects of curcumin in skin cancers, Kuttan *et al.* [191] successfully demonstrated the protective effects of curcumin, on symptomatic relief in patients with external cancerous lesions. Subsequently, these researchers performed a clinical trial to monitor the effect of curcumin administration in reducing the serum levels of cholesterol and lipid peroxides in ten healthy human volunteers who received 500 mg of curcumin per day for 7 days [192]. The authors reported a marked decrease in the level of serum lipid peroxides (33%), an increase in HDL cholesterol (29%), and a decrease in total serum cholesterol (11.63%) following curcumin supplementation, suggesting the chemopreventive role of this compound for treating arterial diseases [192]. Analogous observations were made in another study in which curcumin lowered LDL and increased HDL in atherosclerosis patients [193]. Rasyid *et al*. [194] showed the protective effects of 20 mg of curcumin in improving gallbladder function and reducing gallstone formation. Another trial investigated the effects of curcumin on phosphorylase kinase (PhK) activity in patients with psoriasis [195]. The trial found that curcumin is a potent inhibitor for PhK and has potential beneficial effects in subjects with psoriatic disease.

In a phase I prospective trial, Chen *et al*. [196] examined the toxicology, pharmacokinetics, and biologically effective dose of curcumin in humans with one of the following five high-risk conditions: (i) recently resected urinary bladder cancer; (ii) arsenic Bowen's disease of the skin; (iii) uterine cervical intraepithelial neoplasm (CIN); (iv) oral leucoplakia; and (v) intestinal metaplasia of the stomach. Curcumin (500 – 12 000 mg) was taken orally for 3 months. The study reported no treatment-related toxicity for doses up to 8000 mg/day. Most subjects in this trial showed marked improved in their disease symptoms, and this study clearly showed that curcumin is not toxic at doses up to 8000 mg/day and that it has biologic relevance for the chemoprevention of cancer [196].

In a similar study, Sharma *et al*. [17] examined the pharmacodynamics and pharmacokinetics of curcumin in humans in a dose-escalation pilot study using a novel turmeric preparation that contained 36 – 180 mg of curcumin. Fifteen patients with advanced colorectal cancer refractory to standard chemotherapies received curcumin for up to 4 months. Radiologically stable disease was demonstrated in five patients following 2 to 4 months of treatment. This was followed by another study by these investigators, in which a daily dose of 3.6 g of curcumin resulted in 62 and 57% decreases in inducible PGE_2 production in blood samples taken 1 h after the dose on days 1 and 29, respectively [197]. Based on these studies, they recommended a daily oral dose of 3.6 g of curcumin for phase II evaluation in the prevention or treatment of cancers outside the gastrointestinal tract. Bundy *et al.* [198] assessed the effects of curcumin on inflammatory bowel syndrome symptomology in healthy adults. This study was a partially blinded, randomized, two-dose, pilot study. Two hundred and seven suitable volunteers were randomized, and significant improvements in symptoms after curcumin were observed at the end of the treatment period, suggesting that curcumin may help reduce inflammatory bowel syndrome symptomology. In another study, Shoskes *et al*. [199] found that curcumin therapy improved early graft function and improved early outcomes in cadaveric renal transplantation patients. Durgaprasad *et al.* [200] in their pilot study found that oral curcumin when

Figure 1. Curcumin-based products from around the World. *Colorant*- produces clean and bright hues used by the food industry in an endless variety of applications. China: *Dairy*- goat milk with curcumin. Turkey: *Henna*- natural hair henna set (red) contains ingredients to vary hair color. Each package includes henna (120 g/4.2 oz), curcumin – turmeric (15 g/0.5 oz), Juglans Frustus Ortex (80 g/2.8 oz), Foliuk Lauri (20 g/0.7 oz), Rastik Natural Point (35 g/1.2 oz). United Kingdom: Desserts include Lemmon Sponge Pudding, Alpro Vanilla Flavoured Soya Dessert, and Alpro Custard; *Dairy*-Longley Farm Vanilla Yogurt and Bute Island Food Sheese (Cheese). United States: *Colorant*-natural green color is made from vegetable juice and turmeric (curcumin) extract.

Table 1. A List of Curcumin Products from Around the World

Company/Brand	Website
Asia	
Bangladesh	
Hasan Agro (TF)	tradekey.com/ks-curcumin
China	
Biopharm Co. (P)	www.ecplaza.net/tradeleads/seller/4324626/curcumin.html
Changsha Active Ingredients (E)	www.aigi-herb.com
Chemblink (P)	www.chemblink.com
Deray Biological Industry (E)	www.tradekey.com/ks-curcumin
Edison Trading Co. (E)	ecplaza.net/tradeleads/seller/3926784/sell_curcumin.html
Future Pharmaceutical (E)	plantextract.51.net/pe.htm
GreenSky Biological (E)	www.ecplaza.net/tradeleads/seller/1911272/offer_plant_extracts.html
Guangxi Changzhou Natural Products Development (P)	ecplaza.net/tradeleads/seller/2835559/curcumin_95.html
Healing Herbs (G)	www.alibaba.com/catalog/11354367/Herbal_Cosmetics.html
HeBei Food Additive (CO)	http://pigment100.en.ec21.com/company_info.jsp
HeBei Food Additive (P)	www.tradekey.com/ks-curcumin
Herbal Trading Co. (E)	www.xafeida.cn
Huakang Biotech (E)	www.huakangsw.com
Italmatch International (E)	kelvinmiao.en.ec21.com
Jiang Su Sainty Corp. (E)	www.ecplaza.net/tradeleads/seller/4185036/curcumin_95.html
Kairun Co. (CO)	www.ecplaza.net/tradeleads/seller/2136634/curcumin_turmeric_pigment.html
Nanjing Qingze Medical Technology Development (E)	ecplaza.net/ecmarket/list.asp?cmd=search&keywords=curcumin
Nanjing Sulang Medical Technology Development (E)	www.qzmed.com
NingboTaipioBio-tech (P)	www.tradekey.com/ks-curcumin
Nuchem Source (E)	www.nuchemsource.com
Organic Herb (E)	www.organic-herb.com
Pengyuan Natural Pigment Research Institute (WS,CO)	http://yanger222.en.ec21.com/company_info.jsp
Qingdao Peng Yuan Natural Pigment Research Institute (WS,CO)	http://winner1568.en.ec21.com/company_info.jsp
Qingdao Pengyuan Natural Pigment Research Institute (CO)	www.ecplaza.net/ecmarket/list.asp?cmd=search&keywords=curcumin
Qingdao Winhealth (E)	http://superzdc.en.ec21.com
Research Institute	www.tradekey.com/ks-curcumin
Sciphar (E)	www.sciphar.com/
Shaanxi Sciphar Biotechnology (E)	www.ecplaza.net/tradeleads/seller/3608990/curcumin.html
Shanghai Richem International (E)	http://srichem.en.alibaba.com
Sichuan Xiangzhen Enterprise (R)	www.alibaba.com/catalog/11086811/Organic_Turmeric.html
Trademax Phamaceutial & Chemicals (E)	www.trademaxchem.com
Wuhan Yuancheng Technology Development (E, WS)	www.ecplaza.net/tradeleads/seller/4327063/monocurcumin_95.html
Wuhu Haozhan Trading (P)	www.alibaba.com/catalog/10124094/Curcumin.html
Xi'an Erica Botanical Product (E)	www.plant-extract.com
Xi'an Tianxingjian Natural Bio-products (P)	www.txjherb.com/doce/jj.htm
India	
Adani Pharmachem (OL, P)	www. catalogs.indiamart.com
Advance Chemical Processor (E)	www.ecplaza.net/tradeleads/seller/3975297/sell_curcumin_95_extract.html
Advance Chemical Processor (E)	www.tradekey.com/ks-curcumin
Alchem International (THC)	http://www.ecplaza.net/tradeleads/seller/3897369/tetra_hydro_curcumin.html
Apna Agro Products (P)	www.alibaba.com/catalog/11820469/Turmeric_Powder.html
Aseptik (CR)	www.alibaba.com/catalog/11121534/Aseptik.html
Asian Herbex (CR, P)	www.asianherbex.biz/curcumin.htm
Chemiphar (E)	www.tradekey.com/ks-curcumin
Deepak Engg (E)	www.tradekey.com/buyoffer_view/id/125993.htm
Elango Extraction (E)	www.tradekey.com/ks-curcumin
Enorbis (E)	www.ecplaza.net/tradeleads/seller/1023843/bulk_suppliers_of_annatto.html
Extract Tech Co. (P)	www.alibaba.com/catalog/12011995/Curcumin.html
Fancy India Corp. (E)	ecplaza.net/ecmarket/list.asp?cmd=search&keywords=curcumin
Garuda Exports (E)	www.ecplaza.net/tradeleads/seller/4520473/curcumin95.html

Table 1. Continued

Company/Brand	Website
H. Bilal & Co. (E)	www.alibaba.com/catalog/10990947/Turmeric.html
Harley Carmbel (P)	www.harleycarmbel.com
HR Consultant (E)	www.tradekey.com/buyoffer_view/id/37405.htm
INDSAFF (C)	www.tradekey.com
Jabalpur Motors (E)	www.tradekey.com/ks-curcumin
Jai Radhe Sales (O, R)	www.pharmaceuticaldrugsmanufacturer.com
JaiRamdass Khushiram (E, P)	www.tradekey.com/ks-curcumin
Kancor Ingredients (P)	www.kancor.in
Konark Herbal (O, E, WS, OL)	www.ecplaza.net/tradeleads/seller/4648335/curcumin.html
Krish Enterprises (E)	http://srinivas45.en.ec21.com/
M.S.Drugs ImpEx (E)	www.ecplaza.net/tradeleads/seller/4089411/curcumin.html
Malhar Udyog (E)	tradekey.com/ks-curcumin
Meghalaya Natural Products (CO)	ecplaza.net/tradeleads/seller/510607/birds_eye_chillies.html
Natural Remedies (P)	www.naturalremedy.com
Naturnutra Inc. (E)	ecplaza.net/tradeleads/seller/1735227/herbal_extracts.html
Navshakti Herbal Labs (E)	www.tradekey.com/ks-curcumin
Organic.co.in (P, TF, C)	http://organic.co.in
Phytolipids (E)	ecplaza.net/tradeleads/seller/4396071/curcumin_95.html
Phytopharma (P, TA)	www.alibaba.com
Prakruti Products (P)	www.ecplaza.net/tradeleads/seller/1937068/garciniaglucosaminecurcuminsen-nasalacia.html
Prmc Ltd. (T, F, P)	http://prmcltd.en.ecplaza.net
Protek India Herbals (WS)	www.tradekey.com/ks-curcumin
S.S. Herbals (P)	www.alibaba.com
Sai Lalith Fragrances (E)	www.tradekey.com/buyoffer_view/id/64526.htm
Sears Phytochem (E, O, R)	www.searsphytochem.com
Sami Labs Ltd.	www.samilabs.com
Shinago Exim (P)	www.tradekey.com/ks-curcumin
Shivom Plantation (R)	www.alibaba.com/catalog/11566696/Fresh_Turmeric.html
Sipindia Exports (E, TF, P)	http://sipindia-exports.tradenote.net
Sri Dhanalakshmi Industries (E)	www.evergreen-sdi.com
Synthite	www.synthite.com
Tricon Enterprises (CO)	www.ecplaza.net/tradeleads/seller/878140/curcuminbeet_root_annato.html
UNICO Pharmaceuticals (C)	tradeindia.com
Veekay International (P)	www.alibaba.com/catalog/10881731/Turmeric.html
Vision India Technology (P)	http://www.ecplaza.net/tradeleads/seller/4389650/curcumin_95_hplc_in_-bulk.html
Bazaar of India (C, P, T)	www.bazaarofindia.com
Japan	
Biofirm (DR, TA)	www.rbr.co.jp
Ottogi (C)	www.ottogi.co.kr
Suplinx (O)	www.suplinx.jp/biyou-diet/curcumin-oil.html
Taikokushuzo (DR)	www.okinawab2b.sakura.ne.jp
Yakuryouken (C)	http://curcumin.client.jp
Korea	
M.E.C.O (D)	http://meco.co.kr/meco/nglish/product/eproductlist.aspx
Taeyoung E&T Co. (F)	http://tyent.en.ec21.com
Singapore	
Gen-Gap Bio Sciences (E)	www.gengapbiosciences.com
Thailand	
Beauty by Herb (CR)	www.beautybyherb.com
DHYA (L)	www.ldirectgroup.com
Herbcare (CR)	www.herbalfantasy.net
Thai Tambon (CR)	www.thaitambon.com
Wandee Osot LP (B)	http://thailandbalms.trustpass.alibaba.com
Vietnam	
Chau Giang Co. (E)	http://www.ecplaza.net/tradeleads/seller/3914286/artemisinin_essential.html

Table 1. Continued

Company/Brand	Website
Europe	
Cayman Europe (C)	www.caymaneurope.com
France	
Extrasynthese (P)	www.extrasynthese.com/codeart.asp
Germany	
Spirulife (C)	www.spirulife.de/kurkuma-extrakt-curcuma.php
Spain	
ASAC Pharma	www.asac.net/asac/portada.asp
Switzerland	
Fluka (P)	www.sigmaaldrich.com
United Kingdom	
Bursting With Health (C)	www.burstingwithhealth.co.uk
CBS Formula Tea (P)	www.pavilionhealth.co.uk
Curcumin 98 (C)	www.yourhealthfoodstore.co.uk
Health Aid (E)	www.worldwideshoppingmall.co.uk
Himalaya (C)	www.himalayadirect.com
Lichtwer Pharma Cynara (TA)	www.yourhealthfoodstore.co.uk
Solgar (C)	www.yourhealthfoodstore.co.uk
Viridian Organic Tumeric (C)	www.yourhealthfoodstore.co.uk
North America	
Canada	
AOR (C)	http://aor.ca
Hallelujah Acres (C)	www.hacres.ca
Organika (C)	www.healthmart2000.com
United States	
95% Curcumin (C)	www.turmeric-curcumin.com
Ageless Cures (C)	www.agelesscures.com
Alfa Chem (E)	www.alfachem1.com
Amazon (C)	www.curmax.com
American Color Research Center(CO)	www.acrccolors.com
America's Finest (C)	www.afisupplements.com
America's Finest Super Curcumin(TA)	www.afisupplements.com
Ancient Way Acupuncture/Herbs (P)	www.ancientway.com
Ayur-Curcumin (C)	www.nynaturalhealthcenter.com
Better Health International (C)	www.betterhealthinternational.com
Brain Therapeutics (E)	www.tradekey.com/buyoffer_view/id/146343.htm
Cardiovascular Resarch (C)	www.thenaturalonline.com/
Chong's Health Care Enterprise (C)	www.cljhealth.com
Curcumin Pro (C)	www.naturalhealthconsult.com
CureCumin (NS)	www.bioponic.com/press/press_releases/
Doctor's Best (C)	www.vitacost.com/DoctorsBestBestCurcumin
Doctor's Purest Curcumin (C)	www.agelesscures.com
Doctor's Trust (C)	www.doctorstrust.com
Dr. Donsbach's Let's Talk Health (C)	www.letstalkhealth.com
Eclectic Institute Tumeric (C)	www.eclecticherb.com
Federal Laboratories Corp. (P)	www.federalabs.com
Food Science Of Vermont (C)	www.fslabs.com
GFS Chemicals Inc.	www.gfschemicals.com
Herbal Descriptions (LSE)	www.health-marketplace.com
Herbal Fields Supplements (C)	www.herbalfields.com/curm.html
Herbals (C)	www.qcinutritionals.com
*Himani Gold Turmeric (CR, E)	www.naturalplaza.com
Home Cure (C)	www.homecure.com/newproducts.html
Jarrow Formulas (C)	www.jarrow.com
Life Extension (C)	www.lef.org/newshop/items/item00912.htm

Table 1. Continued

Company/Brand	Website
Life One Formulas (E)	www.lifeonesales.com/lifeone.htm
MSM Glucosamine Curcumin (CR)	www.drsupply.com
Nature's Way (C)	www.swansonvitamins.com
NatXtra (C)	www.indogen.net/
New Chapter (C)	www.Whole-Food-Vitamins.net
Now Foods (C)	www.nowfoods.com
NSI (C)	www.vitacost.com/AlanJamesOptiFormSAMe
Nutriteam (C)	www.nutriteam.com
Paradise Herbs (C)	www.paradiseherbs.com
Physician Formulas (C)	www.physicianformula.com
Pionair (C)	www.pionair.net
Planetary Herbals (C)	www.planetaryherbals.com
Psoria-Gold (CR)	www.psoriagold.com
Pure Encapsulations (C)	www.organicpharmacy.org
Pure Prescriptions (C)	www.pureprescriptions.com
Puritan's Pride (C)	puritan.com/pages/Categories.asp?xs=&CID=212&Page=0
Sabinsa (E)	www.curcuminoids.com
Simply Organic (P)	www.simplyorganic.com
Solaray (C)	www.nutraceutical.com/about/solaray.cfm
Source Naturals (C)	www.sourcenaturals.com
Spectrum Chemical (P)	www.spectrumchemical.com
Springboard (CR)	www.springboard4health.com
Tattva's Herbs (C)	www.tattvasherbs.com
Tropilab (TI, P)	www.tropilab.com/tumulawaktincture.html
Tumeric (E)	www.herbalremedies.com
United Food Ingredients	www.ufi-vitamin.com
Viable Herbal Soltions (C)	www.viable-herbal.com
Vibrant Health (C)	www.vitaminlife.com
Vital Nutrients (C)	www.vitalnutrients.net
Vitamin Research Products (C)	www.vrp.com
Wild Flavors (CO)	www.wildflavors.com
South America	
Peru	
Conaisa Eirl (E)	http://www.alibaba.com/catalog/11537368/Turmeric.html
Worldwide	
Sigma (P)	http://www.sigmaaldrich.com

* Offices also in Singapore, China, Hong Kong and India (Tablet and capsule concentrations range from 300-500 mg) B-Balm, C-Capsule, CO-Colorant, CR-Cream, D-Dairy, DR-Drink, E-Extract, F-Fermented, G-Gel, L-Lotion, LSE-Liquid Seed Extract, NS-Nasal Spray, O-Oil, OL- Oleroresin, P-Powder, R-Root, T-Tea, TA-Tablet, TF-Turmeric Finger, TI-Tincture, WS-Water Soluble

given in conjunction with piperine reversed lipid peroxidation in patients with tropical pancreatitis.

A recent clinical study reported the protective efficacy of curcumin in patients with ulcerative proctitis and Crohn's disease, who were otherwise refractory to conventional 5-aminosalicyclic acid (5ASA) or corticosteroid therapies. Recent study from Hanai *et al.* [201] supported these data: curcumin was again found to be a promising and safe medication for maintaining remission in patients with quiescent ulcerative colitis. In another interesting study, the combination of 480 mg of curcumin and 20 mg of quercetin orally three times a day reduced the number and size of ileal and rectal adenomas in patients with FAP [202].

In addition to the published evidence for the chemopreventive effects of curcumin in humans, several clinical trials are currently underway in the United States and other parts of the world. These clinical trials aim to further investigate the effects of curcumin in phase I and II randomized or non-randomized studies using curcumin alone or in conjunction with other natural substances or NSAID in human malignancies, including colorectal cancer, aberrant crypt foci, FAP, pancreatic cancer, multiple myeloma, Alzheimer's disease, myelodysplastic syndrome, and psoriasis. On the basis of the existing information and the anticipated outcome of ongoing clinical trials, we anticipate that chemoprevention and therapeutic studies will remain popular not only from the standpoints of efficacy and safety but also from a financial standpoint, compared with the conventional chemopreventive or chemotherapeutic regimens adopted to treat these deadly diseases.

6 Current clinical trials of curcumin

Due to the growing literature on curcumin's efficacy to prevent and treat multiple cancers, several human trials investigating chemopreventive effects of curcumin have been completed in the recent years. However, many more similar trials are in progress, and at least 12 such studies are underway in the United States as well as other parts of the world. In majority of these trials, curcumin is being investigated alone, or in conjunction with other compounds including quercetin or sulindac. Some of these clinical studies are currently underway in Japan (colon cancer, gastric cancer and liver cancer), and the details of these are not readily available. However, information regarding various randomized and nonrandomized phase I and II trials on curcumin in the United States can be obtained at www.ClinicalTrials.gov. These clinical trials interrogate curcumin's effects in a variety of human cancers including colon cancer, aberrant crypt foci (ACF), FAP, pancreatic cancer, multiple myeloma (MM), Alzheimer's disease, myelodysplastic syndrome (MDS), hepatocellular cancer, gastric cancer and psoriasis.

In addition to investigating curcumin together with quercetin and sulindac, an Israeli study is interrogating the effects of combined curcumin and gemcitabine in patients with metastatic pancreatic cancers. Similarly, another study is exploring the clinical efficacy of curcumin alone or in combination with coenzyme Q10 in patients with MDS. In yet another trial, curcumin is being investigated in conjunction with bioprine (that increases its bioavailability) in patients with asymptomatic multiple myeloma. Considering the promise curcumin holds in the prevention and treatment of wide variety of human cancers, it is anticipated that completion of these clinical trials will lend further credence to the already established effects of curcumin as a multi-targeted therapeutic regimen for the management of human cancer.

7 Sources and uses of curcumin

Based on all studies performed on curcumin, the FDA has approved curcumin as "generally regarded as safe", and it is being used in the United States in mustard sauce, cheese, butter, chips, and other as both a preservative and a coloring agent. The safety of curcumin, combined with its efficacy and lower cost, makes it an ideal chemopreventative or chemotherapeutic agent. Various countries are already selling curcumin-based products (see Fig. 1); and it is also extensively being sold as food supplement, in cream and other forms (see Table 1).

8 Conclusions

All the studies described above demonstrate that traditional medicines such as turmeric from which curcumin is derived have multiple targets that could explain its role in the treatment of various diseases. This also validates the epidemiological evidences that why certain diseases have lower incidence in countries where agents such as curcumin are consumed more frequently and on a regular basis. This is in agreement with Hippocrates, who stated almost 25 centuries ago, "Let food be thy medicine and medicine be thy food." More studies are needed to validate agents such as curcumin as a therapeutic agent for multiple diseases.

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