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Discovery of Curcumin, a Component of the Golden Spice, and Its Miraculous Biological Activities

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SUMMARY

1. Curcumin is the active ingredient of the dietary spice turmeric and has been consumed for medicinal purposes for thousands of years. Modern science has shown that curcumin modulates various signaling molecules, including inflammatory molecules, transcription factors, enzymes, protein kinases, protein reductases, carrier proteins, cell survival proteins, drug resistance proteins, adhesion molecules, growth factors, receptors, cell-cycle regulatory proteins, chemokines, DNA, RNA, and metal ions.

2. Because of this polyphenol's potential to modulate multiple signaling molecules, it has been reported to possess pleiotropic activities. First shown to have anti-bacterial activity in 1949, curcumin has since been shown to have anti-inflammatory, anti-oxidant, pro-apoptotic, chemopreventive, chemotherapeutic, anti-proliferative, wound healing, anti-nociceptive, anti-parasitic, and anti-malarial properties as well. Animal studies have suggested that curcumin may be active against a wide range of human diseases, including diabetes, obesity, neurologic and psychiatric disorders, and cancer, as well as chronic illnesses affecting the eyes, lungs, liver, kidneys, and gastrointestinal and cardiovascular systems.

3. Although many clinical trials evaluating curcumin's safety and efficacy against human ailments have already been completed, others are still ongoing. Moreover, curcumin is used as a supplement in several countries, including India, Japan, the United States, Thailand, China, Korea, Turkey, South Africa, Nepal, and Pakistan. Although inexpensive, apparently well tolerated, and potentially active, curcumin has yet not been approved for treatment of any human disease.

4. In this article, we discuss the discovery and key biological activities of curcumin, with a particular emphasis on its activities at the molecular, cellular, animal, and human levels.

DISCOVERY OF CURCUMIN

The discovery of curcumin dates to around two centuries ago when Vogel and Pelletier reported the isolation of “yellow coloring-matter” from the rhizomes of *Curcuma longa* (turmeric) and named it curcumin (1). Later, this substance was found to be a mixture of resin and turmeric oil. In 1842, Vogel Jr. obtained a pure preparation of curcumin but did not report its formula (2). In the decades that followed, several chemists reported possible structures of curcumin (3–5). However, it was not until 1910 that Milobedzka and Lampe identified the chemical structure of curcumin as diferuloylmethane, or 1,6-heptadiene-3,5-dione-1,7-bis (4-hydroxy-3-methoxyphenyl)-(1E, 6E) (6). Further work by the same group in 1913 resulted in the synthesis of the compound (7). Subsequently, Srinivasan separated and quantified the components of curcumin by chromatography (8) (Fig 1A and 1B).

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Although turmeric, the major source of curcumin, has been consumed as a dietary spice and a cure for human ailments for thousands of years in Asian countries, the biological characteristics of curcumin were not scientifically identified until the mid-twentieth century. In a paper published in *Nature* in 1949, Schraufstatter and colleagues reported that curcumin is a biologically active compound that has anti-bacterial properties (9). The authors found that curcumin was active against strains of *Staphylococcus aureus*, *Salmonella paratyphi*, *Trichophyton gypseum*, and *Mycobacterium tuberculosis* (Fig 1C). Despite those findings, only five papers were published on curcumin during the next two decades. In the 1970s, curcumin became the subject of scientific investigation, and three independent groups discovered diverse characteristics of curcumin, including cholesterol-lowering (10), anti-diabetic (11), anti-inflammatory (12), and anti-oxidant (13) activities. Later, in the 1980s, Kuttan and colleagues demonstrated the anti-cancer activity of curcumin in both *in vitro* and *in vivo* models (14). In 1995, our group was the first to demonstrate that curcumin exhibits anti-inflammatory activity by suppressing the pro-inflammatory transcription factor nuclear factor (NF)-κB; we also delineated the molecular mechanism of the inhibition (15).

The interest in curcumin research has increased dramatically over the years (Fig 1D). As of June 2011, more than 4000 articles on curcumin were listed in the National Institutes of Health PubMed database (www.ncbi.nlm.nih.gov/sites/entrez). We now know that curcumin can modulate multiple signaling pathways in either a direct or indirect manner. This polyphenol has been shown to possess activities in animal models of many human diseases. In human clinical trials, curcumin has been found to be safe and efficacious, and the U.S. Food and Drug Administration has approved curcumin as a “generally regarded as safe” compound.

Although curcumin has shown therapeutic efficacy against many human ailments, one of the major problems with curcumin is its poor bioavailability (16), which appears to be primarily due to poor absorption, rapid metabolism, and rapid systemic elimination. Therefore, efforts have been made to improve curcumin's bioavailability by improving these features. Adjuvants that can block the metabolic pathway of curcumin have been most extensively used to increase the bioavailability of this polyphenol. For instance, in humans receiving a dose of 2 g curcumin alone, serum levels have been either undetectable or very low, but concomitant administration of piperine was associated with an increase of 2000% in the bioavailability of curcumin (17). Furthermore, the effect of piperine in enhancing curcumin's bioavailability has been shown to be much greater in humans than in rats (16). Other promising approaches to increase the bioavailability of curcumin include use of nanoparticles (18), liposomes (19), micelles (20), phospholipid complexes (21), and structural analogues (22, 23).

Curcumin is now regarded as a “new drug” with great potential and is being used as a supplement in several countries. For example, in India, turmeric containing curcumin has been used in curries; in Japan, it is popularly served in tea; in Thailand, it is used in cosmetics; in China, it is used as a colorant; in Korea, it is served in drinks; in Malaysia, it is used as an antiseptic; in Pakistan, people use it as an anti-inflammatory agent to get relief from gastrointestinal discomfort; and in the United States, it is used in mustard sauce, cheese, butter, and chips, as a preservative and a coloring agent. Curcumin is marketed in several forms including capsules, tablets, ointments, energy drinks, soaps, and cosmetics.

Our laboratory and others have shown that many other nutraceuticals in addition to curcumin have therapeutic potential against inflammatory conditions. Some of these nutraceuticals are resveratrol, ursolic acid, butein, silymarin, caffeic acid phenethyl ester, anethole, berberine, capsaicin, flavopiridol, thymoquinone, gossypin, withanolides, γ-tocotrienol, zerumbone, morin, plumbagin, and celastrol. Although these nutraceuticals have

been shown to exhibit anti-inflammatory activity, very little is known about their efficacy in humans. In the sections to follow, we review the biological activities of curcumin, with a special focus on its major activities at the molecular, cellular, animal, and human levels.

BIOLOGICAL ACTIVITIES OF CURCUMIN

Molecular level

At the molecular level, curcumin has been shown to modulate a wide range of signaling molecules. Curcumin may cause upregulation or downregulation depending on the target and cellular context (Table 1). These targets fall into two categories: those to which curcumin binds directly and those whose activity curcumin modulates indirectly. Included among the indirect targets are transcription factors, enzymes, inflammatory mediators, protein kinases, drug resistance proteins, adhesion molecules, growth factors, receptors, cell-cycle regulatory proteins, cell-survival proteins, chemokines, and chemokine receptors (Table 1). Direct targets include inflammatory molecules, cell-survival proteins, protein kinases, protein reductases, histone acetyltransferase, histone deacetylase, glyoxalase I, xanthine oxidase, proteasomes, HIV1 integrase, HIV1 protease, sarco/endoplasmic reticulum Ca^{2+} ATPase, DNA methyltransferase 1, FtsZ protofilaments, carrier proteins, and metal ions. A comprehensive review of the molecular targets of curcumin and the molecular mechanisms involved can be found in numerous articles published by us and others (24–28).

One of the most important targets of curcumin is pro-inflammatory transcription factors, such as NF-κB, activator protein-1, and signal transducer and activator of transcription (STAT) proteins (29). These transcription factors regulate the expression of genes that contribute to tumorigenesis, cell survival, cell proliferation, invasion, and angiogenesis. Curcumin has been shown to negatively regulate these transcription factors (29). Protein kinases are another major target of curcumin. For instance, the polyphenol has been shown to downregulate epidermal growth factor receptor and the activity of extracellular signal-regulated kinase 1/2 (also called mitogen-activated protein kinase) in pancreatic and lung adenocarcinoma cells (30). Curcumin has also been shown to inhibit the phosphatidylinositol 3 kinase/AKT pathway in malignant glioma cells (31). The polyphenol has been shown to completely inhibit the activity of several protein kinases, including phosphorylase kinase, protein kinase C, protamine kinase, autophosphorylation-activated protein kinase, and pp60c-src tyrosine kinase (29, 32).

Cellular level

Extensive *in vitro* studies over the past half century have shown that curcumin is a highly pleiotropic molecule and that its pleiotropic activity comes from its ability to modulate multiple signaling molecules. In particular, curcumin has been shown in numerous *in vitro* models to possess anti-inflammatory, anti-oxidant, pro-apoptotic, chemopreventive, chemotherapeutic, anti-proliferative, wound healing, anti-nociceptive, anti-parasitic, and anti-malarial properties (Table 2).

Inflammation is an integral component of many chronic diseases. The pro-inflammatory transcription factors NF-κB and signal transducer and activator of transcription 3 (STAT3) play a major role in mediating inflammatory response by modulating the production of pro-inflammatory cytokines (33, 34). Extensive research using a wide range of *in vitro* models over the past several years has indicated that curcumin can reduce inflammatory response by regulating the production of inflammatory molecules (35). For example, in one study, curcumin was shown to inhibit phorbol 12-myristate 13-acetate (PMA)-induced inflammation of mouse fibroblast cells (36). Curcumin has also been shown to act as an anti-inflammatory agent by inhibiting production of pro-inflammatory cytokines in PMA or lipopolysaccharide-stimulated peripheral blood monocytes and alveolar macrophages (37).

Our laboratory was the first to demonstrate that curcumin is a potent inhibitor of STAT3 (38). The hydroxyphenyl unit in curcumin has been shown to be crucial to its anti-inflammatory activity (39). One study specifically identified the presence of a 4-hydroxyphenyl unit as crucial in this role; an increase in the anti-inflammatory activity was found by introducing additional small-sized alkyl or methoxy groups on the adjacent 3- and 5-positions on the phenyl ring (40).

Curcumin activity as an anti-oxidant and free-radical scavenger has been demonstrated from several *in vitro* studies. This activity can arise either from the hydroxyl group or the methylene group of the β-diketone (heptadiene-dione) moiety (41, 42). The importance of the phenolic hydroxyl group to curcumin's anti-oxidant activity is supported by several more studies (43–45). As shown in Table 2, curcumin has demonstrated anti-oxidant activities in blood plasma and platelets and in numerous cell lines. In one study, curcumin was shown to completely inhibit the *in vitro* production of superoxide anions, hydrogen peroxide, and nitrite radical production by rat macrophages (46). A recent study revealed that oxidative stimulation of G proteins in human brain membranes by the metabolic pro-oxidants homocysteine and hydrogen peroxide can be significantly depressed by curcumin (47). In another study, curcumin was shown to inhibit lipid peroxidation in a rat liver microsome preparation (48).

Curcumin has been found to be cytotoxic to a variety of tumor cells. The action of curcumin depends on the cell type, the curcumin concentration, and the length of treatment. The major mechanism by which curcumin induces cytotoxicity is the induction of apoptosis. Curcumin also has the potential to inhibit cancer development and progression by targeting multiple steps in the process of tumorigenesis. It has activity both as a blocking agent, inhibiting the initiation step of cancer, and as a suppressing agent, inhibiting malignant cell proliferation during the promotion and progression of carcinogenesis (49). In addition to its role as a chemopreventive and chemotherapeutic agent, curcumin has been shown to have the potential to help eliminate chemoresistant cells by sensitizing tumors to chemotherapy, in part by inhibiting pathways that lead to treatment resistance (50). For example, adding curcumin to either 5-fluorouracil alone or 5-fluorourcil + oxaliplatin resulted in statistically significant growth inhibition and an enhancement in apoptosis in HCT116 and HT29 colon cancer cells (51). Similarly, many *in vitro* studies have supported the potential chemosensitizing ability of curcumin in multiple cancers and have provided evidence for curcumin's use singly or as an adjunct to current chemotherapeutic drugs (50). In addition to its role as a potentially potent chemosensitizer, curcumin is also a promising radiosensitizer in a wide variety of cancer cells (52–55). Curcumin has also been shown to suppress the growth of numerous cancer cells, including those from cancer cells of the prostate (56), biliary (57), pituitary gland (58), oral (59), and uterine leiomyoma (60).

Curcumin possesses anti-microbial activities as well (61–64). For example, in a recent study of 14 *Candida* strains, curcumin displayed anti-fungal properties against all tested strains (62). In another study, curcumin was shown to improve the activity of common azole and polyene anti-fungals (65). In some cell culture systems, curcumin has been shown to possess anti-viral activities (63, 64). Other common activities of curcumin as demonstrated in *in vitro* cell culture models are wound healing in skin fibroblasts (66), anti-nociceptive activity in ganglion neurons (67), anti-parasitic activity against African trypanosomes (68), schistosomicidal activity against *Schistosoma mansoni* adult worms (69), anti-malarial activity (70), and nematocidal activity (71).

Animal level

Research carried out in animals during the past half century provides strong evidence for the beneficial role of curcumin against various diseases (41, 72, 73); the conditions in which

curcumin appears to be active are listed in Table 3. Most of these studies used rodents, although some used rabbits. For example, curcumin was shown to significantly reduce intestinal inflammation in multidrug resistance gene-deficient mice, which spontaneously develop colitis (74). In another study, curcumin was shown to attenuate colitis in the dinitrobenzene sulfonic acid-induced murine model of colitis (75). In a study investigating the protective effect of curcumin on trinitrobenzene sulfonic acid-induced colitis in mice, treatment with curcumin was associated with significant decreases in diarrhea and in disruption of the colonic architecture in mice (76). Finally, in a rat model, curcumin administration was associated with a significant reduction in chronic inflammation and inflammatory biomarkers (77).

Curcumin has also been shown to improve the symptoms associated with diabetes. For example, in a streptozotocin-induced diabetic mouse model, curcumin (60 mg/kg body weight) was shown to act as an anti-diabetic agent and to maintain the normal structure of the kidney (78). The effect of curcumin on the progression of insulin resistance and type 2 diabetes mellitus (T2DM) was investigated in another study. Insulin resistance and T2DM were induced in male Sprague Dawley rats by high-fat diet feeding for 60 and for 75 days. Curcumin was administered in the last 15 days of high-fat diet feeding after induction of insulin resistance and T2DM. Curcumin showed an anti-hyperglycemic effect and improved insulin sensitivity; these actions were attributed in part to its anti-inflammatory properties and anti-lipolytic effects. The authors concluded that curcumin could be a beneficial adjuvant therapy in T2DM (79). In T2DM mice, curcumin appeared to be a potent glucose-lowering agent, but it had no effect in non-diabetic mice (80).

Obesity is a major risk factor for the development of T2DM, and curcumin's potential to prevent obesity was investigated in a mouse model. Mice were fed a high-fat diet (22% fat) supplemented with 500 mg curcumin/kg for 12 weeks. Supplementing the high-fat diet of mice with curcumin did not affect food intake, but it did reduce body weight gain, adiposity, and microvessel density in adipose tissue, which coincided with reduced expression of vascular endothelial growth factor and its receptor-2, peroxisome proliferator-activated receptor-γ, and CCAAT/enhancer-binding protein-α. These findings suggest that dietary curcumin may have the potential to prevent obesity (81).

Curcumin has also been shown to affect various neurological disorders. In one study, curcumin treatment for 7 days was shown to reduce plaque formation and amyloid beta accumulation in a mouse model of Alzheimer's disease (82). In another mouse model, curcumin was shown to cross the blood-brain barrier, reduce amyloid levels and plaque burden, and exhibit significant activity against Alzheimer's disease (83). One of the pathological hallmarks of another prominent neurological disorder, Parkinson's disease, is the presence of intracellular inclusions called Lewy bodies that consist of aggregates of the presynaptic soluble protein α-synuclein (84). Drug therapy for Parkinson's disease includes replacing or mimicking dopamine in the brain. Whether curcumin can be neuroprotective against a 6-hydroxydopamine model of Parkinson's disease was investigated in a rat model. Rats pretreated with curcumin showed a clear protection in dopamine levels in the striata of rat brain. Curcumin's ability to exhibit neuroprotection against 6-hydroxydopamine was related to its anti-oxidant capability and ability to penetrate into the brain (85). Another study evaluated the protective role of curcumin against dopaminergic neurotoxicity induced by MPTP or the 1-methyl-4-phenylpyridnium ion (MPP^+) in C57BL/6N mice (86). Curcumin was shown to substantially improve behavioral deficits and enhance neuron survival in the substantia nigra in the MPTP-induced Parkinson's disease mouse model. Curcumin treatment was also associated with a significant inhibition of MPTP/MPP^+-induced phosphorylation of c-Jun N-terminal kinase 1/2 and c-Jun. In addition, several other

studies using animal models have shown that curcumin has the potential to be active against Parkinson's disease (87, 88).

Epilepsy is another chronic neurological disorder in which curcumin has shown promise. A recent study examined the effect of curcumin on pentylenetetrazole-induced seizure in a rat model. Rats pretreated with curcumin had less severe seizures and less cognitive impairment than those not pretreated (89). Curcumin exhibited anti-epileptic effects in another rat model in which seizure was induced by kainic acid treatment (90). Other neurological disorders in which curcumin has shown promise in animal models are diabetic encephalopathy (91), encephalomyelitis (92), intracerebral hemorrhage (93), spinal cord injury (94), cerebral malaria (95), convulsions (96), and brain ischemia (97).

During the past two decades, our laboratory and others have demonstrated curcumin's potential as both a chemopreventive and a chemotherapeutic agent against cancer in rodent models. The chemopreventive efficacy of curcumin for colon cancer is particularly well established (98, 99). Other common cancers in which curcumin has shown protective effects in rodent models include esophageal (100), lung (101), kidney (102), stomach (103), liver (104), mouth (105), breast (106), bladder (107), leukemia (106), skin (108), small intestine (109), pancreatic (110), brain (111), and prostate (112) cancers. Accumulating evidence over the past several years has indicated that curcumin can be used for the treatment of established cancers as well. Most of these studies have used orthotopic or xenotransplant models and have employed curcumin either alone or in combination with existing therapies. Curcumin has shown potential for treatment of the following transplanted human cancers: cholangiocarcinoma (113), lymphoma (14), and melanoma (114), and prostate (115), pancreatic (116), colorectal (117), hepatocellular (118), breast (119), ovarian (120), and bladder (121) cancers.

Mounting evidence over the past several years has indicated curcumin's efficacy in various animal models of psychiatric disorders. For example, in a mouse model of depression, curcumin exhibited anti-depressant activity that was potentiated by the concomitant administration of fluoxetine, venlafaxine, or bupropion (122). When curcumin (20 and 40 mg/kg, intraperitoneally) was administered along with the bioavailability-enhancing agent piperine in these mice, enhancement of the anti-depressant action and increased brain penetration of curcumin were observed (122). Curcumin is also known to reverse olfactory bulbectomy-induced major depression in a rat model (123).

Curcumin has also been investigated for its potential to reduce cancer-related symptoms such as fatigue, neuropathic pain, and cognitive deficit. For example, curcumin's ability to reduce immunologically induced fatigue was investigated in a mouse model (124). Reduction of chronic fatigue in these mice was associated with a marked decrease in serum tumor necrosis factor-α levels (124). In another mouse model, curcumin was found to reduce fatigue in association with decreases in the levels of interleukin-β, interleukin-6, and tumor necrosis factor-α in the soleus muscles (125). Another study explored the effect of curcumin against glutamate excitotoxicity, mainly focusing on the neuroprotective effects of curcumin on the expression of brain-derived neurotrophic factor (BDNF), which is involved in the development of depression (126). Exposure of rat cortical neurons to 10 μM glutamate for 24 h caused a significant decrease in the BDNF level, accompanied by reduced cell viability and enhanced cell apoptosis. Pretreatment of neurons with curcumin prevented the declines in BDNF expression and cell viability in a dose- and time-dependent manner. The study concluded that the neuroprotective effects of curcumin might be mediated through the BDNF signaling pathway (126). An investigation into the role of curcumin in reducing neuropathic pain in mice with streptozotocin-induced diabetes found that treating mice with insulin in combination with curcumin significantly reduced diabetic

neuropathic pain that was associated with a reduction in tumor necrosis factor-α level (127). Curcumin has also been shown to improve cognitive function in animal models. One study investigated the effect of curcumin on cognitive function and inflammation in diabetic rats. These rats exhibited cognitive deficits in association with enhancements in serum tumor necrosis factor-α levels, which were significantly attenuated after chronic treatment with curcumin (60 mg/kg) (91).

In addition to the activities discussed above, curcumin has shown potential activity against numerous other disorders and diseases, including those of eyes, lungs, liver, kidneys, and gastrointestinal and cardiovascular systems, as well as conditions such as fibrosis, wound healing problems, aging, asthma, endometriosis, and muscle wasting. The potential of curcumin to enhance memory and ameliorate morphine addiction has also been reported.

Curcumin analogues have also shown potential against animal models of human diseases. One study examined the effect of bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione, a bisdemethoxycurcumin analog (BDMC-A) on 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis in male Wistar rats (128). The study also compared the efficacy of BDMC-A with that of curcumin. Both BDMC-A and curcumin were equipotent in inhibiting the DMH-induced colon tumor incidence and normalizing histological changes. The study concluded that the presence of a terminal phenolic group and the conjugated double bonds in the central seven-carbon chain could be responsible for the agents' beneficial effects (128). In another study, curcumin and demethoxycurcumin were shown to reduce lead-induced memory deficits in male Wistar rats (129). In addition, tetrahydrocurcumin, another analogue of curcumin, has been shown to reduce the development of preneoplastic aberrant crypt foci initiated by 1,2-dimethylhydrazine dihydrochloride in the colons of mice (99). THC has also been shown to ameliorate oxidative stress-induced renal injury in mice (130). The anti-diabetic activity of THC in streptozotocin-nicotinamide-induced diabetes in rats has been investigated (131), and in one study, THC was found to possess more potent anti-diabetic activity than curcumin in type 2 diabetic rats (132).

Human level

Preclinical data obtained over the past several years have provided a strong foundation for testing curcumin's potential in human subjects. To date, approximately 50 clinical trials using human subjects have been completed. Although still in the initial phases, most of these trials have suggested that curcumin is safe and effective in a number of human diseases (Fig 2). The most promising effects of curcumin have been observed with cancer; inflammatory conditions; skin, eye, and neurological disorders; diabetic nephropathy; and pain.

In one of the early studies, curcumin was found to produce remarkable symptomatic relief in 62 patients with external cancerous lesions. The effect continued for several months in many patients, and an adverse reaction was noticed in only one patient (133).

A phase II clinical trial from our group evaluated the efficacy of oral curcumin in 25 patients with advanced pancreatic cancer. Patients received 8 g curcumin daily until disease progression, with disease restaging done every 2 months. Circulating curcumin was detectable in both glucuronide and sulfate conjugate forms, albeit at low steady-state levels, suggesting poor oral bioavailability. Two patients showed clinical biological response to curcumin; nevertheless, one additional patient showed a brief but marked tumor regression by 73%, and one patient had disease stability for >18 months. None of the patients showed toxic effects from curcumin. We concluded that oral curcumin is well tolerated and has biological activity in some patients with pancreatic cancer (134).

In some clinical trials, curcumin has been found to be useful in combination with existing drugs for pancreatic cancer patients. For example, one study evaluated the activity and feasibility of gemcitabine and curcumin combinations in patients with advanced pancreatic cancer. Seventeen patients who enrolled in the study were given 8 g curcumin by mouth daily, concurrently with gemcitabine (1000 mg/m^2, intravenously, three times a week for 4 weeks). Five patients discontinued curcumin after a few days to 2 weeks because of intractable abdominal fullness or pain. In two other patients, the dose of curcumin was reduced to 4 g/day because of abdominal complaints. One of 11 evaluable patients had a partial response, 4 had stable disease, and 6 had tumor progression. Time to tumor progression was 1–12 months (median, 2.5 months), and overall survival was 1–24 months (median, 5 months). It was concluded that low compliance for curcumin at a dose of 8 g/day, when taken with systemic gemcitabine, may prevent the use of high doses of oral curcumin needed to achieve a systemic effect (135).

A phase I/II study also evaluated the safety and efficacy of a combination therapy of curcumin with gemcitabine for pancreatic cancer. The study enrolled 21 patients with gemcitabine-resistant disease; they received 8 g oral curcumin daily in combination with gemcitabine. The primary endpoint was safety for the phase I portion of the trial and the feasibility of oral curcumin for phase II. The phase I portion of the study revealed the absence of limiting toxicities, and 8 g/day oral curcumin was selected as the recommended dose for the phase II portion. Curcumin was found to be well tolerated in this phase as well, and the plasma curcumin concentration ranged from 29 to 412 ng/ml in the five patients tested. It was concluded that combination therapy using 8 g oral curcumin daily with gemcitabine is safe and feasible for patients with pancreatic cancer (136). Other common cancers in which curcumin has shown efficacy either alone or in combination with existing drugs include prostate cancer, breast cancer, multiple myeloma, and adenoma.

The role of curcumin in improving body weight was evident from a recent study of patients with colorectal cancer. Curcumin administration (360 mg/day for 10–30 days) in these patients significantly improved body weight; the effect of curcumin was associated with a significant decrease in serum tumor necrosis factor-α levels (137).

Curcumin has shown promise against cardiac conditions as well. For example, one study evaluated the efficacy of curcumin in reducing lipid content in patients with acute coronary syndrome. Seventy-five patients with acute coronary syndrome participated in the study, and curcumin was administered at three different doses: low (15 mg/day, three times a day), moderate (30 mg/day, three times a day), and high (60 mg/day, three times a day). The effect of curcumin administration on total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels was investigated. Interestingly, curcumin was found to be more effective at low doses than at high doses in reducing total cholesterol and low-density lipoprotein cholesterol levels in these patients (138). Usharani *et al.* recently evaluated the potential of a standardized preparation of curcuminoids (NCB-02) against different oxidative stress and inflammatory markers in patients with T2DM. Seventy-two patients with T2DM were randomized to receive NCB-02 (two capsules containing 150 mg of curcumin, twice a day), atorvastatin (10 mg, once a day), or placebo for 8 weeks. Of the 72 patients, 67 completed the study. Curcumin treatment significantly improved endothelial function and reduced oxidative stress and inflammatory markers in diabetic patients (139).

Curcumin has also been shown to have potential against abnormal eye conditions, most importantly uveitis, an inflammation of the uvea, which is characterized by symptoms such as red eye, infected conjunctiva, pain, and decreased vision. In a clinical trial from Italy, curcumin was administered orally (600 mg, twice a day) for 12–18 months to 106 patients

with uveitis. Curcumin was well tolerated and reduced eye discomfort in more than 80% of patients after a few weeks of treatment (140).

One study investigated the effect of oral curcumin in combination with piperine on pain and the markers of oxidative stress in patients with tropical pancreatitis. Twenty patients were randomized to receive 500 mg of curcumin with 5 mg of piperine, 3 times a day, or placebo for 6 weeks. The effects on the pattern of pain and on the malondialdehyde and glutathione content in red blood cells were assessed. Curcumin therapy in combination with piperine was correlated with a significant reduction in the erythrocyte malondialdehyde content and a significant increase in glutathione levels in patients with tropical pancreatitis (141).

Thus, curcumin's potential as a therapeutic agent against many human diseases is clear. At the time of this writing, a search on clinicaltrials.gov revealed that more than 30 clinical trials are further evaluating curcumin's potential. Considering the promise curcumin holds against various diseases, we expect that completion of these clinical trials will provide further credence to the already established positive effects of curcumin.

CONCLUSIONS AND FUTURE PERSPECTIVES

The medicinal properties of turmeric, the source of curcumin, have been known for thousands of years to ancient people, but advancements in modern science have provided a scientific basis for the practice of using curcumin therapy against numerous human diseases. This polyphenol has been shown to target multiple signaling molecules and has shown activities at the cellular and organism levels that provide a basis for its use against multi-factorial human diseases. Although most of the currently available mono-targeted therapies are associated with numerous side effects, curcumin has been found to be safe for human use at gram doses. However, most of the known activities of curcumin are based only on *in vitro* and *in vivo* studies. Curcumin has yet not been approved for treatment of any human disease. Therefore, more extensive and well-controlled human studies are required to demonstrate this polyphenol's safety and efficacy. Future research should be focused on bringing this fascinating molecule to the forefront of therapeutic agents for the treatment of human diseases.

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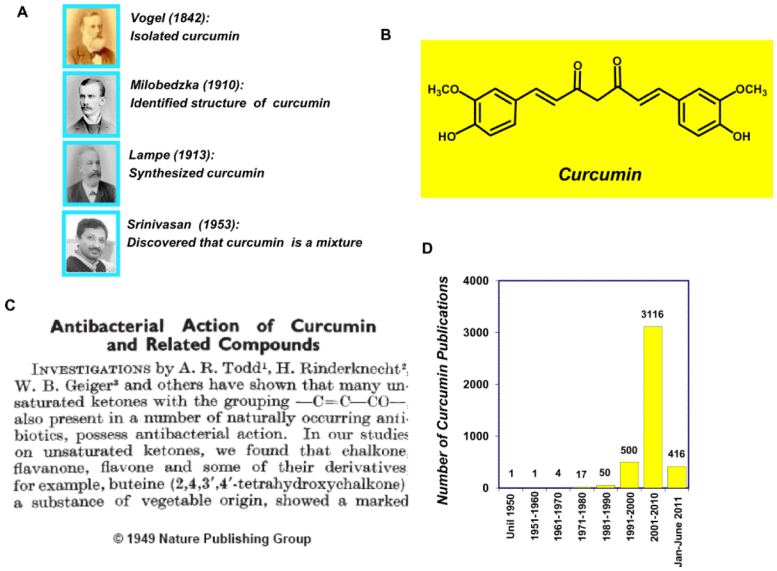

Figure 1.

A, Key curcumin discoverers (courtesy: JP Synder, Emory University, Atlanta, GA). *B*, Chemical structure of curcumin. *C*, The first article published in *Nature* showing curcumin's anti-bacterial activity (image used with permission from the Nature Publishing Group). *D*, The number of publications on curcumin has increased remarkably over the years (source: www.ncbi.nlm.nih.gov/sites/entrez).

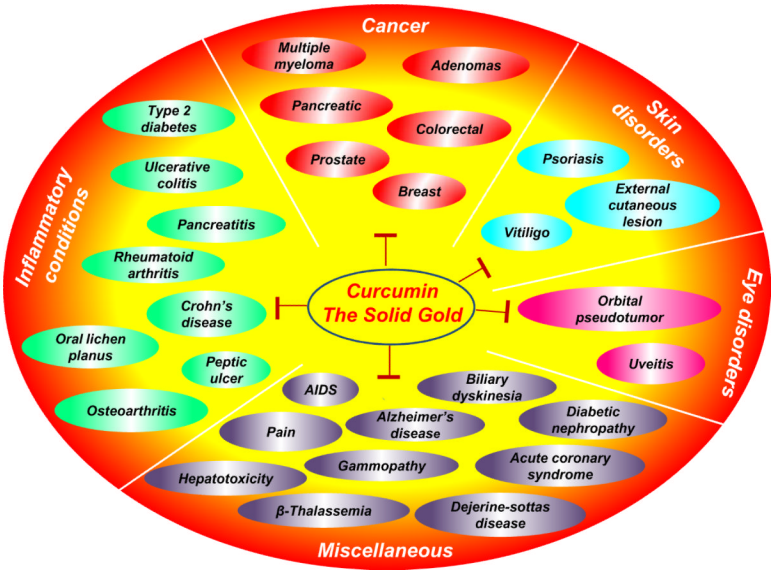

Figure 2.
The variety of human disorders against which curcumin's potential has been revealed by numerous clinical trials.

Table 1

Molecular targets of curcumin

Transcription factors	***Inflammatory mediators***
Activating transcription factor-3 ↓	C-reactive protein ↓
Activator protein-1 ↓	Interleukin-1β ↓
β-catenin ↓	Interleukin-2 ↓
CREB-binding protein ↓	Interleukin-5 ↓
C/EBP homologous protein ↓	Interleukin-6 ↓
Electrophile response element ↑	Interleukin-8 ↓
Early growth response gene-1 ↓	Interleukin-12 ↓
Hypoxia inducible factor-1α↓	Interleukin-18 ↓
Nuclear factor κ-B ↓	Interferon-γ ↓
Notch-1 ↓	Inducible nitric oxide synthase ↓
NFE2 related factor ↑	5-Lipoxygenase ↓
p53↑	Monocyte chemoattractant protein ↓
Peroxisome-proliferator-activated receptor -γ ↑	Migration inhibition protein ↓
Specificity protein-1 ↓	Macrophage inflammatory protein-1α↓
STAT-1 ↓	Prostate specific antigen ↓
STAT-3 ↓	
STAT-4 ↓	***Protein kinases***
STAT-5 ↓	Autophosphorylation-activated protein kinase ↓
Wilms' tumor gene 1 ↓	Ca^{2+}, phospholipid-dependent protein kinase C ↓
	c-jun N-terminal kinase ↓
Enzymes	cAMP-dependent protein kinase ↓
Acetylcholinesterase ↓	CSN-associated kinase ↓
Aldose reductase ↓	EGF receptor-kinase ↓
Arylamine N-acetyltransferases-1 ↓	Extracellular receptor kinase ↓
Beta-site APP-cleaving enzyme-1 ↓	Focal adhesion kinase ↓
CD13 ↓	IL-1 receptor-associated kinase ↓
DNA polymerase I ↓	IκB kinase ↓
DNA topoisomerase-II ↓	Janus kinase ↓
GTPase (microtubule assembly) ↓	Mitogen-activated protein kinase ↓
Glutathione reductase ↓	pp60c-src tyrosine kinase ↓
Glutathione-peroxidase ↓	Phosphorylase kinase ↓
Glutathione S-transferase ↑	Protein kinase A ↓
Hemeoxygenase-1 ↑	PI3K-Akt ↓
Ca^{2+}-dependent ATPase ↓	Protamine kinase ↓
Inosine monophosphate dehydrogenase ↓	
17β-HSD3 ↓	***Drug resistance proteins***
Ornithine decarboxylase ↓	Multi-drug resistance protein-1 ↓
Monoamine oxidase ↓	Multi-drug resistance protein-2 ↓
NADP(H):quinoneoxidoreductase -1 ↓	

Phospholipase D ↓
Thioredoxinreductase 1 ↓
Telomerase ↓
Ubiquitin isopeptidases ↓

Growth factors

Connective tissue growth factor ↓
Epidermal growth factor ↓
Fibroblast growth factor ↓
HER2 ↓
Hepatocyte growth factor ↓
Platelet derived growth factor ↓
Tissue factor ↓
Transforming growth factor-β1 ↓

Receptors

Androgen receptor ↓
Aryl hydrocarbon receptor ↓
Death receptor-5 ↓
EGF-receptor ↓
Endothelial protein C-receptor ↓
Estrogen receptor-α ↓
Fas ↑
Histamine (2)- receptor ↓
Interleukin 8-receptor ↓
Inositol 1,4,5-triphosphate receptor ↓
Integrin receptor ↓
Low density lipoprotein-receptor ↑
Transferrin receptor 1 ↓

Cell-cycle regulatory proteins

Cyclin D1 ↓
Cyclin E ↓
c-Myc ↓
p21 ↓

Adhesion molecules

Intracellular adhesion molecule-1 ↓
Endothelial leukocyte adhesion molecule-1 ↓
Vascular cell adhesion molecule-1 ↓

Cell-survival proteins

B-cell lymphoma protein-xL ↓
Cellular FLICE-like inhibitory protein ↓
Inhibitory apoptosis protein ↓
X-linked IAP ↓

Chemokines and chemokine receptor

Chemokine ligand 1 ↓
Chemokine ligand 2 ↓
Chemokine receptors 4 ↓

Invasion and angiogenesis biomarkers

Matrix metalloproteinase-9 ↓
Urokinase-type plasminogen activator ↓
Vascular endothelial growth factor ↓

Others

cAMP response element binding protein ↓
DNA fragmentation factor 40-kD subunit ↑
Fibrinogen ↓
Ferritin H and L ↓
Heat-shock protein 70 ↑
Iron regulatory protein ↓
Prion fibril ↓

17β-HSD3,17 β-hydroxysteroid dehydrogenase 3; Akt, AKT8 virus oncogenecellular homolog; APP, amyloid precursor protein; ATP, adenosine triphosphate; cAMP, cyclicadenosine monophosphate; CD, cluster of differentiation; CSN, COP9 signalosome; EGF, epidermal growth factor; FLICE, FADD like interleukin-1- β-converting enzyme; GTP, guanosine triphosphate; HER2, human EGF receptor 2; IAP, inhibitor of apoptosis; IL, interleukin; NADP, nicotinamide adenine dinucleotide phosphate; NFE2, nuclear factor-erythroid 2; PI3K, phosphoinositide 3-kinase; STAT, signal transducers and activators of transcription protein.

Table 2

Biological activities of curcumin as revealed by in vitro models

Anti-inflammatory	***Chemosensitization***	***Wound healing***
Mouse fibroblast (36)	Colon cancer (51)	Skin fibroblasts (66)
Blood monocytes (37)	Leukaemia (142)	
Multiple myeloma (38)	Bladder cancer (143)	***Anti-nociceptive***
BNHL (144)	Colorectal cancer (145)	Ganglion neurons (67)
Breast cancer (146)	Glioma (52)	
Mouse macrophage (147)	Ovarian cancer (148)	***Antiparasitic***
Myeloid leukaemia (32)	Breast cancer (148)	African trypanosomes (68)
Oesophageal epithelial cancer (149)	Lung cancer (150)	
	Prostate cancer (53)	***Schistosomicidal***
Antioxidant		*Schistosoma mansoni* (69)
Blood plasma (151)	***Radiosensitization***	
Blood platelets (151)	Glioma (52)	***Antimalarial*** (70)
Rat macrophages (46)	Prostate cancer (53)	
Brain membrane (47)	Cervical carcinoma (54)	***Nematocidal*** (71)
Rat liver microsomes (48)	Squamous cell carcinoma (55)	
Leukaemia (152)		
Multiple myeloma (152)	***Anti-proliferative***	
	Prostate cancer (56)	
Pro-apoptotic	Biliary cancer (57)	
Colon cancer (153)	Pituitary tumor (58)	
Esophageal adenocarcinoma (154)	Oral cancer (59)	
Biliary cancer (57)	Uterine leiomyoma(60)	
Leukaemia (155)		
Medulloblastoma (156)		
Multiple myeloma (152)	***Antimicrobial***	
Osteosarcoma (157)	*Candida albicans* (61)	
Prostate cancer (158)	*Candida glabrata* (62)	
Breast cancer (159)	Coxsackie virus (64)	

BNHL, B cell non-Hodgkin'slymphoma

Table 3

Biological activities of curcumin as revealed by animal models

Disease	Animal model	Disease	Animal model
Inflammatory condition		***Cancer treatment***	
Intestinal inflammation	Mouse (74)	Hepatocellular	Mouse (118)
Inflammatory bowel disease	Mouse (75, 76)	Breast	Mouse (119)
Chronic inflammation	Rat (77)	Ovarian	Mouse (120)
		Bladder	Rat (121)
Diabetes		Cholangiocarcinoma	Hamster (113)
Diabetes	Mouse (78)		
Type 2 diabetes	Rat (79)	***Psychiatric disorders***	
Type 2 diabetes	Mouse (80)	Depression	Mouse (122)
			Rat (123)
Obesity	Mouse (81)		
		Eye disorders	
Neurological disorders		Cataract	Rat (160)
Alzheimer's disease	Mouse (82, 83)	Diabetic retinopathy	Rat (161)
Parkinson's disease	Rat (85)	Corneal neovascularization	Rabbit (162)
Epilepsy	Rat (89, 90)		
Diabetic encephalopathy	Rat (91)	***Lung disorders***	
Encephalomyelitis	Mouse (92)	Acute lung injury	Rat (163)
Intracerebral hemorrhage	Mouse (93)	COPD	Mouse (164)
Spinal cord injury	Rat (94)	Emphysema	Mouse (165)
Cerebral malaria	Mouse (95)		
Convulsions	Mouse (96)	***Liver disorders***	
Brain ischemia	Rat (97)	Liver injury	Rat (166)
		Liver fluke infection	Hamster (167)
Cancer prevention			
Colon	Mouse (99)	***Gastro intestinal disorders***	
Esophageal	Rat (100)	Enterocolitis	Rat (168)
Lung	Mouse (101)	Gastric ulcer	Rat (169)
Kidney	Mouse (102)	*Helicobacter pylori* infection	Mouse (170)
Stomach	Rat (103)	Colitis	Mouse (75)
Liver	Rat (104)		
Mouth	Hamster (105)	***Renal disorders***	
Breast	Mouse (106)	Polycystic kidney disease	Mouse (171)
Bladder	Mouse (107)	Ischemic reperfusion injury	Rat (172)
Leukaemia	Mouse (106)		
Skin	Mouse (108)	***Cardiovascular disorders***	
Small intestine	Mouse (109)	Hypertension	Rat (173)
Pancreatic	Mouse (110)	Atherosclerosis	Mouse (174)
Brain	Mouse (111)	Ischemia reperfusion injury	Rabbit (175)

Disease	Animal model	Disease	Animal model
Prostate	Mouse (112)		
		Fibrosis	Hamster (176)
Cancer treatment			Rat (177)
Lymphoma	Mouse (14)		Mouse (178)
Melanoma	Mouse (114)		
Prostate	Mouse (115)	***Woundhealing***	Rat (179)
Pancreatic	Mouse (116)		Guinea pig (180)
Colorectal	Mouse (117)		Mouse (181)
Aging	Rat (182)		
	Mouse (183)		
	D. melanogaster (184)		
Miscellaneous conditions			
Asthma	Mouse (185)		
Endrometriosis	Rat (186)		
Mercury toxicity	Rat (187)		
Fatigue	Mouse (124, 125)		
Neuropathic pain	Mouse (127)		
Cognitive deficit	Rat (91)		
Coagulopathy	Rat (188)		
Memory enhancer	Rat (189)		
Morphine addiction	Mouse (190)		
Muscle wasting	Mouse (191)		

COPD, chronic obstructive pulmonary disease.