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Curcumin: A wonder anticancer drug

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Curcumin [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5di one] is the major yellow pigment extracted from turmeric, a commonly used spice, derived from the rhizome of the plant Curcuma longa. In India and Southeast Asia, turmeric has long been used as a treatment for inflammation, skin wounds and tumors. Curcumin has broad spectrum cancer chemo preventive activity in preclinical animal models. The anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumor cells, down-regulatetranscription factors NF-κB, AP-1 and Egr-1; down-regulate the expression of COX2, LOX, NOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules and cyclin D1; down-regulate growth factor receptors (such as EGFR and HER2); and inhibit the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases. In several systems, curcumin has been described as a potent antioxidant and anti-inflammatory agent. Evidence has also been presented to suggest that curcumin can suppress tumor initiation, promotion and metastasis. Pharmacologically, curcumin has been found to be safe. Human clinical trials indicated no dose-limiting toxicity when administered at doses up to 10 g/day. All of these studies suggest that curcumin has enormous potential in the prevention and therapy of cancer. The current review describes in detail the data supporting thesestudies.

Key words: Curcumin, Curcuminoids, Anticancer agent, Neurodegenerative disease, Drug delivery

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1. INTRODUCTION

Turmeric is a spice derived from the rhizomes of *Curcuma longa*, which is a member of the ginger family (*Zingiberaceae*). Rhizomes are horizontal underground stems that send out shoots as well as roots (Fig.1). The bright yellow color of turmeric comes mainly from fat-soluble, polyphenolic pigments known as curcuminoids). Curcumin, the principal curcuminoid found in turmeric, is generally considered its most active constituent. Other curcuminoids found in turmeric include demethoxycurcumin and bisdemethoxycurcumin (Fig.2). In addition to its use as a spice and pigment, turmeric has been used in India for medicinal purposes for centuries. More recently, evidence that curcumin may have anti-inflammatory and anticancer activities has renewed scientific interest in its potential to prevent and treat disease.

Tumeric is the dried ground rhizome of *Curcuma longa* Linn [1]. It is used as a spice in Indian, Southeast Asian, and Middle Eastern cuisines. Curcuminoids comprise about 2-9% of turmeric [2]. Curcumin is the most abundant curcuminoid in turmeric, providing about 75% of the total curcuminoids, while demethoxycurcumin provides 10-20% and bisdemethoxycurcumin generally provides <5%. Curry powder contains turmeric along with other spices, but the amount of curcumin in curry powders is variable and often relatively low [3]. Curcumin extracts are also used as food-coloring agents [4].

2. CURCUMIN

2.1 Significance

The health benefits of curcumin are extremely well known, stretching back to ancient times. It has been widely used in medicine as an anti-inflammatory, to treat digestive and liver problems, skin diseases, biliary disorders, anorexia, cough, hepatic disorders, bloody urine, hemorrhage, toothache, rheumatism, sinusitis, bruises and wounds. To take one example, curcumin has been found to inhibit the growth of the Helicobacter pylori bacteria, which has been linked to gastric ulcers and gastric cancer. Studies show that curcumin may help fight infections some cancers, reduce inflammation, and treat digestive problems. Several uses

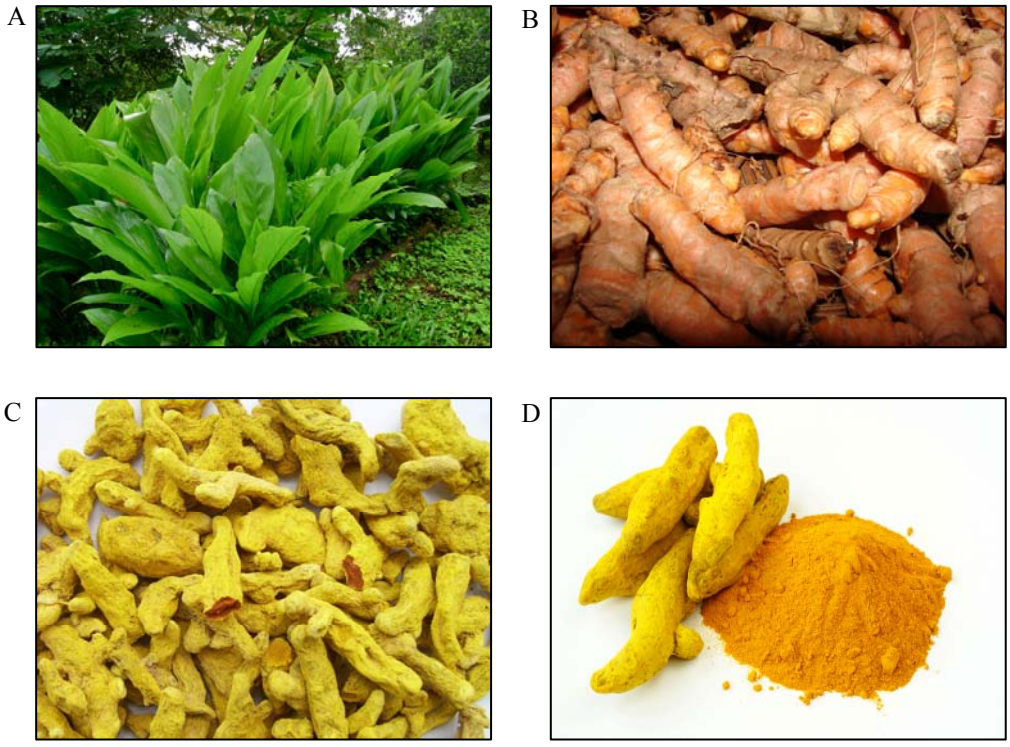

Fig.1. Turmeric (A) Plant, (B) Fresh rhizome, (C) Dried rhizome, (D) Powdered rhizome

have been proposed for Curcumin. Many of these are supported by scientific research. Others are supported by centuries of use and tradition.

2.2 Medical uses

In October, 2010, it was reported that curcumin, when combined with the drug cisplatin, "enhances chemotherapy's suppression of head and neck cancer cell growth." The study, conducted by researchers Eric Srivatsan and Marilene Wong, who have investigated curcumin's anti-cancer properties for six years, builds on previous research demonstrating curcumin's ability to suppress growth of other cancer Curcumin and turmeric are being studied for their effectiveness against a wide range of other conditions, ranging from arthritis to Alzheimer's disease, according to Medline Plus.

2.3 Considerations

Curcumin is used as a coloring agent in many foods, including mustard, margarine, processed cheese, curry powder, soft drinks, cakes and candy. Women in India have long used turmeric as an anti-aging lotion for cramp and and an additive in cosmetics. Turmeric is likely safe when used in food. It is possibly safe when used in medicinal amounts, although side effects can include nausea or diarrhea. Pregnant women should not take curcumin, because it could cause a miscarriage.

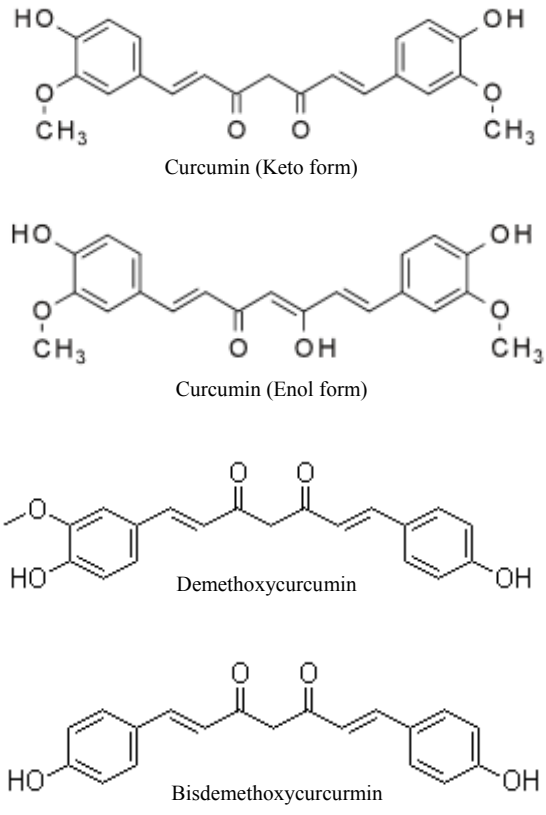

Fig.2. Chemical structure of curcuminoids (Curcumin, Demethoxycurcumin, Bisdemethoxycurcumin)

3. CHEMISTRY OF CURCUMIN

Curcumin incorporates several functional groups. The aromatic ring systems, which are polyphenols are connected by two α,β-unsaturated carbonyl groups. The diketones form stable enols or are easily deprotonated and form enolates, while the α,β-unsaturated carbonyl is a good Michael acceptor and undergoes nucleophilic addition. The structure was first identified in 1910 by J. Miłobędzka, StanisławKostanecki and Wiktor Lampe [3].

4. EXTRACTION OF CURCUMIN

Curcumin is the main component of the spice plant turmeric, which is used in curry and also for medicinal purposes. It is a water soluble orange-yellow colored powder. Quicker and better extraction methods of curcumin will aid research into the medicinal uses of curcumin and turmeric. Up until 2009, curcumin was extracted from the dried roots of turmeric plants by a process called liquid solid extraction. But in a study reported in 2009 in "National Product Communications," researchers found that a better method, one that uses ultrasound in the extraction process, had been discovered.

4.1 Liquid solid extraction

In liquid solid extraction, a solvent is added to a solid, such as a turmeric root. As the website DSB science explains, insoluble material is separated by gravity or vacuum filtration, and soluble material, in this case curcumin is "extracted" in the solvent. A sequence of solvents can be used to separate complex mixtures into separate groups. The filtered solution can then be used as a liquid or the solvent can be evaporated to recover the extracted material in powder or crystalline form.

4.2 Ultrasound-assisted extraction

In 2009, the U.S. National Library of Medicine website, PubMed, published an abstract from a study conducted at Jadavpur University in India. The abstract discussed an effective alternative to the liquid solid extraction of curcumin. Researchers discovered that the ulitilization of ultrasound in extracting curcumin was not only much quicker; 70 minutes as opposed to many hours--the extraction could be done with greater recovery of curcumin on a more consistent basis. "This study clearly shows that this method can be effectively utilized for cutting down long extraction times of botanicals to just a few minutes without the aid of heat," the study authors reported.

5. BIOLOGICAL ACTIVITIES OF CURCUMIN

5.1 Antioxidant Activity

Curcumin is an effective scavenger of reactive oxygen species and reactive nitrogen species in the test tube (*in vitro*) [5,6]. However, it is not clear whether curcumin acts directly as an antioxidantin vivo. Due to its limited oral bioavailability in humans (see Metabolism and Bioavailability above), plasma and tissue curcumin concentrations are likely to be much lower than that of other fat-soluble antioxidants, such as alpha-tocopherol (vitamin E). However, the finding that oral curcumin supplementation (3.6g/day) for seven days decreased the number of oxidative DNA adducts in malignant colorectal tissue suggests that curcumin taken orally may reach sufficient concentrations in the gastrointestinal tract to inhibit oxidative DNA damage [7]. In addition to direct antioxidant activity, curcumin may function indirectly as an antioxidant by inhibiting the activity of inflammatory enzymes or by enhancing the synthesis of glutathione, an important intracellular antioxidant (see below).

5.2 Anti-inflammatory activity

The metabolism of arachidonic acid in cell membranes plays an important role in the inflammatory response by generating potent chemical messengers known as eicosanoids [8]. Membrane phospholipids are hydrolyzed by phospholipase A2 (PLA2), releasing arachidonic acid, which may be metabolized by cyclooxygenases (COX) to form prostaglandins and thromboxanes, or by lipoxygenases (LOX) to form leukotrienes. Curcumin has been found to inhibit PLA2, COX-2, and 5-LOX activities in cultured cells [9]. Although curcumin inhibited the catalytic activity of 5-LOX directly, it inhibited PLA2 by preventing its phosphorylation and COX-2 mainly by inhibiting itstranscription. Nuclear factor-kappa B (NF-kB) is a transcription factor that binds DNA and enhances the transcription of the COX-2 gene as well as other pro-inflammatory genes, such as inducible nitric oxide synthase (iNOS). In inflammatory cells, such as macrophages, iNOS catalyzes the synthesis of nitric oxide, which can react with superoxide to form peroxynitrite, a reactive nitrogen species that can damage proteins and DNA. Curcumin has been found to inhibit NF-kB-dependent gene transcription [10], and the induction of COX-2 and iNOS in cell culture and animal studies [11,12].

5.3 Effects on biotransformation enzymes involved in carcinogen metabolism

Biotransformation enzymes play important roles in the metabolism and elimination of a variety of biologically active compounds, including drugs and carcinogens. In general, phase I biotransformation enzymes, including those of the cytochrome P450 (CYP) family, catalyze reactions that increase the reactivity of hydrophobic (fat-soluble) compounds, preparing them for reactions catalyzed by phase II biotransformation enzymes. Reactions catalyzed by phase

II enzymes generally increase water solubility and promote the elimination of these compounds [13]. Although increasing biotransformation enzyme activity may enhance the elimination of potential carcinogens, some carcinogen precursors (procarcinogens) are metabolized to active carcinogens by phase I enzymes [14]. CYP1A1 is involved in the metabolic activation of several chemical carcinogens. In cell culture and animal studies, curcumin has been found to inhibit procarcinogen bioactivation or measures of CYP1A1 activity [15-18]. Increasing phase II biotransformation enzyme activity is generally thought to enhance the elimination of potential carcinogens. Several studies in animals have found that dietary curcumin increased the activity of phase II enzymes, such as glutathione S-transferases (GSTs) [19-21]. However, curcumin intakes ranging from 0.45-3.6g/day for up to four months did not increase leukocyte GST activity in humans [22].

5.4 Inductions of cell cycle arrest and apoptosis

After a cell divides, it passes through a sequence of stages—collectively known as the cell cycle—before it can divide again. Following DNA damage, the cell cycle can be transiently arrested to allow for DNA repair or, if the damage cannot be repaired, for activation of pathways leading to cell death (apoptosis) [23]. Defective cell-cycle regulation may result in the propagation of mutations that contribute to the development of cancer. Curcumin has been found to induce cell-cycle arrest and apoptosis in a variety of cancer cell lines grown in culture [24,25-29]. The mechanisms by which curcumin induces apoptosis are varied but may include inhibitory effects on several cell-signaling pathways. However, not all studies have found that curcumin induces apoptosis in cancer cells. Curcumin inhibited apoptosis induced by the tumor suppressor protein p53 in cultured human colon cancer cells [30,31] and one study found that curcumin inhibited apoptosis induced by several chemotherapeutic agents in cultured breast cancer cells at concentrations of 1-10 micromoles/liter.

5.5 Effects on autophagic cell death

Autophagy is a catabolic process in which cells break down their own components via engulfment in vacuoles and degradation through the lysosomal system. The hallmark of autophagy is thus the formation of these so-called "autophagosomes", double layered vacuoles which contain cytoplasmic proteins and organelles targeted for degradation upon fusion with the lysosome [32]. Autophagy is a housekeeping process by which cells may dispose of old or damaged cytoplasmic organelles and proteins, and also serves an adaptive function under conditions of nutrient stress by allowing cells to recycle endogenous biosynthetic substrates such as amino acids.[133] In addition to promoting cell survival and function, autophagy is also a method by which cells may undergo programmed cell death [33]. Autophagy is considered Type II programmed cell death (apoptosis is type I and necrosis is type III) and, thus has come under interest as a potential process that may be exploited in the development of anti-cancer chemotherapeutics.The possible roles of autophagy in carcinogenesis as well as tumor regression in response to therapy are still being elucidated, with seemingly conflicting studies suggesting that induction of autophagy enhances cell death in certain tumor types while mediating chemotherapeutic resistance in others. On one hand, there is evidence that autophagy may be employed by cancer cells to facilitate growth under the stressful metabolic conditions commonly encountered in the tumor microenvironment (such as hypoxia and decreased availability of glucose and other nutrients due to poor vascularization) [34-36]. In addition, the induction of autophagy as an adaptive response mediating resistance to chemotherapy has been observed in multiple tumor types including malignant gliomas, lymphoma, breast, lung and hepatocelluar carcinomas (37-43].On the other hand, there is genomic evidence that disruption of autophagy is associated with tumorigenesis, as suggested by the mono-allelic deletion of the autophagy-related gene beclin-1 in a high percentage of breast and ovarian cancers [44]. Studies in mice have demonstrated that monoallelicdeletion of beclin-1 increases the frequency of spontaneous malignancies including hepatocellular carcinoma, B cell lymphoma and lung adenocarcinomas in beclin-1 +/- mice, suggesting beclin-1 as a haploinsufficent tumor suppressor gene [45]. In addition it was found that monoallelic deletion of beclin-1 resulted in increased cellular proliferation, decreased autophagy as measured by expression of the autophagosome membrane protein LC3, and accelerated the development of hepatitis B-induced premalignant lesions [46]. Conversely, transfection of beclin-1 into MCF-7 breast cancer cells (which express a very low baselinelevel of the protein) inhibited the cellular proliferation and tumorigenicity in a nude mouse xenograft model [44].While autophagy appears to play a role in mediating chemoresistance in certain cancers as described above, there is also data supporting that autophagy may also induce non-apoptotic cell death in response to chemotherapy. In human (MCF-7) estrogen-receptor positive breast cancer, both tamoxifen and paclitaxel were found to induce autophagic cell death in cell culture (47-48]. Arsenic trioxide was found to induce autophagic cell death in malignant glioma, leukemia and fibrosarcoma cells, and in leukemia this effect was accompanied by up-regulation of beclin-1 [49-51]. The small molecule tyrosine kinase inhibitor imatinib has been shown to induce cellular autophagy, an effect that may sensitize drug-resistant Kaposi sarcoma cells [52,53]. Interestingly, imatinib's induction of autophagy seems to decrease its effectiveness in chronic myelogenous leukemia (CML) and blocking of autophagy lead to increased apoptotic cell death [54]. Studies done in malignant glioma cells have also yielded varying results; while autophagy induced by arsenic trioxide resulted in increased cell death, treatment with temolozamide and

etoposide led to an increase in ATP that exerted a protective effect(55,56]. Likewise, there is controversy regarding the effect of autophagy induction on radiation sensitivity. Studies in breast cancer have suggested that vitamin D-dependant radiosensitization is mediated through autophagy, while autophagy has demonstrated bothradiosensitizing and dampening effects in malignant gliomas [57-59].Curcumin has been shown to be an inducer of autophagic cell death in chronic myelogenous leukemia, esophageal cancer and malignant glioma cells [60-62]. In malignant glioma cells, curcumin induced G2/M cell cycle arrest and non-apoptotic autophagic death. This effect was mediated through curcumin's inhibition of the Akt/mTOR/p70S6 kinase pathway and inhibition of the ERK1/2 pathway, which are both involved in the regulation of autophagy induced by nutrient stress. In addition, these effects were confirmed via activation of the Akt/mTOR/p70S6 pathway which decreased curcumin-induced autophagic cell death as well as activation of the ERK1/2 pathway, which resulted in inhibition of autophagy and induction of apoptosis [63,64]. While the current data on autophagy and cancer is far from providing a consensus, it is evident that regulation of this process may play an important role in tumorigenesis and response to therapy thus making pharmacologic modulators of autophagy attractive candidates for further study.

5.6 Inhibition of tumor invasion and angiogenesis

Cancerous cells invade normal tissue with the aide of enzymes called matrix metalloproteinases. Curcumin has been found to inhibit the activity of several matrix metalloproteinases in cell culture studies [65-69]. To fuel their rapid growth, invasive tumors must also develop new blood vessels by a process known as angiogenesis. Curcumin has been found to inhibit angiogenesis in cultured vascular endothelial cells [70,71] and in an animal model [72].

Note: It is important to keep in mind that many of the biological activities discussed above were observed in cells cultured in the presence of curcumin at higher concentrations than are likely to be achieved in cells of humans consuming curcumin orally.

6. DISEASE TREATMENT

6.1 Cancer

The ability of curcumin to induce apoptosis in a variety of cancer cell lines and its low toxicity have led to scientific interest in its potential for cancer therapy as well as cancer prevention [73]. To date, most of the controlled clinical trials of curcumin supplementation in cancer patients have been Phase I trials. Phase I trials are clinical trials in small groups of people, which are aimed at determining bioavailability, safety, and early evidence of the efficacy of a new therapy [74]. A phase I clinical trial in patients with advanced colorectal cancer found that doses up to 3.6g/day for four months were well-tolerated, although the systemic bioavailability of oral curcumin was low [75]. When colorectal cancer patients with liver metastases took 3.6g/day of curcumin orally for seven days, trace levels of curcumin metabolites were measured in liver tissue, but curcumin itself was not detected [76]. In contrast, curcumin was measurable in normal and malignant colorectal tissue after patients with advanced colorectal cancer took 3.6 g/day of curcumin orally for seven days [77]. These findings suggest that oral curcumin is more likely to be effective as a therapeutic agent in cancers of the gastrointestinal tract than other tissues. Phase II trials are clinical trials designed to investigate the effectiveness of a new therapy in larger numbers of people, and to further evaluate short-term side effects and safety of the new therapy. Phase II clinical trials of curcumin in patients with colorectal cancer are currently under way [78]. A phase II clinical trial in patients with advanced pancreatic cancer found that curcumin exhibited some anticancer activity in two out of 21 patients; however, bioavailability of curcumin was extremely poor [79]. Due to low systemic bioavailability and the fact that curcumin is hydrophobic, the authors proposed that intravenous administration of liposome-encapsulated curcumin be used in future clinical trials [79].

6.2 Inflammatory diseases

Although the anti-inflammatory activity of curcumin has been demonstrated in cell culture and animal studies, few controlled clinical trials have examined the efficacy of curcumin in the treatment of inflammatory conditions. A preliminary intervention trial that compared curcumin with a nonsteroidal anti-inflammatory drug (NSAID) in 18 rheumatoid arthritis patients found that improvements in morning stiffness, walking time, and joint swelling after two weeks of curcumin supplementation (1,200mg/day) were comparable to those experienced after two weeks of phenylbutazone (NSAID) therapy (300mg/day) [80]. A placebo-controlled trial in 40 men who had surgery to repair an inguinal hernia or hydrocele found that oral curcumin supplementation (1,200mg/day) for five days was more effective than placebo in reducing post-surgical edema, tenderness and pain, and was comparable to phenylbutazone therapy (300mg/day) [81]. Two uncontrolled studies found that oral curcumin (1,125mg/day) for 12 weeks or longer improved anterior uveitis and idiopathic inflammatory orbital pseudotumor, two inflammatory conditions of the eye [82,83]. However, without a control group, it is difficult to draw conclusions regarding the anti-inflammatory effects of curcumin in these conditions. Larger randomized controlled trials are needed to determine whether oral curcumin supplementation is effective in the treatment of inflammatory diseases, such as rheumatoid arthritis.

6.3 Cystic fibrosis

Cystic fibrosis is a hereditary disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [84]. CFTR is a transmembrane protein that acts as a chloride channel and plays a critical role in ion and fluid transport. In the lungs, CFTR mutations ultimately result in increased mucus concentration and decreased mucus clearance, which leads to progressive lung disease. The most common CFTR mutation contributing to the development of cystic fibrosis is the delta F508 mutation, which results in CFTR protein misfolding and degradation before the protein can be targeted to the cell membrane. However, the mutated protein retains some ability to function as a chloride channel if it can be inserted in the cell membrane. In 2004, a study in mice with the delta F508 mutation found that oral curcumin administration corrected abnormal ion transport and improved the survival of these mice [85]. However, unlike humans, mice with the delta F508 mutation experience only the digestive complications of cystic fibrosis without the lung complications, and treatment benefits in the mouse model are not always realized in humans [84]. More recently, another group of scientists was unable to duplicate the beneficial effects of curcumin in the same mouse model given the same dose of curcumin [87]. It is unclear whether curcumin supplementation will be of benefit to humans with cystic fibrosis. In a phase I clinical trial funded by the Cystic Fibrosis Foundation, curcumin did not correct the function of the defective CRTR protein; a follow-up study using higher curcumin dosages is currently under way [88]. Until the safety and efficacy of curcumin in individuals with cystic fibrosis has been evaluated in clinical trials, the Cystic Fibrosis Foundation does not recommend the use of curcumin as a therapy for cystic fibrosis [89].

6.4 Alzheimer's disease

Aging baby boomers are becoming increasingly aware of the risk of Alzheimer's disease, first in their parents and eventually in their own generation. Curcumin may offer some hope as a treatment for this devastating disease. Research is still ongoing, but there is evidence that Curcumin could offer significant protection against neurotoxic and genotoxic agents. One research team concluded that "In view of its efficacy and apparent low toxicity, this Indian spice component shows promise for the prevention of Alzheimer's disease."

In Alzheimer's disease, a peptide called amyloid beta forms aggregates (oligomers), which accumulate in the brain and form deposits known as amyloid plaques [90]. Inflammation and oxidative damage are also associated with the progession of Alzheimer's disease [91]. Curcumin has been found to inhibit amyloid beta oligomer formation *in vitro* [74]. When injected peripherally, curcumin was found to cross the blood brain barrier in an animal model of Alzheimer's disease [92]. In animal models of Alzheimer's disease, dietary curcumin has decreased biomarkers of inflammation and oxidative damage, amyloid plaque burden in the brain, and amyloid beta-induced memory deficits [92-95]. It is not known whether curcumin taken orally can cross the blood brain barrier or inhibit the progression of Alzheimer's disease in humans. As a result of the promising findings in animal models, clinical trials of oral curcumin supplementation in patients with early Alzheimer's disease are under way [96,97]. The results of a 6-month trial in 27 patients with Alzheimer's disease found that oral supplementation with up to 4 g/day of curcumin was safe [98]. Larger controlled trials are needed to determine whether or not oral curcumin supplementation is efficacious in Alzheimer's disease.

7. DISEASE PREVENTION

7.1 Cancer

The ability of curcumin to induce apoptosis in cultured cancer cells by several different mechanisms has generated scientific interest in the potential for curcumin to prevent some types of cancer [99]. Oral curcumin administration has been found to inhibit the development of chemically-induced cancer in animal models of oral [100,101], stomach [102,103], liver [104], and colon [105-107] cancer. $Apc^{Min/+}$ mice have a mutation in the Apc (adenomatous polyposis coli) gene similar to that in humans with familial adenomatous polyposis, a genetic condition characterized by the development of numerous colorectal adenomas (polyps) and a high risk for colorectal cancer. Oral curcumin administration has been found to inhibit the development of intestinal adenomas in $Apc^{Min/+}$ mice [108,109]. In contrast, oral curcumin administration has not consistently been found to inhibit the development of mammary (breast) cancer in animal models [110-112].

Although the results of animal studies are promising, particularly with respect to colorectal cancer, there is presently little evidence that high intakes of curcumin or turmeric are associated with decreased cancer risk in humans. A phase I clinical trial in Taiwan examined the effects of oral curcumin supplementation up to 8 g/day for three months in patients with precancerous lesions of the mouth (oral leukoplakia), cervix (high grade cervical intraepithelial neoplasia), skin (squamous carcinoma in situ), or stomach (intestinal metaplasia) [113]. Histologic improvement on biopsy was intraepithelial neoplasia, two out of six patients with squamous carcinoma in situ, and one out of six patients with intestinal metaplasia. However, cancer developed in one out of seven patients with oral leukoplakia and one out of four patients with cervical intraepithelial neoplasia by the end of the treatment period. This study was designed mainly to examine the bioavailability and safety of oral curcumin, and interpretation of its results is limited by the lack of a control group for comparison. As a result of the promising findings in animal studies, several controlled clinical trials in humans designed to evaluate the effect of oral curcumin

supplementation on precancerous colorectal lesions, such as adenomas, are under way.

In experiments on tumors, Curcumin was shown to "directly and irreversibly" affect the growth of new cancers. It appears to suppress the onset of tumors as well as their growth and metastasis. Doctors at the National Institute of Health are excited about the possibilities of using Curcumin to treat cancer. In their words, Curcumin is, "an exciting compound because it can be taken orally and may not have any side effects for cancer patients."

7.2 Curcumin and lung cancer

Curcumin also appears to reduce the risk of lung cancer associated with smoking. Experiments on Curcumin and nicotine, a powerful cancer-causing chemical, showed that Curcumin reduced the effects of nicotine as a carcinogen by 50%. Curcumin specifically showed significant potential in the reducing the chances of lung cancer, colon cancer, and as a preventive for cancer in the liver, duodenum, and kidneys. Doctors stress that more research is needed, but the initial results about Curcumin and cancer are very encouraging. These scientific findings seem to be confirming what millions of Indians already know about the health benefits of curry, Turmeric, and Curcumin.

7.3 Curcumin and prostate cancer

Curcumin appears to slow or prevent the growth of prostate cancer, the most common cancer in American men. Prostate cancer is the second leading cause of cancer deaths in American men, surpassed only by lung cancer in total number of deaths. On average, an American man has about a 30 percent risk of having prostate cancer in his lifetime. As you age, your risk of prostate cancer increases. By age 50, up to one in four men have some cancerous cells in the prostate gland. By age 80, that number has increased to one in two. In a study of prostate cancer cells, Curcumin inhibited cell growth, thus demonstrating a potential for slowing the progression of prostate cancer. Researchers concluded that Curcumin may provide "an alternative, nontoxic" means of treating prostate cancer in men.

7.4 Curcumin and breast cancer

Curcumin has shown potential as a treatment for breast cancer. Researchers in China found that Curcumin exerts multiple suppressive effects on human breast carcinoma cells. Other researchers note that the results of studies on Curcumin and breast cancer are mixed and that more research is needed. As always, consult your doctor before adding any herbal supplements to your treatment regimen.

7.5 Curcumin and colorectal cancer

Colorectal cancer is one of the leading causes of cancer deaths in the Western world. More than 56,000 newly diagnosed colorectal cancer patients die each year in the United States. Researchers at the University of California studied the effects of Curcumin on colorectal cancer and found that "Curcumin should be considered as a safe, non-toxic, and easy to use chemotherapeutic agent for colorectal cancers arise in the setting of chromosomal instability as well as microsatellite instability." Treatment with Curcumin has fewer side effects than some other cancer treatment. One researcher wrote, "Naturally occurring COX-2 inhibitors such as Curcumin and certain phytosterols have been proven to be effective as chemopreventive agents against colon carcinogenesis with minimal gastrointestinal toxicity."

8. POTENTIAL RISKS AND SIDE EFFECTS

Extensive in vivo toxicity studies have been performed with turmeric Oleoresin (85% curcumin) which led to it being placed on the FDA's GRAS (generally recognized as safe) list [54]. Kawanishi*et al.* (2005) remarked that curcumin, like many antioxidants, can be a "double-edged sword" where, in the test tube, anticancer and antioxidant effects may be seen in addition to pro-oxidant effects [66]. Carcinogenic effects are inferred from interference with the p53tumor suppressor pathway, an important factor in human colon cancer [67]. Carcinogenic and LD_{50} tests in mice and rats, however, have failed to establish a clear relationship between tumorogenesis and administration of curcumin in turmeric oleoresin at >98% concentrations [68]. Other in vitro and in vivo studies suggest that curcumin may cause carcinogenic effects under specific conditions [69,70].

Clinical studies in humans with high doses (2–12g) of curcumin have shown few side effects, with some subjects reporting mild nausea or diarrhea [71]. More recently, curcumin was found to alter iron metabolism by chelating iron and suppressing the protein hepcidin, potentially causing iron deficiency in susceptible patients [72]. Further studies seem to be necessary to establish the benefit/risk profile of curcumin [73].

9. CONCLUSIONS

As a natural product, curcumin is both non-toxic as well as diversified in its inhibitory effects on a multitude of pathways involved in carcinogenesis and tumour formation. While the compound alone has shown some anti-tumour effects in HNSCC, curcumin's lack of systemic toxicity and broad-reaching mechanism of action may make it best suited as an adjuvant therapy for head and neck cancers that are resistant to currently available therapy. Multiple molecular pathways such as NF-κB activation, EGFR and PI3/AKT/Mtor signaling, STAT3 expression, the MAP kinase cascade and VEGF-mediated angiogenesis have been shown to be deregulated in HNSCC and represent potential therapeutic targets. While some promising results from such

targeted therapies have been obtained, the complexity of interaction between these signaling pathways may contribute to the limited clinical response seen with the use of single-agent biologic therapies. Nowadays Curcuminlargly use as a antiinflamatory, antimalarial, analgesicagent. It is one of the best medicines to treat various life threatning diseases like Alzheimer, huntingtons diseases, types of cancer, AIDS.

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