International Journal of Tropical Medicine 11 (6): 226-231, 2016
ISSN: 1816-3319

Proven Health Benefits of Curcumin as a Medicinal Herb

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Abstract: Curcumin, a phytonutrient extracted from the rhizome of Curcuma longa has been found to possess potent pharmacological effects from antioxidant properties to anti-inflammatory, antimicrobial/antiviral and even cancer chemopreventive effects. Since there have been no reports about the toxicity, genotoxicity or teratogenicity of curcumin, this natural phenolic compound has been extensively used as a safe agent in numerous preclinical and clinical studies. Several studies have evaluated the effects of curcumin as a natural anti-inflammatory agent, on the proliferation of blood mononuclear cells and vascular smooth muscle cells based on tritiated thymidine uptake. Curcumin has been proved to suppress mitogen-induced proliferation of blood mononuclear cells and inhibit neutrophil activation, smooth muscle cell proliferation and mixed lymphocyte reaction. Recent research on animal models of cancer has also confirmed the cancer chemopreventive properties of curcumin. A previous study on azoxymethane-induced colon, small intestine and stomach cancers in mice reported the reduced incidence and size of tumors following the dietary administration of 0.5-2% curcumin. The beneficial effects of curcumin can be attributed to its effects on cellular enzymes and ability to regulate gene transcription and induce apoptosis. Moreover, daily administration of curcumin (300-800 mg/day) for 21 days was associated with symptom relief in 67 patients with biliary disease. Curcumin can regulate the activity of various enzymes through either direct interaction (e.g. ,cyclooxygenase-2, 5-lipoxygenase and inducible nitric oxide synthase) or regulation of gene transcription via the inhibition of transcription factors (e.g., adaptor protein complex 1, early growth response factor-1 and STAT-3) and their related signaling pathways. The beneficial effects of curcumin have been documented by numerous animal studies and human clinical trials. This phytonutrient can downregulate blood cholesterol levels, prevent platelet aggregation and myocardial infarction, alleviate the symptoms of type II diabetes and decrease the complications of several diseases including rheumatoid arthritis, multiple sclerosis and Alzheimer's disease. It can also be useful in the treatment of both acute and chronic inflammations. Studies on chemically induced rodent models of colitis have confirmed the benefits of curcumin in the treatment of inflammatory bowel disease. In fact, this phenolic compound was found to significantly reduce mortality, enhance local cytokine and chemokine production, promote neutrophil infiltration and improve colonic morphology.

Key words: Curcumin, drugs, effects, curcumin, morphology

INTRODUCTION

Indian traditional medicine has traditionally used Turmeric for its medicinal values. Also it has been used in "ayurvedic medicine" as an antiseptic and wound healing salve and an anti-inflammatory compound. Curcumin is derived from the rhizome of Curcuma longa. According to the result of continuing studies and clinical trials, Curcumin as a natural phenolic compound possesses various pharmacological potency and can be influential in treatment of a number of diseases thanks to its antioxidant, anti-inflammatory and antimicrobial/antiviral properties; besides, it can be considered as a cancer chemo-preventive agent. Curcuma longa is a perennial herb which measures up to 60-90 cm in height. The plants leaves are 30-40 cm in length and 10-15 cm in width with prominent mid-rib underneath. The flowers are pale-yellow and grow in autumnal spikes. It's over ground stem is usually short and tapered at the base while underground part is modified into a rhizome (Scartezzini and Speroni, 2000). Curcuma Longa belongs to Zingirberaceae (ginger family) and is naturally distributed or widely cultivated

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throughout the tropical and subtropical regions of the world including India, China, Indonesia, Jamaica and Haiti (Anonymus, 2001) . In addition to Curcuma longa there are many other plants that produce phenolic compounds with structural similarities to Curcuminoids (Aggarwal *et al*., 2003) .

MATERIALS AND METHODS

Curcumin can inhibit rancidity of foods due to its antioxidant property and can help providing food stuffs with less free radicals and oxidant fats. The antioxidant property in Curcumin can preserve the curry for longer time while without it the curry can become rancid. Curcumin is almost insoluble in water at acidic and neutral pH but it is practically in oil and alkali. Curcuminoids are hardly soluble in such solvents as hydrocarbon solvents. There have been reports on preparations of water-soluble Curcumin through incorporating it into various surfactant micellar systems (acetone, methanol and ethanol) (Gupta *et al*., 1999). Also in another study the treatment of muscle injury led to faster restoration using Curcumin. Rafatullah in his experimental study observed significant anti ulcerogenic activity in rats by ethanol extract of turmeric. The oral dose of extract 500 mg kg^{-1} showed highly significant protective effect against cytodestructive agents. A paste of fresh rhizome of turmeric, on applying over the cut end of the umbilical cord of a newborn, showed quick healing effect. Cohly investigated the turmeric wound-healing feature who noticed that it lowered the Nitric Oxide Synthetase (NOS) levels and performed effectively in chronic and acute wounds. Concerning antibiotic properties, turmeric demonstrated a variety of antibacterial activities (Omoloso, 2001). Negi in his study put the turmeric oil product of Curcumin processing under anti-bacterial investigation and found it as effective vs. Bacillus cereus, Bacillus coagulans and Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa (Toda *et al*., 1985). Ayurvedic traditional system of medicine considers turmeric as an effective remedy in urinary disorders, on account of its pungent, bitter and hot properties as well as its specific antiseptic property (Nadkarni, 1976). Recent experimental studies have concluded that Curcumin administration could be promising in treatment of renal disorders. As a traditional treatment method the turmeric rhizome in some parts of the world like Brunes etc. Is utilized for urinary infection. Kolamma quoted Vangasena (an ancient Ayurvedic sage) as saying that turmeric was good for calculus. Leskover found that oral administration of Curcumin and Curcuminoids were effective in inhibition of urinary calculi formation Venkatesan investigated the nephroprotective effect of Curcumin in rats. In their study, they investigated the influence of Curcumin on Adriamycin (ADR)-induced nephrosis in rats and concluded that Curcumin was effective in injury prevention. Curcumin could protect the ADR induced proteinuria, albuminuria, hypoalbuminaemia, hyperlipemia and urinary excretion. It restored the renal function.

The understudy rodents treated by intravenous or intraperitoneal administration of Curcumin showed large amounts of Curcumin and its metabolites in their bile. This means that Curcumin transforms during absorption via the intestine and probably recirculates (Ravindranath and Chandrasekhara, 1981). One other study proved that Curcumin coadministrated with piperine a compound found in pepper vine and peppers-escalated the bioavailability of Curcumin after oral dosing possibly due to the inhibition of xenobiotic glucuronidation by piperine (Shoba *et al*., 1998). Hence, it can be concluded that Curcumin indicates low systemic bioavailability in rodents following oral dosing and probably undergoes intestinal metabolism (Lal *et al*., 2000).

MATERIALS AND METHODS

Initially the Curcumin effect on both spontaneous neutrophil apoptosis and apoptosis of neutrophils was investigated after transmigration over a human lung endothelium-epithelium bilayer. Evidences indicated that the constitutive neutrophil apoptosis was increased under the effect of Curcumin and the transbilayer migration induced delay in neutrophil apoptosis was abolished. Also they performed myeloperoxidase activity and migration assessment to determine the Curcumin effect on neutrophil function. The neutrophil migration and myeloperoxidase release were decreased under the effect of Curcumin, showing mitigation of neutrophil activation. They investigated the Curcumin impact on p38 mitogen-activated protein kinase and caspase-3 activity to explain the potential mechanism. A considerable increase in the amount of p38 phosphorylation and caspase-3 activity in Curcumin presence was observed in this experiment. Treatment by SB203580 which is a p38-specific inhibitor was successful in suppressing the Curcumin-induced apoptosis and caspase-3 activation. So, they made conclusion that Curcumin induced the apoptosis in human neutrophil and its effect was mediated by the activation of p38 and caspase-3 activity Kumar *et al*., 1998). Although, the Curcumin is known to show anti-inflammatory behavior in lab animals (Srimal and Dhawan, 1973). For example, recent studies have reported the Curcumin healing effects in sepsis

(Siddiqui *et al*., 2006) . From ancient times, turmeric was linked very much with the traditional ways of treatments based on sorcery. The sorcerers put turmeric paste on the body of the patients with jaundice and performed magical ejection of the disease. Afterwards the sorcerer rinsed the turmeric from the patient's body and the onlookers believed that the sorcerer really conducted a magical treatment (Ravindranath and Chandrasekhara,1981). For afflictions of the liver the turmeric is believed to possess good healing properties. For treatment of jaundice the turmeric is considered to have effective properties and many physicians recommend it to be added in the diet of the patients with jaundice and in some cases, infective hepatitis. Clinical administration of Phyllanthus fraternus together with turmeric has proved very effective with no side effects. Japanese tested the crude turmeric rhizomes' influence on CC14-induced hepatotoxicity in experimental animals. Curcuminoids have represented significant anti hepatotoxic properties. Also that ethanolic derivative of the turmeric has indicated important hepatoprotective effect. The Ecliptaalba and P. fraternus combined with Curcumin proved a promising combination Vs. liver trauma; Curcumin could normalize the lipid level in the liver and in experimental rats, decreased the level of serum bilirubin in CC14-induced hepatotoxicity. In the above study the level of serum triglycerides, pre-α-lipoproteins and cholesterol was regulated and glycogen level after treatment was normalized. there have been reports that turmeric causes contraction of the gallbladder (Jagetia and Aggarwal, 2007). curcumin are especially effective in increasing bile flow in infected bile ducts. Curcumin has anti lithogenic property and a dose of 0.5 g reduced the incidence of cholesterol gallstones in experimental animals (Anonymus, 2001). Hussain and Chandrasekhara reported that Curcumin reduced the gallstone formation rate as a reaction to lithogenic diet. Rasyid investigated the effect of Curcumin on gallbladder volume of a number of healthy volunteers through ultrasonography and concluded that Curcumin could induce the human gallbladder contraction. According to them, sodium Curcuminate was found to stimulate bile flow by action as a hydrocholagogue. Pretreatment of rats with Curcumin 1 h before the ingestion of paracetamol protected them from the vascular changes and necrosis in liver tissue. Pulla Reddy and Lokesh studied the dietary turmeric effect on iron-induced lipid peroxidation in liver of rats and reported decreased lipid peroxide level due to the improvement of antioxidant enzymes activities. Chow investigated the hepatoprotective properties of an aqueous extract of rhizomes of Javanese turmeric (xanthorrhiza) against acute liver damage induced by acetaminophen or CC14 in mice and found substantial alleviation in liver damage (Toda *et al*., 1985). Rajakrishnan *et al*. (2000) reported increased serum cholesterol, phospholipids and free fatty acids in rats fed with ethanol while on Curcumin treatment a significant decrease was observed, thus establishing the protective effect of Curcumin in ethanol toxicity. Deshpande found that turmeric extract produced protective effect on CC14 induced liver injuries in rats; he reported reduced serum levels of cholesterol and bilirubin, reduced activity by Alanine Amino Transferase (ALT), alkaline phosphatase and aspartate aminotransferase (AST). Jeon also found Curcumin very effective in an assay on its protective effect in rat liver (Rajakrishnan *et al*., 2000). according to the literature the Curcumin is a highly pleiotropic molecule which is able to interact with various molecular targets involving in inflammation. Curcumin modulates the inflammatory response by lowering the cyclooxygenase-2 (COX-2), lipoxygenase and inducible nitric oxide synthase (iNOS) enzymes activities; also through preventing the production of the inflammatory cytokines Tumor Necrosis Factor-alpha (TNF-a), interleukin (IL)-1,-2,-6,-8 and-12, Monocyte Chemoattractant Protein (MCP) and migration inhibitory protein as well as reducing the mitogen-activated and Janus kinases (Kumar *et al*., 1998). Curcumin as an anti-inflammatory agent can improve the status of rheumatoid arthritis, psoriasis, tropical pancreatitis orbital inflammatory pseudo-tumours, post-operative inflammation and chronic anterior uveitis (Bundy *et al*., 2004). Curcumin is proved to have anti inflammatory properties. A number of recent researches have shown that cyclooxygenase-1 (COX-1) plays a significant role in carcinogenesis and inflammation. A series of new Curcumin derivatives have been synthesized and assessed in terms of inhibition of COX-1 and COX-2 through measuring PGE2 production to obtain more selective COX-1 inhibitors (Shoba *et al*., 1998).

Curcumin are especially effective in increasing bile flow in infected bile ducts. Curcumin has antilithogenic property and a dose of 0.5g reduced the incidence of cholesterol gallstones in experimental animals (Anonymus, 2001). Jeon also found Curcumin very effective in an assay on its protective effect in rat liver. In his study he administrated Curcuma domestic extract in a daily dose of 2g and found that it could provide pain relief effect identical to ibuprofen that was used to relief the pain of osteoarthritis of the knee. the FDA has declared Curcumin as "generally regarded as safe". The short-and long-term toxicity of turmeric has been evaluated in F344/N rats and B6C3F1 mice by the National Toxicology Program. The animals 13 weeks to 2 year diet contained tumeric extracts with various concentrations. In the 13-week study none of the animals' death could be

attributed to Curcumin and no sign of carcinogenic lesions were found. During the two-year research project, no mortality was observed; however, rats developed chronic inflammation, ulcers and increased incidents of intestinal carcinoma, hepatocellular adenoma and clitoral gland adenom (Aggarwal *et al*., 2003). in a prospective clinical study done by Cheng the toxicology and pharmacokinetics of Curcumin were evaluated in patients with pre-invasive malignancies (Cheng *et al*., 2001). The starting dose of 500 mg day^{-1} and was escalated to 1,000, 2,000, 4,000, 8,000 and 12,000 mg day^{-1}. Total 25 patients participated in this study that was later prolonged for a period of 3 month. No toxicity resulting from the treatment was found up to 8 g day^{-1} but beyond that the patients were reluctant to tolerate the drug. Garcea *et al*. (2005) evaluated the effects of Curcumin on a group of 15 patients suffering from advanced colorectal cancer refractory to standard chemotherapies. Curcumin daily doses of 0.45 and 3.6g were administrated for 4 month. Dose-limiting toxicity was not observed. Other studies confirmed that safety of Curcumin at these doses. Overall, Curcumin has demonstrated high tolerability with few side effects reported (Sharma *et al*., 2001). Curcumin is a powerful preventive of activation of numerous transcription factors namely the Nuclear Factor-κB (NF-κB), Activated Protein-1 (AP-1), Signal Transducer and Activator of Transcription (STAT) proteins, Peroxisome Proliferator-Activated Receptor-g (PPAR-g) and α-catenin (Shoba *et al*., 1998). The transcription factor can regulate the expression of genes that involve in tumorigenesis, inflammation, cell survival, cell proliferation, invasion and angiogenesis) Scartezzini and Speroni, 2000). NF-B. One of the major transcription factors responsive to Curcumin is NF-B: numerous observed biological effects of Curcumin are NF-B dependent processes. Curcumin for example is capable of inhibiting the survival and proliferation of devised human tumor cell lines myeloid leukaemia, B Non-Hodgkin's Lymphoma (NHL), embryonic kidney, mouse macrophage) through suppressing NF-κB-regulated gene products (Bundy *et al*., 2004). STAT proteins. These proteins play a significant and ubiquitous role in tumorigenesis; Curcumin especially prevents from STAT3 activation in human multiple myeloma as well as Hodgkin and Reed-Sternberg lymphoma cells (Chiu *et al*., 2009). This protein dysregulates the cell growth and involves in invasion, angiogenesis, metastasis and resistance to apoptosis (Chen, 2008) PPAR-g. As a transcription factor it exerts anti-cancer, anti-inflammatory and insulin-sensitisingactions. Curcumin can induce the action of this receptor in rat liver cells (Epstein *et al*., 2010). AP-1. It is a transcription factor normally involved in activation of NF-B. Curcumin is proved to prevent from activation of AP-1 induced by tumor promoters (Hatcher *et al*., 2008). Response Element Binding Protein. Along with Histone Acetyl Transferases (HAT), these proteins are involved in cancer cell growth and survival. Studies have shown that Curcumin is a selective HAT inhibitor *in vitro* and *in vivo* (Hong *et al*., 2004). The α catenin it is the core component of the cadherin cell adhesion complex. Curcumin can induce the activation of caspase-3 which in turn involves in cleavage of α catenin and hence destroys the cell- cell adhesion pathways, leading to cell cycle arrest at the G2/M phase and induction of apoptosis in in vitro models (Huang *et al*., 1991) studies have shown the Curcumin capability as a powerful preventive of p53. p53 acts as a tumor suppressor and transcription factor. The p53 plays an important role as regulator of various cellular processes such as cell signal transduction, cellular response to DNA damage, genomic stability, cell cycle control and apoptosis. In this molecular target the role of Curcumin is complex; it has been shown that Curcumin can inhibit p53 in immature B cell lymphoma mouse cell lines, colon cancer cell line and myeloid leukaemic cells. This is while some other studies have shown the induction of p53 by Curcumin. Therefore, it should take into account the different activity of Curcumin in different types of cancer (Huang *et al*., 1991). Tumor Necrosis Factor (TNF) is a cytokine that mediates tumor initiation, promotion and metastasis. Its influence as pro-inflammation are facilitated by its potential for activation of NF-B which promotes the expression of inflammatory genes such as COX-2, LOX-2, cell adhesion molecules, inflammatory cytokines, chemokines and inducible nitric oxide synthase. In a study conducted by Shisodia et al. on mantle cell lymphoma cell lines, they reported the expression inhibition of both TNF mRNA and TNF proteins (Shoba *et al*., 1998).

CONCLUSION

The turmeric oil and its derivative ether as well as chloroform extracts are reportedly anti protozoan, antiviral, antifungal and antibacterial (Chattopadhyay *et al*., 2004). According to experimental studies results the Curcumin could enhance the cutaneous wound healing in guinea pigs and rats through improving the granulation tissue and biosynthesis of extracellular matrix proteins (Joe *et al*., 2004). Clinical testing has proved the bactericidal properties of turmeric (Khanna, 1999).

The importance of Curcumin as a powerful immunomodulatory agent in T cells, B cells, neutrophils, natural killer cells, dendritic cells and macrophages has

been proved in many studies. Immunomodulatory agent in T cells, B cells, neutrophils, natural killer cells, dendritic cells and macrophages has been proved in many studies (Jagetia and Aggarwal, 2007). Similarly the studies have confirmed the Curcumin ability in inducing apoptosis in human neutrophils (Hu *et al*., 2005). Neutrophils constitute the first immune defense against foreign substances so that their biological activities are thoroughly adjusted by the apoptosis. Normally the delayed neutrophil apoptosis is associated with acute lung injury and sepsis (Taneja *et al*., 2004). curcumin treatment inhibits the angiogenic differentiation of human umbilical vein endothelial cells HUVEC and prevents from basic fibroblast growth factor-induced corneal neovascularization in the mouse cornea which is indicative of its antiangiogenic effect. (Arbiser *et al*., 1998). In comparison, the Curcumin is stronger antioxidant than vitamins C and E (Satoskar *et al*., 1986). The pathogenesis of numerous diseases is affected by the oxidative stress as in myocardial ischemia, cerebral ischemia- reperfusion injury, hemorrhage, shock, hypoxia and cancer. In a clinical experiment involving a hemorrhage/resuscitation injury model, the Curcumin administration led to considerable decrease in the liver enzyme as partate transaminase and the liver cytokines, IL-1α, IL-1α, IL-2, IL-6 and IL-10 (Gaddipati, 2003). Nevertheless the most crucial impact of Curcumin lies in its anti-inflammatory properties which we aim to keep the focus of this review on it. Very few clinical researches have been reported in the literature concerning Curcumin administration effect on the inflammatory diseases (Chattopadhyay *et al*., 2004).

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