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Review article

THE CURCUMIN AS AN ANTIOXIDANT NATURAL HERB, WITH EMPHASIZE ON ITS EFFECTS AGAINST SOME DISEASES

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ABSTRACT: The stress of oxidative agents plays an important role in the pathogenesis of some diseases. Since a long time ago, the use of natural compounds plant-derived as potential therapeutic agents for various diseases in human has been studied. The naturally occurring compound (Curcumin) of the curcuminoid family, found in the spice Turmeric (*Curcuma longa)* has broad biological functions particularly antioxidant and activity in a direct and an indirect way by scavenging reactive oxygen species and inducing an antioxidant response, respectively. The various effects of curcumin have been evaluated in several studies. The information presented in the present article through some light on curcumin as an antioxidant natural herb, a powerful scavenger of many free radicals, as anti-inflammatory, anti-carcinogenic, anti-tumoral, anti-viral, antifungal, anti-parasitic, anti-mutagen, anti-infectious and anti-hepatotoxic natural substance.

Key words: Curcumin, Turmeric, C*urcuma longa*, Antioxidant, Reactive Oxygen Species, Natural herb

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INTRODUCTION

The dried ground rhizomes of *Curcuma longa* L. belongs to the family Zingiberaceae. It is called turmeric or curcuma in English, halide in Indian and ukon in Japanese. Curcumin is a perennial herb, the measures up to 1 m high a short stem, distributed throughout tropical and subtropical regions of the world, being widely cultivated in Asiatic countries, mainly India and China. In Malaysia, Indonesia and India, curcumin has been well studied due to its economic importance. The turmeric rhizomes are oblong, ovate, pyriform, often short branched and they are a household remedy in Nepal (Eigner and Scholz, 1999; Araujo and Leon, 2001; Jayaprakasha *et al*., 2005 and Benzie and Wachtel-Galor, 2011). The Latin name, Curcuma, is derived from the Arabic word, Kourkoum, the original name for saffron (Benzie and Wachtel-Galor 2011). In Ayurveda, Turmeric has been used internally as a stomachic, tonic and blood purifier and externally in the prevention and treatment of skin diseases (The Wealth of India, 2001). Traditional Indian medicine claims the use of curcumin powder against biliary disorders, anorexia, coryza, diabetic wounds, hepatic disorders, rheumatism, and sinusitis (Ammon et al., 1992; Araujo and Leon, 2001).

This article aims to provide a summary of curcumin as antioxidant agent from the available literature. Also, we highlight the use of curcumin as a beneficial complementary treatment for some diseases in human and animals.

Curcumin chemical structure and its properties

The curcumin chemical structure was determined by roughly and Whiting (1973). It melts at 176 – 177 $^{\circ}$.c and forms red-brown salt with alkalis. Curcumin is soluble in ethanol, alkalis, ketone, acetic acid, and chloroform; and it is insoluble in water. Curcumin has a molecular weight of 368.37. Commercial grade curcumin contains the curcuminoids desmethoxy curcumin (10–20 % MW 338) and bisdesmethoxy curcumin (less than 5% MW 308). On ultraviolet-visible spectrophotometric investigation, maximum light absorption of curcumin occurs at 420 nm (Sharma *et al.,* 2005).

Curcumin is a bis-α,β unsaturated β-diketone. Curcumin exists in equilibrium with its enol tautomer. The bis-keto form predominates in acidic and neutral aqueous solutions and in the cell membrane (Wang *et al.,* 1997). At pH 3-7, curcumin is an extraordinarily potent H-atom donor, this because in the keto form of curcumin, the heptadienone linkage between the two methoxyphenol rings contain a highly activated carbon atom, and the C-H carbon bonds on this
carbon are very weak due to delocalization of the unpaired electron on the adjacent oxygen (Jovanovic *et al.,* 1999; *Himesh et al.,* 2011).

Curcumin is unstable at basic pH, and degrades within 30 min to trans-6-(4-3-methoxyphenyl)-2-4-dioxo-5-hexanol, ferulic acid, feruloylmethan and vanillin (Lin *et al.,* 2000). If addition of calf serum or human blood or addition of antoxidants such as ascorbic acid, N-acetylcysteine or glutathione occur this leads to blocking this degradation in culture media or phosphate buffer above pH 7. On the other hand in acidic condition, the degradation is much slower, with less than 20% of total curcumin decomposed at 1h (Wang *et al*., 1997).

Wahlstrom and Blennow (1978) in early study showed that the administration a dose of 1g/kg of curcumin in the diet, 75% of the dose was excreted in faeces and negligible amount appeared in the urine. Ravindranath and Chandrasekhara (1980), showed that oral administration of curcumin leads to evidence for presence of glucuronide and sulfate conjugates in urine. By intravenous and intraperitoneal administration in rodents resulted in large quantities of curcumin and metabolites in
bile, which were mainly tetrahydrocurcumin and hexahydrocurcumin glucuronides (Ravindranath and Chandrasekhara, 1981). By intraperitoneal administration in mouse curcumin was transformed to dihydrocurcumin and tetrahydrocurcumin and subsequently to monoglucuronide conjugates (Pan *et al*., 1999). Ireson *et al*., (2001) by using High Performance Liquid Chromatography (HPLC), demonstrated small amount of curcumin in plasma with higher level of curcumin glucuronide and curcumin sulfate , and small quantities of hexahydrocurcumin, hexahydrocurcuminol and hexahydrocurcumin gluccuronide.

Curcumin as ROS (Reactive Oxygen species) scavenger

Curcumin is a powerful scavenger of many free radicals such as anion, hydroxyl radical and nitric oxide (Elizabeth and Rao, 1990; Sreejayan and Rao, 1997 and Barzegar *et a*l., 2011). Jayaprakasha *et al*., (2006) demonstrated in vitro the antioxidant capacities and activities of curcumin, bisdemethoxycurcumin and demethoxycurcumin using the phosphomolybdenum method and linoleic acid peroxidation method. They reported that, by using phosphomolybdeum method curcumin, demethoxycurcumin and bisdemethoxycurcumin exhibited various degrees of antioxidant capacity. The antioxidant capacities of curcuminoids were found to decrease in the order: curcumin > demethoxycurcumin > bisdemethoxycurcumin. Also by using linoleic acid peroxidation method, they found the same orders of antioxidant activities of the three curcuminoid compounds.

Recent studies provide scientific evidence regarding the potential pharmacological, prophylactic or therapeutic use of Cur, as anti-inflammatory, anti-carcinogenic, anti-tumoral, anti-viral, antifungal, anti-parasitic, anti-mutagen, anti-infectious, anti-hepatotoxic and anti-oxidant compound (Chen et al., 2006; Aggarwal *et al*., 2007; Ciftci *et al*., 2010; 2011 and 2012; Shehzad *et al*., 2011).

Sumanont *et al.* (2004) demonstrated that curcumin, curcumin manganese complex, and diacetylcurcumin manganese complex effectively reduced the generation of NO radicals, but curcumin manganese complex and diacetylcurcumin manganese complex showed greater NO radical scavenging than their parent compounds, curcumin, and diacetylcurcumin respectively.

Curcumin inhibits the generation of NO from activated macrophages (Bhaumik *et al.,* 2000). Curcumin has a protective effect against H_2O_2-induced cell damage in NG108-15 cells when added with concentrations (12.5 – 100 μM) with or without FK506 as a reference drug, H_2O_2 alone causes a decrease in cells viability. But the later, increased directly with increase curcumin concentrations (Mahakunakorn *et al*., 2003). The dichloromethane extract of curcumin exhibited significant COX-1 inhibitory activity in COX catalyzed prostaglandin biosynthesis assay in vitro (Selvam *et al.,*
2005). It was found that curcumin was investigated for COX inhibitory activity using bovine seminal vesicles, microsomes and cytosol from homogenates of mouse epidermis showed IC50 value of 2μM, 52μM and 5-10μM respectively (Selvam *et al*., 2005).

Pulla Reddy and Lokesh (1992) observed that curcumin is capable of scavenging oxygen free radicals, such as superoxide anions and hydroxyl radicals, which are the initiators of lipid peroxidation. The lipid peroxidation has a main role in the inflammation, in heart diseases, and in cancer (Jayaprakasha *et al*., 2005). Naik *et al*., (2004) demonstrated the protective effect of curcumin against the cytotoxic effects of ethanol by measuring lipid peroxidation in terms of thiobarbituric acid reactive substances and are expressed in μM of malondialdehyde formed/100gm tissue. They found that the amount of lipid peroxidation was increased by ethanol only with two folds compared to control, but when liver cells pre-treated with curcumin the level of lipid peroxidation lowered to reach control level.

Curcumin is a good antioxidant and inhibits lipid peroxidation in rat liver microsomes, erythrocyte membrane and brain homogenate (Pulla Reddy and Lokesh, 1994). Sreejayan and Rao (1994) have reported that three curcuminoids were inhibitors of lipid peroxidation in rat brain homogenates and rat liver microsomes. All of these curcuminoids were more active than α-tocopherol, as reference, and curcumin showed the better results. Turmeric can lower lipid peroxidation by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase at higher levels. These enzymes play an important role in the regulation of lipid peroxidation (Pulla Reddy and Lokesh, 1992).

By subcutaneous administration of a single dose of cadmium chloride 0.025mM/Kg to rats and 0.03 mM/Kg to mice, lipid peroxidation was increased to 320% of control in rats, 125% of control in mice, pre-treatment with curcumin orally 50mg/Kg leads to significant reduction of lipid peroxidation in both rats and mice (Eybl *et al.,* 2004).

Curcumin has high inhibitory effect for thiobarbituric acid reactive substances formation in lipid peroxidation for rat liver cells mitochondria initiated by 2,2'azobis(2-amidinopropane hydrochloride) Fe^{2+}/VC-induced peroxidation (Wei et al*.,* 2006a). Also in the former study, curcumin and its analogues reduced protein oxidation which indicated by carbonyl formation induced by 2, 2'azobis (2-amidinopropane hydrochloride).

Antioxidant mechanism of curcumin, in the presence of ethyl linoleate as one of the polyunsaturated lipid was reported (Masuda *et al.,* 1999; 2001 and 2002). During the antioxidant process, curcumin reacted with four types of linoleate peroxyl radicals. Six reaction products were observed in the reaction and these have novel tricyclic structures, including a peroxyl linkage. On the basis of the formation pathway for their chemical structure, an antioxidant mechanism of curcumin in polyunsaturated lipids was proposed, which consisted of the curcumin with the lipid and subsequently intramolecular Diels-Alder reaction. Further, a relatively high concentration of curcumin gave three dimmers as radical termination product in addition to the coupling products with curcumin and the lipid hydroperoxide. The structural analysis of those dimmers and quantitative analysis of this production rates revealed that radical termination mainly occurred at the 2-position of curcumin. The contribution of the pathway for production of these dimmers to the antioxidant mechanism of curcumin was estimated from the concentration-dependant data of the antioxidant activity and formation rates of these termination products. The A-A termination (dimmer formation) was estimated to contribute at least about 40% of the entire antioxidant process against ethyl linoleate oxidation.

Curcumin is reported to be a powerful antioxidant to repair both oxidative and reductive damage caused to protein by radiation (Kapoor and priyadarsini, 2001). In gastric mucosal damage
induced by indomethacin-ROS, curcumin stopped or reduced lipid peroxidation when administered (25mg/Kg) 30min prior to indomethacin (48mg/Kg) in rats (Chattopadyay *et al.,* 2006). Chen et al. (2006) studied the antioxidant effect of curcumin and its analogues against free radical initiated peroxidation of human low density lipoprotein. The peroxidation was initiated either by a water-soluble initiator 2, 2'azobis (2-amidino propane hydrochloride), or by cupric ion (Cu^{2+}). The reaction kinetics was monitored either by uptake of oxygen and the depletion of α-tocopherol present in the native LDL, or by the formation of thiobarbituric acid reactive substances. Kinetic analysis of the antioxidant process demonstrated that curcumin and some of its analogues are effective antioxidant against both 2, 2'azobis (2-amidino propane hydrochloride) and cupric ions-initiated LDL peroxidation by H-atom abstraction from the phenolic group.

In curcumin, the methoxy group seems to play a major role. The phenolic hydroxyl and the methoxyl group on the phenyl ring and the 1,3-diketone system seems to be important structural features that can contribute to these effects. The diketone system is a potent legand for metals such as iron. Another fact proposed is that the antioxidant activity increases when the phenolic hydroxyl group is at the ortho position with respect to methoxy group (Sreejayan and Rao, 1994). The photodynamic action of some drugs and pigments is also mediated through $_1O_2$. Light induced diseases including erythropoietic protoporphyria, pellagra and cataractogensis have been attributed in part to the toxicity of $_1O_2$. Thus, curcumin may be used in singlet oxygen-mediated diseases as a pharmacologic agent (Jayaprakasha *et al.,* 2005).

Das and Das (2002) demonstrated that curcumin is a potent singlet oxygen quencher at physiological or pharmacological concentrations. Additionally, singlet oxygen quenching by low concentration of curcumin in aqueous solutions is a physiologically relevant property of this compound, which can explain its effect in protecting skin against UV light. Singlet molecular oxygen is an electronically excited species of oxygen is known to produce in mammalian cells under normal and pathophysiological conditions. Srinivasan (2005) concluded that curcumin inhibited lipid peroxidation by quenching oxygen free radicals and by enhancing the activity of endogenous antioxidant enzymes, superoxide dismutase, catalase, glutathione peroxidase and glutathio-s-transferase.

By Ehrlish's ascites carcinoma cells induction in peritoneal cavity in mice, the activities of SOD and catalase were depressed dramatically due to tumor burden. Curcumin administered orally 50mg/Kg was ameliorate the activities of both enzymes to normal ranges (Pal *et al*., 2005).

Activities of SOD, catalase and peroxidase were measured in the study of Naik *et al.,* (2004) in liver slices culture treated with ethanol alone or ethanol with curcumin; the activities were measured at the end of 2 hours of treatment. In the presence of ethanol alone, the activities of the three enzymes were markedly increased, but in presence of curcumin alone or with ethanol the activities were found to be similar to control. The level of enzymes in the previous study were elevated with ethanol as a response to free radical production (Bandyopadhyay *et al*., 1999), but curcumin reacted with glutathione and also undergone dimerisation by interacting with free radicals (Priyadarisni, 1997 and Masuda et al., 1999). Other antioxidant effects of curcumin include inhibition of cytochrome p450 (Lake *et al*., 1996) and glutathione-s-transferase (Oetari *et al*., 1996), induction of endothelial heamoxygenase (Motterlini *et al*., 2000).

Curcumin elevated peroxidase in gastric mucosa intoxicated with indomethacin to control level (Chattopadhyay, 2006). Inhibition of CYP isoenzymes by curcumin has been demonstrated in cells cultured in vitro (Firozi *et al.,* 1996; Lake *et al.,* 1996) and this may represent a mechanism by which dietary curcumin protects animals against the toxic effects of many chemicals. For example, curcumin in a mammary carcinoma cell line, curcumin's inhibition of CYP 1A1-mediated activation of dimethylbenzanthracene resulted in diminished DNA adduct formation (Ciolino *et al*., 1998). In contrast to CYP enzymes, phase II metabolizing enzymes such as glutathione-s-transferase are regarded as detoxifiers, induction, rather than carcinogensis, potentially conferring a protective effect. Epoxide hydrolase and various hepatic GST isoenzymes were significantly increased upon curcumin feeding in mice (Singh *et al*., 1998) and total GST activity has been induced by dietary
curcumin in both mice and rats (Susan and Rao, 1992; Nijhoff *et al*., 1993; Piper *et al*., 1998 and Dinkova-Kostova *et al*., 2001).

Curcumin also appears to be beneficial in preventing diabetes-induced oxidative stress in rats (Hussein and Abu-Zinadah, 2010; and Lakshmanan *et al*., 2011). The multiple beneficial effects of Cur have also been elaborated in the neurogenesis process which in turn has been reported for its neuroprotective effects in age-related neurodegenerative diseases (Cole *et al*., 2007). Several studies have shown that curcumin exhibits protective effects against oxidative damage and has antioxidant and anticonvulsant properties exerting powerful oxygen free radical scavenging effects and increased intracellular glutathione concentration, thereby protecting lipid peroxidation (Kuhad *et al*., 2007; Kalpana *et al*., 2007; Reeta *et al*., 2009, 2010, 2011; Ataie *et al.,* 2010; Aboul Ezz *et al.,* 2011; Ciftci *et al*., 2011a and b, 2012 a and b; Du *et al*., 2012; Noor *et al*., 2012).

Curcumin in hepatotoxicity and as anti-inflammatory

Hepatotoxicity was induced to rats by subcutaneous injection of CCl_4 (0.2 ml/100gm body weight) twice weekly leads to markedly decrease in hepatic total CYP content to 29% compared to the level of untreated control. In contrast in ingestion of 5gm/kg diet of curcumin significantly moderated the reduction of CYP content to the level of the untreated control group. Similarly the activity of the six types of CYPs were drastically decreased by CCl_4 injection , while ingestion of 5 gm/kg diet of curcumin inhibited the decrease of CYP1A1, CYP1A2, CYP2B, CYP2C9 and CYP3A, but there is any significant changes in CYP2E1 (Sugiyama *et al*., 2006). A structure activity study of the potency of curcumin analogues suggests that their ability to induce phase II enzymes may be linked to the presence of the hydroxyl group at ortho-position on the aromatic rings and β-diketon functionally (Dinkova-Kostova and Talalay, 1999).

Turmeric has been in use as anti-inflammatory substance for a long time. The anti-inflammatory properties of curcumin were investigated in experimental rat models by Reddy and Lokesh (1994). A single oral dose of curcumin inhibited the carrageenan-induced inflammation by
15 – 52%, also lowered the carrageenan-induced edema in the foot pads of rats in a dose dependent manner. Curcumin when fed through the diet, reduced the incidence of carrageenan induced paw edema, delayed the onset of arthritis, and reduced the severity of paw inflammation in arthritic rats (Joe et al., 1997). Arora *et al*., (1971) investigated the anti-inflammatory activity of different fractions of rhizomes of turmeric in animals. It was reported that the extracts reduced the granuloma growth and no toxic effects were observed. Chandra and Gupta (1972) demonstrated the anti-inflammatory and anti-arthritic action of volatile oil in curcumin. Ghatak and Basu (1972) showed the action of sodium curcumonate as an anti-inflammatory agent, being better than curcumin and hydrocortisone acetate in experimental inflammation induced by carrageenin and formalin in albino rats (ED = 144μg/Kg).

Mukhopadhayaya *et al*., (1982) demonstrated the activity of curcumin and other semisynthetic analogues (sodium curcuminate, diacetylcurcumin, triethylcurcumin and tetrahydrocurcumin) in carrageenin-induced rat paw edema and cotton pellets granuloma model of inflammation in rats. In these experiments the authors used ferulic acid and phenylbutazone as reference drug.

Curcumin and its analogues showed similar action in carrageenin-induced paw edema in rats; however, the sodium curcuminate was the most potent analogue and was more water-soluble than curcumin. Among the curcumin analogues, triethylcurcumin was the most potent anti-inflammatory in the chronic models of inflammation, when compared with the others, as well as with a reference drug. Tetrahydrocurcumin showed no activity. In the acute inflammation condition, all the substances were more effective. The authors concluded that the activity of the compounds used in this experiment would depend on the model of inflammation.

Ammon and Wahl (1991) reported that the curcuma extracts showed a high anti - inflammatory effect after parenteral application in standard animal models. Curcumin also protects against inflammatory related changes in the liver prostaniods in animal model of alcohol-caused hepatic injury linked to increased activity in serum enzymes aspartate transaminase and alkaline phosphase. When the diet of the ethanol-consuming rats was supplemented with curcumin , not only
the activity of these serum enzymes was decreased but there was also a reduction in the abnormally raised levels of prostaglandins E1 and E2 in liver as well as in kidney and brain (Rajakrishnan *et al*
., 2000). Administration of 200mg of curcumin suppresses diethylnitrosamine-induced inflammation and hyperplasia in rats (Chuang *et al.,* 2000).

A number of teams have studied the effect of oral curcumin on inflammatory diseases in human. Satoskar *et al.,* (1986) found a significant anti-inflammatory effect objectively and subjectively from 400mg trice daily for 5 days in post-operative patients. Administration of 1200 mg curcumin four times daily to 18 patients with rheumatoid arthritis for 2 weeks made a significant improvement in the patients' inflammatory symptomology without apparent toxicity (Deodhar *at al*., 1980). Administration of 375mg of curcumin trice daily to patients with chronic anterior uveitis for 12 weeks resulted in an improvement in the condition (Lal *et al*., 1999). In a subsequent study , the same dose was administered to eight patients with idiopathic inflammatory orbital pseudotumors for 6–22 month , complete response was observed in half the patients up to 2 years of follow-up (Lal *et al*., 2000).

The mechanism of curcumin anti-inflammatory effects may involve inhibition of the induction of COX-2, iNOS and production of cytokines such as interferon-γ, at least in part due to its suppression of the Janus kinase (JAK)-STAT signaling cascade via its effect on the Src homology 2 domain-containing protein tyrosine phosphatases (SHP)-2 (Kim et al., 2003; Selvam *et al.,* 2005; Sharma et al., 2005 and Tunstall *et al.,* 2006). In myeloma cells, curcumin has also been shown to inhibit STAT3 phosphorylation and thus suppress interleukin 6 production (Bharti *et al.,* 2003). Skrzypezac-Jankum *et al.,* (2000) demonstrated that the effect of curcumin due to inhibition of inflammation-factor lipoxygenase. Surh *et al.,* (2001) reported that curcumin suppress activation of nuclear factor kappa B (NF-κB), which hamper subsequent nuclear translocation of the functionally active subunit of NF-κB. Curcumin is reported as a lead candidate for anti-inflammatory agent as it inhibits protease-activated receptors (PAR2 and PAR4)-mediated mast cell activation through a block of extra cellular signal-regulated kinase (ERK) pathway (Jayaprakasha *et al.,* 2005). The experimental data suggested that curcumin inhibited the formation of arachidonate metabolites (pgE2-leukotrienes) and the secretion of lysosomal enzymes-elastase, collagenase and hyaluronidase by macrophages (reviewed by Srinivasan, 2005).

Curcumin and lipid metabolism

The study of Bhuvaneswaran *et al.,* (1963) one of the pioneering observations is the influence of spices on lipid metabolism, especially demonstration of the hypolipidemic and hypocholesterolemic activities of turmeric and its yellow principle-curcumin. Turmeric and its active principle-curcumin were found to be effective as hypocholesterolemic agent under various conditions of experimentally induced hypercholesterolemia/ hyperlipidemia in rats (Patil and Srinivasan, 1971; Sambaiah and Satyanarayana, 1980; Kempaiah and Srinivasan, 2002; Srinivasan, 2005). In two studies of Kempaiah and Srinivasan (2002 and 2004), experimental hypercholesterolemia and hypertriglyceridemia were induced to rats, the first with 0.5% cholesterol and the second with 30% fat in the diet, by adding curcumin 0.2% this improved hypercholesterolemia and hypertriglyceridemia in these animals. Curcumin had also hypotriglyceridemic action on sucrose-induced hypertriglyceridemia in rats (Srinivasan and Styanarayana, 1988). In streptozotocin-induced diabetic rats hyperlipidemia was improved by 0.5% dietary curcumin (Babu and Srinivasan, 1997). Rats fed with 1% cholesterol in the study of Subba Rao *et al.,* (1970) showed a significant reduction in serum and liver cholesterol by 0.1–0.5%dietary curcumin. Since the hypocholesterolmic activity of curcumin is also accompanied by a hydrocholagognic effect and higher biliary secretion of bile acids (Bhat *et al*., 1984). The influence of Curcumin on cholesterol gall stone formation has been investigated in mice and hamsters maintained on a lithogenic diet (Hussain and Chandrasekhara, 1992; 1993). Further, curcumin effected a marked regression of pre-established gall stones in mice (Hussain and Chandrasekhara, 1994). The anti-lithogenicity of curcumin has been considered to be due not merely to their ability to lower cholesterol saturation index by altering the bile composition but also to their influence on biliary proteins (Hussain and Chandrasekhara, 1994).

In the study of Kempaiah and Srinivasan (2005), female rats fed with high fat diet and another group treated with 0.2% curcumin in the diet, this study approved that plasma triglycerides was elevated by about 85 – 90% in high fat diet animals, most of the elevated triglycerides in this high-fat fed animals resided in LDL–VLDL fraction, plasma triglycerides was lowered by dietary curcumin. Also in the above study, hepatic lipid was raised with high fat diet, and by treatment with 0.2% curcumin in the diet hepatic triglyceride was decreased near to normal range.

Curcumin and diseases

Since the curcumin does not exhibit side effects, it has been designated for several clinical trials as a treatment for some human diseases.

An investigation by Ramirez-Tortsa *et al.,* (1999) has dealt with the effect of ZCl_4-extract of curcumin in a model of experimental atherosclerosis in rabbits based on the administration of a diet with a high content of saturated fat and cholesterol. The simultaneous intake 1.6mg/Kg of ZCl_4-extract in the diet resulted in a decreased oxidation of serum LDL-cholesterol. The experimental works of Miquel *et al*. (1995 and 2002) showed that turmeric induced decrease in lipoperoxides in mouse blood and liver. Clinical research on human volunteers, a daily dose of 200mg of ZCl_4 curcuma extract was administered to men ranging in age from 27 – 67 years, at the end of treatment period of 45 days there was a significant decrease in the levels of serum lipid peroxides (Ramirez-Bosca et al., 1995). By the clinical research of Ramirez-Bosca *et al.,* (1997) on healthy 18 men and 12 women received 200mg of ZCl_4-extract of curcumin for 60 days, HDL and LDL-peroxides were significantly decreased 20-50%. This lowering effect of curcuma antioxidants on lipid-related atherogenic risk factors agrees with the work of Suresh Babu and Srinivasan (1997), who showed that the administration of curcumin to rats in which diabetes had been induced by streptozotocin decreased the blood levels of LDL and VLDL-cholesterol, triglycerides and phospholipids. In addition, the hydro-alcoholc extract of curcuma administered to rabbits, decreased the plasma cholesterol level and the susceptibility of the LDL to oxidation (Ramirez-Tortosa *et al.,* 1999).

Induction of tumor with Ehrlich's ascites carcinoma cells intraperitoneally caused immune cells number reduction. Particularly, it severely affected bone marrow as was evident from the depletion in bone marrow progenitor cell number. When Ehrlich's ascites carcinoma (EAC) cells was grown for three weeks in the peritoneal cavity of mice, the bone marrow progenitor cell number decreased from 55 million in normal to 21 million. Oral administration of 50mg/Kg curcumin showed significant restoration of bone marrow cellularity to 50 million in tumor-bearing mice in a span of three weeks (Pal *et al.,* 2005).

In the previous study, at third week after tumor inoculation there was a significant decrease in thymocyte cell number in the untreated mice from 65 million in normal to 23 million. Administration of 50mg/Kg curcumin orally showed appreciable recovery of up to 90% of normal values. Also spleenic lymphocytes which decreased in tumor-bearing mice from 182 million to 101 million rose significantly with curcumin treatment. Hematological data as RBCs, WBCs count and Hb% which decreased in tumor bearing mice were elevated again near to normal control (Pal *et al.,*
2005).

Recent studies have shown significant potential of pharmacological, prophylactic or therapeutic use of curcumin (Cur) in many beneficial activities in the body including neuroprotection in neurodegenerative diseases and antioxidant properties (Ahmad, 2013). In his study, the previous author described anticonvulsive effects of Cur in lithium–pilocarpine (Li–Pc) induced status epilepticus (SE) in young rats. He found that the Cur has effects on the intensity and frequency of SE, cognitive behavior in water maze as well as on oxidative stress related enzymes in the brain. Also, Cur significantly ameliorates SE-induced cognitive dysfunction and oxidative damages in the hippocampus and striatum areas of the brain.

Curcumin and its analogues acted as inhibitory factor for RBCs hemolysis which induced by various concentrations of 2,2'azobis (2-amidino propan hydrochloride), curcumin with concentration 10μM when added to 5% human RBCs solution inhibited the hemolytic effect of 2,2'azobis (2-amidino propan hydrochloride) for 60 min (Deng et al., 2006). Structural integrity of RBCs and hence , the osmotic fragility are affected in hyperchlosterolemic situation induced by an atherogenic diet , as a result of alteration in membrane cholesterol/phospholipids ratio, dietary curcumin offer protective influence on this altered fluidity of erythrocyte in hypercholesterolemic condition (Kempaiah and Srinivasan, 2002; 2005). Examination of the osmotic fragility of erythrocytes in normal, hyperlipidemic and hypolipidemic rats with dietary curcumin groups in the study of Kempaiah and Srinivasan (2006), indicated that the red blood cells of hyperlipidemic rats displayed a slight resistance to osmotic fragility .In hyperlipidemic with dietary curcumin ,improvement occurred in osmotic fragility of RBCs.

Kempaiah and Srinivasan (2004) examined the antioxidant status of erythrocytes of hypercholesterolemic rats and observed that the depleted intracellular thiol and glutathione content as well as the lowered activity of glutathione reductase in hypercholesrolemic situation were effectively countered by dietary curcumin.

Curcumin exhibits antimutagenic effect towards 4-nitro-O-phenylene-diamine and diamino fluorine in *Salmonella typhimurium* (Azuine *et al*., 1992). It has also been found to protect cisplatin induced clastogenesis by acting as a free-radical scavenger (Antunes *et al*., 2000). Curcumin has been identified to reduce radiation induced DNA damage in rat lymphocytes (Thersiamma et al., 1998). Turmeric exhibits antimutagenic potential towards urthan in somatic mutation recombination assay in Drosophila (El-Hamms *et al.,* 1999).

In the study of Shukla *et al.,* (2002), a single dose of cyclophosphamide 40mg/Kg in rats interaperitoneally leads to many chromosomal aberrations including breaks, fragment, exchanges and multiple aberrations, also mitotic index decreased significantly from control . On the other hand pre-treatment with curcumin 100 or 200mg/Kg leads to a highly significant prevention of these chromosomal aberrations and declining in mitotic index. Curcumin diminished damage induced by UV radiation by modulating SOS repair system (Oda, 1995). Furthermore, it has been observed that
turmeric given in dose of 1.5g per day for 30 days significantly reduced urinary excretion of mutagens in smokers (Polasa *et al*., 1991).

Curcumin has been identified to play a major role in detoxification of lipid peroxidation products in K562 human leukemia cells (Singhanl *et al*., 1991). Also there is association between agents which show antioxidant activity to act as antimutagens (Renner, 1984). The modulatory role of curcumin in inhibition of mutagenicity and carcinogenicity can also be implied to its antioxidant activity (Nagabhushan and Bhide, 1987).

Curcumin has two p-hydroxy groups and scavenges free-radical DNA damage thereby acting as potent antioxidant, scince mutation induced at cytogenetic level are probable causes of cancer, therefore the inhibition of chromosomal aberration by curcumin suggest that the antimutagenic potential of curcumin is related to antioxidant and anticarcingenic activity (Shukla *et al.,* 2002).

DNA adducts, serving as a biomarker, are thought to correlate with tumorgenicity (Otteneder and Lutz, 1999; Li *et al.,* 2003), and protein adducts can serve as the surrogates for the DNA adduct (Wu *et al.,* 1997). In *in vitro* and *in vivo* study of Li *et al.,* (2003), curcumin significantly diminished nitrobenzene-DNA adducts and suppressed nitrobenzene-Hb adduct. There are several possible ways of curcumin on the *in vivo* binding of nitrobenzene to modulation of carcinogen metabolism is often considered an important pathway for inhibitory effects of many types of chemopreventive agents, these agents detoxify carcinogens through the phase I and/or phase II enzymatic system: inhibition of the procarcinogen activation which catalyzed by the phase II enzymes such as glutathione-s-transferase, epoxide hydrolase, glutathione peroxidase and glutathione reductase (Offord *et al.,* 1997). Also, Curcumin inhibition capacity through scavenging reactive intermediates, interfering with the interaction between metabolites and DNA , altering the DNA repair rates and scavenging the reactive oxygen and other free radical species (Manson *et al.,*
2000).

It was observed that Curcumin can inhibit cancer promotion effect of 12-O-tetradecanoylphorbol-13-acetate (TPA) on mouse skin (Huang *et al.,* 1988). In another study,
Huang et al. (1997) reported that application of 100nM of curcumin together with 5nM TPA twice a week for 18 weeks markedly inhibited TPA-induced tumor promotion. Carcinogensis which initiated with 7,12dimethylbenz (a) anthracene (DMBA) and promoted with TPA was inhibited with curcumin (Limtrakul *et al*., 1997). Potential mechanism of these effects considered to involve inhibition of arachidonic acid-induced inflammation, inhibition of ornithine decarboxylase activity/transcription, which is a rat-limiting step in polyamine biosynthesis (Conney, 2003).

Radiation-induced tumor in rat mammary gland was inhibited with the chemopreventive effect of curcumin (Inano *et al*., 2000). Oral administration of curcumin prevents cancer in the colon, skin, soft palate, and breast of rodents (NCI, DCPC, 1996). Administration 2000ppm of curcumin for 14 weeks orally leads to a significant increase in the apoptotic histological index in intestinal cancer induced by azoxymethan in mice (Samaha *et al.,* 1997).

Curcumin was found to decrease the EAC cell number by the induction of apoptosis in the tumor cells (Pal *et al.,* 2001; 2005). An apoptosis enhancing capability of curcumin in EAC cell by modulating the cell cycle progression as well as the cross-talk of various pro- and anti-apoptotic factors has implications for the clinical use. The apoptotic response of EAC cells suggests promise for the efficacy and possible application of this plant product in cancer prevention and perhaps also in cancer therapy (Pal *et al.,* 2005).

Parsai *et al*., (2014) tested the anticancer activity of new curcumin-like compounds (E21cH and Q012095H). They identified several enzymes that are targeted by curcumin, aldo-keto reductase family 1 member B10 (AKR1B10), serine/threonine-protein kinase, protein kinase C, matrix metalloproteinase (MMP), cyclooxygenase and epidermal growth factor receptor, which were tested as targets for these anticancer chemicals.

Turmeric have been experimentally documented to possess anti-diabetic potential by various investigators has been reviewed by Srinivasan (2005). The first report on the hypoglycemic effect of turmeric was in fact an observation consistently made on one self-diabetic individual (Srinivasan, 1972) . Daily intake of curcumin not only reduced the fasting blood sugar level, but also lowered
the dosage of insulin needed for normoglycemia. In experimental studies to examine the potential beneficial effects of curcumin against diabetes, curcumin has been shown to reduce hyperlipidemia (Babu and Srinivasan, 1997), delay the development of cataract (Suryanarayana et al., 2005), ameliorate renal lesions (Babu and Srinivasan, 1998), and reduce the cross-linking of collagen (Sajithlal *et al.*,1998) in a streptozotocin-treated diabetic animal model.

Curcumin has also been shown to lower blood glucose levels in type 2 diabetic KK-Ay mice (Nishiyama *et al.,* 2005) and streptozotocin-treated rats (Mahesh *et al.,* 2005). Curcumin supplementation promotes wound healing in streptozotocin-treated diabetic rats and genetically diabetic mice (Sidhu *et al.,* 1999) and attenuated the phenylephrin-induced increase in vascular reactivity of aorta in streptozotocin-treated diabetic rats (Majithiya and Balaraman, 2005). In their study, Jain *et al.,* (2006) demonstrated that curcumin supplementation prevents increased hemoglobin glycosylation and decreases oxidative stress in erythrocytes exposed to high levels of glucose (mimicking diabetes).

Experimental and clinical studies suggests that oxidative stress plays a major role in the pathogensis of diabetes mellitus (Mercuri *et al.,* 2000; Brownlee, 2001; Rosen *et al.,* 2001; Bonnefont-Rousselat, 2002; Ceriello, 2003; Balasubramanyam *et al.,* 2003). Thus, the antioxidant activity and the inhibition of cellular reactive oxygen species generation of curcumin give it the anti-diabetic properties (Balasubramanyam *et al*., 2003).

By induction of oxidative renal damage with a single dose of ferric nitroacetate 5mg/Kg in mice, the level of TBRS and 8-hydroxy-2'-deoxyguanosine formation rates in kidney homogenate were increased significantly compared to control in the study of Okada *et al.,* (2001). These elevations were reduced and improved with pre-treatment with curcumin or tetrahydrocurcumin 0.5% in the diet for 1 month. Also in the same study, the levels of glutathione-s-transferase, glutathione peroxidase and NADPH:QR activities in kidney homogenate were reduced significantly with ferric nitroacetate, and improved with pre-treatment of curcumin or tetrahydrocurcumin, but tetrahydrocurcumin was more effective than curcumin itself, this due to tetrahydrocurcumin has better absorption properties in gastrointestinal tract than curcumin. The effects of curcumin and tetrhydrocurcumin, in Okada *et al.,* (2001) study, occurred due to direct chelating or scavenging effects and induction of phase II antioxidant enzymes.

The anti-diabetic potential of curcumin also ameliorated kidney lesions, one of the major secondary complications in diabetes, as indicated by decreased proteinuria and leaching of renal tubular enzymes, correction of the alteration in renal cellular enzymes, and countering of the altered renal membrane ATPase and fatty acid composition (Babu and Srinivasan, 1998; Dong-wei Zhang *et al.,* 2013). Hypocholesterolemic effect of curcumin and its ability to lower the extent of lipid peroxidation under diabetic condition are implicated in the amelioration of renal lesions (Babu and Srinivasan, 1995; 1997).

Induction of EAC cells intera-peritoneally in mice in the study of Pal *et al.,* (2005) caused hepatotoxicity, the serum levels of ALT, AST, and ALP activities as clinical indicators of tumor-induced toxicity were increased significantly, and on the other hand curcumin by oral gavage 50mg/Kg lowered these enzymes to normal levels. Also in the same study total bilirubin which increased in tumor-bearing animals was decreased to normal level.

CONCLUSION

Recent review article has provided the scientific basis for “natural herb” curcumin as a reactive oxygen species scavenger, an antioxidant agent and emphasized the important role of curcumin in the prevention and treatment of some diseases. Despite the potential tremendous benefits of this multifaceted natural product, extensive studies are needed to overcome limited solubility and poor bioavailability of curcumin. These include synthesis of curcuminoids and development of new formulations of curcumin, such as nanoparticles, emulsions, and sustained released drugs.

Conflict of Interests

The authors declare that they have no conflicting of interests.

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