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Curcumin-The Yellow Magic

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ABSTRACT

Plants are nature's remedies and have been used on earth for food and medicine since ancient times. Today the global movement towards more natural life style has brought about resurgence of interest in herbs as they are capable of bringing the body into harmony and health. The use of plants and their active principles in the prevention and treatment of chronic diseases is based on the experience of traditional system of medicine from different ethnic societies but there use in modern medicines is limited by the lack of scientific data. Few medicinal plants have attracted the interest of scientists and been the subject of scientific investigations. One plant that has been investigated thoroughly is the turmeric (*Curcuma longa*). Its active constituent is curcumin which gives it yellow colour. The ongoing laboratories and clinical research indicate that curcumin has a broad range of biological activities. The aim of this review article is to explain some of its relevant medicinal properties.

Key words: Curcumin, therapeutic effects, antioxidant property, alzheimer disease, anticancer activity

INTRODUCTION

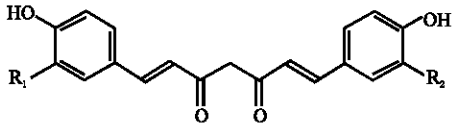
Curcumin is the most biologically active constituent of turmeric. The characteristic yellow colour of turmeric is due to curcumin. The turmeric plant is also known as Curcuma longa which is a perennial herb belonging to the ginger family: Zingiberacae. This plant is cultivated extensively in India and Southeast Asia. The most useful part of the plant is rhizome which is a horizontal underground stem that send out shoots as well as root. Turmeric is highly esteemed by the Indians and has religious importance because of its yellow colour resembling sunlight. As Indian culture worshipped solar system turmeric is specially protected as it contains sun coloured yellow dye. Turmeric has 46 synonyms but it is best known as Haridra in Sanskrit and Pita: yellow, Gauri: brilliant, Rajini : night in Hindi. It belongs to group of aromatic spices and when added to various food preparations preserved their freshness and nutritive value. Curcumin is the principal curcuminoid found in turmeric.

STRUCTURE and CHEMICAL PROPERTIES OF CURCUMIN

It was isolated by Vogel and Pelletier (1818) but obtained in crystalline form by Daube (1870). Chemically it is known as diferuloylmethane. Its IUPAC name is 1, 6- heptadiene-3,5-dione -1,7-bis (4-hydroxyl - 3 - methoxy phenyl) - (1E,6E). Milobedzka *et al.* (1910) confirmed its structure by synthesis. The molecular formula of curcumin is $C_{21}H_{20}O_6$ and molecular weight is 368.37. It is insoluble in water but soluble in dichloromethane, chloroform, methanol, ethanol, ethyl acetate,

dimethylsulfoxide and acetone. Curcumin shows λ_{max} at 430 nm in methanol.The other curcuminoids present along with curcumin (1) in turmeric are demethoxy curcumin (2) and bisdemethoxy curcumin (3). It exists in two tautomeric structures i.e., keto and enol forms. Curcumin contains two para hydroxyl groups, two keto groups, two methoxy groups, an active methylene group and two double bonds. Analysis of the chemical structure of curcumin and its biological activity has established following facts:

- The presence of hydroxyl groups on phenyl ring is responsible for antioxidant activity of curcumin
- The presence of keto groups and double bonds is essential for antiinflammatory, anticancer and antimutagen activities



(1) R1 = R2 = OCH3
(2) R1 = OCH3, R2 = H
(3) R1 = R2 = H

THERAPEUTIC EFFECTS OF CURCUMIN

Curcumin is a non-nutritive and non-toxic chemical that has been used in Indian and Chinese traditional medicine for hundreds of years. It has generated great attention as it possesses large number of biological activities. Several scientific studies revealed the curative properties of curcumin which are as follows:

Antioxidant property: It has been suggested by Priyadarsini *et al.* (2003) that the antioxidant activity of curcumin depends upon the presence of the phenolic group but recently it has been reported by Weber *et al.* (2005) that both the central methylene hydrogens and the phenolic hydrogens are involved in the mechanism of formation of the phenoxy radicals which are likely the basis of the antioxidant activity. It has a unique conjugated structure and shows a typical radical trapping ability as a chain breaking antioxidant suggested by Daniel *et al.* (2004). Generally, it has dual effect in oxygen radical reactions, thus it can act as a scavenger of hydroxyl radicals or it catalyses the formation of hydroxyl radicals explained by Toshiya *et al.* (2001) The antioxidant activity of curcumin could be mediated through antioxidant enzymes such as superoxide dismutase, catalases and glutathione peroxidase. It serves as a Michael acceptor given by reacting with glutathione and thio redoxin (Adams *et al.*, 2005; Simanjuntak *et al.*, 2010; Foda, 2007).

According to Khopde *et al.* (1999) curcumin is at least ten times more active as an antioxidant than even vitamin E. The antioxidant mechanism of curcumin may include one or more of the following interactions (Adams *et al.*, 2005; Simanjuntak *et al.*, 2010; Foda, 2007):

- Scavenging or neutralizing of free radicals
- Inhibition of oxidative enzymes
- Oxygen quenching and making it less available for oxidative reactions
- Interacting with oxidative cascade and preventing its outcome
- Chelating or disarming oxidative properties of metal ions like iron (Fe)

So, the curcumin effectively inhibit the free radical damage to bimolecules both *in vitro* and *in vivo* conditions by prevention and intervention processes which makes it very unique natural antioxidant.

Antiinflammatory activity: Inflammation results from the complex series of reactions triggered by the body's immunological response to tissue damage. Many diseases and surgery induce inflammatory reactions. These reactions sometimes create painful conditions. Arachidonic acid is a compound metabolized in the body and forms some substances which cause inflammation. This arachidonic acid is released by the hydrolysis of membrane phospholipids by the enzyme phospholipase A_2 (PLA_2). Arachidonic acid is metabolized by the enzyme cyclooxygenase (COX) to prostaglandin and thromboxanes, or by the action of the enzyme lipoxygenase (LOX) to leucotrienes (LT). Some prostaglandins dilate the blood vessels causes redness, swelling and pain of the inflamed part and leucotrienes cause tissue swelling.

Curcumin inhibits the lipoxygenase pathway or cyclooxygenase pathway without any side effects (Ammon *et al*., 1993). Curcumin possesses anti inflammatory activity in different experimental models e.g., mice, rats, rabbits and pigeons explained by Arora *et al*. (1971), Ghatak and Basu (1972). The oral doses of curcumin required to reduce the inflammatory edema or tissue swelling to half the size (ED_{50} - a dose effective in reducing edema by 50%) (Srimal and Dhawan, 1973; Chakravarty *et al*., 2009; Ao *et al*., 2008). Nuclear factor kappa B (NF-kB) is a transcription factor that binds DNA and enhances the transcription of the COX-2 gene and other pro-inflammatory genes, such as inducible nitric oxide synthase (iNOS). Curcumin has been found to inhibit NF-kB- dependent gene transcription (Plummer *et al*., 1999) and to inhibit the induction of COX-2 and iNOS in cell culture and animal studies suggested by Brouet and Obshima (1995). According to Chen *et al*. (1999) most inflammatory stimuli are known to activate three independent MAPK pathways, leading to activation of p 44/42 MAPK, JNK and P^{38} MAPK pathway. His group observed that curcumin inhibits JNK activation. In transfection assays, curcumin moderately suppressed mitogen-activated protein kinase kinase (MEKK)-I-induced JNK activation, which shows the potent antiinflammatory action of this natural pigment.

Besides this, curcumin is also found to be effective in MS., which is an inflammatory disease of the Central Nervous System (CNS). The main symptoms of this disease are the destruction of oligodendrocytes and myelin sheath in the CNS. Experimental Allergic Encephalomyelitis (EAE) serves as an animal model for MS show that curcumin inhibits EAE thus it can be use for the treatment of MS (Natarajan and Bright, 2002; Banerjee *et al*., 2010; Tajik *et al*., 2007; Tajik *et al*., 2008).

Later on Verbeek *et al*. (2005) examined the effect of curcumin on EAE and he found that oral curcumin had overall mild but beneficial effects. The antiinflammatory activity of cucumin was evaluated (Mukopadhyaya *et al*., 1982; Padhye *et al*., 2009) in group of patients who underwent surgery or suffered from trauma. A double-blind controlled trial (Satoskar *et al*., 1986) in which three group of patients received curcumin (400 mg), a placebo (250 mg of lactose powder) or phenyl butazone (100 mg), respectively, three times a day for five consecutive days after surgery (for hernia or hydrocele) curcumin reduced inflammation and was an equally effective as the treatment with phenyl butazone.

Alzheimer disease: Alzheimer disease is due to the deposits of amyloid plaques in the brain. The amyloid plaques are the aggregates of amyloid beta forms which are a peptide and it is a principal

constituent of senile plaque, the yellowish junk that destroys the brain cells of Alzheimer's victims. Yang *et al.* (2005) observed that curcumin is very effective in inhibiting the amyloid beta oligomers formation *in vitro*.

Curcumin also helps in the generation of heat-shock proteins or stress proteins. The primary role of these heat shock proteins is to try to control and repair the damage done to other proteins which are vulnerable to the effects of heat and other forms of stress. In the brain of Alzheimer's victims, researchers have found the presence of a particular heat shock protein called heme oxygenase-1 (HO-1) along with amyloid plaques. The enzyme is apparently released in a damage associated with neuro degeneration. Curcumin is a good inducer of HO-1 in vascular endothelial cells it may therefore be able to help forestall the development of Alzheimer's disease (Motterlini *et al.*, 2000; Calabrese *et al.*, 2003).

Although, metal ions are vital for many life processes but certain metal ions e.g., copper, iron and zinc are known to induce the aggregation of amyloid beta molecules into senile plaques. Scientists at the Chinese University of Hong Kong established the fact that curcumin is an effective chelator of Baun and Ng (2004) copper and iron but not of zinc. They used a mixture containing 80% curcumin, 15% demethoxycurcumin and 5% bis demethoxycurcumin. The concentration of the metals that could be chelated were lower than those in Alzheimer's brain and lower even than those in normal brains which means that chelation of the actual (higher) concentration would also occur.

Ono *et al.* (2004) group reported that a beta (beta-amyloid fibril) formation can be inhibited by curcumin. The effect of curcumin did not depend on a beta sequence but on fibril related conformation. *In vivo* studies showed that curcumin injected peripherally into aged Tg mice crossed the blood-brain barrier and bound plaques and reduced amyloid levels and plaque burden. Hence, curcumin directly binds small beta-amyloid species to block aggregation and fibril formation in vitro and *in vivo* suggesting that curcumin can be used in clinical trials preventing or treating Alzheimer diseases.

Anticancer activity: Many substances caused the cancer which one k/a carcinogenesis. Several synthetic chemicals, drugs and cosmetics, environmental pollutants and some food contaminants also act as a causing agent of cancer. The cancer development is a step wise process in which the carcinogenic agents produces cancer or/and promote the cancerous cells. The cancer/tumor initiation or promotion stages are prevented by some substances which are called as anti carcinogens and curcumin is one of them.

Cuncumin is a important anticancer agent and it decreases the cancer initiation of skin (Huang *et al.*, 1988), mammary gland (Kuttan *et al.*, 1985), oral cavity (Kuttan *et al.*, 1987), fore stomach (Rao *et al.*, 1984), esophagus (Lee *et al.*, 2005), stomach (Chuang *et al.*, 2000a), intestine (Chuang *et al.*, 2000b), colon (Deshpande *et al.*, 1998), lung (Ushida *et al.*, 2000) and liver (Limtrakul *et al.*, 1997). The curcumin induces the apoptosis in the various cancerous cells in culture with a minimum toxicity. Therefore curcumin have led to scientific interest in its ability for cancer therapy as well as cancer persecution (Deshpande *et al.*, 1998; Ushida *et al.*, 2000).

The previous study explained the anti cancerous properties of cuncumin or different types of cancers, including suppression of inflammation, inhibition of cell proliferation, suppression of certain oncogenes (e.g., Cha-ras, C-jun and C-fos) inhibition of transcription factors NF-KB and AP-1, suppression of COX-2, inhibition of chromosomal damage, inhibition of tumor implantation, inhibition of tyrosine kinase and protein kinase C activity, inhibition of biotransformation of carcinogenesis and induction of gluthione S-transferase (GST) activity (Limtrakul *et al.*, 1997;

Karunagaran *et al.*, 2005; Sharma *et al.*, 2005; Sharma *et al.*, 2001a; Chuang *et al.*, 2002; Tanaka *et al.*, 2004; Hiroshi *et al.*, 1999).

The development of oral (Krishnaswamy *et al.*, 1998), stomach (Ikezaki *et al.*, 2001; Huang *et al.*, 1994) liver (Chuang *et al.*, 2000b) and colon (Pereira *et al.*, 1996; Rao *et al.*, 1995; Kawamori *et al.*, 1999) cancer in animal models induced by chemicals are found to be decreased by administration of oral curcumin. The development of intestinal adenomas in Apc min/+ mice, are also decreased by the oral curcumin administration (Mahmoud *et al.*, 2000; Perkins *et al.*, 2002). In humans, there are little evidence that high dose of turmeric or curcumin are associated with decreased cancer risk.

The patients with advanced colorectal cancer (Singletary *et al.*, 1998; Huang *et al.*, 1998); found that dose up to 3.6 g day^{-1} for 4 months were well tolerated, during a Phase I clinical trial, although the systamine (RKG) bioavailability of oral curcumin was low (Mall and Kunzelmann, 2005). When 3.6 g day^{-1} of curcumin is given orally for 7 day to the patient of colorectal cancer with liver metastatis, trace levels of curcumin metabolites were measured in liver tissues, but curcumin itself was not detected (Garcea *et al.*, 2004; Garcea *et al.*, 2005).

Curcumin inhibits the proliferation of head and neck squamous cell carcinoma and in another study curcumin shows the significant inhibition of growth of human gastric carcinoma (AGS) cells in a dose and time dependent manner (Mall and Kunzelmanu, 2005; Ward *et al.*, 1995; Berger *et al.*, 2002; Egan *et al.*, 2004). The curcumin is recommended for the patient with colorectal cancer in phase II trial and many clinical trials of curcumin are under the way in patient with pancreatic cancer (Si *et al.*, 2007). These finding suggests that the curcumin (Piper *et al.*, 1998) is a potent anti cancerous agent which tells many types of cancer/tumor development.

Cystic fibrosis: The disease cystic fibrosis is hereditary disease, which is caused by mutation in a specific gene called cystic fibrosis transmembrane conductance regulator (CFTR) and is characterized by abnormal chloride transport in many tissues, including liver, lungs, gastrointestinal tract, sweat glands, pancreas and male reproductive ducts (Rai *et al.*, 2008; Chattopadhyay *et al.*, 2004). The cystic fibrosis transmembrane conductance regulator (CFTR) gene is a trans membrane protein and acts as a chloride channel and play a major role in transportation of fluids and ions. The very common delta F 508 mutation in CFTR resulting the production of an immature protein that retained in the endoplasmic reticulum and targeted for degradation (Li *et al.*, 1993).

There are several studies which demonstrated the role of curcumin to correct the defective, delta F 508 CFTR mutation in cells and mouse models (De *et al.*, 2009; Shankar and Murthy, 1979). The curcumin used as a remedy in cystic fibrosis comes from the observation that endoplasmic reticulum calcium pump inhibitor thapsigangin restores functional surface expression of delta F 508-CFTR (Rao *et al.*, 1970). According to Soni and Kuttan (1992). curcumin also correct the trafficking defect in delta F 508 - CFTR - transected baby hamester kidney cells and in homozygous delta F 508 - CFTR mice and to improve the survival rate in transgenic mice.

Antimicrobial activity: Curcumin inhibits the growth of varieties of microbes such as viruses, bacteria and some pathogenic fungi (Chai *et al.*, 2005). Turmeric studied as an important antiviral agent against Human Immunodeficiency Virus (HIV) and curcumin inhibits the activation of long terminal repeat (ltr), which is the essential part of common system in HIV and decreases the replication of human immunodeficiency virus.

In a study at a dose of 50 mg mL^{-1} of alcoholic extract of turmeric showed in vitro bactericidal activity. Curcumin was recently been shown antimicrobial activity against Helicobacter pylori (*H. pylori*) growth. *H. pylori* showing inhibition with MIC of curcumin range from 5 to 50 microg (μ_g mL^{-1}). *In vitro* growth of staphylococcus aureus was also inhibited by curcumin at concentration of 2.5-50 mg/100 mL.

Choesterol level: Several *in vivo* studies on animals suggest that administration of curcumin decreased the cholesterol level in blood. The effect of curcumin on serum cholesterol levels and on LPO in the liver, kidney, brain and lungs of mice treated with carbon tetrachloride, panaquat and cyclophosphamide was investigated by Soudamini *et al.* (1992). The curcumin significantly decreases the increased peroxidation of lipids in these tissues, produced by these chemicals. The curcumin intake also significantly decreases the tissue and serum cholesterol level, indicating the fact that it helps in peroxide induced injury like liver damage and arterial diseases.

In another study investigated that the serum level of cholesterol and lipid peroxides is decreased by the using 500 mg of curcumin per day for 7 days, decreases serum cholesterol level by 12%, decreases in serum lipid peroxides level with 33% and increases high density lipoproteins (HDL) cholesterol with 29% significantly.

Rheumatoid arthritis: Curcumin play a major role in curing the patients suffering from arthritis. In case of arthritis reactive oxygen species or free radicals are responsible for inflammation and pain in joints.

The effect of curcumin of rheumatoid arthritis was first demonstrated by Deodhan *et al.* (1980) in definite rheumatoid arthritis patients. They observed a significant effect of curcumin (1200 mg day^{-1}) with compared to phenylbutazone (300 mg day^{-1}) in arthritis patients and found that curcumin produces significant improvement in walking time, reduce joint swelling and morning stiffness within two weeks treatment. Curcumin may also help underlying causes of inflammation and reduce damage to bone and cartilage (Bharat, 2007) and has worked as well as cortisone or phenylbutazone for rheumatoid arthritis, osteoarthritis and post operative inflammation with no side effect.

Cataract: Cataract is an age related typical problem with the risk factors including diabetes, excess sunlight exposure, steroid uses, nutritional deficiencies, genetic factors etc. In a study on rats (Suryanarayana *et al.*, 2003) reported that diabetes and the duration of the problem increases the risk of formation of cataracts. The effect of curcumin was investigated on galactsose induced cataract in rats by Suryanarayana *et al.* (2005). In that study they divided the 21 days old Sprague - Dawley rat into 5 groups. The control group (one) received an AIN-93 diet, the group (second) received 30% galactose in the diet, the test group (Third and fourth) received the second group diet plus 0.002% and 0.01% curcumin respectively and group (fifth) received the control diet plus 0.01% curcumin all for 4 weeks. Their observation indicate that curcumin at 0.002% (group third) delayed the onset and maturation of cataract. The slight delay was found in the onset of cataract at the 0.01% level (group four), maturation of cataract was faster when compare to group second. Bio chemical analysis showed that curcumin at the 0.002% level appeared to exert antioxidant and anti glycating effects as it inhibit lipid per oxidation (LPO) advanced glycated and product (AGE) - fluorescence and protein aggregation. Though the reasons for faster on set and maturation of cataract in group fourth, rats was not clear, the data suggested that higher levels of curcumin

(0.01%) in the diet may increase oxidative stress, AGE formation and protein aggregation under hyper glycemic condition. However, feeding of curcumin to normal rats up to a 0.01% level did not result in any change in lens morphology or bio chemical parameters. These finding suggest that curcumin is effective against galactose induced cataract only at very low amounts (0.002%) in the diet. On the other hand at and above a 0.01% level curcumin seems to not be beneficial under hyper glycemic conditions, at least with the model of galactose cataract.

In another study Suryanarayana *et al.* (2005) demonstrated that curcumin are effective against development of diabetes cataract in rats. The observation suggest they curcumin delayed the progression and maturation of cataract. The study suggest that curcumin treatment appear to have countered the hyperglycemia induced oxidative stress, because there was a reversal of changes with respect to lipid per oxidation, protein carbonyl content, reduced glutathione and activities of antioxidant enzymes in a significant manner.

Stress: Curcumin induces the hemoxygenase-1 (HO-1), a redox sensitive inducible protein that provides protection against various forms of stress. Study suggested that curcumin stimulates the expression of Nrf 2, an increase associated with a significant increase in hemoxygenase-1 (HO-1) protein expression and HO-1 activity (Balogun *et al.*, 2005). In a study, MG induced cell death and apoptotic biochemical changes such as mitochondrial cytochrome-C, cleavage of poly [ADP-ribose] polymerase (PARP) and caspase-3 activation found to be prevented by curcumin (Li *et al.*, 2002). The study demonstrate that MG induced ROS formation significantly attenuated by curcumin and suggest that ROS triggers cytochrome C release, caspase activation and subsequent apoptic bio chemical changes. According to Sharma *et al.* (2001b) curcumin blocks the detrimental effects of RTV, which is associated with various types of vascular dysfunction induced by oxidative stress.

CONCLUSION

The long established image of turmeric as a commercial dye stuff, food preservative and component of curry was probably responsible for overshadowing its importance as medicinal herbs. Discovery of its active constituent-'curcumin' has considerably changed the significance of turmeric and it looks like as though it is medicinal treasure. Now it is indisputable fact that curcumin possesses more than 25 biological activities, only 10 important medicinal properties are described in this review article. The great potential of curcumin is due to the fact that it acts upon several important molecular targets (Pandey *et al.*, 2010). As a result it is used to treat various disorders. Curcumin is supposed to be the safe drug which does not show any adverse effect even up to doses as high as 8 g day^{-1}. In addition there are no reports on development of resistance against curcumin.

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