CURCUMIN: A NATURAL PRODUCT OF BIOLOGICAL IMPORTANCE

Asif Nawaz[1], Gul Majid Khan[1], Abid Hussain[1], Akhlaq Ahmad[1], Arshad Khan[2] and Muhammad safdar[3]

[1]*Department of Pharmaceutics, Faculty of Pharmacy, Gomal University, D.I.Khan, KPK Pakistan*
[2]*Health Care& Clinical Research Center, Faculty of Pharmacy, Gomal University D.I.Khan*
[3]*Department of Microbiology, Kohat University of Science and Technology, Kohat, KPK, Pakistan*

ABSTRACT

Curcumin is a small molecular weight, polyphenolic compound, isolated from the roots of *curcuma longa* L. (family zingiberaceae), has been used traditionally for centuries in Asia for medicinal, culinary and other purposes. A large number of *in vitro* and *in vivo* studies in both animals and man have indicated that Curcumin has strong antioxidant, anti-inflammatory, anti-carcinogenic, anti-microbial, anti-parasitic and other activities. The mechanisms of some of these actions have recently been intensively investigated. Safety evaluation studies indicate Curcumin is well tolerated at a very high dose without any toxic effects. Thus, Curcumin has the potential for the development of modern medicine for the treatment of various diseases.

INTRODUCTION

Natural plant products have been used throughout human history for various purposes; hundreds of studies were conducted to investigate the effects of natural origin compounds on human health and prevention and treatment of dieses (Schmidt *et al*., 2007). Among studied compounds of natural origin polyphenols appear as one of the most important group. These polyphenols have recently received much attention in disease prevention and treatment due to their antioxidant properties (Zern and Fernandez, 2005). Among polyphenols, Curcumin is one of the most studied substances (Fig. 1). It is hydrophobic, low molecular weight polyphhenol widely used in the form of spice, turmeric (Anand *et al*., 2007).

Curcuma spp. contain tumerin (a water soluble peptide), essential oils (such as tumerones, atlantones and zingiberene) and curcuminioids including Curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione].

Curcuminoids can be defined as phenolic compounds derived from the roots of curcuma spp. (Zingiberaceae).

Fig.1: source of Curcumin

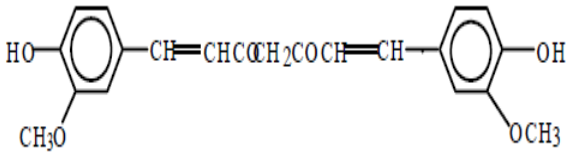

Fig.2: Chemical structure of Curcumin

Curcumin use for health purposes is nothing new. The long list of uses of Curcumin include, antioxidant, anti-inflammatory, anticancer, antimalarial, insectrepellant, antiseptic, analgesic and wound healing activities (Araujo and Leon, 2001).

The aim of this article is to invite researchers to investigate new curcuminoid derivatives with chemical modifications based in structure and biological activity relationships, in order to find new drugs that can be less toxic to humans and also can be used for the treatment of many diseases.

Chemical Properties of Curcumin

Curcumin [1, 7-bis (hydroxyl-3-methoxyphenyl)-1,6- heptadiene-3, 5-dione] (Fig. 2), is the most important active ingredient responsible for the biological activity of turmeric. It was first isolated from the drug in 1815, but its structure was not elucidated until 1913. Curcumin is insoluble in water, but soluble in ethanol and acetone. The naturally occurring ratios of curcuminoids in curcumin are about 5% bisdemethoxycurcumin, 15% demethoxycurcumin, and 80% Curcumin (Ireson *et al*., 2001).

Curcumin is relatively unstable in phosphate buffer at pH 7.4, and the stability is strongly improved by either lowering the pH, or by adding glutathione, *N* acetyl cysteine, ascorbic acid or rat liver microsomes (Oetari S et al 1996). Chemical synthesis of curcumin analogues has resulted in compounds with stronger anti-oxidant and cancer chemoprotective activities (Youssef et al., 2004).

Bioavailability and Pharmacokinetics

Various studies have shown the biotransformation of Curcumin. It was first biotransformed to dihydrocurcumin

and tetrahydrocurcumin, these compounds were than subsequently converted to monoglucuronide conjugates (Lin *et al*., 2000). Thus the major metabolites of Curcumin are Curcumin-glucuronide, dihydrocurcumin glucuronide, tetrahydrocurcumin-glucuronide and tetrahydrocurcumin. Biotransformation of Curcumin occurs mainly in the liver, although some metabolism occurs in the kidney and gastrointestinal tract.

The systemic bioavailability of Curcumin is very low; therefore the pharmacological activity of Curcumin may be mediated, in parts, by its metabolites. The major metabolites of Curcumin in the suspension of human hepatocytes are hexahydrocurcumin and hexahydrocurcuminol while the predominant metabolites of Curcumin in human plasma *in vivo* are Curcumin glucuronide and Curcumin sulfate.

Curcumin has poor bioavailability due to its rapid metabolism in the liver and intestinal wall. Curcumin bioavailability can be increased by administration of piperine, a known inhibitor of hepatic and intestinal glucuronidation. Piperine enhances the serum concentration, extent of absorption and bioavailability of Curcumin in humans (Shoba *et al*., 1998).

Pharmacological Properties

Curcumin and its derivatives and many other extracts from the rhizomes were found to be bioactive. Some of the pharmacological and biological properties of Curcumin and is derivatives are discussed as below.

Antioxidant property of Curcumin

The antioxidant property of Curcumin and its three derivatives are studied by Unnikrishnan and Rao (Ruby *et al*., 1995). The authors demonstrated that the use of Curcumin provides the protection of hemoglobin from oxidation at very low concentration as 0.08 mM. Diacetyl Curcumin has little effect in the inhibition of nitrite induced oxidation of hemoglobin. The antioxidant property of Curcumin could be mediated through antioxidant enzymes such as superoxide dismutase, glutathione peroxide and catalase. Curcumin has been found to be ten times more active than vitamin E. In Curcumin, the phenolic and methoxy group on the phenyl ring and the 1.3-diketone system semm to be important structural features that can contribute to

the antioxidant property of the Curcumin (Motterlini *et al*., 2000).

Anti-inflammatory activity

Anti-inflammatory drugs like steroids and NSAIDs are associated with numerous side effects, probably the best example is the cardiovascular complications caused by the use of most coxibs. Curcumin is one of the most promising candidates of natural origin having anti-inflammatory activity with no side effects (Aggarwal and Sung, 2009).

Mechanism of anti-inflammatory activity (Jurenka, 2009).

- It suppresses the activation of transcription factor NF-kB, which is responsible to regulate the expression of pro-inflammatory gene products.
- It is responsible for the down-regulation of the expression of cyclooxygenase-2 (COX-2), an enzyme linked with most types of inflammation.
- It is responsible for decreasing the expression of various inflammatory cytokines, including TNF, IL-1, IL-6, IL-8 and chemokines.

All these effects are responsible to lower the formation of inflammatory compounds and suppress the inflammatory response.

Anticancer property of Curcumin

Curcumin is a potent anticancer agent. Curcumin suppresses the cancer of the skin, mammary gland, oral cavity, lung, liver, forestomach, oesophagus, stomach, intestine and colon.

The mechanism of anticancer activity of Curcumin is as (Kuttan *et al*., 1985).

- Curcumin has the activity to inhibit cell proliferation.
- It inhibits cytochrome P450 isoenzymes.
- It suppress certain oncogenes e.g. cHa-ras, c-jun and c-fos.
- It inhibits cell-cycle-related proteins (PCNA, cyclin E, p34cdc2).
- It inhibits tumor implantation.
- It inhibits biotransformation of carcinogens and
- Induction of gluthathione S-transferase (GST) activity.

Curcumin effects in cardiovascular diseases

Curcumin is one of the most effective natural origin agent used for the

treatment of various cardiovascular diseases. Some of the important actions of Curcumin on the cardiovascular system are as follows

- Curcumin has effects on the proliferation of pheripheral blood mononuclear cells (PBMC) and vascular smooth muscle cells from the uptake of [3H] thymidine, which is a hallmark of atherosclerosis (Huang *et al*., 1992).
- Curcumin lowers the serum cholesterol level. Oral administration of Curcumin lowers the increased peroxidation of lipids in liver, lung, kidney and brain and also lowers the serum and tissue cholesterol level. The 3D structural data shows that Curcumin interacts with fatty acid-metabolizing enzyme, soybean lopoxygenase. Curcumin binds to lipoxygenase enzyme noncompetitively.
- Curcumin inhibits the platelet activating factor (PAF) and arachidonic acid (AA), much higher concentration of Curcumin is required to inhibit aggregation induced by other platelet agonist. Curcumin also inhibits the formation of thromboxane A2 (TXA2) by platelets (Shah *et al*., 1999).

Curcumin enhances wound healing

Tissue repair and wound healing are complex processes. Curcumin has very effective wound healing activity, examined in rats and guinea pigs (Sidhu *et al*., 1998). *In situ* hybridization and PCR analysis shows an increase in the mRNA transcripts of transforming growth factor beta 1 (TGFβ1) and fibronectin in Curcumin treated wounds. Transforming growth factor beta 1 enhance wound healing, therefore it is possible that Curcumin modulates TGF β1 activity.

Antibacterial and anti-fungal actions:

Kim et al reported *in vivo* the action of Curcumin and materials derived from *Curcuma longa* rhizomes against several plant pathogenic fungi. The responses varied with the tested pathogen. Fungicidal action comparable to that of the fungicidal agent chlorothalonil was observed with Curcumin. More recently, Mishra et al tested various synthesized Curcumin bioconjugates viz. 4,4′-di-*O*-glycinoyl-curcumin, 4,4′-di-*O*-D-alaninoyl-curcumin, curcumin-4,4′-di-*O*-β-Dglucopyranoside and 4,4′-di-*O*-acetylcurcumin, along with piperoyl

glycine, against different bacteria and fungi *in vitro*. The 4,4′-di-*O*-(glycinoyl-di-*N* piperoyl)- curcumin and 4,4′-di-*O*-acetylcurcumin were found to be more effective than Cefepime, a commercially available antibacterial drug, at the same concentration. These bioconjugates synthesized from Curcumin were found to be more potent than Curcumin itself against many common strains of bacteria, as well as fungi. The enhanced activity of these bioconjugates in comparison with Curcumin may be due to either improved cellular uptake or reduced metabolism of these bioconjugates, resulting in the building up of a sufficient concentration inside the infected cells. This report suggests that suitably designed Curcumin bioconjugates have the potential to become useful antibacterial/antifungal drugs.

Toxicological Properties

Curcumin is considered to have a low toxicity in man and animals. In a clinical trial with 25 volunteers, administration of up to 8 gm of Curcumin per day has no apparent toxic sign. In another clinical trial in which humans were given 1.25-2.5 gm Curcumin per day confirmed the apparent safety of the substance (Chainani-Wu, 2003). There are no reports of adverse effects of either Curcumin or its analogues except for rare cases of contact dermatitis. Many women in Asia apply turmeric to their skin in an effort to minimize unwanted hair growth, but few experience dermatitis. Oral administration of Curcumin to rats at doses up to 5 g/kg caused no overt signs of toxicity. The American Herbal Association classifies turmeric as a menstrual stimulant and some sources recommended avoiding Curcumin in pregnancy. Its use is not recommended during breast-feeding, as effects on breast-feeding infants are unknown (Oetari *et al*., 1996). Turmeric may have an antiplatelet activity (Shah *et al*., 1999), and its concurrent use with anticoagulants may lead to an additive effect. Although there are no reports of this in humans, its use should be avoided in patients with bleeding disorders and bile duct obstruction and should only be used under the supervision of a physician in patients with gallstones.

CONCLUSIONS

Curcumin is a natural substance with many pharmacological activities, some

of which have been experimentally and clinically utilized in both man and animals. Notable among these are the antioxidant, anti-inflammatory and anti-carcinogenic properties, all three of which seem to be interrelated. It is encouraging that Curcumin is of low toxicity. Despite a plethora of phytochemical, pharmacological, biochemical and toxicological data on Curcumin, large well-designed clinical trials and epidemiological data are warranted to substantiate it usefulness in the treatment and/or prevention of cancer, rheumatoid arthritis and other conditions of human patients.

REFERENCES

Aggarwal B B and Sung B (2009). Pharmacological basis for the role of Curcumin in chronic diseases: an age-old spice with modern targets. Trends in Pharmacological Sciences 30: 85-94.

Anand P, Kunnumakkara A B, Newman R A and Aggarwal B B (2007). Bioavailability of curcumin: problems and promises. Molecular Pharmaceutics., 4: 807–818.

Araujo C A C and Leon L L (2001). Biological activities of Curcuma longa L. Mem. Inst. Oswaldo Cruz. Riode Janeiro., 96: 723 - 728.

Chainani-Wu N (2003). Safety and anti-inflammatory activity of curcumin: A component of turmeric (*Curcuma longa*). *Journal of Alternative and Complementary Medicine., 9*: 161-168.

Huang MT, Wang ZY, Georgiadis CA, Laskin JD and Conney AH (1992). Inhibitory effects of Curcumin on tumor initiation by benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene.

Carcinogenesis., 13(11): 2183–2186.

Ireson C, Orr S and Jones DJL (2001). Characterization of metabolites of the chemopreventative agent curcumin in rat and human hepatocytes and in rat *in vivo*, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. *Cancer Research., 61*: 1058-1064.

Jurenka J S (2009). Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Alternative Medicine Review: A Journal of Clinical Therapeutic 14: 141-153.

Kuttan R, Bhanumathy P, Nirmal K, and George MC (1985). Potential anticancer activity of turmeric (*Curcuma longa*). *Cancer Lett.,* 29(2): 197–202.

Lin JK, Pan MH and Lin-Shiau SY (2000). Recent studies on the biofunctions and biotransformations of curcumin. *Biofactors.,* 13(1–4): 153–158.

Mishra S, Narain U, Mishra K and Misra K (2005). Design, development and synthesis of mixed bioconjugates of piperic acid-glycine, curcumin-glycine/alanine and curcumin-glycine-piperic acid and their antibacterial and antifungal properties. *Bioorganic and Medicinal Chemistry., 13*: 1477-1486.

Motterlini R, Foresti R, Bassi R and Green CJ (2000). Curcumin, an antioxidant and anti-inflammatory agent, induces heme oxygenase-1 and protects endothelial cells against oxidative stress. *Free Radic Biol Med.,* 28(8): 1303–1312.

Oetari S, Sudibyo M, Commandeur JN, Samhoedi R and Vermeulen NP (1996). Effects of curcumin on cytochrome P450 and glutathione S-transferase activities in rat liver. *Biochemical Pharmacology., 51*: 39-45.

Ruby AJ, Kuttan G, Babu KD, Rajasekharan KN and Kuttan R (1995). Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer Lett.,* 94(1): 79–83.

Schmidt BM., Ribnicky D M, Lipsky P E and Raskin I (2007). Revisiting the ancient concept of botanical therapeutics. Nature Chemical Biology 3: 360 – 366.

Shah BH, Nawaz Z, Pertani SA, Roomi A, Mahmood H, Saeed SA and Gilani AH (1999). Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor- and arachidonic acidmediated platelet aggregation through inhibition of thromboxane formation and Ca2+ signaling. *Biochem Pharmacol.,* 58(7): 1167–1172.

Shah BH, Nawaz Z and Pertani SA (1999). Inhibitory effect of curcumin, a food spice from turmeric, on platelet-activating factor and arachidonic and acid-mediated platelet aggregation through inhibition of thromboxane and Ca2+ signaling. *Biochemical Pharmacology., 58*: 1167-1180.

Shoba G, Joy D, Joseph T, Majeed M, Rajendran R and Srinivas PS (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med.,* 64(4): 353–336.

Youssef KM, El-Sherbeny MA, El-Shafie FS, Farag HA, Al-Deeb OA and Awadalla SR (2004). Synthesis of curcumin analogues as potential antioxidant, cancer chemopreventative agents. *Archiv der Pharmazie (Weinheim.,) 337*: 42-54.

Zern T L and Fernandez M L (2005). Cardioprotective effects of dietary polyphenols. The Journal Nutrition 135: 2291-2294.