Curcumin: Nutraceutical and Pharmaceutical Applications

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ABSTRACT

Medicinal plants can be used for the treatment of many diseases is associated to folk medicine from different parts of the world. Natural and herbal products from some plants, fungi, bacteria’s and other organisms, continue to be used in pharmaceutical formulations either as pure compounds or as extracts. There is a great variety of compounds that can be extracted and characterized from plants, herbs and roots. One good example is the harmaline, one of the indole alkaloids found in Peganum harmala (Zygo-phylaceae), used in the treatment of dermatosis. Extensive scientific research on curcumin, a natural compound present in the rhizomes of plant Curcuma longa Linn. The natural product curcumin (diferuloylmethane, 1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione), obtained from the spice turmeric is a rhizomatous herbaceous plant belonging to the family Zingiberaceae, exhibits numerous biological activities. It is the major constituent of the oleoresin of turmeric. In the crude extract of rhizomes of C. longa about 70-76% curcumin is available along with about 16% demethoxycurcumin and 8% bisdemethoxycurcumin. Curcumin which is commonly used as a spice is also well documented for its medicinal properties in Indian and Chinese systems of medicine. It is extensively used for imparting color and flavor to the food. Extensive scientific research on curcumin had demonstrated a wide spectrum of therapeutic effects such as anti-inflammatory, antibacterial, antiviral, antifungal, antitumor, antispasmodic, hepato-protective, anti-angiogenic, anti-oxidant, wound healing, anti-cancer effects, nematocidal activities, anti-protozoal activity, anti-venom activity. Recently, its potential utility in Auto-Immune Deficiency Syndrome (AIDS) had been demonstrated. A number of curcumin based pyrazoles an isoxazoles and a diazepine had been synthesized and evaluated for their antibacterial activities.

Keywords: Curcumin, anti-inflammatory, antibacterial, antiviral, antifungal, antitumor, antispasmodic, hepato-protective, anti-angiogenic.
INTRODUCTION

The increasing importance in traditional medicine, chiefly plants-based medicine has headed to wide research on the potentials of natural origin substances. Large amount of studies were carried-out to explore the effects of natural origin compounds on human health and prevention and treatment of chronic diseases (Schmid et al., 2007). Among the various compounds studied, polyphenols are found as one of the most promising groups. In plants, polyphenols plays an important role in growth and protection against pathogens. In recent times polyphenol have received greater attention due to their demonstrated antioxidant capabilities against prevention and treatment of disease (Zern and Fernandez, 2005). Polyphenols are derived from components of the human food such as peanuts, dark chocolate, green and black tea and turmeric etc. Ayurveda, Unani, Siddha and Chinese medicines recommend turmeric for a wide range of disorders and diseases. Turmeric has been used traditionally for many ailments because of its wide spectrum of biological and pharmacological activities. Among the various polyphenols present, curcumin is currently one of the most studied substances. Curcumin has been identified as the active principle of turmeric. Curcumin has been used in traditional medicine for many centuries mainly in Asian countries such as India and China (Shishodia et al., 2005). It is chemically a yellow hydrophobic polyphenol, diferuloylmethane extracted from the rhizomes of turmeric (Curcuma longa), it is a bis-α, β-unsaturated β-diketone that exhibits keto-enol tautomerism, which exhibits keto-enol tautomerism having a predominant keto form in acidic and neutral solutions and stable enol form in alkaline medium. Commercial curcumin contains approximately 77% diferuloylmethane, 17% demethoxycurcumin, and 6% bisdemethoxycurcumin. Curcumin has been shown to exhibit antioxidant, anti-inflammatory (Srimal and Dhawan, 1973; Sherma, 1976; Ruby et al., 1995; Sugiyama et al., 1996) , antimicrobial and anti-carcinogenic activities (Kuttan et al., 1985; Jordan and Drew, 1996; Kim et al., 2003; Reddy et al., 2005). Additionally, the hepato-protective and nephro-protective (Kiso et al., 1998; Venkatesan, 1998; Venkatesan et al., 2000), thrombosis suppressing (Dikshit et al., 1987), myocardial infarction protective (Dikshit et al., 1995; Nirmala and Puvanakrishnan, 1996ab), hypoglycemic (Srinivasan, 1972 ; Babu and Srinivasan, 1995; Babu and Srinivasan, 1997; Arun and Nalini, 2002) and anti-rheumatic (Deodhar et al.,1980) antitumor, anti-amyloid effects of curcumin are also well established. Various animal models (Shankar et al., 1980; Qureshi et al., 1992) or human studies (Lao et al., 1996ab; Shoba et al., 1998; Cheng et al., 2000) proved that curcumin is extremely safe even at very high doses as, it possesses low intrinsic toxicity. Inspite of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent. Curcumin is known to possess low systemic bio-availability (Ireson et al., 2001), attributed to a generally poor aqueous solubility poor absorption and faster metabolic alterations (Ireson et al., 2001; 2002) and intense staining color of curcumin have been highlighted as major problems.

History

The structure of curcumin (C21H20O6) was first described in 1910 by Lampe and Milobedesa and shown to be diferuloylmethane (Aggarwal et al., 2003). However Curcumin the major constituent of Curcuma longa L. (turmeric), was been isolated first early in 1815 by Vogel and Pelletier, but it has attracted few modern studies, then it was crystallized in 1870 by Daube and the structure was revealed in 1910 by Lampe and co-workers, who future completed a synthesis. Renewed interest has been evoked by the recent discovery of relative sharing the 1,7-diaryl skeleton.

Cultivation & Extraction

Turmeric (Curcuma longa) is a rhizomatous herbaceous plant belonging to the family Zingiberaceae. It is native to tropical South Asia and requires the temperatures in between 20-30°C and a considerable amount of yearly rainfall to flourish. Sangli a town in the southern part of the Indian state of Maharashtra is the leading and most significant trading centre for turmeric in Asia or possibly in the whole world.

Plants are collected annually for their rhizomes and re-seeded from some of those rhizomes in the following season. The gathered
rhizomes are then boiled for several hours and are dried in hot ovens after which they are pulverized into a deep orange-yellow powder i.e. turmeric powder which are commonly used as a spice in curries.

The obtained turmeric powders are then extracted with 95% alcohol in soxhlet assembly until all the coloring matter is completely extracted. The Alcoholic extracts are distilled of to a semisolid brown colored mass (about 4.5%) (Figure 1).

![Figure 1: The extraction of curcumin](image)

The crude extract is then dissolved in 50 ml of benzene and extracted two times with the same volume of 0.1% sodium hydroxide solution. The alkaline extracts are then combined and acidified with dilute hydrochloric acid. A yellow colored precipitate is thus formed. It is then allowed to settle down for 15 min, after settling down of precipitate (ppt). The extract is concentrated by boiling on water bath and at the same time dissolving the precipitate in boiling water. During this process of boiling the resinous material is agglomerated and lumpy mass is formed. The solution is then filtered in hot condition and the filtrate is concentrated to very small volume and finally cooled to get curcumin (1.5%). The final product obtained is recrystallized using 95% alcohol (Kokate, 1993).

**Structure of Curcumin**

Curcumin is an orange–yellow crystalline powder. Lampe and Milobedeska in 1910 first described the structure of curcumin (C_{21}H_{20}O_{6}) and shown to be diferuloylmethane. Curcumin 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a natural polyphenolic phytochemical extracted from the powdered rhizomes of turmeric (Curcuma longa). Hydroxyl groups of the benzene rings, double bonds in the alkene part and the central b-diketone moiety are suggested to be likely responsible for the high beneficial activities of this polyphenolic molecule (Figure 2).

![Figure 2: Structure of Curcumin (Keto form of curcumin and Enol form of curcumin)](image)

**Properties of Curcumin**

Curcumin belongs to the linear diarylheptanoid class of natural products in which two oxy-substituted aryl moieties are joined together by a seven-carbon chain. The C7 chain of linear diarylheptanoids is known to have unsaturation, oxo functions, enone moiety, and a 1,3-diketone group. Excluding for the oxo and hydroxy functions, the C7 chain is usually unsubstituted. This unsaturation in the linker unit has an E-configuration (trans C=C bonds). The aryl rings could be substituted symmetrically or unsymmetrically; the most prevalent natural substituents are of the oxy type, such as hydroxy or methoxy elements (Anand et al., 2008). Curcumin which has a molecular formula (C_{21}H_{20}O_{6}) is chemically known as 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione, it has a molecular weight of 368.37 g/mol and melting point of 183°C. Curcumin is poorly soluble in water (Zaveri et al., 2011), however it completely dissolves in methanol which is
further followed by acetone, normal amyl methyl ketone, ethanol, tetrahydrofuran, acetylacetone, chloroform, acetic acid, dimethyl sulfoxide, benzene, toluene, and CCl₄. Lambda max of curcumin in UV-Vis spectrophotometric investigation, where maximum light absorption of curcumin occurs around 400-430 nm depending upon organic solvent (Ganpati et al., 2011).

Figure 3: Structure of Curcumin and its metabolites

Figure 4: Biological properties of Curcumin
Metabolism and Elimination
The orally administered curcumin is absorbed from the alimentary tract and present in the general blood circulation after mainly being metabolized to the form of glucuronide/sulfate conjugates (Asai and Miyazawa, 2000). Once absorbed, Curcumin is subjected to conjugations like sulfation and glucuronidation at various tissue sites. Curcumin undergoes rapid metabolism in the liver particularly via glucuronidation, while curcumin given intraperitoneally or systemically undergoes reduction (Aggarwal and Sung, 2009). Metabolites produced from these pathways show low or no pharmacological activity (Aggarwal et al., 2007; Aggarwal and Harikumar, 2009). The major biliary metabolites of curcumin are glucuronides of dihydrocurcumin (DHC), tetrahydrocurcumin (THC) and hexahydrocurcumin (HHC). A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid (Holder et al., 1978). Various other metabolites of curcumin that have been reported, includes, octahydrocurcumin (OHC), curcuminolucuronide and curcumin sulfate. Tetrahydrocurcumin (THC), a partially reduced derivative of curcumin not found in turmeric, is one of the major metabolites of curcumin. Other reduced forms of curcumin, HHC and OHC, have also been considered curcumin metabolites, but have not been examined as extensively as THC. Tetrahydrocurcumin (THC) is obtained by partial hydrogenation of curcumin; it is colorless and more hydrophilic than curcumin.

A large amount of ingested curcumin is excreted mainly through the feces unmetabolized, the minor portion that is absorbed is extensively converted to its water-soluble metabolites, i.e. glucuronides and sulfate, and thus excreted. This seriously limits curcumin to reach targets distant from the gut and exert its beneficial action. The major route of eradication of the curcumin is through feces; the urinary excretion of curcumin is very low regardless of the dose. The elimination pattern of orally administered curcumin exhibit’s unchanged excretion mostly in the feces of the single oral administration over a period of 8 days. Maximum fecal excretion of curcumin occurs during first 24 h and gradually declines thereafter. Excretion of intact curcumin in the urine is only minimal (Suresh and Srinivasan, 2010) (Figure 3).

Safety Evaluation
Human clinical trials indicate that curcumin has no toxicity when administered at dose of 1-10g/day.

Stability
Curcumin has a poor light stability. It suffers photo-degradation when being exposed to light in solution as well as in solid form. curcumin is unstable at basic pH and undergoes alkaline hydrolysis in alkali (higher pH) solution. Hydrolytic decomposition also occurs even in in-vitro physiological condition (isotopicphosphate buffer. pH 7.2). Under acidic conditions, the degradation of curcumin is much slower. Curcuminin basic pH solution degrades with in 30 min to form trans- $6(4'$-hydroxy-3'$-methoxyphenyl)-2,4-dioxo-5-hexanal, ferulic acid, feruloylniethane and vanillin. Whereas in acidic conditions the degradation is less than 20% of total curcumin at 1 hour. When being exposed to sun light, both in ethanolic and methanolic extracts and as a solid curcumin degrades to give vanillin, vanillic acid, ferulic aldehyde and ferulic acid as final products (wikipedia.org/ wiki/ curcumin).

Adverse Reaction
No major side effect has been noted for curcumin for higher dose. Curcumin have shown few side effects, with some subjects reporting mild nausea or diarrhea.

Biological Properties of Curcumin
The various medicinal properties exhibited by the curcumin are as follows: anti-inflamatory, antioxidant, anti-carcinogenic activities, antimicrobial, antibacterial, antiviral, anti-protozoan, hepato- protective, nephro-protective, thrombosis suppressing and anticoagulant, myocardial infarction protective, nematocidal activities, hypoglycemic, hypolipemic, anti-rheumatic, antitumor, anti-amyloid effects, antispasmodic, anti-angiogenic, anti-venom activity (Figure 4).

Pharmacological Effect of Curcumin
1. Anti-inflamatory
The curcumin exhibits its anti-inflamatory activities by one of the following ways.
Perhaps one of curcumin’s most important activities in the human body is its ability to inhibit activation of the transcription factor, nuclear factor-kappa B (NF-κB), a potent inducer of chronic inflammation and also the anti-inflammatory effect of curcumin is mediated through its ability to inhibit COX-2, lipoxygenase and inducible nitric oxide synthase. It is a protein that acts as a sort of switch, turning on inflammation by activating genes involved in the production of inflammatory compounds. As NF-κB activation has been implicated in all the stages of carcinogenesis, this transcription factor is a potential target in cancer chemoprevention and is the subject of intensive research (Kiefer, 2012). The various tumor promoters, including phorbol ester, tumor necrosis factor (TNF), and H₂O₂, activate NF-κB and that curcumin down regulates the activation. Subsequently, the curcumin-induced down regulation of NF-κB is mediated through suppression of IκBα kinase activation. It also reported that curcumin suppresses the constitutively active NF-κB activation in mantle cell lymphoma. This led to the down regulation of cyclin D1, COX-2, and matrix metalloproteinase (MMP)-9 by curcumin (Aggarwal et al., 2007).

The other mechanisms implicated in the anti-inflammatory potential of curcumin may include:

1) Inhibition of arachidonic acid metabolism via lipoxygenase and scavenging the free radicals generated in this pathway
2) Down-regulation of the expression of various cell surface adhesion molecules that have been linked with inflammation
3) Decreasing the expression of various inflammatory cytokines, including TNF, IL-1, IL-6, IL-8, and chemokines
4) Curcumin is a potent antioxidant, which contributes to its anti-inflammatory action.

All these effects are thought to lead to lowering the formation of inflammatory compounds and suppressing the inflammatory response. This outcome is considered to be beneficial in many abnormal conditions such as autoimmune diseases (Sharma, 1976).

2. Antioxidant

The various authors demonstrated that antioxidant effect of curcumin is exhibited by following ways.

The antioxidant activity of curcumin arises mainly from scavenging of several biologically relevant free radicals that are produced during physiological processes. The curcumin act by protecting haemoglobin from oxidation even at a low concentration, several authors have studied the effect of curcumin on LPO in various models. Curcumin a good antioxidant acts by inhibiting LPO in rat liver microsomes, erythrocyte membranes, and brain homogenates. The LPO plays a major role in the inflammation, in heart diseases, and in cancer. The antioxidant action is mainly mediated through the antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase (Ruby et al., 1995; Sugiyama et al., 1996; Adams et al., 2000). Curcumin acts as a Michael acceptor, there by reacting with glutathione and thioredoxin thus interaction of curcumin with these agents decreases intracellular GSH in the cells (Adams et al., 2000). It has been demonstrated that curcumin is at least ten times more active as an antioxidant than even vitamin E (Khopde et al., 1999). The methoxy and phenolic group on the phenyl ring and the 1,3-diketone system may be considered important to show antioxidant property of curcumin. Additional information in the literature is exhibits that the antioxidant action of curcumin increases when the phenolic group with a methoxy group is at the ortho position (Motterlini et al., 2000).

3. Anti-carcinogenic

A broad examination of the works carried on curcumin characterises it as one of the excellent molecule among many naturally occurring compounds for cancer therapeutics.

Researchers of University of Alabama have published report in the Journal of Cancer Research, describing one of possibly various mechanisms by which curcumin functions as an anticancer agent. The investigators grew prostate cancer cells in the laboratory, and exposed them to varying concentrations of curcumin. Accordingly curcumin acts by decreasing the cell’s production of MDM2 a known protein, which is mainly associated with the formation of malignant tumors. Simultaneously, curcumin stimulates the cells to produce another protein which is associated with the promotion of programmed cell death (apoptosis) (Li et al., 2007). MDM2 have been recommended as
innovative target for human cancer therapy. Thus the curcumin acts by reducing the expression of MDM2. This down regulation exerts its anticancer activity which is considered as one of its mechanism against cancer.

The other mechanism involves pleiotropic properties of the curcumin which permit it to target the genome (DNA), messengers (RNA) and enzymes (proteins) within cells, actions that can be consecutive or instantaneous. Unlike other chemotherapeutic agents, curcumin exhibits pleiotropic properties that includes the modulation of nuclear factor-kappaB (NF-kB), transcription factor activator protein-1 (AP-1), tumor protein 53 (p53), mitogen-activated protein kinase (MAPK), nuclear b-catenin signaling and serine/threonine protein kinase (AKT) signalling pathways (Hatcher et al., 2008). It also down regulates the expression of estrogen receptors and epidermal growth receptor that are cancer-associated growth factors (Kunnumakkara et al., 2008). It has also been verified that it sensitizes tumor cells to first-line chemotherapies and radiation (Landis-Piwowar et al., 2010; Page and Yang, 2010; Maher et al., 2010). In cancer therapy development of multidrug resistance (MDR) causes minimal responses to regular cytotoxic agents and targeted biological therapies (Ejendal and Hrycyna, 2002; Loo and Clarke, 1999; Szakács et al., 2006). This result’s due to over expression of ATP-binding cassette transporters, which performs as drug-efflux pumps involved in the aggressive exclusion of drug molecules from the cells, thereby reducing the intracellular levels of these therapeutic molecules. This mechanism can be overcome by curcumin treatment, which reduces P-glycoprotein (P-gp), breast cancer resistance protein (ABCG2) and multidrug resistance protein (MRP-1) expression (Um et al., 2008).

4. Protection against Alzheimer’s disease

Curcumin also provides protection against the most common cause of dementia: Alzheimer’s disease. This disease is mainly characterized by the accumulation of amyloid-beta a malformed protein. generally, immune cells known as macrophages recognizes these defective proteins, engulf them, and kills them. In Alzheimer’s disease macrophages proves incompetent to perform this crucial function (Fiala et al., 2005).

CLCLUSION

The curcumin works by enhancing the clearance of amyloid-beta, and reducing fibrils, which are also associated with Alzheimer’s pathology. Curcumin’s ability of curcumin to cross the blood-brain barrier and to bind directly to plaques plays an important role in its anti-amyloid activity.

REFERENCES


