Biological Activities of *Curcuma longa* L.

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There are several data in the literature indicating a great variety of pharmacological activities of Curcuma longa *L. (Zingiberaceae), which exhibit anti-inflammatory, anti-human immunodeficiency virus, anti-bacteria, antioxidant effects and nematocidal activities. Curcumin is a major component in* Curcuma longa *L., being responsible for its biological actions. Other extracts of this plant has been showing potency too. In vitro, curcumin exhibits anti-parasitic, antispasmodic, anti-inflammatory and gastrointestinal effects; and also inhibits carcinogenesis and cancer growth. In vivo, there are experiments showing the anti-parasitic, anti-inflammatory potency of curcumin and extracts of* C. longa *L. by parenteral and oral application in animal models. In this present work we make an overview of the pharmacological activities of* C. longa *L., showing its importance.*

Key words: *Curcuma longa* L. - curcumin - medicinal plants

MEDICINAL PLANTS

The use of medicinal plants for the treatment of many diseases is associated to folk medicine from different parts of the world. Natural products from some plants, fungi, bacterias and other organisms, continue to be used in pharmaceutical preparations either as pure compounds or as extracts. There is a great variety of compounds that can be extracted and characterized from plants. One good example is the harmaline, one of the indole alkaloids found in *Peganum harmala* (Zygophyllaceae), used in the treatment of dermatosis (Iwu et al. 1994). Another substance that can be found in plants is the morphine from the opium poppy, which has highly analgesic action and is still used. Its molecule is used as a model for design to reach new drugs (Phillipson 1994). The isolation of artemisinin showed the real importance to investigate plants that can be sources of new compounds with clinical activities. Based on these facts, we can conclude that plants produce a large number of substances, which can provide a wide spectrum of biological properties.

The idea 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.

HISTORICAL BACKGROUND

Curcuma longa L., which belongs to the Zingiberaceae family, is a perennial herb that measures up to 1 m high with a short stem, distributed throughout tropical and subtropical regions of the world, being widely cultivated in Asiatic countries, mainly in India and China. In India is popularly known as "Haldi", in Malaysia, Indonesia and India has been well studied due to its economic importance. Its rhizomes are oblong, ovate, pyriform, often short-branched and they are a household remedy in Nepal (Eigner & Scholz 1999). As a powder, called turmeric, it has been in continuous use for its flavoring, as a spice in both vegetarian and non-vegetarian food preparations and it also has digestive properties (Govindarajan 1980). Current traditional Indian medicine claims the use of its powder against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorder, rheumatism and sinusitis (Ammon et al. 1992).

The coloring principle of turmeric was isolated in the 19th century and was named curcumin, which was extracted from the rhizomes of *C. longa* L., with yellow color and is the major component of this plant, being responsible for the anti-inflammatory effects. In old Hindu medicine, is extensively used for the treatment of sprains and swellings caused by injury (Ammon & Wahl 1991). The traditional medicine in China uses *C. longa* L. in diseases, which are associated with abdominal pains. Religious ceremonies still use turmeric in many forms.

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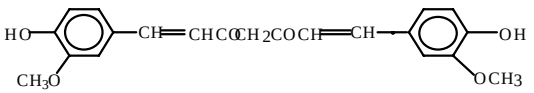
CHEMISTRY

The major constituent, curcumin (diferuloylmethane) is in the most important fraction of *C. longa* L. and its chemical structure (Figure and Table), was determined by Roughley and Whiting (1973). It melts at 176-177°C and forms red-brown salts with alkalis. Curcumin is soluble in ethanol, alkalis, ketone, acetic acid and chloroform; and is insoluble in water. In the molecule of curcumin, the main chain is aliphatic, unsaturated and the aryl group can be substituted or not.



Chemical structure of curcumin

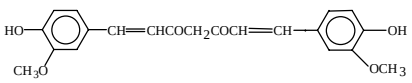
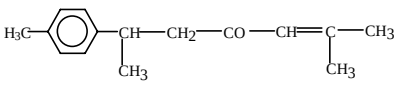
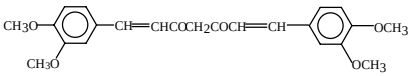
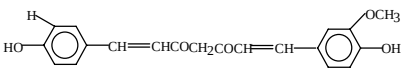
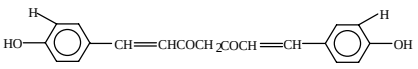
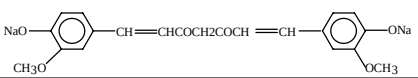
ACTIVITIES OF *CURCUMA LONGA* L.

Anti-inflammatory activity - There is a great number of papers in the literature relating the activity of compounds extracted from *C. longa* L. being potent inhibitors of inflammation. These substances can be classified as curcuminoids, analogues of diarylheptanoids. There are two models of inflammation to be studied: chronic models (cotton pellet and granuloma pouch), where the inflammation and granulomas develop during a period of time (several days), indicating the proliferative phase of inflammation; and acute models, where acute effects of anti-inflammatory agents can be studied, testing their inhibitory action on the development of rat paw edema.

Mukophadhyay et al. (1982) demonstrated the activity of curcumin and other semi-synthetic analogues (sodium curcuminate, diacetyl curcumin, triethyl curcumin and tetrahydro curcumin) in carrageenin-induced rat paw edema and cotton pellet granuloma models of inflammation in rats. In these experiments the authors used ferulic acid and phenylbutazone (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, triethyl curcumin was the most potent anti-inflammatory in the chronic model of inflammation, when compared with the others and with the drug reference; and tetrahydro curcumin 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 these experiments, would depend on the model of inflammation. Arora et al. (1971) investigated the anti-inflammatory activity in different fractions of the petroleum ether extract of the rhizomes of turmeric (two constituents) in animals. They found that the extracts reduced the granuloma growth and no toxic effects were ob-

TABLE

Curcumin and derivatives from *Curcuma longa* L. with biological activities

Compounds	Chemical structure	Activity
Curcumin		anti-bacteria *Leishmania amazonensis* anti-HIV antioxidant anti-inflammatory anti-tumor
Ar-turmerone		snakebite
Methylcurcumin		*L. amazonensis*
Demethoxy curcumin		antioxidant
Bisdemethoxy curcumin		antioxidant
Sodium curcuminate		anti-inflammatory

served. Chandra and Gupta (1972) demonstrated the anti-inflammatory and anti-arthritic actions of volatile oil of *C. longa* L. Ghatak and Basu (1972) showed the action of sodium curcuminate as an anti-inflammatory agent, being better than curcumin and hydrocortisone acetate, in experimental inflammation induced by carrageenin and formalin in albino rats (ED_{50} = 144 µg/kg), its more soluble in water than curcumin and no side effects were observed.

Pharmacological actions of curcumin as an anti-inflammatory agent have been examined by Srimal and Dhawan (1973). In this work, the authors reported that the compound was effective in acute as well as chronic models of inflammation. The potency of this drug is approximately equal to phenylbutazone in the carrageenin-induced edema test, but it is only half as active in the chronic experiments. It was observed that curcumin was less toxic than the reference drug (no mortality up to a dose of 2 g kg^{-1}). Huang et al. (1992) examined the inhibitory effects of curcumin on the proliferation of blood mononuclear cells and vascular smooth muscle cells. In blood mononuclear cells, curcumin was capable to impair the response of cells to mitogen, PHA and the response to alloantigen, MLR. The investigators suggested that curcumin could be use clinically in transplant atherosclerosis. The cinnamic acid derivatives were less active than curcumin. Ammon et al. (1992) demonstrated curcumin as an inhibitor of leucotriene formation in rat peritoneal polymorphonuclear neutrophils (PMNL), with an EC_{50} of 27 x 10^{-7} M, in contrast, the hydrocortisone did not show any effect.

Antioxidant activity - Unnikrishnan and Rao (1995) studied the antioxidative properties of curcumin and its three derivatives (demethoxy curcumin, bisdemethoxy curcumin and diacethyl curcumin). The authors demonstrated that these substances provide a protection of hemoglobin from oxidation at a concentration as low as 0.08 mM, except the diacethyl curcumin which has little effect in the inhibition of nitrite induced oxidation of hemoglobin.

The effect of curcumin on lipid peroxidation has also been studied in various models by several authors. Curcumin is a good antioxidant and inhibits lipid peroxidation in rat liver microsomes, erythrocyte membranes and brain homogenates (Pulla Reddy & Lokesh 1994). The lipid peroxidation has a main role in the inflammation, in heart diseases, and in cancer.

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 & Lokesh 1992). Pulla Reddy and Lokesh (1992) observed that curcumin is capable of scavenging oxygen free radicals such as superoxide anions and hydroxyl radicals, which are important to the initiation of lipid peroxidation. Another article about curcuminoids as potent inhibitors of lipid peroxidation was described by Sreejayan Rao (1994), in which the authors showed that three curcuminoids were inhibitors of lipid peroxidation in rat brain homogenates and rat liver microsomes. All of these compounds were more active than α-Tocopherol (drug reference) and curcumin showed the better results. In the case of curcumin, the methoxy group seems to play a major role. The phenolic and the methoxy 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 ligand for metals such as iron, used in these experiments. Another fact proposed in the literature is that the antioxidant activity increases when the phenolic group with a methoxy is at the ortho position. The mechanism of action of curcumin is still unknown.

Anti-protozoal activity - The first work to relate the activity of curcumin and some semi-synthetic derivatives in the literature against tripanosomatids was studied in promastigotes (extracellular) and amastigotes (intracellular) forms of *Leishmania amazonensis*. The authors showed that curcumin (a phenolic curcuminoid) in experiments in vitro has an excellent activity (LD_{50} = 24 µM or 9 mg/ml) and the semi-synthetic derivative, methylcurcumin (a non-phenolic curcuminoid), has the best action with a LD_{50} < 5 µg/ml and LD_{90} = 35 µM against promastigotes forms. This derivative was tested in vivo in mice and showed a good activity with 65.5% of inhibition of the lesion size of the footpad of the animals, when compared with the group inoculated with the parasites alone (Araújo et al. 1998, 1999). Another interesting point mentioned by the authors is that they did not observe any inflammatory reaction in the area where the drugs were injected, perhaps because curcuminoids are potent inhibitors of inflammation. Rasmussen et al. (2000) reported the efficacy of an ethanolic extract from *C. longa* against *Plasmodium falciparum* and *L. major*, which was able to inhibit the in vitro growth of these parasites.

Nematocidal activity - Curcuma oil was studied on *Paramecium caudatum* in different concentrations, varying from 1 in 2,000 to 1 in 5,000. The ciliates became sluggish and ultimately died (Chopra et al. 1941). Kiuchi et al. (1993) demonstrated the activity of fractions (methanolic and chloroformic) of turmeric against *Toxocara canis*. In this work they isolated a new curcuminoid, the

cyclocurcumin. All the substances did not show activity when applied independently, but the activity was observed when they were mixed, suggesting a synergistic action between them.

Anti-bacterial activity - Curcuma oil was tested against cultures of *Staphylococcus albus*, *S. aureus* and *Bacillus typhosus*, inhibiting the growth of *S. albus* and *S. aureus* in concentrations up to 1 to 5,000 (Chopra et al. 1941).

Bhavani Shankar and Murthy (1979) investigated the activity of turmeric fractions against some intestinal bacteria in vitro. In this work, total inhibition of growth of *Lactobacilli* in the presence of whole turmeric was observed (4.5-90 µl/100 ml). The other fraction, the alcoholic extract, was effective too (10-200 mg/ml), but the inhibition was not equal as the whole turmeric. Curcumin (2.5-50 mg/ml) only inhibited *S. aureus*.

Antivenom activity - A potent antivenom was tested against snakebite. The fraction consisting of ar-turmerone, isolated from *C. longa* L., neutralized both the hemorrhagic activity and lethal effect of venom in mice. In this study ar-turmerone was capable of abolishing the hemorrhagic activity of *Bothrops* venom and about 70% of the lethal effect of *Crotalus* venom. Ar-turmerone can act as an enzymatic inhibitor in the case of venom enzymes, with proteolytic and hemorrhagic activities (Ferreira et al. 1992).

Anti-HIV - Mazumber et al. (1995) demonstrated that curcumin has an antiviral activity, being a HIV-1 integrase inhibitor (IC_{50} = 40 µM) and suggested that curcumin analogs may be developed as anti-Aids drugs. Data showed that curcumin inhibited the replication of HIV-1 integrase protein. Eigner and Scholz (1999) reported that curcumin was claimed for anti-HIV-1 and HIV-2 activities in a recent patent application.

Anti-tumor activity - Huang et al. (1988), studying the effect of curcumin, chlorogenic acid, caffeic acid and ferulic acid on tumor promotion in mouse skin by 12-O-tetradecanoyl-13-acetate (TPA), observed that all these compounds inhibit the epidermal ornithine decarboxilase (ODC) and epidermal DNA synthesis, being curcumin the most efficient. In another work (1991), the results suggested that curcumin was a potent inhibitor of TPA- and arachidonic acid-induced inflammation and of lipoxygenase and cyclooxygenase activities in mouse epidermis. The IC_{50} for curcumin-dependent inhibition of these enzyme activities was 5-10 µM. In this study the results indicated that curcumin inhibited the epidermal metabolism of arachidonic acid via the lipoxygenase and cyclooxygenase pathways.

Furthermore, Ozaki et al. (2000), examining the action of curcumin on rabbit osteoclast apoptosis, demonstrated that curcumin drastically inhibits bone resorption in parallel with its stimulation of apoptosis in the cells. Since cancer and bone inflammation are diseases that increase bone resorption, the authors suggest that curcumin may be useful in the therapy of these pathogenies.

Other activities - Curcumin and its sodium salt have been showing a strong anti-inflammatory activity in carragenin and caoline-induced edema. Turmeric powder protects the gastric mucosa against irritants. Curcumin can decrease high cholesterol levels like statine and have antimutagenic activity (Scartezzini & Speroni 2000). Chuang et al. (2000) showed that curcumin at concentrations of 200 mg/kg or 600 mg/kg could effectively inhibit diethylnitrosamine-induced liver inflammation in rats. Other interesting action of this substance was demonstrated by Park et al. (2000), when acute hepatotoxicity was induced by intraperitoneal injection of carbon tetrachloride in rats. After these animals had been treated with curcumin and the results showed that the liver injury was inhibited.

STRUCTURE-ACTIVITY RELATIONSHIPS

It is known that curcumin, which can be extracted from *C. longa* L., belongs to the class of curcuminoids and is very similar to diarylheptanoids. In the literature we can find some authors that associate the anti-inflammatory activity of curcumin and its derivatives to the presence of hydroxyl and phenol groups in the molecule, being essential for the inhibition of prostaglandins (PG synthetase) and leucotrienes (LT) (Kiuchi et al. 1982, 1992, Iwakami et al. 1986). On the other hand, some authors suggested that the anti-inflammatory action is associated to the existence of the β-dicarbonylic system, which has the conjugated double bonds (dienes), being responsible for this activity (Claeson et al. 1993, 1996). This system seems to be responsible not only for anti-inflammatory power, but also to antiparasitic activity (Araújo et al. 1998, 1999). The presence of diene ketone system provides a lipophylicity to the compounds, and thus probably better skin penetration. Other factors can be mentioned here, like the presence of double bonds (α, β unsaturated system), which seems to increase the potency of some substances.

PHARMACOKINETIC STUDIES

Experiments involving rats, administrating curcumin orally were made by Wahlström and Blennow (1978). They demonstrated that this compound in a dose of 1 to 5 g/kg given to rats apparently did not cause any adverse effect and it was excreted in the faeces in about 75%, while traces

appeared in the urine. Curcumin (up to 5 µg/ml) added to microsomes suspensions disappeared within 30 min and it was similar in hepatocyte suspensions. It was capable of disappearing from the blood after intravenous or after addition to the liver perfusion system. It seems that curcumin is rapidly metabolized in circulation (Whalstöm & Blennow 1978). Little is known about the pathway of curcumin and its derivatives. It is necessary to study more about it.

CLINICAL STUDIES

There are data in the literature showing the administration of *C. longa* L. powder in different patients with respiratory diseases and it was observed that these treated patients have relief in symptoms like dyspnoea, cough and sputum or physical signs. Other authors reported the treatment of 18 patients with rheumatoid arthritis and found a real improvement on them, treated with 120 mg/day of the drug, administered orally in patients (Ammon & Wahl 1991).

CONCLUDING REMARKS

Based in the literature already described in this review, we can say that many works have been done trying to find compounds with low side effects and pharmacologically activities. The phytochemical seems to be a potential source, having different substances to be investigated, including alkaloids, curcuminoids, terpenoids, flavonoids, etc, which have been commonly used in folk medicine and have efficacy against many diseases. The herbal preparations used in India traditional medicine can be important to understand their use in the past as well as nowadays. Knowing that plants have a large number of chemical substances, which have several pharmacological actions, we should exploit more natural products, which in the future could show the cure for many illnesses. Finally, we hope that phytotherapies in official health care signal a new cycle of natural products research.

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