Pharmacology of *Curcuma longa*

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Received: May 2, 1990

Abstract

The data reviewed indicate that extracts of *Curcuma longa* exhibit anti-inflammatory activity after parenteral application in standard animal models used for testing anti-inflammatory activity. It turned out that curcumin and the volatile oil are at least in part responsible for this action. It appears that when given orally, curcumin is far less active than after *i.p.* administration. This may be due to poor absorption, as discussed. Data on histamine-induced ulcers are controversial, and studies on the secretory activity (HCl, pepsinogen) are still lacking. *In vitro*, curcumin exhibited antispasmodic activity. Since there was a protective effect of extracts of *Curcuma longa* on the liver and a stimulation of bile secretion in animals, *Curcuma longa* has been advocated for use in liver disorders. Evidence for an effect on liver disease in humans is not yet available.

From the facts that after oral application only traces of curcumin were found in the blood and that, on the other hand, most of the curcumin is excreted via the faeces it may be concluded that curcumin is absorbed poorly by the gastrointestinal tract and/or underlies presystemic transformation. Systemic effects therefore seem to be questionable after oral application except that they occur at very low concentrations of curcumin. This does not exclude a local action in the gastrointestinal tract.

Key words

Curcuma longa, curcumin, medicinal plants, anti-inflammatory activity, pharmacology.

Preface

The use of medicinal plants is based on the experience of many generations of physicans and traditional systems of medicine from different ethnic societies. The use of medicinal plants in modern medicine suffers from the fact that though hundreds of plants are used in the world to prevent or to cure diseases scientific evidence in terms of modern medicine is lacking in most cases. However, today it is necessary to provide scientific proof as to whether or not it is justified to use a plant or its active principles. Only few of medicinal plants have attracted the interest of scientists and been the subject of scientific investigations.

As far as modern drugs are concerned they must be further characterized after their pharmacological screening, that is a study of their pharmacokinetic properties and toxicity. Moreover, clinical studies must follow. Thus, by employing healthy volunteers there should be proof of whether or not pharmacological actions which have been found in animal and *in vitro* studies are also relevant to humans and, finally, it is necessary to study in a controlled manner whether or not medicinal plant preparations or active principles will in fact help to prevent or cure diseases in man.

Having this in mind the authors of the present review surveyed the literature available on *Curcuma longa* and tried to critically evaluate the scientific data. The editors feel that this is a very welcome way to initiate scientific research on medicinal plants and active principles. Reviews of this sort should be organized in such a way that finally also medicinal plants will have a scientific background and can, to a certain extent, compete with drugs of synthetic origin.

The idea for this review was given by the Thailand Government who invited the authors of this article to help to improve the scientific standard of some medicinal plants being used in Thailand and to point out where in the future research has to be initiated to complete a scientific profile of *Curcuma longa*. The editor of Planta Medica would welcome further review articles following these lines.

Historical Background

Curcuma longa L. (Zingiberaceae) is a perennial herb widely cultivated in tropical regions of Asia. Its rhizome is extensively used for imparting colour and flavour to food. As a powder, called turmeric, it is also used for medicinal purposes. In old Hindu texts it is ascribed for its aromatic, stimulant, and carminative properties. Turmeric mixed with slaked lime is known as a household remedy for the treatment of sprains and swellings caused by injury. For this purpose it is applied locally over the affected area.

Current traditional Indian medicine claims the use of turmeric against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis (1) – when translated into terms of modern medicine. The traditional medicine in China uses *Curcuma longa* in diseases which are associated with abdominal pains, icterus etc. (2).

Ethnologically, *Curcuma longa* still occupies an important position as every food should contain it in India. Religious ceremonies always make use of turmeric in any form.

Chemistry

The chemical study of different samples of turmeric has yielded essential oil (4.2 to 14 %), fatty oil (4.4 to 12.7 %), and moisture (10 to 12.0 %) (3). Srinivasan (4) has demonstrated the presence of three major constituents whereby curcumin (diferuloylmethane) formed the most important fraction, the two others being derivatives of curcumin [*p*-hydroxycinnamoyl(feruloyl)methane and *p,p'*-dihydroxydicinnamoylmethane]. The chemical structure of curcumin (Fig. 1) was determined by Lampe et al. (5).

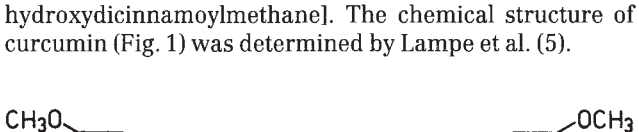

Fig. 1 Curcumin.

Pharmacodynamic Studies

Tremendous work has been performed on this plant, especially by Indian scientists (6).

Anti-inflammatory activity

Acute inflammation

A classical model for studying acute effects of anti-inflammatory agents is to test their inhibitory action on the development of rat paw edema – the exudative phase of inflammation – induced, for instance, by the local injection of carrageenin. This inflammation is thought to be in part due to the action of prostaglandin deriving from arachidonic acid metabolism. Yegnanarayan et al. (7) investigated various dried extracts of *Curcuma longa* (petroleum ether, alcohol, and water) after *i.p.* administration for their anti-inflammatory activity in the acute carrageenin-induced rat paw edema. They found that after 4 hours the water extract was the most active with an ED_{50} of 4.7 mg/kg. The alcoholic extract exhibited less activity (ED_{50} 309 mg/kg). In the same study the ED_{50} of the petroleum ether extract was 40.7 and that of curcumin 8.7 mg/kg. Unfortunately at that time no exact information was available as to the amount of active principles present in the various extracts. Possibly curcumin is of major significance.

Curcumin: Ghatak and Basu (8) reported high anti-inflammatory activity of curcumin as well as of sodium curcuminate in the carrageenin-induced edema test in rats with an ED_{50} of 2.1 and 0.36 mg/kg *i.p.*, respectively. In the same experiment hydrocortisone inhibited the edema by 47.8 % at a dose of 10 mg/kg *(i.p.)*. A systematic investigation on the anti-inflammatory activity of the rhizome of *Curcuma longa* was undertaken at the Central Drug Research Institute, Lucknow in 1969 (6). These studies indicated curcumin to be the major constituent responsible for the anti-inflammatory activity of extracts. A detailed evaluation of curcumin as a potential non-steroidal anti-inflammatory agent was, therefore, carried out and the results were reported by Srimal and Dhawan (6). Curcumin was found to be effective in the acute carrageenin-induced edema test in mice as well as rats after *oral* administration. The oral doses required to produce an anti-inflammatory effect, however, were much higher than the doses which were necessary for intraperitoneal administration giving a similar effect. Thus, the oral ED_{50} was 100.2 mg/kg in mice and 48.0 mg/kg in rats.

The effect of locally injected curcumin on inflammation produced by kaolin (0.05 ml of 25 % suspension) and carrageenin (0.05 ml of 1 %) in rats was also studied. A dose of 3 mg curcumin injected in the paw inhibited the kaolin-induced edema by 19.7 % at 24 h and by 22.4 % at 48 h. In the carrageenin test at 4 h the same dose was inactive (6), Mukhopadhyay et al. (9), however, found that 3 mg of curcumin was effective in rats against carrageenin edema when injected locally in the paw.

Naturally occurring analogues of curcumin, i.e. feruloyl-(4-hydroxycinnamoyl)-methane (FHM) and bis-[4-hydroxycinnamoyl]-methane (BHM), were screened for anti-inflammatory activity after oral administration also using the carrageenin-induced rat paw edema and compared with sodium curcuminate and phenylbutazone. FHM was the most potent among the 3 curcumin analogues studied. Curcumin analogues revealed a dose-dependent effect up to the dose of 30 mg/kg. Further increase of the dose of curcumin analogues (60 mg/kg) resulted in decreased anti-inflammatory activity (10).

Moreover, the oral administration of ferulic acid esters was shown to exert an inhibitory action in the carrageenin-induced rat paw edema model (11); 200 mg/kg produced an apparent inhibition of 25 %. Unfortunately comparisons of oral ED_{50} between curcumin, FHM, BHM, and ferulic acid esters are of no value since they include the pharmacodynamic and pharmacokinetic properties of the drugs which may differ among the compounds in question.

Volatile oil: Chandra and Gupta (12) found that the volatile oil (orally 0.1 ml/kg per day) of *Curcuma longa* suppressed acute edema. The activity of the essential oil has been attributed to its ability to stimulate the adrenohypophyseal axis because it was not effective in adrenalectomized animals. Tripathi et al. (13) reported that the volatile oil of the *Curcuma longa* plant inhibited trypsin and hyaluronidase enzymes.

Chronic models (granuloma pouch, cotton pellet)

In the above models, inflammation and granulomas develop during a period of several days. These models are indications for the proliferative phase of inflammation.

Extracts: Employing the cotton pellet method, the formalin-induced arthritis and the granuloma pouch method, Arora et al. (14) reported anti-inflammatory activity of the petroleum ether extract of *Curcuma longa*. Two of its fractions, i.e. a deep red viscous oil and a white crystalline solid, were positive in the Liebermann-Burchard test for steroids. After intraperitoneal administration of one of the three preparations in the rat, the activity of doses of 1.0 mg/100 g was well comparable with the effect of 0.5 mg/100 g hydrocortisone in the cotton pellet, formalin-induced, and granuloma pouch tests. Yegnanarayan et al. (7) investigated various extracts of *Curcuma longa* for anti-inflammatory activity in the granuloma pouch and the cotton pellet model in rats. They also observed significant activity at doses of 10 to 20 mg/kg *(i.p.)* daily.

Curcumin: In formalin-induced arthritis in rats Ghatak and Basu (8) found an almost 45 to 50 % inhibition by 0.1 mg/kg of sodium curcuminate, 3 mg/kg of curcumin (both orally), and in comparison 5 mg/kg of hydrocortisone *(i.p.)*.

In the studies of Srimal and Dhawan (6) curcumin inhibited the formalin-induced arthritis in rats with an ED_{50} of about 40 mg/kg being equipotent to phenylbutazone. In the subacute granuloma pouch (10 days) and cotton pellet tests (7 days), curcumin was found to be half as potent as phenylbutazone. However, such comparisons are difficult to interpret since the pharmacokinetics after *i.p.* administration of drugs are known to differ from those after oral application.

Volatile oil: Also the use of volatile oil (orally 0.1 ml/kg per day) suppressed the polyarthritis induced by Freund's adjuvant in the rat (12).

Considerations of the mechanism of action

Taken together, curcumin and the volatile oil from *Curcuma longa* appear to be responsible for the well documented anti-inflammatory action in the acute and subchronic models. Srimal and Dhawan (6) found curcumin to be less effective in adrenalectomized rats suggesting a participation of corticoidal steroids in the anti-inflammatory action of curcumin. On the other hand, Mukhopadhyay et al. (9) did not find any effect of low doses of sodium curcuminate on steroid release from the adrenal cortex. Sharma et al. (15) reported curcumin to be an effective agent inhibiting lipid peroxide formation in liver during inflammation and attributed this effect to an antioxidant property to explain the anti-inflammatory activity. A similar effect was obtained with phenylbutazone. Curcumin also inhibited the lipid peroxide formation *in vitro* (16). Anyway the predominant mechanism by which curcumin will inhibit inflammation still remains obscure. From the fact that quite high oral doses of curcumin [50–100 mg/kg (6)] are necessary to achieve an anti-inflammatory activity comparable to the effect of *i.p.* administration of the water extract [5–10 mg/kg (7)], it seems that curcumin possesses only little bioavailability after oral administration. Comparison of the anti-inflammatory activity of orally given extracts of *Curcuma longa* and its active constituents with the effect of orally given reference drugs must therefore be interpreted with caution.

Wound healing

A wound healing property of turmeric powder was reported by Gujral et al. (17). They applied turmeric powder over septic as well as aseptic wounds in rats and rabbits and found that the healing process was accelerated to an extent of 23–24 % in both cases which was comparable to the effect of scarlet red. Sulfanilamide powder, copper sulfate solution (0.1 %), and silver nitrate solution (0.1 %) were less effective.

Effects on the gastrointestinal system

Stomach

Curcuma powder has been reported by Mukherjee et al. (18) to increase the mucin content of gastric juice in rabbits. It may thus be beneficial in protecting the gastric mucosa against irritants.

Controversial data exist regarding an anti-ulcerogenic activity of curcumin. Sinha et al. (19) reported such an effect of curcumin whereas Bhatia et al. (20) did not find any protective action of curcumin in guinea pigs against histamine-induced gastric ulceration. Moreover, even an ulcerogenic effect of high doses of curcumin was reported by Prasad et al. (21): when administered at a daily oral dose of 100 mg/kg over 6 days curcumin produced gastric ulceration in albino rats. Pretreatment with adrenergic, cholinergic, and histaminergic (H_1) receptor antagonists provided partial protection against curcumin-induced gastric ulcers; metiamide, an H_2-antagonist almost completely prevented the development of gastric lesions and prevented a decrease in mucin secretion (22). However, it appears that the ulcerogenic activity may depend on the doses used since the ulcerogenic index reported by Srimal and Dhawan (6) when feeding curcumin to rats via a stomach tube was about one third compared to phenylbutazone, although it was significantly higher than in the untreated control group.

Intestines

Intestinal smooth muscle (antispasmodic activity): Employing the isolated guinea pig ileum, Srihari Rao et al. (10) calculated the ED_{50} of sodium curcuminate for antagonizing the effect of several spasmogens. They observed that curcuminate was inhibiting in a nonspecific manner, the ED_{50} values being against nicotine 30.2 µg/ml, acetylcholine 77.2 µg/ml, 5-hydroxytryptamine 82.8 µg/ml, histamine 81.8 µg/ml, and barium chloride 171.4 µg/ml.

However, such concentrations will not appear in the blood after oral administration (see below). Thus, *in vivo* a possible antispasmodic effect will only be conceivable – if at all – locally in the gastrointestinal tract.

Intestinal gas formation: The effect of curcumin on gas formation was studied by adding curcumin to *Clostridium perfringens* of intestinal origin *in vitro* and to chickpea flour diet known to be a flatulent food, which was then given to rats. *In vitro* there was a gradual reduction of gas formation from 0.005 % to 0.035 % curcumin in the diet. No gas formation was observed at 0.05 %. In the *in vivo* studies gas formation was 3.45 ml in animals receiving flatulent diet compared to 1.36 ml during control diet. Addition of curcumin to chickpea diet decreased the amount of gas produced. For a reduction to normal 0.1 % curcumin was required (23). This effect seems not to be due to antibacterial activity since the glucose utilization of *Clostridium perfringens* was not inhibited by 0.035 % of curcumin. It remains to be established whether or not therapeutical use of turmeric or curcumin will provide curcumin concentrations in the intestine sufficient to inhibit gas formation in man.

Liver

Using cultured rat hepatocytes, Hikino (24) showed the protective action of *Curcuma longa* against CCL_4-, D-galactosamine-, peroxide-, and ionophore-induced cytotoxicity. In further studies, Kiso et al. (25) supported these findings by following GOT and GPT in cultured rat hepatocytes. They found that curcumin (1 mg/ml) diminished CCl_4-induced GOT to 53 % and GPT to 20 % of the control. D-Galactosamine-induced increase of GPT was reduced to 44 % of the control. *p*-Coumaroyl(feruloyl)methane and di-*p*-coumaroylmethane, two analogues of the curcumoids, showed a similar activity.

Bile

Ramprasad and Sirsi (26) studied the effect of sodium curcuminate on bile secretion from the cannulated bile duct in anaesthetized dogs. They found it to cause a maximal increase of about 100 % in quantity after intravenous administration of 25 mg/kg. The essential oil had similar effects but it was less potent. They also found that even though there was a decrease in the concentration of solids in the bile, the total amount of bile salts, cholesterol, and bilirubin excreted under the effect of the drug was increased. Fatty acid content remained constant. In addition, gall-bladder muscles were stimulated (27, 28). Increase in bile production by curcumin (25 mg/kg) in cannulated male rats was also reported by Jentzsch et al. (29).

The doses used *i.v.* were, however, very large and therefore of no clinical relevance. It would therefore be of interest to determine whether oral administration would produce choleresis and cholekinesis by a possible indirect effect, i.e. through the release of gastrointestinal hormones.

An increase of bile flow total bile acids and solid dry matter by the essential oil of *Curcuma longa* (300 mg/kg orally) was reported by Ozaki and Liang (30). These authors ascribed the effect to its content of *d*-camphor. However, the high dose of the volatile oil used raises the question of practical relevance when related to the intake of turmeric.

Pancreas

Extensive studies with the pancreas were carried out by Chey et al. (31). In this connection 1-phenyl-1-hydroxy-*n*-pentane (PHP), a synthetic derivative of *p*-tolylmethylcarbinol, the latter being an ingredient of *Curcuma longa*, was employed. The effects of PHP on release of secretin, gastrin and pancreatic secretion of bicarbonate and protein were studied in both dogs and humans. In fasting dogs with gastric fistulas and modified Herrera's pancreatic fistulas, intraduodenal administration of PHP (pH 6.7) resulted in a significant increase in both plasma secretin concentration and bicarbonate output. The increases were dose related from 25 to 100 mg/kg. The bicarbonate output and plasma secretin concentration produced by PHP correlated well. No significant change occurred in either protein output or plasma gastrin concentration. The effect of intragastric PHP on release of secretin and pancreatic secretion was also studied in the digestive state. While gastric pH was maintained at 5.5 by intragastric titration with 1 N NaOH after intragastric administration of 5 % liver extract solution, PHP treatment (100 mg/kg) resulted in significant increases in both plasma secretin concentrations and pancreatic bicarbonate output. In the same experiment, the plasma gastrin concentration did not change significantly, whereas gastric acid secretion decreased. In 6 human volunteers, both plasma secretin concentration and pancreatic bicarbonate output significantly increased when 30 ml of a PHP solution (2 %), were infused during 30 min in the upper jejunum. Again, no increase in the protein output was detected. Secretin is apparently released by an agent other than acid and the increased pancreatic bicarbonate secretion is probably attributed to the increased plasma concentration of secretin.

Cardiovascular system

Sinha et al. (32) found a sharp and transient hypotensive effect of curcumin (7.5 mg/kg *i.v.*) in dogs which was resistant to block by atropine, antihistaminics, and beta-adrenergic antagonists. They also reported a depressant effect of curcumin on isolated guinea pig heart. Whether or not such effects occur also in response to oral administration has not been studied and for pharmacokinetic reasons appears to be unlikely.

Anticoagulant activity

1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (curcumin), *p,p'*-dihydroxydicinnamoylmethane, and *p*-hydroxycinnamoyl(feruloyl)methane were found to be the principles of *Curcuma longa* with anticoagulative activity when recalcification time in male mice (33) was measured. Srivastava et al. (34) stated that curcumin at doses between 25 and 100 mg/kg *(i.p.)* inhibits collagen- and adrenaline-induced aggregation of platelets *in vitro* as well as *ex vivo* but does not affect prostacyclin (PGI_2) synthesis by rat thoracic aorta. Collagen-induced platelet aggregation is known to be associated with an increase in

the thromboxane A_2 (TXA_2) levels. It is, therefore, conceivable that curcumin may have an anti-TXA_2 activity.

Hormonal system and metabolism

Antifertility action

Garg (35) observed that petroleum ether and aqueous extracts showed 100 % antifertility in rats at a dose of 200 mg/kg fed orally whereas no anovulatory action was seen. In another study by the same group (36), implantation was completely inhibited by the use of 100–200 mg/kg (oral) of a petroleum ether or aqueous extract of *Curcuma longa* rhizomes. Rao and Kotagi (37) demonstrated that administration of 0.1 ml/day of an alcohol extract to immature male rats for 10 days resulted in significant decrease in testes weight and testosterone concentration.

Lipid metabolism

Rao et al. (38) reported that rats fed with curcumin and cholesterol in diet had only half to one-third of the serum and liver cholesterol levels compared to the control group receiving cholesterol alone. The effective concentration was found to be less than 0.1 % of the diet. A similar effect was observed by Pachauri and Mukherji (39) in feeding 1 g of an ether extract of *Curcuma longa* to hypercholesterolemic rabbits. The data suggest hypolipemic activity of *Curcuma longa*. Whether these observations are due to inhibition of cholesterol absorption and/or synthesis in the liver remains to be established.

In another study (40) the effect of an ethanolic (50 %) extract (dried extract) of *Curcuma longa* (300 mg/100 g) given orally every 6 hours over a period of 48 hours in triton WR 1339-pretreated rats was tested. In this model the authors observed a significant fall of elevated plasma cholesterol and triglyceride as well as VLDL-, LDL-, and HDL-cholesterol levels; the HDL-cholesterol/total-cholesterol ratio was increased. Again, since the dose of extract used was extremely high, the practical impact of this finding must be established.

Microorganisms

Antibacterial effects

In connection with infectious cholecystitis, an alcoholic extract and active ingredients from *Curcuma longa* inhibited growth of most microorganisms occurring in cholecystitis including *Sarcinia, Gaffkya, Corynebacterium, Streptococcus*, and *Bacillus* strains. The concentrations used were 0.5–5.0 mg/ml curcumin or 5–100 µg/ml of the essential oil. Nearly all tested Gram-negative rods, some yeasts and molds were not susceptible to treatment with high concentrations of the examined substances. Standard and hospital strains developed an identical susceptibility to the substances tested. An alcoholic extract (50 mg/ml) and the essential oil (100 µg/ml) of *Curcum longa* showed bactericidal activity. Curcumin reacted as a bacteriostatic agent with respect to *Staphylococci* (41).

Bhavani Shankar and Sreenivasa Murthy (23) investigated the effect of *Curcuma longa* fractions on the growth of some intestinal and pathogenic bacteria *in vitro*. They found a significant suppression of growth of a wide variety of microorganisms by the oil-fraction (4.5–90 µl/100 ml). Curcumin (2.5–50 mg/100 ml) only inhibited *Staphylococcus aureus*, the alcoholic extract (10–200 mg/100 ml) of *Curcuma longa* induced morphological changes in *Streptococci, Lactobacilli*, and *Staphylococci*. Ramprasad and Sirsi (42) reported the antibacterial activity of sodium curcuminate. They found that *Micrococcus pyogenes* was specifically inhibited in a dilution of 1 part sodium curcuminate in 1 million parts of the solvent. The essential oil of *Curcuma longa* had a similar effect but only when used undiluted. Banerjee and Nigam (43) reported activity of essential oil from *Curcuma longa* against Gram-negative bacteria up to a dilution of 1 : 1000.

Antifungal effects

The crude ether and chloroform extracts of *Curcuma longa* stem were found to show fungistatic activity against several dermatophytes *in vitro* (44). Antifungal activity is reported from rhizomes of *Curcuma longa* by Venkitraman (45); Banerjee and Nigam (43) showed that the essential oil in dilution (1 : 10) inhibited the growth of different pathogenic fungi. The ethanol extract of rhizomes of *Curcuma longa* has been reported to have anti-amoebic activity against *Entamoeba histolytica in vitro* (46).

In terms of practical relevance of antimicrobial effects of *Curcuma longa* again it appears that they will be effective only when applied topically. This does not exclude an effect in gastrointestinal infections though remarkable amounts of curcumin are not absorbed.

Antitumor activity

12-*O*-Tetradecanoylphorbol 13-acetate (TPA) is a tumor promoting agent. It is used to produce skin tumors in mice. Topical application of 1, 3, or 10 µmol of curcumin together with 5 nmol TPA twice weekly for 20 weeks to mice previously initiated with 7,12-dimethylbenz[*a*]anthracene inhibited the number of TPA-induced tumors by 39, 77, and 98 %, respectively. This was also the case with the use of ferulic acid; the effect being, however, less in comparison to curcumin (47).

A potential anticancer activity of turmeric is also claimed by Kuttan et al. (48) from studies with tumor cell cultures where an ethanol extract of rhizomes of *Curcuma longa* inhibited cell growth of Chinese hamster ovary cells at a concentration of 0.4 mg/ml and was cytotoxic to lymphocytes and Dalton's lymphoma cells at the same concentration. The same effect was shown for curcumin, where 1–4 µg/ml have been effective. In the same study *i.p.* injection of liposome encapsulated curcumin inhibited tumor formation and increased survival rate of mice injected Dalton's lymphoma cells.

Toxicity Studies

Acute toxicity

In rats, Wahlstrom and Blennow (49) found no apparent toxic effects after doses up to 5 g/kg curcumin when given orally. Using guinea pigs, rats, and monkeys the

acute oral toxicity of *Curcuma longa* has been tested by Bhavani Shankar et al. (50) by evaluating histology and cytology of heart, liver, and kidney.

The whole spice turmeric or curcumin fed to rats at doses normally consumed by humans or at much higher doses (1.25–125-fold) did not cause any adverse effects on growth, feeding efficiency ratio, erythrocytes, leucocytes, or on the levels of blood constituents (Hb, total serum protein, albumin, globulin, serum aminotransferases, and alkaline phosphatase). At the highest level tried (10% curcumin), the feeding efficiency was much lower than normal because of low diet intake possibly due to unpalatability (51).

Teratogenic activity

Testing genotoxic effects of orally administered turmeric showed no significant changes in bone-marrow cells of mice in either chromosomal aberrations (52) or the micronucleus test (53). When extracts from fresh rhizomes of *Curcuma longa* were used, chromosome breakage and other aberrations were found *in vitro* (54).

Pharmacokinetic Studies

Absorption

When administered orally, in doses of 1 g/kg in rats, curcumin was excreted in the faeces for about 75% while only traces appeared in the urine (49). Oral doses of 0.6 mg/rat [^3H]curcumin led to the fecal excretion (72 h observation time) of about 89%, and 6% of the radioactivity was excreted in the urine. After *i.p.* administration, fecal excretion was about 73% of the radioactivity, 11% were found in the bile (55). Ravindranath and Chandrasekhare (56) reported 60% absorption of curcumin after oral administration of 400 mg to rats by determination of the amount excreted by the faeces. They found that at the end of 24 hours the concentration of curcumin remaining in the lower part of the gut (caecum, colon) amounted to 38% of the quantity administered. Nevertheless, they could not detect curcumin in portal or heart blood samples, only traces were measured in liver and kidney tissue when observed between 0.25 and 24 h after administration. From these data absorption into blood is unlikely. Nevertheless, the fate of the remaining amount not excreted in the faeces is unexplained. A possible explanation would be absorption (and transformation?) in the intestinal wall.

Distribution and blood levels

From their data on absorption, metabolism, and excretion, Wahlstrom and Blennow (49) concluded that it is unlikely that substantial concentrations of curcumin occur in the body after oral ingestion. Ravindranath and Chandrasekhare (56) could not detect curcumin colorimetrically in heart blood samples taken in a time range between 15 min and 24 hours after oral administration of 400 mg curcumin, ruling out levels higher than 0.5 µg/ml. In portal vein blood only traces (less than 5 µg/ml) and quantities of less than 20 µg/g from liver and kidney were observed in the same interval.

Metabolism/excretion

When *i.v.* injected or when added to the perfusate of isolated liver, curcumin was actively transported into the bile against concentration gradients of several hundred times. The major part of the drug was, however, metabolized. In suspensions of isolated hepatocytes or liver microsomes 90% of the added curcumin was metabolized within 30 min (50). In another study Holder et al. (55) reported that the major biliary metabolites of curcumin were glucuronides of tetrahydrocurcumin and hexahydrocurcumin. A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid. No urinary excretion of curcumin was observed as shown by the study of Ravindranath and Chandrasekhare (56). Thus, curcumin, if it is absorbed at all, after metabolism in the liver is mainly excreted through the bile.

Clinical Studies

A number of clinical studies were reported by Srimal and Dhawan (6), nevertheless only little detailed information is available.

Deodhar et al. (57) published the result of a short time, double blind crossover clinical trial in 18 patients with "definite" rheumatoid arthritis. They found significant improvement of morning stiffness, walking time, and joint swelling following two weeks of therapy with doses of 120 mg/day administered orally in all the patients.

Jain et al. (58) administered *Curcuma longa* powder in different forms to patients with various respiratory diseases (ayurvedic nomenclature; no specification according to modern medicine was given in the paper). They pretreated the patients for 3 to 7 days with placebo and bed rest. Then they administered capsules containing the drug and found significant relief in symptoms like cough, dyspnoea, sputum or physical signs on the basis of subjective patients reports.

In patients undergoing surgery the effect of oral curcumin (400 mg) three times a day on postoperative inflammation was studied in a double blind manner over 6 days. Inflammation was roughly scored as a total intensity score (TIS). The patients received also ampicillin. Phenylbutazone 100 mg also three times a day was given as a reference drug. Though curcumin significantly decreased TIS in comparison to placebo unfortunately the curcumin group started with a very high TIS of inflammation so that there was no homogeneous distribution of cases between the three groups (59). Further evidence is necessary to prove oral antiphlogistic activity of curcumin in man.

Acknowledgements

This work was supported by the Gesellschaft für technische Zusammenarbeit (GtZ), Eschborn.

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