

Turmeric – Nature's precious gift

N. M. Khanna

Turmeric (Curcuma longa) is a well-known indigenous herbal medicine. Its major constituents, curcumin, various curcuminoids, curcuma oil – particularly dl-ar-turmerone – exhibit a wide range of biological activities, e.g. anti-bacterial, anti-inflammatory, hypolipidemic, hepatoprotective, lipoxygenase, cyclooxygenase, protease inhibitory effects, besides being effective active oxygen species scavengers and lipid peroxidase inhibitors.

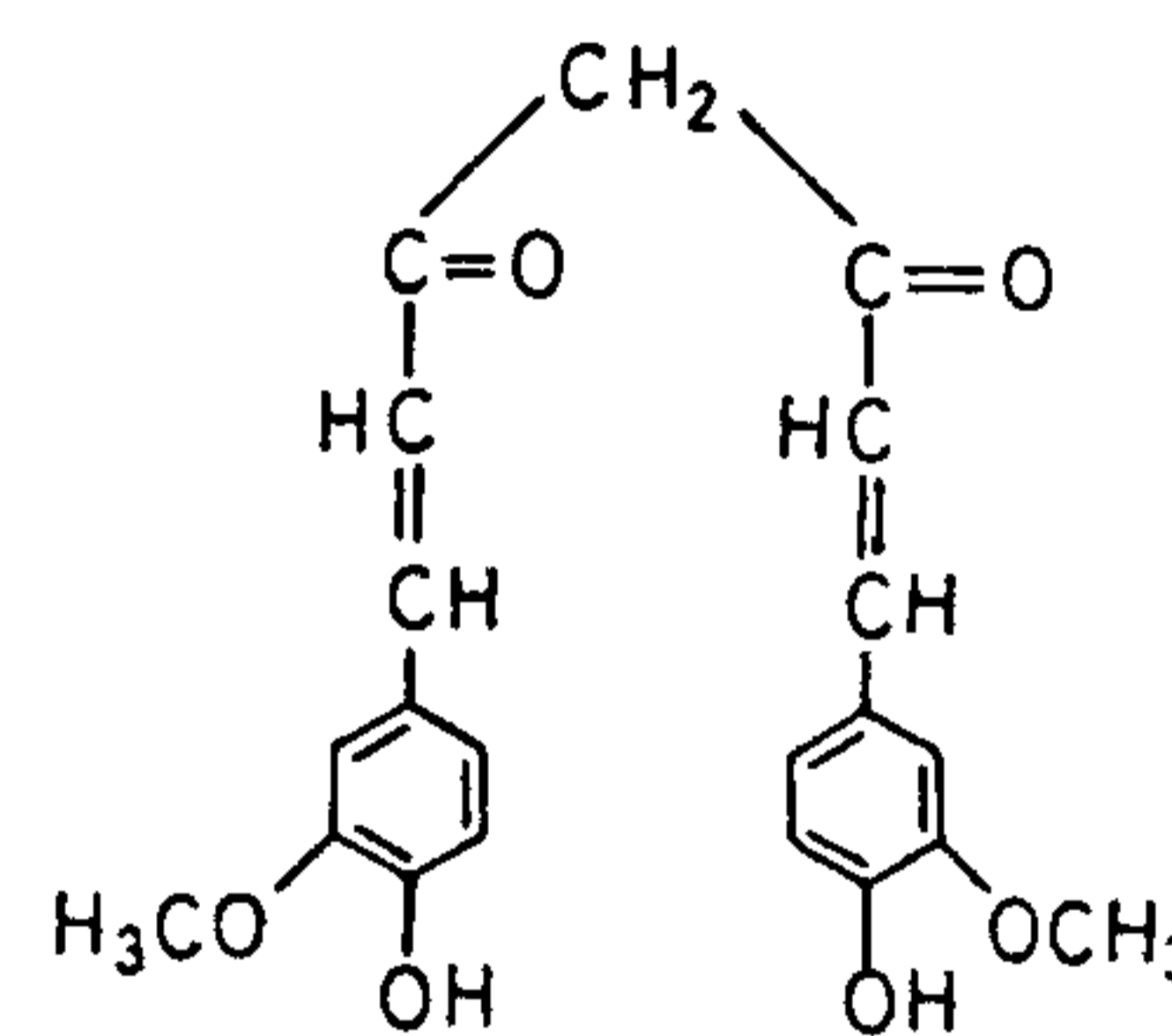
A Persian physician came to India to confer with the Hindu pandits. Together they studied the Charak Samhita and all other medical texts. They realized that the medical texts are like an ocean and they were like pearl divers who plunged into the ocean to grasp the pearls.

From Kavi Taranga, 1703 A.D.

THE herbal renaissance has produced a profound effect on the Western medicine which is now trying to acknowledge methods of healing that have existed for millenia in the traditional medicine throughout the world, especially Asia. The surge in research on drugs from natural sources is now moving out of the herbalists' shop away from the core texts into the drugs research laboratories. India's herbal tradition is as old as China's. We have rich resources but we have been complacent. In the present day world with numerous challenges facing us, particularly those relating to intellectual property rights, we must brace ourselves up and focus on areas of potential competitive advantage to emerge as winners. The grant of a patent to two non-resident Indian doctors in USA who claimed that they were the first to use turmeric (*Curcuma longa*) and its extract in powder form for healing wounds is yet another example of blatant plagiarism and an attempt to obtain exclusive rights over a traditional medicine that Indians and Chinese have known for centuries. It is a case that pits East against the West. This article is an attempt to put the record straight in respect of one of the most versatile and benign medicine given by God/Nature (or luck as you may call it), namely turmeric (*Curcuma* species especially *C. longa*, Haldi). Since the future is likely to be replete with such examples, the information given here should be helpful to research scientists, physicians, health officials and the public to take a firm stand and safeguard this and other precious gifts of nature that are part of our traditional medicine and heritage.

In the indigenous system of medicine, turmeric enjoys the reputation as a stomachic, blood purifier, useful in common cold, leprosy, intermittent fevers, affections of

the liver, dropsy, purulent ophthalmia, otorrhea, indolent ulcers, pyogenic affections, wound healing and inflammation. A review of literature reveals that turmeric is useful in treating a variety of ailments and metabolic disorders. Turmeric roots are known¹⁻³ to be antiseptic and aromatic. Its paste is used in cleansing and disinfecting the skin and skin ulcers without drying out its natural oils. The bactericidal properties of turmeric have been proved by clinical testing to have a greater medicinal effect than being merely cosmetic. *In vitro* evaluation of the antibacterial potency of *C. longa* constituents – curcumin, other curcuminoids (Scheme 1)



Curcumin

and the essential oil showed them to be active. The sodium salt of curcumin inhibits *Microoccus pyogenus var aureus* in 1 in 1 million dilution⁴. The inhibitory concentration against *Staphylococcus aureus* was 1:640,000 (refs 5, 6). One of the constituents of the volatile oil, *p*-tolyl methyl carbinol and its isomer phenylethyl carbinol have a strong action against *B. coli* commune⁷. The oil kills *Paramecium caudatum* in 10 to 30 min in dilutions of 1 in 30,000 (ref. 8), *S. aureus* and *S. albus* in 1:5000. Curcumin and other curcuminoids inhibit growth of *S. aureus*, *S. paratyphi*, *Trichophyton gypseum*, *Mycobacterium tuberculosis* in concentrations varying from 1 in 20,000 to 1 in 640,000 (ref. 9). The essential oils show marked anti-microbial activity against gram negative (*Vibrio cholerae*, *Salmonella typhi*, *Klebsiella [enterobacter] aerogenes*, *B. coli*) and gram-positive organisms (*Corynebacterium diphtheriae*, *β-hemolytic streptococci*)¹⁰⁻¹⁵.

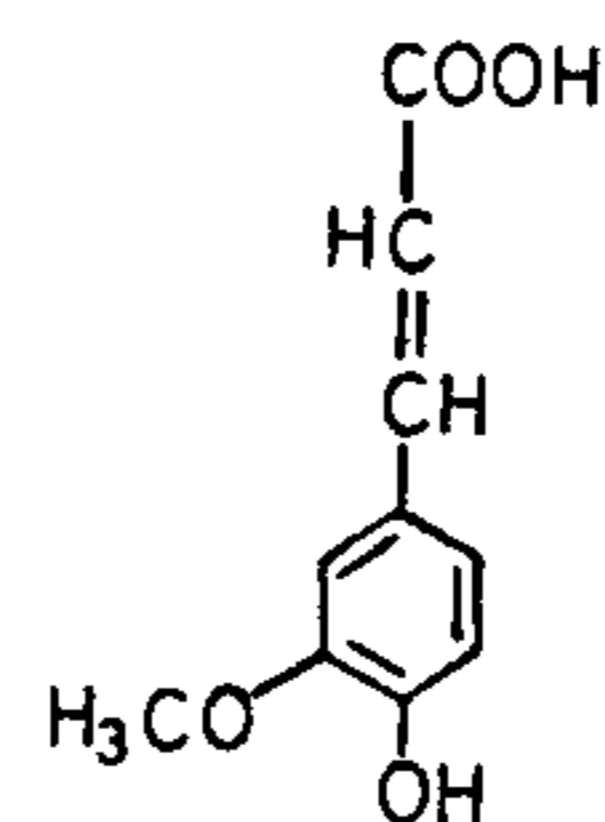
N. M. Khanna lives at 21/26, Tilak Marg, Near Moti Mahal East, Lucknow 226 001, India.

The essential oil fractions from *C. longa* rhizomes of various habitats exhibit fungistatic activity^{16,17} particularly against *Aspergillus niger in vitro* and *Physalospora tucumanensis*, *Ceratocystis paradoxa*, *Sclerotium solfsii*, *curvularia lunata*, *Helminthosporium sacchari*, *Fusarium moniliforme* vaz. Subglutinans and *cephalosporium sacchari*.

Turmeric powder significantly increases the mucus content in gastric juices and Indian cuisine lays emphasis on turmeric's therapeutic effect against gastric disorders. Curcuma oil, curcumin and its alkali salts prevent histamine induced gastric ulceration^{18,19}. While proving the non-toxicity of turmeric extract before recommending its use as a colouring agent for hydrogenated oils, it was observed²⁰⁻²² that liver cholesterol levels were lower in rats fed with hydrogenated groundnut oil containing turmeric extracts. Curcumin and the essential oils of *C. longa* particularly sodium curcuminatate differentially affect the individual constituents of bile²³. Though the concentrations of the solids decrease in the bile flow stimulated by it, this is compensated by the increased volume of bile excreted. Absolute values for the entire period of choleresis indicate increased total excretion of bile salts, bilirubin and cholesterol. The fatty acid content remains almost constant. Sodium curcuminatate stimulates the flow of bile, the degree and duration of activity depends upon the dosage administered. In conditions where hydrocholagogic effect is desired, it may be found useful. Increased bile salt excretion in higher doses favours the use of curcumin in digestive disorders of fat metabolism. The increased cholesterol secretion may be clinically useful in atherosclerosis and other conditions involving cholesterol metabolism and bilirubin secretion in hastening the recovery from jaundiced conditions. Curcumin seems to combine the choleric and hydrocholagogic action with the antiseptic property and probably would be an ideal therapeutic agent in conditions of suspected staphylococcal infections. The low toxicity and absence of adverse pharmacodynamic action of curcumin also favour its clinical use. The relaxation of intestines while maintaining the spontaneous contractions would probably assist thorough digestion of the food and complete absorption of the digested material. Other active constituents of *C. longa* and a synthetically derived constituent of turmeric manifest useful therapeutic choleric and cholagogic action in humans²⁴⁻²⁸. In rats fed with cholesterol and curcumin, an important constituent of turmeric, levels of serum and liver cholesterol decreased to one-half or one third of those in rats fed with cholesterol alone²⁹. Deposition of cholesterol was found to be high in liver sections from rats fed with cholesterol and least in specimens from animals concurrently fed with curcumin. Curcumin increased fecal excretion of bile acids and cholesterol both in normal and hypercholesterolemic rats. This biliary drainage is a plausible explanation for

the reduction of tissue cholesterol on curcumin feeding. α -Lipoprotein and β -lipoprotein in blood plasma were affected by addition of curcumin and the imbalance in these two lipoproteins brought about by cholesterol feeding was nearly corrected by simultaneous feeding of curcumin. The above beneficial effects of curcumin were about the same with 0.1% or 0.5% of the drug in the diet suggesting that the effective level of curcumin may even be lower than 0.1%. All levels of curcumin maintained body and liver weights, correcting the ill-effects in this respect caused by ingested cholesterol. The effect of curcumin in keeping down cholesterol in conditions which otherwise induced hypercholesterolemia was not through alterations in cecal microflora which are known to dismutate and utilize bile acids in the gut. In hypercholesterolemic rats, 0.05% dietary curcumin decreased serum and hepatic cholesterol within four weeks³⁰. Ar-turmerone, the active constituent of curcuma oil also exhibits significant cholagogic activity³¹.

Extracts of *C. longa* rhizomes exhibit good preventive activity against carbon tetrachloride induced liver injury *in vivo* and *in vitro*³². After fractionation, the curcuminoids showed significant anti-hepatotoxic action. Ferulic



Ferulic acid

acid, *p*-coumaric acid and their respective analogs (probable metabolites of curcuminoids) also possess marked liver protective effects. In rats, oral administration of paracetamol (100, 200 and 400 mg/kg) caused increase in serum glutamic pyruvic transaminase (SGPT), serum alkaline phosphatase and serum cholesterol. The two higher doses of paracetamol caused vascular changes with scattered areas of necrosis in liver tissue. Pretreatment of rats one hour before with curcumin protected them from paracetamol-induced lesions^{33,34}. The induction of gastric ulcers in guinea pigs by intramuscular injection of 5-hydroxytryptamine (serotonin) creatinine sulphate (20 mg/kg) was inhibited by curcumin (5-20 mg/kg orally)¹⁹.

Curcumin inhibits intestinal gas formation³⁵ by *Clostridium perfringens* at 0.05% concentration. Its effect was evaluated at 0.005, 0.013, 0.025 and 0.05% on gas formation by *C. perfringen* of intestinal origin. Gas formation decreased gradually as the curcumin concentration increased and there was no gas when curcumin

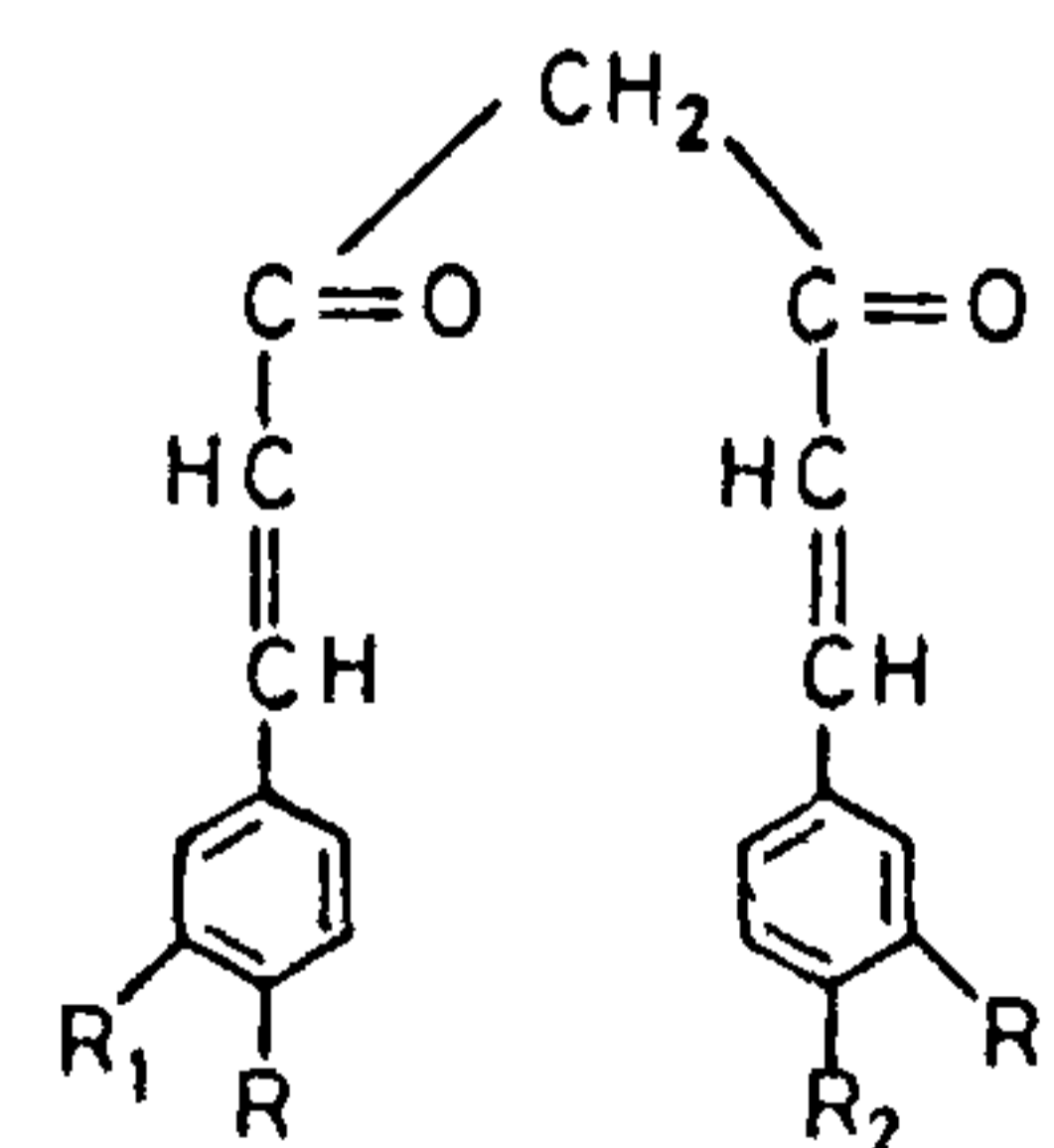
concentration was 0.05%, the level at which bacterial growth was inhibited completely.

Oral administration of curcumin and curcuminoids (750 mg/kg) has been reported³⁶ to prevent the formation and dissolution of urinary calculi.

In the indigenous system of medicine turmeric (*C. longa*) rhizomes are widely used for treatment of various inflammatory conditions. The use of turmeric paste with or without slaked lime and/or onion juice is a household remedy^{37,38} for reducing pain and swelling due to sprains, wound injuries and various types of inflammation. *C. longa* total extracts, its active constituents the curcuminoids and the oil have been extensively investigated³⁹⁻⁵⁰ for anti-inflammatory activity in acute and chronic models of inflammation in experimental animals and were found to exhibit significant anti-inflammatory activity. Of these, curcumin is currently under Phase-2 clinical trials⁵⁰. In curcumin and other curcuminoids, the regression line paralleled with that of cortisone but not with phenylbutazone which is another anti-inflammatory agent. The anti-inflammatory effect of curcumin was significantly less in adrenalectomized rats which suggested an indirect mechanism of action. Curcumin inhibited chemically-induced acute edema in mice as well as subacute arthritis in rats. It inhibited cotton pellet-induced granuloma formation in rats. It had no side-effects on the central nervous system nor any effect on the cardiovascular system of anaesthetized cats up to a dose of 10 mg/kg administered intravenously. Curcumin prevented the increase in serum glutamic oxalacetic transaminase and glutamic pyruvic transaminase seen in inflammation. It had a lower ulcerogenic index than phenylbutazone and had no analgesic, antipyretic effects in mice and rats. The volatile oil also gave protection against injection of talc in the left intratarsal joint in pigeons⁴² and was effective against both early and late inflammation. The early protective effect may be due to antihistaminic activity while the late effect may be a result of activation of the adrenohypophyseal axis. Using a newly developed combination of prostaglandin synthesizing cyclooxygenase system from sheep seminal vesicles and an HPLC separation technique for the metabolites of arachidonic acid, curcuma oil and curcumin exhibited significant activity as inhibitors of prostaglandin biosynthesis. Inflammation induced by carrageenin in mice was accompanied by an increase in the *in vitro* formation of lipid peroxides by liver. Pretreatment of mice with curcumin (500 mg/kg p.o.) prevented both edema development and lipid peroxide formation.⁵¹ Curcumin inhibits *in vitro* lipoxygenase and cyclooxygenase activities in mouse epidermis. Topical application of curcumin markedly inhibits TPA and arachidonic acid, induced epidermal inflammation (ear edema) in mice⁵². *In vitro* addition of 3, 10, 30 or 100 μ M curcumin to cytosol from homogenates of mouse epidermis inhibited the metabolism of arachidonic acid to 5-

hydroxyeicosatetraenoic acid (5 HETE) by 40, 60, 66 or 83%, respectively and the metabolism of arachidonic acid to 8 HETE was inhibited by 40, 51, 77 and 85%, respectively (IC₅₀, concentration needed for 50% inhibition: 5–10 μ M). The metabolism of arachidonic acid to prostaglandin E₂, prostaglandin F_{2x} and prostaglandin D₂ epidermal microsomes was inhibited approximately 50% by the *in vitro* addition of 5 to 10 μ M curcumin. The inhibitory effect of curcumin on TPA-induced tumor promotion in mouse epidermis parallels its inhibitory effect on TPA-induced epidermal inflammation and epidermal lipoxygenase and cyclooxygenase activities.

Turmeric powder, extracts and curcumin exhibit antioxidant property^{53,54} as observed by the induction period and oxygen absorption of coconut, groundnut, safflower, sesame, mustard, cotton seed oils and ghee at 95°C to 220°C for periods up to 144 h. In food, the antioxidant property of turmeric was effective in preventing peroxide development⁵⁵. *C. longa* extract also protects the oil in water emulsion against oxygen absorption⁵⁶. Curcumin at 10⁻⁶ M showed anti-oxidative activity⁵⁷ to linoleic acid. Five antioxidative components of turmeric (*C. longa*) oleoresin were detected and identified by comparing with authentic compounds on TLC and HPLC and studied by a TLC fluorescent method developed to separate and evaluate the activity of the individual antioxidative components. Curcumin, demethoxy curcumin and bis-demethoxy curcumin were the major antioxidative components⁵⁸. Curcumin markedly antagonized the lipid peroxide in homogenates of brain, heart, spleen, liver and kidney of NIH mice⁵⁹. The antioxidant activity was dose-dependent with the range of 0.128–20.4 mg/100 ml of curcumin. In a study of the diethyl ether extracts of 23 spices, turmeric extract proved to be the second most active⁶⁰. Turmeric extract was separated into basic, strongly acidic, weakly acidic and neutral fractions. The antioxidative activity was detected in the weakly acidic fraction. To isolate the active compounds C₁₈ reversed phase HPLC, C₈ preparative HPLC and high performance TLC (RP-8) were employed. Besides



Other curcuminoids:

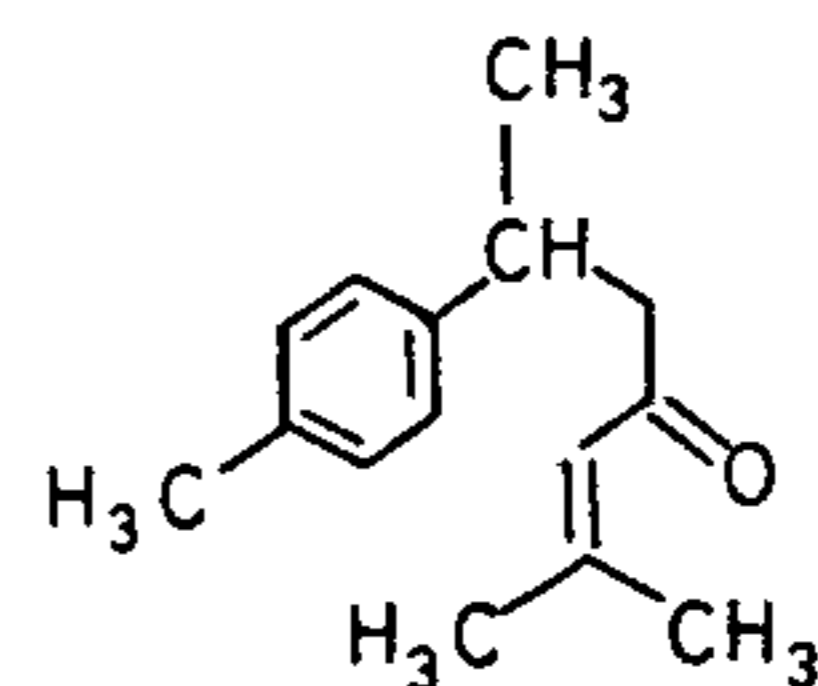
R = R₁ = R₂ = R₃: Dicinnamoyl methane
 R = R₂ = OH; R₁ = R₃ = H: Bis-demethoxy-curcumin
 R = R₂ = OH, R₁ = OCH₃, R₃ = H: Demethoxy curcumin

the main component curcumin, six other compounds were found, one of which was identified as dicinnamoyl methane. In a study of the anti-oxidative activity of curcumin and related compounds, structure-activity relationship was determined⁶¹ for the inhibition of lipid peroxide formation in rat brain homogenates. Demethylated derivatives of curcumin and trans-ferulic acid, e.g. bis(3,4-dihydroxy trans-cinnamoyl) methane ($1.03 \times 10^{-6} - 1.03 \times 10^{-3}$ M) and trans-caffeic acid ($1.03 \times 10^{-6} - 1.03 \times 10^{-3}$ M) were potent. Complete methylation abolished antioxidant activity. The OH group in the benzene ring had to be in the para position.

Anti-oxidants are the frontline of defence against free radicals. They are able to neutralize free radicals and put an end to the destructive chain reactions. The anti-oxidant action of curcumin, other curcuminoids and curcuma oil works in many ways. Probably the most important activity as antioxidant is the vital role in the antioxidant enzyme superoxide dismutase (SOD). SOD is a primary defender against free radicals and is so important to survival that it is the fifth most prevalent protein (of more than 100,000 in the body). SOD eliminates destructive superoxide molecules, a common free radical produced in the body^{61,62}. SOD apparently blocks the oxidation of harmful LDL cholesterol, thereby inhibiting the initial stages of atherosclerosis. Liver cells produce a free radical known as malondialdehyde (MDA) while human neutrophils (a type of white blood cell) produce superoxide. Active oxygen species (AOS) including superoxide, hydrogen peroxide, hydroxyl and ferryl radicals are considered to be generated or formed subsequent to reduction of molecular oxygen in living organisms. The hydroxyl radical and the ferryl radical, a complex of oxygen radical and iron are the most reactive and thought to be the major species responsible for oxidative injury of enzymes, lipid membranes and DNA in living cells and tissues, a process which causes much damage and contributes to cancer, atherosclerosis, heart attacks and stroke. Nerve cell damage can be caused by free radicals generated by/from breakdown of certain proteins, oxidative stress resulting from increased free radical production and/or defects in antioxidation defences could be central to the degenerative processes. Cells and tissues are protected from attack by AOS under normal conditions by certain enzymes – SOD, catalase, peroxidase, etc. and some low molecular weight substances such as ascorbic acid, tocopherol which exhibit mild AOS scavenging effect. Caffeic acid also inhibits⁶³ 5-lipoxygenase and lipid peroxidation. Turmeric (*C. longa*) extracts and its constituents – curcumin, the other curcuminoids and curcuma oil are highly effective antioxidants, inhibitors of lipid peroxidation, leukotriene biosynthesis, 5-lipoxygenase, cyclooxygenase,^{64,65} AOS scavengers⁶⁵ and are able to prevent increased free radical generation or accumulation in the body. They fight free radicals by

competing with peroxidant metals (iron and copper) for cell binding sites which decreases the possibility of free radical formation. Further, they appear to protect against free radical damage by defending sulfhydryl groups against oxidation. In the body sulfhydryl groups are a common part of many molecules and are easily oxidized forming free radicals. These unique properties make turmeric and its constituents useful as hypolipidemics,^{66,67} anti-inflammatory, anti-allergy, antimicrobial agents particularly wound healers including bed sores⁶⁸, liver injury, certain forms of cancer and treatment of various metabolic disorders and other degenerative processes.

Like curcumin and other curcuminoids considered to be derived from two caffeic acid molecules combined through a methylene bridge, ar-turmerone the main constituent of curcuma oil also has an α - β -unsaturated keto system in its molecular framework which is an important pharmacophore for most biological activities^{66,67,69}. Curcuma oil too is an effective inhibitor of 5-lipoxygenase, cyclooxygenase, leukotriene biosynthesis, lipid peroxidation and AOS scavenger. For pharmaceutical purposes curcuma oil can be easily standardized on the basis of its ar-turmerone content.



DL-ar-turmerone

Curcumin (30 mg/kg) prevents hypertrophy and other inflammatory changes in the rat uterus induced by IUCD⁷⁰.

Curcuma oil is an effective mosquito repellent⁷¹ and compares favourably with dimethyl phthalate in its repellent action against mosquitoes, the time of protection being 282 min compared to 240 for dimethyl phthalate. Curcuma oil has a quick knock-down effect on housefly (*Musca nebulosa*)⁷² nearly comparable with Lethane 384 and Thanite.

Many plant phenolics especially the curcuminoids possess anti-carcinogenic property due to their oxygen radical scavenging property⁷³. Turmeric extracts and curcumin reduced the expression of papillomas in mouse skin induced by 7,12-dimethylbenz(a) anthracene followed by croton oil promotion. Curcumin also inhibited tumour formation induced by 20-methylcholanthrene. Curcumin, curcuminoids and curcuma oil derived from turmeric may, therefore, be anti-carcinogens. Evaluation of anti-cancer activity of turmeric rhizomes⁷⁴ *in vitro* using tissue culture methods and *in vivo* in mice using

Dalton's lymphoma cells grown as ascites showed that turmeric extract inhibited cell growth in Chinese hamster ovary (CHO) cell culture at a concentration of 4 µg/ml and was cytotoxic to lymphocytes and Dalton's lymphoma cells at the same concentration. Cytotoxic effect was found within 30 min at room temperature. The active cytotoxic constituent was curcumin. Other curcuminoids and the oil also showed promise. Turmeric extracts and curcumin reduce the development of tumours in animal. Plant phenolics including caffeic, ferulic acids at levels of 4% in diet for one week prior to challenge by benzo[a]pyrene (100 mg/kg body weight) inhibited⁷⁵ the nuclear damage (micro nuclei, pyknotic nuclei, karyorrhectic bodies) in colonic epithelial cells of C57BL/8J mice. A cytotoxic sesquiterpene active against L 1210 cells was isolated from the roots of *C. domestica* and identified as β -sesquiphellandrene. The cytotoxicity potentiating substance was identified as (+) ar-turmerone⁷⁶. Turmerone potentiated the cytotoxicity of β -sesquiphellandrene 5-fold in ED₅₀ value. It also potentiated the cytotoxic activities of Me CCNO (10-fold) and cyclophosphamide (10-fold). Although all the effective cytotoxic substances possess relatively good lipophilicity, no relationship between their structure and increase of cytotoxicity by turmerone was found. Curcumin and its derivatives inhibit HIV protease⁷⁷. Derivatives containing boron had enhanced inhibitory activity and one of them irreversibly inhibited the HIV 1 protease. DNA polymerase and human immunodeficiency virus and avian myeloblastosis virus reverse transcriptase inhibition has also been reported⁷⁸.

Curcumin and other 3,4-dihydroxylated compounds structurally related to trans-cinnamic acid inhibit the binding of [125 I] bovine TSH to human thyroid membrane⁷⁹.

Curcumin inhibits ADP epinephrine and collagen-induced platelet aggregation in monkey plasma⁸⁰ and may be preferable in patients requiring antiarthritic therapy who are prone to vascular thrombosis. Curcumin protects⁸¹ mice against thrombotic challenge, the anti-thrombotic activity being dose-related and its inhibitory effect on mouse platelet TXB₂ and cyclooxygenase; the latter indicated by the inhibition of synthesis of malondialdehyde. Anti-coagulant activity of curcumin, *p*, *p'*-dihydroxy dicinnamoyl methane and *p*-hydroxy cinnamoyl ferulyl methane isolated from turmeric rhizomes (*C. longa*) has also been reported⁸². During the isolation process, plasma recalcification time in mice was used to follow the anti-coagulant activity of the compounds. Drug compositions for treating hyperlipidemia, inhibiting blood platelet aggregation and metabolic disorders, comprising curcumin^{83,84} and curcuma oil^{66,67} along with other plant-based constituents which enhance the biological activity are also known⁶⁷.

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