

SIGNIFICANCE OF TURMERIC AS SPICE IN INDIA

India is the land of spices from time immemorial, and holds the premier position in terms of the number of spices grown, the area under cultivation, and the volume of spices produced. One among the spices is turmeric, an integral component of the cultural, religious and culinary practices in the country. The total acreage under turmeric in India has been estimated variously from 60,000 to 100,000 acres, and the production is nearly 100,000 tons of rhizomes per annum.

Turmeric is the rhizome or underground stem of a ginger-like plant, *Curcuma longa* L. belonging to the Zingiberaceae family. It is usually available ground, as a fine, bright yellow powder. The whole turmeric is a tuberous rhizome, with a rough, segmented skin. The rhizome is yellowish-brown with a dull orange interior that looks bright yellow when powdered. The main rhizome measures 2.5 - 7 cm (1" - 3") in length with a diameter of 2.5 cm (1"), with smaller tubers branching off. In fresh state, the rootstock has an aromatic and spicy fragrance, which by drying gives way to a more medicinal aroma. On storing, the smell rather quickly changes to earthy and unpleasant. Similarly, the color of ground turmeric tends to fade if stored too long.

Turmeric has always been considered an auspicious material in the Indian sub-continent, both amongst the Aryan cultures (mostly northern) and the Dravidian cultures (mostly southern) and its value extends far in history to the beliefs of ancient Indian population. Yellow and yellow-orange are colors with sacred and auspicious connotations in India, yellow being associated with Vishnu, and as the color of the space between chastity and sensuality. Orange signifies sacrifice, renunciation and courage. In Buddhism yellow is the color of the Bodhisattva Ratnasambhava. In South India, turmeric is considered very auspicious and therefore, is the first item on the grocery list. The turmeric plant is tied around the vessel used to make Sweet pongal on the harvest festival, which is celebrated on the Makarshankranti Day, universally celebrated on 14th of January, every year.

Indian cooking employs turmeric liberally. It is added to nearly every dish, be it meat or vegetables. Its principal place is in curries and curry powders. When used in curry powders, it is usually one of the main ingredients, providing the associated yellow color. In current day practice, turmeric has found application in canned beverages, baked products, dairy products, ice cream, yogurts, yellow cakes, biscuits, popcorn-color, sweets, cake icings, cereals, sauces, gelatins, direct compression tablets, etc. In combination with annatto, it has been used to color cheeses, dry mixes, salad dressings, winter butter and margarine.

Turmeric also is a highly valued cosmetic ingredient. The Friday oil bath routines with the application of Haldi are almost sacrosanct with the South Indian women, resulting in beautiful skin, and hairless bodies! Pieces of the rhizomes are added to water to make an infusion that is used in baths. It is reported that washing in turmeric improves skin tone and reduces hair growth. Turmeric is currently used in the formulation of some sun screens.

SIGNIFICANCE OF TURMERIC IN AYURVEDA

The medicinal history of turmeric is at least 2500 years old. Ayurveda, Unani, Siddha and Chinese medicine recommend turmeric for a large number of disorders and diseases. Susruta's Ayurvedic *Compendium*, dating to 250 BC, recommends an ointment containing turmeric to relieve the effects of poisoned food.

Traditional Indian medicine use the powder against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorders, rheumatic disorders, sprains and swellings caused by injury, and sinusitis. Externally, the dried rhizome has been applied to fresh wounds and to insect stings and to help the healing process in chickenpox and smallpox. Traditional Chinese medicine uses curcuma in diseases associated with abdominal pain, amenorrhea, dysmenorrhea, distending or pricking pain in the chest and abdomen; impairment of consciousness in febrile diseases, epilepsy, and mania; jaundice with dark urine.

It is also applied topically for ulcers, wounds, eczema, and inflammations. In both the Ayurvedic and Siddha systems of medicine, a turmeric paste is used topically to treat ulcers and scabies. The Himalayan system of medicine recommends turmeric for contraception, swelling, insect stings, wounds, whooping cough, inflammation, internal injuries, pimples, injuries, and as a skin tonic.

Chinese medicine recommends turmeric for promoting flow of Qi and removing blood stasis, clearing away heat from the heart to relieve depression, and cooling blood to arrest bleeding. The herb is credited with powers to stop hemorrhage and dissolve clots. In Unani medicine, turmeric has been used for conditions such as liver obstruction and jaundice and has been applied externally for ulcers and inflammation. Roasted turmeric has been used as an ingredient of a preparation used for dysentery. Turmeric has also been used in tooth powder or paste.

TURMERIC GROWN IN VARIOUS PARTS OF INDIA

Turmeric is grown in many Asian countries with India as the largest producer. About 30 varieties of *Curcuma* are known, but what is known as turmeric in commerce is derived from *Curcuma longa* L., with rhizomes from other species with low curcumin content being passed off as turmeric. For example, turmeric grown in parts of Japan¹ and Indonesia² have low curcumin content and low yield per hectare. The price of turmeric is directly related to its curcumin content^{3, 4}.

The main turmeric growing states in India are Andhra Pradesh, Maharashtra, Orissa, Tamil Nadu, Karnataka and Kerala. Turmeric requires a hot and moist climate. It thrives the best on loamy or alluvial, loose, friable and fertile soils. It grows at all places ranging from sea level to an altitude of 1220m above sea level. It is very sensitive to low atmospheric temperature. It is grown both under rain fed and irrigated conditions. *Curcuma longa* accounts for about 96% of the total area under cultivation, the remaining 4% being accounted for by *C. aromatica* which is grown mostly in small areas in East and West Godavari district of Andhra Pradesh, and Thanjavur and South Arcot districts in Tamil Nadu⁵. Because climatic conditions vary from state to state, the curcumin content and yield of turmeric vary from state to state. For example, 27 accessions of *C. longa* grown in the climatic conditions of North Indian plains at Lucknow had curcumin content varying from 0.61% to 1.45% on dry weight basis⁶. Similarly, turmeric grown in Kandhamal district of Orissa had hardly 1.5% curcumin³, while that grown in Laxmipur block of Koraput district of the same state has curcumin content as high as 7 percent⁷.

Recently, the Kerala Agricultural University developed and released two high-yielding varieties⁴, with curcumin contents above 7%. These two varieties with high curcumin content would fetch a premium price in the market, according to the scientists who developed the varieties. Thus, owing to favorable climatic conditions, the best quality turmeric is available from the southern and eastern parts of India.

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VARIOUS HEALTH BENEFITS OF TURMERIC

Since the Ayurvedic times (1900 BC), numerous therapeutic activities have been assigned to turmeric for a wide variety of diseases and conditions, including those of the skin, pulmonary, and gastrointestinal systems, aches, pains, wounds, sprains, and liver disorders. Turmeric is also recommended under the Unani, Sidha and Chinese systems of medicine. Modern research has confirmed and provided a scientific basis for these various health claims, unlike many other traditional medicines. Since the isolation of curcumin as the main active constituent of turmeric about two centuries ago, much of the scientific interest has shifted to this molecule rather than on turmeric. Observational studies point to the substantially reduced prevalence of Alzheimer's disease, rheumatoid arthritis and disease of the gastrointestinal tract such as colon cancer and inflammatory bowel diseases in Asian countries compared to the western world as a consequence of the daily consumption of turmeric as a curry spice. For this reason, curcumin has been termed "the spice of life".

GROWING AWARENESS FOR TURMERIC

Research on curcumin is exploding with more than 2000 reports presently available. This is because of an extremely wide array of biological activities exhibited by the molecule. Curcumin acts at multiple targets and at multiple levels. The number of transcription factors and signaling pathways modulated by curcumin is, indeed, bewildering^{1,2}. For this reason, curcumin is fast emerging as a cure-all, for valid reasons. Curcumin has demonstrated benefit for most, if not all, chronic diseases afflicting mankind. It is an antioxidant several times more potent than α -tocopherol and can effectively scavenge oxygen- and nitrogen free radicals. It is a complete anti-inflammatory modulating all the agents involved in the complex process of inflammation, including cytokines, chemokines, adhesion molecules, growth factors and transcription factors such as NF-KB and AP-1, and a large number of kinases, notably the MAP kinases p38 and JNK. It is an inhibitor of histone acetyltransferases^{3,4} thereby preventing the transcription of inflammatory genes. In heart disease, curcumin can affect all the steps believed to be involved in the pathologic process of atherosclerosis. In diabetes, it can potentially reverse insulin resistance, the first clinically relevant stage of the disease. Further, it can sensitize insulin by inducing the transcription factor PPAR γ , similar to the thiazolidinediones currently used for the purpose. Curcumin can be shown to be the only agent who can effectively address all the multiple factors involved in Alzheimer's disease and rheumatoid arthritis. As an anticancer agent, it is a chemo preventive, affect cell cycle progression and transformation, cause apoptosis of malignant cells by more than one mechanism, prevents angiogenesis and metastasis, and is effective even against drug-resistant cancers. Whereas the present day cancer drugs are specific for one type of cancer, curcumin has been shown in preclinical studies to be effective against virtually all forms of human cancers. While common chemotherapeutic agents cause serious side effects, curcumin produces none. While the common anticancer drugs are Immuno-suppressors, curcumin is an immuno-restorer^{5,6}. Furthermore, whereas the common anticancer drugs cannot cross the blood-brain barrier, curcumin can. Curcumin exhibits activities similar to recently discovered drugs such as TNF inhibitors (e.g., Humira, Remicade, and Enbrel), a vascular endothelial cell growth factor (VEGF) blocker (e.g., Avastin), human epidermal growth factor receptor (EGFR) inhibitors (e.g., Erbitux, Erlotinib, and Gefitinib), and the HER2 blocker (e.g., Herceptin), minus their toxic side effects.

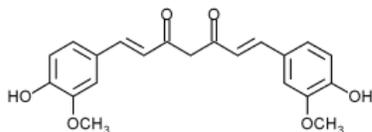
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CHEMICAL CONSTITUENTS OF TURMERIC

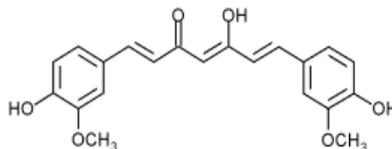
Turmeric may contain well over a hundred chemical species, most of these originating from the essential oil part of turmeric. A complete analysis of all these constituents has not so far been undertaken. However, the major and characteristic components of turmeric are the three curcuminoids and volatile compounds of turmeric.

Curcuminoids: Curcumin, Desmethoxy curcumin, Bisdesmethoxy curcumin

Curcuminoids exist as a mixture of the keto- and enol tautomeric forms, their relative composition dependent on the pH of the medium.



Keto-form of curcumin



Enol form of curcumin

ACTIVITY OF VARIOUS CURCUMINOIDS

The curcuminoids are diferuloylmethanes with curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, see structure) as the main and the most active constituent. Compounds lacking either one or two methoxy groups in the aromatic rings (desmethoxycurcumin, and bisdesmethoxycurcumin, respectively) form the other two constituents of the curcuminoids fraction. Other functional groups, namely the phenolic OH- group and α,β -unsaturated diketo Michael acceptor functions, are identical. The Michael acceptor property may be considered crucial for most of curcumin's biological activity, the methoxy groups have apparently supportive roles in these activities because compounds lacking these groups are less active, with desmethoxycurcumin (lacking one methoxy group) being less active than curcumin, and bisdesmethoxycurcumin, lacking both methoxy groups, the least active. However, a recent report suggests that bis-desmethoxycurcumin was the most potent in correcting immune defects in AD patients¹. The Michael acceptor functionality allows the curcuminoids to react or form complexes with a number of molecules, notably proteins, both covalently and non-covalently. For example, curcumin forms stable complexes with serum albumin which may be important in its transport within the human body.

A recent study² compared the relative anti-inflammatory, anti-proliferative, and antioxidant properties of the three curcuminoids, along with tetrahydrocurcumin and the turmerones. The relative potency for suppression of tumor necrosis factor (TNF)-induced nuclear factor-kappaB (NF-KB) activation was curcumin > desmethoxycurcumin > bisdesmethoxycurcumin; thus suggesting a critical role of methoxy groups on the phenyl rings. Tetrahydrocurcumin, which lacks the conjugated bonds in the central seven-carbon chain, was completely inactive for suppression of the transcription factor. Turmerones also failed to inhibit TNF-induced NF-KB activation. The suppression of NF-KB activity also correlated with down-regulation of cyclooxygenase-2 (COX-2), cyclin D1 and vascular endothelial growth factor (VEGF), all regulated by NF-KB. In contrast to NF-KB activity, the suppression of proliferation of various tumor cell lines by the three curcuminoids was found to be comparable; indicating the methoxy groups play minimum role in the growth-modulatory effects of curcumin. Tetrahydrocurcumin and turmerones were also found to be active in suppression of cell growth but to a much lesser extent than curcumin, DMC and BDMC. The antioxidant potential of all the curcuminoids were comparable, not influenced by the structural features.

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COMMERCIALY NOT FEASIBLE TO STANDARDIZE TO 100% CURCUMIN

Curcumin is presently commercially sold as 95% curcuminoids mixture, of which about 14% is constituted by desmethoxycurcumin and about 4-5% by bisdesmethoxycurcumin. The close similarity between their chemical structures makes their separation by routine methods not possible. Expensive chromatographic methods can separate the three molecules, but would push up the cost of the final product to uneconomical levels. For this reason no attempts are presently made to prepare 100% pure curcumin. This is also probably not necessary because the activity profile of the two minor curcuminoids is similar to that of curcumin, albeit to a lesser degree. Thus, the benefits of preparing 100% pure curcumin are not in proportion to the cost involved.

SCIENTIFIC BASIS FOR THE UNUSUALLY HIGH ACTIVITY RANGE OF THE CURCUMIN MOLECULE

The structural features of curcumin, though not complex chemically, makes it a highly reactive molecule with a capacity to interact with a range of biologically relevant molecules, notably proteins and metal ions. The main structural features which distinguish curcumin are the two α,β -unsaturated diketo functions in conjugation, which may be involved in its interaction with proteins, and the two phenolic hydroxyls which would confer antioxidant properties. The extended conjugation may add a degree of stability and reactivity to the molecule. The remaining feature is the presence of two methoxy groups. Though not a reactive group chemically, these two groups are apparently very important for curcumin's activity, as borne out by the lower biological activities of the other two Curcuminoids lacking one or two of these groups.

The unusually high biological activity profile of curcumin arises from its unique combination of antioxidant and anti-inflammatory properties. These two activities are complementary, and an effective antioxidant should also be an anti-inflammatory because oxidative stress elicits an inflammatory response. Modern drugs fall awfully short of this requirement. These drugs, with the exception of the new generation biological, aim mostly at blocking the cyclooxygenase (COX) pathway of Arachidonic acid metabolism. However, blocking COX is not equivalent to inhibiting inflammation. Blocking the COX pathway, more particularly COX-2, prevents the formation of prostaglandin E2 (PGE2), which sense pain, and treatment with these drugs provides only symptomatic relief from pain, and not inflammation. In fact blocking COX makes it worse, because the same enzyme is required at the resolution phase of inflammation^{1,2}. Indeed, cellular infiltration and edema are present for longer in COX-2-deficient mice than in wild-type mice indicating that during the resolution phase of inflammation, COX-2 may have a more significant role. This results in the persistence of inflammation without its symptoms. All chronic diseases such as coronary artery diseases, cancer, diabetes, rheumatoid arthritis, Alzheimer's disease, to cite a few, all have inflammation as an obligatory component. Inhibiting COX-2 is harmful in other ways, too! COX-2, though originally believed to be an inducible enzyme, is constitutively present in some tissues, including the brain and the kidneys^{3,4}. COX-2 may also play an important part in the homeostasis of other functions and body areas, including the kidneys, gastric tissue repair, cardiovascular system, and bone repair⁵⁻¹². COX-2 is also involved in the process of ovulation, implantation and neonatal development¹³⁻¹⁸; it is particularly essential for normal renal development. The deleterious effects of COX-2 inhibitors on the gastrointestinal system are well known. This is because COX-2 has essential roles in maintaining mucosal integrity and barrier functions of the gut. Furthermore, COX-2 induction is only an effect and not the cause for inflammation. An effective anti-inflammatory should tackle the causative factors and mediators, which only curcumin does.

Most chronic diseases are multifactorial and a disease-modifying drug should address all these simultaneously. Modern drugs can target only one of such factors, and hence polypharmacy is the rule rather than the exception. For example, current practice guidelines recommend the routine use of several cardiac medications in hospital survivors of acute coronary infarction¹⁹. Aspirin, β -blockers, angiotensin converting enzyme (ACE) inhibitors, lipid lowering agents (statins) are routinely administered in such patients. Even then, the percentage of survivors in 2005 was only 58%. Curcumin has been found beneficial in so many disease conditions because of its ability to act at multiple targets and at multiple levels.

An important aspect of the usefulness of curcumin in therapeutic applications is its non-toxic nature. It is enlightening to see why curcumin does not produce any toxic side effects although the pathways modulated by curcumin and other drugs are the same. All drugs produce side effects, some minor, and some severe or even fatal. From 1998 through 2005, reported serious adverse drug events reported to the FDA²⁰ increased 2.6-fold from 34,966 to 89,842, and fatal adverse drug events increased 2.7-fold from 5519 to 15,107. Reported serious events increased 4 times faster than the total number of outpatient prescriptions during the period. For 13 new biotechnology products, reported serious events grew 15.8-fold, from 580 reported in 1998 to 9181 in 2005. The increase was influenced by relatively few drugs: 298 of the 1489 drugs identified (20%) accounted for 407,394 of the 467,809 events (87%).

These results highlight the importance of this public health problem and underscore the need for improved systems to manage the risks of prescription drugs. Under normal disease-free conditions, our body achieves homeostasis by a delicate balance of opposing factors. Various signaling cascades are put into action to keep the biological processing going. These signaling cascades are also intricately interrelated. These are generally transiently activated and then put out to avoid over expression or persistent activation of a particular pathway. What is crucial to maintaining homeostasis is the timing and duration of the signals in response to internal and external stimuli. Derangement of this balance leads to disease, or vice versa.

Modern drug development is based on the naïve assumption that one or more of these pathways can be independently manipulated. Drugs normally aim at complete inhibition of a particular pathway, and in the case drugs taken for the life time, permanently. This affects other pathways directly or indirectly. We just saw that heart patients are routinely administered 4 or more drugs, and if the patient also has co-morbidities such as diabetes or hypertension, then the number of medications taken daily for life multiplies, each harming the body processes to some extent. Repercussions of these manifest themselves are side effects of the drugs. If such repercussions need to be handled

safely, we need a molecule with pleiotropic action such as curcumin. Importantly, curcumin also do not block the pathway totally, but only down regulate the overactive pathway to basal levels.

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VARIOUS CLINICAL TRIALS PERFORMED ON CURCUMIN

More than 20 clinical trial results have been reported on various disease conditions: cancer¹⁻⁵, familial adenomatous polyposis⁶, tropical pancreatitis⁷, renal transplantation⁸, inflammatory bowel disease^{9,10}, gall bladder function¹¹, psoriasis¹², chronic anterior uveitis¹³, peptic ulcer¹⁴, *Helicobacter pylori* infection¹⁵.

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WHY NO CLINICAL TRIALS HAVE PROGRESSED BEYOND PHASE I

The dark side of the curcumin story is its poor systemic availability due to poor absorption from the intestines and rapid metabolism of the compound in the body. This has largely curtailed its progress from the lab to the clinic, and no clinical trials have progressed beyond the phase I stage. All these have led to the general impression that curcumin's benefits are largely unrealizable in the human body.

Early experiments indicated that curcumin undergoes transformation during absorption from the intestine. When administered orally to rats in a dose of 1 g/kg, curcumin was excreted in the feces to about 75%, while negligible amounts of curcumin appeared in the urine¹. Measurements of blood plasma levels and biliary excretion showed that curcumin was poorly absorbed from the gut. No apparent toxic effects were seen after doses of up to 5 g/kg. When intravenously injected or when added to the perfusate of the isolated liver, curcumin was actively transported into bile, against concentration gradients of several hundred times. The major part of the absorbed drug was, however, metabolized. In suspensions of isolated hepatocytes or liver microsomes 90% of the added curcumin was metabolized within 30 min. The authors concluded that in view of the poor absorption, rapid metabolism and excretion of curcumin, it is unlikely that substantial concentrations of curcumin occur in the body after ingestion. This study, which appeared as early as 1978, appears to summarize our current understanding of the metabolic fate of curcumin *in vivo*.

Later studies have more or less confirmed these findings. Oral and intraperitoneal doses of [³H] curcumin led to the fecal excretion of most of the radioactivity². Intravenous and intraperitoneal doses of [³H] curcumin were well excreted in the bile of cannulated rats. The major biliary metabolites were glucuronides of tetrahydrocurcumin and hexahydrocurcumin. The major route of elimination of the label was the feces; the urinary excretion of the label was very low regardless of the dose; however, its metabolites, namely, glucuronide and sulfate, were present³.

After *i.p.* administration of curcumin (0.1 g/kg) to mice, about 2.25 µg/ml of curcumin appeared in the plasma in the first 15 min⁴. One hour after administration, the levels of curcumin in the intestines, spleen, liver, and kidneys were 177.04, 26.06, 26.90, and 7.51 µg/g, respectively. Only traces (0.41 µg/g) were observed in the brain at 1 h. Thus, in mice, absorption of curcumin appears to be significantly higher compared to rats.

The intestinal tract plays an important role in the metabolic disposition of curcumin. Accordingly, a study explored curcumin metabolism in the subcellular fractions (cytosolic and microsomal) of human and rat intestinal tissue, and compared it with metabolism in the corresponding hepatic fractions⁵. Quantitatively, major differences were observed between human and rat tissues. In humans, microsomal glucuronidation occurred to a much higher level in the intestine than liver, while the reverse was true in the case of rat.

In the rat, dietary curcumin yielded low drug levels in the plasma, between 0 and 12 nM, whereas tissue concentrations of curcumin in liver and colon mucosa were 0.1 to 0.9 nmol/g and 0.2 to 1.8 µmol/g, respectively⁶. In comparison with dietary administration, suspended curcumin given *i.g.* resulted in more curcumin in the plasma but much less in the colon mucosa. The authors conclude that curcumin mixed with the diet achieves drug levels in the colon and liver sufficient to explain the pharmacological activities observed and suggest that this mode of administration may be preferable for the chemoprevention of colon cancer.

A prospective phase-I study⁷ evaluated pharmacokinetics, toxicology and biologically effective dose of curcumin in cancer patients. Curcumin was given orally for 3 months. Biopsy of the lesion sites was done immediately before and 3 months after starting curcumin treatment. The starting dose was 500 mg/day. If no toxicity ≥ grade II was noted in at least 3 successive patients, the dose was then escalated to another level in the order of 1,000, 2,000, 4,000, 8,000, and 12,000 mg/day. The concentration of curcumin in serum and urine was determined. A total of 25 patients were enrolled in this study. There was no treatment-related toxicity up to 8,000 mg/day. Beyond 8,000 mg/day, the bulky volume of the drug was unacceptable to the patients. The serum concentration of curcumin usually peaked at 1 to 2 hours after oral intake of curcumin and gradually declined within 12 hours. The average peak serum concentrations after taking 4,000 mg, 6,000 mg and 8,000 mg of curcumin were clinically relevant at 0.51 ± 0.11 µM, 0.63 ± 0.06 µM and 1.77 ± 1.87 µM, respectively. Urinary excretion of curcumin was undetectable. This study demonstrated that curcumin is not toxic to humans up to 8,000 mg/day when taken by mouth for 3 months.

In another phase I study⁸, 15 patients with advanced colorectal cancer refractory to standard chemotherapies consumed curcumin (0.45 to 3.6 g per day) for up to 4 months. Blood, urine and feces were collected on days 1, 2, 8, and 29. Blood was collected before dosing and after 0.5, 1, 2, 3, 6, and 8 h after dose. Curcumin was detected in plasma samples taken 0.5 and 1 h postdose from 3 patients consuming 3.6 g of curcumin daily, with a mean concentration of 11.1 ± 0.6 nmol/L on day 1, 2, 8, and 29 of intervention. Glucuronides and sulfates of curcumin were detected at levels of 15.8 ± 0.9 and 8.9 ± 0.7 nmol/L, respectively. Presence of metabolites arising out of metabolic reduction, e.g. hexahydrocurcumin, was not reported. They were apparently absent. Curcumin and its metabolites, unexpectedly, were present in high amounts in the urine of the 6 patients consuming 3.6 g curcumin daily, but not in the urine of patients consuming lower doses. The urinary levels varied between 0.1 and 1.3 μ mol/L (curcumin), 19 and 45 nmol/L (curcumin sulfate), and 210 and 510 nmol/L (curcumin glucuronide). This is the only study which found unchanged curcumin in the urine. Considering that curcumin is insoluble in water, this result needs reconfirmation. The quantities excreted through feces amounted to 25 to 116 nmol/g dried feces.

In another trial, 12 patients with confirmed colorectal cancer received curcumin at dose levels of 450, 1800, or 3600 mg per day (4 patients per dose level) for 7 days prior to colectomy⁹. Samples of peripheral blood were taken 1 h post dose and surgery was done 6-7 h after the last dose of curcumin. Curcumin levels in the plasma of patients were below the limit of quantization (3 nmol/L). Levels in the normal and malignant tissues ranged from 7 to 20 nmol/g tissue. Normal mucosa from the caecum and ascending colon contained more curcumin than normal mucosa from the transverse, splenic flexure, and the descending colon. In patients who had received 1800 or 3600 mg curcumin, the concentration of curcumin was 21.7 ± 8.2 and 6.8 ± 3.7 nmol/g in the right and left colon, respectively. This difference was not reflected by curcumin levels in tumor tissue originating from different sites of the bowel. Curcumin metabolites were not detected in the plasma. Extracts of colorectal mucosa of 7 of the 8 patients who received 1800 or 3600 mg curcumin showed the presence of curcumin sulfate, and two patients from the highest dose indicated the presence of curcumin glucuronide. However, the concentrations of these conjugates were very low at about 1 pmol/g tissue. The results of this study thus suggest that a daily dose of 3.6 g curcumin achieves pharmacologically efficacious levels in the colorectum.

Curcumin's metabolic fate is decided by the phase I, II and III detoxifying enzymes. Curcumin is, simultaneously, a substrate for these enzymes, an inducer of these enzymes, as well as an inhibitor of these enzymes, depending on context. Curcumin was shown to inhibit sulfotransferases²⁸⁻³⁰. Inhibition^{29,31-33}, as well as induction^{34,35}, of UDP-glucuronosyl-transferase have been described. A similar situation exists with glutathione S-transferase (GST) another phase II enzyme, where again curcumin has been shown to be an inhibitor as well as an inducer. The chemo preventive action of curcumin significantly depends on the induction of these enzymes. Inhibition of these enzymes is relevant in the context of overcoming drug resistance in cancer chemotherapy. Thus, the metabolism of curcumin may depend on many external factors, and probably may explain the confusing results reported.

Although some questions remain unanswered regarding the pharmacokinetics of curcumin in humans, there is no denying the fact that considerable proportion of ingested curcumin is excreted through feces, and at least about one-half of absorbed curcumin is metabolized. The quantity of curcumin that reaches tissues outside the gut are probably pharmacologically insignificant.

These results have, apparently, dampened the spirits of researchers and halted curcumin's progress from Phase 1 trials.

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HAVE THERE BEEN ATTEMPTS TO IMPROVE THE BIOAVAILABILITY OF CURCUMIN?

Yes. A number of curcumin analogues have been tested, but in most cases they were found to be less effective than curcumin itself. One exception has been dimethoxycurcumin¹. This derivative was found to be more bioavailable. Nearly 100% of curcumin, but < 30% of dimethoxycurcumin was degraded in HT116 cells treated for 48 h, and incubation with liver microsomes confirmed the limited metabolism of dimethoxycurcumin. The absence of free phenolic groups in dimethoxycurcumin probably prevents its conversion to glucuronide and sulfate.

Piperine, an inhibitor of glucuronosyltransferase, administered along with curcumin has been found to significantly enhance the plasma curcumin concentration in animals and in humans². However, piperine is toxic at least to experimental animals. Curcumin formulated with lecithin was found to increase its bioavailability in rats about 5-fold³. In contrast, curcumin concentrations in the gastrointestinal mucosa after ingestion of the formulation were somewhat lower than those observed after administration of unformulated curcumin. Fluorometric data on the association of curcumin with phosphatidylcholine indicate that one molecule of curcumin could bind six molecules of phosphatidylcholine⁴. Thus, the formulated products would have low curcumin content, and large amounts of lecithin would have to be consumed in relation to the required curcumin dose.

Enhancing the bioavailability of curcumin by using compounds naturally present in turmeric itself has been successfully adopted by Arjuna Natural Extracts Ltd, India⁵. This product has been trade-named as **Biocurcimax®/ BCM-95®**. In healthy human volunteers, the blood levels of curcumin after ingestion of this composition were increased about 8-fold⁶. This composition assumes synergism between curcumin and the volatile compounds of turmeric, to enhance bioavailability and bio-efficacy of curcumin. Supporting this assumption, Curcuminoids along with volatile components of turmeric was found to be more effective in inhibiting LPS-induced PGE2 production in HL-60 cells⁷. Similarly, Curcuminoids along with the essential oil components of turmeric was more effective in lowering blood glucose levels in diabetic KK-Ay mice⁸.

Improved delivery systems are currently being explored to enhance bioavailability of curcumin. These include liposomal curcumin⁹⁻¹², encapsulated^{13,14}, and more recently, nano particle-encapsulated curcumin formulations¹⁵⁻¹⁷ have been developed and tested. The techno-economic feasibility of these formulations remains to be tested.

At the moment, **Biocurcimax®/ BCM-95®** appears to be most effective way to enhance the bioavailability of curcumin. Efforts are underway to test the therapeutic potential of this formulation in various disease conditions.

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WHAT IS BCM-95®

BCM-95® is 100% Natural Extract of Turmeric Rhizome standardized to blend of Curcuminoids COMPLEX to maintain the Natural Spectrum and synergy of the turmeric rhizome.

Curcuminoids COMPLEX is a blend with right ratios of various Curcuminoids and Volatile Oils of turmeric rhizome.

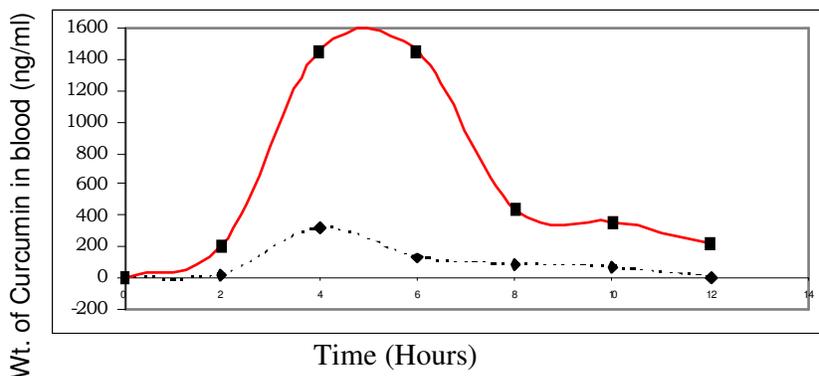
Human clinical studies have proven that BCM-95® is several times more bioavailable and retains longer in blood than the commercially available Turmeric 95% Extracts.

ADVANTAGES OF BCM-95® OVER COMMERCIALLY AVAILABLE TURMERIC 95% EXTRACTS

BCM-95®	Turmeric 95% Extract
Several times more bioavailable confirmed via Human Clinical Studies	Poor bioavailability
Retains longer in the blood, confirmed via Human Clinical Studies (up to 8 hours)	Major concern on retention (up to 4-5 hours)
High ORAC value (+13,000)	Low ORAC value (2,000 – 4,000)

- BCM-95® is 100% Natural
- Undergone Toxicity Study (Toxicity not detected)
- Patent Pending
- Undergoing various clinical studies and long term plans

A well conducted Single Dose, Human Clinical, and Crossover study showed than BCM-95 is several times more bioavailable and retains longer in blood than commercially available turmeric 95% extract.



TOXICITY STUDY ON BCM-95®

The results of the study indicated that treatment of Sprague Dawley rats with BCM-95® for a prolonged period of 45 days (dose of 75mg/100gm of body weight) did not significantly affect the feed intake and body weight. There was no significant change in the haematological and biochemical parameters. There was decrease in serum cholesterol level. Histopathological evaluations did not reveal any histological lesions in rats.

DOSAGE COMPARISON OF BCM-95®

BCM-95®	Turmeric 95% Extract
250 mg	1,750 mg

ONGOING AND PROPOSED CLINICAL STUDIES ON BCM-95®

1. Bioavailability Study sponsored by Department of Biotechnology (Government of India) in comparing BCM-95® with commercially available Turmeric extracts + Bio-enhancers. Results shows the BCM-95® is superior
2. In-Vitro study to examine intestinal cell (Caco-2) uptake of curcumin from micelles generated during the digestion of Curcugel (Softgel consisting of 250mg of BCM-95®) at Ohio State University sponsored by Tishcon Corporation NY.
3. Efficacy and Safety of BCM-95® in Oral Pre-malignant Lesions/Cervical Cancer (A Multi Centre, Phase II, Double Blind, Placebo controlled, Chemoprevention study, Sponsored by Department of Biotechnology Government of India).
4. Bioavailability study comparing BCM-95® against commercially available Turmeric 95% Extract and Turmeric extract + Phosphatidylcholine (as a bio-enhancer). Results show BCM-95® is superior.
5. To study the effect of BCM-95® in formulation for Type II Diabetes (sponsored by Department of Bio-Chemistry, Little Flower Hospital, India).
6. In-vitro study on dosage related Anti-Cancer Mechanism of commercially available Turmeric 95% Extract and BCM-95® in (Sponsored by Rajiv Gandhi Institute of Biotechnology, Trivandrum - Dept of Biotechnology, Government of India)
 - Expression of VEGF (Vascular endothelial growth factor)
 - NF-KB (Nuclear factor Kappa - B)
 - Inhibition of BCL 2 Expression
 - AP-1 Inhibition
7. Efficacy, safety and tolerability in subjects with prostate cancer - a randomized, double blind, placebo controlled, parallel, multi-center study using BCM-95® sponsored by Department of Biotechnology Government of India.