Curcumin

Curcumin is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family (Zingiberaceae). The other two curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin. The curcuminoids are polyphenols and are responsible for the yellow color of turmeric. Curcumin can exist in at least two tautomeric forms, keto and enol. The enol form is more energetically stable in the solid phase and in solution.

Chemistry

Curcumin incorporates several functional groups. The aromatic ring systems, which are polyphenols are connected by two α,β-unsaturated carbonyl groups. The two carbonyl groups form a diketone. The diketone form stable enols or are easily deprotonated and form enolates, while the α,β-unsaturated carbonyl is a good Michael acceptor and undergoes nucleophilic addition.

Biosynthesis

The biosynthetic route of curcumin has proven to be very difficult for researchers to determine. In 1973 Roughly and Whiting proposed two mechanisms for curcumin biosynthesis. The first mechanism involved a chain extension reaction by cinnamic acid and 5 malonyl-CoA molecules that eventually arylized into a curcuminoid. The second mechanism involved two cinnamate units being coupled together by malonyl-CoA.16. Both mechanisms utilize cinnamic acid as their starting point, which is derived from the amino acid phenylalanine. This is noteworthy because plant biosyntheses employing cinnamic acid as a starting point are rare compared to the more common use of p-coumaric acid. Only a few identified compounds, such as anigorufone and pinosylvin, use cinnamic acid as their start molecule.
It was not until 2008 in which an experimentally backed route was presented. This proposed biosynthetic route follows both the first and second mechanisms suggested by Roughley and Whiting. However, the labeling data supported the first mechanism model in which 5 malonyl-CoA molecules react with cinnamic acid to form curcumin. However, the sequencing in which the functional groups, the alcohol and the methoxy, introduce themselves onto the curcuminoid seems to support more strongly the second proposed mechanism. Therefore it was concluded that the second pathway proposed by Roughley and Whiting was correct.

Curcumin Keto form

Curcumin Enol form

Curcumin can be used for boron quantification in the so-called curcumin method. It reacts with boric acid forming a red colored compound, known as rosocyanine.

Curcumin is brightly colored and may be used as a food coloring. As a food additive, its E number is E100.

*Potential medical uses*

Turmeric has been used historically as a component of Indian Ayurvedic medicine since 2000 BC to treat a wide variety of ailments.
Research in the latter half of the 20th century has identified curcumin as responsible for most of the biological activity of turmeric. *In vitro* and animal studies have suggested a wide range of potential therapeutic or preventive effects associated with curcumin. At present, these effects have not been confirmed by doing extensive humans studies.

However, as of 2008, numerous clinical trials in humans were underway, studying the effect of curcumin on numerous diseases including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis, and Alzheimer's disease.

*In vitro* and animal studies have suggested the curcumin may have antitumor, antioxidant, antiarthritic, anti-amyloid, anti-ischemic, and anti-inflammatory properties.

Anti-inflammatory properties may be due to inhibition of eicosanoid biosynthesis. In addition it may be effective in treating malaria, prevention of cervical cancer, and may interfere with the replication of the HIV virus.

In HIV, it appears to act by interfering with P300/CREB-binding protein (CBP). It is also hepatoprotective. A 2008 study at Michigan State University showed that low concentrations of curcumin interfere with Herpes simplex virus-1 (HSV-1) replication. The same study showed that curcumin inhibited the recruitment of RNA polymerase II to viral DNA, thus inhibiting the transcription of the viral DNA. This effect was shown to be independent of effect on histone acetyltransferase activities of p300/CBP. A previous (1999) study performed at University of Cincinnati indicated that curcumin is significantly associated with protection from infection by HSV-2 in animal models of intra-vaginal infections.

Curcumin acts as a free radical scavenger and antioxidant, inhibiting lipid peroxidation and oxidative DNA damage. Curcuminoids induce glutathione S-transferase and are potent inhibitors of cytochrome P450.
A 2004 UCLA-Veterans Affairs study involving genetically altered mice suggests that curcumin might inhibit the accumulation of destructive beta-amyloid in the brains of Alzheimer’s disease patients and also break up existing plaques associated with the disease.

There is also circumstantial evidence that curcumin improves mental functions; a survey of 1010 Asian people who ate yellow curry and were between the ages of 60 and 93 showed that those who ate the sauce ‘once every six months’ or more had higher MMSE results than those who did not. From a scientific standpoint, though, this does not show whether the curry caused it, or people who had healthy habits also tended to eat the curry, or some completely different relationship.

Numerous studies have demonstrated that curcumin, amongst only a few other things such as high impact exercise, learning, bright light, and antidepressant usage, has a positive effect on neuro-genesis in the hippocampus and concentrations of brain-derived neuro-trophic factor (BDNF), reductions in both of which are associated with stress, depression, and anxiety.

Curcumin has also been demonstrated to be a selective monoamine oxidase inhibitor (MAOI) of type MAO-A.

In 2009 an Iranian group demonstrated the combination effect of curcumin with 24 antibiotics against *Staphylococcus aureus*. It is showed that in the presence of sub-inhibitory concentration of curcumin the antibacterial activities of cefixime, cefotaxime, vancomycin and tetracycline have been increased against test strain. Increase in inhibition zone surface area for these antibiotics was 52.6% (cefixime), 24.9% (cephotaxime), 26.5% (vancomycin), 24.4% (tetracycline). Also it is showed that curcumin has the antagonist effect on the antibacterial effect of Nalidixic acid against test strain.

**Anticancer effects**
Its potential anticancer effects stem from its ability to induce apoptosis in cancer cells without cytotoxic effects on healthy cells. Curcumin can interfere with the activity of the transcription factor NF-κB, which has been linked to a number of inflammatory diseases such as cancer.

A 2009 study suggests that curcumin may inhibit mTOR complex I via a novel mechanism.

Another 2009 study on curcumin effects on cancer states that curcumin modulates growth of tumor cells through regulation of multiple cell signaling pathways including cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53, p21) death receptor pathway (DR4, DR5), mitochondrial pathways, and protein kinase pathway (JNK, Akt, and AMPK).

When 0.2% curcumin is added to diet given to rats or mice previously given a carcinogen, it significantly reduces colon carcinogenesis.

**Bioavailability of curcumin**

Very little curcumin, when eaten, is absorbed: from 2 to 10 grams of curcumin eaten alone resulted in undetectable to very low serum levels. Curcumin is stable in the gut, and the traces that pass through the GI tract rapidly degrade or are conjugated through glucuronidation.

Co-supplementation with 20 mg of piperine (extracted from black pepper) significantly increased the absorption of curcumin by 2000% in a study funded by a prominent manufacturer of piperine. However, the increase in absorption only occurred during the first hour, in which the difference between the piperine curcumin and the regular curcumin was almost the same as far as absorption. Due to its effects on drug
metabolism, piperine should be taken cautiously (if at all) by individuals taking other medications.

Some benefits of curcumin, such as the potential protection from colon cancer, may not require systemic absorption. Alternatively, dissolving curcumin in hot water or in warm oils prior to ingestion may possibly increase bioavailability; however, no published studies to date have documented this. Cooking with curcumin and oil may increase absorption, but peer-reviewed scientific literature has not documented this, while the literature has documented concerns regarding the heat stability of curcumin and its degradation in the gut.¹

In 2007, a polymeric nanoparticle-encapsulated formulation of curcumin (nanocurcumin) has been synthesized which has the potential to bypass many of the shortcomings associated with free curcumin, such as poor solubility and poor systemic bioavailability. Nanocurcumin particles have a size of less than 100 nanometers on average, and demonstrate comparable to superior efficacy compared to free curcumin in human cancer cell line models. However, actual in vivo absorption has not been demonstrated with this nanoparticle.

In July 2008, researchers from the aforementioned team in UCLA’s Department of Neurology announced results on a form of ‘lipidated curcumin’ that was noted to achieve more than 5 micromolar in the brain in vivo, 50 times that found in clinical studies. Another method to increase the bioavailability of curcumin was filed in a patent in 2006 and involves a simple procedure creating a complex with soya phospholipids; the plasma concentration of curcumin using this method increased by 5-fold reaching 33.4 nanomolar in comparison to 6.5 nanomolar obtained with an equal molar quantity of unformulated curcumin administered as control.

Potential risks and side-effects

Kawanishi et al. (2005) remarked that curcumin, like many antioxidants, can be a ‘double-edged sword’ where in the test tube,
anti-cancer and antioxidant effects may be seen in addition to pro-
oxidant effects. Carcinogenic effects are inferred from interference
with the p53 tumor suppressor pathway, an important factor in
human colon cancer. Carcinogenic and LD$_{50}$ tests in mice and rats,
however, have failed to establish a relationship between tumoro-
genesis and administration of curcumin in turmeric oleoresin at
>98% concentrations.

In animal studies, hair loss (alopecia) and lowering of blood pressure
have been reported.

Clinical studies in humans with high doses (2–12 grams) of curcumin
have shown few side effects, with some subjects reporting mild
nausea or diarrhea. More recently, curcumin was found to alter iron
metabolism by chelating iron and suppressing the protein hepcidin,
potentially causing iron deficiency in susceptible patients.

**Clinical Summary**

Derived from the rhizome and root, this supplement is used as a spice
and coloring agent, and in traditional medicine in Asia. The active
constituents are thought to be turmerone oil and water soluble
curcuminoids, including curcumin. Turmeric may help alleviate
symptoms of irritable bowel syndrome as well as quiescent ulcerative
colitis. Data from an epidemiological study are suggestive of improved
cognitive performance in elderly Asians who consume turmeric in the
form of curry powder; however, no benefits of curcumin
supplementation were detected in patients with Alzheimer’s.

In vitro and animal studies suggest anti-proliferative and preventative
effects of turmeric against cancer. Furthermore, curcumin was shown to
induce apoptosis in human colon cancer and promyelocytic leukemia
cells. Curcumin potentiated gemcitabine action in both in vitro and in
vivo studies of pancreatic cancer. In a phase II trial in pancreatic cancer
patients, down-regulation of NF-kappa B and cyclooxygenase-2 were
observed. Oral administration is well tolerated, but bioavailability is
relatively low. Following absorption, curcuminoids are rapidly metabolized. Recent animal studies indicate that dietary turmeric may inhibit the antitumor action of chemotherapeutic agents such as cyclophosphamide in treating breast cancer. More research is necessary, but it is advisable for cancer patients undergoing chemotherapy to limit intake of turmeric. Patients with gastrointestinal disorders or those predisposed to kidney stone formation should use this supplement with caution.

**Mechanism of Action**

Turmeric has anti-inflammatory and choleretic actions. Anti-inflammatory action may be due to leukotriene inhibition. Its curcuminoids (curcumin) and volatile oils are both responsible for the anti-inflammatory activity. Curcuminoids induce glutathione S-transferase and are potent inhibitors of cytochrome P450. Turmeric acts as a free radical scavenger and antioxidant, inhibiting lipid peroxidation and oxidative DNA damage. It also inhibits activation of NF-kB 17, 20, c-jun/AP-1 function, and activation of the c-Jun NH2-terminal kinase (JNK) pathway.

In vitro and animal models of breast cancer showed that turmeric may inhibit chemotherapy-induced apoptosis via inhibition of the JNK pathway and generation of reactive oxygen species (ROS). The isolated constituent ar-turmerone has been shown to arrest the growth and cytotoxic activity of human lymphocytes, which may contribute to its anti-inflammatory action. In vitro studies suggest that curcumin induces apoptosis in human colon cancer cells independent of p21 expression. In addition, in vitro and in vivo studies report that NF-kB-mediated resistance of cancer cells to gemcitabine and γ-radiation was repressed by curcumin administration. In laboratory tests, curcumin’s antitumor actions appear to be due to interactions with arachidonate metabolism and its in vivo antiangiogenic properties.
**Pharmacokinetics**

Bioavailability of curcumin is approximately 60-65% following oral administration. Metabolism is primarily via glucuronidation to glucuronide and glucuronide/sulfate metabolites. In vitro studies indicate inhibition of Cytochrome P450s (CYPs) such as CYP1A1, CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2B6. Excretion of parent compound is primarily in the feces with metabolites present in the urine.

**Warnings**

Recent laboratory findings indicate that dietary turmeric may inhibit the anti-tumor action of chemotherapeutic agents such as cyclophosphamide in treating breast cancer. More research is necessary, but it is advisable for cancer patients undergoing chemotherapy to limit intake of turmeric and turmeric-containing foods.

**Contraindications**

Patients with bile duct obstruction, gallstones, and GI disorders (including stomach ulcers and hyperacidity disorders) should not take this supplement.

**Herb-Drug Interactions**

**Anticoagulants / Antiplatelets:** Turmeric may increase risk of bleeding.

**Camptothecin:** Turmeric inhibits camptothecin-induced apoptosis of breast cancer cell lines in vitro.

**Mechlorethamine:** Turmeric inhibits mechlorethamine-induced apoptosis of breast cancer cell lines in vitro.

**Doxorubicin:** Turmeric inhibits doxorubicin-induced apoptosis of breast cancer cell lines in vitro.

**Cyclophosphamide:** Dietary turmeric inhibits cyclophosphamide-induced tumor regression in animal studies.
Kidney related problems

The results of study indicate that ADR-induced kidney injury was remarkably well prevented by treatment with curcumin. Treatment with curcumin markedly protected against ADR-induced proteinuria, albuminuria, hypoalbuminemia and hyperlipidemia. Curcumin restored renal function in ADR rats, as judged by the increase in GFR. The data also demonstrate that curcumin protects against ADR-induced renal injury by suppressing oxidative stress and increasing kidney glutathione content and glutathione peroxidase activity. This suggests that administration of curcumin is a promising approach in the treatment of nephrosis caused by ADR.

Chemoprevention of colon carcinogenesis

This study was designed to investigate the chemopreventive action of dietary curcumin on azoxymethane-induced colon carcinogenesis and the modulating effect of curcumin on the colonic mucosal and tumor phospholipase A2, phospholipase C gamma 1, lipoxygenase, and cyclooxygenase activities in male F344 rats. The results indicate that the administration of curcumin significantly inhibited incidence of colon adenocarcinomas (p<0.004) and the multiplicity of invasive, non-invasive, and total adenocarcinomas. Curcumin also significantly suppressed the colon tumor volume by more than 57% compared to the control diet. Although the precise mechanism by which curcumin inhibits colon tumorogenesis remains to be elucidated, it is likely that the chemopreventive action, at least in part, may be related to the modulation of arachidonic acid metabolism.

1. Prevention of Diseases such as Cancer and Alzheimer’s

Curcumin has been shown to help prevent cancer in all its stages by inducing the infected cells to kill themselves but leaving the healthy ones alone. Due to its powerful anti-inflammatory properties it can help to keep the neural pathways clear, helping with dementia like Alzheimer’s. With many expected to suffer from some kind of
dementia in our lifetime, any one can benefits by taking curcumin daily is that we can help to prevent this from happening.

2. Healthy Immune System

With it having the most powerful antioxidant properties of any natural substance, it is hardly surprising that it can boost your immune system, helping you prevent those annoying coughs and colds, while maintaining optimum health, perhaps one of the best everyday curcumin benefits.

3. Detox

Curcumin has a detoxifying effect on the body by improving liver function and helping the body eliminate toxins at a greater and more efficient rate, helping to keep you even healthier on the inside.

4. Low Cholesterol

The lowering of our bad or LDL cholesterol has had a lot of press recently with many people’s levels too high. One of the benefits of taking curcumin daily is that you can lower your level and help to prevent a stroke or heart attack for occurring.

5. A Natural Solution

What better way to get all these benefits than from a natural substance with no side effects. When you consider that after taking a course of antibiotics your immune system is severely lowered for up to six months, unlike with curcumin, while treating the problem it also boosts your immune system! Combining with other nutrients like black pepper will increase the absorption by up to 2000%, leaving no need for high doses.