Here are some research papers on curcumin and curcuminoids. This is in relationship to RELEVIT, a very successful product used for chronic pain such as low back and arthritis pain. It works in 30 minutes and is safe. The active and primary ingredient is a highly refined curcuminoid although there are synergist effects from the other ingredients.

Turmeric in Latin is Curcuma longa. Turmeric is the yellow spice that gives flavor to curried dishes. In the Far East, Turmeric is valued for more than just its culinary uses. The herb has been employed in the Ayurvedic healing tradition for centuries. The active ingredient in turmeric is the intense yellow pigment that is called curcumin. Curcumin is composed of three curcuminoids and is generally thought of as an antioxidant although it is also a powerful COX2 inhibitor without side effects.

Unlike other antioxidants, there are two particular modes of antioxidant action of curcuminoids. The “prevention mode” prevents the formation of free radicals. The second mechanism, known as the “intervention mode”, neutralizes the already formed free radicals by the action of free radical scavenging. The active ingredients in Curcuma longa are a group of plant substances called curcuminoids. Known collectively as “curcumin”, curcuminoids have demonstrated potent antioxidant properties in scientific studies. Curcuminoids benefit joints and other tissues by helping to neutralize free-radicals. Through its antioxidant mechanisms, curcumin supports colon health, exerts neuroprotective activity and helps maintain a healthy cardiovascular system.

The process of inflammation which occurs after an injury of some kind, whether it be trauma from physical means or injury by chemical means within the body produces a cascade of responses. The cardinal three signs of inflammation are rubor (redness signifying intense blood accumulation), tumor (swelling signifying accumulation of fluid), and dolor (signifying pain because of irritation of sensory nerves). In an external injury this is easily seen and felt, but internal inflammation is more insidious. This inflammation is a necessary part of the first response to an injury and without it we would suffer greatly. As with every function in the body, we have checks and balances to control inflammation and not allow it to get out of control. COX2 enzymes are present to stimulate the process so repair can proceed quickly but there are balancing chemicals to stop the stimulation of COX2. Under certain circumstances, the COX2 enzyme is allowed to continue its stimulation of the inflammatory process and then we have chronic pain such as in low back conditions, arthritis, lupus, etc.

It has long been known that the salicylates are capable of inhibiting the COX2 enzymes and aspirin, ibuprofen and others have been extensively used. But the downside of these inhibitors is the lack of specificity, they also inhibit COX1 enzymes which protect the mucous membranes of the stomach and urinary tract and respiratory tract. They also act as an anticoagulant with side effects that are well known and caution is the rule of the day. Most of the natural COX2 inhibitors do not have these side effects and can be used with full safety.

The isolated curcuminoid found in RE-LEV-IT is such a safe antiinflammatory and has been used for years without any known side effects reported with the exception of a rare gastric upset. Following are some of the other benefits of using highly concentrated curcumin as a dietary supplement.
Curcumin is the principal active ingredient of the popular Indian curry spice turmeric. The curcuminooids 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.[1] It is also hepatoprotective.[2]

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. Since curcumin is brightly colored, it may be used as a food coloring. As a food additive, its E number is E100.

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

Potential medical uses
Curcumin is known for its antitumor,[3][4] antioxidant, antiarthritic, anti-amyloid, anti-ischemic[5] and anti-inflammatory properties.[6] Anti-inflammatory properties may be due to inhibition of eicosanoid biosynthesis.[7] In addition it may be effective in treating malaria, prevention of cervical cancer, and may interfere with the replication of the HIV virus.[8] In HIV, it appears to act by interfering with P300/CREB-binding protein (CBP). A 2008 study at Michigan State University showed that low concentrations of curcumin interfere with Herpes simplex virus-1 (HSV-1) replication.[9] The same study showed that curcumin inhibited the recruitment of RNA polymerase II to viral DNA, thus inhibiting the transcription of the viral DNA.[9] This effect was shown to be independent of effect on histone acetyltransferase activities of p300/CBP.[9] 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 intravaginal infections.[10]

Curcumin acts as a free radical scavenger and antioxidant, inhibiting lipid peroxidation[11] and oxidative DNA damage. Curcuminooids induce glutathione S-transferase and are potent inhibitors of cytochrome P450.

For the last few decades, extensive work has been done to establish the biological activities and pharmacological actions of curcumin. Its 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-$\kappa$B, which has been linked to a number of inflammatory diseases such as cancer.[12] Indeed, when 0.2% curcumin is added to diet given to rats or mice previously given a carcinogen, it significantly reduces colon carcinogenesis (Data from sixteen scientific articles reported in the Chemoprevention Database). A 2007 report indicates that curcumin may suppress MDM2, an oncogene involved in mechanisms of malignant tumor formation.[13]
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.[14]

**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.[15] 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 affect on neurogenesis in the hippocampus and concentrations of brain-derived neurotrophic factor (BDNF), reductions in both of which are associated with stress, depression, and anxiety.[16] [17] [18]

**Little curcumin, when eaten, is absorbed:** from 2 to 10 grams of curcumin eaten alone resulted in undetectable to very low serum levels.[19] Curcumin is unstable in the gut, and the traces that pass through the GI tract rapidly degrades or is 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.[19] (ED. NOTE: THIS IS WHY WE ADD PIPERINE TO THE FORMULA OF RELEVIT.)

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

In 2007, a polymeric nanoparticle encapsulated formulation of curcumin (“nanocurcumin”[20]) 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.[20] 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.[21] Another method to increase the bioavailability of curcumin filed a patent in 2006 that involves a simple procedure creating a complex with soy phospholipids, however the plasma concentration of curcumin using this formulation only reached 0.033 micromolar.[22]

[edit] Potential Risks & Side Effects
Kawanishi et al. (2005) of NCBI 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. [23] Carcinogenic effects are inferred from interference with the p53 tumor suppressor pathway, an important factor in human colon cancer. [24] Carcinogenic and LD50 tests in mice and rats, however, have failed to establish a relationship between tumorogenesis and administration of curcumin in turmeric oleoresin at >98% concentrations. [25] This may prove curcumin medicinally useful as it helps activate p53. When a cell is inhibited by cancer the concentrations of p53 increase, helping cells defend against cancer mechanisms. Clinical studies in humans with high doses (>2-12 grams) curcumin supplementation have shown some subjects reporting diarrhea and nausea; however, curcumin has also been indicated for these conditions as well. [26]

References
impaired hippocampal neurogenesis and increases serotonin receptor 1A mRNA and brain-derived neurotrophic factor expression in chronically stressed rats”. Brain Res 1162: 9. doi:10.1016/j.brainres.2007.05.071. PMID 17617388.


22. European patent EP20060004820


• Aggarwal, Bharat et al; December 2006; “Curcumin: The Indian Solid Gold” [2]
• Aggarwal BB, Kumar A, Bharti AC; “Anticancer potential of curcumin: preclinical and clinical studies.” Anticancer Res. ’2003 Jan-Feb;23(1A):363-98. (PMID 12680238)
• Can a Common Spice Be Used to Treat Cancer?, Dianne C. Witter, OncoLog, September 2007, Vol. 52, No. 9
• Turmeric, (University of Maryland info on complementary and alternative medicines)
• Sloan-Kettering Herbal Guide
• Curcumin at M.D. Anderson
• Curcumin: A Powerful Brain Protection Supplement, 2005-2008, John Smart, Acceleration Studies Foundation.
• Turmeric, (University of Maryland info on complementary and alternative medicines)
• Clinical trials info on Curcuma Longa at HerbMed
• Curcumin (metabolism, effects, bioavailability,..., Linus Pauling Institute, Oregon State U.)
• Spice Healer--An ingredient in curry shows promise for treating Alzheimer’s, cancer and other diseases, Gary Stix, Scientific American, Feb 2007
• Curcumin & Alzheimer’s and Cancer, ongoing studies at Alzheimer’s research lab, UCLA, plus human drug trial [3]
• Nanocurry vs. cancer Technology Review, June 12, 2007
• Bioavailability of Curcumin: Problems and Promises, Preetha Anand, Ajaikumar B. Kunnumakkara, Robert A. Newman, and Bharat B. Aggarwal
• Tumour tripper -- Turmeric can boost the immune system in cancer., The Telegraph, June 11, 2007
• Treatment of human multiple myeloma by curcumin; US Patent Issued on March 27, 2007
Curcumin Update
New Research on the Multiple Benefits of this Potent Health-Promoting, Disease-Fighting Agent  By Dale Kiefer

From powerful heart medications and antibiotics to simple aspirin, many modern pharmaceuticals have been derived directly from ancient plant and fungal sources that exhibit remarkable abilities to improve well being and intervene in disease processes at the molecular level. Scientists continue to discover medically useful plant compounds that demonstrate powerful anti-inflammatory, anticancer, antibiotic, and antiaging properties. Turmeric is a case in point. This tropical root delivers a smorgasbord of powerful health benefits. **New research shows that turmeric—and its main bioactive compound, curcumin—has the power to block inflammation, stop cancer, kill infectious microbes, and improve heart health.**

Turmeric is perhaps most familiar as the star ingredient in powdered curry mixes. Curcumin, a group of polyphenolic plant pigments, is responsible for turmeric’s characteristic canary yellow color. Curry is the signature seasoning and fragrant dish of the Indian subcontinent.

India’s relationship with turmeric, and thus curcumin, goes back thousands of years. Both ginger and turmeric have been cultivated in India and southeast Asia for millennia. India produces and consumes most of the world’s turmeric. A cousin of ginger, turmeric was revered by the ancient Romans and Greeks, who valued its medicinal properties. Indeed, its English name derives from its Latin moniker, which roughly translates as “earth-merit.”

Unlike their Western counterparts, most native Indians would probably not be surprised to learn that modern science has begun to investigate and catalogue turmeric’s various health-promoting properties. Turmeric is familiar to Indians not only as a spice but also as an important element of folk medicine. In the ancient Indian system of Ayurvedic holistic medicine, turmeric is revered for its ability to quell inflammation and to treat a variety of maladies. Indeed, Ayurvedic medicine recommends mixing turmeric in a small amount of honey for the treatment of numerous ailments. It is taken orally at the first sign of the common cold, and the sticky paste is applied to the skin as a topical ointment for the treatment of skin infections and irritations.

**Turmeric powder also is a popular remedy for stomach complaints throughout Asia. In Hawaii, it is reportedly used to treat swimmer’s ear (infection) and sinus infections. Perhaps one of its most important applications is as an anti-inflammatory for the treatment of arthritis; it has been used as such in China and India for thousands of years.**

Modern Science Meets Ancient Faith
Modern scientists have examined these largely faith-based claims and have subjected them to rigorous testing over the last 50 years. Although few large-scale human trials have been completed, hundreds of experiments conducted by researchers around the globe have demonstrated curcumin’s ability to halt or prevent certain types of cancer,1-20 stop inflammation,21-26 improve cardiovascular health,27-31 prevent cataracts,32 kill or inhibit the toxic effects of certain microbes including fungi33 and dangerous parasites,34,35 and protect, at least in the laboratory, against the damaging effects of heterocyclic amines (potentially carcinogenic compounds found in some cooked foods).36 **As one investigative
team declared: “[Curcumin] has been proven to exhibit remarkable anticarcinogenic, anti-inflammatory, and antioxidant properties.”

As if that were not enough, this hard-working spice shows promise as a potential treatment for multiple sclerosis, and may ameliorate the damaging effects of long-term diabetes. It is even being investigated as a topical treatment to speed diabetic wound healing. Some researchers also have noted an exciting link between turmeric consumption and a dramatically decreased incidence of Alzheimer’s disease, an effect that may well be related to curcumin’s ability to block signaling pathways that lead to inflammation.

Cancer-Fighting Capabilities Documented
Numerous studies published in peer-reviewed medical journals detail curcumin’s ability to protect against cancer. In addition to its capacity to intervene in the initiation and growth of cancer cells and tumors—and to prevent their subsequent spread throughout the body by metastasis—curcumin also has been shown to increase cancer cells’ sensitivity to certain drugs commonly used to combat cancer, rendering chemotherapy more effective in some cases. Much research has focused on curcumin’s anti-inflammatory properties, and some new research suggests that curcumin may protect the heart and circulatory system, and prevent the onset of Alzheimer’s disease. Still other studies have examined curcumin’s potential ability to counteract the effects of fungal toxins in the food supply, and to protect the eyes from cataracts and uveitis, an inflammation of a portion of the eye that may result in glaucoma.

Turmeric Patent Granted and Revoked
Several years ago, two expatriate Indians associated with the University of Mississippi Medical Center filed for a US patent on turmeric. The patent was granted in 1995, but after an outcry from an Indian agriculture group, it was promptly revoked. Protesters challenged the patent’s validity on the grounds that turmeric is a previously available product that has been used medicinally in Asia for centuries. Since “novelty” is a condition of patent protection, it was determined that turmeric is not subject to such protection. The patent was revoked.

As an anticancer agent, curcumin is promising enough to warrant serious attention from the National Cancer Institute (NCI). In its 2002 annual report, the Chemopreventive Agent Development Research Group, a subset of the NCI’s Division of Cancer Prevention, details its efforts to encourage and support research on curcumin’s utility in cancer prevention and treatment. Because curcumin is a non-patentable product (see sidebar), such support is crucial, especially for research involving all-important human trials, as other sources of funding are virtually nonexistent. At least one human trial, focusing on dosing, bioavailability, and pharmacokinetics (how curcumin is used, metabolized, and eliminated by the body), is under way at the University of Michigan Comprehensive Cancer Center. Other curcumin studies have been proposed to the NIC and are awaiting approval.

Test-tube and animal-model studies have demonstrated that curcumin exhibits significant anti-cancer activity. Numerous experiments have shown that curcumin inhibits the progression of chemically induced colon and skin cancers. In colon cancer, in particular, curcumin seems to significantly inhibit both the promotional and progression stages of the disease. Various studies have reported that curcumin reduces the number and size of existing tumors, and decreases the incidence of new tumor formation.
Much discussion lately has focused on the use of cyclooxygenase-2 (COX-2) inhibitors—such as the prescription medications Celebrex® and Vioxx®—as potential colon cancer preventive agents. This new approach arose from the observation that people who routinely take anti-inflammatory non-steroidal drugs (NSAIDs) are statistically less likely to develop cancer than those who do not. Unfortunately, NSAIDs are poorly tolerated by some and can even cause bleeding in the gastrointestinal tract. Regarding curcumin’s potential benefits for the prevention and treatment of colon cancer, one research team commented: “Naturally occurring COX-2 inhibitors such as curcumin and certain phytosterols have been proven to be effective as chemopreventive agents against colon carcinogenesis with minimal gastrointestinal toxicity.”18

Additionally, other studies using cancer cells grown in the laboratory in vitro have demonstrated curcumin’s ability to prompt apoptosis, or programmed cell death, among leukemia, B lymphoma, and other cancerous cells. Curcumin has been used as a topical application to successfully induce apoptosis in skin cancer cells both in vitro and in animal models. Curcumin is under investigation as a preventive agent for increasingly common non-melanoma skin cancers, and as a potential preventive or treatment agent in breast, prostate, oral, pancreatic, and gastric cancers, among others.1-21 One researcher understated the matter, noting, “…curcumin…should be considered for further development as [a] cancer preventive agent.”43

Curcumin also has been shown to enhance the effectiveness of certain anti-cancer drugs, and, amazingly, to potentially improve the effectiveness of anti-cancer radiation treatment by preventing tumor cells from developing radiation resistance.33 Protein kinase C (PKC) has been suggested as a possible mechanism by which tumor cells develop resistance to radiation therapy. Curcumin’s helpful effect may be due to its ability to inhibit radiation-induced PKC activity. Additionally, one study found that curcumin protected study animals from the tumor-producing effects of deadly gamma radiation,44 while another found that it protects against damaging ultraviolet light, which is known to play a role in the development of skin cancer.8

Earlier this year, researchers at the University of Texas M.D. Anderson Cancer Center declared: “...curcumin has enormous potential in the prevention and treatment of cancer.” They noted that curcumin has been found to be safe for human consumption, even in doses ranging as high as 10 grams per day.10 But other researchers have observed that more is not necessarily better. A recently published study out of India found that among rats fed a diet causing high blood sugar, those given low doses of curcumin did not develop experimentally induced cataracts as often as control subjects. But rats receiving high doses of curcumin actually developed cataracts somewhat faster, possibly due to increased oxidative stress.32 The difference in dosing was extreme, but these findings underscore the importance of further inquiry into the uses of curcumin in humans for a variety of diseases and under a variety of conditions.
**Curcumin arthritis**  
by Nathan Wei, MD, FACP, FACR

Nathan Wei is a board-certified rheumatologist

Turmeric, a component of curry spice mixtures, has long been used for anti-inflammatory treatment in traditional Chinese and Ayurvedic medicine. The active ingredient in turmeric is curcumin. Dr Nadir Arber (Lev-Ari S, Strier L, Kazanov D, et al. Curcumin synergistically potentiates the growth-inhibitory and pro-apoptotic effects of celecoxib in osteoarthritis synovial adherent cells. Rheumatology 2006; 4:171-177 ) reports that curcumin not only has anti-inflammatory properties but also synergistically potentiates the beneficial effects of celecoxib (Celebrex). The effects of curcumin are due to inhibition of COX-2, resulting in a 95% reduction in production of prostaglandins, but also to non-COX-2 processes. The synergy with celecoxib was so striking that adding curcumin might permit the use of much lower doses of celecoxib, thereby reducing the risk of side effects such as cardiovascular problems.

Curcumin inhibits COX-2 and has been the subject of considerable interest in cancer treatment and prevention. Arber reasoned that combining curcumin with a COX-2 inhibitor with a different mechanism of action might also be useful for treating joint inflammation such as OA or rheumatoid arthritis (RA).

Arber used bits of human synovial tissue collected during total-knee-replacement surgery to prepare cultures of OA synovial adherent cells. These cells were then exposed to different concentrations of celecoxib and curcumin and combinations of the two. A synergistic effect was observed in inhibition of cell growth when the cells were exposed to various concentrations of celecoxib combined with curcumin. Although Arber’s studies use pharmaceutical-grade curcumin, clinicians might also face questions from patients interested in taking nonprescription curcumin dietary supplements or just in eating more curry.

The effects of curcumin are only partly due to reductions in COX-2 activity. Curcumin affects numerous molecular targets, including transcription factors such as NF- B, cell-cycle proteins such as cyclin D1 and p21, and cytokines such as TNF, IL-1, and IL-6. It also appears able to directly protect cartilage from inflammation-related damage. Shakibaei et al found that curcumin protected cultured human chondrocytes from IL-1- (IL-1b)-induced degradation by preventing activation of matrix-degrading enzymes, preventing downregulation of matrix production, and reducing chondrocyte apoptosis (Shakibaei M, Schulze-Tanzil G, John T, et al. Curcumin protects human chondrocytes from IL-1-beta-induced inhibition of collagen type II and beta-1-integrin expression and activation of caspase-3: an immunomorphological study. Ann Anat 2005; 187:487-497).