Curcumin and Fermented Soy Capsules and Fermented Soy/Curcumin Nutritional Beverage

Studies that used the Jiva Ingredient: Curcumin C3 Complex®

Inflammatory Bowel Disease

- Numerous therapies used for inflammatory bowel disease (IBD) target the transcription factor NF-kappaB, which is involved in the production of cytokines and chemokines integral for inflammation. The authors show that curcumin, is able to attenuate colitis in the dinitrobenzene sulfonic acid (DNB)-induced murine model of colitis. They also show that the immunohistochemical signal is dramatically attenuated at the level of the mucosa by curcumin. They conclude that curcumin is able to attenuate experimental colitis through a mechanism correlated with the inhibition of the activation of NF-kappaB and effects a reduction in the activity of p38 MAPK with therapeutic implications for human IBD.

Title: Curcumin attenuates DNB-induced murine colitis.
Authors: Salh B, Assi K, Templeman V, Parhar K, Owen D, Gomez-Munoz A, Jacobson K.

Antitumor /Anticancer/Antimutagenic

- In several systems, curcumin has been described as a potent antioxidant and anti-inflammatory agent. Evidence has also been presented to suggest that curcumin can suppress tumor initiation, promotion and metastasis. Pharmacologically, curcumin has been found to be safe. Human clinical trials indicated no dose-limiting toxicity when administered at doses up to 10 g/day. All of these studies suggest that curcumin has enormous potential in the prevention and therapy of cancer. The current review describes in detail the data supporting these studies, and discusses the mechanism of action of curcumin.

Source: Anticancer Res. 2003 Jan-Feb;23(1A):363-98.
Title: Anticancer potential of curcumin: preclinical and clinical studies.
Authors: Aggarwal BB, Kumar A, Bharti AC.

- Effect of aqueous extracts of turmeric, cloves, pepper, chili, cinnamon, onion and also their respective active principles viz., curcumin, eugenol, pipercine, capsaicin, cinnamaldehyde, quercetin, and allyl sulfide were tested on human PMNL 5-LO activity by spectrophotomeric and HPLC methods. The formation of 5-LO product 5-HETE was significantly inhibited in a concentration-dependent manner by aqueous extracts of spices and the respective active principles. Quercetin, eugenol and curcumin with one or more phenolic ring and methoxy groups in their structure showed high inhibitory effect, while the non-phenolic spice principle allyl sulfide showed least inhibitory effect on 5-LO. The inhibitory effect of quercetin, curcumin and eugenol was similar to that of synthetic 5-LO inhibitors phenidone and NDGA. These findings clearly suggest that phenolic compounds present in spices might have physiological role in modulating 5-LO pathway.

Title: Spice phenolics inhibit human PMNL 5-lipoxygenase.
Authors: Prasad NS, Raghavendra R, Lokesh BR, Naidu KA.

- The effects of curcumin on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced expression of cyclooxygenase-2 (COX-2) in female ICR mouse skin were assessed. Topical application of the dorsal skin of female ICR mice with 10 nmol TPA led to maximal induction of cox-2 mRNA and...
protein expression at approximately 1 and 4 h, respectively. When applied topically onto shaven backs of mice 30 min prior to TPA, curcumin inhibited the expression of COX-2 protein in a dose-related manner. Taken together, suppression of COX-2 expression and NF-kappaB activation may represent molecular mechanisms underlying previously reported antitumor promoting effects of curcumin in mouse skin tumorigenesis.

**Title:** Curcumin inhibits phorbol ester-induced expression of cyclooxygenase-2 in mouse skin through suppression of extracellular signal-regulated kinase activity and NF-kappaB activation.
**Authors:** Chun KS, Keum YS, Han SS, Song YS, Kim SH, Surh YJ.

- Based on the hypothesis that natural agents capable of modulating both lipoxygenase and COX may advance the efficacy of cancer therapy, an overview and discussion is presented of dietary modifications and selected nutritional and botanical agents (notably, omega-3 fatty acids, antioxidants, boswellia, bromelain, curcumin, and quercetin) that favorably influence eicosanoid production.

**Source:** Integr Cancer Ther. 2002 Mar;1(1):7-37; discussion 37.
**Title:** Nutritional and botanical modulation of the inflammatory cascade--eicosanoids, cyclooxygenases, and lipoxygenases--as an adjunct in cancer therapy.
**Authors:** Wallace JM

- Gene deletion studies have shown that receptor activator of NF-kappabligand (RANKL) is one of the critical mediators of steoclastogenesis. Curcumin inhibited both RANKL- and TNF-induced osteoclastogenesis and pit formation. Curcumin suppressed osteoclastogenesis maximally when added together with RANKL and minimally when it was added 2 days after RANKL. The results indicated treatment with curcumin inhibits both the NF-kappaB activation and osteoclastogenesis induced by RANKL.

**Title:** Curcumin (diferuloylmethane) inhibits receptor activator of NF-kappab ligand-induced NF-kappaB activation in osteoclast precursors and suppresses osteoclastogenesis.
**Authors:** Bharti AC, Takada Y, Aggarwal BB.

- Incidence of cancer at different sites may be related to oxidative damage to host genome by genotoxicants. These oxidative actions may be modified by phytochemicals present in foods. The non-nutritive dietary constituents which possess antimutagenic property appear to be promising chemopreventive agents.

   This study reports the protective effect of curcumin on B(a)P induced DNA damage in human peripheral blood lymphocyte cells.

   The study group consisted of 10 male smokers, 10 non-smokers and 10 non-smoking females aged between 25 and 45. The DNA damage was assessed using comet assay. In all the groups curcumin showed a dose-dependent inhibitory effect. The effect appeared to be sex dependent.

**Source:** Mutat Res. 2004 Feb 14;557(2):203-13.
**Title:** Inhibition of B(a)P induced strand breaks in presence of curcumin.
**Authors:** Polasa K, Naidu AN, Ravindranath I, Krishnaswamy K.

- In this study the authors examined the modulatory effects of turmeric on nitrosodiethylamine (NDEA)-induced hepatocarcinogenesis in rats. NDEA-treated rats receiving 1 or 5% turmeric before, during and after carcinogen exposure showed significant decrease in number of gamma glutamyl transpeptidase (GGT) positive foci and decrease in the incidence of NDEA-induced focal dysplasia (FD) and hepatocellularcarcinomas

**Source:** Toxicol Lett. 2003 Mar 20;139(1):45-54.
**Title:** Inhibition of nitrosodiethylamine-induced hepatocarcinogenesis by dietary turmeric in rats.
**Curcumin and osteoarthritis**

- P54FP is an extract of Indian and Javanese turmeric, Curcuma domestica and Curcuma xanthorrhiza respectively, which contains a mixture of active ingredients including curcuminoids and essential oils. A randomised, double-blind, placebo-controlled, parallel group clinical trial of P54FP as a treatment for osteoarthritis of the canine elbow or hip was conducted to assess its efficacy and safety. Sixty-one client-owned dogs with osteoarthritis were recruited through first-opinion practices and examined at a single centre. After a two-week wash-out period, they were randomly allocated to receive P54FP or a placebo orally twice daily for eight weeks, and were re-examined after four, six and eight weeks of treatment. The investigators’ overall assessment showed a statistically significant treatment effect in favour of P54FP (P=0.012), but the owners’ assessment just failed to reach statistical significance (P=0.063). No serious adverse effects were recorded, but two P54FP-treated dogs and four placebo-treated dogs were withdrawn from the study because their condition deteriorated.

**Gastroprotective /antiulcer:**

- Matrix metalloproteinases (MMPs) are suggested to play a critical role in extracellular matrix (ECM) degradation and remodeling during inflammation and wound healing processes. The anti-inflammatory and antioxidant properties of curcumin, an active component of turmeric suggest that...
Curcumin may exert anti-ulcer activity either through scavenging reactive oxygen species (ROS) or by regulating MMP activity, or both. The authors studied the effect of curcumin in indomethacin-induced gastric ulcer. The results show that curcumin exhibits potent antiulcer activity in acute ulcer in rat model by preventing glutathione depletion, lipid peroxidation and protein oxidation, and denudation of epithelial cells during damage of gastric lumen is reversed by curcumin through re-epithelialization. The results also revealed that both oral and intraperitoneal administration of curcumin blocks gastric ulceration in a dose dependent manner. It accelerates the healing process and protects gastric ulcer through attenuation of MMP-9 activity and amelioration of MMP-2 activity.

_Source: J Biol Chem. 2004 Dec 22; [Epub ahead of print]_
_Title: Curcumin regulates expression and activity of matrix metalloproteinases-9 and -2 during prevention and healing of indomethacin-induced gastric ulcer._
_Authors: Swarnakar S, Ganguly K, Kundu P, Banerjee A, Maity P, Sharma AV._

**Inhibition of gall bladder stone formation**

- Our previous study demonstrated that curcumin, an active compound of Curcuma xanthorrhiza and C. domestica, produces a positive cholekinetic effect. A 20 mg amount of curcumin is capable of contracting the gall bladder by up to 29% within an observation time of 2 h. (From the article: The finding that curcumin causes contraction of the gall bladder indicates that it may be potentially useful in preventing gall bladder stone formation, and may be used clinically to enhance biliary flow or to push out biliary sludge in the gall bladder - cholekinetic effects )

_Source: Asia Pac J Clin Nutr. 2002;11(4):314-8._
_Title: Effect of different curcumin dosages on human gall bladder._
_Authors: Rasyid A, Rahman AR , Jaalam K, Lelo A._

**AntiViral**

- Inhibition of the accumulation of protease-resistant prion protein (PrP-res) is a prime strategy in the development of potential transmissible spongiform encephalopathy (TSE) therapeutics. It is shown that curcumin potently inhibits PrP-res accumulation in scrapie agent-infected neuroblastoma cells (50% inhibitory concentration, approximately 10 nM) and partially inhibits the cell-free conversion of PrP to PrP-res. In vivo studies showed that dietary administration of curcumin had no significant effect on the onset of scrapie in hamsters. Nonetheless, other studies have shown that curcumin is nontoxic and can penetrate the brain, properties that give curcumin advantages over inhibitors previously identified as potential prophylactic and/or therapeutic anti-TSE compounds.

_Source: J Virol. 2003 May;77(9):5499-502_  
_Title: Inhibition of protease-resistant prion protein accumulation in vitro by curcumin._

- **Safety:** A large number of studies on curcumin were identified using literature and web sources. These included studies on the antioxidant, anti-inflammatory, antiviral, and antifungal properties of curcuminoids. Studies on the toxicity and anti-inflammatory properties of curcumin have included in vitro, animal, and human studies. A phase 1 human trial with 25 subjects using up to 8000 mg of curcumin per day for 3 months found no toxicity from curcumin. Five other human trials using 1125-2500 mg of curcumin per day have also found it to be safe. Curcumin has been demonstrated to be safe in six human trials and has demonstrated anti-inflammatory activity. It may exert its anti-inflammatory activity by inhibition of a number of different molecules that play a role in inflammation.

_Title: Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa)._  
_Authors: Chainani-Wu N._
Fermented Soy Studies

The fermented soy used in Jiva products is comprised of cooked organic soy bean that is fermented by L. acidophilus, L. bulgaricus, L. casei, L. plantarum and S. thermophilus, probiotic bacteria. Beneficial probiotic bacteria used in fermentation yield healthy cell wall contents and metabolites which promote optimal immune function and intestinal health. The Soy isoflavones used exhibit enhanced availability by the bacteria in the small intestine due to its conversion to more absorbable forms.

- **Prolonged stabilization of platinum-resistant ovarian cancer in a single patient consuming a fermented soy therapy.**
  Fermented soy products are known to contain high concentrations of the isoflavone, genistein, and other compounds that exhibit anticancer activity in preclinical models. This case report supports the prospective evaluation of alternative therapies such as these in patients with platinum-refractory ovarian cancer.

  **Source:** Division of Medical Oncology, Massachusetts General Hospital, Cox 640, 100 Blossom Street, Boston, MA 02114, U
  **Authors:** Klein A, He X, Roche M, Mallett A, Duska L, Supko JG, Seiden MV.

- **Intake of fermented soybeans, natto, is associated with reduced bone loss in postmenopausal women: Japanese Population-Based Osteoporosis (JPOS) Study.**
  Japanese fermented soybeans (natto in Japanese), which contain a large amount of menaquinone-7, may help prevent the development of osteoporosis. We assessed the possibility of an association between habitual natto intake and bone mineral density (BMD) and BMD change over time in healthy Japanese women who participated in a large representative cohort study (Japanese Population-based Osteoporosis Study: JPOS study). The BMD was measured at the spine, hip, and forearm in 944 women (20-79 y old) at baseline and at a follow-up conducted 3 y later. Dietary natto intake was assessed by a FFQ on both occasions. Additional covariates including age, height, weight, lifestyle factors, dietary calcium intake, and the intake of other soybean products, were also measured. The total hip BMD at baseline increased (P for trend = 0.0034) with increasing habitual natto intake in the postmenopausal women, although this was not the case at other skeletal sites. There were significant positive associations between natto intake and the rates of changes in BMD at the femoral neck (P < 0.0001) and at the distal third of the radius (P = 0.0002) in the postmenopausal women. The association in the femoral neck persisted even after adjusting for covariates. No significant association was observed between the intake of tofu or other soybean products and the rate of BMD change in the postmenopausal women. Natto intake may help prevent postmenopausal bone loss through the effects of menaquinone 7 or bioavailable isoflavones, which are more abundant in natto than in other soybean products.

  **Source:** JPOS Study Group, Department of Public Health, Kinki University School of Medicine, Osaka, Japan.
  **Authors:** Ikeda Y, Iki M, Morita A, Kajita E, Kagamimori S, Kagawa Y, Yoneshima H

- **Soy intake is associated with lower lung cancer risk: results from a meta-analysis of epidemiologic studies.**
  Although several in vitro and animal in vivo studies have suggested that soy or soy isoflavones may exert inhibitory effects on lung carcinogenesis, epidemiologic studies have reported inconclusive results on the association between soy intake and lung cancer. The aim of this meta-analysis was to investigate whether an association exists between soy and lung cancer in epidemiologic studies. We
searched PubMed, EMBASE, and the Cochrane Library from their inception to February 2011 for both case-control and cohort studies that assessed soy consumption and lung cancer risk. Study-specific risk estimates were combined by using fixed-effect or random-effect models. A total of 11 epidemiologic studies that consisted of 8 case-control and 3 prospective cohort studies were included. A significantly inverse association was shown between soy intake and lung cancer with an overall RR of 0.77 (95% CI: 0.65, 0.92). Findings were slightly different when analyses were restricted to 5 high-quality studies (RR: 0.70; 95% CI: 0.45, 0.99). In a subgroup meta-analysis, a statistically significant protective effect of soy consumption was observed in women (RR: 0.79; 95% CI: 0.67, 0.93), never smokers (RR: 0.62; 95% CI: 0.51, 0.76), and Asian populations (RR: 0.86; 95% CI: 0.74, 0.98). Our findings indicate that the consumption of soy food is associated with lower lung cancer risk. Because of different methods used to assess soy consumption across studies, more well-designed cohort studies or intervention studies that use unified measures of soy intake are needed to fully characterize such an association.

Source: State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, China.
Authors: Yang WS, Va P, Wong MY, Zhang HL, Xiang YB.

- **Higher bioavailability of isoflavones after a single ingestion of aglycone-rich fermented soybeans compared with glucoside-rich non-fermented soybeans in Japanese postmenopausal women.**

Eleven healthy postmenopausal Japanese women were recruited for a randomised, double-blind, crossover trial and consumed Fsoy or Soy powder dissolved in hot water. Blood samples were collected 0, 1, 2, 3, 4, 6, 8, 12 and 24 h and urine samples from 0 to 48 h after ingestion of the powders. The Fsoy and Soy powders ingested had the same total isoflavone content (95 µmol), but the former was rich in aglycone (90.6 µmol) while the latter was rich in glucoside (81.9 µmol). Serum concentrations of total isoflavones after 1-4 h were significantly higher in the Fsoy group than in the Soy group. The Fsoy group showed significantly higher maximum concentration (Cmax: 2.79 ± 0.13 vs 1.74 ± 0.13 µmol L(-1)) and area under the curve (AUC(0-24 h) : 23.78 ± 2.41 vs 19.95 ± 2.03 µmol day L(-1)) and lower maximum concentration time (Tmax: 1.00 ± 0.00 vs 5.00 ± 0.67 h) compared with the Soy group. The cumulative urinary excretion of total isoflavones after 2 h was significantly higher in the Fsoy group than in the Soy group. Individual isoflavones (daidzein, genistein and glycitein) showed similar trends to total isoflavones. Equol (a metabolite from daidzein) did not differ between the two groups. The results of this study demonstrated that the isoflavones of aglycone-rich Fsoy were absorbed faster and in greater amounts than those of glucoside-rich Soy in postmenopausal Japanese women.

Source: Research Institute for Health Fundamentals, Ajinomoto Co., Inc., 1-1, Suzuki-cho, Kawasaki 210-8681, Japan.
Authors: Okabe Y, Shimazu T, Tanimoto H.

- **Antidiabetic effects of fermented soybean products on type 2 diabetes.**

Historically, the incidence of type 2 diabetes has been lower in Asian populations compared with those in Western countries. One possible reason for the lower incidence among Asians is that they consume fermented soybean products, which are unique to the traditional Asian diet. Some have hypothesized that dietary phytoestrogens and soy peptides in fermented soybean foods consumed in traditional Asian diets may help prevent and slow the progression of type 2 diabetes. This review evaluates the existing evidence from animal studies and clinical and epidemiologic investigations on fermented soybeans in the prevention and treatment of type 2 diabetes. Nutritional studies performed in animals and intervention studies with humans suggest that the ingestion of soy protein with isoflavones improves glucose control and reduces insulin resistance. Korean fermented soybean products such as doenjang, kochujang, and chungkookjang contain alterations in the structures and content of isoflavonoids and small bioactive peptides, which are produced during fermentation. Several studies revealed improvements in insulin resistance and insulin secretion with the consumption of these fermented products. Therefore, fermented soybean products may help prevent or attenuate the progression of type 2 diabetes. Although the lack of human intervention trials does not permit definitive conclusions, the
evidence does suggest that fermented soy products may be better for preventing or delaying the progression of type 2 diabetes compared with nonfermented soybeans.

**Source**: Emerging Innovative Technology Research Division, Korean Food Research Institutes, Sungnam, Korea.

**Author**: Kwon DY, Daily JW 3rd, Kim HJ, Park S.

- **Lipid profile lowering effect of Soypro* fermented with lactic acid bacteria isolated from Kimchi in high-fat diet-induced obese rats.**

Lactic acid bacteria are known to exert various physiologic functions in humans. In the current study, we investigated the effects of Soypro, a new soymilk fermented with lactic acid bacteria, like Leuconostoc kimchii, Leuconostoc citreum, and Lactobacillus plantarum, isolated from Kimchi, on adipocyte differentiation in preadipocyte 3T3-L1 cell lines and weight gain or the plasma lipid profile in Sprague-Dawley rats. Adipocyte 3T3-L1 cells treated with Soypro (10 microg/ml) significantly reduced the contents of cellular triglyceride and inhibited cell differentiation by Oil red O staining. Treatment with Soypro (10 microg/ml) for an additional two days in adipocytes inhibited the expression of peroxisome proliferator-activated receptor-gamma2 and CCAAT/enhancer binding protein-alpha, transcription factors of adipocyte differentiation. Based on these in vitro studies, we examined the anti-obesity effect of Soypro in rats for six weeks. Soypro had no significant effect on high-fat diet-induced increases in body weight, food intake, or feed gain ratio. However, the administration of Soypro significantly reduced the concentration of the plasma low density lipoprotein cholesterol. Changes in the plasma levels of total cholesterol and glucose were inclined to decrease in Soypro administrated groups compared with saline treated group. Triglyceride and high density lipoprotein cholesterol values in Soypro fed groups were similar compared to those of saline fed groups. Although further research is needed, these findings suggest that Soypro decreased the levels of low density lipoprotein cholesterol in high-fat diet-induced obesity and might partially inhibit the adipocyte differentiation through the suppression of a transcription factors peroxisome proliferator-activated receptor-gamma2 and CCAAT/enhancer binding protein-alpha.

**Source**: Department of Pharmacology, College of Oriental Medicine, Kyung Hee University, Seoul, Republic of Korea

**Authors**: Kim NH, Moon PD, Kim SJ, Choi IY, An HJ, Myung NY, Jeong HJ, Um JY, Hong SH, Kim HM.

- **Quantification of genistein and genistin in soybeans and soybean products.**

It has been suggested that the isoflavone, genistein,, may have some role as a chemopreventive agent against cancer in humans. Levels of genistein and its beta-glucoside conjugate, genistin, ingested in soybeans and related bean products by the Japanese were quantified by HPLC, to estimate daily intake of these compounds. Amounts of genistein and genistin in soybeans, soy nuts and soy powder were in the range of 4.6 to 18.2 and 200.6 to 968.1 micrograms/g food, respectively. The values for soy milk and tofu (bean curd) were 1.9 to 13.9 and 94.8 to 137.7 micrograms/g food, respectively. Levels of isoflavones in fermented soybean products, miso (bean paste) and natto (fermented soybeans), were 38.5 to 229.1 micrograms/g food for genistein and 71.7 to 492.8 micrograms/g food for genistin. Thus, the level of genistein in the fermented soybean products was higher than in soy beans and soybean products such as soy milk and tofu. From these observations, it is suggested that the beta-glycosyl bond of genistin is cleaved to produce genistein by microbes during fermentation to yield miso and natto. Soy sauce was also found to contain both isoflavones, but at levels lower than in miso and natto. On the basis of these data for average annual consumption of soybeans and related products, daily intake of genistein and genistin by the Japanese is calculated to be 1.5-4.1 and 6.3-8.3 mg/person, respectively. These levels are much higher than those for Americans or Western Europeans, whose mortality rates for breast, colon and prostate cancers are greater than the Japanese.

**Source**: Biochemistry Division, National Cancer Center Research Institute, Tokyo, Japan.

**Authors**: Fukutake M, Takahashi M, Ishida K, Kawamura H, Sugimura T, Wakabayashi K
Early intake appears to be the key to the proposed protective effects of soy intake against breast cancer.

There is a large variation in breast cancer incidence and mortality rates worldwide. Migration studies have indicated that this variation is primarily the result of lifestyle influences. Although there has been much research conducted, definitively identifying dietary factors that impact breast cancer risk has proven difficult. In part this may be because most clinical and epidemiologic studies have focused on adult dietary exposure. However, evidence suggests that childhood and/or adolescence is the period of life when the breast is most sensitive to dietary influences. Further, the available epidemiologic and animal data suggest that early soy intake reduces breast cancer risk. Soy foods are unique dietary sources of isoflavones, diphenolic compounds that exert estrogen-like effects under certain experimental conditions. The protection effects of soy may result from the soybean isoflavones stimulating differentiation of the breast in much the same way that the elevated estrogen levels do during pregnancy. More specifically, in rats, the primary isoflavone genistein reduces mammary tumorigenesis and increases mammary tissue differentiation by leading to a reduction in the number of terminal end buds (TEB) and an increase in the number of differentiated lobules. There is need and justification for continued investigation of the early soy intake hypothesis, particularly to determine the cellular targets of soy action and to identify the signaling pathways mediating the effects on mammary gland morphology and susceptibility to breast cancer.

Source: Loma Linda University, Loma Linda, California, USA. markm@olympus.net
Authors: Messina M, Hilakivi-Clarke L.