

Selected *Curcuma longa* Published Scientific Abstracts

Cancer Lett. 2007 Apr 18;

Curcumin for chemoprevention of colon cancer.

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The most practical approach to reduce the morbidity and mortality of cancer is to delay the process of carcinogenesis through the use of chemopreventive agents. This necessitates that safer compounds, especially those derived from natural sources must be critically examined for chemoprevention. A spice common to India and the surrounding regions, is turmeric, derived from the rhizome of *Curcuma longa*. Pre-clinical studies in a variety of cancer cell lines including breast, cervical, colon, gastric, hepatic, leukemia, oral epithelial, ovarian, pancreatic, and prostate have consistently shown that curcumin possesses anti-cancer activity in vitro and in pre-clinical animal models. The robust activity of curcumin in colorectal cancer has led to five phase I clinical trials being completed showing the safety and tolerability of curcumin in colorectal cancer patients. To date clinical trials have not identified a maximum tolerated dose of curcumin in humans with clinical trials using doses up to 8000mg per day. The success of these trials has led to the development of phase II trials that are currently enrolling patients. Overwhelming in vitro evidence and completed clinical trials suggests that curcumin may prove to be useful for the chemoprevention of colon cancer in humans. This review will focus on describing the pre-clinical and clinical evidence of curcumin as a chemopreventive compound in colorectal cancer. PMID: 17448598

Cancer Res. 2007 Apr 15;67(8):3853-61.

Curcumin Potentiates Antitumor Activity of Gemcitabine in an Orthotopic Model of Pancreatic Cancer through Suppression of Proliferation, Angiogenesis, and Inhibition of Nuclear Factor- κ B-Regulated Gene Products.

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Gemcitabine is currently the best treatment available for pancreatic cancer, but the disease develops resistance to the drug over time. Agents that can either enhance the effects of gemcitabine or overcome chemoresistance to the drug are needed for the treatment of pancreatic cancer. Curcumin, a component of turmeric (*Curcuma longa*), is one such agent that has been shown to suppress the transcription factor nuclear factor- κ B (NF- κ B), which is implicated in proliferation, survival, angiogenesis, and chemoresistance. In this study, we investigated whether curcumin can sensitize pancreatic cancer to gemcitabine in vitro and in vivo. In vitro, curcumin inhibited the proliferation of various pancreatic cancer cell lines, potentiated the apoptosis induced by gemcitabine, and inhibited constitutive NF- κ B activation in the cells. In vivo, tumors from nude mice injected with pancreatic cancer cells and treated with a combination of curcumin and gemcitabine showed significant reductions in volume ($P = 0.008$ versus control; $P = 0.036$ versus gemcitabine alone), Ki-67 proliferation index ($P = 0.030$ versus control), NF- κ B activation, and expression of NF- κ B-regulated gene products (cyclin D1, c-myc, Bcl-2, Bcl-xL, cellular inhibitor of apoptosis protein-1, cyclooxygenase-2, matrix metalloproteinase, and vascular endothelial growth factor) compared with tumors from control mice treated with olive oil only. The combination treatment was also highly effective in suppressing angiogenesis as indicated by a decrease in CD31(+) microvessel density ($P = 0.018$ versus control). Overall, our results suggest that curcumin potentiates the

antitumor effects of gemcitabine in pancreatic cancer by suppressing proliferation, angiogenesis, NF-kappaB, and NF-kappaB-regulated gene products. PMID: 17440100

Indian J Exp Biol. 2007 Mar;45(3):272-7.

Curcuma longa as feed additive in broiler birds and its pathophysiological effects.

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Broiler birds (Vencob chicken of 3 days old) when given feed mixed with powdered rhizome of *Curcuma longa* (CL; @ 1 g/kg) for 42 days of age, showed significant decrease in serum uric acid and albumin as compared to control, whereas significant increase was recorded in the level of serum total protein and globulin. Level of serum glucose, alkaline phosphatase, aspartate amino transferase and calcium showed no significant variation between the two groups. Micronutrient assay revealed significantly higher level of manganese, zinc, iron and copper in treated group as compared to control group. HA/HI test revealed better humoral response against RD vaccine in CL administered birds. Haematological study showed significantly higher haemoglobin and absolute neutrophil count in treated group. Addition of CL as feed additive also resulted in better growth rate, feed consumption and F:C efficiency in the treated birds. Thus, it could be concluded that powdered CL might be a useful feed additive, since it enhanced the F:C efficiency and had nephroprotective properties. PMID: 17373373

Methods Find Exp Clin Pharmacol. 2007 Jan-Feb;29(1):19-25.

Possible neuroprotective mechanisms of curcumin in attenuating 3-nitropropionic acid-induced neurotoxicity.

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3-Nitropropionic acid (3-NP) is a well known fungic toxin causing neurotoxicity. Systemic administration of 3-NP causes motor and cognitive deficits that are associated with excessive free radical generation. Recently, curcumin has been implicated as a neuroprotectant in the treatment of various neurological disorders. The present study was designed to investigate the effects of curcumin in 3-NP-induced cognitive impairment and oxidative stress in rats. Curcumin, a potent antioxidant of dietary polyphenol, containing a standardized extract of *Curcuma longa* root (Zingiberaceae), has been reported to possess free radical scavenging, iron chelating and antiinflammatory activities. Intraperitoneal administration of 3-NP (20 mg/kg for 4 days) showed loss in body weight, declined motor function, poor retention of memory and changes in oxidative stress (lipid peroxidation, reduced glutathione and nitrite level) parameters in brain. Chronic treatment with curcumin (10, 20 and 50 mg/kg, p.o.) once daily for a period of 8 days beginning 4 days prior to 3-NP administration dose-dependently improved the 3-NP-induced motor and cognitive impairment. Biochemical analysis revealed that curcumin administration significantly attenuated 3-NP-induced oxidative stress (lipid peroxidation estimation, reduced glutathione and nitrite activity) in the brains of rats. It also significantly restored the decreased succinate dehydrogenase activity. The results of the present study clearly indicate that curcumin by its antioxidant activity showed neuroprotection against 3-NP-induced behavioral and biochemical alteration. PMID: 17344940

Int Immunopharmacol. 2007 Mar;7(3):333-42. Epub 2006 Dec 18.

Curcumin, a Curcuma longa constituent, acts on MAPK p38 pathway modulating COX-2 and iNOS expression in chronic experimental colitis.

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Ulcerative colitis (UC) is a nonspecific inflammatory disorder characterized by oxidative and nitrosative stress, leucocyte infiltration and up-regulation of pro-inflammatory cytokines. Mitogen-activated protein kinases (MAPKs), such as the p38 and the c-Jun N-terminal kinase (JNK) modulate the transcription of many genes involved in the inflammatory process. Curcumin is a polyphenol derived from *Curcuma longa*, which is known to have anti-inflammatory activity. The aim of this study was to study the effects and mechanisms of action of curcumin, on chronic colitis in rats. Inflammation response was assessed by histology and myeloperoxidase activity (MPO). We determined the production of Th1 and Th2 cytokines and nitrites in colon mucosa, as well as the expression of inducible nitric oxide synthase (iNOS), cyclo-oxygenase(COX)-1 and-2 by western blotting and immunohistochemistry. Finally, we studied the involvement of MAPKs signaling in the protective effect of curcumin in chronic colonic inflammation. Curcumin (50-100 mg/kg/day) were administered by oral gavage 24 h after trinitrobenzenesulfonic acid (TNBS) instillation, and daily during 2 weeks before sacrifice. Curcumin significantly attenuated the damage and caused substantial reductions of the rise in MPO activity and tumour necrosis factor alpha (TNF)-alpha. Also curcumin was able to reduce nitrites colonic levels and induced down-regulation of COX-2 and iNOS expression, and a reduction in the activation of p38 MAPK; however, no changes in the activation of JNK could be observed. In conclusion, we suggest that inhibition of p38 MAPK signaling by curcumin could explain the reduced COX-2 and iNOS immunosignals and the nitrite production in colonic mucosa reducing the development of chronic experimental colitis. PMID: 17276891

Basic Clin Pharmacol Toxicol. 2007 Jan;100(1):43-8.

Curcumin and kolaviron ameliorate di-n-butylphthalate-induced testicular damage in rats.

Farombi EO, Abarikwu SO, Adedara IA, Oyeyemi MO.

The present study was carried out to evaluate the ameliorative effects of kolaviron (a biflavonoid from the seeds of *Garcinia kola*) and curcumin (from the rhizome, *Curcuma longa* L.) on the di-n-butylphthalate (DBP)-induced testicular damage in rats. Administration of DBP to rats at a dose of 2 g/kg for 9 days significantly decreased the relative testicular weights compared to the controls, while the weights of other organs remained unaffected. Curcumin or kolaviron did not affect all the organ weights of the animals. While only DBP treatment significantly increased the testicular malondialdehyde level and gamma-glutamyl transferase activity (gamma-GT), it markedly decreased glutathione level, the testicular catalase, glucose-6-phosphate dehydrogenase, superoxide dismutase, sperm gamma-GT activities and serum testosterone level compared to the control group. Data on cauda epididymal sperm count and live/dead ratio were not significantly affected in the DBP-treated rats. Alone, DBP treatment resulted in a 66% decrease in spermatozoa motility and a 77% increase in abnormal spermatozoa in comparison to control. DBP-treated rats showed marked degeneration of the seminiferous tubules with necrosis and defoliation of spermatocytes. The DBP-induced injuries in biochemical, spermatological parameters and histological structure of testis were recovered by treatment with kolaviron or curcumin. The pattern in the behaviour of these compounds might be correlated with their structural variations. Our results indicate that kolaviron and curcumin protect against testicular oxidative damage induced by DBP. The chemoprotective effects of these compounds may be due to their intrinsic

antioxidant properties and as such may prove useful in combating phthalate-induced reproductive toxicity. PMID: 17214610

J Clin Immunol. 2007 Jan;27(1):19-35. Epub 2007 Jan 9.

"Spicing up" of the immune system by curcumin.

Jagetia GC, Aggarwal BB.

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA. Curcumin (diferuloylmethane) is an orange-yellow component of turmeric (*Curcuma longa*), a spice often found in curry powder. Traditionally known for its antiinflammatory effects, curcumin has been shown in the last two decades to be a potent immunomodulatory agent that can modulate the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells. Curcumin can also downregulate the expression of various proinflammatory cytokines including TNF, IL-1, IL-2, IL-6, IL-8, IL-12, and chemokines, most likely through inactivation of the transcription factor NF-kappaB. Interestingly, however, curcumin at low doses can also enhance antibody responses. This suggests that curcumin's reported beneficial effects in arthritis, allergy, asthma, atherosclerosis, heart disease, Alzheimer's disease, diabetes, and cancer might be due in part to its ability to modulate the immune system. Together, these findings warrant further consideration of curcumin as a therapy for immune disorders. PMID: 17211725

Anticancer Res. 2006 Nov-Dec;26(6B):4379-89.

Curcumin-induced apoptosis of human colon cancer colo 205 cells through the production of ROS, Ca²⁺ and the activation of caspase-3.

Su CC, Lin JG, Li TM, Chung JG, Yang JS, Ip SW, Lin WC, Chen GW.

Curcumin (diferuloylmethane), the yellow pigment in turmeric (*Curcuma longa*), is known to inhibit proliferation of cancer cells by arresting them at various phases of the cell cycle and to induce apoptosis in tumor cells. Curcumin-induced apoptosis mainly involves the activation of caspase-3 and mitochondria-mediated pathway in various cancer cells of different tissue origin. In the present study, the induction of apoptosis and cytotoxicity by curcumin in colon cancer colo 205 cells was investigated by using flow cytometry. The results demonstrated that curcumin induced cytotoxicity and apoptosis dose- and time-dependently. Curcumin induced the production of reactive oxygen species (ROS) and Ca²⁺, decreased the levels of mitochondria membrane potential and induced caspase-3 activity. Curcumin also promoted the expression of Bax, cytochrome C, p53 and p21 but inhibited the expression of Bcl-2. These observations suggest that curcumin may have a possible therapeutic potential in colon cancer patients. PMID: 17201158

Anticancer Res. 2006 Nov-Dec;26(6B):4361-71.

Curcumin-induced cell cycle arrest and apoptosis in human acute promyelocytic leukemia HL-60 cells via MMP changes and caspase-3 activation.

Curcumin (diferuloylmethane), is a natural product derived from the root of the plant *Curcuma longa*. For centuries, it has been used as a spice and as a herbal medicine in Chinese populations. Curcumin has been shown to inhibit cell proliferation, cell cycle arrest, cyclooxygenase (COX)-1 and -2 expression and apoptosis in several human cancer cell lines. The aim of this investigation was to clarify the mechanisms by which curcumin induced cytotoxicity and apoptosis in human leukemia HL-60 cells. The effects of curcumin on the levels of reactive oxygen species (ROS), Ca²⁺ production, cyclin E, cdc25c, wee1, Bcl-2, Bax, the changes of mitochondrial membrane potential (MMP), cytochrome c release and the activation of caspase-3 were also investigated in the HL-60 cells. Results of flow cytometry and DAPI staining assays indicated that curcumin induced

cytotoxicity and apoptosis in the examined cells. The results from flow cytometry assay indicated that curcumin induced ROS and Ca²⁺ productions, decreased the levels of MMP and increased the activity of caspase-3, leading to cell apoptosis. Western blot assay also revealed that curcumin increased the levels of Bax and the release of cytochrome c, and decreased the levels of Bcl-2 in the examined cells. The inhibition of caspase-3 activation by z-VAD-fmk (broad-spectrum caspase inhibitor) completely blocked curcumin-induced apoptosis in HL-60 cells. PMID: 17201156

Gynecol Oncol. 2007 Apr;105(1):104-12. Epub 2006 Dec 15.

Curcumin enhances Apo2L/TRAIL-induced apoptosis in chemoresistant ovarian cancer cells.

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OBJECTIVE.: Curcumin, the active component of turmeric (*Curcuma longa*), exhibits growth inhibitory activity against prostate, colon, and breast cancer; however, the effect of curcumin on ovarian cancer cells is not known. We hypothesized that curcumin could induce cell death in ovarian cancer cells, and enhance apoptosis induced by tumor necrosis factor-related apoptosis inducing Apo2 ligand/TRAIL. **METHODS.:** Chemoresistant ovarian cancer cell lines SKOV3 and ES-2 were used. The cytotoxic effect of curcumin, Apo2L/TRAIL, and curcumin+Apo2L/TRAIL in combination was determined by sulforhodamine assay. Apoptotic fraction was determined by staining cells with propidium iodide followed by analysis of the sub-G(0) DNA content of cells by flow cytometry. Caspase activation was determined by immunoblotting. **RESULTS.:** Curcumin alone had a cytotoxic effect in cisplatin-resistant cells at 25 µM. Curcumin at low doses (5-15 µM) or Apo2L/TRAIL alone was not significantly cytotoxic to the cell lines tested. Preincubating cells with curcumin at low doses prior to treating with Apo2L/TRAIL resulted in markedly enhanced cell death. The combined treatment of curcumin and Apo2L/TRAIL resulted in activation of both the extrinsic, receptor-mediated apoptotic pathway (cleavage of caspase-8) and the intrinsic, mitochondria-mediated apoptotic pathway (cleavage of caspase-9). **CONCLUSIONS.:** Combined curcumin and Apo2L/TRAIL treatment results in enhanced induction of apoptotic cell death. Because curcumin and Apo2L/TRAIL together can activate both the extrinsic and intrinsic pathways of apoptosis, they may circumvent chemoresistance to conventional chemotherapeutic agents. PMID: 17174384

J Ethnopharmacol. 2007 Mar 21;110(2):356-63. Epub 2006 Oct 17.

Behavioral, neurochemical and neuroendocrine effects of the ethanolic extract from *Curcuma longa* L. in the mouse forced swimming test.

Xia X, Cheng G, Pan Y, Xia ZH, Kong LD.

Curcuma longa L. (turmeric) has been used for centuries in traditional Chinese medicine as a treatment for mental disorders including depression. The studies described here were undertaken to determine the behavioral, neurochemical and neuroendocrine effects of the ethanolic extract from *Curcuma longa* using the forced swimming test (FST) in male ICR strain of mice. The ethanolic extract was found to reduce the duration of immobility in the mouse FST when orally administered for 21 days. The extract markedly attenuated swim stress-induced decreases in serotonin, 5-hydroxyindoleacetic acid, noradrenaline and dopamine concentrations, as well as increases in serotonin turnover. Furthermore, the ethanolic extract of *Curcuma longa* significantly reversed the swim stress-induced increases in serum corticotropin-releasing factor and cortisol levels. Under these conditions, the ethanolic extract of *Curcuma longa* was partly different from fluoxetine and amitriptyline. These results suggested that antidepressant properties of the ethanolic extract of *Curcuma longa* was mediated through

regulations of neurochemical and neuroendocrine systems and it may be a useful agent against depression.

PMID: 17134862

J Agric Food Chem. 2006 Nov 29;54(24):9055-62.

Effects of ingested turmeric oleoresin on glucose and lipid metabolisms in obese diabetic mice: a DNA microarray study.

Honda S, Aoki F, Tanaka H, Kishida H, Nishiyama T, Okada S et al.

Turmeric, the rhizome of *Curcuma longa* L., has a wide range of effects on human health. Turmeric oleoresin, an extract of turmeric, is often used for flavoring and coloring. Curcuminoids and turmeric essential oil are both contained in turmeric oleoresin, and both of these fractions have hypoglycemic effects. In the present study, we comprehensively assessed the effect of turmeric oleoresin on hepatic gene expression in obese diabetic KK-Ay mice using DNA microarray analysis and quantitative real-time polymerase chain reaction (PCR). Female KK-Ay mice aged 6 weeks (n = 6/group) were fed a high-fat diet containing turmeric oleoresin, curcuminoids, and essential oil for 5 weeks. The same diet without any of these fractions was used as a control diet. Ingestion of turmeric oleoresin and essential oil inhibited the development of increased blood glucose and abdominal fat mass, while curcuminoids only inhibited the increase in blood glucose. DNA microarray analysis indicated that turmeric oleoresin ingestion up-regulated the expression of genes related to glycolysis, beta-oxidation, and cholesterol metabolism in the liver of KK-Ay mice, while expression of gluconeogenesis-related genes was down-regulated. Real-time PCR analysis was conducted to assess the contribution of the curcuminoids and essential oil in turmeric oleoresin to the changes in expression of representative genes selected by DNA microarray analysis. This analysis suggested that curcuminoids regulated turmeric oleoresin ingestion-induced expression of glycolysis-related genes and also that curcuminoids and turmeric essential oil acted synergistically to regulate the peroxisomal beta-oxidation-related gene expression induced by turmeric oleoresin ingestion. These changes in gene expression were considered to be the mechanism by which the turmeric oleoresin affected the control of both blood glucose levels and abdominal adipose tissue masses. All of these results suggest that the use of whole turmeric oleoresin is more effective than the use of either curcuminoids or the essential oil alone. PMID: 17117790

Arthritis Rheum. 2006 Nov;54(11):3452-64.

Efficacy and mechanism of action of turmeric supplements in the treatment of experimental arthritis.

Funk JL, Frye JB, Oyarzo JN, Kuscuoglu N, Wilson J, McCaffrey G et al.

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OBJECTIVE: Scientific evidence is lacking for the antiarthritic efficacy of turmeric dietary supplements that are being promoted for arthritis treatment. Therefore, we undertook studies to determine the antiarthritic efficacy and mechanism of action of a well-characterized turmeric extract using an animal model of rheumatoid arthritis (RA). **METHODS:** The composition of commercial turmeric dietary supplements was determined by high-performance liquid chromatography. A curcuminoid-containing turmeric extract similar in composition to these supplements was isolated and administered intraperitoneally to female Lewis rats prior to or after the onset of streptococcal cell wall-induced arthritis. Efficacy in preventing joint swelling and destruction was determined clinically, histologically, and by measurement of bone mineral density. Mechanism of action was elucidated by analysis of turmeric's effect on articular transcription factor activation, microarray analysis of articular gene expression, and verification of the physiologic effects of alterations in gene expression. **RESULTS:** A turmeric fraction depleted of essential oils profoundly inhibited joint inflammation and periarticular joint destruction in a dose-dependent manner. In vivo treatment

prevented local activation of NF-kappaB and the subsequent expression of NF-kappaB-regulated genes mediating joint inflammation and destruction, including chemokines, cyclooxygenase 2, and RANKL. Consistent with these findings, inflammatory cell influx, joint levels of prostaglandin E(2), and periarticular osteoclast formation were inhibited by turmeric extract treatment. **CONCLUSION:** These translational studies demonstrate in vivo efficacy and identify a mechanism of action for a well-characterized turmeric extract that supports further clinical evaluation of turmeric dietary supplements in the treatment of RA. PMID: 17075840

Nutr Cancer. 2006;55(2):185-94.

Mechanisms of curcumin- and EGF-receptor related protein (ERRP)-dependent growth inhibition of colon cancer cells.

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Numerous dietary and pharmacological agents have been proposed as alternative strategies for treatment and prevention of colorectal cancer. Curcumin, an active ingredient of turmeric, that inhibits growth of malignant neoplasms, has a promising role in the prevention and treatment of colorectal cancer. EGF-R related protein (ERRP), a recently identified pan-erbB inhibitor, is a potential therapeutic agent for colorectal cancer. Here we examine whether curcumin together with ERRP will cause a greater inhibition of growth of colon cancer cells than either agent alone and the mechanisms of this inhibition. Human colon cancer HCT-116 or HT-29 cells were incubated with increasing doses of curcumin (up to 10 microM) or ERRP (up to 5 microg/ml), or a combination of both for 48 h. We observed that the cell growth inhibition and stimulation of apoptosis in response to the combinatorial treatment was significantly greater than that caused by either agent alone. These changes were associated with decreased activation (tyrosine phosphorylation) of EGFR, ErbB-2, ErbB-3, and/or IGF-1R. Whereas curcumin inhibited constitutive activation of both EGFR and IGF-1R, ERRP decreased activation of EGFR, ErbB-2, and ErbB-3 but had no effect on IGF-1R. Further, the combination therapy caused a greater attenuation of downstream effectors such as NF-kappaB, Akt and BAD activation, and down-regulation of procaspase-3 than that noted with either agent alone. The superior effects of the combinatorial treatment could partly be attributed to inhibition of constitutive activation of EGFRs and IGF-1R signaling pathways. PMID: 17044774

J Clin Rheumatol. 2004 Oct;10(5):236-245.

A 32-Week Randomized, Placebo-Controlled Clinical Evaluation of RA-11, an Ayurvedic Drug, on Osteoarthritis of the Knees.

Chopra A, Lavin P, Patwardhan B, Chitre D.

BACKGROUND:: The ancient Indian (Asian) Ayurvedic medicinal system uses herbomineral drugs to treat arthritis. Despite centuries of use, very few have been tested by drug trials. RA-11 (ARTREX, MENDAR), a standardized multiplant Ayurvedic drug (*Withania somnifera*, *Boswellia serrata*, *Zingiber officinale*, and *Curcuma longa*) is currently used to treat arthritis. **OBJECTIVE::** The objective of this study was to evaluate the efficacy and safety of RA-11 in patients with symptomatic osteoarthritis (OA) of the knees. **METHODS::** A total of 358 patients with chronic knee pain were screened free-of-cost in "arthritis camps" in an Indian metropolis. Ninety patients with primary OA of the knees (ACR classification; Arthritis Rheum 1986;29:1039-1049) were found eligible (postanalgesic washout pain visual analog score [VAS] \geq 40 mm in either or both knees on body weight-bearing activities) to enroll into a randomized, double-blind, placebo-controlled, parallel efficacy, single-center, 32-week drug trial (80% power to detect 25% difference, P = 0.05, 2-sided). Concurrent analgesics/nonsteroidal antiinflammatory drugs and steroids in any form were not

allowed. Lifestyle and/or dietary restrictions, as per routine Ayurveda practices, were not imposed. Pain VAS (maximum pain in each knee recorded by the patient during the preceding 48 hours) and modified WOMAC (Western Ontario McMaster University OA Index, Likert scale, version 3.0) were the primary efficacy variables. The WOMAC section on "physical function difficulty" was modified for Indian use and validated before the trial. Routine laboratory testing was primarily done to monitor drug safety. At baseline, the groups (active = 45, placebo = 45) were well matched for several measures (mean pain VAS: active = 6.17; placebo = 6.5). RESULTS:: 1) Efficacy: Compared with placebo, the mean reduction in pain VAS at week 16 (active = 2.7, placebo = 1.3) and week 32 (active = 2.8, placebo = 1.8) in the active group was significantly (P <0.05, analysis of variance [ANOVA]) better. Similarly, the improvement in the WOMAC scores at week 16 and week 32 were also significantly superior (P <0.01, ANOVA) in the active group. 2) Safety: Both the groups reported mild adverse events (AE) without any significant difference. 3) Withdrawals: Twenty-eight patients were discontinued. None reported drug-related toxicity. The majority failed follow up/compliance. No differences were observed between the groups. CONCLUSION:: This controlled drug trial demonstrates the potential efficacy and safety of RA- 11 in the symptomatic treatment of OA knees over 32 weeks of therapy. PMID: 17043520

Brain Res. 2006 Nov 29;1122(1):56-64. Epub 2006 Oct 3.

Curcumin reverses the effects of chronic stress on behavior, the HPA axis, BDNF expression and phosphorylation of CREB.

Xu Y, Ku B, Tie L, Yao H, Jiang W, Ma X, Li X.

Curcuma longa is a major constituent of the traditional Chinese medicine Xiaoyao-san, which has been used to effectively manage stress and depression-related disorders in China. Curcumin is the active component of curcuma longa, and its antidepressant effects were described in our prior studies in mouse models of behavioral despair. We hypothesized that curcumin may also alleviate stress-induced depressive-like behaviors and hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Thus in present study we assessed whether curcumin treatment (2.5, 5 and 10 mg/kg, p.o.) affects behavior in a chronic unpredictable stress model of depression in rats and examined what its molecular targets may be. We found that subjecting animals to the chronic stress protocol for 20days resulted in performance deficits in the shuttle-box task and several physiological effects, such as an abnormal adrenal gland weight to body weight (AG/B) ratio and increased thickness of the adrenal cortex as well as elevated serum corticosterone levels and reduced glucocorticoid receptor (GR) mRNA expression. These changes were reversed by chronic curcumin administration (5 or 10 mg/kg, p.o.). In addition, we also found that the chronic stress procedure induced a down-regulation of brain-derived neurotrophic factor (BDNF) protein levels and reduced the ratio of phosphorylated cAMP response element-binding protein (pCREB) to CREB levels (pCREB/CREB) in the hippocampus and frontal cortex of stressed rats. Furthermore, these stress-induced decreases in BDNF and pCREB/CREB were also blocked by chronic curcumin administration (5 or 10 mg/kg, p.o.). These results provide compelling evidence that the behavioral effects of curcumin in chronically stressed animals, and by extension humans, may be related to their modulating effects on the HPA axis and neurotrophin factor expressions. PMID: 17022948

Clin Exp Pharmacol Physiol. 2006 Oct;33(10):940-5.

Curcumin, the active principle of turmeric (Curcuma longa), ameliorates diabetic nephropathy in rats.

Sharma S, Kulkarni SK, Chopra K.

Chronic hyperglycaemia in diabetes leads to the overproduction of free radicals and evidence is increasing that these contribute to the development of diabetic

nephropathy. Among the spices, turmeric (*Curcuma longa*) is used as a flavouring and colouring agent in the Indian diet every day and is known to possess anti-oxidant properties. The present study was designed to examine the effect of curcumin, a yellow pigment of turmeric, on renal function and oxidative stress in streptozotocin (STZ)-induced diabetic rats. Diabetes was induced by a single intraperitoneal injection of STZ (65 mg/kg) in rats. Four weeks after STZ injection, rats were divided into four groups, namely control rats, diabetic rats and diabetic rats treated with curcumin (15 and 30 mg/kg, p.o.) for 2 weeks. Renal function was assessed by creatinine, blood urea nitrogen, creatinine and urea clearance and urine albumin excretion. Oxidative stress was measured by renal malonaldehyde, reduced glutathione and the anti-oxidant enzymes superoxide dismutase and catalase. Streptozotocin-injected rats showed significant increases in blood glucose, polyuria and a decrease in bodyweight compared with age-matched control rats. After 6 weeks, diabetic rats also exhibited renal dysfunction, as evidenced by reduced creatinine and urea clearance and proteinuria, along with a marked increase in oxidative stress, as determined by lipid peroxidation and activities of key anti-oxidant enzymes. Chronic treatment with curcumin significantly attenuated both renal dysfunction and oxidative stress in diabetic rats. These results provide confirmatory evidence of oxidative stress in diabetic nephropathy and point towards the possible anti-oxidative mechanism being responsible for the nephroprotective action of curcumin. PMID: 17002671

Am J Epidemiol. 2006 Nov 1;164(9):898-906. Epub 2006 Jul 26.

Curry consumption and cognitive function in the elderly.

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Curcumin, from the curry spice turmeric, has been shown to possess potent antioxidant and anti-inflammatory properties and to reduce beta-amyloid and plaque burden in experimental studies, but epidemiologic evidence is lacking. The authors investigated the association between usual curry consumption level and cognitive function in elderly Asians. In a population-based cohort (n = 1,010) of nondemented elderly Asian subjects aged 60-93 years in 2003, the authors compared Mini-Mental State Examination (MMSE) scores for three categories of regular curry consumption, taking into account known sociodemographic, health, and behavioral correlates of MMSE performance. Those who consumed curry "occasionally" and "often or very often" had significantly better MMSE scores than did subjects who "never or rarely" consumed curry. The authors reported tentative evidence of better cognitive performance from curry consumption in nondemented elderly Asians, which should be confirmed in future studies. PMID: 16870699

Int J Mol Med. 2006 Aug;18(2):227-31.

Curcumin inhibits telomerase activity in human cancer cell lines.

Cui SX, Qu XJ, Xie YY, Zhou L, Nakata M, Makuuchi M, Tang W.

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Curcumin, one of the major components of tumeric, the dried rhizome of *Curcuma longa* L, has been shown to have anti-proliferating and anti-carcinogenic properties. In this study, we examined the effects of curcumin on cell growth and telomerase activity in human cancer cell lines Bel7402, HL60 and SGC7901.

Curcumin (1-32 microM) showed anti-proliferating effects on these cell lines in a dose-dependent manner in vitro, and anti-tumor effects when curcumin (50-200 mg/kg) was orally administered to nude mice transplanted with the cancer cells. When the cells were treated with 1 microM of curcumin for 120 h, apoptotic cells were observed by means of the adridine orange/ethidium bromide staining

method, single cell microgel electrophoresis and flow cytometric analysis. On the other hand, suppression of telomerase activity in extracts of the cells treated with 1 microM of curcumin was observed by means of a telomeric repeat amplification protocol - silver staining assay. These results suggest that curcumin could suppress telomerase activity in the cancer cell lines and that the decrease of telomerase expression followed by induction of apoptosis might be involved in the anti-proliferating effect of curcumin.

PMID: 16820928

J Nat Prod. 2006 Mar;69(3):351-5.

Turmeric extracts containing curcuminoids prevent experimental rheumatoid arthritis.

Funk JL, Oyarzo JN, Frye JB, Chen G, Lantz RC, Jolad SD et al

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Turmeric has been used for centuries in Ayurvedic medicine as a treatment for inflammatory disorders including arthritis. On the basis of this traditional usage, dietary supplements containing turmeric rhizome and turmeric extracts are also being used in the western world for arthritis treatment and prevention. However, to our knowledge, no data are available regarding antiarthritic efficacy of complex turmeric extracts similar in composition to those available for use as dietary supplements. Therefore, the studies described here were undertaken to determine the in vivo efficacy of well-characterized curcuminoid-containing turmeric extracts in the prevention or treatment of arthritis using streptococcal cell wall (SCW)-induced arthritis, a well-described animal model of rheumatoid arthritis (RA). Arthritic index, a clinical measure of joint swelling, was used as the primary endpoint for assessing the effect of extracts on joint inflammation. An essential oil-depleted turmeric fraction containing 41% of the three major curcuminoids was efficacious in preventing joint inflammation when treatment was started before, but not after, the onset of joint inflammation. A commercial sample containing 94% of the three major curcuminoids was more potent in preventing arthritis than the essential oil-depleted turmeric fraction when compared by total curcuminoid dose per body weight. In conclusion, these data (1) document the in vivo antiarthritic efficacy of an essential oil-depleted turmeric fraction and (2) suggest that the three major curcuminoids are responsible for this antiarthritic effect, while the remaining compounds in the crude turmeric extract may inhibit this protective effect. PMID: 16562833

Ann N Y Acad Sci. 2005 Nov;1056:206-17.

Curcumin: getting back to the roots.

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The use of turmeric, derived from the root of the plant *Curcuma longa*, for treatment of different inflammatory diseases has been described in Ayurveda and in traditional Chinese medicine for thousands of years. The active component of turmeric responsible for this activity, curcumin, was identified almost two centuries ago. Modern science has revealed that curcumin mediates its effects by modulation of several important molecular targets, including transcription factors (e.g., NF-kappaB, AP-1, Egr-1, beta-catenin, and PPAR-gamma), enzymes (e.g., COX2, 5-LOX, iNOS, and hemeoxygenase-1), cell cycle proteins (e.g., cyclin D1 and p21), cytokines (e.g., TNF, IL-1, IL-6, and chemokines), receptors (e.g., EGFR and HER2), and cell surface adhesion molecules. Because it can modulate the expression of these targets, curcumin is now being used to treat cancer, arthritis, diabetes, Crohn's disease, cardiovascular diseases, osteoporosis, Alzheimer's disease, psoriasis, and other pathologies. Interestingly, 6-gingerol, a natural analog of curcumin derived from the root of ginger (*Zingiber officinalis*),

exhibits a biologic activity profile similar to that of curcumin. The efficacy, pharmacologic safety, and cost effectiveness of curcuminoids prompt us to "get back to our roots." PMID: 16387689

Anticancer Agents Med Chem. 2006 May;6(3):259-70.

Biological effects of curcumin and its role in cancer chemoprevention and therapy.

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Centre for Cellular and Molecular Biology, Uppal Road, Hyderabad 500007, India. Curcumin, a natural component of the rhizome of *curcuma longa* has emerged as one of the most powerful chemopreventive and anticancer agents. Its biological effects range from antioxidant, anti-inflammatory to inhibition of angiogenesis and is also shown to possess specific antitumoral activity. The molecular mechanism of its varied cellular effects has been studied in some details and it has been shown to have multiple targets and interacting macromolecules within the cell. Curcumin has been shown to possess anti-angiogenic properties and the angioinhibitory effects of curcumin manifest due to down regulation of proangiogenic genes such as VEGF and angiopoitin and a decrease in migration and invasion of endothelial cells. One of the important factors implicated in chemoresistance and induced chemosensitivity is NFkB and curcumin has been shown to down regulate NFkB and inhibit IKK kinase thereby suppressing proliferation and inducing apoptosis. Cell lines that are resistant to certain apoptotic inducers and radiation become susceptible to apoptosis when treated in conjunction with curcumin. Besides this it can also act as a chemopreventive agent in cancers of colon, stomach and skin by suppressing colonic aberrant crypt foci formation and DNA adduct formation. This review focuses on the various aspects of curcumin as a potential drug for cancer treatment and its implications in a variety of biological and cellular processes vis-a-vis its mechanism of action. PMID: 16712454

Mol Cell Biochem. 2006 Aug;288(1-2):115-23.

Curcumin combats against cigarette smoke and ethanol-induced lipid alterations in rat lung and liver.

Vanisree AJ, Sudha N.

BACKGROUND: Human population, in spite of the medical and scientific achievements, still fall as a prey to the evils of habitual smoking and alcohol, thus necessitating safer counteracting measures. Objective: To evaluate the effect of cotreatment of curcumin (*Curcuma longa*) in rats subjected to acute exposure to cigarette smoke (CS) and ethanol (EtOH). METHODOLOGY: Of the four groups of experimental rats, a set of rats was subjected to whole body exposure to cigarette smoke along with ethanol administration serving as a model of CS+EtOH injury. Curcumin treatment was given to two sets of rats: (i) one set receiving simultaneous CS+EtOH and (ii) one set of normal rats without any administration. The other group of rats served as control. Blood, liver and lung of rats were selected for assessment of CS+EtOH injury as well as curcumin treatment. RESULT: Altered lipid, lipoprotein profile and bile acid excretion were observed in CS+EtOH rats along with premalignant pathological state in tissues. In treated rats, the levels were maintained at near-normal levels along with near-normal histology. CONCLUSION: This biochemical picture on cotreatment with curcumin suggests that curcumin could counteract the injurious effects of combined CS and EtOH and thus might help to reduce the risk of hyperlipidemic disorders which develop due to smoking and drinking. PMID: 16691314

Biol Pharm Bull. 2006 May;29(5):938-44.

Ethanolic extracts from *Curcuma longa* attenuates behavioral, immune, and neuroendocrine alterations in a rat chronic mild stress model.

Xia X, Pan Y, Zhang WY, Cheng G, Kong LD.

The ethanolic extracts from the rhizome of *Curcuma longa* L. (turmeric), possesses a wide variety of biological activities related to the treatment and prevention of affective disorders. To study their antidepressant effects, the impacts of chronic mild stress (CMS) and of the subsequent administration of ethanolic extracts of *C. longa* were investigated. Male Sprague-Dawley rats subjected to the CMS procedure demonstrated increased serum interleukin-6 and tumor necrosis factor- α levels, as well as a reduction of natural killer cell activity in splenocytes. In addition, CMS-treated rats exhibited elevated corticotropin-releasing factor in serum and medulla oblongata and cortisol levels in serum, with no significant change in serum adrenocorticotropin hormone levels. The preferential behavior of reduction in sucrose intake was also observed. These findings indicate that the alterations in immune and hypothalamic-pituitary-adrenal (HPA) axis systems could participate in the behavioral response to the CMS procedure in animals. Administration of ethanolic extracts of *C. longa* largely reversed the above effects. These results demonstrate the antidepressant-like activity of ethanolic extracts of *C. longa* in the rat CMS model of depression, at least in part by improving the abnormalities in immune and the HPA axis functions. PMID: 16651723

Przegl Lek. 2005;62(10):1180-1.

[Preventive role of curcumin in lung cancer] [Article in Polish]

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Carcinogens from cigarette smoke form the link between nicotine addiction and lung cancer, which is the leading cause of cancer-related mortality in the world. One of the most frequently studied chemopreventive agents is a curcumin, a natural compound extracted from turmeric that inhibits cell proliferation and induces apoptosis in human leukaemia, prostate cancer, and non-small cell lung cancer. Curcumin (diferuoylmethane) is a major yellow pigment in turmeric (*Curcuma longa*) and is widely used as a spice. Curcumin exhibits a variety of pharmacological effects, and has been reported to have anti-inflammatory and anti-tumor activities.

PMID: 16521985

Life Sci. 2006 Mar 27;78(18):2081-7. Epub 2006 Jan 18.

Multiple biological activities of curcumin: a short review.

Maheshwari RK, Singh AK, Gaddipati J, Srimal RC.

Turmeric (*Curcuma longa* rhizomes), commonly used as a spice is well documented for its medicinal properties in Indian and Chinese systems of medicine. It has been widely used for the treatment of several diseases. Epidemiological observations, though inconclusive, are suggestive that turmeric consumption may reduce the risk of some form of cancers and render other protective biological effects in humans. These biological effects of turmeric have been attributed to its constituent curcumin that has been widely studied for its anti-inflammatory, anti-angiogenic, anti-oxidant, wound healing and anti-cancer effects. As a result of extensive epidemiological, clinical, and animal studies several molecular mechanisms are emerging that elucidate multiple biological effects of curcumin. This review summarizes the most interesting in vitro and in vivo studies on the biological effects of curcumin.

PMID: 16413584

Cell Biol Int. 2006 Mar;30(3):221-6. Epub 2005 Dec 22.

Antiproliferation and apoptosis induced by curcumin in human ovarian cancer cells.

Shi M, Cai Q, Yao L, Mao Y, Ming Y, Ouyang G.

Curcumin, an active ingredient from the rhizome of the plant, *Curcuma longa*, has antioxidant, anti-inflammatory and anti-cancer activities. It has recently been demonstrated that the chemopreventive activities of curcumin might be due to its ability to inhibit cell growth and induce apoptosis. In the present study, we have investigated the effects of curcumin on growth and apoptosis in the human ovarian cancer cell line Ho-8910 by MTT assay, fluorescence microscopy, flow cytometry and Western blotting. Our data revealed that curcumin could significantly inhibit the growth and induce apoptosis in Ho-8910 cells. A decrease in expression of Bcl-2, Bcl-X(L) and pro-caspase-3 was observed after exposure to 40 microM curcumin, while the levels of p53 and Bax were increased in the curcumin-treated cells. These activities may contribute to the anticarcinogenic action of curcumin.

PMID: 16376585

Biol Pharm Bull. 2005 Dec;28(12):2220-4.

Curcuma longa extract protects against gastric ulcers by blocking H2 histamine receptors.

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Curcuma longa has been commonly used as a traditional remedy for a variety of symptoms such as inflammation, gastritis and gastric ulcer. When *C. longa* extract was administered per os to pylori-ligated rat stomachs, it reduced gastric acid secretion and protected against the formation of gastric mucosal lesions. We therefore tested whether *C. longa* extract inhibits gastric ulcers by blocking the H(2) histamine receptor. Dimaprit, a H(2) histamine receptor agonist, induced intracellular cAMP production in U937 and HL-60 promyelocytes. Pretreatment with *C. longa* extract significantly blocked dimaprit-induced cAMP production in a concentration dependent manner, but had no effect on the elevation of cAMP levels triggered by isoproterenol-induced beta(2)-adrenoceptor activation in U937 cells. To identify the active component(s) of *C. longa* extract, we sequentially fractionated it by extraction with ethyl acetate, n-butanol and water. We found that the ethyl acetate extract showed the most potent H(2)R antagonistic effect against dimaprit-induced cAMP production. However, curcumin, a major component of *C. longa* extract, showed no H(2)R blocking effect. *C. longa* ethanol extract and ethylacetate extract also blocked the binding of [(3)H]-tiotidine to membrane receptors on HL-60 cells. These findings suggest that the extract from *C. longa* specifically inhibits gastric acid secretion by blocking H(2) histamine receptors in a competitive manner.

PMID: 16327153

Phytomedicine. 2005 Jun;12(6-7):445-52.

The effect of turmeric extracts on inflammatory mediator production.

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Department of Cell Biology and Anatomy, University of Arizona, Tucson, AZ, USA. Major compounds of several commonly used botanicals, including turmeric, have been purported to have anti-inflammatory actions. In order to test the anti-inflammatory activity of compounds isolated from rhizomes of *Curcuma longa* L. (Zingiberaceae), we have established an in vitro test system. HL-60 cells were differentiated and exposed to lipopolysaccharide (LPS) from *Escherichia coli* (1 microg/ml) in the presence or absence of botanical compounds for 24 h. Supernatants were collected and analyzed for the production of tumor necrosis factor alpha (TNF-alpha) and prostaglandin E2 (PGE2) using standard ELISA

assays. Water-soluble extracts were not cytotoxic and did not exhibit biological activity. Organic extracts of turmeric were cytotoxic only at concentrations above 50 microg/ml. Crude organic extracts of turmeric were capable of inhibiting LPS-induced TNF-alpha (IC50 value = 15.2 microg/ml) and PGE2 (IC50 value = 0.92 microg/ml) production. Purified curcumin was more active than either demethoxy- or bisdemethoxycurcumin. Fractions and subfractions of turmeric extracts collected via preparative HPLC had differing biological activity, ranging from no activity to IC50 values of < 1 microg/ml. For some fractions, subfractionation resulted in a loss of activity, indicating interaction of the compounds within the fraction to produce an anti-inflammatory effect. A combination of several of the fractions that contain the turmeric oils was more effective than the curcuminoids at inhibiting PGE2. While curcumin inhibited COX-2 expression, turmeric oils had no effect on levels of COX-2 mRNA.
PMID: 16008121

Eur J Pharmacol. 2005 Jul 25;518(1):40-6.

The effects of curcumin on depressive-like behaviors in mice.

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Curcuma longa is a major constituent of Xiaoyao-san, the traditional Chinese medicinal formula, which has been used effectively to treat depression-related diseases in China. There is no information available about the antidepressant activity of curcumin, the active component of *curcuma longa*. In the present study, we analyzed the effects of curcumin on depressive-like behaviors in mice, using two animal models of depression. Our results showed that curcumin treatment at 5 and 10 mg/kg (p.o.) significantly reduced the duration of immobility in both the tail suspension and forced swimming tests. These doses that affected the immobile response did not affect locomotor activity. In addition, the neurochemical assays showed that curcumin produced a marked increase of serotonin and noradrenaline levels at 10 mg/kg in both the frontal cortex and hippocampus. Dopamine levels were also increased in the frontal cortex and the striatum. Moreover, curcumin was found to inhibit monoamine oxidase activity in the mouse brain. These findings suggest that the antidepressant-like effects of curcumin may involve the central monoaminergic neurotransmitter systems.
PMID: 15987635

Curr Alzheimer Res. 2005 Apr;2(2):131-6.

A potential role of the curry spice curcumin in Alzheimer's disease.

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There is substantial in-vitro data indicating that curcumin has antioxidant, anti-inflammatory, and anti-amyloid activity. In addition, studies in animal models of Alzheimer's disease (AD) indicate a direct effect of curcumin in decreasing the amyloid pathology of AD. As the widespread use of curcumin as a food additive and relatively small short-term studies in humans suggest safety, curcumin is a promising agent in the treatment and/or prevention of AD. Nonetheless, important information regarding curcumin bioavailability, safety and tolerability, particularly in an elderly population is lacking. We are therefore performing a study of curcumin in patients with AD to gather this information in addition to data on the effect of curcumin on biomarkers of AD pathology.
PMID: 15974909