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<http://www.sciencemag.org/cgi/content/abstract/1179052v1?&searchid=1&usestrictdates=yes&resourcetype=HWCI&T&ct>

Science Express > Lombardi et al.  
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#### REPORTS

Submitted on July 14, 2009  
 Accepted on August 31, 2009

#### **Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome**

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These authors contributed equally to this work.

#### ESSENCE OF ARTICLE

“These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS. “

#### ARTICLE

Chronic fatigue syndrome (CFS) is a debilitating disease of unknown etiology that is estimated to affect 17 million people worldwide. Studying peripheral blood mononuclear cells (PBMCs) from CFS patients, we identified DNA from a human gammaretrovirus, xenotropic murine leukemia virus-related virus (XMRV), in 68 of 101 patients (67%) compared to 8 of 218 (3.7%) healthy controls. Cell culture experiments revealed that patient-derived XMRV is infectious and that both cell-associated and cell-free transmission of the virus are possible. Secondary viral infections were established in uninfected primary lymphocytes and indicator cell lines following exposure to activated PBMCs, B cells, T cells, or plasma derived from CFS patients. These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS.

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#### PERSPECTIVES

#### VIROLOGY

A New Virus for Old Diseases?

John M. Coffin and Jonathan P. Stoye (23 October 2009)

Science 326 (5952), 530. [DOI: 10.1126/science.1181349]

#### THIS ARTICLE HAS BEEN CITED BY OTHER ARTICLES:

A New Virus for Old Diseases?.

J. M. Coffin and J. P. Stoye (2009)

Science 326, 530-531

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<http://www.nature.com/bjc/journal/v101/n9/abs/6605308a.html>

Molecular Diagnostics

British Journal of Cancer (2009) 101, 1585–1595. doi:10.1038/sj.bjc.6605308

[www.bjcancer.com](http://www.bjcancer.com)

Published online 6 October 2009

#### **Curcumin induces apoptosis-independent death in oesophageal cancer cells**

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Received 1 June 2009; Revised 10 August 2009; Accepted 17 August 2009; Published online 6 October 2009.

#### ESSENCE OF ARTICLE

“Curcumin can induce cell death by a mechanism that is not reliant on apoptosis induction, and thus represents a promising anticancer agent for prevention and treatment of oesophageal cancer.”

## ARTICLE

### Abstract

#### BACKGROUND:

Oesophageal cancer incidence is increasing and survival rates remain extremely poor. Natural agents with potential for chemoprevention include the phytochemical curcumin (diferuloylmethane). We have examined the effects of curcumin on a panel of oesophageal cancer cell lines.

#### METHODS:

MTT (3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide) assays and propidium iodide staining were used to assess viability and DNA content, respectively. Mitotic catastrophe (MC), apoptosis and autophagy were defined by both morphological criteria and markers such as MPM-2, caspase 3 cleavage and monodansylcadaverine (MDC) staining. Cyclin B and poly-ubiquitinated proteins were assessed by western blotting.

#### RESULTS:

Curcumin treatment reduces viability of all cell lines within 24 h of treatment in a 5–50  $\mu$ M range. Cytotoxicity is associated with accumulation in G2/M cell-cycle phases and distinct chromatin morphology, consistent with MC. Caspase-3 activation was detected in two out of four cell lines, but was a minor event. The addition of a caspase inhibitor zVAD had a marginal or no effect on cell viability, indicating predominance of a non-apoptotic form of cell death. In two cell lines, features of both MC and autophagy were apparent. Curcumin-responsive cells were found to accumulate poly-ubiquitinated proteins and cyclin B, consistent with a disturbance of the ubiquitin–proteasome system. This effect on a key cell-cycle checkpoint regulator may be responsible for the mitotic disturbances and consequent cytotoxicity of this drug.

#### CONCLUSION:

Curcumin can induce cell death by a mechanism that is not reliant on apoptosis induction, and thus represents a promising anticancer agent for prevention and treatment of oesophageal cancer.

#### Keywords:

curcumin, apoptosis, mitotic catastrophe, autophagy, oesophageal cancer

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[19676105]ADDITIONAL ARTICLES ON CURCUMIN AND CANCER..  
Mol Carcinog. 2009 Aug 12. [Epub ahead of print]

#### **Curcumin-induced apoptosis in ovarian carcinoma cells is p53-independent and involves p38 mitogen-activated protein kinase activation and downregulation of Bcl-2 and survivin expression and Akt signaling.**

Watson JL, Greenshields A, Hill R, Hilchie A, Lee PW, Giacomantonio CA, Hoskin DW.  
Faculty of Medicine, Department of Surgery, Dalhousie University, Halifax, Nova Scotia, Canada.

New cytotoxic agents are urgently needed for the treatment of advanced ovarian cancer because of the poor long-term response of this disease to conventional chemotherapy. Curcumin, obtained from the rhizome of *Curcuma longa*, has potent anticancer activity; however, the mechanism of curcumin-induced cytotoxicity in ovarian cancer cells remains a mystery. In this study we show that curcumin exhibited time- and dose-dependent cytotoxicity against monolayer cultures of ovarian carcinoma cell lines with differing p53 status (wild-type p53: HEY, OVCA429; mutant p53: OCC1; null p53: SKOV3). In addition, p53 knockdown or p53 inhibition did not diminish curcumin killing of HEY cells, confirming p53-independent cytotoxicity. Curcumin also killed OVCA429, and SKOV3 cells grown as multicellular spheroids. Nuclear condensation and fragmentation, as well as DNA fragmentation and poly (ADP-ribose) polymerase-1 cleavage in curcumin-treated HEY cells, indicated cell death by apoptosis. Procaspase-3, procaspase-8, and procaspase-9 cleavage, in addition to cytochrome c release and Bid cleavage into truncated Bid, revealed that curcumin activated both the extrinsic and intrinsic pathways of apoptosis. Bax expression was unchanged but Bcl-2, survivin, phosphorylated Akt (on serine 473), and total Akt were downregulated in curcumin-treated HEY cells. Curcumin also activated p38 mitogen-activated protein kinase

(MAPK) without altering extracellular signal-regulated kinase 1/2 activity. We conclude that p53-independent curcumin-induced apoptosis in ovarian carcinoma cells involves p38 MAPK activation, ablation of prosurvival Akt signaling, and reduced expression of the antiapoptotic proteins Bcl-2 and survivin. These data provide a mechanistic rationale for the potential use of curcumin in the treatment of ovarian cancer. (c) 2009 Wiley-Liss, Inc.

PMID: 19676105 [PubMed - as supplied by publisher]

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Cancer Lett. 2008 Aug 18;267(1):133-64. Epub 2008 May 6.

### **Curcumin and cancer: an "old-age" disease with an "age-old" solution.**

Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB.  
Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA.

Cancer is primarily a disease of old age, and that life style plays a major role in the development of most cancers is now well recognized. While plant-based formulations have been used to treat cancer for centuries, current treatments usually involve poisonous mustard gas, chemotherapy, radiation, and targeted therapies. While traditional plant-derived medicines are safe, what are the active principles in them and how do they mediate their effects against cancer is perhaps best illustrated by curcumin, a derivative of turmeric used for centuries to treat a wide variety of inflammatory conditions. Curcumin is a diferuloylmethane derived from the Indian spice, turmeric (popularly called "curry powder") that has been shown to interfere with multiple cell signaling pathways, including cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and down-regulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1), survival (PI3K/AKT pathway), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR-4) and inflammation (NF-kappaB, TNF, IL-6, IL-1, COX-2, and 5-LOX). The activity of curcumin reported against leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma reflects its ability to affect multiple targets. Thus an "old-age" disease such as cancer requires an "age-old" treatment.

PMID: 18462866 [PubMed - indexed for MEDLINE]

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Clin Cancer Res. 2007 Jun 1;13(11):3423-30.

### **Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor-kappaB pathway.**

Lin YG, Kunnumakkara AB, Nair A, Merritt WM, Han LY, Armaiz-Pena GN, Kamat AA, Spannuth WA, Gershenson DM, Lutgendorf SK, Aggarwal BB, Sood AK.  
Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA.

**PURPOSE:** Curcumin, a component of turmeric, has been shown to suppress inflammation and angiogenesis largely by inhibiting the transcription factor nuclear factor-kappaB (NF-kappaB). This study evaluates the effects of curcumin on ovarian cancer growth using an orthotopic murine model of ovarian cancer.

**EXPERIMENTAL DESIGN:** In vitro and in vivo experiments of curcumin with and without docetaxel were done using human ovarian cancer cell lines SKOV3ip1, HeyA8, and HeyA8-MDR in athymic mice. NF-kappaB modulation was ascertained using electrophoretic mobility shift assay. Evaluation of angiogenic cytokines, cellular proliferation (proliferating cell nuclear antigen), angiogenesis (CD31), and apoptosis (terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling) was done using immunohistochemical analyses.

**RESULTS:** Curcumin inhibited inducible NF-kappaB activation and suppressed proliferation in vitro. In vivo dose-finding experiments revealed that 500 mg/kg orally was the optimal dose needed to suppress NF-kappaB and signal

transducers and activators of transcription 3 activation and decrease angiogenic cytokine expression. In the SKOV3ip1 and HeyA8 *in vivo* models, curcumin alone resulted in 49% ( $P = 0.08$ ) and 55% ( $P = 0.01$ ) reductions in mean tumor growth compared with controls, whereas when combined with docetaxel elicited 96% ( $P < 0.001$ ) and 77% reductions in mean tumor growth compared with controls. In mice with multidrug-resistant HeyA8-MDR tumors, treatment with curcumin alone and combined with docetaxel resulted in significant 47% and 58% reductions in tumor growth, respectively ( $P = 0.05$ ). In SKOV3ip1 and HeyA8 tumors, curcumin alone and with docetaxel decreased both proliferation ( $P < 0.001$ ) and microvessel density ( $P < 0.001$ ) and increased tumor cell apoptosis ( $P < 0.05$ ).

**CONCLUSIONS:** Based on significant efficacy in preclinical models, curcumin-based therapies may be attractive in patients with ovarian carcinoma.

PMID: 17545551 [PubMed - indexed for MEDLINE]

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Cancer Lett. 2007 Oct 8;255(2):170-81. Epub 2007 Apr 19.

### **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 [PubMed - indexed for MEDLINE]

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Cancer Biol Ther. 2007 Feb;6(2):178-84. Epub 2007 Feb 5.

### **Curcumin induces G2/M arrest and apoptosis in cisplatin-resistant human ovarian cancer cells by modulating Akt and p38 MAPK.**

Weir NM, Selvendiran K, Kutala VK, Tong L, Vishwanath S, Rajaram M, Tridandapani S, Anant S, Kuppusamy P. Davis Heart and Lung Research Institute and Comprehensive Cancer Center, Department of Internal Medicine, Ohio State University, Columbus, OH 43210, USA.

Curcumin, a major active component of turmeric, is known to induce apoptosis in several types of cancer cells, but little is known about its activity in chemoresistant cells. Hence, the aim of the present study was to investigate the anticancer properties of curcumin in cisplatin-resistant human ovarian cancer cells *in vitro*. The results indicated that curcumin inhibited the proliferation of both cisplatin-resistant (CR) and sensitive (CS) human ovarian cancer cells almost equally. Enhanced superoxide generation was observed in both CR and CS cells treated with curcumin. Curcumin induced G(2)/M phase cell-cycle arrest in CR cells by enhancing the p53 phosphorylation and apoptosis through the activation of caspase-3 followed by PARP degradation. Curcumin also inhibited the phosphorylation of Akt while the phosphorylation of p38 MAPK was enhanced. In summary, our results showed that curcumin inhibits

the proliferation of cisplatin-resistant ovarian cancer cells through the induction of superoxide generation, G(2)/M arrest, and apoptosis.

PMID: 17218783 [PubMed - indexed for MEDLINE]

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

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

Wahl H, Tan L, Griffith K, Choi M, Liu JR.

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Michigan, 4219 CCGC, 1500 East Medical Center Drive, Ann Arbor, MI 48128, USA.

**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-G0 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 microM. Curcumin at low doses (5-15 microM) 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 [PubMed - indexed for MEDLINE]

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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.

Key Laboratory of China Education Ministry for Cell Biology and Tumor Cell Engineering, School of Life Sciences, Xiamen University, Xiamen 361005, China.

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 [PubMed - indexed for MEDLINE]

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Life Sci. 2006 Apr 11;78(20):2391-8. Epub 2005 Nov 16.

### **Curcumin modulates drug metabolizing enzymes in the female Swiss Webster mouse.**

Valentine SP, Le Nedelec MJ, Menzies AR, Scandlyn MJ, Goodin MG, Rosengren RJ.

Department of Pharmacology and Toxicology, 18 Frederick Street, Adams Building, University of Otago, Dunedin, New Zealand.

Curcumin, the yellow pigment found in turmeric, exhibits potent chemopreventative properties in both in vivo and in vitro cancer models. We hypothesized that this effect may occur via curcumin-mediated changes in enzymes involved in both carcinogen bioactivation and estrogen metabolism. Female Swiss Webster mice were treated with either curcumin (200 mg/kg or 400 mg/kg, p.o.) or vehicle control for 1 or 2 weeks. The results demonstrated that curcumin had no effect on the catalytic activities of ovarian aromatase, hepatic catechol-O-methyltransferase or hepatic UDP-glucuronosyltransferase. However, both doses of curcumin caused a 25% decrease in CYP1A catalytic activity, but not polypeptide levels, following 2 weeks of treatment. Additionally, following 2 weeks of curcumin at 400 mg/kg, there was a 20% decrease in the catalytic activity and a 28% decrease in polypeptide levels of CYP3A. While 2 weeks of curcumin treatment (400 mg/kg) caused a 20% increase in glutathione S-transferase activity, there was no parallel increase in hepatic stores of the co-factor glutathione. In conclusion small changes in CYP1A, CYP3A and GST following long term treatment (2 weeks) suggest that the combination of all three metabolic pathways may play a small role in curcumin's chemopreventative action.

PMID: 16297412 [PubMed - indexed for MEDLINE]

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J Huazhong Univ Sci Technolog Med Sci. 2004;24(1):55-8.

### **Growth-inhibitory effects of curcumin on ovary cancer cells and its mechanisms.**

Zheng L, Tong Q, Wu C.

Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022.

To study the growth-inhibitory effects of curcumin on human ovary cancer A2780 cells in vitro and its molecular mechanisms, the growth inhibition rates of A2780 cancer cells, after being treated with 10 micromol/L-50 micromol/L curcumin for 6-24 h, were examined by MTT method. The morphological changes of cancer cells were observed under inversion microscopy. Cellular apoptotic rates were determined by using TUNEL. The protein expression levels of bcl-2, p53 and MDM2 in cancer cells were examined by SP immunohistochemistry. After being treated by various concentrations of curcumin, the growth of cancer cells was inhibited significantly. Some cancer cells presented characteristic morphological changes of apoptosis. The rates of apoptosis were 6.41%-28.48% ( $P < 0.01$ ). The expression of bcl-2 and p53 was decreased, which depended on the action time ( $P < 0.01$ ). There were no obvious changes in MDM2 expression. It was concluded that curcumin could significantly inhibit the growth of ovary cancer cells. The induction of apoptosis by down-regulating the expression of bcl-2 and p53 was probably one of its molecular mechanisms.

PMID: 15165116 [PubMed - indexed for MEDLINE]

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Ai Zheng. 2002 Dec;21(12):1296-300. [Article in Chinese]

### **Inhibitory effects of curcumin on apoptosis of human ovary cancer cell line A2780 and its molecular mechanism**

Zheng LD, Tong QS, Wu CH.

Department of Pathology, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, P. R. China. ld\_zheng@hotmail.com

**BACKGROUND & OBJECTIVE:** Curcumin is the major effective component of curcuma, which is a kind of traditional Chinese medicine. It has been paid more attention to curcumin recently for its specific proliferation inhibition and apoptosis inducing effects on tumor cells; however, the involved mechanisms were not clear. This

study was designed to explore the apoptosis inducing effects of curcumin on human ovary A2780 cell line and its related molecular mechanisms.

**METHODS:** A2780 cancer cells were treated with 10-50  $\mu\text{mol/L}$  curcumin for 6-24 h and the growth inhibition rates of A2780 cancer cells were measured by MTT method. Cell apoptosis was inspected by flow cytometry (FCM) and acridine orange-ethidium bromide fluorescent staining method. The protein levels of NF-kappa B (P65) and Caspase-3 in cancer cells were observed by SP immunohistochemistry.

**RESULTS:** The growth inhibition rates of the cancer cells reached 62.05%-89.24%, with the peak of sub G1 appeared on DNA histogram in FCM. Partial cells presented the characteristic morphological changes of apoptosis under the fluorescent microscope; the apoptosis rates were 21.5%-33.5%. The NF-kappa B (p65) expression was decreased while Caspase-3 expression was increased, which depended on the action time.

**CONCLUSIONS:** Curcumin could significantly inhibit the growth of ovary cancer cells; inducing apoptosis through up-regulating Caspase-3 and down-regulating expression of NF-kappa B was probably one of its molecular mechanisms.

PMID: 12520734 [PubMed - indexed for MEDLINE]

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Cell Stress Chaperones. 2001 Oct;6(4):368-76.

**Induction of stress response renders human tumor cell lines resistant to curcumin-mediated apoptosis: role of reactive oxygen intermediates.**

Khar A, Ali AM, Pardhasaradhi BV, Varalakshmi CH, Anjum R, Kumari AL.  
Centre for Cellular and Molecular Biology, Hyderabad, India. khar@ccmb.ap.nic.in

Curcumin, a well-known dietary pigment derived from *Curcuma longa*, has been shown to be a potent antiinflammatory, antioxidant, and anticarcinogenic compound. The present study was designed to investigate the cytotoxic potential of curcumin against a range of human tumor cell lines in an attempt to understand its mechanism of action, which may lead to its possible therapeutic applications. We have shown that different cancer cell lines differ in their sensitivity to curcumin. Cell lines established from malignancies like leukemia, breast, colon, hepatocellular, and ovarian carcinomas underwent apoptosis in the presence of curcumin, whereas cell lines from lung, kidney, prostate, cervix, CNS malignancies, and melanomas showed resistance to the cytotoxic effects of curcumin. Sensitivity of the cancer cell lines to curcumin correlated with the generation of superoxide radicals as determined by the reduction of ferricytochrome C. Curcumin-resistant tumor cell lines showed significantly higher production of Hsp70, thus mounting a stress response and protecting the cells from the apoptotic cell death. These observations yield clues toward understanding the regulation of the cell death machinery by the stress proteins. Interestingly, curcumin had no effect on nontransformed cell lines, which showed neither superoxide generation nor the induction of a stress response. These observations demonstrate that curcumin is an interesting molecule with varied actions, depending on the cell type.

PMID: 11795474 [PubMed - indexed for MEDLINE]

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J Nat Prod. 1998 Dec;61(12):1531-4.

**Cytotoxicity of curcuminoids and some novel compounds from *Curcuma zedoaria*.**

Syu WJ, Shen CC, Don MJ, Ou JC, Lee GH, Sun CM.  
Institute of Microbiology and Immunology, National Yang-Ming University, Taipei.

Bioassay-directed fractionation of an EtOH extract of *Curcuma zedoaria* led to isolation of an active curcuminoid, which was identified as demethoxycurcumin (2) by comparison of its <sup>1</sup>H and <sup>13</sup>C NMR spectra with literature data and by direct comparison with synthetic material. Curcumin (1) and bisdemethoxycurcumin (3) were also obtained. Curcuminoids (1-3) were synthesized and demonstrated to be cytotoxic against human ovarian cancer OVCAR-3 cells. The observed CD50 values of 1, 2, and 3 were 4.4, 3.8, and 3.1  $\mu\text{g/mL}$ , respectively. Three additional

novel compounds, 3, 7-dimethylindan-5-carboxylic acid (4), curcolanol (5), and guaidiol (6), were also isolated from the EtOH extract. The structures and relative stereochemistry of 4-6 were determined by spectroscopic methods and X-ray crystallographic analysis.

PMID: 9868158 [PubMed - indexed for MEDLINE]

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Med Oncol. 2009 Oct 27. [Epub ahead of print]

### **Cell cycle inhibition and apoptosis induced by curcumin in Ewing sarcoma cell line SK-NEP-1.**

Singh M, Pandey A, Karikari CA, Singh G, Rakheja D.  
All India Institute of Medical Sciences, New Delhi, India, mansher4u@yahoo.com.

Curcumin is a naturally occurring polyphenolic compound found in the turmeric, which is used as food additive in Indian cooking and as a therapeutic agent in traditional Indian medicine. Curcumin is currently under investigation as a chemotherapeutic and chemopreventive agent in adult cancer models at both pre-clinical and clinical levels. In this preliminary study, we show that curcumin is effective in causing cell cycle arrest, inducing apoptosis, and suppressing colony formation in the Ewing sarcoma cell line SK-NEP-1. Curcumin causes upregulation of cleaved caspase 3 and downregulation of phospho-Akt, producing apoptosis in Ewing sarcoma cells at an inhibitory concentration 50% (IC<sub>50</sub>) of approximately 4 μM. Our findings indicate a need for further evaluation of curcumin in chemotherapy and chemoprevention of Ewing sarcoma.

PMID: 19859844 [PubMed - as supplied by publisher]

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Appl Biochem Biotechnol. 2009 Oct 18. [Epub ahead of print]

### **Antifungal and Antiproliferative Activities of Lectin from the Rhizomes of *Curcuma amarissima* Roscoe.**

Kheeree N, Sangvanich P, Puthong S, Karnchanat A.  
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A lectin was purified from the rhizomes of *Curcuma amarissima* Roscoe by aqueous extraction, fractionation with 80% saturated ammonium sulfate, and a combination of affinity and gel chromatography on ConA Sepharose and Superdex G-75, respectively. The molecular mass of the purified lectin was 32.4 kDa, as estimated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The lectin showed no significant specificity in its ability to hemagglutinate erythrocytes from human blood groups (A, B, AB, and O), but for other animals, it only agglutinated rabbit and rat, and not mouse, guinea pig, goose, and sheep erythrocytes. The lectin was stable at temperatures below 40 degrees C, but the hemagglutinating activity halved when it was heated to 45-85 degrees C and was completely lost at 95 degrees C. The hemagglutinating activity was more stable at 80 degrees C than at 70 degrees C and was rapidly inactivated at 90 degrees C. It showed a maximum hemagglutination activity within the pH range of 8.0-11.0. The deduced amino acid sequence of an internal tryptic peptide sequence of this purified lectin showed sequence similarity (homology) to other members of the leucoagglutinating phytohemagglutinin precursor family, whilst the complete lectin inhibited the in vitro growth of three plant pathogenic fungi, *Fusarium oxysporum*, *Exserohilum turcicum*, and *Colectrotrichum cassiicola*, at a concentration of 17.5 to 35 microg, and showed in vitro cytotoxicity against the BT474 breast cancer cell line with an IC<sub>50</sub> of approximately 21.2 μg.

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Mol Biol Rep. 2009 Oct 15. [Epub ahead of print]

### **Curcumin modulates eukaryotic initiation factors in human lung adenocarcinoma epithelial cells.**

Chen L, Tian G, Shao C, Cobos E, Gao W.

Department of Environmental Toxicology and The Institute of Environmental and Human Health (TIEHH), Texas Tech University, Lubbock, TX, 79409, USA.

Curcumin, a polyphenolic compound, is the active component of *Curcuma longa* and has been extensively investigated as an anticancer drug that modulates multiple pathways. Eukaryotic initiation factors (eIFs) have been known to play important roles in translation initiation, which controls cell growth and proliferation. Little is known about the effects of curcumin on eIFs in lung cancer. The objective of this study was to examine the curcumin cytotoxic effect and modulation of two major rate-limiting translation initiation factors, including eIF2 $\alpha$  and eIF4E protein expression levels in lung adenocarcinoma epithelial cell line A549. Cytotoxicity was measured by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and protein changes were determined by Western blot. A549 cells were treated with 0-240  $\mu$ M curcumin for 4-96 h. The inhibitory effects of curcumin on cytotoxicity were dose- and time-dependent ( $P < 0.001$ ). The 50% inhibitory curcumin concentrations (IC<sub>50</sub>s) at 24, 48, 72, and 96 h were 93, 65, 40, and 24  $\mu$ M, respectively. Protein expressions of eIF2 $\alpha$ , eIF4E, Phospho-4E-BP1 were down-regulated, while Phospho-eIF2 $\alpha$  and Phospho-eIF4E were up-regulated after A549 cells were treated with 20 and 40  $\mu$ M curcumin for 24 h. In addition, the effects of curcumin on these protein expression changes followed a significant dose-response ( $P < 0.05$ , trend test). These findings suggest that curcumin could reduce cell viability through prohibiting the initiation of protein synthesis by modulating eIF2 $\alpha$  and eIF4E.

PMID: 19826913 [PubMed - as supplied by publisher]

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Mol Cell Biochem. 2009 Oct 14. [Epub ahead of print]

#### **Multifocal signal modulation therapy of cancer: ancient weapon, modern targets.**

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Although safe in most cases, ancient treatments are ignored because neither their active components nor their molecular targets are well defined. This is not the case, however, with curcumin, a yellow-pigment substance and component of turmeric (*Curcuma longa*), which was identified more than a century ago. Recently, extensive research has addressed the chemotherapeutic potential of this relatively nontoxic-plant-derived polyphenol. Because most cancers are caused by deregulation of as many as 500 different genes, agents that target multiple gene products are needed for prevention and treatment of cancer. In this regard, curcumin has been reported to have immense potentiality for being used in cancer chemotherapy because of its control over the machineries of cell survival, proliferation, invasion, and angiogenesis. The mechanisms implicated are diverse and appear to involve a combination of cell signaling pathways at multiple levels. This review seeks to summarize the unique multifocal signal modulatory properties of the "ancient weapon," curcumin, which may be exploited for successful clinical cancer prevention.

PMID: 19826768 [PubMed - as supplied by publisher]

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Eur J Pharmacol. 2009 Oct 7. [Epub ahead of print]

#### **Demethoxycurcumin suppresses migration and invasion of MDA-MB-231 human breast cancer cell line.**

Yodkeeree S, Ampasavate C, Aggarwal BB, Limtrakul P.

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Demethoxycurcumin (DMC) is one of the main active compounds of curcuminoids found in turmeric powder, which is used as a spice in Asian cooking and traditional medicine. Recent studies reveal that DMC has several biological activities including anti-inflammation and anti-cancer activities. However, the molecular mechanism by which DMC

has anti-metastasis activity in breast cancer cells remains poorly understood. Here, we report for the first time that DMC inhibited adhesion, migration and invasion of MDA-MB-231 human breast cancer cells. For cancer cell migration and invasion, extracellular matrix (ECM) degradation processes are required. MDA-MB-231 cells treated with DMC had decreased levels of ECM degradation-associated proteins including matrix metalloproteinase-9 (MMP-9), membrane type-1 matrix metalloproteinase (MT1-MMP), urokinase plasminogen activator (uPA) and uPA receptor (uPAR), while the level of uPA inhibitor (PAI-1) was up-regulated. Moreover, DMC also reduced the expression of intercellular adhesion molecule-1 (ICAM-1) and chemokine receptor 4, (CXCR4), which is involved in modulation of the tumor metastasis process. We also found that DMC treatment inhibited the DNA binding activity of nuclear factor-kappa B (NF-kappaB), which is known to mediate the expression of MMPs, uPA, uPAR, ICAM-1, and CXCR4. These findings strongly suggest that the mechanism of DMC-mediated anti-invasive activity involves modulation of the expression of invasion-associated proteins, possibly by targeting NF-kappaB in MDA-MB-231 cells.

PMID: 19818349 [PubMed - as supplied by publisher]

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Mol Pharmacol. 2009 Sep 24. [Epub ahead of print]

**An Anticancer Effect of Curcumin Mediated by Down-regulating PRL-3 Expression on Highly Metastatic Melanoma Cells.**

Wang L, Shen Y, Song R, Sun Y, Xu J, Xu Q.  
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Phosphatase of regenerating liver-3 (PRL-3) has been suggested as a potential target for anti-cancer drugs based on its involvement in tumor metastasis. However, little is known about small molecule inhibitor against PRL-3. In this study, we report that curcumin, the component of the spice turmeric, shows its anti-tumor effect by selectively down-regulating the expression of PRL-3 but not its family members PRL-1 and -2 in a p53-independent way. Curcumin inhibited the phosphorylation of Src and stat3 partly through PRL-3 down-regulation. Cells with PRL-3 stably knocked down show less sensitivity of curcumin treatment, which reveals that PRL-3 is the very upstream target of curcumin. Curcumin treatment also remarkably prevented B16BL6 from invading the draining lymph nodes in the spontaneous metastatic tumor model, which is likely of relevance to PRL-3 down-regulation. Our results reveal a novel capacity of curcumin to down-regulate oncogene PRL-3, raising its possibility in therapeutic regimen against malignant tumor.

PMID: 19779032 [PubMed - as supplied by publisher]

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Int J Radiat Oncol Biol Phys. 2009 Oct 1;75(2):534-42.

**Curcumin modulates the radiosensitivity of colorectal cancer cells by suppressing constitutive and inducible NF-kappaB activity.**

Sandur SK, Deorukhkar A, Pandey MK, Pabón AM, Shentu S, Guha S, Aggarwal BB, Krishnan S.  
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**PURPOSE:** Radiation therapy is an integral part of the preoperative treatment of rectal cancers. However, only a minority of patients achieve a complete pathologic response to therapy because of resistance of these tumors to radiation therapy. This resistance may be mediated by constitutively active pro-survival signaling pathways or by inducible/acquired mechanisms in response to radiation therapy. Simultaneous inhibition of these pathways can sensitize these tumors to radiation therapy.

**METHODS AND MATERIALS:** Human colorectal cancer cells were exposed to clinically relevant doses of gamma rays, and the mechanism of their radioresistance was investigated. We characterized the transcription factor nuclear

factor-kappaB (NF-kappaB) activation as a mechanism of inducible radioresistance in colorectal cancer and used curcumin, the active ingredient in the yellow spice turmeric, to overcome this resistance.

**RESULTS:** Curcumin inhibited the proliferation and the post-irradiation clonogenic survival of multiple colorectal cancer cell lines. Radiation stimulated NF-kappaB activity in a dose- and time-dependent manner, whereas curcumin suppressed this radiation-induced NF-kappaB activation via inhibition of radiation-induced phosphorylation and degradation of inhibitor of kappaB alpha, inhibition of inhibitor of kappaB kinase activity, and inhibition of Akt phosphorylation. Curcumin also suppressed NF-kappaB-regulated gene products (Bcl-2, Bcl-x(L), inhibitor of apoptosis protein-2, cyclooxygenase-2, and cyclin D1).

**CONCLUSIONS:** Our results suggest that transient inducible NF-kappaB activation provides a prosurvival response to radiation that may account for development of radioresistance. Curcumin blocks this signaling pathway and potentiates the antitumor effects of radiation therapy.

PMID: 19735878 [PubMed - indexed for MEDLINE]

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Biochem Pharmacol. 2009 Sep 6. [Epub ahead of print]

**Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo.**

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Curcumin, a yellow pigment present in the spice turmeric (*Curcuma longa*), has been linked with antioxidant, anti-inflammatory, antiproliferative, anticancer, antidiabetic, antirheumatic, and antiviral effects, but its optimum potential is limited by its lack of solubility in aqueous solvents and poor oral bioavailability. We employed a polymer-based nanoparticle approach to improve bioavailability. Curcumin was encapsulated with 97.5% efficiency in biodegradable nanoparticulate formulation based on poly (lactide-co-glycolide) (PLGA) and a stabilizer polyethylene glycol (PEG)-5000. Dynamic laser light scattering and transmission electron microscopy indicated a particle diameter of 80.9nm. This curcumin, renamed from hereon "as curcumin (NP)", was characterized for its biological activity. In vitro curcumin (NP) exhibited very rapid and more efficient cellular uptake than curcumin. Estrase staining revealed that curcumin (NP) was at least as potent as or more potent than curcumin in inducing apoptosis of leukemic cells and in suppressing proliferation of various tumor cell lines. When examined by electrophoretic gel shift mobility assay, curcumin (NP) was more active than curcumin in inhibiting TNF-induced NF-kappaB activation and in suppression of NF-kappaB-regulated proteins involved in cell proliferation (cyclin D1), invasion (MMP-9), and angiogenesis (VEGF). In mice, curcumin (NP) was more bioavailable and had a longer half-life than curcumin. Overall we demonstrate that curcumin-loaded PLGA nanoparticles formulation has enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo over curcumin.

PMID: 19735646 [PubMed - as supplied by publisher]

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Ann N Y Acad Sci. 2009 Aug;1171:436-47.

**Effect of curcumin on nuclear factor kappaB signaling pathways in human chronic myelogenous K562 leukemia cells.**

Reuter S, Charlet J, Juncker T, Teiten MH, Dicato M, Diederich M.  
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Curcumin, a natural product isolated from the plant *Curcuma longa*, has a diverse range of molecular targets that influence numerous biochemical and molecular cascades. Curcumin has been shown to inhibit nuclear factor kappaB (NF-kappaB) activation at several steps in the NF-kappaB signaling pathways and thereby controls numerous NF-kappaB-regulated genes involved in various diseases. In the present study, we investigated the effect of curcumin

pretreatment on 84 tumor necrosis factor-alpha (TNF-alpha)-activated genes of NF-kappaB pathways in K562 cells, using a real-time PCR array. Our results show that transcription of 29 NF-kappaB-related mRNAs was significantly downregulated (CARD4, CCL2, CD40, CSF2, F2R, ICAM1, IKBKB, IKBKE, IL1A, IL1B, IL6, IL8, IRAK2, MALT1, MAP3K1, MYD88, NFKB1, NFKB2, NFKBIA, PPM1A, RAF1, RELB, STAT1, TLR3, TNF, TNFalphaIP3, TNFSF10, and TICAM1), whereas 10 mRNAs were induced (AGT, CASP1, CSF3, FOS, IFNG, IL10, TICAM2, TLR2, TLR9, and TNFRSF7). Western blot analysis of CD40, NFKB1 (p50), RELB, NFKBIA (IkappaBalpha), and IL10 as well as an IL8 secretion assay confirmed our results. Taken together, we show that curcumin regulates an impressive number of NF-kappaB genes within the different NF-kappaB signaling pathways.

PMID: 19723087 [PubMed - indexed for MEDLINE]

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Nutr Hosp. 2009 May-Jun;24(3):273-81.

### **Plant-derived health: the effects of turmeric and curcuminoids.**

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Plants contain numerous polyphenols, which have been shown to reduce inflammation and hereby to increase resistance to disease. Examples of such polyphenols are isothiocyanates in cabbage and broccoli, epigallocatechin in green tea, capsaicin in chili peppers, chalcones, rutin and naringenin in apples, resveratrol in red wine and fresh peanuts and curcumin/curcuminoids in turmeric. Most diseases are maintained by a sustained discreet but obvious increased systemic inflammation. Many studies suggest that the effect of treatment can be improved by a combination of restriction in intake of proinflammatory molecules such as advanced glycation end products (AGE), advanced lipoperoxidation end products (ALE), and rich supply of antiinflammatory molecules such as plant polyphenols. To the polyphenols with a bulk of experimental documentation belong the curcuminoid family and especially its main ingredient, curcumin. This review summarizes the present knowledge about these turmeric-derived ingredients, which have proven to be strong antioxidants and inhibitors of cyclooxygenase-2 (COX-2), lipoxygenase (LOX) and nuclear factor kappa B (NF-kappaB) but also AGE. A plethora of clinical effects are reported in various experimental diseases, but clinical studies in humans are few. It is suggested that supply of polyphenols and particularly curcuminoids might be value as complement to pharmaceutical treatment, but also prebiotic treatment, in conditions proven to be rather therapy-resistant such as Crohn's, long-stayed patients in intensive care units, but also in conditions such as cancer, liver cirrhosis, chronic renal disease, chronic obstructive lung disease, diabetes and Alzheimer's disease.

PMID: 19721899 [PubMed - indexed for MEDLINE]

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Biochem Pharmacol. 2009 Aug 12. [Epub ahead of print]

### **Curcumin potentiates the antitumor effects of gemcitabine in an orthotopic model of human bladder cancer through suppression of proliferative and angiogenic biomarkers.**

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Little progress has been made in the last three decades in the treatment of bladder cancer. Novel agents that are nontoxic and can improve the current standard of care of this disease are urgently needed. Curcumin, a component of *Curcuma longa* (also called turmeric), is one such agent that has been shown to suppress pathways linked to oncogenesis, including cell survival, proliferation, invasion and angiogenesis. We investigated whether curcumin has potential to improve the current therapy for bladder cancer, using an orthotopic mouse model. Curcumin potentiated the apoptotic effects of gemcitabine against human bladder cancer 253JBV cells in culture. Electrophoretic mobility shift assay revealed that curcumin also suppressed the gemcitabine-induced activation of the cell survival transcription factor NF-kappaB. In an orthotopic mouse model, bioluminescence imaging revealed that while curcumin alone significantly reduced the bladder tumor volume, maximum reduction was observed when curcumin was used in combination with gemcitabine ( $P < 0.01$  versus vehicle;  $P < 0.01$  versus gemcitabine alone). Curcumin also significantly decreased the proliferation marker Ki-67 and microvessel density (CD31) ( $P < 0.01$  versus vehicle;  $P < 0.01$  versus gemcitabine alone), but maximum reduction occurred when it was combined with

gemcitabine (P<0.01 versus vehicle; P<0.01 versus gemcitabine alone). Curcumin abolished the constitutive activation of NF-kappaB in the tumor tissue; induced apoptosis, and decreased cyclin D1, VEGF, COX-2, c-myc and Bcl-2 expression in the bladder cancer tissue. Overall our results suggest that curcumin alone exhibits significant antitumor effects against human bladder cancer and it further potentiates the effects of gemcitabine, possibly through the modulation of NF-kappaB signaling pathway.

PMID: 19682434 [PubMed - as supplied by publisher]

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Mol Carcinog. 2009 Aug 12. [Epub ahead of print]

**Curcumin-induced apoptosis in ovarian carcinoma cells is p53-independent and involves p38 mitogen-activated protein kinase activation and downregulation of Bcl-2 and survivin expression and Akt signaling.**

Watson JL, Greenshields A, Hill R, Hilchie A, Lee PW, Giacomantonio CA, Hoskin DW.  
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New cytotoxic agents are urgently needed for the treatment of advanced ovarian cancer because of the poor long-term response of this disease to conventional chemotherapy. Curcumin, obtained from the rhizome of *Curcuma longa*, has potent anticancer activity; however, the mechanism of curcumin-induced cytotoxicity in ovarian cancer cells remains a mystery. In this study we show that curcumin exhibited time- and dose-dependent cytotoxicity against monolayer cultures of ovarian carcinoma cell lines with differing p53 status (wild-type p53: HEY, OVCA429; mutant p53: OCC1; null p53: SKOV3). In addition, p53 knockdown or p53 inhibition did not diminish curcumin killing of HEY cells, confirming p53-independent cytotoxicity. Curcumin also killed OVCA429, and SKOV3 cells grown as multicellular spheroids. Nuclear condensation and fragmentation, as well as DNA fragmentation and poly (ADP-ribose) polymerase-1 cleavage in curcumin-treated HEY cells, indicated cell death by apoptosis. Procaspase-3, procaspase-8, and procaspase-9 cleavage, in addition to cytochrome c release and Bid cleavage into truncated Bid, revealed that curcumin activated both the extrinsic and intrinsic pathways of apoptosis. Bax expression was unchanged but Bcl-2, survivin, phosphorylated Akt (on serine 473), and total Akt were downregulated in curcumin-treated HEY cells. Curcumin also activated p38 mitogen-activated protein kinase (MAPK) without altering extracellular signal-regulated kinase 1/2 activity. We conclude that p53-independent curcumin-induced apoptosis in ovarian carcinoma cells involves p38 MAPK activation, ablation of prosurvival Akt signaling, and reduced expression of the antiapoptotic proteins Bcl-2 and survivin. These data provide a mechanistic rationale for the potential use of curcumin in the treatment of ovarian cancer. (c) 2009 Wiley-Liss, Inc.

PMID: 19676105 [PubMed - as supplied by publisher]

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Anticancer Res. 2009 Aug;29(8):3185-90.

**Curcumin inhibits proliferation of colorectal carcinoma by modulating Akt/mTOR signaling.**

Johnson SM, Gulhati P, Arrieta I, Wang X, Uchida T, Gao T, Evers BM.  
Department of Surgery, The University of Texas Medical Branch, Galveston, TX 77550, USA.

**BACKGROUND:** Curcumin, a natural polyphenol product of the plant *Curcuma longa*, has been shown to inhibit the growth and progression of colorectal cancer; however, the anticancer mechanism of curcumin remains to be elucidated.

**MATERIALS AND METHODS:** Colorectal cancer cells were treated with curcumin and changes in proliferation, protein and mRNA levels were analyzed.

**RESULTS:** Curcumin inhibited proliferation of colorectal cancer cells. This effect was mediated by inhibition of mammalian target of rapamycin (mTOR) signaling as evidenced by decreased phosphorylation of downstream effectors of mTOR complex 1 (mTORC1), p70S6K and 4E-BP1. Curcumin decreased total expression of mTOR, Raptor and Rictor protein and mRNA levels. Surprisingly, curcumin induced phosphorylation of Akt(Ser 473); this effect may be attributed to a decrease in levels of the PHLPP1 phosphatase, an inhibitor of Akt.

**CONCLUSION:** Our data suggest that curcumin, a natural compound, may exert its antiproliferative effects by inhibition of mTOR signaling and thus may represent a novel class of mTOR inhibitor.

PMID: 19661333 [PubMed - indexed for MEDLINE]

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Environ Health Perspect. 2009 Jul;117(7):1155-61. Epub 2009 Mar 23.

**Diarylheptanoid phytoestrogens isolated from the medicinal plant *Curcuma comosa*: biologic actions in vitro and in vivo indicate estrogen receptor-dependent mechanisms.**

Winuthayanon W, Piyachaturawat P, Suksamrarn A, Ponglikitmongkol M, Arao Y, Hewitt SC, Korach KS.  
Department of Physiology, Faculty of Science, Mahidol University, Bangkok, Thailand.

**BACKGROUND:** Diarylheptanoids isolated from *Curcuma comosa* Roxb. have been recently identified as phytoestrogens. However, the mechanism underlying their actions has not yet been identified. **OBJECTIVES:** We characterized the estrogenic activity of three active naturally occurring diarylheptanoids both in vitro and in vivo.

**METHODS:** We characterized mechanisms of estrogenic action of the diarylheptanoids (3S)-1,7-diphenyl-(6E)-6-hepten-3-ol (D1), 1,7-diphenyl-(6E)-6-hepten-3-one (D2), and (3R)-1,7-diphenyl-(4E,6E)-4,6-heptadien-3-ol (D3) by using a real-time polymerase chain reaction assay, a mammalian transfection model, and a uterotrophic assay in mice.

**RESULTS:** All diarylheptanoids up-regulated estrogen-responsive genes in estrogen-responsive breast cancer cells (MCF-7). In HepG2 cells transfected with estrogen receptor (ER) beta or different ERalpha functional receptor mutants and the Vit-ERE-TATA-Luc reporter gene, all diarylheptanoids induced transcription through a ligand-dependent human ERalpha-ERE-driven pathway, which was abolished with ICI 182,780 (ER antagonist), whereas only D2 was active with ERbeta. An ERalpha mutant lacking the functional AF2 (activation function 2) region was not responsive to 17beta-estradiol (E(2)) or to any of the diarylheptanoids, whereas ERalpha lacking the AF1 domain exhibited wild-type-like activity. D3 markedly increased uterine weight and proliferation of the uterine epithelium in ovariectomized mice, whereas D1 and D2 were inactive. D3, like E(2), up-regulated lactoferrin (Ltf) gene expression. The responses to D3 in the uterus were inhibited by ICI 182,780. In addition, D3 stimulated both classical (Aqp5) and nonclassical (Cdkn1a) ER-mediated gene regulation.

**CONCLUSIONS:** The results suggest that the D3 diarylheptanoid is an agonist for ER both in vitro and in vivo, and its biological action is ERalpha selective, specifically requiring AF2 function, and involves direct binding via ER as well as ERE-independent gene regulation.

PMID: 19654927 [PubMed - indexed for MEDLINE]

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Menopause. 2009 Jul 22. [Epub ahead of print]

**Curcumin delays development of medroxyprogesterone acetate-accelerated 7,12-dimethylbenz[a]anthracene-induced mammary tumors.**

Carroll CE, Benakanakere I, Besch-Williford C, Ellersieck MR, Hyder SM.  
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**OBJECTIVE::** Combined hormone therapy (HT) containing estrogen and progestin (medroxyprogesterone acetate [MPA]) leads to increased risk of breast cancer in postmenopausal women, compared with HT regimens containing estrogen alone or placebo. We previously reported that in animal models, progestins can accelerate the development of mammary tumors by increasing vascular endothelial growth factor (VEGF) levels. We furthermore showed that curcumin, an Indian spice derived from the turmeric root, specifically inhibits MPA-induced VEGF secretion from

breast cancer cells in vitro. In the present study, we investigated whether curcumin inhibits 7,12-dimethylbenz[a]anthracene (DMBA)-induced, MPA-accelerated tumors in Sprague-Dawley rats.

**METHODS::** On day 0, virgin female Sprague-Dawley rats (age, 55 d) were given DMBA (20 mg/rat). Sixty-day timed-release pellets containing 25 mg MPA were implanted into the rats on day 30. Curcumin was administered daily at a rate of 200 mg kg day from days 26 to 50, and animals were killed on day 52 (n = 15-19 per group).

**RESULTS::** Treatment with curcumin delayed the first appearance of MPA-accelerated tumors by 7 days, decreased tumor incidence by the end of the experiment, and reduced tumor multiplicity in DMBA-induced MPA-accelerated tumors. Curcumin also prevented many of the gross histological changes seen in the MPA-treated mammary gland. Immunohistochemical analyses of mammary tumors showed that curcumin decreased MPA-induced VEGF induction in hyperplastic lesions, although it did not affect the levels of estrogen and progesterone receptors.

**CONCLUSIONS:** We suggest that curcumin be tested as a dietary chemopreventive agent in women already exposed to MPA, in an effort to decrease or delay the risk of breast cancer associated with combined HT.

PMID: 19629015 [PubMed - as supplied by publisher]

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Int J Cancer. 2009 Nov 1;125(9):2187-97.

**Curcumin sensitizes human colorectal cancer to capecitabine by modulation of cyclin D1, COX-2, MMP-9, VEGF and CXCR4 expression in an orthotopic mouse model.**

Kunnumakkara AB, Diagaradjane P, Anand P, Kuzhuvilil HB, Deorukhkar A, Gelovani J, Guha S, Krishnan S, Aggarwal BB.  
Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA.

Because of the poor prognosis and the development of resistance against chemotherapeutic drugs, the current treatment for advanced metastatic colorectal cancer (CRC) is ineffective. Whether curcumin (a component of turmeric) can potentiate the effect of capecitabine against growth and metastasis of CRC was investigated. The effect of curcumin on proliferation of CRC cell lines was examined by mitochondrial dye-uptake assay, apoptosis by esterase staining, nuclear factor-kappaB (NF-kappaB) by electrophoretic mobility shift assay and gene expression by Western blot analysis. The effect of curcumin on the growth and metastasis of CRC was also examined in orthotopically implanted tumors in nude mice. In vitro, curcumin inhibited the proliferation of human CRC cell lines, potentiated capecitabine-induced apoptosis, inhibited NF-kappaB activation and suppressed NF-kappaB-regulated gene products. In nude mice, the combination of curcumin and capecitabine was found to be more effective than either agent alone in reducing tumor volume (p = 0.001 vs. control; p = 0.031 vs. capecitabine alone), Ki-67 proliferation index (p = 0.001 vs. control) and microvessel density marker CD31. The combination treatment was also highly effective in suppressing ascites and distant metastasis to the liver, intestines, lungs, rectum and spleen. This effect was accompanied by suppressed expression of activated NF-kappaB and NF-kappaB-regulated gene products (cyclin D1, c-myc, bcl-2, bcl-xL, cIAP-1, COX-2, ICAM-1, MMP-9, CXCR4 and VEGF). Overall, our results suggest that curcumin sensitizes CRC to the antitumor and antimetastatic effects of capecitabine by suppressing NF-kappaB cell signaling pathway. (c) 2009 UICC.

PMID: 19623659 [PubMed - indexed for MEDLINE]

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Altern Med Rev. 2009 Jun;14(2):141-53.

**Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: a review of preclinical and clinical research.**

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*Curcuma longa* (turmeric) has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions. Turmeric constituents include the three curcuminoids: curcumin (diferuloylmethane; the primary constituent and the one responsible for its vibrant yellow color), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins. While numerous pharmacological activities, including antioxidant and antimicrobial properties, have been attributed to curcumin, this article focuses on curcumin's anti-inflammatory properties and its use for inflammatory conditions. Curcumin's effect on cancer (from an anti-inflammatory perspective) will also be discussed; however, an exhaustive review of its many anticancer mechanisms is outside the scope of this article. Research has shown curcumin to be a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. Based on early cell culture and animal research, clinical trials indicate curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis, as well as certain types of cancer. Because of curcumin's rapid plasma clearance and conjugation, its therapeutic usefulness has been somewhat limited, leading researchers to investigate the benefits of complexing curcumin with other substances to increase systemic bioavailability. Numerous in-progress clinical trials should provide an even deeper understanding of the mechanisms and therapeutic potential of curcumin.

PMID: 19594223 [PubMed - indexed for MEDLINE]

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AAPS J. 2009 Sep;11(3):495-510. Epub 2009 Jul 10.

### **Curcumin and cancer cells: how many ways can curry kill tumor cells selectively?**

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Cancer is a hyperproliferative disorder that is usually treated by chemotherapeutic agents that are toxic not only to tumor cells but also to normal cells, so these agents produce major side effects. In addition, these agents are highly expensive and thus not affordable for most. Moreover, such agents cannot be used for cancer prevention. Traditional medicines are generally free of the deleterious side effects and usually inexpensive. Curcumin, a component of turmeric (*Curcuma longa*), is one such agent that is safe, affordable, and efficacious. How curcumin kills tumor cells is the focus of this review. We show that curcumin modulates growth of tumor cells through regulation of multiple cell signaling pathways including cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53, p21) death receptor pathway (DR4, DR5), mitochondrial pathways, and protein kinase pathway (JNK, Akt, and AMPK). How curcumin selectively kills tumor cells, and not normal cells, is also described in detail.

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