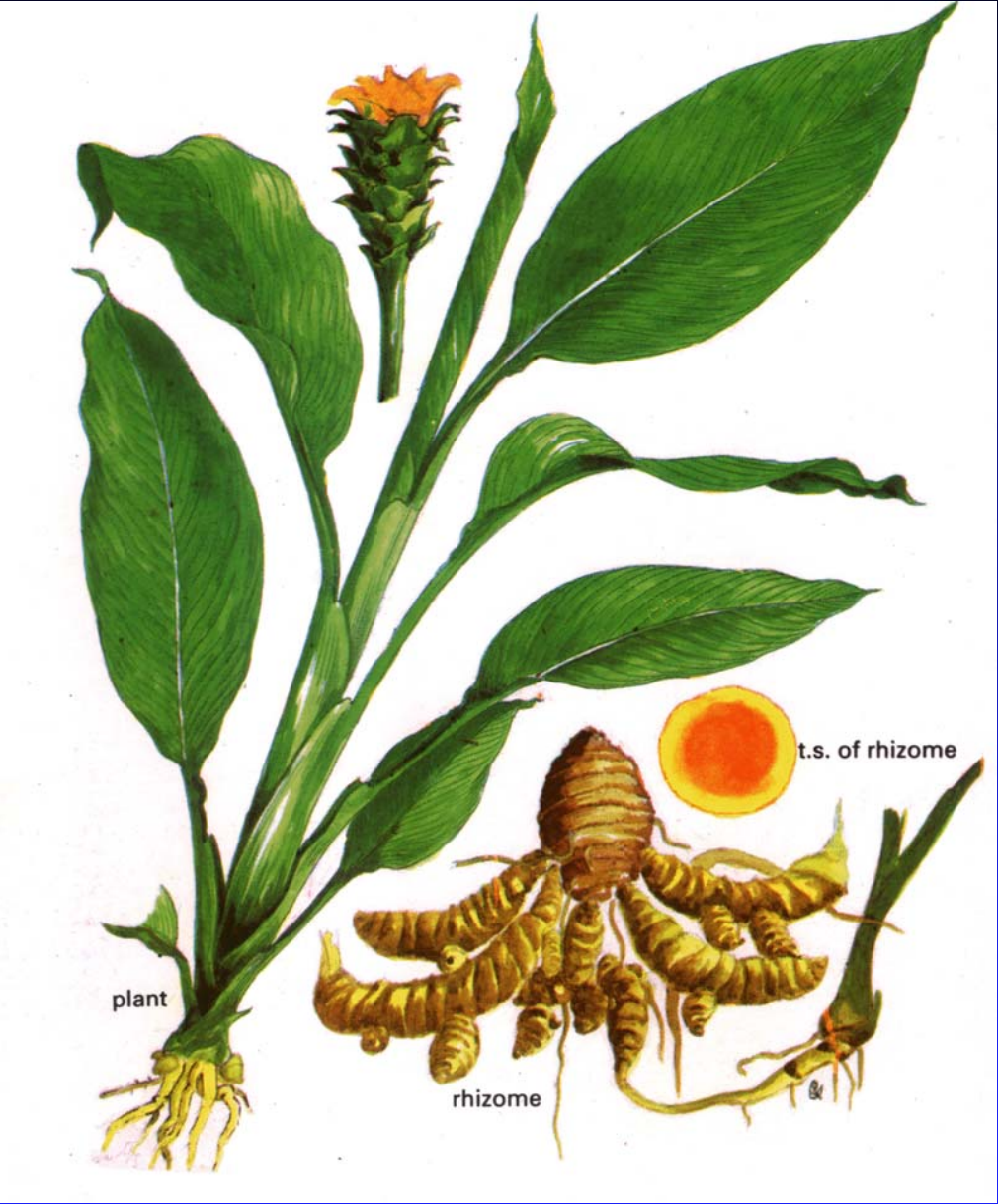


# **Anticancer potential of curcumin**

**Bharat B. Aggarwal, Ph.D.**

**Cytokine Research Section,  
Department of Bioimmunotherapy,  
The University of Texas M.D. Anderson Cancer Center,  
Houston, Texas, U.S.A.**

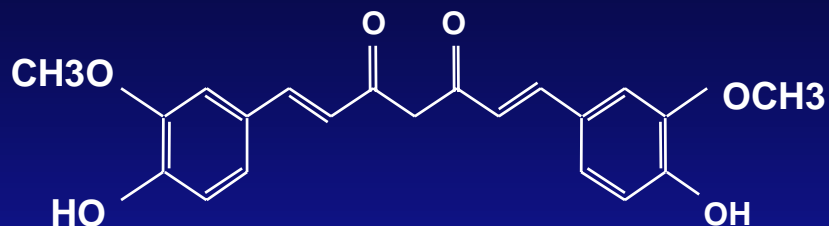


# Source of Curcumin

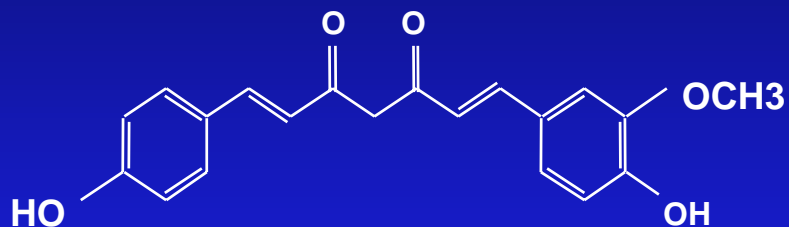


**Turmeric**  
(*Curcuma longa*)

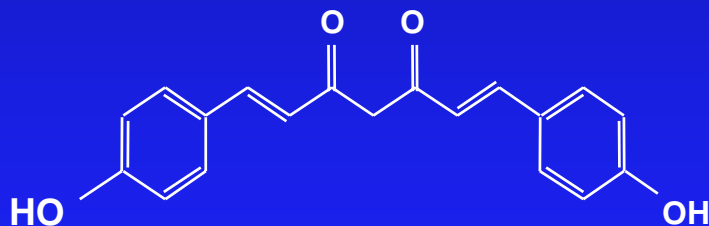
# Structure of curcumin



**Curcumin I**  
(77%)



**Curcumin II**  
Demethoxycurcumin  
(17%)



**Curcumin III**  
Bis-Demethoxycurcumin  
(3%; less active)

# Different stages of cancer progression and its suppression by curcumin

## Constitutive activation of transcription factors

➤ AP-1 & NF- $\kappa$ B

➤ Tumor Suppressor genes

## Overexpression of

➤ Oncogenes

➤ HER2

➤ Growth factors

(e.g; EGF, PDGF, FGF)

➤ Growth factor receptors

➤ Survival factors

(e.g; Survivin, Bcl-2 and Bcl-xl)

➤ Cyclin D1

➤ Decoy receptor

## Overexpression of

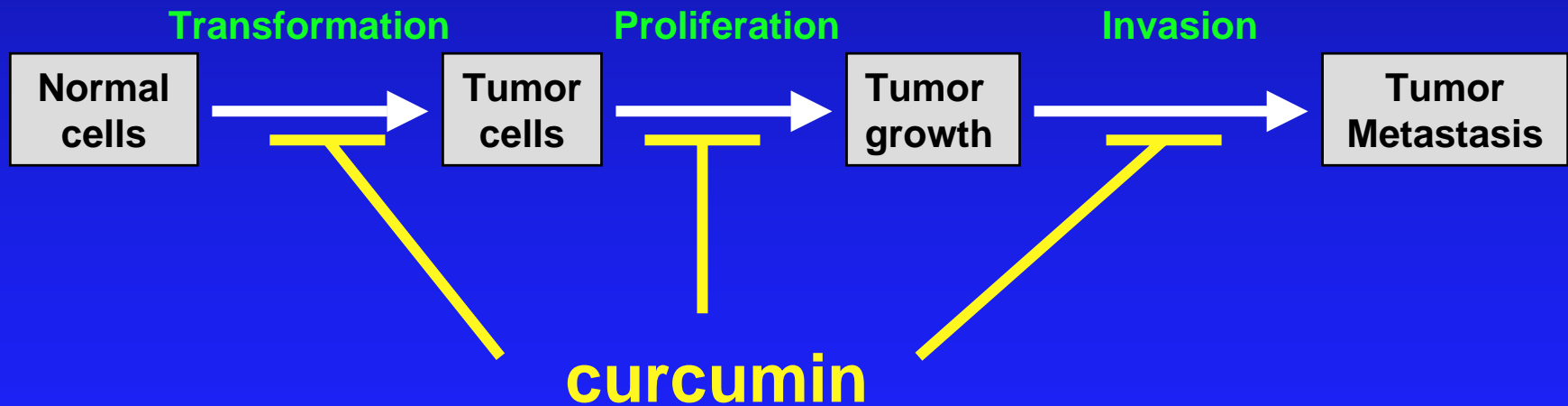
➤ Matrix metalloproteases

➤ Cyclooxygenase-2

➤ Adhesion molecules

➤ Chemokine

➤ TNF

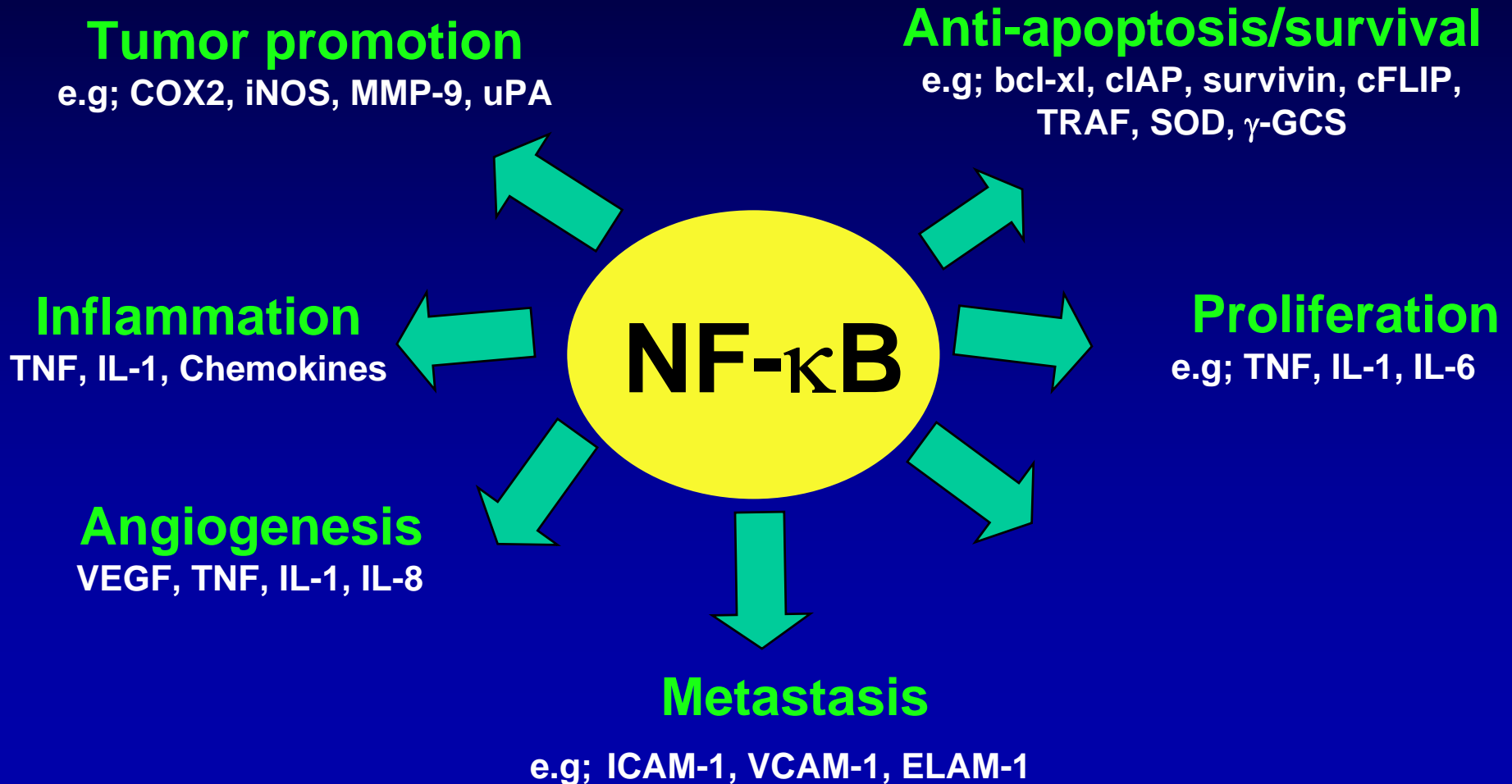


**Activation of transcription factor  
Nuclear Factor-kappa B is  
suppressed by curcumin**

*Singh S, and Aggarwal BB.*

*J Biol Chem. 1995 Oct 20;270 (42):24995-5000.*

# *Role of NF- $\kappa$ B in Development of Cancer*



**Curcumin inhibits constitutive NF- $\kappa$ B, I $\kappa$ B $\alpha$  kinase, inhibits proliferation, and induces apoptosis in human multiple myeloma cells**

*Bharti A., Donato N., Singh S., Aggarwal B.B.*

*BLOOD, 101, 2003, 1053-1062*



# **Curcumin Inhibits Constitutive and Interleukin-6-Inducible STAT3 Phosphorylation in Human Multiple Myeloma Cells**

*Alok C. Bharti, Nicholas Donato, and  
Bharat B. Aggarwal*

*(Journal of Immunology, in press)*

**Nuclear Factor- $\kappa$ B and STAT3  
are Constitutively Active in  
CD138+ Cells Derived from  
Multiple Myeloma Patients and  
Their Suppression Leads to  
Apoptosis**

*Alok C. Bharti, James M. Reuben, Donna Weber,  
Raymond Alexanian, Moshe Talpaz and  
Bharat B. Aggarwal*

*(submitted)*

**Curcumin inhibits TNF-mediated NF- $\kappa$ B activation leading to suppression of expression of cell surface adhesion molecules in endothelial cells**

*Kumar A. and Aggarwal B. B.,*

*Biochem. Pharmacol. 55, 775-783, 1998*

**Curcumin induces apoptosis  
through activation of caspase-8,  
BID cleavage and cytochrome C  
release**

*Anto R. J., Mukhopadhyay A., Denning K., and  
Aggarwal B.B.,*

*Carcinogenesis, 23, 143, 2002*

# **Curcumin inhibits cyclin D1 expression through transcriptional and post-transcriptional regulation**

*Mukhopadhyay A., Banerjee S., Stafford LJ,  
Xia CX., Liu M., and Aggarwal BB,*

*ONCOGENE, 21, 8852, 2002*

**Curcumin Inhibits Receptor  
Activator of NF- $\kappa$ B Ligand-  
Induced NF- $\kappa$ B Activation in  
Osteoclast Precursors and  
Suppresses Osteoclastogenesis**

*Alok C. Bharti and Bharat B. Aggarwal*

*(submitted)*

# **Antiproliferative effect of curcumin against human breast tumor cell lines.**

*Mehta K, Pantazis P, McQueen T,  
Aggarwal BB.*

*Anticancer Drugs. 1997 Jun;8(5):470-81.*

# **Curcumin Suppresses Metastasis in a Human Breast Cancer Xenograft Model:**

**Association With Suppression of Nuclear Factor- $\kappa$ B,  
Cyclooxygenase-2 and Matrix Metalloproteinases**

***Bharat B. Aggarwal, Shishir Shishodia, Sanjeev  
Banerjee, Robert A. Newman,  
Carlos E. Bueso-Ramos and Janet E. Price***

***(submitted)***



# **Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines**

*Mukhopadhyay A, Bueso-Ramos C, Chatterjee D, Pantazis P, Aggarwal BB.*

*Oncogene. 2001 Nov 15; 20 (52):7597-609.*

# Curcumin and prostate cancer

## Therapeutic potential of curcumin in human prostate cancer

III. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo

Dorai T, Cao YC, Dorai B, Buttyan R, Katz AE

Prostate. 2001 Jun 1;47(4):293-303.

**Curcumin Downregulates the  
Constitutive Activation of NF- $\kappa$ B  
and I $\kappa$ B $\alpha$  Kinase  
in Human Head and Neck  
Squamous Cell Carcinoma Cells  
Leading to Suppression of  
Proliferation and Induction of  
Apoptosis:**

Modulation of Cyclin D1, MMP-9 and COX-2

*S. Aggarwal, Y. Takada, S. Singh, J. Myers and B. B. Aggarwal,  
(submitted)*

**Curcumin Downregulates Cigarette  
Smoke -Induced NF- $\kappa$ B Activation  
Through Inhibition of I $\kappa$ B $\alpha$  Kinase  
in Human Lung Epithelial Cells:  
Correlation with Suppression of  
COX-2, MMP-9 and Cyclin D1**

***S. Shishodia, P. Potdar, C. G. Gairola and  
B. B. Aggarwal,***

***Carcinogenesis 24, 2003, 1269-1279***

**Nuclear Factor- $\kappa$ B and I $\kappa$ B Kinase  
are Constitutively Active in  
Human Pancreatic Cells and their  
Down-regulation by Curcumin is  
Associated with Suppression of  
Proliferation and Induction of  
Apoptosis**

*Lan Li, Bharat B. Aggarwal, Shishir Shishodia,  
James Abbruzzese and Razelle Kurzrock*

*(submitted)*

# Molecular targets of curcumin

## Gene expression

### Chemokines

Cyclin D1  
MMP9  
COX2  
5-LOX  
iNOS  
IL-12  
TNF  
IL-6  
IL-8

### Others

ICAM-1  
VCAM-1  
ELAM-1  
TF  
Bcl-2  
Bcl-xl  
P53  
AR/ARP  
MDR  
Telomerase  
CyclinD1

**Curcumin**

```
graph TD; Curcumin((Curcumin)) --> GeneExpression[Gene expression]; Curcumin --> TranscriptionFactor[Transcription factor]; Curcumin --> ProteinKinases[Protein Kinases]; Curcumin --> Enzymes[Enzymes]; Curcumin --> Others[Others];
```

## Transcription factor

NF- $\kappa$ B  
AP-1  
Egr-1  
STAT1  
STAT3  
STAT5  
PPAR- $\gamma$   
EpRE  
CBP  
 $\beta$ -catenin

## Protein Kinases

I $\kappa$ B $\alpha$  kinase  
EGFR  
HER2  
AKT  
JAK2  
TYK2  
JNK  
PKC  
Src  
PKA

## Enzymes

FTPase  
Xanthine oxidase  
Hemeoxygenase  
uPA  
GST  
GSH-px

# Clinical studies with curcumin in human subjects

Study	Patients	Dose	Comments	Ref.
Double blind, cross-over	18 pts. (22-48 yrs)	1200 mg /day x 2wks	Antirheumatic	Deodar et al (1980)
	46 male pts. (15-68)	400 mg; 3x/day x5 days	Inguinal hernia	Satosakar etal (1986)
	111 pts. (40-85yrs.)	Topical	HNSCC, Breast Vulva, Skin	Kuttan etal 1987
	10 volun.	500 mg/day x7 days	Serum cholesterol & LPO	Soni & Kuttan (1992)
	40 pts.	625 mg; 4x/day x 8 wks	well-tolerated	James (1994)
	53 pts.	375 mg; 3x/day x12 wks	Chronic anterior uveitis	Lal etal (1999)
	8 pts.	375 mg; 3x/day 6-22 months	Idiopathic inflamm. orbital pseudotumors	Lal etal (2000)
Prospective Phase I	25 pts.	500 mg-12,000mg/day x3 months	H&N cancers	Cheng etal (2001)
	15 pts.	36-180 mg 4 months	Colorectal Serum GST-down	Sharma etal (2001)

# Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions.

Cheng AL, et al Anticancer Res. 2001 Jul-Aug;21(4B):2895-900.

➤ Tested on **25 pts** (13 men & 12 women) with a median age of 60 yrs (36-77)

➤ Curcumin was administered orally **8000 mg/day**

➤ Patients	No.	Histological response
Recently resected bladder cancer;	2	1/2
Oral leukoplakia,	7	2/7
Intestinal metaplasia of the stomach;	6	1/6
CIN	4	1/4
Bowen's disease	6	2/6

➤ All pts (except 2) completed **3 months** treatment regimen

➤ Peak serum conc. of curcumin at 1-2 h after oral intake was **0.4-1.6 uM**

➤ **Conclusion:**

Curcumin is not toxic to humans even at the high dose (8000 mg/day).



# Influence of piperine (Trikatu) on the pharmacokinetics of curcumin in animals and human volunteers

Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS.

Planta Med. 1998;64:353-6.

- Due to its rapid metabolism in the liver and intestinal wall curcumin has **poor bioavailability**.
- Piperine, an inhibitor of hepatic and intestinal glucuronidation, enhances the bioavailability of curcumin in rats and healthy human volunteers.
- In rats, a dose of 2g/kg curcumin, gave moderate serum levels over 4 h period, but combining with piperine 20 mg/kg increased the **bioavailability by 154%**.
- In humans, at dose of 2 g curcumin, serum levels were undetectable , but concomitant with piperine 20 mg, **increased the bioavailability by 2000%**.
- Conclusion: Piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects

# Sources of curcumin (60-98%)

## Human use:

**Sabinsa** ([http://www.sabinsa.com/products/circumin\\_book.htm](http://www.sabinsa.com/products/circumin_book.htm); Piscataway, NJ)

**Kalsec** ([http://www.kalsec.com/products/turmeric\\_over.cfm](http://www.kalsec.com/products/turmeric_over.cfm); Kalamazoo, MI )

**Life Extension** (<http://www.lef.org/newshop/items/item00552.html?source=WebProtProd> )

**Turmeric Curcumin** (<http://www.turmeric-curcumin.com/>)

**Iherb** (<http://www.iherb.com/curcumin1.html>)

**Club Natural** (<http://www.clubnatural.com/curex9550180.html>, Irvine, California)

**American Nutrition** ([www.AmericanNutrition.com](http://www.AmericanNutrition.com))

**Amerifit** ([www.amerifit.geomerx.com/items/categories.cfm?categoryid=2](http://www.amerifit.geomerx.com/items/categories.cfm?categoryid=2), Bloomfield, CT);

**XKMS** ([www.xkms.org/WebVitamins-32/Curcumin-Power-60C.htm](http://www.xkms.org/WebVitamins-32/Curcumin-Power-60C.htm));

**Immune Support** (<https://www.Immunesupport.com/shop/prodlisting.cfm?NOTE=NOC>);

**Nature's** ([www.naturesnutrition.com/SKU/55114.htm](http://www.naturesnutrition.com/SKU/55114.htm))

**Big Fitness** ([www.bfwse.com/jr-021.html](http://www.bfwse.com/jr-021.html))

**Powerhouse Gym** (<http://store.yahoo.com/musclespot/curcumin95.html>), MMS

**MMS Pro** (<http://www.mmspro.com/>.)

**Herbal Fields** (<http://www.herbalfields.com/curcumin.html>)

## Research use:

**Sigma Aldrich**

([http://www.sigmaaldrich.com/cgi-bin/hsrun/Distributed/HahtShop/HAHTpage/HS\\_CatalogSearch](http://www.sigmaaldrich.com/cgi-bin/hsrun/Distributed/HahtShop/HAHTpage/HS_CatalogSearch))

**Calbiochem** ([http://www.calbiochem.com/Products/ProductDetail\\_CBCB.asp?catNO=239802](http://www.calbiochem.com/Products/ProductDetail_CBCB.asp?catNO=239802))

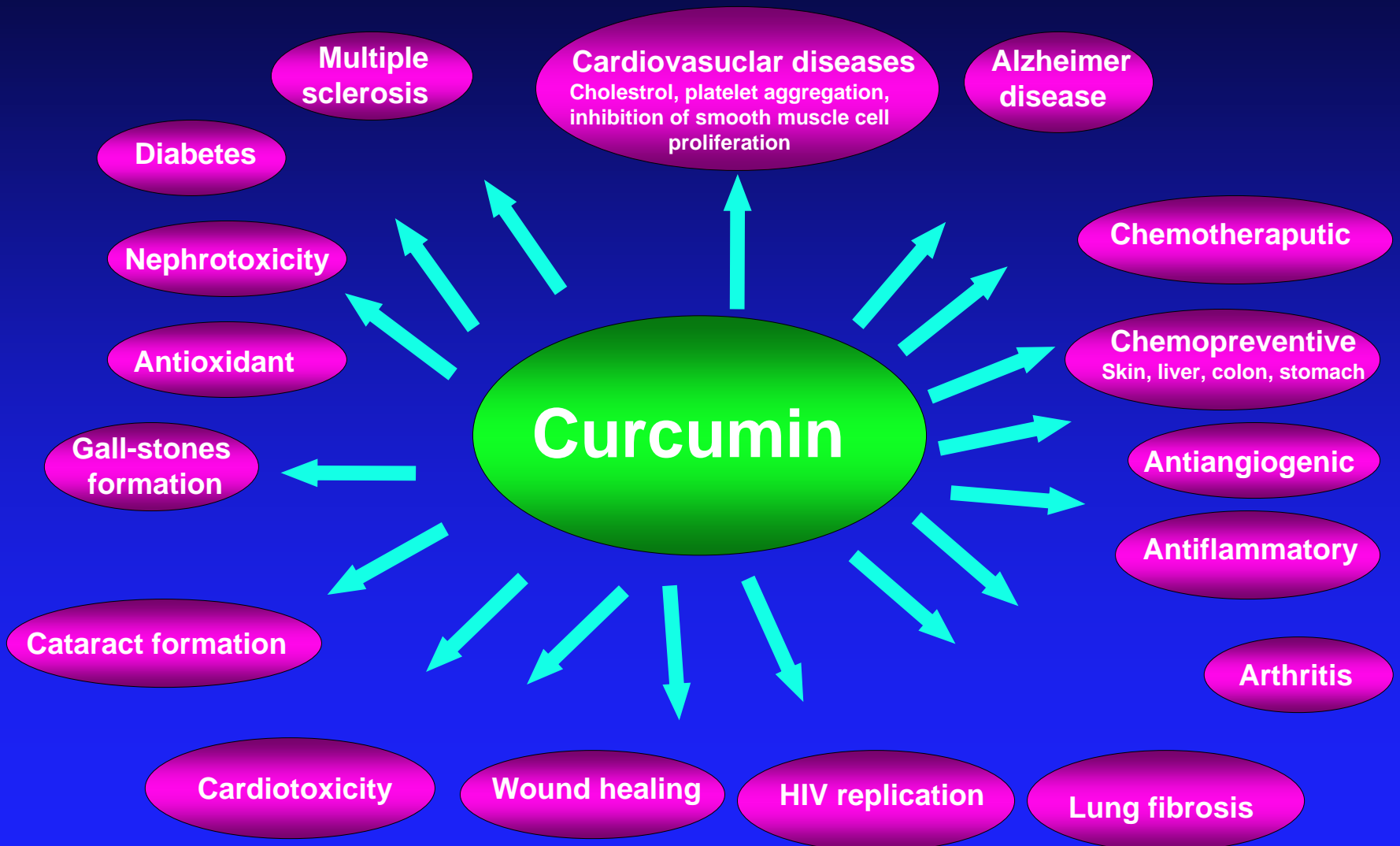
**LKT laboratories.** ([www.lkmlabs.com](http://www.lkmlabs.com))

# **Anticancer potential of curcumin: preclinical and clinical studies**

*Aggarwal BB, Kumar A, Bharti AC.*

*Anticancer Res. 2003 Jan-Feb;23(1A):363-98.  
Review.*

# Therapeutic potential of curcumin



# Hypothesis!

**NF- $\kappa$ B activation mediates  
carcinogenesis/  
tumorigenesis and  
inhibition of NF- $\kappa$ B  
activation suppresses  
tumorigenesis**

# Turmeric can reduce radiotherapy-induced side-effects (Date :10/15/2002)

- Close on the heels of the report regarding the effectiveness of turmeric curcumin in treating radiation therapy burns, an **Oxford University** scientist at the Research Institute of Oxford's Churchill Hospital has invented a new non-toxic compound therapy, based on turmeric, which has shown positive results in the treatment of radiotherapy-induced side effects.
- More than **50% of cancer patients** receive radiotherapy at one stage in their course of treatment, and normal tissue damage is the most important limiting factor in using this method. A particular side effect of the treatment of **head and neck cancers** is a disorder known as **mucositis**, where the lining of the mouth becomes inflamed and can disintegrate altogether. This can be an extremely painful and debilitating problem for patients who may quickly be forced to forgo solid food.
- Other possible side effects of radiotherapy are **damage to the spinal chord**, possibly leading to paralysis, and damage to the brain which can cause dementia. At present there is no standard treatment for these disorders and the damage caused will often lead to a reduction in the dose of the radiation that may be administered, thereby affecting its efficacy.
- Now a **combination therapy** has been identified that significantly reduces the incidence and shortens the duration of **radiation-induced mucositis**. The therapy has been studied in a biological model and in this model its effectiveness was startling, according to the research. It has also shown efficacy in **preventing central nervous system and skin damage**. Furthermore, as the compound is non-toxic, quick advancement to the clinical trial stage is possible.

# Turmeric good for Radiation Burn

Date :10/10/2002

- Researchers in the United States have found that turmeric, a spicy ingredient in many curries, and widely used in Asian cuisines, may **prevent skin blistering and redness** associated with **cancer radiation therapy**.
- The compound, which gives the spice turmeric its yellow color, was effective in tests on mice. Turmeric is found in everything from mild Kormas to the hottest Vindaloos. The crucial chemical - curcumin - has long been used as a traditional medicine. It is now being investigated for the treatment of **colon cancer and Alzheimer`s disease as well as burns**. The spice is thought to work as an anti-inflammatory agent. It is said to have a number of other health benefits as well, such as aiding digestion and helping fight infection.
- In the latest study, a team at the **University of Rochester`s** Wilmot Cancer Center tested the ingredient on 200 mice. Mice given curcumin had fewer blisters and burns after a single dose of radiation, said **Dr Ivan Ding**, who helped carry out the study.
- The authors of the US study however, warn that curcumin must be tested in other animals, and then in people, before it is accepted as valid. **Professor Andy Gescher of the department of Oncology at Leicester University, UK**, is part of a team testing **curcumin capsules on colon cancer** sufferers. He believes there is anecdotal evidence to suggest that members of the Asian community in the city may be better able to resist colon cancer because they use the spice in cooking.

# Common Spice May Protect Skin During Radiation Therapy for Cancer

10/07/2002 ; Leslie White; (585) 273-1119; leslie\_white@urmc.rochester.edu

Cancer researchers at the University of Rochester Medical Center have found that curcumin, a substance in curry long believed to have health benefits, seems to protect skin during radiation therapy. Doctors say that while further study is needed, cancer patients could consider eating foods with curry during their radiation treatment.

Curcumin, the substance that gives turmeric its yellow color, is a natural anti-inflammatory compound and scientists have already shown that it can suppress tumor blood vessel growth. This process, called anti-angiogenesis, can strangle tumors. Now, James P. Wilmot Cancer Center researchers have discovered through a study of mice that curcumin may protect skin from the burns and blisters that often occur during radiation treatment.

“This is significant because skin damage is a real problem for patients undergoing radiation to treat their tumors. If a non-toxic, natural substance can help prevent this damage and enhance the effectiveness of our radiation, that’s a winning situation,” said Paul Okunieff, M.D., chief of radiation oncology at the Wilmot Cancer Center. Scientists presented results of the pilot study at the 44th annual meeting of the American Society for Therapeutic Radiology and Oncology on Monday, Oct. 7, in New Orleans. The team of researchers, led by Ivan Ding, M.D., assistant professor of radiation oncology, studied the impact of various doses of curcumin on skin protection in mice given radiation therapy. The difference in skin damage was dramatic. “There were far fewer blisters or burns on the mice who had been given curcumin,” Ding said.

In the study, 200 mice were given three different doses of curcumin for five to seven days. On the fifth day, mice were given a single dose of radiation and scientists waited 20 days to assess skin damage. The mice who received curcumin had minimal skin damage caused by radiation. Scientists also found the substance suppresses development of new cells in the area of tumor, thus furthering the effectiveness of radiation. While doctors are not ready to say that curcumin is the answer to preventing skin damage, researchers believe the results demonstrate the need for more extensive study. Researchers plan further scrutiny of curcumin and combinations with other anti-inflammatory compounds to determine what could be the best way to prevent skin damage, Ding said.

“Nearly all cancer patients who get radiation treatment experience some form of skin damage – from mild sunburn all the way to blisters – that is painful for many,” Okunieff said. “If we can find a simple way to help prevent that, it would make treatment a bit easier.”



# Turmeric may help inhibit tumor growth

Date :10/12/2002

- Close on the heels of the discovery that curcumin, a compound found in turmeric, may prevent skin blistering and redness associated with cancer radiation therapy, researchers at the **Kumamoto University** in Japan have now found that the compound may be capable of working as a potent agent that reduces tumor promotion in the body.
- The study showed that curcumin **suppresses production of a protein, interleukin-8 (IL-8)**, that spurs tumor growth in the body.
- The researchers mixed **human pancreatic cancer cells** with different amounts of curcumin. It was found that curcumin inhibited the production of IL-8, a protein that attracts white blood cells to a particular site and leads to inflammation. Curcumin also reduced the activity of **NF-kappaB**, a molecule that helps regulate the gene that produces IL-8.
- While tumor cells are known to secrete high levels of inflammation-promoting proteins like IL-8, the exact role of these proteins in cancer is unclear. Previous research suggests that the compounds (proteins) may spur the proliferation of tumor cells and suppress the immune system. “Regardless of the mechanism, controlling levels of these compounds (proteins) may have an important role in therapy for patients with malignant disease,” **Dr. Hideki Hidaka** and his colleagues from the University conclude.

# Spice that stems liver disease caused by liquor

Washington, Mar 20 (ANI): A new study has found that a **curcumin, an essential ingredient of curry, prevents alcohol-related liver damage.**

The study on **rats** has found that the substance that gives the spice turmeric its distinctive yellow colour, stopped the changes caused by excessive alcohol consumption that lead to liver disease.

The research, published in **American Journal of Physiology - Gastrointestinal and Liver Physiology**, adds to the repertoire of benefits already shown by curcumin, which include anti-oxidant properties and anti-cancer activity. However, it does not mean that people eating curries can safely drink more alcohol, warns **Kalle Jokelainen**, one of the team of Finnish and American researchers.

"Curcumin is not harmful, and it may protect your liver from liver disease if you have very high amounts - but this has only been seen in rats," he says.

For the study, the team gave rats **fish oil with either ethanol** or dextrose added for four weeks. The rats that also received doses of **curcumin did not develop the fatty livers**, necrosis and inflammation seen in those not given the spice extract.

Furthermore, the doses used in the experiments were much greater than would ever be used in cooking with turmeric, he says. Alcoholic liver disease is a serious problem, he says, but the answer is to drink less.

Jokelainen, at **Helsinki University Central Hospital**, said that curcumin somehow blocks the activation of a key molecule called **NFkB**.

This molecule directs the chain of events that leads to inflammation and death of tissue. It is activated by many stimuli including radiation, heat shock and endotoxins - the toxins associated with bacteria.

"If you drink too much, that leads to **leaky gut syndrome**," Jokelainen told New Scientist.

"Somehow **endotoxins** from the gut reach the blood and are carried to the liver. The liver is a filter and inactivates the endotoxin, but the price paid is that **NFkB** is activated." (ANI)

# More evidence curry ingredient may fight cancer

2003-03-13 10:00:26 -0400 ; By Alison McCook

NEW YORK (Reuters Health) - An ingredient in the curry spice turmeric may help suppress and destroy a blood cancer, early lab research shows--suggesting yet another health benefit from this long-heralded substance. Turmeric is a common ingredient in Indian food and yellow mustard. Its active ingredient is curcumin, which gives turmeric its yellow color. Adding curcumin to human cells with the blood cancer [multiple myeloma](#), [Dr. Bharat B. Aggarwal of the University of Texas MD Anderson Cancer Center in Houston](#) and his colleagues found, stopped the cells from replicating. And the cells that were left died. Although the study did not test the benefits of curcumin in patients, previous research has shown the substance may fight other types of cancers, Aggarwal told Reuters Health. Studies have also shown that curcumin, even in large quantities, does not produce any known side effects in humans, the researcher noted. Based on this evidence, Aggarwal recommended that people with cancer should try to eat more curcumin, if possible. "Whichever way you can take it, as much as possible," he said. Aggarwal added, however, that further research is needed to determine how much curcumin people need to get the most benefits. Previous laboratory research has shown that curcumin may have antioxidant and anti-inflammatory properties, as well as treat and prevent cancer. Studies in the lab and in animals also suggest that the compound might help [heal wounds](#) and fight [Alzheimer's disease](#) and [multiple sclerosis](#). Patients with multiple myeloma are in particular need of new treatments, Aggarwal and his colleagues point out in their report in the journal *Blood*. Once diagnosed with this blood cancer, patients typically live between [two and three years](#). During the current study, the researchers added curcumin to a sample of human cells with multiple myeloma, and observed how the substance influenced the progression of the cancer. In an interview, Aggarwal explained that curcumin appears to block the activity of a "light switch" called [nuclear factor kappa-B \(NF-kappaB\)](#). When turned on, he said, NF-kappaB appears to then turn on many genes linked to cancer. Examining the multiple myeloma cells before adding the curcumin, the authors found that virtually all contained activated forms of NF-kappaB. After adding curcumin, however, NF-kappaB activity was inhibited, the multiple myeloma cells no longer replicated and the remaining cells died, Aggarwal said. Aggarwal explained that it is somewhat difficult to study the effects of curcumin in a large number of patients because these experiments cost a lot of money. Funding for similar research is often provided by a company that stands to benefit if the tested treatment works; however, in the case of curcumin, a natural compound, no company can reap the benefits if turmeric shows itself to be an effective anti-cancer drug, he said. However, Aggarwal said that he hopes the new findings and previous research suggesting curcumin's benefits inspire other researchers to continue investigating its properties. If curcumin is, in fact, an effective and safe treatment for cancer, studying it further can only be a "win-win situation," Aggarwal predicted.

SOURCE: [Blood 2003;101:1053-1062.](#)

# Leading Pigment in a Common Indian Spice Can Prevent Onset of Alcoholic Liver Disease, Study Finds

Donna Krupa: 703.527.7357; Cell: 703.967.2751 or [djkrupa1@aol.com](mailto:djkrupa1@aol.com)

The yellow substance found in the pigment for curry prevents activation of a genetic factor leading to liver inflammation and necrosis.

Source: February 2003 edition of the *American Journal of Physiology—Gastrointestinal and Liver Physiology*.

The authors of “Curcumin Prevents Alcohol-Induced Liver Disease in Rats by Inhibiting the Expression of NF-KB-Dependent Genes,” are Amin A. Nanji, from the University of Pennsylvania Medical Center, Philadelphia, PA; Kalle Jokelainen, at the Helsinki University Central Hospital, Helsinki, Finland; George L. Tipoe, from the University of Hong Kong, Hong Kong; Amir Rahemtulla, from the Harvard Medical School, Boston, MA; Peter Thomas, from the Boston University School of Medicine in Boston; and Andrew J. Dannenberg from the Weill Medical College of Cornell University and Anne Fisher Nutrition Center at the Strang Cancer Prevention Center, New York, NY.

## **A little more than what grandma said: Haldi might keep cancer away Mumbai lab to launch human trials as part of global effort under the aegis of National Institute of Health, USA** Reshma Patil

Mumbai, January 15: Can eating a little bit of haldi every day keep cancer away? Could the next cancer drug be stirred in spoonfuls of curry? Well, turmeric is grandma's home remedy for everything from cold to injuries. Now the humble Indian spice is being tested in differing fashions in two national laboratories — with stunning results — against cancer. “Turmeric shows a lot of promise in delaying the onset of cancer,” says **Girish Maru, head of the carcinogenesis division at Mumbai's Tata Memorial Centre**. TMC is one of eight global centres where human trials with a constituent of turmeric are about to be launched. It all starts from the cages of Swiss Albino mice at a TMC lab. When the groups of five mice scurrying around their cages are thirsty, they **sip water laced with curcumin** — an anti-oxidant and anti-inflammatory yellow pigment that makes up nearly **five per cent of turmeric**. The mice have been exposed to carcinogens and the curcumin diet continues for several weeks before, during and after carcinogen exposure. The result: “**A remarkable decrease in tumour incidence and multiplicity**” for stomach, colon, skin, liver and breast cancer, says Maru.

The human trials in Mumbai will focus on the prevention of **oral cancer in “several thousand” active and passive smokers** — the mice have also been exposed to chemicals that mimic diesel exhaust or tobacco smoke.

These trials on cancer survivors, patients and volunteers across the globe come under the aegis of the **National Institute of Health (NIH) in the US**. American backing came last year, **a decade after** Tata scientists first started probing cheap turmeric brought from the markets. For now, it isn't clear what form anti-cancer turmeric medication might take if the trials succeed. Maybe a **turmeric lozenge** popped every day to keep cancer away. Or **turmeric paste** applied inside the cheeks on pre-malignant patches of **leukoplakia** in reverse smokers — as it's done at the **National Institute of Nutrition (NIN) in Hyderabad**.

## **A little more than what grandma said: Haldi might keep cancer away Mumbai lab to launch human trials as part of global effort under the aegis of National Institute of Health, USA** Reshma Patil

Mumbai, January 15: “Our studies on mice and humans over the last 8-10 years have shown potential biological activity in turmeric to prevent cancer,” former NIN director **Kamala Krishnaswamy** told The Indian Express. She’s not worried about US competition. “Whole turmeric ingested through diet is better for cancer prevention than isolated curcumin. Of course, if USA develops a drug, nobody in India will take it. They could just eat 1-2 gm haldi every day,” she says. Before Mumbai’s clinical trials can begin, the 20-member Tata team headed by Maru, who has devoted the last 12 years to chemoprevention, is busy developing bio markers funded by the Indian Council of Medical Research (ICMR). The three-year development period started 2002 and markers will verify doses taken by volunteers. “People may be **unwilling to apply turmeric paste inside the mouth** because of staining, so we have to work out doses and alternative methods,” says Maru. Time is running out and competition is keen. International research backs Indian advances. “Doctors say that while future study is needed, **cancer patients should consider eating food with curry during their radiation treatment**,” the **University of Rochester** announced last October, pleased with the health of 200 mice fed a diet of curcumin. “Curcumin is a substance in curry long believed to have health benefits. It seems to protect skin during radiation therapy,” says the university’s research posted online.

The **Ohio State University of Columbus** has also posted exciting reports that turmeric has “demonstrated anti-cancer effects at all stages of tumor development in rodents and showed **potential to kill cancer cells and prevent normal cells from being cancerous.**”

# Curry Spice May Inhibit Tumor Growth

**NEW YORK OCT 08, 2002 (Reuters Health) - A compound found in the curry spice turmeric may suppress production of a protein that spurs tumor growth in the body, researchers report.**

**According to their study, curcumin inhibited the production of interleukin-8 (IL-8), a protein that attracts white blood cells to a particular site and leads to inflammation. The compound also reduced the activity of NF-kappaB, a molecule that helps regulate the gene that produces IL-8.**

**While tumor cells are known to secrete high levels of inflammation-promoting proteins like IL-8, the exact role of these proteins in cancer is unclear. Previous research suggests that the compounds may spur the proliferation of tumor cells and suppress the immune system.**

**Regardless of the mechanism, controlling levels of these compounds "may have an important role in therapy for patients with malignant disease," Dr. Hideki Hidaka from Kumamoto University in Kumamoto, Japan and colleagues conclude.**

**The researchers mixed human pancreatic cancer cells with different amounts of curcumin, which is the substance that gives turmeric its yellow color. The production of IL-8 and the activity of NF-kB fell with increasing doses of curcumin.**

**If the spice component does indeed reduce IL-8 activities as the findings suggest, "curcumin is capable of working as a potent agent that reduces tumor promotion," the researchers conclude.**

**The study, in a recent issue of the journal Cancer, is not the first to link curcumin, a compound thought to be a potent anti-inflammatory agent, with certain health benefits. Studies also suggest that the compound might help heal wounds and fight Alzheimer's disease and multiple sclerosis.**

**\* Cancer 2002;95:1206-1214.**

# The British are investigating the possible connection between curcumin and treatment for Alzheimer's disease. Anything to this?

Richard Bray (Published 06/12/2002)

The Brits aren't alone in this effort. Researchers here in the United States have been pursuing clues to the effects of curcumin, a compound found in the spice turmeric that is responsible for the yellow color of Indian curry and American mustard. Studies show that elderly villagers in India appear to have the lowest rate of Alzheimer's disease in the world. Researchers speculate that curcumin, which has powerful antioxidant and anti-inflammatory properties might play a role, because Indians eat turmeric with almost every meal.

In a recent study at the University of California at Los Angeles, scientists fed curcumin to rats prone to accumulate beta-amyloid plaque in their brains – the abnormality associated with Alzheimer's disease in humans. Curcumin blocked the accumulation of beta-amyloid plaque and also appeared to reduce inflammation related to Alzheimer's disease in neurologic tissue. The rats fed curcumin also performed better on memory tests than rats on normal diets.

The UCLA study isn't the only one that suggests that curcumin might prove helpful for treatment and prevention of Alzheimer's. Researchers at the University of Illinois have also found that it helps prevent plaque formation. And preliminary studies at Vanderbilt University suggest that curcumin may block the progression of multiple sclerosis. Mice with an MS-like illness showed little or no signs of disease after being injected with curcumin, while their untreated counterparts went on to severe paralysis. New research from Japan also suggests that turmeric may help prevent colitis, an inflammation of the colon.

My friend Paul Schulick of New Chapter, Inc., who brought me up to speed on the latest curcumin research, tells me that only low dose curcumin reduced plaque in the Alzheimer's disease studies. This is good news since it suggests that curcumin is most effective at doses well below pharmaceutical strength. Schulick also emphasizes that turmeric contains many other compounds besides curcumin and points out that people in India consume the whole spice not an isolated element. Turmeric appears to have significant anti-inflammatory and cancer-protective effects as well, so I think it is good to find ways to include it in our diets.



# Important substance in curry conciliate Inflamed Colon

Medindia Health News June 9, 2002

According to a research, on laboratory animals, the curry spice turmeric may help reduce and even prevent inflammation of the intestines. The spice contains curcumin, a compound thought to be a potent anti-inflammatory agent effective in wound healing.

Dr. Ken Sugimoto, of the department of internal medicine at the Hamamatsu University School of Medicine, Japan, showed that curcumin can improve experimental colitis. The researchers induced severe colitis, or colon inflammation, in mice using a chemical and immediately gave the mice a diet containing 1% to 2% curcumin for a week. The mice are used to study inflammatory bowel disease, a group of conditions in humans that can result in intestinal inflammation, cramping and chronic diarrhea.

The researchers also gave some of the mice a 2% diet of curcumin before the colitis was induced, in order to see whether the compound had a preventive effect, and 2 days after colitis was induced, to see whether the substance had healing powers if administered at a later point. The mice who received no curcumin had a 30% death rate due to colitis.

# Curry Spice May Slow Multiple Sclerosis Progression

Interest in the potential neuroprotective properties of curcumin rose after studies found very low levels of neurological diseases, such as Alzheimer's disease, in elderly Indian populations. Added to this were studies confirming curcumin as a potent anti-inflammatory agent, effective in wound healing. And just last fall, researchers at the University of California, Los Angeles reported that curcumin appeared to slow the progression of Alzheimer's disease in mice. Preliminary studies in mice suggest that curcumin, a compound found in the curry spice turmeric, may block the progression of multiple sclerosis (MS). Dr. Chandramohan Natarajan, of Vanderbilt University in Nashville, Tennessee, observed that mice injected with curcumin showed little or no disease symptoms, while untreated animals went on to develop severe paralysis.

"We got a very good inhibition of the disease by treating with curcumin," Dr. Natarajan told Reuters Health. He presented the findings here Tuesday at the annual Experimental Biology 2002 conference. In their 30-day study, Dr. Natarajan and co-researcher Dr. John Bright administered 50- and 100-microgram doses of curcumin, three times per week, to a group of mice bred to develop experimental autoimmune encephalomyelitis (EAE). They then monitored the mice for signs of MS-like neurological impairment.

In contrast, mice given the 50-microgram dose of the curry compound showed only minor symptoms, such as a temporarily stiff tail. And mice given the 100-microgram dose appeared completely unimpaired throughout the 30 days of the study. The results did not surprise Dr. Natarajan. In Asian countries, such as India and China, where people eat more spicy foods and more yellow compounds like curcumin, reports of MS are "very, very rare," he pointed out. He said the doses the mice received were roughly equivalent in human terms to those found in a typical Indian diet.

Just how curcumin might work to thwart the progression of demyelination remains unclear. But the Nashville researchers believe it may interrupt the production of IL-12, which plays a key role in signaling immune cells to attack the myelin sheath. Dr. Natarajan stressed that "we have to do a lot of work on this," including examining other potential mechanisms by which curcumin slows EAE and, potentially, MS. The work remains preliminary, and MS patients should follow their doctor's advice when it comes to treating the disease. Still, Dr. Natarajan said adding a little curry to the diet couldn't hurt. "I think using this spice in their food could be of help," he said.

# "Nuclear Factors Associated with Transcriptional Regulation"

(No. 6,410,516), June 25th, 2002

<http://164.195.100.11/net/html/srchnum.htm> or <http://www.ariad.com/patents>

**Selected NF- $\kappa$ B scientific papers is also available at**

[http://www.ariad.com/related\\_resources](http://www.ariad.com/related_resources).

Three patents in the U.S. and one in Europe, awarded. The latest patent includes **203 claims** and provides coverage relating to NF- $\kappa$ B treatment methods through the year **2019**.

NF- $\kappa$ B can be generally thought of as a "biological switch" that can be turned off in cells to treat these diseases. The activity of NF- $\kappa$ B has been implicated in **atherosclerosis, arthritis, inflammatory bowel disease, rheumatoid arthritis, and septic shock, malignant transformation and tumor growth (e.g., certain blood cancers and solid tumors), and bone breakdown and rebuilding (e.g., osteoporosis).**

NF- $\kappa$ B inventors include **Drs. David Baltimore, Phillip Sharp, Thomas Maniatis, Patrick Baeuerle, Albert Baldwin, Roger Clerc, Lynn Corcoran, Chen-Ming Fan, Jonathan LeBowitz, Michael Lenardo, Ranjan Sen, Harinder Singh, and Louis Staudt.**

## **ARIAD NF- $\kappa$ B drug targets:**

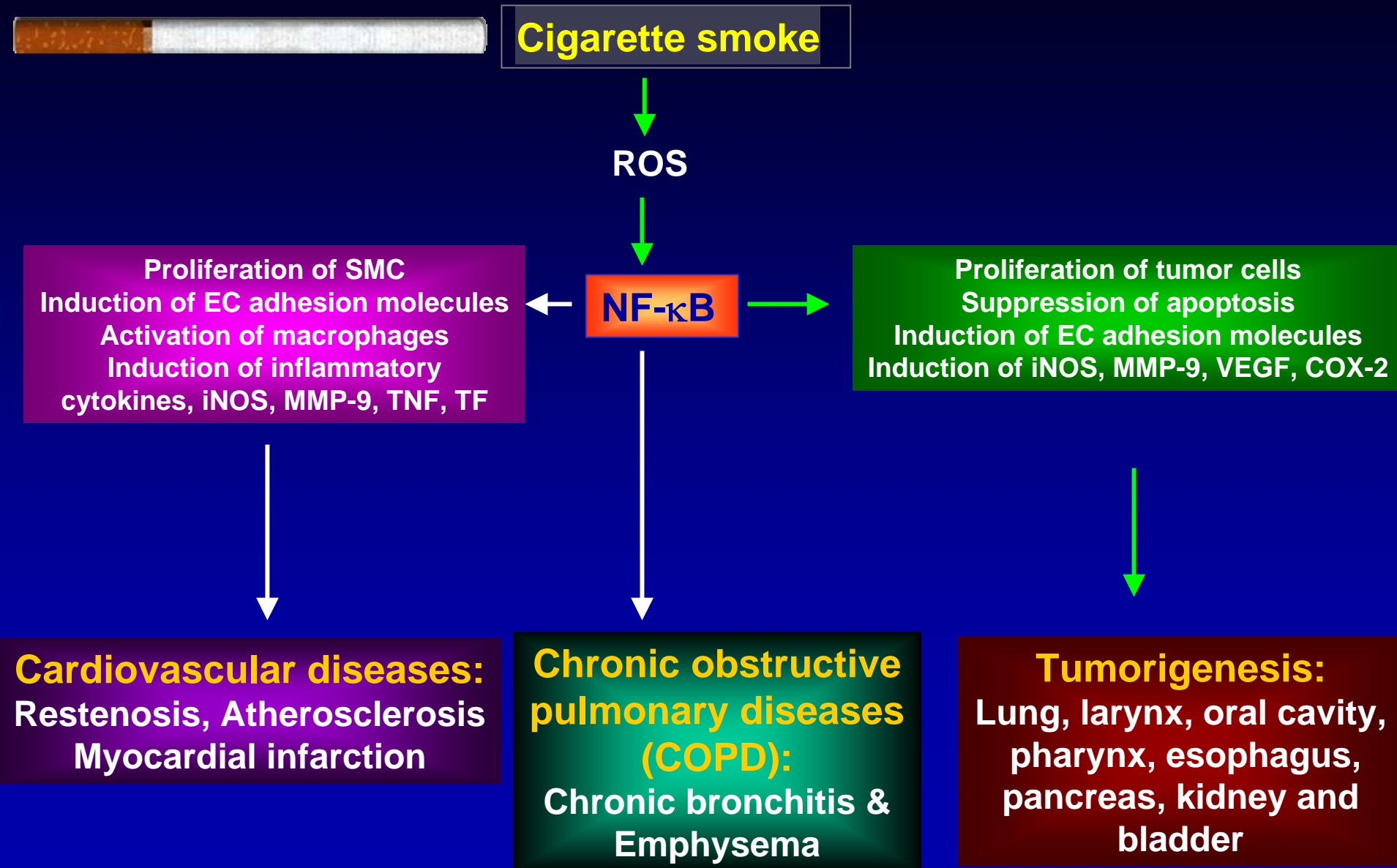
- Controls cell proliferation and nutrient uptake by tumors to treat cancer.**
- Bone-targeted drug candidate to treat the complications of cancer that has spread to bone.**
- Regulated protein therapy product candidate to treat anemia in which the production of erythropoietin is controlled in vivo using an orally administered drug.**
- T cell immunotherapy product candidate in which a non-immunosuppressive drug may be used to treat graft-vs-host disease following donor bone marrow transplantation - a therapy for cancer and other immune and blood diseases**
- Dual-action drug candidates that block bone resorption and stimulate bone formation to treat osteoporosis.**

# Cancers incidence comparison between developed countries (USA) and developing countries (India) (1983-1987)

<b>Cancer</b> (Rates per 100,000)		<b>United States</b>	<b>India</b>
<b>Prostate</b>	<b>(Men)</b>	<b>61.8</b>	<b>6.9</b>
<b>Breast</b>	<b>(Women)</b>	<b>89.2</b>	<b>24.6</b>
<b>Colon/rectum</b>	<b>(Men)</b>	<b>46.3</b>	<b>6.4</b>
	<b>(Women)</b>	<b>33.2</b>	<b>5.1</b>
<b>Stomach</b>	<b>(Men)</b>	<b>8.0</b>	<b>7.3</b>
	<b>(Women)</b>	<b>3.5</b>	<b>4.3</b>
<b>Lung</b>	<b>(Men)</b>	<b>64.3</b>	<b>14.0</b>
	<b>(Women)</b>	<b>29.9</b>	<b>3.0</b>
<b>Oesophagus</b>	<b>(Men)</b>	<b>4.0</b>	<b>11.4</b>
	<b>(Women)</b>	<b>1.3</b>	<b>8.4</b>

*Source: Food, Nutrition and the Prevention of Cancer: a global perspectives by American Institute for Cancer Research, 1997*

# Working Model for Cigarette Smoke-Induced Damage



# **Why NF- $\kappa$ B is a good targets for cancer drug development?**

**Activation of NF- $\kappa$ B blocks apoptosis and mediates tumor cell proliferation**





**Tumor cells frequently express constitutively activated form of NF- $\kappa$ B**

**Tumor microenvironment can induce NF- $\kappa$ B activation**

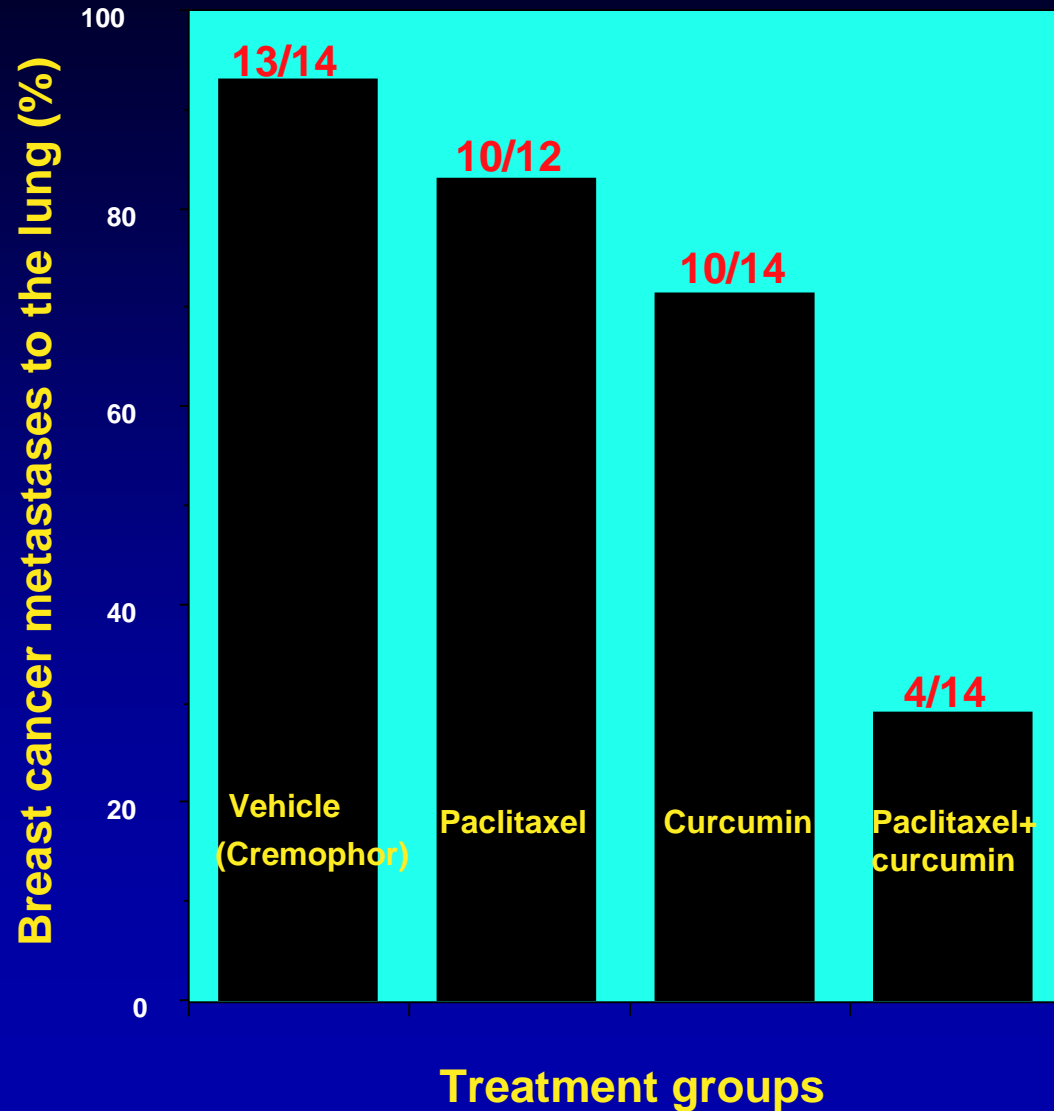
**NF- $\kappa$ B activation induces resistance to chemotherapeutic agents**

**Several genes involved in tumor initiation, promotion, and metastasis are regulated by NF- $\kappa$ B.**

# Curcumin potentiates the effect of paclitaxel by inhibiting the metastasis of the human breast cancer to the lung in mouse xenograft model

- ❖ Inject mammary fat pad of female nude mice with human breast cancer cells (MDA-MB-435, 2 million cells)
- ❖ Allow the tumors to reach to palpable size (10 mm mean diameter)
- ❖ Anesthetize the mice and resect the tumors and close the skin incisions
- ❖ Then randomize the mice into four treatment groups to receive:
  1. Control diet (vehicle injection, i.p.) 
  2. Curcumin diet, (vehicle injection, i.p.) 
  3. Control diet, paclitaxel (10 mg/kg, i.p.) 
  4. Curcumin diet, paclitaxel (10 mg/kg, i.p.) 
- ❖ Paclitaxel was injected on day 10, 17 and 24 after tumor removal
- ❖ Animals were given diet containing 2% curcumin (w/w) 5 day after tumor removal
- ❖ Five weeks after tumor removal, mice were killed and incidence of metastases to the lung and other organs was recorded

# Curcumin potentiates the effect of paclitaxel by suppressing the metastasis of the human breast cancer to the lung in mouse xenograft model





**Does curcumin enhances the effect of paclitaxel by inhibiting the metastasis of the human breast cancer to the lung in mouse xenograft model?**

*Aggarwal B. B, Shishodia S., Banerjee S., Newman R., Bueso-Ramos C. and Price J.*

*(manuscript in prepration)*

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# Treatment of human multiple myeloma by curcumin

(filed 5/30/02)

# Curcumin, analogues of curcumin and novel uses thereof.

Aggarwal, B.B. as inventor(s).

*International Publication No. WO95/18606, date 7/13/95.*