Targets Inflammatory Pathways by Dietary Spices For Prevention and Treatment of Cancer

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(Talk on Nov 5th; 2:10-2:40 PM)
Molecular Targets of Nutraceuticals Derived from Dietary Spices: Potential Role in Suppression of Inflammation and Tumorigenesis

Aggarwal B, Van Kuiken ME, Iyer LH, Harikumar KB, Sung B

Experimental Biology & Medicine
2009 Jun 2.
Change in the US Death Rates* by Cause, 1950 & 2002

<table>
<thead>
<tr>
<th>Cause</th>
<th>1950 Rate Per 100,000</th>
<th>2002 Rate Per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Diseases</td>
<td>586.8</td>
<td>240.1</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>180.7</td>
<td>56.0</td>
</tr>
<tr>
<td>Pneumonia/Influenza</td>
<td>48.1</td>
<td>22.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>193.9</td>
<td>193.4</td>
</tr>
</tbody>
</table>

* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
Why We're Losing The War On Cancer! And How To Win It?

By Clifton Leaf Additional Reporting Doris Burke
March 22, 2004 (FORTUNE Magazine)

Avastin, Erbitux, Gleevec ... The new wonder drugs might make you think we're finally beating this dreaded scourge. We're not. Here's how to turn the fight around.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cancer</th>
<th>Target</th>
<th>OS (mo)</th>
<th>Year</th>
<th>Cost ($/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erbitux (cetuximab)</td>
<td>SCCHN, CRC</td>
<td>EGFR</td>
<td>1.5</td>
<td>2004</td>
<td>~144,000</td>
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<tr>
<td>Iressa (gefitinib)</td>
<td>NSCLC</td>
<td>EGFR</td>
<td>4.3</td>
<td>2003</td>
<td>~26,000</td>
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<tr>
<td>Tarceva (erlotinib)</td>
<td>NSCLC, PC</td>
<td>EGFR</td>
<td>6.7, 6.4</td>
<td>2004</td>
<td>~43,300</td>
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<tr>
<td>Vectibix (panitumumab)</td>
<td>CRC, NSCLC</td>
<td>EGFR</td>
<td>None</td>
<td>2006</td>
<td>~50,400</td>
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<td>Herceptin (trastuzumab)</td>
<td>Breast cancer</td>
<td>HER2</td>
<td>None</td>
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<td>~69,500</td>
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<td>Tykerb (lapatinib ditosylate)</td>
<td>Breast cancer</td>
<td>HER1/2</td>
<td>None</td>
<td>2007</td>
<td>~44,400</td>
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<tr>
<td>Sutent (sunitinib)</td>
<td>GIST, ARCC</td>
<td>VEGFR</td>
<td>NDA</td>
<td>2006</td>
<td>~48,000</td>
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<tr>
<td>Nexavar (sorafenib)</td>
<td>HCC, RCC</td>
<td>VEGFR</td>
<td>10.7</td>
<td>2005/7</td>
<td>~77,000</td>
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<tr>
<td>Avastin (bevacizumab)</td>
<td>CRC, BC, NSCLC</td>
<td>VEGF</td>
<td>4.7</td>
<td>2004</td>
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<td>Velcade (bortezomib)</td>
<td>MM, MCL</td>
<td>Proteasome</td>
<td>6</td>
<td>2008</td>
<td>~43,500</td>
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<tr>
<td>Gleevec (imatinib)</td>
<td>BP-CML</td>
<td>Bcr-abl</td>
<td>6.5</td>
<td>2001</td>
<td>~61,000</td>
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<td>Sprycel (dasatinib)</td>
<td>ALL, CML</td>
<td>Bcr-abl</td>
<td>N/A</td>
<td>2006</td>
<td>~47,000</td>
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<tr>
<td>Tasigna (nilotinib)</td>
<td>CP-CML</td>
<td>Bcr-abl</td>
<td></td>
<td>2007</td>
<td></td>
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<tr>
<td>Celebrex (celecoxib)</td>
<td>FAP</td>
<td>COX-2</td>
<td></td>
<td></td>
<td></td>
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<td>Rituxan (rituximab)*</td>
<td>NHL</td>
<td>CD20</td>
<td>1.5</td>
<td>1997</td>
<td>~143,000</td>
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<td>Revlimid (lenalidomide)</td>
<td>MM</td>
<td>TNF,</td>
<td></td>
<td>2006</td>
<td>~97,200</td>
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<tr>
<td>Thalomid (thalidomide)</td>
<td>MM</td>
<td>TNF</td>
<td>18</td>
<td>2006</td>
<td>~11-66,000</td>
</tr>
</tbody>
</table>
Today’s Magic bullets or targeted therapies

Cost of treating advanced colorectal cancer patient was $500 in 1999 and $250,000 in 2007

Leonard Saltz, MD
(Memorial Sloan-Kettering cancer Center)
Cancer Is a Preventable Disease That Requires Major Changes in Life Style

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
## Life style and cancer

<table>
<thead>
<tr>
<th>Prostate cancer</th>
<th>per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese from Shanghai</td>
<td>2</td>
</tr>
<tr>
<td>Chinese in USA for five years</td>
<td>23</td>
</tr>
<tr>
<td>Chinese born in USA</td>
<td>37</td>
</tr>
<tr>
<td>Caucasian born in USA</td>
<td>58</td>
</tr>
</tbody>
</table>

*Ho E, 2007; IJC*
Different faces of inflammation and its role in tumorigenesis

**Stress**
(Chemical, physical, and psychological)

**Food Factors**
(Grill, Fried, red meat)

**Environmental pollutants**
(Cigarette smoke, Diesel)

**Viruses**
(HTLV1, HPV, HCV, HBV, EBV)

**Bacteria**
(e.g; Helicobacter pylori)

**Acute inflammation**
- Innate Immunity
- Humoral immunity
- Immune surveillance

**Chronic inflammation**
- Tumor cell survival
- Tumor cell proliferation
- Tumor cell invasion
- Tumor angiogenesis
- Tumor metastasis
- Tumor chemoresistance
- Tumor radioresistance

**Pathological inflammation**

**Reactive oxygen species**
- Tumor necrosis factor
- Interleukin-1
- Interleukin-6
- Interleukin-8
- Interleukin-18

**Nuclear Factor-κB**

**Hypoxia-inducible factor**

**Cyclooxygenase-2**

**5-Lipoxygenase**

**Inducible nitric oxide-synthase**

**Matrix metallo-proteinase-9**

**Chemokines**

**Therapeutic inflammation**

Inflammatory networking in cancer

Survival & Chemoresistance:
c-FLIP, Bcl-x<sub>L</sub>
IAP-1, IAP-2, XIAP, survivin

Proliferation:
Cyclin D1, 5-LOX, COX-2, IL-6

NF-κB

IL-6

STAT 3

Angiogenesis
VEGF

Bone loss
RANKL, IL-1, TNF

Invasion and metastasis
Chemokines

Cross-talk between NF-κB and other transcription factors

Liu G, 2008
Deng J, 2002
Remels, 2009
Webster, 1999
Suzawa, 2003
Du Q, 2009
Role of inflammation in tumorigenesis

**NF-κB**

- DNA damage
- Oncogenes
- Bcl-xI
- Bcl-2
- Survivin
- C-FLIP
- cIAP-1
- cIAP-2
- XIAP
- Cyclin D1
- C-myc
- TNF
- IL-1
- IL-6
- COX2
- MMP-9
- uPA
- ICAM-1
- ELAM-1
- VCAM-1
- VEGF
- CXCR4
- TWIST

**Transformed**

- 10-20 Years
- 10 Years

**Inflammation**
Constitutive activation of NF-κB has been linked with most cancers

- Hodgkin’s disease
- Non-Hodgkin’s lymphoma
- B cell lymphoma
- T cell lymphoma
- Mantle cell lymphoma
- Multiple myeloma

- Acute myelogenous leukemia

- Tobacco-linked cancers
  - Esophageal cancer
  - Laryngeal cancer
  - Pharyngeal cancer
  - Pancreatic cancer
  - Renal carcinoma
  - Colon cancer
  - Head and neck SCC
  - Lung cancer
  - Bladder cancer

- Viral cancers
  - Acute lymphoblastic leukemia
  - Adult T cell leukemia
  - Cervical cancer
  - Nasopharyngeal carcinoma

- UV light
  - Melanoma

Shishodia and Aggarwal, *Biochemical Pharmacology*, 2004
Working Hypothesis

- Stress
- NF-kappaB
- Inflammation
- Cancer
How to suppress NF-κB activation safely!
Inflammation and Cancer

Fig. 3

Pharmaceuticals

Celecoxib

Nutraceuticals
Promiscuity is becoming a virtue in drug development!

(Mencher SK, 2005)
Identification of inhibitors of NF-κB from natural sources
Spices can block NF-κB activation
<table>
<thead>
<tr>
<th>Common Herbs and Spices in America</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardamom</strong></td>
</tr>
<tr>
<td>Amomum subulatum</td>
</tr>
<tr>
<td><strong>Oregano</strong></td>
</tr>
<tr>
<td>Origanum vulgare</td>
</tr>
<tr>
<td><strong>Nutmeg</strong></td>
</tr>
<tr>
<td>Myristica Fragrans</td>
</tr>
<tr>
<td><strong>Red Pepper</strong></td>
</tr>
<tr>
<td>Capsicum frutescens</td>
</tr>
<tr>
<td><strong>Parsley</strong></td>
</tr>
<tr>
<td>Petroselinum crispum</td>
</tr>
<tr>
<td><strong>Basil</strong></td>
</tr>
<tr>
<td>Ocimum basilicum</td>
</tr>
<tr>
<td><strong>Chervil</strong></td>
</tr>
<tr>
<td>Anthriscus cerefolium</td>
</tr>
<tr>
<td><strong>Cinnamon</strong></td>
</tr>
<tr>
<td>Cinnamomum zeylanicum</td>
</tr>
</tbody>
</table>

*Aggarwal et al, 2008*
Spices as NF-κB Inhibitors

- **Capsicum annum** (Red chilli)
  - Capsaicin

- **Curcuma longa** (Turmeric)
  - Curcumin

- **Foeniculum vulgare** (Fennel)
  - Anethole

- **Eugenia caryophyllata** (Cloves)
  - Eugenol

- **T. foenum-graecum** (Fenugreek)
  - Diosgenin

- **Ocimum sanctum** (Holi basil)
  - Ursolic Acid
Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a potent inhibitor of NF-κB activation by diverse agents.


Capsaicin is a novel blocker of constitutive and interleukin-6-inducible STAT3 activation.

Ginger

Zerumbone abolishes NF-κB and IκBα kinase activation leading to suppression of antiapoptotic and metastatic gene expression, upregulation of apoptosis, and downregulation of invasion.

Takada Y, Murakami A, Aggarwal BB.

Zerumbone down-regulates chemokine receptor CXCR4 expression leading to inhibition of CXCL12-induced invasion of breast and pancreatic tumor cells.

Cancer Research. 2008 Nov 1;68(21):8938-44.

Zerumbone abolishes RANKL-induced NF-κB activation, inhibits osteoclastogenesis, and suppresses human breast cancer-induced bone loss in athymic nude mice.

Sung B, Murakami A, Oyajobi BO, Aggarwal BB.
Zerumbone Down-regulates Chemokine Receptor CXCR4 Expression Leading to Inhibition of CXCL12-Induced Invasion of Breast and Pancreatic Tumor Cells

Bokyung Sung,1 Sonia Jhurani,1 Kwang Seok Ahn,1 Yoichi Mastuo,2 Tingfang Yi,3 Sushovan Guha,2 Mingyao Liu,3 and Bharat B. Aggarwal1

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**Image Description:**

**Panel A** shows a comparison of CXCR4 expression levels in different cell lines: Panc1, Panc20, and MIA PaCa-2, with and without ZER treatment. The results indicate a reduction in CXCR4 expression with ZER treatment.

**Panel B** presents a bar graph showing the percent invasion of tumor cells treated with CXCL12 and ZER. The graph indicates a significant reduction in invasion with ZER treatment (*p < 0.05)*.

**Panel D** displays Western blots for CXCR4 and β-actin expression over time (0, 3, 6, 12, 24 hours) with ZER treatment. The blots show a decrease in CXCR4 expression over time with ZER treatment.
Black cumin

Targeting **NF-kB** activation pathway by thymoquinone: role in suppression of **antiapoptotic** gene products and enhancement of apoptosis.

Sethi G, Ahn KS, Aggarwal BB.

Thymoquinone inhibits tumor **angiogenesis** and tumor growth through suppressing **AKT** and extracellular signal-regulated kinase signaling pathways.

Diosgenin inhibits osteoclastogenesis, invasion, and proliferation through the downregulation of Akt, IkB kinase activation and NF-κB-regulated gene expression.

Shishodia S, Aggarwal BB.

Anethole blocks both early and late cellular responses transduced by TNF: effect on NF-κB, AP-1, JNK, MAPKK and apoptosis.

Chainy GB, Manna SK, Chaturvedi MM, Aggarwal BB.

Curcumin: Getting Back to Our Roots!
Structure of Curcumin
From turmeric (curry powder)

Diferuloylmethane
Pharmacology of curcumin

IL-17 in human disease
Discovering GAPCs
Plasticity of adult hippocampal progenitors
Activation of transcription factor Nuclear Factor-kappa B is suppressed by curcumin

Singh S, and Aggarwal BB.

Curcumin Downregulates Expression of Cell Proliferation, Antiapoptotic and Metastatic Gene Products Through Suppression of IκBα Kinase and AKT Activation

Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB.

Molecular Pharmacology
[2006 Jan; 69(1): 195-206]
Curcumin & cancer
Different stages of cancer progression and its suppression by curcumin

Constitutive activation of transcription factors
- AP-1 & NF-κB
- 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

Transformation
Normal cells → Tumor cells

Proliferation
Tumor cells → Tumor growth

Invasion
Tumor growth → Tumor Metastasis

curcumin

From Aggarwal B et al, Anticancer Research 23, 2003, 363-398
Curcumin in cell culture models!
Preclinical data with curcumin against various cancers

- Gastrointestinal cancers (Esophagus, Intestine, Liver, Stomach, Pancreas, Colorectal)
- Genitourinary cancers (Bladder, Kidney, Prostate)
- Brain tumors
- Breast cancer
- Gynecologic cancers (Cervix, Ovary, Uterus)
- Thoracic/ H&N Cancers (Lung, Oral, Thymus)
- Melanoma
- Bone cancer
- Hematological cancers (Leukemia, Lymphoma, Multiple myeloma)

Anand et al., CL, 2008
Modulation of Cell Signaling by Curcumin

TNF → TNFR1 → TRADD → EGFR → EGF → RANKL

TRAF2 → RIP → PI3K → NIK → TRAF6 → RANK

AP-1 → JNK → TAK1 → AKT → PTEN

XIAP → GSK3β → IKK-β → mTOR

Shp-2 → Notch-1

NF-κB (p50-p65)

p50-p65-IκBα → pκBα → Ub-pκBα

Wnt/beta catenin/Tcf

βTrCP

DR5

pκBα

GADD153/CHOP

Ub-pκBα

NF-κB (p50-p65)

p53 PIAS3 STAT3 PPAR-γ Myocardin

Nur1 Shh

Elk-1

Ac-p50-p65

HIF-1α

MDM2

DR5

p53

GADD 45

p21

COX-2 5-LOX TLR4

Aggarwal and Sung; Trends in Pharmaceutical. Sciences, 2009
Curcumin Potentiates the Effect of Chemotherapy

Chemosensitization *in vitro*:

- Potentiates cytotoxic effects of doxorubicin, 5-FU, and paclitaxel against prostate cancer cells. (Hour TC, 2002)
- Sensitizes multiple myeloma cells to vincristine and melphalan. (Bharti AC, 2003)
- Enhances cytotoxicity of cisplatin against ovarian cancer cells in culture. (Chan MM, 2003)
- Potentiated antitumor effects of sodium butyrate against erythroleukemic cells. (Indap MA, 2003)
- Potentiates growth inhibition effects of 5-FU against human gastric carcinoma cells in culture. (Koo JY, 2004)
- Exhibits both additive and sub-additive for antitumor and apoptotic effects of doxorubicin against hepatocellular carcinoma cells in culture. (Notarbartolo M, 2005).
- Potentiates the antitumor and apoptotic effects of cisplatin against hepatocellular carcinoma cells. (Notarbartolo M, 2005)
- Enhances antitumor effects of taxol against cervical cancer cells in culture. (Bava SV, 2005)
- Potentiates the cytotoxicity of paclitaxel toward breast cancer cells in culture. (Aggarwal BB, 2005)
- Potentiates apoptotic effects of celecoxib against human pancreatic cancer cells. (Lev-Ari S, 2005)
- Enhances apoptotic effects of cisplatin against cervical cancer SiHa cells, but not HeLa cells. (Venkatraman M, 2005)
- Enhances apoptotic effects of vinorelbine against human squamous cell lung carcinoma cell line. (Sen S, 2005)
- Augments apoptotic effects of cisplatin against ovarian cancer and breast cancer cell lines. (Chirnomas D, 2006)
- Has no effect on cytotoxic effects of paclitaxel against human ovarian cancer and breast cancer cell lines. (Chirnomas, 2006)
- Potentiates apoptosis induced by gemcitabine and paclitaxel in bladder cancer cells in culture. (Kamat AM, 2007)
- Potentiates antitumor activity of docetaxel against ovarian cancer cell lines. (Lin YG, 2007)
- Increases antitumor effects of oxaliplatin against colorectal cancer cells in culture. (Howells LM, 2007)
- Augments cytotoxic effects of gemcitabine on pancreatic adenocarcinoma cell line. (Lev-Ari S, 2007; Kunnumakkara AB, 2007)
- Enhances the antitumor effects of gemcitabine against prostate cancer cells in culture. (Li M, 2007)
- Potentiates cytotoxicity of cisplatin, etoposide, camptothecin, and doxorubicin against human and rat glioma cells. (Dhandapani KM, 2007)
- Enhances antitumor effects of oxaliplatin against colorectal cancer cell lines. (Li L, 2007)
- Enhanced the antitumor effects of vincristine and PDE4 inhibitors in B-CLL from patients (Everett PC, 2007)
- Enhances antitumor effects of 5-FU and FOLFOX (5-FU plus oxaliplatin) against colon cancer cells (Patel 2008; Du B, 2006)
Curcumin Potentiates the Effect of Chemotherapy

**Chemosensitization in vivo:**
- Enhances antitumor effects of oxaliplatin against colorectal cancer in mice. (Li L, 2007)
- Potentiates antitumor activity of gemcitabine against pancreatic cancer in mice. (Kunnumakkara AB, 2007)
- Potentiates antitumor activity of docetaxel against ovarian cancer in mice. (Lin YG, 2007)
- Enhances the antitumor effects of gemcitabine against prostate cancer in mice. (Li M, 2007)

**Chemoresistance in vitro:**
- Antagonizes apoptotic effects of camptothecin, mechlorethamine, and doxorubicin in human breast cancer cells. (Somasundaram S, 2002)
- Reduces nephrotoxicity of cisplatin in rats. (Kuhad A, 2007)

**Chemoresistance in vivo**
Antagonizes apoptotic effects of cyclophosphamide in mice. (Somasundaram S, 2002)

5-FU, 5-fluorouracil; HeLa, a cervical carcinoma cell line derived from Henrietta Lacks; SiHa, a cervical carcinoma cell line; Gy, gray units; UVA, ultraviolet A light; UVB, ultraviolet B light
Curcumin in animal models!
### Cancer prevention by curcumin in animals

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Carcinogen</th>
<th>Animal</th>
<th>Dose</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Gastrointestinal cancers:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ACF</td>
<td>AOM</td>
<td>Rat</td>
<td>2000 ppm</td>
<td>Rao et al, 1993</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Mice</td>
<td>0.5 to 0.2 % w/w</td>
<td>Huang et al, 1994</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>DMH</td>
<td>Mice</td>
<td>0.5%</td>
<td>Kim et al, 1998</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>2000 ppm</td>
<td>Rao et al, 1995</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>0.2 or 0.6% w/w</td>
<td>Kawamori et al, 1999</td>
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<tr>
<td>Colon cancer</td>
<td>PhIP</td>
<td>Apc mice</td>
<td>2000 ppm</td>
<td>Collett et al, 2001</td>
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<tr>
<td>Colon cancer</td>
<td>AOM</td>
<td>Rat</td>
<td>1 or 2% w/w</td>
<td>Pereira et al, 1996</td>
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<td>AOM</td>
<td>Rat</td>
<td>0.6% w/w</td>
<td>Kwon et al, 2004</td>
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<tr>
<td>Colon cancer</td>
<td>DMH</td>
<td>Rat</td>
<td>0.6%</td>
<td>Shiptz B, 2006</td>
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<tr>
<td>Colitis</td>
<td>TNBS</td>
<td>Mice</td>
<td>0.5-5%, diet</td>
<td>Sugimoto K, 2002</td>
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<tr>
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<td>DNB</td>
<td>Mice</td>
<td>0.25%; diet</td>
<td>Salh B, 2003</td>
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<tr>
<td>Colitis</td>
<td>TNBS</td>
<td>Mice</td>
<td>50mg/kg</td>
<td>Ukil A, 2003</td>
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<td>Ulcerative colitis</td>
<td>TNCB</td>
<td>Rat</td>
<td>30-60 mg/kg</td>
<td>Jung H, 2006</td>
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<tr>
<td>Ulcerative colitis</td>
<td>DNCB</td>
<td>Rat</td>
<td>25-100 mg/kg</td>
<td>Venkatarangana MV, 2007</td>
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<tr>
<td>Duodenal tumor</td>
<td>MNNG</td>
<td>Mice</td>
<td>0.5 to 2.0% w/w</td>
<td>Huang et al, 1994</td>
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<tr>
<td>Esophageal cancer</td>
<td>NMBA</td>
<td>Rat</td>
<td>500 ppm</td>
<td>Usida et al, 2000</td>
</tr>
<tr>
<td>FAD*</td>
<td>AOM</td>
<td>Mice</td>
<td>2%</td>
<td>Huang et al, 1992</td>
</tr>
<tr>
<td>FAP*</td>
<td>---</td>
<td>Min/+ mice</td>
<td>0.1, 0.2 or 0.5% w/w</td>
<td>Perkins et al, 2002</td>
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<tr>
<td>Forestomach neoplasia</td>
<td>B[a]P</td>
<td>Mice</td>
<td>2% w/w</td>
<td>Azuine et al, 1992</td>
</tr>
<tr>
<td>Forestomach cancer</td>
<td>B[a]P</td>
<td>Mice</td>
<td>2% w/w</td>
<td>Singh et al, 1998</td>
</tr>
<tr>
<td>Forestomach neoplasia</td>
<td>B[a]P</td>
<td>Mice</td>
<td>2% w/w</td>
<td>Nagabhushan et al, 1992</td>
</tr>
<tr>
<td>Stomach cancer</td>
<td>MNNG</td>
<td>Rat</td>
<td>0.05% w/w</td>
<td>Ikezaki et al, 2010</td>
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<tr>
<td><strong>Liver cancers:</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Hepatic hyperplasia</td>
<td>DNM</td>
<td>Rat</td>
<td>200 or 600 mg/kg</td>
<td>Chuang et al, 2000</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>DNM</td>
<td>Mice</td>
<td>0.2% w/w</td>
<td>Chuang et al, 2000</td>
</tr>
<tr>
<td><strong>Lung cancers:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood cancers:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma/leukemia</td>
<td>DMBA</td>
<td>Sencar mice</td>
<td>2% w/w</td>
<td>Huang et al, 1998</td>
</tr>
</tbody>
</table>

*Goel et al, Biochem. Pharm., 2007*
# Cancer prevention by curcumin in animals

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Carcinogen</th>
<th>Animal</th>
<th>Dose</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>Breast cancers:</strong></td>
<td></td>
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</tr>
<tr>
<td>Mammary tumor</td>
<td>DMBA</td>
<td>Rat</td>
<td>0.8 to 1.6% w/w</td>
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<td>Mammary tumor</td>
<td>DMBA</td>
<td>Rat</td>
<td>50 to 200 mg/kg</td>
<td>Singletary et al, 1996</td>
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<td>DMBA</td>
<td>Rat</td>
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<td>Deshpande et al, 1998</td>
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<td>Mammary tumor</td>
<td>DMBA</td>
<td>Sencar mice</td>
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<td>Huang et al, 1998</td>
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<tr>
<td>Mammary tumor</td>
<td>γ-radiation</td>
<td>Rat</td>
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<td>Inano et al, 1999</td>
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<td>Mammary tumor</td>
<td>DMBA</td>
<td>Rat</td>
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<td>Inano et al, 2002</td>
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<tr>
<td>Mammary tumor</td>
<td>DMBA</td>
<td>Sencar mice</td>
<td>2% w/w</td>
<td>Lin et al, 2001</td>
</tr>
<tr>
<td>Mammary tumor</td>
<td>γ-radiation</td>
<td>Rat</td>
<td>1% w/w</td>
<td>Inano et al, 2002</td>
</tr>
<tr>
<td>Oral cancers:</td>
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</tr>
<tr>
<td>Oral cancer</td>
<td>MNA</td>
<td>Hamster</td>
<td>500 ppm</td>
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<tr>
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<td>500 ppm</td>
<td>Tanaka et al, 1994</td>
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<td>Prostate cancer</td>
<td>DMAB &amp; PhilPRat</td>
<td>15 to 500 ppm</td>
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<td>Imaida et al, 2001</td>
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<td>Skin cancers:</td>
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<tr>
<td>Dermatitis</td>
<td>TPA + UV-A</td>
<td>Mice</td>
<td></td>
<td>Ishizaki et al, 1996</td>
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<td>Skin tumor</td>
<td>TPA</td>
<td>Mice</td>
<td></td>
<td>Huang et al, 1988</td>
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<tr>
<td>Skin tumor</td>
<td>DMBA</td>
<td>Mice</td>
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<td>Azuine et al, 1992</td>
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<td>10 &amp; 30 nmol</td>
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<td>Skin tumor</td>
<td>TPA</td>
<td>Mice</td>
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<td>Huang et al, 1995</td>
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<tr>
<td>Skin tumor</td>
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<td>Mice</td>
<td>1, 10, 100 or 3000 nmol</td>
<td>Huang et al, 1997</td>
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<td>Skin tumor</td>
<td>DMBA</td>
<td>Mice</td>
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<td>Soudamini, 1989</td>
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<td>Skin tumor</td>
<td>B[a]P and</td>
<td>Mice</td>
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<td>Nagabhushan et al, 1992</td>
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<td>Other cancers:</td>
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<tr>
<td>Multi-organ cancer</td>
<td>DHPN, EHEN</td>
<td>Rat</td>
<td>1% w/w</td>
<td>Takaba et al, 1997</td>
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*Goel et al, Biochem. Pharm., 2007*
## Treatment of cancer by curcumin in animals

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Route</th>
<th>Dose</th>
<th>Model</th>
<th>References</th>
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<tr>
<td>Ascites²</td>
<td>IP</td>
<td>50 mg/kg</td>
<td>Ascites</td>
<td>Kuttan et al, 1985</td>
</tr>
<tr>
<td>Ascites</td>
<td>IP</td>
<td>50 mg/kg</td>
<td>Ascites</td>
<td>Ruby et al, 1995</td>
</tr>
<tr>
<td>Breast¹</td>
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<td>Orthotopic</td>
<td>Aggarwal et al, 2006</td>
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<tr>
<td>Breast¹</td>
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<td>Orthotopic</td>
<td>Bachmeier et al, 2007</td>
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<tr>
<td>Colon²</td>
<td>IV</td>
<td>40 mg/kg</td>
<td>Orthotopic</td>
<td>Li et al, 2007</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Oral</td>
<td>50-200 mg/kg</td>
<td>Xenograft</td>
<td>Cui et al, 2006</td>
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<tr>
<td>Glioblastoma</td>
<td>IT</td>
<td>10 mg/kg</td>
<td>Orthotopic</td>
<td>Aoki et al, 2007</td>
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<tr>
<td>HCC³</td>
<td>Oral</td>
<td>100-200 mg/kg</td>
<td>Xenograft</td>
<td>Ohashi et al, 2003</td>
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<tr>
<td>Hepatoma</td>
<td>Oral</td>
<td>50-200 mg/kg</td>
<td>Xenograft</td>
<td>Cui et al, 2006</td>
</tr>
<tr>
<td>HNSCC</td>
<td>Sub cute</td>
<td>50-250 µmol/L</td>
<td>Xenograft</td>
<td>LoTempio et al, 2005</td>
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<tr>
<td>Leukemia</td>
<td>Oral</td>
<td>50-200 mg/kg</td>
<td>Xenograft</td>
<td>Cui et al, 2006</td>
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<tr>
<td>Melanoma</td>
<td>IP</td>
<td>25 mg/kg</td>
<td>Xenograft</td>
<td>Odot et al, 2004</td>
</tr>
<tr>
<td>Ovarian</td>
<td>IP</td>
<td>500 mg/kg</td>
<td>Orthotopic</td>
<td>Lin et al, 2007</td>
</tr>
<tr>
<td>Pancreas</td>
<td>IV</td>
<td>40 mg/kg</td>
<td>Xenograft</td>
<td>Li et al, 2005</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Gavage</td>
<td>1 gm/kg</td>
<td>Orthotopic</td>
<td>Kunnumakkara et al, 2007</td>
</tr>
<tr>
<td>Prostate</td>
<td>Diet</td>
<td>2% w/w</td>
<td>Xenograft</td>
<td>Dorai et al, 2001</td>
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<tr>
<td>Prostate</td>
<td>Gavage</td>
<td>5 mg/kg</td>
<td>Orthotopic</td>
<td>Hong et al, 2006</td>
</tr>
<tr>
<td>Prostate</td>
<td>Gavage</td>
<td>5 mg/day</td>
<td>Xenograft</td>
<td>Li et al, 2007</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Gavage</td>
<td>1 gm/kg</td>
<td>Orthotopic</td>
<td>Kunnumakkara et al, 2008</td>
</tr>
</tbody>
</table>

1. Lung metastases; 2. Liposomal curcumin; 3. Intrahepatic metastasis; IP, intraperitoneal; IT- intratumoral; IV- intravenous

Goel et al, Biochem. Pharm., 2007
Liposome-encapsulated curcumin: in vitro and in vivo effects on proliferation, apoptosis, signaling, and angiogenesis.

Li L, Braiteh FS, Kurzrock R
Cancer
Liposome-encapsulated curcumin inhibits the growth of human pancreatic tumors in nude mice.
Liposome-encapsulated curcumin inhibits angiogenesis in human pancreatic tumors in nude mice
Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of NF-κB-regulated gene products.

Kunnumakara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, Aggarwal BB.

Experimental Design for treatment of pancreatic tumors in orthotopic mouse model

Curcumin (sesamine oil) at 500 mg/kg (42 mg/kg in man) oral gavage
Curcumin potentiates the effect of Gemzar against pancreatic cancer in orthotopic mouse model.
Curcumin downregulates the expression of Ki67 and CD31 in human pancreatic tumors in mice

Kunnumakkara AB, et al, 2007
Curcumin decreases the expression of NF-κB regulated gene products in human pancreatic tumors in mice.
Curcumin in human clinicals!
## Completed clinical trials with curcumin

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dose/Frequency</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>2000 mg/day</td>
<td>10</td>
</tr>
<tr>
<td>Phase-I</td>
<td>500-12,000 mg/day x 90 days</td>
<td>25</td>
</tr>
<tr>
<td>Phase 1</td>
<td>500-12,000 mg/day</td>
<td>24</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1200 mg/day x 14 days</td>
<td>18</td>
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<tr>
<td>Postoperative inflammation</td>
<td>400 mg; 3 x/day x 5 d</td>
<td>46</td>
</tr>
<tr>
<td>External cancerous lesions</td>
<td>1% ointment x several months</td>
<td>62</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>500 mg/day x 7 d</td>
<td>10</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>10 mg; 2x/day x 28 d</td>
<td>12</td>
</tr>
<tr>
<td>HIV</td>
<td>625 mg; 4x/day x 56 d</td>
<td>40</td>
</tr>
<tr>
<td>Gall bladder function</td>
<td>20 mg, single dose (2 h)</td>
<td>12</td>
</tr>
<tr>
<td>Gall bladder function</td>
<td>20-80 mg, single dose (2 h)</td>
<td>12</td>
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<tr>
<td>Chronic anterior uveitis</td>
<td>375 mg; 3x/day x 84 days</td>
<td>32</td>
</tr>
<tr>
<td>Idiopathic Inflamm Orbital pseudotumors</td>
<td>375 mg; 3x/day x 180-660 days</td>
<td>8</td>
</tr>
</tbody>
</table>

*Goel et al, Biochem. Pharm., 2007*
## Completed clinical trials with curcumin

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dose/Frequency</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>1% curcumin gel</td>
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<tr>
<td>Psoriasis</td>
<td>4.5g/day x 84 days</td>
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<tr>
<td>Colorectal cancer</td>
<td>36-180 mg/day x 120 days</td>
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</tr>
<tr>
<td>Colorectal cancer</td>
<td>450-3600 mg/day x 120 days</td>
<td>15</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>72-144 mg/day x 56 days</td>
<td>207</td>
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<tr>
<td>Liver metastasis of CRC</td>
<td>450-3600 mg/day x 7 day</td>
<td>12</td>
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<tr>
<td>Colorectal cancer</td>
<td>450-3600 mg/day x 7 days</td>
<td>12</td>
</tr>
<tr>
<td>Cadaveric renal transplantation</td>
<td>480 mg; x1-2/day x 30 days</td>
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<tr>
<td>Tropical pancreatitis</td>
<td>500 mg/day x 42 days</td>
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<tr>
<td>Ulcerative proctitis</td>
<td>550 mg; x 2-3/day x 60 days</td>
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<tr>
<td>Crohn’s disease</td>
<td>360 mg; x 3/day x 30 days</td>
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<tr>
<td>Ulcerative colitis</td>
<td>2000 mg/day x 180 days</td>
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<tr>
<td>Familial adenomatous polyposis</td>
<td>480 mg; x3/day x 180 days</td>
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<tr>
<td>Cognitive function</td>
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<tr>
<td>Prostatic intra-epithelial neoplasia (PIN)</td>
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<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>300 mg/day x 7 days</td>
<td>25</td>
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</tbody>
</table>

*Goel et al, Biochem. Pharm., 2007*
# Ongoing clinical trials with curcumin

<table>
<thead>
<tr>
<th>Disease</th>
<th>Study Type/Design</th>
<th>Patients #</th>
<th>Trial Site</th>
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</thead>
<tbody>
<tr>
<td>Colorectal cancer, ACF</td>
<td>Phase-I, Randomized</td>
<td>-</td>
<td>Rockefeller University Hospital</td>
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<tr>
<td>Colon cancer</td>
<td>Phase-III, Randomized</td>
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<td>Tel-Aviv Sourasky Med. Center</td>
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<tr>
<td>Colorectal cancer, ACF</td>
<td>Phase-II, Non-randomized</td>
<td>48</td>
<td>University of Illinois, Chicago</td>
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<tr>
<td>FAP</td>
<td>Phase-II, Randomized</td>
<td>68</td>
<td>University of Pennsylvania</td>
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<tr>
<td>FAP</td>
<td>Phase-II, Non-randomized</td>
<td>-</td>
<td>Johns Hopkins University</td>
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<tr>
<td>Aberrant crypt foci</td>
<td>Prevention, Randomized</td>
<td>60</td>
<td>Cancer Institute of New Jersey</td>
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<tr>
<td>Pancreatic cancer</td>
<td>Phase-II, Non-randomized</td>
<td>45</td>
<td>Rambam Medical Center, Haifa</td>
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<tr>
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<td>Phase-II, Non-randomized</td>
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<td>M.D. Anderson Cancer Center</td>
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<tr>
<td>Pharmacokinetics</td>
<td>Treatment, Non-randomized</td>
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<td>Massachusetts General Hospital</td>
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<tr>
<td>Myelodysplastic syndrome</td>
<td>Phase II</td>
<td>30</td>
<td>Univ. Massachusetts, Worcester</td>
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<tr>
<td>Alzheimer’s disease</td>
<td>Phase-II, Randomized</td>
<td>33</td>
<td>Univ. of California Los Angeles</td>
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<tr>
<td>Alzheimer’s disease</td>
<td>Phase-I &amp;II, Randomized</td>
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<td>Chinese University of HK</td>
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<tr>
<td>Multiple myeloma</td>
<td>Randomized</td>
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<td>Myelodysplastic syndrome</td>
<td>Phase-I &amp;II, Non-randomized</td>
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<td>Hadassah Medical Organization</td>
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</table>

Goel et al, Biochem. Pharm., 2007
## Ongoing clinical trials with curcumin

<table>
<thead>
<tr>
<th>Disease</th>
<th>Study Type/Design</th>
<th>Patients #</th>
<th>Trial Site</th>
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<tbody>
<tr>
<td>Psoriasis</td>
<td>Phase-II, Non-randomized</td>
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<tr>
<td>Epilepsy</td>
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<tr>
<td>Advanced HNSCC</td>
<td>Phase II (1-8 g/day; 56 d)</td>
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<tr>
<td>Cervical cancer (Stage IIb, IIIb)</td>
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<td>100</td>
<td>AIIMS, Delhi</td>
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<tr>
<td>Oral premalignant lesions</td>
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<td>90</td>
<td>Tata Memorial Cancer Ctr</td>
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<td>Oral premalignant lesions</td>
<td>Phase II/III DBRPC</td>
<td>96</td>
<td>Amrita Institute, Kerala</td>
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<td>Oral leukoplakia</td>
<td>Phase II (curcumin gel)</td>
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<td>Gall bladder cancer</td>
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<td>Banaras Hindu univ, Varanasi</td>
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<td>Pancreatic cancer</td>
<td>Phase II (8 g/day)</td>
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<td>PSC</td>
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<td>Amsterdam Medical Ctr.</td>
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<td>Ulcerative colitis</td>
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<td>Barretts Metaplasia</td>
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<td>MGUS</td>
<td>Phase 1 (3.4 g/day)</td>
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<td>St. George Hospital, Sydney</td>
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</table>

*Goel et al, Biochem. Pharm., 2007*
Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis.

Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD, Giardiello FM.

Five FAP patients with prior colectomy (4 with retained rectum and 1 with an ileal anal pouch) received curcumin 480 mg and quercetin 20 mg orally 3 times a day. The number and size of polyps were assessed at baseline and after therapy. The Wilcoxon signed-rank test was used to determine differences in the number and size of polyps. Treatment side effects and medication compliance also were evaluated. All 5 patients had a decreased polyp number and size from baseline after a mean of 6 months of treatment with curcumin and quercetin. The mean percent decrease in the number and size of polyps from baseline was 60.4% (P < .05) and 50.9% (P < .05), respectively. Minimal adverse side effects and no laboratory abnormalities were noted.

CONCLUSIONS: The combination of curcumin and quercetin appears to reduce the number and size of ileal and rectal adenomas in patients with FAP without appreciable toxicity. Randomized controlled trials are needed to validate these findings.
Curcumin for clinical trials

- Pill (1000 mg)
- Capsule (500 mg)
- Losegens (100 mg)
Constitutive activation of NF-κB in PBMC from MM Patients and its Suppression by Curcumin (2g/day)

Patient #4 (482480)

<table>
<thead>
<tr>
<th>Time</th>
<th>Pre</th>
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<th>8w</th>
<th>12w</th>
<th>20w</th>
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<tr>
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<td>+</td>
<td>-</td>
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Patient #6 (337641)

<table>
<thead>
<tr>
<th>Time</th>
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<th>16w</th>
<th>20w</th>
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<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

A, B, C, D, E, F, and G represents Pre, 4, 8, 12, 16, 20 and 24 wks after curcumin administration
Phase II trial of curcumin in patients with advanced pancreatic cancer

Dhillon N, Aggarwal BB, Newman RA, Wolff RA, Kunnunakkara AB, Abbruzzese JL, Ng CS, Badmaev V, Kurzrock R.

Phase II Trial of Curcumin in Patients with Advanced Pancreatic Cancer


- The only FDA-approved therapies- gemcitabine and erlotinib- produce objective responses in less than 10% of patients.
- The objectives of this trial were to evaluate the toxicity and activity of curcumin, as well as its impact on survival and biologic correlates.
- Patients were treated with 8 grams of curcumin (Sabinsa Corp.) daily by mouth for two months and evaluated radiographically using the RECIST criteria.
- Maintenance therapy was continued at the same dose and schedule until disease progression.
- RESULTS: Seventeen patients were enrolled as of the date of analysis.
- Six were inevaluable: noncompliance (n=1), never dosed (n=1), noted to have gastric obstruction after one dose (n=1), and too early (n=3).
- Eleven patients were evaluable for response and 15 were evaluable for toxicity.

To date, four patients have stable disease (2+, 2+, 3+ and 7 months) and one patient had a brief partial remission (73% reduction in tumor size by RECIST) that lasted one month.

- No toxicity was observed. Serum was available for evaluation of pre-and post-dose cytokine levels in thirteen patients. Interestingly, the patient with the partial remission had marked increases in (4-35 fold) in serum IL-1 receptor antagonist, IL-6, IL-10 and IL-8 levels. One to three other patients also had post-treatment increases one or more of the above cytokines, albeit to a lesser extent (2-6 folds).

- CONCLUSIONS: We conclude that curcumin is well tolerated and our preliminary results suggest biologic activity in pancreatic cancer.

From ASCO-2006
"If you want to do something, do it now. Don't wait."

This advice come from a patient with end-stage pancreatic cancer who was given an unexpected gift of time, thanks to curcumin, the main ingredient in the spice tumeric. When Duane Jacobson first came to the Clinical Center for Targeted Therapy (CCTT) at M. D. Anderson, he had less than three months to live, estimated his oncologist Razelle Kurzrock, M.D., principal investigator of the curcumin trial and also chair of the Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program). More than two years later, he is traveling around the world with his wife Hildrud while enrolled in an NIH-sponsored, phase II clinical trial of curcumin in advanced pancreatic cancer.
Adding celecoxib and curcumin to standard therapy has a beneficial effect in patients with metastatic pancreatic cancer.

E. Shacham-Shmueli, L. Galazan, V. Badmaev, M. Inbar, N. Arber, A. Figer; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Sabisna corporation, Piscataway, NJ

Background: Pancreatic cancer, one of the most difficult cancers to treat harbors poor prognosis. The anti-metabolite gemcitabine has become the standard treatment. Series of phase III trials examined efficacy of gemcitabine and a second agent, but these doublets demonstrated no survival advantage over single-agent gemcitabine. However, the rationale for continuing to study gemcitabine-based combinations remains compelling. Curcumin derived from the rhizome of Curcuma Longa, commonly called turmeric, has shown to possess potent anti-inflammatory and anti-oxidative properties. Phase I-II studies found curcuminoids to be safe with no dose-limiting toxicity at doses up to 10 g/day PO. Studies showed stabilizing effect of Curcuminoids in some pancreatic cancer patients. COX-2 inhibitors have very broad applications in oncology, from prevention to treatment of advanced malignancies. The COX-2-specific inhibitors celecoxib has anti-inflammatory effect and cancer protection without gastrointestinal toxicity associated with the older non-specific NSAIDs. In vitro combination celecoxib and curcuminoids demonstrated synergistic growth inhibitory effect in several colonic and pancreatic cell lines.

Methods: In a preliminary study that had been performed at Tel Aviv Medical Center, 20 patients with inoperable pancreatic cancer were recruited. They had received gemcitabine + celecoxib (400 mg qd) and curcuminoids (8 g qd) (13) or placebo (7).

Results: While there were no side effects related to the use of curcuminoids or celecoxib the disease progressed in all subjects receiving gemcitabine and placebo. Stabilization of the disease was achieved in 50% of the patients receiving the combination therapy.

Conclusions: The results in this small study are encouraging. Adding celecoxib and curcuminoids to standard therapy in pancreatic cancer seems to be very promising. A multi center study, with this protocol, has been initiated in Israel.
Obesity and Cancer

Fig. 5. Various cancers that have been linked to obesity. In the USA overweight and obesity could account for 14% of all deaths from cancer in men and 20% of those in women (see 51).

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
Role of curcumin in diabetes and hyperlipidemia

- Reduces blood glucose and increase plasma insulin
- Prevents diabetes-induced oxidative stress
- Reduces the accumulation and cross-linking of collagen
- Reduces serum and liver cholesterol, triglycerides, free fatty acids
- Attenuate cognitive deficit, cholinergic dysfunction
- Decreases glycosylated haemoglobin
- Reduces hyperglycemia-induced vascular endothelial growth factor
- Prevents brain lipid peroxidation
- Suppresses the development of retinopathy
- Suppresses diabetic neuropathic pain
- Ameliorates diabetic nephropathy
- Attenuates thermal hyperalgesia (neuropathic pain).
- Prevents the cataractogenesis
- Induces hypoglycemia in genetically diabetic KK-Ay mice
- Enhances wound healing in genetically diabetic rat
- Ameliorate renal lesions
- Reduces the development of fatty streaks in rabbits
Curcumin suppresses the expression of TNF, NO and MCP-1 in macrophages stimulated by mesenteric adipose tissue CM
Curcumin protects pancreatic beta cells!

- Curcumin treatment *enhances islet recovery* by induction of heat shock response proteins, Hsp70 and heme oxygenase-1, during cryopreservation (Kanitkar, 2008).
- Curcumin prevents streptozotocin-induced *islet damage* by scavenging free radicals: a prophylactic and protective role (Meghana, 2007).
- Regulation of heme oxygenase-1 expression by demethoxy curcuminoids through Nrf2 by a PI3-kinase/Akt-mediated pathway in mouse *beta-cells* (Pugazhenthi, 2007).
- Curcumin induces electrical activity in rat pancreatic *beta-cells* by activating the volume-regulated anion channel (Best, 2007).
- Curcumin inhibits in vitro MCP-1 release from mouse *pancreatic islets* (Amoli, 2006).
- Protection of *pancreatic beta-cell* by the potential antioxidant bis-o-hydroxycinnamoyl methane, analogue of natural curcuminoid in experimental diabetes (Srinivasan, 2003).
- Protection against the *diabetogenic effect* of feeding tert-butylhydroquinone to rats prior to the administration of streptozotocin (Nishizono, 2000).

*Pancreatic islet cell death is the cause of deficient insulin production in diabetes mellitus*
Curcumin ameliorates ethanol and nonethanol experimental pancreatitis (Gukovsky, 2003).

- Effects of curcumin on TNF-alpha and IL-6 in the late phase of experimental acute pancreatitis (Gulcubuk, 2006).

- A pilot study of the antioxidant effect of curcumin in tropical pancreatitis. (Durgaprasad, 2005)

- Heme oxygenase-1 inhibits the proliferation of pancreatic stellate cells by repression of the ERK1/2 pathway (Schwer C, 2008)


- Curcumin blocks activation of pancreatic stellate cells (Mesamune, 2006).

- Pathologic alterations detected in acute pancreatitis induced by sodium taurocholate in rats and therapeutic effects of curcumin, ciprofloxacin and metronidazole combination (Gulcubuk, 2005).

Activation of pancreatic stellate cells (PSCs) is the key process in the development of pancreatic fibrosis, a common feature of chronic pancreatitis and pancreatic cancer.
This pilot study was undertaken to evaluate the effect of oral curcumin with piperine on the pain, and the markers of oxidative stress in patients with tropical pancreatitis (TP).

Twenty consecutive patients with tropical pancreatitis were randomized to receive 500 mg of curcumin with 5 mg of piperine, or placebo for 6 wk.

There was a significant reduction in the erythrocyte malonyldialdehyde (MDA) levels following curcumin therapy compared with placebo; with a significant increase in GSH levels.

There was no corresponding improvement in pain.

CONCLUSION: Oral curcumin with piperine reversed lipid peroxidation in patients with tropical pancreatitis.
Effect of curcumin on blood sugar as seen in a diabetic subject.

Srinivasan M.

Indian Journal of Medical Sciences.
Multi-targeted

Inflammatory cytokines
IL-1, IL-2, IL-5, IL-6, IL-8, IL-12, IL-8, MCP-1, MIP-1, MalP

Enzymes
ATFase, ATPase, Desaturase, FPTase, GST, GCL, HO-1, iNOS, MMPs, NQO-1, ODC, PhPD, TIMP-3, 5-LOX, Telomerase

Growth factors
TGF β, FGF, HGF, PDGF, TF

Receptors
AR, AHR, CXCR4, DR, EGFR, ER-α, FasR, H2R, IL-8R, ITPR, IR, LD-R

Adhesion molecules
ELAM-1, ICAM-1, VCAM-1

Anti-apototic proteins
Bcl-2, BclxL, IAP-1

Protein Kinases
IKK, AAPK, Ca2+ PK, EGFR, ERK, FAK, IL-1 RAK, JAK, JNK, MAPK, PhK, PK, PKA, PKB, PKC, pp60c-src tk, PTK

Transcriptional factors
AP-1, β-Catenin, CBP, ERG-1, ERE, HIF-1, Notch-1, Nrf-2, NF-κB, PPAR-γ, STAT-1, STAT-3, STAT-4, STAT-5, WTG-1

Others
Cyclin D1, Cyclin E, HsP 70, MDR

Mono-targeted

COX-2
Celecoxib

EGFR
Erbitux

TNF
Remicade
Humira
Enbrel

HER-2
Herceptin

Bcr-Abl
Gleevac

VEGF
Avastin

Tubulin
Paclitaxel

Topoisomerase
Camptothecin

Curcumin Targets

Kunnumakkara et al, CL, 2008
Nonocurcumin has higher cellular uptake than curcumin.
Cancer is less in spice consuming countries

Figure 1. Relationship between production of spices and cancer incidence. Data is modified from 2000 faostat.fao.org (http://www.foodmarketexchange.com/datacenter/product/herb/herb/detail/dc_pi_hs_herb0406.htm) and cancer data from the World Health Organization GLOBOCAN 2002. A color version of the figure is available in the online journal.
**TNF blockers (>16B$)**

TNF blockers have been approved for osteoarthritis, psoriasis & Crohn’s disease

<table>
<thead>
<tr>
<th>Blocker</th>
<th>Name</th>
<th>Company</th>
<th>Yr approved</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anti-Fc-DcR fusion</td>
<td>Enbrel</td>
<td>Amgen</td>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>2. Chimeric antibody</td>
<td>Remicade</td>
<td>Centocor</td>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>3. Fully human antibody</td>
<td>Humira</td>
<td>Abbott</td>
<td>2003</td>
<td>Biweekly</td>
</tr>
<tr>
<td>4. Pegylated anti-TNF</td>
<td>Cimzia</td>
<td>UCB</td>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>5. Anti-TNF; IgGk</td>
<td>Symponi</td>
<td>Centocor</td>
<td>2009</td>
<td>Monthly</td>
</tr>
<tr>
<td>6. Denosumab</td>
<td>?</td>
<td>Amgen</td>
<td>Filed</td>
<td></td>
</tr>
</tbody>
</table>

Sale for 1, 2 and 3 for 2008 is >$16; All TNF blockers have black-box warning labels for increased infections, CNS demyelinating disorder. There are 22 TNF family ligand-receptor pairs; Beromun, is a recombinant TNF approved for cancer by Beringer and Ingelheim; TM-TNF mediates immune system mediated protection from infection (Allenbach, 2008, Fremond, 2005)
Hippocrates proclaimed
~2500 years ago

“Let food be thy medicine
and medicine be thy food”
National Cancer Institute

Eat 8 servings of fruits and vegetables every day!
Role of life style in cancer development

- Environment
- Diet
- Smoking
- Viruses
- Bacteria
- Meat
- Alcohol
- Spices
- Fruits
- Exercise (e.g., yoga)
- Grains
- Vegetables
- Legumes
- Breast
- Prostate
- Skin
- Lung
- Leukemia
- Colon
- Multiple Myeloma

CANCER

NF-κB
TNF, IL-1, IL-6, Chemokines, iNOS, MMP, COX2, ICAM

20-30 years

LIFESTYLE