Inflammation and chronic disease: Role of spices

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6th International Congress of Vegetarian Nutrition
February 24-26, 2013.
Krystal Sky Gheen, MPH RD; Tara Johnson; Sujatha Rajaram
School of Public Health; Loma Linda University, Loma Linda, California
February 25th, 2013 (4:40-5:05 PM)
According to the Centers for Disease Control and Prevention (CDC), chronic diseases today account for 70% of the deaths of all Americans and 75% of this country’s annual health care costs.

Unless we take steps now to deal effectively with chronic diseases, our nation is headed for a serious financial and quality-of-life crisis.

Among the contributing factors to this crisis are the aging of our population; increases in obesity, particularly among adolescents; and the tragedy of tobacco addiction.
The top 10 countries, in numbers of people with diabetes, are:

- India
- China
- USA
- Indonesia
- Japan
- Pakistan
- Russia
- Brazil
- Italy
- Bangladesh

Prevalence of diabetes in persons 35 - 64 years:
- People with diabetes (millions):
  - 2000: 31.7
  - 2030: 79.4
  - People with diabetes (millions):
  - 2000: 20.8
  - 2030: 42.3
  - People with diabetes (millions):
  - 2000: 17.7
  - 2030: 30.3

Source: Wild et al., 2004
The World Health Organization predicts there will be 2.3 billion overweight adults in the world by 2015 and more than 700 million of them will be obese.
Several age-related chronic diseases such as metabolic syndrome, cardiovascular disease, and neurodegenerative disease have an inflammatory component.
Inflammation, Lifestyle and Chronic Diseases: The Silent Link

Bharat B. Aggarwal, Ph.D. (Editor), Sunil Krishnan, M.D. (Editor), Sushovan Guha, M.D. (Editor)

(Francis and Taylor)
# Inflammation, Lifestyle and Chronic Diseases: The Silent Link

## Vegetables (95)
- Artichoke
- Arugula
- Asparagus
- Banana blossoms
- Bamboo shoots
- Basil
- Beet greens
- Beet root
- Bell pepper
- Bitter melon
- Bok choy
- Bottle gourd
- Broad beans
- Broccoli
- Broccoli sprouts
- Broccoli sprouts
- Cabbage
- Calabacita
- Collard greens
- Carrot
- Celeriac
- Celery
- Chayote
- Chervil
- Chinese cabbage
- Chinese chives
- Chufa
- Cilantro
- Cluster beans
- Collard greens
- Cucumber
- Calabacita
- Daikon
- Dill
- Drumstick tree
- Eggplant
- Elephant yam
- Endive
- Epazote leaves
- Fennel bulbs
- Gardening chrysanthemum
- Garlic
- Hairy basil
- Head lettuce
- Ivy gourd
- Jalapeño pepper
- Kale
- Kohlrabi
- Leek
- Lemon grass
- Lettuce
- Long bean
- Malanga
- Mint
- Morning glory
- Mustard green
- Mushrooms
- Napa cabbage
- Okra
- Olives
- Onion
- Parsley
- Parsnip
- Peppers
- Potato
- Pumpkin
- Radicchio
- Radish
- Ridge gourd
- Romain lettuce
- Rutabaga
- Savoy
- Serrano pepper
- Shallot
- Shiitake mushrooms
- Snake gourd
- Snap bean
- Snow peas
- Spinach
- Sponge gourd
- Sweet potatoes
- Swiss chard
- Taro plant
- Tomatillos
- Tomato
- Turnip
- Watercress
- Winter squash
- Yam

## Fruits (215)
- Alligator apple
- Apple
- Apricot
- Avocado
- Acai
- Acerola
- Ackee
- Araza
- Babaco
- Bael
- Banana
- Barbados cherry
- Barbados cherry
- Bayberry
- Bearberry
- Barberry
- Betel nut
- Beech nut
- Beach plum
- Bignay
- Bilimbi
- Blackberry
- Black cherry
- Black currant
- Black mulberry
- Black raspberry
- Black sapote
- Blueberry
- Boesemania
- Boysenberry
- Brazil nut
- Breadfruit
- Buffalo pear
- Burdekin plum
- Burmese grape
- Cacao
- Calimyrna
- Caromana
- Calabash
- Camu camu
- Carrot
- Cantaloupe
- Cape gooseberry
- Carambola
- Cardon
- Carob
- Cashew
- Cempedak
- Cedar Bay
- Cherry
- Ceylon gooseberry
- Chee
- Chenet
- Cherry
- Cherimoya
- Chinese bayberry
- Chinese mulberry
- Chokeberry
- Citron
- Clementine
- Cluster fig
- Cloudberry
- Coconut
- Cocoplum
- Coffee
- Cornelian cherry
- Crabapple
- Cranberry
- Crowberry
- Cudrania
- Currant
- Cupuacu
- Custard apple
- Damson
- Date
- Date palm
- Date plum
- Davidson's plum
- Desert lime
- Dewberry
- Douba
- Dragonfruit
- Dorrain
- Elephant apple
- Elderberry
- Emblica
- Emu apple
- Etrog
- Feijoa
- Fig
- Finger lime
- Fibrous watercress
- Galia
- Gandaria
- Genipap
- Genip
- Giant granadilla
- Goumi
- Greengage
- Grape
- Grapple
- Grenadilla
- Guarana
- Guava
- Guanabana
- Guavaberry
- Hackberry
- Hardy kiwi
- Hawthorn
- Hog plum
- Honeysuckle
Inflammation, Lifestyle and Chronic Diseases: The Silent Link
Signalling pathways of the TNF superfamily: a double-edged sword.

Aggarwal BB. Nature Reviews Immunology 2003 Sep;3(9):745-56.

Historical perspectives on tumor necrosis factor and its superfamily: twenty-five years later, a golden journey.

THE SECRET KILLER

- The surprising link between inflammation and heart attacks, cancer, Alzheimer's and other diseases
- What you can do to fight it
The Fires Within

Inflammation is the body's first defense against infection, but when it goes awry, it can lead to heart attacks, colon cancer, Alzheimer's and a host of other diseases.

Illustration for TIME by Brian Stauffer

By CHRISTINE GORMAN and ALICE PARK

WHAT DOES A STABBED TOE OR A splinter in a finger have to do with your risk of developing Alzheimer's disease, suffering a heart attack or succumbing to colon cancer? More than you might think. As scientists delve deeper into the fundamental causes of those and other illnesses, they are starting to see links to an age-old immunological defense mechanism called inflammation—the same biological process that turns a piece of trash into a splinter red and causes swellings in an injured toe. If they are right—and the evidence is strong and already proving to look pretty good—it could radically change doctors' concept of what makes us sick. It could also prove a bonanza to pharmaceutical companies looking for new ways to keep us well.

Most of the time, inflammation is a lifesaver that enables our bodies to fight off various disease-causing bacteria, viruses and parasites. (Yes, even the industrialized world, we are constantly bombarded by pathogens.) The instant any of these potentially deadly microbes slips into the body, inflammation marshals a defensive attack that lays waste to both invader and any tissue it may have infected. Then, just as quickly, the process extrudes and healing begins.

Every once in a while, however,

the whole feverish production doesn't shut down on cue. Sometimes the problem is a genetic predisposition; other times something like smoking or high blood pressure keeps the process going. In any event, inflammation becomes chronic rather than transitory. When that occurs, the body turns on itself—like an errant child, who can't resist picking a scab—with aftereffects that seem to underlie a wide variety of diseases. Suddenly, inflammation has become one of the hottest areas of medical research.

TIME Feb. 23, 2004
Inflammation/Flame/Fire

Controlled

Uncontrolled
Life style Carcinogens/Risk factors
Cancer is a preventable disease that requires major changes in life style.

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
6 actions YOU can take to reduce your cancer risk

1. Eliminate Tobacco Exposure
   Tobacco use accounts for 33% of cancer incidence

2. Reduced Alcohol Intake
   Excessive alcohol consumption accounts for 33% of cancer incidence

3. Healthy Diet
   Poor diet accounts for 5% of cancer incidence and being overweight or obese accounts for 20% of cancer incidence

4. Preventive Medicines
   Infection with pathogenic organisms account for 5% of cancer incidence

5. Reduced Sun Exposure
   Exposure to UV and ionizing radiation accounts for 2% of cancer incidence

6. Physical Activity
   Lack of exercise accounts for 5% of cancer incidence
Reduce your risk of cancer by 30 to 40% by adopting healthier eating habits.

Visit: http://www.mdanderson.org/cancerawareness
Potential Sources of Inflammation

- **Bacteria**
  - Helicobacter pylori
  - Salmonella typhi
  - Chlamydia pneumoniae
  - Streptococcus bovis
  - Escherichia coli

- **Viruses**
  - Herpes simplex virus 8,
  - Hepatitis viruses, HPVs
  - HIV, EBV

- **Stress**
  - pH, hypoxia,
  - heavy metals,
  - chemotherapy

- **Cigarette smoke**

- **Food Factors**
  - Grill,
  - Fried,
  - red meat

- **Environmental pollutants**
  - Industrial pollutant,
  - Diesel, Acid rain

- **Ultraviolet radiation**

- **Alcoholic beverages**

- **Environmental pollutants**
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Expt subjects: (N=9; BMI=25; non-diabetic; 29-38y) fasted overnight, came to clinic between 8-9 AM.

Mixed meals:
Egg muffin,
sausage,
muffin sandwiches,
2 hash browns
(81g CHO, 51g fat; 32 g protein=910 kcal) finished in 15 min.

Control subject: (N=8; BMI=24.3; 26-50 y) given 300ml water

Blood samples: 1, 2, 3 h after the meal.
Working Hypothesis:

Dysregulated chronic inflammation caused by life style factors mediate chronic diseases including cancer!
# Inflammation as a risk factor for most cancers

<table>
<thead>
<tr>
<th>Inducer</th>
<th>Inflammation</th>
<th>Cancers</th>
<th>% predisposed progress to cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoke</td>
<td>Bronchitis</td>
<td>Lung Cancer</td>
<td>11-24</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Gastritis</td>
<td>Gastric Cancer</td>
<td>1 - 3</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>Cervicitis</td>
<td>Cervical cancer</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hepatitis B &amp; C virus</td>
<td>Hepatitis</td>
<td>HCC</td>
<td>10</td>
</tr>
<tr>
<td>Bacteria, GBS</td>
<td>Cholecystitis</td>
<td>Gall bladder cancer</td>
<td>1 – 2%</td>
</tr>
<tr>
<td>Gram- uropathogens</td>
<td>Cystitis</td>
<td>Bladder cancer</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tobacco, genetics</td>
<td>Pancreatitis</td>
<td>Pancreatic cancer</td>
<td>≤10%</td>
</tr>
<tr>
<td>GA, alcohol, tobacco</td>
<td>Esophagitis</td>
<td>Esophageal cancer</td>
<td>15</td>
</tr>
<tr>
<td>Asbestos fibers</td>
<td>Asbestosis</td>
<td>Mesothelioma</td>
<td>10–15</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Mononucleosis</td>
<td>Burkitt’s lymphoma</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gut pathogens</td>
<td>IBD</td>
<td>Colorectal cancer</td>
<td>1*</td>
</tr>
<tr>
<td>Ultraviolet light</td>
<td>Sunburn</td>
<td>Melanoma</td>
<td>≤9%</td>
</tr>
<tr>
<td>Infections, STD</td>
<td>PIA</td>
<td>Prostate cancer</td>
<td>?</td>
</tr>
</tbody>
</table>

GA, gastric acid; GBS, gall bladder stones; HCC, hepatocellular carcinoma; STD, sexually transmitted diseases; PIA, prostate inflammatory atrophy.

Hypothesis!

NF-κB activation is a major mediator of inflammation in most chronic diseases (including cancer) & inhibition of NF-κB can prevent/delay the onset of the chronic diseases!
NF-κB-regulated genes

Cytokines
- LT-α, LT-β, TNF-α, TNFβ, TRAIL, Fas-Ligand, CD40 ligand
- BMP-2, IL-1α, IL-10, G-CSF, M-CSF, GM-CSF, VEGF-C, EPO
- ICOS, LAG4, NK-1R, NK 4, TSP-1, TSP-2, ENA-78, PDGF β chain, Proenkephalin

Acute phase proteins
- Tissue factor-1, C-reactive protein, C4b binding protein, Complement factor B, Complement factor C4, β-defensin-2, Urokinase-type plasminogen activator

Early response genes
- p62, TIEG, B 94, p22/PRG1

Enzymes
- NGAL, CRAD1, CRAD2, Cathepsin L, Collagenase 1, Gelatinase B, H^+ K—ATPase, Xanthine Oxidase, 5-Lipoxygenase, 12-Lipoxygenase, Hemeoxygenase-1, Transglutaminase, ABC Transporters, Hyaluronan synthase, Ceramide glycosyl transferase

Viruses
- CMV, EBV, JC Virus, HPV type 16, Adenovirus, Avian Leukosis Virus, Bovine Leukemia Virus

Receptors
- Gal 1 Receptor, PAF receptor 1, Androgen receptor, μ-opioid receptor, IL-1 receptor antagonist, A1 adenosine receptor, Glucocorticoid receptor, IL-2 receptor α-chain, Immunoglobulin Cγ 1, Immunoglobulin γ4, MHC class I (H-2Kb), MHC Class I (HLA-B7), Polymorphic I g receptor, T-cell receptor β chain, T-cell receptor/CD 3γδ, TNF- Receptor 1, 2, 7, 8, 10, 12, 18, Bradikinin B 1-Receptor, Neuropeptide Y Y1-receptor, Immunoglobulin k light chain, Immunoglobulin e heavy chain, NMDA receptor subunit 1A, NMDA receptor subunit NR-1, Amiloride-sensitive sodium channel

NF-κB

Transcription factors
- c-myb, c-myc, Nurr 1, ELYS, ETR 101, p53, Stat 5a, Lef 1, NF-κB1, NF-κB2

Cell cycle regulators
- p21, Cyclin D1, Gadd 45β, Cyclin D3

Miscellaneous

Inflammatory networking in cancer

**Survival & Chemoresistance:**
- c-FLIP, Bcl-xL
- IAP-1, IAP-2, XIAP, survivin

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

**Invasion and metastasis**
- Chemokines

**Bone loss**
- RANKL, IL-1, TNF

**Angiogenesis**
- VEGF

**NF-κB**

**STAT3**

**IL-6**

**TNF**

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

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

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

Carcinogens

UV light
- Melanoma

Shishodia and Aggarwal, *Biochemical Pharmacology*, 2004
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

Normal cell → Transformation → Survival → Proliferation → Invasion → Angiogenesis → Metastasis

10-20 Years → 10 Years

Inflammation

Aggarwal et al., CCR, 2010
NF-kappa B activation has been linked to most major diseases.

Cigarette Smoke Activates Nuclear Factor-κB and Induces Cyclooxygenase-2

Anto R. J., Mukhopadhyay A., Gairola C. G. and Aggarwal B. B.,

Carcinogenesis, 23, 1511, 2002
Cigarette smoke-induced NF-κB activation is persistent

Shishodia S, and Aggarwal BB.
NF-κB expression in the pathogenesis of lung cancer

Tang et al, 2006
Obesity and Cancer

- Esophageal cancer
- Colon cancer
- Multiple myeloma
- Renal cancer
- Non-Hodgkin’s lymphoma
- Cervical cancer
- Pancreatic cancer
- Rectal cancer
- Uterine cancer
- Endometrial cancer
- Gall bladder cancer
- Gastric cancer
- Ovarian cancer
- Breast cancer
- Liver cancer

Obesity
♂ 14%
♀ 20%

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
NF-κB

NF-κB: the enemy within.

NF-κB: a friend or a foe in cancer?
Shishodia S, Aggarwal BB.

NF-κB in Cancer:
A Matter of Life and Death.
Aggarwal BB, Sung B.
NF-κB: a pivotal transcription factor in chronic inflammatory diseases.

Barnes PJ, Karin M.


Working Hypothesis

- Stress
- NF-kappaB
- Inflammation
- Cancer
Nearly 43% of patients with ulcerative colitis develop colorectal cancer after 25-35 years!

Ekbom A, 1998
Dietary modification can reduce this cancer burden by 70%.

Colorectal cancer is the second most common cause of cancer deaths in affluent countries.

Processed red meat (beef, mutton, lamb, veal, pork, and offal) intake is closely linked with the risk of CRC.

Heterocyclic amines, high saturated fat, carcinogenic N-nitroso compounds, high protein cholesterol and salt contents and heme iron are some of the components of meat linked with CRC.
Inflammatory bowel disease: a survey of the epidemiology in Asia.


PREVALENCE RATES OF ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>CASES/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAPAN</td>
<td>7.9</td>
</tr>
<tr>
<td>INDIA</td>
<td>44.3</td>
</tr>
<tr>
<td>USA</td>
<td>229.0</td>
</tr>
</tbody>
</table>

- Migrant studies of South Asians in the UK, where second-generation immigrants have assumed incidence rates as high as the indigenous whites and Asian Jews who develop high incidence rates comparable to Jews from Europe or North America in Israel point to the role of environmental factors.

- Studies have suggested a change in diet to a more Westernized one may underlie this epidemiological change in the Asian population.

- It is likely that there are racial groups amongst Asians who are more susceptible to IBD and who will demonstrate a higher frequency of IBD when exposed to putative environmental factors.
Global Prostate cancer Incidence per 100,000 (Age-standardized) in 2002

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence</th>
</tr>
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<tbody>
<tr>
<td>USA</td>
<td>124.8</td>
</tr>
<tr>
<td>China</td>
<td>1.6</td>
</tr>
<tr>
<td>India</td>
<td>4.4</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Breast cancer among immigrants from Japan to USA!
A Fire Extinguisher!

How to suppress NF-κB activation safely?
....Sloan School of Management at M.I.T. and the Harvard Business School has created *Pharmer’s Market*, however, we need a *Farmer’s Market*...

New York Times, November, 2009
Hippocrates proclaimed ~2500 years ago

“Let food be thy medicine and medicine be thy food”

Sept 21st, 2012
Farmer’s Market

Fruits

Spices & condiments

Vegetables

Cereals

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
Farmaceuticals!

Refers to medically valuable compounds produced from modified agricultural crops or animals.
Antiinflammatory life style

Spices
- Asian ginger (Alpinia galanga)
- Cloves (Eugenia caryophyllus)
- Fennel (Foeniculum vulgare)
- Fenugreek (Trigonella foenum-graecum)
- Gamboge (Garcinia hanburyi)
- Onion seed (Nigella sativa)
- Holy basil (Ocimum sanctum)
- Onion (Allium cepa)
- Onion seed (Nigella sativa)
- Poppy seed (Papaver somniferum)
- Pomegranate (Punica granatum)

Traditional Chinese Medicine
- Evodia (Evodia rutaecarpa)
- Goldenrod (Solidago canadensis)
- God of thunder vine (Tripterygium wilfordii)
- Indigo (Polygonum tinctorium)
- Lacquer tree (Rhus verniciflua)
- Magnolia (Magnolia officinalis)
- Smoke tree (Cotinus coggyria)
- Songgen (Phellinus linteus)

Ayurvedic Medicine
- Aloe (Aloe vera)
- Ashwagandha (Withania somnifera)
- Boswellia (Boswellia serrata)
- Chitrak (Plumbago zeylanica)
- Clove (Eugenia caryophyllus)
- God of thunder vine (Tripterygium wilfordii)
- Guggulu (Commiphora mukul)
- Himalayan fir (Abies webbiana)
- Indigo (Polygonum tinctorium)
- Picroliv (Picrorhiza kurroa)

Others
- Cashew nut (Anacardium occidentale)
- Cork bush (Euphorbia virosa)
- Elephant’s foot (Euphorbia ssp)
- Fire lily (Glochidion superba)
- Ginger lily (Hedychium coronarium)
- Hop (Humulus lupulus)
- Horse chestnut (Aesculus hippocastanum)
- Palm (Elaeis guineensis)
- Oleander (Nerium oleander)
- Tropical rose mallow (Hibiscus mutabilis)

Fruits & Vegetables
- Artichoke (Cynara cardunculus)
- Cauliflower (Brassica oleracea)
- Grapes (Vitis vinifera)
- Mulberry (Morus nigra)
- Soybean (Glycine max)

Life style
**Spices**

- 1'-Actoxychavicolacetate
- Anethole
- Capsaicin
- Gurmar
- Dicagenin
- Ellagic acid
- Gambogic acid
- Noscapine
- Quercetin
- Sesamin
- Thymoquinone
- Ursolic acid

**Fruits & Vegetables**

- Indole 3-carbinol
- Genistein
- Morin
- Resveratrol
- Silymarin

**Traditional Chinese Medicine**

- Butein
- Berberin
- Celastrol
- Fisetin
- Evodiamine
- Hispolon
- Honokiol
- Indirubin

**Ayurvedic Medicine**

- Betulinic acid
- Crotopoxide
- Embelin
- Emodin
- Flavopiridol
- Guggulsterone
- Indirubin 3'-monoxime
- Nimbolida
- Piceatannol
- Picroliv
- Pinitol
- Plumbagin
- Withanolide
- Zerumbone

**Others**

- Coronarin-D
- Deguelin
- Gossypin
- Gossypol
- Isodeoxyeletophantoin
- Pentamethoxyflavone
- Oleandrin
- Thiocichicoside
- γ-Tocotrienol
- Xanthohumol

- Anacardic acid
- Betulinic acid
- Chimonanthoside
- Coralin-D
- Emodin
- Gossypol
- Isodeoxyeletophantoin
- Oleandrin
- Plumbagin
- Pinitol
- Pentamethoxyflavone
- Quercetin
- Resveratrol
- Silymarin
- Thymoquinone
- Ursolic acid
- Flavopiridol
- Guggulsterone
- Indirubin 3'-monoxime
- Nimbolida
- Piceatannol
- Picroliv
- Pinitol
- Plumbagin
- Withanolide
- Zerumbone
Add spices to your life!
Spice Route

Vasco da Gama lands at Calicut, May 20, 1498.

The route followed in Vasco da Gama's first voyage (1497 - 1499).
Dietary Spices
Spices as functional foods

Universidad Miguel Hernández, Orihuela Alicante.

• Spices and aromatic herbs have been used since antiquity as preservatives, colorants, and flavor enhancers.

• Spices, which have long been the basis of traditional medicine in many countries, have also been the subject of study, particularly by the chemical, pharmaceutical, and food industries, because of their potential use for improving health.

• Both in vitro and in vivo studies have demonstrated how these substances act as antioxidants, digestive stimulants, and hypolipidemics and show antibacterial, anti-inflammatory, antiviral, and anticancerigenic activities.

• These beneficial physiological effects may also have possible preventative applications in a variety of pathologies. The aim of this review is to present an overview of the potential of spices and aromatic herbs as functional foods.
Spice Healer [Preview]

An ingredient in curry shows promise for treating Alzheimer's, cancer and other diseases

By Gary Stix

Searching for new drugs by milling through ancient folk pharmacopoeia or by just picking a plant while walking in the woods has a decidedly checkered history. Many well-established therapeutic compounds originated in trees, shrubs, mollusks, even dirt. Aspirin came from willow bark, cholesterol-lowering statins from a mold, and the antimalarial artemisinin from a shrub used in traditional Chinese medicine.
Is it a coincidence or luck?
TNF blockers

HEALING Spices

Use Spices to Boost Health and Beat Disease

Bharat B. Aggarwal, PhD
TNF blockers

MOLECULAR TARGETS AND THERAPEUTIC USES OF SPICES

Modern Uses for Ancient Medicine

edited by Bharat B Aggarwal (The University of Texas M D Anderson Cancer Center, Houston, Texas, USA) & Ajaikumar B Kunnunnakkara (National Institute of Health, Bethesda, MD, USA)

Most therapeutics available today are highly toxic,

Contents:
The global demand for more affordable therapeutics and concerns about side effects of commonly used drugs are refocusing interest on Eastern traditional medicines, particularly those of India and China.
Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals.

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 234(8):825-49.
Herbs and Spices in Cancer Prevention and Treatment.

Kaefer CM, Milner JA.
Nutritional Science Research Group, National Cancer Institute, Rockville, MD 20892, USA.


The role of herbs and spices in cancer prevention.

Kaefer CM, Milner JA.
Antioxidant capacity and phytochemical content of herbs and spices in dry, fresh and blended herb paste form.


basil, chili, cilantro, dill, garlic, Ginger, lemongrass, oregano, parsley
Spices as NF-κB Inhibitors

**Curcuma longa**  
Turmeric  
*Curcumin*

**Capsicum annum**  
Red chilli  
*Capsaicin*

**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.

More than spice: capsaicin in hot chili peppers makes tumor cells commit suicide

Surh YJ.

Journal National Cancer Institute

2002 Sep 4;94(17):1263-5.

Comment on
Examining the role of mitochondrial respiration in vanilloid-induced apoptosis.
[J Natl Cancer Inst. 2002]
Ginger

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

Takada Y, Murakami A, Aggarwal BB.

Oncogene.
2005 Oct 20;24(46):6957-69
Ginger abolishes RANKL-induced NF-κB activation, inhibits osteoclastogenesis, and suppresses human breast cancer-induced bone loss in athymic nude mice.

Black cumin

Targeting NF-κB 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, IκB kinase activation and NF-κB-regulated gene expression.

**Fennel**

Inhibitory Effects of Black Pepper (*Piper nigrum*) Extracts and Compounds on Human Tumor Cell Proliferation, Cyclooxygenase Enzymes, Lipid Peroxidation and Nuclear Transcription Factor-kappa-B

Yunbao Liu¹, Vivek R. Yadev², Bharat B. Aggarwal² and Muraleedharan G. Nair¹∗
Long pepper
(Piper longam)

Selective killing of cancer cells by a small molecule targeting the stress response to ROS.


Nature.
Cardamonin Sensitizes Tumor Cells to TRAIL Through ROS- and CHOP-Mediated Upregulation of Death Receptors and Downregulation of Survival Proteins.

Cinnamon has been used as a spice and as traditional herbal medicine for centuries.

The available in vitro and animal in vivo evidence suggests that cinnamon has anti-inflammatory, antimicrobial, antioxidant, antitumor, cardiovascular, cholesterol-lowering, and immunomodulatory effects.

In vitro studies have demonstrated that cinnamon may act as an insulin mimetic, to potentiate insulin activity or to stimulate cellular glucose metabolism. Furthermore, animal studies have demonstrated strong hypoglycemic properties.

However, there are only very few well-controlled clinical studies, a fact that limits the conclusions that can be made about the potential health benefits of cinnamon for free-living humans.

The use of cinnamon as an adjunct to the treatment of type 2 diabetes mellitus is the most promising area, but further research is needed before definitive recommendations can be made.
Curcumin: Getting Back to Our Roots!
Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets.

Aggarwal BB, Sung B.

Discovery of curcumin, a component of golden spice, and its miraculous biological activities.

Gupta SC, Patchva S, Koh W, Aggarwal BB.
Structure of Curcumin
From turmeric (curry powder)

### Turmeric Names In Ayurveda

<table>
<thead>
<tr>
<th>Turmeric Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>anestha</td>
<td>(not offered for sacrifice or homa)</td>
</tr>
<tr>
<td>bhadra</td>
<td>(auspicious or lucky)</td>
</tr>
<tr>
<td>bahula</td>
<td>(plenty)</td>
</tr>
<tr>
<td>dhirgharaja</td>
<td>(long in appearance)</td>
</tr>
<tr>
<td>gandhaplashika</td>
<td>(which produces good smell)</td>
</tr>
<tr>
<td>gauri</td>
<td>(to make fair)</td>
</tr>
<tr>
<td>gharshani</td>
<td>(to rub)</td>
</tr>
<tr>
<td>haldi</td>
<td>(that draws attention to its bright color)</td>
</tr>
<tr>
<td>haridra</td>
<td>(dear to hari, Lord Krishna)</td>
</tr>
<tr>
<td>harita</td>
<td>(greenish)</td>
</tr>
<tr>
<td>hemaragi</td>
<td>(exhibits golden color)</td>
</tr>
<tr>
<td>hemaragini</td>
<td>(gives the golden color)</td>
</tr>
<tr>
<td>hridayavilasini</td>
<td>(gives delight to heart; charming)</td>
</tr>
<tr>
<td>jayanti</td>
<td>(one that wins over diseases)</td>
</tr>
<tr>
<td>jawarantika</td>
<td>(which cures fevers)</td>
</tr>
<tr>
<td>kanchani</td>
<td>(exhibits golden color)</td>
</tr>
<tr>
<td>kaveri</td>
<td>(harlot)</td>
</tr>
<tr>
<td>krimighni or kashpa</td>
<td>(killer of worms)</td>
</tr>
<tr>
<td>kshamata</td>
<td>(capability)</td>
</tr>
<tr>
<td>laxmi</td>
<td>(prosperity)</td>
</tr>
<tr>
<td>mangalprada</td>
<td>(who bestows auspiciousness)</td>
</tr>
<tr>
<td>Mangalya</td>
<td>(auspicious)</td>
</tr>
<tr>
<td>mehagni</td>
<td>(killer of fat)</td>
</tr>
<tr>
<td>nisha</td>
<td>(night)</td>
</tr>
<tr>
<td>nishakhya</td>
<td>(known as night)</td>
</tr>
<tr>
<td>nishawa</td>
<td>(clears darkness and imparts color)</td>
</tr>
<tr>
<td>patwaluka</td>
<td>(perfumed powder)</td>
</tr>
<tr>
<td>pavitra</td>
<td>(holy)</td>
</tr>
<tr>
<td>pinga</td>
<td>(redish-brown)</td>
</tr>
<tr>
<td>pinja</td>
<td>(yellow-red powder)</td>
</tr>
<tr>
<td>pita</td>
<td>(yellow)</td>
</tr>
<tr>
<td>pitika</td>
<td>(which gives yellow color)</td>
</tr>
<tr>
<td>rabhargavasa</td>
<td>(which dissolves fat)</td>
</tr>
<tr>
<td>ranjani</td>
<td>(which gives color)</td>
</tr>
<tr>
<td>ratrimanika</td>
<td>(as beautiful as moonlight)</td>
</tr>
<tr>
<td>shifa</td>
<td>(fibrous root)</td>
</tr>
<tr>
<td>shobhna</td>
<td>(brilliant color)</td>
</tr>
<tr>
<td>shiva</td>
<td>(gracious)</td>
</tr>
<tr>
<td>shyama</td>
<td>(dark colored)</td>
</tr>
<tr>
<td>soubhagaya</td>
<td>(lucky)</td>
</tr>
<tr>
<td>survana</td>
<td>(golden color)</td>
</tr>
<tr>
<td>suvarnavara</td>
<td>(which exhibits golden color)</td>
</tr>
<tr>
<td>tamasini</td>
<td>(beautiful as night)</td>
</tr>
<tr>
<td>Umavara</td>
<td>(Parvati, wife of Lord Shiva)</td>
</tr>
<tr>
<td>vairagi</td>
<td>(who remains free from desires)</td>
</tr>
<tr>
<td>varavarnini</td>
<td>(which gives fair complexion)</td>
</tr>
<tr>
<td>varna datri</td>
<td>(enhancer of body complexion)</td>
</tr>
<tr>
<td>varnini</td>
<td>(which gives color)</td>
</tr>
<tr>
<td>Vishagni</td>
<td>(killer of poison)</td>
</tr>
<tr>
<td>yamini</td>
<td>(night)</td>
</tr>
<tr>
<td>yoshitapriya</td>
<td>(beloved of wife)</td>
</tr>
<tr>
<td>yuvati</td>
<td>(young girl)</td>
</tr>
</tbody>
</table>
Antibacterial action of curcumin and related compounds.

SCHRAUFSTATTER E, BERNT H.

Nature.
1949 Sep 10;164(4167):456.
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 $\text{i} \kappa \text{B} \alpha$ Kinase and AKT Activation
Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB.

*Molecular Pharmacology*  
[2006 Jan;69(1):195-206]
Preclinical data with curcumin against various cancers

Gastrointestinal cancers
(Esophagus, Intestine, Liver, Stomach, Pancreas, Colorectal)

Genitourinary cancers
(Bladder, Kidney, Prostate)

Hematological cancers
(Leukemia, Lymphoma, Multiple myeloma)

Bone cancer

Melanoma

Thoracic/H&N Cancers
(Lung, Oral, Thymus)

Gynecologic cancers
(Cervix, Ovary, Uterus)

Brain tumors

Breast cancer

Anand et al., Cancer Letters, 2008
Spicy approach to cancer treatment.

Nath S.
Journal of National Cancer Institute

Curry compound fights cancer in the clinic

Carter A.
Journal of National Cancer Institute
2008 May 7;100(9):616-7.
Multi-targeted Approach to Prevention of Colorectal Cancer by Curcumin/Turmeric
Curcumin as a chemo-sensitizer
Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs.

Suppression of orthotopic implanted human colorectal cancer in mice by turmeric force
Turmeric inhibits the growth of human PaCa and acts as a chemo-sensitizer.
Cancer treatment requires suppression of multiple cell-signaling/survival pathways!
Curcumin binders

Curcumin Interactors

Docking studies

*Ahmed T, 2009  
Zsila F, 2004  
Reddy S, 1994  
Matsunaga T, 2009  
Lin R, 2008  
Muthenna P, 2009  
Snehari AH, 2009  
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Shim JS, 2004  
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Rai D, 2008  
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Su Z, 1993  
Mazumder A, 1995  
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Jung KH, unpublished  
Dairaku I, 2010  
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Jankun J, 2006  
Wang SS, 2009  
Kulkarni SK, 2008  
Gradisar H, 2007  
Wortelboer HM, 2003  
Gupta KK, 2006  
Nafisi S, 2009  
Sahoo BK, 2009  
Ji HF, 2009  
Hafner-Bratkovic I, 2008  
Chearwae W, 2004  
Marcu MG, 2006  
Jutooru I, 2010  
Martin-Cordero C, 2003  
Fang J, 2005  
Pullakhandam R, 2009  
Mullally JE, 2002  
Shen L, 2008  
Sui Z, 1993  
Mazumder A, 1995  
Hu, 2010  
Jung KH, unpublished  
Dairaku I, 2010  
Liu Y, 2008  
Jankun J, 2006  
Wang SS, 2009  
Kulkarni SK, 2008  
Gradisar H, 2007  
Wortelboer HM, 2003  
Gupta KK, 2006  
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Ji HF, 2009  
Hafner-Bratkovic I, 2008  
Chearwae W, 2004  
Marcu MG, 2006  
Jutooru I, 2010  
Martin-Cordero C, 2003  
Fang J, 2005  
Pullakhandam R, 2009  
Mullally JE, 2002  
Shen L, 2008
Multitargeting by curcumin as revealed by molecular interaction studies

Subash C. Gupta, Sahdeo Prasad, Ji Hye Kim, Sridevi Patchva, Lauren J. Webb, Indira K. Priyadarshini and Bharat B. Aggarwal

Fig. 2 Direct molecular targets of curcumin and curcumin analogues.
Multi-targeted

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

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

Growth factors
- TGFβ, 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-apoptotic 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

Inflammatory cytokines
- COX-2
- Celecoxib

Enzymes
- EGFR
- Erbitux

Growth factors
- TNF
- Remicade
- Humira
- Enbrel

Receptors
- HER-2
- Herceptin

Adhesion molecules
- Bcr-Abl
- Gleevec

Anti-apoptotic proteins
- VEGF
- Avastin

Protein Kinases
- Tubulin
- Paclitaxel

Transcriptional factors
- Topoisomerase
- Camptotheacin

Kunnumakkara et al, CL, 2008
Curcumin: gene profile


- Performed gene expression profiling study to identify novel targets of curcumin action.
- A cDNA array comprised of 12,625 probes was used to compare total RNA extracted from curcumin-treated, and untreated, MDA-1986 cells for differential gene expression.
- Identified 202 up-regulated mRNAs and 505 transcripts decreased 2 fold or more.
- The pro-apoptotic activating transcription factor 3 (ATF3) was induced over 4 fold. Two negative regulators of growth control (antagonizer of myc transcriptional activity, Mad, and p27kip1) were induced 68 and 3 fold respectively.
- Additionally, two dual-activity phosphatases (CL 100 and MKP-5) which inactivate the JNKs showed augmented expression, coinciding with reduced expression of the upstream activators of JNK (MEKK and MKK4).
- Of the repressed genes, the expression of Frizzled-1, (Wnt receptor), was most strongly attenuated (8 fold).
- Growth control genes (K-sam, encoding the KGF receptor and HER3) as well as the E2F-5 transcription factor, which regulates genes controlling cell proliferation also showed down-regulated expression.
- Treatment of MDA-1986 cells, yielded a rapid, dose-dependent increase in ATF3 protein. Moreover, expression of an exogenous ATF3 cDNA synergized with curcumin in inducing apoptosis.
- In conclusion, we have identified several putative, novel biological targets of curcumin and demonstrated that one (ATF3) contributes to the pro-apoptotic effects of this compound.
Curcumin is an Orally Bioavailable TNF Blocker
Regulation of production and action of TNF by curcumin

- Ets
- ATF2/Jun
- Sp-1
- NFAT
- AP-1
- NF-κB
- EGR-1
- CREB
- C/EBPα/β
- Nrf-1

TNF-α
- TNFR1
- TRADD
- TRAF2
- RIP
- TAK1
- IKK
- JNK
- P38 MAPK
- ERK
- STAT3
- IL-6R
- IL-6
- NF-κB
- AP-1
- PI3K/AKT

TNF-β
- TNFR2
- PI3K/AKT

- COX2
- INOS
- IL-8
- MMP-9
The 3 main binding regions for curcumin were identified.

Curcumin docked at the receptor-binding sites of TNF-α.

Covalent π–π aromatic interactions or π–cation interactions were found between and curcumin and the TNF-α.

Curcumin is the strong inhibitor of TNF-α because of the covalent bonds it forms with TNF-α.

Curcumin bound to Cys129–in TNF-α.
Evidence that curcumin is an orally bioavailable TNF-a blocker in human

Placebo

N=21

Curcumin
(150 mgx2 daily)

Serum TNF-α (pg/ml)

Pre  Post

N=23

6.0
4.0
2.0
0.0
8 wks

Usharani, 2008
Regulation of production and action of TNF by curcumin
Curcumin increased the phosphorylation of AMP-activated protein kinase (AMPK) and its downstream target acetyl-CoA carboxylase (ACC) with 400 times (curcumin) to 100,000 times (THC) the potency of metformin (Kim, 2009).
White vs Yellow Curcumin

Curcumin (Cur)

Tetrahydrocurcumin (THC)

Sandur, 2007
Curcumin
As An Antioxidant
Curcumin is a better antioxidant than most vitamins.
Curcumin is more potent antioxidant than Vitamin C or Vitamin E

<table>
<thead>
<tr>
<th>Antioxidant</th>
<th>NBT superoxide scavenging activity (IC50 in um)</th>
<th>DPPH free radical scavenging activity (IC50 in uM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>Demethoxycurcumin</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Bis demethoxycurcumin</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Curcumin (no hydroxyl)</td>
<td>810</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Curcumin (hexahydroxy)</td>
<td>4.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>852</td>
<td>25.1</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>726</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Butylated hydroxyanisol (BHA)</td>
<td>966</td>
<td>34</td>
</tr>
<tr>
<td>Butylated hydroxyltoluene (BHT)</td>
<td>381</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Venkateswarlu S, 2005
Curcumin Clinical Trials?
To date, more than 65 human clinical trials of curcumin, which included more than 1000 patients, have been completed, and as many as 35 clinical trials are underway!
Therapeutic Role of Curcumin: Lessons Learned from Clinical trials

Gupta, Patchva and Aggarwal: AAPS J. (in press)
Curcumin Clinical Trials?

**Inflammatory diseases**
- Crohn disease
- Ulcerative proctitis
- Ulcerative colitis
- Inflammatory bowel disease
- Irritable bowel syndrome
- Rheumatoid arthritis
- Osteoarthritis
- Chronic anterior uveitis
- Recurrent anterior uveitis
- Postoperative inflammation
  - Gastric ulcer
  - Peptic ulcer
  - H. pylori infection
- Idiopathic orbital inflammatory pseudotumor

**Skin diseases**
- Vitiligo
- Psoriasis

**Neurodegenerative diseases**
- Dejerine-Sottas disease
- Alzheimer's disease

**Cardiovascular diseases**
- Acute coronary syndrome
- Atherosclerosis

**Metabolic diseases**
- Diabetes
- Diabetic nephropathy
- Diabetic microangiopathy
- Lupus nephritis

**Renal diseases**
- Renal transplantation
- Viral diseases
- Acquired immunodeficiency syndrome

**Cancer**
- Colorectal cancer
- Pancreatic cancer
- Breast cancer
- Prostate cancer
- Multiple myeloma
- Lung cancer
- Cancer lesions
- Head and neck cancer

**OTHERS**
- β-Thalassemia
- Biliary dyskinesia
- Gallbladder contraction
- Recurrent respiratory tract infections
- Cholecystitis
- Hepatoprotection
- Chronic arsenic exposure
- Alcohol intoxication
- Chronic bacterial prostatitis

Curcumin

Gupta, Patchva and Aggarwal; AAPS J. (in press)
TURMERIC (CURCUMIN) IN BILIARY DISEASES

Albert Oppenheimer M.D.

(ASSISTANT PROFESSOR OF ROENTGENOLOGY TO THE AMERICAN UNIVERSITY OF BEIRÛT, LEBANON)

The Lancet, Volume 229,
Issue 5924, Pages 619 - 621, 13 March 1937
Curcumin & Cancer Clinical Trials
Ingestion of 440 mg of Curcuma extract (36 mg curcumin) for 29 days was accompanied by a 59% decrease in lymphocytic glutathione S-transferase activity.

At higher dose levels, this effect was not observed.

Sharma et al., 2001, Clinical Cancer Research
Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis

After six months, the mean percent decrease in the number and size of polyps from baseline was 60.4% and 50.9%, respectively.

Cruz-Correa et al., 2006, Clinical Gastroenterology Hepatology
Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial.

Eighty-nine patients with quiescent UC were recruited.

Forty-five patients received curcumin, 1g after breakfast and 1g after the evening meal, plus sulfasalazine (SZ) or mesalamine, and 44 patients received placebo plus SZ or mesalamine for 6 months.

Of 43 patients who received curcumin, 2 relapsed during 6 months of therapy, whereas 8 of 39 patients in the placebo group relapsed.

Furthermore, curcumin improved both CAI (P=.038) and EI (P=.0001), thus suppressing the morbidity associated with UC.

A 6-month follow-up was done during which patients in both groups were on SZ or mesalamine.

Curry for the cure?

Inflammatory Bowel Disease. 2007

Hanai et al., 2006, Clinical Gastroenterology Hepatology
Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia

Forty-one subjects completed the study (30 days).

Neither dose of curcumin reduced PGE₂ or 5-HETE within ACF or normal mucosa or reduced Ki-67 in normal mucosa.

A significant 40% reduction in ACF number occurred with the 4-g dose, whereas ACF were not reduced in the 2-g group.
A pilot study of the antioxidant effect of curcumin in tropical pancreatitis.

MDA and GSH levels in patients with tropical pancreatitis after oral administration of curcumin for 6 weeks

Durgaprasad et al., 2005, Indian Journal Medical Research
Combined inhibitory effects of soy isoflavones and curcumin on the production of prostate-specific antigen

Serum PSA levels at the baseline (pre) and after administration of isoflavones (40 mg/day) and curcumin (100 mg/day) supplements or placebo (post) for 6 months in participants with PSA < 10 or PSA ≥ 10

Ide et al., 2010, Prostate.
Patients suffering from submucous fibrosis were given a total oral dose of turmeric oil (600 mg TO mixed with 3 g turmeric/day).

Turmeric oleoresin (600 mg + 3 g turmeric/day) and 3 g turmeric/day as a control for 3 months.

It was observed that all three treatment modalities decreased the number of micronucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes.

Turmeric oleoresin was found to be more effective in reducing the number of Mn in oral mucosal cells, but in circulating lymphocytes the decrease in Mn was comparable in all three groups.
Curcumin, the active principle of turmeric, is known to act as an anti-oxidant, anti-mutagen and anti-carcinogen in experimental animals. In the present study, anti-mutagenic effects of turmeric were assessed in 16 chronic smokers.

It was observed that turmeric, given in doses of 1.5 g/day for 30 days, significantly reduced the urinary excretion of mutagens in smokers.

In contrast, in six non-smokers, who served as control, there was no change in the urinary excretion of mutagens after 30 days.

Turmeric had no significant effect on serum aspartate aminotransferase and alanine aminotransferase, blood glucose, creatinine and lipid profile.

These results indicate that dietary turmeric is an effective anti-mutagen and it may be useful in chemoprevention.
Curcumin & CRC patients

126 pts; 360 mg curcumin; thrice/day

(Apoptosis & p53 proteins)

(He et al, 2011)
Curcumin downregulates NF-κB and related genes in patients with multiple myeloma: Results of a phase 1/2 study.


Blood

29 patients with asymptomatic, relapsed, or plateau phase multiple myeloma.

Curcumin was given either alone (orally at 2, 4, 6, 8, or 12 g/d in two divided doses) or in combination with bioperine (10 mg in two divided doses) for 12 weeks.

Peripheral blood mononuclear cells from 28 patients examined at baseline showed constitutively active NF-κB, COX-2, and STAT3.

Furthermore, oral administration of curcumin was associated with significant down-regulation in the constitutive activation of NF-κB and STAT3, and it suppressed COX-2 expression in most of the patients. These observations suggest the potential of curcumin against multiple myeloma.
Constitutive activation of NF-κB in PBMC from MM Patients and its Suppression by Curcumin (2g/day)

<table>
<thead>
<tr>
<th>Patient #4 (482480)</th>
<th>Pre</th>
<th>4w</th>
<th>8w</th>
<th>12w</th>
<th>20w</th>
<th>TNF</th>
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</table>

A, B, C, D, E, F, and G represents Pre, 4, 8, 12, 16, 20 and 24 wks after curcumin administration
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.
"If you want to do something, do it now. Don't wait."
This advice comes 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 turmeric. 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.
Phase II trial of curcumin in patients with advanced pancreatic cancer.

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

Curcumin & Arthritis Clinical Trials
Randomized, Pilot Study to Assess the Efficacy and Safety of Curcumin in Patients with Active Rheumatoid Arthritis

Levels of C-reactive protein in patients with active rheumatoid arthritis at baseline and after curcumin treatment.

Forty-five patients diagnosed with RA were randomized into three groups with patients receiving curcumin (500 mg) and diclofenac sodium (50 mg) alone or their combination.

The primary endpoints were reduction in Disease Activity Score (DAS) 28.

The secondary endpoints included American College of Rheumatology (ACR) criteria for reduction in tenderness and swelling of joint scores.

Patients in all three treatment groups showed statistically significant changes in their DAS scores.

Interestingly, the curcumin group showed the highest percentage of improvement in overall DAS and ACR scores (ACR 20, 50 and 70) and these scores were significantly better than the patients in the diclofenac sodium group.

Chandran and Goel, 2012, Phytother Res
Efficacy and safety of curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients

After three months of treatment, the global WOMAC score decreased by 58%, walking distance in the treadmill test was prolonged from 76 m to 332 m, and CRP levels decreased from 168 +/- 18 to 11.3 +/- 4.1 mg/L in the subpopulation with high CRP.

In comparison, the control group experienced only a modest improvement in these parameters (2% in the WOMAC score, from 82 m to 129 m in the treadmill test, and from 175 +/- 12.3 to 112 +/- 22.2 mg/L in the CRP plasma concentration), while the treatment costs (use of anti-inflammatory drugs, treatment and hospitalization) were reduced significantly in the treatment group.
Efficacy and safety of Meriva®, a curcumin-phosphatidylcholine complex, during extended (8 months) administration in osteoarthritis patients

The treatment consisted of two 500-mg tablets daily, one after breakfast and one after dinner (1,000 mg/day, corresponding to 200 mg curcumin/day).

The composition of the test material was a natural curcuminoid mixture (20%), phosphatidylcholine (40%), and microcrystalline cellulose (40%).

The composition of the curcuminoid mixture was 75% curcumin, 15% demethoxycurcumin, and 10% bisdemethoxycurcumin.

N = 100

Belcaro et al., 2010, Alternate Medicine Review
Curcumin & Psoriasis Clinical Trials
Treatment of psoriasis with Psoria-Gold

Before
11-07-2003

After
4 weeks
12-05-2003

MCY Heng, MK Song, J. Harker and MK Heng, Br. J. Dermatology, 143, 2000, 937-949

Courtesy of Dr. Madeline Heng from UCLA
http://www.psoria-gold.com/RESEARCH.html
Drug-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. 

Elevated PhK activity correlates with psoriatic activity. PhK activity was assayed in four groups, each with 10 patients:

(i) active untreated psoriasis;
(ii) resolving psoriasis treated by calcipotriol, a vitamin D3 analogue and an indirect inhibitor of PhK;
(iii) curcumin, a selective PhK inhibitor;
(iv) 10 normal non-psoriatic subjects.

PhK activity in units mg\(^{-1}\) protein was highest in active untreated psoriasis (1204 +/- 804.3; mean +/- SD), lower in the calcipotriol-treated group (550.7 +/- 192.9), lower in curcumin-treated group (207.2 +/- 97.6), and lowest in normal skin (105.4 +/- 44.6).

One-way analysis of variance performed on log-transformed PhK activity measure showed significant differences among the four groups, F\(_{3,36}\) = 48.79, P < 0.0001.

Our results demonstrate that drug-induced suppression of PhK activity is associated with resolution of psoriatic activity.
Curcumin & Skin Diseases

Curcumin-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters

MCY Heng, MK Song, J. Harker and MK Heng, Br. J. Dermatology, 143, 2000, 937-949

Psoriasis, Actinic keratosis, Acne, Warts, Dermatitis, Eczema
Wound healing, Sunburn, Skin cancer
Uveitis

- Uveitis is the inflammation of uvea.
- Symptoms include red eye, injected conjunctiva, pain and decreased vision.
- Uveitis is estimated to be responsible for approx 10% of the blindness in the USA.
- Treated with steroids, topical cycloplegics, such as atropine or homatropine, methotrexate, anti-TNFs' infusions.


- Administered 600 mg curcumin, twice a day, orally.
- Consisted of 106 patients.
- More than 80% of patients responded.
- Benefits in eye inflammatory and degenerative conditions, such as dry eye, maculopathy, glaucoma, and diabetic retinopathy.

Indicates therapeutic role of curcumin and its efficacy in eye relapsing diseases, such as anterior uveitis, and points out other promising curcumin-related benefits in eye inflammatory and degenerative conditions, such as dry eye, maculopathy, glaucoma, and diabetic retinopathy.

Allegri et al., 2010, Clinical Ophthalmology
Curcumin & Heart Clinical Trials
Currying favor for the heart

Jonathan A. Epstein

Department of Cell and Developmental Biology, Cardiovascular Institute, and Institute for Regenerative Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
Effect of oral curcumin administration on serum peroxides and cholesterol levels in human volunteers

N = 10

![Graphs showing the decrease in MDA, total cholesterol, and HDL cholesterol levels after curcumin administration.]

7 day trial

Soni KB, Kuttan R. Indian J Physiol Pharmacol. 1992
Enrolled 19 healthy men and women, ages 40 to 60 years, in a four-week long study. Subjects received a supplement containing 80 mg curcumin, daily; an age-matched group of 19 other subjects were given placebo and served as controls.

Curcumin supplementation significantly lowered plasma triglyceride levels, lowered salivary amylase while raised salivary radical scavenging capacities, raised plasma catalase activities, lowered plasma soluble intercellular adhesion molecule levels, and increased plasma nitric oxide.

Collectively, these results demonstrate that a low dose of a curcumin-lipid preparation can produce a variety of potentially health promoting effects in healthy middle aged people.”
Curcumin & Diabetes Clinical Trials
Effect of curcumin on blood sugar as seen in a diabetic subject.

Srinivasan M.

Indian J Med Sci.

Effect of NCB-02 (Curcumin), atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-controlled, 8-week study.

Curcumin decreases serum inflammatory biomarkers in DM2 Patients

8 wks

Placebo

Atorvastatin (10 mg/day)

Curcumin (NCB-02 150 mgx2 daily)

Usharani, 2008

<table>
<thead>
<tr>
<th>Biomarkers level</th>
<th>ET-1 (pg/ml)</th>
<th>IL-6 (pg/ml)</th>
<th>TNF-α (pg/ml)</th>
<th>MDA (nmol/ml)</th>
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<tbody>
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<td><strong>Pre</strong></td>
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<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Post</strong></td>
<td>1.0</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

N=21

N=23

N=23
Curcumin extract for prevention of type 2 diabetes

Number of newly diagnosed diabetic subjects after treatment with curcumin

After 9 months of treatment, 16.4% of subjects in the placebo group were diagnosed with T2DM, whereas none were diagnosed with T2DM in the curcumin-treated group.

In addition, the curcumin-treated group showed a better overall function of β-cells, with higher changes in β-cell functions (homeostasis model assessment [HOMA]-β (61.58 vs. 48.72; P < 0.01) and lower C-peptide (1.7 vs. 2.17; P < 0.05).

The curcumin-treated group showed a lower level of HOMA-IR (3.22 vs. 4.04; P < 0.001) and higher adiponectin (22.46 vs. 18.45; P < 0.05) when compared with the placebo group.

Chuengsamarn et al., 2012, Diabetes Care.

A 9-month curcumin intervention in a prediabetic population significantly lowered the number of prediabetic individuals who eventually developed T2DM. Curcumin treatment appeared to improve overall function of β-cells, with very minor adverse effects. This study demonstrated that the curcumin intervention in a prediabetic population may be beneficial.
Curcumin increases the postprandial serum insulin levels in healthy subjects (n=14)

![Graph showing the effect of Curcumin and Placebo on insulin levels over time.](image)

Wickenberg J, 2010
Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-\(\beta\) and interleukin-8 levels in patients with overt type 2 diabetic nephropathy:

*a randomized, double-blind and placebo-controlled study.*

40 patients with overt type 2 diabetic nephropathy, randomized into a trial group (\(n = 20\)) and a control group (\(n = 20\)).

Each patient in the trial group received one capsule with each meal containing 500 mg turmeric, of which 22.1 mg was the active ingredient curcumin (three capsules daily) for 2 months.

The control group received three capsules identical in colour and size containing starch for the same 2 months.

Serum levels of TGF-\(\beta\) and IL-8 and urinary protein excretion and IL-8 decreased significantly comparing the pre- and post-turmeric supplementation values.

Short-term turmeric supplementation can attenuate proteinuria, TGF-\(\beta\) and IL-8 in patients with overt type 2 diabetic nephropathy and can be administered as a safe adjuvant therapy for these patients.

---

Khajehdehi et al., 2011, Scand J Urol Nephrol
**Curcuma longa and Tinospora cordifolia formulation to prevent anti-tuberculosis treatment induced hepatotoxicity**

Curcumin enriched (25%) CL and a hydro-ethanolic extract enriched (50%) TC 1 g each divided in two doses comprised the herbal adjuvant.

Hemogram, bilirubin and liver enzymes were tested initially and monthly till the end of study to evaluate the result.

Incidence and severity of hepatotoxicity was significantly lower in trial group (incidence: 27/192 vs 2/316, P<0.0001).

Mean aspartate transaminase (AST) (195.93+/−108.74 vs 85+/−4.24, P<0.0001), alanine transaminase (ALT) (75.74+/−26.54 vs 41+/−1.41, P<0.0001) and serum bilirubin (5.4+/−3.38 vs 1.5+/−0.42, P<0.0001).

A lesser sputum positivity ratio at the end of 4 wk (10/67 vs 4/137, P=0.0068) and decreased incidence of poorly resolved parenchymal lesion at the end of the treatment (9/152 vs 2/278, P=0.0037) was observed.

Improved patient compliance was indicated by nil drop-out in trial vs 10/192 in control group (P<0.0001).

The herbal formulation prevented hepatotoxicity significantly and improved the disease outcome as well as patient compliance without any toxicity or side effects.

Adhvaryu et al., 2008, World J Gastroenterol.
Synergistic action of curcumin

**Resveratrol**
Majumdar AP, 2009; Csaki, 2009

**Green Tea**

**Quercetin***
Pereiera MA, 1996; Shoskes D, 2006; Cruz-Correa M, 2006; Jackson JK, 2006

**Piperine**
Shoba G, 1998; Kakarala M, 2009

**Genistein**
Mandeville, 2009; Verma, 1997

*inhibits sulfoconjugation (Eaton EA, 1996); ** antagonism when exposed together but synergism when given sequentially.
Cancer incidence 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.
Recruited a group of overweight and obese women, average age 23 years, for a study in which each subject either consumed a glass (330 mL) of tomato juice a day, or water (control beverage), for 20 days.

Among the women who drank tomato juice, IL-8 was reduced by 11.77 pg/mL, and TNF-a was reduced by 5.44 pg/mL, as compared to 6.22 and 0.07 pg/mL, respectively, among the control group.
Add *spice* to your life, not years to your life!
<table>
<thead>
<tr>
<th>Cancer</th>
<th>USA</th>
<th></th>
<th>India</th>
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<tr>
<td></td>
<td>Cases</td>
<td>Deaths</td>
<td>Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>Breast</td>
<td>660</td>
<td>160</td>
<td>79</td>
<td>41</td>
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<tr>
<td>Prostate</td>
<td>690</td>
<td>130</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Colon/Rectum</td>
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<td>220</td>
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<td>18</td>
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<tr>
<td>Lung</td>
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<td>580</td>
<td>38</td>
<td>37</td>
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<tr>
<td>Head &amp; Neck SCC</td>
<td>140</td>
<td>44</td>
<td>153</td>
<td>103</td>
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<tr>
<td>Liver</td>
<td>41</td>
<td>44</td>
<td>12</td>
<td>13</td>
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<tr>
<td>Pancreas</td>
<td>108</td>
<td>103</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Stomach</td>
<td>81</td>
<td>50</td>
<td>33</td>
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<tr>
<td>Melanoma</td>
<td>145</td>
<td>27</td>
<td>1.8</td>
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<td>Testis</td>
<td>21</td>
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<td>Bladder</td>
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<td>Kidney</td>
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<td>Brain, Nervous system</td>
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<td>Endometrial Cancers</td>
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<td>90</td>
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<td>Hodgkin’s disease</td>
<td>20</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

Showing cases per 1 million persons calculated on the basis of current consensus: Endometrial cancers include Cervix uteri and Corpus uteri.

Thank you,