Add Spice to your life for Wellness
Targeting Inflammatory Pathways Linked to Cancer by Dietary Agents

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Hosted by
February 2nd, 2019

Power of Wellness Symposium on Health is Wealth!
(Sponsored by EKAL Vidyalaya; UCSD School of Medicine, San Diego)
Food for Thought
How complicated is the human disease?

- Human body is made up of 13 trillion cells and each cell contains 24,000 different genes.
- Almost 98% of human DNA thought to be junk, is no longer junk.
- The human brain contains nearly 100 billion neurons of at least 1000 different varieties.
- These nerve cells make at least a 100 trillion connections.
- Just like no two human beings are alike, no two cells alike and no two genes are alike.
- Almost 90% of human body is made up of bacteria (>100 trillions) with over 1000 species; and almost one million genes (only 58% identified)-microbiome.
- If so, how do we expect to have a cure to any disease by targeting a single gene, when all chronic diseases are mediated through dysregulation of multiple genes.
Global Cancer Incidence

Cases of cancer per 100,000 population:

- Under 100
- 100-150
- 151-200
- 201-250
- 251-300
- 301 and above

From Parkin DM, EJC, 37, 2000, 4-66
Projection for Global Cancer Incidence and Cancer Deaths

Year

- **2002**
  - New Cases: 10
  - Deaths: 7

- **2020**
  - New Cases: 16
  - Deaths: 10

- **2030**
  - New Cases: 20
  - Deaths: 14

Millions
Working Hypothesis:

Dysregulated chronic inflammation caused by life style factors mediate chronic diseases including cancer!
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.

Aggarwal BB, Gupta SC, Kim JH.
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 stubbed 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 the tissue around a splinter red and causes swelling in an injured toe. If they are right—and the evidence is starting 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 fend off various disease-causing bacteria, viruses and parasites. (Yes, even in 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 extricates 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.
Inflammation/Flame/Fire

**Controlled**

**Uncontrolled**
Inflammation, a Double-Edge Sword for Cancer and Other Age-Related Diseases

Subash Chandra Gupta\textsuperscript{1*}, Ajaikumar B. Kunnumakkara\textsuperscript{2}, Sadhna Aggarwal\textsuperscript{3} and Bharat B. Aggarwal\textsuperscript{4*}

\textsuperscript{1} Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India, \textsuperscript{2} Department of Biosciences and Bioengineering, Indian Institute of Technology, Guwahati, India, \textsuperscript{3} Department of Biotechnology, All India Institute of Medical Sciences, New Delhi, India, \textsuperscript{4} Inflammation Research Center, San Diego, California, CA, United States
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
Inflammation and cancer

Redness, swelling, heat and pain

Rudolf Virchow (1821-1902; in 1850)

His Pathology laboratory in Wurzburg, Germany

Linked Inflammation with atherosclerosis, rheumatoid arthritis, multiple sclerosis, cancer, asthma, Alzheimer’s

From Heidland A et al, History of Nephrology, 2006
Inflammation is “itis”

Arthritis is inflammation of the joints
Bronchitis.......................... Bronchus
Sinusitis.......................... Sinus
Gastritis.......................... Stomach
Esophagitis........................ Esophagus
Pancreatitis........................ Pancreas
Meningitis.......................... Brain
Rhinitis.......................... Rhina
Gingivitis.......................... Gum
**Inflammation-mediated diseases**

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**Inflammation-mediated diseases**

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- Typhlitis
- Tonsillitis
- Urethritis
- Uveitis
- Vaginitis
- Valvulitis
- Vulvitis
- Vulvovaginitis
Inflammatory bowel disease: a survey of the epidemiology in Asia.

Prevalence of rates of Ulcerative Colitis:

**JAPAN** 7.9 per 100,000

**INDIA** 44.3 per 100,000

**USA** 229.0 per 100,000

- 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.
Inflammation as a risk factor for most cancers.

- Hepatitis B&C Virus
- Helicobacter pylori
- Tobacco smoke
- High fat Diet
- Radiation
- Uropathogens
- Alcohol

- Bronchitis
- Hepatitis
- Cervicitis
- Colitis
- Pancreatitis
- Gastritis
- Prostitis
- Cystitis
- Cholecystitis

- Lung Cancer
- Liver Cancer
- Cervical Cancer
- Colon Cancer
- Pancreatic Cancer
- Stomach Cancer
- Prostate Cancer
- Bladder Cancer
- Gall bladder Cancer

**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

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

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

**Invasion and metastasis**
- Chemokines

**Angiogenesis**
- VEGF

NF-κB

IL-6

STAT3

TNF

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

**Tobacco-linked cancers**

- Acute Myelogenous leukemia
- Hodgkin’s disease
- Non-Hodgkin’s lymphoma
- B cell lymphoma
- T cell lymphoma
- Mantle cell lymphoma
- Multiple myeloma
- Thyroid cancer
- Liver cancer
- Breast cancer
- Ovarian cancer
- Prostate cancer

**Viral cancers**

- Acute lymphoblastic leukemia
- Adult T cell leukemia
- Cervical cancer
- Nasopharyngeal carcinoma
- Melanoma

**UV light**

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

Shishodia and Aggarwal, *Biochemical Pharmacology*, 2004
NF-κB addiction and its role in cancer: “One size does not fit all”

Chaturvedi MM, Sung B, Yadav VR, Kannappan R, and Aggarwal BB

ONCOGENE
2011 Apr 7;30 (14):1615-30
Cross Talk between NF-κB and other transcription factors

Chaturvedi et al., 2010
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

Role of inflammation in tumorigenesis

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
NF-κB expression in the pathogenesis of lung cancer

Tang et al, 2006
Obesity and Cancer

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

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

♂ 14% ♂ 20%
NF-κB

NF-κB: the enemy within.

NF-κB: a friend or a foe in cancer?

NF-κB in Cancer:
A Matter of Life and Death.
Working Hypothesis

- Stress
- NF-kappaB
- Inflammation
- Cancer
Neutralizing tumor-promoting chronic inflammation: a magic bullet?

Steroids
NSAID
Celebrex
Metformin
Statins
Natural Products & Traditional Medicine
<table>
<thead>
<tr>
<th>Fruits &amp; Vegetables</th>
<th>Spices</th>
<th>Ayurvedic Medicine</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artichoke (Cynara cardunculus)</td>
<td>Asian ginger (Alpinia galanga)</td>
<td>Aloe (Aloe vera)</td>
<td>Cashew nut (Anacardium occidentale)</td>
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<tr>
<td>Cauliflower (Brassica oleracea)</td>
<td>Cloves (Eugenia caryophyllus)</td>
<td>Ashwagandha (Withania somnifera)</td>
<td>Cork bush (Murraya koenigii)</td>
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<td>Grapes (Vitis vinifera)</td>
<td>Fennel (Foeniculum vulgare)</td>
<td>Boswellia (Boswellia serrata)</td>
<td>Elephant’s foot (Elephantopus scaber Linn)</td>
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<td>Mulberry (Morus nigra)</td>
<td>Fenugreek (Trigonella foenum-graecum)</td>
<td>Hymalayan fir (Abies webbiana)</td>
<td>Fire ily (Selaginella spicata)</td>
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<td>Soybean (Glycine max)</td>
<td>Gambooe (Sambula hardy)</td>
<td>Pink trumpet tree (Tabebuia avellanedae)</td>
<td>Ginger lily (Hedychium spicatum)</td>
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<td>Traditional Chinese Medicine</td>
<td>Onion seed (Nigella sativa)</td>
<td>Holy basil (Ocimum sanctum)</td>
<td>Elephant’s foot (Elephantopus scaber Linn)</td>
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<td>Onion (Allium cepa)</td>
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<td>False pepper (Embelia ribes)</td>
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<td>False pepper (Embelia ribes)</td>
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</tbody>
</table>

**Spices**
- Fennel (Foeniculum vulgare)
- Asian ginger (Alpinia galanga)
- Red chili (Capsicum annum)
- Sesame seed (Sesamum indicum)
- Turmeric (Curcuma longa)
- Gamboge (Garcinia hanburyi)
- Onion seed (Nigella sativa)
- Holy basil (Ocimum sanctum)
- Onion (Allium cepa)
- Poppy seed (Papaver somniferum)
- Pomegranate (Punica granatum)
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- Asian ginger (Alpinia galanga)
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- Turmeric (Curcuma longa)
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- Onion seed (Nigella sativa)
- Holy basil (Ocimum sanctum)
- Onion (Allium cepa)
- Poppy seed (Papaver somniferum)
- Pomegranate (Punica granatum)

**Ayurvedic Medicine**
- Aloe (Aloe vera)
- Ashwagandha (Withania somnifera)
- Boswellia (Boswellia serrata)
- Beauty berry (Celastruss nana)
- Chitrak (Plumbago zeylanica)
- False pepper (Embelia ribes)
- Guggulu (Commiphora mukul)
- God of thunder vine (Tripterygium wilfordii)
- Himalayan fir (Abies webbiana)
- Indigo (Polygonum tinctorium)
- Lacquer tree (Rhus verniciflua)
- Magnolia (Magnolia officinalis)
- Smoke tree (Cotinus coggygria)
- Senggen (Phellinus linkiu)
- Veldt-grape (Cissus quadrangularis)

**Others**
- Cottonseed oil (Gossypium)
- Cashew nut (Anacardium occidentale)
- Cork bush (Murraya koenigii)
- Elephant’s foot (Elephantopus scaber Linn)
- Fire ily (Selaginella spicata)
- Ginger lily (Hedychium spicatum)
- Hop (Humulus lupulus L.)
- Horse chestnut (Aesculus hippocastanum)
- Palm (Elaeis guineensis)
- Oleander (Nerium oleander)
- Tropical rose mallow (Hibiscus rosasinensis)
Hippocrates proclaimed ~2500 years ago

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

Sept 21st, 2012
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)
Farmer's Market

### Vegetables (95)
- Artichoke
- Arugula
- Asparagus
- Tomato
- Bamboo shoot
- Basil
- Beet greens
- Beet root
- Bell pepper
- Butter melon
- Broccoli
- Bottle gourd
- Broad Bean
- Brussel sprouts
- Brussels sprouts
- Cabbage
- Calabacita
- Cauliflower
- Carrot
- Celery
- Cabbage
- Chives
- Chinese cabbage
- Chinese chive
- Chula
- Chives
- Cilantro
- Cluster beans
- Collard
- Cucumber
- Cilantro
- Dill
- Drumstick
- Eggplant
- Elephant Yam
- Endive
- Epazote leaves
- Fenugreek

### Pulses (30)
- Adzukki Beans
- Amaranth
- Autumn Lentil
- Black Beluga Lentils
- Black Chickpeas
- Black Eyed Beans
- Black bean
- Black Soy Beans
- Brown Lentils
- Cannellini Beans
- Chick Peas
- Cranberry Beans
- Fava Beans
- French green Lentils
- Giant Peruvian Lima
- Golden Lentils
- Green pea
- Green lentils
- Green pea
- Ivory white bean
- Kidney Beans
- Lima Beans
- Mung bean
- Navy Peas
- Pigeon pea
- Pinto Beans
- Porso millet
- Red Lentils
- Scarlet beans
- Soya bean
- Yellow Peas

### Nuts (11)
- Almonds
- Brazil Nuts
- Cashews
- Coconut
- Hazelnuts
- Pecan
- Macadamia nuts
- Peanuts
- Pine nuts
- Pistachia

### Cereals (11)
- Barley
- Corn
- Finger millet
- Oat
- Rice
- Pearl millet
- Sorghum
- Spelt
- Triticale
- Wheat
- Wild Rice
Farmer’s Market

Fruits

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
### Farmer’s Market

#### Spices (108)

- Ajowan
- Allspice
- Almond
- Anchar
- Angelica
- Aniseed
- Anatto
- Arrowroot
- Asafoetida
- Barberry
- Basil
- Bay leaf
- Bergamot
- Black Cumin
- Black Lime (Loomi)
- Black pepper
- Boldo (Holdina)
- Bush Tomato
- Calamus
- Candle
- Capers
- Caraway
- Cardamom
- Cashew nut
- Cayenne pepper
- Celery seed
- Chervil
- Christmas
- Chives
- Chicory
- Cinnamon
- Clove
- Coriander
- Coriander seed
- Cubeb
- Cumin
- Curry leaf
- Dates
- Dill
- Epazote
- Fenugreek
- Garlic
- Ginger
- Galangal
- Horseradish
- Hoja santa
- Hyssop
- Indian gooseberry
- Jamaican Sorrel
- Juniper
- Kaffir lime
- Kokum
- Lavender
- Lemongrass
- Lemon Myrtle
- Lemon peel
- Lemon Verbena
- Licorice
- Long pepper
- Lovage
- Mace
- Mahlab
- Mango
- Marjoram
- Mastic
- Moquegua pepper
- Mountain pepper
- Mint
- Mustard
- Myrtle
- Neem
- Nigella
- Nutmeg
- Onion
- Oregano
- Orris root
- Peprika
- Parsley
- Pomegranate
- Poppy seed
- Rosemary
- Saffron
- Sage
- Sassafras
- Savory
- Scented Geranium
- Screw-pine
- Sesame
- Shallot
- Soapwort
- Sorrel
- Star Anise
- Sumac
- Szechwan pepper
- Tamarind
- Taragon
- Terminalia chebula
- Tetracanth Cum
- Thyme
- Tarragon
- Vanilla
- Wasabi
- Watercress
- Wattleseed
- White pepper
- Zedoary

---

Anand P, Harikumar K and Aggarwal BB; Pharmaceutical Research, 2009
Resveratrol can block NF-κB Activation

Figure 1. Sources of resveratrol from different plants.
Resveratrol addiction: to die or not to die.


Chemosensitization of tumors by resveratrol.
Indole-3-Carbinol can block NF-kB activation

Figure 1. I3C is produced by members of the family Cruciferae, and particularly members of the genus Brassica.
Commentary

Tocotrienols, the vitamin E of the 21st century: Its potential against cancer and other chronic diseases

Bharat B. Aggarwal *, Chitra Sundaram, Seema Prasad, Ramaswamy Kannappan

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 143, Houston, TX 77030, USA
Tocopherols
37,323 pub

Tocotrienols
1127 pub

Alfa

Beta

Gamma

Delta

Alfa

Beta

Gamma

Delta
Natural Sources of Tocotrienols

- Oryza sativa (Rice)
- Hordeum distichon (Barley)
- Avena sativa (Oat)
- Triticum vaccinimum (Wheat)
- Elaeis guineensis (Palm)

http://www.tocotrienol.org/index.html
Sources of tocotrienols

- Red annatto: 940 mg/kg
- Palm oil: 910 mg/kg
- Barley: 465 mg/kg
- Rice bran: 380 mg/kg
- Grape fruit seed oil: 25.1 mg/kg
- Oat: 210 mg/kg
- Hazelnut: 200 mg/kg
- Maize: 200 mg/kg
- Wheat germ oil: 189 mg/kg
- Olive oil: 180 mg/kg
- Buckthorn Berry: 130 mg/kg
- Rye: 92 mg/kg
- Flax seed oil: 25.1 mg/kg
- Poppy seed oil: 20.5 mg/kg
- Safflower oil: 11.8 mg/kg

From: Red annatto, Barrie, Tan; Palm oil, Schroeder, 2006; Rice bran, Sookwong, 2010; Grape fruit seed oil, maize, Wheat germ oil-Hassanein, 2009; Hazel nut, Amaral, 2006; Olive oil, Cunha, 2006; Buckthorn berry, Kallio, 2002; Rye-milagros Delgado-Zamarreno, 2009; Oat and barley, Panfili, Fratianni, 2000; Flax oil, poopy oil, safflower oil, Bozan, 2008

From Aggarwal et al, 2010
γ-tocotrienol but not tocopherol inhibits NF-κB signaling pathway through inhibition of RIP and TAK1 leading to suppression of antiapoptotic gene products and potentiation of apoptosis.

Ahn KS, Sethi G, Krishnan K, Aggarwal BB.

Journal of Biological Chemistry.
Role of γ-Tocotrienols in Treatment of Human Pancreatic Cancer
{gamma}-Tocotrienol Inhibits Pancreatic Tumors and Sensitizes Them to Gemcitabine Treatment by Modulating the Inflammatory Microenvironment.


Cancer Research
2010 Nov 1;70(21):8695-705.
From traditional Ayurvedic medicine to modern medicine: identification of therapeutic targets for suppression of inflammation and cancer.


Expert Opin Therapeutic Targets 2006 Feb;10(1):87-118.
Identification of Novel Anti-inflammatory Agents from Ayurvedic Medicine for Prevention of Chronic Diseases: “Reverse Pharmacology” and “Bedside to Bench” Approach

Bharat B. Aggarwal*, Sahdeo Prasad, Simone Reuter, Ramaswamy Kannappan, Vivek R. Yadav, Byoungduck Park, Ji Hye Kim, Subash C. Gupta, Kanokkarn Phromnoi, Chitra Sundaram, Seema Prasad, Madan M. Chaturvedi and Bokyung Sung
Guggul is one of the most ancient medicines described in Ayurveda.

The Veda says, "Yakshma (disease), it cannot appear in sunlight.

Guggulu is the best medicine, because it develops through the rays of hot sun on specific circumstances.

Guggulu has an aromatic odor. It removes the disease, like a deer that runs away on seeing the horse.

A mixture of Guggulu and common salt remove the disease along with their complications"

Structure of guggulsterone

![Structure of Guggulsterone](image)
Googling the Guggul (Commiphora and Boswellia) for Prevention of Chronic Diseases

Ajaikumar B. Kunnunakkara\textsuperscript{1*}, Kishore Banik\textsuperscript{1}, Devivasha Bordoloi\textsuperscript{1}, Choudhary Harsha\textsuperscript{1}, Bethsebie L. Sailo\textsuperscript{1}, Ganesan Padmavathi\textsuperscript{1}, Nand K. Roy\textsuperscript{1}, Subash C. Gupta\textsuperscript{2} and Bharat B. Aggarwal\textsuperscript{3*}

\textsuperscript{1} Cancer Biology Laboratory, DBT-AIST International Laboratory for Advanced Biomedicine (DAILAB), Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, Assam, India, \textsuperscript{2} Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India, \textsuperscript{3} Inflammation Research Center, San Diego, CA, United States
Dietary natural products and their potential to influence health and disease including animal model studies – a review*

Andy Wai Kan Yeung¹**, Bharat Bhushan Aggarwal², Davide Barreca³,
Guggulsterone inhibits osteoclastogenesis induced by receptor activator of NF-kB ligand and by tumor cells by suppressing NF-kB activation.


Guggulsterone [4,17 (20)-pregnadiene-3,16-dione], a plant sterol derived from the gum resin (guggulu) of the tree Commiphora mukul.

The resin has been used in Ayurvedic medicine for centuries to treat a variety of ailments, including obesity, bone fractures, arthritis, inflammation, cardiovascular disease, and lipid disorders.

The anti-arthritic and anti-inflammatory activity of gum guggul was shown as early as 1960 by Gujral et al. followed by a report of activity in experimental arthritis induced by mycobacterial adjuvant.

Guggulsterone Suppresses Osteoclastogenesis and another on the effectiveness of guggul for treating osteoarthritis of the knee.

Guggulsterone is an antagonist for the bile acid receptor farnesoid X receptor.

Guggulsterone enhances transcription of the bile salt export pump, thereby regulating cholesterol homeostasis.
AKBA potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis by suppressing NF-kB and NF-kB-regulated gene expression.

The plant Withania somnifera Dunal (Ashwagandha), also known as Indian ginseng, is widely used in the Ayurvedic system of medicine to treat tumors, inflammation, arthritis, asthma, and hypertension.

Withanolides potentiate apoptosis, inhibit invasion, and abolish osteoclastogenesis through suppression of NF-kB activation and NF-kB-regulated gene expression.

Ichikawa H, Takada Y, Shishodia S, Jayaprakasam B, Nair MG, Aggarwal BB. 
Long pepper
(Piper longam)

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


Nature.
Piperlongumine chemosensitizes tumor cells through interaction with cysteine 179 of IkBα kinase, leading to suppression of NF-κB-regulated gene products.

NEEM tree (Azadirachta indica)

Sanskrit- “sarva roga nivarini” (the curer of all ailments).

Nimbolide
Modification of Cysteine 179 of IκBα Kinase by Nimbolide Leads to Down-regulation of NF-κB-regulated Cell Survival and Proliferative Proteins and Sensitization of Tumor Cells to Chemotherapeutic Agents

Received for publication, July 6, 2010, and in revised form, September 6, 2010  Published, JBC Papers in Press, September 9, 2010, DOI 10.1074/jbc.M110.161984

Subash C. Gupta†, Sahdeo Prasad‡, Simone Reuter‡, Ramaswamy Kannappan‡, Vivek R. Yadav‡, Jayaraj Ravindran‡, Padmanabhan S. Hema§, Madan M. Chaturvedi‡1, Mangalam Nair§, and Bharat B. Aggarwal‡2

From the †Cytokine Research Laboratory, Department of Experimental Therapeutics, University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030 and the §Organic Chemistry Section, National Institute for Interdisciplinary Science and Technology (Council for Scientific and Industrial Research), Trivandrum, 695 019 Kerala, India
Nimbolide, a Limonoid Triterpene, Inhibits Growth of Human Colorectal Cancer Xenografts by Suppressing the Proinflammatory Microenvironment

Subash C. Gupta¹,², Sahdeo Prasad¹, Dhanya R. Sethumadhavan³, Mangalam S. Nair³, Yin-Yuan Mo², and Bharat B. Aggarwal¹
From exotic spice to modern drug?

Singh S.
Cell. 2007 Sep 7;130(5):765-8.

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.
Chronic diseases, inflammation, and spices: how are they linked?

Ajaikumar B. Kunnumakkara¹*, Bethsebie L. Sailo¹, Kishore Banik¹, Choudhary Harsha¹, Sahdeo Prasad², Subash Chandra Gupta³, Alok Chandra Bharti⁴ and Bharat B. Aggarwal⁵*
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
Healing Spices
TNF blockers

Connecting Great Minds

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 Kunnumakkara (National Institute of Health, Bethesda, MD, USA)

Contents:
Add Spice to your Life!
Curry in Hurry!
Spice it up!
Spice Queen!
Spice Goddess!
Spicy Names

Anise
Ginger
Rosemary
Mace
Pepper
Basil
Tulsi
Sage
Jasmine
Angelica
Curry
Chilli
Tamarind
Dietary nutraceuticals as backbone for bone health

Manoj K. Pandey\textsuperscript{a,*}, Subash C. Gupta\textsuperscript{b}, Deepkamal Karelia\textsuperscript{c}, Patrick J. Gilhooley\textsuperscript{a}, Mehdi Shakibaei\textsuperscript{d}, Bharat B. Aggarwal\textsuperscript{e}

\textsuperscript{a} Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ, USA
\textsuperscript{b} Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India
\textsuperscript{c} Department of Pharmacology, Penn State College of Medicine, Hershey, PA, USA
\textsuperscript{d} Musculoskeletal Research Group and Tumour Biology, Chair of Vegetative Anatomy, Institute of Anatomy, Ludwig-Maximilian-University, Munich, Germany
\textsuperscript{e} Inflammation Research Center, San Diego, CA, USA
Healing with Spices

Julie Chugh
<table>
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<tr>
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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.
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.
Ginger

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

Takada Y, Murakami A, Aggarwal BB.

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

Targeting \textit{NF-\kappa B} activation pathway by thymoquinone: role in suppression of antiapoptotic gene products and enhancement of apoptosis.
Sethi G, Ahn KS, Aggarwal BB.

Thymoquinone inhibits tumor \textit{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-kB-regulated gene expression.

Black pepper
(Piper indica)

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

RANKL Signaling and Osteoclastogenesis Is Negatively Regulated by Cardamonin

Bokyung Sung¹⁰, Sahdeo Prasad¹⁰, Vivek R. Yadav¹, Subash C. Gupta¹, Simone Reuter¹, Norio Yamamoto², Akira Murakami³, Bharat B. Aggarwal¹*

¹ Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America, ² Food Science Research Center, House Wellness Foods Corporation, Itami, Japan, ³ Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto, Japan
Curcumin: Getting Back to Our Roots!
Structure of Curcumin
From turmeric (curry powder)

Diferuloylmethane

Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets.

Aggarwal BB, Sung B B.

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

Gupta SC, Patchva S, Koh W, Aggarwal BB.
Curcumin From turmeric

Curcuma longa

CH3O

HO

Dried rhizome

Blend (Turmeric)

Extract in 95% ethanol for 24 h, filter and dry

Curcumin based products

Tetrahydrocurcumin (THC)
Antibacterial action of curcumin and related compounds.

SCHRAUFSTATTER E, BERNT H.

Nature.

1949 Sep 10;164(4167):456.
Curcumin is as potent as hydrocortisone and phenylbutazone

Anti-inflammatory and irritant activities of curcumin analogues in rats. Mukhopadhyay A et al Agents Actions. 1982
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]
Preclinical data with curcumin against various cancers

Curcumin and cancer: an "old-age" disease with an "age-old" solution.
Regulation of production and action of TNF by curcumin
Curcumin binders

Curcumin Interactors

Docking studies

Kim 11-03-2010
TNF blockade: an inflammatory issue


Ernst Schering Res Found Workshop.

2006;(56):161-86. Review.
Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. 
**Selected FDA approved TNF blockers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Disease</th>
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<td>Infliximab</td>
<td>mAbs</td>
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<tr>
<td>Etanercept</td>
<td>RD</td>
<td>RA, PA, psoriasis, ALS, juvenile RA</td>
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<tr>
<td>Adalimumab</td>
<td>mAbs</td>
<td>RA, PA, psoriasis, ALS, juvenile RA, Crohn's disease</td>
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<td>Certolizumab</td>
<td>mAbs</td>
<td>RA, Crohn's disease</td>
</tr>
<tr>
<td>Golimumab</td>
<td>mAbs</td>
<td>RA, PA, AS</td>
</tr>
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</table>

*Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey.*

Various diseases that have been closely linked to TNF-α and members of its family.
TNF Blockers
($20 billion/year)

- Lymphoma
- Infections
- Develop resistance
- T cell Non-Hodgkins Lymphoma
- Cutaneous T Cell lymphoma
- Injectable only
- Sezary syndrome

Deepak, 2012; Askling, 2005a, 2005b; Siegel, 2009; Herrinton, 2011; Parakkal, 2011; Adams, 2004; Dalle, 2005; Michot, 2009; Dauendorffer, 2007; Lourari, 2009; Schmidt, 2009; Mackey, 2007
**REVIEW**

Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers

Bharat B Aggarwal, Subash C Gupta and Bokyung Sung

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
Evidence that curcumin is an orally bioavailable TNF-a blocker in human

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<td>Post</td>
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<td>Serum TNF-α (pg/ml)</td>
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Curcumin Clinical Trials (120)

- Panahi, 2015
- Panahi, 2014
- Lopresti, 2014
- Nakayama, 2014
- Henrotin, 2014
- Panahi, 2014
- Ganjali, 2014
- Abidi, 2014
- Kuptniratsaikul, 2014
- Soare, 2014
- Panahi, 2014
- Klickovic, 2014
- Takahashi, 2014
- Jager, 2014
- Singla, 2014
- Sanmukhani, 2014
- Belcaro, 2014
- Cheungsamarn, 2014
- Basu, 2013
- Hejazi, 2013
- Morimoto, 2013
- Marciani, 2013
- Moreillon, 2013
- Ryan, 2013
- Elad, 2013
- Bergman, 2013
- Peek, 2013
- Kanai, 2013
- Muglikar, 2013
- Mohammadi, 2013
- Suskind, 2013
- Sahebkar, 2013
- Na, 2013
- Vaolak, 2013
- Irving, 2013
- Ledda, 2012
- Steigerwalt, 2012
- Akazawa, 2012
- Panahi, 2012
- Kudva, 2012
- DiSilvestro, 2012
- Cheungsamarn, 2012
- He, 2012
- Wongharoen, 2012
- Golombick, 2012
- Sugawara, 2012
- Chandran, 2012
- Vitaglione, 2012
- Chainani-Wu, 2012
- Kusuhara, 2012
- Araujo, 2012
- Pinsornsak, 2012
- Wolff, 2012
- Panahi, 2012
- Chainani-Wu, 2012
- Khajehdehi, 2012
- Kanai, 2012
- Appendino, 2011
- Mishra, 2011
- Pungcharoenkul, 2011
- Agarwal, 2011
- Khajehdehi, 2011
- Sasaki, 2011
- Cuomo, 2011
- Carroll, 2011
- Aggarwal, 2011
- Kanai, 2011
- He, 2011
- Belcaro, 2010
- Asawanonda, 2010
- Ide, 2010
- Sannia, 2010
- Koosirirat, 2010
- Dominiak, 2010
- Biswas, 2010
- Bayet-Robert, 2010
- Kalpravidh, 2010
- Burns, 2009
- Golombick, 2009
- Masouni, 2009
- Cai, 2009
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- Marczylo, 2007
- Everett, 2007
- Juan, 2007
- Tuntipopipat, 2006
- Hanai, 2006
- Cruz-Correa, 2006
- Loa, 2006
- Durgaprasad, 2005
- Shoskes, 2005
- Holt, 2005
- Ringman, 2005
- Garcea, 2005
- Sharma, 2004
- Bao, 2003
- Rasyid, 2002
- Plummer, 2001
- Cheng, 2001
- Sharma, 2001
- Heng, 2000
- Ramirez Bosca, 2000
- Niederau, 1999
- Lal, 1999
- Rasyid, 1999
- Shoba, 1998
- James, 1996
- Satoskar, 1986
- Deodhar, 1980
- Pilz, 1975

Stefan, R. (1934) Quoted by Vetterlein.

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 Bioavailability

How big is the problem?
**Curcumin Bioavailability**

<table>
<thead>
<tr>
<th>Title</th>
<th>Cited By</th>
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<tr>
<td>Bioavailability of curcumin: problems and promises</td>
<td>2717</td>
<td>2007</td>
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<td>Anticancer potential of curcumin: preclinical and clinical studies</td>
<td>2437</td>
<td>2003</td>
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<td>Signalling pathways of the TNF superfamily: a double-edged sword</td>
<td>2431</td>
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<td>Human tumour necrosis factor: precursor structure, expression and homology to lymphotoxin</td>
<td>2064</td>
<td>1984</td>
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<td>Oxidative stress, inflammation, and cancer: how are they linked?</td>
<td>1982</td>
<td>2010</td>
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<td>Recombinant human tumor necrosis factor-alpha: effects on proliferation of normal and transformed cells in vitro</td>
<td>1839</td>
<td>1985</td>
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<td>Molecular targets of dietary agents for prevention and therapy of cancer</td>
<td>1664</td>
<td>2006</td>
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<td>Nuclear factor-kB: the enemy within</td>
<td>1576</td>
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<td>Curcumin as &quot;Curcumin&quot;: from kitchen to clinic</td>
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<td>Cancer is a preventable disease that requires major lifestyle changes</td>
<td>1465</td>
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<td>Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies</td>
<td>1360</td>
<td>2004</td>
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<td>Activation of transcription factor NF-kB is suppressed by curcumin (diferuloylmethane)</td>
<td>1313</td>
<td>1995</td>
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<td>Curcumin: the Indian solid gold</td>
<td>1289</td>
<td>2007</td>
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Biodistribution of $^{125}$I-Curcumin in normal mice

Curcumin level (ID/g) vs. Time (min)

Ryu, 2006
Curcumin as local application on the lesion of a Bulgarian tumor stage CTCL patient
Curcumin & Psoriasis Clinical Trials
Treatment of psoriasis with Psoria-Gold

Before
11-07-2003

R Knee  L Knee  L Leg  L Elbow

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
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.
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/detial/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.
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<td>Prostate</td>
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<td>Colon/Rectum</td>
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<td>Lung</td>
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<td>Head &amp; Neck SCC</td>
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<td>Liver</td>
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<td>Pancreas</td>
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<td>Endometrial Cancers</td>
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<td>Ovary</td>
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</table>

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

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.
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.

Image no longer available.

The full versions of this and other articles from the print edition—including all graphics and sidebars—are available for purchase at Scientific American Digital.

Click here to go to Scientific American Digital
Is it a coincidence or luck?
Haldi (Turmeric) is Healthy

Bharat B. Aggarwal, Ph.D.
Anti-Inflammation Research Institute, San Diego, California;

Former Professor & Chief, Cytokine Research, Department of Experimental Therapeutics,
The University of Texas, M.D. Anderson Cancer Center, Houston, Texas, U.S.A.

Former Senior Scientist, Genentech Inc., South San Francisco, California
PDF, University of California, San Francisco; Ph.D., University of California, Berkeley, CA

Plenary Talk on Wednesday, August 3rd, 2016
Hosted by Dr. Sanni Raju, Ph.D., R.Ph., CEO & Chairman
Natreon Inc.; 2D Janine Place; New Brunswick, NJ 08901
(732) 296-1080; (732) 296-1075; info@natreoninc.com
In Curry Hill, a New Kid on the Block
Haldi in Midtown South

MARCH 19, 2015

Eric Marsh Moran for The New York Times
Haldi means turmeric in Hindi, thus the sunny yellow chairs, under chandeliers of green bottles and copper wok-like pans called kadhai, inverted and fixed to the ceiling.

Although chemotherapy is routinely used in the treatment of almost all cancers, the development of eventual resistance to chemotherapy is one of the major problems in the treatment. Thus chemosensitization to Cancer is needed. The compounds derived from natural sources, which are usually multi-targeted can overcome chemoresistance. This includes:

- Curcumin,
- Resveratrol,
- Indole 3-carbinol,
- Tocotrienols,
- Ursolic acid,
- Fisetin,
- Celastrol,
- gambogic,
- Butein,
- Catechins,
- Silymarin.
First International Conference On Nutraceuticals and Chronic Diseases September 9-11, 2016

Cochin, Kerala, India

Abstract Submission Deadline: 31st July 2016

Sponsored by International Society of Transitional Cancer Research
Indian Institute of Technology, Guwahati, Assam, India

Organizing Committee

Theme

Extensive research over the last half a century has revealed that most chronic diseases are caused by the dysregulation of multiple genes. However, most of the drugs designed by men (pharmaceutical companies) are highly specific and lack sufficient chemicals that target single genes. Thus such drugs are not so effective and exhibit side effects when taken for a long period of time. In contrast, most drugs designed by “mother nature” are multi-targeted, highly effective over long-term and exhibit minimal side effects. Until very recently, almost 80% of all drugs had their roots in natural products that are also some time referred to as “Nutraceuticals”. The history of these nutraceuticals goes back thousands of years as indicated by Ayurveda (Science of long life), “Sidhha”, “Himachalpatri”, and other ancient branches of disease treatment. The current conference is designed to explore the scientific basis for the role of nutraceuticals in chronic diseases. Nutraceuticals derived from spices, other dietary sources, and medicinal plants will be included. Chronic diseases such as diabetes, obesity, cancer, mental diseases, arthritis, cardiovascular, pulmonary, and infectious diseases will be covered. Topic such as changes in epigenomics, biofilms, microbiome, omics by nutraceuticals will also be covered. Scientists who are totally devoted to this topic are invited from around the world.

Advisors

Sen Puithok (USA)
Soni Kauf (Japan)
Resa Watanow (Japan)
Sicheriah Chauhan (USA)
Guatam Sethi (Singapore)
Vigya Kumar (USA)
Maden Kumar Georgiev (Bulgaria)
Forid Badia (Egypt)
Kannan Parkhutikram (India)
Altej C. Surati (India)
Karanadakar D (India)
S.V. Choppa (India)
Ram Raja (India)
Ramdasan Kuttram (India)
Prabhudas Patil (India)
Rahul Patwardhan (India)
Mangalam Nair (India)
Hind S. Singh (India)
Vijay Pratap Shukla (India)
Ruby Anil Ante (India)
Murli Abraham (India)
Santwana Chakraborty (India)

Contact us

Aajikumar B. Kunnumakkara, Ph.D.
kunnumakkara@itc.ernet.in
Ph: 09909343234

Registration details

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Venue:
Riviera Suites, Thirva Waterfront, Cochin, Kerala, India

For more details: Please visit www.itc.ernet.in/kunnumakkara2016/pare-main.html
Acknowledgement

Klara Totpal
Raj Pandita
Henry Chan,
Yash Gad,
Santosh Kumar, PhD,
Madan Chaturvedi, PhD,
Bokyung Sung, PhD,
Ramawamy Kannappan, PhD,
Simone Reuter, PhD,
Vivek R. Yadav, PhD,
Byoungduck Park, PhD,
Subash Chandra Gupta, PhD,
Ji Hye Kim, PhD,
Vrushali Van Kuiken, PhD,
Mathew John, PhD.
Toshihiko Utsumi, PhD,
Venkat Sharma, PhD,
H Raghava Reddy, PhD,
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Sinjini Singh, Ph.D.
Qaisar Manzoor,
Arfaa Sajid,
Sasha Raman,
Suresh Devabhakutuni,
Meena Sundaresan
Thank you,

Grazie

Namste

Thank you,

Gracias!

Arigato!

Teşekkür ederim!

Obrigado!

Merci!

Gamsa hamnida!

Kiitos!

Shalom!

Shei-shei!

Do Jeh!

Danke!
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Aggarwal Talks and interviews

Radio Interview  http://www.youtube.com/watch?v=Zht2Q5D0RdY
McGill University  http://www.youtube.com/watch?v=XT7vXV7MCmE
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Samidirect (CURCUMIN C3 POWER), Cancer Testimonial Team Chairman Club
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