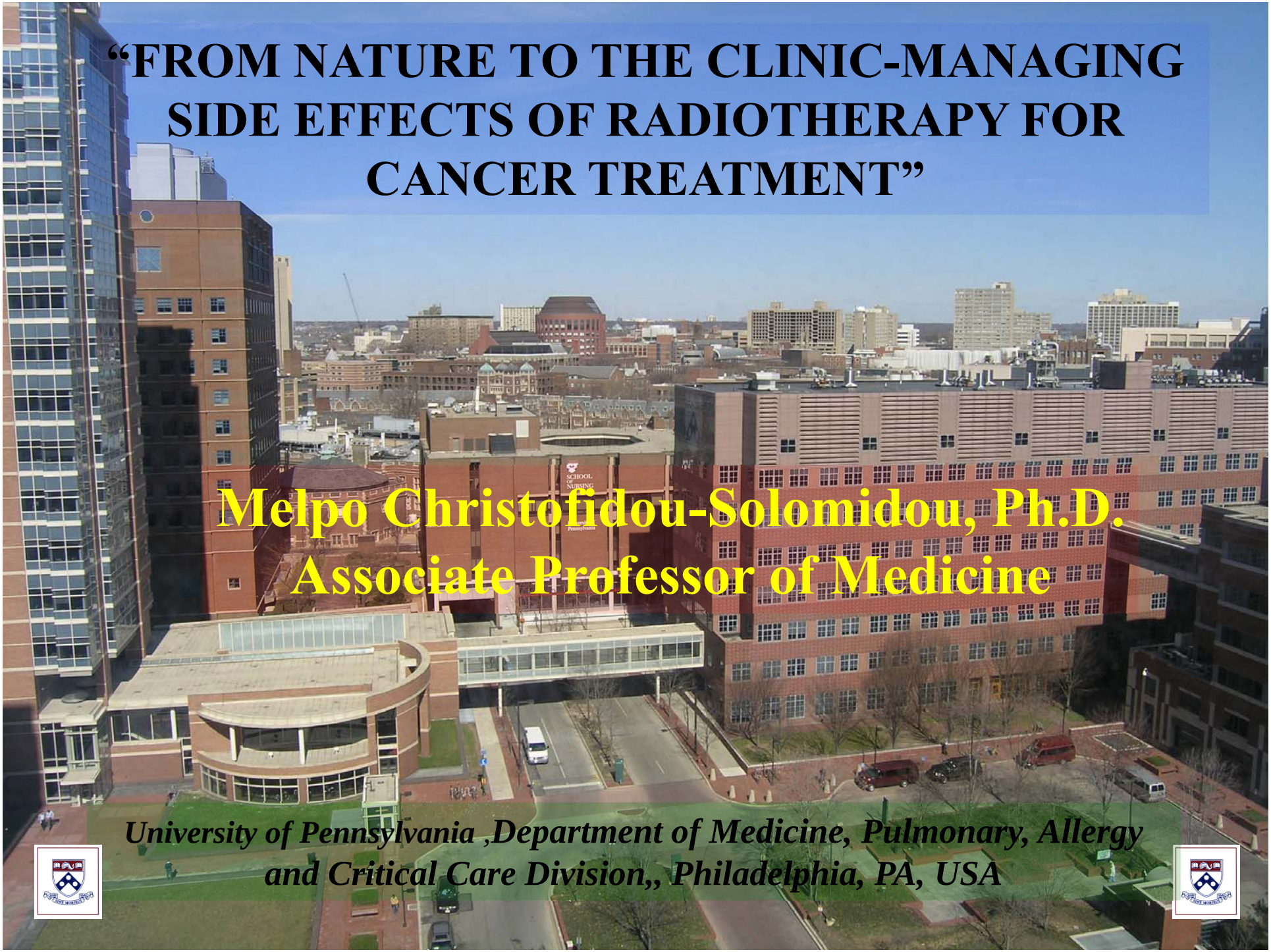
"FROM NATURE TO THE CLINIC-MANAGING SIDE EFFECTS OF RADIOTHERAPY FOR CANCER TREATMENT"



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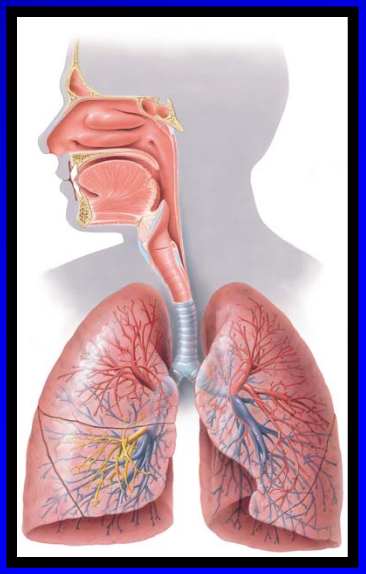
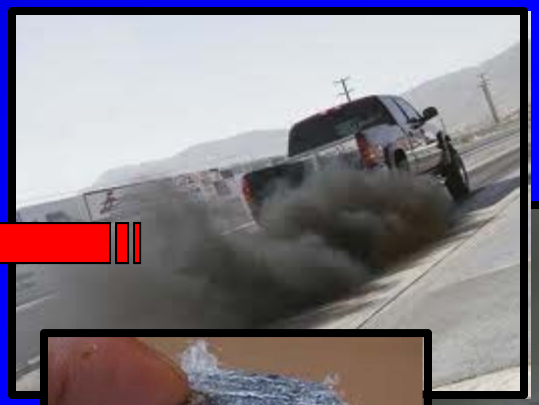
Presentation Outline

1. Introduce oxidative lung damage.
2. Radiation toxicity of normal lung tissues
3. Natural products and their use in mitigating radiation lung damage.
4. Modeling lung toxicity in rodents to study adverse effects of therapeutic radiation
5. Designing Effective Radioprotecting agents

Oxidative Lung Damage

Airborne Toxins





Asbestos fibers

Blood-borne Toxins

Radiation

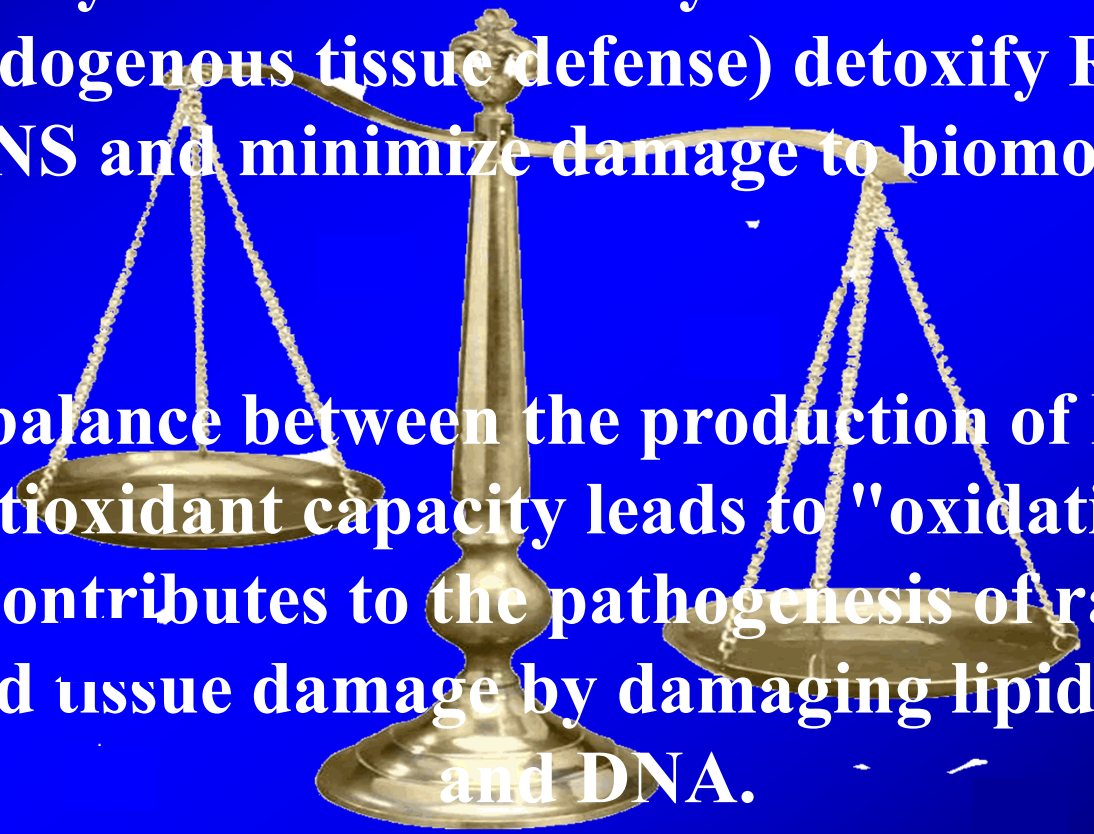
Oxidative/Nitrosative Stress and Radiation Lung Damage

The lung is one of the most sensitive tissues to ionizing radiation, and damage to normal lung tissue remains a major obstacle in the treatment of a variety of cancers.

An immediate effect of tissue irradiation is the generation of reactive oxygen (ROS) and nitrogen (RNS) species that can produce oxidative damage to DNA, lipids, and proteins resulting in cell injury or death

Oxidative/Nitrosative Stress and Tissue Damage

Enzymatic and nonenzymatic antioxidants (endogenous tissue defense) detoxify ROS and RNS and minimize damage to biomolecules.



An imbalance between the production of ROS/RNS and antioxidant capacity leads to "oxidative stress" that contributes to the pathogenesis of radiation-induced tissue damage by damaging lipids, protein, and DNA.

RADIATION PNEUMONOPATHY

Radiation Pneumonopathy

Radiation Therapy is commonly used to treat lung cancer and other thoracic malignancies (mesothelioma, breast cancer, esophageal cancer, lymphomas).

Up to 30% of patients irradiated for lung cancer and 10-15% of other thoracic oncology patients develop clinically significant radiation lung injury.

Radiation Damage to the Lung is characterized by:
A) Pneumonia-like symptoms (inflammation)
B) Fibrotic lung damage (irreversible).

Scoring of Clinical Manifestations of Radiation Damage of Lung Tissues

RTOG/EORTC Late Radiation Morbidity Scoring Schema

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency / Continuous O_2/ Assisted ventilation	Death directly related to radiation late effects

http://rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx

Current Readings: Improvements in Intensity-Modulated Radiation Therapy for Malignant Pleural Mesothelioma

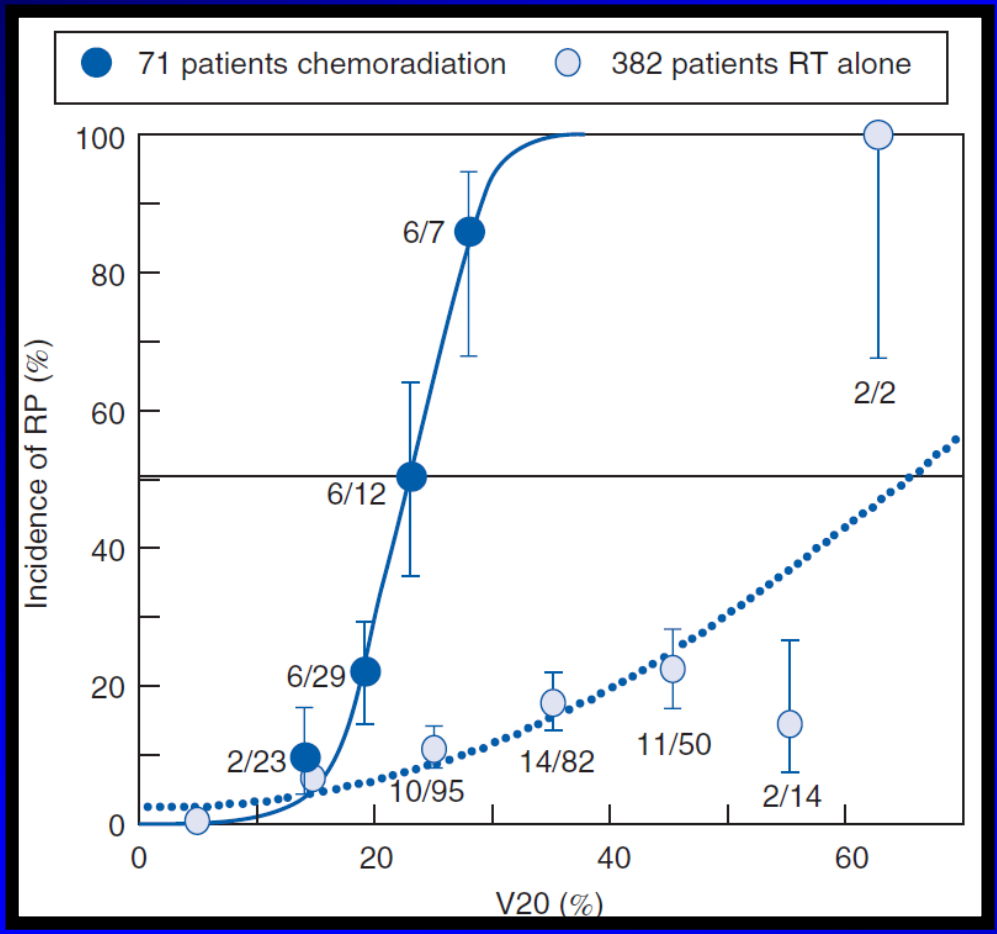
Table 1. Comparison of Dosimetric Parameters, Toxicity, and Outcome in Patients Receiving IMRT After Extrapleural Pneumonectomy

Reference	Number of Patients	Technique	Dose (Gy)	Boost (Gy)	V5 (%)	V20 (%)	Mean Lung Dose (Gy)	Grade 3 + RP (%)	Grade 5 RP (%)	2-Year OS (%)
Giraud et al[9]	24	HT	50	4-6	99	4	11	16	8	–
Patel et al[8]	30	IMRT	45	8-25	56	4	7.2	13	3	
Gomez et al[7]	86	IMRT	45-50	10			8	12	6	32

Gy, Gray; V5 and V20, dose of lung receiving 5 and 20 Gy, respectively; RP, radiation pneumonitis; OS, overall survival.

Seminars in Thoracic Surgery, 25:245-250, 2013

Incidence of Radiation Pneumonitis (RP) in Relation to V20 and Effects of Concurrent Chemoradiation.



Incidence of Grade 2 radiation pneumonitis as a function of the relative lung volume irradiated to more than 20 Gy (V20) of patients treated with radiotherapy alone (open circles) or with chemo-radiotherapy (closed circles) .

Patients receiving chemotherapy had a sharper increase in risk of radiation pneumonitis as the volume of normal lung exposed to 20 Gy increased.

International Journal of Radiation Oncology, Biology, Physics 55(1): 110–115, 2005

Radiation Toxicity to Normal Tissues

The usefulness of thoracic radiotherapy in the treatment of cancer is greatly limited by toxicity of ionizing radiation (radiation pneumonopathy).

Therefore, if we protect "normal" lung parenchyma from radiation injury, we will increase the ability to deliver tumoricidal radiotherapy doses.

Pharmacologic Treatment of Radiation Pneumonopathy

Despite active research in the development of tissue radioprotectors, there is no known effective pharmacologic therapy for the **prevention** of radiation pneumonopathy.

Steroids are used to treat **Acute** radiation pneumonitis, but do not alter risk of developing long term, **Chronic**, fibrotic complications

Use of Botanicals And Dietary Supplements Derived From Natural Substances

An expanding body of preclinical evidence suggests that a number of botanicals have the potential to impact a variety of human diseases including lung disease.

Therefore, non-toxic natural agents could be useful either alone or in combination with conventional therapeutics for the prevention or therapy of oxidative lung disease.

Usefulness of Dietary Supplements

Annual sale of Medicinal Herbs in the US is > 3 Billion $$$

More than 60 million consumers in the U.S. take herbal remedies. More physicians are recommending herbal medicines and some health insurance plans offer coverage for alternative health treatments such as herbal remedies.

In 1993 the NIH opened the National Center for Complementary and Alternative Medicine (NCCAM), now NCCIH, which along with the Office of Dietary Supplements (ODS) aim to promote the safety, effectiveness, and biological action of botanical products.

Complementary & Integrative Health Approaches

Natural Products

This group includes a variety of products, such as herbs (also known as botanicals), vitamins and minerals, and probiotics. They are widely marketed, readily available to consumers, and often sold as **dietary supplements**.

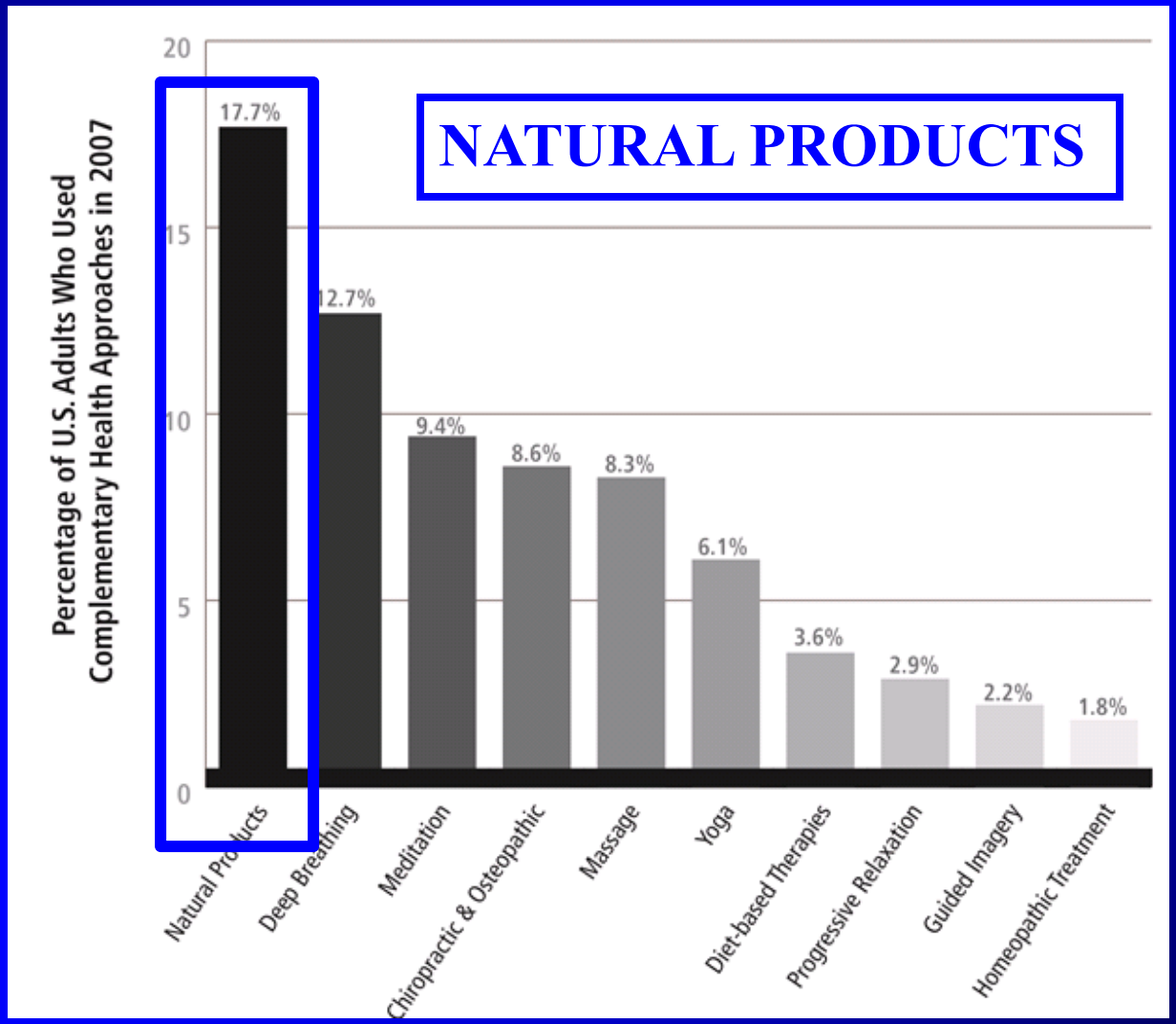
Mind and Body Practices

Mind and body practices include a large and diverse group of procedures or techniques administered or taught by a trained practitioner or teacher.

Other Complementary Health Approaches

The practices of **traditional healers**, **Ayurvedic medicine** from India, **traditional Chinese medicine, homeopathy,** and **naturopathy**.

The Ten Most Common Complementary Health Approaches Among Adults (2007)



Barnes et al, 2007; CDC National Health Statistics Report#12, 2008

Spices


Asian ginger (1)
(*Alpinia galanga*)


Fennel (2)
(*Foeniculum vulgare*)


Sesame seed (3)
(*Sesamum indicum*)


Turmeric (4)
(*Curcuma longa*)


Cloves (5)
(*Eugenia caryophyllu*)


Red chili (6)
(*Capsicum annum*)


Fenugreek (7)
(*Trigonella foenum graecum*)


Poppy seed (8)
(*Papaver somniferum*)


Gamboge (9)
(*Garcinia hanburyi*)


Onion (10)
(*Allium cepa*)


Onion seed (11)
(*Nigella sativa*)


Holy basil (12)
(*Ocimum sanctum*)


Pomegranate (13)
(*Punica granatum*)

Ayurvedic Medicine


Aloe (1)
(*Aloe vera*)


Veldt-grape (2)
(*Cissus quadrangularis*)


Picroliv (3)
(*Picrorhiza kurroa*)


Himalayan fir (4)
(*Abies webbiana*)


Chitrak (5)
(*Plumbago zeylanica*)


Boswellia (7)
(*Boswellia serrata*)


Beauty berry (7)
(*Callicarpa macrophylla*)


Pink trumpet tree (8)
(*Tabebula avellanedae*)


Bloodroot (9)
(*Sanguinaria canadensis*)


Guggulu (10)
(*Commiphora mukul*)


False pepper (11)
(*Embelia ribes*)


Rohitukine (12)
(*Dysoxylum binectariferum*)


Ashwagandha (13)
(*Withania somnifera*)


Indigo (14)
(*Polygonum tinctorium*)


Pinecone ginger (15)
(*Zingiber zerumbet*)

Fruits & Vegetables


Cauliflower (1)
(*Brassica oleracea*)


Mullberry (2)
(*Morus nigra*)


Artichoke (3)
(*Cynara cardunculus*)


Grapes (4)
(*Vitis vinifera*)


Soybean (5)
(*Glycine max*)

Traditional Chinese Medicine


Lacquer tree (1)
(*Rhus vernicifiua*)


Goldenseal (2)
(*Hydrastis canadensis*)


God of thunder vine (3)
(*Tripterygium wilfordii*)


Smoke tree (4)
(*Cotinus coggygria*)


Evodia (5)
(*Evodia rutaecarpa*)


Song gen (6)
(*Phellinus linteus*)


Magnolia (7)
(*Magnolia officinalis*)

Others

Cashew nut (1)
(*Anacardium occidentale*)

Horse chestnut (2)
(*Aesculus hippocastanum*)

Palm (3)
(*Elaeis guineensis*)

Elephant's foot (4)
(*Elephantopus scaber Linn*)

Hop (5)
(*Humulus lupulus L.*)

Ginger lily (6)
(*Hedychium coronarium*)

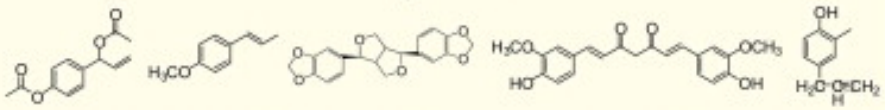
Cork bush (7)
(*Mundulea sericea*)

Tropical rose mallow (8)
(*Hibiscus vitifolius*)

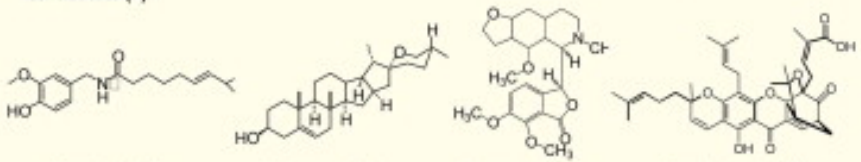
Oleander (9)
(*Nerium oleander*)

Gullet et. al, 2010

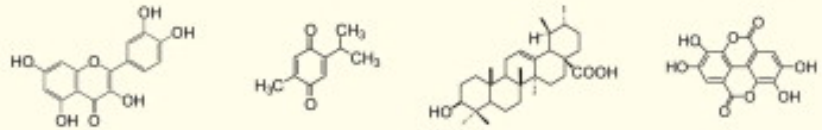
Spices



1'-Actoxychavicol acetate (1) | Anethole (2) | Sesamin (3) | Curcumin (4) | Eugenol (5)

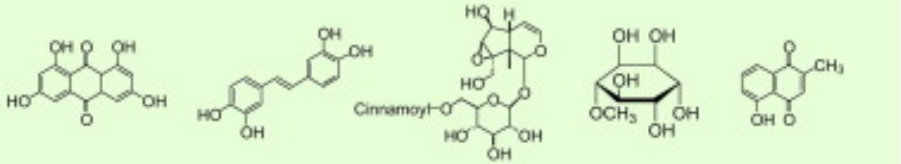


Capsaicin (6) | Diosgenin (7) | Noscapine (8) | Gambogic acid (9)

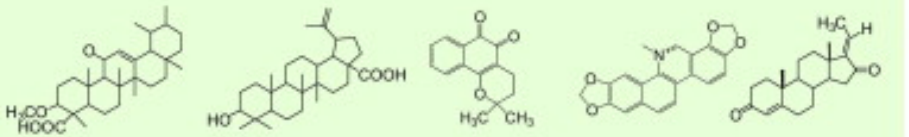


Quercetin (10) | Thymoquinone (11) | Ursolic acid (12) | Ellagic acid (13)

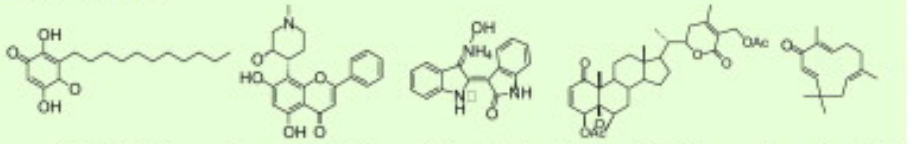
Ayurvedic Medicine



Emodin (1) | Piceatannol (2) | Picroliv (3) | Pinitol (4) | Plumbagin (5)

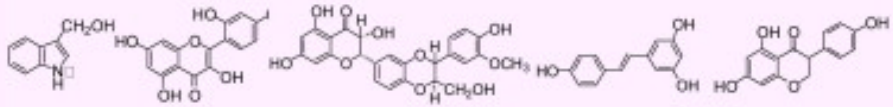


Acetyl-11-keto-β-boswellic acid (6) | Betulinic acid (7) | β-Lapachone (8) | Sanguinarine (9) | Guggulusterone (10)



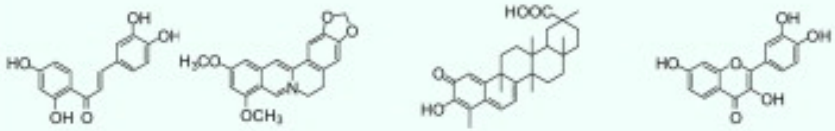
Embelin (11) | Flavopiridol (12) | Indirubin 3'-monoxime (13) | Withanolide (14) | Zerumbone (15)

Fruits & Vegetables

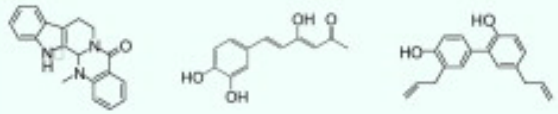


Indole 3-carbinol (1) | Morin (2) | Silymarin (3) | Resveratrol (4) | Genistein (5)

Traditional Chinese Medicine

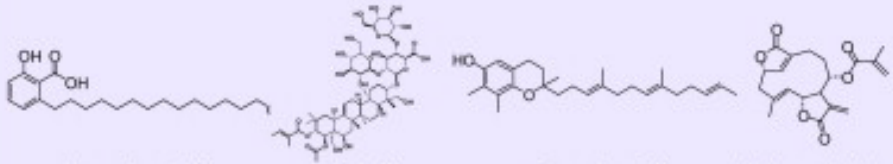


Butein (1) | Berberin (2) | Celastrol (3) | Fisetin (4)

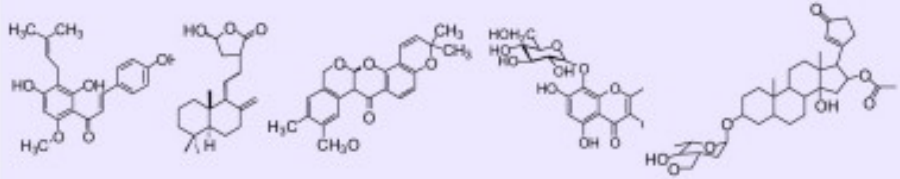


Evodiamine (5) | Hispolon (6) | Honokiol (7)

Others



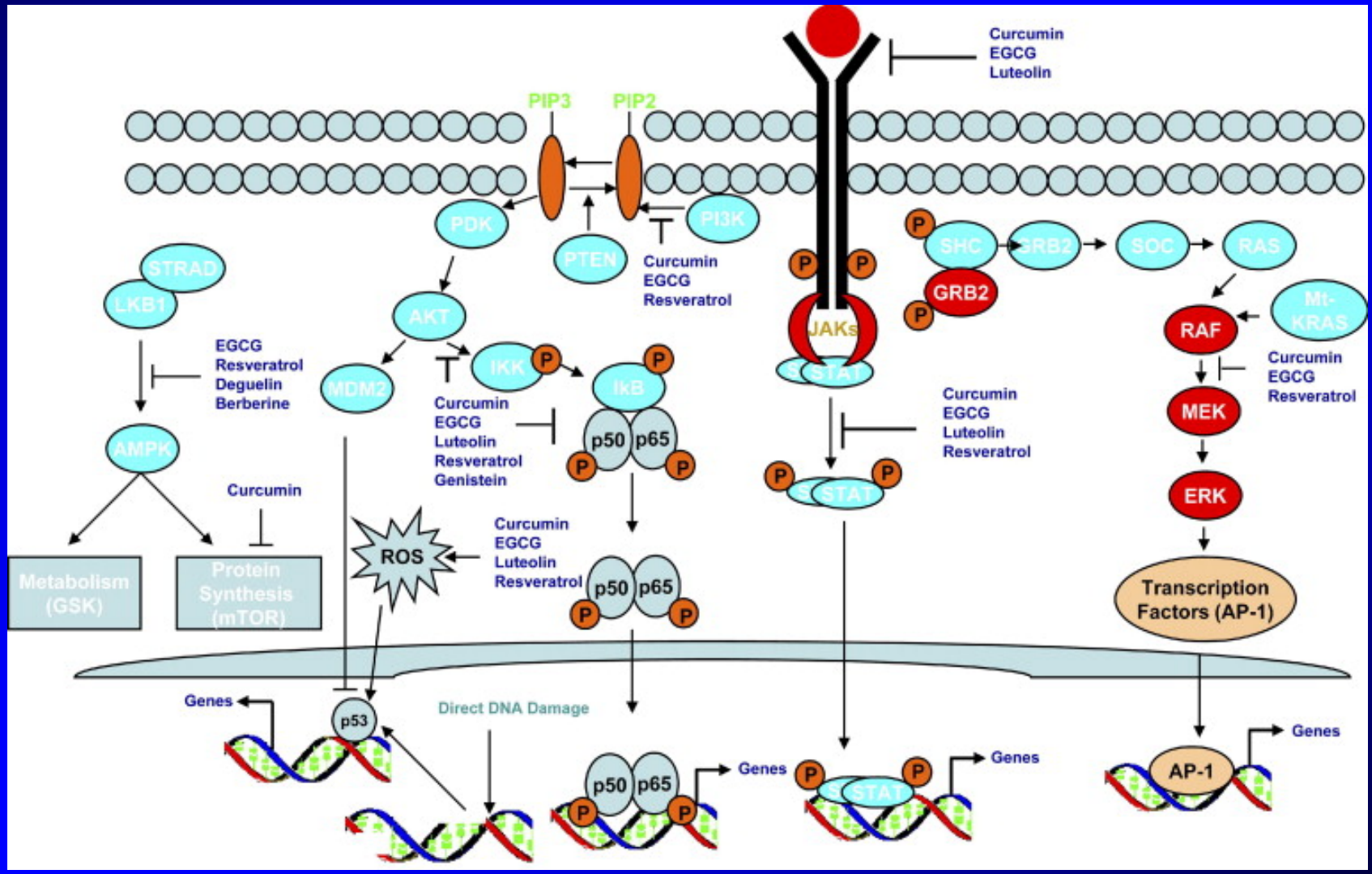
Anacardic acid (1) | Escin (2) | γ-Tocotrienol (3) | Isodeoxyelephantopin (4)



Xanthohumol (5) | Coronarin-D (6) | Deguelin (7) | Gossypin (8) | Oleandrin (9)

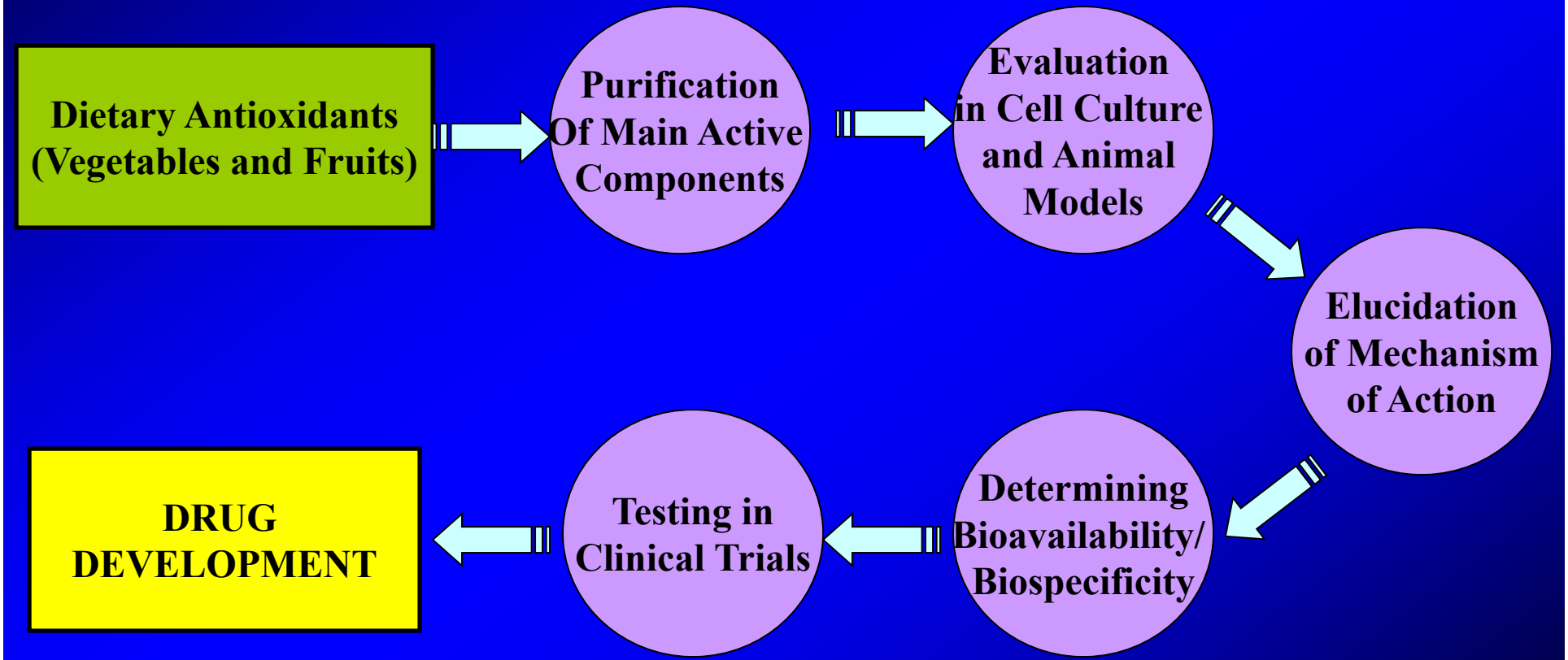
Gullet et. al, 2010

Molecular Pathways Affected by Common Botanicals



Gullet et. al, 2010

Drug Development From Bioactive Dietary Agents



Botanicals with antioxidant properties currently being evaluated in lung disease and cancer

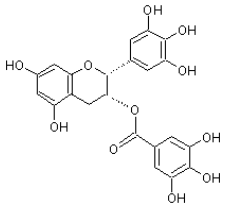
Dietary Agents

Green Tea

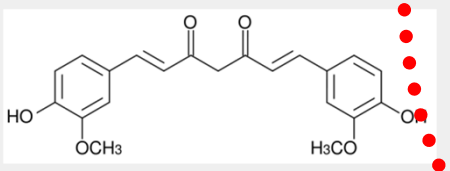
Turmeric

Flaxseed

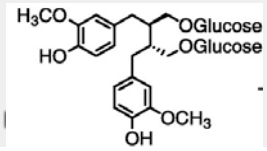
Chemical Structures



Epigallocatechin-3-gallate (EGCG)



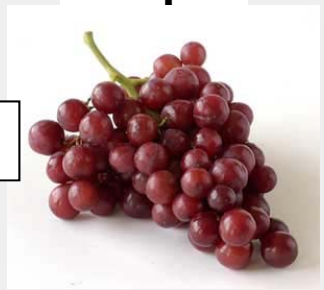
Curcumin



Secoisolariciresinol Diglucoside (SDG)

Dietary Agents

Grapes

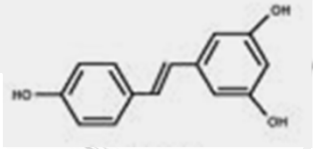


Tomatoes

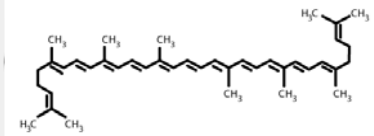
Pomegranate

Broccoli

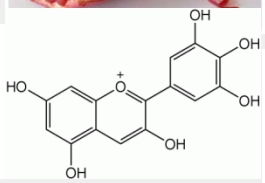
Chemical Structures



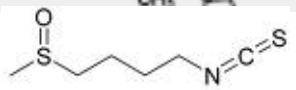
Resveratrol



Lycopene

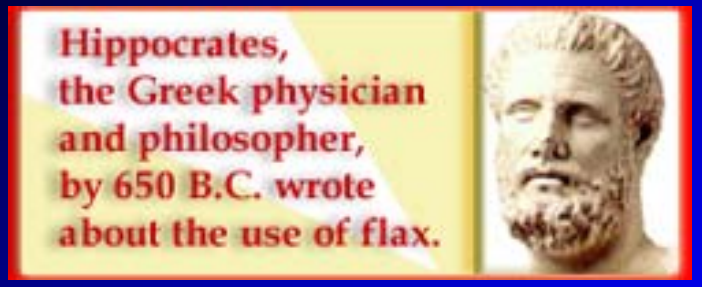


Delphinidin

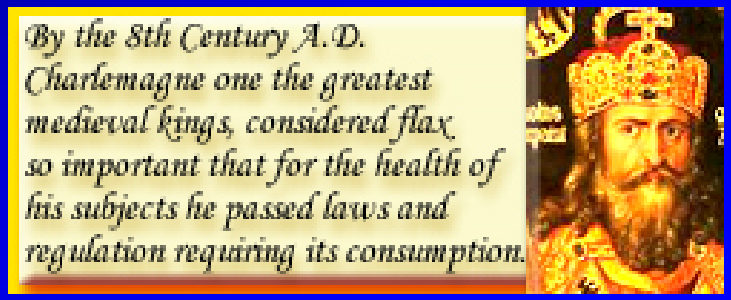


Sulforaphane


Flaxseed:
“an ancient remedy
in a modern world”



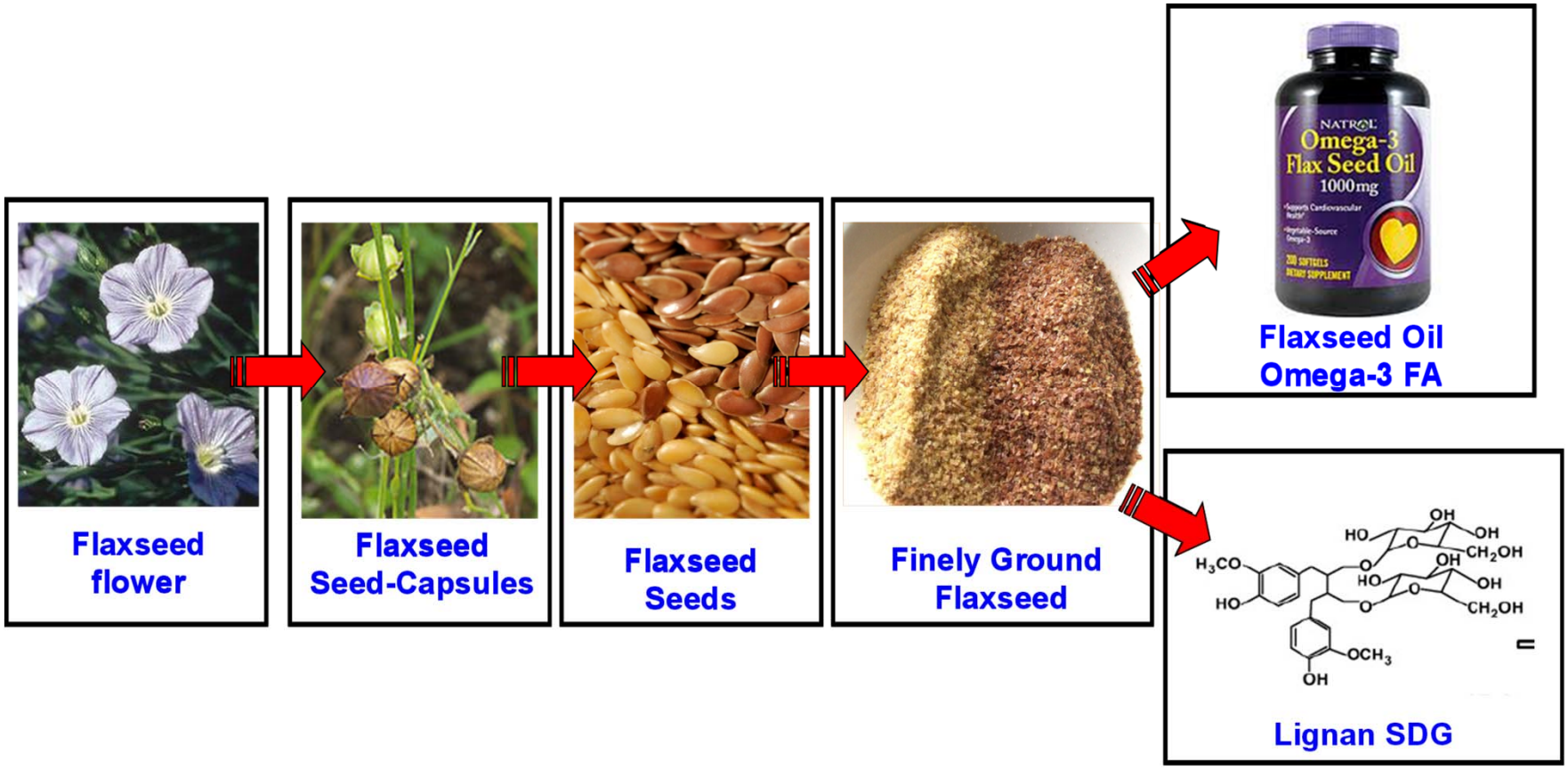
The father of modern medicine, Hippocrates, the Greek physician, by 650 B.C. wrote about the use of flax to relieve inflammation of mucous membrane and for the relief of abdominal pains and diarrhea.



By the 8th Century A.D. Charlemagne one the greatest medieval kings, considered flax so important that for the health of his subjects he passed laws and regulation requiring its consumption.

Mahatma Ghandi said that when flaxseed was added to people's diet their health improved.

Flaxseed - a Natural Product



FLAXSEED

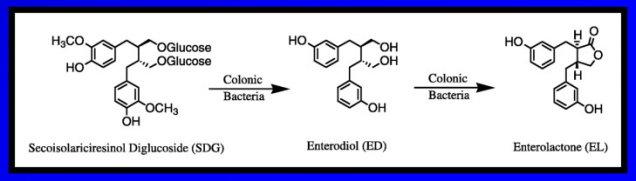
Plant Lignan Precursors

- Secoisolarisiresinol diglycoside (SDG)
- matairesinol

Intestinal Bacteria

Lignans

- Enterodiol (ED)
- Enterolactone (EL)



Biological Properties

- ***Antioxidative
- Antiproliferative
- Antiangiogenic
- Estrogenic/Antiestrogenic

Omega-3 Fatty Acids

α-Linolenic Acid

EPA

(eicosapentanoic Acid)

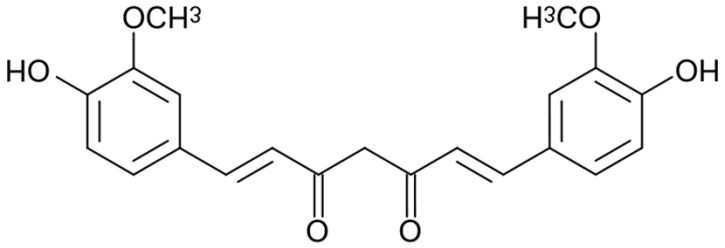
DHA

(Docosahexanoic Acid)

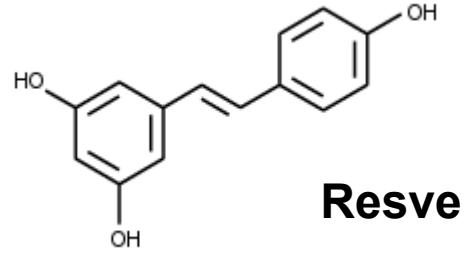
Cancer Protection

****Anti-inflammatory**

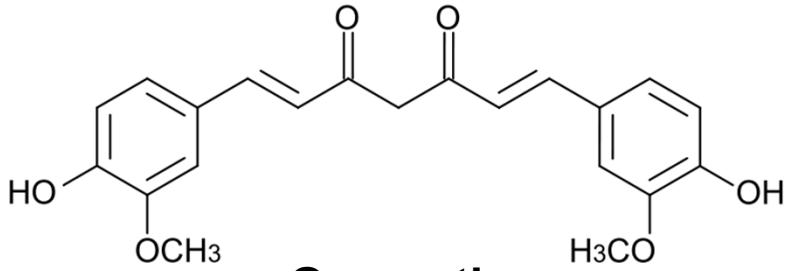
Flaxseed Lignan Structure



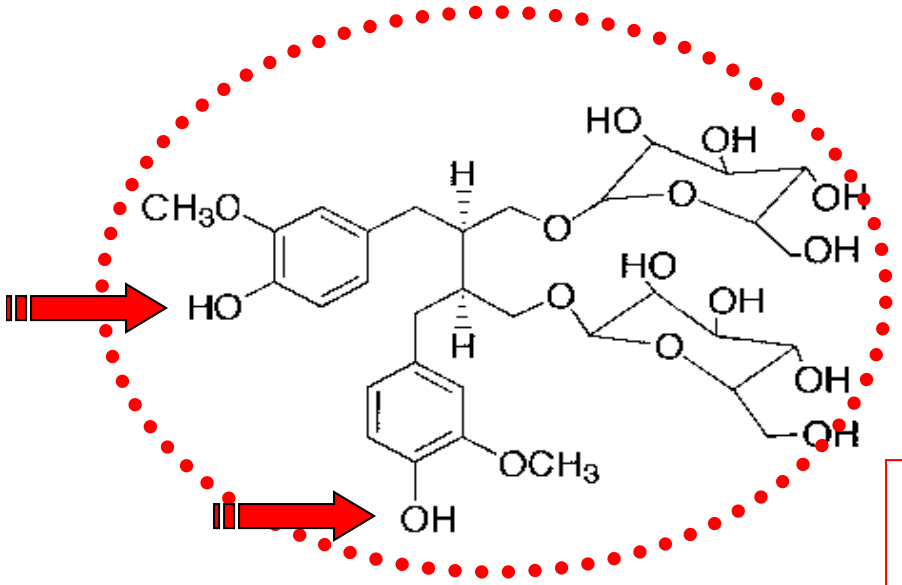
Curcumin



Resveratrol



Quercetin



Secoisolariciresinol diglucoside (SDG)

A bi-phenolic with potent antioxidant properties

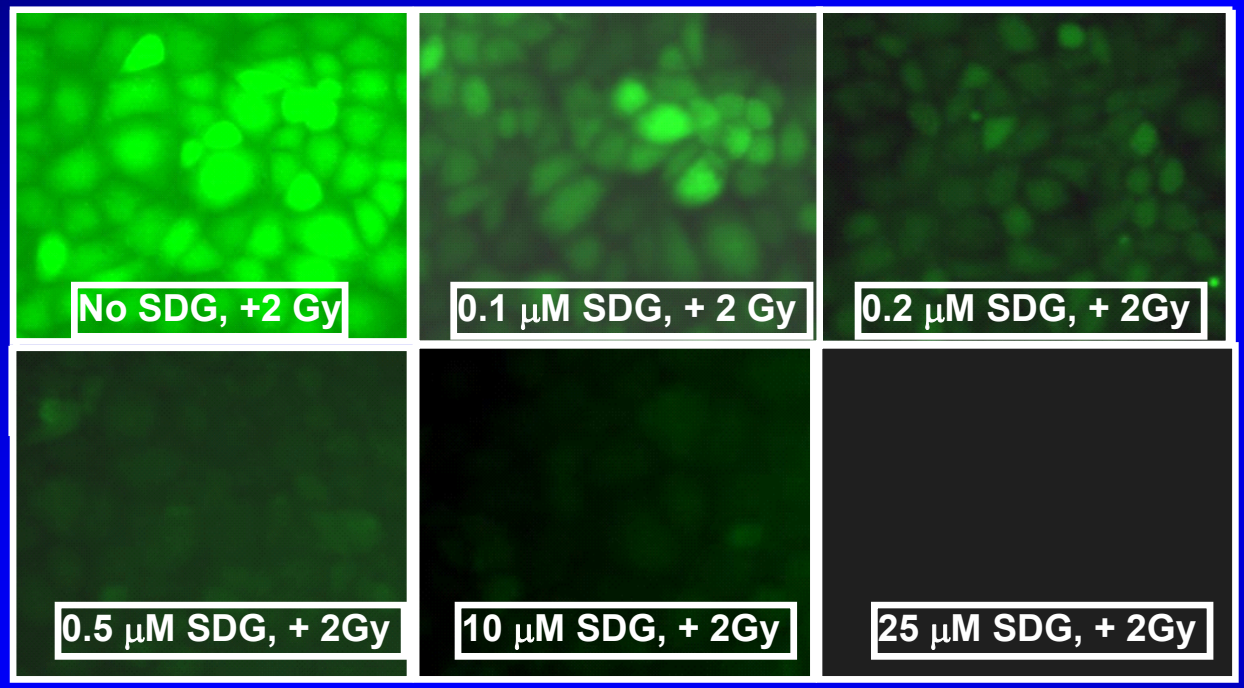
Our Group Has Identified Flaxseed As A Potent Inhibitor Of Oxidative Lung Injury In A Number Of Animal Models

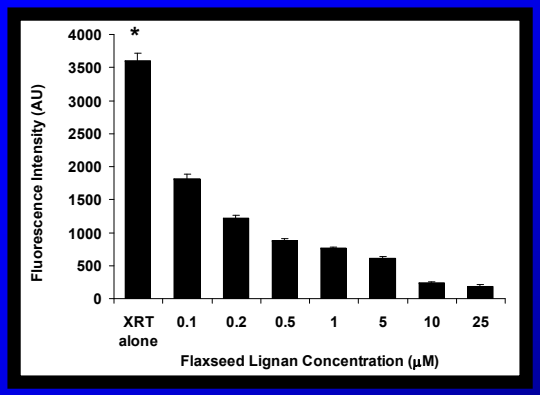
Protective Properties of Flaxseed in Preclinical Models of Cancer & Acute/Chronic Lung Damage

FLAXSEED (wholegrain) & SDG

- THORACIC RADIATION PNEUMONOPATHY
- HYPEROXIC LUNG DAMAGE
- ISCHEMIA-REPERFUSION LUNG DAMAGE
- ACID ASPIRATION-INDUCED LUNG DAMAGE
- ASBESTOS-INDUCED MESOTHELIOMA
- TOBACCO CARCINOGEN-INDUCED LUNG CANCER

Direct Free Radical Scavenging by Flaxseed Lignan- Antioxidant action in γ-irradiated lung Endothelial cells

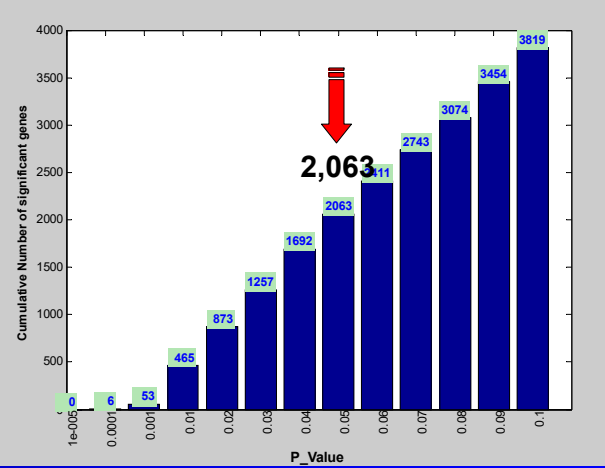




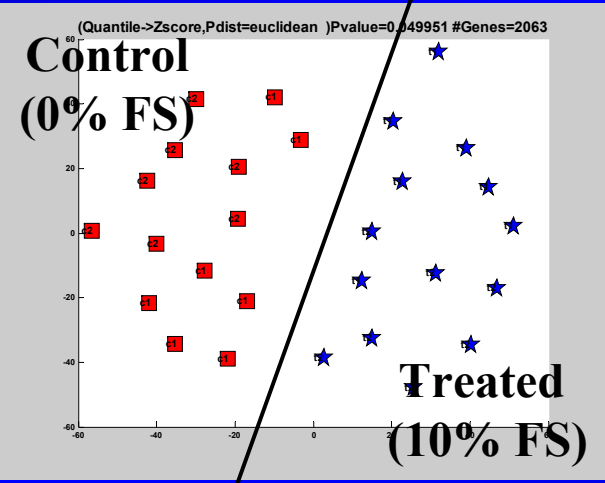
Lee et.al, 2009

Genetic profiling of flaxseed in lung
(30,000 gene array of entire mouse genome)

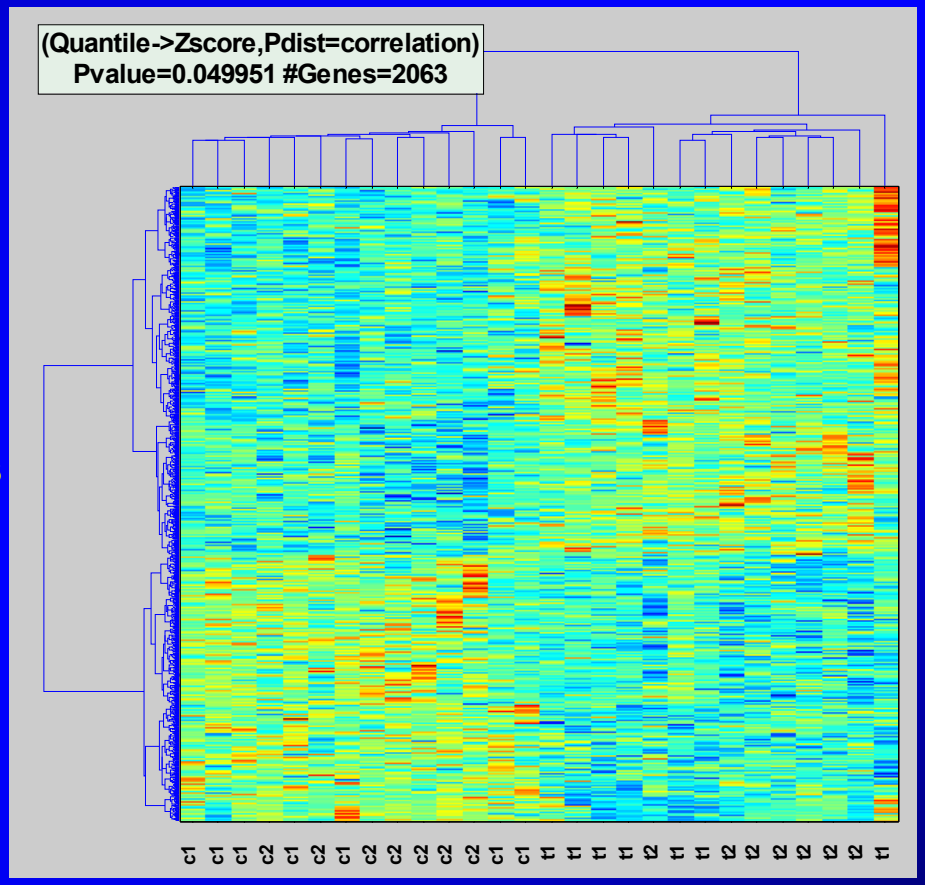
6.8% of all mouse genes in lung tissues are significantly modified by flaxseed



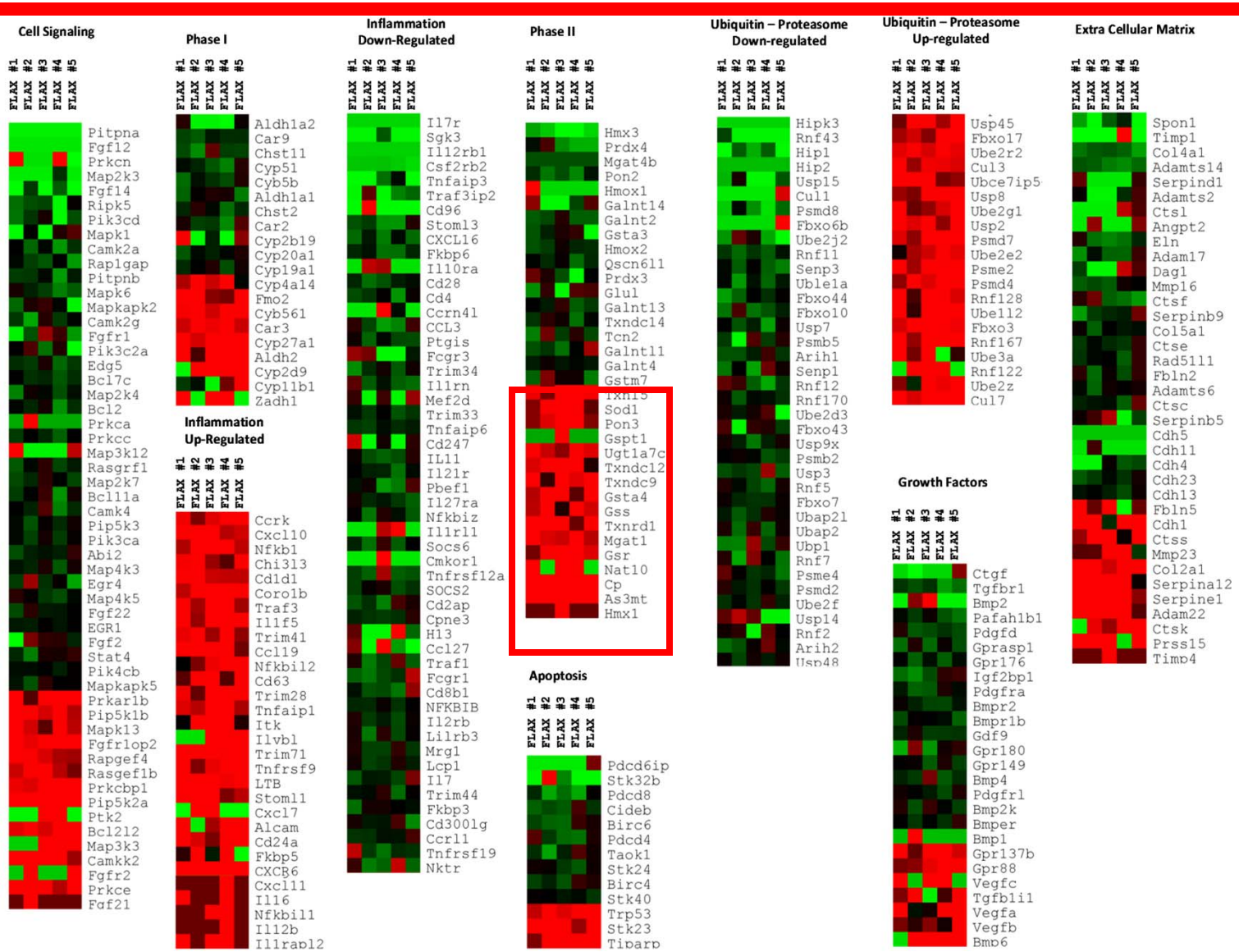
Principle Component Analysis



Dukes et.al, 2012



Pulmonary Gene Expression Profiling of Genes With >1.5x fold Change in Individual Flax-fed Mice as Compared to Mean of Control



Red indicates up-regulation, green down-regulation

Dukes et.al, 2012

HYPOTHESIS

Given the direct free radical scavenging properties of the flaxseed lignans and the robust boost of antioxidant tissue defenses,

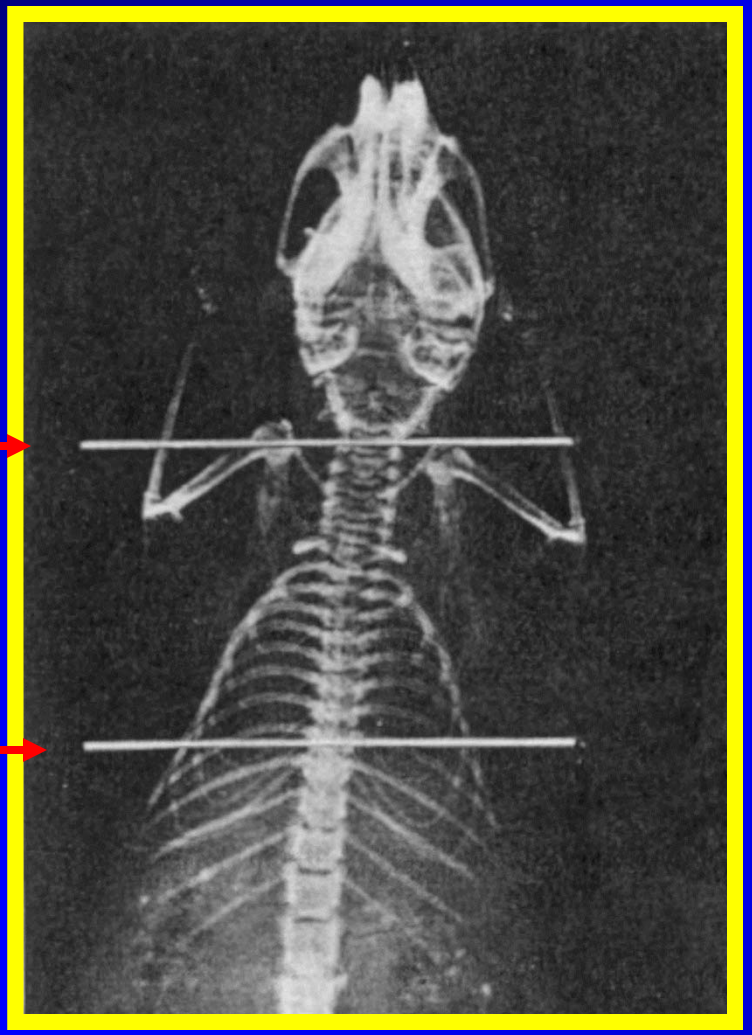
We Hypothesized, That Dietary Flaxseed and Will Ameliorate Oxidative Acute and Chronic Lung Damage such as that resulting from Radiation Exposure, Modeled In Mice

Mouse Model of Thoracic Radiation Damage

Mouse Radiographs

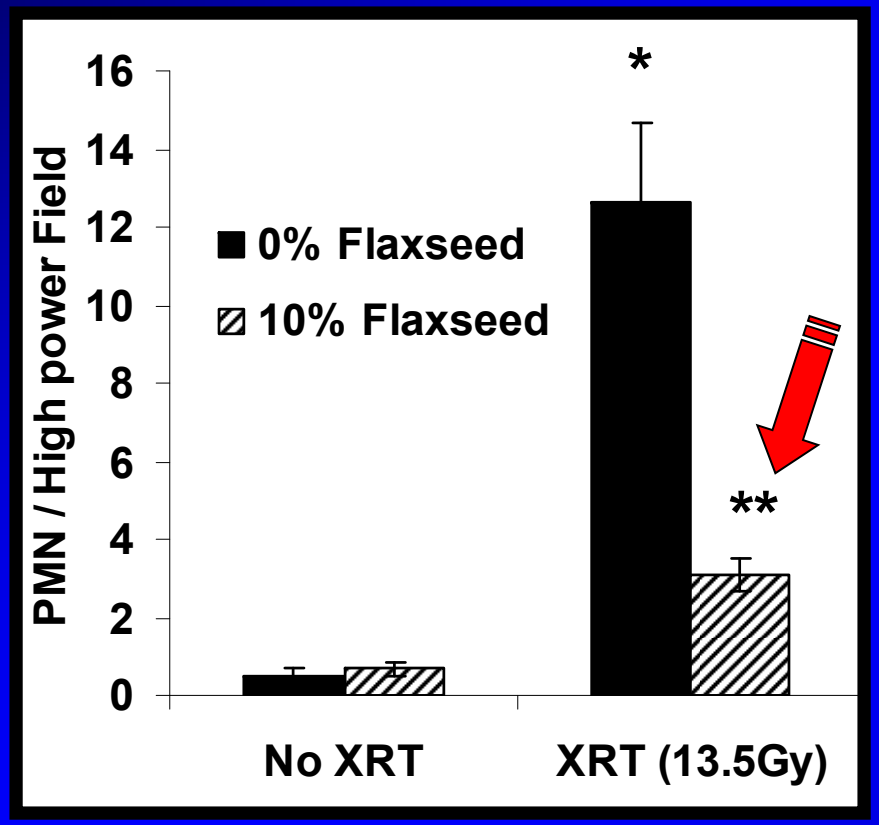
Cephalic margin

Caudal margin

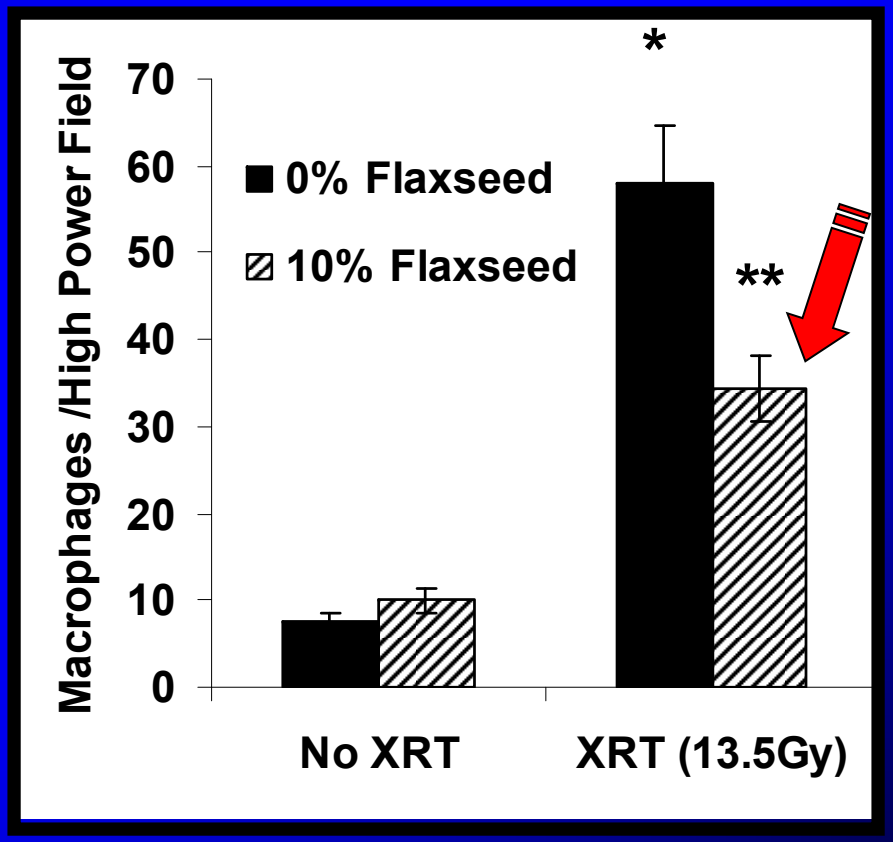


(XRT=X-Ray Treatment)

Dietary Flaxseed Ameliorates Radiation-Induced Pneumonitis (Inflammation) in Mice



Alveolar Neutrophils

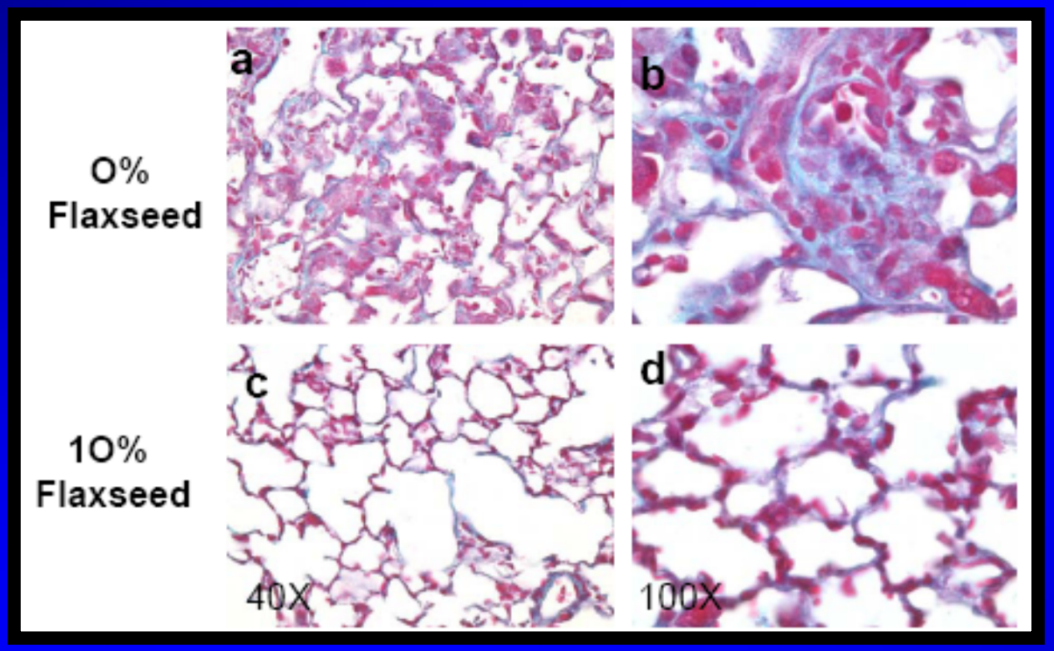


Alveolar Macrophages

Lee et.al, 2009

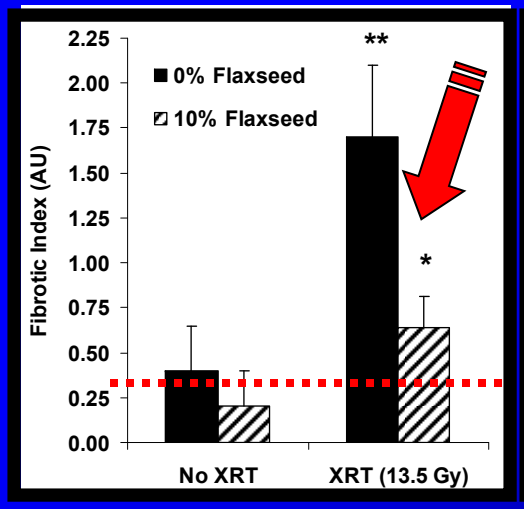
Antifibrotic Role of Flaxseed

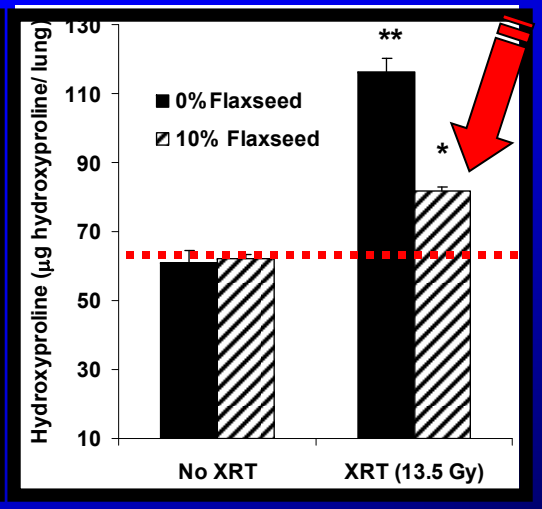
Flaxseed Decreased Radiation-Induced Collagen Deposition in Lungs



Trichrome Blue Staining for Collagen (Marker for Lung Fibrosis)

Fibrotic Index (Pathology)

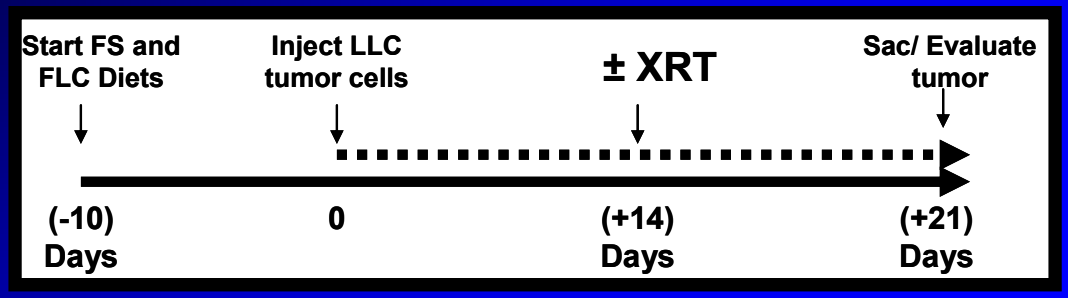


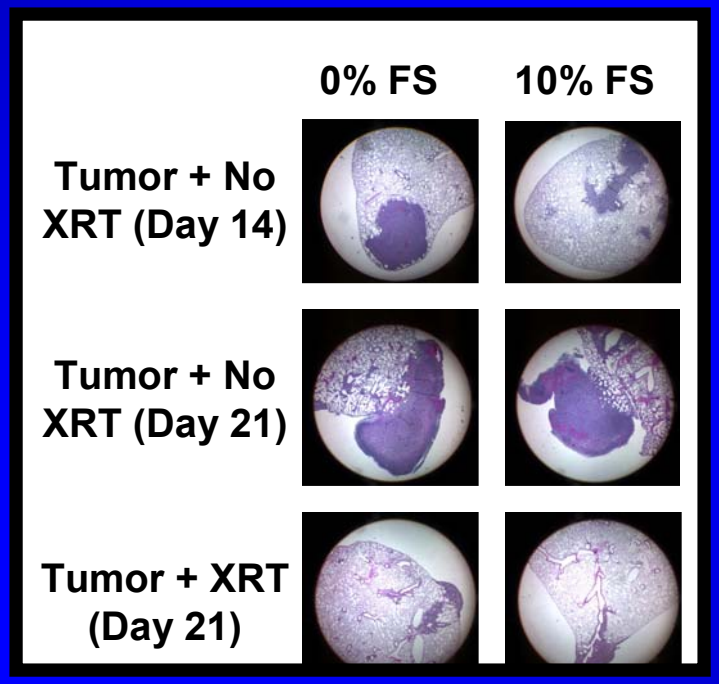


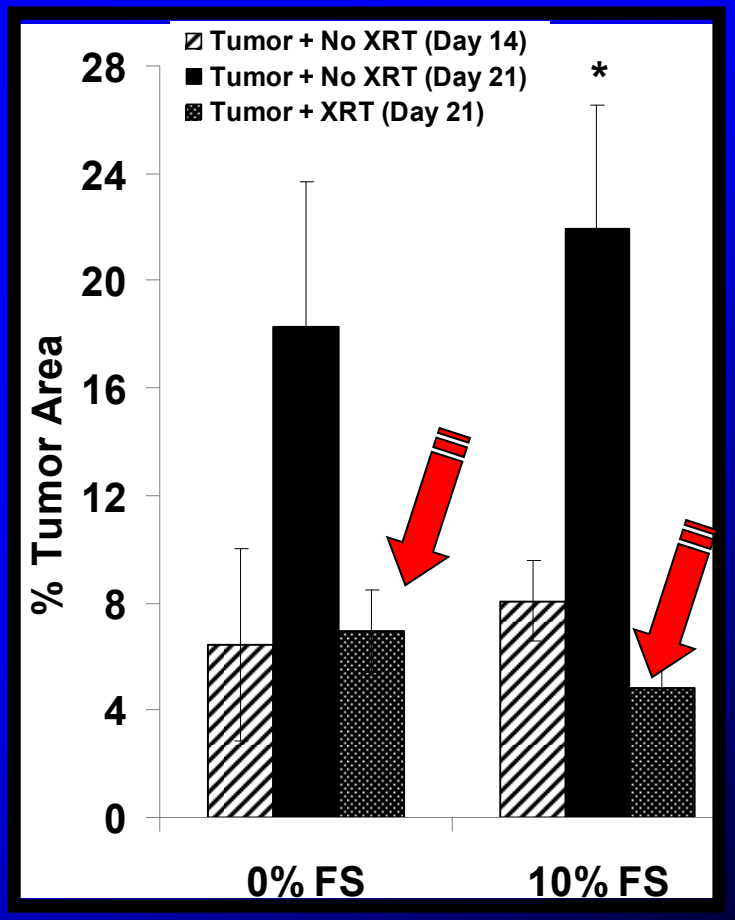
OH-Proline Content

Cancer Biology and Therapy, 2009

Flaxseed Does Not Impair Tumor Eradication By Radiation





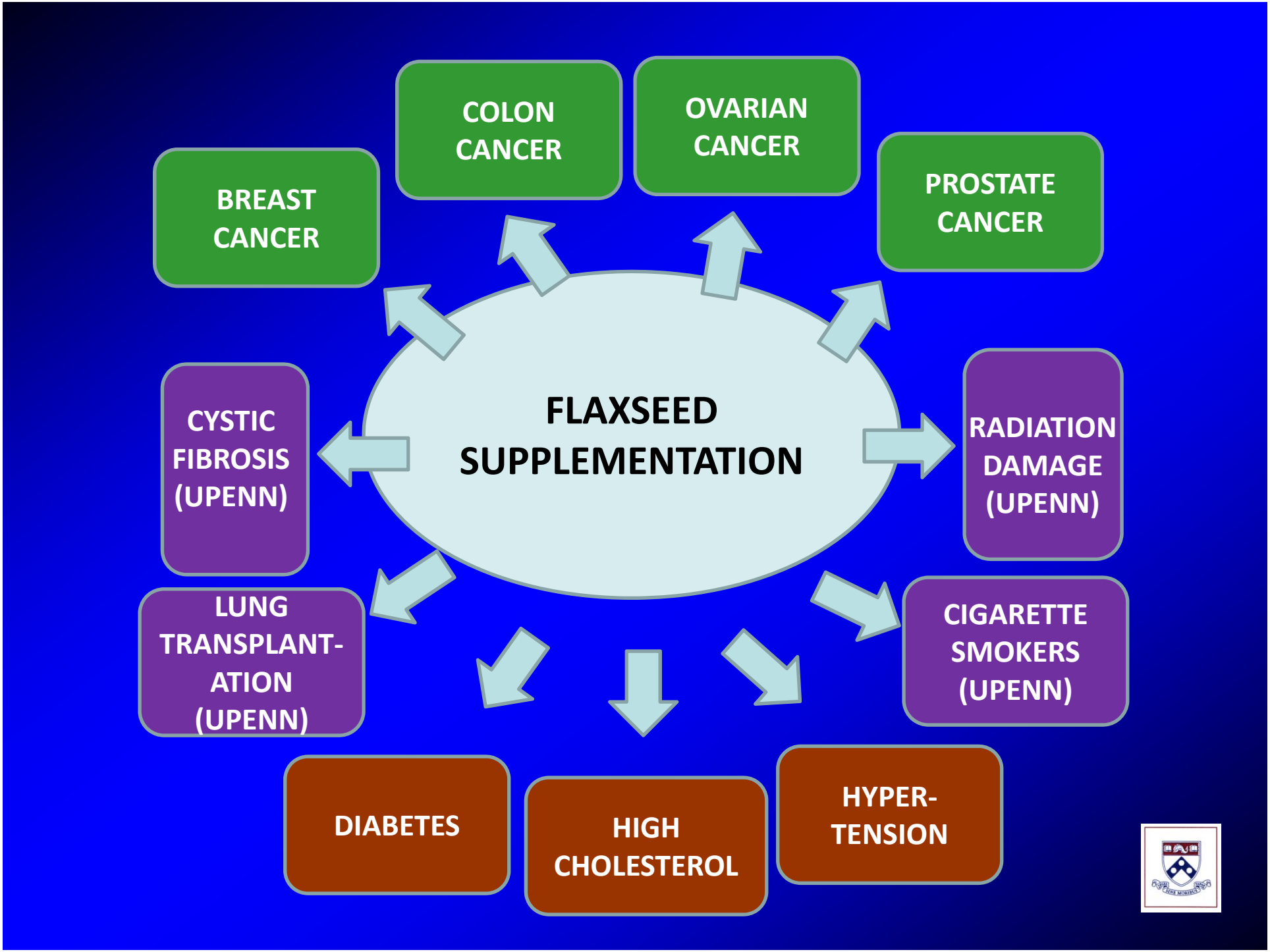


Christofidou-Solomidou et.al., Radiation Research, 2012

Summary

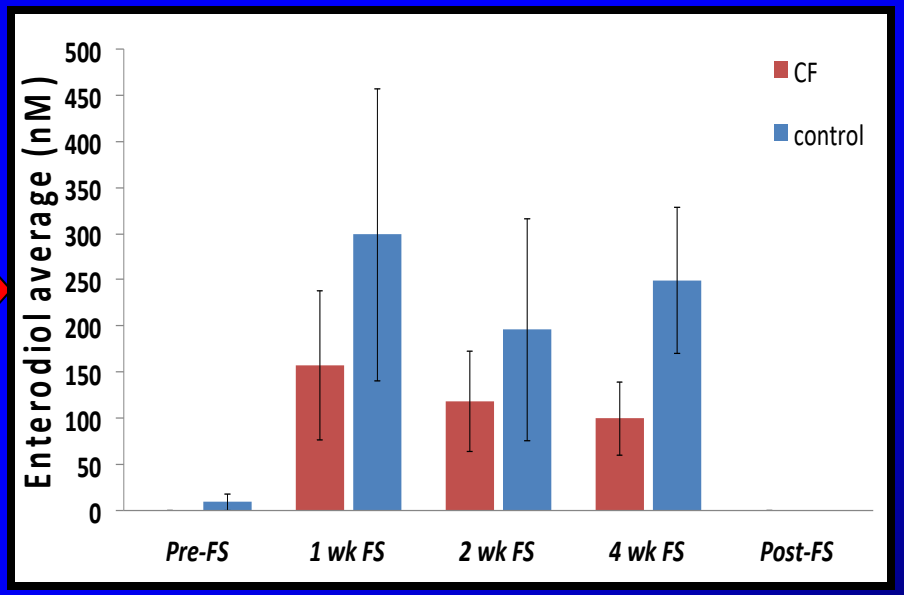
Dietary Flaxseed:

- Improves Survival
- Prevents Radiation-induced
  - Oxidative Tissue Injury
  - Pneumonitis
  - Inflammation
  - Lung Fibrosis
  - Cytokine Secretion
  - Does NOT protect Tumor


FLAXSEED SUPPLEMENTATION
COLON CANCER
OVARIAN CANCER
BREAST CANCER
PROSTATE CANCER
CYSTIC FIBROSIS (UPENN)
RADIATION DAMAGE (UPENN)
LUNG TRANSPLANT-ATION (UPENN)
CIGARETTE SMOKERS (UPENN)
DIABETES
HIGH CHOLESTEROL
HYPER-TENSION

DIETARY FLAXSEED IS WELL TOLERATED BY HEALTHY VOLUNTEERS AND CYSTIC FIBROSIS PATIENTS

Dietary Flaxseed (40g daily) Supplementation



Plasma Lignan Concentration Increases after Flaxseed Consumption

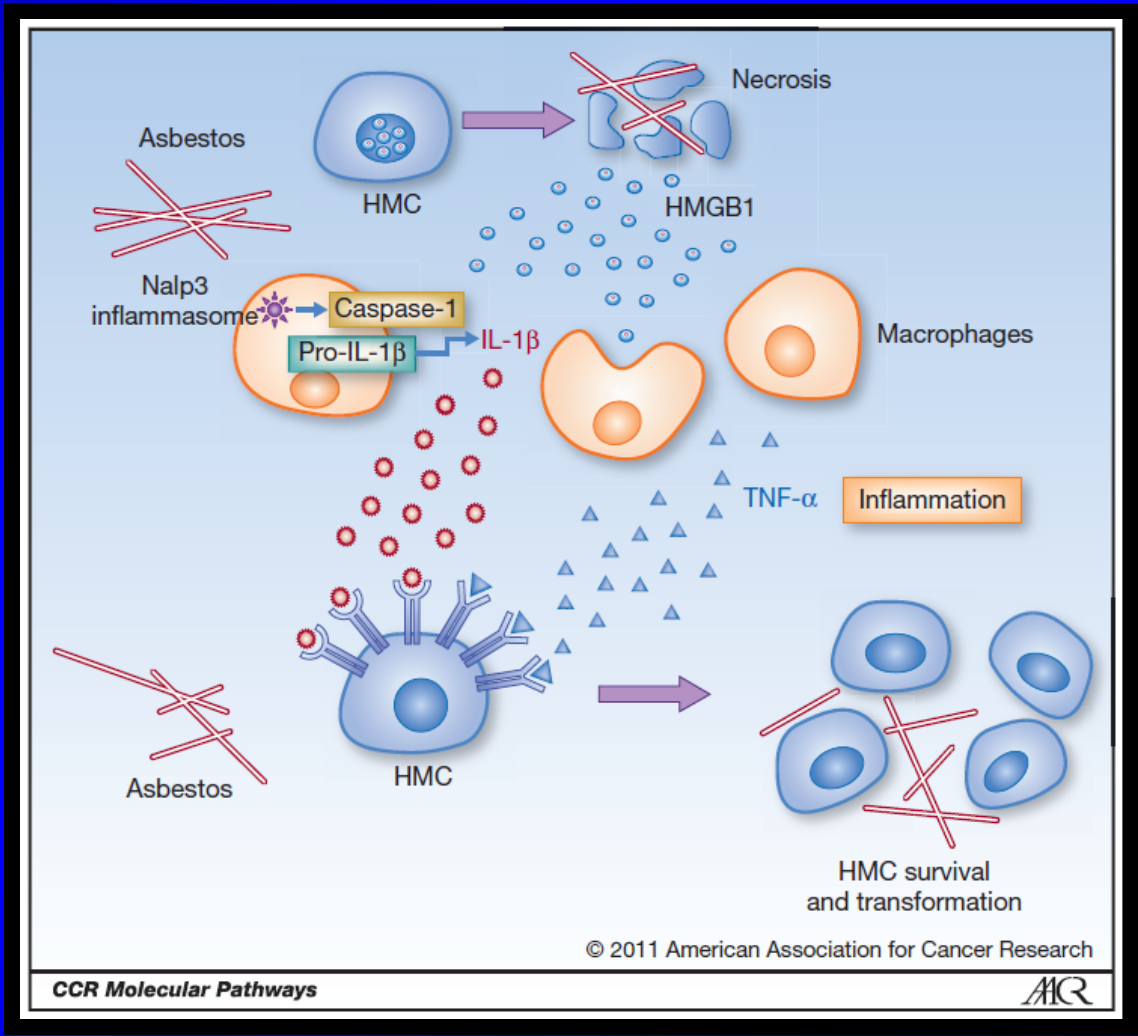
Future Plans: Determine if Flaxseed Supplementation Modulates systemic inflammation and disease exacerbations in CF patients

Turowski et al, in review

ROS/Inflammation in Mesothelioma:

The working paradigm of mesothelioma carcinogenesis is that asbestos induces a state of chronic inflammation in the pleura that ultimately leads to mutagenesis and tumor formation (especially in those with a genetic predisposition).

Key roles of:
HMGB1, TNFα, IL-1ß
AND
REACTIVE OXYGEN SPECIES



Hypothesis

Inhibition of inflammation and/or ROS will delay or prevent the induction of asbestos-induced mesothelioma.

We want to test this using Flaxseed and the main lignan found in Flaxseed: the SDG

LEGAL NEWSLINE

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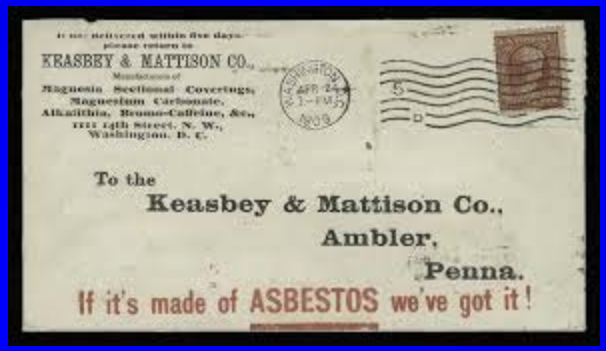
University of Pennsylvania receives $10M to study Superfund asbestos site

July 11, 2014 9:52 AM

By HEATHER ISRINGHAUSEN GVILLO

PHILADELPHIA (Legal Newsline) – Researchers with the U
million grant to study asbestos and how the toxic fiber leads t
America's 10 Superfund sites.

The grant, which came from the National Institute of Environ
to help researchers from the school's Center of Excellence in
Perelman School of Medicine to study asbestos, mesotheliom
next four years.



University of Pennsylvania researchers receive $10 million to study asbestos in Ambler

Published: Tuesday, June 24, 2014

By Eric Devlin
edevlin@montgomerynews.com

The University of Pennsylvania recently announced it has received a $10 million grant from the National Institute of Environmental Health Sciences to study asbestos and its impact on the Ambler community.

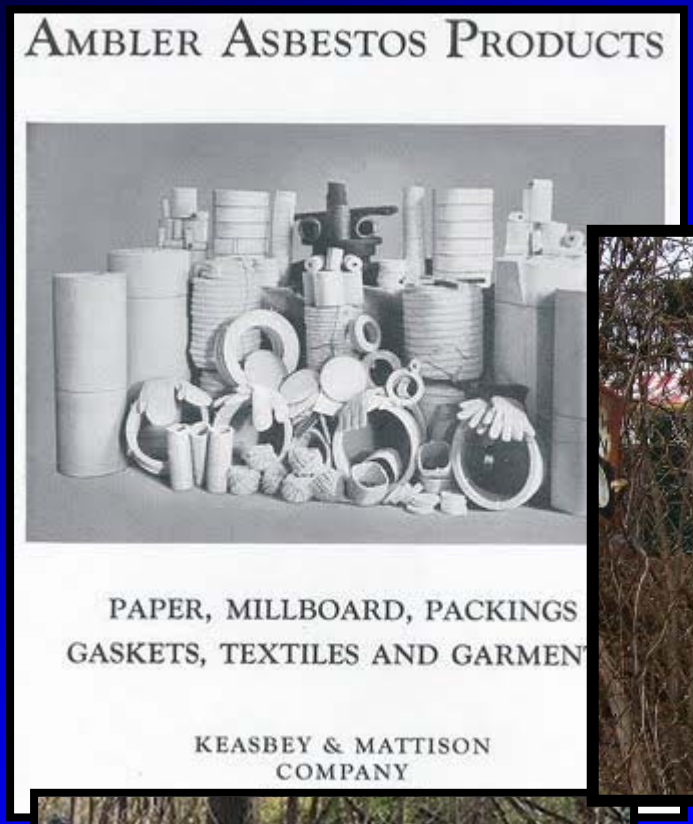
The grant will allow researchers from Penn's Center of Excellence in Environmental Toxicology to, over the next four years, study asbestos, the rare asbestos-related cancer, mesothelioma, and other asbestos-related diseases, according to a press release. Researchers from the Abramson Cancer Center, the Penn School of Arts and Sciences and Fox Chase Cancer Center are also lead investigators on the grant.

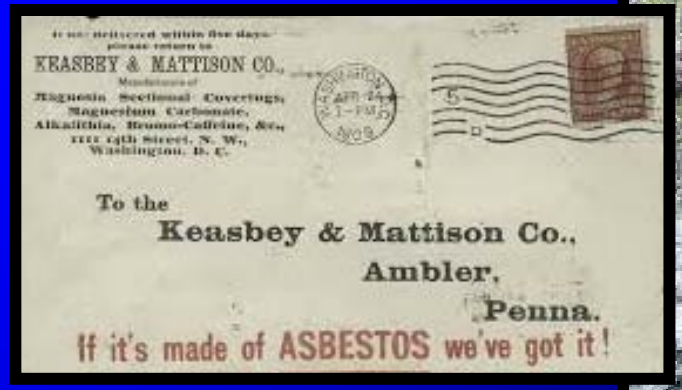
A 2010 aerial view of the BoRit asbestos site following two phases of removal action. Photo by: salbocutti.com

View and purchase photos

The BoRit site where research will take place, located in Ambler Borough, Upper Dublin and Whitpain townships between Butler Avenue, North Maple Street and the Wissahickon Creek, was placed on the Environmental Protection Agency's Superfund National Priorities List in April 2009.

Asbestos Contamination-Ambler PA



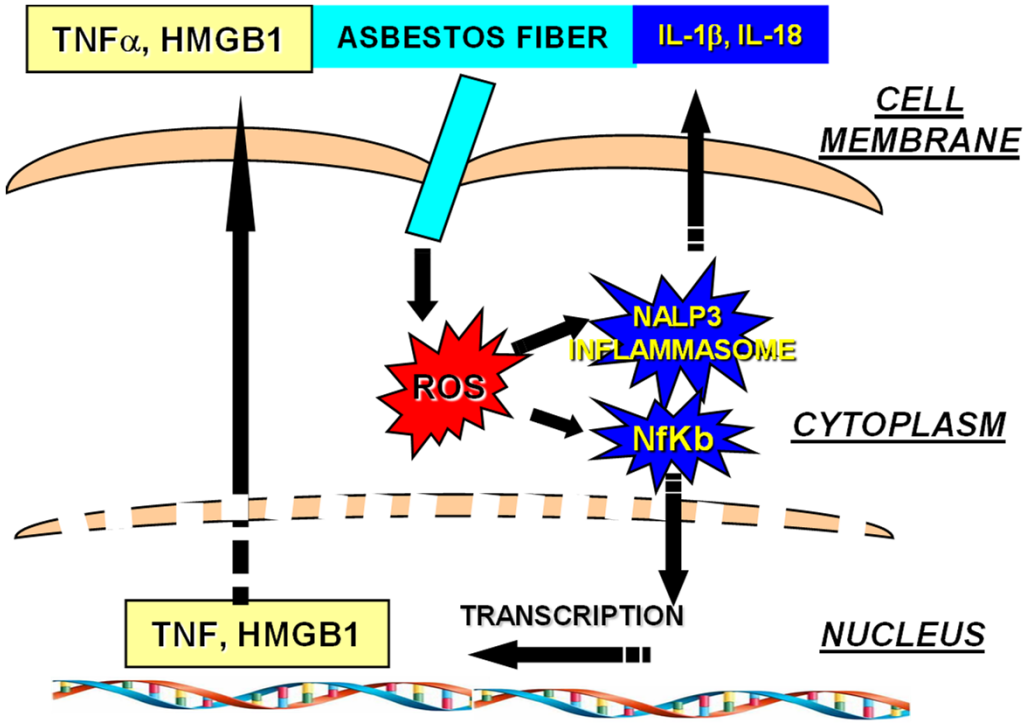


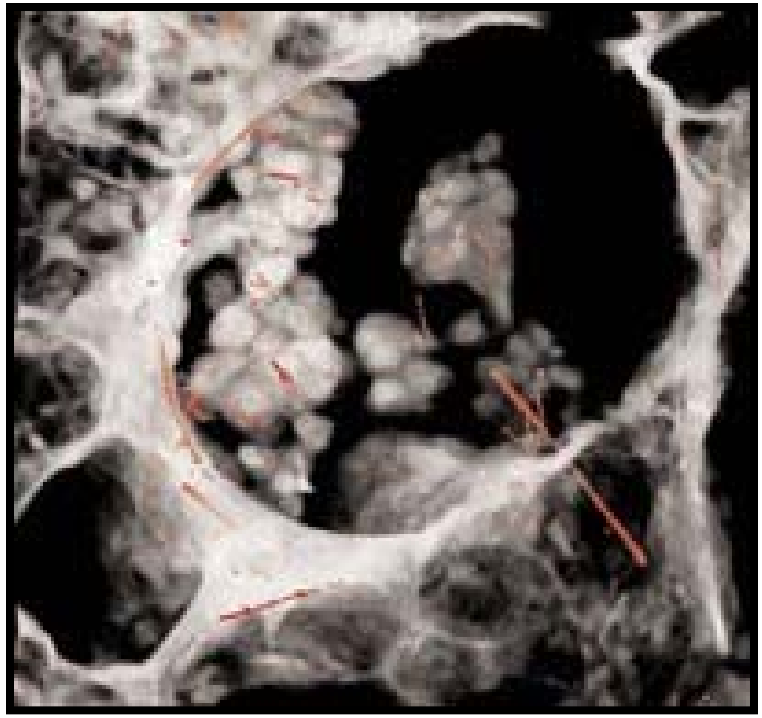
"Asbestos fate, exposure, remediation, and adverse health effects"

1. Can we remediate asbestos without moving it from the original disposal site?
2. What do we know about the fate and transport of asbestos in the environment by water and air?
3. What do we know about the exposure pathways that were responsible for the mesothelioma cluster in Ambler? And why is the incidence higher in women?
4. Is susceptibility to mesothelioma genetic?
5. **Can asbestos-related disease be prevented?**
6. Is there a blood test to determine whether a person will get asbestos-related disease?

USEFULNESS OF FLAXSEED TO PREVENT MM FROM ASBESTOS EXPOSURE

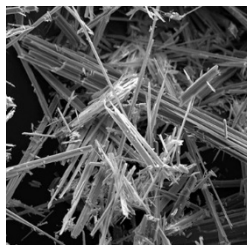
Role of Flaxseed and SDG in Preventing Asbestos-Induced Mesothelioma in Mice





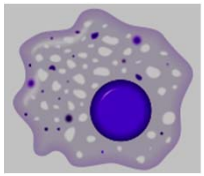
We hypothesize that SDG or flaxseed diets will decreased asbestos induced ROS/inflammation leading to: 1) ROS, 2) decreased cytokines, 3) decreased HMGB1, 4) less tumorigenic foci, and 5) less tumors

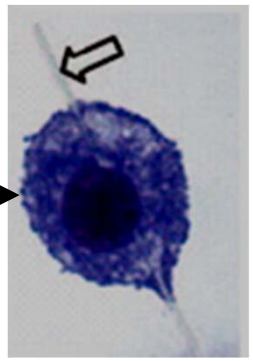
EXPOSING CELLS TO ASBESTOS



Asbestos Exposure

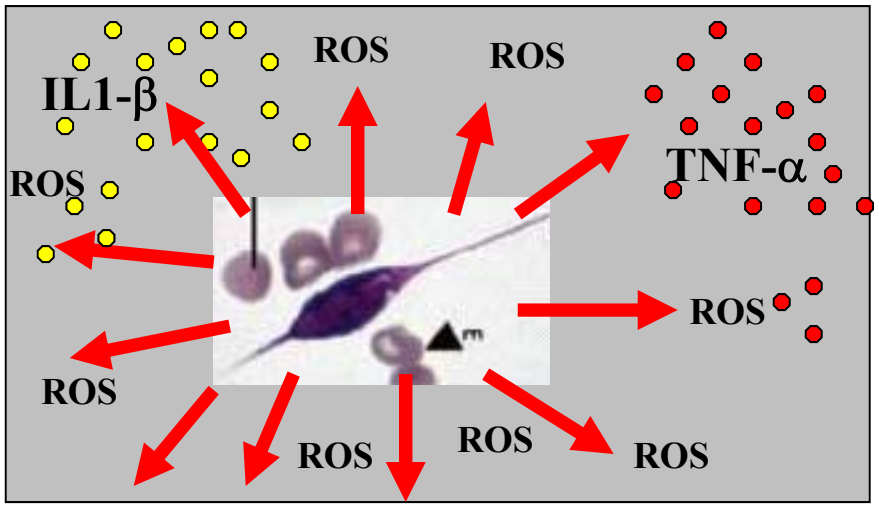
SDG incubation





0 hrs

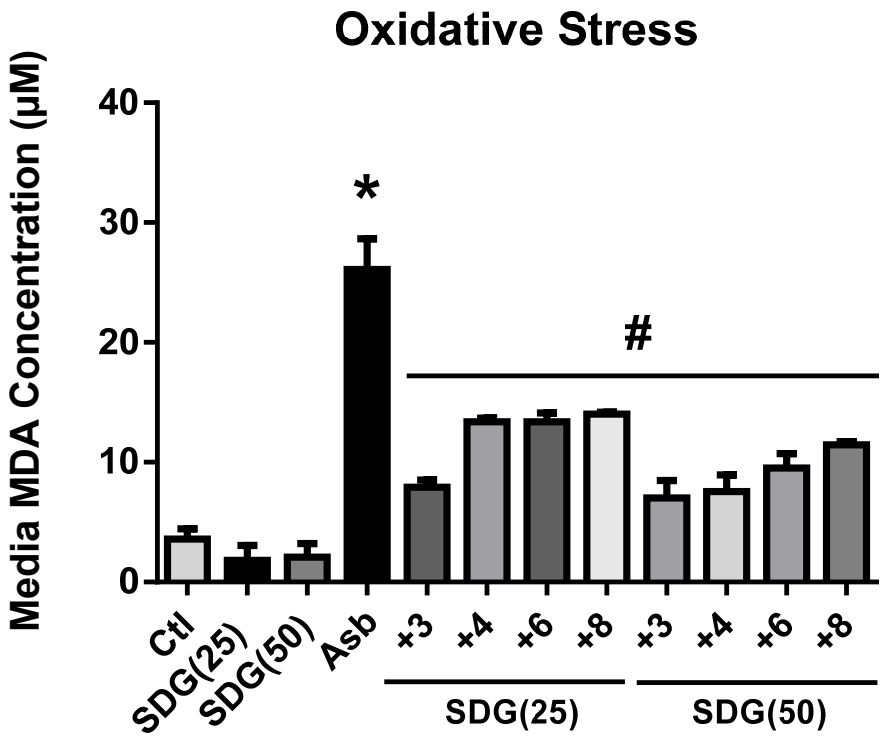
+3 hrs +4 hrs +6 hrs +8 hrs

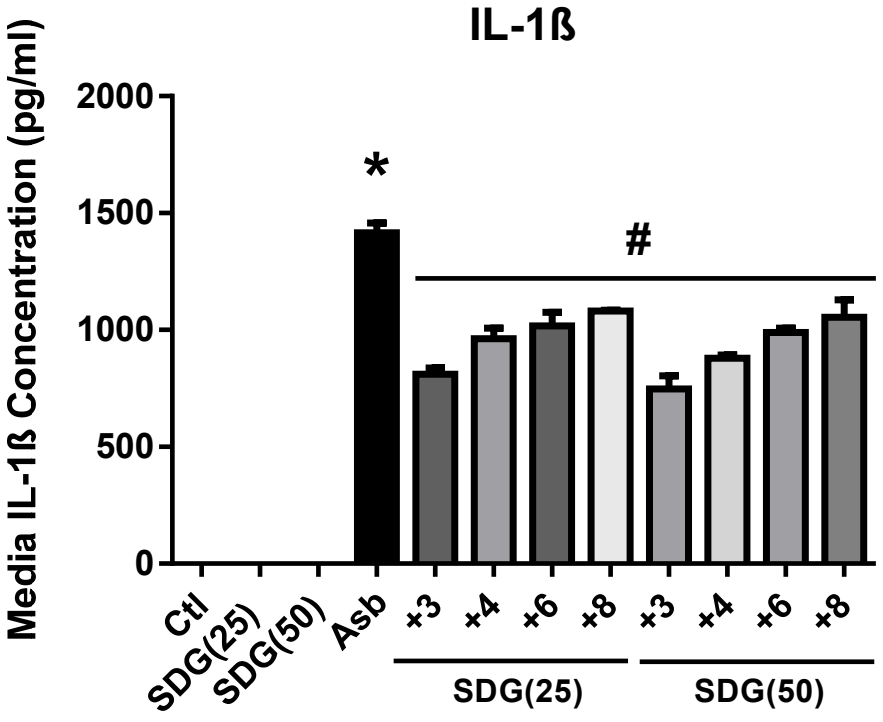


24h

1. ROS levels using H_2DCFDA
2. Supernatant⟶ Cytokine (TNF-α; IL-1β)
3. Cells ⟶ Inflammasome activation
4. MDA (Lipid Peroxidation)
5. Nitrite/Nitrate levels

SDG given to Macrophages Post Asbestos-Exposure Decreases Oxidative Stress and Inflammatory Cytokines



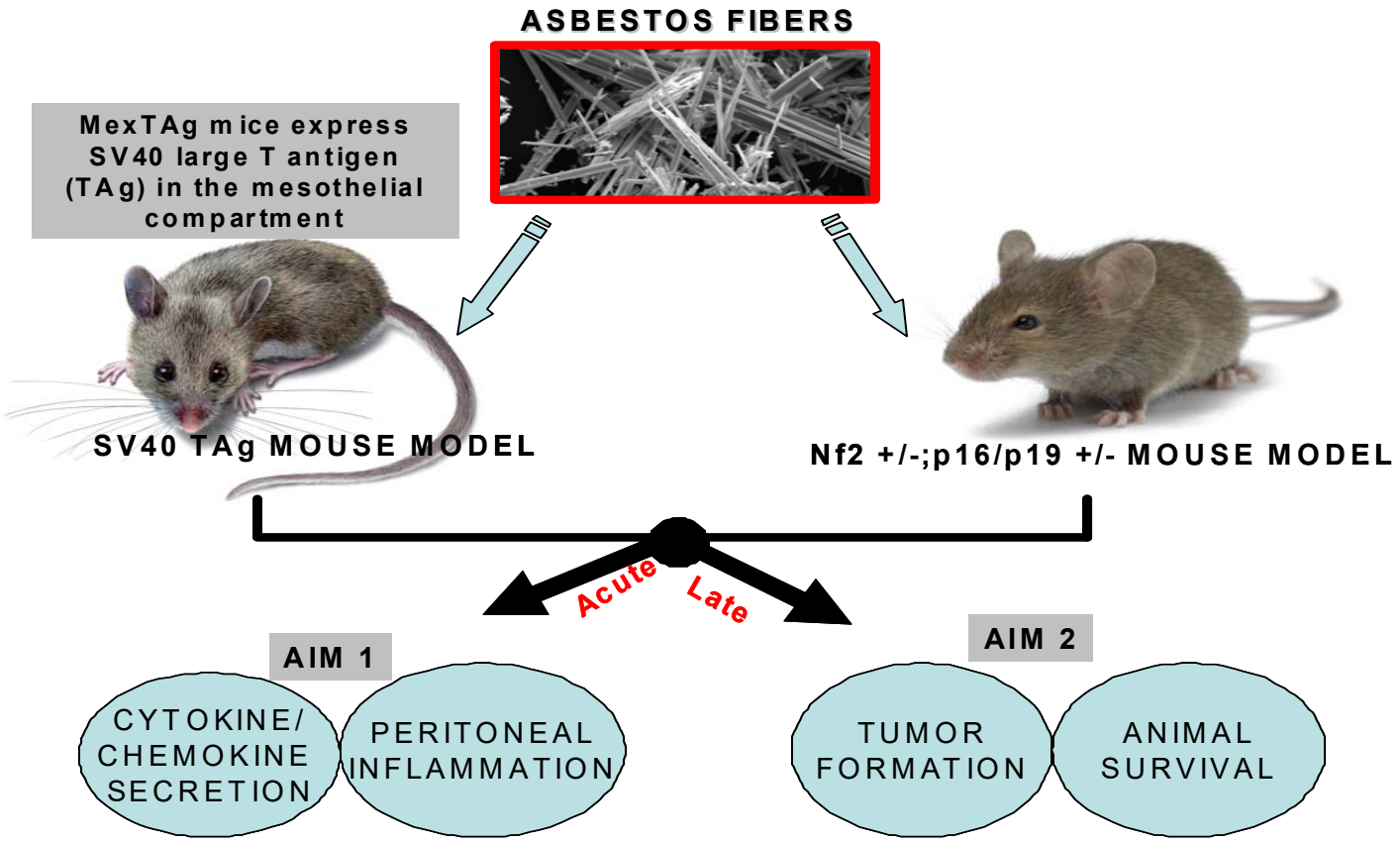


Summary of Findings

1. SDG blocks asbestos-induced ROS macrophages.
2. SDG blocks inflammatory cytokine secretion by mouse peritoneal macrophages exposed to asbestos
3. SDG blocks oxidative (lipid peroxidation) and nitrosative stress (nitrite levels) in mouse peritoneal macrophages exposed to asbestos

Findings from cell experiments justify pre-clinical experimentation to determine the usefulness of flaxseed and its lignan SDG in blunting chronic inflammation and ultimately malignancy due to asbestos exposure

Testing Flaxseed and SDG in Asbestos-Induced Malignant Mesothelioma



Using 2 models of mice genetically predisposed to develop mesothelioma after asbestos exposure, we will: Evaluate the acute effects of Flaxseed and SDG on asbestos exposed mice; test whether Flaxseed and SDG inhibits the development of tumors in genetic models of accelerated, asbestos induced MM.

Chemoprevention of Asbestos-Induced Malignant Mesothelioma Using Dietary Flaxseed

Data from this work will provide important evidence for the usefulness of this bioactive natural product in blunting cancer development from asbestos exposure and provide insight in the mechanisms involved.

If our studies show efficacy with safety, our long-term goal would be the evaluation of Flaxseed and SDG as chemopreventive agents for mesothelioma in exposed populations.

Funding Provided by:

National Institute of Allergy and Infectious Diseases (NIAID)
RC1AI081251

National Cancer Institute (NCI/NIH)
NIH-1R01CA-133470
NIH-1R21CA-118111

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