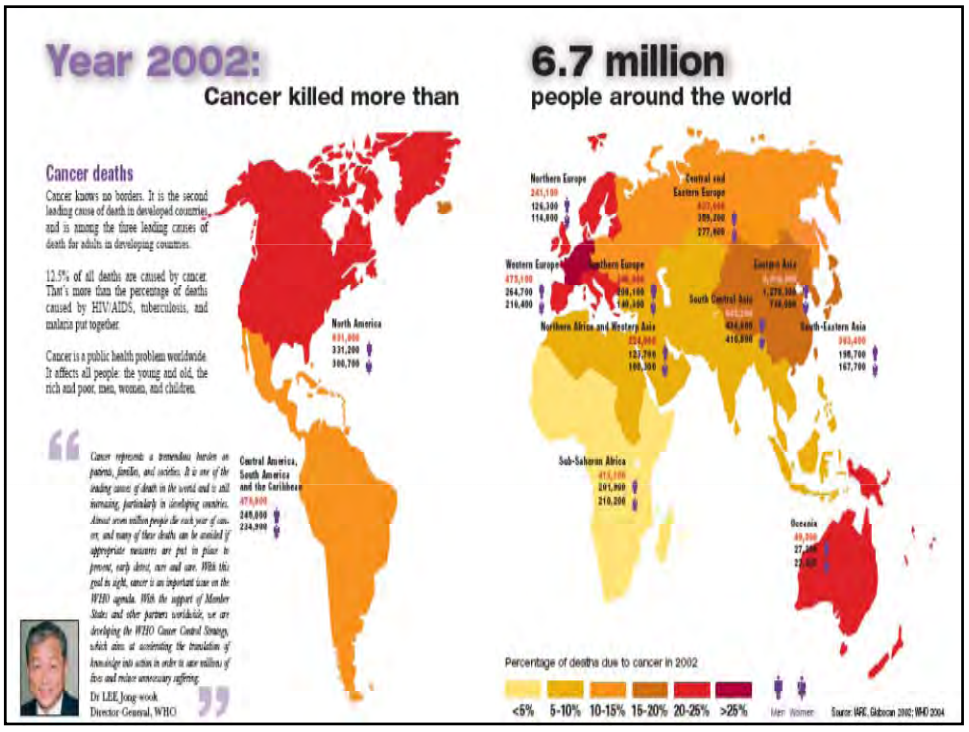
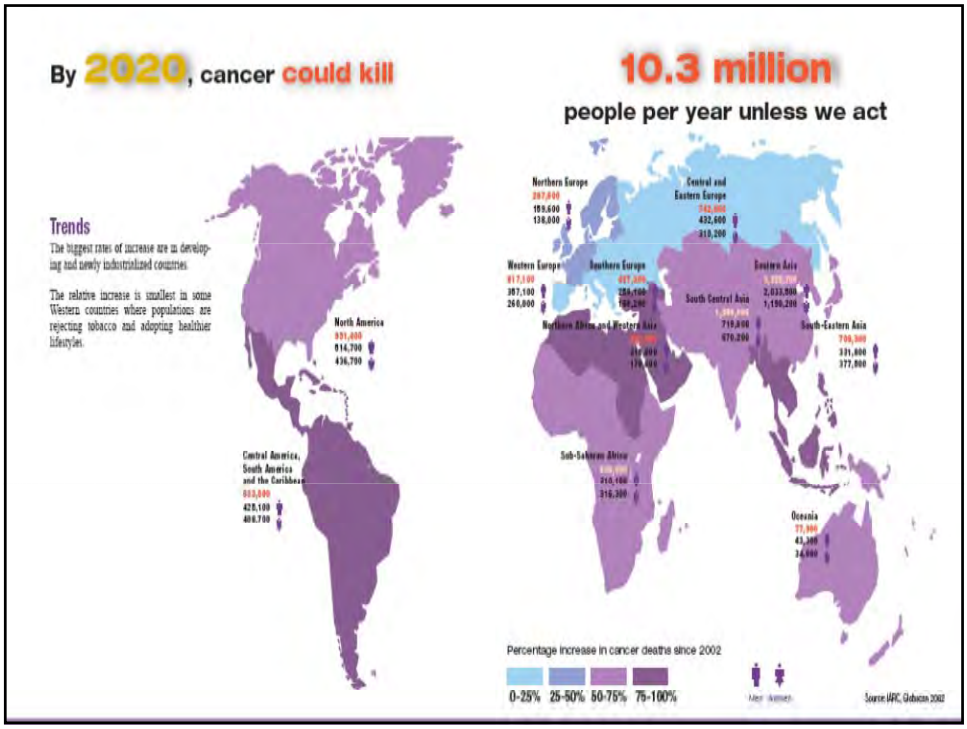
And when I am ill, it is [God] who cures me." (Ash-Shu'ara (The Poets: 26:80) (A supplication of Prophet Abraham)

"What you (O humanity) have been given of knowledge is but little." [Sūrah al-Isrā: 85]

Acknowledgements

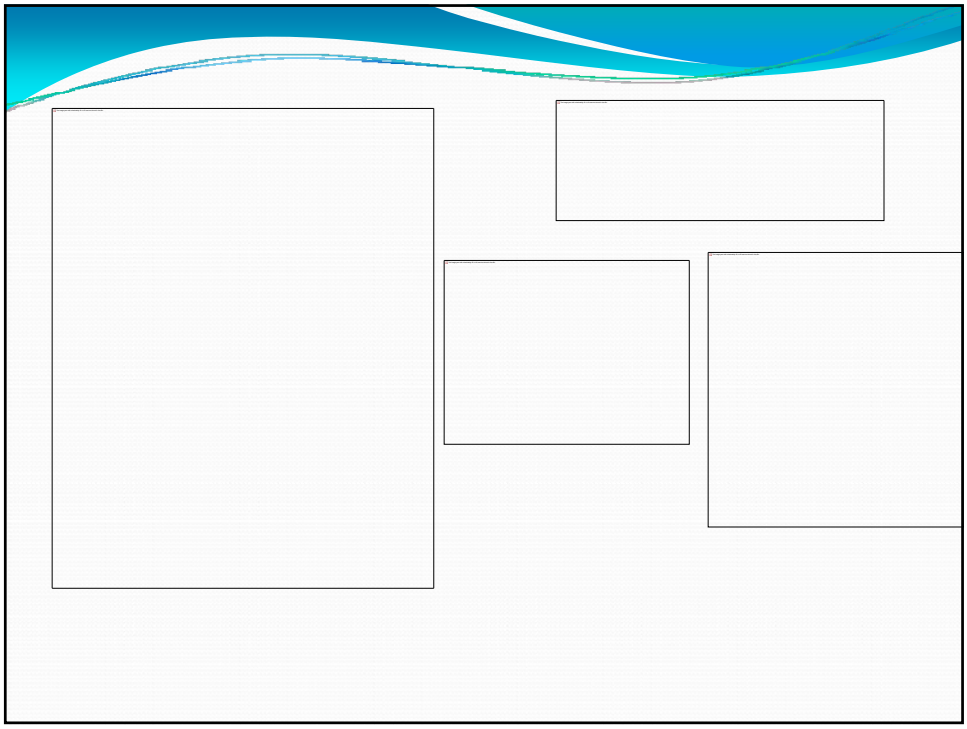
- All the postgraduate students
- Prof Zhari Ismail
- Dr Khadeer Ahmad
- Dr Aman Shah
- Dr Sven Peterson
- Dr Oon Chern Ein
- Prof Nur Hayati Othman
- Dr Rosnani Anwarul Haq
- Prof Othman Sulaiman
- Prof Zaini Asmawi
- Prof Chan Kit Lam
- Prof Mohamad Suhaimi Jaafar
- Prof Munawar Zubaid





Global Market Sales on Cancer Health Supplements

- The global cancer market in 2010 was valued at US$54bn, an increase of 5.1% reaching US$81bn in 2016.
- Global cancer prevalence rates are on the rise owing to an aging population and changing lifestyle.
- Herbal Supplements market valued at US$ 90 bn
- Hence the increase in hoax medicinal products.



Can Herbal products become therapeutic agents to treat cancer?

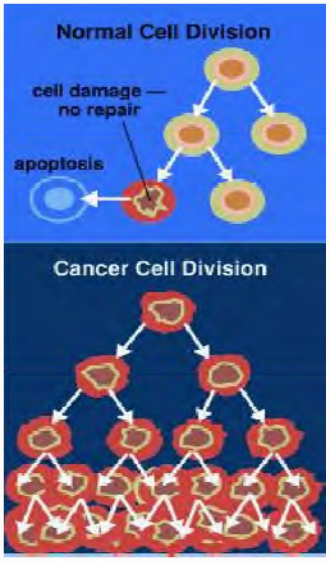
- Why not? 70 % of current drugs originate from nature.
- Drugs isolated from plants include the anticancer agent paclitaxel (Taxol) from the yew tree, and the antimalarial agent artemisinin from Artemisia annua.
- Current regulatory guidelines allows herbs to become therapeutic drugs similar to current drugs in the market.
- Requires preclinical and clinical data, a good CMC (Chemical, manufacturing & controls) , certified plantation sources and manufacturing facilities.

Why many herbs product failed to become drugs?

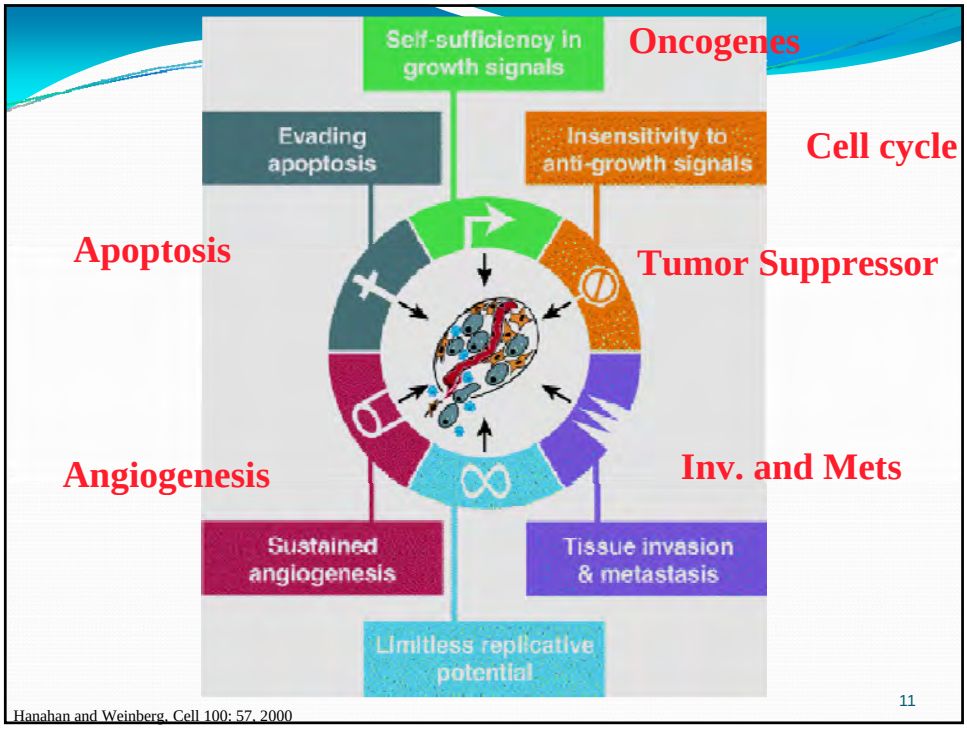
- Poor IP protection
- Lack of funding to do proper preclinical & clinical studies
- Insufficient raw materials
- Science too complex, too many biological targets & compounds, unidentified active principles.
- Lack of quality controls

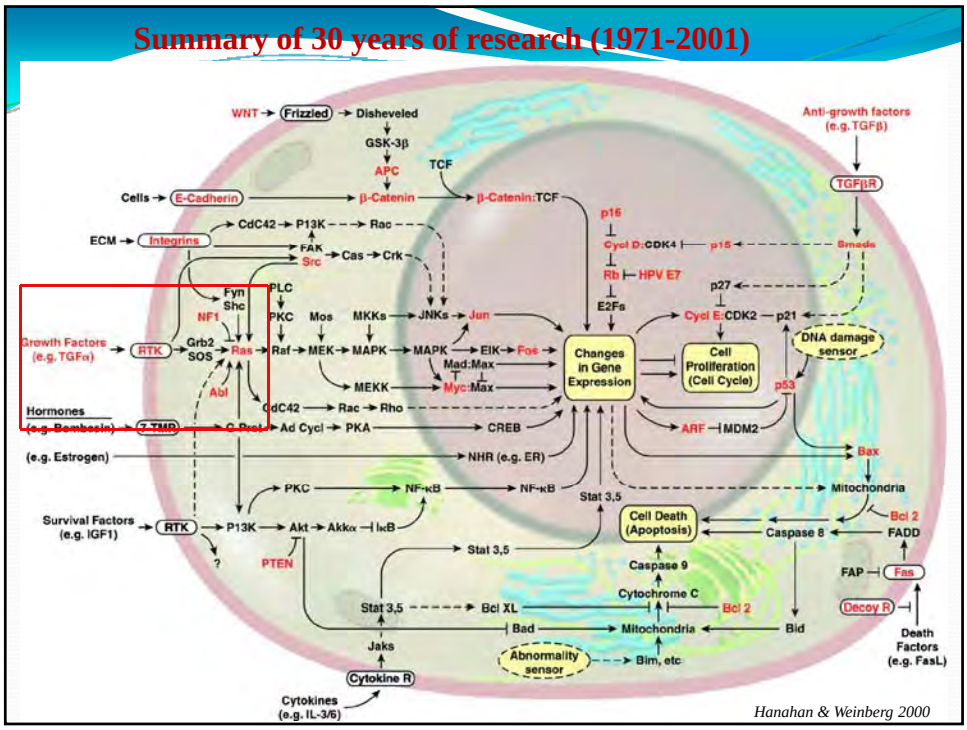
What is Cancer ?

- **Cancer is a collection of diseases characterized by abnormal and uncontrolled growth**
- **Cancer arises from a loss of normal growth control**
- **In normal tissues, the rates of new cell growth and old cell death are kept in balance**
- **In cancer, this balance is disrupted**
- **This disruption can result from**
  1) uncontrolled cell growth or
  2) loss of a cell's ability to undergo apoptosis

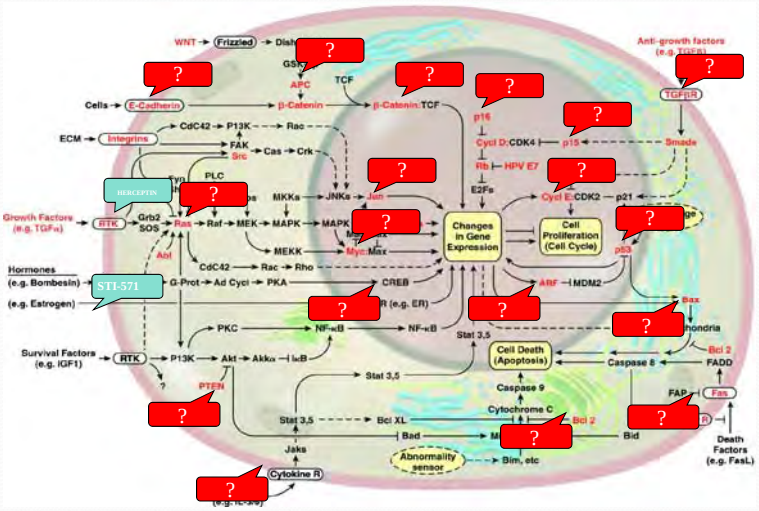


10


Self-sufficiency in growth signals
Oncogenes
Evading apoptosis
Insensitivity to anti-growth signals
Cell cycle
Apoptosis
Tumor Suppressor
Angiogenesis
Inv. and Mets
Sustained angiogenesis
Tissue invasion & metastasis
Limitless replicative potential
11
Hanahan and Weinberg, Cell 100: 57, 2000


Summary of 30 years of research (1971-2001)
WNT
Frizzled
Disheveled
GSK-3β
APC
TCF
β-Catenin
β-Catenin:TCF
Cells
E-Cadherin
ECM
Integrins
CdC42
P13K
Rac
FAK
Src
Cas
Crk
PLC
Fyn
Shc
NF1
PKC
Mos
MKKs
JNKs
Jun
Growth Factors (e.g. TGFα)
RTK
Grb2
SOS
Ras
Raf
MEK
MAPK
MAPK
EIK
Pos
Mad:Max
Myc:Max
MEKK
Abl
CdC42
Rac
Rho
Hormones
(e.g. Bombesin)
7-TMD
G Prot
Ad Cycl
PKA
CREB
(e.g. Estrogen)
NHR (e.g. ER)
PKC
NF-κB
NF-κB
Survival Factors (e.g. IGF1)
RTK
P13K
Akt
Akkα
IκB
?
PTEN
Stat 3,5
Stat 3,5
Stat 3,5
Bcl XL
Bad
Jaks
Cytokine R
Cytokines (e.g. IL-3/6)
Abnormality sensor
Bim, etc
Mitochondria
Cytochrome C
Bcl 2
Bid
Caspase 9
Cell Death (Apoptosis)
Caspase 8
FADD
FAP
Fas
Decoy R
Death Factors (e.g. FasL)
Bax
Bcl 2
Mitochondria
Anti-growth factors (e.g. TGFβ)
TGFβR
Smads
p16
Cycl D:CDK4
p15
Rb
HPV E7
E2Fs
p27
Cycl E:CDK2
p21
DNA damage sensor
p53
ARF
MDM2
Changes in Gene Expression
Cell Proliferation (Cell Cycle)
Hanahan & Weinberg 2000

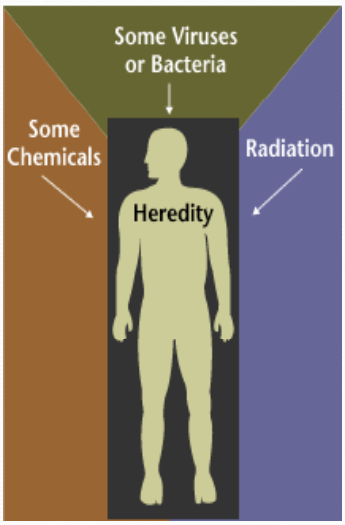
Thousands of Targets



13

What causes Cancer?

- Cancer is caused by alterations or mutations in the genetic code
- Can be induced in somatic cells by:
  - Carcinogenic chemicals
  - Radiation
  - Some viruses
  - Diet
- Heredity - 5%



14

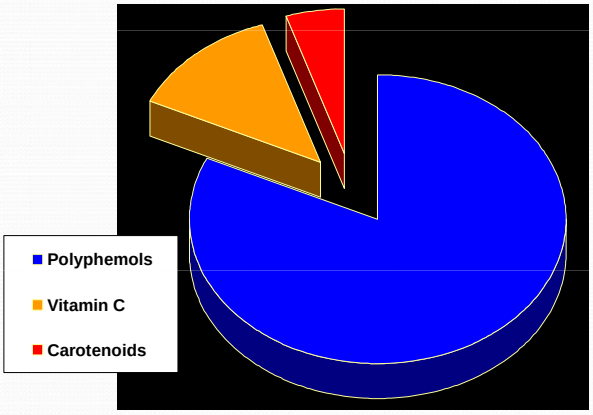
Natural product properties useful for anti-cancer activity

- Antioxidants: defense against radicals
- Phase 1 enzyme inducers
- Phase 2 enzyme inducers
- Anti-proliferative agents
- Anti-hormonal compounds
- Disruption of mutational gain or loss of functio
- Epigenetic effects

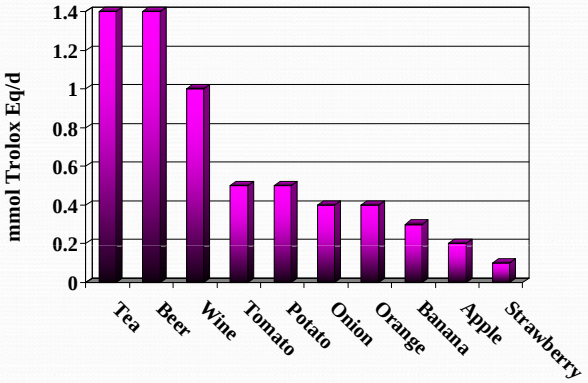
Antioxidants

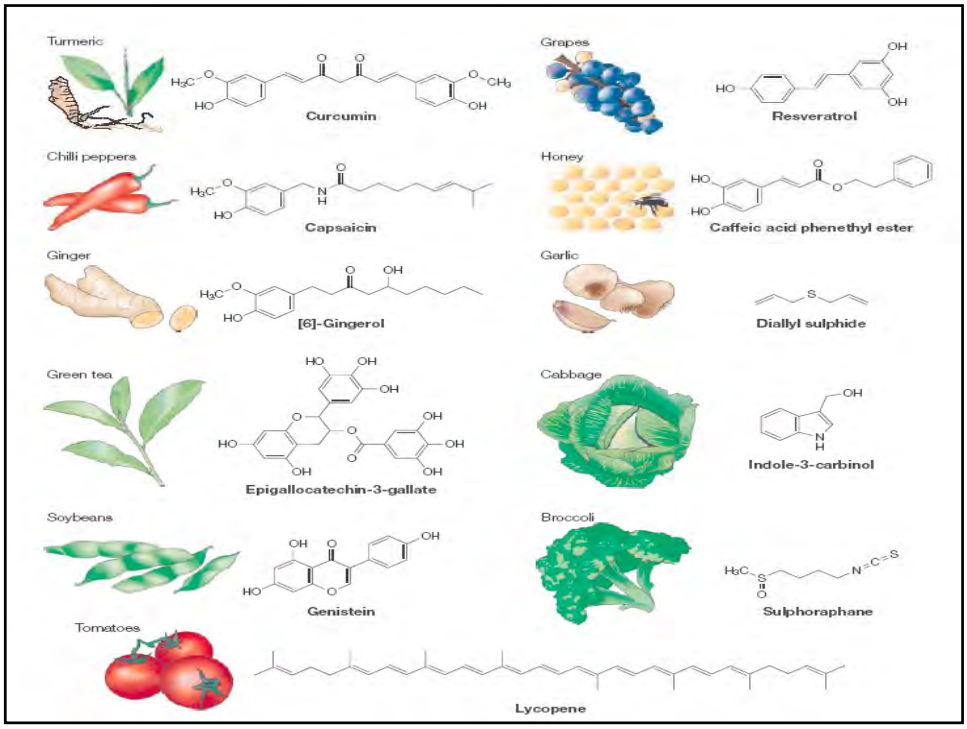
- Oxygen is actually a very toxic substance
- Antioxidants are the first line defense mechanism against oxidative damage in plants
- Plant based natural products are loaded with antioxidant substances

Total Daily Intake of Antioxidants



Antioxidant Potential of Fruits and Vegetables



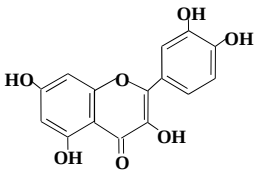


Flavonoids: naturally occurring low molecular wt phenols consisting of 2 benzene rings linked via a heterocyclic pyrone or pyran ring

- **Anthocyanin** - berries
- **Flavanone** - citrus
- **Flavanol** - red wine
  teas
  chocolate
  fruit
- **Flavonol** - fruit
  vegetables
- **Hydroxycinnamates** - most fruit & some vegetables

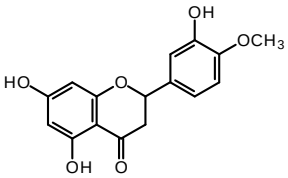
Flavonol

***e.g.* quercetin**
onion, cranberry, red apple many fruit and vegetables



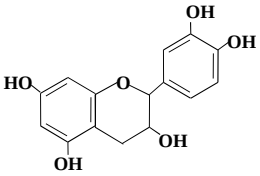
Flavanone

e.g. hesperetin
Citrus fruit, orange



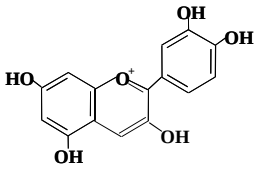
Flavanol

***e.g.* epicatechin**
red wine, green tea, as procyanidins in apple, chocolate



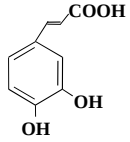
Anthocyanidin

***e.g.* cyanidin**
major constituents of dark red fruit berries e.g. raspberries

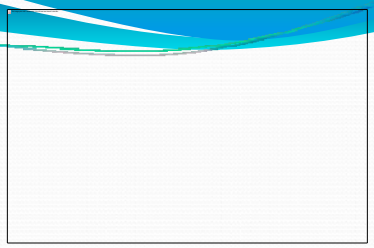


Hydroxycinnamate

***e.g.* caffeic acid**
most fruit especially tomato, apple some vegetables e.g. egg plant grains

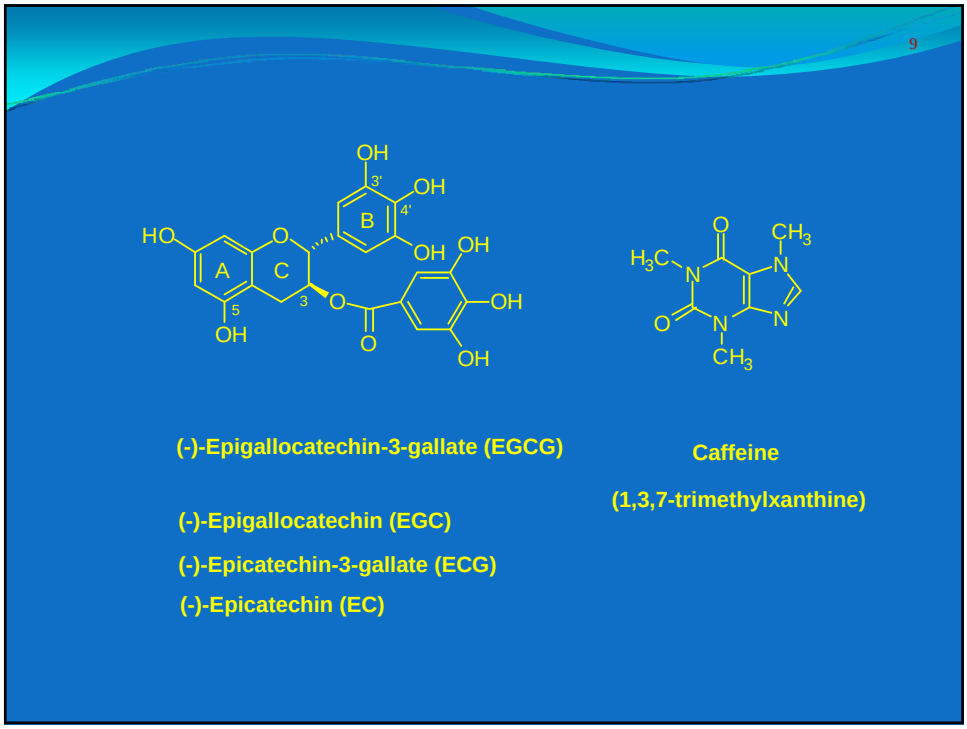


Green Tea



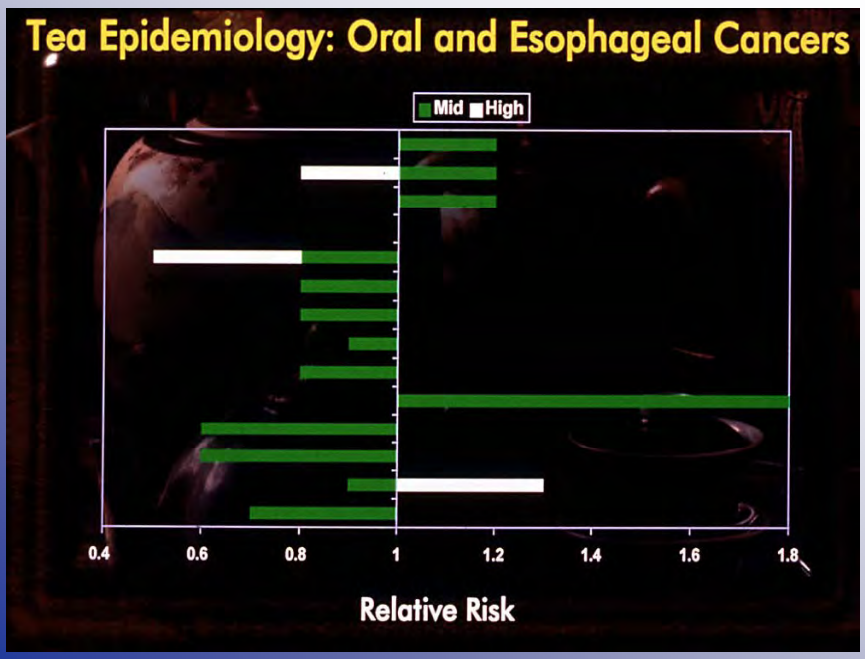
Camellia sinensis

- Epidemiologic studies support a protective effect for green tea but not black tea in prevention of certain cancers
- Animal studies are highly supportive of a preventive effect of green teaand purified polyphenols, especially EGCG against certain cancers



Evidence for Tea Drinking and Prevention of Human Cancer

- Ecological Studies
- Cohort Studies
- Case-Control Studies



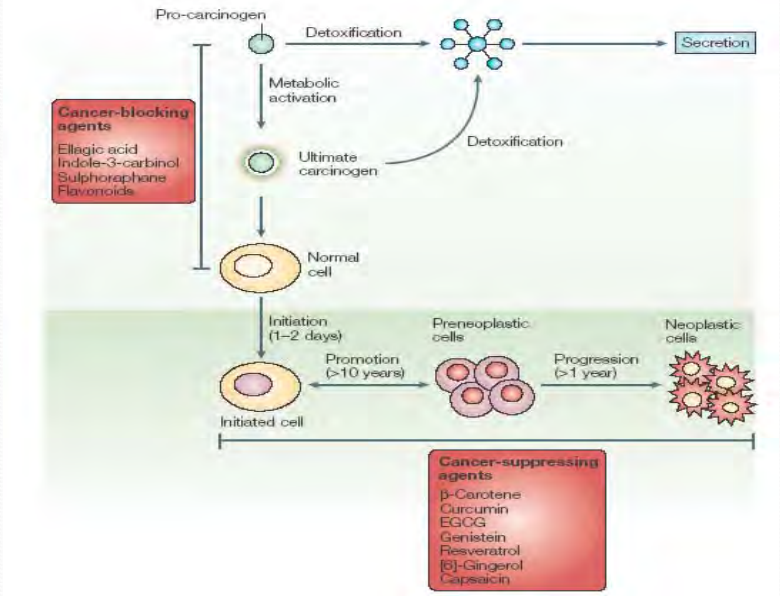
Bioflavonoids

- Naturally occurring chemicals present in many fruits and vegetables
- Major flavonoids in onion are quercetin and its glycoside, rutin
- Can reach appreciable levels in onions but tea also is a major source

Bioflavonoids and Reduced Risk for Heart Disease

- Quercetin inhibits oxidation of LDL cholesterol
- Inhibits development of fatty streaks in animals

Agents That Influence Drug Metabolism

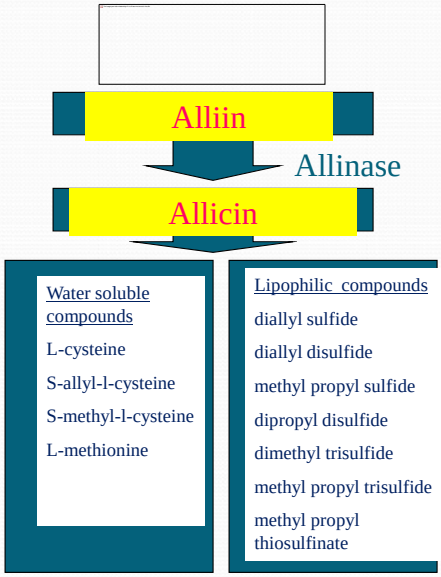


Garlic

Allium sativum

- Consumption in China and Italy linked to lower gastric cancer risk
- Sulfur compounds inhibit cancers of colon, breast, esophagus, lung, skin
- Primarily acts through modulation of Phase 1 (activation) and Phase 2 (detoxification) enzymes

Organosulfur Compounds in Garlic



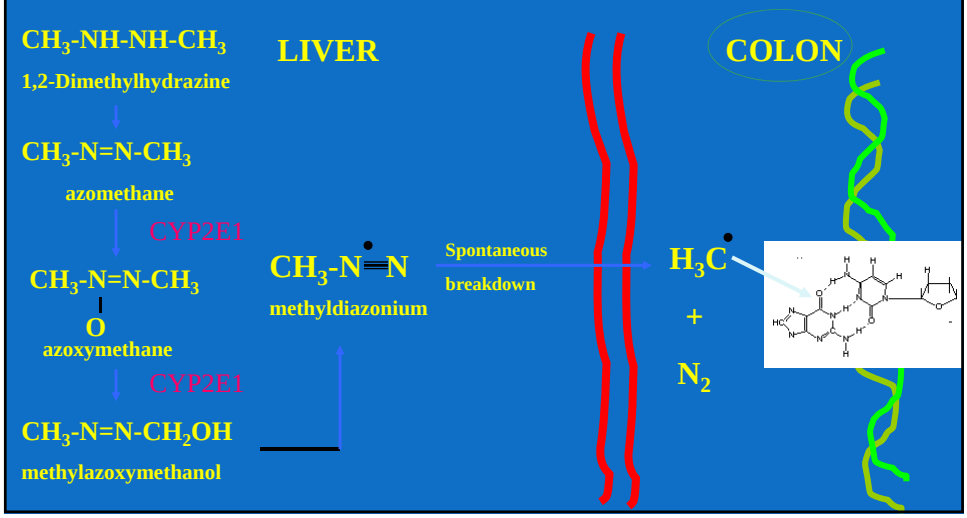
- Member of the plant genus *Allium*
- Over 20 different compounds in garlic are being tested for cancer inhibition.
- Diallyl sulfide was the first organosulfur compound known to inhibit experimentally-induced cancer.
- Proposed mechanisms of chemoprotection lie in modification of carcinogen metabolism and/or detoxification.

Cyp2e1

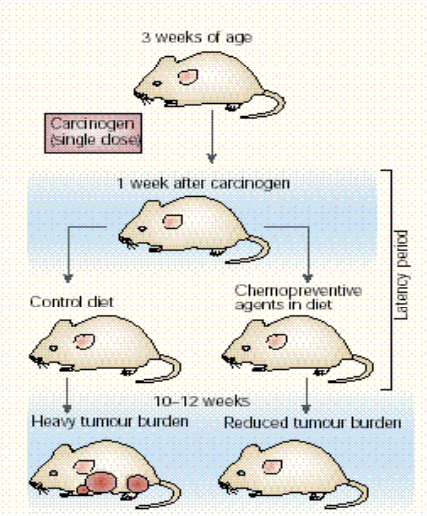
- **One subset of many cytochromes P450**
- **Main task is to activate compounds; eliminate them from the body**
- **This enzymes metabolizes many small molecular weight compounds**
- **Ethanol, nitrosamines, hydrazines**

CYP2E1 and Colon Cancer

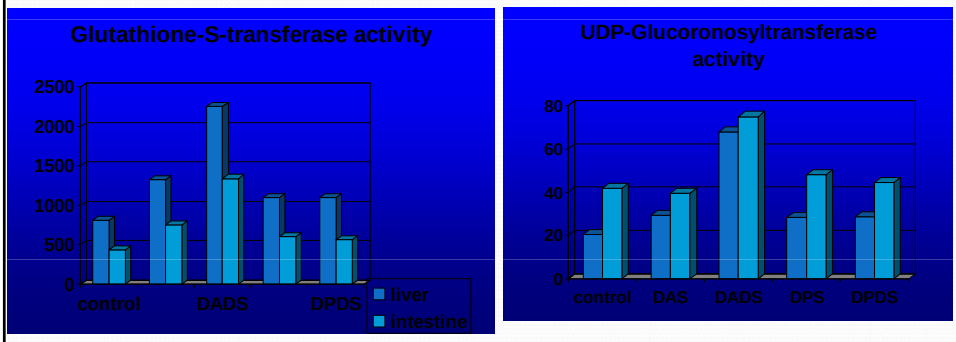
Dimethylhydrazine (DMH) Model

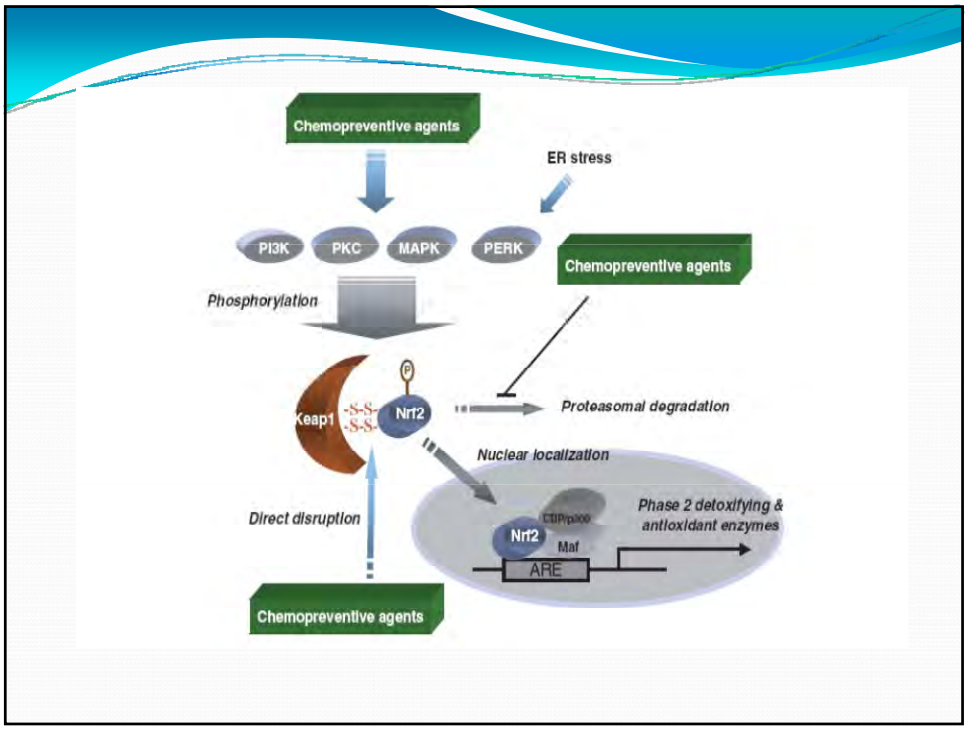


Typical Chemoprevention Assays in Rodents

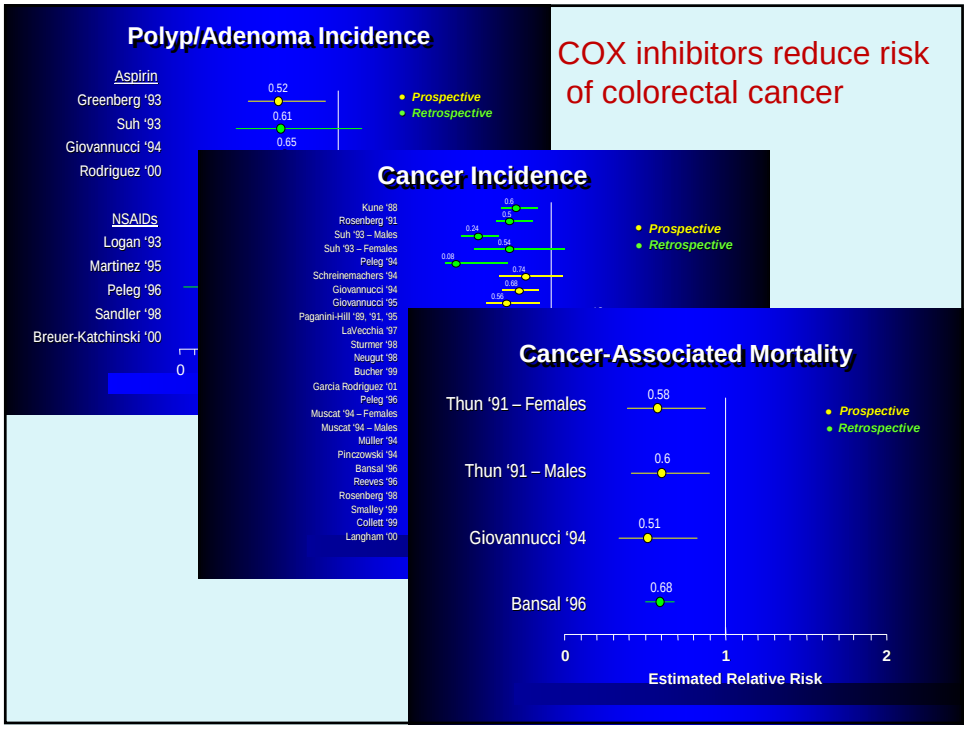


Garlic Compounds and Phase II Enzymes





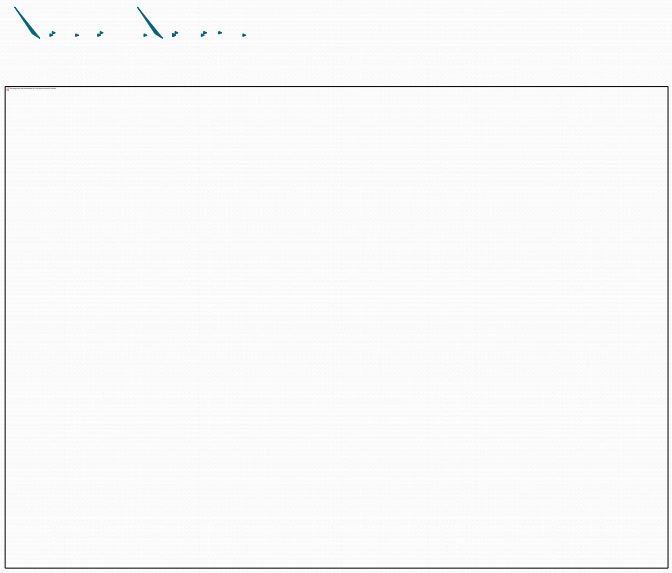
Antiproliferative or Growth Suppressing Agents: Modulation of Cell Signaling



COX inhibitors reduce risk of colorectal cancer

How Do NSAIDs Work?

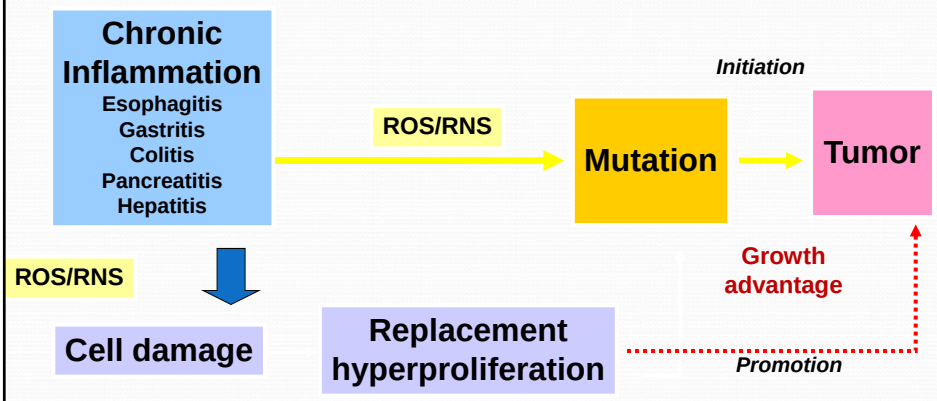
- Aspirin transfers acetyl group to serine on the cyclooxygenase enzyme, blocking its affinity for arachidonic acid
- All other NSAIDs are competitive inhibitors of the COX enzymes

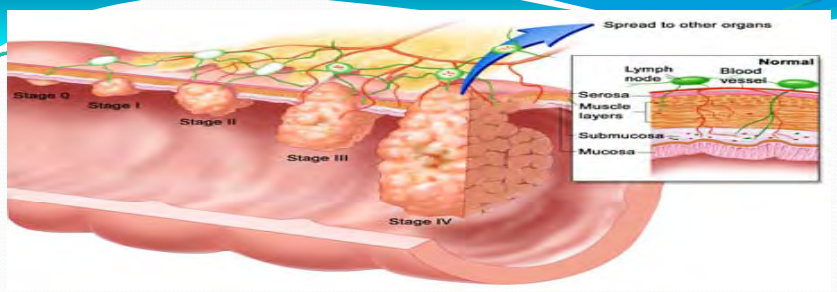


Inflammation and Cancer

- Chronic, clinically invisible, unresolved inflammation may create a very high risk for common cancers
- Tumors corrupt the inflammatory pathway to survive

A model of chronic inflammation setting a threshold for cancer





APC mutation

COX-2 Overexpression

K-ras mutation

p53 mutation

Loss of 18q

Multistage Colon Carcinogenesis

Plant-based NSAIDS…

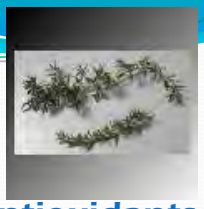
Are there plant-based NSAIDS?

- If so, the source should:
  - Have anti-inflammatory effects
  - Be available for oral use
  - Be safe
  - Efficacious

Resveratrol (Red Grapes)

- A phytoalexin in red grapes
- Inhibits cell transformation in cultured tumor cells
- Inhibits cell proliferation in cells in culture and in tumors grown in mice
- Inhibits mammary cancer in rats
- Induces apoptosis

Rosemary

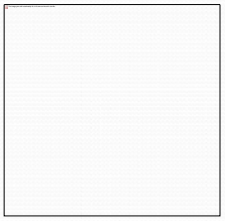


- Rosemary is a potent source of antioxidants
- Three antioxidants have cancer preventive properties:
  - rosmarinic acid
  - ursolic acid
  - caffeic acid

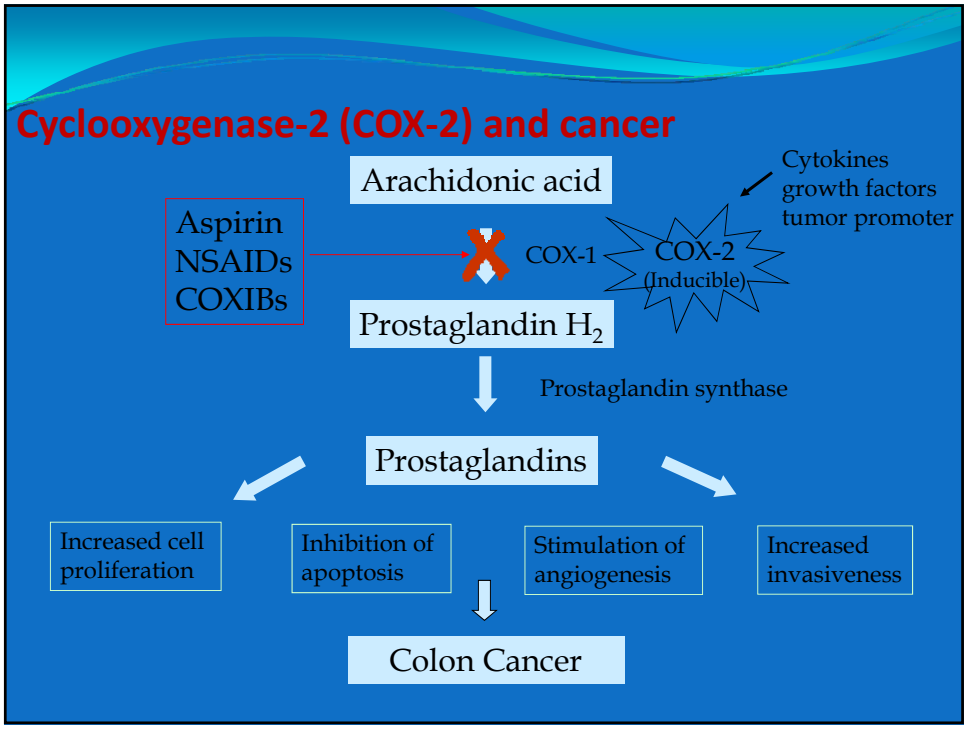
Gingko biloba

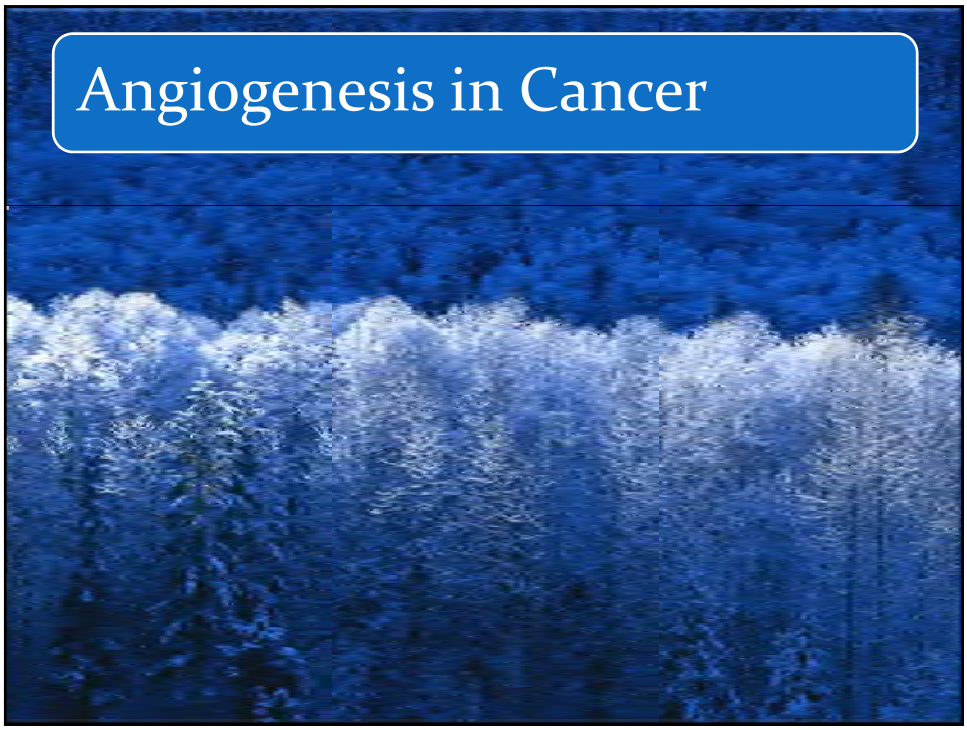
- Widely used in Europe
- ↑ cognitive function
- No side effects in > 10,000 patients
- Useful in dementia and Alzheimer's
- Anti-inflammatory
- Anti-oxidant

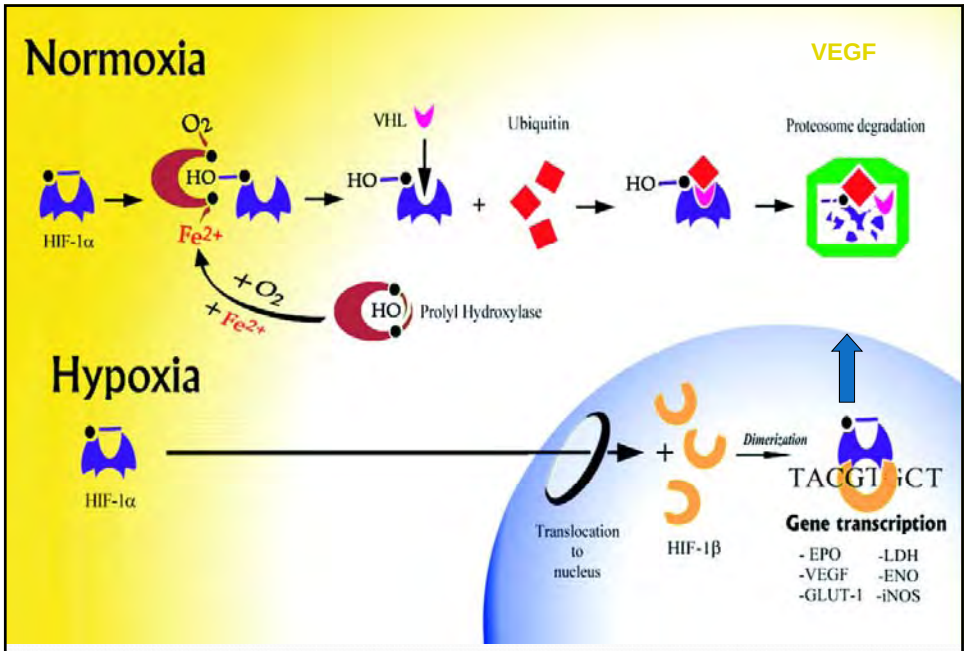
Turmeric



- The yellow spice used in cooking Malaysian dishes
- Yellow color due to phenolic compound-curcumin
- Strongly antioxidant
- Suppress many types of tumors in animal
- Clinical studies underway


Cyclooxygenase-2 (COX-2) and cancer
Arachidonic acid
Cytokines
growth factors
tumor promoter
Aspirin
NSAIDs
COXIBs
COX-1
COX-2
(Inducible)
Prostaglandin H2
Prostaglandin synthase
Prostaglandins
Increased cell proliferation
Inhibition of apoptosis
Stimulation of angiogenesis
Increased invasiveness
Colon Cancer


Angiogenesis in Cancer

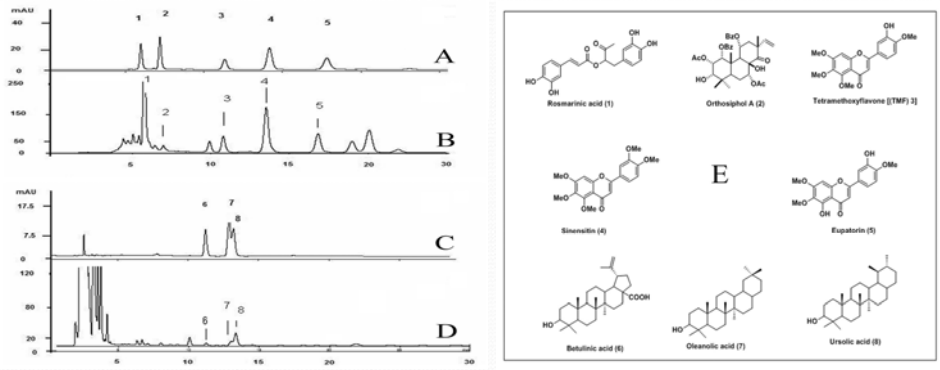


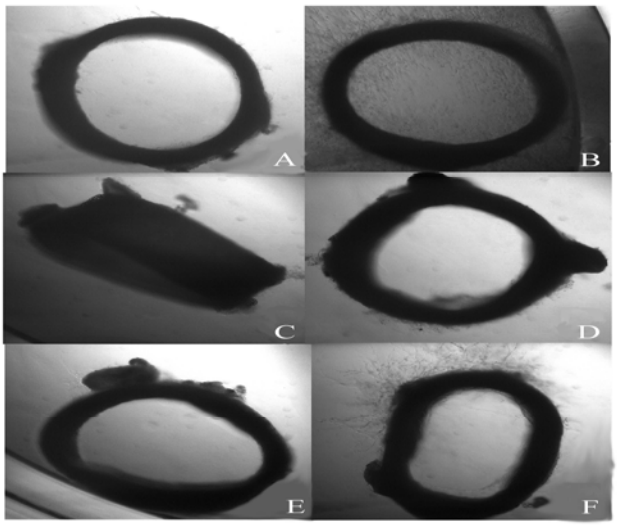
LaManna, J. C. et al. J Exp Biol 2004;207:3163-3169

Orthosiphon stamineus (Misai Kucing)

- *Widely used in South East Asia*
- *Used for diabetes, hypertension, rheumatoid arthritis , kidney stones.*
- *Anti-inflammatory*
- *Anti-oxidant*

- Standardized 50% ethanolic extract of *O. stamineus (Msai kucing)* with 8 marker compounds: sinensetin, eupatorin, rosmarinic acid, Orthosiphol A, methylripariochromene, TMF, oleanolic acid and betulinic acid.

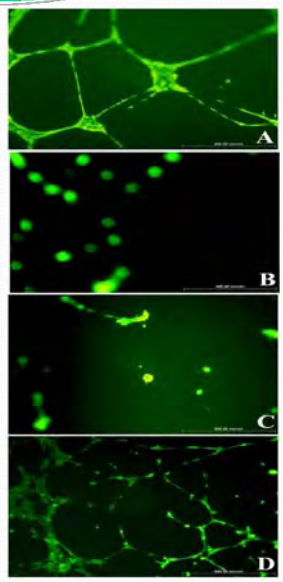


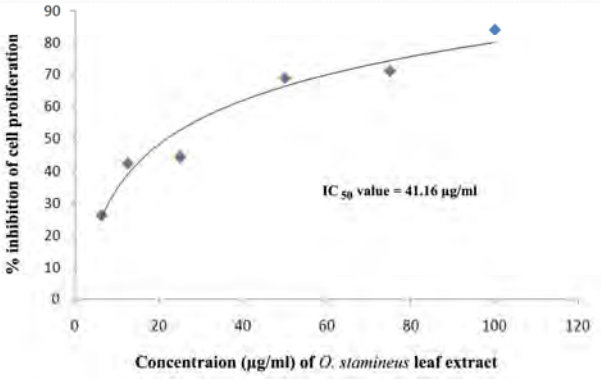


Rat Aortic Arch Ring Assay. A is the positive control Suramin, B is the negative control, C is petroleum ether extract of O.S, D is Chloroform extract, E is methanol extract of O.S and F is the water extract of O.S.

Inhibition of HUVECs Proliferation and Tube Formation

Effect of O.S 50% ETOH extract on endothelial Tube formation. A: - Control B: EtOH 50% extract C: EtOH 50% fraction D: + Control (Suramin)





Effect of O.S 50% ETOH extract on endothelial Cell proliferation (HUVECs)

Inhibition of VEGF Production and suppression of its receptor

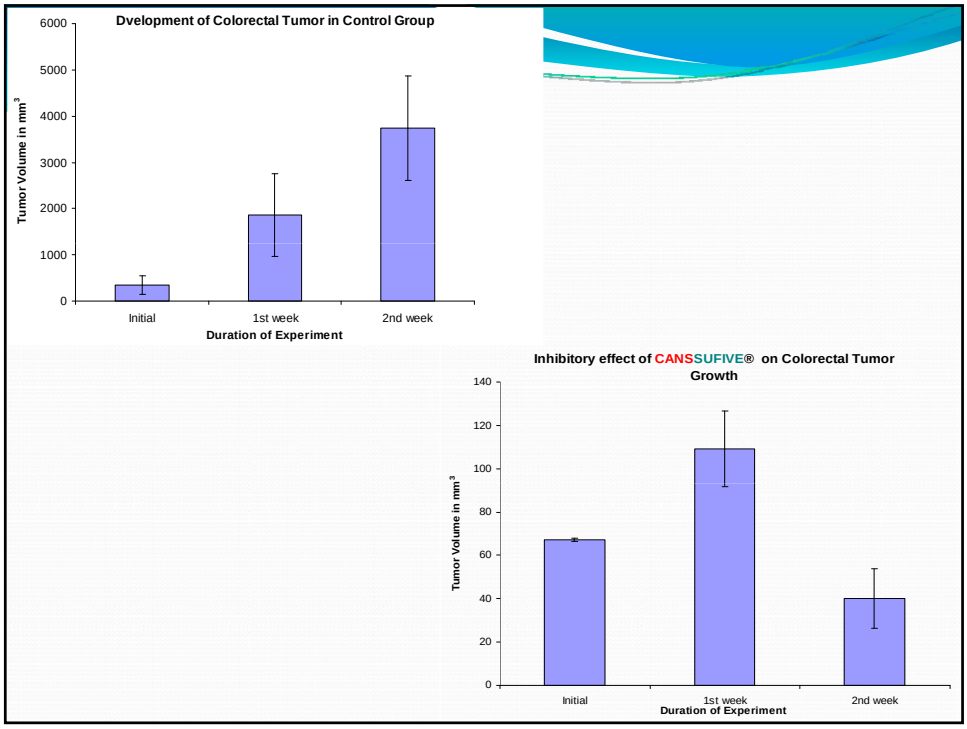
Western Blotting Analysis of VEGF-R2

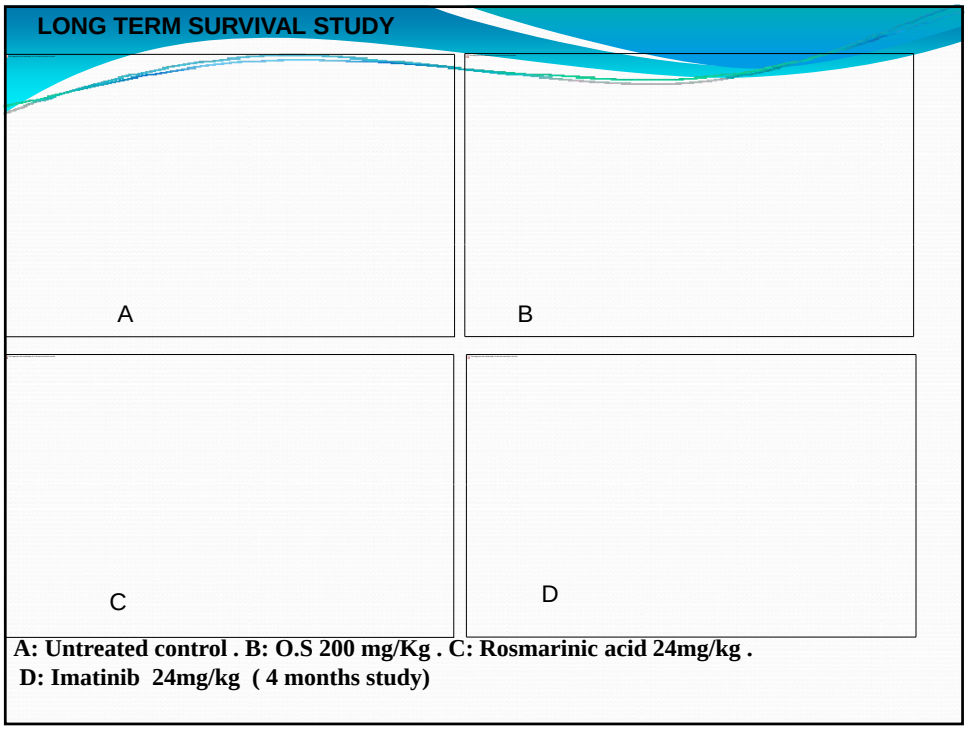
O.S

Inhibits angiogenesis in vivo
Matrigel gel plug assay

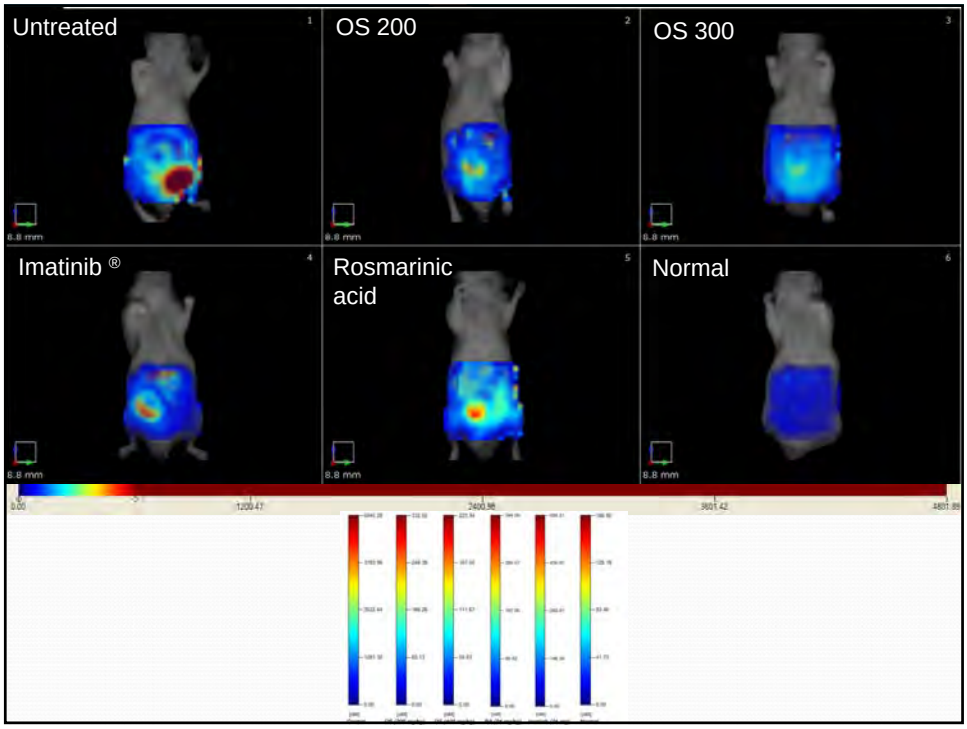
Anti-tumor Property of CANSSUFIVE O.S extract

Inhibition of Colorectal Tumor

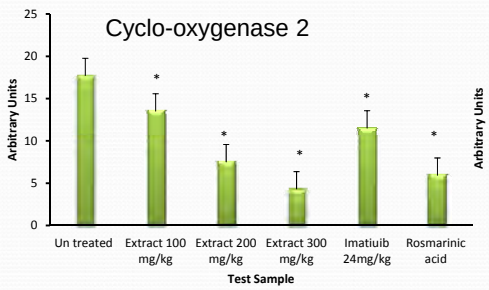


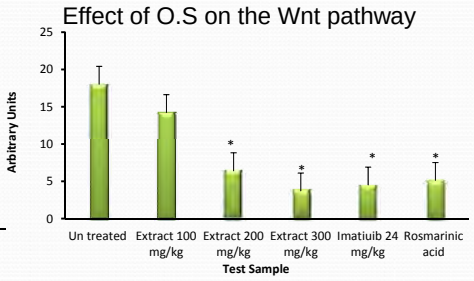


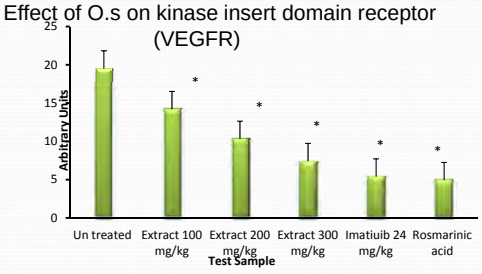
A: Untreated control . B: O.S 200 mg/Kg . C: Rosmarinic acid 24mg/kg . D: Imatinib 24mg/kg (4 months study)

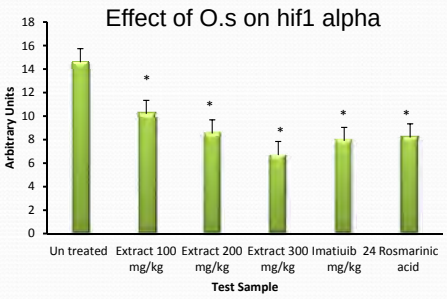


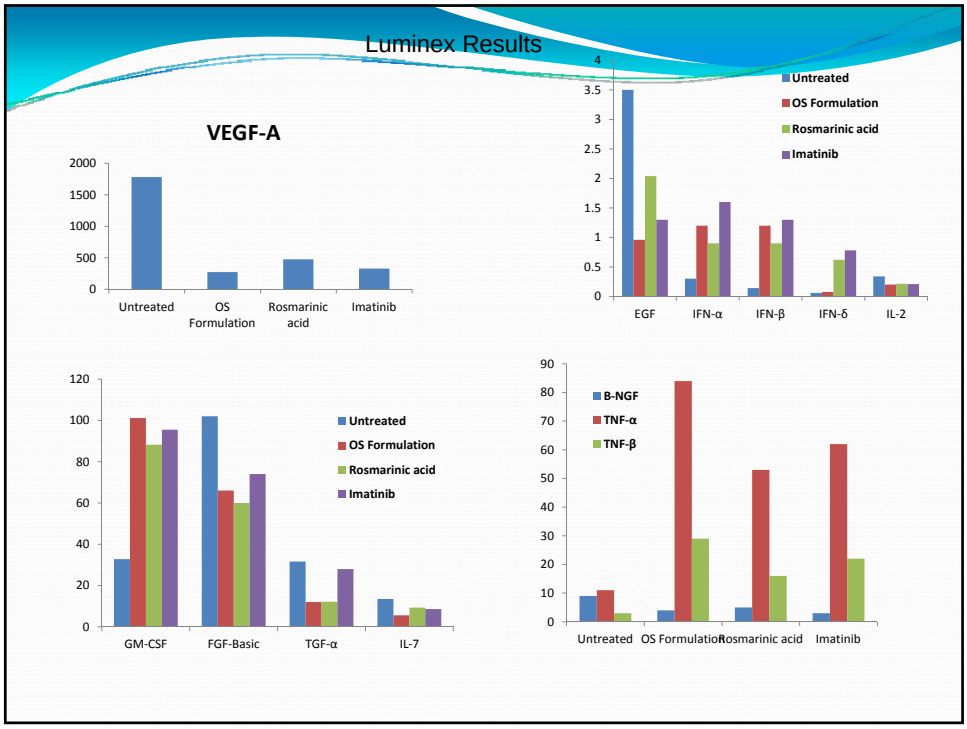
O.s on Colon tumor homogenate











Clinical Trials

Canssufive ® has been on pilot clinical studies since 2007.

- 50 patients with end stage cancers have been enrolled.
- Phase 1a clinical studies have been completed on 12 healthy volunteers.
- IND pivotal phase 1 studies is expected to commence January 2014.
- Phase 2 and 3 as adjuvant therapy for breast and colon cancer is expected to be completed end of 2017.

Conclusion

- Herbal products as anti-cancer agents is not a hype
- Requires good fundamental research
- Must have robust clinical data
- Chemical and manufacturing control is vital with robust QC standards and certified plantation source.
- Maintaining consistency in product quality and efficacy is paramount.

Thank You