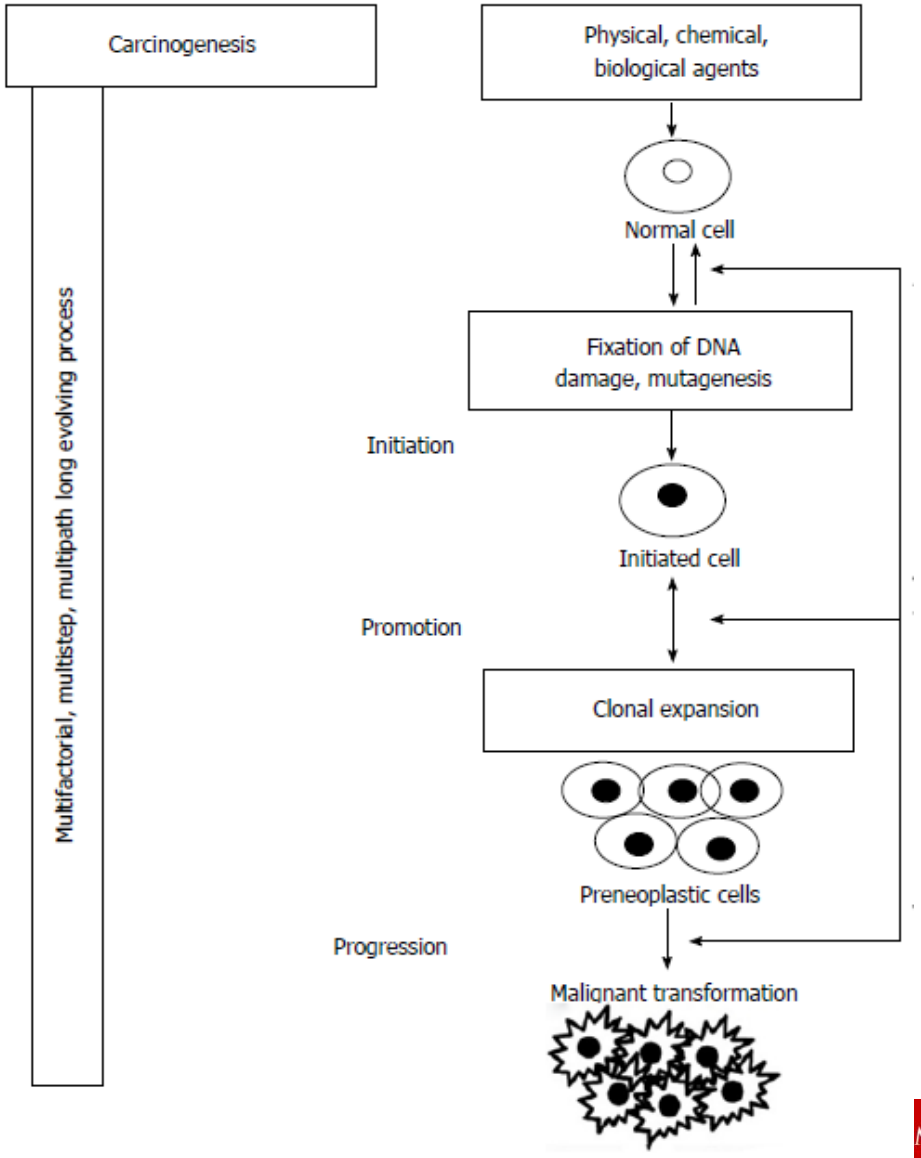
Nutraceuticals in chemoprevention

Novi Sad, 14 December 2016

What is Cancer?



Cancer is a disease characterized by out-of-control cell growth leading to spread of abnormal cells to other body parts by local invasion and/or distant metastasis.

It is one of the major and growing public health problem, currently accounting for over 12% deaths globally.

Cancer risk factors

Genetic factors contribute only around 5–10% of the cancer risk, while environmental factors account for 90–95% (10–15% from chemical and industrial carcinogens, 15–20% from infections, 25–30% from tobacco, and 30–35% from diet)

Biomed. Pharmacother. 61 (2007) 640–658.

Lifestyle represents the major determinant of cancer risk, practical approaches in cancer prevention interventions include pursuing lifestyle or dietary changes.

Chemoprevention

- “Chemoprevention” is defined as the use of natural dietary agents able to prevent or interfere with the development or progression of neoplastic processes that lead to the appearance of cancer.

World J Biol Chem 2016 February 26; 7(1): 88-99

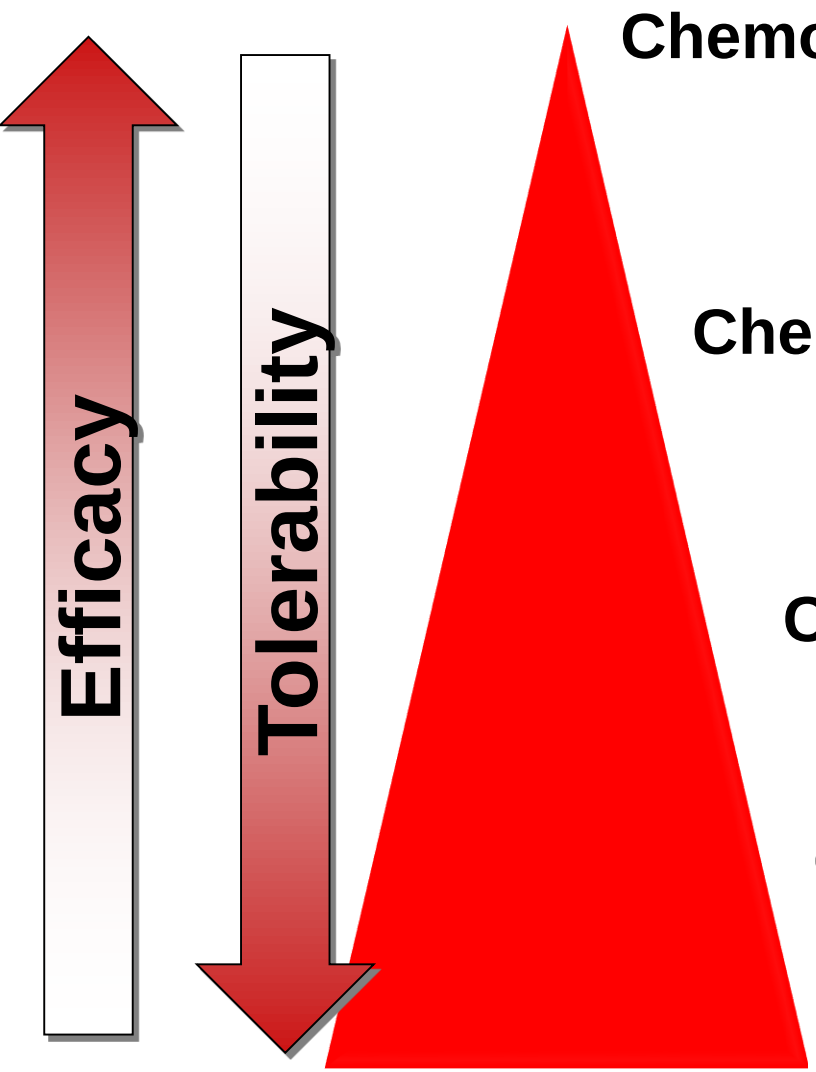
-**Primary Chemoprevention**: aims to prevent the development of disease in the general population.

Chemoprevention

-**Secondary Chemoprevention**: this focuses on individuals who have been diagnosed with some type of premalignant lesions that may progress to invasive cancer. This strategy aims to limit the development and progression of malignant lesions.

-**Tertiary Chemoprevention**: this type of chemoprevention is directly aimed at preventing the recurrence of new secondary tumours in individuals who have developed a cancer.

Chemoprevention



Chemotherapy

Chemoprevention (tertiary)

Chemoprevention (secondary)

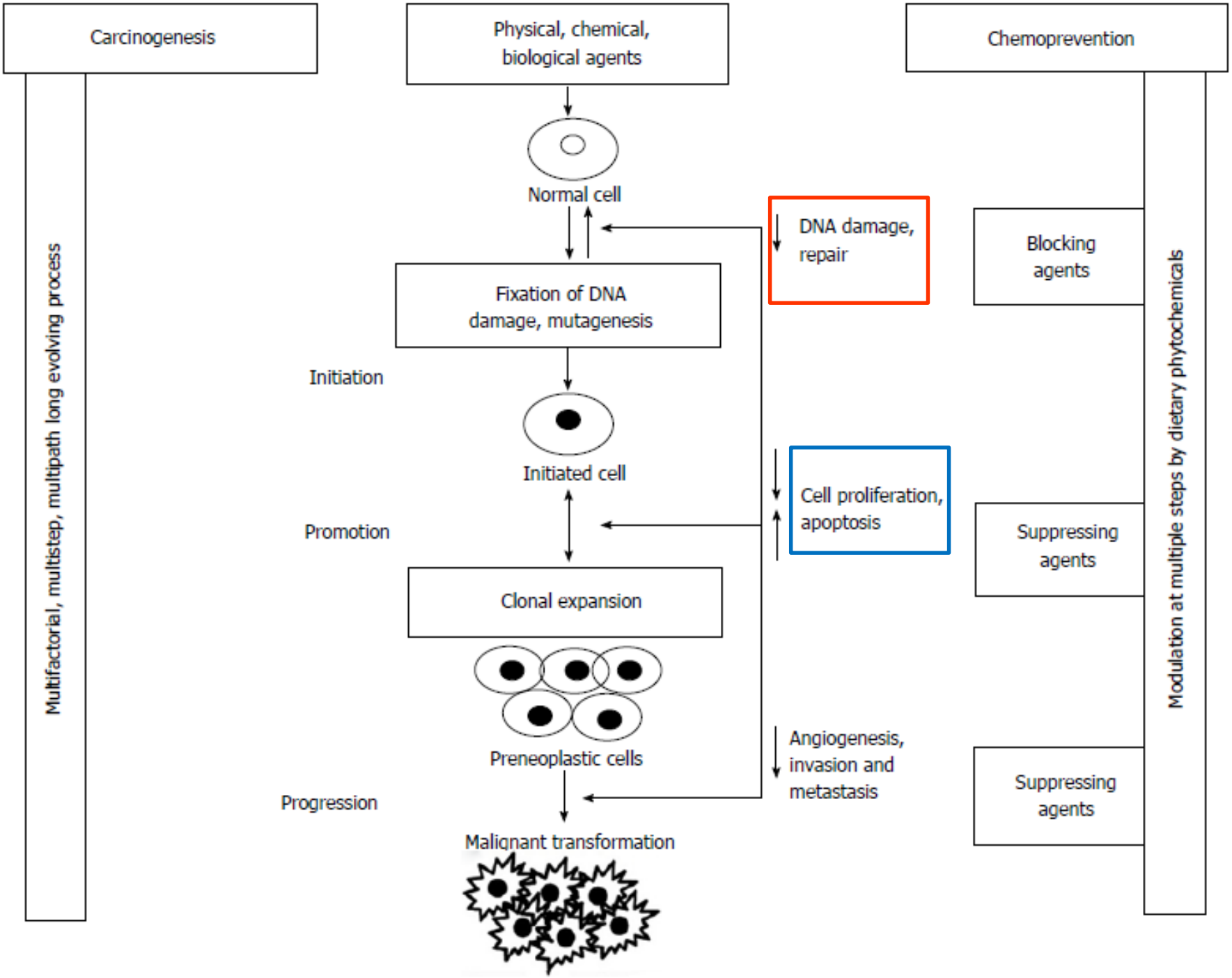
Chemoprevention (population at high risk)

Chemoprevention (primary)

Chemopreventive agents

Risk Level	
Low	Calcium, vitamin D, β-carotene, green tea polyphenols, resveratrol
Moderate	Aspirin, Ibuprofen
High	Retinoid acid

Front. Nutr., 12 April 2016 | http://dx.doi.org/10.3389/fnut.2016.00008


Carcinogenesis
Physical, chemical, biological agents
Chemoprevention
Multifactorial, multistep, multipath long evolving process
Normal cell
DNA damage, repair
Blocking agents
Fixation of DNA damage, mutagenesis
Initiation
Initiated cell
Cell proliferation, apoptosis
Promotion
Suppressing agents
Clonal expansion
Preneoplastic cells
Angiogenesis, invasion and metastasis
Progression
Suppressing agents
Malignant transformation
Modulation at multiple steps by dietary phytochemicals

A good chemopreventive

Chemoprevention, through the use of synthetic or natural compounds, represents the possibility to inhibit, stop or reverse the process of carcinogenesis.

Blockage of carcinogen formation, the induction of detoxification enzymes,

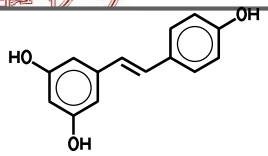
Slowing of cell division, induction of apoptosis and induction of differentiation of neoplastic cells constitute important chemopreventive actions.

A promising chemopreventive agent must show selectivity towards cancer cells and low toxicity on non-transformed cells.

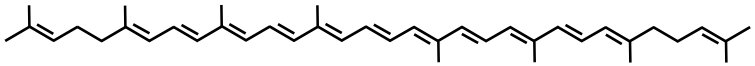
CHEMOPREVENTIVE AGENTS: EXPERIMENTAL STUDIES

Large number of pure compounds and extracts from dietary sources has been evaluated in various experimental models for testing their chemopreventive efficacy.

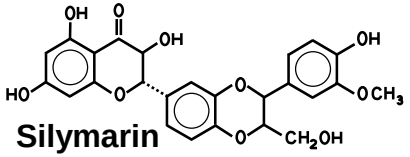
Dietary cancer chemopreventive compounds



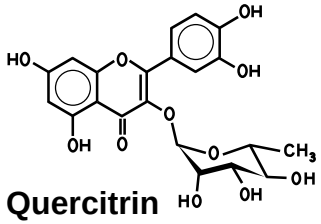
Resveratrol
Grape and red wine
Vinca vinifera



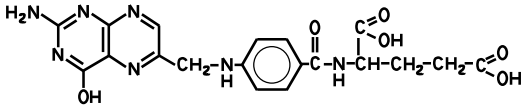
Lycopene
Tomato
Lycopersicon esculente, Solanaceae



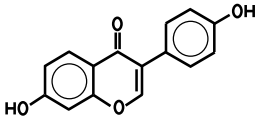
Silymarin
Milk thistle,
Silybum marianum, Compositae



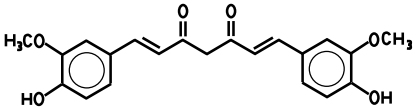
Quercitrin
Blueberry
Vaccinium myrtillus,
Ericaceae



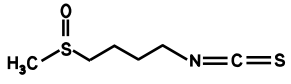
Folate



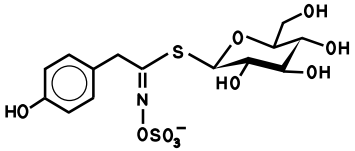
Daidzein
Soya beans
Glycine max, Leguminosae



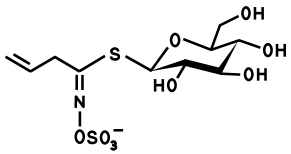
Curcumin
Turmeric
Curcuma domestica, Zingiberaceae



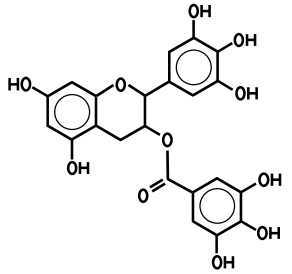
Sulforaphane
Broccoli, Brasica oleracea
Cruciferae



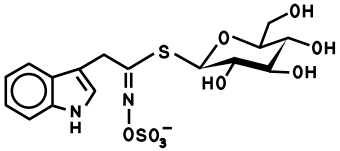
Sinalbin
White mustard
Sinapis alba, Cruciferae



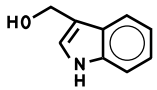
Sinigrin
Black mustard
Brassica nigra, Cruciferae



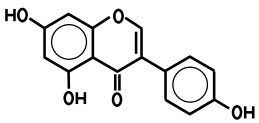
(-)Epigallocatechin-3-O-gallate
EGCG
Green tea
Camellia sinensis, Theaceae



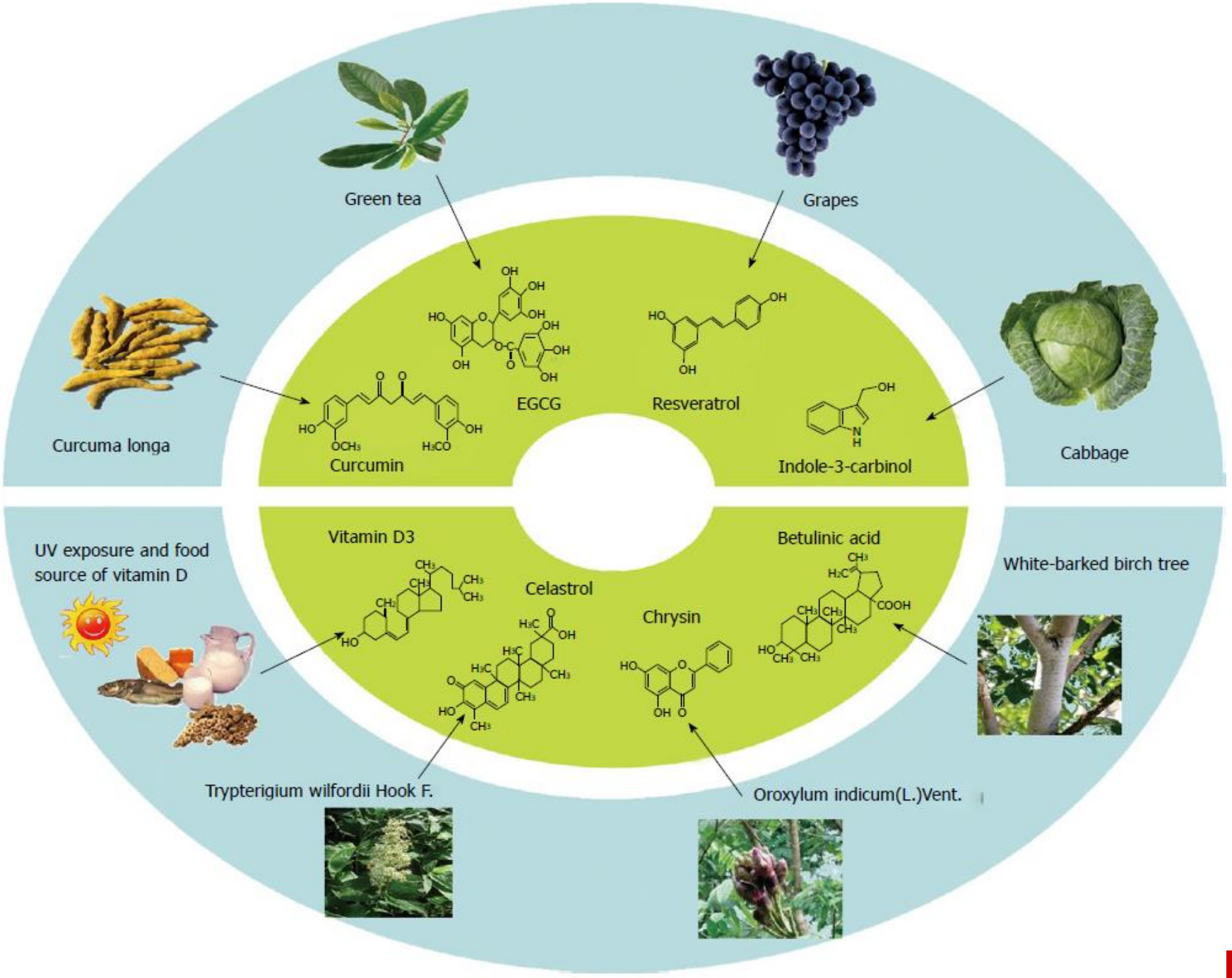
Glucobrassicin
Horseradish
Armoracia rusticana, Cruciferae



Indole-3-carbinol
Cruciferous vegetables
Cruciferae



Genistein
Soya beans
Glycine max, Leguminosae


Green tea
Grapes
Curcuma longa
EGCG
Resveratrol
Curcumin
Indole-3-carbinol
Cabbage
UV exposure and food source of vitamin D
Vitamin D3
Celastrol
Chrysin
Betulinic acid
White-barked birch tree
Trypterigium wilfordii Hook F.
Oroxylum indicum(L.)Vent.

CHEMOPREVENTIVE AGENTS: EXPERIMENTAL STUDIES

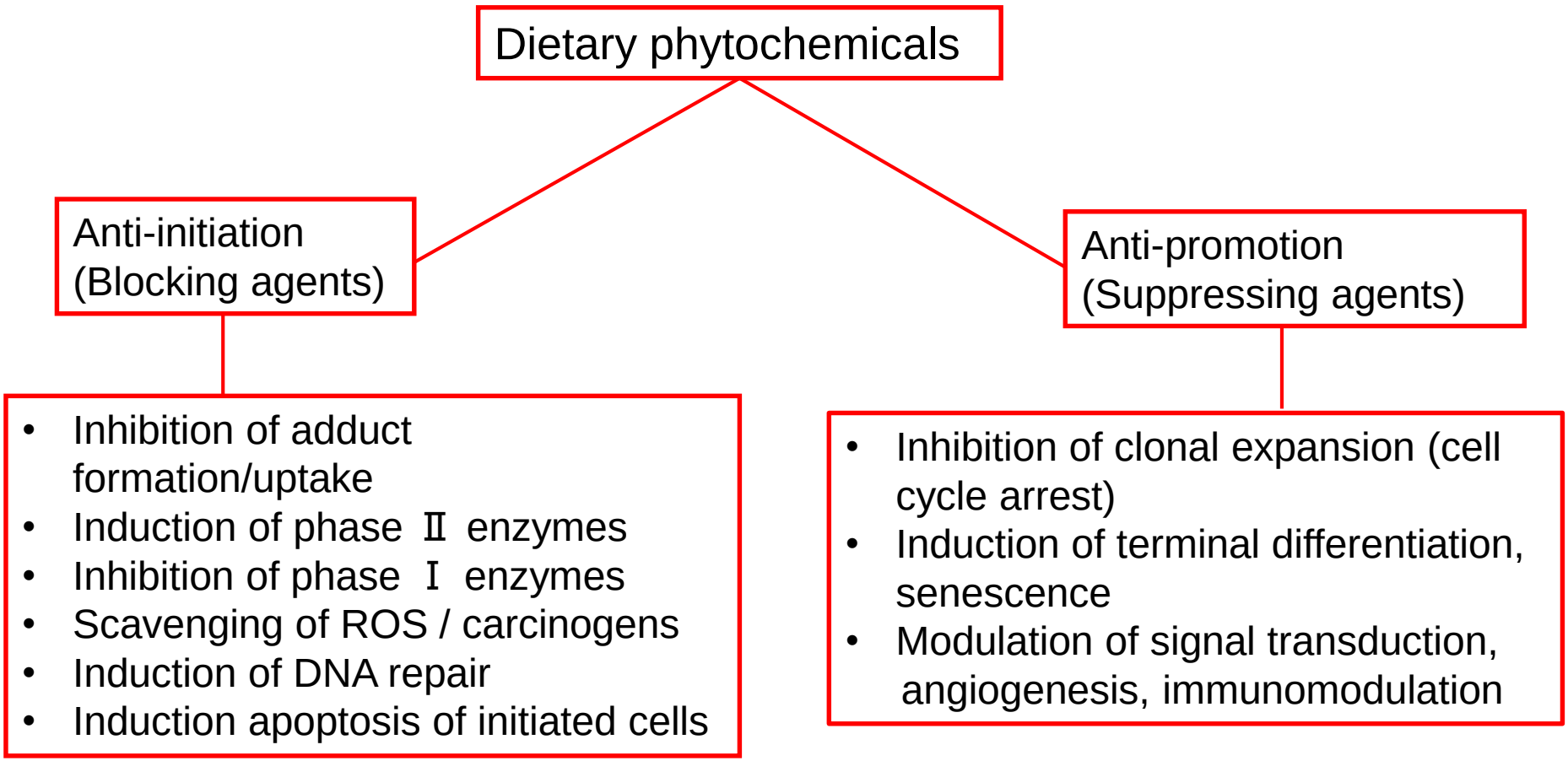
Chemopreventive activity is generally investigated employing:

- cancer cell lines to investigate apoptosis, cell proliferation detoxification pathways and specific biochemical pathways.

- animal models with induced tumor to evaluate latency period and/or decrease in incidence.

Many dietary phytochemicals have been demonstrated to be effective reducing incidence and/or affecting latency period of carcinogen induced tumors at various organ sites in experimental rodent models.

Mechanisms of chemopreventive actions



Overall findings of experimental studies

1. Relatively long and repeated exposures to dietary phytochemicals have generally been needed for observing protective effects;

2. Most of the dietary phytochemicals have been demonstrated to be effective against several classes of environmental carcinogens at multiple organ sites;

3. Bioavailability of dietary phytochemicals and their metabolites have not been reported from most of the experimental studies that demonstrated their chemopreventive efficacy;

4. In most of these studies doses of chemopreventive agent(s) administered or effective doses appear to be much higher than normal dietary exposures in human.

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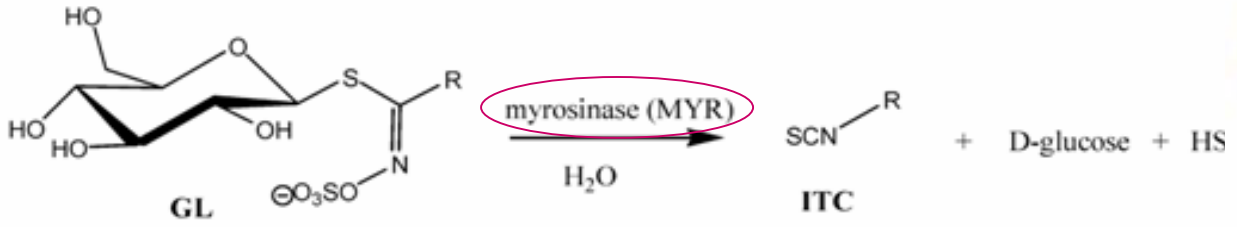
Some examples

Isothiocyanates

Anthocyanins

Castanea sativa bark extract

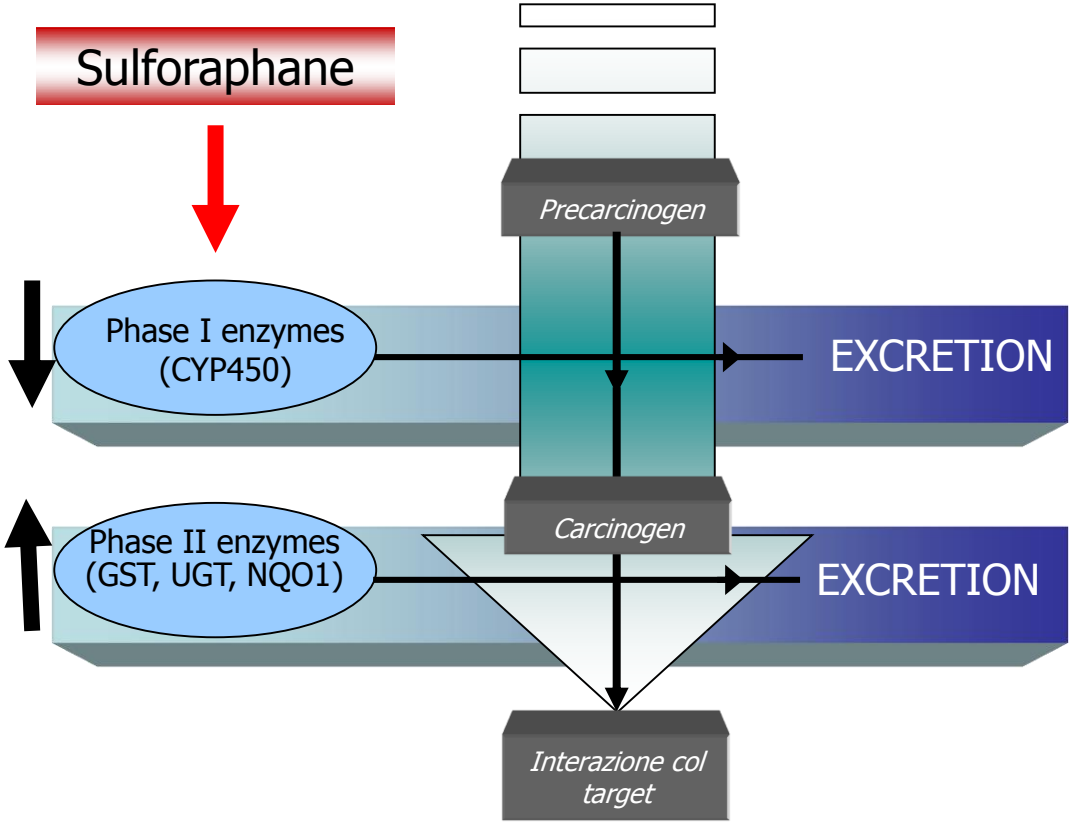
Isothiocyanates

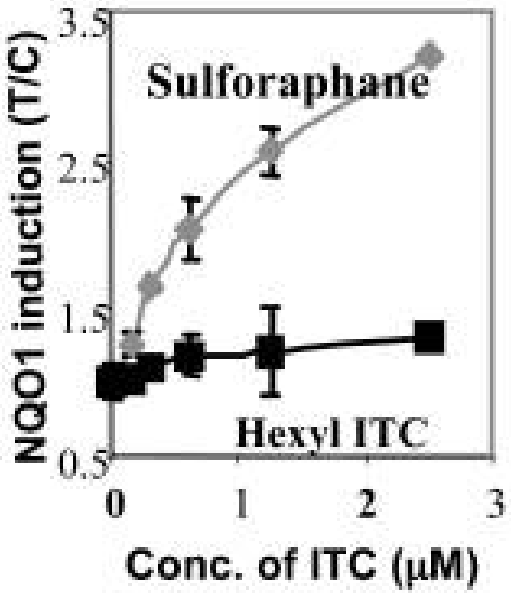


Side chain (R)	*Chemical name*	***GL**s trivial name* **Glucosinolate**	***ITC**s trivial name* **Isothiocyanate**
$CH_3S(O)CH_2CH_2CH_2CH_2$-	4-methylsulfinylbutyl-	Glucoraphanin (GRA)	Sulforaphane (SFN)
$CH_3SCH_2CH_2CH_2CH_2$-	4-methylthiobutyl-	Glucoerucin (GER)	Erucin (ERN)
$CH_3S(O)CH{=}CHCH_2CH_2$-	4-methylsulfinyl-3-butenyl-	Glucoraphenin (GRE)	Sulforaphene (GRE-ITC)
$CH_3SCH{=}CHCH_2CH_2$-	4-methylthio-3-butenyl-	Glucoraphasatin (GRH)	Raphasatin (GRH-ITC)

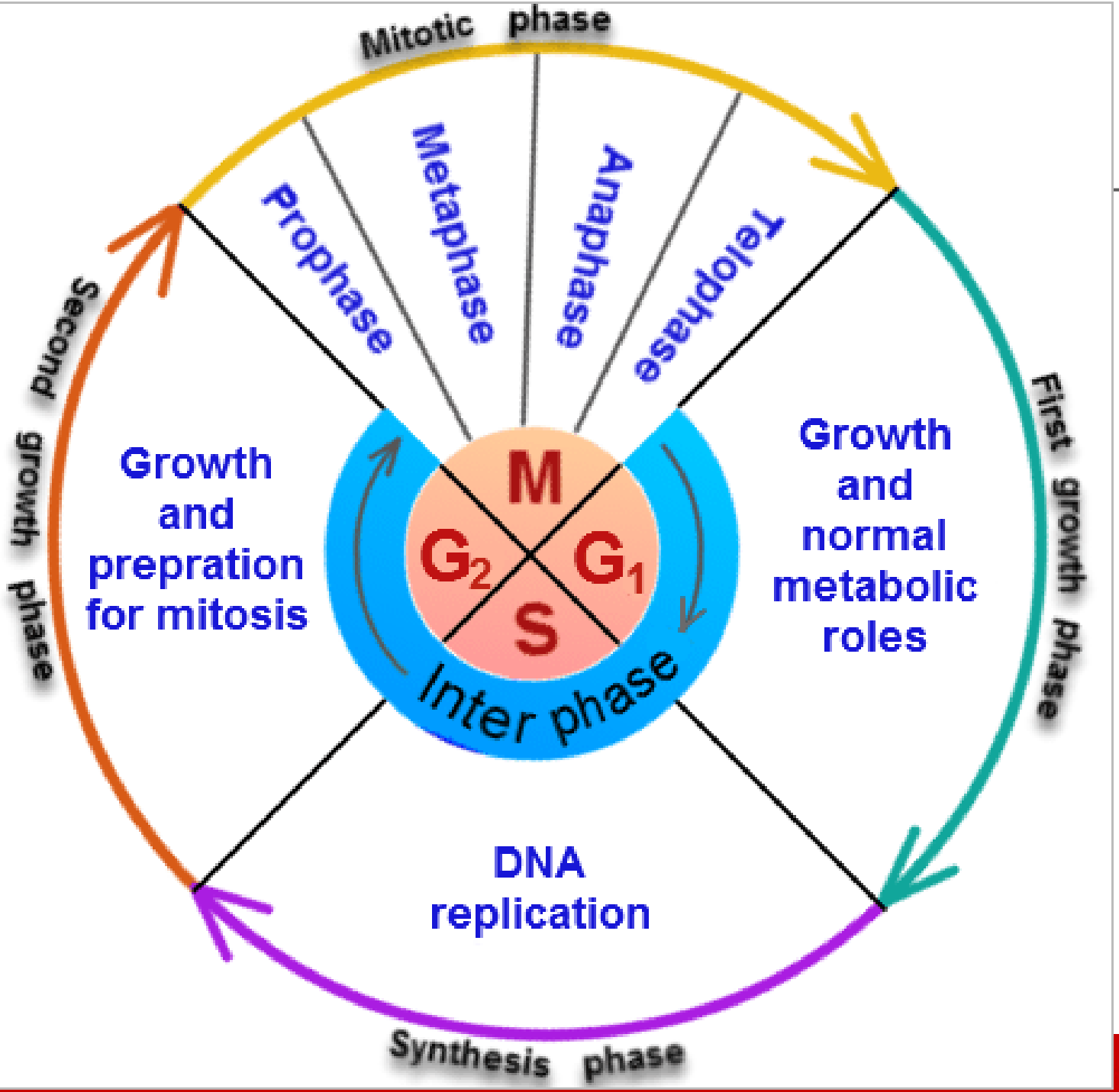
Da: J Agric Food Chem 56: 875-883, 2008. DOI: 10.1021/jf073123c

Sulforaphane modulates carcinogens activation

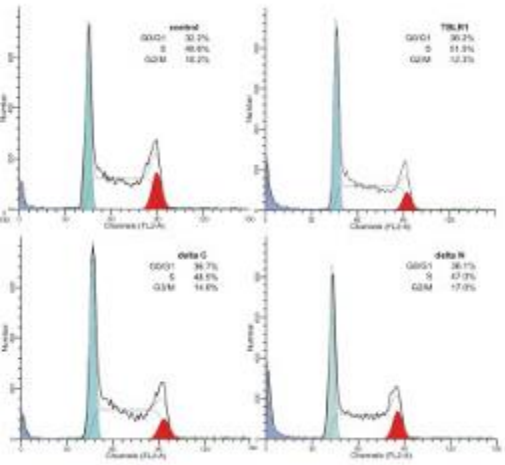


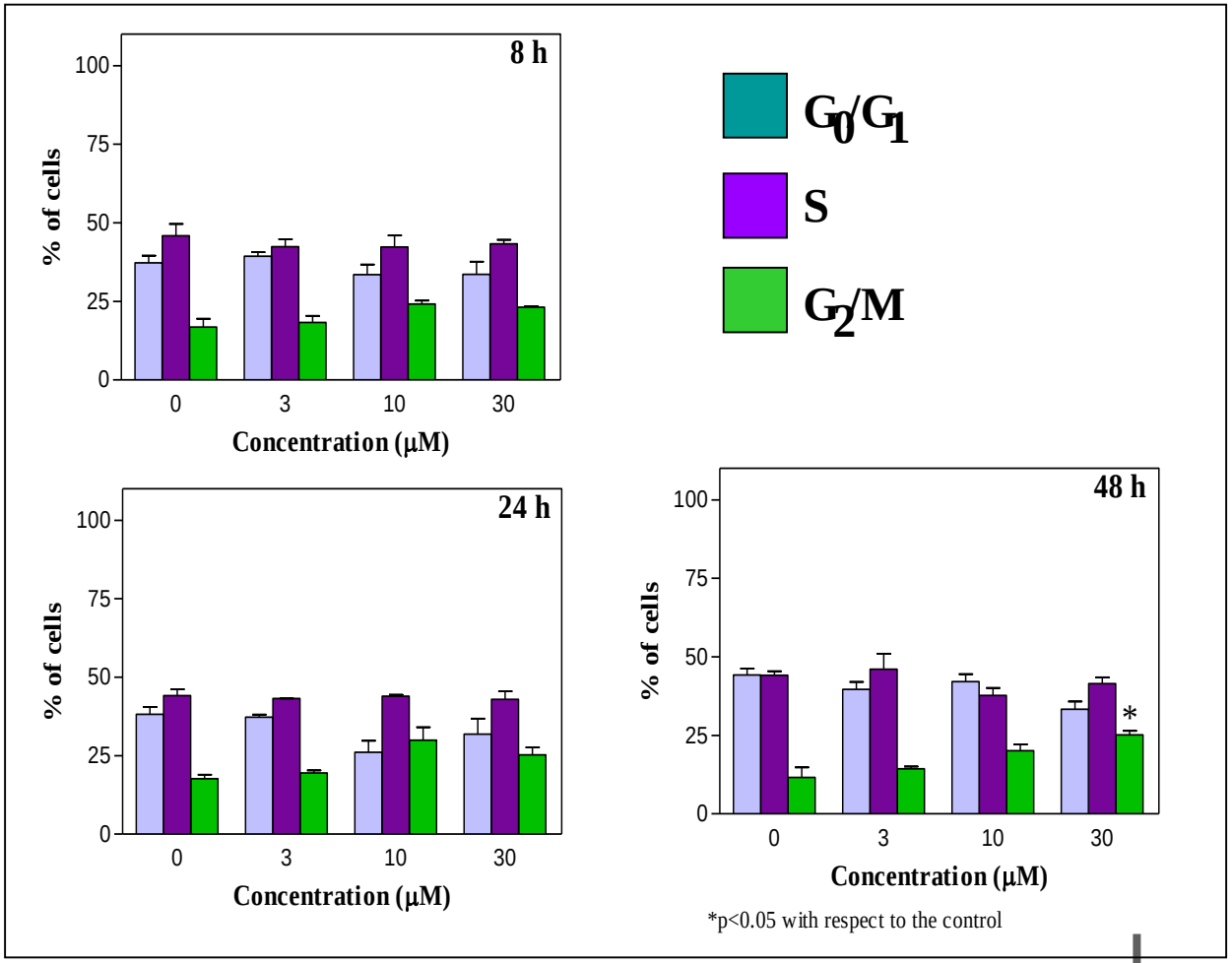


Proc Natl Acad Sci USA 89: 2399-403, 1992; Cancer Res 58: 4632-39, 1998; Carcinogenesis 22: 1987-92, 2002


Mitotic phase
Prophase
Metaphase
Anaphase
Telophase
First growth phase
Growth and normal metabolic roles
Synthesis phase
DNA replication
Second growth phase
Growth and prepration for mitosis
M
G2
G1
S
Inter phase

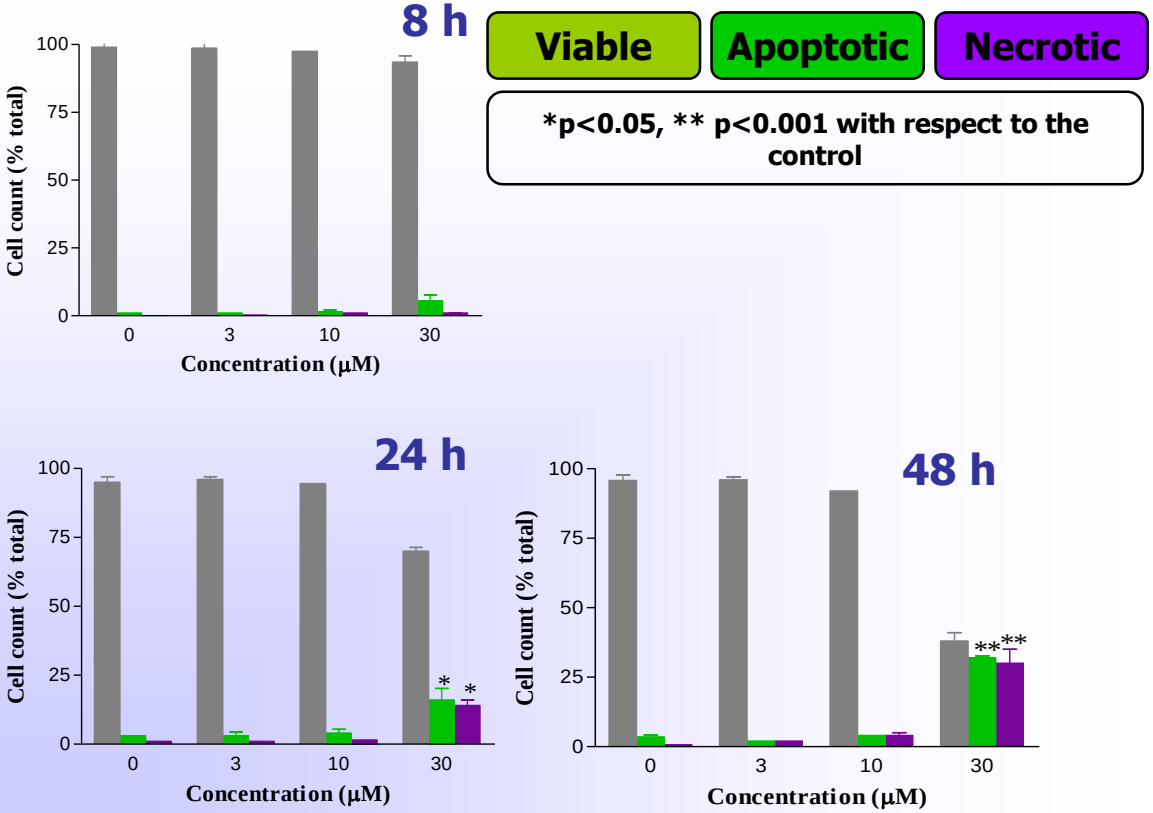
SF induces cell cycle arrest in Jurkat cells

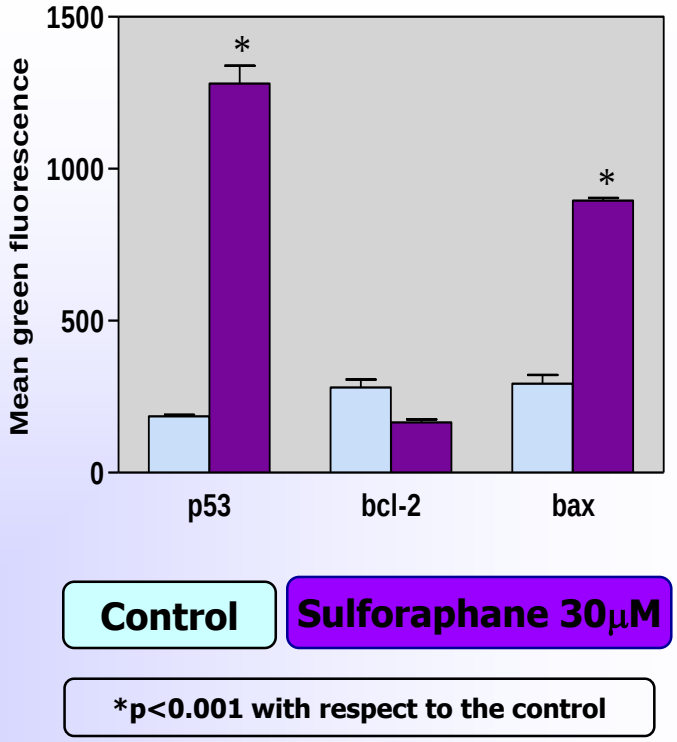




Carcinogenesis 23: 581-6, 2002; Biochem Pharmacol 68: 1133-8, 2004;
Mutat Res. Reviews 635: 90-104, 2007

SF induces apoptosis in Jurkat cells





Carcinogenesis 23: 581-6, 2002; Biochem Pharmacol 68: 1133-8, 2004

Molecular Targets of Sulforaphane

Apoptosis
Caspases ↑
Bcl-2 ↓
Bax ↑
Bax:Bcl-2 ↑
p53 ↑
PARP ↑
IAP ↓
Smac/Diablo ↑
Calpain ↑
$p21^{Cip1/Waf1}$ ↑
Acetylated histones ↑

Phase I enzymes
CYP1A1 ↓
CYP2B1/2 ↓
CYP3A4 ↓
CYP2E1 ↓

Phase II enzymes
GST1A1 ↑
GSTA1/2 ↑
GSTM1 ↑
UGT1A1 ↑
NQO1 ↑
γ-glutamylcysteine synthetase ↑

SULFORAPHANE

Angiogenesis
KDR ↓
HIF-1 ↓
VEGF ↓
c-Myc ↓

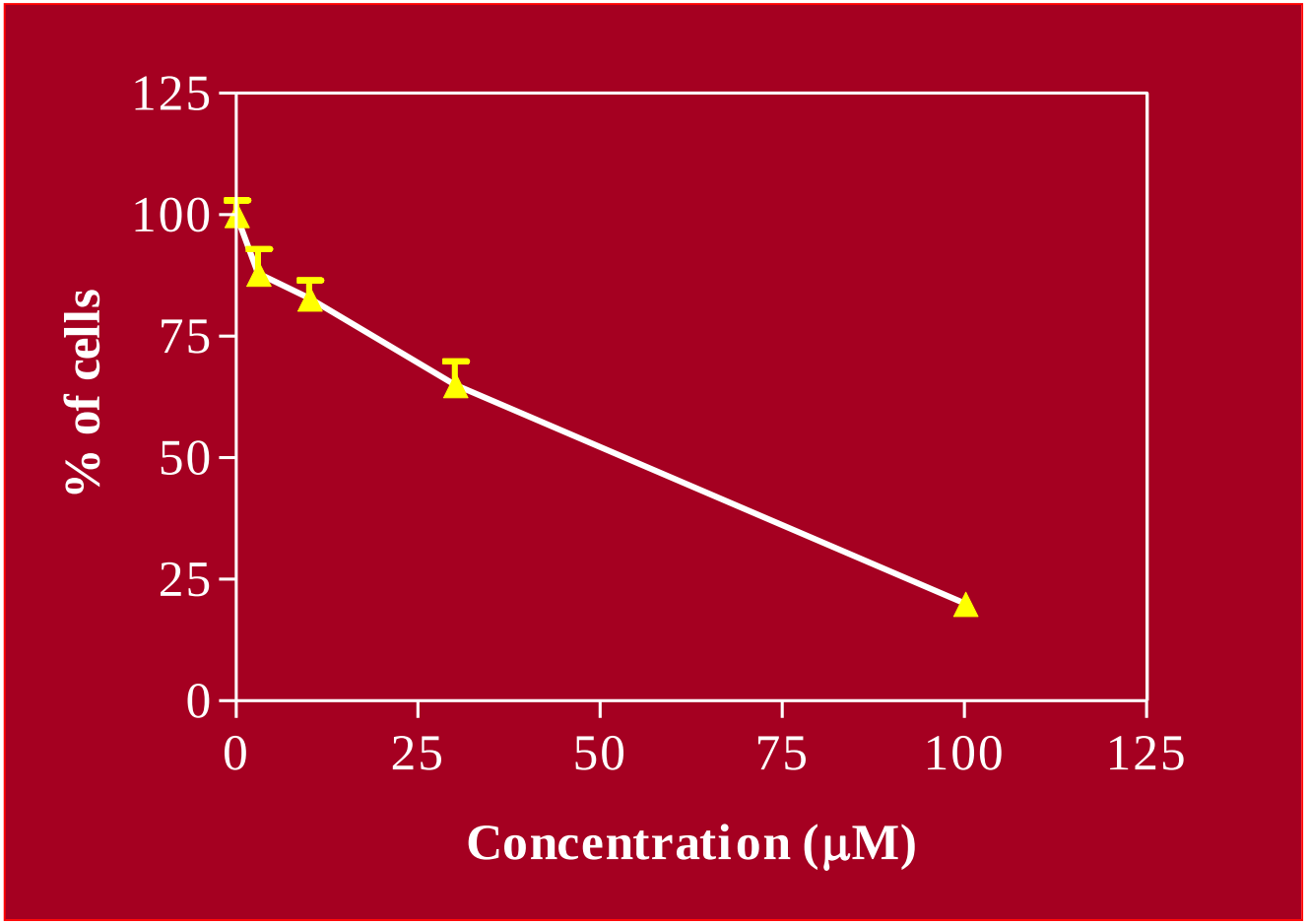
Metastasis
MMP-2 ↓
Tissue inhibitor of metalloproteinase-2 ↓

Cell cycle
Cyclin A ↑
Cyclin B1 ↑
Cyclin D1 ↓
Cdk4 ↓
$p21^{Cip1/Waf1}$ ↑
Cdc25C ↓
Kruppel-like factor 4 ↑
GADD45b ↑
$PC3^{TIS21/BTG2}$ ↑
SMAR1 ↑
CKSHS2↑
MCM4 ↓
MCM7 ↓

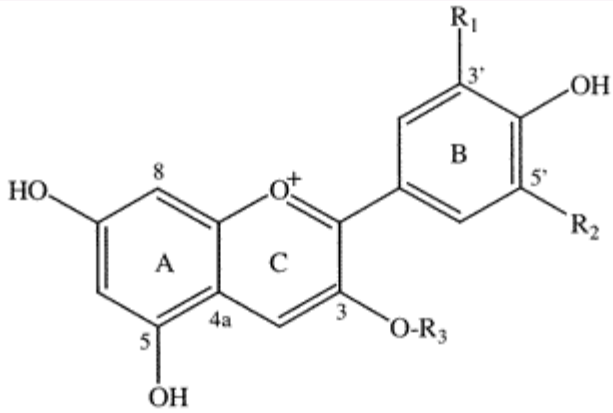
Cancer Treat Res. 2014;159:207-23. **Sulforaphane as a promising molecule for fighting cancer.**

SF is selective towards cancer cells

IC_{50}=50 μM
Normal cells
vs
IC_{50}=15 μM
Jurkat cells



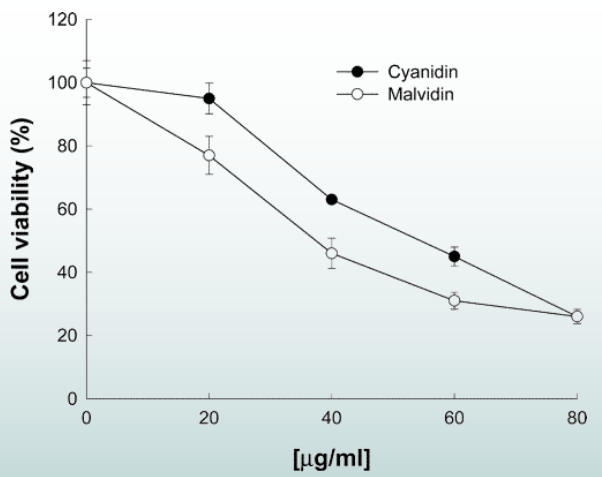
Anthocyanins in chemoprevention

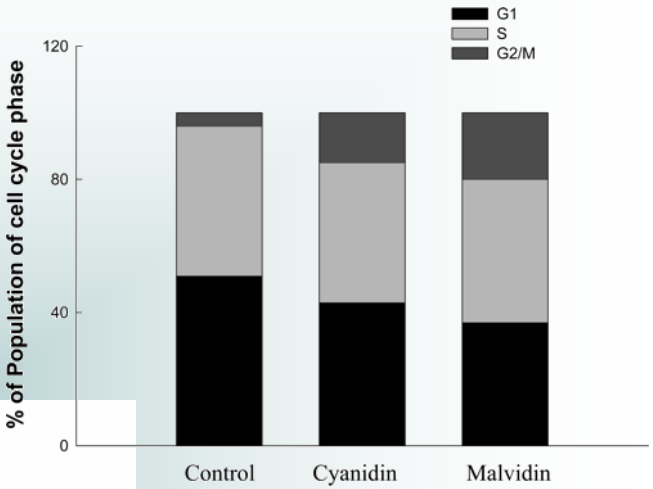


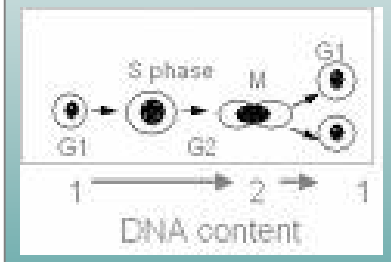
Anthocyanidins & Anthocyanins	R_1	R_2	R_3
Pelargonidin	H	H	H
Cyanidin	OH	H	H
Delphinidin	OH	OH	H
Peonidin	OMe	OH	H
Malvidin	OMe	OMe	H
Pelargonidin-3-galactoside	H	H	galactose
Cyanidin-3-galactoside	OH	H	galactose
Cyanidin-3-rutinoside	OH	OH	rutinose
Cyanidin-3-glucosylrutinoside	OH	OH	glucose-rutinose
Delphinidin-3-galactoside	OH	OH	galactose

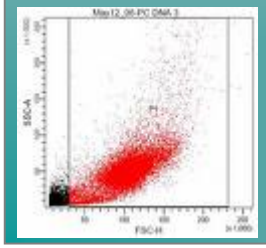
Malvidin and cyanidin hinibit cancer cells proliferation

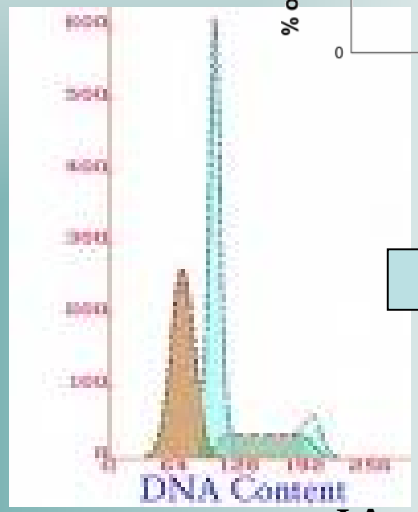
leukemia cell line (U937)



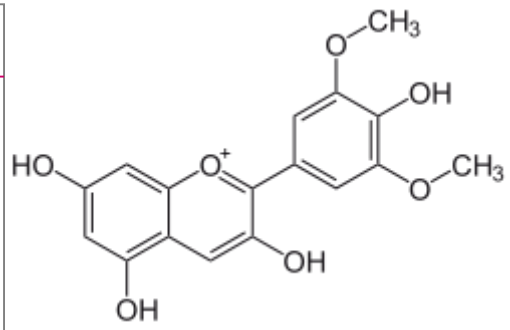




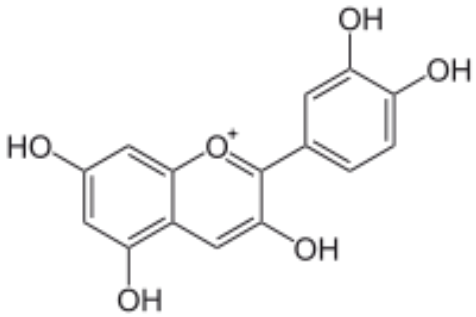




J Agric Food Chem 52: 2213-17, 2004

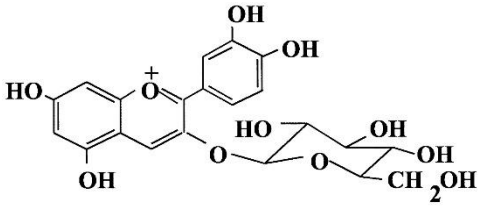


Malvidin

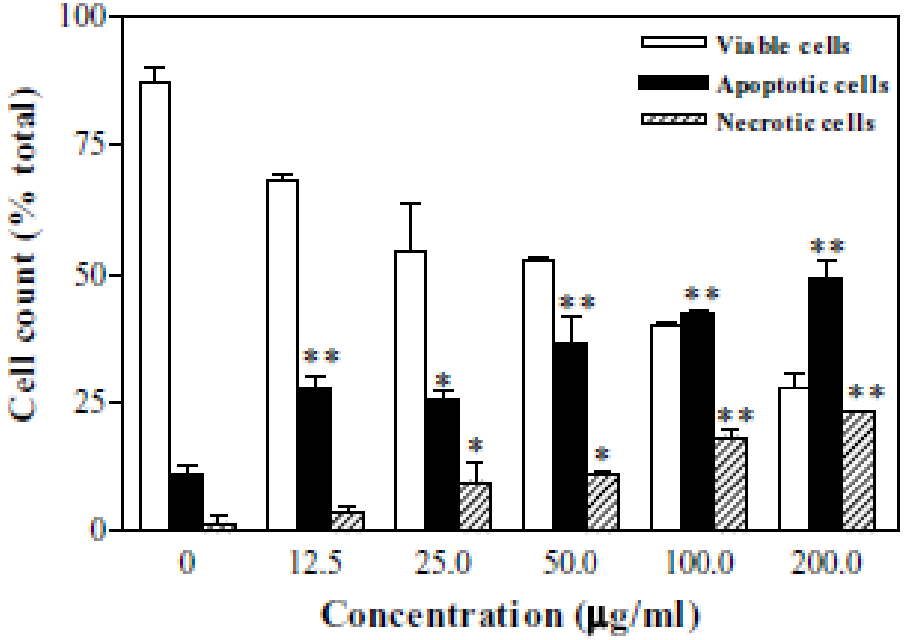


Cyanidin

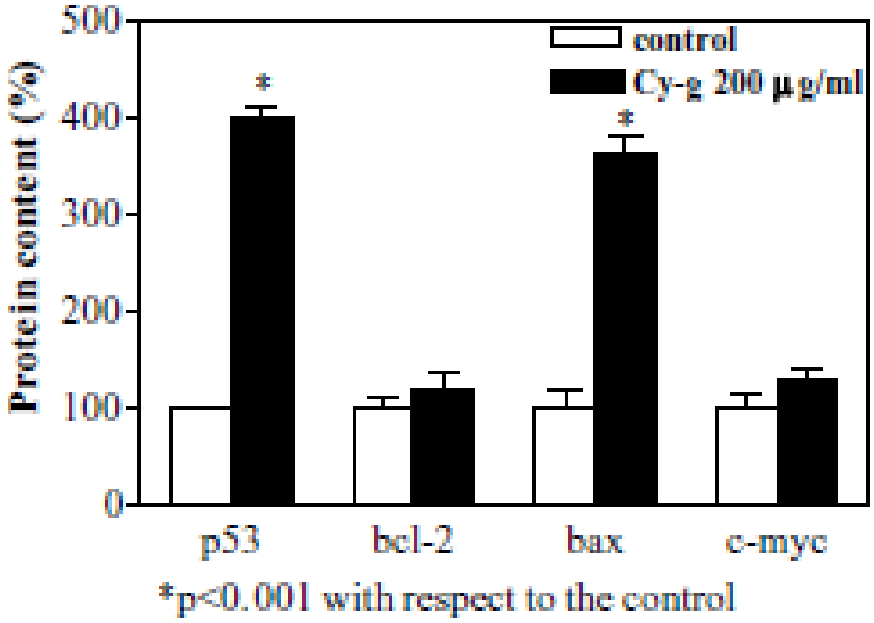
Cyanidin 3-O-β-glucopyranoside induces apoptosis in Jurkat cells



Cyanidin 3-*O*-β-D-glucoside



*P<0.05, **P<0.01 with respect to controls (Dunnet test)



*p<0.001 with respect to the control

Biochem Pharmacol 67: 2047-56, 2004

Overall findings of clinical trials

Overall findings of clinical trials

1. In most of the trials chemopreventive agents were administered to patients with cancer or high risk individuals, *i.e*., after occurrence of damage or disease;
2. Though there are several clinical trials conducted using dietary phytochemicals, results from only approximately 20% trials have been reported. Other trials have either not been completed or their results are not reported due to issues of toxicity, bioavailability and other unknown reasons under the conditions employed for the trials;
3. Bioavailability issues have been reported for curcumin, genistein, resveratrol, lycopene and green tea;
4. Toxicity issues have been reported in clinical trials conducted with tocopherols and retinoids;
5. Very few trials with curcumin and green tea have shown beneficial effects as judged by modulation of biomarkers and symptoms.

World J Biol Chem 2016 February 26; 7(1): 88-99

Clinical trials *vs.* experimental studies


EAT MORE FRUITS
EXERCISE
DRINK MORE WATER
READ SPIRATIONAL BOOKS
HEALTHY LIFESTYLE
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