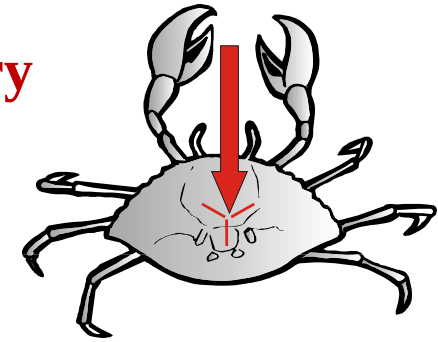
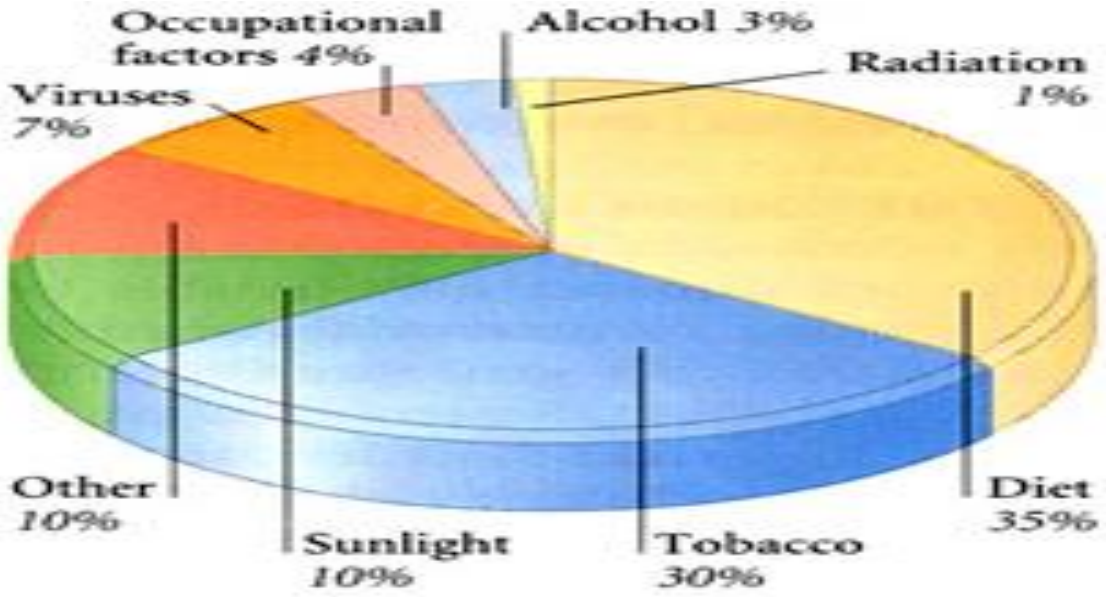
CANCER CHEMOPREVENTIVE POTENTIAL OF PHYTOCHEMICALS DERIVED FROM MEDICINAL PLANTS

Dr. P. K. Goyal
Professor & Head
President - Indian Society for Radiation Biology
President - Indo Global Health Care Research Foundation



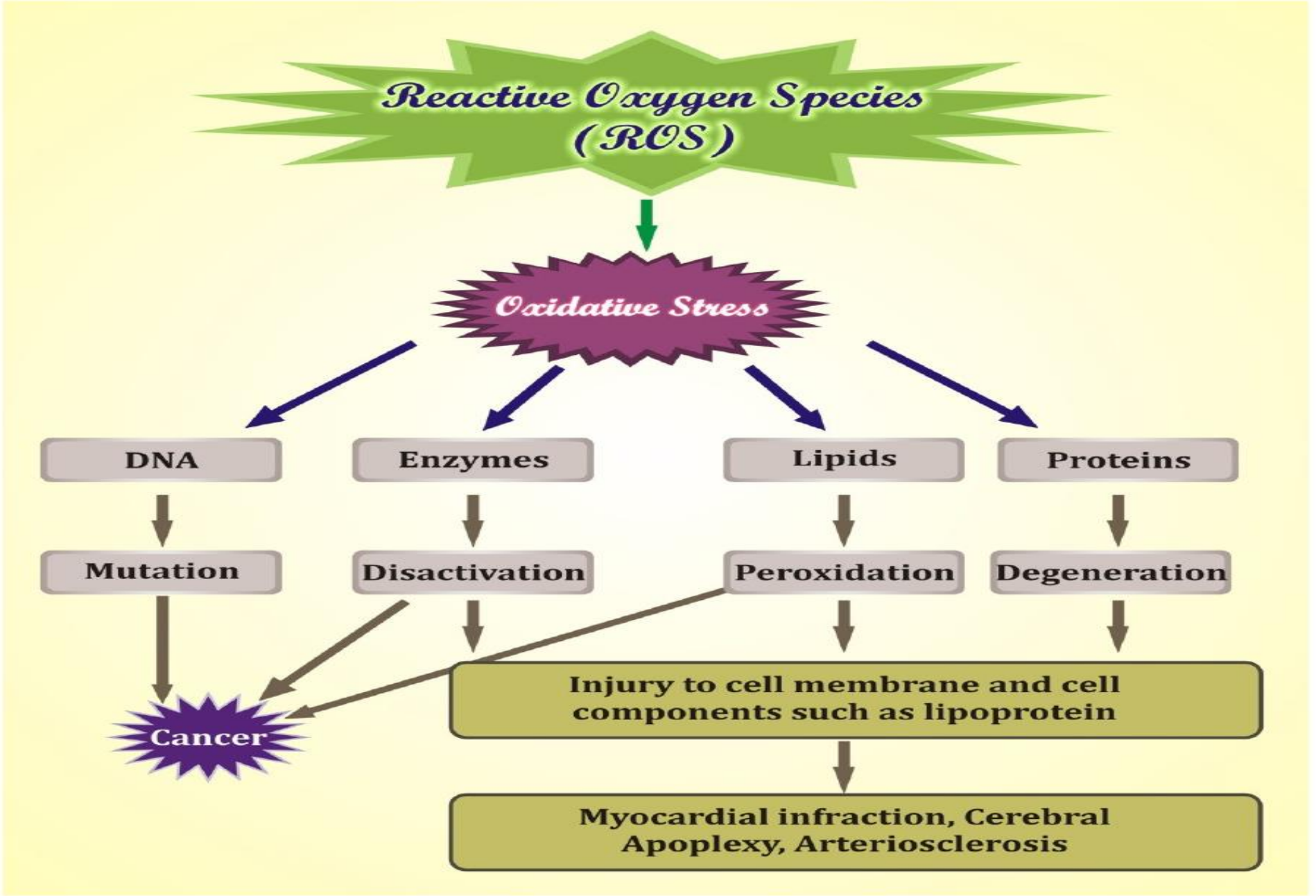
Radiation & Cancer Biology Laboratory
Department of Zoology
University of Rajasthan
Jaipur (India)







Key Causes of Cancer

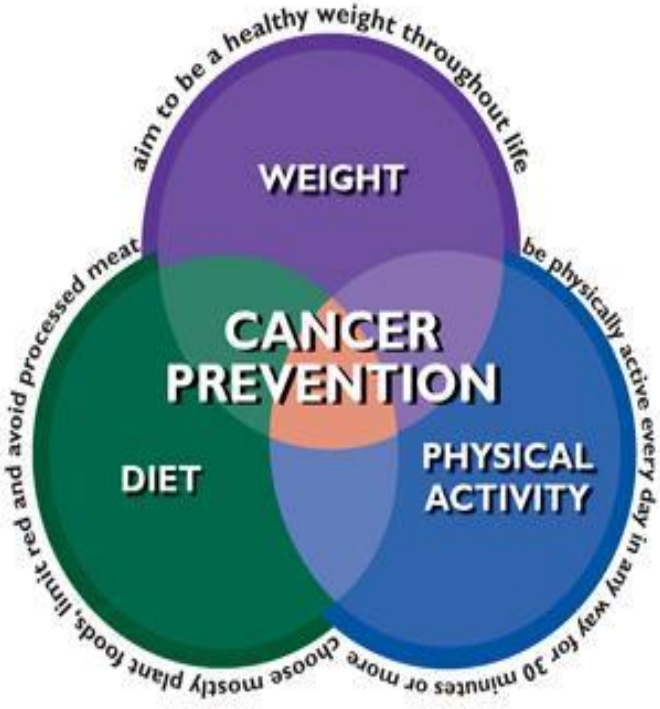


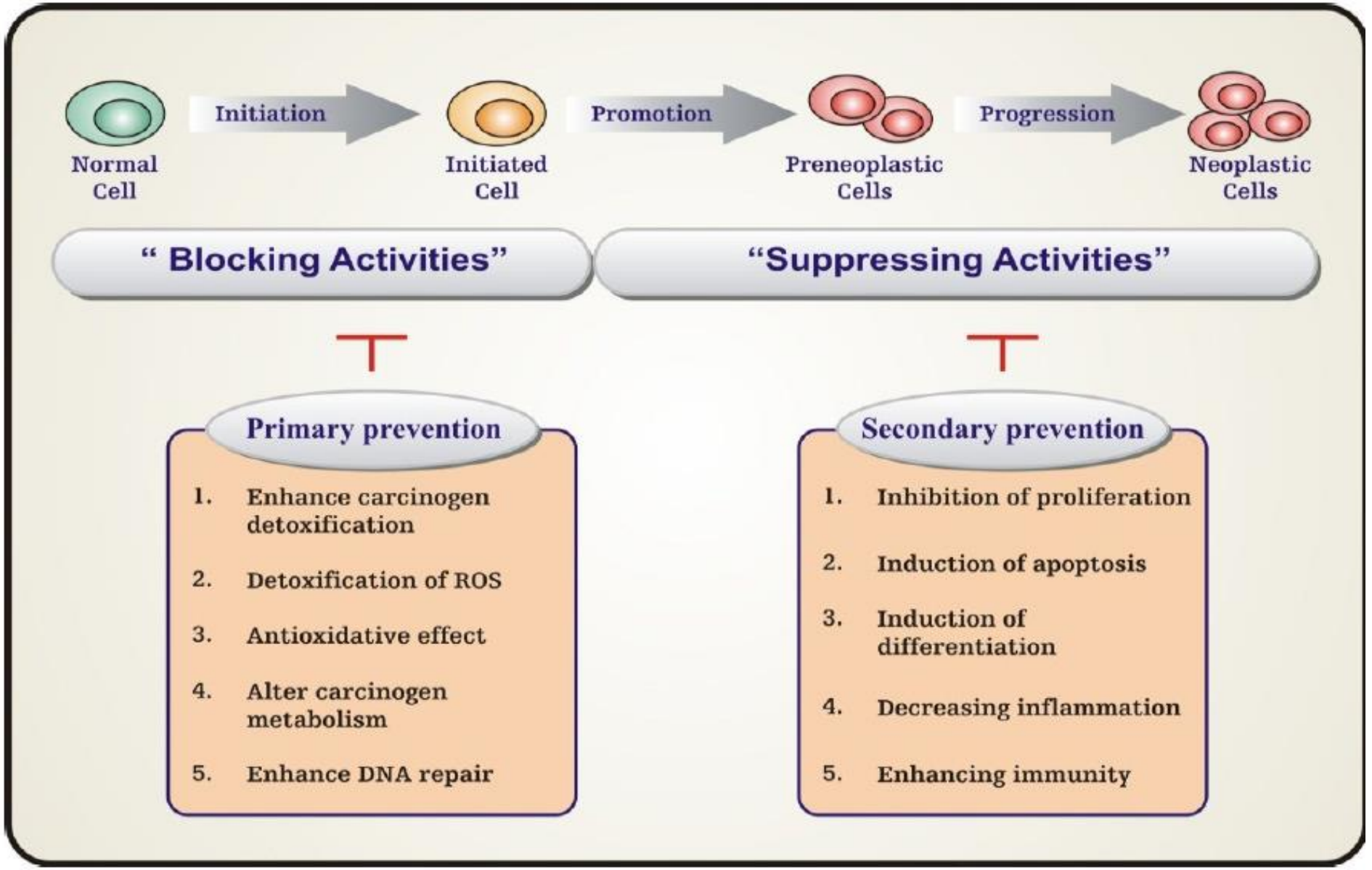
Reactive oxygen species induced oxidative stress and pathogenesis

Chemoprevention of Cancer

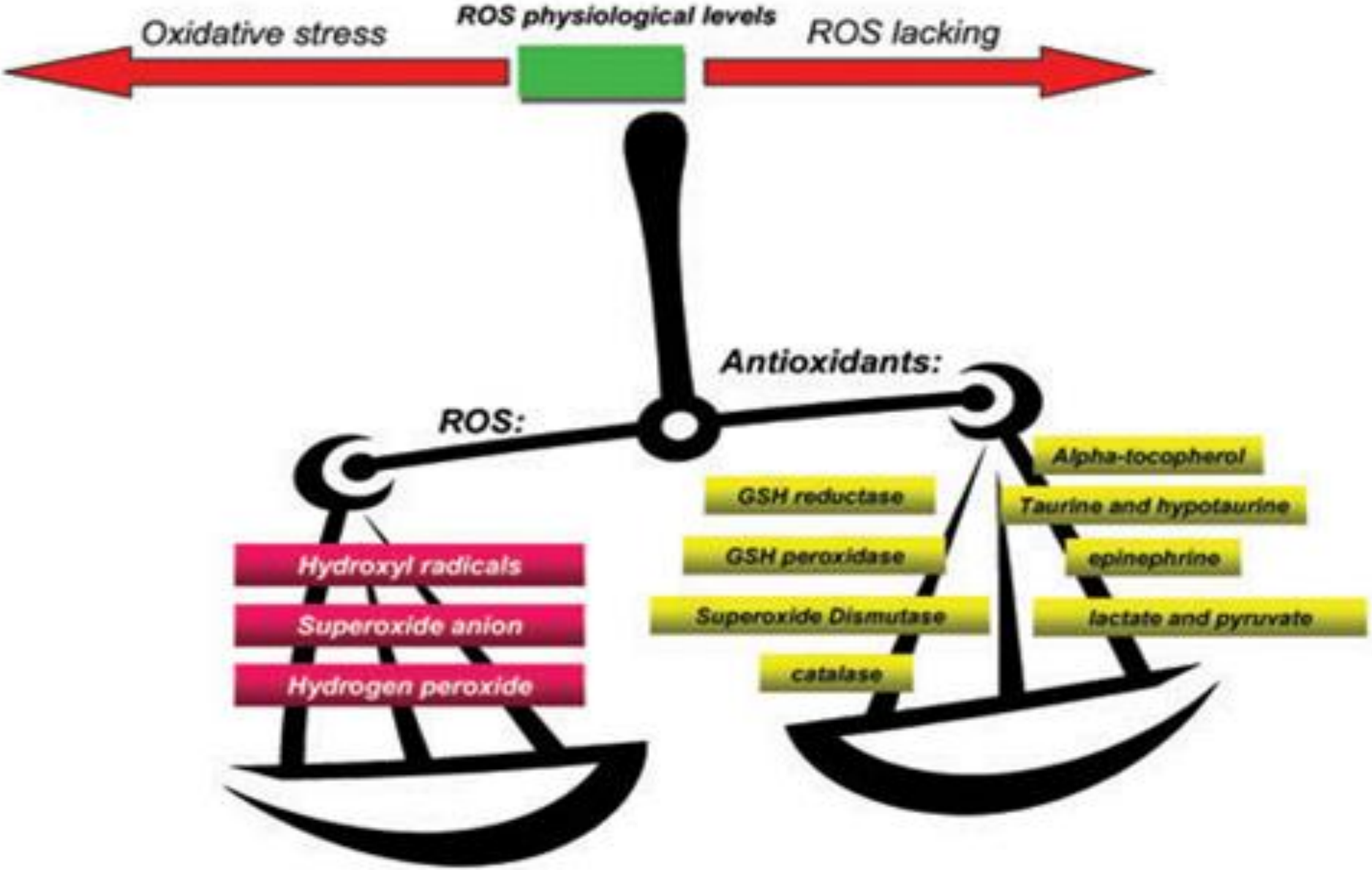
- About 40 % of cancers may be avoidable or preventable
- Risk of cancer may be reduced by-
  - ↑ consumption of nutraceuticals, fruits & vegetables (rich in anti-oxidants)
  - ↓ high-fat content
  - ↓ intake of tobacco & alcohol
  - Regular exercise



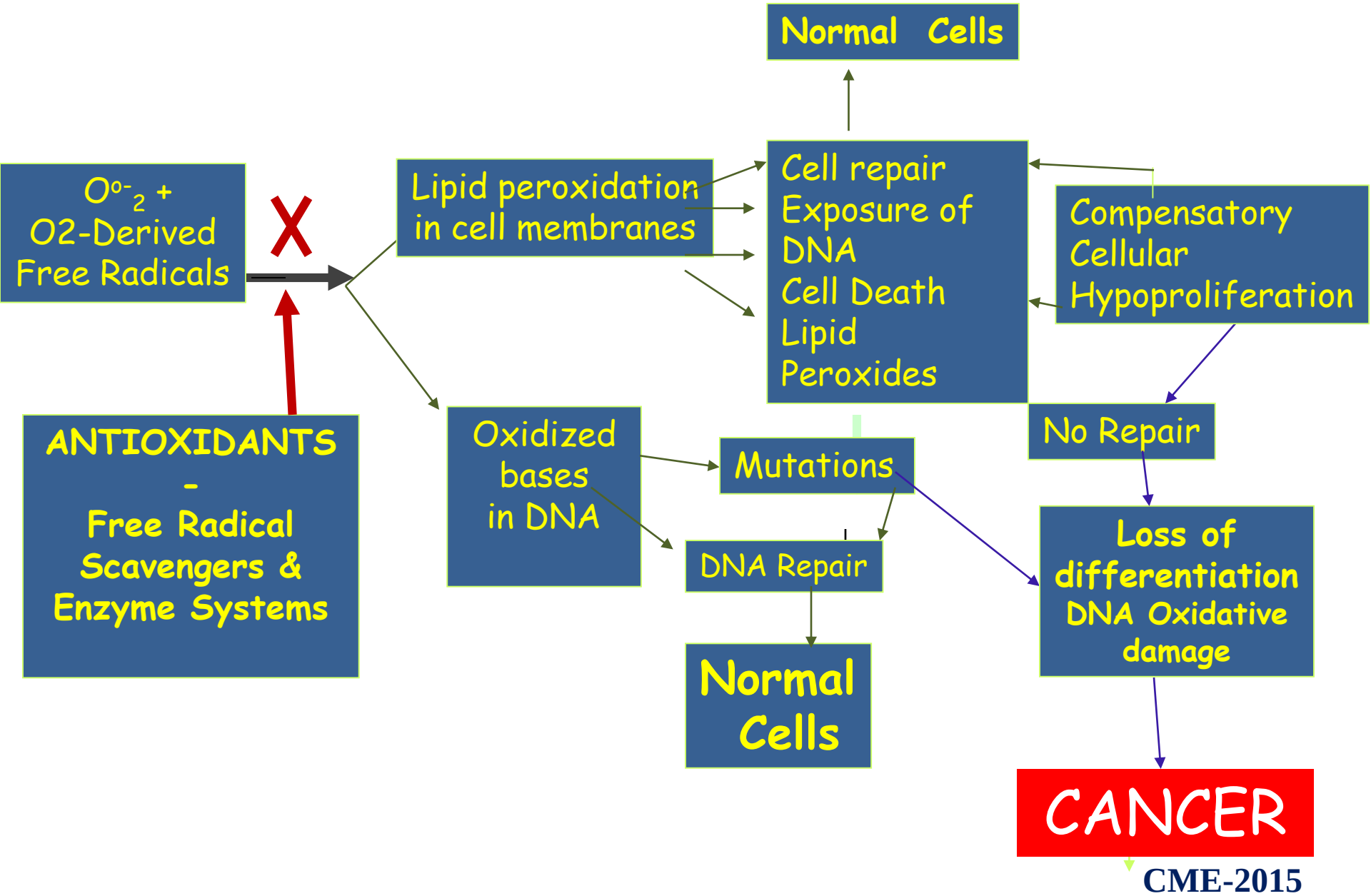




Stages of carcinogenesis and their intervention using chemo-preventive agents


Oxidative stress
ROS physiological levels
ROS lacking
Antioxidants:
ROS:
Hydroxyl radicals
Superoxide anion
Hydrogen peroxide
Alpha-tocopherol
GSH reductase
Taurine and hypotaurine
GSH peroxidase
epinephrine
Superoxide Dismutase
lactate and pyruvate
catalase

Anticancer Activity of Antioxidants



Why herbal medicine ?

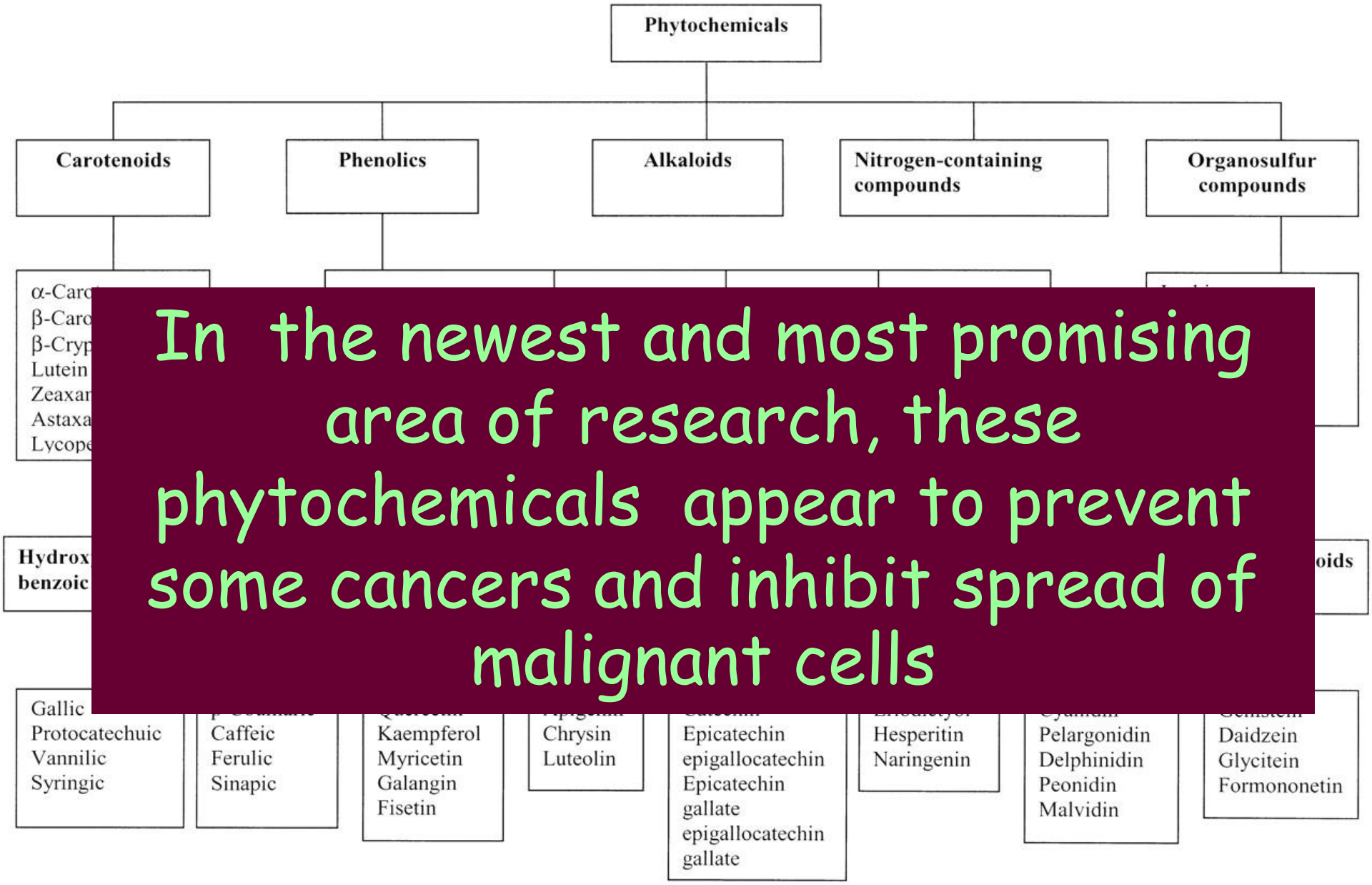


- ***Prevalence of Herbal Medicine in over 75% of the world population, it is preferred over chemicals because***

  - ***Better cultural acceptability***
  - ***better efficacy***
  - ***better compatibility with the human body***
  - ***lesser side effects***

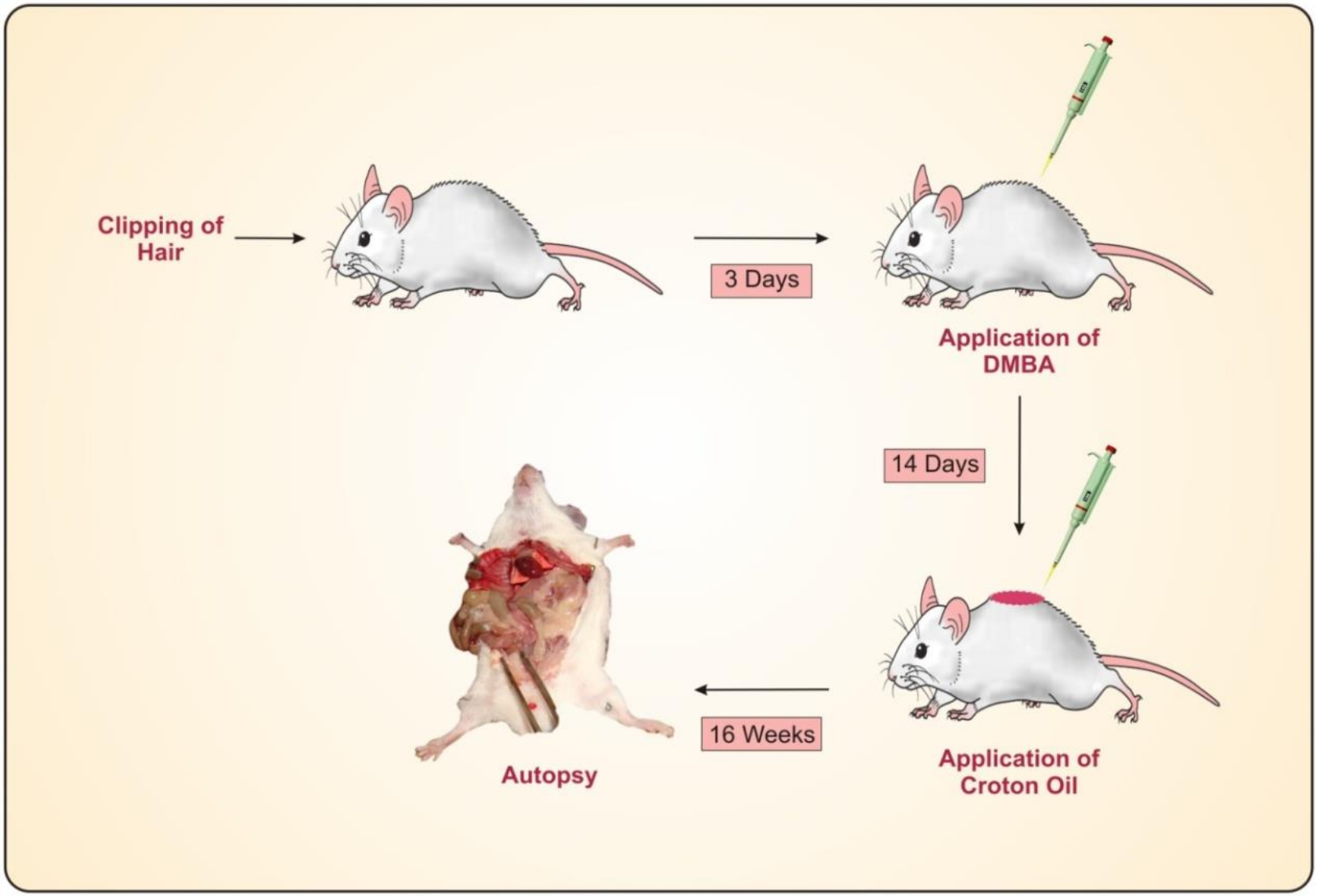
- ***A systemic approach is needed for identifying active constituents from different medicinal plants, using modern techniques.***

Phytochemicals in Dietary Vegetables & Fruits

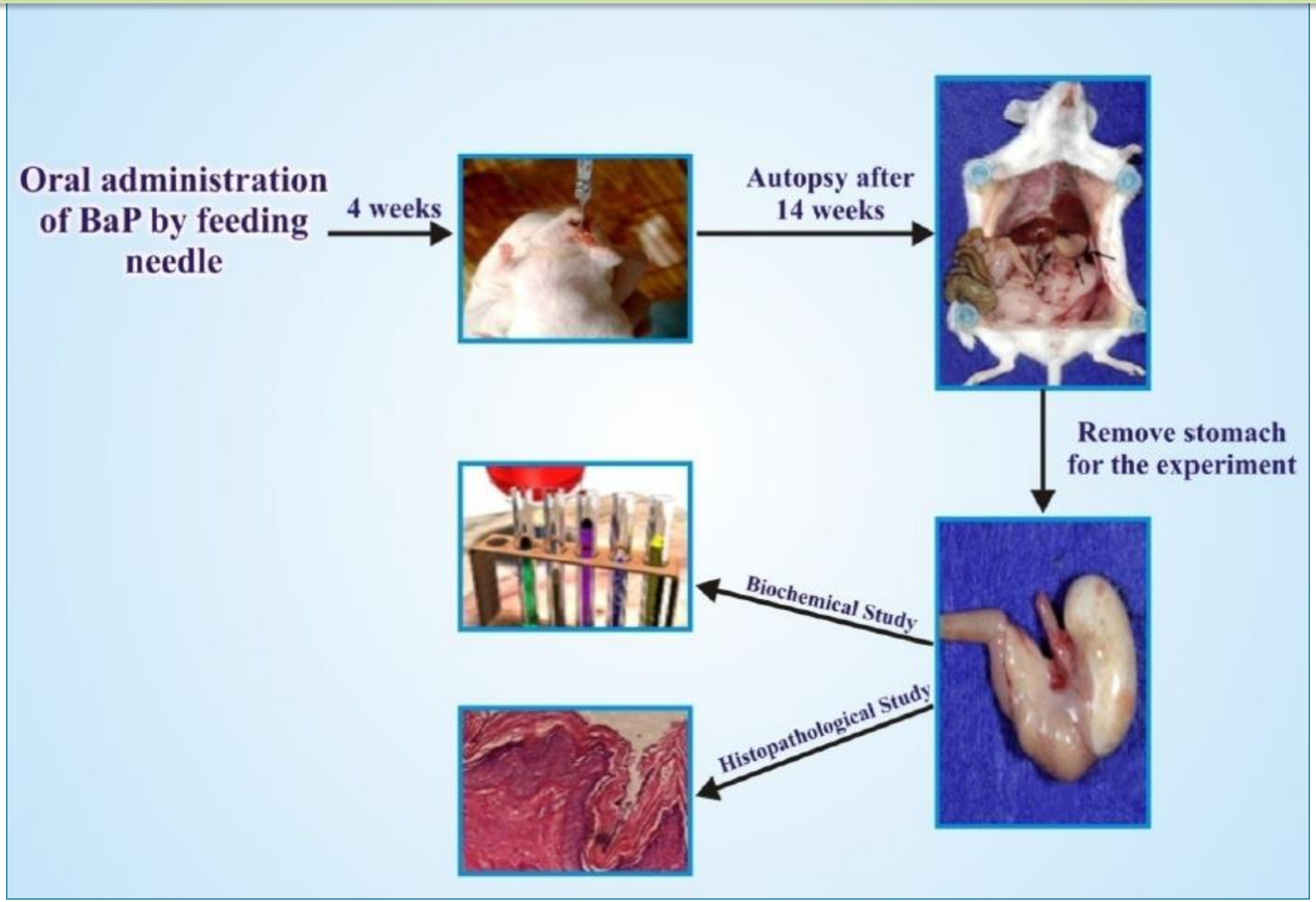


In the newest and most promising area of research, these phytochemicals appear to prevent some cancers and inhibit spread of malignant cells

General protocol for the induction of skin tumor



General protocol for the induction of stomach tumor



General protocol for the induction of hepatic tumor



3 weeks old Animals

Single i.p. injection of Diethyl nitrosamine (DENA) in normal saline



After 2 weeks

Oral administration of CCl_4, 3 times in a week by gavage with 1:1 dilution in corn oil



Necropsy after 24 weeks



Medicinal Plants & Natural Products Screened/ under Screening in our Laboratory for the Management of Cancer by using Skin, Hepatic & Gastric Cancer Models



CME-2015



Emblica officinalis(Fruit)



Rosemarinus officinalis (leaves)



Aloe vera (leaves)



Trigonella foenum (leaves)



Alstonia scholaris (Bark)



Syzygium cumuni (Seed)



Tinospora cordifolia (Root)



Panax ginseng (Root)



Aegle marmelos (Fruit)



Linum usitatissimum (Seed oil)



Averrhoa carambola (Fruit)



Carissa carandas (Fruit)



Capparis decidua (Fruit)



Trachyspermum ammi (Seed)

Chemopreventive Potential of Flax/Linseed oil against chemical induced skin carcinogenesis

Materials & Methods



Animals

Swiss Albino Mice

6-8 weeks old



Carcinogen/Promoter

7, 12-Dimethyl Benz (a) anthracene (DMBA)

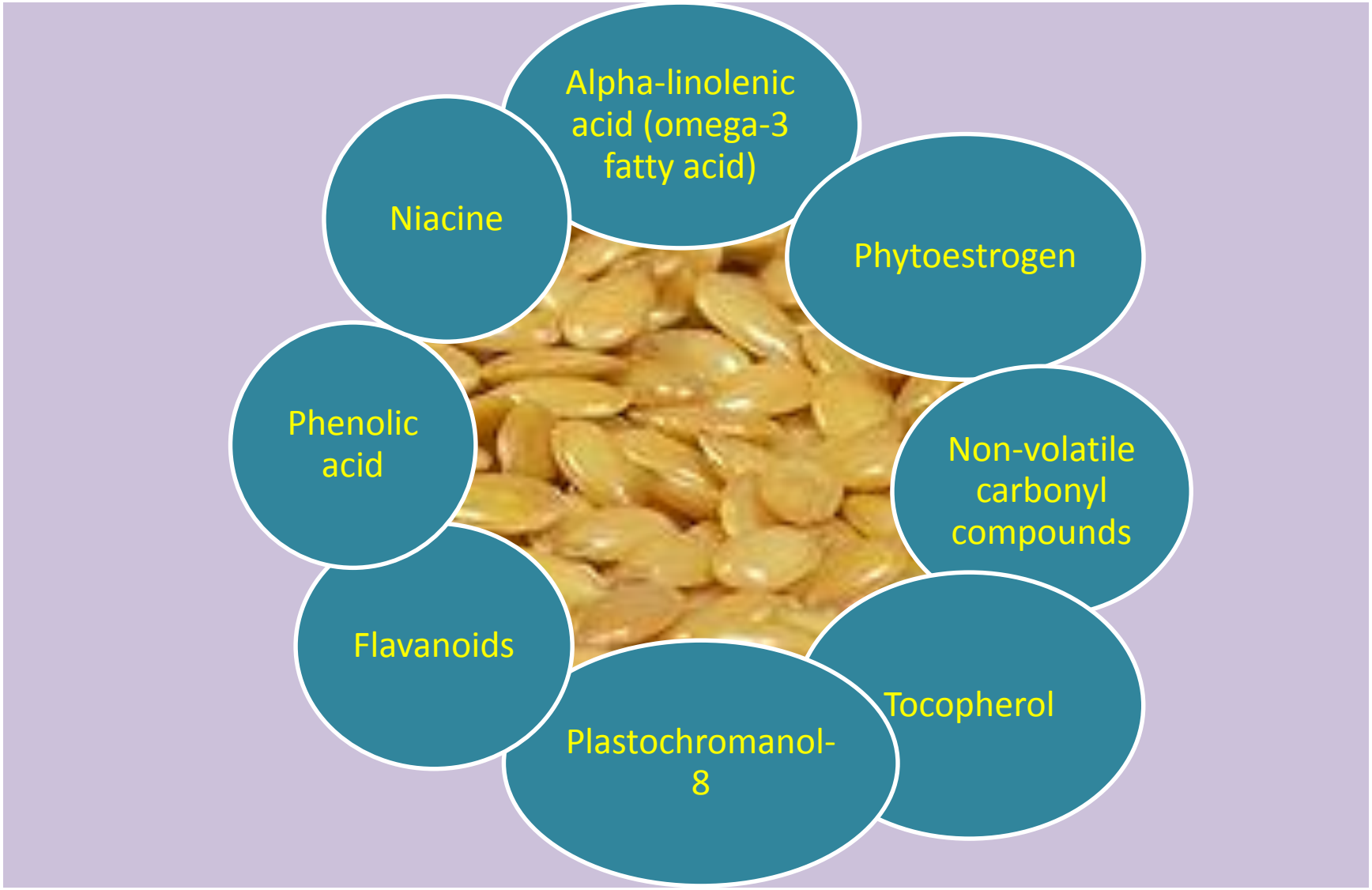
Croton oil

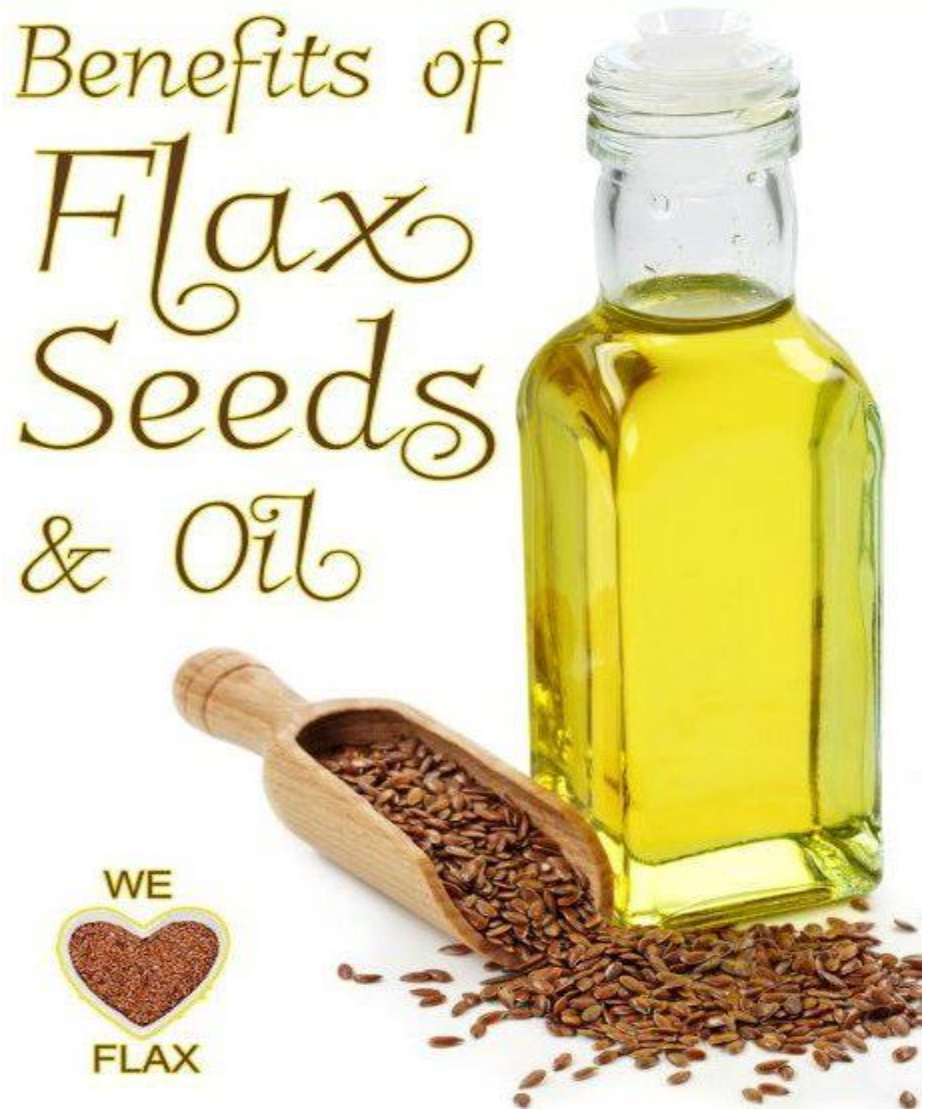


Plant Material

Cold pressed Flaxseed oil

Chemical constituents present in flaxseed oil





Flaxseed oil contains

1. OMEGA-3 FATTY ACIDS
   (Improve circulation, strengthen body and reduce cholesterol, diabetes)

2. PHYTOESTROGENS
   (Maintain hormonal levels)

3. ANTI-INFLAMMATORY PROPERTIES
   (Reduce cysts in breasts and inflammation in bowels, digestive tracts & joints)

Parameters Studied



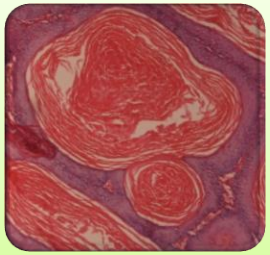
Morphological

- **Tumor Incidence**
- **Cumulative no. of tumors**
- **Tumor yield**
- **Tumor burden**
- **Average latent period**
- **Inhibition of tumor multiplicity**



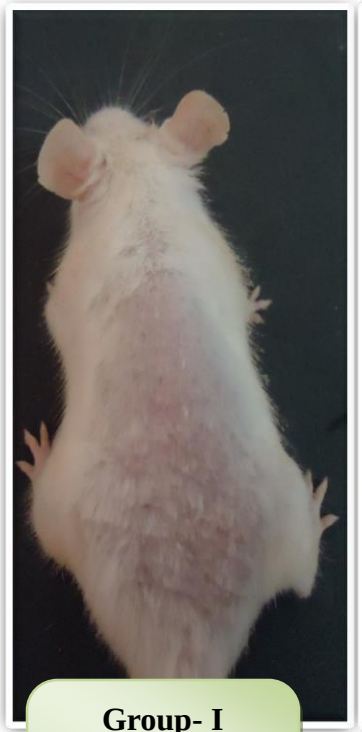
Biochemical

- Lipid peroxidation (LPO) (Ohkhawa *et al.* 1979)
- Reduced glutathione (GSH) (Moron *et al.* 1979)
- Superoxide dismutase (Marklund & marklund, 1974)
- Catalase (Aebi, 1984)
- Total Proteins (Lowry *et. al.*, 1951)



Histopathological

- Skin
- Tumor



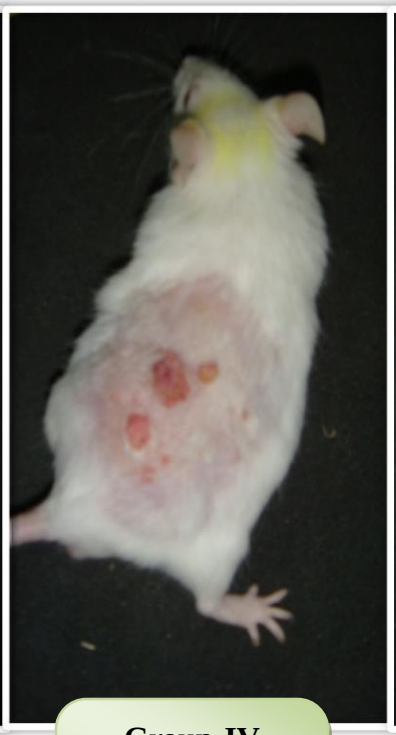
Group- I

Vehicle treated Control



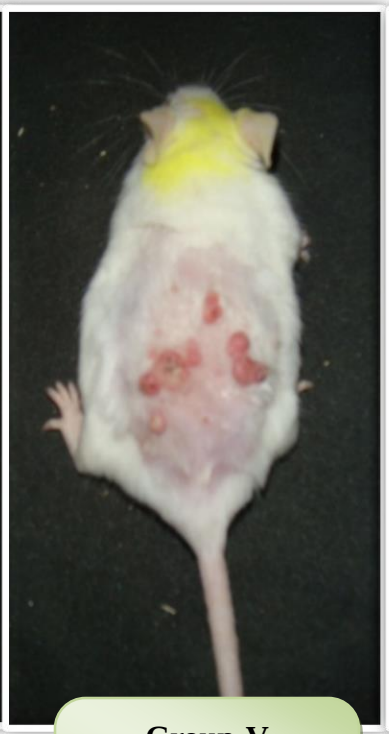
Group–III

Carcinogen treated Control



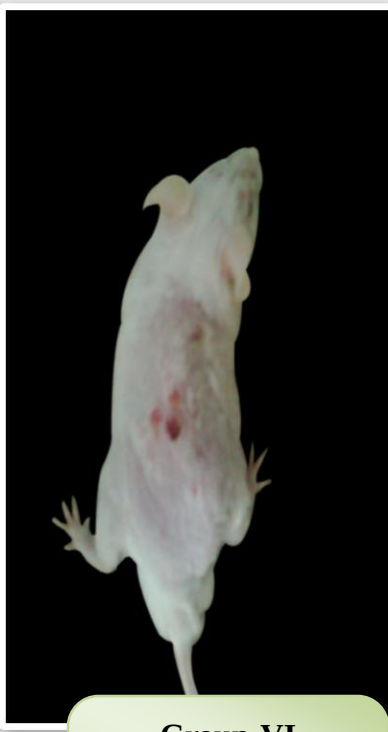
Group-IV

FSO treated Experimental-1



Group-V

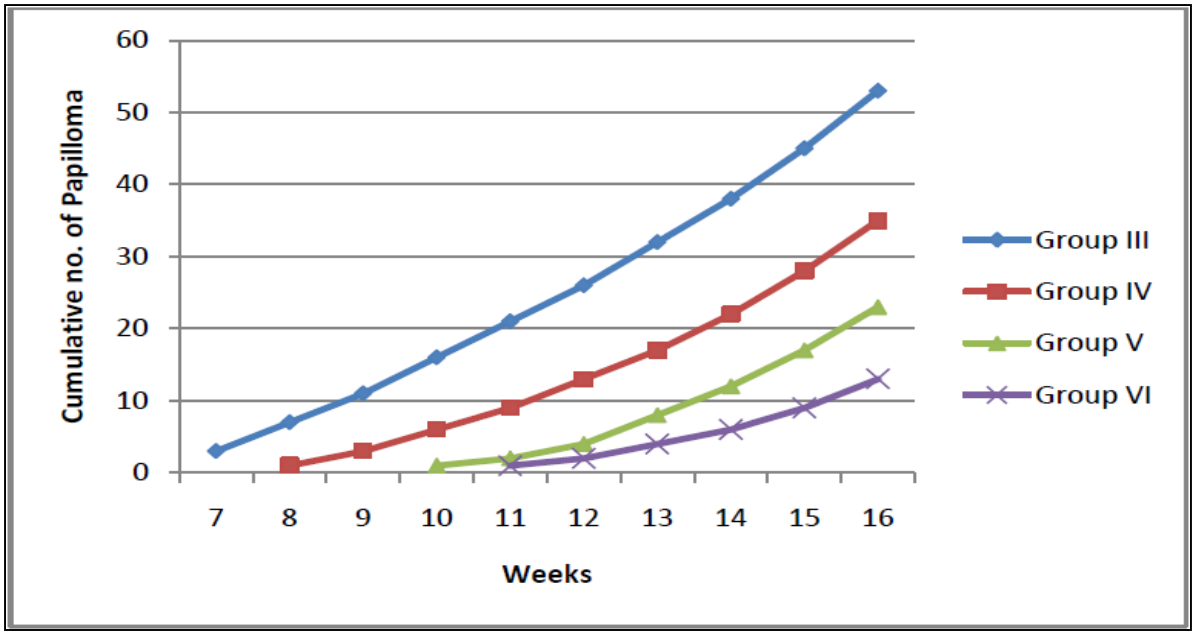
FSO treated Experimental-II



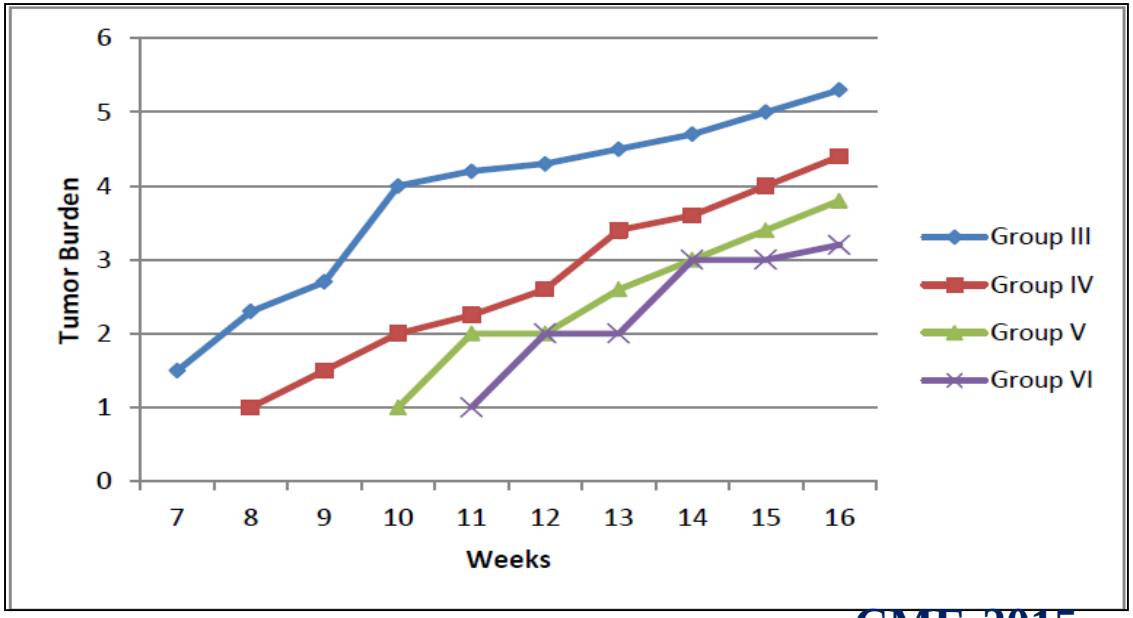
Group-VI

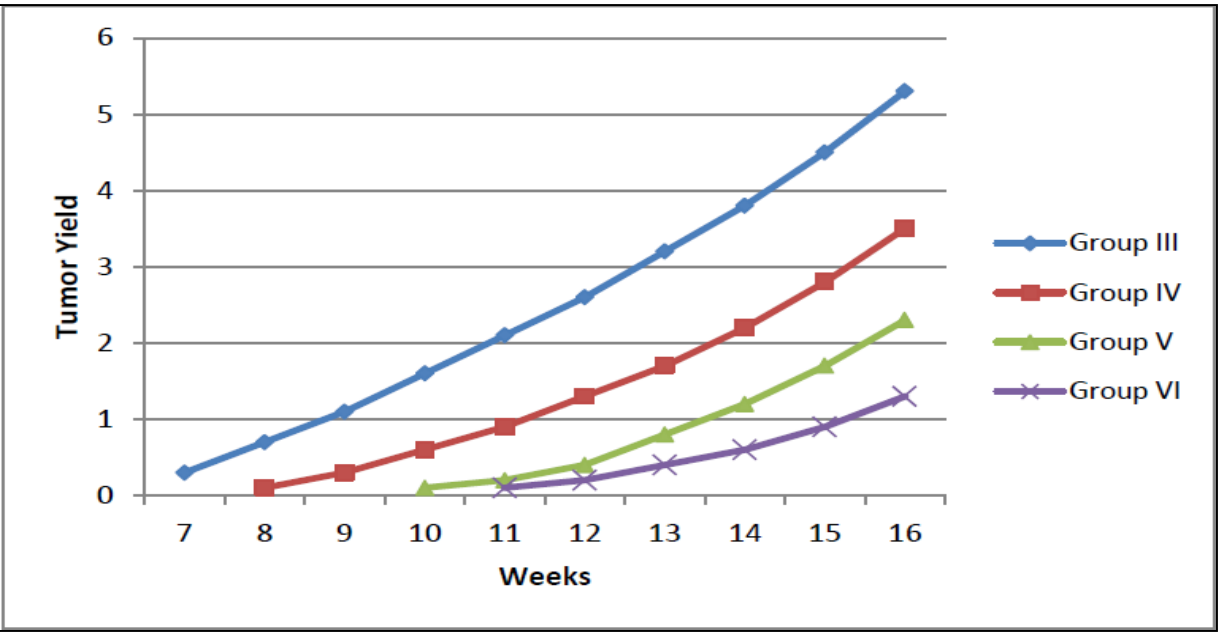
FSO treated Experimental- III

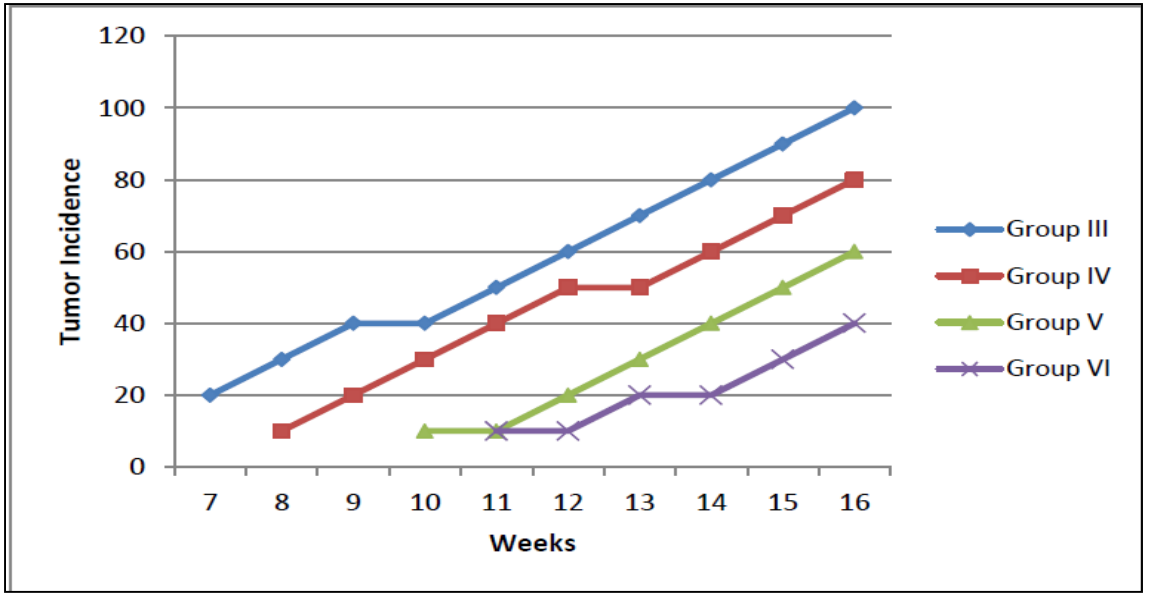
Fig. The gross appearance of skin tumors in mice of different groups during chemical induced skin carcinogenesis with or without flaxseed oil



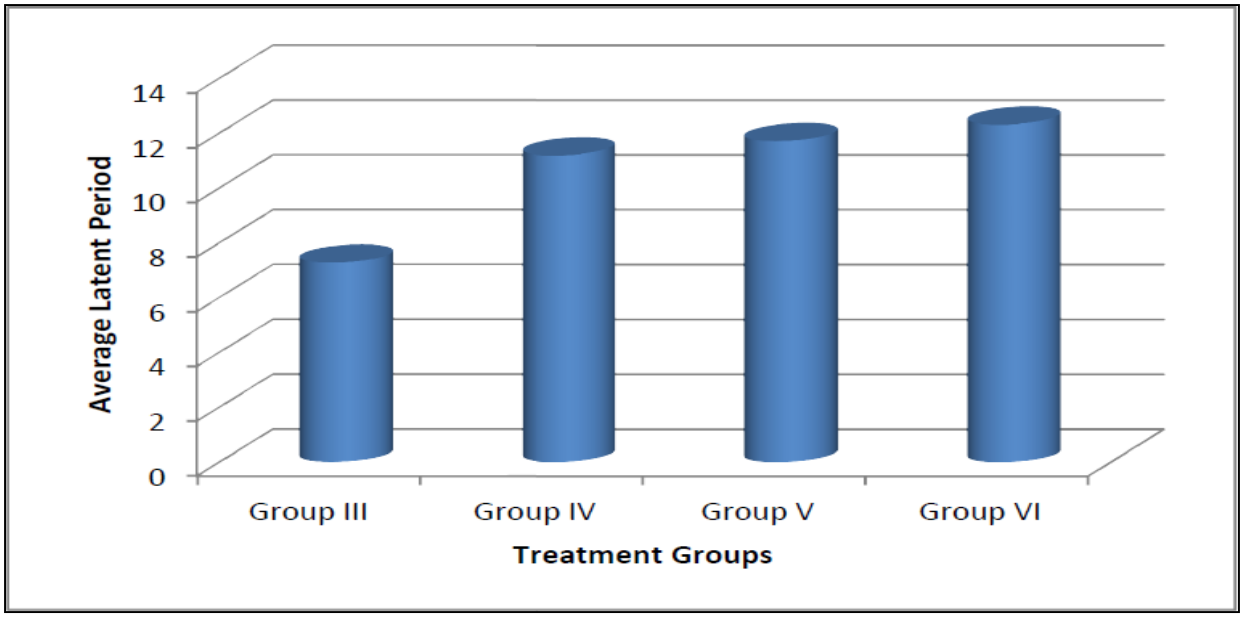
- **Gr. I: DDW alone; Gr. II: FSO alone**
- **Gr. III: DMBA+ Croton oil**
- **Gr. IV : Peri-initiation (FSO-50µl/animal/day)**
- **Gr. V : Post-initiation (FSO-50µl/animal/day)**
- **Gr. VI: Peri-Post initiation (FSO-50µl/animal/day)**

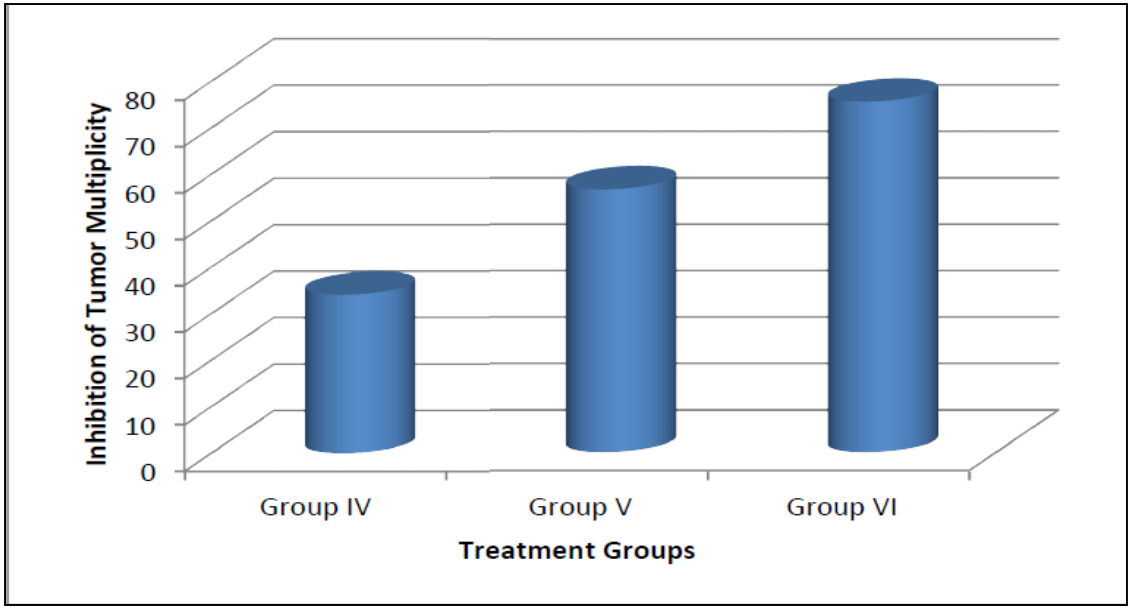




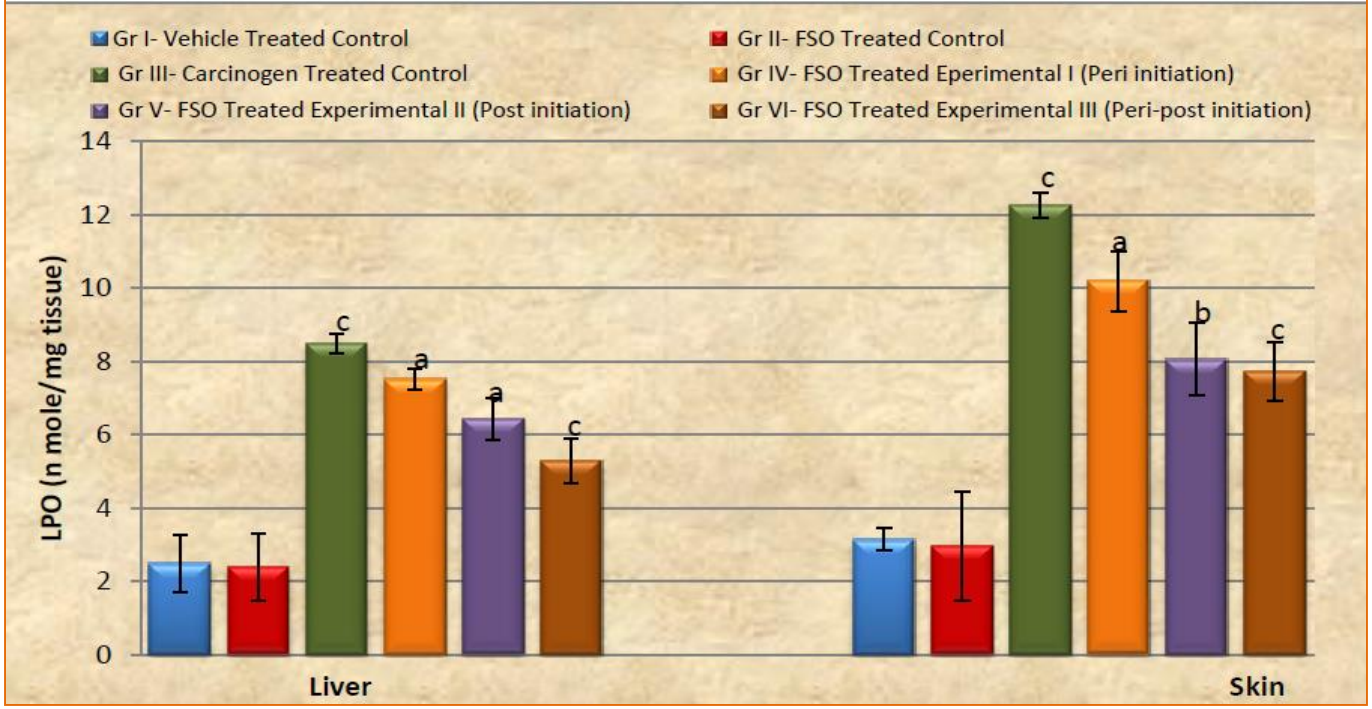


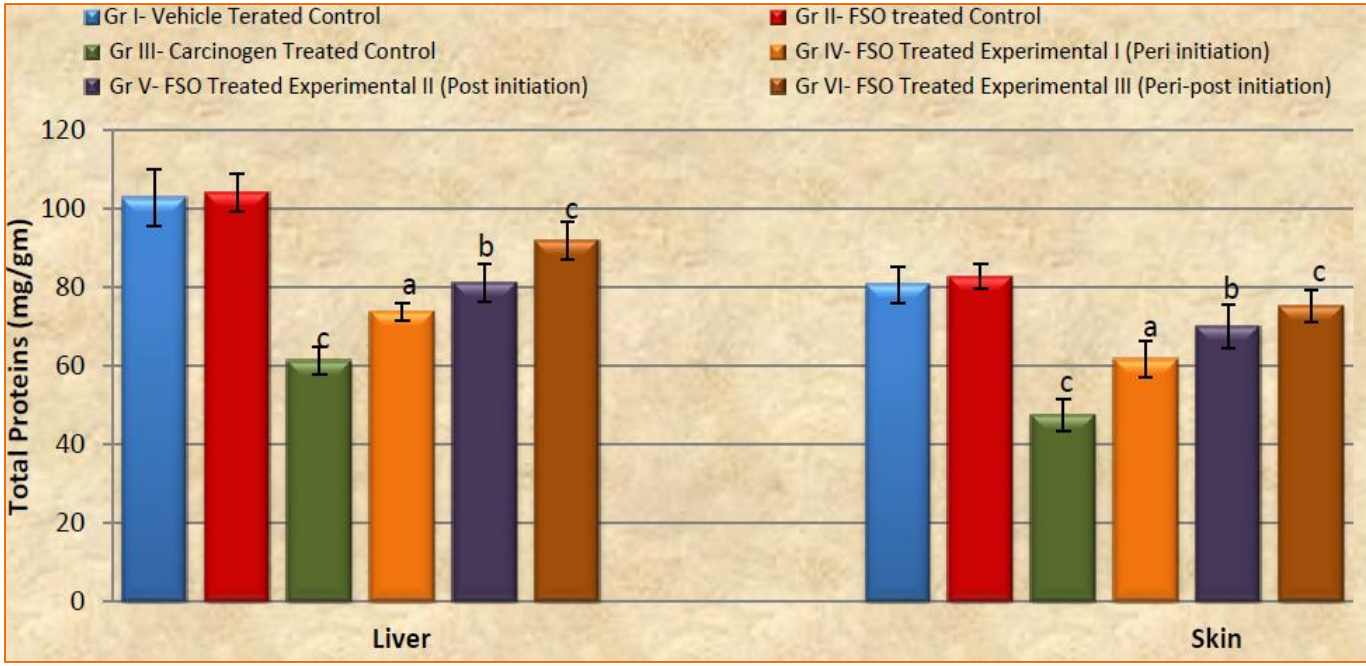
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- **Gr. VI: Peri-Post initiation (FSO-50µl/animal/day)**



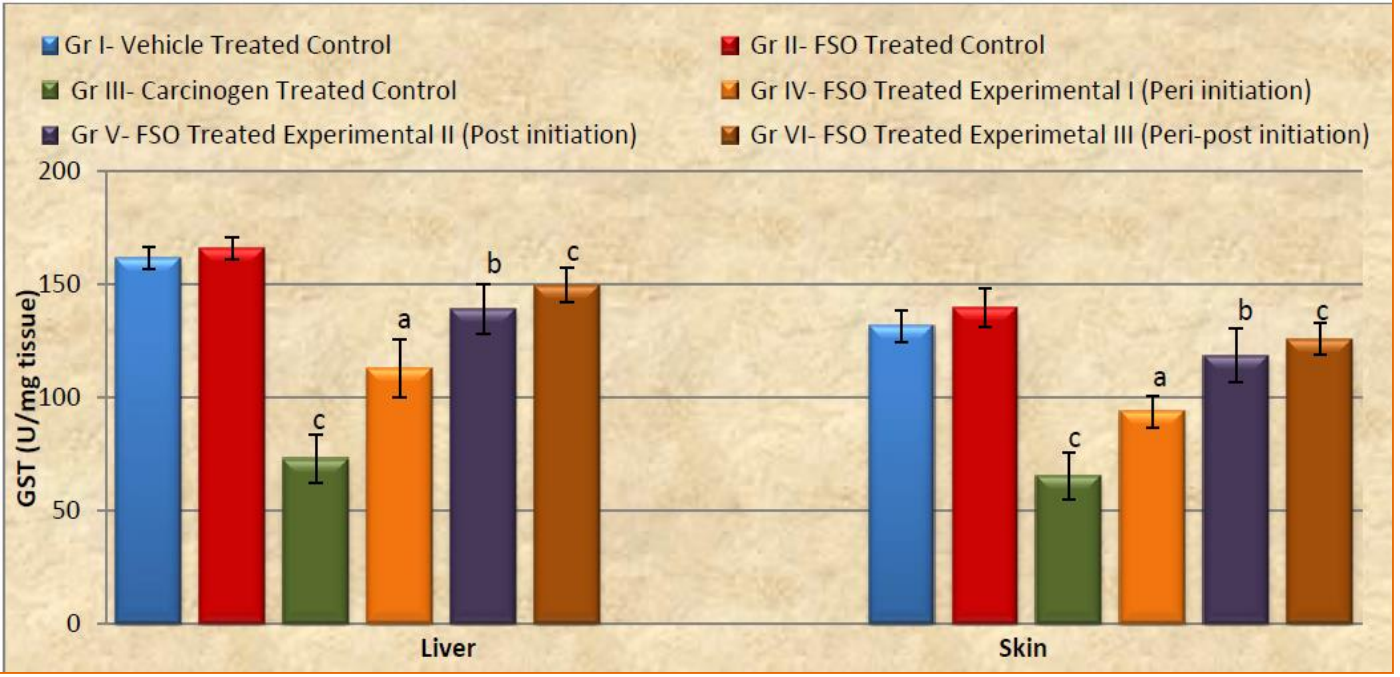


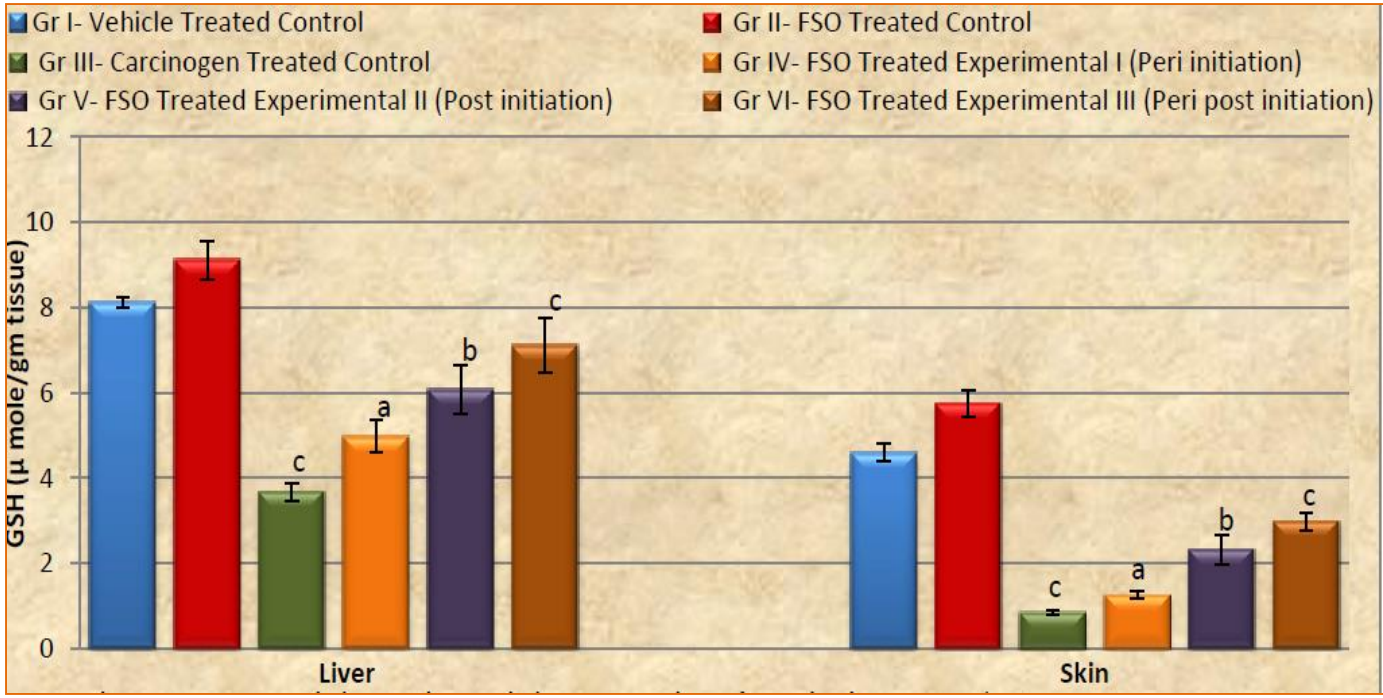
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- **Gr. VI: Peri-Post initiation (FSO-50µl/animal/day)**



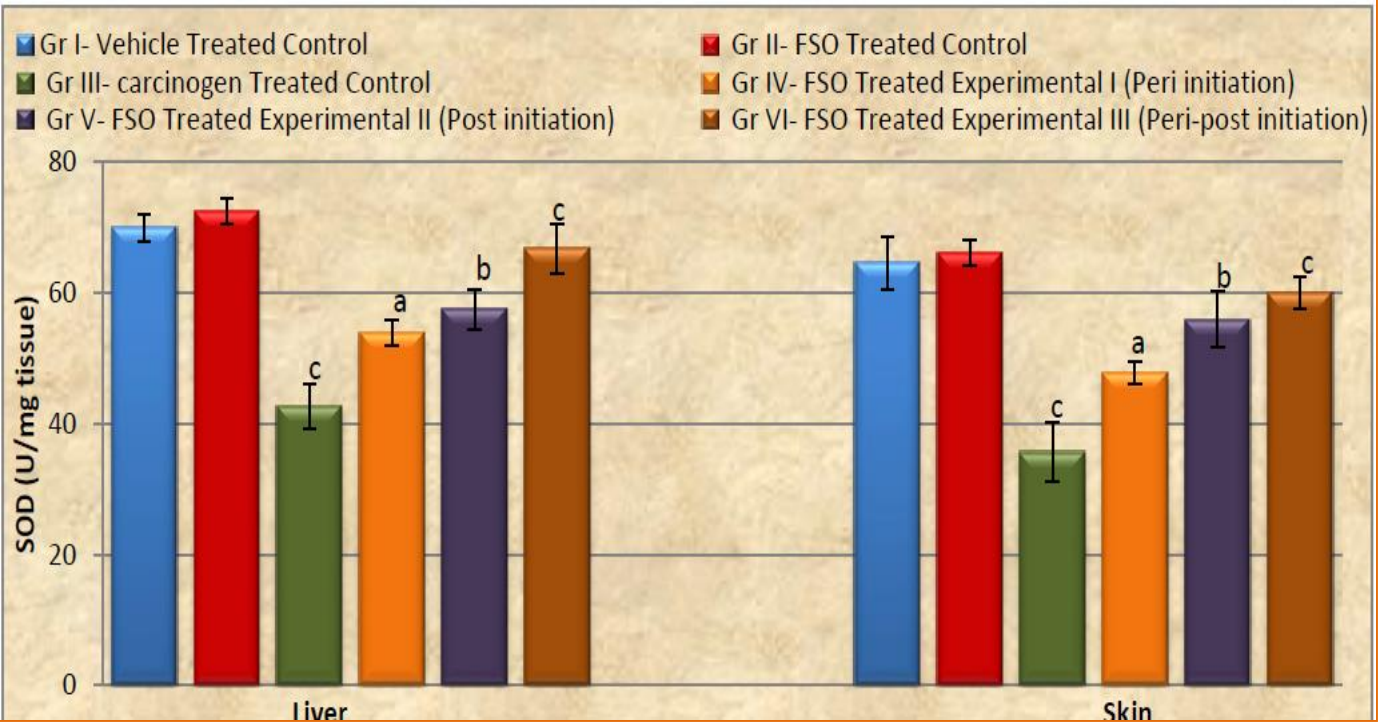


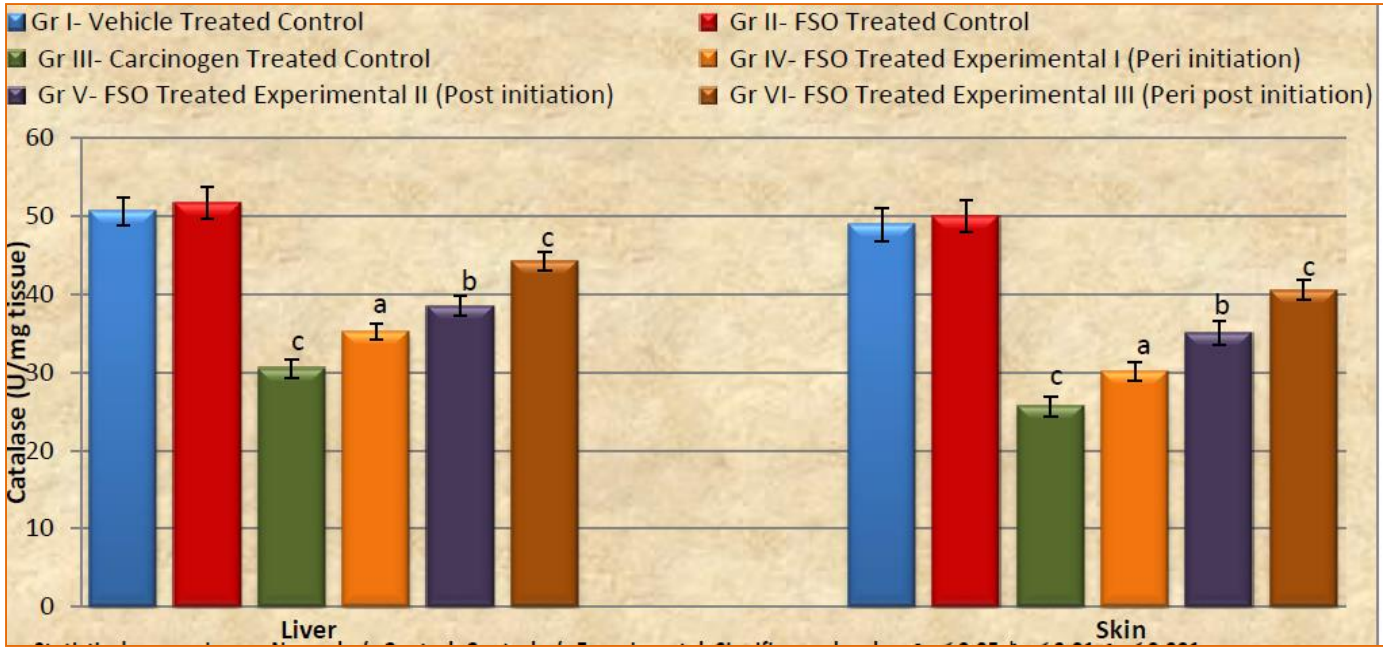
Significance level:
$^{a}p \leq 0.05$, $^{b}p \leq 0.01$, $^{c}p \leq 0.001$





Significance level:
$^{a}p \leq 0.05$, $^{b}p \leq 0.01$, $^{c}p \leq 0.001$





Significance level:
[a]p≤0.05, [b]p≤0.01, [c]p≤0.001

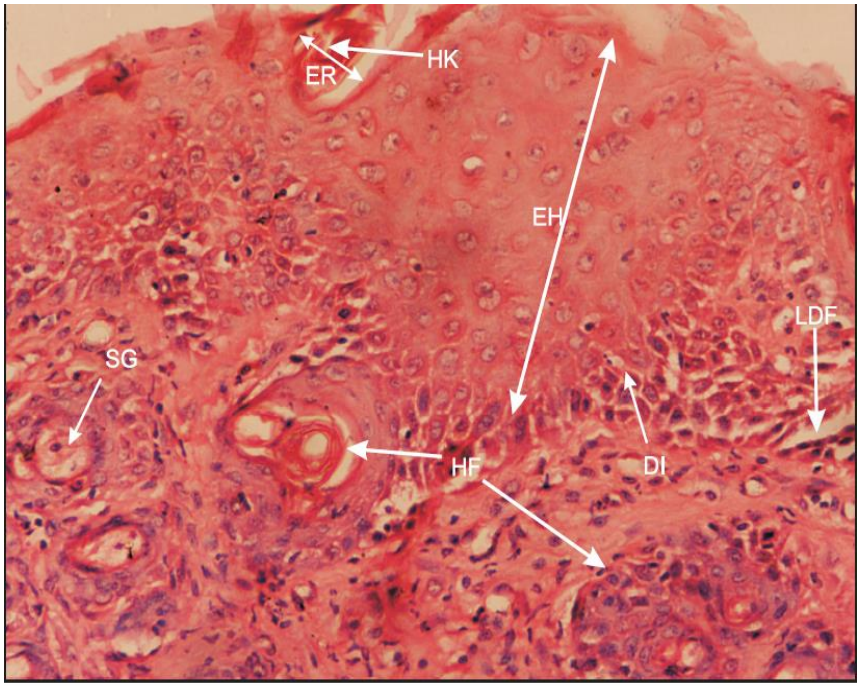


Plate- 1

Photomicrograph of skin in DMBA/ croton oil treated mice illustrating skin lesions in the form of:

X 200

Severe:

(i) ER- Erosion
(ii) HK- Hyperkeratosis
(iii) EH- Epidermal hyperplasia
(iv) DI- Dermal invasion
(v) LDF- Loosening of dermal fibers, and

Severely damaged:

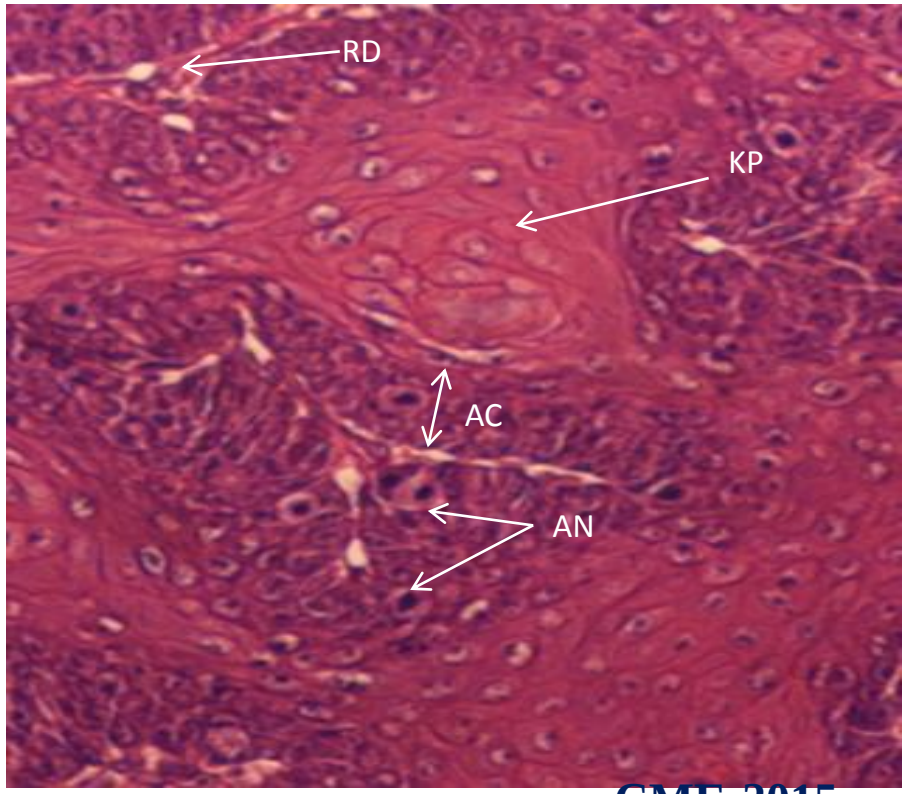
(i) SG- Sebaceous gland
(ii) HF- Hair follicle

Plate- 2

Photomicrograph of T. S. of tumor in DMBA/ croton oil treated mice illustrating:

Ac- Acanthosis, Sr- reduced stroma with lymphocytes, KP- Keratinous Pearl,

AN- Atypic nuclei



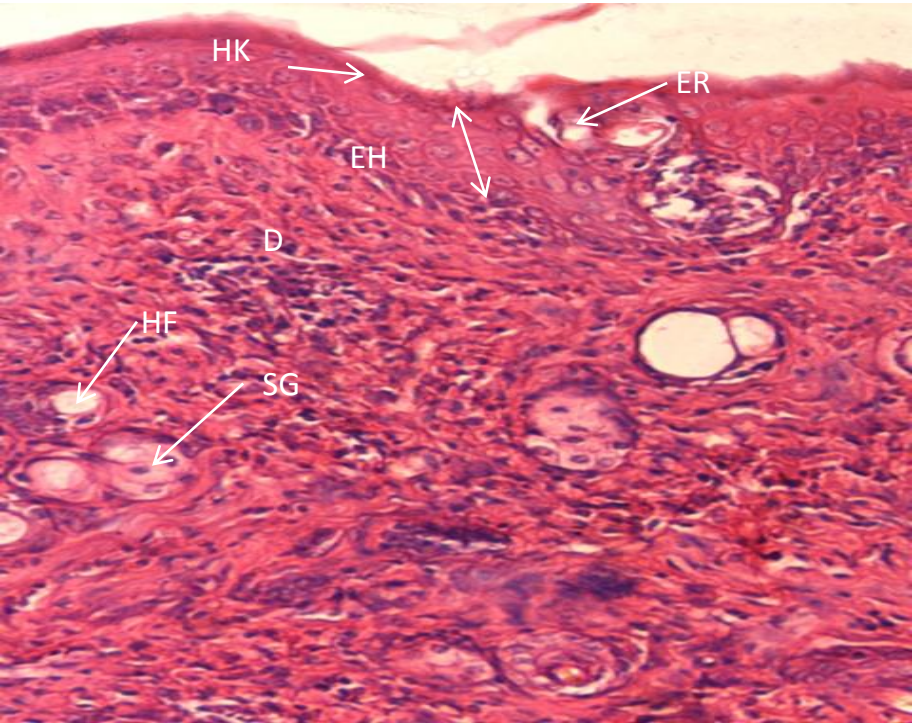


Plate- 3

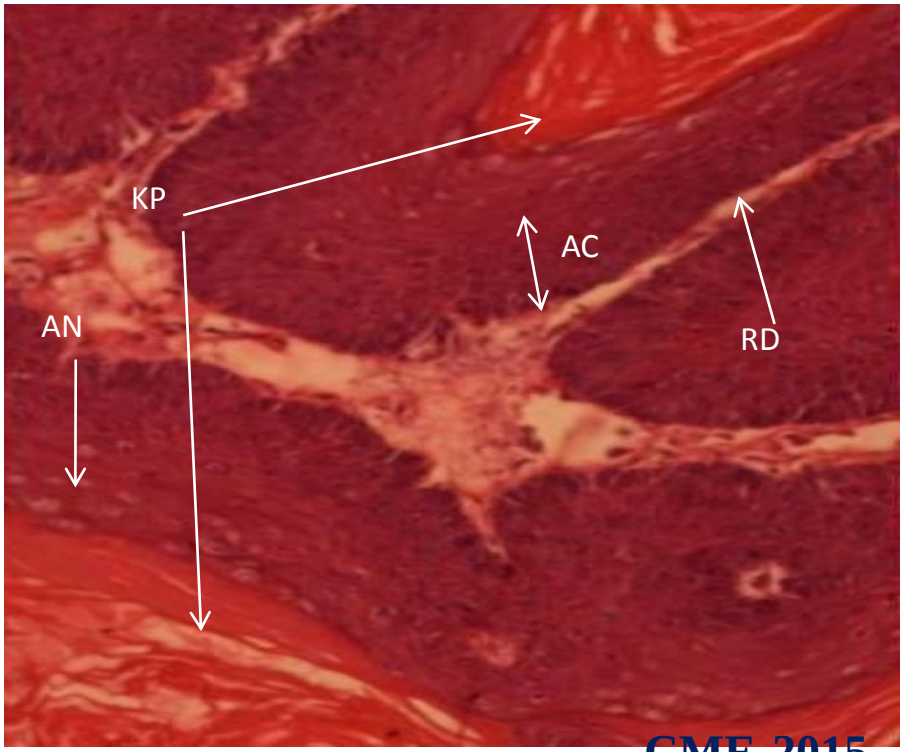
Photomicrograph of V.S. of skin in mice, received FSO (50 µl/animal/day) during peri-initiation stage.

X 200

Plate- 4

Photomicrograph of T. S. of tumor in mice, received FSO (50 µl/animal/day) during peri-initiation stage.

X 200



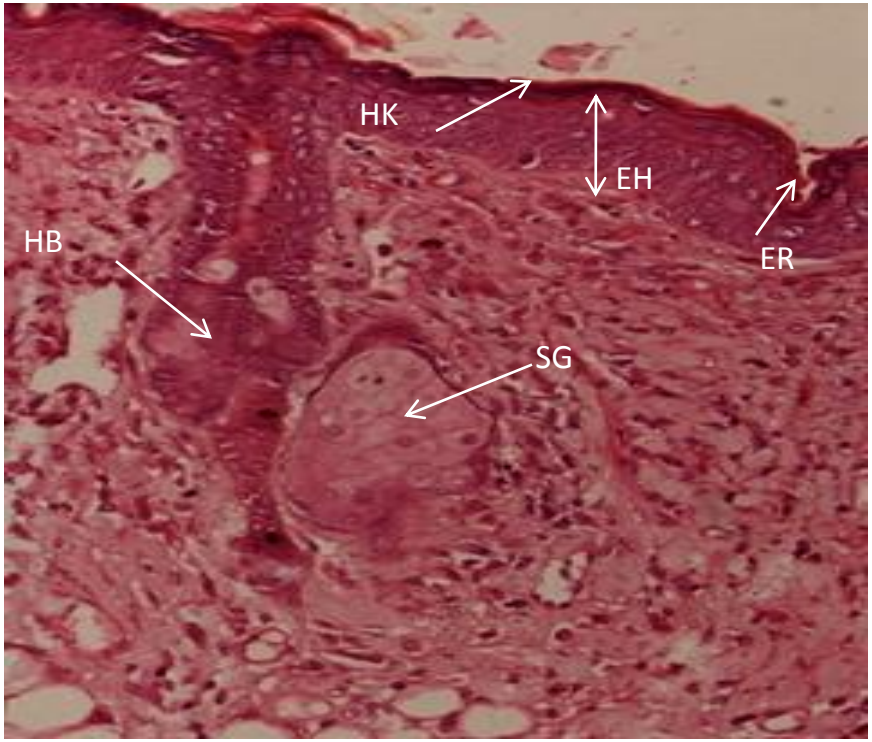


Plate- 5

Photomicrograph of V.S. of skin in mice, received FSO (50 µl/animal/day) during post-initiation stage.

X 100

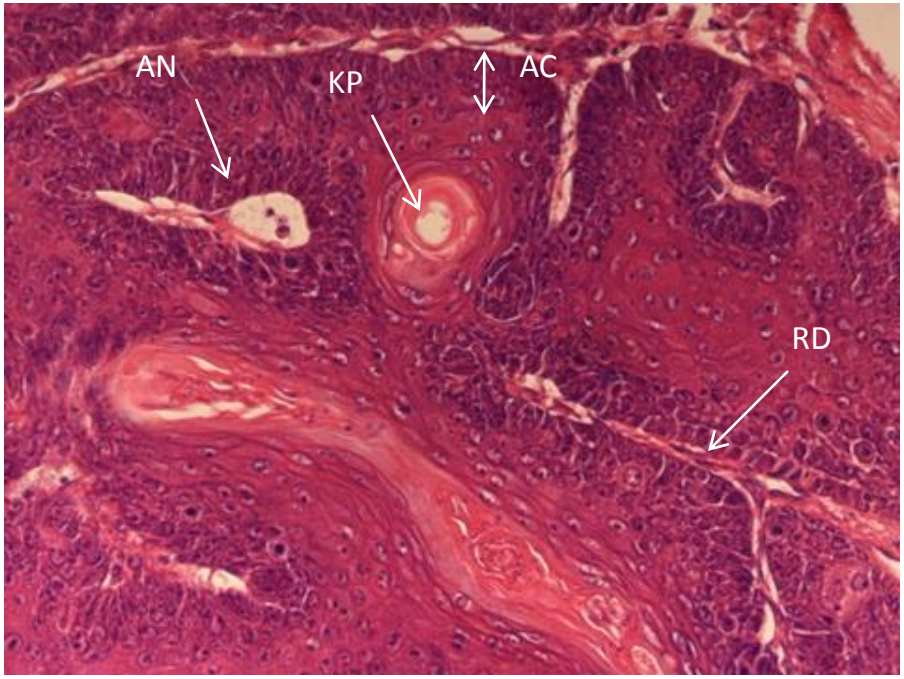


Plate- 6

Photomicrograph of T. S. of tumor in mice, received FSO (50 µl/animal/day) during post-initiation stage.

X200

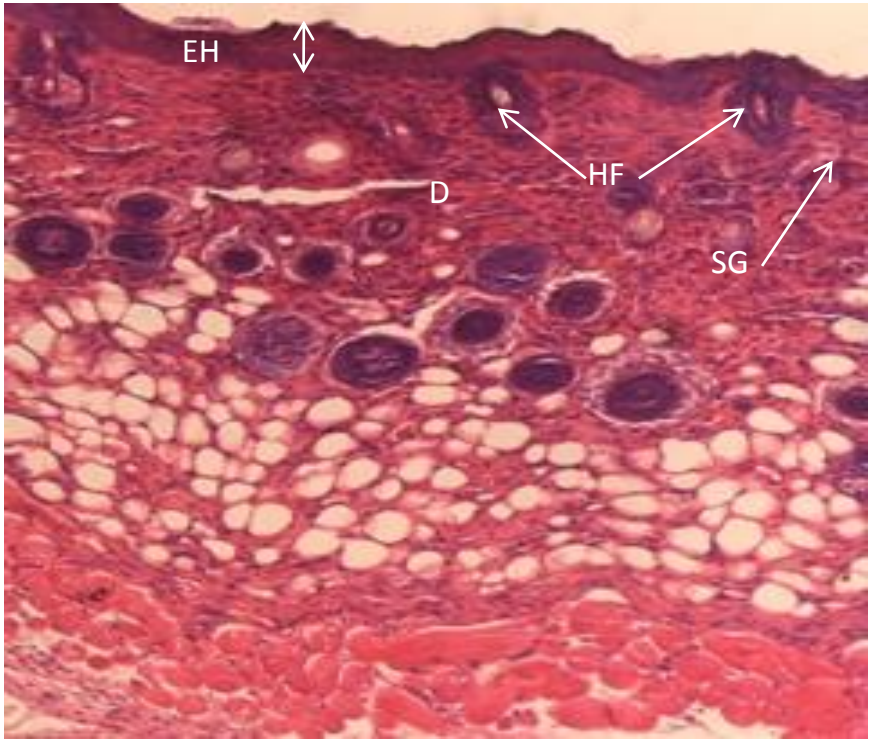


Plate- 7

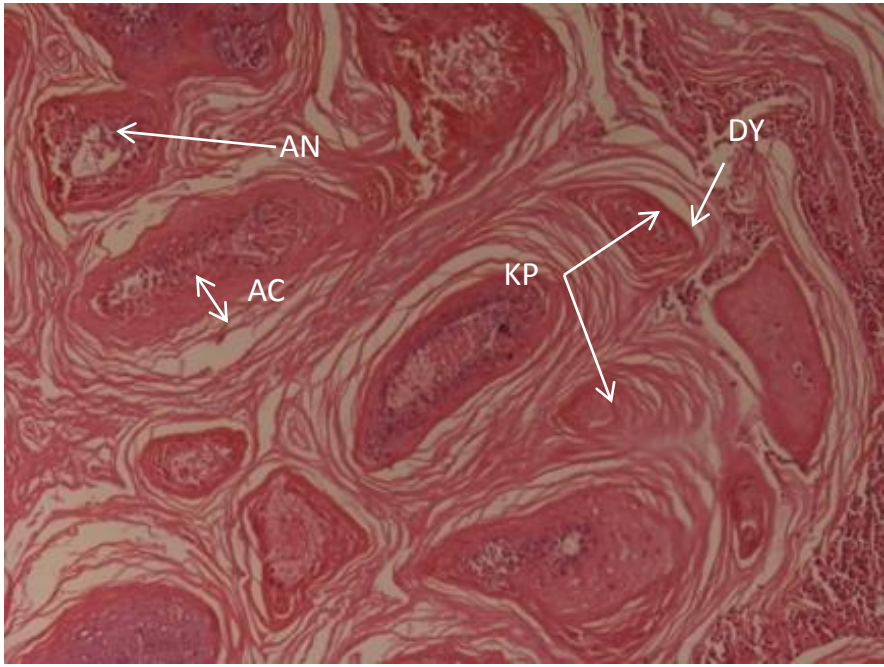
Photomicrograph of V.S. of skin in mice, received FSO (50 µl/animal/day) during peri- & post-initiation stage.

X 100

Plate- 8

Photomicrograph of T.S. of Tumor in mice, received FSO (50 µl/animal/day) during peri- & post-initiation stage.

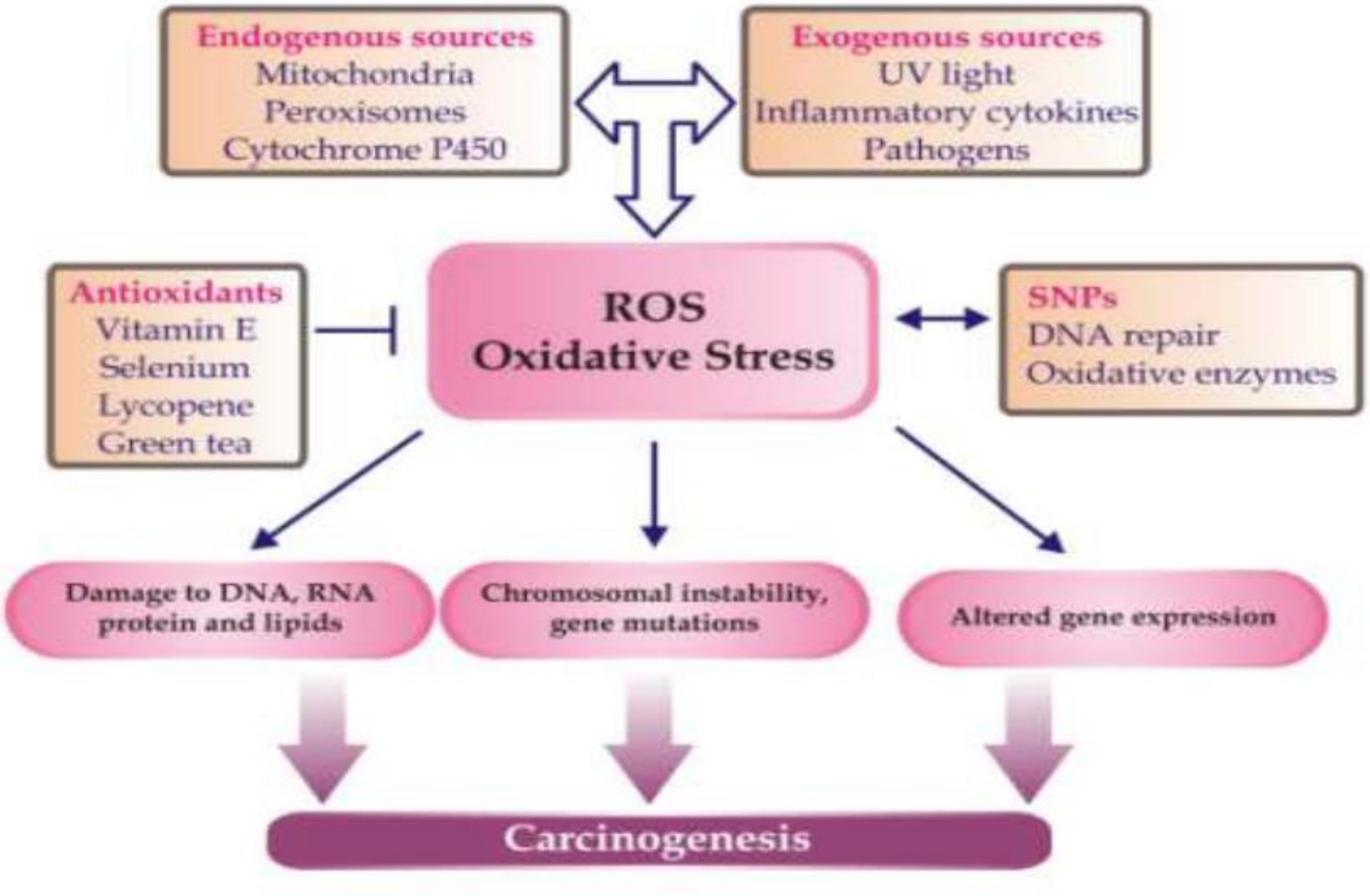
X 100



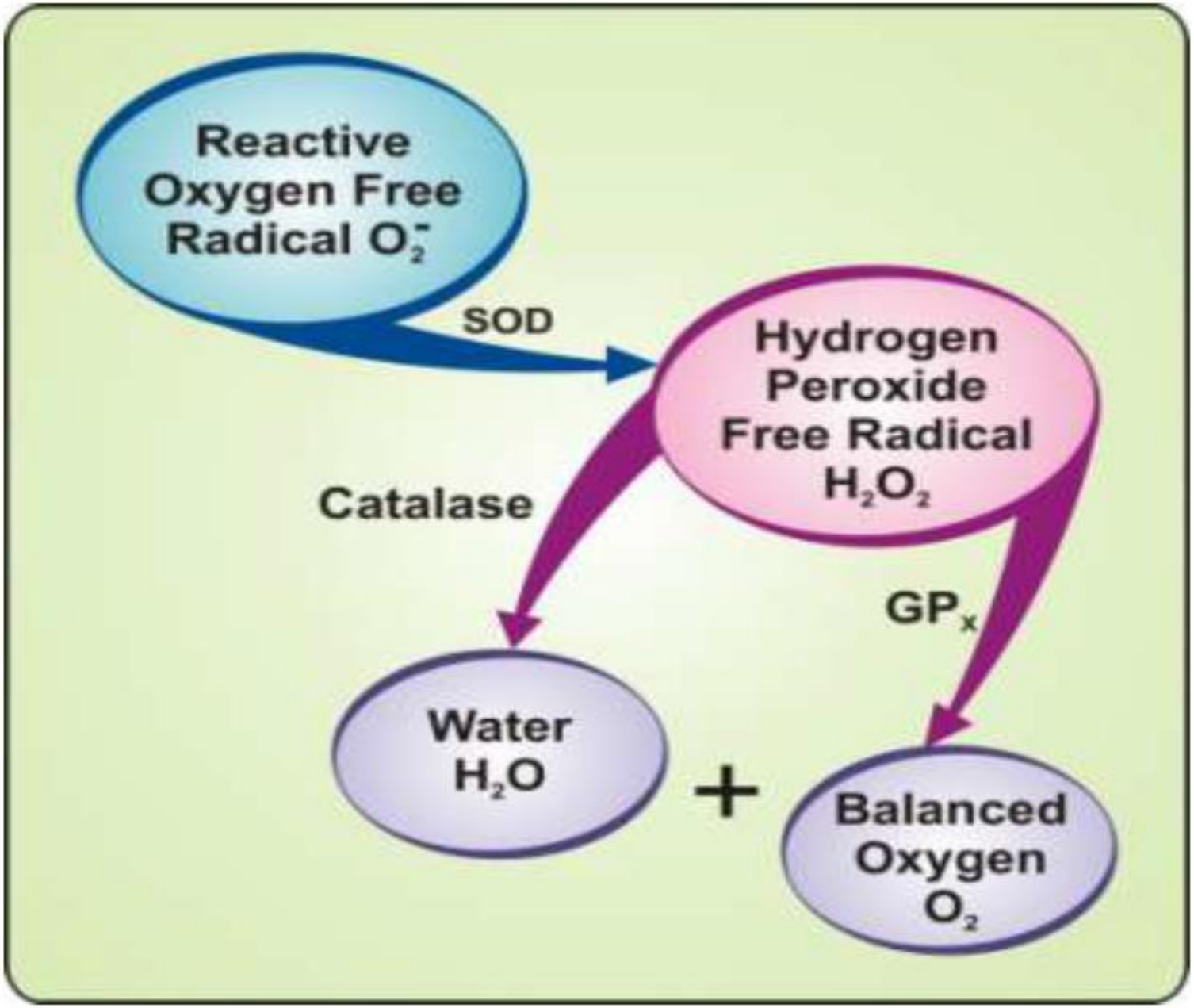
TUMOR STATISTICS WITH DIFFERENT PLANT EXTRACTS

Treatment	Tumor Incidence (%)	Tumor Burden	Tumor Yield	Average Latent Period
Carcinogen treated control (DMBA+ Croton oil)	+ + +	+ + +	+ + +	-
Tinospora cordifolia (100mg/ kg.b. wt.) + DMBA+ Croton oil	+ +	+ +	+ +	+ +
Syzygium cumini((125mg/kg. b.wt.) + DMBA+ Croton oil	+ +	+ +	+ +	+ +
Phyllanthus niruri (1000mg/ kg.b. wt.) + DMBA+ Croton oil	+ +	+ +	+ +	+ +
Alstonia scholaris (100mg/ kg.b. wt.) + DMBA+ Croton oil	+ +	+ +	+ +	+ +
Rosmarinus officinalis(750mg/kg. b.wt) + DMBA + Croton oil	+	+	+	+ + +
Aegle marmelos (100mg/ kg. b.wt) + DMBA+ Croton oil	+ +	+ +	+ +	+ +
Flaxseed Oil (100mg/ kg. b.wt) + DMBA + Croton oil	+ +	+ +	+ +	+ +

Treatment	LPO (nmole/mg tissue)	GSH (µmole/gm tissue)	CAT (U/mg tissue)	Protein (mg/ ml)	SOD (U/mg of protein)
Carcinogen treated control (DMBA+ Croton oil)	+ + +	- - -	- - -	- - -	- - -
Tinospora cordifolia (100mg/ kg.b. wt.)+ DMBA+ Croton oil)	+ +	- -	- -	- -	- -
Syzygium cumini (125mg/kg. b.wt.) + DMBA+ Croton oil	+ +	- -	- -	- -	- -
Phyllanthus niruri (1000mg/ kg.b. wt.)+ DMBA+ Croton oil)	+ +	- -	- -	- -	- -
Alstonia scholaris (100mg/ kg.b. wt.)+ DMBA+ Croton oil	+ +	- -	- -	- -	- -
Rosmarinus officinalis (750mg/ kg. b.wt)+ DMBA+ Croton oil	+ +	- -	- -	- -	- -
Aegle marmelos (100mg/ kg. b.wt)+ DMBA+ Croton oil	+ +	- -	- -	- -	- -
Flaxseed Oil (50 µl// kg. b.wt)+ DMBA+ Croton oil	+ +	- -	- -	- -	- -

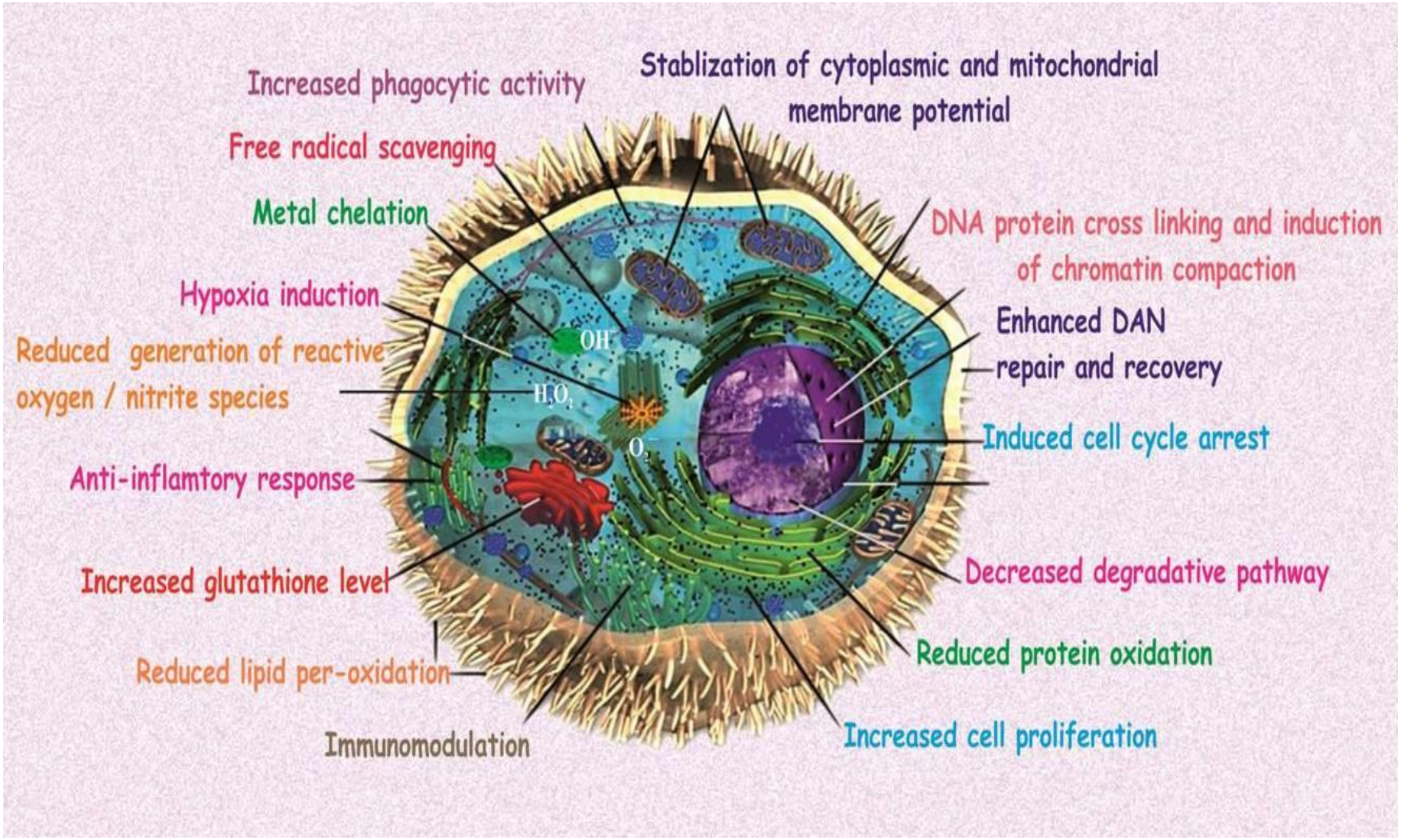


ROS induced oxidative stress leading to carcinogenesis



Free radicals and their neutralization by antioxidants

CHEMO PREVENTIVE MECHANISM BY NATURAL PRODUCTS



Cancer Economics : Cancer Prevention

- High expenditure in cancer treatments
- Cancer is preventable
- Therefore, cancer prevention is necessary
- Most cancers likely develop from a complex interplay of diet, lifestyle and environmental factors
- Nutrition and diet are the most important way for cancer prevention.
- Dietary Prevention: Edible vegetables/fruits and medicinal plants

What can we do to prevent cancer?



Be good

healthy diet
exercise regularly
maintain healthy weight
don't smoke
alcohol in moderation

Know your risk

seek appropriate evaluation or therapy for your risk level

Support prevention research

Conclusions

- Cancer is an important health problem in the world these days. It is the second largest non-communicable disease that has a sizable contribution in the total number of deaths.
- The increasing trend of cancer incidence has forced the humanity to work more on the cancer prevention and treatments.
- The quest of identifying new chemopreventive agents from plant sources has become an ideal strategic paradigm to combat cancer.
- Natural compounds have practical advantages with regard to availability, suitability for oral application, low toxicity, regulatory approval and mechanisms of action.
- Much progress has been made in this field, but more work remains before widespread use and practice of cancer prevention by natural products.
- Various medicinal plants extracts demonstrate their ability in reducing the chemical induced tumors and oxidative stress.
- These findings suggest the possible preventive and therapeutic use of herbal medicine in the management of cancer.
- It may also be recommended that more medicinal plants and natural products should be trialed in the laboratory to access their anti-carcinogenic potential.

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