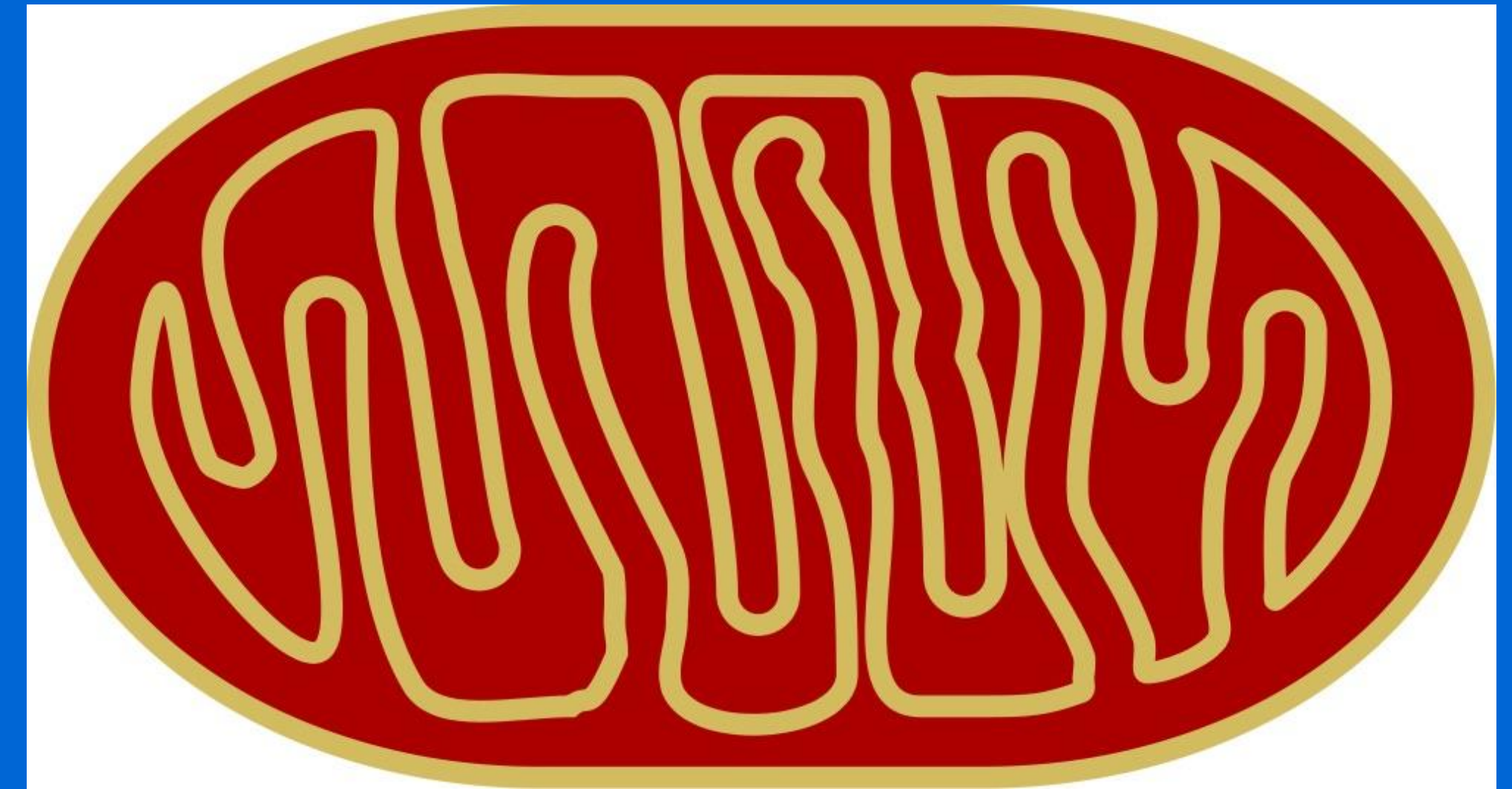
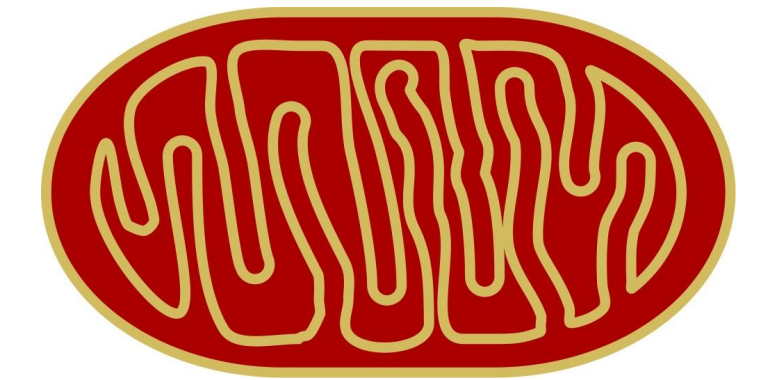


CARE AND FEEDING OF MITOCHONDRIA



**CHEMO-PROTECTIVE NATURAL COMPOUNDS
THAT MODULATE MITOCHONDRIAL FUNCTION**

Dr. Nalini Chilkov, L.Ac., OMD. drchilkov@aimore.com



DISCLOSURES

Independent Contractor and Lecturer Providing Educational & Consulting Services to Nutritional Supplement Companies: Designs for Health, Inc., Pure Encapsulations/Atrium Inc., Invivo Clinical, Ltd. (UK)

Principal and Founder, *American Institute of Integrative Oncology Research and Education and Integrative Cancer Answers* that derive revenue from Educational Products and Services and Sales of Supplements




**EVASION OF PROGRAMMED CELL DEATH
REVERSAL of INHIBITION of APOPTOSIS
With Natural Compounds**

Bcl-2

p53

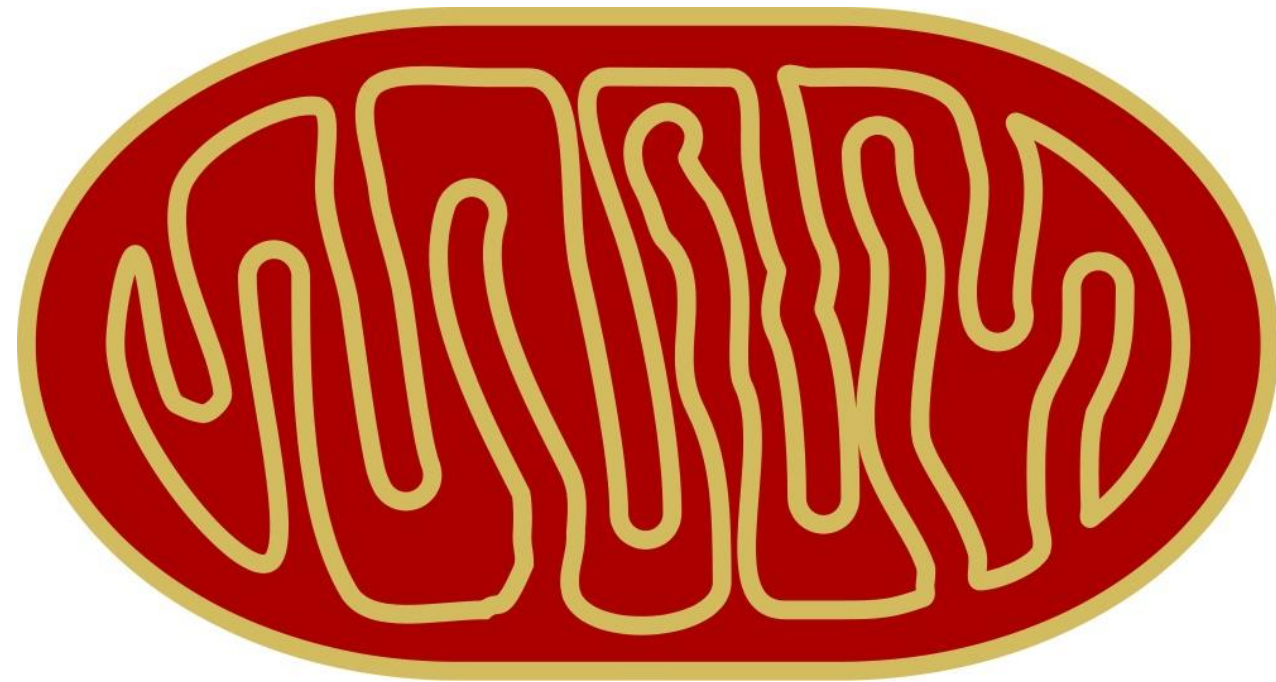
Hexokinase 2

miRNA



There is more to mitochondrial function and cancer than the Warburg Effect and a shift from Oxidative Phosphorylation to Aerobic Glycolysis

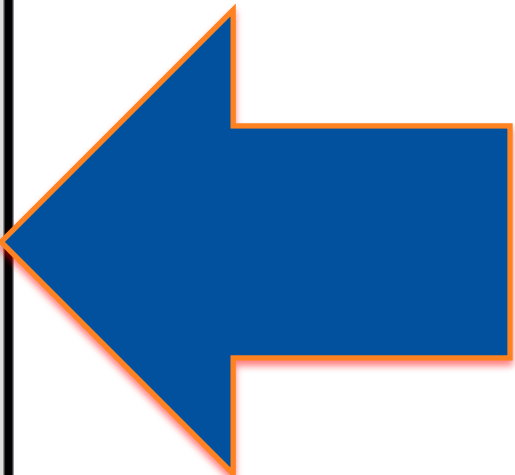
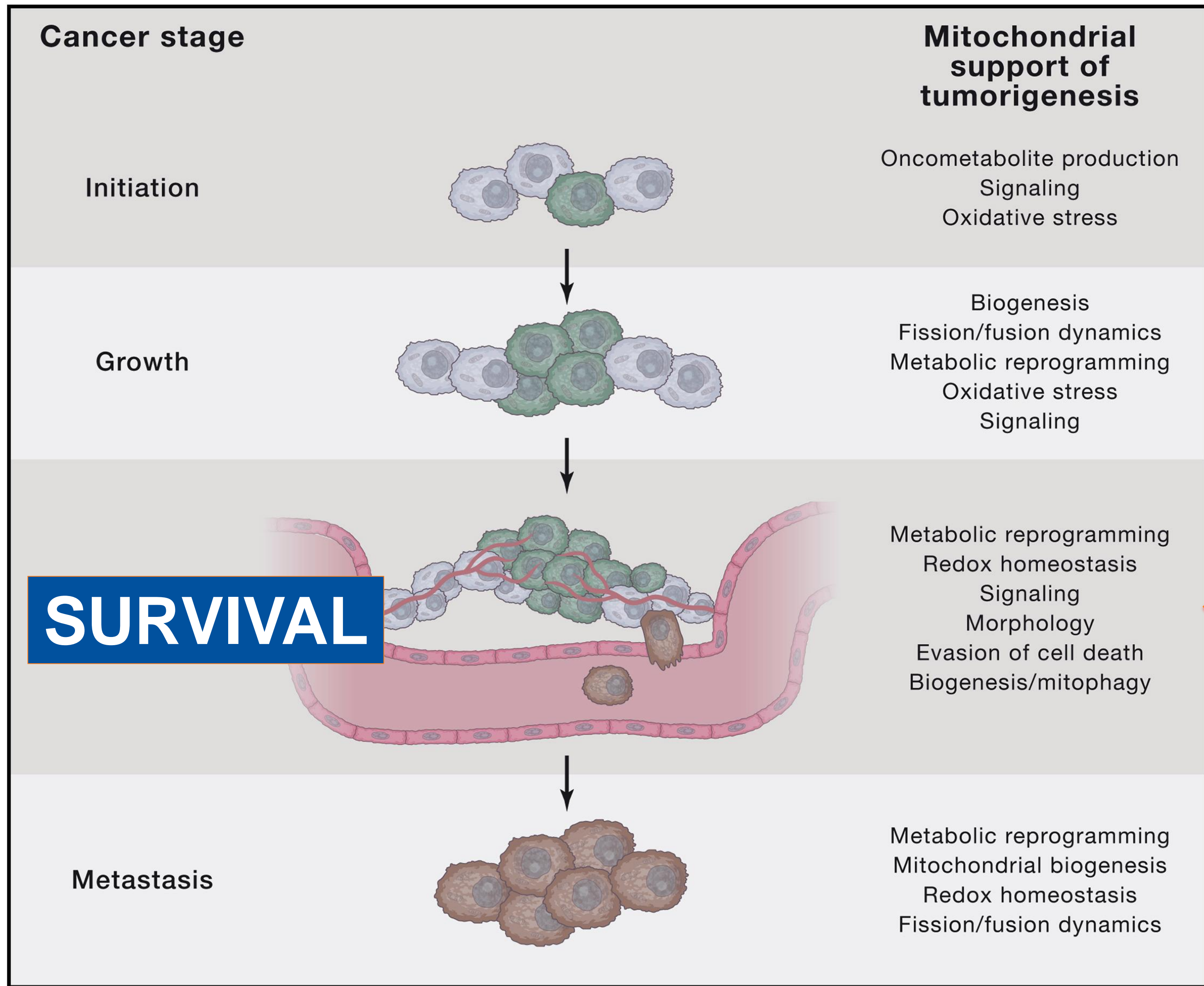
**Mitochondria are crucial cell monitoring sentinels
Governing Cell Death through
Autophagy Mitophagy & Apoptosis**



MITOCHONDRIA AND STAGES OF TUMORIGENESIS



Volume 166, Issue 3, Pages
555-566 (July 2016)
DOI: 10.1016/j.cell.2016.07.002



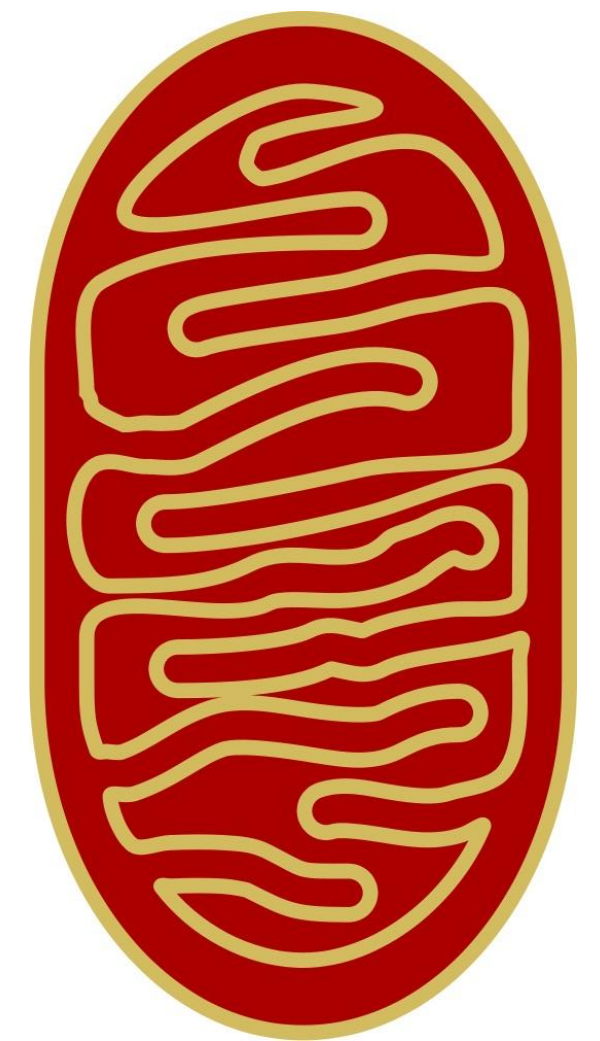
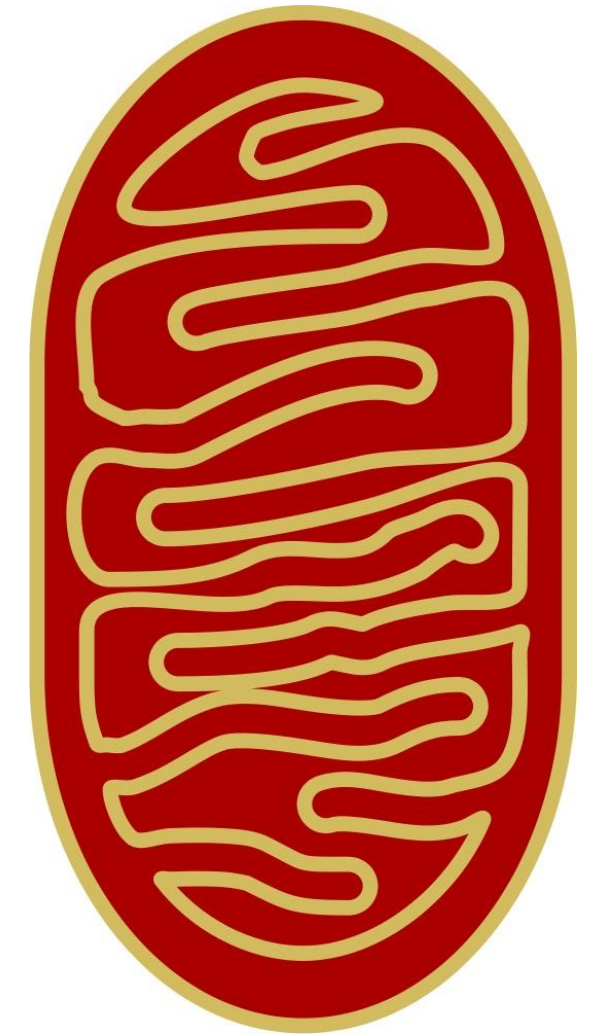
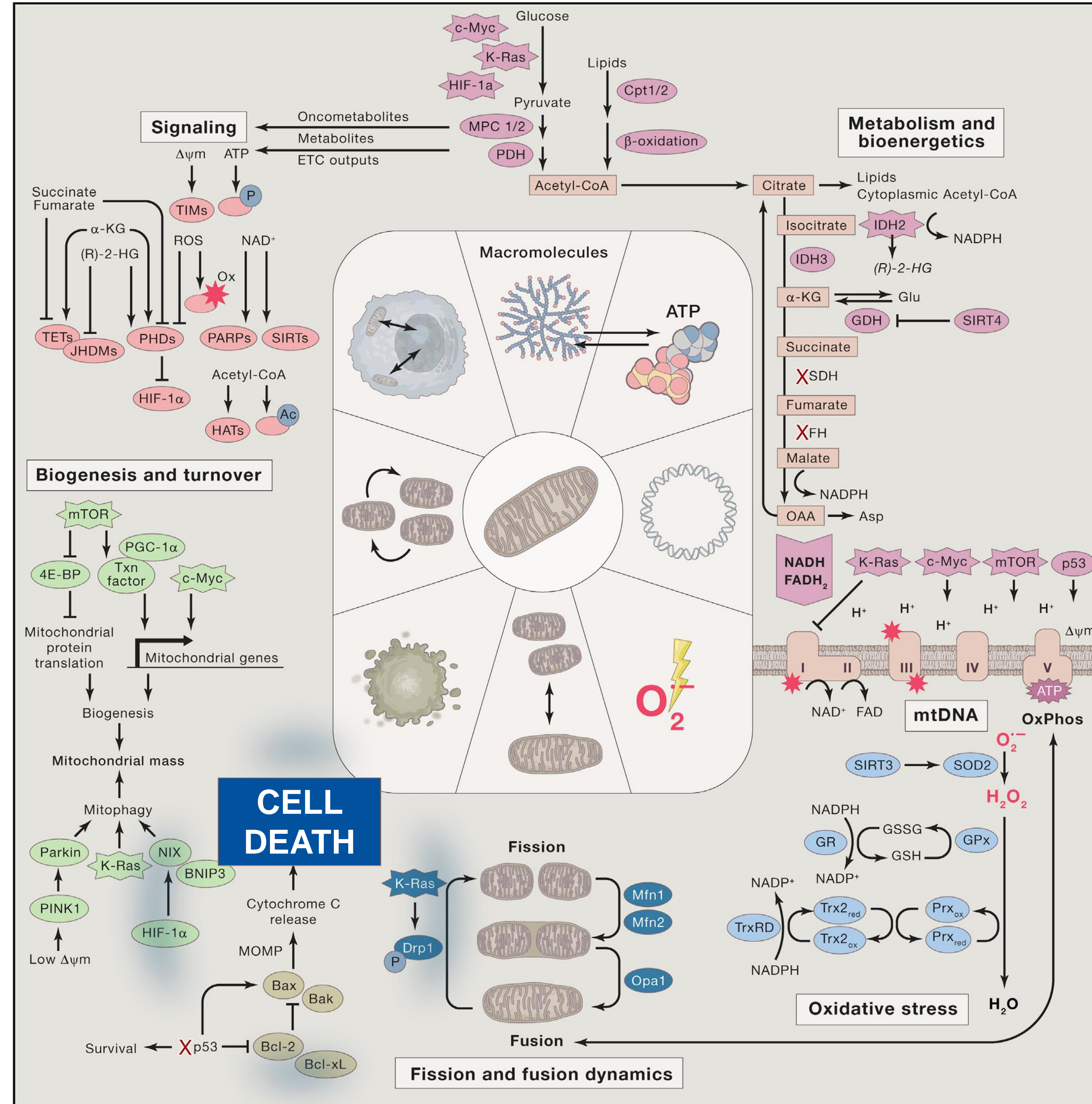
Mitochondria and Cancer

Sejal Vyas
Elma Zaganjor
Marcia C. Haigis

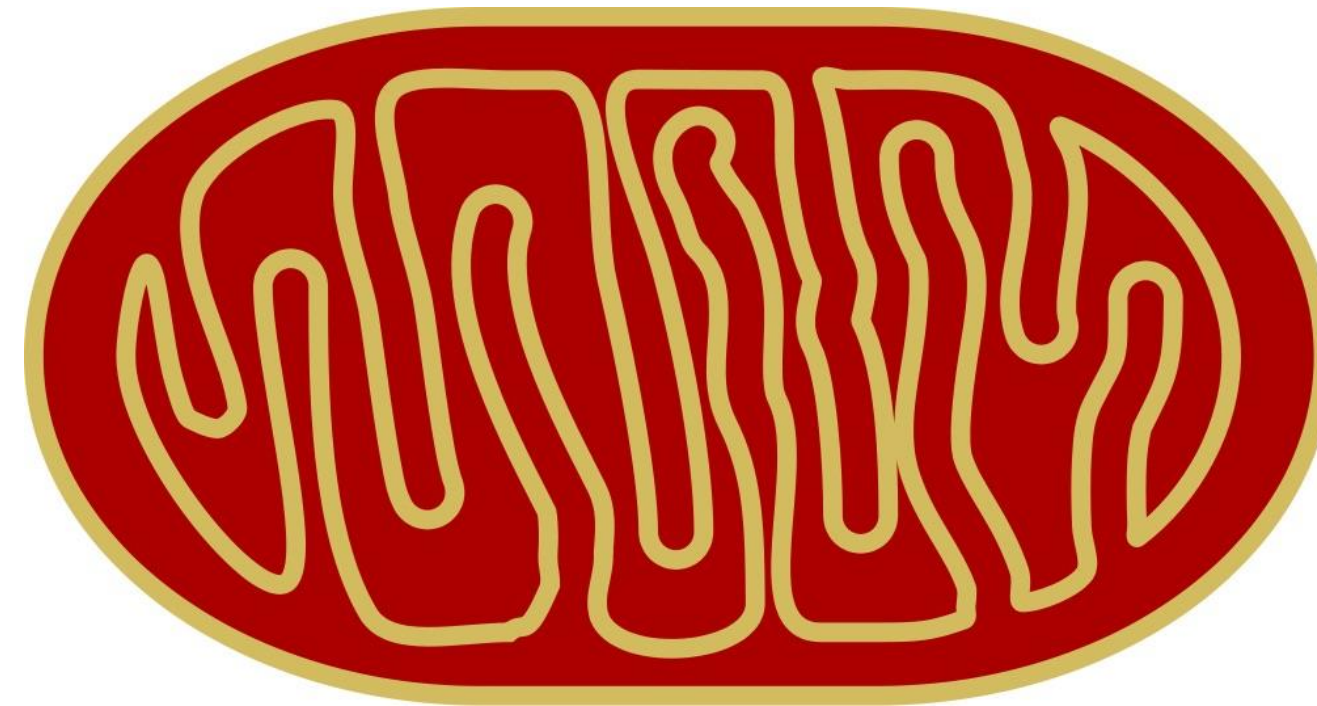
[Cell](#)
Vol166 Issue 3

555–566,
28 July 2016

- CELL DEATH
- SIGNALING
- BIOGENESIS & TURNOVER
- FISSION & FUSION
- METABOLISM & BIOENERGETICS
- OXIDATIVE STRESS



Chemoprevention by Promotion of Apoptosis



Bcl-2

p53

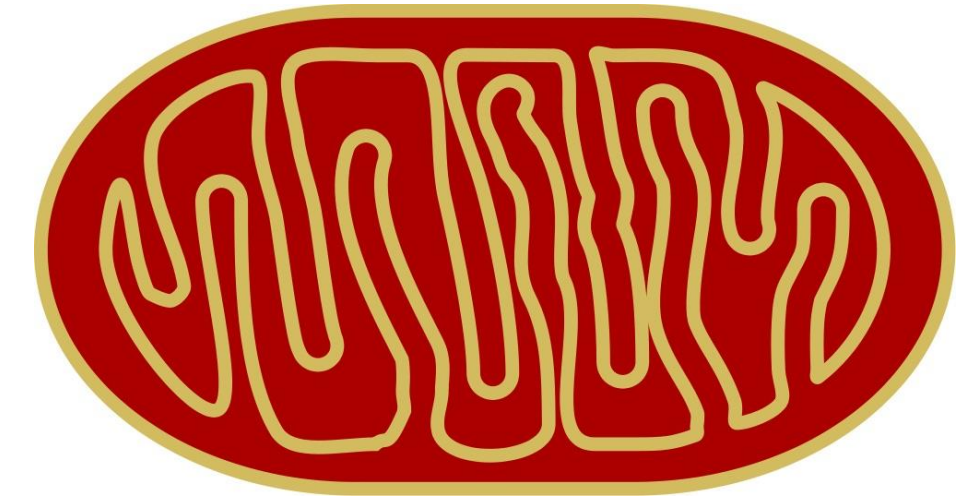
Induction of apoptosis is the key for successful tumor regression or elimination of abnormal

HK-2

miRNA

Curcumin Induces Apoptosis of Upper Aerodigestive Tract Cancer Cells by Targeting Multiple Pathways
[A. R. M. Ruhul Amin](#) et al [PLoS One](#). 2015; 10(4): e0124218.

Chemoprevention by Promotion of Apoptosis



The initiation of the apoptotic process directly determines the 'fate' of the cell

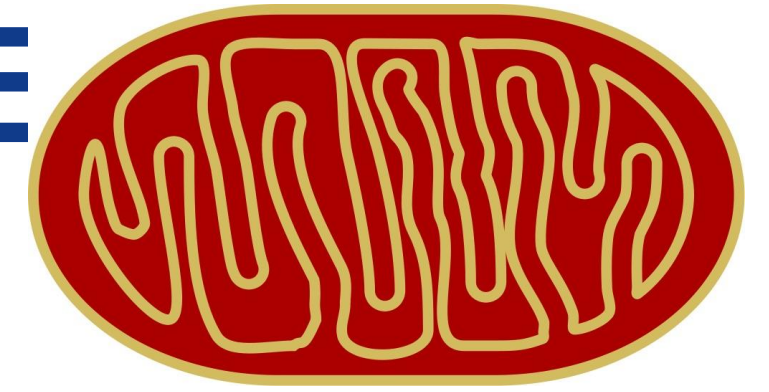
Cancer cells have hyperpolarized mitochondrial membranes compared to normal cells, preventing them from throwing the apoptotic off-switch no matter how old or mutated they become.

Lemasters JJ, et al E. Voltage-dependent anion channel (VDAC) as mitochondrial governor—thinking outside the box. *Biochim Biophys Acta.* 2006 Feb;1762(2):181-90.

HALLMARK OF CANCER: APOPTOSIS RESISTANCE

ESCAPE of PROGRAMMED CELL DEATH

OVEREXPRESSION of ANTI-APOPTOTIC PROTEIN Bcl-2



The initiation of the apoptotic process directly determines the 'fate' of the cell

In 371 cases of breast cancer a positive expression of Bcl-2 is as high as 79.3%

Normal cells undergo a spontaneous death process known as apoptosis, which includes mitochondrial regulation.

This process is active, highly ordered, signal-dependent, and controlled by genes and a series of enzymes.

A high expression of the Bcl-2 gene maintains cell survival.

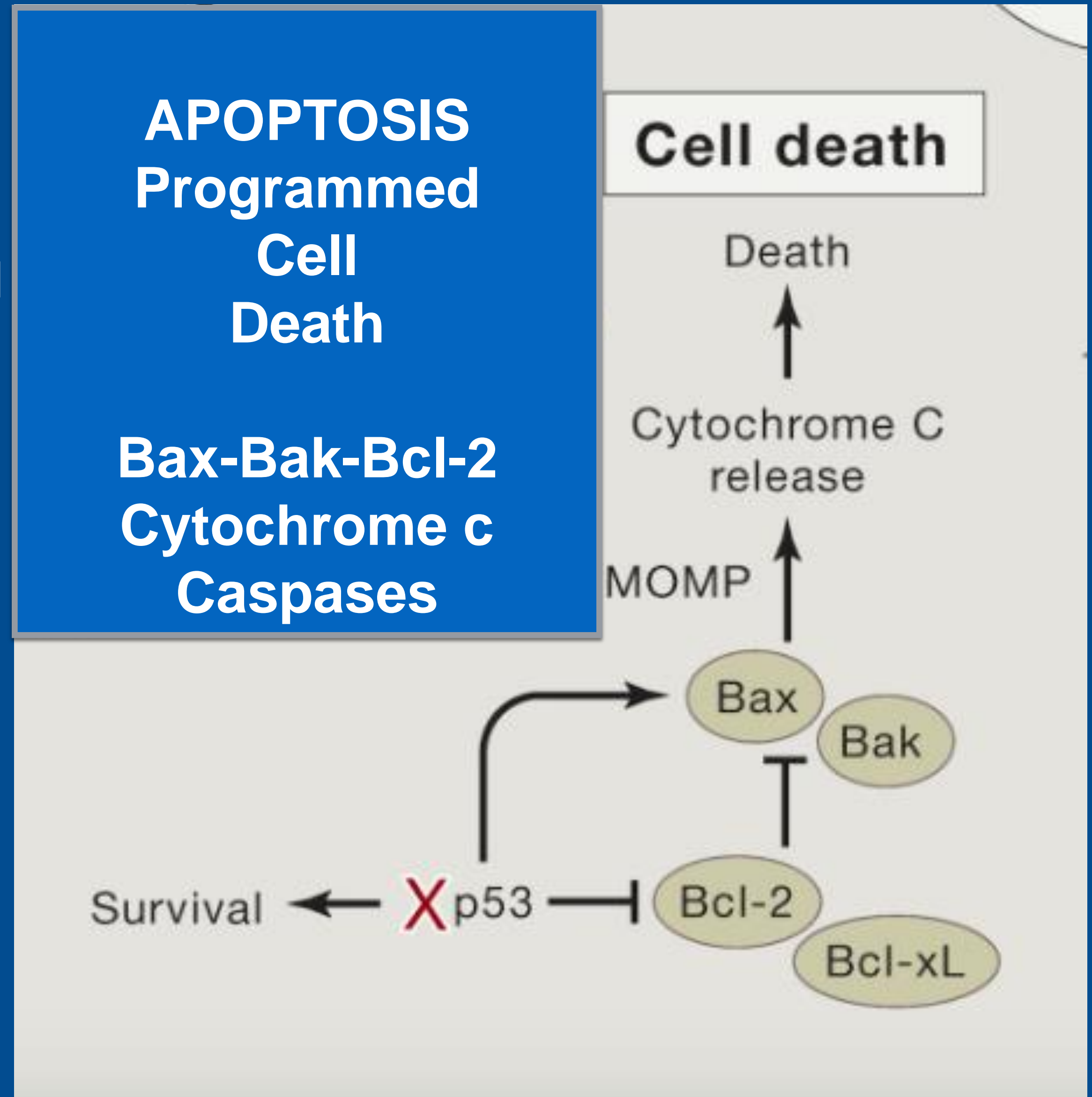
The main physiological function of the Bcl-2 protein is inhibition of apoptosis, thereby prolonging the life of cells

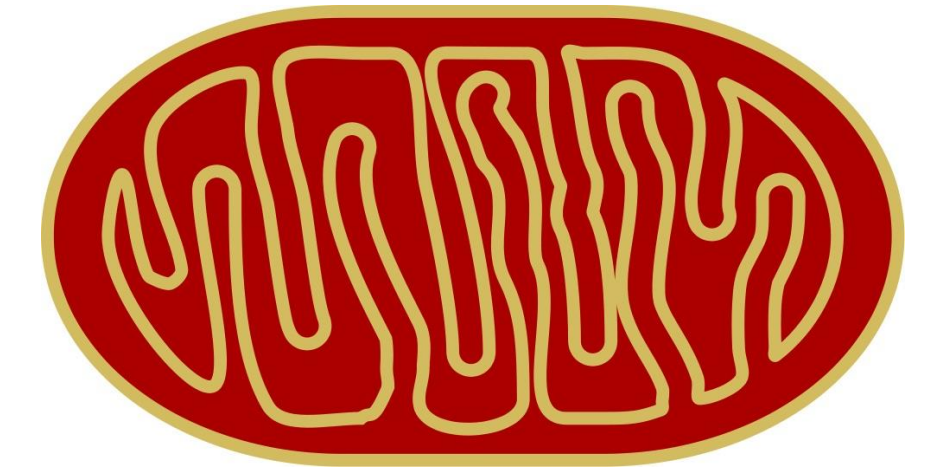
A Hallmark of Cancers is their ability to Evade Cell Death, a phenomenon tightly linked to mitochondria.

The pro-apoptotic Bcl-2 family members Bax and Bak are recruited to the OMM and oligomerize to mediate Mitochondrial Outer Membrane Permeabilization (MOMP)

resulting in Pore Formation and Cytochrome c Release from mitochondria into the cytosol to Activate Caspases, the executors of programmed cell death.

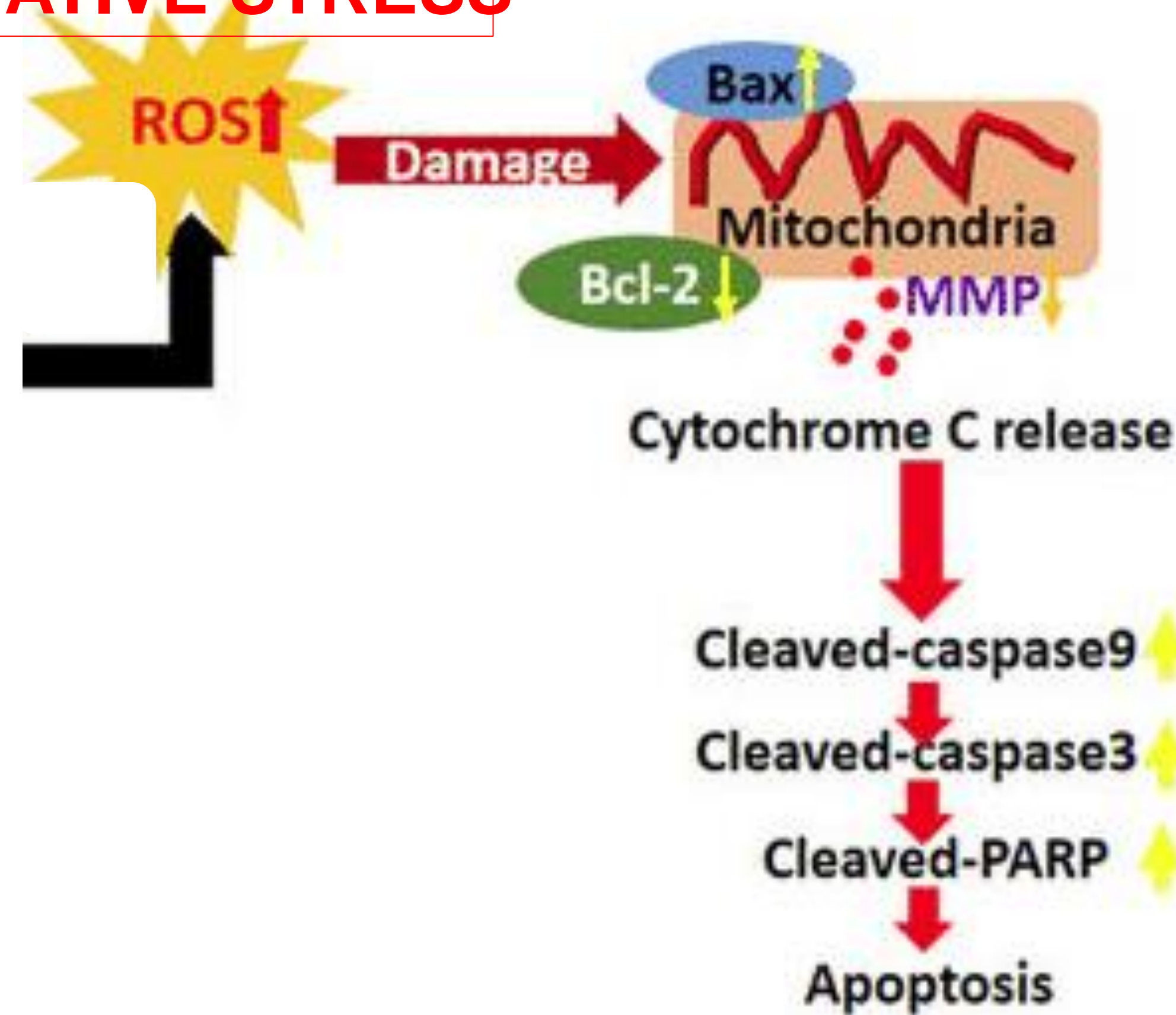
Tumor cells escape apoptosis by downregulating pro-apoptotic Bcl-2 genes and/or upregulating anti-apoptotic Bcl-2 genes





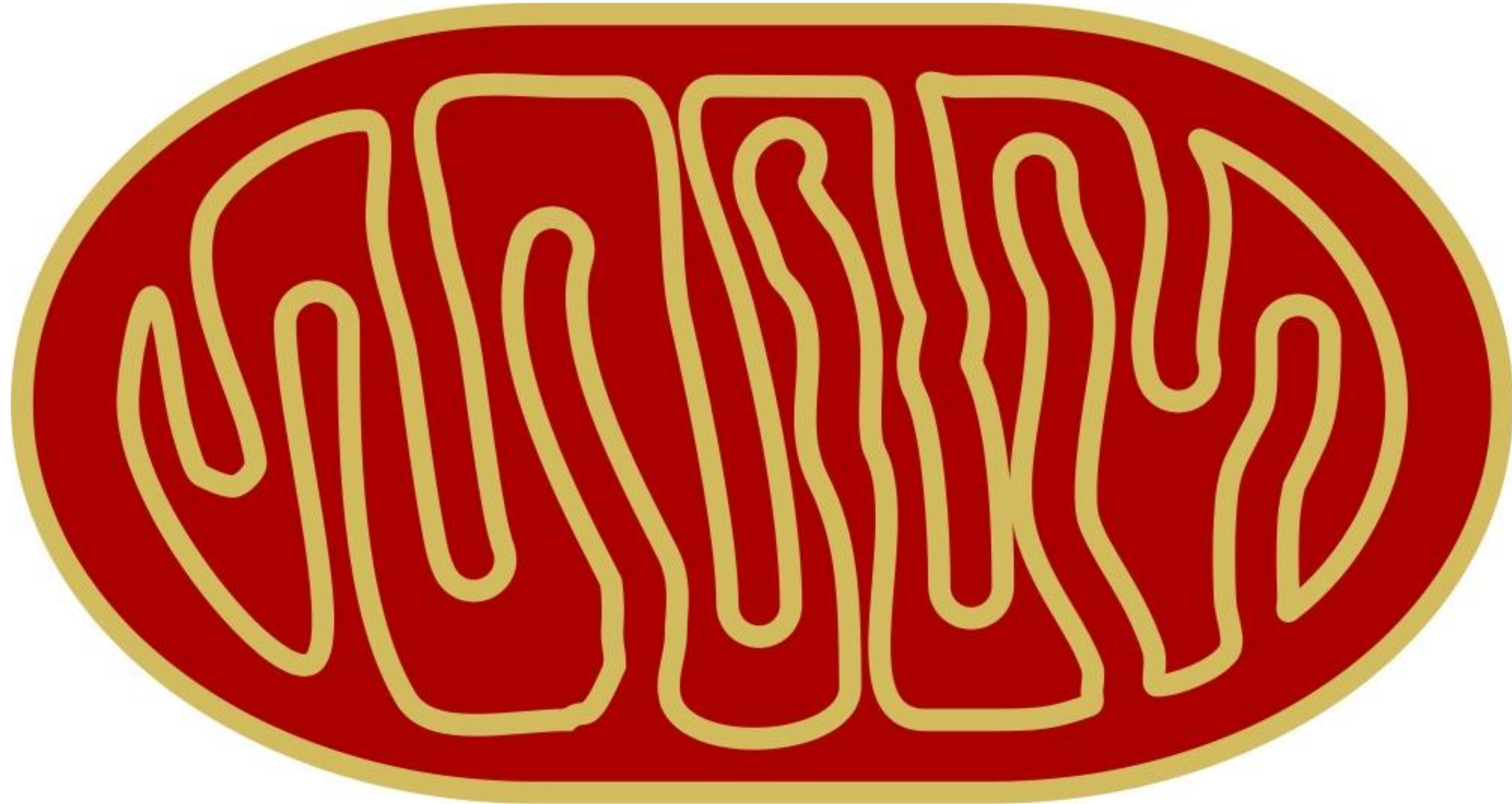
OXIDATIVE STRESS

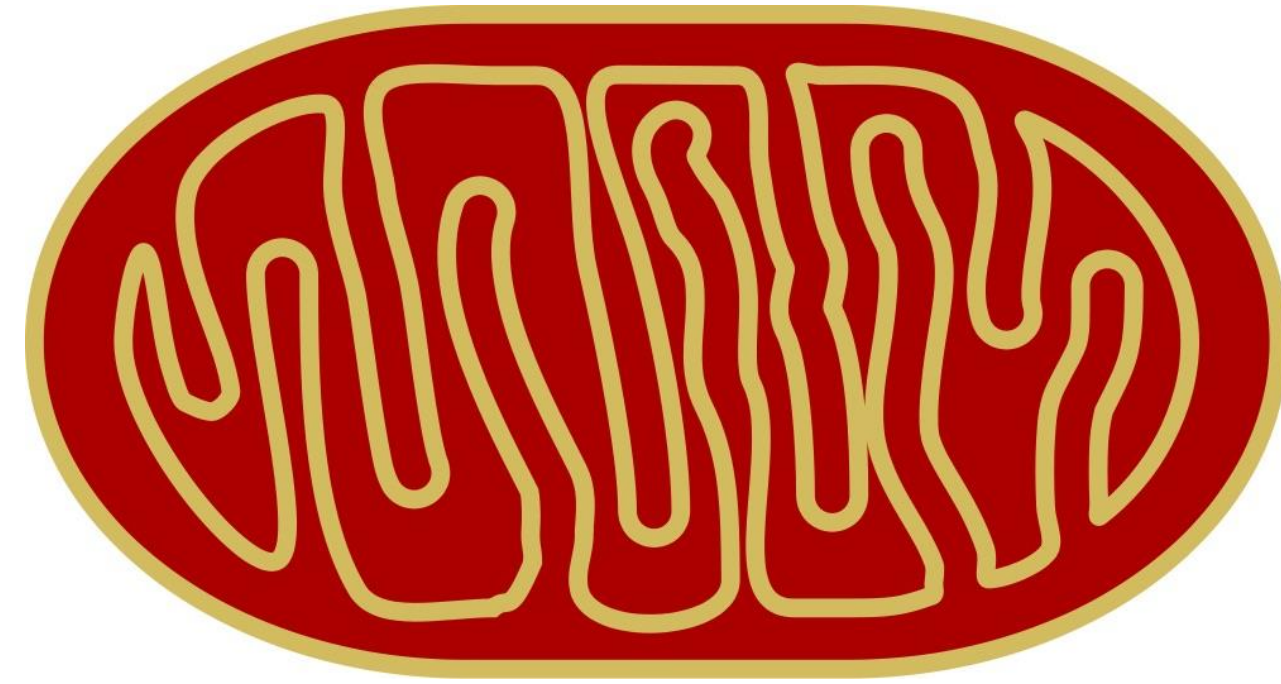
**NORMAL
APOPTOTIC
SIGNALLING**
in response to
**INCREASED
OXIDATIVE
STRESS**



CELL DEATH

MODULATION OF MITOCHONDRIAL-DEPENDENT APOPTOSIS PATHWAYS BY NATURAL COMPOUNDS





**High levels of mutated Bcl-2 are associated
with most types of human cancer**

**Overexpression of Bcl-2 prevents efflux of cytochrome c
from the mitochondria and the initiation of apoptosis.**

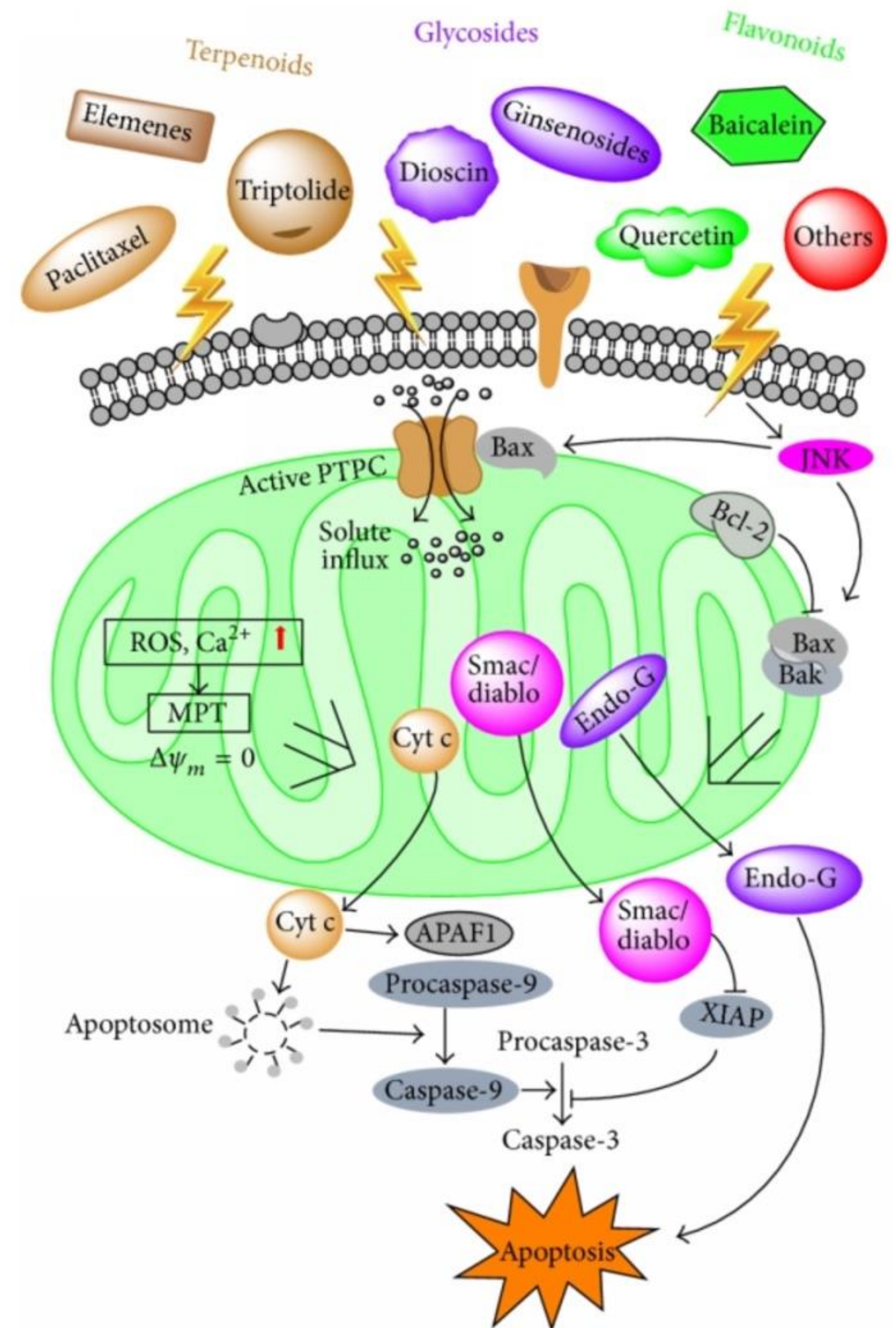
Prevention of Apoptosis by Bcl-2: Release of Cytochrome c from Mitochondria Blocked

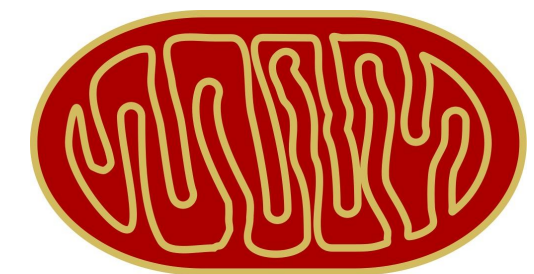
Jie Yang, et al *Science* 21 Feb 1997: Vol. 275, Issue 5303, pp. 1129-1132

Modulation of mitochondrial-dependent apoptosis pathways by natural compounds

Bioactive compounds can act on mitochondria to trigger the permeabilization of the mitochondrial outer membrane and lead to the impairment of the mitochondria, including the alteration of electron transport, the loss of mitochondrial transmembrane potential, and the cytosolic release of apoptotic proteins such as

cytochrome c
Evidence-based Complementary and Alternative
Medicine 2015(5):1-14 · November 2015





Phytochemicals in Foods and Spices that Promote Normal Apoptosis by inhibition of Bcl-2

Modulation of Apoptosis in Colon
Cancer Cells by Bioactive Compounds
<http://dx.doi.org/10.5772/63382>



Garlic
Parsley
Celery
Broccoli
Kale
Tumeric
Ginger
Rosemary
Oregano
Cayenne



**Red & Purple
grapes**
Red Onions
Red Apples
Pomegranate
Red Berries
Blackberries
Blueberries
Green Tea
Soybeans

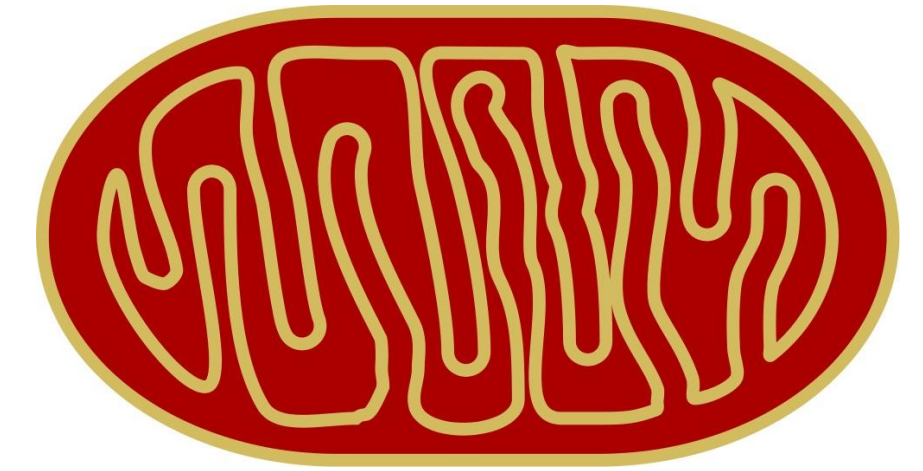


Alicillin
Apigenin
Carnosol
Sulphoraphanes
I3C
Curcumin
Gingerol
Chrysin

EGCG
Resveratrol
Pterostilbene
Quercetin
Genestein
Capsaicin
Gallic acid



Botanicals that Promote Normal Apoptosis by inhibition of Bcl-2



Rhizoma Curcuma longa

Rdx Panax ginseng

Polygonum cuspidatum

Rabdosia rubescens

Camelia sinensis

Cortex Magnolia

Andrographis paniculatus

Ctx-Tips Taxus brevifolia

Rdx Scutellaria baicensis

Rdx Salvia miltiorrhiza

Rdx Dioscorea spp

Rdx Salvia miltiorrhiza

Ganoderma lucidum

Pleurotus pulmonaris

Inontus obliquus

Rosmarinus officinalis

Tanacetum parthenium

Tababueia spp.

Rz Zingiber off,

Withania somnifera

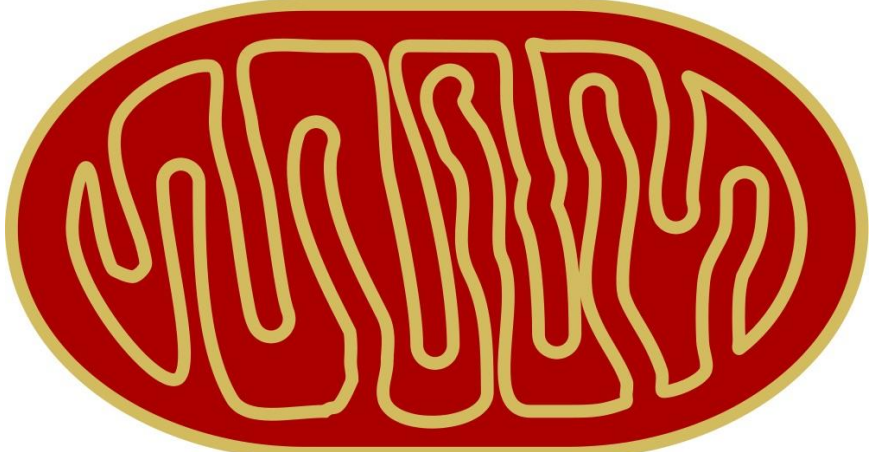
Berberis vulgaris

Coptis chinensis

Viscum album



Nutriceutical Supplements that Promote Normal Apoptosis by inhibition of Bcl-2



Curcumin



EGCG



Quercetin

Resveratrol



Berberine



Pterostilbene



Tanshinone

Honokiol

Reishi mushroom

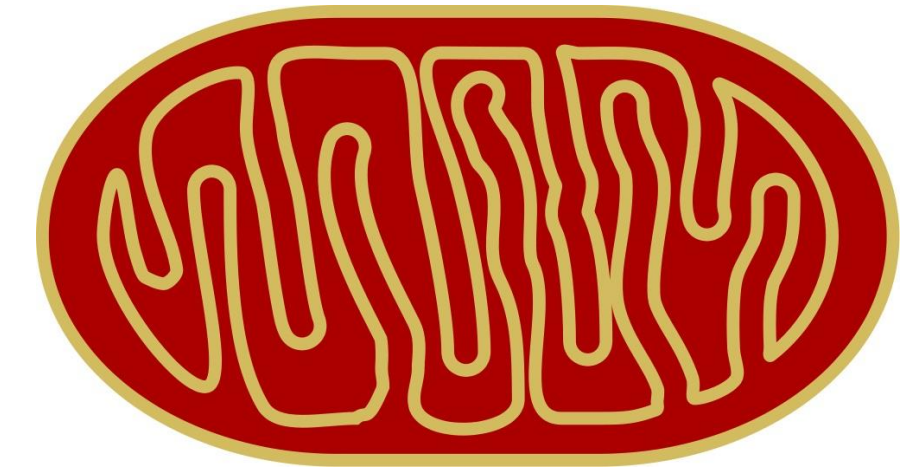
Indole-3-Carbinol



**500-1000mg
tid**

Polygonatum odoratum and apoptosis

Solomon's Seal 1-3g tid



- Downregulation of Bcl-2 and upregulation of Bax
- Increase in the ratio of apoptotic breast cancer cells

The majority of tumors develop drug resistance
Adequately sensitive apoptosis cannot be induced

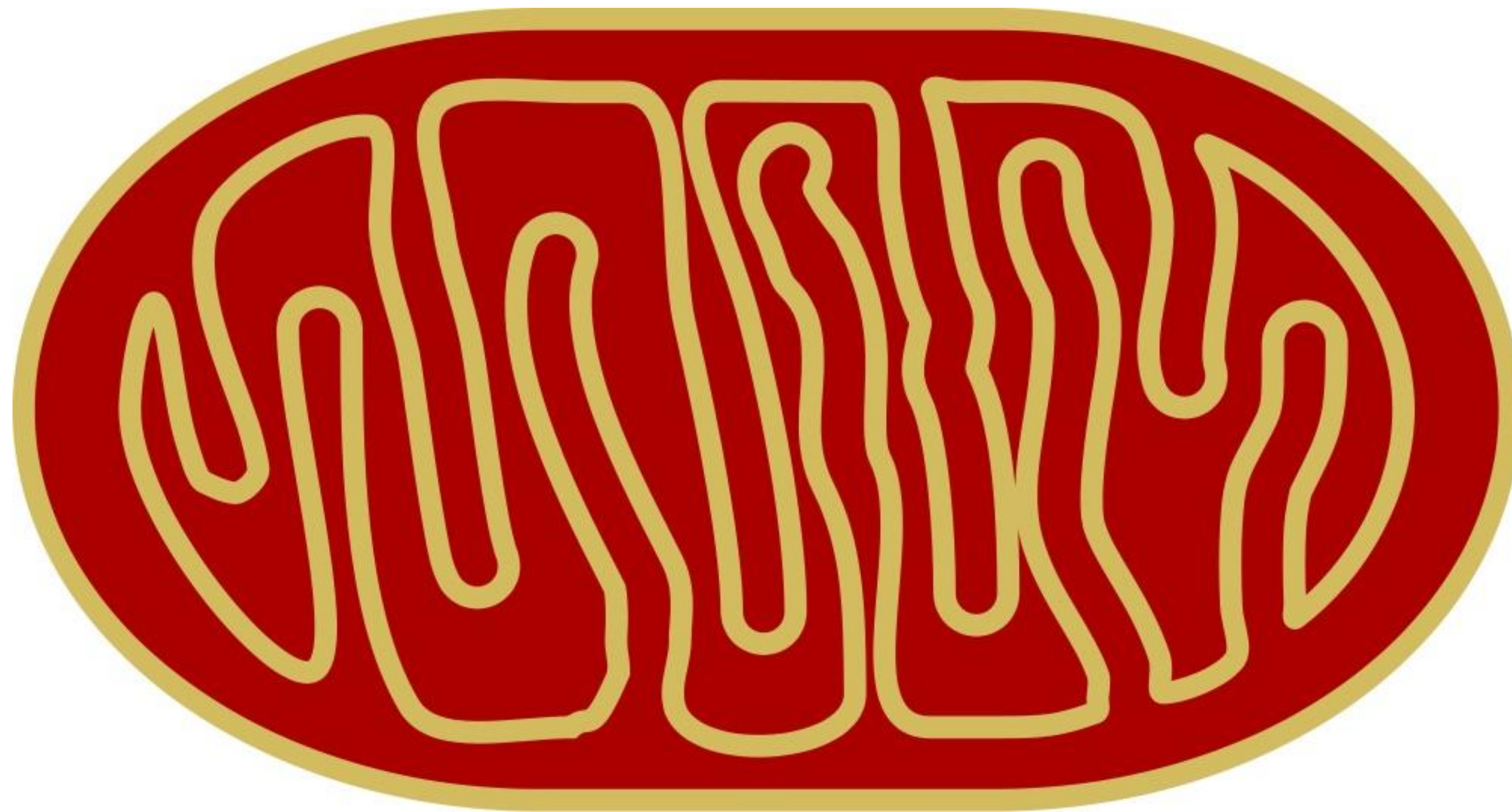


Effect of *Polygonatum odoratum* extract on human breast cancer MDA-MB-231 cell proliferation and apoptosis EXPERIMENTAL AND THERAPEUTIC MEDICINE 12: 2681-2687, 2016 YU TAI et al

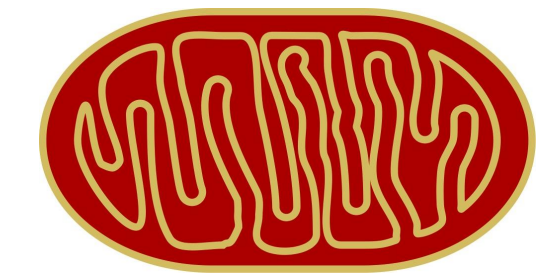
Role of caspases, Bax and Bcl-2 in chrysin-induced apoptosis in the A549 human lung adenocarcinoma epithelial cells.

- Chrysin treatment resulted in the activation of caspase-3 and -9 and an increase in the Bax/Bcl-2 ratio ($p < 0.01$).
- Bax protein expression was increased but Bcl-2 protein expression decreased in chrysin-treated cells
- Chrysin inhibits the growth of the lung cancer cells by **inducing cancer cell apoptosis via the regulation of the Bcl-2 family and also activation of caspase-3 and -9**, which may, in part, explain its anticancer activity.

APOPTOSIS INDUCED BY DEPOLARIZATION of MITOCHONDRIAL MEMBRANE



URSOLIC ACID PROMOTES APOPTOSIS



Oldenlandia diffusa Bai Hua She She Cao and Holy Basil Ocimum sanctum Tulsi

URSOLIC ACID caused depolarization of mitochondrial membrane potential, cell arrest in G0/G1 phase and apoptosis/necrosis in a dose-dependent manner.

[Sci Rep.](#) 2014 May 21;4:5006. Synergism of ursolic acid derivative US597 with 2-deoxy-D-glucose to preferentially induce tumor cell death by dual-targeting of apoptosis and glycolysis. [Wang J et al](#)

URSOLIC ACID promoted apoptosis was associated with the depolarization of mitochondrial membrane potential.

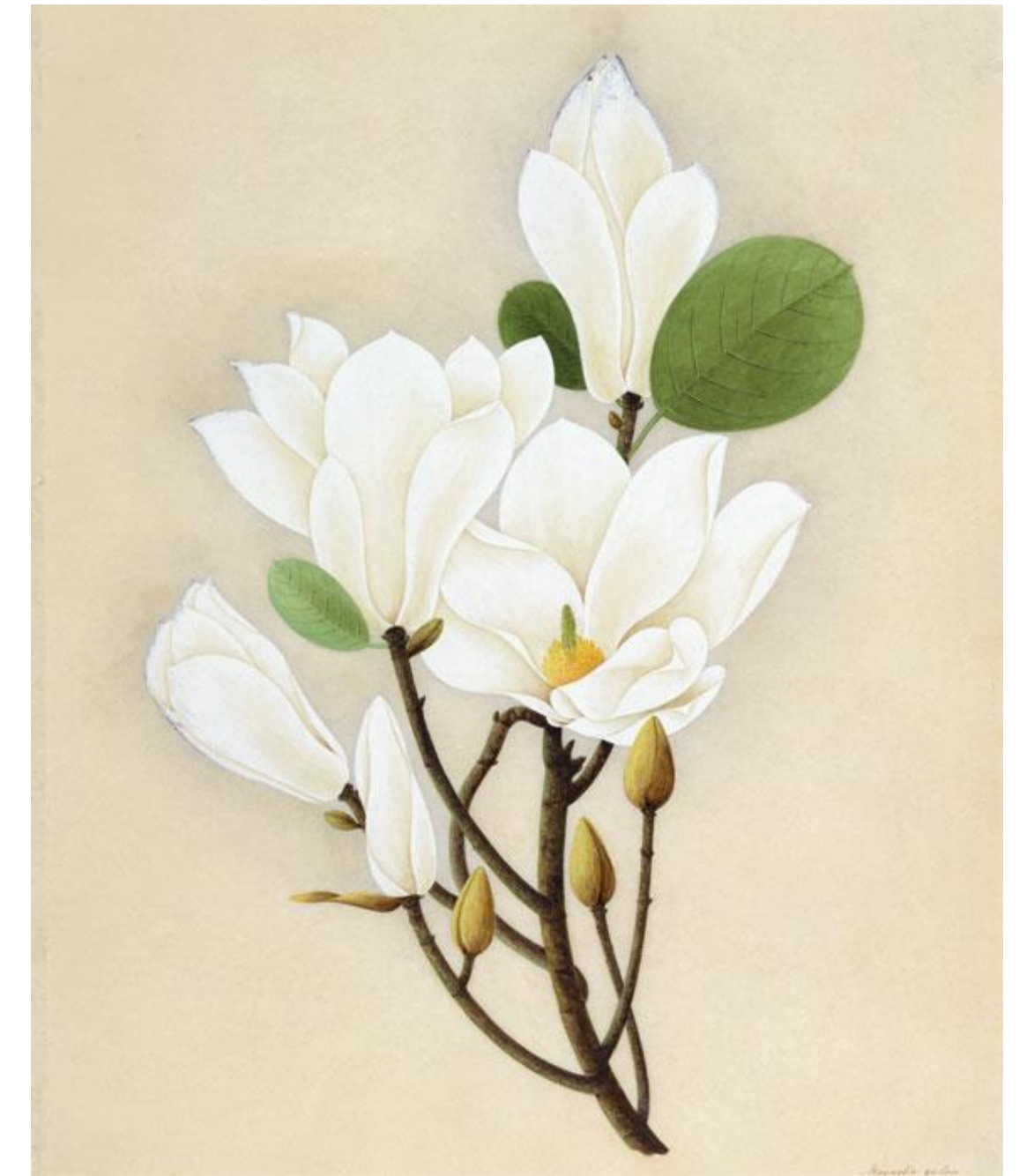
[Apoptosis.](#) 2017 Jun;22(6):800-815. Ursolic acid-mediated changes in glycolytic pathway promote cytotoxic autophagy and apoptosis in phenotypically different breast cancer cells. [Lewinska A et al](#)

[PLoS One.](#) 2013 May 30;8(5):e63872. Ursolic acid simultaneously targets multiple signaling pathways to suppress proliferation and induce apoptosis in colon cancer cells. Wang J et al



Honokiol inhibits lung tumorigenesis through inhibition of mitochondrial function.

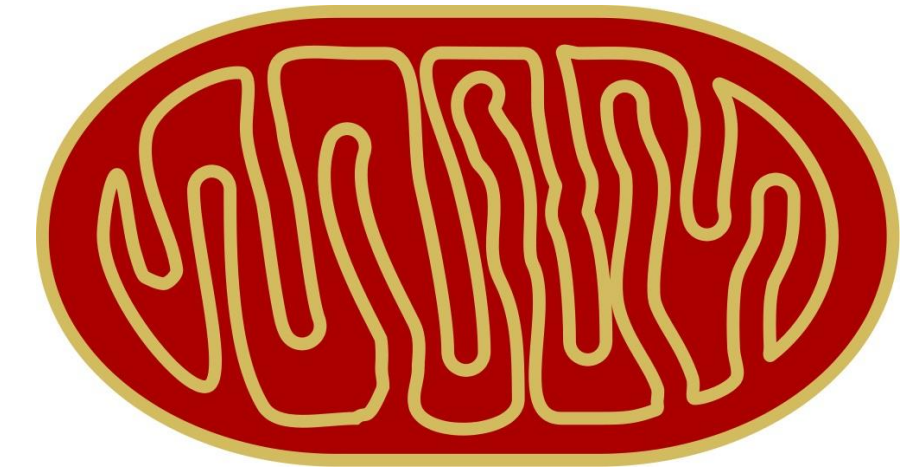
- **ANTI-APOPTOTIC.** Triggers apoptosis by interfering with mitochondrial respiration and redox status
- **CHECKPOINT INHIBITION,** arresting cell cycle
- **REDUCES PROLIFERATION** of cells in vitro



Pan J, Zhang Q, Liu Q, Komasa SM, Kalyanaraman B, Lubet RA, Wang Y, You M. [Honokiol inhibits lung tumorigenesis through inhibition of mitochondrial function.](#) *Cancer Prev Res (Phila)*. 2014 Nov;7(11):1149-59

Honokiol, a multifunctional tumor cell death inducer.
Tian W, et al. *Pharmazie*. 2012 Oct;67(10):811-6

INDOLE 3 CARBINOL Promotes APOPTOSIS



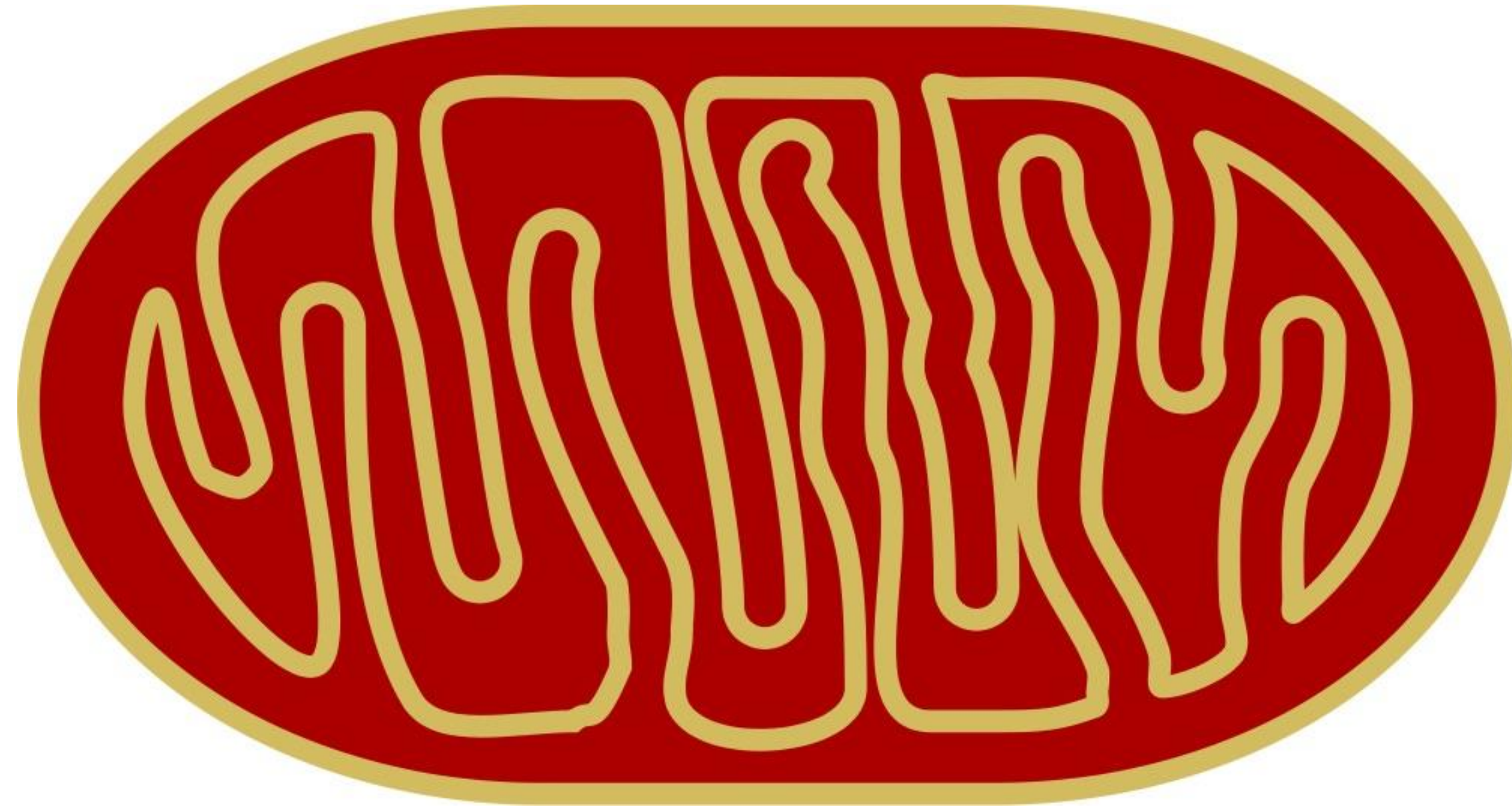
Indole-3-carbinol has a potent effect on upregulation of Bax in mitochondria, causing membrane depolarization and activation of

Cruciferous vegetables: cauliflower, cabbage, broccoli, broccoli sprouts, kale+

Rahman KM, Aranha O, Glazyrin A, Chinni SR, Sarkar FH. **Translocation of Bax to mitochondria induces apoptotic cell death in indole-3-carbinol (I3C) treated breast cancer cells.** *Oncogene*. 2000 Nov 23;19(50):5764-71.

Rahman KM, Aranha O, Sarkar FH. **Indole-3-carbinol (I3C) induces apoptosis in tumorigenic but not in nontumorigenic breast epithelial cells.** *Nutr Cancer*. 2003;45(1):101-12.

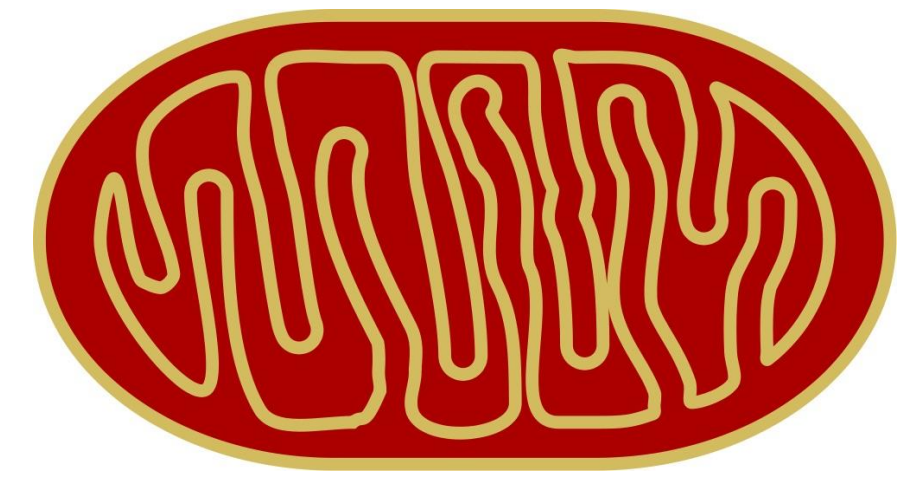
TUMOR SUPPRESSOR GENE p53 GUARDIAN of the GENOME



p53 is inhibited in a vast majority of cancers

Tumor Suppressor p53

Induces Apoptosis in Response to Stress



- **Commonly mutated tumor suppressor gene**
- **Transcriptional regulation of cell cycle and apoptotic genes**
- **Directly functions at the mitochondria to induce apoptosis in response to stress**
- **Interacts with Bcl-2 to trigger MOMP mitochondrial outer membrane permeabilization**
- **Upregulates synthesis of Cytochrome c**

Upon activation, p53 leads to cell-cycle arrest and promotes DNA repair or induces apoptosis

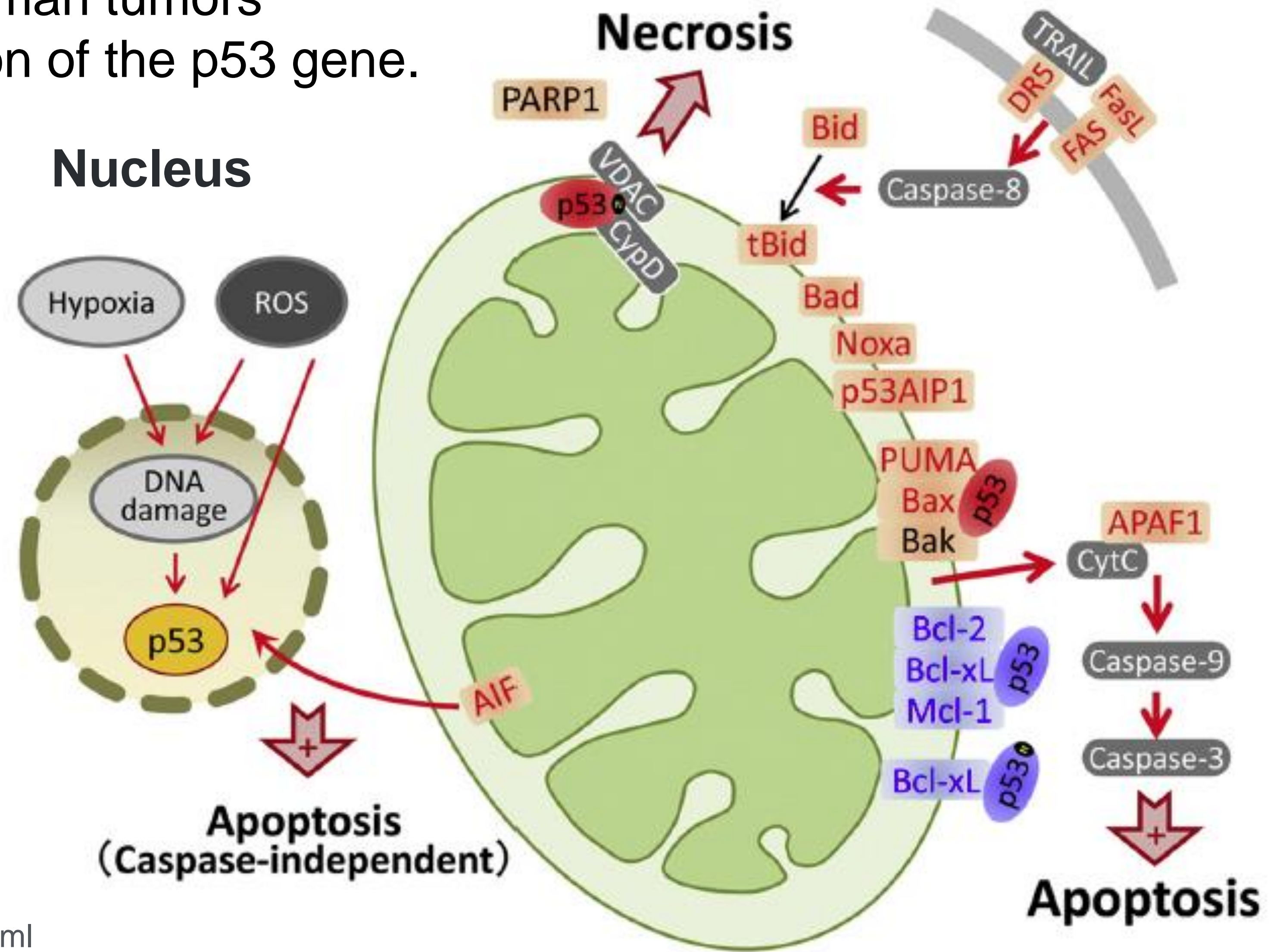
Loss of wild-type p53 function is often associated with aggressive tumor growth, poor prognosis, and resistance to chemotherapy.

Restoration of p53 function in mice suffering from lymphomas or sarcomas has been shown to induce tumor regression

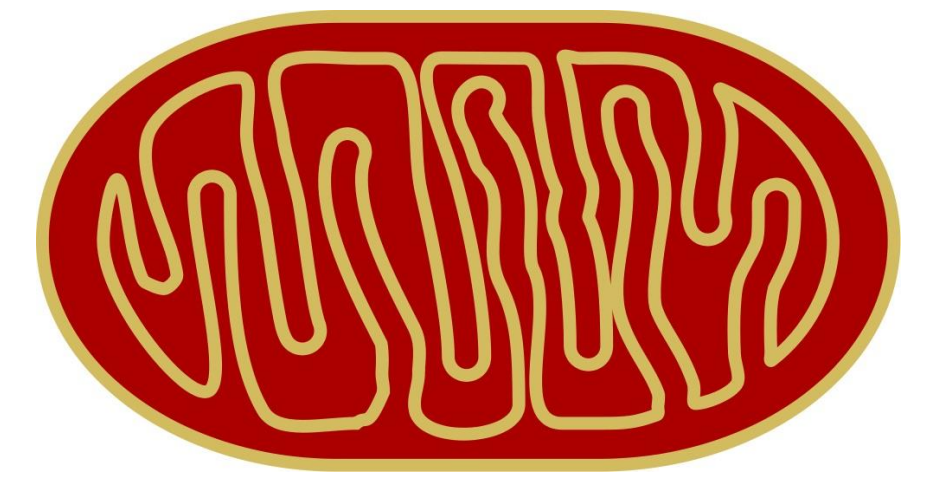
Front. Oncol., 21 October 2014 p53 family and cellular stress responses in cancer J Pflaum et al

More than **50 percent** of human tumors contain a mutation or deletion of the p53 gene.

APOPTOSIS p53 Nuclear & Mitochondrial Signaling



Natural Compounds that Normalize p53 Function



Rhizoma Curcuma longa

Curcumin



Rdx Panax ginseng

Ginsenosides



Polygonum cuspidatum

Resveratrol

5-Methyl-Tetrahydrofolate

Rabdosia rubescens

Oridonin

Tocotrienols

Camelia sinensis

EGCG

Vitamin E Succinate



Rz Zingiber off,

6-Gingergol

Withania somnifera

Withanone

Rehmannia glutinosa

Polysaccharides

Ganoderma lucidum

Ganodermic acid

Coriolus versicolor

Polysaccharides

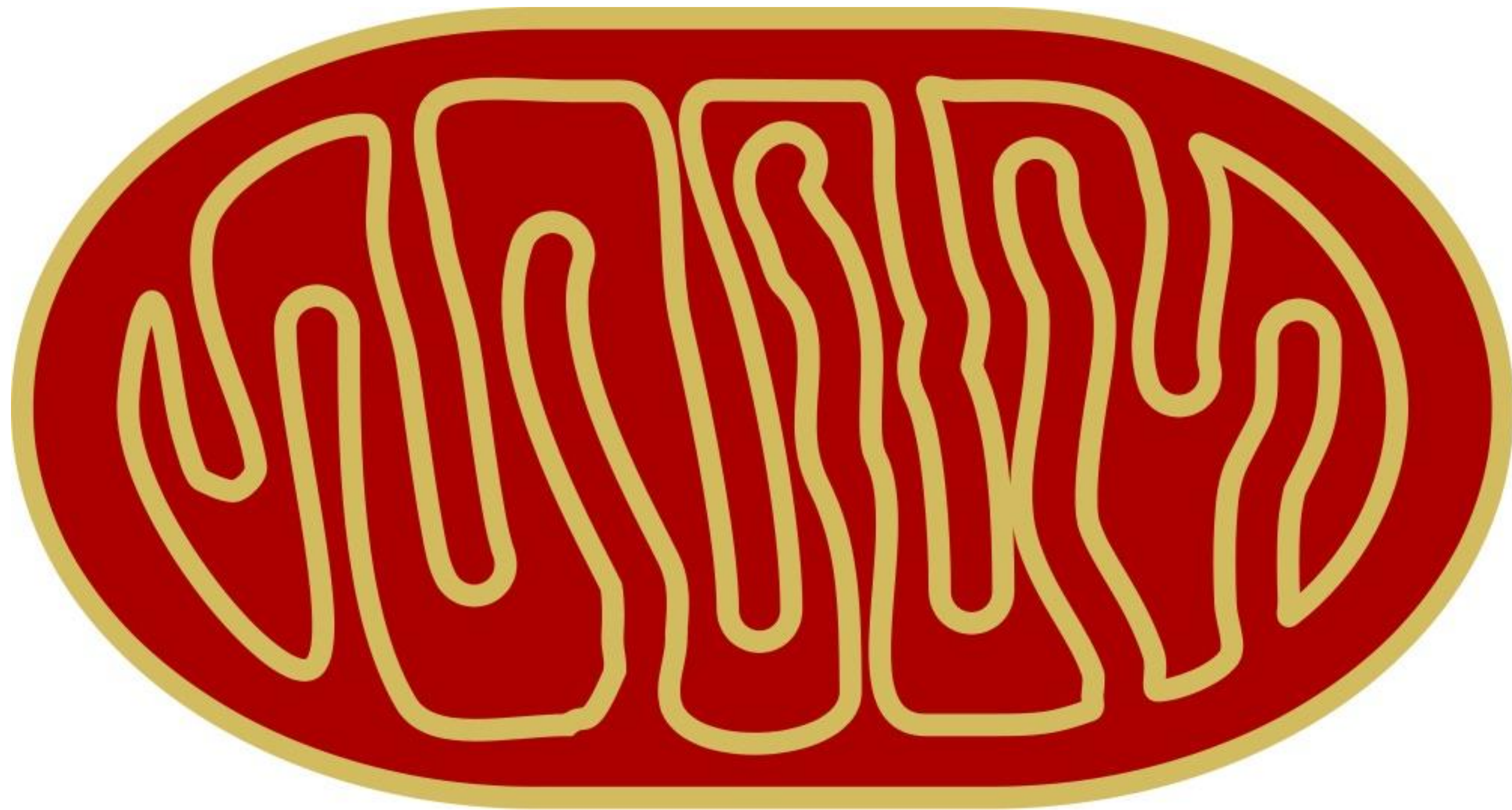
Coptis chinensis

Berberine



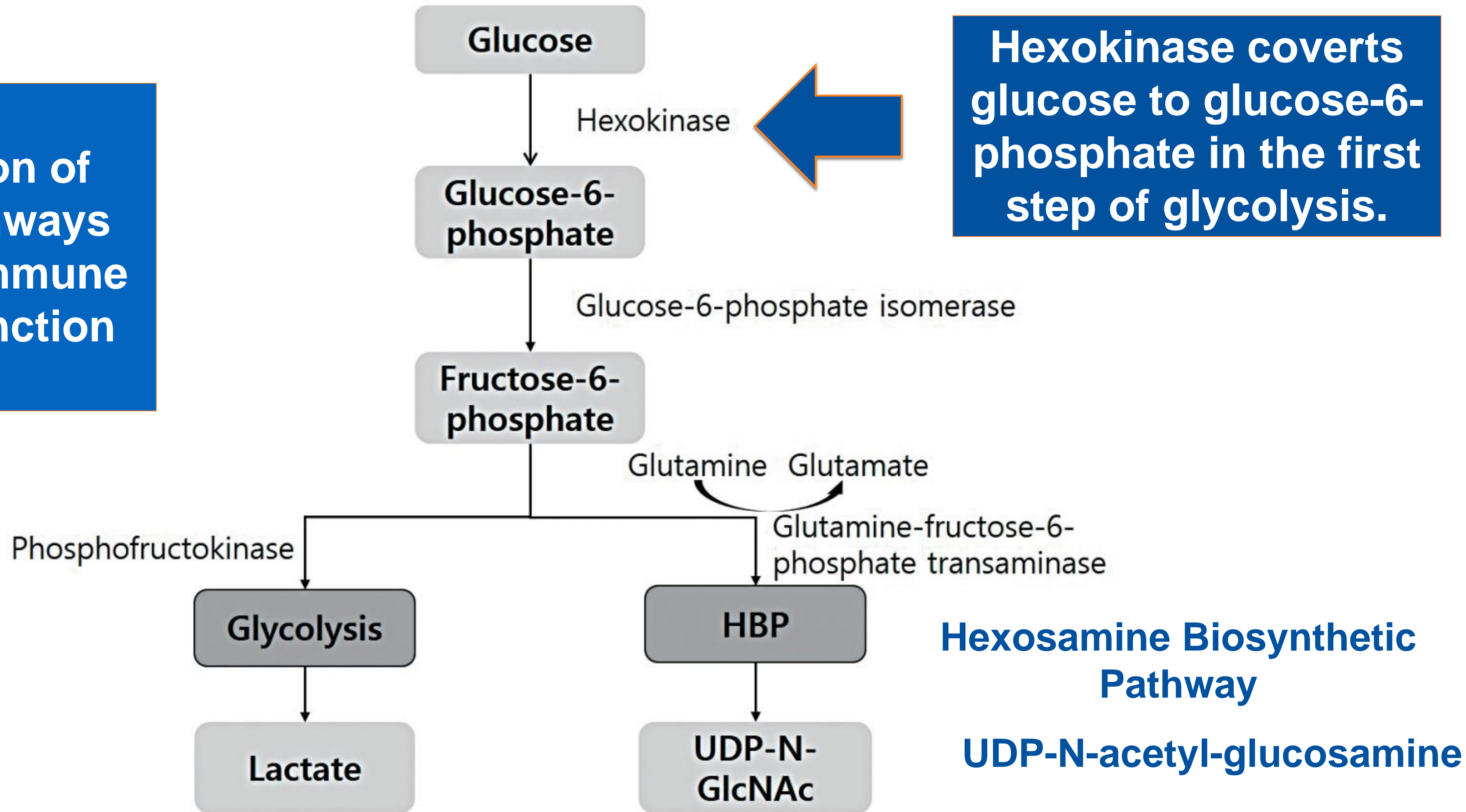
From Donald Yance, CNH

APOPTOSIS | HEXOKINASE 2



Modulation of these pathways can alter immune system function

Hexokinase converts glucose to glucose-6-phosphate in the first step of glycolysis.



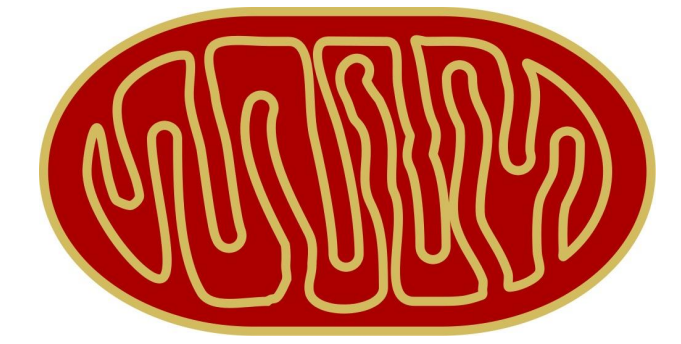
Hexokinase II–derived cell-penetrating peptide targets mitochondria and triggers apoptosis in cancer cells

HK II depolarized mitochondrial membrane potential, inhibited mitochondrial respiration and glycolysis, and depleted intracellular ATP levels.

Promoted release of Cytochrome c and Triggered Apoptosis

[Abiy D. Woldetsadik](#), et al [FASEB J.](#) 2017 May; 31(5): 2168–2184.

Curcumin inhibits aerobic glycolysis and induces mitochondrial-mediated apoptosis through hexokinase II in human colorectal cancer cells in vitro. [Wang K et al](#)

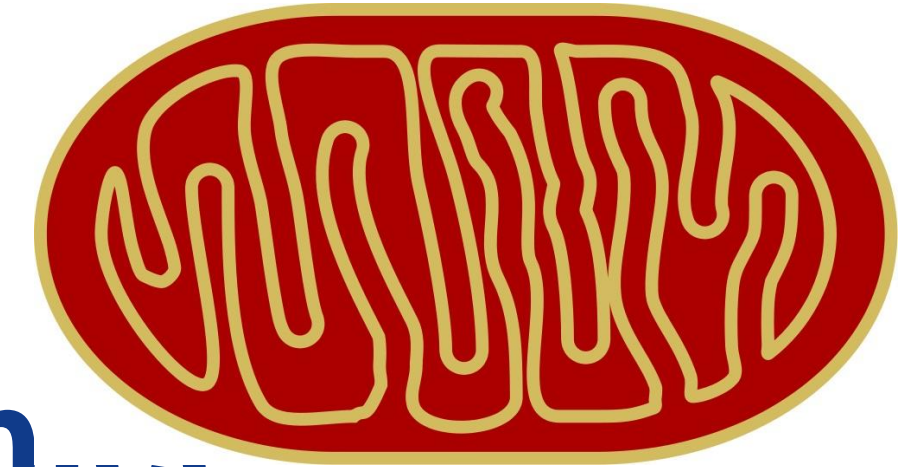


- Important implications for the metabolism reprogramming effect and the susceptibility to curcumin-induced mitochondrial cytotoxicity through the regulation of HKII
- Downregulated the expression and activity of hexokinase II (HKII) in a concentration-dependent manner
- Induced dissociation of HKII from the mitochondria,



[Oncotarget](#). 2015 May 30;6(15):13703-17. Dai, W et al

By reducing hexokinase 2, Resveratrol induces apoptosis in HCC cells addicted to aerobic glycolysis and inhibits tumor growth in mice.



Resveratrol sensitized aerobic glycolytic HCC cells to apoptosis

Induction of mitochondrial apoptosis was associated with the decrease of HK2 expression by Resveratrol



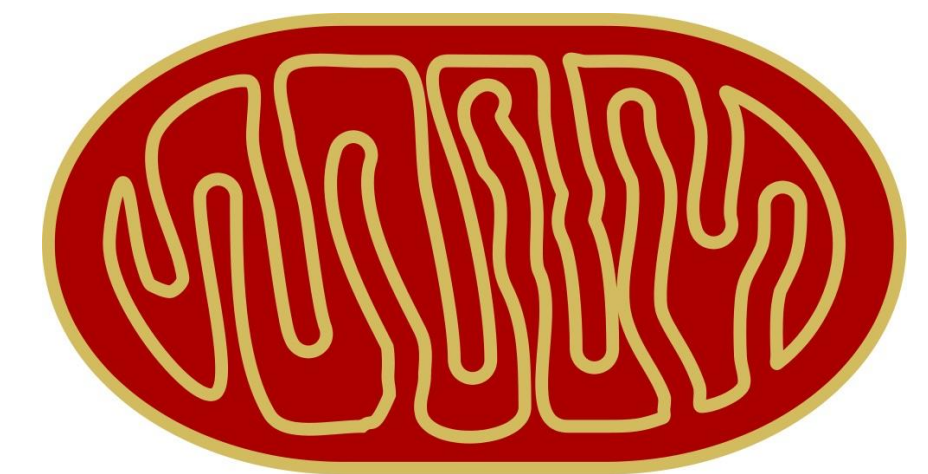
1-4 grams per day

Chrysin flavone inhibited tumor glycolysis and induced apoptosis in hepatocellular carcinoma by targeting hexo

Honey. PROPOLIS Passiflora spp

500-1000mg
tid

- Chrysin is a natural flavone found in plant extracts
- HK-2 expression was substantially elevated in the majority of tumor cell lines and tumor tissue
- **After chrysin treatment, HK-2 on mitochondria significantly declined, resulting in the transfer of Bax (PRO APOPTOTIC) from cytoplasm to mitochondria and induction of cell apoptosis**
- **Chrysin suppressed glycolysis and induced apoptosis**



Polygonatum cyrtonema (Solomon's Seal. Yu Zhu)



lectin, a potential antineoplastic drug

targeting programmed cell death pathways

Polygonatum cyrtonema lectin (PCL), a mannose/sialic acid-binding plant lectin, has recently drawn a rising attention for cancer biologists because PCL bears remarkable anti-tumor activities and thus inducing programmed cell death (PCD) including apoptosis and autophagy in cancer cells. In this review, we focus on exploring the precise molecular mechanisms by which PCL induces cancer cell apoptotic death such as the caspase-dependent pathway, mitochondria-mediated ROS-p38-p53 pathway, Ras-Raf and PI3K-Akt pathways. In addition, we further elucidate that PCL induces cancer cell autophagic death via activating mitochondrial ROS-p38-p53 pathway, as well as via blocking Ras-Raf and PI3K-Akt pathways, suggesting an intricate relationship between autophagic and apoptotic death in PCL-induced cancer cells. In conclusion, these findings may provide a new perspective of Polygonatum cyrtonema lectin (PCL) as a potential anti-tumor drug targeting PCD pathways for future cancer

Polygonatum (Solomon's Seal Yu Zhu) and Hexokinase II Lectin PCL inhibits the Warburg effect of PC3 cells by combining with EGFR & inhibiting HK2.

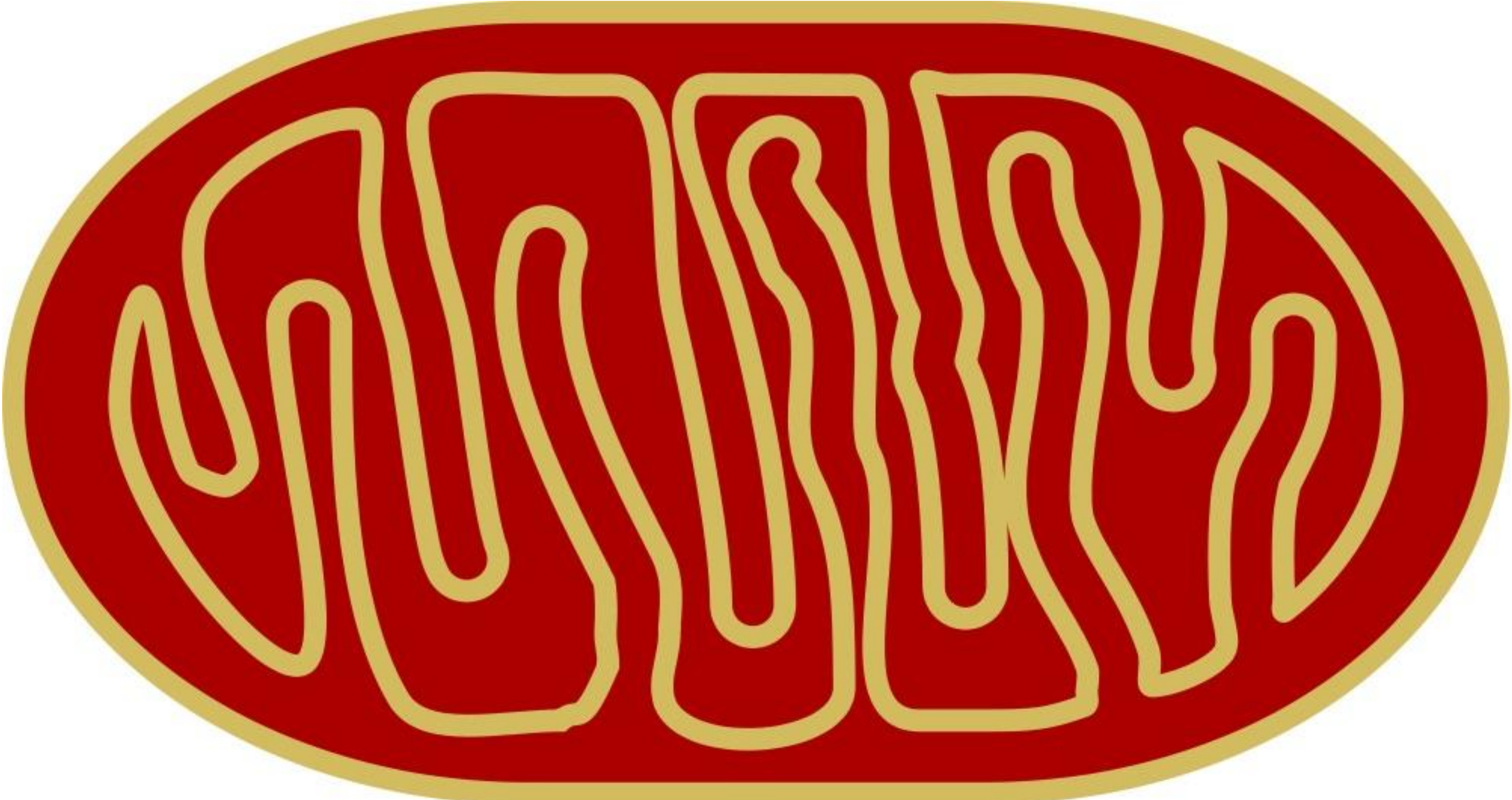


Hexokinase 2 (HK2), a major rate-limiting enzyme involved in Warburg effect, is selectively upregulated.

The lectin PCL (Polygonatum lectin) could lower glucose consumption and lactate production, shift the Warburg effect by inhibiting the expression of HK2 in Prostate cancer

Zhang, Du, Sun, et al., *Lectin PCL Inhibits the Warburg Effect of PC3 Cells by Combining with EGFR and Inhibiting HK2*, *Oncol. Rep.* 2017 Jan. 16, DOI: [10.3892/or.2017.5367](https://doi.org/10.3892/or.2017.5367). PMID: 28098871

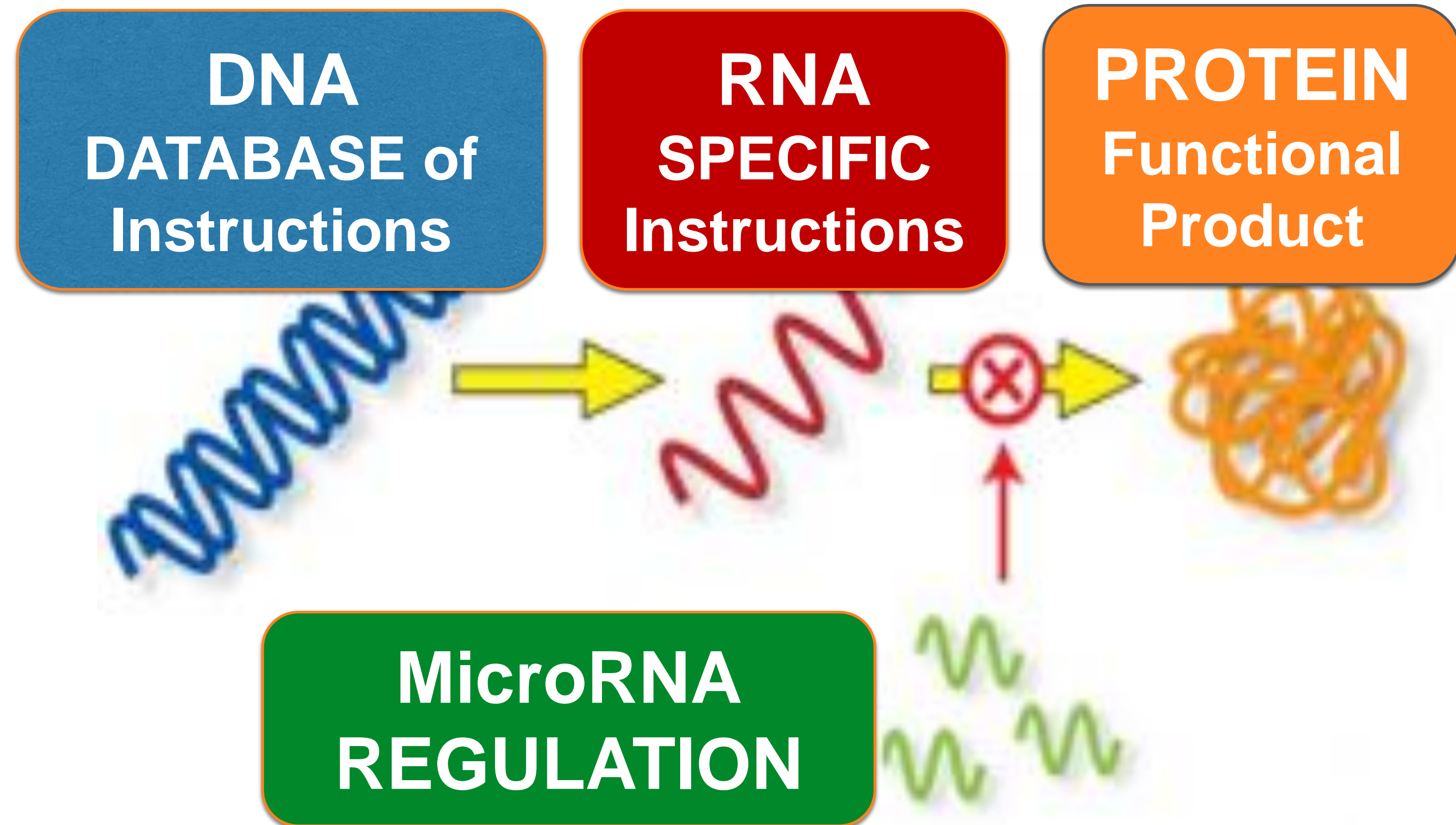
Botanical MicroRNA | Regulation of Gene Expression



WHAT ARE MicroRNA'S (MiRNA)?

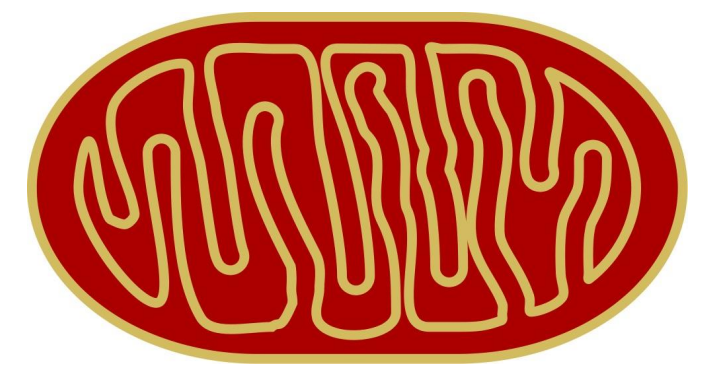
miRNAs are very small 19 to 25 nucleotide, **non-coding RNAs** that **negatively regulate gene expression post-transcriptionally** by inhibiting translation and degrading mRNAs.

- miRNAs **control biological processes** such as **cell proliferation, differentiation, angiogenesis and apoptosis.**
- miRNA **deregulation is involved in the occurrence of many types of cancer**

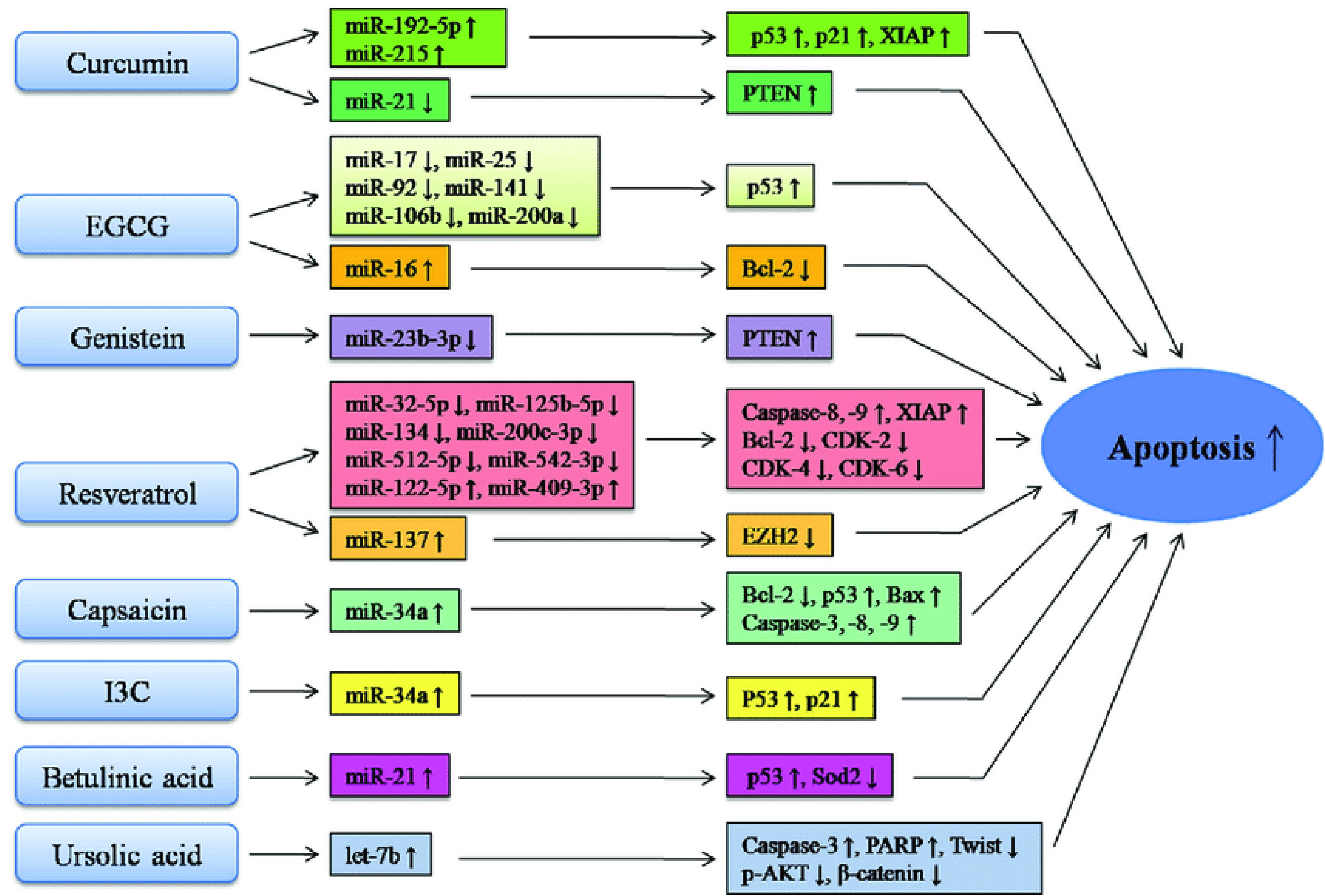
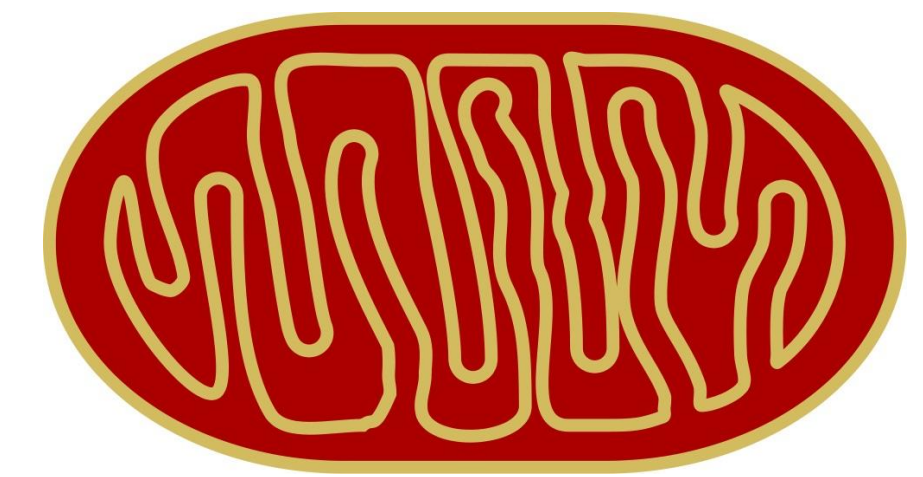


MicroRNA (miRNA) Plant based

Regulate a diverse range of biological pathways



- class of single-stranded non-coding RNA molecules
- approximately 22 nucleotides
- play crucial roles in gene expression
- bind to complimentary sequences of specific protein-coding genes
- are highly pleiotropic
- a single miRNA can recognize hundreds of mRNA transcripts, allowing them to regulate a diverse range of biological pathways
- can function as active signaling molecules to regulate mammalian genes

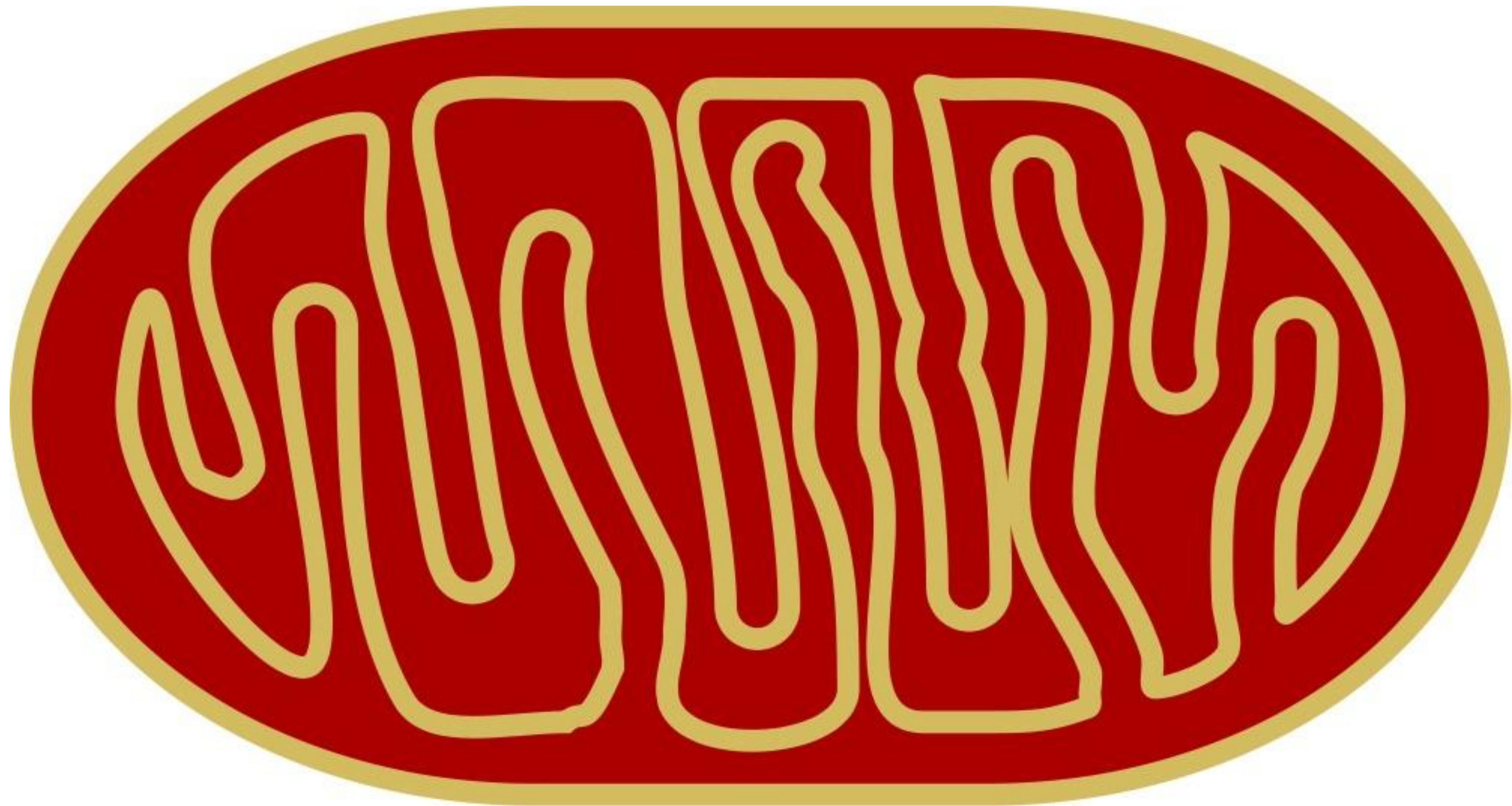


Regulation of apoptosis related miRNAs and their targets in cancers by dietary phytochemicals

[Biomedicine & Pharmacotherapy](#)
94C:1197-1224

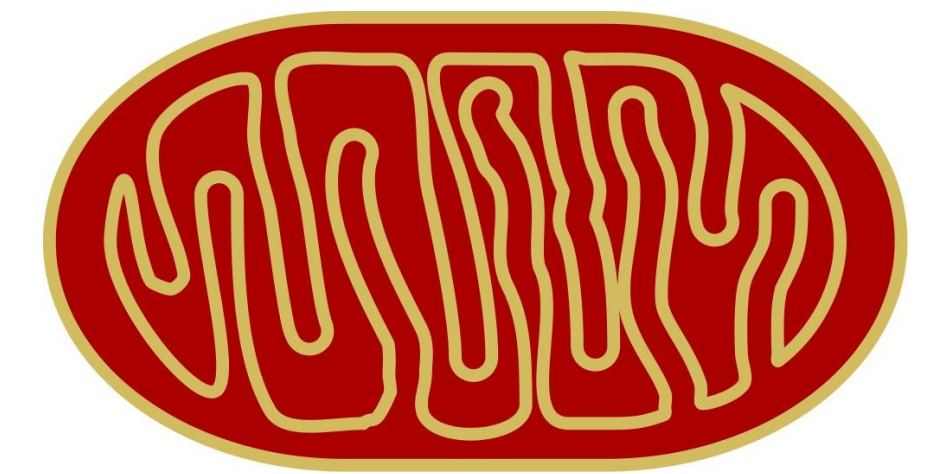
THE PROBLEM WITH POLYPHENOLS

Short half life Low bioavailability

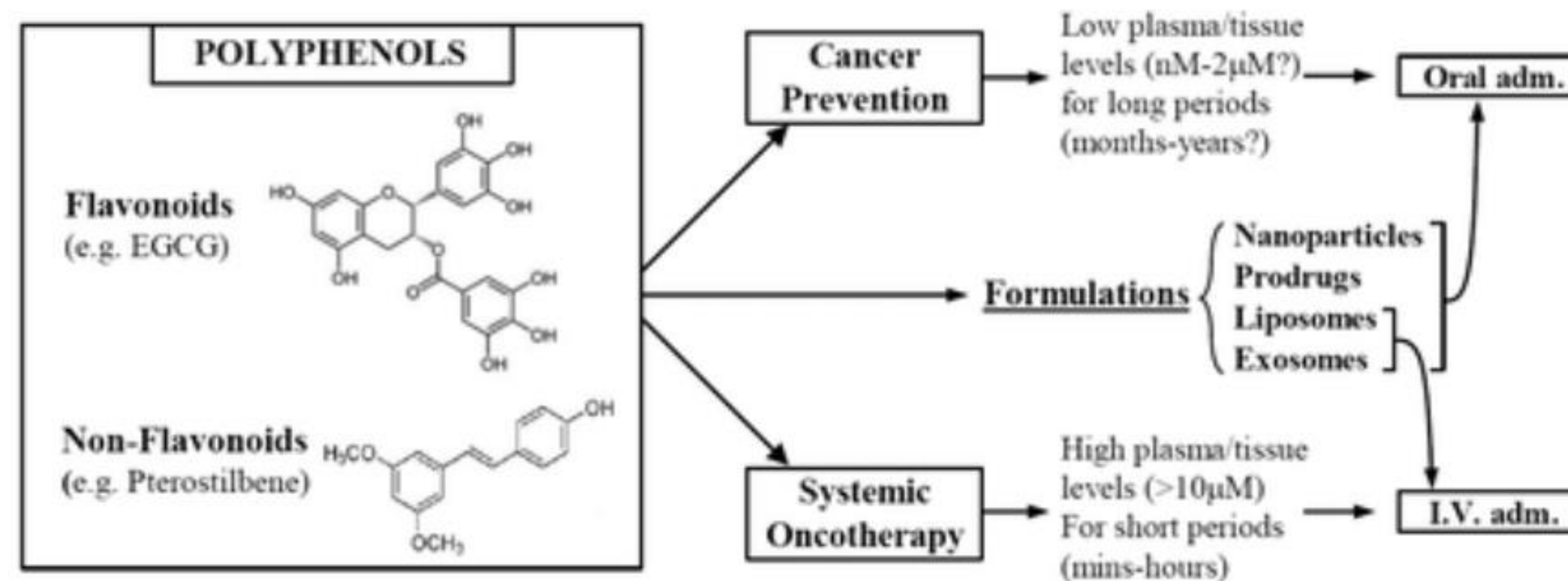


Polyphenolic Phytochemicals in Cancer Prevention and Therapy: Bioavailability versus Bioefficacy

José M. Estrela. *J. Med. Chem.* 60, 23, 9413-9436 2017



Short half life. Low bioavailability



Healthy Microbiome & Phytophenol BioAccessability

Two Way Gut Microbiota <---> Polyphenol Interactions

Dietary polyphenols and their metabolites modulate gut microbial balance through stimulation of the growth of beneficial bacteria

including Lactobacillus and Bifidobacterium
and inhibition of pathogen bacteria exerting pre-biotic like effects

Polyphenols depend upon gut microbiota for their transformation to active metabolites
which positively influence inflammation, carcinogenesis, apoptosis, cell proliferation and modulation of enzymes

J. Ethnopharm. 2016 Feb 17: 179:253-64 **Could gut microbiota reconcile oral bioavailability conundrum of traditional herbs?** Chen, Wen, Jiang, et al

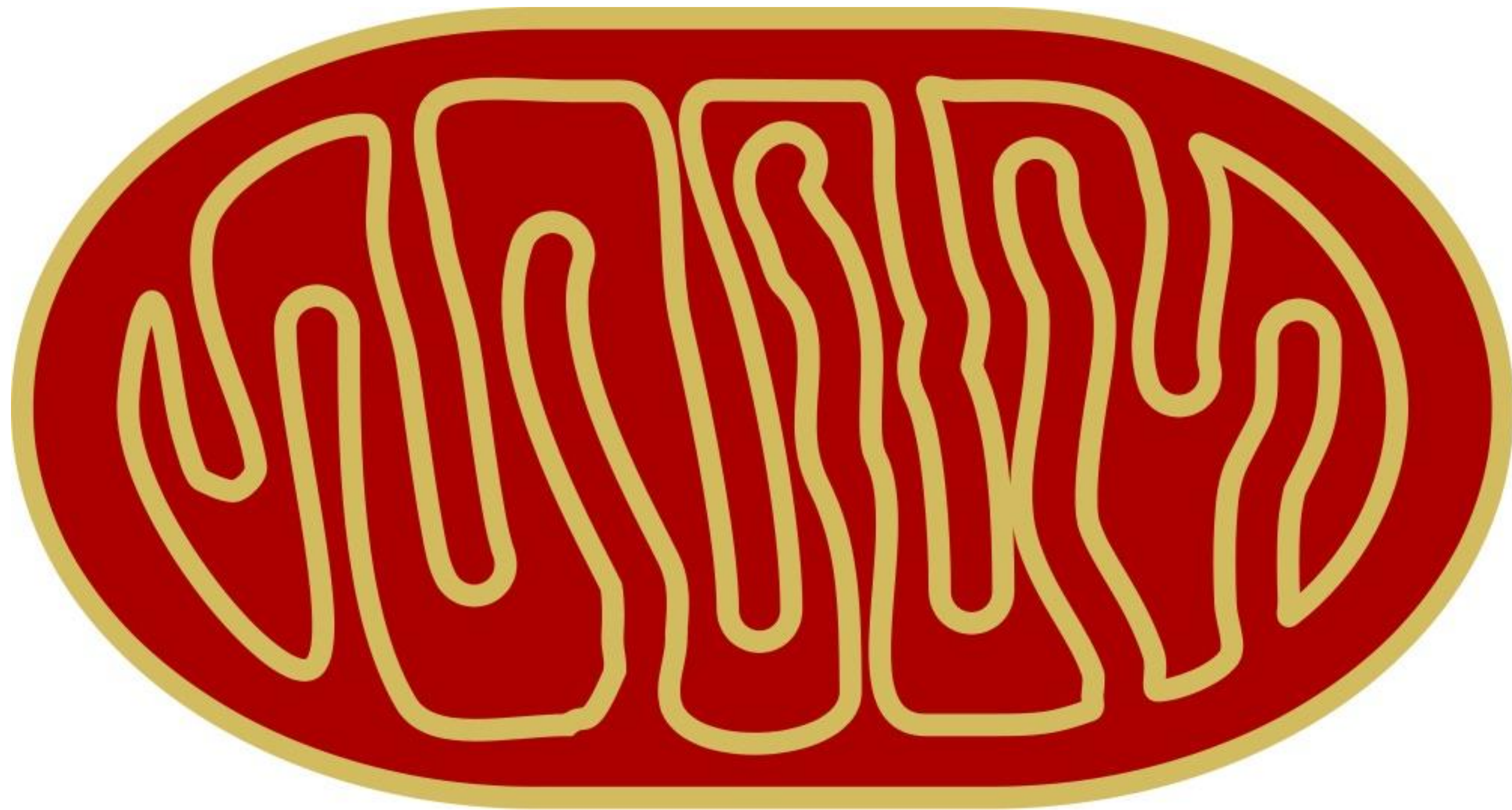
Healthy Microbiome & Phytophenol BioAccessibility

- Bioavailability and effects of polyphenols greatly depend on their transformation by components of the gut microbiota.
- Phytochemicals and their metabolic products may also inhibit pathogenic bacteria while stimulate the growth of beneficial bacteria, exerting prebiotic-like effects.
- Intestinal microbiota is both a target for nutritional intervention and a factor influencing the biological activity of other food compounds acquired orally.

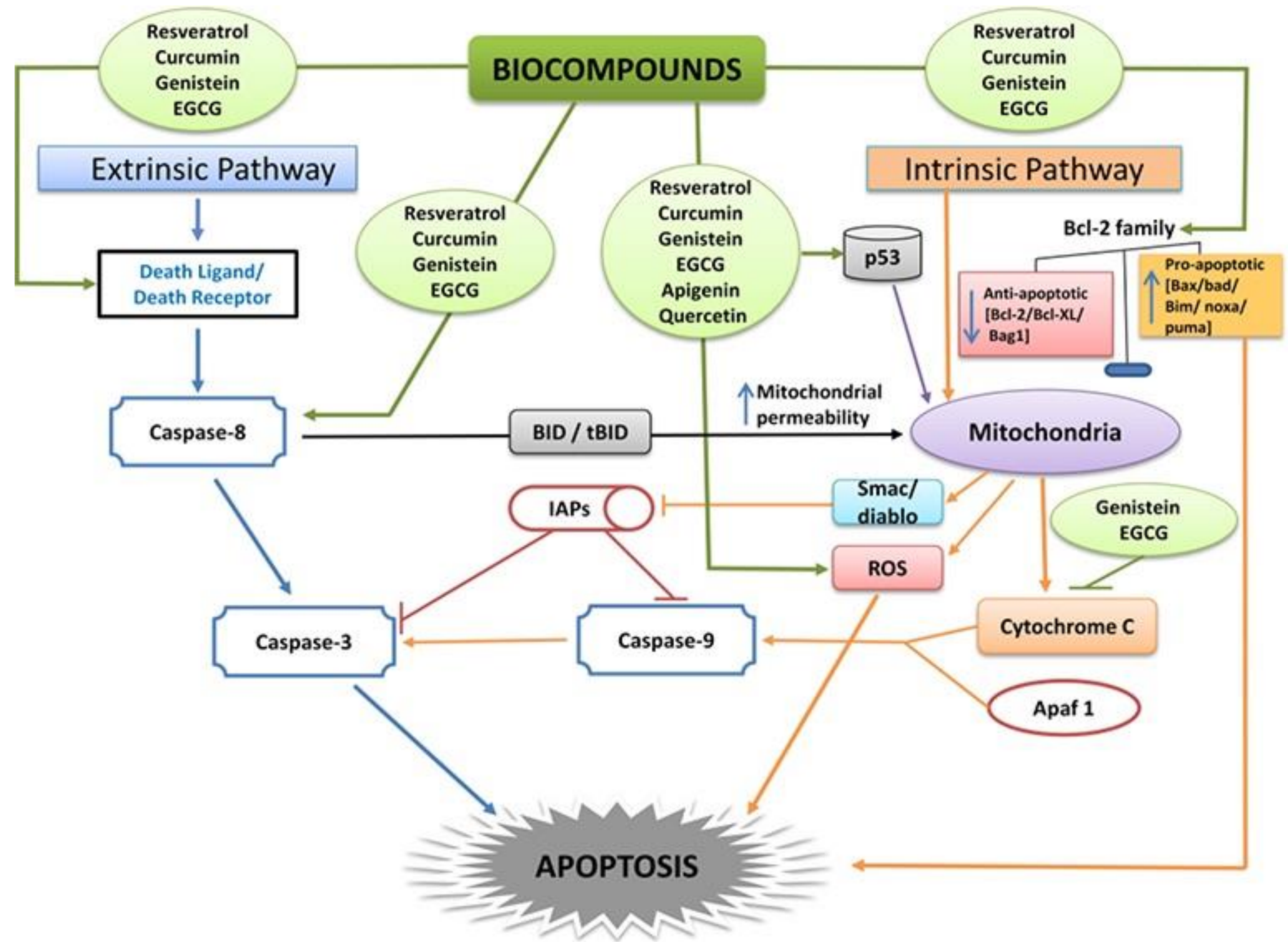
The Reciprocal Interactions between Polyphenols and Gut Microbiota and Effects on Bioaccessibility.

Ozdal T, et al Nutrients. 2016 Feb 6;8(2):78. Review

SUMMARY



Modulation of Apoptosis in Colon Cancer Cells by Bioactive Compounds
<http://dx.doi.org/10.5772/63382>





SAMPLE COMPREHENSIVE TREATMENT PLAN

ONCO Targeted CAPSULES tid

Curcumin	1000-2000mg
Resveratrol	1000-1500mg
Indole 3 Carbinol.	500mg
Berberine	1000mg
Quercetin	500-1000mg
EGCG	1000-2000mg
Honokiol	500mg + 500mg hs
Tocotrienols	500mg
5-MTHF	1000mcg

Add to Daily Therapeutic Shake

Chaga Mushroom.	1 gram
Pleurotus Mushroom	1 gram
Ganoderma Mushroom	1

CUSTOM COMPOUNDED Herbal Tonic

240ml 2 teaspoons qd

- 40 H Oldenlandia diffusa/Bai Hua She She
- 40 Rdx Scutellaria baicalensis/Huang Qin
- 40 Rdx Salvia milthiorrhiza/Dan Shen
- 20 Rdx Panax ginseng/Ren Shen
- 20 Rdx Withania/Ashwaganda
- 20 H Tanacetum parthenium/Feverfew
- 20 H Camelia Sinsensis/Green Tea
- 15 H Rabdosia rubescens
- 15 H Polygonatum odoratum/Solomon's Seal
- 15 Ctx Magnolia/Hou Po
- 15 H Tabuebia/Pau d Arco
- 10 Rz Zingiberis/Ginger Root

Dietary Guidelines-Meal Plans-Recipes-Intermittent Fasting
 Exercise-Sleep-Meditation-Stress Management-Resilience

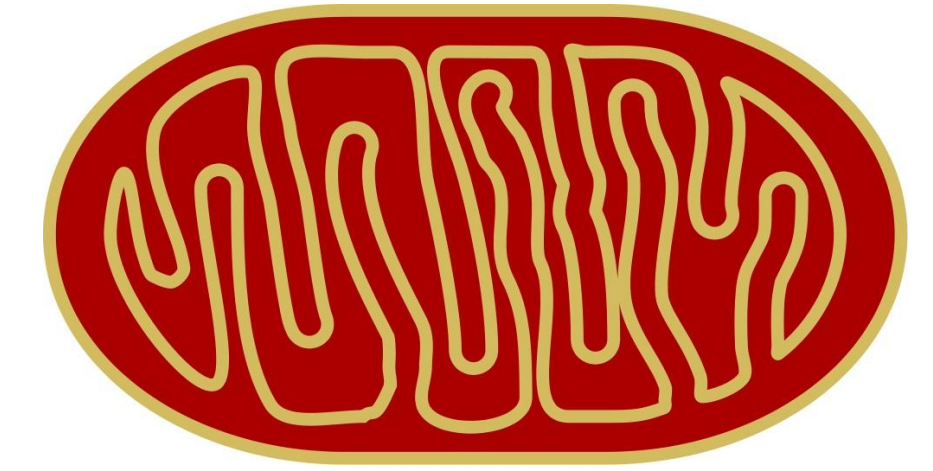
FOUNDATION NUTRIENTS

- Cu-Fe Free Multi
- Omega 3 FA
- Probiotics
- Magnesium glycinate
- Vitamin D3
- Bone Minerals s Cu
- Vitamin C
- Zinc + Mb
- (CoQ10 , NAC)

THERAPEUTIC SHAKE

- Protein, Solube-
- Insoluble Fiber, Fatty
- Acids, MCT, Plant
- Antioxidants,
- Moringa,
- L-Carnitine, Sacha
- inchi, Goji-Lycium
- ETC

Additional References



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Evidence-Based Complementary and Alternative Medicine Volume 2015, Article ID 539260

Plants Against Cancer: A Review on Natural Phytochemicals in Preventing and Treating Cancers and Their Druggability. [Anticancer Agents Med Chem. 2012 Dec; 12\(10\): 1281–1305.](#) [Hu Wang](#), et al

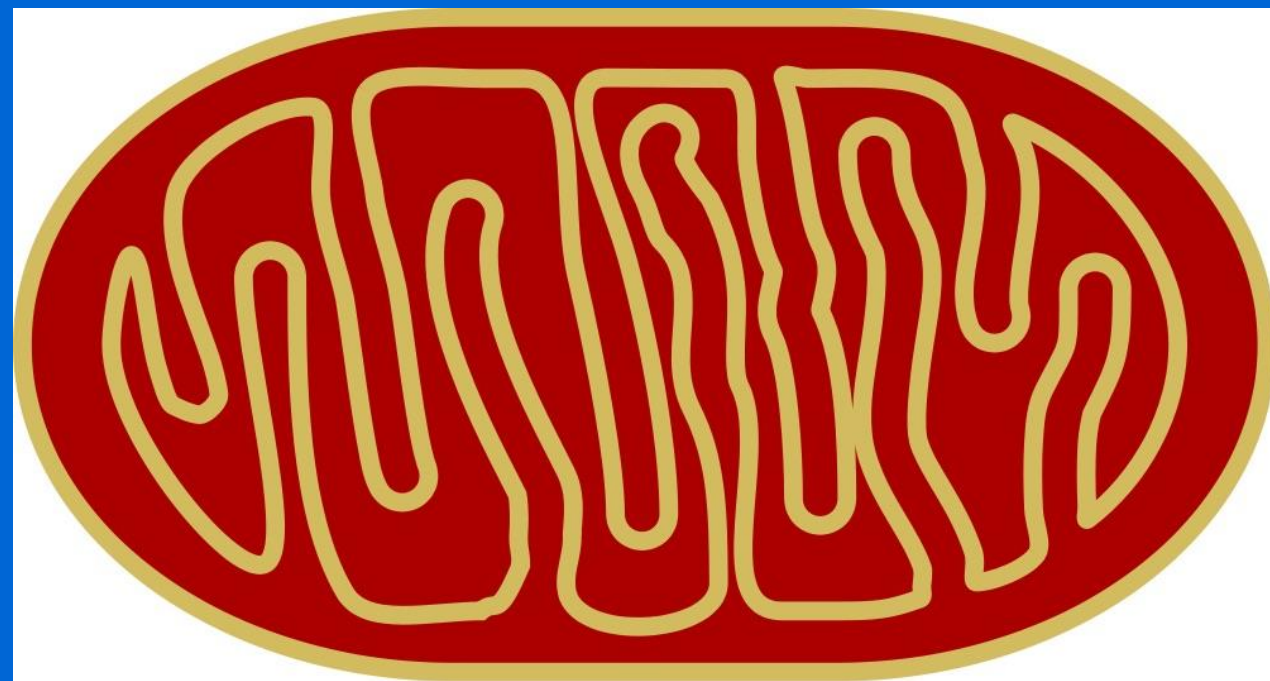
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MicroRNAs and Chinese Medicinal Herbs: New Possibilities in Cancer Therapy
[Cancers \(Basel\).](#) 2015 Sep; 7(3): 1643–1657. [Ming Hong](#)

Role of phytochemicals in colorectal cancer prevention.
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BONUS



THANK YOU!

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ADDITIONAL RESOURCES

STUDY GUIDE

Lecture Summary Notes

Most Current Lecture Slides
References

DOWNLOAD

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