



Minor Components In Palm Oil And Their Health Benefits

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Composition of crude palm oil.

Component	Percentage
Triglycerides (TAG)	~ >90
Diglycerides (DAG)	~ 2-7
Monoglycerides (MAG)	~ <1
Free Fatty Acids (FFA)	~ 3-5
Phytonutrients	~1



Value Addition

- Crude palm oil contains about 1% valuable components (phytonutrients) that are beneficial to health. These phytonutrients include
 - Carotenes,
 - Vitamin E (tocopherols and tocotrienols),
 - Sterols,
 - Squalene,
 - Co-enzyme Q and
 - Phospholipids
- The presence of these phytonutrients will increase the demand for palm oil

Major Phytonutrients in Palm Oil

Phytonutrients	Concentration (ppm)
Tocols (Tocotrienols, Tocopherols)	600-1000
Carotenoids (α -carotene, β -carotene, lycopene, phytoene)	500-1000
Phytosterols (Sitosterol, Stigmasterol, Campesterol)	300-620
Squalene	250-800
Lecithin (Phospholipids)	20-100
Co-enzyme Q10 / Ubiquinones	10-80
Polyphenols (Phenolic acids, Flavonoids)	40-70

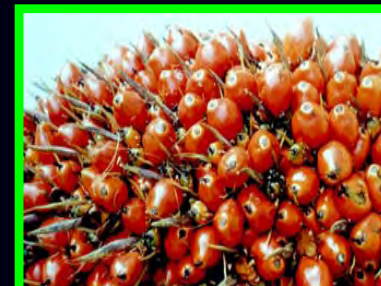
Choo *et al.* 2008.

Unsaponifiable Matter

Sample	Vitamin E (ppm)	Sterols (ppm)	Squalene (ppm)
Palm Oil	1060	1243	762
Olive oil	143	680	992



Health Promoting Phytonutrients



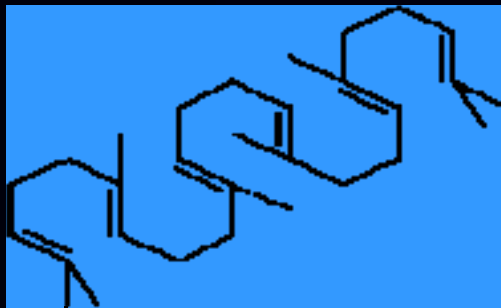
SQUALENE

Cardiovascular Benefits

- Inhibition of cholesterol synthesis (Strandberg et al., 1989)

Anti-cancer effects

- Protection against colon, breast and skin cancer (Owen et al., 2000)
- Suppress skin carcinogenesis (Murakoshi et al., 1992)
- Anti-tumor activity (Yamaguchi et al., 1985, Newmark 1997)
- Suppress colon carcinogenesis (Rao et al., 1998)
- Inhibition of lung tumorigenesis (Smith et al., 1998)



DEEP SEA SHARK
LIVER OIL



OLIVE OIL



PALM OIL



WHEAT GERM
OIL



AMARANTH OIL



BEEF

-

MACKEREL

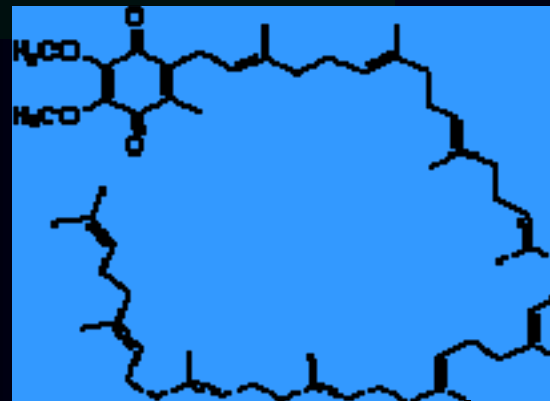
- 
- A photograph showing a tall glass of white milk and a small bowl filled with golden-brown wheat grains. Some grains are spilled on the surface next to the bowl.

SOY

- 

SPINACH

- 



PEANUTS

PHYTOSTEROL

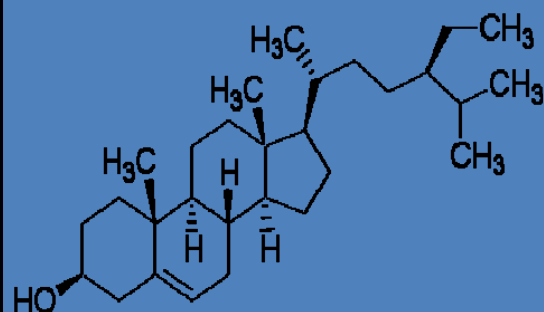
Cardiovascular benefits

- Cholesterol lowering effect (zadak et al, 2006)
- Inhibition of cholesterol absorption (Miettinen et al, 2006)

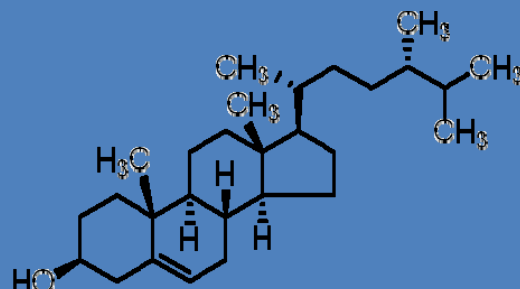
Anticancer properties (Awad et al, 2000)

Immune functions

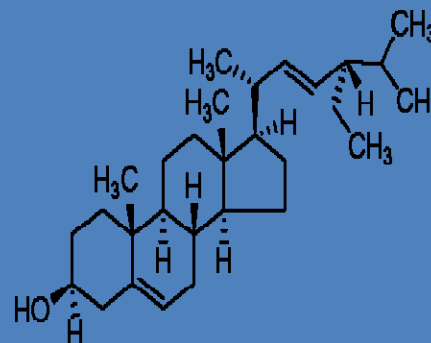
- Stimulates lymphocytes proliferation (Bouic et al, 1996)



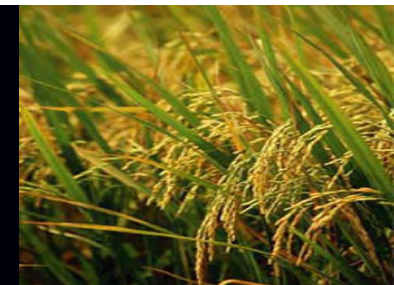
B-sitosterol



campesterol



stigmasterol



RICE BRAN OIL



CORN OIL



WHEAT GERM OIL



FLAX SEED OIL



COTTON SEED OIL

PHOSPHOLIPIDS

Brain function

- Restore age related memory loss (Suzuki et al, 2001)

Energy Endurance

- Optimal sports performance (Jager et al, 2007)
- Combat exercise induced stress (Starks et al, 2008)

Structural integrity of cells

- Rapid membrane proliferation (Lochmann et al, 1997)

Eases digestion and nutrition absorption

- Improved weight gain (Lochmann et al, 1997)



EGG YOLK



LIVER



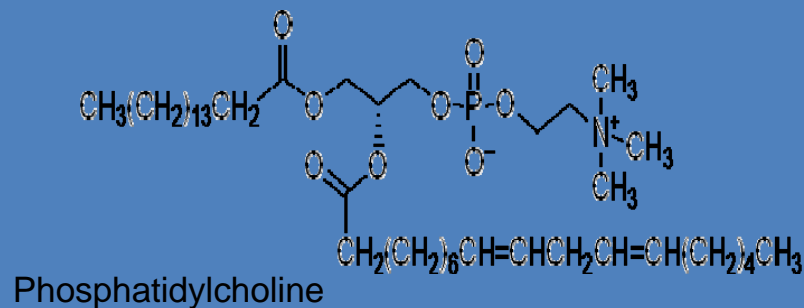
PEANUTS



CORN



SPINACH



POLYPHENOLS

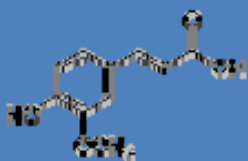
Antioxidants (Ebrahimzadeh et al, 2008)

Free radical scavengers (Pourmorad et al, 2006)

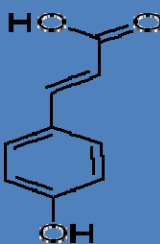
Iron chelating activity (Ebrahimzadeh et al, 2008)

Anticarcinogenic

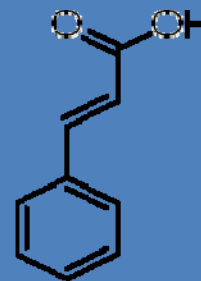
- Breast cancer (Fink et al, 2007)
- Prostate cancer (Nair et al, 2004)



Ferulic acid



Coumaric acid



Cinnamic acid



ONIONS



APPLES



TEA



RED WINE



GRAPES

Carotene and Vitamin E Composition

Carotene (1000 ppm)

- * 30% alpha carotene
- * 60% beta carotene
- * 1% lycopene
- * 9% others

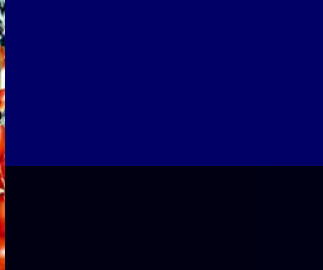
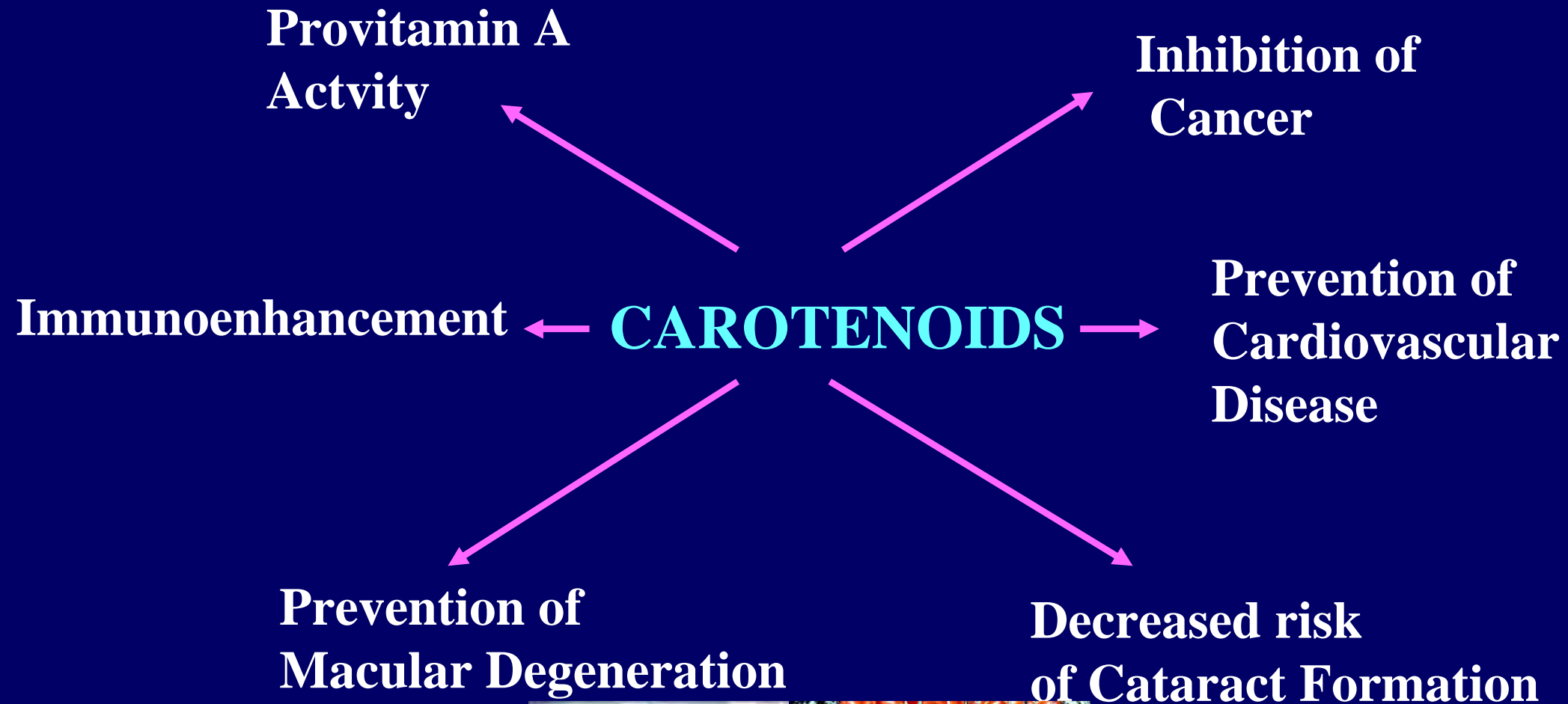


Vitamin E (600-1000 ppm)

- * 70% tocotrienols
- * 30% tocopherols



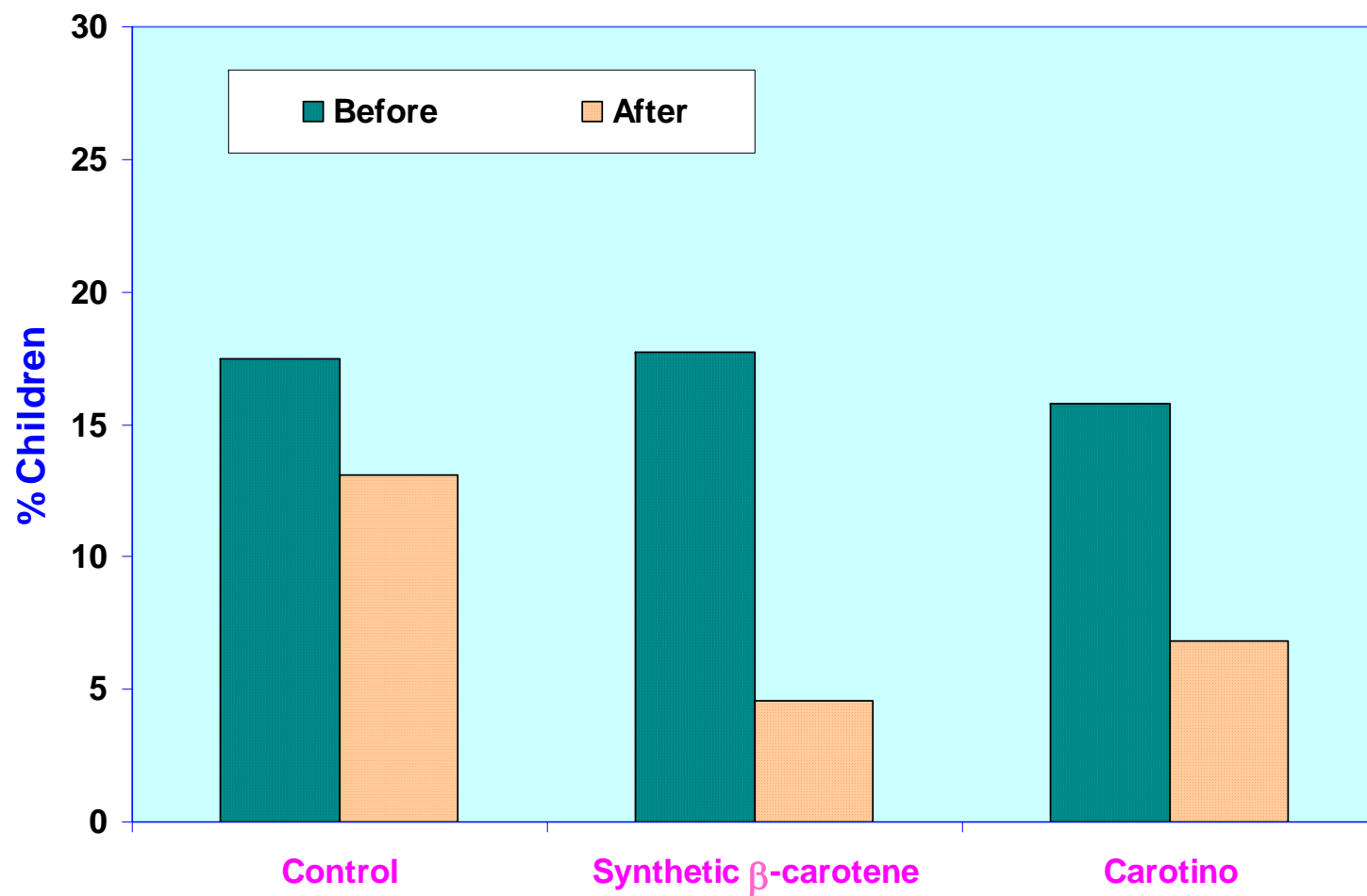
HEALTH-PROMOTING FUNCTIONS OR ACTIONS ATTRIBUTED TO CAROTENOIDS







**Prevalence of Low Serum Vitamin A levels (<15 ug/dL)
Before and After 5 Month Intervention**



Tocotrienols

Vitamin E content in Fats & Oils

Palm Kernel Oil

Olive Oil

Peanut Oil

Cottonseed Oil

Safflower Oil

Palm Oil

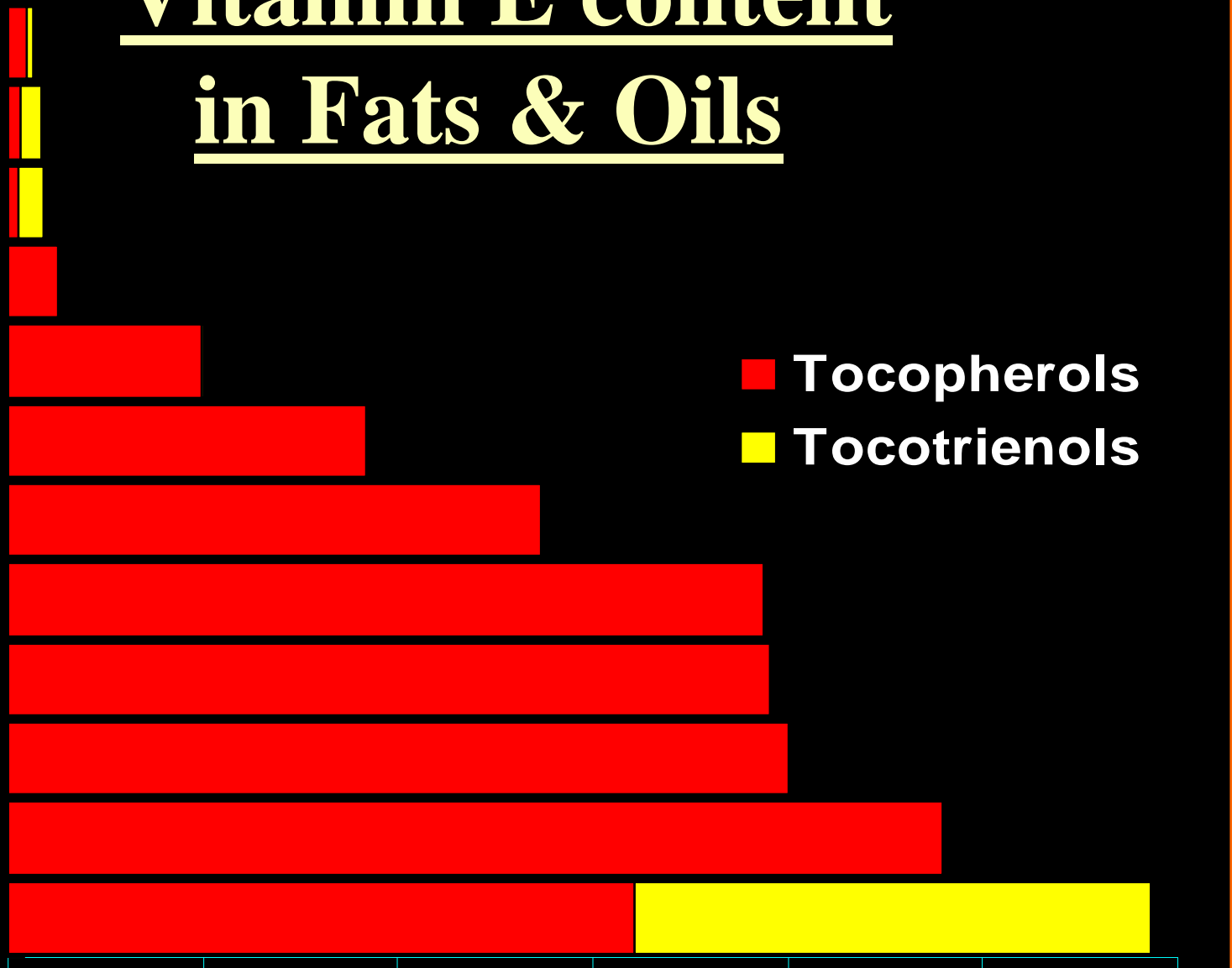
■ Tocopherols

■ Tocotrienols

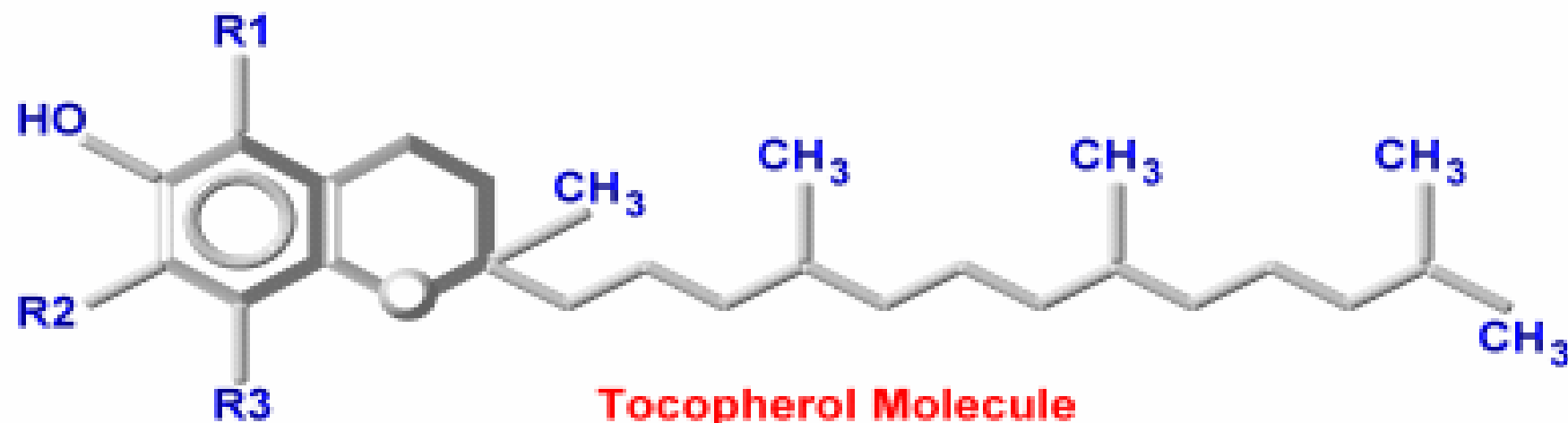
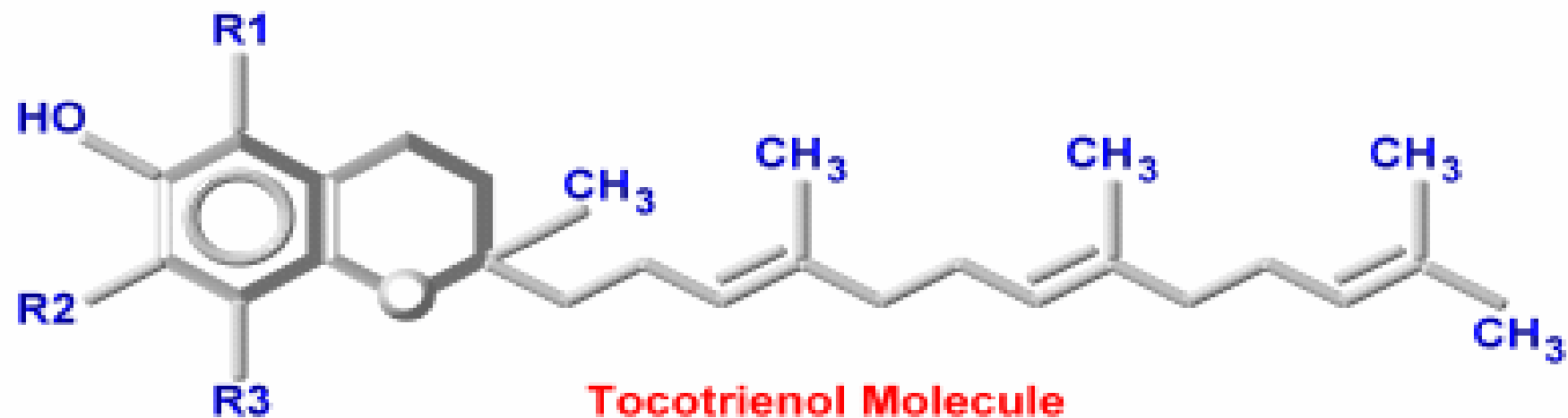
0 200 400 600 800 1000 1200

ppm










Refs: H.T. Slover, Lipids 6:291 (1971); F.D. Gunstone (1986)



VITAMIN E STRUCTURE



RESEARCH ON TOCOTRIENOLS TO DATE

-  T3 and Breast and Prostate Cancer
-  T3 and Neuroprotection
-  T3 and Pre-eclampsia
-  T3 and Immune Response
-  T3 and Anti-inflammation
-  T3 and Atherosclerosis
-  T3 and Cholesterol Lowering
-  T3 and Opthamology-Cataracts
-  T3 and Platelet Aggregation

TOCOTRIENOLS

Anti-cancer effects

- Human prostate cancer cells (Srivastava & Gupta 2006, Nesaretnam *et al.* 2008)
- Breast cancer cells (Nesaretnam *et al.* 1995, 1998, 2004, Yu *et al.* 2005)
- Anti-angiogenesis (Miyazawa *et al.* 2008, Weng-Yew *et al.* 2009)

Neuroprotection

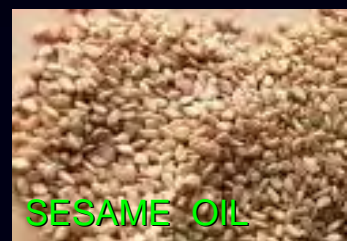
α -tocotrienols at nanomolar concentration provide neuroprotection (Sen *et al.* 2000)

Independent of anti-oxidant property

Tocotrienols inhibit c-Src activity in glutamate-induced neurodegeneration (Khanna *et al.* 2002)

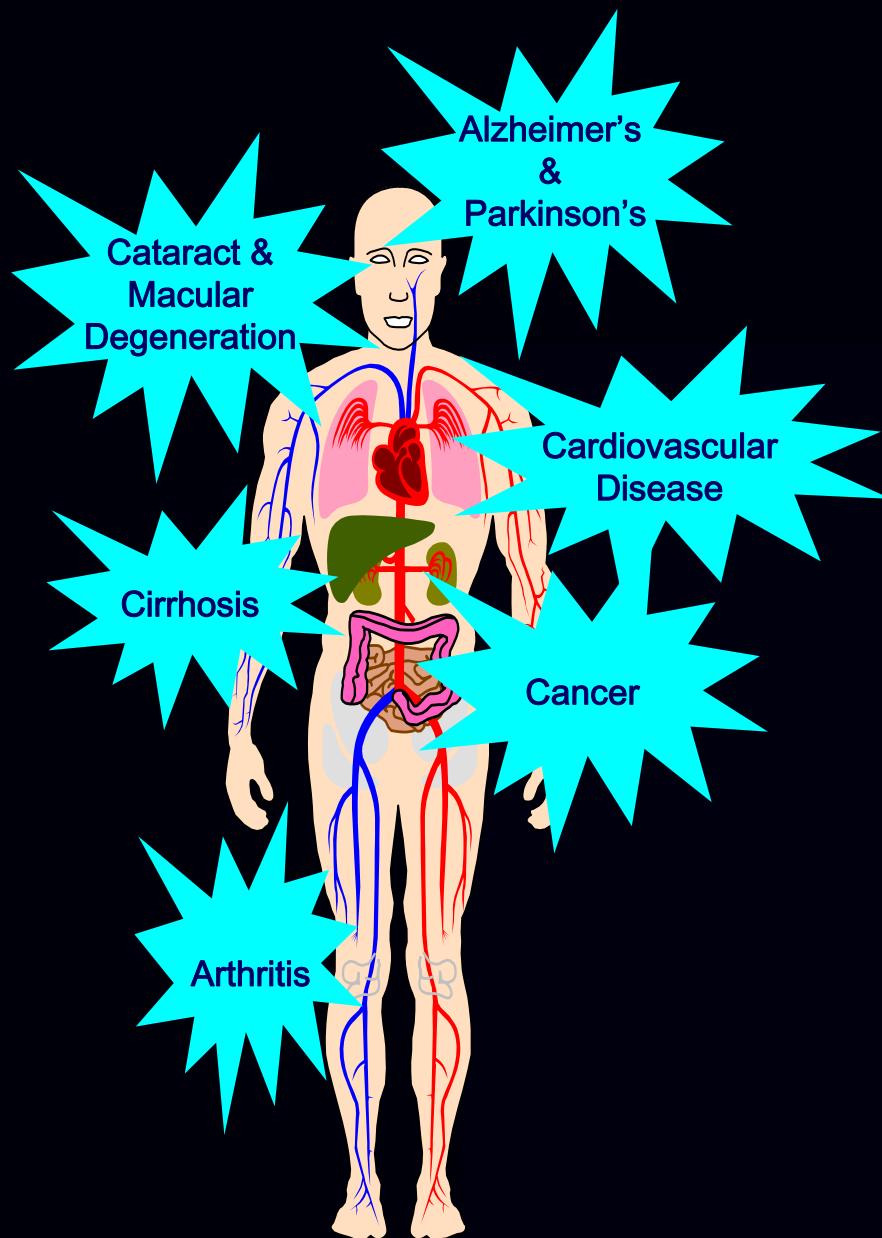
Cardiovascular Protection

- Inhibition of cholesterol synthesis (Qureshi *et al.* 1991, Parker *et al.* 1993, Song *et al.* 2006)
- Reversing Artherosclerosis (Tomeo *et al.* 1995)



ANTIOXIDANTS





Antioxidants may prevent or slow the oxidative damage to protein, lipid & DNA that is implicated in ageing and age-related, degenerative diseases – the so-called '*diseases of civilization*'

INTRODUCTION

- **Antioxidants represent a first line of defense against oxidative stress produced by the generation of free radicals.**
- **Unchecked these compounds can cause damage to tissues**

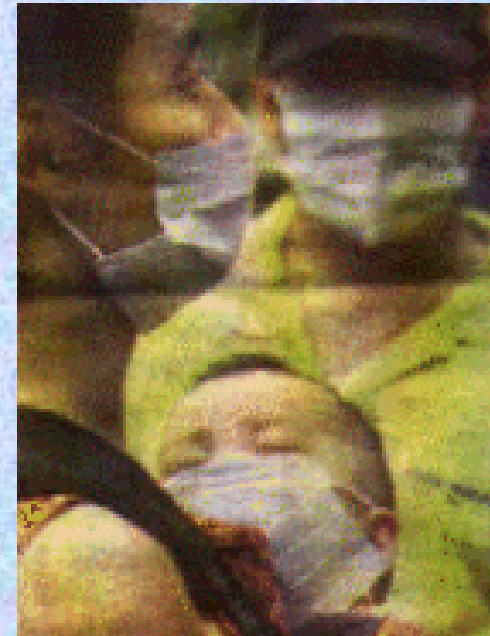
FREE RADICALS



Smoking



UV Rays



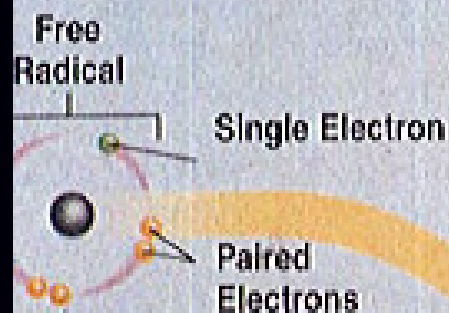
Pollution

What is a free radical?

- A free radical is any molecule that contains one or more unpaired electron. Examples of free radicals include ($\text{O}_2^{\cdot-}$) and hydroxyl ($\cdot\text{OH}$)
- Extremely reactive molecules and can cause cell injury and death. Cell components damaged by free radicals include
- PUFA in cell membranes
- proteins, such as enzymes and membrane ion transporters
- DNA

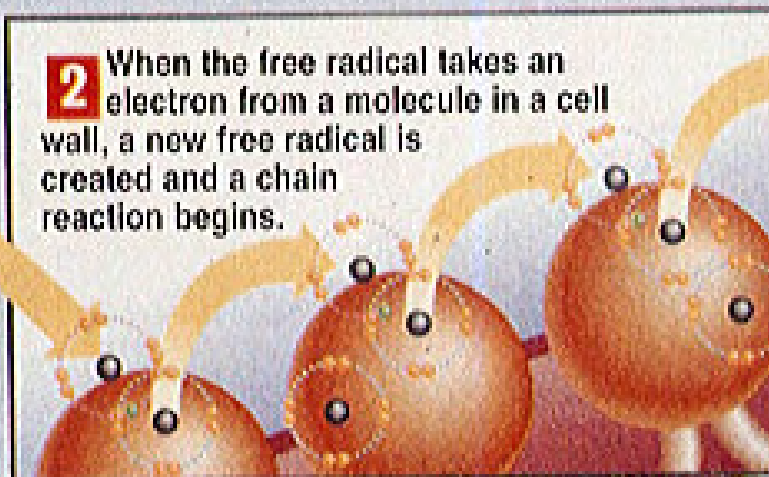
How Antioxidants Work

Scientists believe that compounds like vitamin E, known as antioxidants, may help thwart many common diseases by neutralizing harmful molecules known as free radicals.

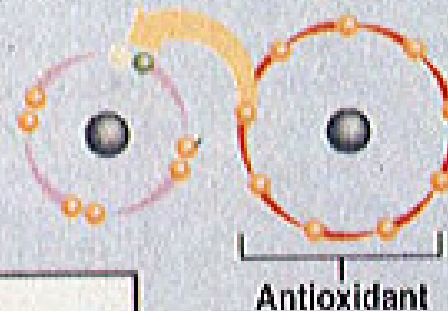


1 A normal oxygen atom has four pairs of electrons. The body's natural metabolism can rob the atom of an electron. It is now a free radical, which tries to replace the lost electron by attacking other molecules.

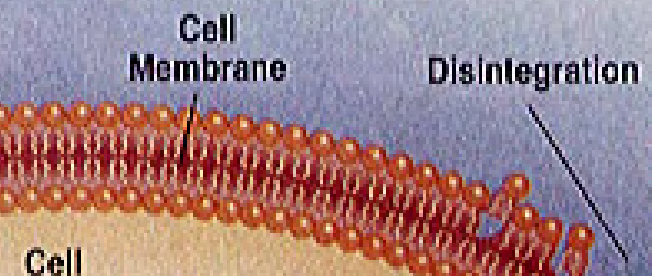
2 When the free radical takes an electron from a molecule in a cell wall, a new free radical is created and a chain reaction begins.

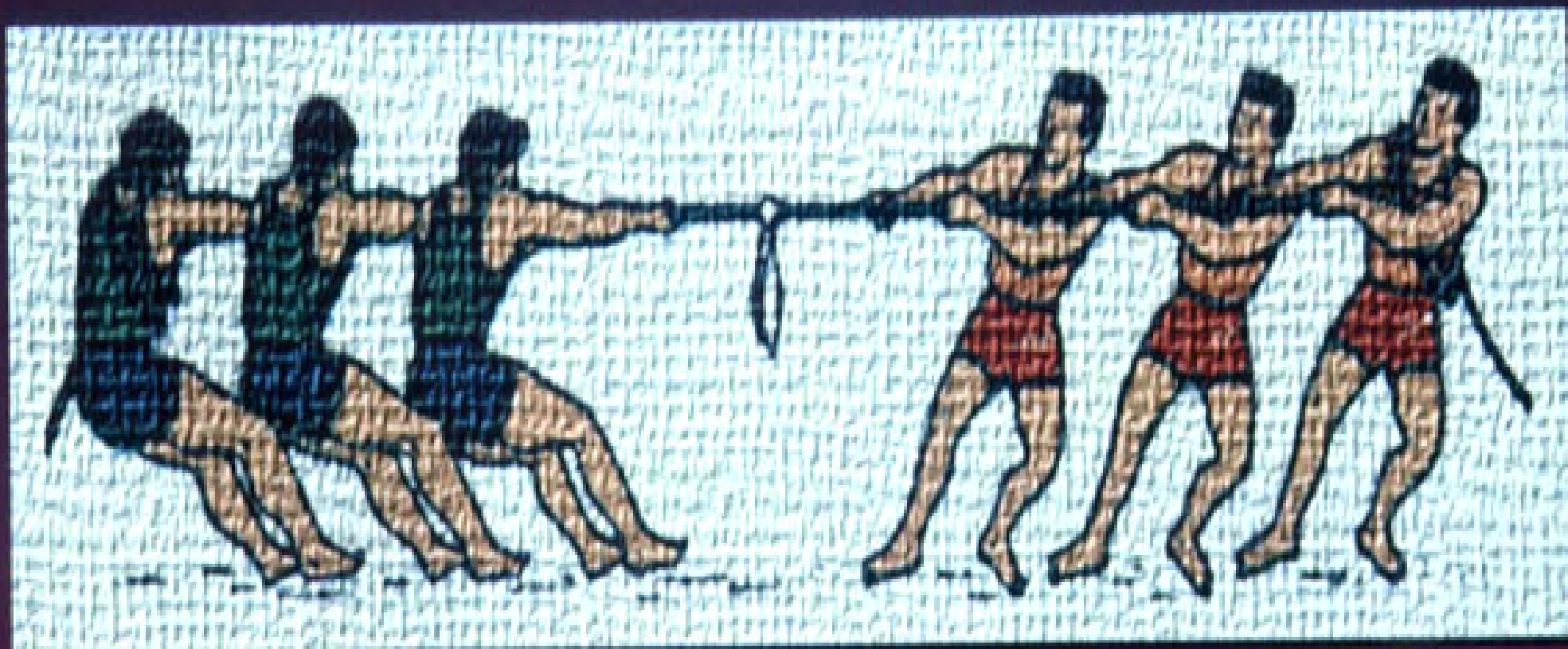


3 The chain of electron theft erodes the cell membrane, leading to disintegration of the cell and opening the door to cancer and other ills.



4 Because of their molecular structures, antioxidants can give up electrons to free radicals without becoming harmful, heading off the dangerous chain reaction.





**Protection
from
Disease**

Antioxidants

Free Radicals

**Tissue
Damage &
Disease**

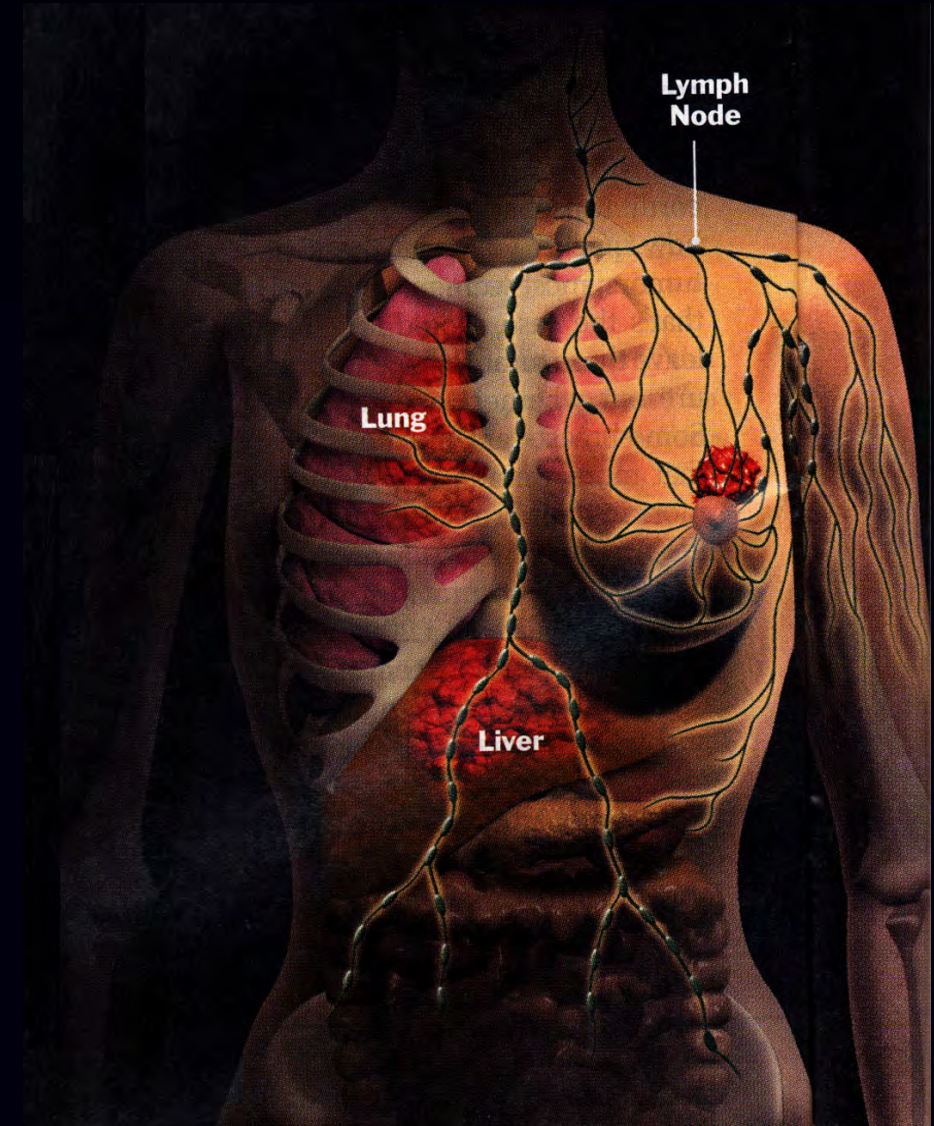
Deficiencies in the antioxidant system

- Low intake of dietary antioxidants
- Diseases that reduce the absorption of antioxidant nutrients from food
- Total parenteral nutrition
- Renal dialysis
- In these situations the AS struggles to protect the body from free radical attack and the result free radical mediated diseases

Tocotrienols and Breast Cancer

Breast Cancer

- The most common cancer in women worldwide. WHO reported a total of 910,000 new cases in 2008
- In Malaysia breast cancer incidence in 2008 was 4500 cases



BREAST CANCER

Risk Factors

- Family History of Breast Cancer
- Early Menarche
- Late Menopause
- Late Age At First Child-Birth
- Hormone Replacement Therapy



ESTROGEN

TREATMENT OF BREAST CANCER

◆ Estrogen Antagonists

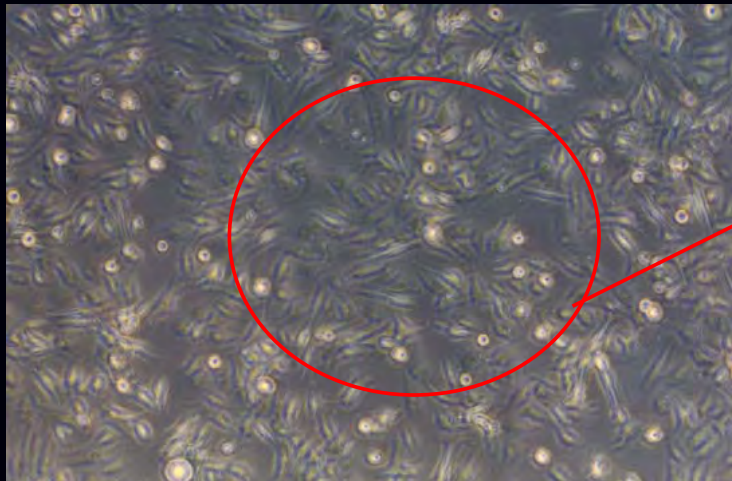
- Tamoxifen
- Pure antiestrogens-ICI 182,780

BIOLOGICAL THERAPIES

- The development of more effective biological therapies for breast cancer is under intense investigation.
- Naturally occurring agents such as the fat soluble vitamins A,D,E and K have been investigated for anticancer properties and found to possess antiproliferative effects.

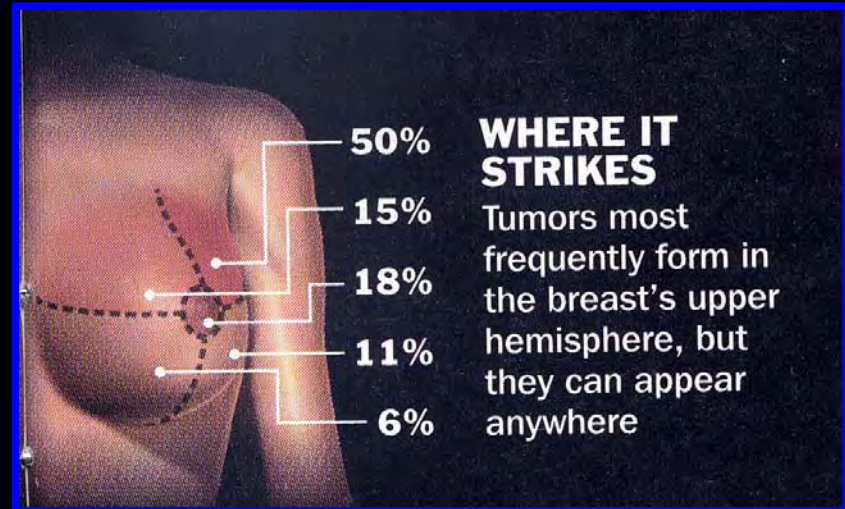
THERAPEUTIC POTENTIAL OF TOCOTRIENOLS

IN VITRO



MCF 7
Human
Breast
Cancer
cells

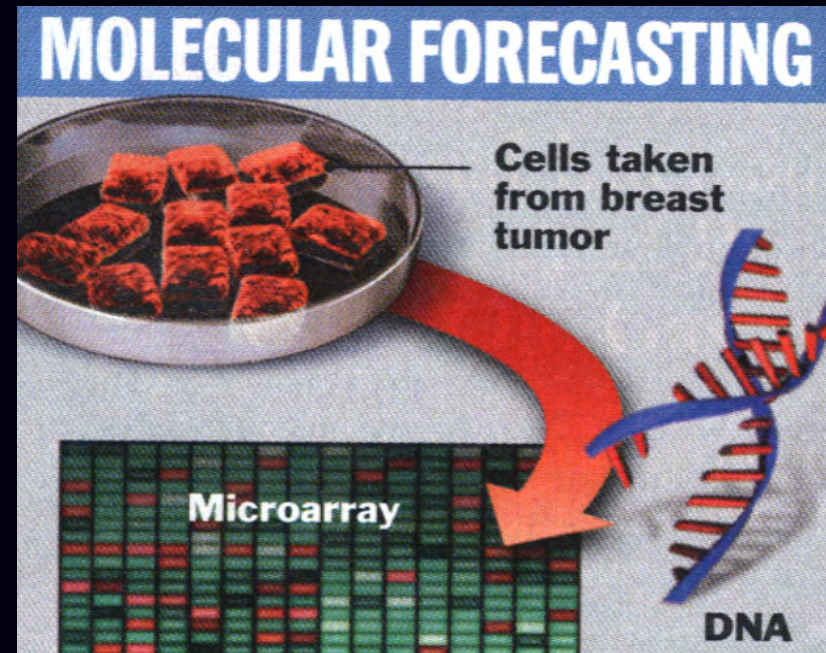
CLINICAL TRIAL



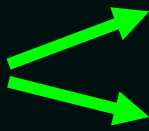
IN VIVO



GENE EXPRESSION



CLINICAL TRIAL

- 240  *120 Tamoxifen+ placebo*
120 Tamoxifen + Tocotrienol
- Primary Breast Cancer ER+
- Stage 1 & 2
- Lymph nodes

Anatomy of a Tumor

Every breast cancer is a little different, but many follow a fairly standard course. How each is treated depends on how early it is discovered, how aggressively it grows, and how it responds to antihormone treatment.

PRECANCEROUS



Normal
The cells lining the duct are uniform and well-differentiated.



Hyperplasia
A few extra cells accumulate.



Atypical ductal hyperplasia
The cells start looking more and more abnormal.

STAGE 0



■ THE DEFINITION

Cells that look like cancer but are still contained within the duct and do not have the ability to spread outside the duct. The reason it may be long to find may be up to 10 years.

■ THE OPTIONS

Patients whose lesions are not focused can be treated with tamoxifen or surgery. For surgery, the margins should be sufficient to prevent relapse.

■ THE OUTLOOK

Very good. Virtually no one dies from breast cancer within 5 years of diagnosis. The one exception is if the cancer is found late.

STAGE I

■ THE DEFINITION

The cancer has mostly spread to the lymph nodes. Even a tumor less than 1 cm in size is considered Stage I if several lymph nodes were involved.

■ THE OPTIONS

Mastectomy or lumpectomy plus radiation. Chemotherapy or tamoxifen for breast cancer. If that response is adequate.

■ THE OUTLOOK

Depending on tumor size and other characteristics, 85% to 95% of women survive at least 5 years after diagnosis.

STAGE I



Invasive Ductal Cancer

■ THE DEFINITION

Some of the cells from the tumor, which now measures 2 cm or less, spill out of the duct. There is no evidence of cancer in the lymph nodes.

■ THE OPTIONS

Mastectomy or lumpectomy plus radiation. Lymph nodes are biopsied. Chemotherapy or tamoxifen may be recommended for some women.

■ THE OUTLOOK

Anywhere from 95% to 98% of women are doing fine five years after treatment. Most will live much longer.

Actual size, Stage I

Stage II

Anatomy of a Tumor

Every breast cancer is a little different. How early it is discovered, how aggressive it is, and how it responds to antihormonal therapy.

PRECANCEROUS

- Normal**
The cells lining the duct are orderly and well-differentiated.
- Hyperplasia**
A few extra cells accumulate.
- Atypical ductal hyperplasia**
The cells start looking more and more abnormal.

STAGE 0

- THE DEFINITION**
Cells that look abnormal but haven't started spreading to other parts of the breast. The tumor is small and may grow up to 1 cm.
- THE OPTIONS**
Patients often choose to have a lumpectomy or mastectomy. Radiation is often used after a lumpectomy. Surgeons check if lymph nodes are sufficient to confirm.
- THE OUTLOOK**
Very good. Almost all breast cancer within Stage 0 is cured. The five-year survival rate is nearly 100%.

STAGE I

- THE DEFINITION**
The cancer has spread to the lymph nodes. It is up to 2 cm in size.
- THE OPTIONS**
Mastectomy or lumpectomy plus radiation. Chemotherapy is often prescribed for those cancers that respond to estrogen.
- THE OUTLOOK**
Depending on tumor size and other characteristics, 76% to 88% of women live at least five years after their diagnosis.

STAGE II

■ THE DEFINITION

Most tumors in this category measure 2-5 cm but have not spread to the lymph nodes.

■ THE OPTIONS

Mastectomy or lumpectomy plus radiation. Chemotherapy is used for any cancers that have spread to the lymph nodes and may even be indicated for larger node-negative tumors. Tamoxifen is prescribed for those cancers that respond to estrogen.

■ THE OUTLOOK

Depending on tumor size and other characteristics, 76% to 88% of women live at least five years after their diagnosis.

WHERE IT STRIKES

Tumors most frequently form in the breast's upper half, but they can appear anywhere.

IN

1 category of breast cancer.

usually plus therapy is used for an approach to this is given for early-stage cancer, followed by surgery for advanced stages.

Age and 1. 10% to 15% of breast cancer.

DEFINITION

1. Stage 0 breast cancer is called DCIS, or ductal carcinoma in situ.

PERIODS

Patients are given an option to have a lumpectomy or mastectomy. Radiation is often used after a lumpectomy. Chemotherapy is often prescribed for those cancers that respond to estrogen. Tamoxifen is prescribed for those cancers that respond to estrogen.

OUTLOOK

Depending on tumor size and other characteristics, 76% to 88% of women live at least five years after their diagnosis.

Anatomy of a Tumor

Every breast cancer is a little different, but many follow a fairly standard course. How each is treated depends on how

50% WHERE IT STRIKES
45% Tumors spread frequently from the breast to lymph nodes
40%

STAGE III

■ THE DEFINITION

The cancer has really taken hold in the lymph nodes. Even a tumor less than 1 cm in size is considered Stage III if several lymph nodes are involved

■ THE OPTIONS

Mastectomy or lumpectomy plus radiation. Chemotherapy. Tamoxifen for those cancers that respond to estrogen

■ THE OUTLOOK

Depending on tumor size and other characteristics, 49% to 56% of women live at least five years after diagnosis

TIME Graphic by Ed Gabel

Sources: M. D. Anderson Cancer Center; National Cancer Institute

STAGE IV

■ THE DEFINITION

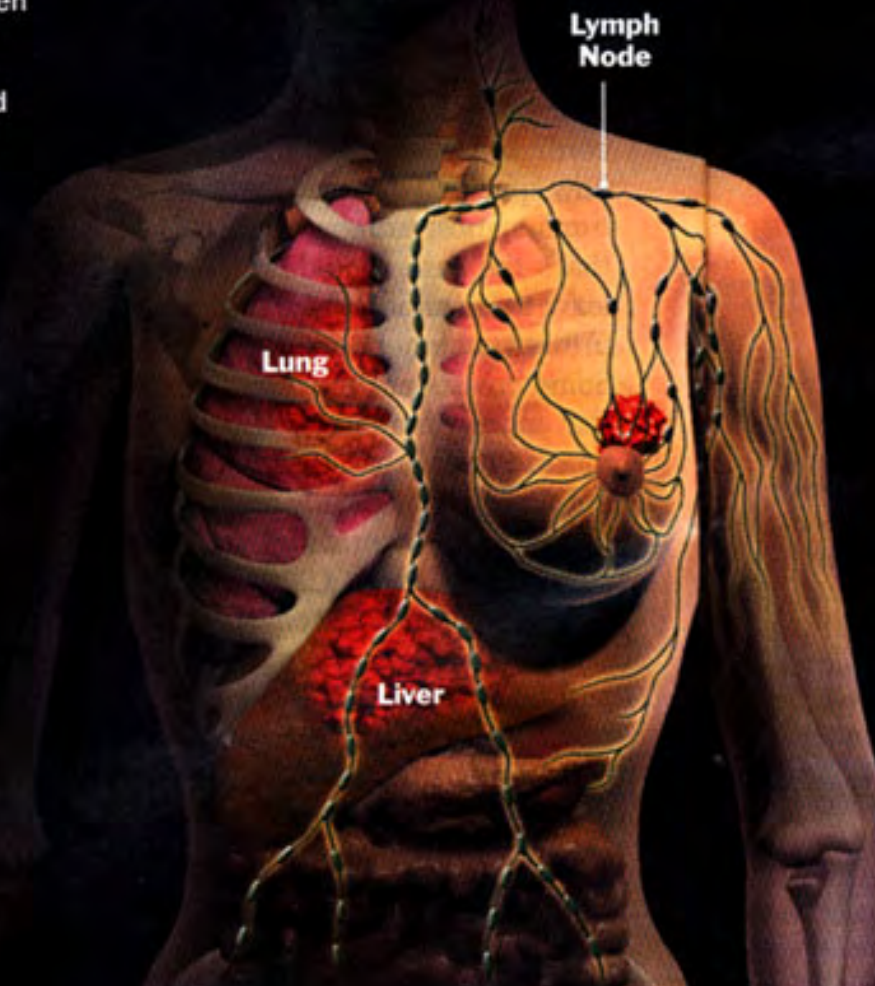
The cancer has spread beyond the breast, leading to secondary tumors in the liver, lungs, brain or elsewhere

■ THE OPTIONS

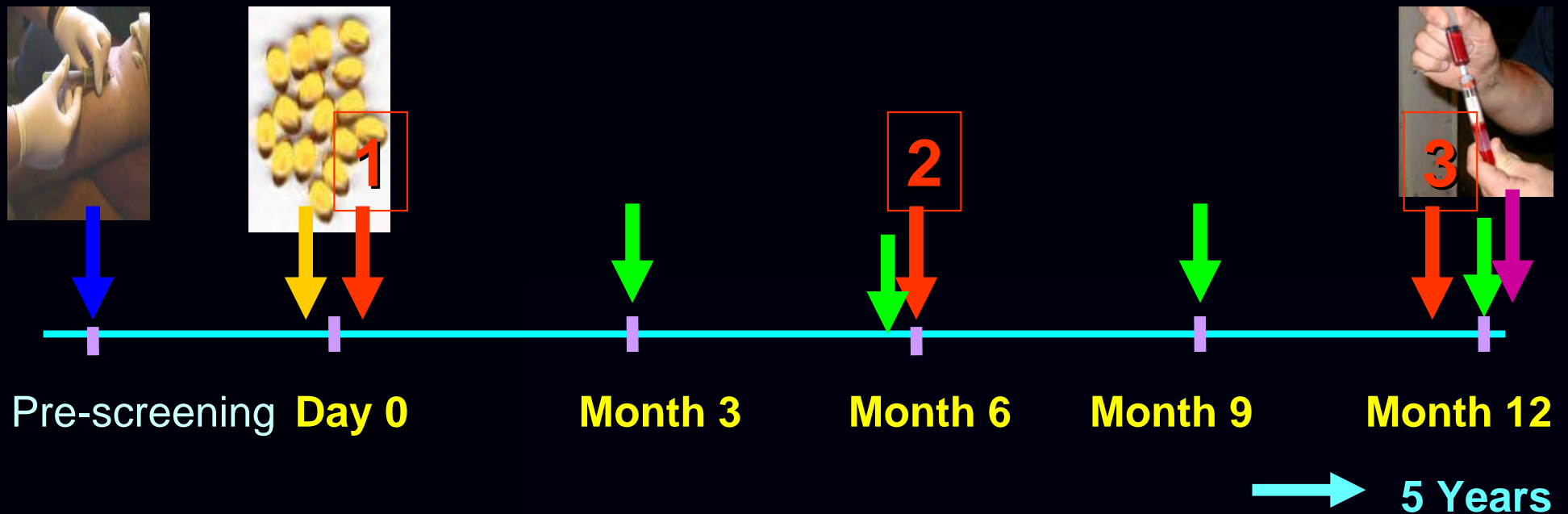
Most treatments are aimed at relieving symptoms or prolonging life a few months or years. Surgery or radiation to remove or at least try to shrink any tumors. Chemotherapy. Herceptin for those cancers that express an excess of the Her2 receptor. Tamoxifen or an aromatase inhibitor, if they haven't already been used, for those tumors that respond to estrogen. (Clinical trials of both herceptin and aromatase inhibitors in earlier stages of breast cancer are under way)

■ THE OUTLOOK

Studies indicate an average survival time of 18 months to 24 months. From 15% to 20% live at least five years after diagnosis



Time-Line (1 Year)



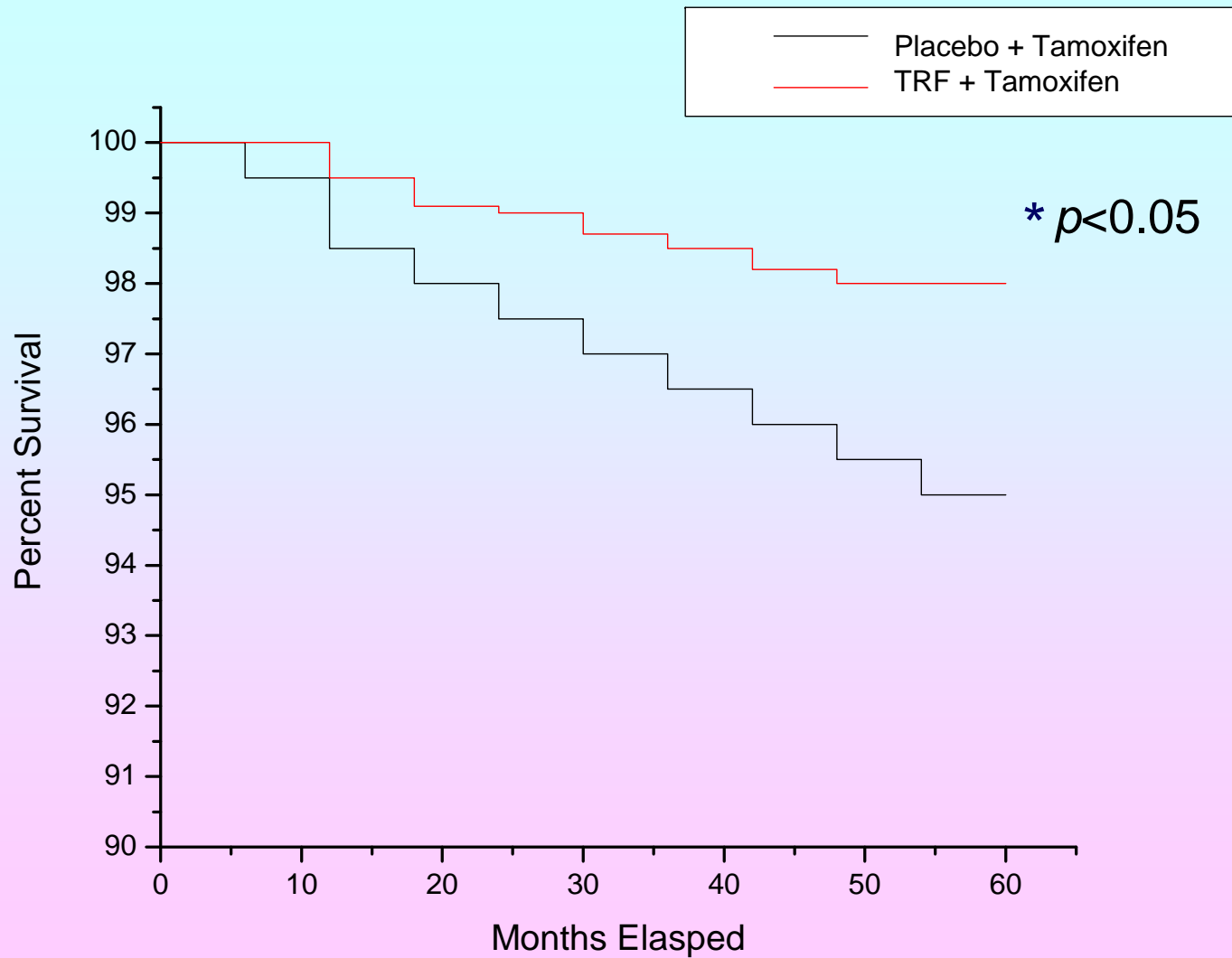
KEY

- Pre-screening
- Supplementation (Vit. E or Placebo + Tamoxifen) starts
- Monitoring (Mammogram, Oncology)
- Blood collection, Full Blood Count, LFT, HPLC, Flow Cytometry,
- Additional blood for IFN- γ

RESULTS

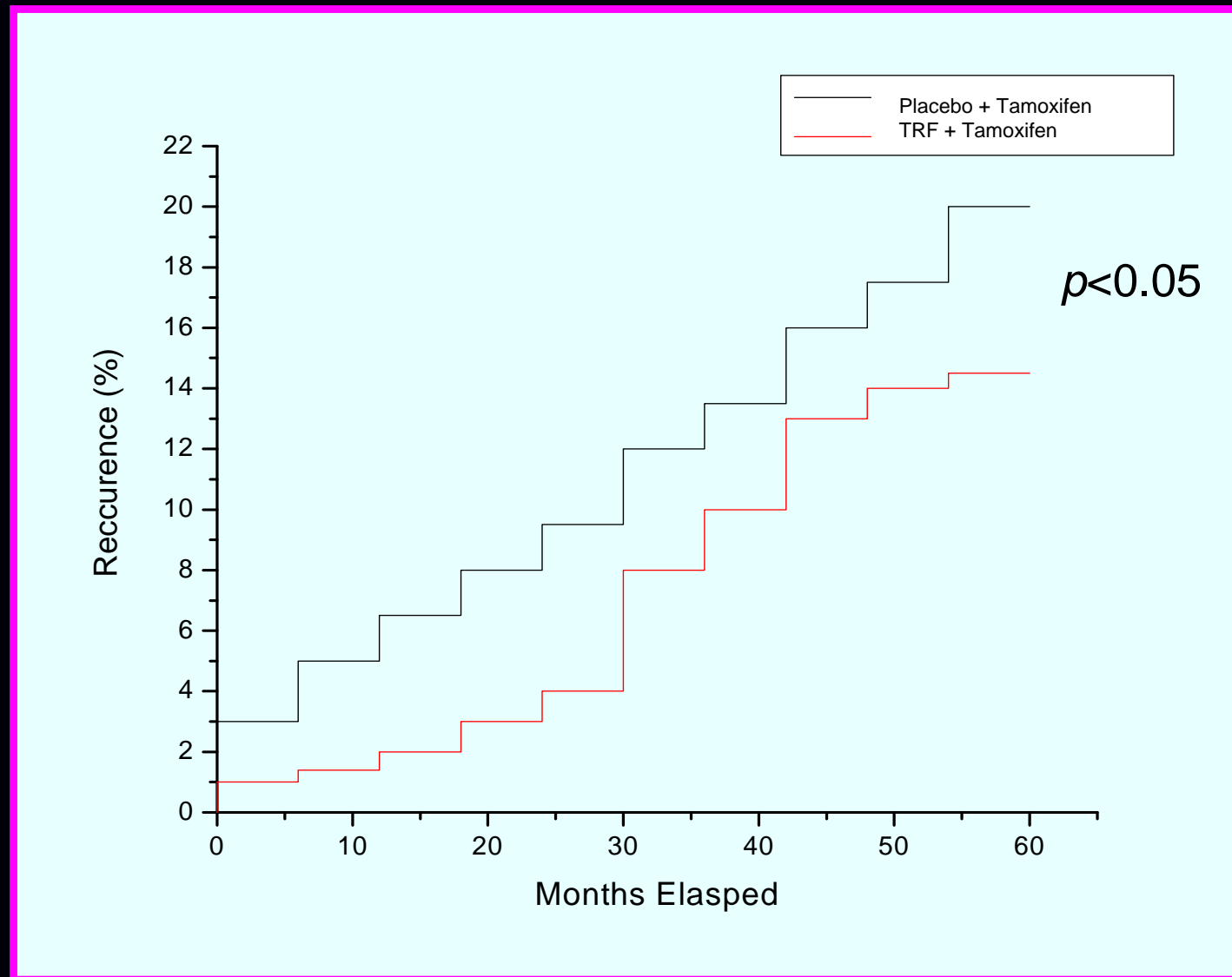
- SURVIVAL & RECURRENCE
- BLOOD PARAMETERS
- LIVER FUNCTION TESTS
- IMMUNE MARKERS
- VITAMIN E PLASMA
- IFN- γ

Survival



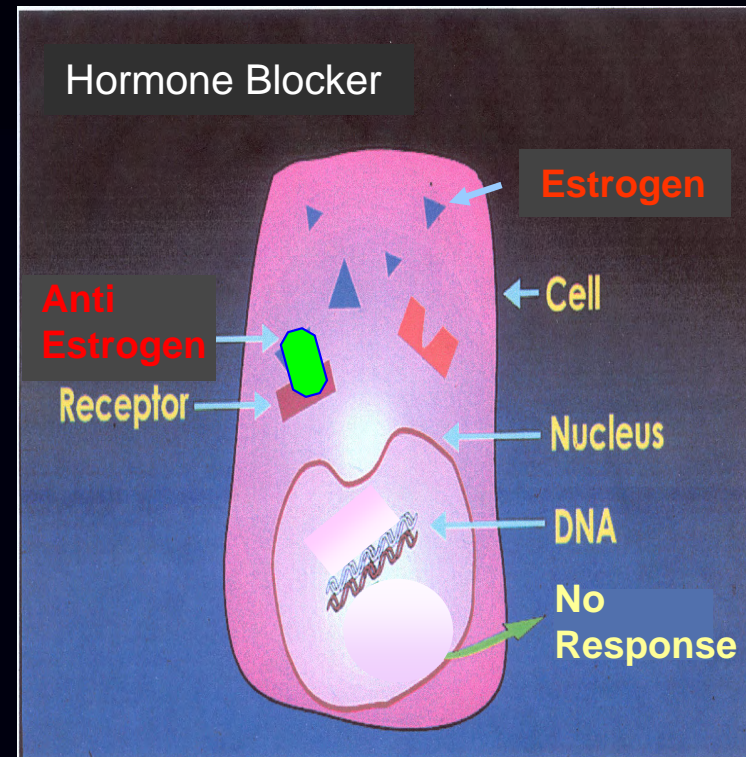
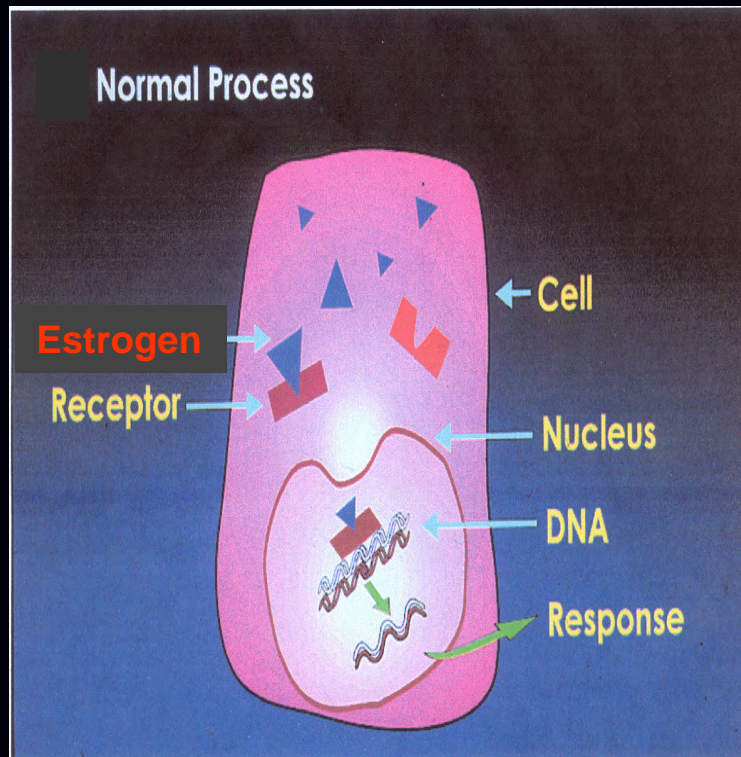
Kaplan Meier Survival Analysis

Time to Tumour Progression

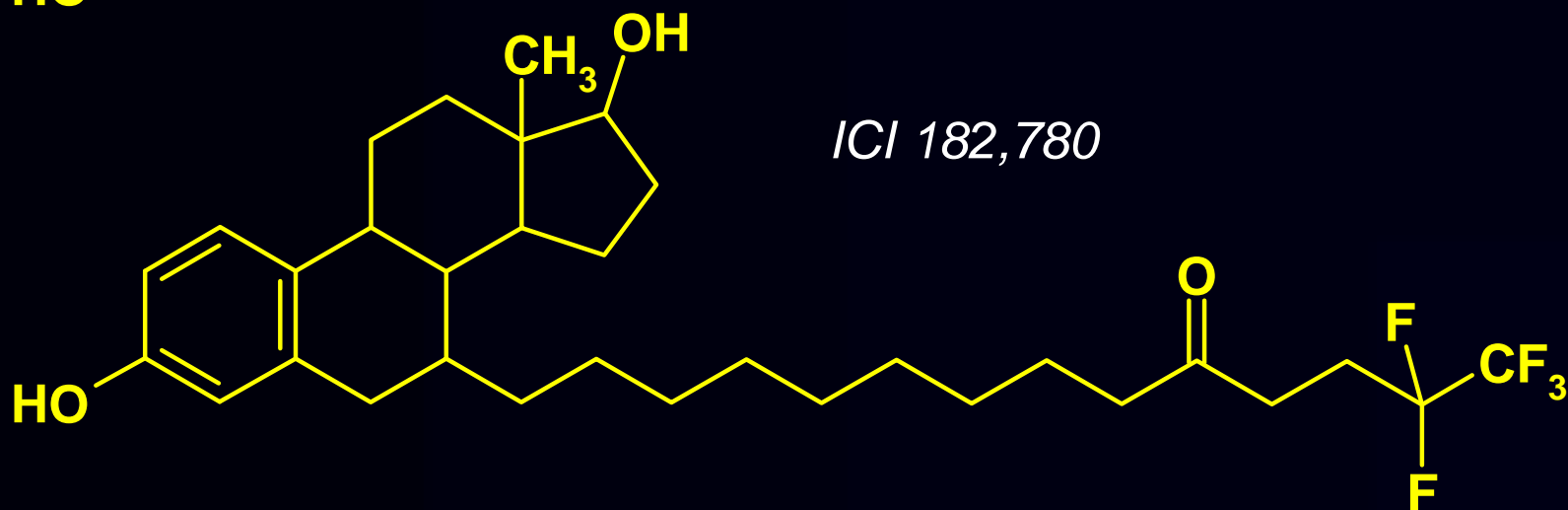


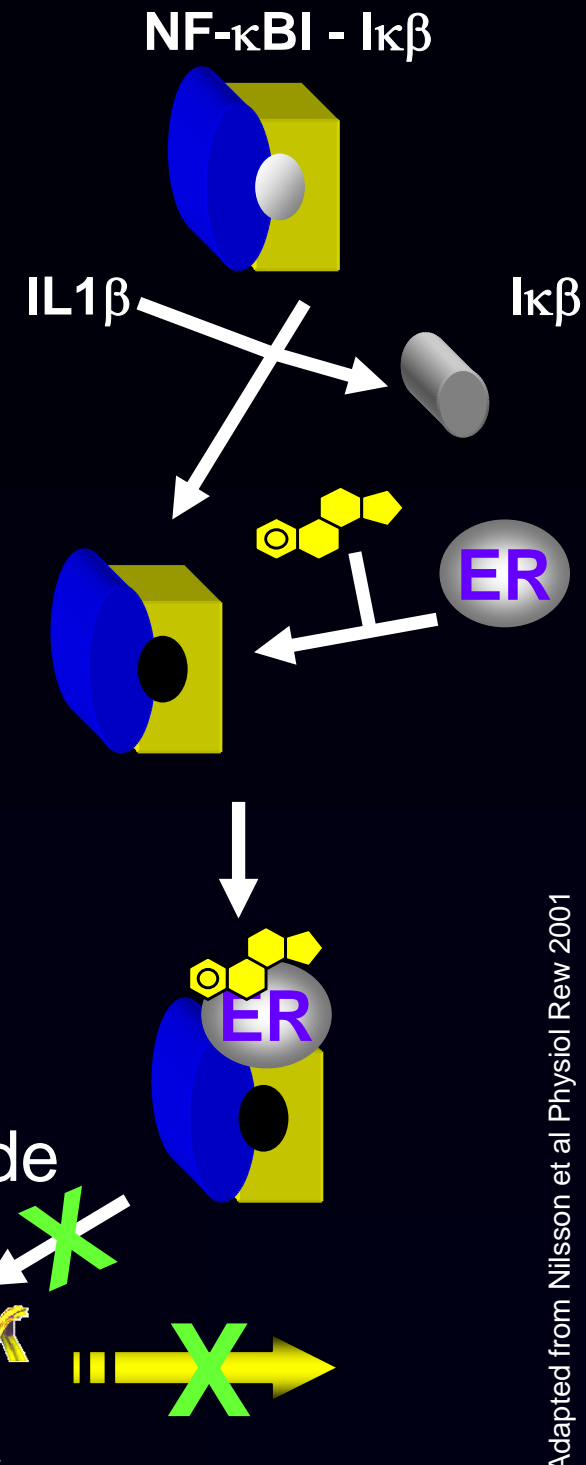
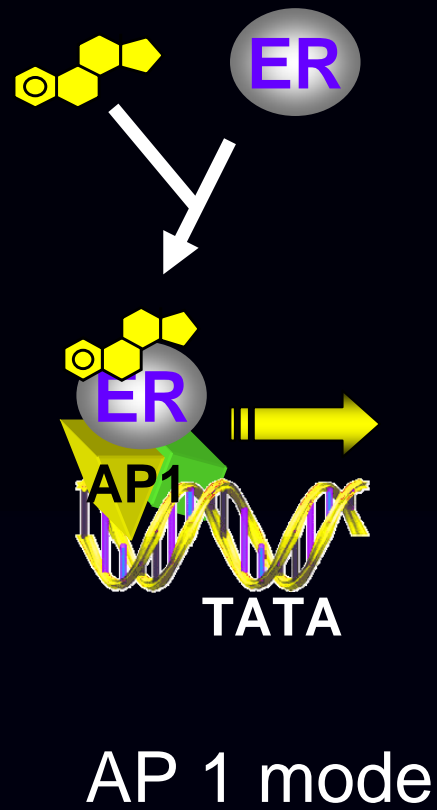
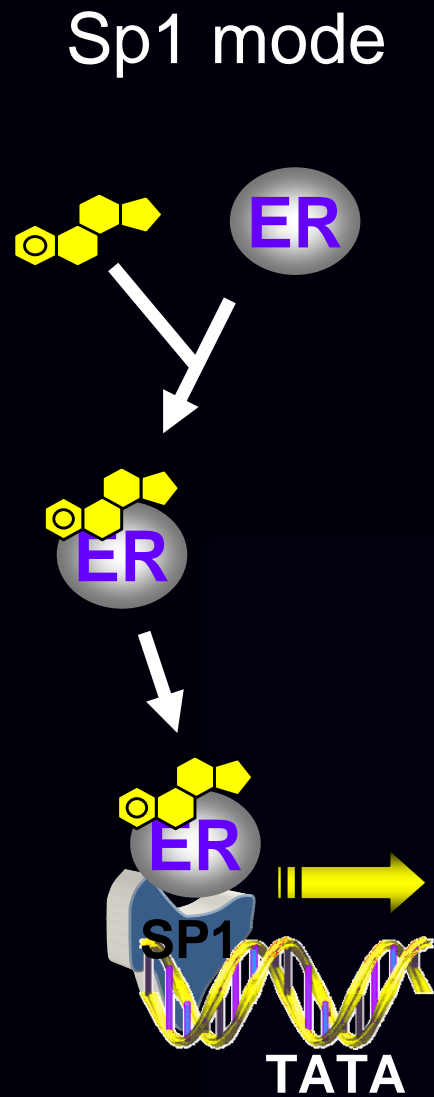
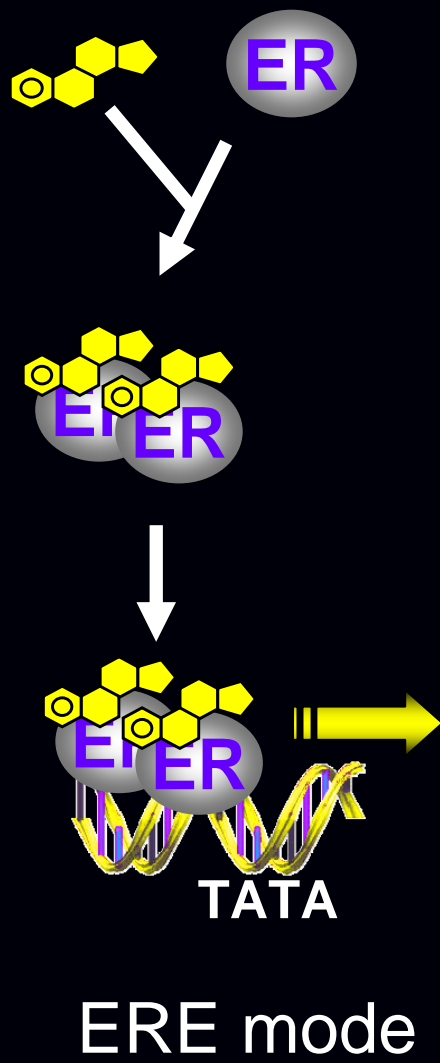
MECHANISM

ER MEDIATED MECHANISM



Structural Similarity





Ligand independent mode
(via receptor phosphorylation)

Commercial Potential

POTENTIAL - Cancer

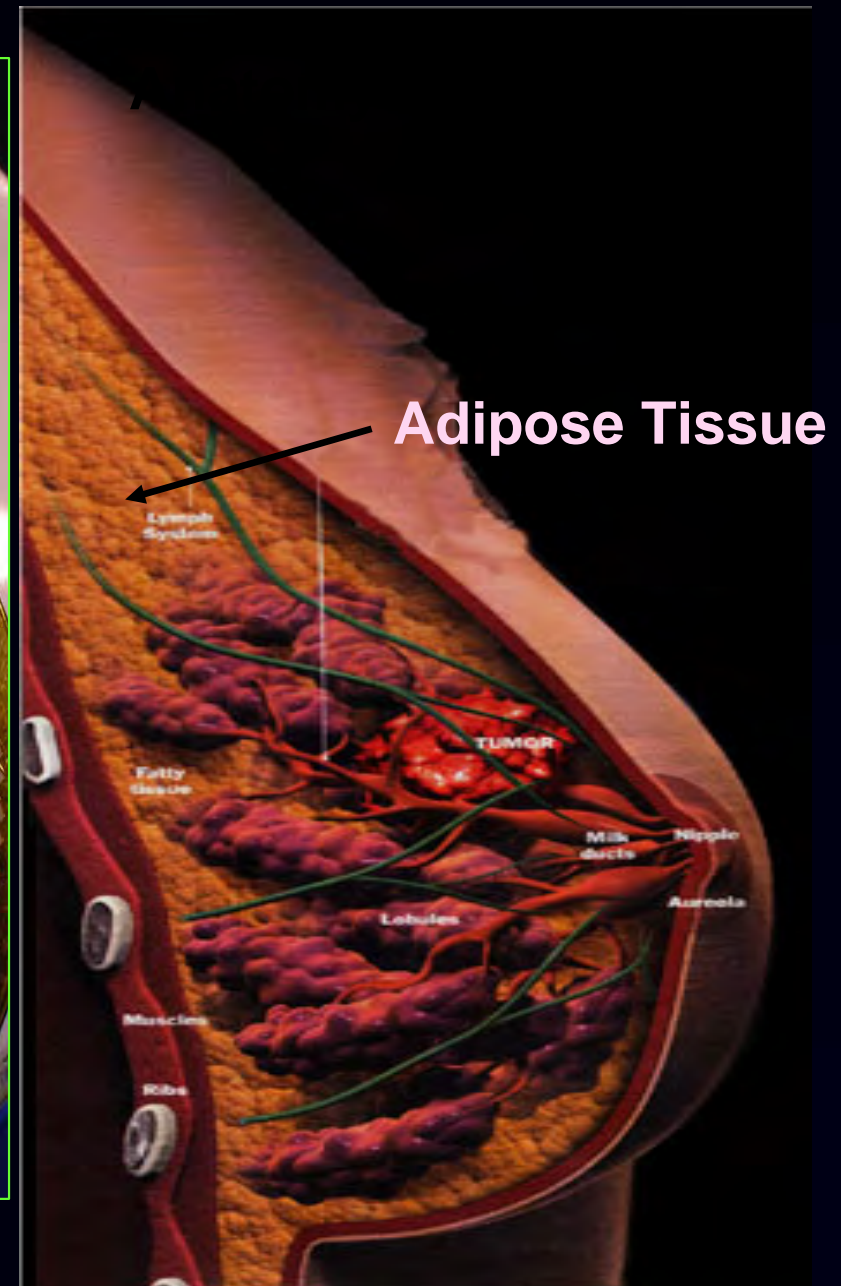
From our very positive results so far we believe that

- tocotrienols can be used for the prevention and treatment of breast cancer
- tocotrienols can substitute and/or supplement tamoxifen
- tocotrienols can be used as a biomarker for the prognosis of breast cancer
- tocotrienols can be used to enhance the immune system especially after chemotherapy and vaccination.

Transdermal Breast Cream



Patent Filed



SUMMARY AND CONCLUSION

- Palm oil is a rich source of essential phytonutrients and enhances the value of the oil
- MPOB has developed a number of processes to extract these phytonutrients
- Commercially carotenoids and tocotrienols from palm oil are available in the market
- Many health benefits have been demonstrated for tocotrienols particularly in breast cancer and neuroprotection
- Various modes through which tocotrienols can modulate transcription of genes. Interaction of ERE, protein-protein interaction with Sp1, AP1 and NFkB proteins



T3 Nutritional Benefits

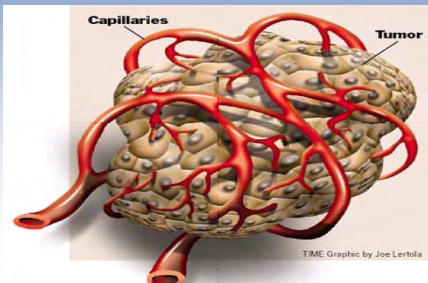
1. Women with malignant tumour had 65% less T3
2. T3 inhibits cancer cell growth *in vivo*
3. T3 causes apoptosis of cancer cells
4. T3 enhances immune system
5. T3 can convert potent estradiol to weak estrone
6. Delta T3 increases efficacy of tamoxifen by 75% at cellular level
7. Promising neuro-and vascular protective effects
8. Potent antioxidant effects

Properties of Tocotrienol: The forgotten Vitamin E

Tocotrienols



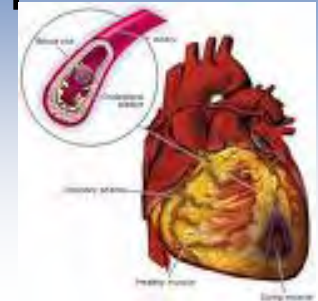
Anti-tumour



Neuroprotection



Cardiovascular
protection



Anti-tumour properties

1. Antioxidant activity
2. Anti-angiogenic activity
3. Anti-proliferation activity
4. Apoptosis induction

1. Antioxidant activity

- phenolic group in the chromane ring binds and neutralizes damaging free radicals

Mechanisms

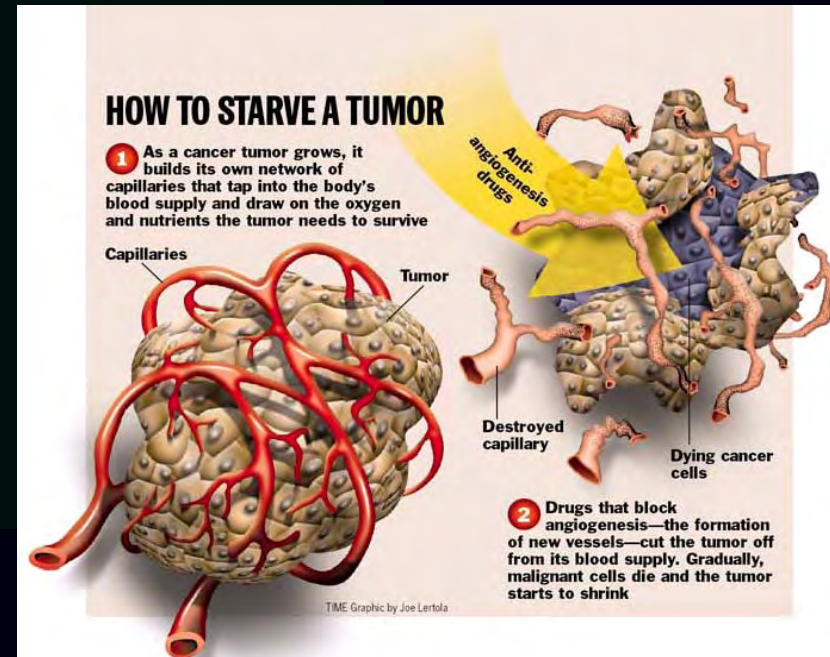
Inhibits lipid peroxidation and its formation of reactive products.

Inhibits the formation of powerful mutagenic nitric oxide species

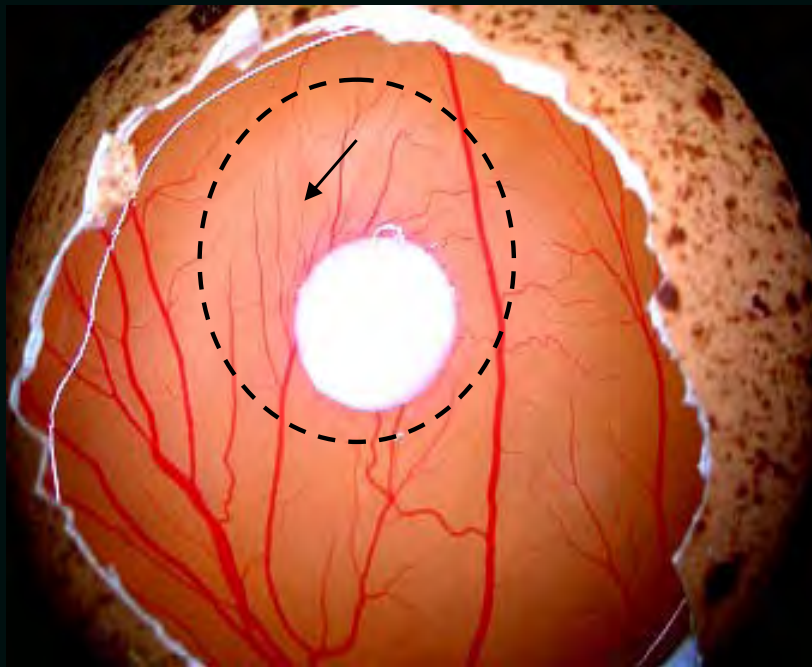
1. peroxynitrite
2. nitosamines.

2. Anti-angiogenic activity

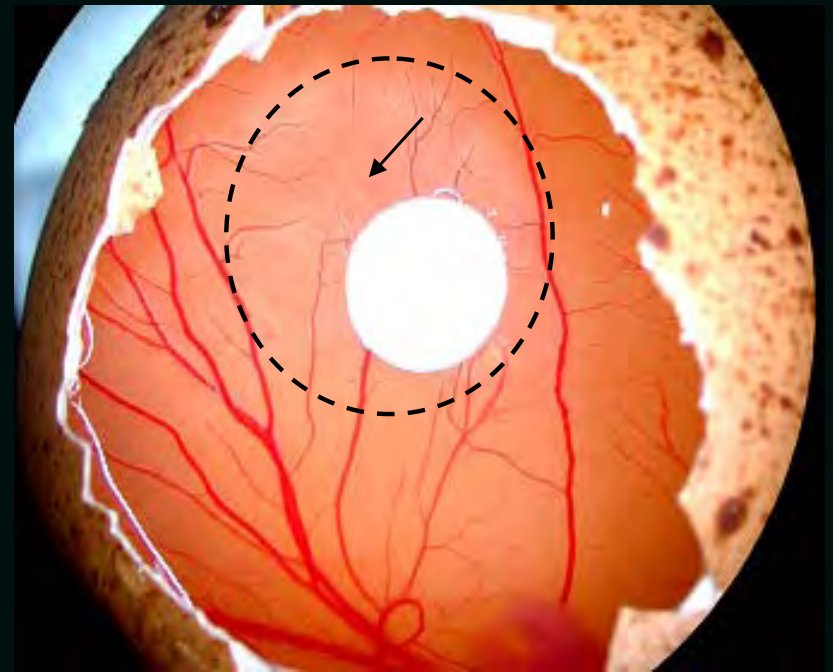
- Prevents formation of blood vessels in cancer.
- Inhibits HUVECs proliferation and migration
- Reduces serum VEGF *in vivo*



- Our laboratory results showed disruption of vascular network in Chick Embryo Chorioallantoic Membrane (CAM) assay with TRF (Weng-Yew *et al.* 2009)



TRF 200 ug/ml at 0 hr



TRF 200 ug/ml at 24 h

3. Anti-proliferation

- Inhibits the growth and proliferation of cancerous cells such as prostate cancer and breast cancer (Nesaretnam *et al.* 1995, 2004), liver and lung cancer (Wada *et al.* 2005)

Mechanisms

PC-3 Human Prostate cancer cells (Nesaretnam *et al.* 2008)

- TRF and T3 induced a specific G2 phase cell cycle arrest

MDA-MB-231 Breast cancer cells (Nesaretnam *et al.* 2004)

- TRF modulated

A) c-myc binding protein MM-1

B) 23-kDa highly basic protein (23-kDa HBP)

C) interferon-inducible protein 9-27 (IFITM-1)

4. Apoptosis induction

- Tocotrienols induce apoptosis of tumours (Nesaretnam *et al.* 2008;Takahasi and Loo 2004)

Mechanisms

PC-3 Human Prostate cancer cells (Nesaretnam *et al.* 2008)

- TRF and dT3 induce Fas receptor/FasL apoptotic pathway

MDA-MB-231 Breast cancer cells (Takahasi and Loo 2004)

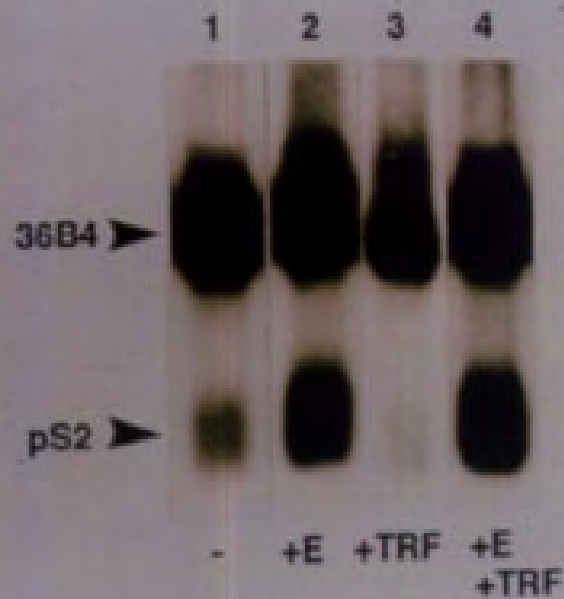
- γ -tocotrienol induced mitochondria-mediated apoptotic pathway
- Mitochondria Membrane Potential (MMP) collapses and initiates apoptosis

Neuroprotection

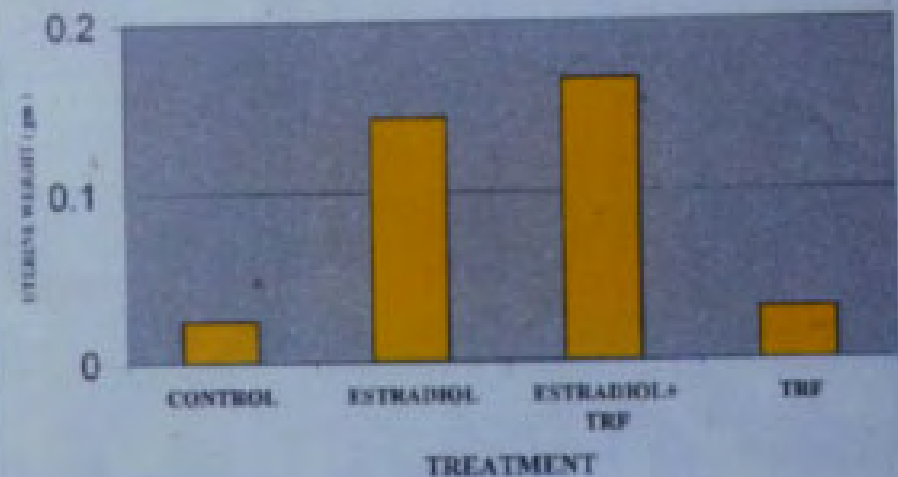
- α -tocotrienols at nanomolar concentration provide neuroprotection (Sen *et al.* 2000)
- Independent of tocotrienols anti-oxidant property
- Tocotrienols inhibit c-Src activity in glutamate-induced neurodegeneration (Khanna *et al.* 2002)



Effect of tocotrienols on pS2 and uterine weight



EFFECT OF OESTRADIOL AND TRF ON UTERINE WEIGHT



Conclusion

- ✓ T3 increased survival time and inhibited recurrence of cancer
- ✓ T3 showed no effect on blood parameters
- ✓ T3 showed an increase in B cells, NK cells and IFN- γ and stimulation of the immune system
- ✓ Various modes through which tocotrienols can modulate transcription of genes. Interaction of ERE, protein-protein interaction with Sp1, AP1 and NFkB proteins
- ✓ An alternative pathway under investigation is in the interaction of T3s with Pregnane receptors PXR (orphan receptor)

CAROTENOIDS

Provitamin A activity

- Improves vitamin A status of lactating women and their infants (Canfield & Kaminsky, 2000., Lietz et al 2000)
- Improve serum retinol concentrations (Stuijvenberg & Benade 2000)
- Combat vitamin A deficiency (Rao, 2000, Scrimshaw, 2000)

Anti-cancer effects

- Breast cancer cells (Nesaretnam et al 2002, Toniolo et al 2001, Zhang et al 1999, Tamimi et al 2005)

Cardiovascular Benefits

- Protection against Ischemia/ Reperfusion heart injury (Rooyen et al 2008)



CARROTS



TOMATOES



EGG YOLK



GRAPE FRUIT



APRICOT

