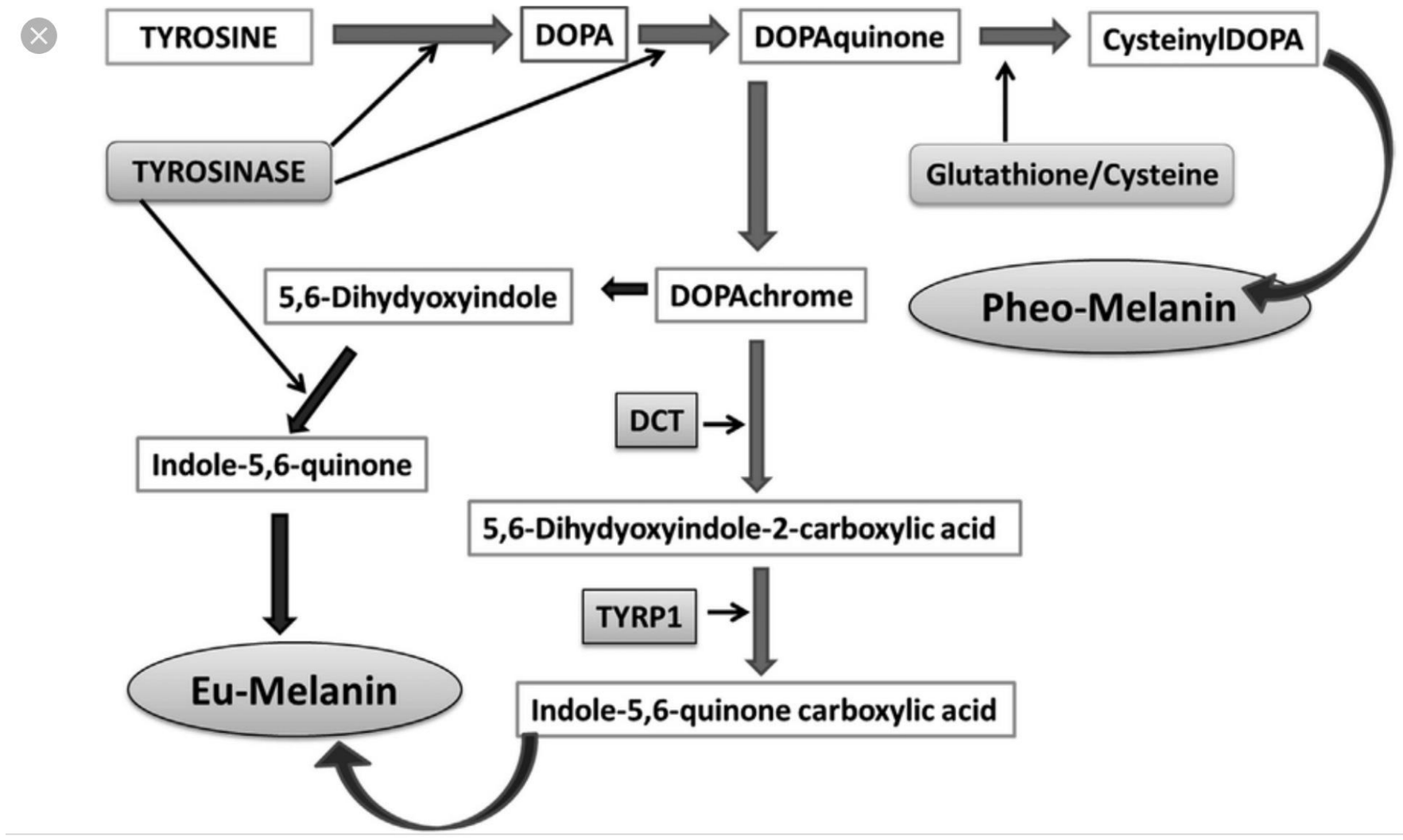
Anti-Tyrosinase Activity of Tocotrienol in Skin Blemishes

Melanin are responsible for skin and hair colors. They play an important role in the defense against harmful UV radiation

The formation of pigment melanin occurs within the melanosome of skin melanocytes

Increased production and accumulation of melanin are characteristics of a large number of skin diseases, including melasma, post-inflammatory hyperpigmentation and lentigo.



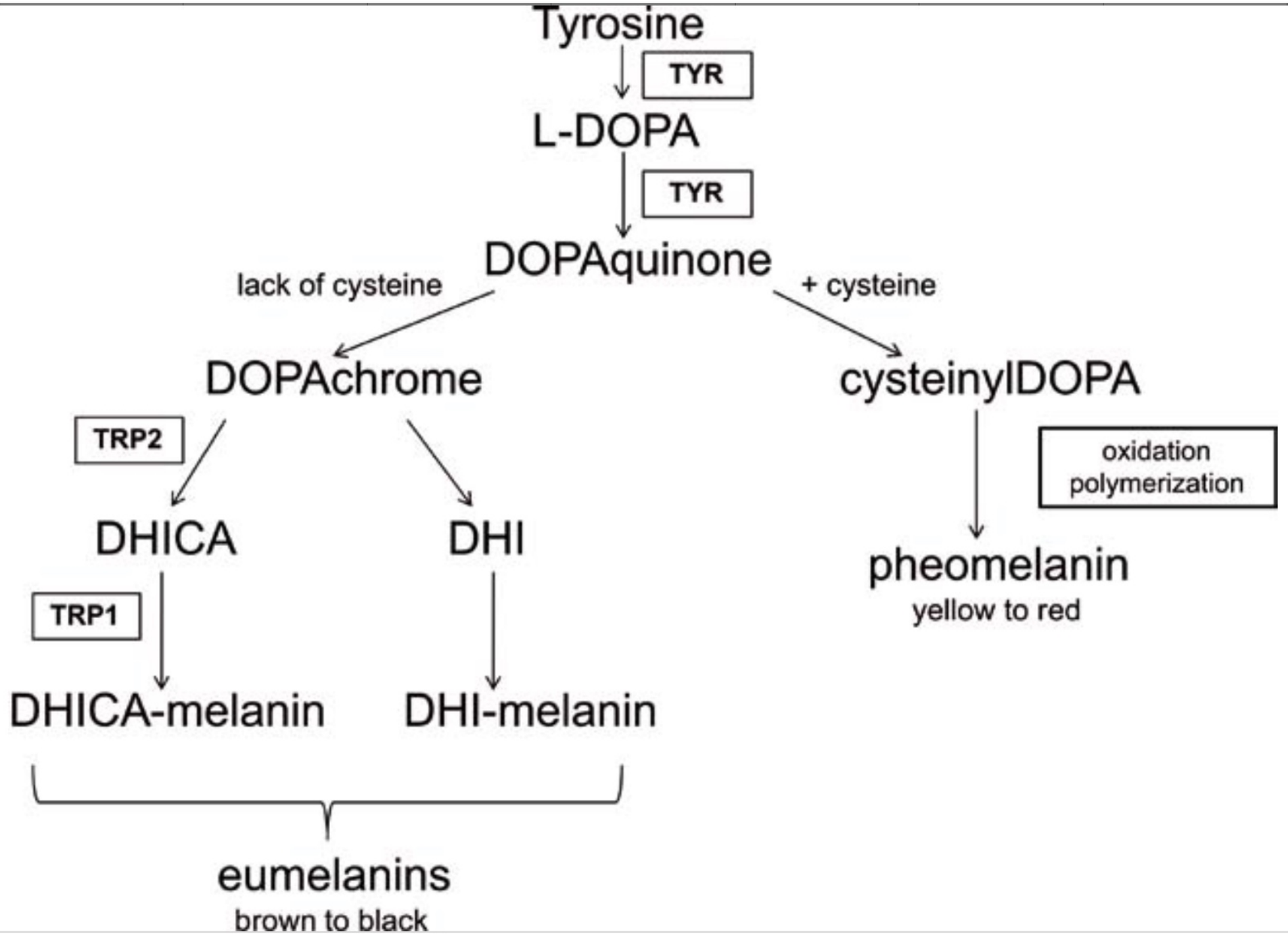
researchgate.net

Figure 12.3 Schematic overview of melanin synthetic pathway and the involvement of melanogenic

- Modulation of tyrosinase activities therefore represents a key process for the regulation of cutaneous melanogenesis

Tyrosinase is a pivotal enzyme in melanin synthesis. The majority of whitening or lightening agents act by specifically reducing the activity of tyrosinase via several mechanisms:

1) **prior to melanin synthesis (interfering with its transcription and/or glycosylation)**
2) **during melanin synthesis (tyrosinase inhibition, peroxidase inhibition and reduction of byproducts)**
3) **and after melanin synthesis (tyrosinase degradation, inhibition of melanosome transfer, acceleration of skin turnover)**


Tyrosine
TYR
L-DOPA
TYR
DOPAquinone
lack of cysteine
+ cysteine
DOPAchrome
cysteinylDOPA
TRP2
oxidation
polymerization
DHICA
DHI
pheomelanin
yellow to red
TRP1
DHICA-melanin
DHI-melanin
eumelanins
brown to black

Gamma- and delta-tocotrienols are lipid soluble agents that can penetrate skin lipids effectively to release natural nutrients and produce whitening of the skin. Compared to other water soluble agents (kojic acid, arbutin, sodium lactate), tocotrienols can penetrate more deeply through the skin to deliver the active ingredients in a controlled and constant manner," said Dr. Daniel Yap, the leading scientists for the study and head of R&D at Davos Life Science.

The study found that tocotrienols are effective in suppressing the activity of tyrosinase – an enzyme that is essential for the production of melanin in skin cells. Specifically, two isomeric forms of tocotrienols – gamma and delta – have been found to significantly suppress the action of tyrosinase in melanin-generating cells from human and mouse. Also of great interest is that since skin pigmentation is a hallmark of melanoma – a malignant form of skin cancer – the control of tyrosinase activity may provide a basis for treating patients with this type of cancer.

In the study, researchers treated both human and mouse melanoma cells with tocotrienols. They found that gamma- and delta-tocotrienols significantly suppressed tyrosinase activity, even when used in very low doses compared to other common skin whitening agents. These results suggest that the unsaturated isoprenoid side chain of tocotrienols – a unique structural property of this class of compounds – may account for their capability in inhibiting melanin production.

Gamma and delta-tocotrienols produced the same inhibitory effect on tyrosinase as much higher concentrations of kojic acid, arbutin and sodium lactate. In fact, tocotrienols are shown to have at least 150 times more potency than sodium lactate, kojic acid and arbutin in suppressing the biosynthesis of melanin. Interestingly, when tocotrienols are combined with kojic acid, the two compounds work in synergy and reinforce the inhibition of tyrosinase activity.

HISTORICAL DEVELOPMENT

1922

- Herbert Evans and Katherine Bishop (Berkeley researchers)
- discovered Vitamin E in green leafy vegetables
- supported fertility and named TOCOPHEROL in 1924
- Greek Tokos -childbirth, phero – to bring forth, ol – alcohol properties of molecule
- deficiency caused severe degenerative diseases – ataxia, muscular degeneration and infertility

1938

- Vitamin E chemically synthesized by Karrer

1965

- Schwartz rediscovered it as a factor 2 antioxidant

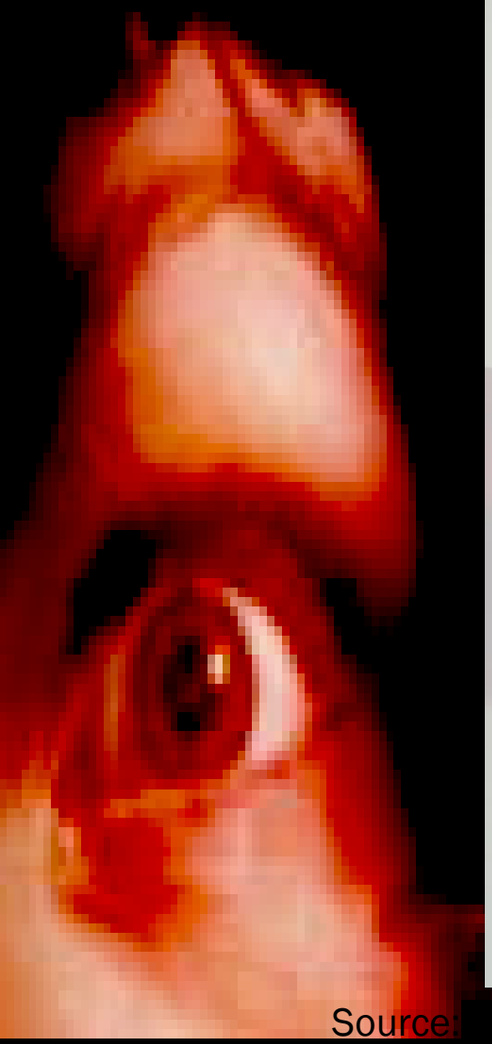
HISTORICAL DEVELOPMENT

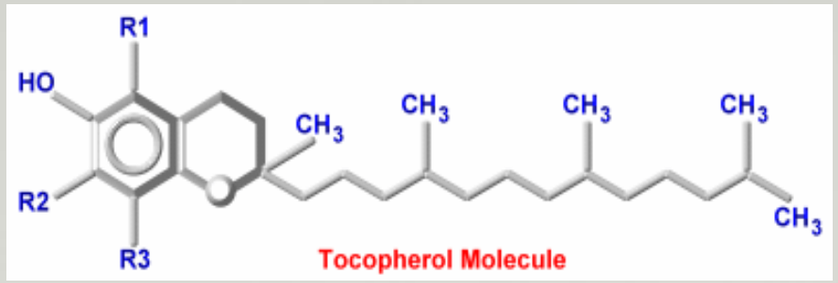
1964

- Tocotrienols discovered
- Anticholesterol, anticancer etc. activities noted in vitro, in animals and humans over the past 20 years only

Tocotrienol is not the same as Tocopherol

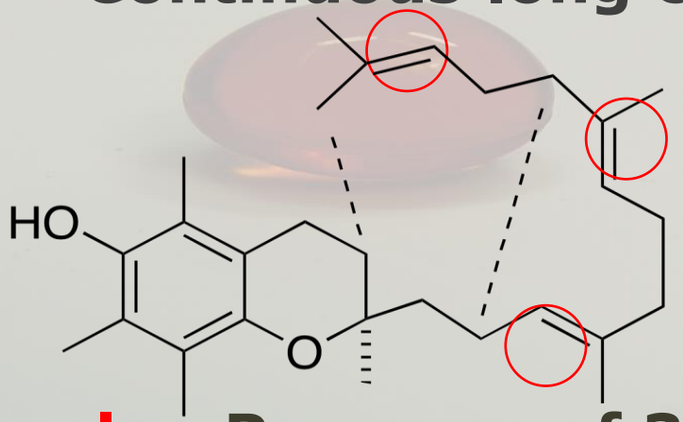
Chemical Structure





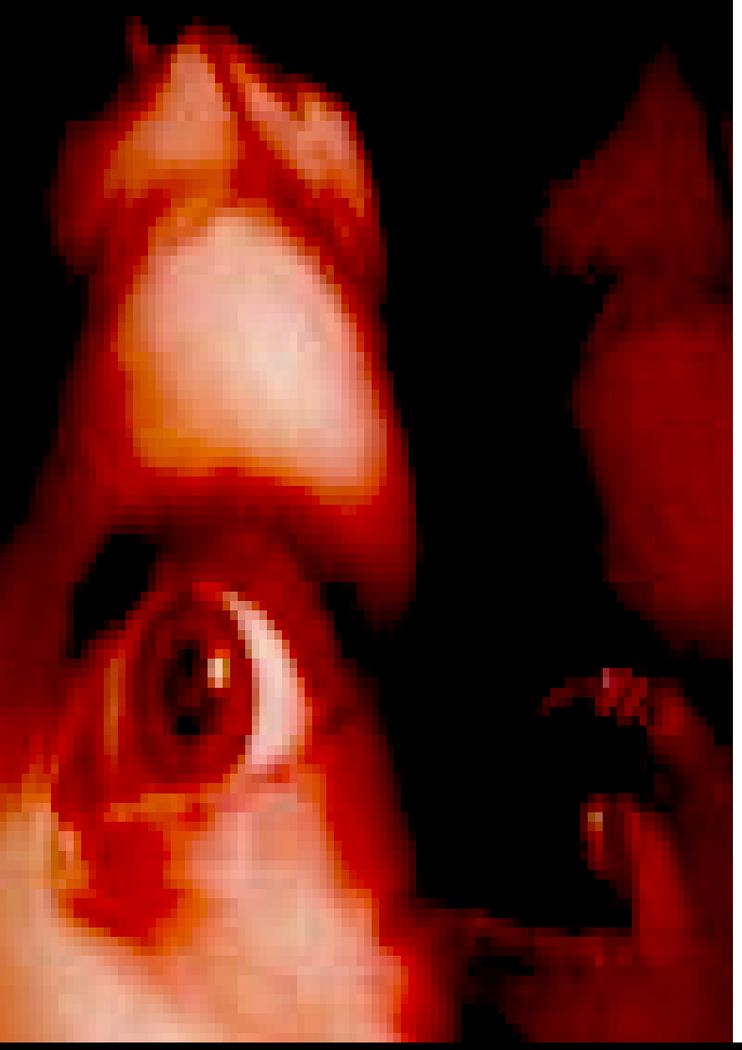
Tocopherol Molecule

Continuous long chain



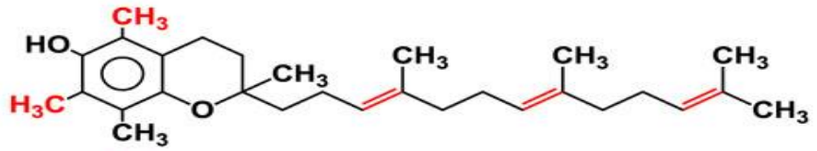
Tocotrienols - Presence of 3 double bonds which enhance antioxidant and anti-carcinogenic properties

Source: tural Forms of Radical Biology) and Medici

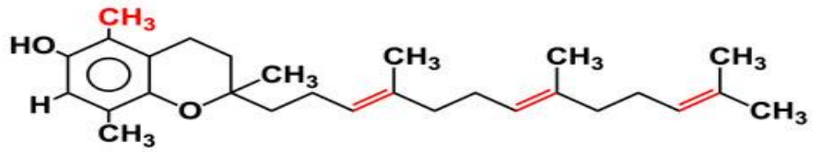


Tocotrienols

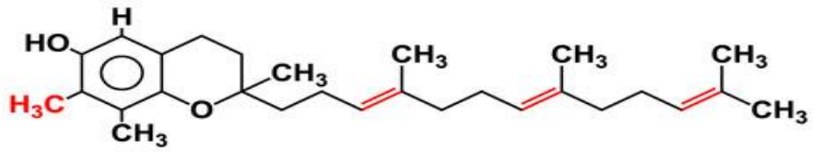
Alpha



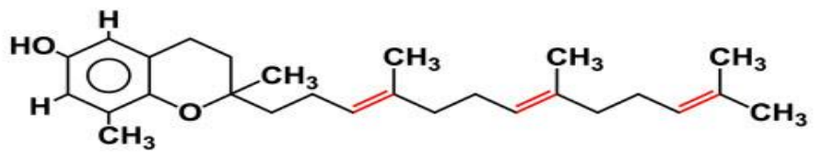
Beta



Gamma

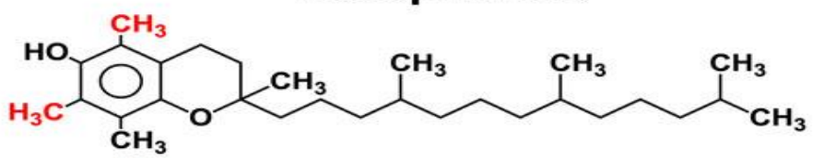


Delta



Tocopherols

Alpha



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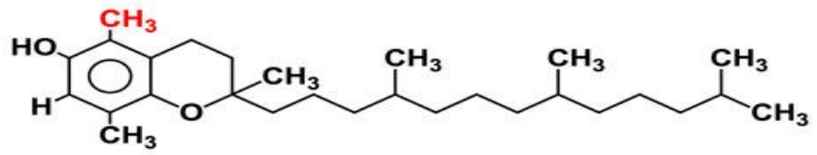
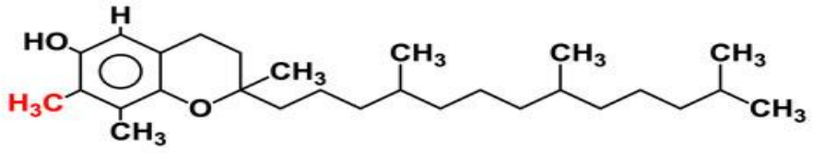
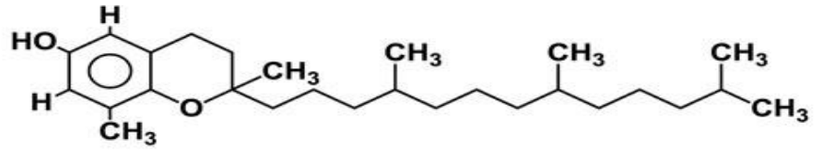


Gamma



Delta



TOCOTRIENOLS

SOURCE

- in a small fraction of plants and mostly in seed endosperm of most monocots
- Cereal grains (wheat, rice, barley), palm oil, annatto oil
- Very limited in dicots – tobacco
- found rarely in vegetative tissues of plants
- inedible plant products – Rubber Latex
- safe for human consumption from 200-1000 mg/day (Yu et al 2006)

TOCOTRIENOL

* Natural fat-soluble vitamin
* Richest source: Palm fruit/Annatto seeds
* Has 4 isomers

Tocotrienols (T3)	α (alpha)-tocotrienol	Mixed tocotrienols
	β (beta)- tocotrienol	
	γ (gamma)- tocotrienol	
	δ (delta)- tocotrienol	

Red annatto

Palm oil
940 mg/kg

Barley
910 mg/kg

Rice bran
465 mg/kg

Grape seed oil
380 mg/kg

Oat
210 mg/kg

Hazelnut
209 mg/kg

Maize
200 mg/kg

Wheat germ oil
189 mg/kg

Olive oil
180 mg/kg

Buckthorn Berry
130 mg/kg

Rye
92 mg/kg

Flax seed oil
25.1 mg/kg

Poppy seed oil
20.5 mg/kg

Safflower oil
11.8 mg/kg

TOCOTRIENOLS

Changing Trends in Vitamin E Research

- less than 1% of entire literature over the past 30 years on Vitamin E addresses tocotrienols
- more than 2/3 of PubMed literature on tocotrienols published after 2000

TOCOTRIENOLS

Why has Tocotrienols not been studied as well?

1. Discovered late – 1964

- isolated in latex of rubber plant

- 1990's when cholesterol lowering and anticancer effects described

2. Alpha tocopherol transfer protein (TTP)

- selectively transports tocopherols

- 1997 discovery that oral tocotrienol not transported by TTP and does not reach vital organs

- natural isomers of vitamin E get transported to vital organs in the absence of TTP

TOCOTRIENOLS

- isomers COMPETE with specific transporting mechanisms
- tocotrienol supplementation should be performed with minimized co-presence of tocopherols
- when given together, more favorable uptake of alpha tocopherol over alpha tocotrienol

Tocopherol-tocotrienol ratios

Rice Bran oil– 50:50

Palm oil – 25:75

Annato oil 1:99.9 (90% delta and 10% gamma)

Other Therapeutic Benefits of Tocotrienols

✓ Hair Growth Promotion

- **Efficacy of Tocotrienols in a Double-blind Placebo-controlled Clinical Trial 28 volunteers with mild to moderately severe ongoing hair loss, 8-month study conducted at the School of Pharmaceutical Sciences, Universiti Sains Malaysia; Tocotrienol 50mg 2x daily**

41.8% increase in no. of hair for 8-month treatment

✓ Inhibition of Breast Cancer Cell Growth

* Delta-tocotrienol **is 3 times more powerful than Tamoxifen** in stopping multiplication of breast cancer cells. When use in combination, the effect is **45 times more effective than using Tamoxifen alone** (synergistic effect)

Carrolis KK (U.of Western Ontario, presented at 7th Asian Congress of Nutrition 1995

Tocotrienol effects on human subjects

Anti-aging effect
• T3 (160 mg × 8 mo) reduced DNA damage in older healthy adults (64)
• T3 improves long-term clinical outlook and survival in patients with neurodegenerative familial dysautonomia
Skin disease
• Topical α-T3 supplementation inhibited lipid peroxidation after benzoyl peroxide treatment of human skin

Tocotrienol shows distinct Biological Activities

Area	Characteristics / Health Properties
Brain Health / Neuroprotection	•Nanomolar concentration prevents glutamate-induced neurotoxicity •Slows down progression of white matter lesion
Liver Health	•Attenuates non-alcoholic fatty liver disease (NAFLD) •Mitigates liver stiffness •Maintains healthy liver function
Heart Health	•Cholesterol-lowering property •Regression of atherosclerosis •Supports arterial compliance •Maintains healthy lipid profile (total cholesterol & low density lipoprotein)
Skin Nutrition / Hair Health	•Surgical scar treatment •Burn wound healing •Biopsy wound healing •Improved skin characteristics •Promotes hair growth
Antioxidative Properties	•40-60 times stronger antioxidant than alpha-tocopherol
Immune Support	•Improved cell-mediated immune response

BIOLOGICAL FUNCTIONS OF TOCOTRIENOLS

Prostate Cancer

- Gamma tocotrienol increases efficacy of radiotherapy (Kumar et al 2006)
- significant apoptosis seen

Liver Cancer

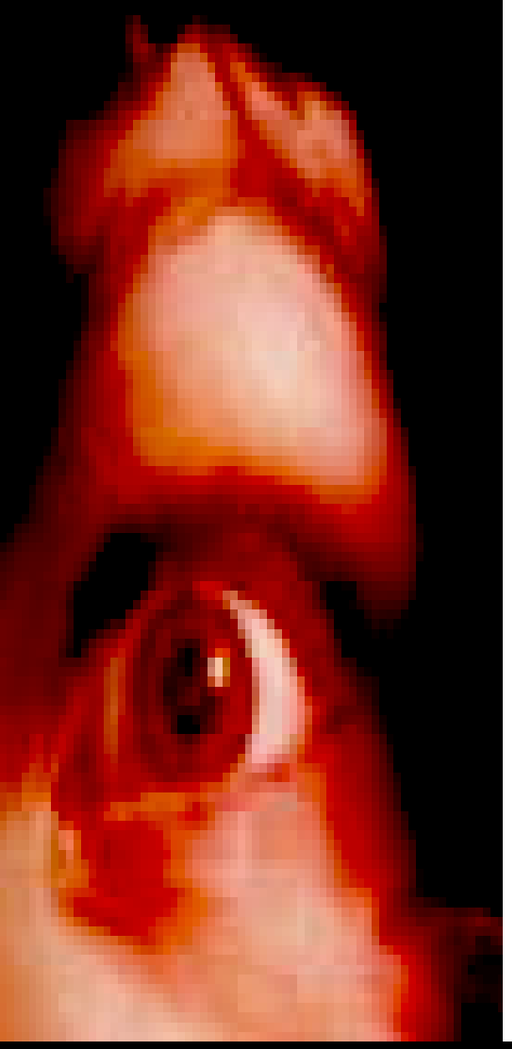
- induced apoptosis of hepatoma cells by capsace 3 acitvation (Har and Keong 2005)
- Gamma tocotrienol more effective

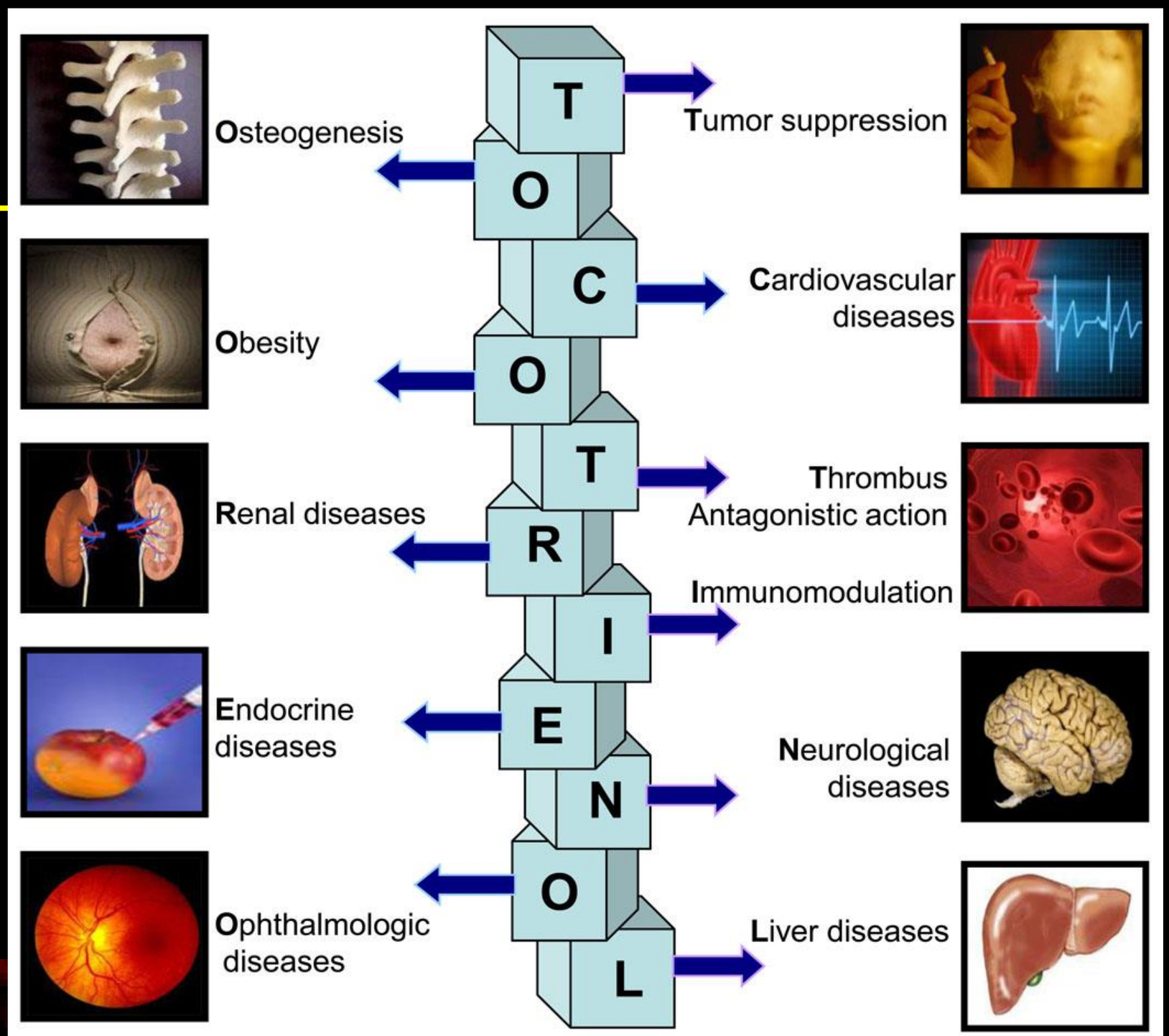
Colon Cancer

- inhibits telomerase activity of colorectal adenocarcinoma cells (Shay et al 2006)

Melanoma

- only cancer where both tocotrienol and tocopherol were significantly effective




Osteogenesis
Obesity
Renal diseases
Endocrine diseases
Ophthalmologic diseases
T
O
C
O
T
R
I
E
N
O
L
Tumor suppression
Cardiovascular diseases
Thrombus Antagonistic action
Immunomodulation
Neurological diseases
Liver diseases