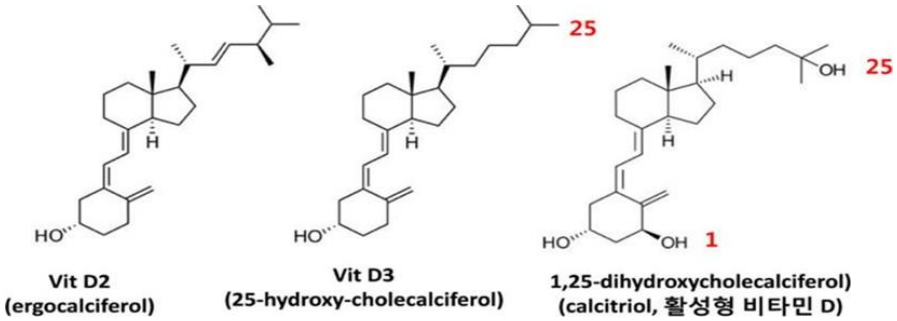


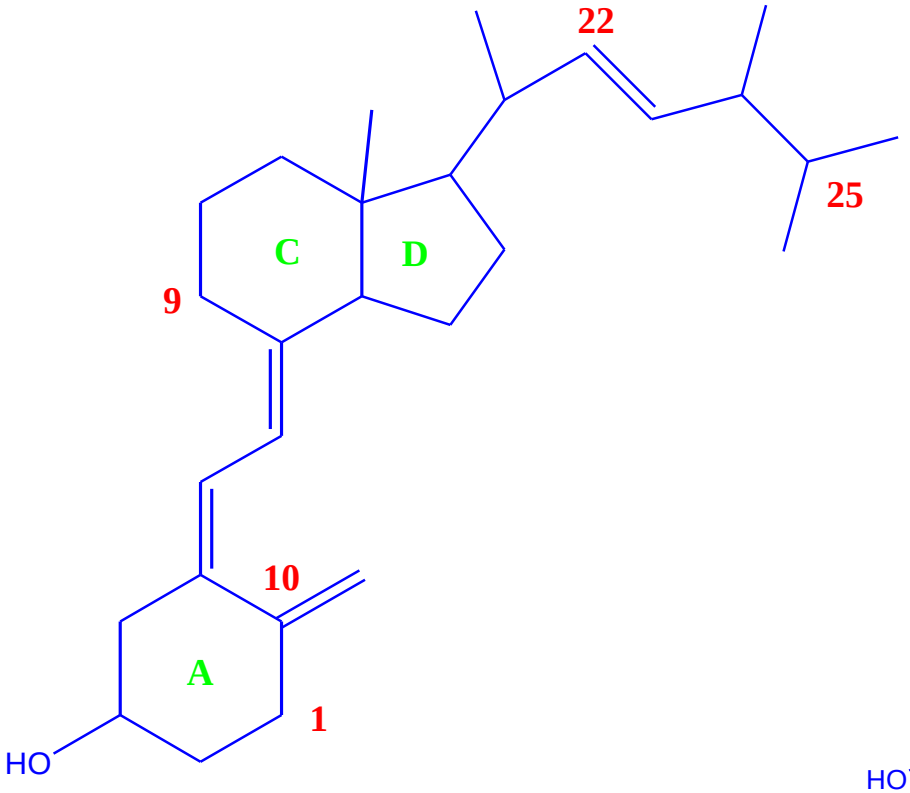
Vit D2
(ergocalciferol)

Vit D3
(25-hydroxy-cholecalciferol)

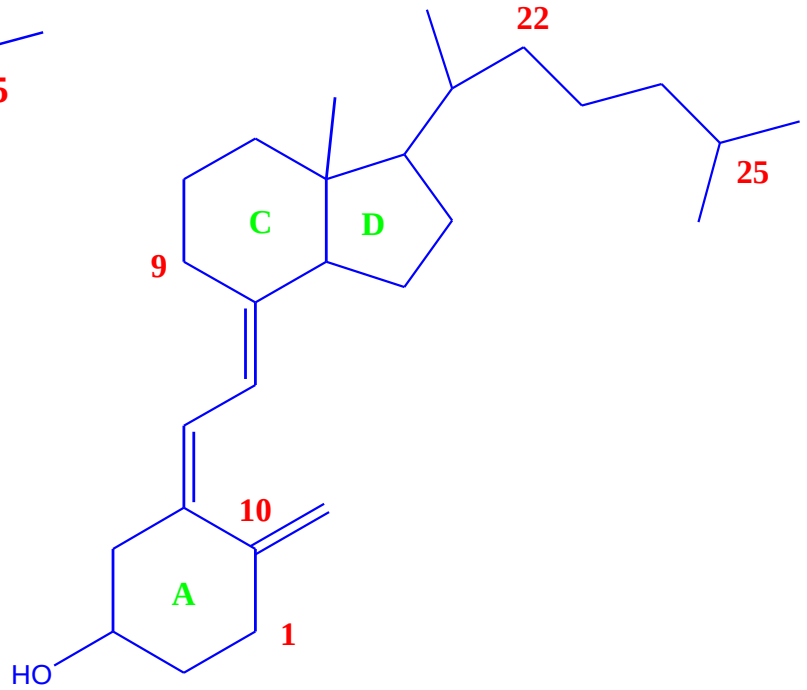
1,25-dihydroxycholecalciferol)
(calcitriol, 활성형 비타민 D)

2- Vitamin D

- Vitamin D is a group of fat-soluble secosteroids.
- Several vitamers are available.
- The two major forms are vitamin D_2 or ergocalciferol, and vitamin D_3 or cholecalciferol.
- vitamin D without a subscript refers to either D_2 or D_3 or both.
- They are known collectively as calciferol.
- Vitamin D_3 is not itself biologically active, but must be modified by the body to have any physiologic effects.



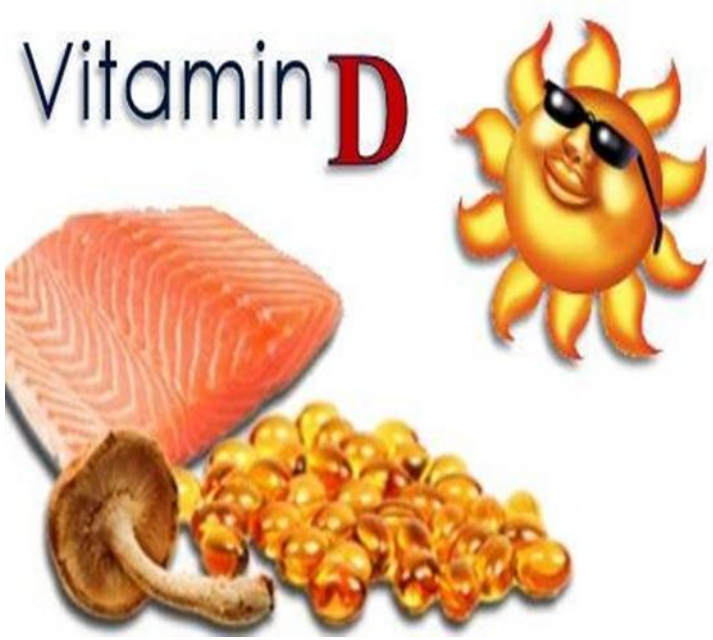
Vitamin D_2



Vitamin D_3

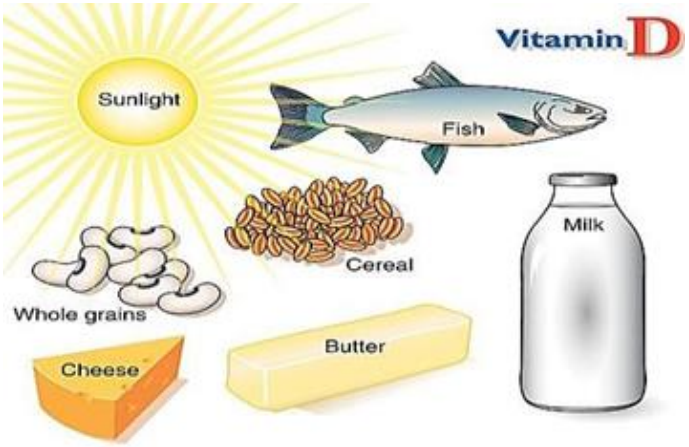
Significance of Vitamin D

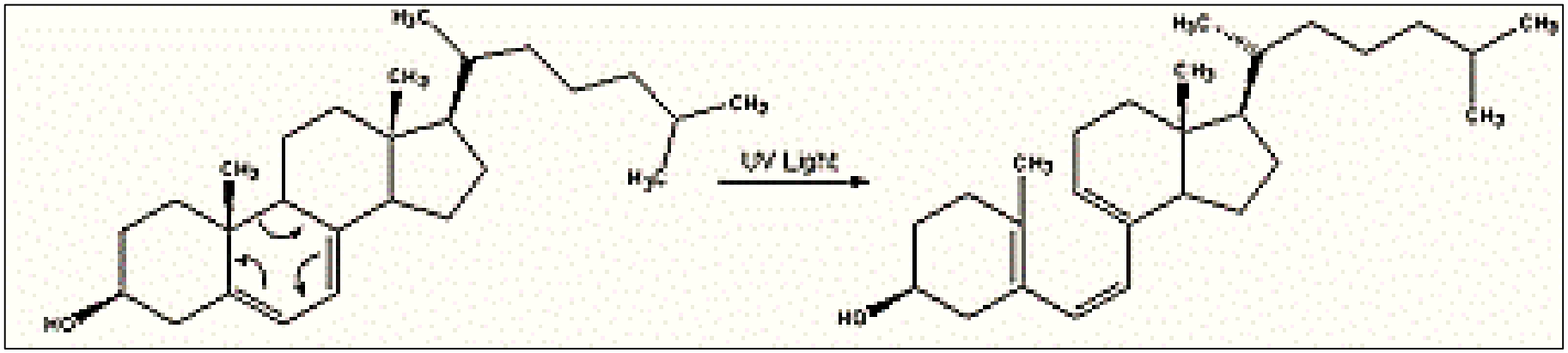
- It is the sunshine vitamin.
- It is produced in the body by the photolytic action of ultraviolet light on the skin (considered as hormone).
- It is important in the maintenance of healthy bones and teeth.

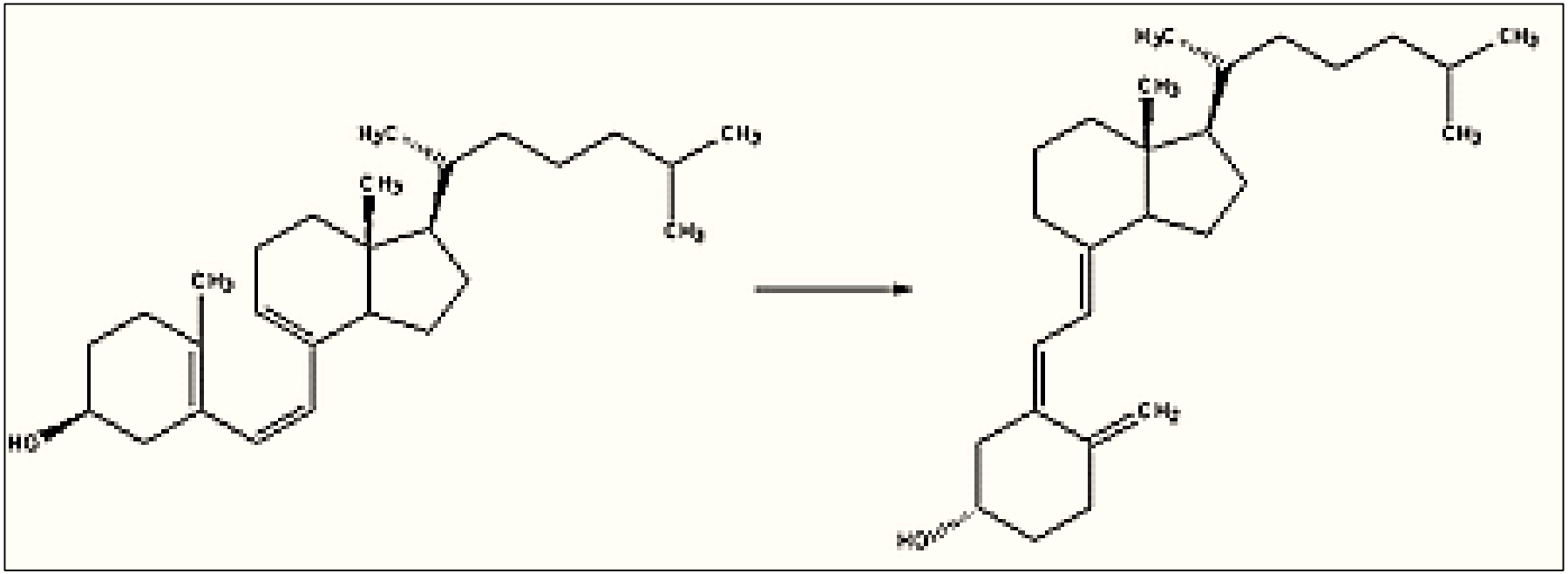


Source of vitamin D

- Sun light.
- Affected by many factors such as skin types, age and environment.
- Vitamin D producing UV irradiation is greatest at noon (10 AM and 2 PM).




UV Light



- Vitamin D, as ergocalciferol (D_2) or cholecalciferol (D_3) is sparsely represented in nature.
- The provitamins are common in both plants (ergosterol) and animals (7-dehydrocholesterol).
- Tuna, fish liver oil and salmon are good source of vitamin D.
- Generally, most foods contain low amounts of vitamin D and it has become the practice in many countries to fortify certain foods

Absorption of vitamin D

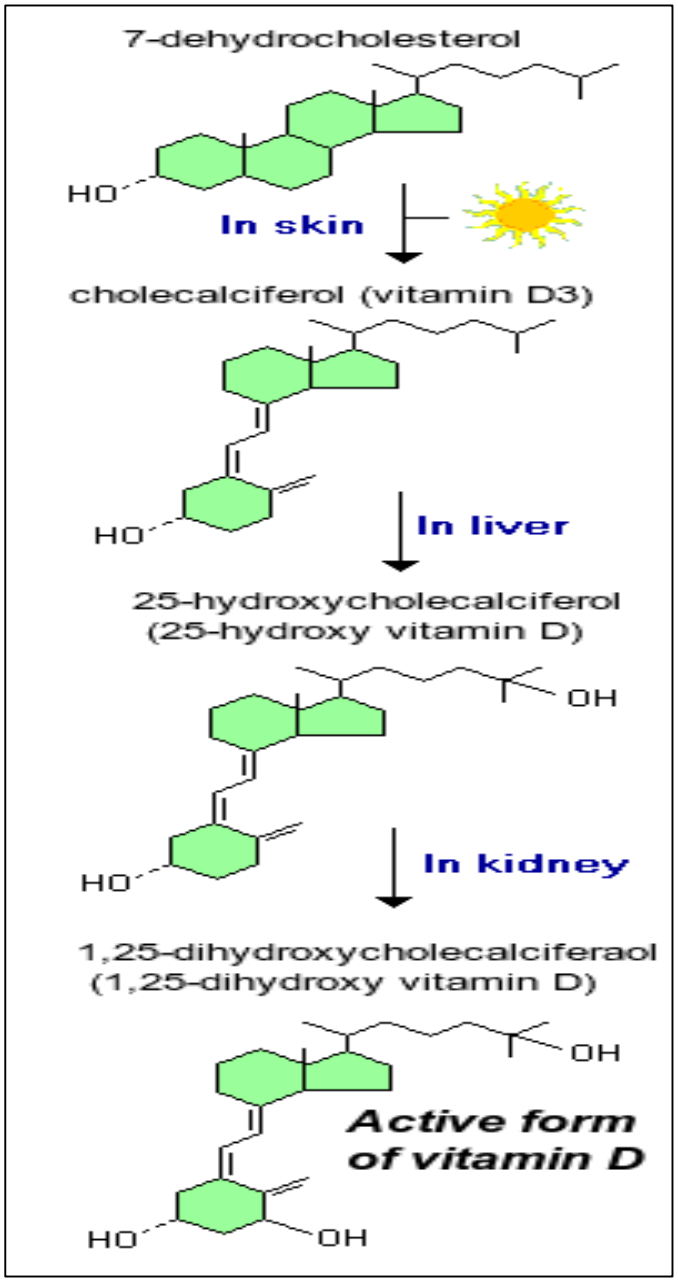
- It is absorbed from small intestine.

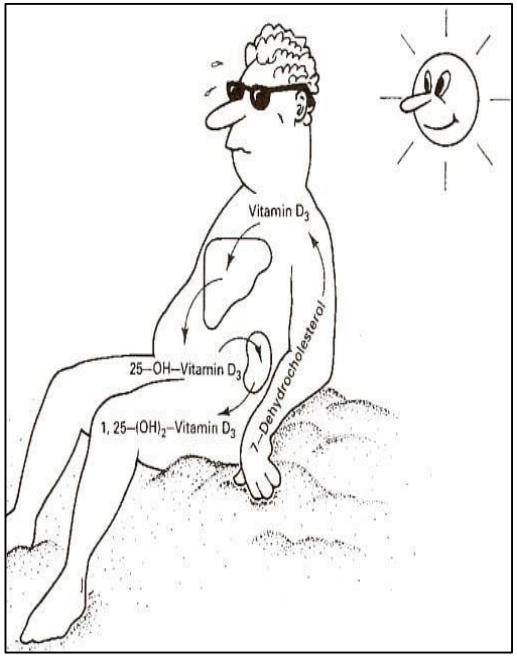
Transport of vitamin D

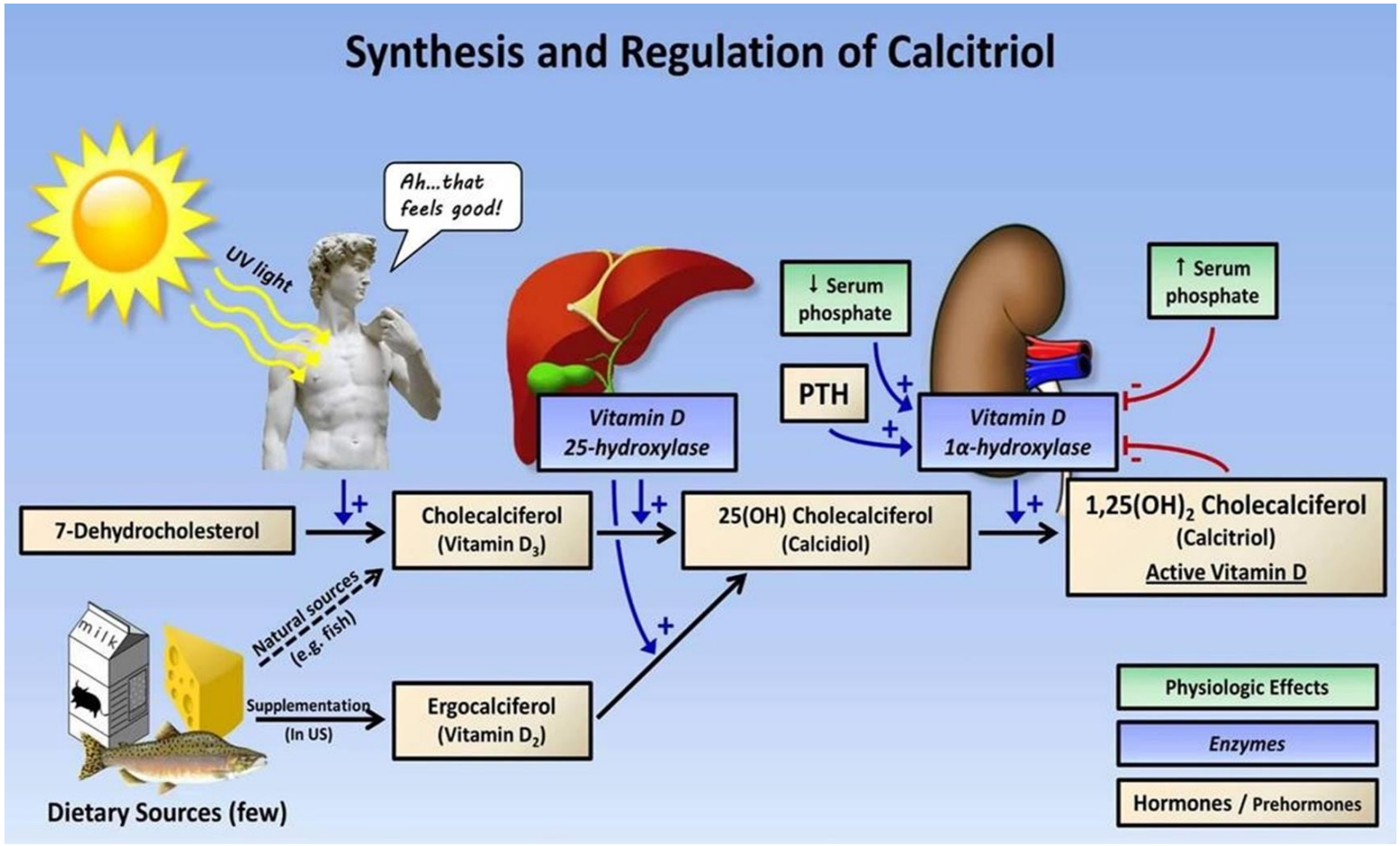
- It is transported in the plasma in association with DBP.
- It is stored in fatty tissues like adipose in the form of D_3 and 25-OH-D_3.
- Tissues of kidneys, liver, lungs, aorta and heart tend to accumulated 25-OH-D_3.
- 25-0H-D_3 crosses placenta.
- 1,25-$(OH)_2$-D_3 is distributed intracellularly and bound to VDR.

- 1,25-$(OH)_2$-D_3 and its receptors are distributed in certain tissues such as kidney, intestine, bone and other tissues like placenta, parathyroid, pancreatic islets, and certain gastric and brain cells.
- Metabolism of vitamin D
- Vitamin D is converted in the liver by hydroxylation of C-25 to yield 25-OH-D_3 (calcidiol).
- 25-OH-D_3 (calcidiol) is the major circulating form of the vitamin.
- It is not biologically active.
- The enzyme involved for the hydroxylation is vitamin D 25-hydroxylase.
- The enzyme is only poorly regulated by hepatic concentration of vitamin D, with little or no inhibition by 25-OH-D_3.

- 25-OH-D_3 is further hydroxylated at C-1 to yield 1,25-$(OH)_2$-D_3 (calcitriol).
- The reaction is catalyzed by 25-OH-1-hydroxylase, which is located in the kidney.
- This enzyme is tightly regulated by many factors such as PTH, calcitonin, hypo and hypercalcemia, 1,25-$(OH)_2$-D_3, hypo and hyperphosphatemia.


7-dehydrocholesterol
HO
In skin
cholecalciferol (vitamin D3)
HO
In liver
25-hydroxycholecalciferol
(25-hydroxy vitamin D)
OH
HO
In kidney
1,25-dihydroxycholecalciferaol
(1,25-dihydroxy vitamin D)
OH
Active form
of vitamin D
HO
OH


Vitamin D_3
25–OH–Vitamin D_3
1, 25–$(OH)_2$–Vitamin D_3
7–Dehydrocholesterol


Synthesis and Regulation of Calcitriol
Ah…that feels good!
UV light
Vitamin D 25-hydroxylase
↓ Serum phosphate
PTH
Vitamin D 1α-hydroxylase
↑ Serum phosphate
7-Dehydrocholesterol
Cholecalciferol (Vitamin D3)
25(OH) Cholecalciferol (Calcidiol)
1,25(OH)2 Cholecalciferol (Calcitriol)
Active Vitamin D
Natural sources (e.g. fish)
Supplementation (In US)
Ergocalciferol (Vitamin D2)
milk
Dietary Sources (few)
Physiologic Effects
Enzymes
Hormones / Prehormones

Metabolic function of vitamin D

1- The maintenance of calcium and phosphate homeostasis through genomic and non genomic pathways.

- 1,25-$(OH)_2$-D_3 induces the production of calcium binding protein (CaBP).
- Increase the intestinal Calcium absorption.
- Increase the intestinal phosphate absorption.
- 1,25-$(OH)_2$-D_3 stimulates the resorption of both phosphate and calcium in the distal renal tube (phosphate more than calcium).

- Vitamin D plays role both in the formation (mineralization) of bone as well as in the mobilization of bone mineral (demineralization).
- At hypocalcemia case, PTH is secreted, which causes:

A- Phosphate diuresis from kidney.

B- Stimulation of 25-OH-1-hydoxylase and leads to formation of 1,25-$(OH)_2$-D_3.

C- Both 1,25-$(OH)_2$-D_3 and PTH act in bone to promote the mobilization of calcium and phosphate.

- Under hypercalcemia, Calcitonin (CT) is secreted from thyroid gland and causes:

A- Suppression of bone mobilization.

B- Increases the renal excretion of both calcium and phosphate.

C- 25-OH-1-hydroxylase feedback inhibited by 1,25-$(OH)_2$-D_3.

- Vitamin D function can be affected by some trace elements such as zinc and iron.
- Deprivation of zinc diminishes the 1,25-$(OH)_2$-D_3 response to low calcium intake.
- Zinc may indirectly affect renal 25-OH-D_3-1-hydroxylase.
- Iron deficiency has been shown to reduce 25-OH-D_3 response to supplementation with vitamin D.
- Iron deficiency also known to impair the absorption of fat, vitamin A and D.

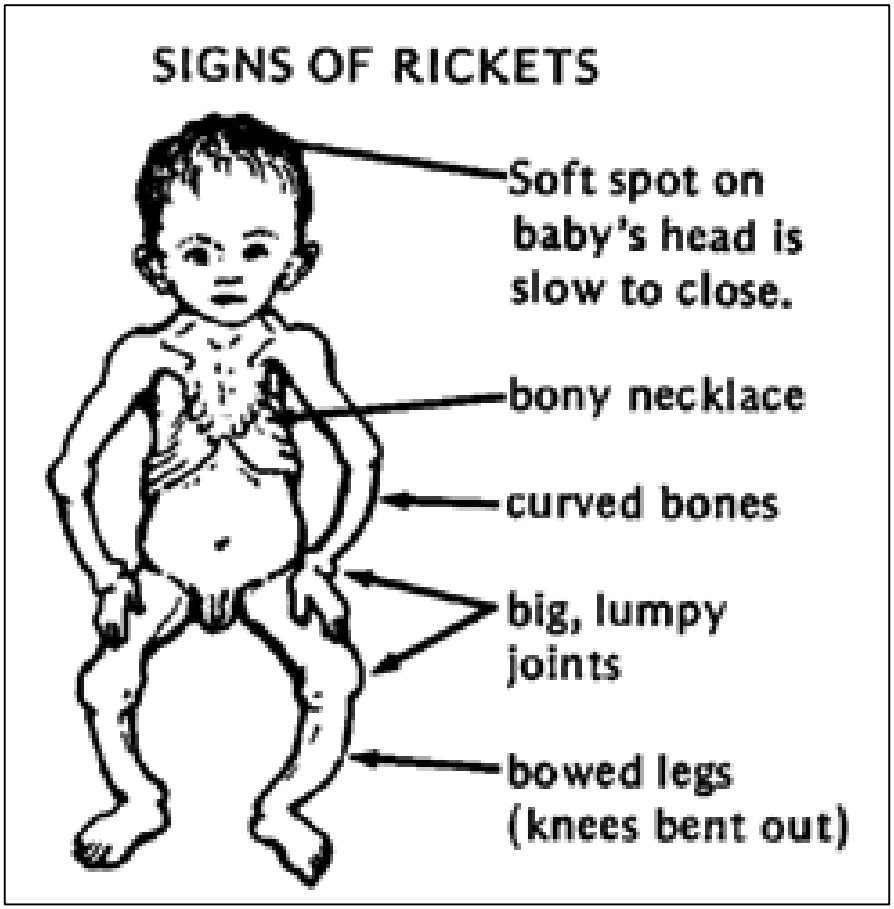
- Nonclassical functions of vitamin D
- Presence of 1,25-$(OH)_2$-D_3 in many tissues such as pancreas, skin, brain and some endocrine glands suggests a more general function in these tissues.
- All these effects are still speculative, however, it may be involved in regulating the temporal/spatial distribution of intracellular calcium.
- Studies have shown that 1,25-$(OH)_2$-D_3 can decrease keratinocyte sensitivity to EGF-receptor-mediated growth factors can increase the transcription of transforming growth factor β1 and can regulate a cytokine cascade involved in the accumulation of leukocytes during skin inflammation.

Recommended Daily Allowance (RDA)

- 600 IU/day (15 µg/day) for healthy people from age of one year and older.
- 400 IU/day for younger.

Vitamin D deficiency

- Primary vitamin D deficiency.
- Secondary vitamin D deficiency.
- It leads to privational rickets in children and privational osteomalacia in adult.
- Rickets appears in 6 to 24 month old children, with impaired mineralization of the growing bone and accompanying bone pain, muscular tenderness and hypocalcemic tetany.
- Old children show deformations of the softened femurs leads to bow leg.


SIGNS OF RICKETS
Soft spot on baby's head is slow to close.
bony necklace
curved bones
big, lumpy joints
bowed legs (knees bent out)


Normal anatomy
Rickets

- Osteomalacia characterized by muscular weakness and bone tenderness.
- It involves the failure to mineralize bone matrix and results in increase in the ratio of nonmineralized bone to mineralized bone.
- Patients with osteomalacia are at increased risk of fractures of all types, but particularly those of the wrist and pelvis.

Nonprivational causes of vitamin D deficiency

1- Anticonvulsant drugs

- E.g., Phenobarbital, Phenylhydrantoin induce the catabolism of 25-OH-D_3 and 1,25-$(OH)_2$-D_3.

2- Hypoparathyroidism.

3- Nephrotic syndrome.

- Clinical condition involving renal tubular degeneration and characterized by edema, albuminuria, hypoalbumunemia and usually hypercholesterolemia.
- Osteoporosis refers to the degeneration of already constructed bone making them brittle, while osteomalacia is an abnormality in the building process of bone making them soft.

Uses of vitamin D

- Vitamin D deficiency, which can be treated with sunlight 5-10 minutes two days per week or vitamin D supplements.
- Dose is dependent on the severity of the deficiency and blood level of 25-OH-D_3 (40-70 ng/ml).

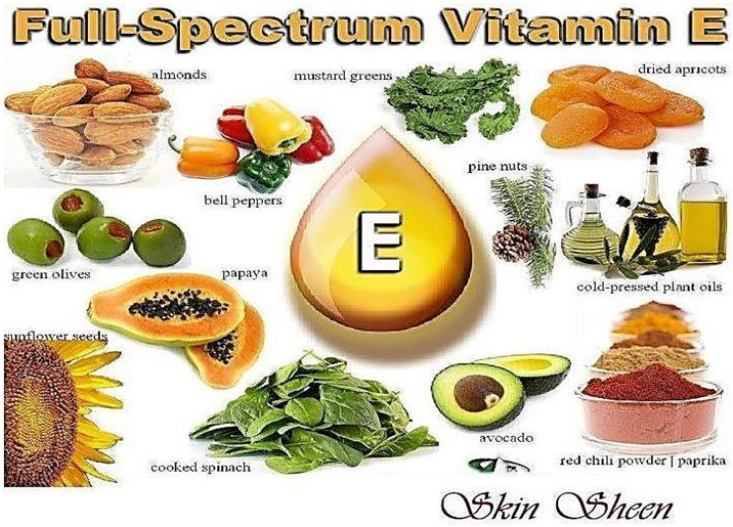
Note

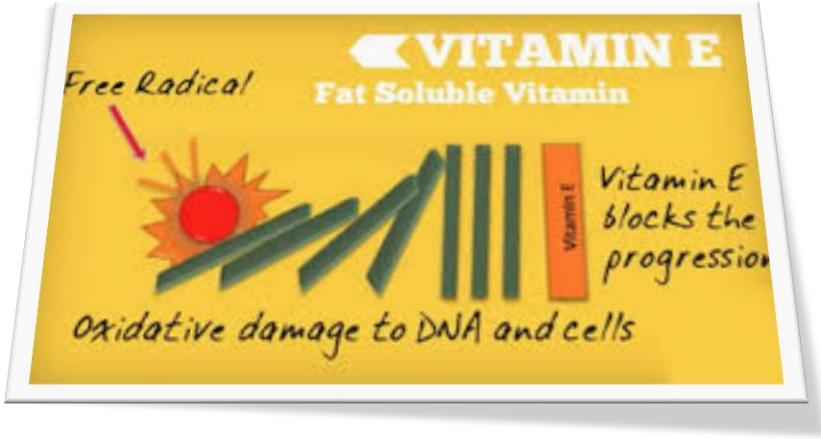
- Prolonged exposure to sunlight degrades the vitamin D precursor in the skin, preventing its conversion to the active vitamin. It also causes skin cancer.

Vitamin D toxicity

- Excessive intakes of vitamin D are associated with increases of 25-OH-D_3.
- Vitamin D_3 is 10-20 times more toxic than D_2.
- Hypervitaminosis D resulted in increases of enteric absorption and bone resorption of calcium and decreases in serum PTH and glomerular filtration rate.
- It also increases the concentration of zinc from reserve.
- The persons with toxicity show anorexia, vomiting, headache, drowsiness, diarrhea and polyuria and at chronic cases calcinosis may occur.

3- Vitamin E


Full-Spectrum Vitamin E
almonds
mustard greens
dried apricots
bell peppers
pine nuts
E
green olives
papaya
cold-pressed plant oils
sunflower seeds
avocado
cooked spinach
red chili powder | paprika
Skin Sheen

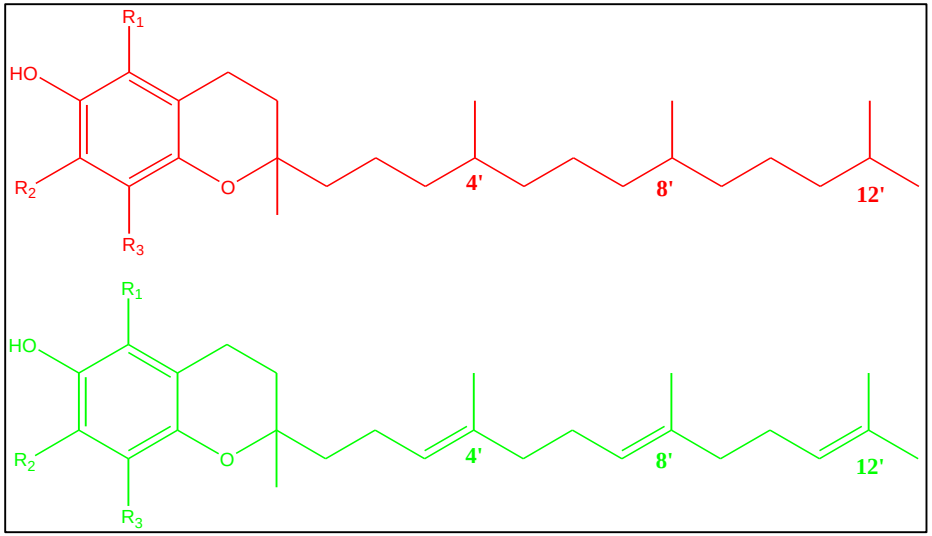

VITAMIN E
Fat Soluble Vitamin
Free Radical
Vitamin E
Vitamin E blocks the progression
Oxidative damage to DNA and cells

Definition & Types

- Vitamin E is a group of fat-soluble compounds that include both tocopherols and tocotrienols.

- **Vitamin E** is a term that refers to a family of eight related compounds, the **tocopherols** and the **tocotrienols**.
- The four major forms of vitamin E are designated **α, β, γ, δ,** that have varying levels of biological activity. Alpha- (or **α**-) tocopherol is the most active form. β-, γ-, and δ -tocopherols, possess only low levels of vitamin E activity.

Vitamin E is stored extensively in **adipose tissues** of the body; the stored vitamin E in normal situations represents up to **4 years' requirements.**



Vitamer	R_1	R_2	R_3
α-Tocopherol/α-tocotrienol	CH_3	CH_3	CH_3
β-Tocopherol/β-tocotrienol	CH_3	H	CH_3
γ-Tocopherol/γ-tocotrienol	H	CH_3	CH_3
δ-Tocopherol/δ-tocotrienol	H	H	CH_3
Tocol/tocotreinol	H	H	H

- Vitamin E is the generic descriptor for all tocol and tocotrienol derivatives that exhibit qualitatively the biological activity of α-tocopherol.
- *R,R,R*-form of α-tocopherol is the only stereoisomer occurs in nature.
- Vitamin E from synthesis has 2*RS*-α-tocopherol and all-*rac*- form structure.
- The esterified and unesterified forms are used.

Significance of vitamin E

- It has no specific deficiency disease.
- It is important for the normal metabolism of all cells.
- It is nontoxic vitamin and may have beneficial effects at supranutritional levels.

Source of the vitamin E

- Vitamin E is primarily available in plant products.
- Green plants contain more vitamin E than yellow plants.
- Plant oils, seeds and cereal grains.
- Tocopherols are exist in free alcohols, while tocotrienols occur in esterified form.
- Very little and variable of vitamin E in animal source.

Vitamin E storage

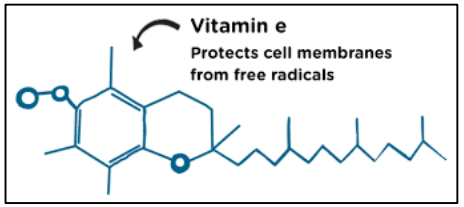
- It is stored in two forms;
- Labile and fixed pool.
- Labile form in tissues such as liver and plasma.
- Fixed form in adipose tissue.

Metabolic function of vitamin E

- It works as antioxidant.
- Its antioxidant function involves the reduction of free radicals, thus protecting against the potentially deleterious reactions of such highly reactive oxidizing species.
- Free radicals ($X^{\cdot}$) are produced in cells under normal conditions either by:

A- Homolytic cleavage of covalent bond.

B- Univalent electron transfer reaction.



Types of free radicals

1. Superoxide, O_2^-
2. Hydrogen peroxide, H_2O_2
3. Hydroxyl radical, OH^-
4. Singlet oxygen, $^1O_2$
5. Hydroperoxy radical, HOO^-
6. Lipid peroxide radical, ROO^-
7. Nitric oxide, NO^-
8. peroxynitrite, $ONOO^-$

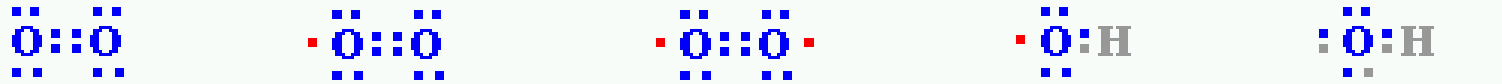
Sources of reactive oxygen species

1- Normal oxidative metabolism.

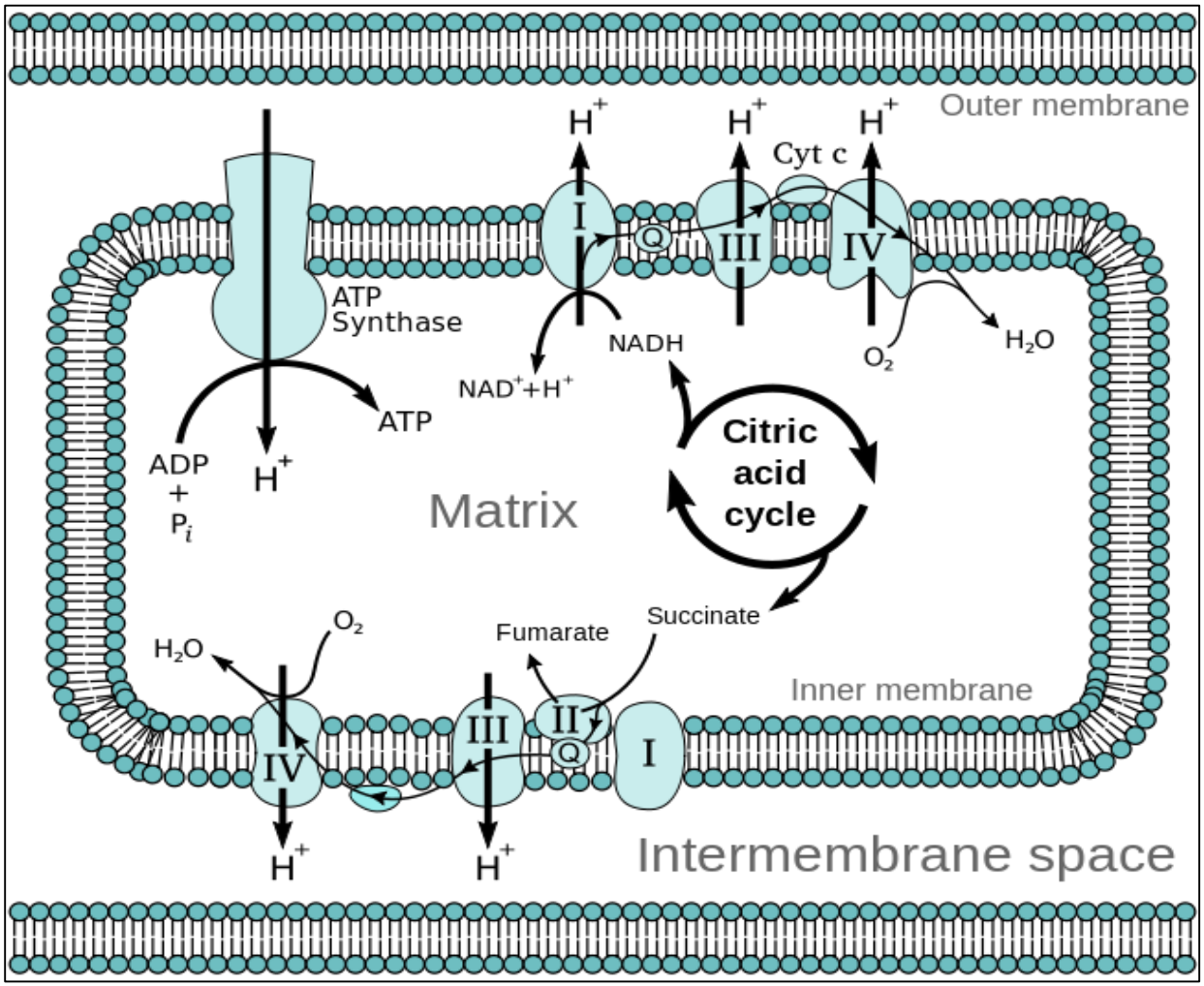
2- Microsomal cytochrome P-450 activity.

3- Respiratory burst of stimulated phagocytes.

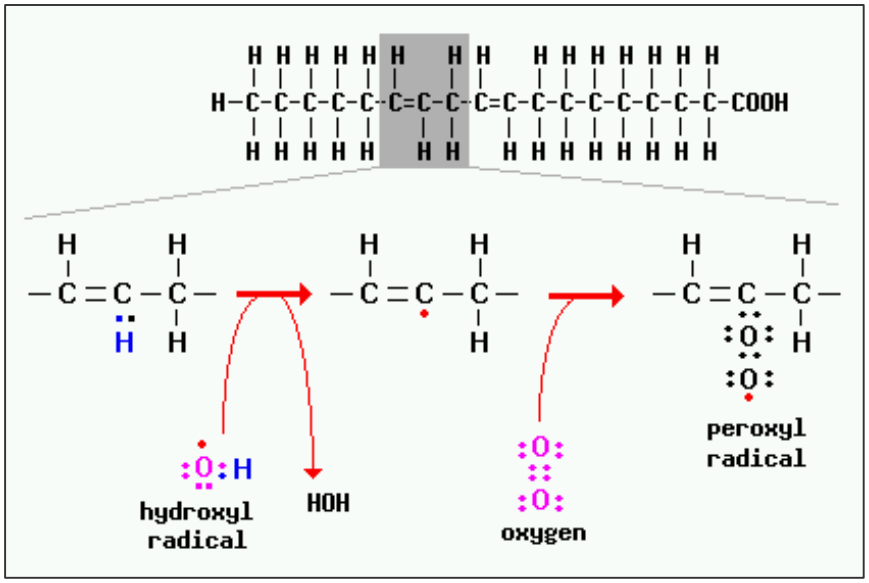
Reactive oxygen species (· unpaired electrons)

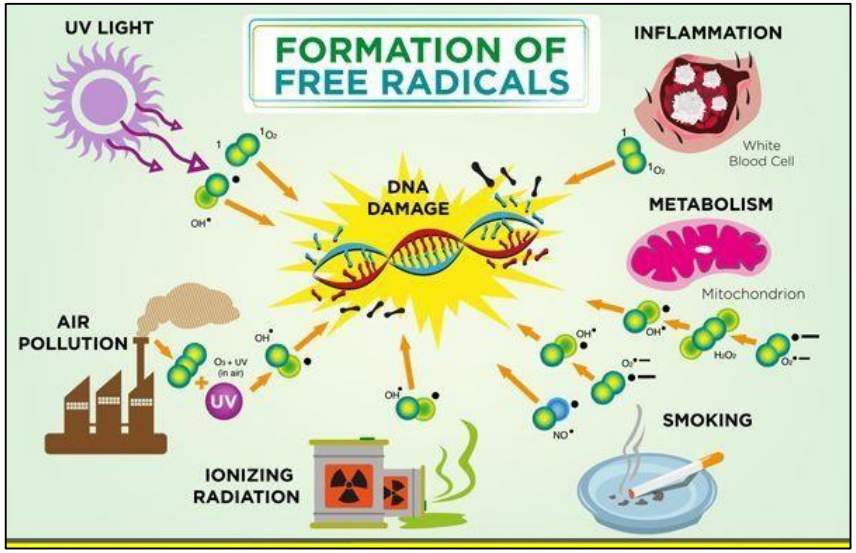


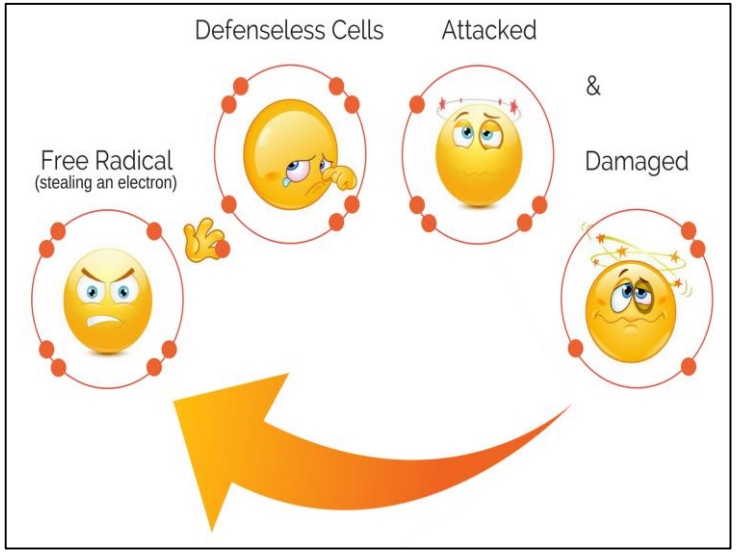
Oxygen	Superoxide anion	Peroxide	Hydroxyl radical	Hydroxyl ion
O_2	$O_2^{\bullet -}$	$O_2^{\bullet -2}$	$\bullet OH$	OH^-

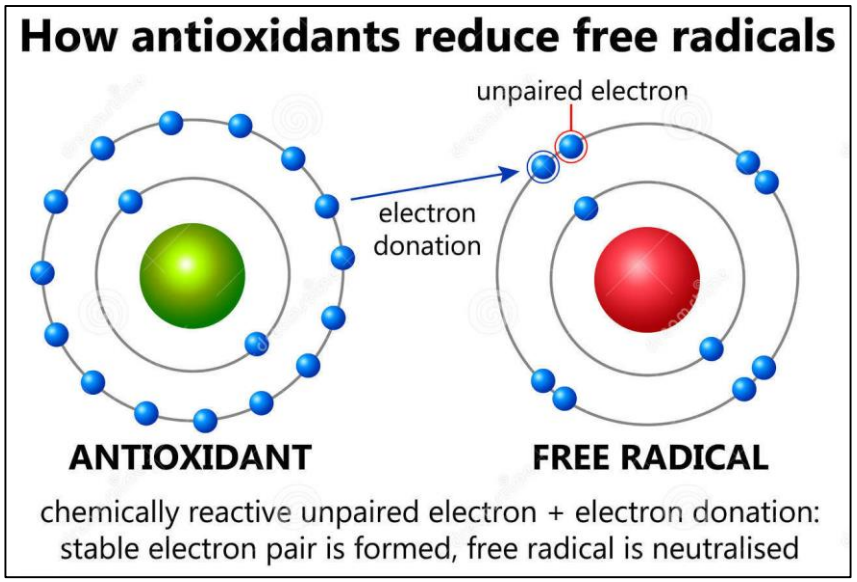

Outer membrane
H+
H+
H+
Cyt c
I
Q
III
IV
ATP
Synthase
NADH
NAD+ + H+
O2
H2O
ATP
ADP
+
Pi
H+
Matrix
Citric
acid
cycle
Succinate
Fumarate
O2
H2O
Inner membrane
IV
III
II
Q
I
H+
H+
Intermembrane space

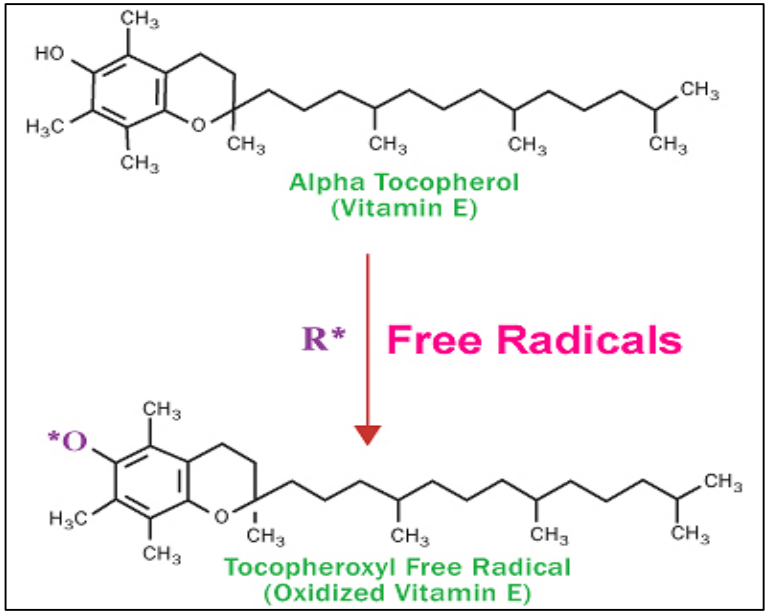
- Despite their beneficial activities, reactive oxygen species clearly can be toxic to cells. By definition, radicals possess an unpaired electron, which makes them highly reactive and thereby able to damage all macromolecules, including lipids, proteins and nucleic acids.

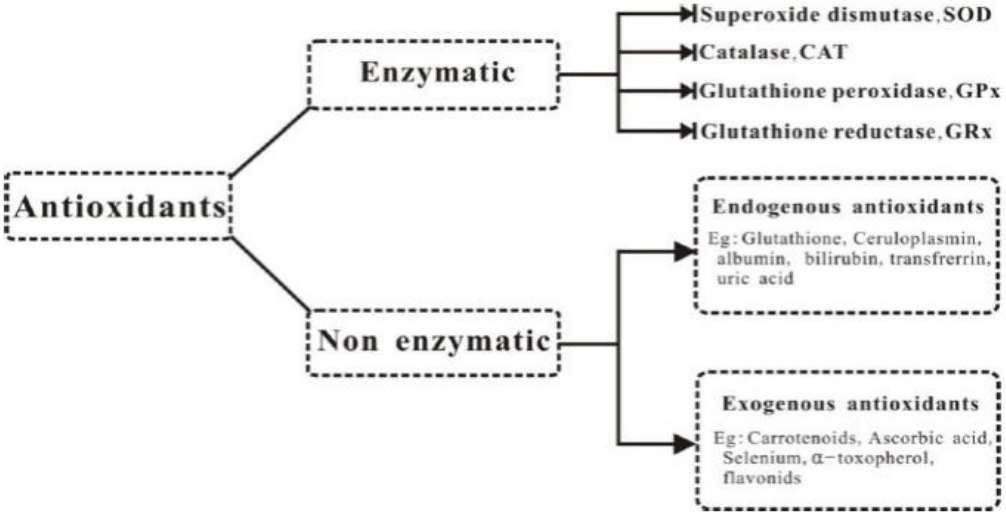



UV LIGHT
FORMATION OF FREE RADICALS
INFLAMMATION
White Blood Cell
DNA DAMAGE
METABOLISM
Mitochondrion
AIR POLLUTION
UV
IONIZING RADIATION
SMOKING

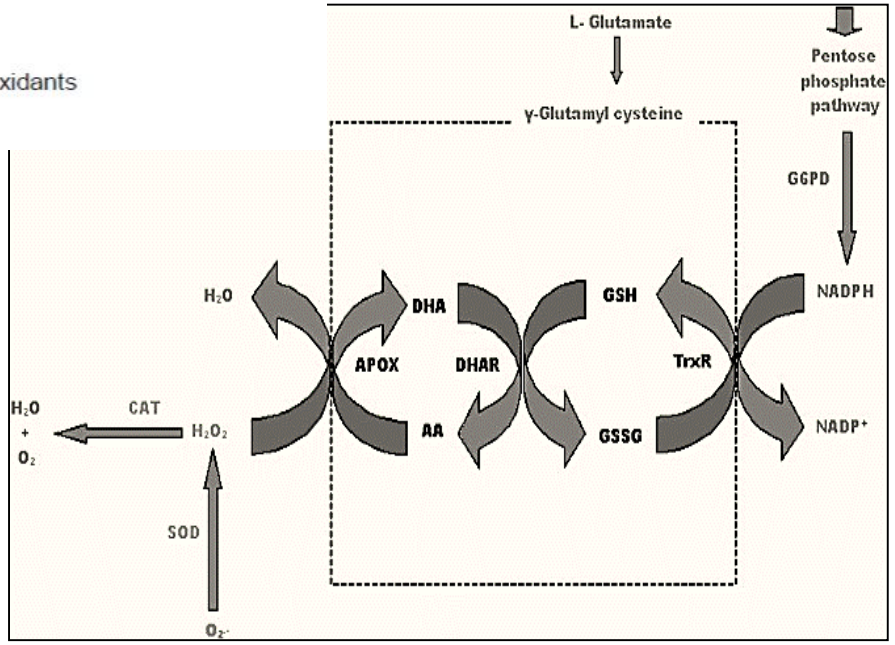

Defenseless Cells
Attacked
&
Damaged
Free Radical
(stealing an electron)


How antioxidants reduce free radicals
unpaired electron
electron donation
ANTIOXIDANT
FREE RADICAL
chemically reactive unpaired electron + electron donation:
stable electron pair is formed, free radical is neutralised


Alpha Tocopherol
(Vitamin E)
R*
Free Radicals
Tocopheroxyl Free Radical
(Oxidized Vitamin E)



Enzymatic and non-enzymatic classification of antioxidants



Other functions

- It inhibits the activity of protein kinase C, an important cell-signaling molecule.
- It appears to affect the expression and activities of molecules and enzymes in immune and inflammatory cells.
- It inhibits platelet aggregation and to enhance vasodilation.

Recommended Daily Allowance (RDA)

- 22.5 IU/day (15 mg/day) for healthy people from age of 14 years and older.

Vitamin E deficiency

- It can result from insufficient dietary intake or impaired absorption of the vitamin.
- Low selenium and high polyunsaturated fatty acids PUFA.
- The main symptoms are hemolytic anemia and neurologic deficits especially children.
- Diagnosis is based on measuring the ratio of plasma α-tocopherol to total plasma lipids; a low ratio suggests vitamin E deficiency.

vitamin E toxicity

- Generally, vitamin E is nontoxic.
- At high doses (1000 IU/day) showed signs of fatigue, headache, nausea and muscular weakness.
- It also, can antagonize the functions of other fat soluble vitamins (vitamin K) **(i.e. may affect the blood clotting effects of vitamin K and may lead to increased risk of hemorrhage)**.

Drug interactions

- Increase the risk of bleeding in individuals taking anticoagulant drugs, antiplatelet drugs and NSNIDs.
- Individual s who are vitamin K deficient.
- Anticonvulsant drugs may decrease the plasma levels of vitamin E.
- Any medications that reduce the absorption of vitamin E.