AL- MUSTAQBAL UNIVERSITY
College Of Health And Medical Techniques
Prosthetic Dental Techniques Department
Second Grade
Second Semester

Advanced chemistry

Lecture 20 (The theoretical part)

(Vitamins)

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Giving the lecture

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Introduction to Vitamins

* Vitamins are organic molecules that function in a wide variety of capacities within the body.

** The most prominent function is as cofactors for enzymatic reactions.

The distinguishing feature of the vitamins is that they generally cannot be synthesized by mammalian cells and, therefore, must be supplied in the diet. The vitamins are of two distinct types:

1. **Water Soluble Vitamins:** Thiamin (B_1) -Riboflavin (B_2) -Niacin (B_3) -Pantothenic Acid (B_5)-Pyridoxal, Pyridoxamine, Pyridoxine (B_6)-Biotin-Cobalamin (B_{12})-Folic Acid -Ascorbic Acid.
2. **Fat Soluble Vitamins**: Vitamin A-Vitamin D, Vitamin E, Vitamin K.

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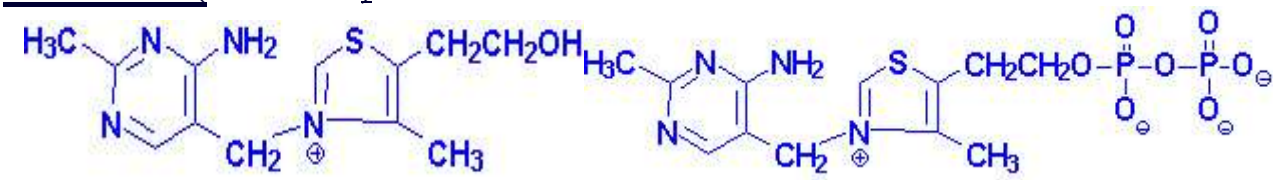
1. Thiamin (vitamin B_1)



Thiamin structure **Thiamin pyrophosphate**

- Thiamin is rapidly converted to its active form, **thiamin pyrophosphate, TPP**, in the brain and liver by a specific enzymes, ***thiamin diphosphotransferase***.

TPP is necessary as a cofactor for: 1-***pyruvate dehydrogenase*** 2-***α-ketoglutarate dehydrogenase*** 3- ***transketolase***

@ A deficiency in thiamin intake leads to a severely reduced capacity of cells to generate energy as a result of its role in these reactions.

The dietary requirement for thiamin ranges **from 1.0 - 1.5 mg/day** for normal adults.

- **Beriberi:** The severe thiamin deficiency disease
- Wernicke-Korsakoff syndrome. This disease is most commonly found in chronic alcoholics due to their poor dietetic lifestyles.

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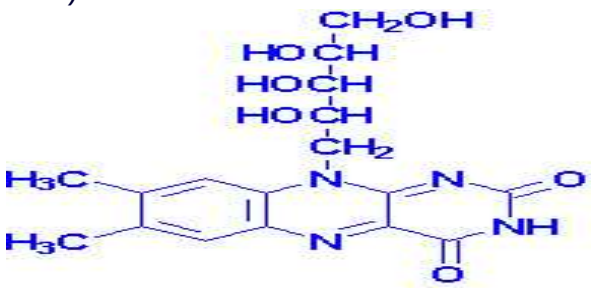
2. Riboflavin (vitamin B_2)

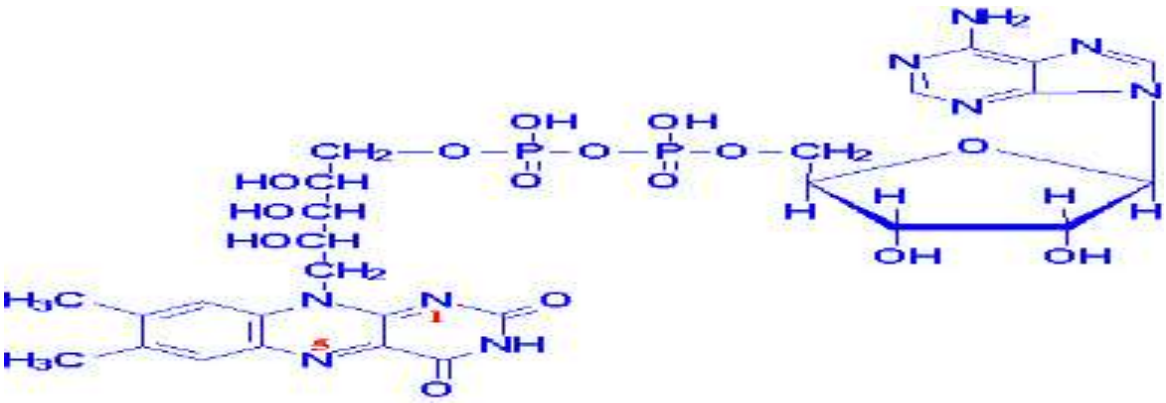


Riboflavin structure

- Riboflavin is the precursor for the coenzymes, **flavin mononucleotide (FMN)** and **flavin adenine dinucleotide (FAD)**.

@@The enzymes that require FMN or FAD as cofactors are termed flavoproteins. Several flavoproteins also contain metal ions and are termed metalloflavoproteins.

- Both classes of enzymes are involved in a wide range of redox reactions, e.g. ***succinate dehydrogenase*** and ***xanthine oxidase***. During the course of the enzymatic reactions involving the flavoproteins the reduced forms of FMN and FAD are formed, $FMNH_2$ and $FADH_2$, respectively.
- The normal daily requirement for riboflavin is **1.2 - 1.7 mg/day** for normal adults.
- Riboflavin decomposes when exposed to visible light. This characteristic can lead to riboflavin deficiencies in newborns treated for hyperbilirubinemia by phototherapy.



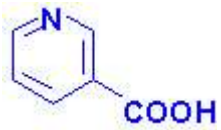
Structure of FAD-------nitrogens 1 & 5 carry hydrogens in $FADH_2$

Q/ Why Riboflavin deficiencies are rare.

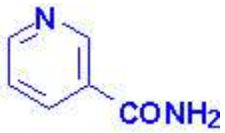
A/ Due to the presence of adequate amounts of the vitamin in eggs, milk, meat and cereals.

- Riboflavin deficiency is often seen in chronic alcoholics due to their poor dietetic habits.

3. Niacin



Nicotinic Acid



Nicotinamide

- Niacin (nicotinic acid and nicotinamide) is also known as **vitamin B_3**.
- Niacin is required for the synthesis of the active forms of vitamin B_3, **nicotinamide adenine dinucleotide (NAD^+)** and **nicotinamide adenine dinucleotide phosphate ($NADP^+$)**. Both NAD^+ and $NADP^+$ function as cofactors for numerous dehydrogenase, e.g., ***lactate*** and ***malate dehydrogenases***.

Q/ Why Niacin is not a true vitamin in the strictest definition.

A/ Because it can be derived from the amino acid tryptophan.

The recommended daily requirement for niacin is **13 - 19 mg** of free niacin.

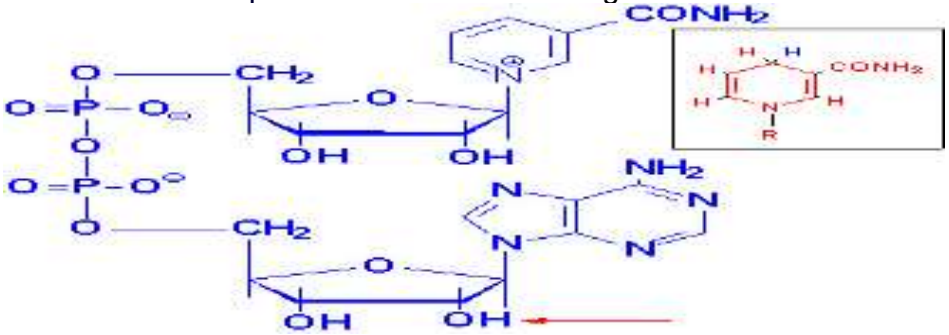
- Causes of Niacin deficiency: **1**-**Pellagra** **2**-Hartnup disease and malignant carcinoid syndrome) **3**-drug therapies (e.g. isoniazid).

@@ nicotinic acid therapy causes:

1- lowers blood cholesterol

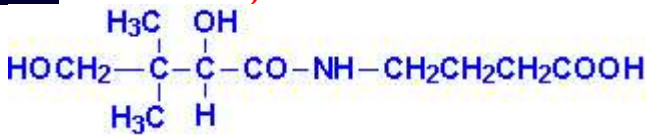
2- depletion of glycogen stores and fat reserves in skeletal and cardiac muscle

3-an elevation in blood glucose and uric acid production. For these reasons nicotinic acid therapy is not recommended for diabetics or persons who suffer from gout.



Structure of NAD^+----NADH is shown in the box insert.
The -OH phosphorylated in $NADP^+$ is indicated by the red arrow.

4. Pantothenic Acid (vitamin B_5)

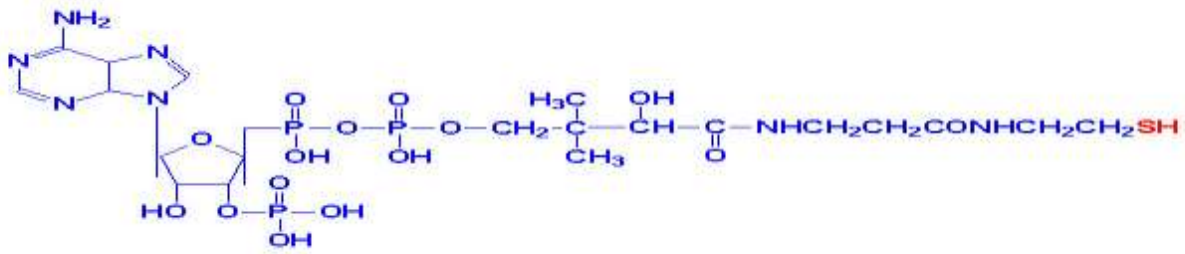


Pantothenic Acid

- Pantothenic acid is formed from β-alanine and pantoic acid.

- Pantothenate is required for: **1-**Synthesis of coenzyme A(CoA) **2-**Component of the acyl carrier protein (ACP) domain of fatty acid synthase **3-**required for the metabolism of carbohydrate via the TCA cycle and all fats and proteins.
- At least 70 enzymes have been identified as requiring CoA or ACP derivatives for their function.

@Deficiency of pantothenic acid is extremely rare.



Coenzyme A

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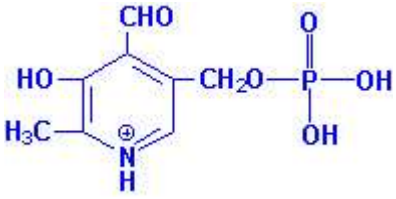
5. Vitamin B_6

Pyridoxine

Pyridoxal

Pyridoxamine

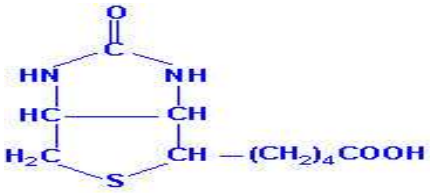


Pyridoxal Phosphate

- **Pyridoxal, pyridoxamine** and **pyridoxine** are as a group known as **vitamin B_6**.
- All three compounds are efficiently converted by ***pyridoxal kinase*** to the biologically active form of vitamin B_6, **pyridoxal phosphate**.
- Pyridoxal phosphate functions as **1-**cofactor in enzymes involved in transamination reactions **2-**required for the synthesis and catabolism of the amino acids **3-** in glycogenolysis as a cofactor for ***glycogen phosphorylase***.
- The requirement for vitamin B_6 in the diet is proportional to the level of protein consumption ranging from **1.4 - 2.0 mg/day** for a normal adult.

#During pregnancy and lactation the requirement for vitamin B_6 increases approximately 0.6 mg/day.

6-Biotin



Biotin

- Biotin is the cofactor required of enzymes that are involved in carboxylation reactions, e.g. ***acetyl-CoA carboxylase*** and ***pyruvate carboxylase***.
- Deficiencies of the vitamin are rare because **1-**Biotin is found in numerous foods **2-** synthesized by intestinal bacteria.
- Note: Deficiencies are generally seen only after 1- long antibiotic therapies which deplete the intestinal fauna 2-following excessive consumption of raw eggs because of the affinity of the egg white protein, **avidin**, for biotin preventing intestinal absorption of the biotin.

7-Cobalamin (vitamin B_{12})

- Vitamin B_{12} is composed of a complex tetrapyrrol ring structure (corrin ring) and a cobalt ion in the center.
- The vitamin must be hydrolyzed from protein in order to be active. Hydrolysis occurs in the stomach by gastric acids or the intestines by trypsin digestion following consumption of animal meat. The vitamin is then bound by **intrinsic factor**, a protein secreted by parietal cells of the stomach, and carried to the ileum where it is absorbed. Following absorption the vitamin is transported to the liver in the blood bound to **transcobalamin II**.
  ##There are only two clinically significant reactions in the body that require vitamin B_{12} as a cofactor:1-. ***methylmalonyl-CoA mutase***, 2- ***methionine synthase***.

Clinical Significances of B_{12} Deficiency

1. The liver can store up to six years worth of vitamin B_{12}, hence deficiencies in this vitamin are rare.
2. Pernicious anemia: is a megaloblastic anemia resulting from vitamin B_{12} deficiency that develops as a result a lack of intrinsic factor in the stomach leading to malabsorption of the vitamin. The anemia results from impaired *DNA synthesis due to a block in purine and thymidine biosynthesis*. The block in nucleotide biosynthesis is a consequence of the effect of vitamin B_{12} on folate metabolism. When vitamin B_{12} is deficient essentially all of the folate becomes trapped as the N^5-methylTHF derivative as a result of the loss of functional ***methionine synthase***. This trapping prevents the synthesis of other THF derivatives required for the purine and thymidine nucleotide biosynthesis pathways.

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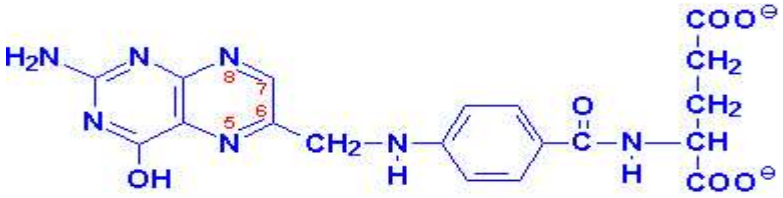
8. Folic Acid

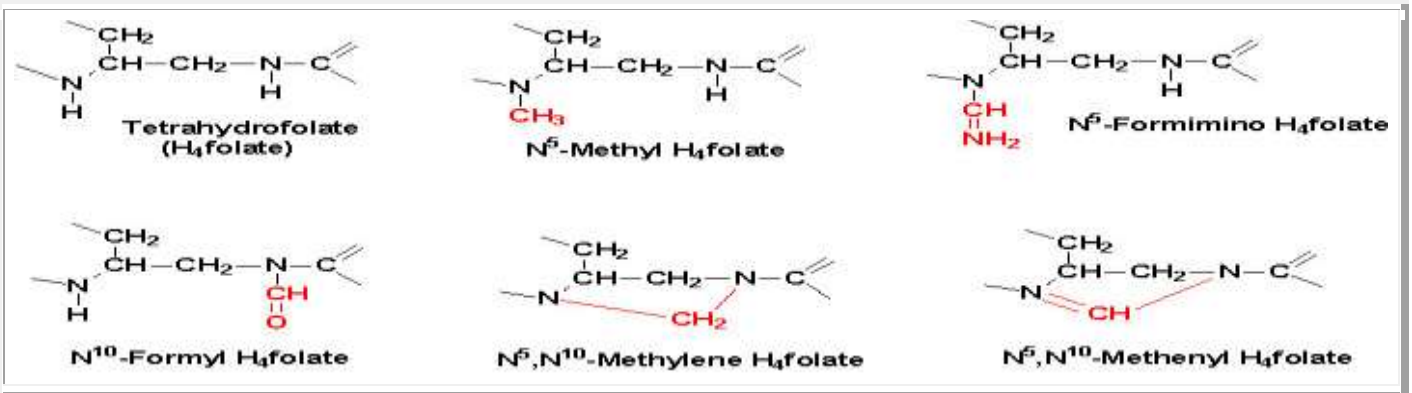
- Folic acid is obtained primarily from yeasts and leafy vegetables as well as animal liver.
- Folic acid is reduced within cells (principally the liver where it is stored) to tetrahydrofolate (THF also H_4folate) through the action of ***dihydrofolate reductase*** **(DHFR)**, an NADPH-requiring enzyme.



Folic Acid

positions 7 & 8 carry hydrogens in dihydrofolate (DHF)
positions 5-8 carry hydrogens in tetrahydrofolate (THF)

- The function of THF derivatives is to carry and transfer various forms of one carbon units during biosynthetic reactions. The one carbon units are either methyl, methylene, methenyl, formyl or formimino groups.



Active center of tetrahydrofolate (THF). Note that the N^5 position is the site of attachment of methyl groups, the N^{10} the site for attachment of formyl and formimino groups and that both N^5 and N^{10} bridge the methylene and methenyl groups.

- These one carbon transfer reactions are required in the biosynthesis of serine, methionine, glycine, choline and the purine nucleotides and dTMP.

Clinical Significance of Folate Deficiency

Folate deficiencies are rare due to the adequate presence of folate in food

a) The most pronounced effect of folate deficiency on cellular processes is upon DNA synthesis. This is due to an impairment in dTMP synthesis which leads to cell cycle arrest in S-phase of rapidly proliferating cells, in particular hematopoietic cells. The result is **megaloblastic anemia** as for vitamin B_{12} deficiency.

b) The inability to synthesize DNA during erythrocyte maturation leads to abnormally large erythrocytes termed **macrocytic anemia**.
metabolism.

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9. Ascorbic Acid (vitamin C)

Ascorbic Acid

- Ascorbic acid is derived from glucose via the uronic acid pathway. The enzyme responsible for the conversion of gulonolactone to ascorbic acid is ***L-gulonolactone oxidase***.
- The main function of ascorbate is as a reducing agent in a number of different reactions.
    1. To reduce cytochromes a and c of the respiratory, molecular oxygen.
    2. As a cofactor in the hydroxylation of proline residues in collagen.
    3. Maintenance of normal connective tissue- wound healing since synthesis of connective tissue is the first event in wound tissue remodeling.
    4. as a cofactor for 1-catabolism of tyrosine 2- synthesis of epinephrine from tyrosine3- Synthesis of the bile acids.
    5. It is also believed that vitamin C is involved in the process of steroidogenesis.

##Deficiency in vitamin C leads to the disease **scurvy** due to the role of the vitamin in the post-translational modification of collagens. Scurvy is characterized by easily bruised skin, muscle fatigue, soft swollen gums, decreased wound healing and hemorrhaging, osteoporosis, and anemia.

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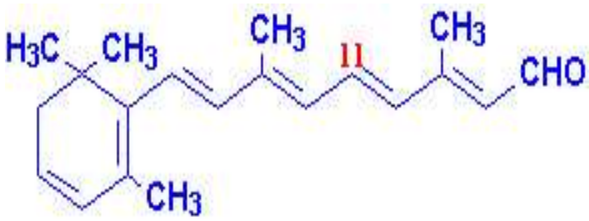
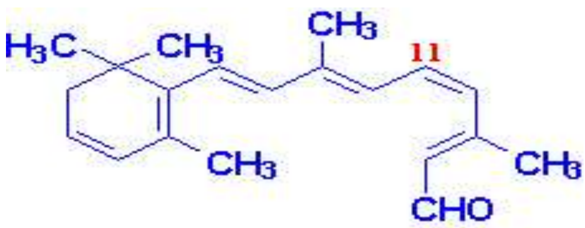
10.Vitamin A

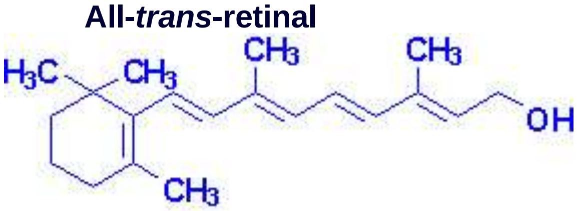
Vitamin A consists of three biologically active molecules, **retinol, retinal** (retinaldehyde) and **retinoic acid**.



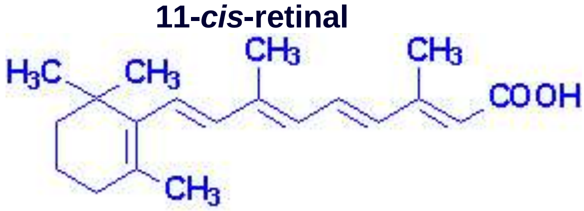
All-*trans*-retinal



11-*cis*-retinal



Retinol



Retinoic Acid

- All derived from the plant precursor molecule, **β-carotene** (a member of a family of molecules known as **carotenoids**).
- β-carotene dioxygenase retinaldehyde reductase
- Ingested β-carotene ⟶ Retinal ⟶ Retinol
- NADPH NAD+
- Retinol also functions in the synthesis of certain glycoproteins and mucopolysaccharides necessary for mucous production and normal growth regulation.

Vision and the Role of Vitamin A

- The rod and cone cells in retina (specialized cells in the retina) contain a photoreceptor pigment in their membranes.
- **opsin** The photosensitive compound of most mammalian eyes. It is a protein covalently coupled with an aldehyde of vitamin A.
- **scotopsin**: The opsin of rod cells.
- **rhodopsin** or **visual purple:** The photoreceptor imbedded in the membrane of the rod cells. This compound is a complex between scotopsin and the 11-*cis*-retinal (also called 11-*cis*-retinene) form of vitamin A.

Q/ How the vision occurs?

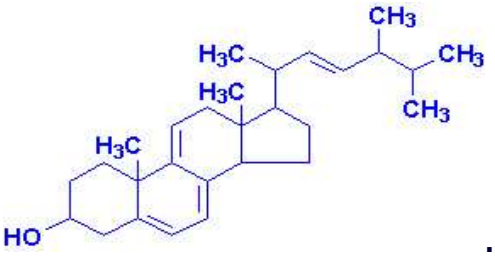
A/ When the rhodopsin is exposed to light it is **bleached** releasing the **11-*cis*-retinal** from **opsin.** Absorption of photons by 11-*cis*-retinal triggers a series of conformational changes on the way to conversion **all-*trans*-retinal**. This conformational change activates transducin, leading to an increased GTP-binding by the a-subunit of transducin. Binding of GTP releases the α-subunit from the inhibitory β- and γ-subunits. The GTP-activated α-subunit in turn activates an associated ***phosphodiesterase***; an enzyme that hydrolyzes cyclic-GMP (cGMP) to GMP. Cyclic GMP is required to maintain the Na^+ channels of the rod cell in the open conformation. The drop in cGMP concentration results in complete closure of the Na^+ channels. Metarhodopsin II appears to be responsible for initiating the closure of the channels. The closing of the channels leads to hyperpolarization of the rod cell with concomitant propagation of nerve impulses to the brain.

Clinical Significances of Vitamin A Deficiency

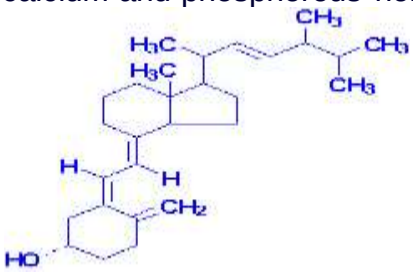
- Vitamin A is stored in the liver and deficiency of the vitamin occurs only after prolonged lack of dietary intake.
- The earliest symptoms of vitamin A deficiency are **night blindness**.
- Additional early symptoms include (follicular hyperkeratinosis, increased susceptibility to infection and cancer and anemia equivalent to iron deficient anemia).

11-Vitamin D

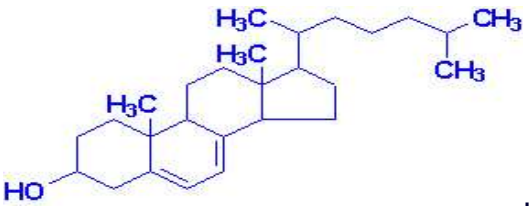
- Vitamin D is a steroid hormone.
- The biologically active form of the hormone is **1,25-dihydroxy vitamin D_3** ($1,25\text{-}(OH)_2D_3$, also termed **calcitriol**).
- Calcitriol functions: primarily to regulate calcium and phosphorous homeostasis.



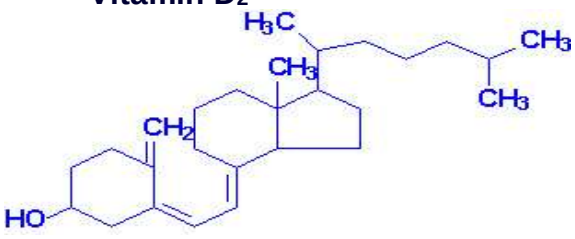
Ergosterol



Vitamin D_2



7-Dehydrocholesterol



Vitamin D_3

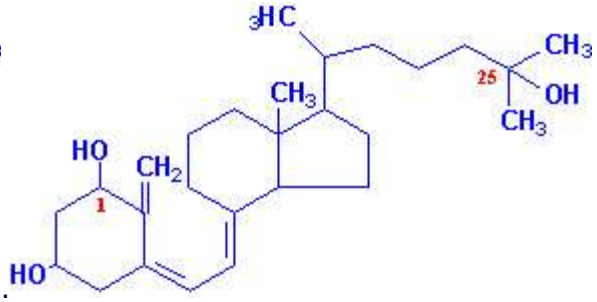
- **in plants**: Active calcitriol is derived from **ergosterol** (produced in plants) and form **Ergocalciferol** (vitamin D_2) by uv irradiation of ergosterol.
- **In the skin: 7-dehydrocholesterol** is converted to **cholecalciferol** (vitamin D_3) following *uv* irradiation.

Synthesis of active Vitamin D:

Cholecalciferol (or egrocalciferol) $\xrightarrow[D_3\text{-1-hydroxylase}]{}$ Intestine $\xrightarrow{}$ liver $\xrightarrow{D_3\text{-25-hydroxylase}}$ 25-hydroxy-D_3 [25-(OH)D_3]

In (kidneys bone and placenta) **calcitriol**

25-hydroxyvitamin D3



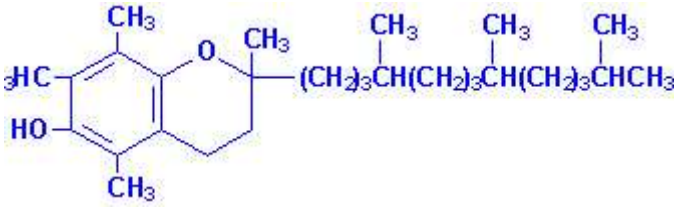
1,25-dihydroxyvitamin D3

Calcitriol functions in concert with **parathyroid hormone (PTH)** and **calcitonin** to regulate serum calcium and phosphorous levels.

Clinical Significance of Vitamin D Deficiency

1. Vitamin D deficiency in children causes **rickets** Rickets is characterized improper mineralization during the development of the bones resulting in soft bones.
2. Vitamin D deficiency in adults causes **osteomalacia**. Osteomalacia is characterized by demineralization of previously formed bone leading to increased softness and susceptibility to fracture.

12.Vitamin E



α-Tocopherol

Vitamin E is a mixture of several related compounds known as **tocopherols**.

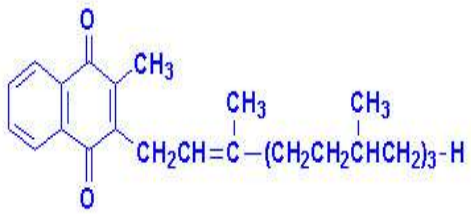
@ **The major function of vitamin E is:** to act as a natural **antioxidant** by scavenging free radicals and molecular oxygen. In particular vitamin E is important for preventing peroxidation of polyunsaturated membrane fatty acids.

@ **Clinical significances of Vitamin E Deficiency**:

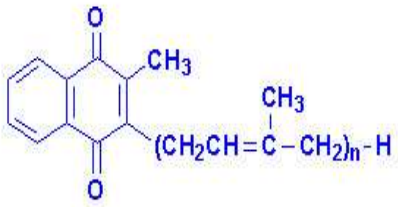
1-an increase in red blood cell fragility. 2-Neurological disorders have been associated with vitamin E deficiencies associated with fat malabsorptive disorders.

13.Vitamin K

The K vitamins exist naturally as: **1**-K_1 (phylloquinone) in green vegetables **2**-K_2 (menaquinone) produced by intestinal bacteria **3**-K_3 is synthetic water soluble menadione. When administered, vitamin K_3 is alkylated to one of the vitamin K_2 forms of menaquinone.



Vitamin K1



VitaminK2

Vitamin K3

"n" can be 6, 7 or 9 isoprenoid groups

##The major function of the K vitamins is:

1. in the maintenance of normal levels of the blood clotting proteins, **factors II, VII, IX, X**.
2. Vitamin K reactions are the site of action of the **dicumarol** based anticoagulants such as **warfarin**.

Clinical significance of Vitamin K Deficiency

- Naturally occurring vitamin K is absorbed from the intestines only in the presence of bile salts and other lipids through interaction with chylomicrons. Therefore, fat malabsorptive diseases can result in vitamin K deficiency.

@The synthetic vitamin K_3 is water soluble and absorbed regardless of the presence of intestinal lipids and bile.

- Since the vitamin K_2 form is synthesized by intestinal bacteria, deficiency of the vitamin in adults is rare. However, long term antibiotic treatment can lead to deficiency in adults.

@ The intestine of newborn infants is sterile, therefore, vitamin K deficiency in infants is possible if lacking from the early diet. The primary symptom of a deficiency in infants is a **hemorrhagic syndrome**.