Chapter six

Vitamins

Introduction:

Vitamins are organic compounds that are required in small quantities for a variety of biochemical functions. Vitamins cannot be synthesized by the body and must be supplied by the diet. Some can be synthesized by intestinal microorganisms, but in quantities that are not sufficient to meet our needs.

Classification of vitamins:

Vitamins can be classified into two groups based on their solubility:

1- Fat soluble vitamins.

2- Water soluble vitamins.

Storage of vitamins in the body:

The vitamins can be stored in the body to a slight extent. The liver cells are, however, rich in certain **fat-soluble vitamins**. For instance, the amount of ***vitamin A*** contained in the liver is sufficient to meet its requirement without any additional intake for about 6 months. Similarly, the quantity of ***vitamin D*** stored ordinarily in the liver is sufficient to maintain a person without any additional intake of vitamin D for about 2 months. The storage of ***vitamin K*** is, however, relatively slight.

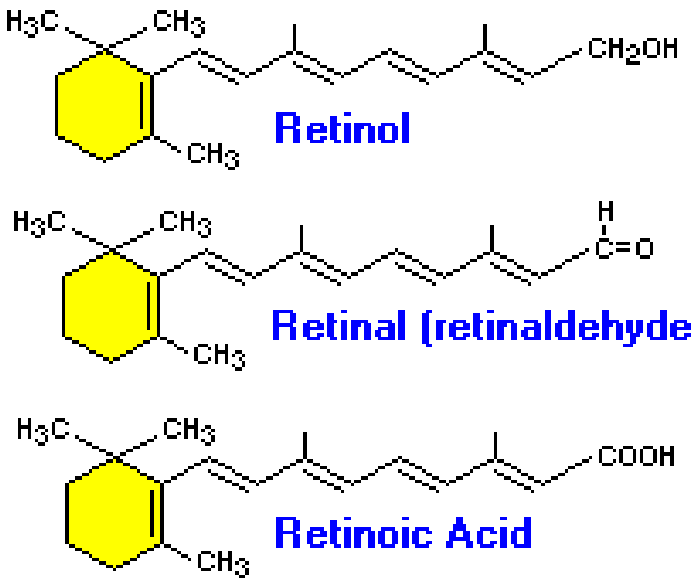
The **water-soluble vitamins** are stored even in lesser amounts in the cells. Evidently, in cases of deficiency of *vitamin B compounds*, clinical symptoms appear rather early, that is within a few days. Similarly, absence of *vitamin C* can induce deficiency symptoms within a few weeks. Vitamin C is stored in the adrenal cortex.

Fat soluble vitamins:

These are vitamins which insoluble in water but soluble in organic solvents like benzene, CCL4, CHCL3,…. Fat soluble vitamins can be stored in the body, in liver. However, because fat soluble vitamins are storage, excessive intakes can result in toxic conditions (hyper vitaminoses).

1- Vitamin A:

Vitamin A is fat soluble vitamin and exists in three forms: **retinol, retinal and retinoic acid**.



Vitamin A is found in animal sources such as liver, egg yolk and fish oil, Yellow and dark green vegetables and fruits are good dietary sources of the carotenes known as a provitamin A (present in carrot, potatoes and tomatoes ….), which serve as precursors of vitamin A and cleaved in the small intestine by carotene dioxygenase yielding retinaldehyde which reduced to retinol and retinoic acid.

Functions of vitamin A:

Vitamin A has important roles in the body, which include:

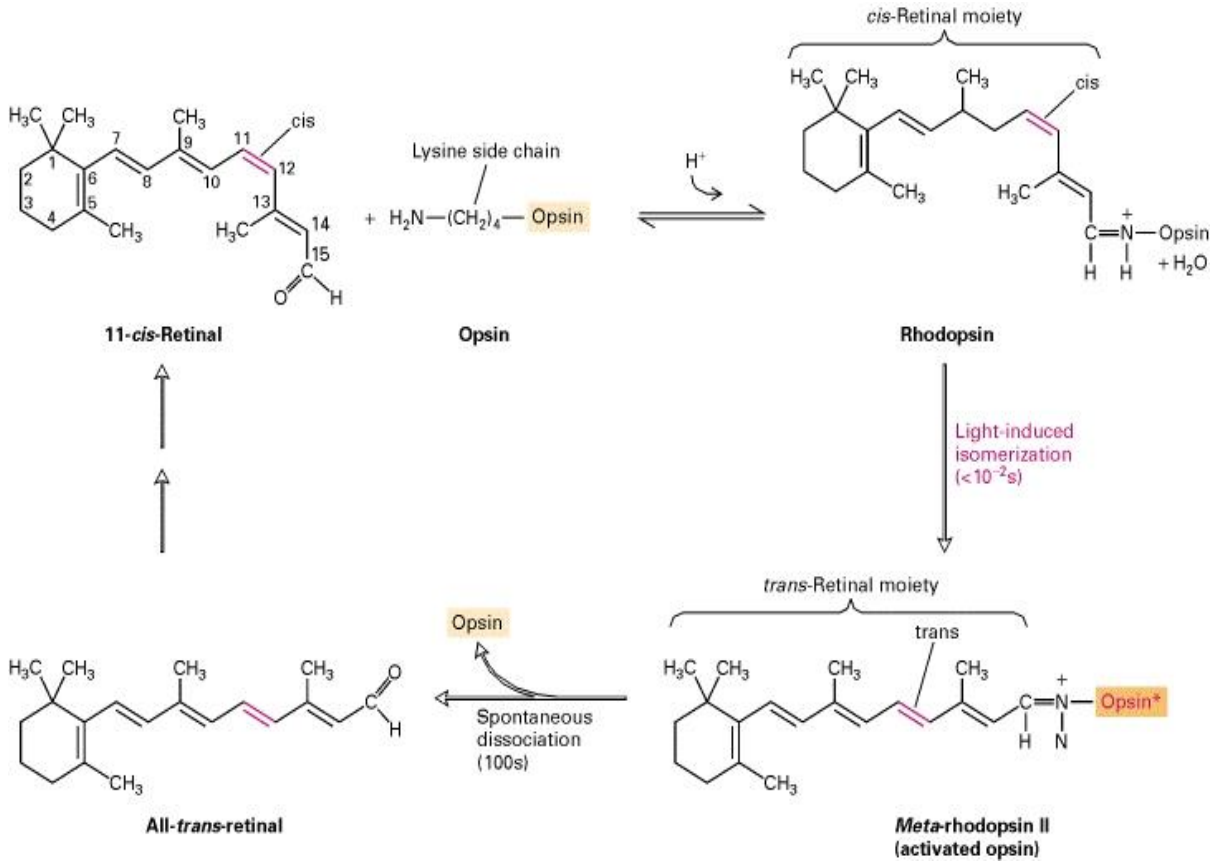
1- Vitamin A is critical for vision.

2- In the maintaining of healthy epithelial tissues and skin.

4- Necessary for the synthesis of mucopolysaccharides of the brain.

5- Have the role in reproduction system.

6- Involved in the electron transport chain and oxidative phosphorylation.



Deficiency of vitamin A;

Vitamin A is stored in the liver and deficiency of the vitamin occurs only after prolonged lack of dietary intake. Deficiency causes:

1- Hardening of skin cells

2- Night blindness or total blindness

3- Failure of growth in children.

4- Teeth become unhealthy due to thinning of enamel.

The current recommended dietary allowance (RDA) is 5000 I.U = 1µg of retinol or 6 µg of β- carotene.

Toxicity of vitamin A:

Because vitamin A is fat soluble and can be stored, primarily in the liver, routine consumption of large amounts of vitamin A over a period of time can result in toxic symptoms, including

1- Liver damage

2- Bone abnormalities and joint pain.

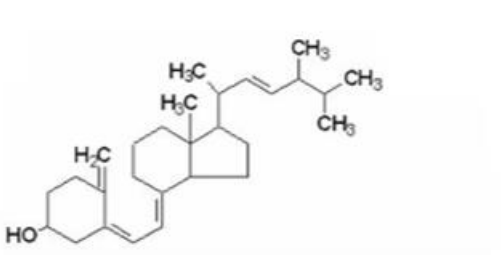
3- Hair loss and headaches

4- Double vision, nausea and vomiting.

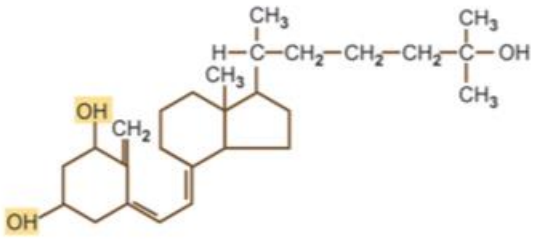
Vitamin D:

The D Vitamins are a group of steroid compound that have a hormone like function. The best sources of vitamin D are fish liver oil, egg, milk …and sunlight induced synthesis of vitamin D3 in skin.

There are two forms of vitamin D: vitamin D3 or (cholecalciferol) found in animals and vitamin D2 (ergosterol) found in plant sources.

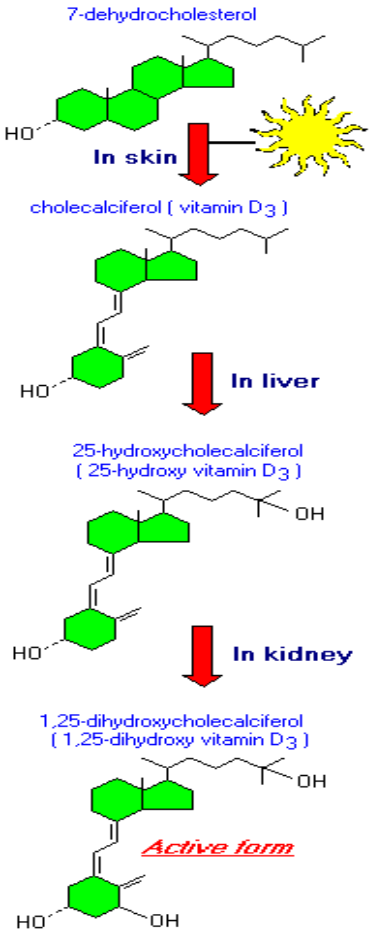


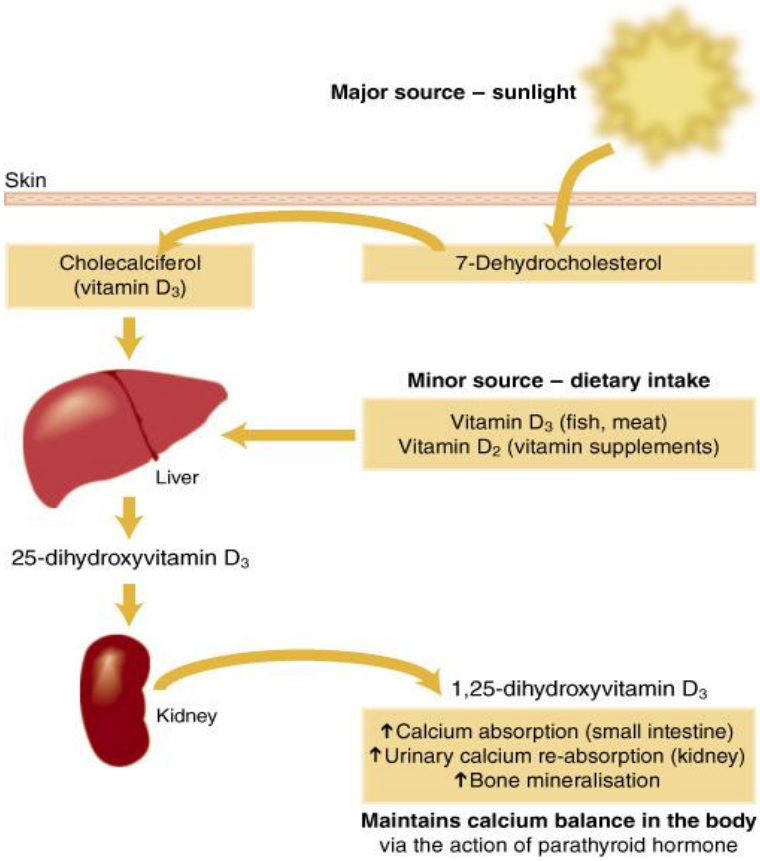
Vitamin D_2



1.25-dihydroxycholecalciferol: an active form of V. D3

Vitamin D3 is not active form of the vitamin D, but it is converted to active form **(1,25 dihydroxycholecalciferol also known as calcitriol)** by a series of reactions:





Functions of Vitamin D

1. Vitamin D (Calcitriol) plays an essential role as a hormone in the regulation of **calcium** and **phosphorus** metabolism.

2. It maintains the normal plasma level of calcium and phosphorus by acting on **intestine**, **kidneys** and **bones**

3. More recently suggested affecting a wide-range of diseases, including autoimmune disorders, cancer, metabolic syndrome.

RDA for vitamin D is 200 IU to age 50, and 400-600 IU for infants, pregnant women, lactating mothers and after age 50.

Deficiency of vitamin D:

Vitamin D deficiency in nutrition causes

1- Causes Rickets in children and osteomalacia in adults.

2- Liver disease and kidney failure leads to decrease formation of active form of vit.D.

3- This vitamin with parathyroid hormone stimulates the reabsorption of calcium so that it is not lost in the urine, therefore, lack of parathyroid hormone causes hypocalcemia**.**

Toxicity of vitamin D:

Vitamin D can be stored in the body and high doses of vitamin D can causes

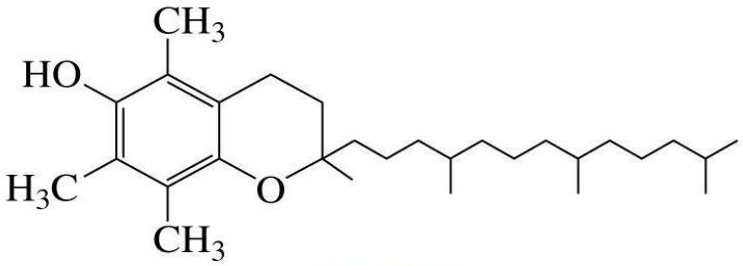
1- Loss of appetite, nausea, polyuria, weakness, headache and thirst.

2- Enhance calcium absorption and bone resorption causes hypercalcemia, which can be lead to deposition of calcium in many organs particularly kidney and arteries.

UV light is required to make vitamin D and prolonged exposure to can cause damage to skin cells

Vitamin E:

Vitamin E refers to a family of eight compounds called tocopherol, which differ in the number and position of the methyl group on the ring, in which **α- tocopherol is the active form**.



vitamin E
α-tocopherol

The major source of vitamin E are vegetable oils and some fruits like olive and palm, also present in small amount in meat, milk, eggs.

Functions of vitamin E

1- Vitamin E act as antioxidants, i.e., they can prevent the oxidation of unsaturated fatty acids contained in the phospholipids.

2- Suppression of activity of HMG CoA reductase (cholesterol synthesis)

3- Protection of erythrocyte membrane from oxidant is the major role of vitamin E in humans.

Recommended Dietary Allowance (RDA) for vitamin E was 10 mg (15. I.U) for men and 8 mg (12. I.U) for women.

Deficiency of Vitamin E:

The major symptom of vitamin E deficiency in human is:

1- Hemolytic anemia due to increased red blood cell fragility.

2- Increased oxidation of polyunsaturated fatty acids in the muscle with a rise in O2 consumption and peroxide production, peroxide leads to hydrolysis of intracellular.

Toxicity of vitamin E:

Vitamin E does not seem to have toxic effects in high doses.

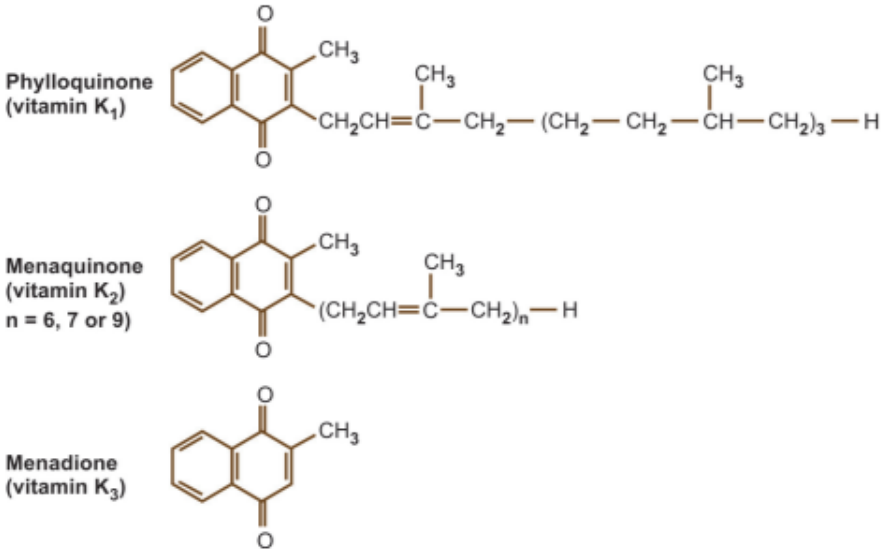
Vitamin K:

There are three forms of vitamin K:

VitaminK1 (Phylloquinone) derived from plants.

Vitamin K2 (Menaquinone) produced by intestinal bacteria

Vitamin K3 (Menadione) is a synthetic product, which produced by alkylation of Vit.K2.

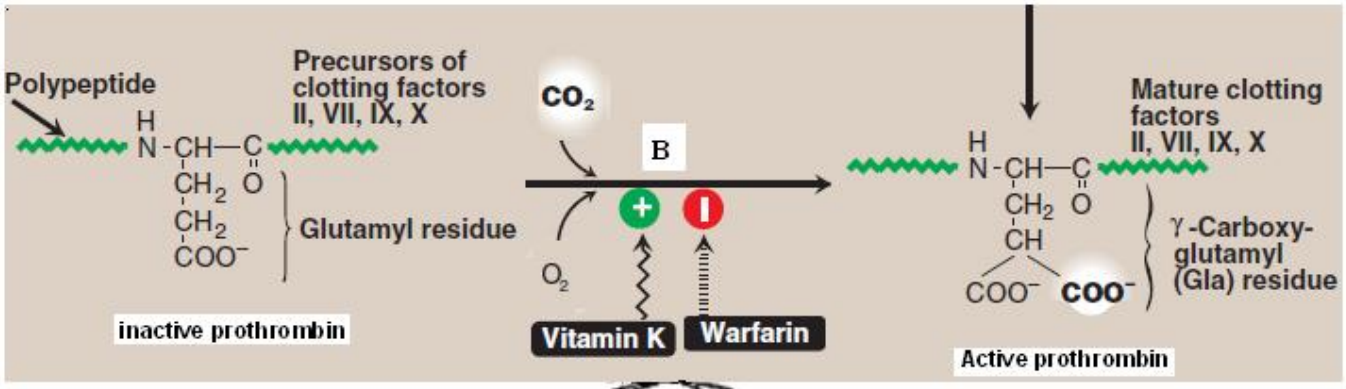


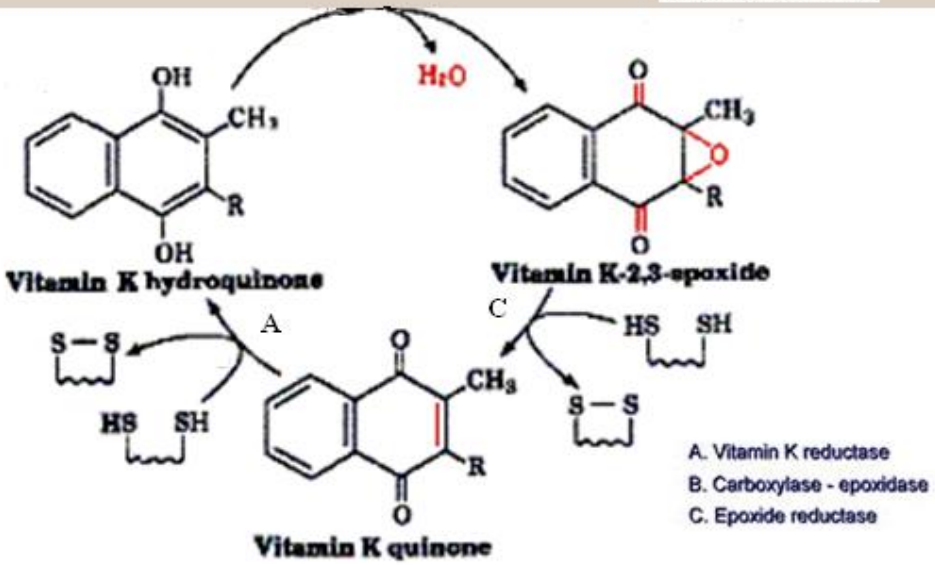
Vitamin K is found in cabbage, spinach, egg yolk, and liver. There is also extensive synthesis of the vitamin by the bacteria in the gut.

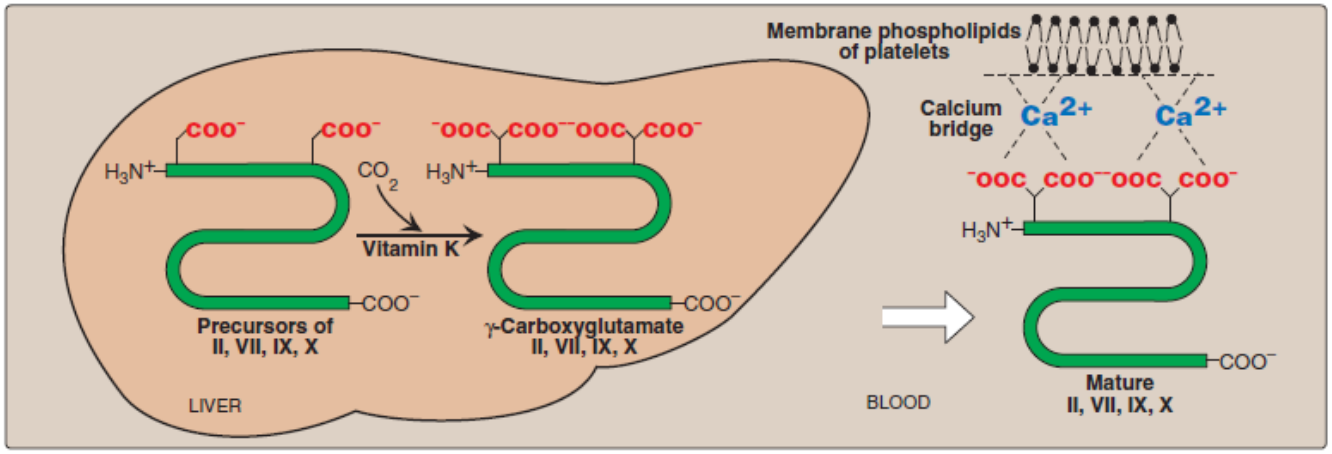
Functions of vitamin K:

1. Vitamin K plays an important role in **blood coagulation.** Vitamin K is required for the activation of blood clotting factors, prothrombin (II), factor VII, IX and X. These blood clotting proteins are synthesized in liver in inactive form, and are converted to active form by vitamin K dependent carboxylation reaction. In this, vitamin K dependent carboxylase enzyme adds the extra carboxy group at γ-Carboxyglutamyl (Gla) residues of inactive blood clotting factors.

2. Vitamin K is also required for the carboxylation of glutamic acid residues of osteocalcin, a Ca2+ binding protein present in bone.







Role of vitamin K in blood coagulation.

Deficiency of Vitamin K:

Vitamin K is widely distributed in nature and its production by the intestinal bacteria ensures that dietary deficiency does not occur. Vitamin K deficiency however found in:

1- Patients with liver disease and biliary obstruction due to intestinal of entry of the bile salts to the intestine.

2- In new born infants, due to absence of intestinal bacteria flora.

3- Prolonged antibiotic therapy will kill the intestine bacteria.

4- Malabsorption of dietary lipids.

Toxicity of vitamin K

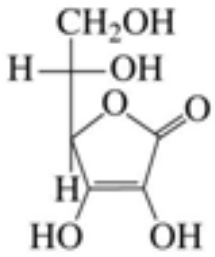
Excessive doses of vitamin K produce a **hemolytic anemia** (due to increased breakdown of RBCs) and **jaundice** (in infants).

Water soluble vitamins:

Many of the water-soluble vitamins are precursors of coenzymes for metabolic reactions. Since these vitamins are water soluble, they are not stored in the body like fat soluble vitamins. They dissolve in water and are excreted from the body in urine. Therefore, it is important to consume foods rich in these vitamins each day in order to fulfill the body's need.

1- Vitamin C:

Vitamin C is also known as ascorbic acid. Easily lost through cooking and sensitive to heat, and oxygen. **Ascorbic acid** itself is an active form of vitamin C. Most animals can synthesize ascorbic acid. But humans cannot synthesize ascorbic acid, due to lack of the enzyme gluconolactone oxidase which is required for the synthesis of ascorbic acid. Thus, humans have a dietary requirement of ascorbic acid. Vitamin C found in vegetables like green pepper, spinach, tomatoes, potatoes, and in citrus fruits such as orange, lemon, and pineapple.



vitamin C
ascorbic acid

Function of vitamin C:

1- Acts as a natural antioxidant.

2- Vitamin C is a coenzyme in the hydroxylation of lysine and proline, and these compounds are essential for the production of collagen.

3- Also facilitates the absorption of dietary iron from the intestine.

4- Helping the enzyme folate reductase to reduce folic acid to tetra hydro folate (active form). Thus it helps the maturation of RBC.

Deficiency of Vitamin C:

Deficiency of Vitamin C causes:

1- Scurvy.

2-Defective in connective tissue this can be explained by a deficiency in the hydroxylation of collagen

Recommended Daily Allowance: 75 mg for women and 90 mg for men but Smokers need an extra 35 mg/day.

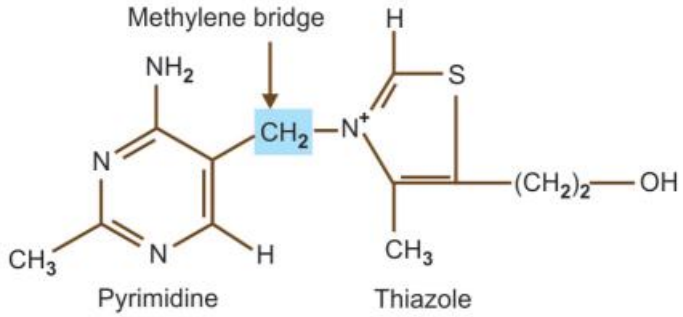
Toxicity of vitamin C:

Some adverse effects have been reported with excessive supplementation (1000 mg daily) for long periods of time, such as kidney stone development, diarrhea or Flatulence, skin rash, anemia, burning sensation during urination, and low blood sugar.

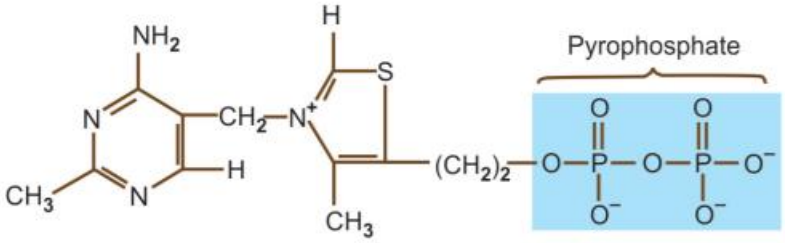
B- Complex vitamins:

1- Thiamine (vitamin B_1):

Thiamine, also known as vitamin B_1, it is abundant in liver, meat, milk, cereals, heart, kidney, whole grain and green leafy vegetables.



The active coenzyme form of thiamine is **thiamine pyrophosphate (TPP)**.



Functions of Thiamin in the body:

1. Thiamine is required mainly for carbohydrate metabolism

2. Thiamine pyrophosphate (TPP) is a coenzyme involved in several enzymatic reactions mainly for oxidative decarboxylation and transketolase reactions as follows:

a. TPP is a coenzyme for pyruvate dehydrogenase complex which catalyzes the conversion of pyruvate into acetyl CoA by oxidative decarboxylation

b. TPP is a coenzyme for α-ketoglutarate dehydrogenase which catalyzes the conversion of α-ketoglutarate to succinyl-CoA in TCA cycle

c. TPP is a coenzyme for the enzyme transketolase, in the pentose phosphate pathway of glucose oxidation.

Deficiency of thiamine:

Thiamine deficiency leads to

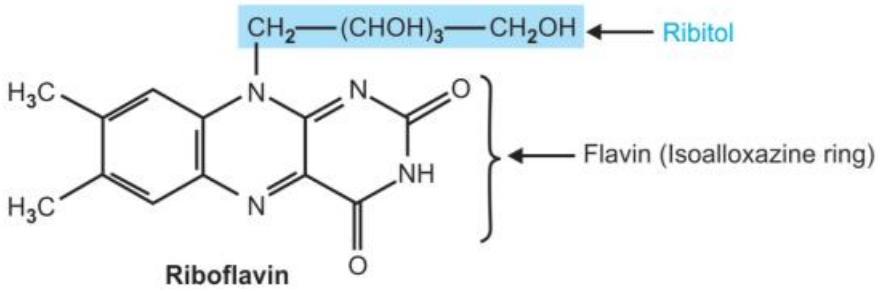
1- Failure of carbohydrate metabolism, resulting in decreased production of ATP and thus impaired cellular functions of central nervous, heart and gastrointestinal tract.

2- Leads to beriberi, a disease characterized by muscle weakness, mental stability, fatigue poor appetite, deep muscle pain and pain on contact with the skin.

Daily Thiamine needs (RDA): men: 1.2 mg/day; women: 1.1 mg/day

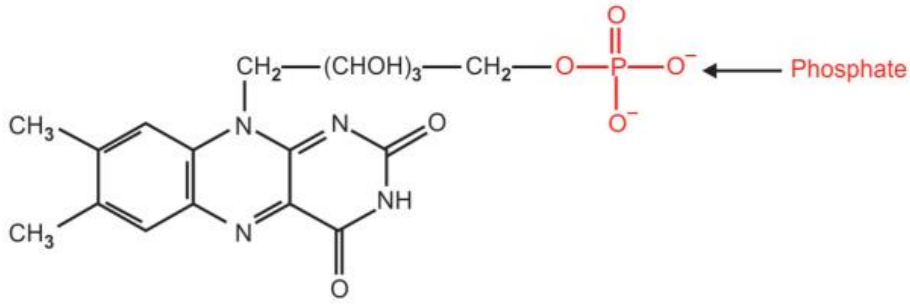
2- Riboflavin (vitamin B2):

Riboflavin ($C_{17}H_20N_4O_6$) belongs to a class of water-soluble pigments called lyochromes. Rich source of riboflavin are liver, heart, kidney, milk, egg, whole cereals, fish, green leafy vegetable and some fruits.

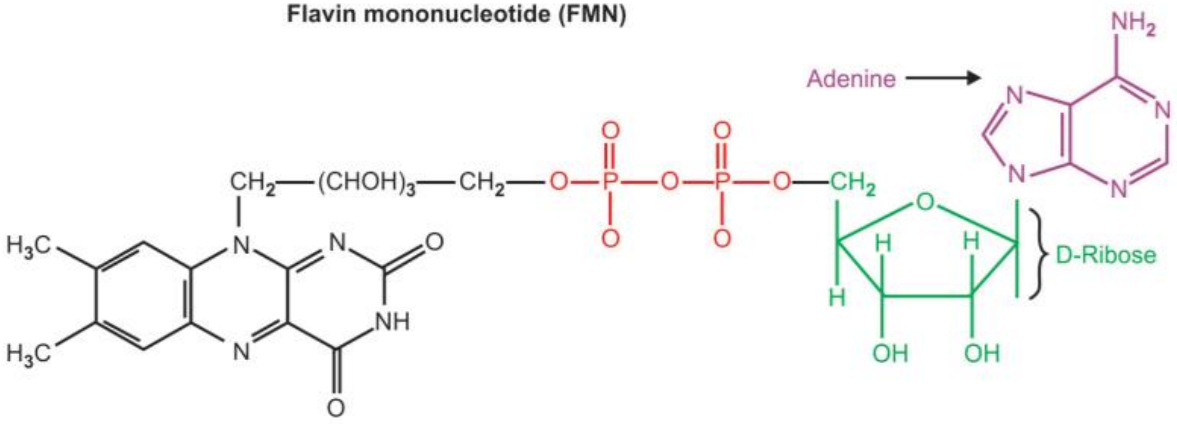


Riboflavin

The active forms of riboflavin are **Flavin Mono Nucleotide (FMN)** and **Flavin Adenine Dinucleotide (FAD)** in the liver.



Flavin mononucleotide (FMN)



Flavin Adenine dinucleotide (FAD)

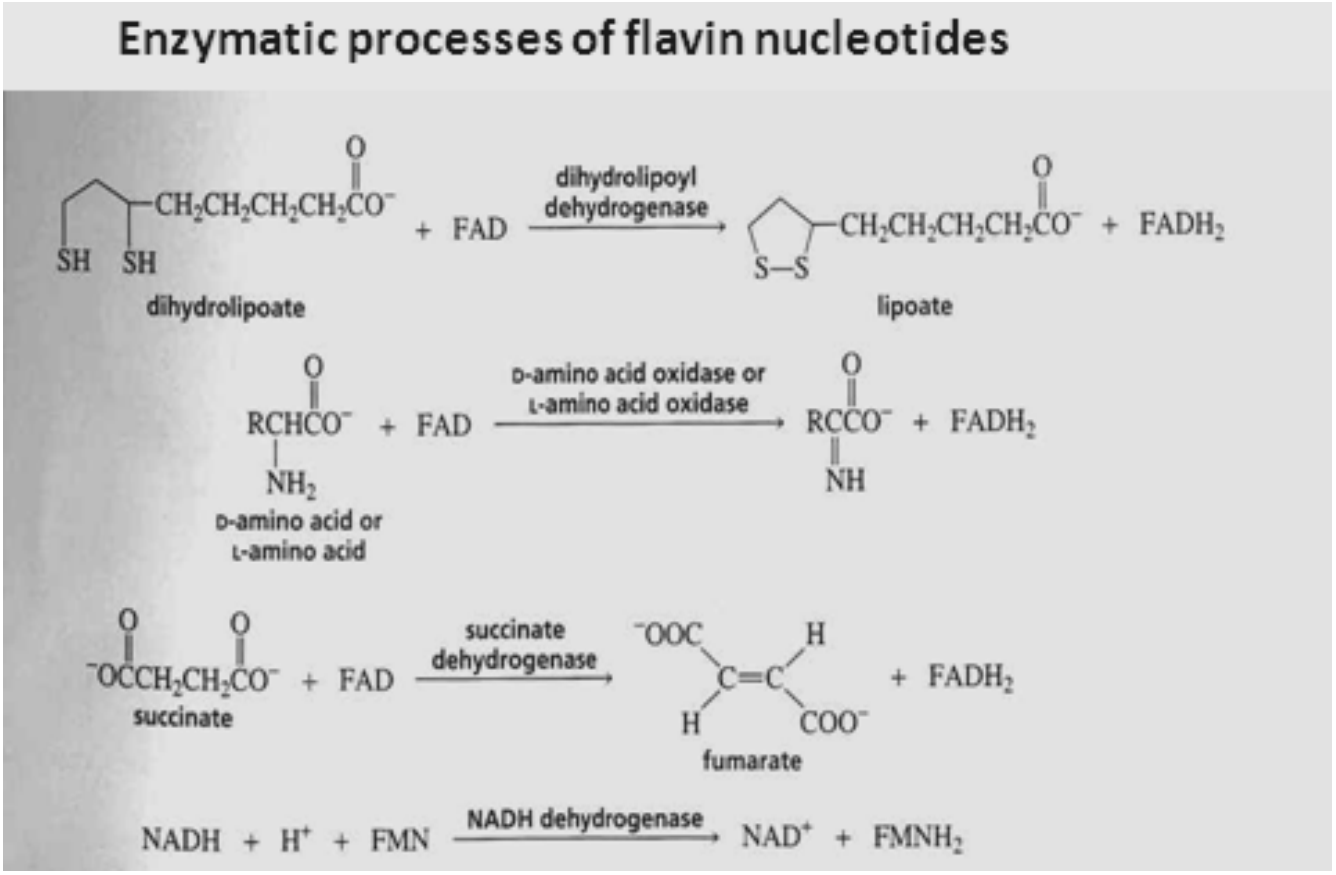
Functions of riboflavin:

1- FMN and FAD serve as coenzymes for several oxidation reduction reactions in metabolism pathways and in energy production via the respiratory chain.

2- Involved in the metabolism of iron, pyridoxine, folate.

3- Involved in protection against peroxidation in metabolism of xenobiotics.

4- Riboflavin is also needed to help the body convert vitamin B_6 and folate into active forms.



Deficiency of riboflavin:

Plants, microorganisms and intestinal micro flora synthesize riboflavin. Riboflavin deficiency is rare as it has a wide distribution in foodstuffs. It is usually seen along with deficiencies of other vitamins of B-complex group. Deficiency symptoms include

1- Dermatitis.

2- Cheilosis (fissuring at the corners the mouth)

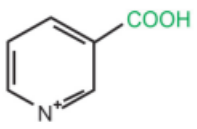
3- Glossitis (the tongue appearing smooth and purplish.

However, patients suffering from pellagra and beriberi are usually also deficient in riboflavin content.

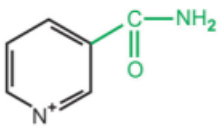
Recommended Daily Allowance: in men: 1.3 mg/day and women: 1.1 mg/day

3- Niacin (Vitamin B_3):

Niacin is also known as vitamin B_3. It is a pyridine derivative. Niacin is a general name for the nicotinic acid or nicotinamide. Niacin is widely distributed in nature in plant and animal tissues.



Nicotinic acid



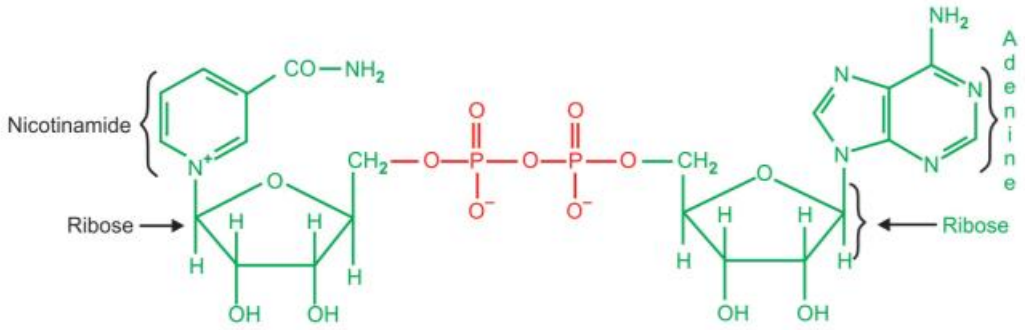
Nicotinamide

Niacin found in the liver, meat and milk. Limited quantities of niacin can be obtained from the metabolism of tryptophane.

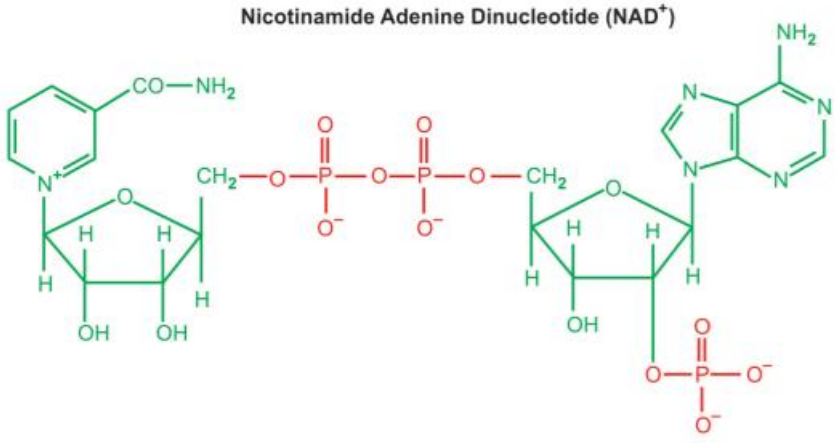
60 mg tryptophan synthesize —(PLP)→ 1mg Niacin

Synthesize of niacin from tryptophan requires pyridoxal phosphate (PLP).

Active forms of niacin are **Nicotinamide Adenine Dinucleotide (NAD^+) and Nicotinamide Adenine Dinucleotide Phosphate ($NADP^+$)**



Nicotinamide Adenine Dinucleotide (NAD^+)



Nicotinamide Adenine Dinucleotide Phosphate ($NADP^+$)

Function of niacin:

1. Niacin is a precursor of coenzymes, ***nicotinamide adenine dinucleotide (NAD+)*** and ***nicotinamide adenine dinucleotide phosphate (NADP+).***

2. NAD+ and NADP+ are involved in various ***oxidation*** and ***reduction reactions*** catalyzed by dehydrogenases in metabolism.

3. They are involved carbohydrate, lipid and protein metabolism. Generally, ***NAD+*** linked dehydrogenases catalyze oxidation-reduction reactions in ***oxidative pathways,*** e.g. citric acid cycle and glycolysis.

4. Whereas ***NADP+*** linked dehydrogenases or reductases are often found in pathways concerned with ***reductive synthesis,*** e.g. synthesis of cholesterol, fatty acid and pentose phosphate pathways.

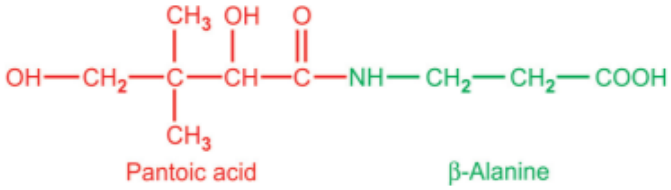
Deficiency of niacin:

1- Pellagra, a disease involving the skin, gastrointestinal tract and central nervous system. The symptoms of pellagra are characterized by three D s: Dermatitis, diarrhea, and dementia.

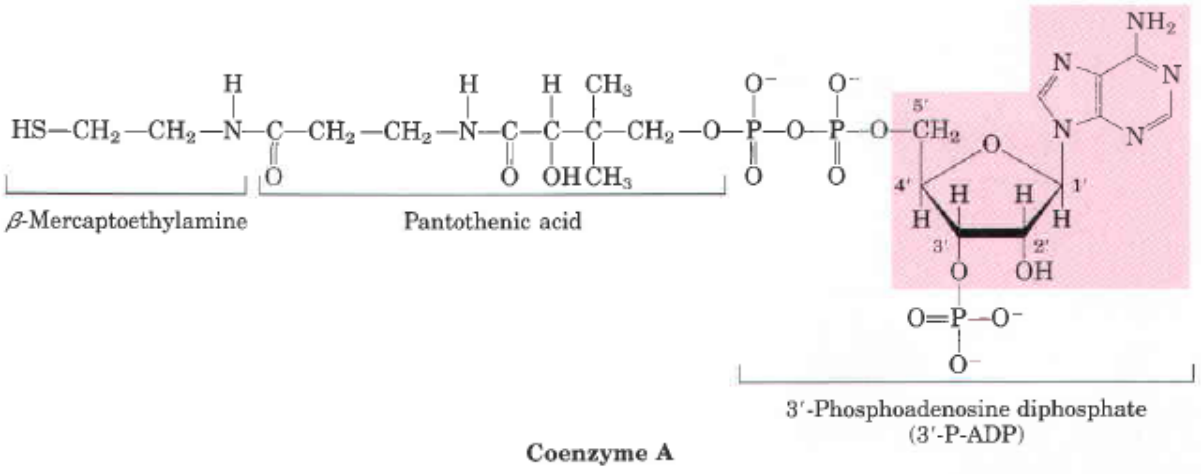
2- Also deficiency of V.B_9 leads to deficiency of niacin, because it is involved in the synthesis of niacin from tryptophan. Recommended Daily Allowance: in men: 16 mg NE/day and women: 14 mg NE/day. Niacin is measured in milligrams (mg) of niacin equivalents (NE). One NE equals 1 milligram of niacin or 60 mg of tryptophan.

4- Pantothenic acid (vitamin B5):

Pantothenic acid (C9H17NO5) is formed by a combination of pantoic acid and β-alanine. The important sources of pantothenic acid are liver, egg, yeast, potatoes, tomatoes and skimmed milk, although the vitamin is widely distributed.



Active forms of pantothenic acid are **Coenzyme-A** (CoA-SH) and **Acyl carrier protein** (ACP).



Coenzyme A

Function of pantothenic acid:

1- Pantothenic acid is a component of coenzyme A (CoA-SH) and acyl carrier protein (ACP). The thiol group of CoA-SH and ACP acts as a carrier of acyl groups.

2- Coenzyme A is required for the metabolism of all fat, protein, and carbohydrate via the citric acid cycle.

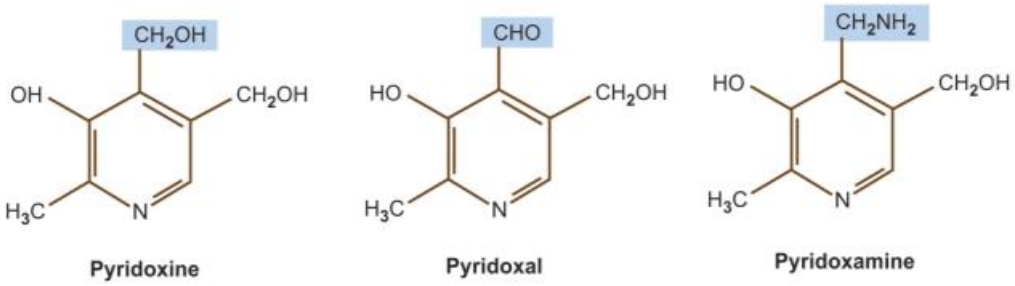
Deficiency of pantothenic acid:

Pantothenic acid deficiency is not well characterized in human because it is widespread in natural foods and when pantothenic deficiency dos occur, it is usually associated with multiple nutrient deficiencies, thus making it difficult to discern symptoms specific to the pantothenic acid.

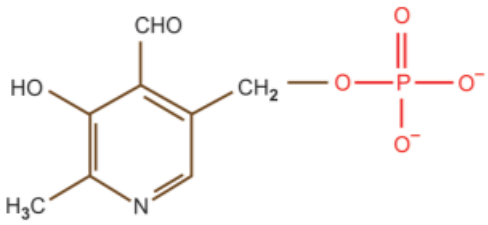
Daily Pantothenic Acid needs for adults (RDA): 5 mg/day

5- Vitamin B_6 (pyridoxine):

Vitamin B_6 consists of three related pyridine derivatives pyridoxine, pyridoxal, and pyridoxamine. All the 3 forms of vitamin B6 are derivatives of pyridine. Vitamin B_6 are widely distributed in nature in plant and animal tissues and found in many foods, such as fish, meat, milk, egg, green leafy vegetables and potatoes. Vitamin B6 can be synthesized by the intestinal bacteria.



Active form of vitamin B_6 is **pyridoxal phosphate**, and it's synthesized from phosphorylation of all three forms of this vitamin.



Structure of pyridoxal phosphate: an active form of vitamin B6

Function of Vitamin B_6 (pyridoxine):

1- Keep immune and nervous systems healthy

2- Pyridoxal-phosphate (PLP, active form of vitamin B_6) is required in carbohydrates, amino acid and fatty acid metabolism

3- It is also essential in the metabolism of hydroxy amino acids, sulfur containing amino acids and also to convert tryptophan to niacin.

4- Pyridoxal or its phosphate derivative also possibly acts as a carrier in the active transport of amino acids across cell membranes.

5- Helps to make red blood cells.

6- The various forms of vitamin B_6 serve as growth factors to a number of bacteria.

Deficiency of vitamin B_6:

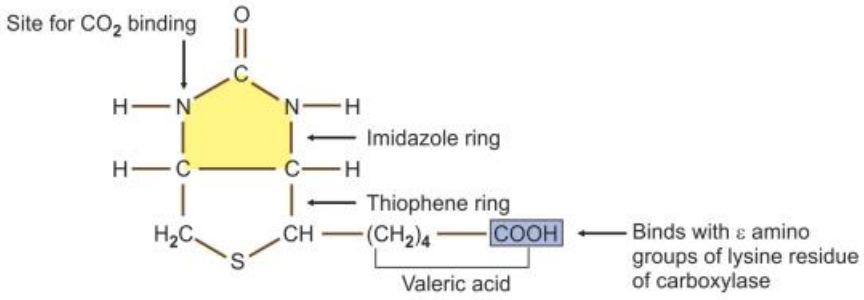
The deficiencies of vitamin B_6 is rare in human but have been observed in women taking oral contraceptive, alcoholics, and used of some drugs like pencillamide which combine with pyridoxal phosphate forming inactive derivatives of pyridoxal phosphate. Deficiency symptoms are:

1. Dermatitis
2. Anemia
3. Depression, confusion, and abnormal brain

Daily vitamin B_6 needs (RDA): men 1.3-1.7 mg/day; women 1.3-1.5 mg/day, depending on age.

6- Biotin:

Biotin ($C_{10}H_{16}O_3N_2S$) is an imidazole derivative. The active coenzyme form of biotin is **biotin** itself. Biotin and thiamine are the only sulfur-containing vitamins isolated to date. Biotin has a wide range of distribution in both the animal and the vegetable kingdoms. Biotin found in liver, kidney, milk, egg yolk, soya bean, tomatoes and vegetables. In addition, intestinal bacteria provide sufficient amounts of biotin.



Biotin occurs in nature usually in combined state as biocytin. Biotin is covalently bound to amino group of lysine of an enzyme to form biocytin

Function of biotin:

This vitamin serves as a coenzyme in energy metabolism, fat synthesis, amino acid metabolism, and glycogen synthesis.

Deficiency of biotin:

Deficiency of biotin is rare in human because it is widely distributed in foods. However, deficiency of biotin occurs in consuming large amounts of raw egg white, because egg white contains a glycoprotein avidin, which binds to biotin and prevent biotin absorption. In addition, intake sulphonamide drugs or oral antibiotics for prolonged periods, that

inhibit the growth of intestinal bacteria, eliminate this source of biotin and lead to biotin deficiency.

1- Dermatitis

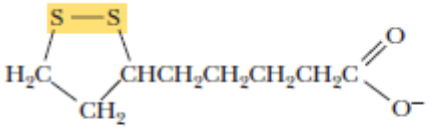
2- Loss of hair

3- Decrease in weight, sleepiness, depress and nausea.

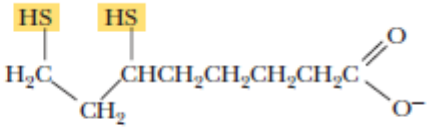
Daily Biotin needs for adults (RDA): 30 µg/day.

7- Lipoic acid:

Lipoic acid also known as alpha-lipoic acid, is a sulfur-containing fatty acid and found in yeast, liver, and the compound occurs widely in nature. Lipoic acid exists in oxidized and reduced form.



Lipoic acid, oxidized form



Reduced form

Function of Lipoic acid:

Lipoic acid acts as a coenzyme for the oxidative decarboxylation of pyruvic acid by pyrovate dehydrogenase multienzyme complex and α-ketoglutaric acid by α- ketogltarate dehydrogenase multi-enzyme complex.

Deficiency of lipoic acid:

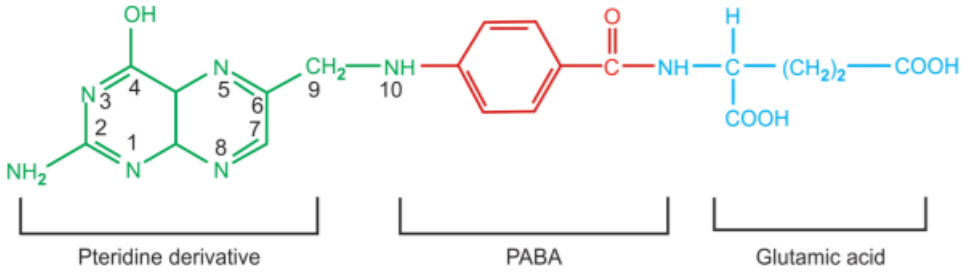
A deficiency of lipoic acid usually does not occur because it is widespread in the nature and most animals in small intestine synthesize it.

Recommended Daily Allowance: There is no Recommended Dietary Allowance (RDA) for alpha-lipoic acid, but studies have found that 100 milligrams taken twice daily is enough.

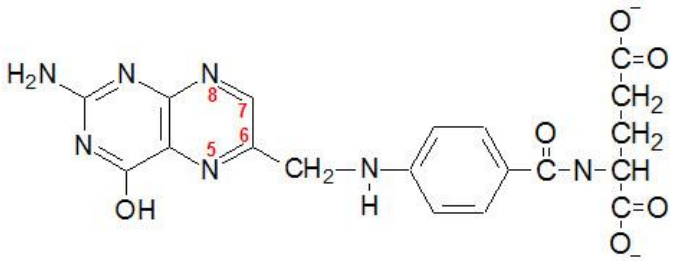
8- Folic acid:

Folic acid is widely distributed in the word. A good source of this vitamin are liver, kidney, green leafy vegetables, tomatoes, potatoes,…

A molecule of folic acid consists of 3 units: glutamic acid, p-amino benzoic acid and a derivative of the heterocyclic fused-ring compound pterin. Its molecular formula is $C_{19}H_{19}O_6N_7$.



The active form of folic acid is **tetrahydrofolate (THF)**



Function of Folic acid:

1- Tetrahydrofolate acts as a carrier of one carbon unit (may be methyl -CH_3, methylene -CH_2, formyl -CHO, formate-COOH….) during metabolism.

2- FH_4 is used in the synthesis of purines and pyrimidines, and therefore for the formation of DNA and RNA in all cells including maturing blood cells- synthesis of RBC and WBC.

3- FH_4 is needed for the synthesis of amino acid methionine.

4- Recent studies have shown that folic acid provides protection against Alzheimer's disease.

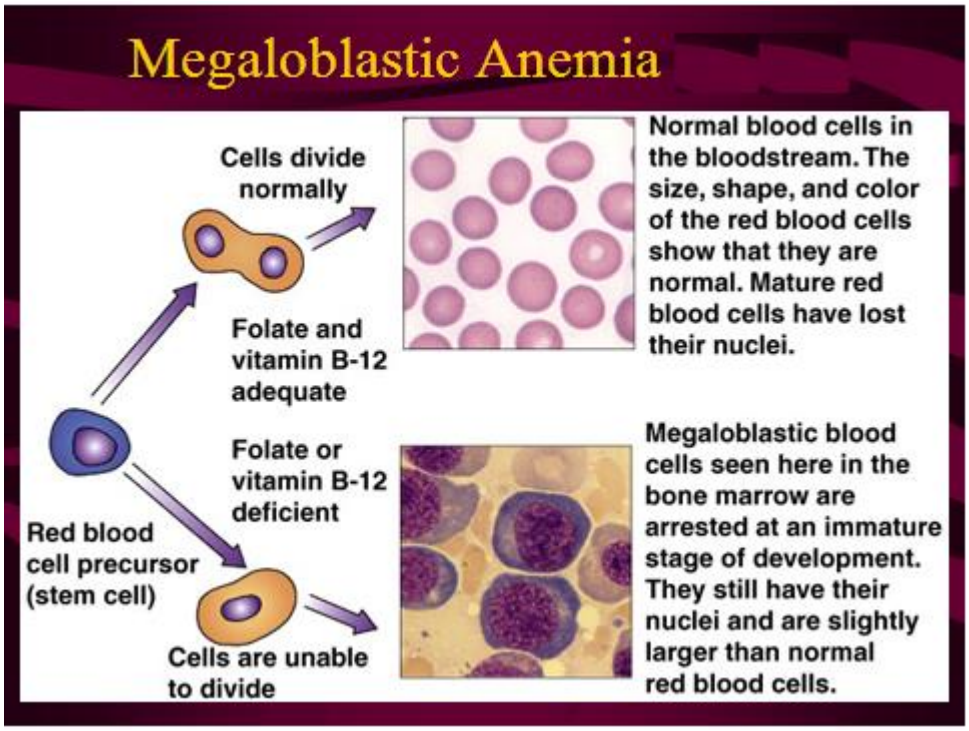
Deficiency of folic acid:

A nutritional deficiency of this vitamin causes:

1- Megaloblastic anemia, leads to impairment of synthesis of DNA. This leads to change in size and shape of the nuclei and slower maturation of red blood cells, causing production of abnormality large red blood cells with fragile membranes.

2- Gastrointestinal disorders.

Recommended Daily Allowance: 400 mg\ day. Folic acid is especially necessary for children and pregnant women



9- Vitamin B_{12} (cobalamine):

Vitamin B_{12} has been found only in animals; the chief source is liver, although it is also present in milk, meat, eggs, and fish. Vitamin B_{12} is absent in plant foods.

The intestinal microorganisms in the human may synthesize small amounts of vitamin B12. In general, cyanocobalamin is not present in plant foods except in Spirulina, a blue-green alga. However, it occurs in foods bound to proteins and is apparently split off by proteolytic enzymes.

Cobalamins exists in three forms that differ in the group attached to cobalt. Cynocobalamin is the commercial available form of vitamin B12

The active coenzyme forms of vitamin B_{12} are **methyl cobalamine** and **deoxyadenosyl cobalamine**. Vitamin B_{12} is the only water-soluble vitamin that is stored in significant amounts in the liver, bone marrow and other tissues.

Function of vitamin B_{12}:

The main functions of vitamin B_{12} are:

1- Helps in production of Methionine.

2- Red blood cells

3- DNA synthesis

4- Allows the use of Folic acid

Deficiency of vitamin B_{12}:

Deficiency of this vitamin is not observed because it is widespread in foods of animal origin. Vitamin B_{12} deficiency causes folate deficiency (because the generation of FH_4 depends on the presence of Vitamin B_{12}), therefore, all the manifestation of folate deficiency are also seen.

In addition, the deficiency causes

1- Pernicious anemia, a disease that is characterized by the presence of large, immature of red blood cells in the blood. The damage to the central nervous system can even cause demyelination of the peripheral nerves in the arms and legs.

2- Depression and Neurological problems

3- Weakness or fatigue

Recommended Daily Allowance: 2.4 μg\ day