وزارة التعليم العالي و البحث العلمي

جامعة البـصرة / كلية الصـيدلـــة

فرع العلوم المختبــرية و السـريرية

وزارة التعليم العالي والبحث العلمي

Ministry of Higher Education & Scientific Research

Vitamins

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Vitamins

Vitamins :- (Vital-amines) are group of organic nutrients that required in small quantities for a variety of biochemical functions and which, generally, cannot be synthesized by the body and therefore, it must be supplied in the diet.

***Vitamins can be classified into two mains classes** :-

1. **Lipid-soluble vitamins** (Lipophilic) \ it is can only be absorbed efficiently when there is normal the fat absorption. They are transported in the blood, like any other non-polar lipids, as lipoproteins or attached to specific binding proteins. They have diverse functions, e.g :- Vit. A (for vision), Vit. D (For Calcium and Phosphate metabolism),Vit. E (as Anti-oxidant) and Vit. K (For blood clotting). The malabsorption of these vitamins due to dietary inadequacy or diseases can lead to deficiency syndromes, includes :-

a) Night blindness and xerophthalmia (deficiency of Vit. A).

b) Rickets in children and osteomalacia in adults (deficiency of Vit.D).

c) Neurologic disorders and anemia in newborns (deficiency of Vit.E).

d) The hemorrhage in newborns (deficiency of Vit.K).

Being lipophilic, these vitamins have a long half-life and deficiency syndromes are rare, therefore, often, the body suffers from toxicity resulted from excessive intake of vitamins A, D, E and K.

2. Water-soluble vitamins \ they are the water-soluble vitamins comprise the B complex and vitamin C and their main function as coenzyme factors. Although, all diets contain a suitable concentration of water-soluble vitamins, specific deficiency of individual vitamins, the syndromes are appeared due to the high solubility in the water, especially, in the case of Diabetes , e.g :-

a) Beriberi (deficiency of thiamin B_1).
b) Cheilosis, glossitis, seborrhea (deficiency of riboflavin B_2).
c) Pellagra (deficiency of niacin B_3).
d) Peripheral neuritis (deficiency of pyridoxine B_6).
e) Megaloblastic and pernicious anemia (deficiency of vitamin B_{12}).
f) Megaloblastic anemia (deficiency of folic acid).
g) Scurvy disease (deficiency of Vitamin C).

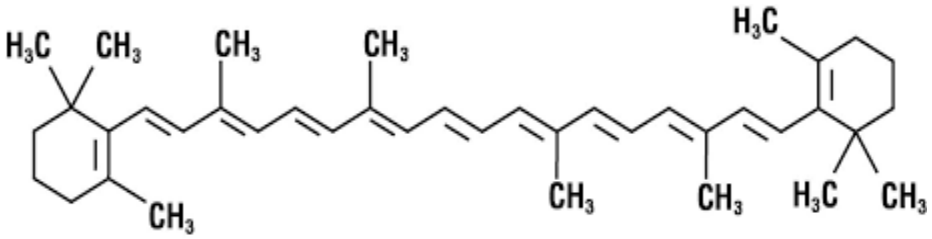
A vitamin is defined as an organic compound that is required in the diet in small amounts for the maintenance of normal metabolic integrity. However, vitamins D, which can be made in the skin after exposure to sunlight, and niacin, which can be formed from the essential amino acid tryptophan, do not strictly conform to this definition.

[A] Lipid-soluble vitamins :-

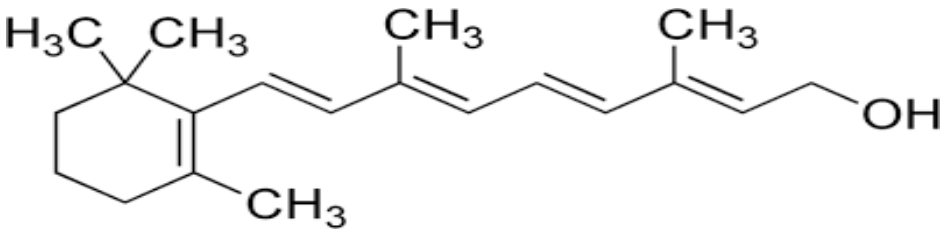
1. Vitamin A :-

Retinoids comprise retinol, retinaldehyde, and retinoic acid (preformed vitamin A, found only in foods of animal origin); carotenoids, found in plants, comprise carotenes and related compounds, known as provitamin A, as they can be cleaved to yield retinaldehyde and thence retinol and retinoic acid. The α-, β-, and γ-carotenes and cryptoxanthin are quantitatively the most important provitamin A carotenoids.

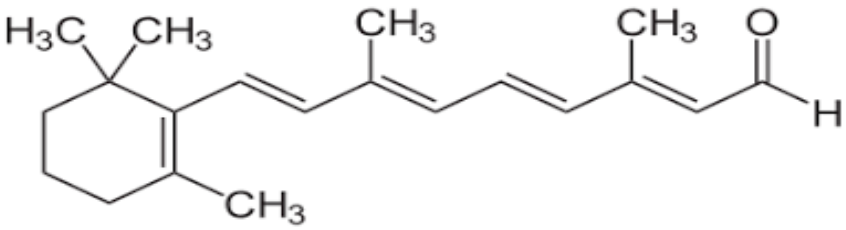
Beta-carotene and other provitamin A carotenoids are cleaved in the intestinal mucosa by carotene dioxygenase, yielding retinaldehyde, which is reduced to retinol, esterified, and secreted in chylomicrons together with esters formed from dietary retinol.



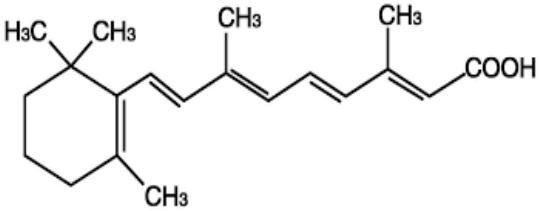
β-carotene structure



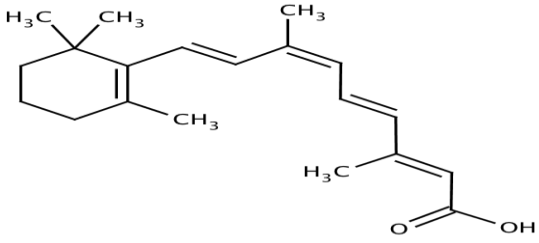
Retinol structure



Retinaldehyde structure



All-*trans*-retinoic acid



9-*cis*-retinoic acid

Figure show **β-Carotene and the major vitamin A vitamers.**

(3)

Vitamin A has main Function in Vision In the retina, where in retina retinaldehyde act as the prosthetic group of the light-sensitive proteins, opsin, forming rhodopsin (in rods) and iodopsin (in cones). Any one cone cell contains only one type of opsin and is sensitive to only one colour. In the pigment epithelium of the retina, all-*trans*-retinol is isomerized to 11-*cis*-retinol and oxidized to 11-*cis*-retinaldehyde. This reacts with a lysine residue in opsin, forming the holoprotein rhodopsin. The absorption of light by rhodopsin causes isomerization of the retinaldehyde from 11-*cis* to all-*trans,* and a conformational change in opsin, which lead to release of retinaldehyde from the protein and the initiation of a nerve impulse which occurs within picoseconds of illumination. There is then a series of conformational changes leading to the formation of metarhodopsin II, which initiates a guanine nucleotide amplification cascade and then a nerve impulse. The final step is hydrolysis to release all-*trans*-retinaldehyde and opsin. The key to initiation of the visual cycle is the availability of 11-*cis*-retinaldehyde, and hence vitamin A.

The most another important function of vitamin A is in the control of cell differentiation and turnover. All-*trans*-retinoic acid and 9-*cis*-retinoic acid regulate growth, development, and tissue differentiation. Like the steroid hormones and vitamin D, retinoic acid binds to nuclear receptors that bind to response elements of DNA and regulate the transcription of specific genes.

****There are two families of nuclear retinoid receptors** :-**

1) **The retinoic acid receptors (RARs) bind all-*trans*-retinoic acid or 9-*cis*-retinoic acid.**
2) **The retinoid X receptors (RXRs) bind only with 9-*cis*-retinoic acid.**

****Vitamin A deficiency is the most important preventable cause of blindness. The earliest sign of deficiency is a loss of sensitivity to green light, followed by impairment of adaptation to dim light, followed by night blindness.**

More prolonged deficiency leads to xerophthalmia (keratinization of the cornea and skin and blindness). Vitamin A also has an important role in differentiation of immune system cells, and mild deficiency leads to increased susceptibility to infectious diseases.
There is only a limited capacity to metabolize vitamin A, and excessive intakes lead to accumulation beyond the capacity of binding proteins, so that unbound vitamin A causes tissue damage in the CNS, liver, skin, and disorders of calcium homeostasis.

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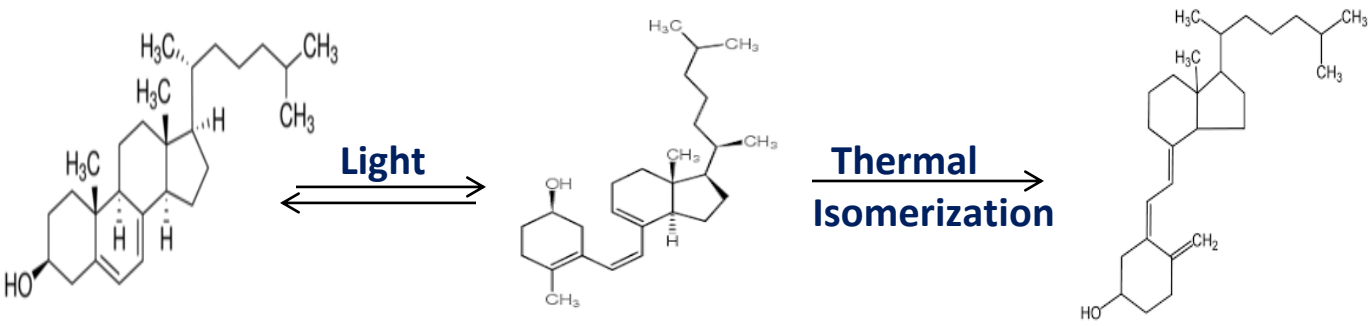
2. Vitamin D \

Vitamin D is not strictly a vitamin since it can be synthesized in the skin, and under most conditions that is its major source. Only when sunlight is inadequate is a dietary source required. The main function of vitamin D is in the regulation of calcium absorption and homeostasis and most of its actions are mediated by way of nuclear receptors that regulate gene expression.

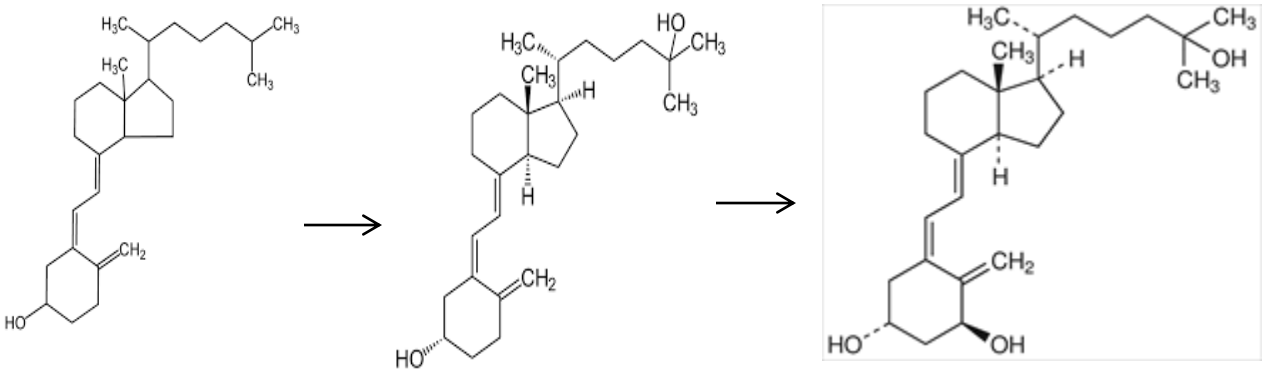
Vitamin D is Synthesized in the Skin

7-Dehydrocholesterol (an intermediate in the synthesis of cholesterol that accumulates in the skin), undergoes a non-enzymic reaction on exposure to ultraviolet light, yielding previtamin D. This undergoes a further reaction over a period of hours to form the vitamin itself, cholecalciferol, which is absorbed into the bloodstream.

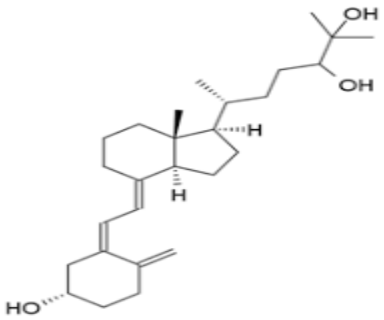


7-Dehydrocholesterol previtamin D cholecalciferol (vitamin D)

In the liver, cholecalciferol, which has been synthesized in the skin or derived from food, is hydroxylated to form the 25-hydroxy derivative calcidiol. This is released into the circulation bound to a vitamin D-binding globulin which is the main storage form of the vitamin. In the kidney, calcidiol undergoes either 1-hydroxylation to yield the active metabolite 1,25-dihydroxyvitamin D (calcitriol) or 24-hydroxylation to yield an inactive metabolite, 24,25-dihydroxyvitamin D (24- hydroxyl-calcidiol). Ergocalciferol from fortified foods undergoes similar hydroxylations to yield ercalcitriol.



Vit. D Calcidiol Calcitriol (1,25-hydroxycholecalciferol)

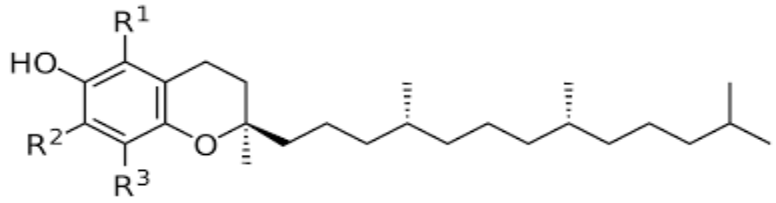


"Figure about metabolism of Vit. D" calcidiol (24-hydroxycalcidiol)

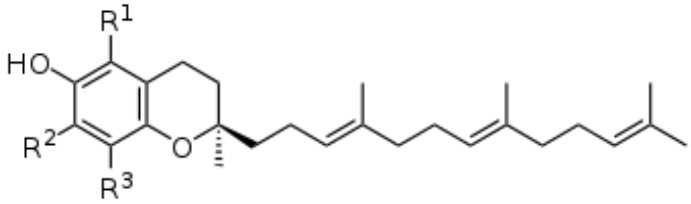
Vitamin D deficiency leads to appear the rickets disease in the children and Osteomalacia in adults due to demineralization of bones, especially, in women who have little exposure to sunlight, often after several pregnancies. By contrast, the excessive intakes of Vit. D can lead to elevate the blood concentration of calcium, which in turn leads to contraction of blood vessels, high blood pressure, and calcinosis (Calcification of soft tissues). (6)

3. Vitamin E \

Vitamin E acts as a lipid-soluble anti-oxidant in cell membranes. This Vitamin comprises two generic families of compounds, the tocopherols and the tocotrienols. The different vitamers (compounds having similar vitamin activity) have different biologic potencies; the most active is D-α-tocopherol.



Tocopherols



Tocotrienol

The main function of vitamin E is as a chain-breaking, free radical trapping antioxidant in cell membranes and plasma lipoproteins. It reacts with the lipid peroxide radicals formed by peroxidation of polyunsaturated fatty acids before they can establish a chain reaction. The tocopheroxyl free radical product is relatively unreactive and ultimately forms nonradical compounds. Commonly, the tocopheroxyl radical is reduced back to tocopherol by reaction with vitamin C from plasma.

In experimental animals, vitamin E deficiency results in resorption of fetuses and testicular atrophy. Dietary deficiency of vitamin E in humans is unknown, though patients with severe fat malabsorption, cystic fibrosis, and some forms of chronic liver disease. Also, some premature infants suffer from hemolytic anemia due to abnormal fragile of erythrocyte membranes as a result of peroxidation.

4. Vitamin K \

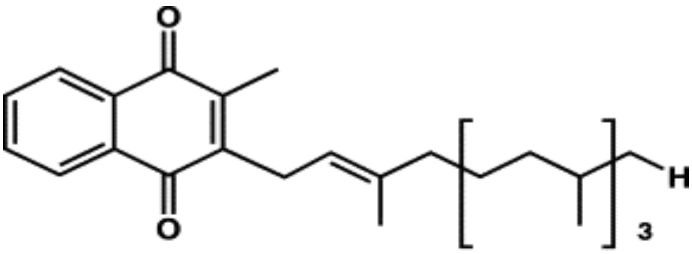
Vitamin K was discovered as a result of investigations into the cause of a bleeding disorder (hemorrhagic) disease.

****There are three compounds have the biologic activity of vitamin K :-**

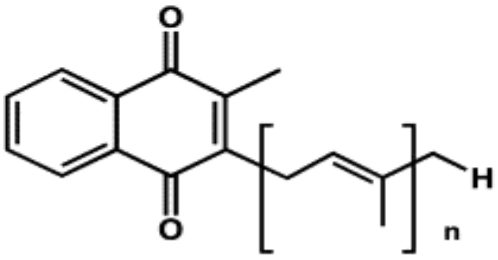
(a) Phylloquinone, the normal dietary source, found in green vegetables.

(b) Menaquinones is synthesized by intestinal bacteria.

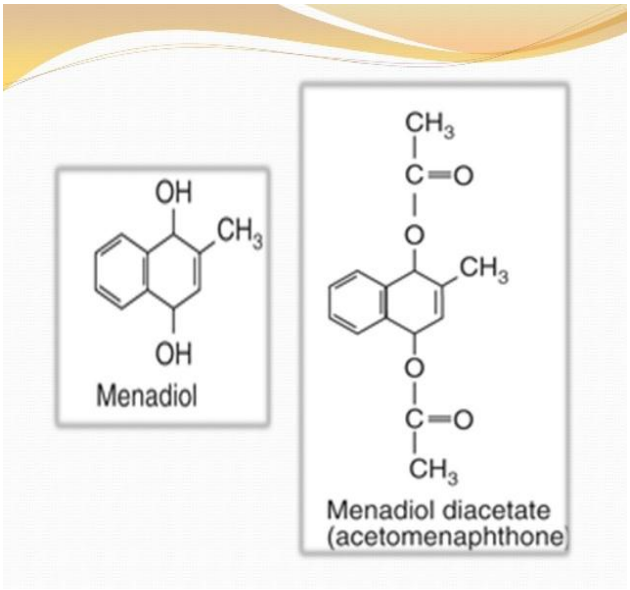
(c) Menadione, Menadiol and Menadiol diacetate synthetic compounds that can be metabolized to phylloquinone.



Vitamin K_1 (Phylloquinone)



Vitamin K_2 (Menaquinone-n)

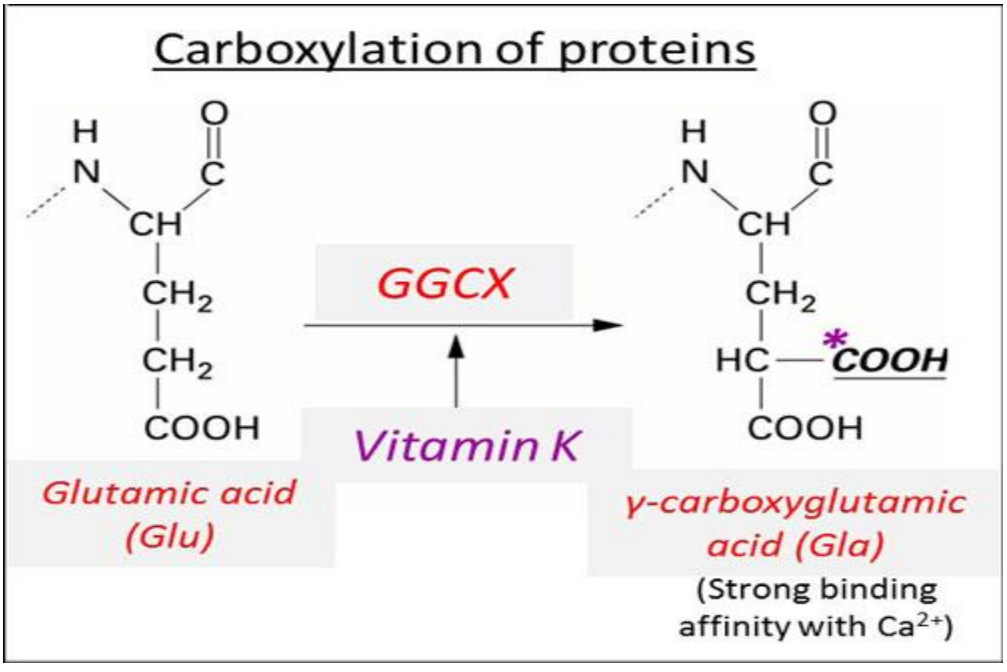


Vitamin K is the cofactor for the carboxylation of glutamate residues in the post-synthetic modification of proteins to form the unusual amino acid γ-carboxyglutamate (Gla), which chelates the calcium ion. Initially, vitamin K hydroquinone is oxidized to the epoxide, which activates a glutamate residue in the protein substrate to a carbanion, that reacts non-enzymically with carbon dioxide to form γ-carboxyglutamate.

Vitamin K epoxide is reduced to the quinone by a warfarin-sensitive reductase, and the quinone is reduced to the active hydroquinone by either the same warfarin-sensitive reductase or a warfarin-insensitive quinone reductase. In the presence of warfarin, vitamin K epoxide cannot be reduced but accumulates, and is excreted. If enough vitamin K (a quinone) is provided in the diet, it can be reduced to the active hydroquinone by the warfarin-insensitive enzyme, and carboxylation can continue, therefore a high dose of vitamin K is the antidote to an overdose of warfarin.

Prothrombin and several other proteins of the blood clotting system (Factors VII, IX and X, and proteins C and S) each contain between four and six γ-carboxyglutamate residues which chelate calcium ions and so permit the binding of the blood clotting proteins to membranes.

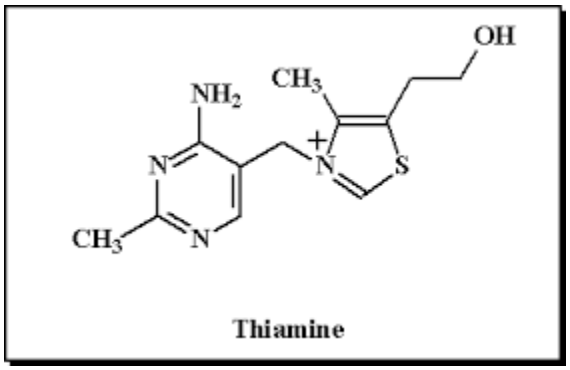
In vitamin K deficiency or in the presence of warfarin, an abnormal precursor of prothrombin (preprothrombin) containing little or no γ-carboxyglutamate, and incapable of chelating calcium, is released into the circulation.



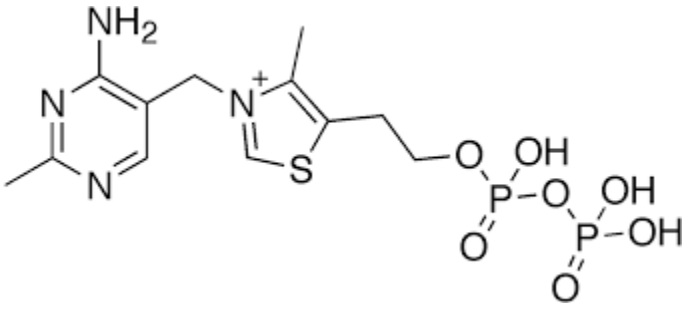
[B] Water-soluble vitamins \

1. Vitamin B_1 (Thiamin) \

Thiamin has a central role in energy-yielding metabolism, and especially the metabolism of carbohydrate. Thiamin diphosphate is the coenzyme for three multi-enzyme complexes that catalyze oxidative decarboxylation reactions.



Thiamine



Thiamin diphosphate

****Thiamin deficiency can result in three distinct syndromes :-**

(A) A chronic peripheral neuritis, beriberi, which may or may not be associated with heart failure.

(B) Edema, acute pernicious (fulminating) beriberi (shoshin beriberi), in which heart failure and metabolic abnormalities predominate, Without peripheral neuritis.

(C) Wernicke's encephalopathy with Korsakoff's psychosis, which is associated especially with alcohol and drug abuse.

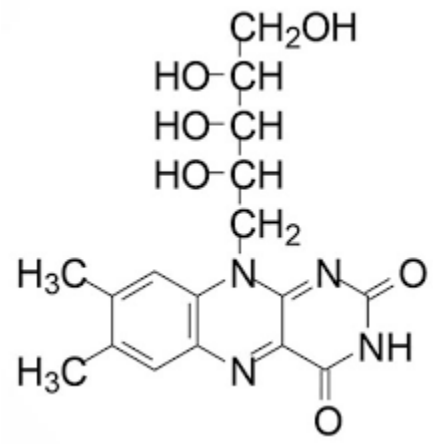
****The central role of thiamin diphosphate in pyruvate dehydrogenase means that in deficiency there is impaired conversion of pyruvate to acetyl CoA. In subjects on a relatively high carbohydrate diet, this results in increased plasma concentrations of lactate and pyruvate, which may cause life-threatening lactic acidosis.**

2. Vitamin B_2 (Riboflavin) \

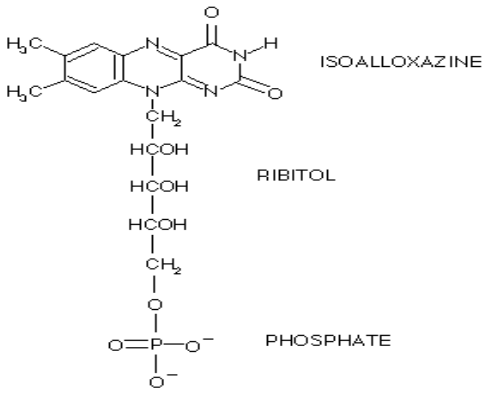
Riboflavin fulfills its role in metabolism as the coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). FMN is formed by ATP-dependent phosphorylation of riboflavin, whereas FAD is synthesized by further reaction of FMN with ATP in which its AMP moiety is transferred to the FMN. The main dietary sources of riboflavin are milk and dairy products. In addition, because of its intense yellow color, riboflavin is widely used as a food additive.

The Coenzymes of Riboflavin are involved the mitochondrial respiratory chain, key enzymes in fatty acid and amino acid oxidation, and the citric acid cycle.

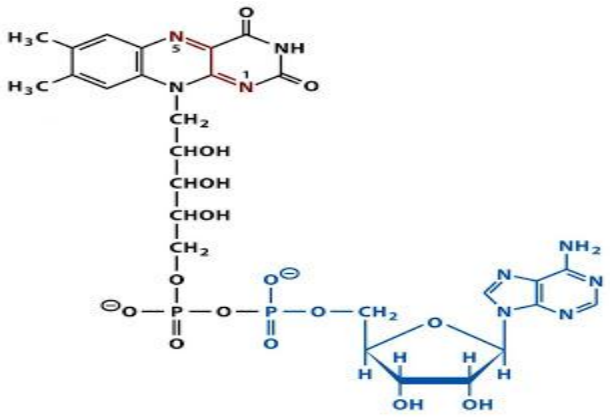
Riboflavin deficiency is characterized by cheilosis, lingual desquamation and a seborrheic dermatitis.



Riboflavin



Flavin mononucleotide (FMN)



Flavin adenine dinucleotide (FAD).

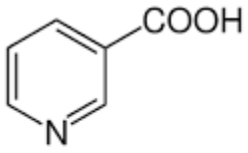
3. Vitamin B_3 (Niacin) \

Niacin was discovered as a nutrient during studies of pellagra. It is not strictly a vitamin since it can be synthesized in the body from the essential amino acid tryptophan. Two compounds, nicotinic acid and nicotinamide, have the biologic activity of niacin; its metabolic function is as the nicotinamide ring of the coenzymes NAD and NADP in oxidation-reduction reactions.

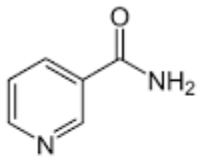
In addition to its coenzyme role, NAD is the source of ADP-ribose for the ADP-ribosylation of proteins and poly ADP-ribosylation of nucleoprotein involved in the DNA repair mechanism.

Pellagra is characterized by a photosensitive dermatitis, dementia, possibly diarrhea, and, if untreated, death.

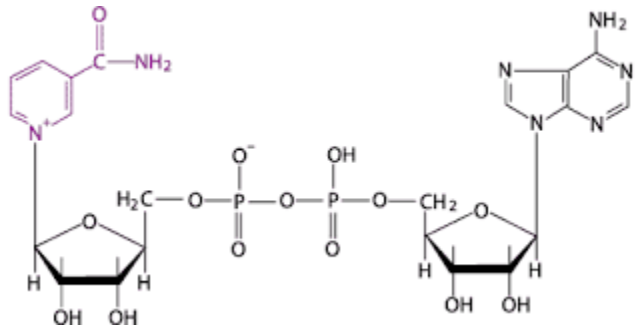
A number of genetic diseases that result in defects of tryptophan metabolism are associated with the development of pellagra despite an apparently adequate intake of both tryptophan and niacin, e.x:- Hartnup disease and carcinoid syndrome.



Niacin or nicotinic acid



Nicotinamide



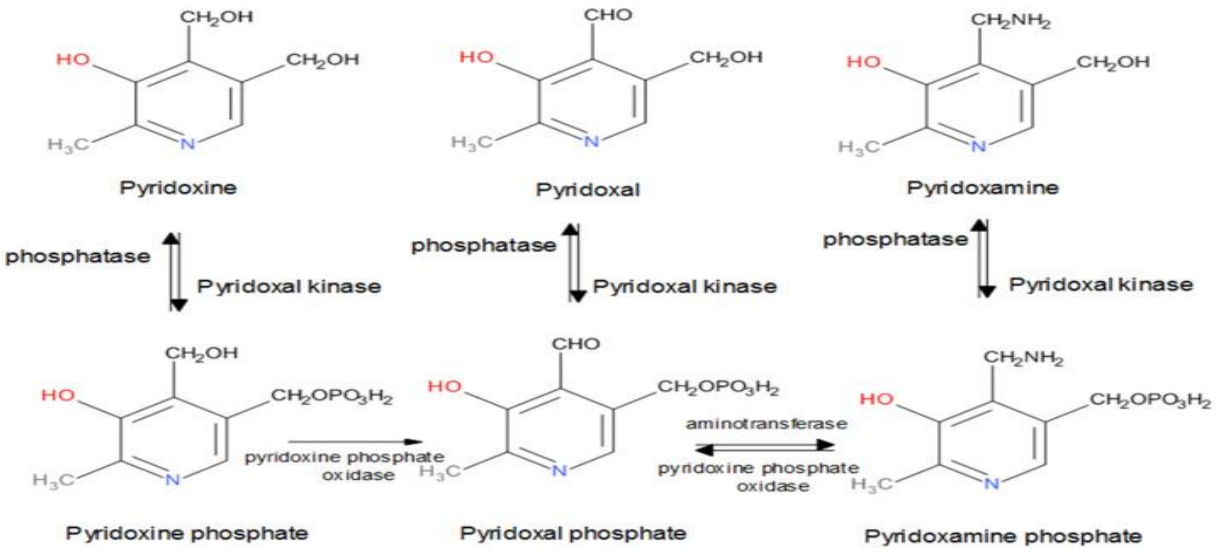
NAD (Nicotinamide adenine dinucleotide)

4. Vitamin B6 (pyridoxine) \

Six compounds have vitamin B6 activity : pyridoxine, pyridoxal, pyridoxamine, and their 5'-phosphates. The active coenzyme is pyridoxal 5'-phosphate. Approximately 80% of the body's total vitamin B6 is present as pyridoxal phosphate in muscle, mostly associated with glycogen phosphorylase.

Pyridoxal phosphate is a coenzyme for many enzymes involved in amino acid metabolism, especially in transamination and decarboxylation. It is also the cofactor of glycogen phosphorylase. In addition, vitamin B6 is important in steroid hormone action where it removes the hormone-receptor complex from DNA binding, terminating the action of the hormones.

Although clinical deficiency disease is rare, the Moderate deficiency results in abnormalities of tryptophan and methionine metabolism. Also this deficiency, results in increased sensitivity to the actions of low concentrations of estrogens, androgens, cortisol, and vitamin D. This Increased sensitivity to steroid hormone action may be important in the development of hormone dependent cancer of the breast, uterus, and prostate. While the excess uptakes of Vitamin B6 (200 mg/d) will result in neuropathy (neurologic damage).



5. Vitamin B_{12} (cobalamins) \

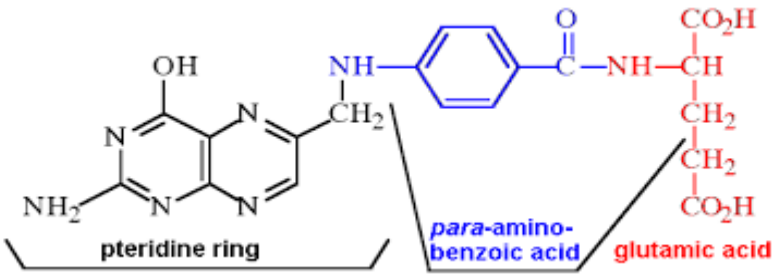
The term "vitamin B_{12}" is used as a generic descriptor for the cobalamins (cobalt containing compounds possessing the corrin "porphorin"ring) having the biologic activity of the vitamin which presents growth factors for microorganisms. This is vitamin is synthesized exclusively by microorganisms, therefore, it found only in foods of animal origin, because of containing the cyanide group, also termed Cyanocobalamine"

Vitamin B_{12} is absorbed bound to intrinsic factor, a small glycoprotein secreted by the parietal cells of the gastric mucosa. Gastric acid and pepsin release the vitamin from protein binding in food and make it available to bind to cobalophilin, a binding protein secreted in the saliva. In the duodenum, cobalophilin is hydrolyzed, releasing the vitamin for binding to intrinsic factor, then it absorbed and moved in the blood and stored in the liver.

Pernicious anemia arises when vitamin B_{12} deficiency blocks the metabolism of folic acid, leading to functional folate deficiency. This impairs erythropoiesis, causing immature precursors of erythrocytes to be released into the circulation (megaloblastic anemia). The commonest cause of pernicious anemia is failure of the absorption of vitamin B_{12} rather than dietary deficiency. This can be due to failure of intrinsic factor secretion caused by autoimmune disease of parietal cells or to generation of antibodies for intrinsic factor.

6. Folic acid (Petroyl glutamate) \

The active form of folic acid is. The folates in foods may have up to seven additional glutamate residues linked by γ-peptide bonds.

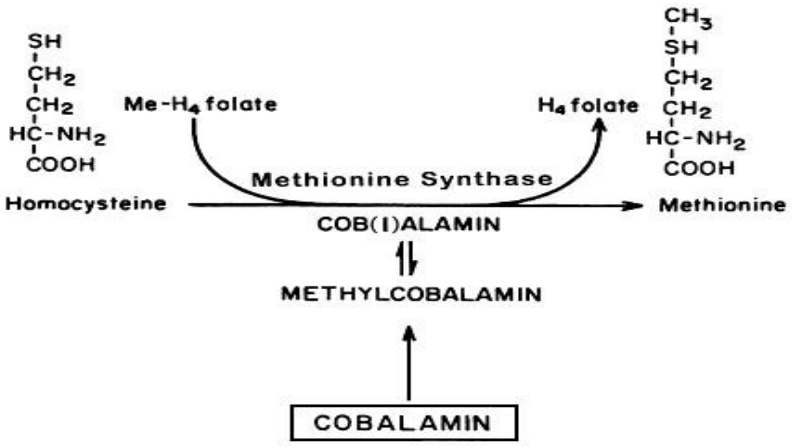


Tetrahydrofolate

The tetrahydrofolate can carry one-carbon fragments at position N-5 or N-10, or as bridging N-5 to N-10 (methylene or methenyl groups). Where 5-Formyl-tetrahydrofolate (H-CO-group attached at N-5) is more stable than folate and is therefore used pharmaceutically in the agent known as folinic acid. The methylation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (TMP), catalyzed by thymidylate synthase, is essential for the synthesis of DNA. The reduction of tetrahydrofolate metabolism into tetrahydrofolate is catalyzed by dihydrofolate reductase. These two enzymes, Thymidylate synthase and dihydrofolate reductase are especially active in tissues with a high rate of cell division. Methotrexate, an analog of 10-methyl-tetrahydrofolate, act as inhibitor for dihydrofolate reductase and has been exploited as an anti-cancer drug. Sometimes,The dihydrofolate reductases of some bacteria and parasites differ from the human enzyme; where inhibitors of these enzymes can be used as antibacterial drugs, e.x, trimethoprim.

The conversion homocysteine into methionine is catalyzed by action of methionine synthase, a vitamin B_{12}-dependent enzyme. This conversion is achieved accompanying with the conversion of methyltetra-hydrofolate (methyl donor) to tetrahydrofolate.

Impairment of methionine synthase in B_{12} deficiency results in the accumulation of methyl-tetrahydrofolate and of homocycteine, to result what is called the folate trape and homocycteinuria. So, there is functional deficiency of folate due to the deficiency of vitamin B_{12}.



Deficiency of folic acid itself, or deficiency of vitamin B_{12}, which leads to functional folic acid deficiency which affects cells that are dividing rapidly because they have a large requirement for thymidine for DNA synthesis, which in turn, this effects on the bone marrow, leading to megaloblastic anemia.

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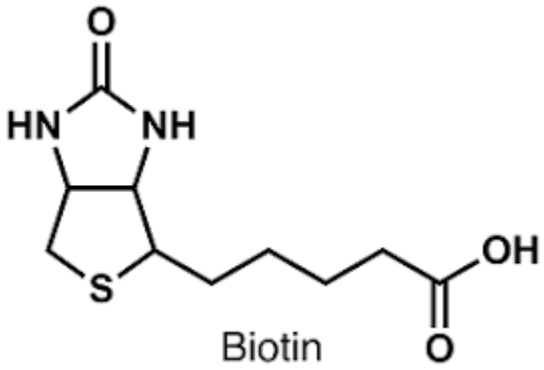
(7) Biotin vitamin \

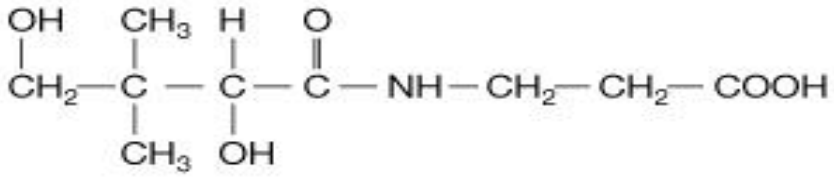
Biotin is widely distributed in many foods and It is synthesized by intestinal flora, where the deficiency of this vitamin is unknown except among people maintained for many months on parenteral nutrition and a very small number who eat abnormally large amounts of uncooked egg white, which contains **avidin,** a protein that binds biotin and prevent the absorption of it. Biotin functions to transfer carbon dioxide in a small number of carboxylation reactions.



Biotin

(8) Pantothenic acid \

Pantothenic acid has a central role in acyl group metabolism when acting as the pantetheine functional moiety of coenzyme A or acyl carrier protein (ACP). This vitamin is widely distributed in all foodstuffs, and deficiency has not been reported in human.



Pantothenic acid

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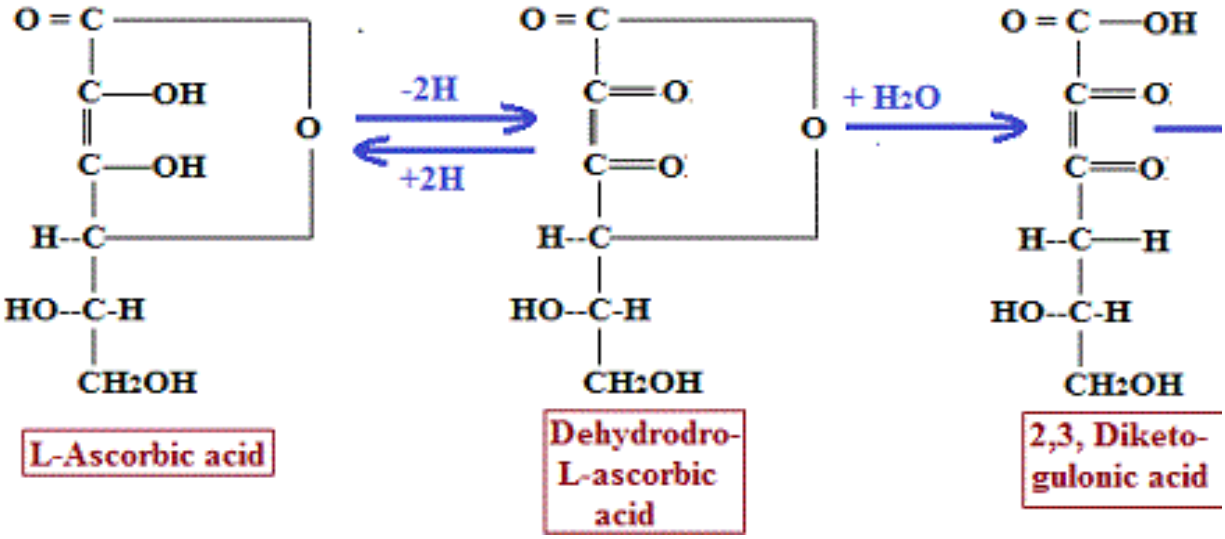
(9) Vitamin C (Ascorbic acid) \

The discovery of vitamin C is associated with the scurvy disease, which has been known for centuries especially among sailors. Ascorbic acid is a white, crystalline, odorless substance with sour taste. It has strong reducing properties and the L-isomer is active but the D-isomer is inactive.



****Signs of vitamin C deficiency in scurvy disease include **

1. Skin changes. 2. Fragility of blood capillaries. 3. Gum decay.

4. Tooth loss. 5. Bone fracture, many of which can be attributed to deficient collagen synthesis.

-With all my wishes for you by success ---Khalaf N. Abood….12/5/2018.