

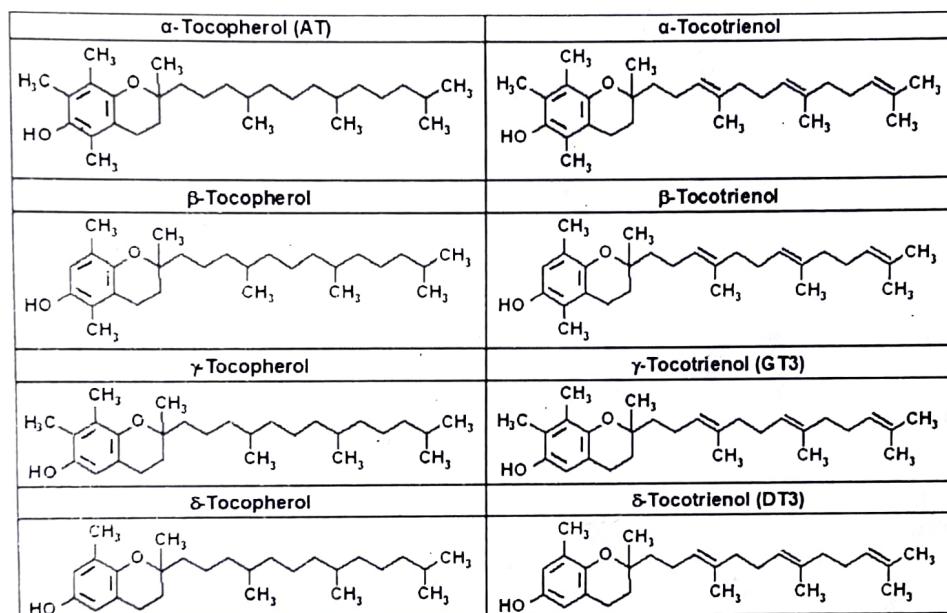
## VITAMIN E (Tocopherol or fertility hormone)

Vitamin E is required in the human diet but its deficiency is rare except in pregnancy and the new born, where it is associated with hemolytic anaemia

- It exists in the diet as a mixture of eight closely related compounds called tocopherols.

### STRUCTURE OF VITAMIN E

Vitamin E occurs naturally as tocopherol and as tocotrienols. Tocopherols and tocotrienols have the same basic chemical structure, which is characterised by a long isoprenoid side chain attached at the 2<sup>nd</sup> position of a 6-chromanol ring. Tocotrienols have unsaturated 3 C-C double bonds in the isoprenoid side chains while tocopherols have saturated ones.



### Sources

Wheat germ oil	Safflower oil	Corn oil	Kiwifruit
Sunflower seeds	Hazelnuts	Spinach	Mango
Almonds	Peanut butter	Broccoli	Tomato
Sunflower oil	Peanuts	Soybean oil	Spinach

### Functions

#### a) Antioxidant

Vitamin E is a potent chain-breaking antioxidant that inhibits the production of reactive oxygen species molecules when fat undergoes oxidation and during the propagation of free radical reaction. It acts as the first line of defence against lipid peroxidation, protecting the cell membranes from free radical attack.

#### b) Protection of the Cell Membranes

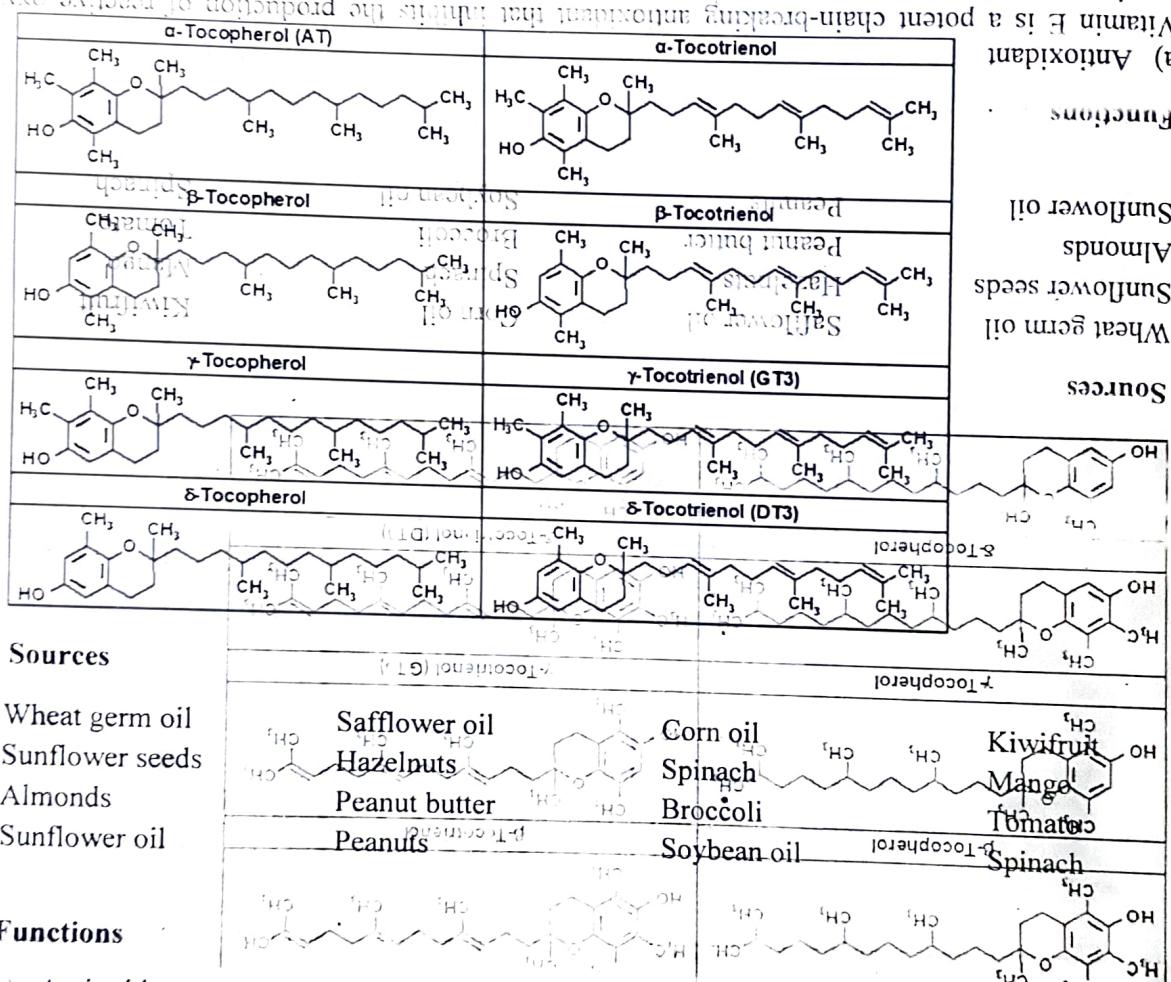
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Vitamin E increases the orderliness of the membrane lipid packaging, thus allowing for a tighter packing of the membrane and, in turn, greater stability to the cell (alpha-tocopherol promotes plasma membrane repair)

- c) Vitamin E helps to keep the immune system strong against viruses and bacteria.
- d) Important in the formation of red blood cells.
- e) It helps the body use vitamin K.
- f) It also helps widen blood vessels and keep blood from clotting inside them.
- g) Vitamin E plays an important role in the production of hormone-like substances called prostaglandins, which are responsible for regulating body processes, such as blood pressure and muscle contraction.
- h) Vit E improves cardiovascular functions by increasing the activity of nitric oxide synthase, which produces vessel-relaxing nitric oxide that traps the reactive nitrogen species (peroxynitrite) molecules and thus enhancing the endothelial function of blood vessels
- i) Vit E inhibits of human platelet aggregation hence can be used as a blood thinner.

### **Vitamin E deficiency**

- A vitamin E deficiency is very rare in humans, though some people are more prone to a vitamin E deficiency than others.

### **Causes**

- Infants, people with fat malabsorption and abetalipoproteinemia (a condition that prevents the body from completely absorbing certain dietary fats) are more likely to have vitamin E deficiency.
  - Abetalipoproteinemia can lead to poor transmission of nerve impulses, muscle weakness, and retinal degeneration that leads to blindness
- Ataxia and vitamin E deficiency (AVED)  
Ataxia is another rare, inherited disorder in which the liver's alpha-tocopherol transfer protein is defective or absent. People with AVED have such severe vitamin E deficiency that they develop nerve damage and lose the ability to walk unless they take large doses of supplemental vitamin E. There is lack of voluntary coordination of muscle movements that can include gait abnormality, speech changes, and abnormalities in eye movements.

### **Signs and symptoms of deficiency**

Anemia, skeletal myopathy, ataxia, peripheral neuropathy, retinopathy, impairment of the immune response and nerve damage, numbness, poor sense of balance.

### **Toxicity**

Vitamin E can accumulate to toxic levels over time due to overdosing. Excess vitamin E can cause excessive bleeding and other symptoms, including fatigue, nausea, blurred vision and gonadal dysfunction. The vitamin is also a mild blood thinner, so high doses are discouraged prior to surgery.

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#### **Toxicity**

#### **Vitamin E deficiency**

- Vitamin E can accumulate to toxic levels over time due to overdosing. Excess vitamin E can cause excessive bleeding and other symptoms, including fatigue, nausea, blurred vision and genital dysfunction. The vitamin is also a mild blood thinner, so high doses are problematic before surgery.

- b) Vitamin E improves cardiovascular function by increasing the density of nitric oxide, which relaxes blood vessels, when we are performing for maintaining body processes, such as blood pressure regulation.
- c) It also helps widen blood vessels and help the body to move faster.
- d) Important in the formation of red blood cells.
- e) Vitamin E helps to keep the immune system strong against viruses and bacteria.

- f) It increases the orderliness of the membrane lipid packaging, thus allowing for a tight packing of the membrane and, in turn, greater stability to the cell (alpha-tocopherol promotes plasma membrane repair).

## VITAMIN K

- Occurs in plants and bacteria and is involved in the clotting of blood.
- During this process a protein zymogen known as **prothrombin** is converted to **thrombin** and this conversion **requires vitamin K**.
- Deficiency of vitamin K disturbs the whole process of clotting leading to loss of blood.
- The structure of vitamin K is shown below (Fig. 4.40).

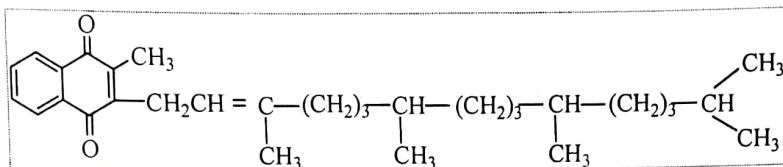


Figure 4.40: Structure of vitamin K.

- Vitamin K is involved in the blood-clotting cascade of reaction as illustrated below (Fig. 4.41).

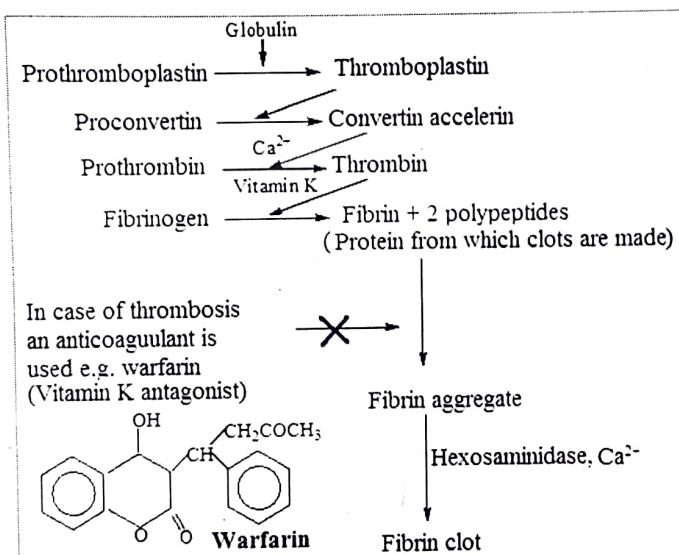


Figure 4.41: Vitamin K plays a key role during blood clotting process.

### Biochemical tests

#### i) Coagulation time

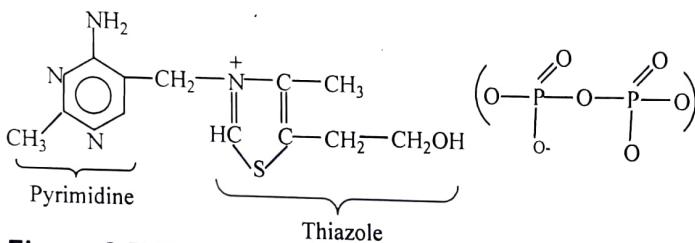
- Take 1ml of whole blood in vitamin K deficient sample.
- In a tube, add thromboplastin, shake the tube and observe clotting time.
- Repeat with whole blood from a normal individual.
- Clotting time is prolonged in vitamin K deficient sample.

#### ii) Prothrombin time determinant

- This test is performed by adding thromboplastin and excess Ca<sup>2+</sup> to a blood sample. Allow the sample to stand for a few minutes.
- The clotting time for normal individuals is between 12 - 15 seconds, while in deficient cases, coagulation process takes several minutes.

## **VITAMIN B<sub>1</sub> (Thiamin)**

- Vitamin B<sub>1</sub> (thiamin) is a component of thiamin pyrophosphate, which is a cofactor used in the oxidative decarboxylation of alpha-keto acids such as pyruvate and alpha-ketoglutarate.
- Vitamin B<sub>1</sub> (thiamin) contains two ring systems, a pyrimidine and a thiazole (Fig. 2.7).



**Figure 2.7:** The structure of vitamin B<sub>1</sub>. The structural formula on the right is PPi.

- Thiamin is converted in the body to thiamin pyrophosphate (TPP) by the transfer of PPi from ATP to thiamine by an ATP-dependent *thiamine pyrophotransferase* present in the *brain and liver*.
- TPP is the metabolically active form of B<sub>1</sub>
- TPP is a cofactor for *transketolase* (an enzyme of Pentose Phosphate Pathway).

## **Sources of vitamin B<sub>1</sub>**

The main sources of this vitamin include; beef, liver, eggs, peas, pork, yeast and outer layers of whole grains and fruits.

## **Deficiency of vitamin B<sub>1</sub>**

- Causes the disease known as **beriberi** characterized by extensive damage to the nervous and circulatory systems, muscular wasting, and oedema.
- Deficiency occurs because of subsisting on polished grain or overdrinking.
- There are two types of beriberi; **dry** and **wet beriberi**.
  - In **dry beriberi**, there is no accumulation of water i.e. lack of oedema. The symptoms of dry beriberi include; muscular wasting, neuritis (inflammation of nerves) and paralysis, while those of
  - **Wet beriberi** are; oedema, heart palpitations; high diastolic blood pressure and high systolic blood pressure that could lead to heart failure. Wet beriberi includes infantile beriberi; characterized by restlessness, bout of screaming and amnesia.

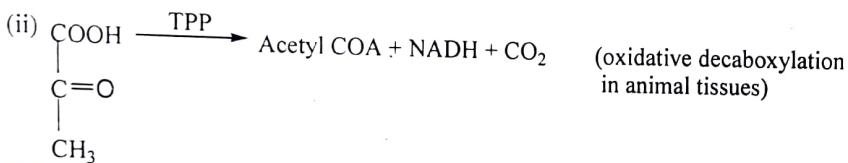
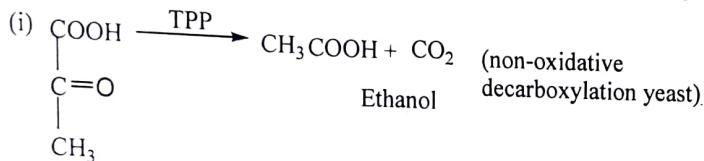
## **Functions of vitamin B<sub>1</sub>**

### **(a) Decarboxylation of pyruvate**

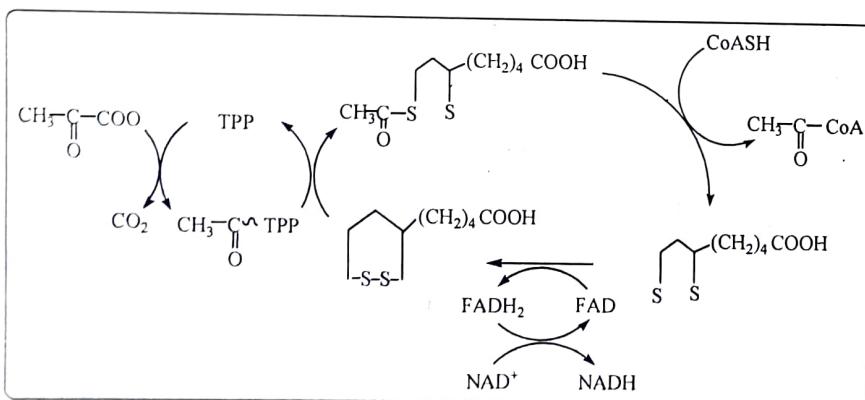
## Mechanism of decarboxylation in animal tissues

The oxidative decarboxylation of pyruvate to yield acetyl CoA requires TPP and other factors such as NAD, FAD, lipoic acid, and coenzyme A (CoA) (Figures 2.8, 2.9).

Oxidative decarboxylation: Are oxidative reactions in which a carboxylate group is removed forming  $\text{CO}_2$  (refer to TCA cycle).



**Figure 2.8:** Roles of thiamine pyrophosphate (TPP) in decarboxylation. The above 3-Carbon structure in (i) & (ii) is Pyruvate.

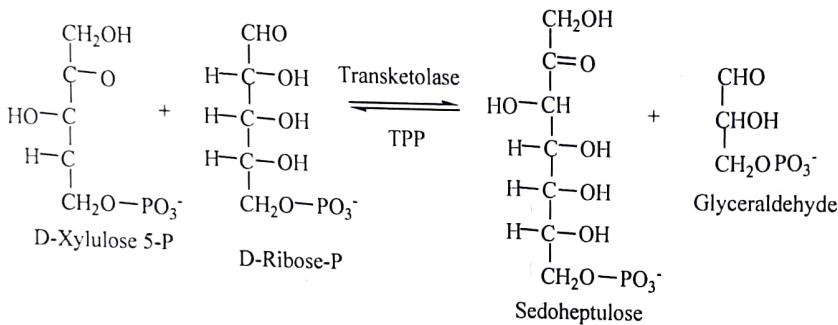


**Figure 2.9:** Shows the mechanism of decarboxylation. Thiamine pyrophosphate (TPP) is a co-enzyme that covalently binds to the substrate to stabilize its negative charge. Lipoamide (reduced) is oxidized in a FAD-dependent step. Acyl-TPP reacts with the oxidized lipoamide to form Acyl-lipoate that is then converted into reduced lipoamide and acetyl CoA through the action of CoASH.

### (b) Transketolase Reaction

- Thiamin pyrophosphate (TPP) also functions as a co-enzyme in transketolase reactions (Fig. 2.10) in the pentose phosphate pathway/hexose monophosphate shunt.

- In deficiency situations, pentose sugars accumulate and growth is retarded since the formation of NADPH and production of riboses and deoxyriboses and subsequently the synthesis RNA and DNA are affected.



**Figure 2.10:** Thiamin pyrophosphate (TPP) is a co-enzyme in transketolase reactions. The reaction requires  $\text{Mg}^{2+}$  and thiamin diphosphate (vitamin  $\text{B}_1$ ) as coenzyme. Thus, transketolase catalyzes the transfer of the two-carbon unit from xylulose 5-phosphate to ribose 5-phosphate, producing the seven-carbon ketose sedoheptulose 7-phosphate and the aldose glyceraldehydes 3-phosphate. Ribose-5-phosphate functions in synthesis of nucleotides (RNA and DNA).

### Deficiency of thiamin pyrophosphate, TPP

#### Wernicke-korsakoff syndrome (*cerebral beriberi*)

- A higher incidence is found among Europeans as a result of a genetic defect i.e. the transketolase from these patients bind thiamin 10 $\times$  less avidly (very high  $K_m$ ) compared normal individuals.
- Pyruvate dehydrogenase and  $\alpha$ -ketoglutarate dehydrogenase are not affected.
- The malnourished or alcoholic groups are prone to this disorder.
- This condition comes about due to the severely impaired transketolase reaction in the brain and is characterized by:
  - i) Paralysis of eye movements/ophthalmoplegia- loss of control of eye movements
  - ii) Abnormal stance and gait, ataxia/unsteady gait
  - iii) Marked deranged mental functions/confusion
  - iv) Severely disoriented and impaired memory

#### Diagnostic test

- This entails administering a normal dose of glucose to a patient and then measuring the lactate/pyruvate ratios as a measure of energy state of an individual.
- Since lactate concentration is constant, high **pyruvate:lactate ratio** indicates low rates of conversion of pyruvate and hence thiamin deficiency.

## Erythrocyte transketolase activity

- The transketolase activity is determined by haemolysing the erythrocytes and dividing the blood into two sets: In one set the pentose sugars ribose 5-P and xylulose-5P are added, while in another set, TPP is introduced in addition to the sugars. The activity is compared under both set-ups.
- In deficiency cases, activity will be lower and addition of TPP leads to significant increase in activity as follows; normal: 0-15% increase, moderate deficiency: 15-25% increase, severe deficiency: 25-100% increase.

## VITAMIN B<sub>2</sub> (Riboflavin)

- The name riboflavin reflects presence of D-ribitol and flavin (Figure 2:11).
- Riboflavin has a characteristic **yellow color** resulting from strong absorptions in the violet and blue regions. It is odorless but bitter in taste and in crystalline form it is stable to heating up to 120°C.

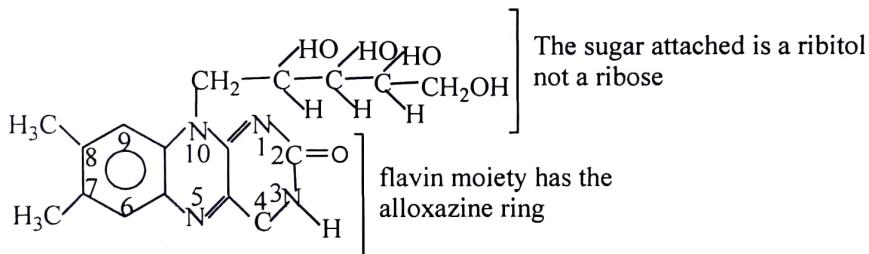


Figure 2.11: Structure of vitamin B<sub>2</sub>.

### Functions of riboflavin

- Riboflavin functions as a co-enzyme in oxido-reductions reactions because it has ability to undergo redox reactions, i.e. it can carry two hydrogen atoms and is able to donate them to acceptors; this is possible because of the isoalloxazine ring (Fig. 2.12).

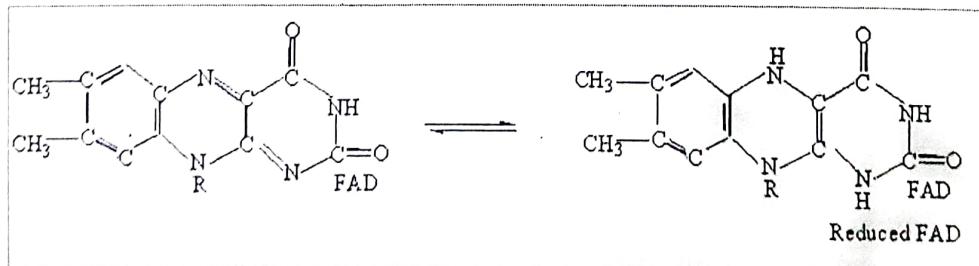


Figure 2.12: Vitamin B<sub>2</sub> functions as a co-enzyme in oxido-reduction reactions.

- The FMN is a prosthetic group in cytochrome reductase, monoamine oxidase and L-amino acid oxidase while; FAD is a prosthetic group in xanthine oxidase and succinate dehydrogenase among other enzymes. FAD and FMN are usually tightly bound to enzymes than are NAD and NADH; therefore, are regarded as prosthetic groups rather than cofactors.

### Clinical signs and symptoms of Vitamin B<sub>2</sub> deficiency

- Oral mucosal and tongue alterations; tongue is abnormally smooth and purplish in color
- Angular stomatitis (fission at angles of mouth), cheilosis (vertical fissions)/dry lips, seborrheic dermatitis in the facial area; seborrhea may also occur on the scrotum in males and vulva in females.

### Biochemical determination

- The erythrocytes are used to determine the activity of glutathione reductase as shown in Figure 2.13.

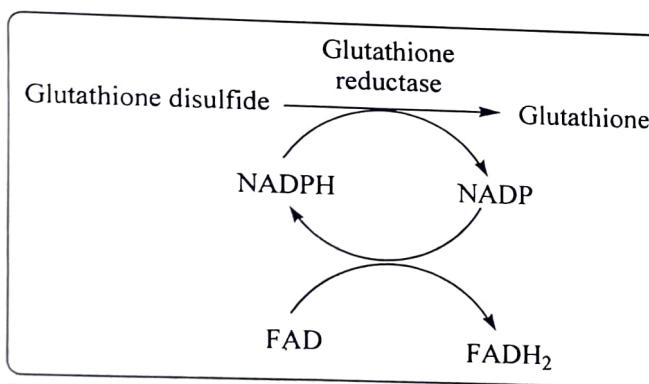
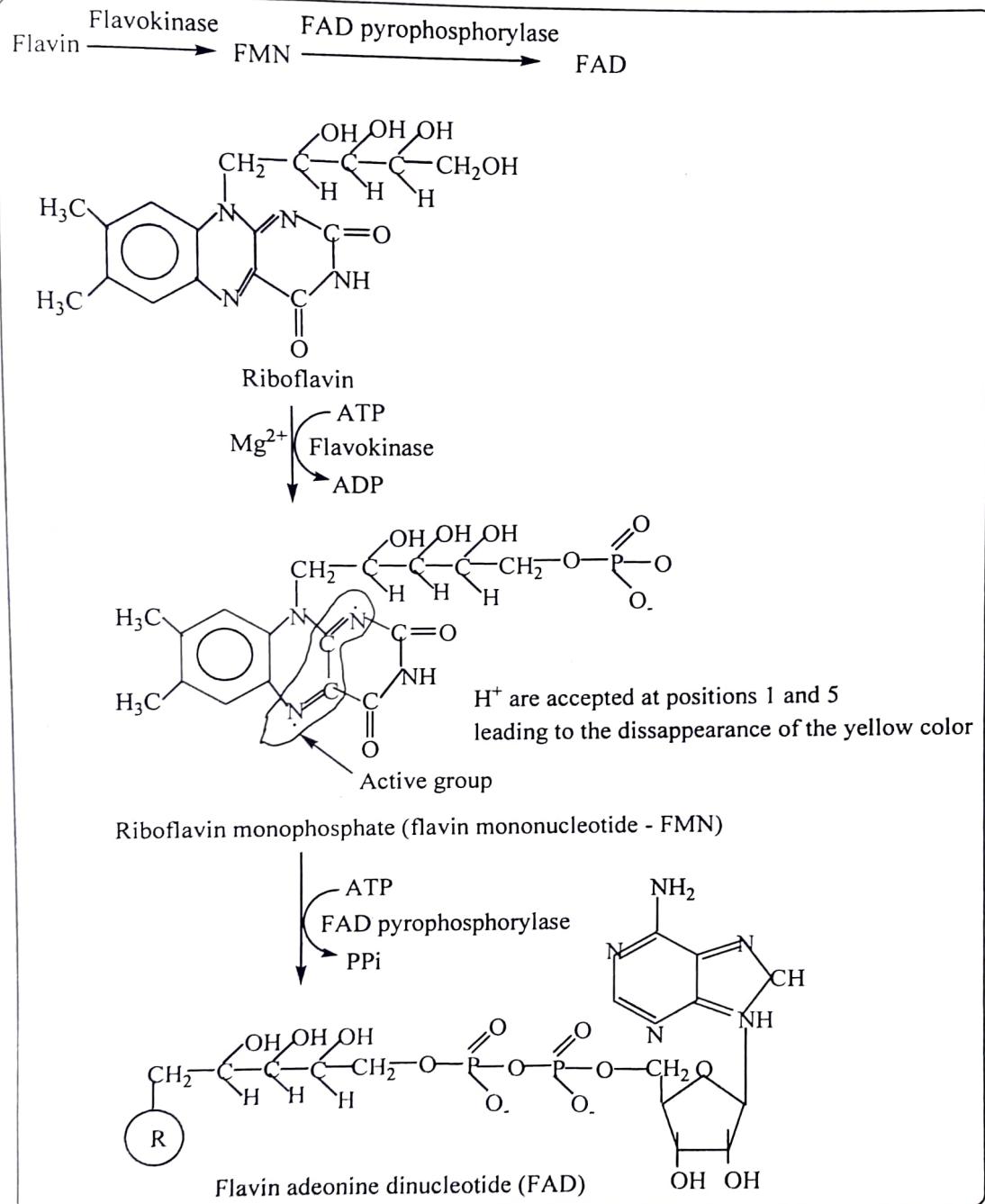


Figure 2.13: Role of glutathione reductase.

- Erythrocyte Glutathione Reductase (EGR) activity coefficient of greater than two in the presence and absence of FAD signifies deficiency. The causes of deficiency include inadequate intake, decreased assimilation, increased requirement or increased destruction.

### Hormonal control of vitamin B<sub>2</sub> activity

- Riboflavin is phosphorylated by ATP to yield riboflavin 5'-phosphate or flavin mononucleotide, FMN.
- The Flavin adenine dinucleotide (FAD) is formed from FMN by the transfer of an AMP moiety from a second molecule of ATP (Fig. 2.14).



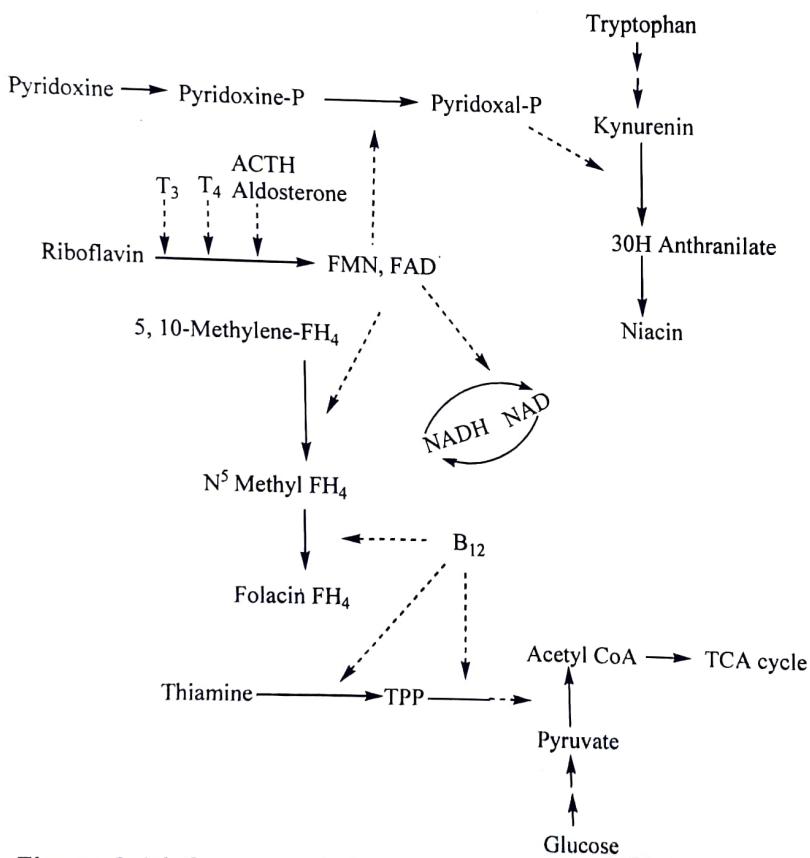
**Figure 2.13:** Synthesis of FAD from riboflavin.

- The thyroid hormones increase the rates of conversion of FMN to FAD by augmenting FAD pyrophosphorylase and under hypothyroidism state; there is decreased formation of the riboflavin coenzymes FMN and FAD.

- Aldosterone and ACTH also enhance the formation of FMN and FAD in adrenal cortex, liver and kidney.
- The interaction is cyclic in that riboflavin deficiency impairs synthesis of triiodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ).

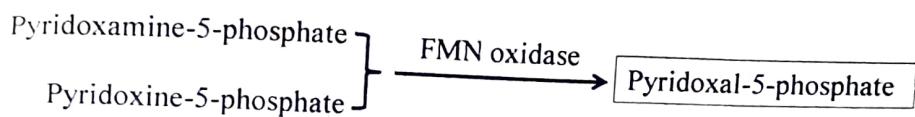
### Interrelationships between vitamin **B**<sub>2</sub>, hormones and other vitamins

- Riboflavin levels in man are influenced by numerous factors and its deficiency affects several metabolic pathways (Fig. 2.14).



**Figure 2.14:** Summary of the reactions in the body that require riboflavin.

- The clinical signs and symptoms of arriboflavinosis have always been associated with pyridoxine and niacin deficiencies.
- Patients diagnosed with clinical and biochemical riboflavin deficiency responds positively to pyridoxal supplementation.
- However, such a therapy does not improve EGR (erythrocyte glutathione reductase) activity. Riboflavin is necessary for the aerobic conversion of pyridoxine to pyridoxal phosphate.



- By virtue of its role in the production of pyridoxal-5-phosphate, riboflavin is also important in tryptophan metabolism and formation of niacin.

### Drug interactions

- Phenothiazine, a major tranquilizer, inhibits conversion of riboflavin to FAD.
- This occurs due to its structural similarity to riboflavin.
- Phenothiazine causes high urinary excretion and alters overall riboflavin status resulting in increased EGR activity.