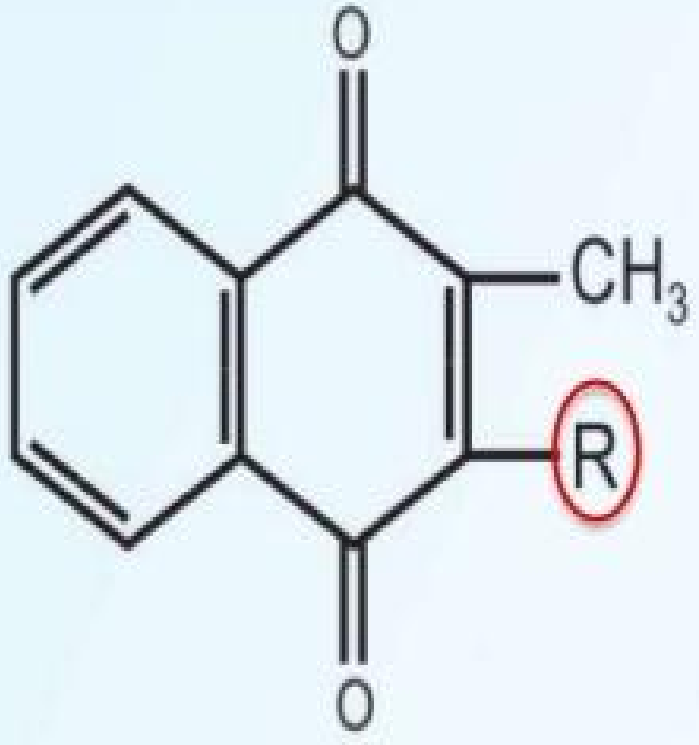
VITAMIN K

- "K " is the abbreviation of the German word "Koagulation "
- Anti-hemorrhagic factor
- Specific coenzyme function required for coagulation
- VITAMIN K are Naphthoquinone derivatives and have long side Isoprenoid chain.
- 1929 – Henrick Dam – isolation of Vitamin K1 –(Noble Prize)
- 1939 – Edward Doisy – isolation of Vitamin K2 –(Noble Prize 1943)

Vitamin K- Chemistry

- Vitamin K represents a group of lipophilic and hydrophobic vitamins.
- Three compounds have the biological activity of vitamin K
- Phylloquinone (Vitamin K1), the normal dietary source, found in green vegetables
- Menaquinones (vitamin K2), synthesized by intestinal bacteria, with differing lengths of side chain; and
- Menadione and menadiol diacetate, synthetic compounds that can be metabolized to phylloquinone

Vitamin K are naphthoquinone derivatives

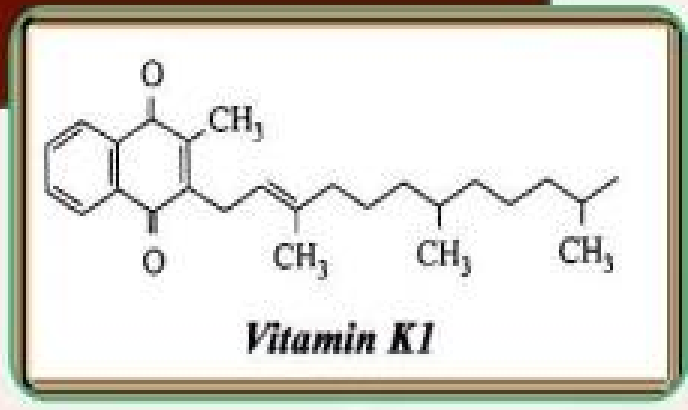


R = 20C in (Phylloquinone) in K_1
R = 30C in (Menaquinone) in K_2
R = H in Menadione

Vitamin K1

- Phylloquinone

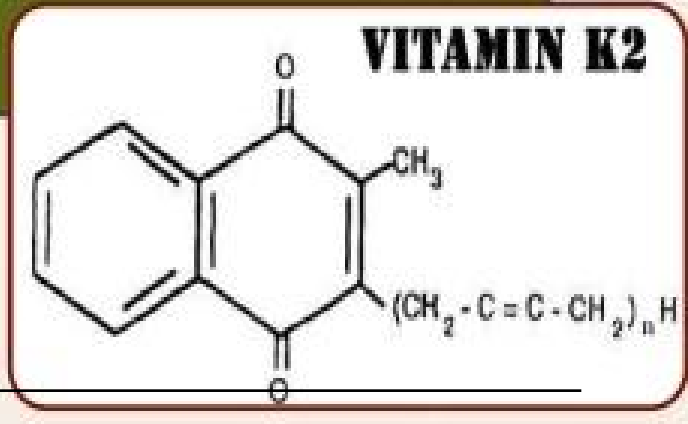
Present in plants



Vitamin K2

- Menaquinone

Produced by the intestinal bacteria



Vitamin K3

- Menadione

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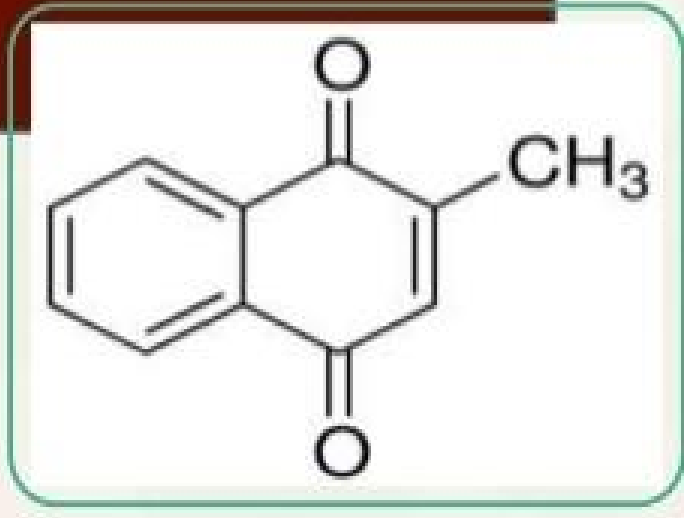
Synthetic product



ABSORPTION

- Absorption takes place in intestine in the presence of bile salts.
- The transportation from intestine is carried out through chylomicrons.
- Storage occurs in liver
- Transportation from liver to peripheral cells is carried out bound with beta lipoproteins.

Biochemical Functions of vitamin K

- Vitamin K act as a coenzyme for the carboxylation of glutamic acid residues present in the protein and this reaction is catalyzed by a carboxylase (microsomal)
- Although vitamin K-dependent gamma-carboxylation occurs only on specific glutamic acid residues in a small number of vitamin K-dependent proteins, it is critical to the calcium-binding function of those proteins

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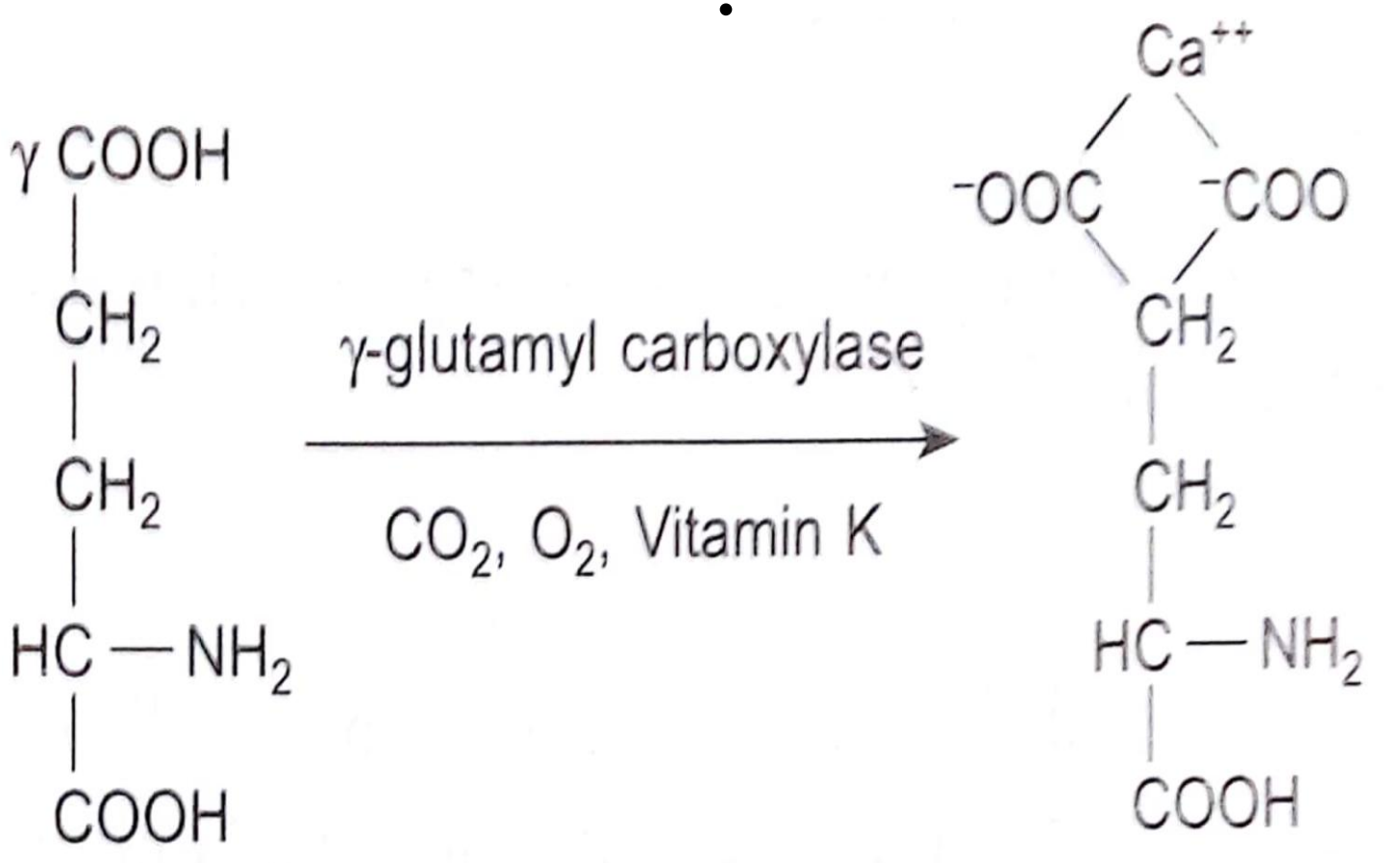
- It involves the conversion of glutamate (Glu) to γ-carboxyglutamate (Gla) and requires vitamin K,O2 and CO2
- The formation of γ - carboxyglutamate is inhibited by dicumarol, an anticoagulant found in spoilt sweet clover
- Warfarin is a synthetic analogue that can inhibit vitamin K action

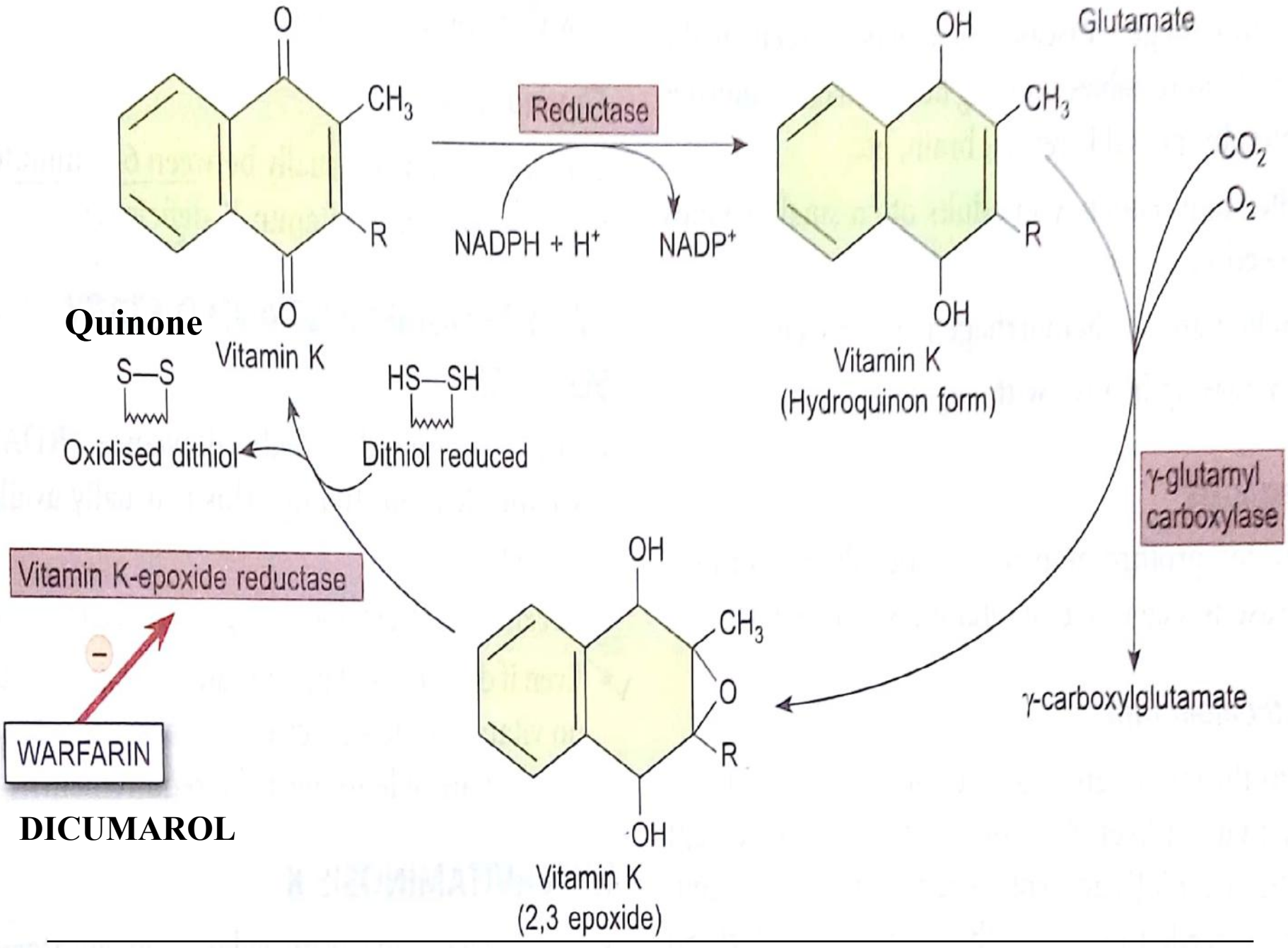


Glutamate (Glu)

γ-carboxylglutamate (Gla)

Vitamin K cycle

- Vitamin K is a fat-soluble vitamin, the body stores very little of it, and its stores are rapidly depleted without regular dietary intake.
- Because of its limited ability to store vitamin K, the body recycles it through a process called the vitamin K cycle.
- The vitamin K cycle allows a small amount of vitamin K to function in the gamma-carboxylation of proteins many times, decreasing the dietary requirement.



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- Vitamin K hydroquinone (active form) is oxidized to the Epoxide form during the process of enzymatic reaction.
- The initial form (hydroquinone form) is regenerated by two steps process.
- Vitamin K Epoxide is reduced to the quinone by a Epoxide reductase, and
- the quinone is reduced to the active hydroquinone by

  --either the same reductase or

  ---by a vitamin K reductase(quinone reductase).

…Role In Clotting

- The functions of vitamin K are concerned with blood clotting process.
- The clotting factors II, VII, IX and X are synthesized as inactive precursors in the liver.
- Vitamin K brings about post-translational modification i.e.γ carboxylation of glutamic acid residues of these blood clotting factors.

- γ - Carboxyglutamic acid (Gla) residues of clotting factors are negatively charged (COO-) and they combine with positively charged calcium ions (Ca2+) to form a complex
- The complex binds to the phospholipids on the membrane surface of the platelets.
- Leads to increased conversion of prothrombin to thrombin

OTHER FUNCTIONS

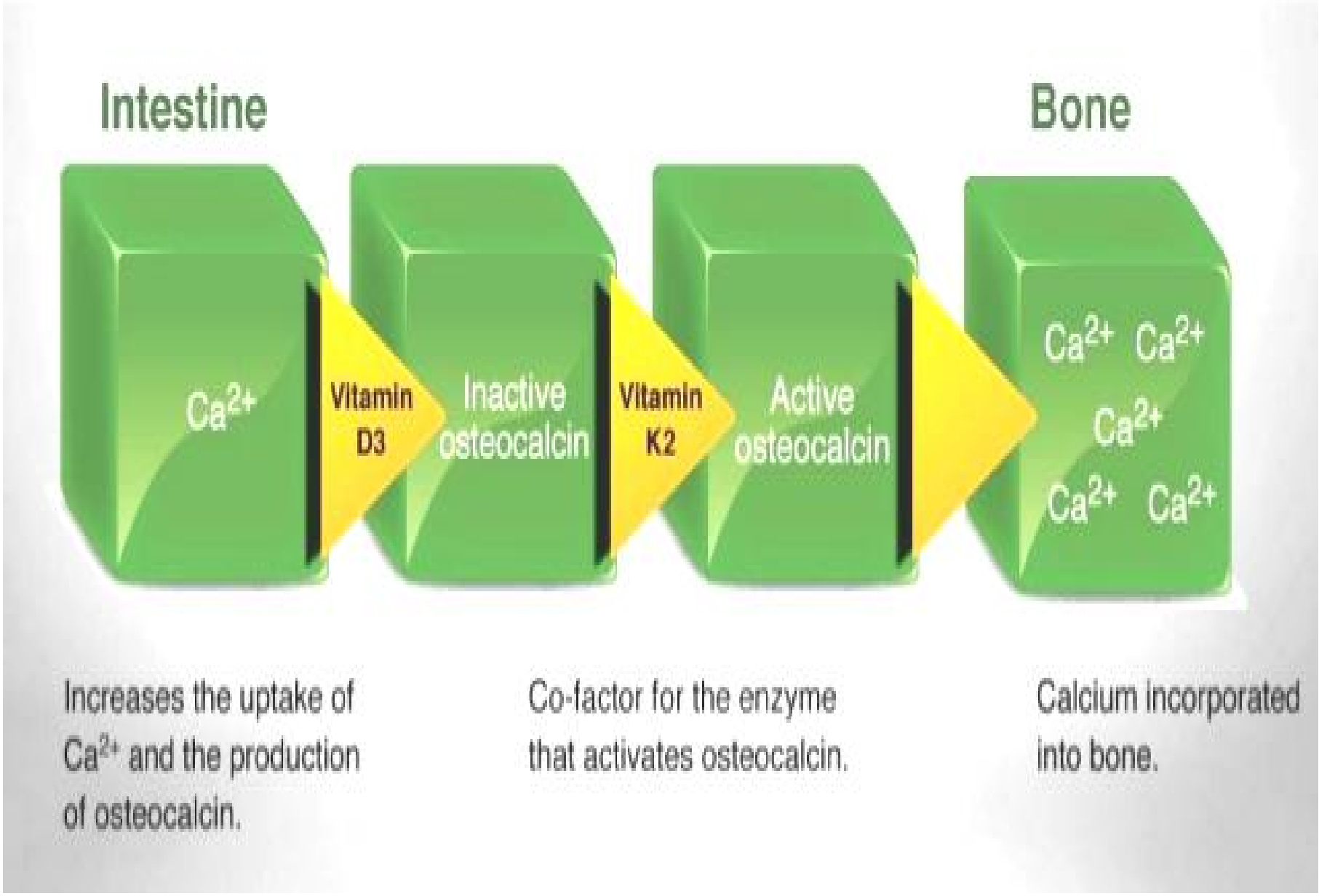
- Vitamin K is also important in synthesis of two proteins that contain γ-carboxyglutamate that are present in bone-

  1. Osteocalcin and
  2. Bone matrix Gla protein.

1. Osteocalcin is a protein synthesized by osteoblasts.

- The synthesis of osteocalcin by osteoblasts is regulated by the active form of vitamin D, 1,25(OH)2D3 or calcitriol. .

- The mineral-binding capacity of osteocalcin requires vitamin K-dependent gamma-carboxylation of three glutamic acid residues
- After gamma carboxylation osteocalcein binds tightly to calcium.
- Osteocalcin also contains hydroxy proline, so its synthesis is dependent on both vitamins K and C; in addition, its synthesis is induced by vitamin D.
- The release into the circulation of osteocalcin provides an index of vitamin D status.



2.Matrix Gla protein- .

- MGP has been found in bone, cartilage, and soft tissue, including blood vessels.
- MGP prevents the calcification of soft tissues and cartilages, while facilitating normal bone growth and development

3. Protein S-

- The vitamin K-dependent anticoagulant protein S
- Children with inherited protein S deficiency suffer complications related to increased blood clotting as well as decreased bone density.

4. Nephrocalcin in kidney
5. Product of the growth arrest specific gene (Gas6)- which is involved in both the regulation and differentiation and development of nervous system, and control of apoptosis in other tissues.
6. Vitamin K is required for ETC and oxidative phosphorylation

   - Vitamin K antagonists such as dicumarol act as uncouplers of oxidative phosphorylation

Vitamin K deficiency

Causes

- Lack of vitamin K in the diet
- Fat malabsorption
- Disease or surgical interventions that affect the ability of intestinal tract to absorb vitamin K
- Chronic liver diseases
- Prolonged use of oral antibiotics
- Prolonged use of Warfarin

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- Pre mature infants and new born babies

- Transplacental transfer of vitamin K is very limited during pregnancy,

-The storage of vitamin K in neonatal liver is also limited.

- Breast milk is a poor source of vitamin K.

- newborn infants to mother with poor vitamin K stores

Deficiency manifestations

- The main symptom is bleeding (hemorrhage)
  —into the skin (causing bruises),
  --from the nose,
  --from a wound,
  ---in the stomach, or
  ---in the intestine.
- Blood may be seen in the urine or stool.
- Having a liver disorder increases the risk of bleeding because clotting factors are made in the liver.
- Vitamin K deficiency may also weaken bones.

- In newborns, life-threatening bleeding within or around the brain may occur.
- Intracranial hemorrhage can occur during the delivery process and can lead to severe complications.
- Soft tissue hemorrhages may be there.

⇦ Bruising

Nosebleeds ⇨

Bleeding gums

A deficiency of vitamin K can lead to extreme bleeding, which can begin as a gum or nose discharge or bruising

Diagnosis

- A prolonged Prothrombin Time (PT) in the absence of liver disease is usually the first laboratory test result to be abnormal in vitamin K deficiency bleeding.
- Prothrombin time is measured before and after giving vitamin K in situation of doubt. If it returns to normal after vitamin K injection, it suggests vitamin k deficiency and rules out liver diseases. If not, liver disease is the likely cause.

- Clotting Time

The clotting time is usually between 6-8 minutes. It is also increased in vitamin K deficiency

RDA

ADULTS - 50-100 μg/day

SOURCES

- Vitamin K is found in green leafy vegetables such as kale and spinach
- Appreciable amounts are also present in margarine and liver.
- Vitamin K is present in vegetable oils and is particularly rich in olive, canola, and soybean oils.
- Some amount is contributed by intestinal bacteria

Prevention

- A vitamin K injection in the muscle is recommended for all newborns to reduce the risk of bleeding within the brain after delivery
- Intramuscular (IM) vitamin K prophylaxis at birth is the standard of care.
- These measures have served to make vitamin K deficiency bleeding a rarity.

Hypervitaminosis K

- Large dose (>5 mg) of menadione can cause toxicity.
- Hypervitaminosis K leads to
  1. Hemolytic anemia
  2. Jaundice (hyperbilirubinemia and kernicterus-leading to brain damage