
Biochemistry of Vitamin K

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Objectives

By the end of this lecture, the Second Year students will be able to:

- Identify the types and sources of vitamin K
- Understand the role of vitamin K in blood coagulation
- Recognize the importance of γ -carboxylation of glutamic acid in coagulation proteins
- Understand the role of anticoagulant drugs in affecting vitamin K function
- Discuss the causes and disorders of vitamin K deficiency

Overview

- Types, chemistry and sources of vitamin K
 - Sources and daily requirements
 - Functions:
 - Synthesis of γ -carboxyglutamate in:
 - Prothrombin and blood clotting factors
 - Interaction of prothrombin with platelets
 - Osteocalcin
 - Protein C and S (anticogaulant proteins)
 - Deficiency and disorders
 - Clinical manifestations
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Types and Sources



Occurs in several forms:

- Vitamin K₁ (Phylloquinone)
- Vitamin K₂ (Menaquinone)
- Vitamin K₃ (Menadione) – synthetic form

Dietary sources:

- Cabbage, kale, spinach, egg yolk, liver



Cabbage

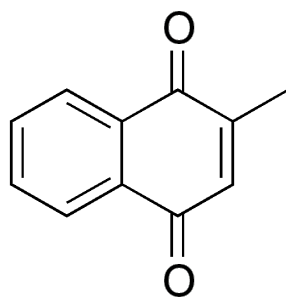
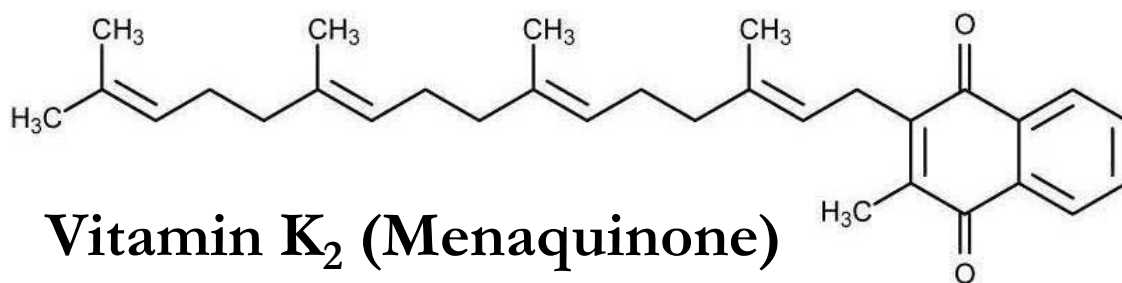
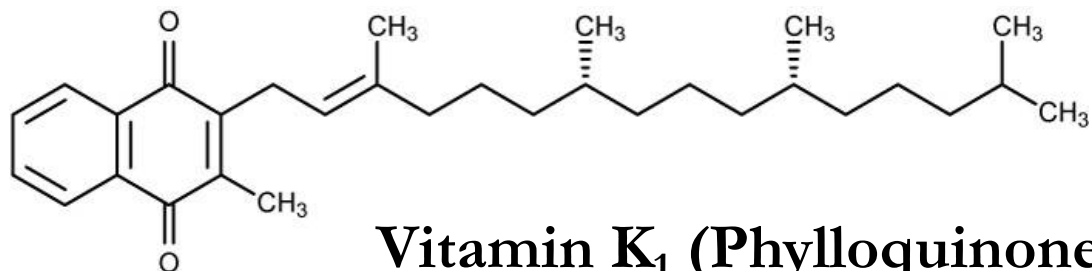


Kale



Spinach

Chemistry of Vitamin K



Sources of Vitamin K



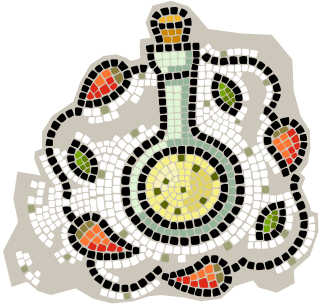
- **Phylloquinone:** Green leafy vegetables
- **Menaquinone:** Intestinal bacteria
 - Intestinal bacterial synthesis meets the daily requirement of vitamin K even without dietary supplement
- **Menadione:** synthetic form
 - A precursor of menaquinone

RDA for Vitamin K

($\mu\text{g}/\text{day}$)



- **Infant (0-1 year): 2-2.5**
 - **Children (1-8): 30-55**
 - **Men (19+): 120**
 - **Women (19+): 90**
 - **Pregnancy / lactation: 90 / 90**
 - **UL: Not established**
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Functions of Vitamin K



- Coenzyme for the synthesis of prothrombin and blood clotting factors in the liver
 - Prothrombin and other clotting factors are protein in nature
 - Synthesis of prothrombin, clotting factors VII, IX, X require carboxylation of their glutamic acid (Glu) residue

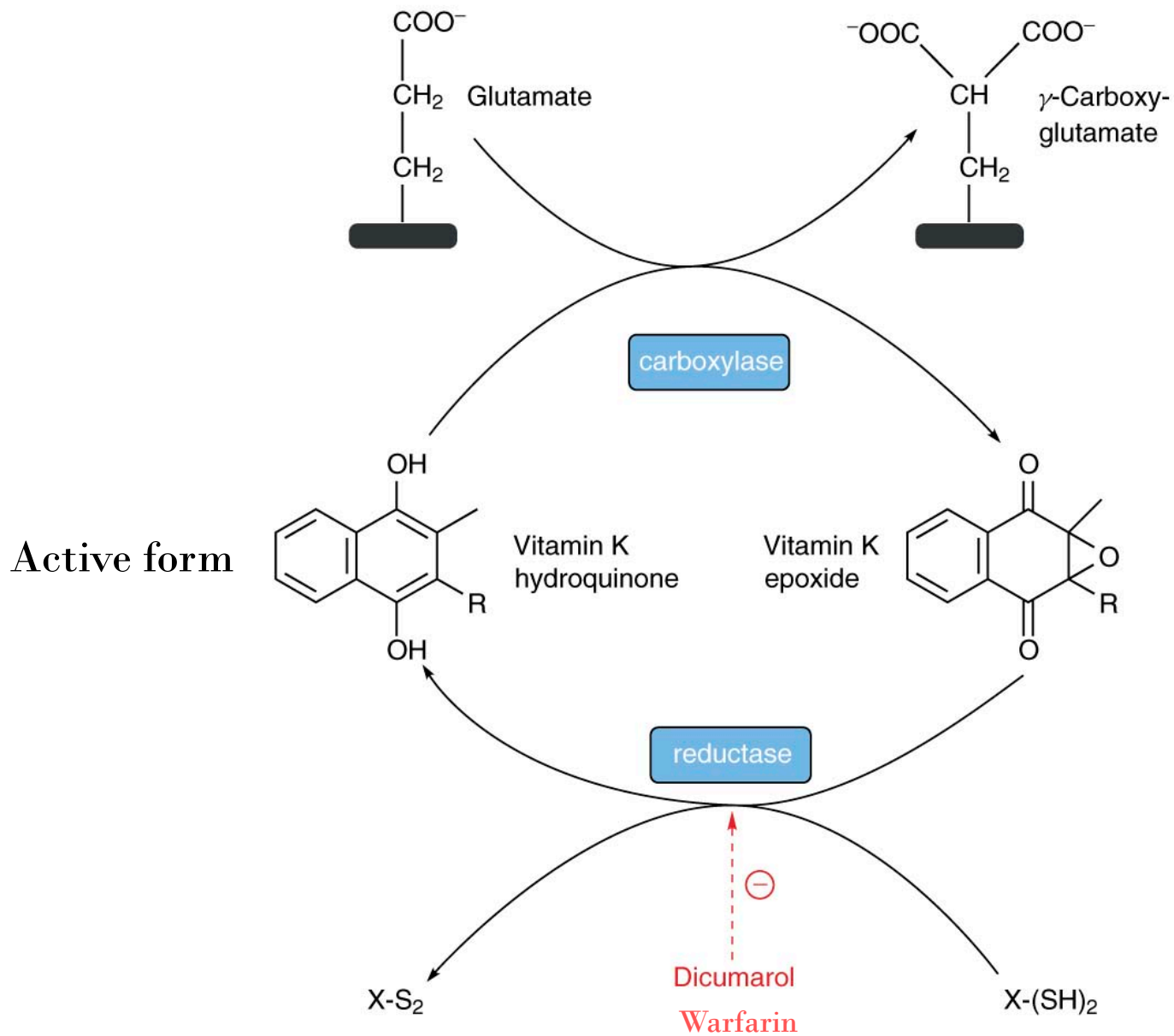
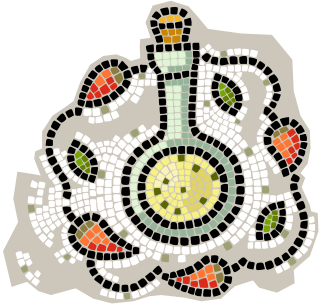


Figure 28.7. Function of Vitamin K.



Functions of Vitamin K



- ❑ Mature prothrombin and clotting factors contain γ -carboxyglutamate (Gla) after carboxylation reaction
- ❑ Vitamin K is essential for the carboxylase enzyme involved
- ❑ Dihydroquinone form of vitamin K is essential for this reaction

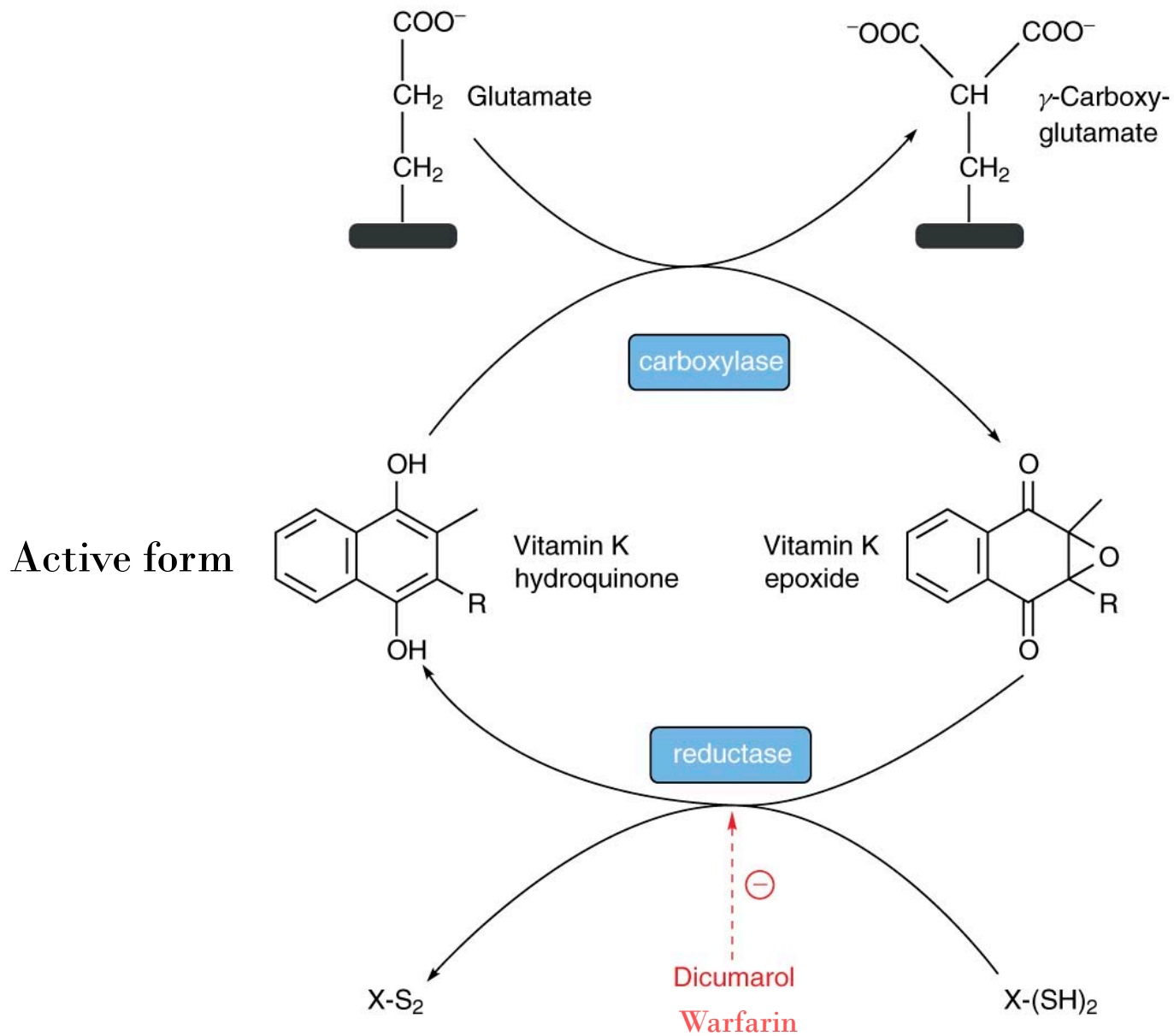
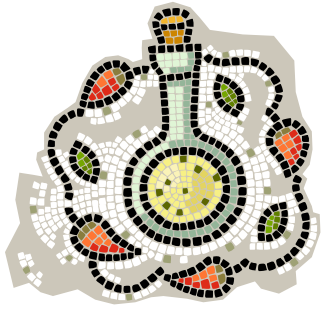


Figure 28.7. Function of Vitamin K.

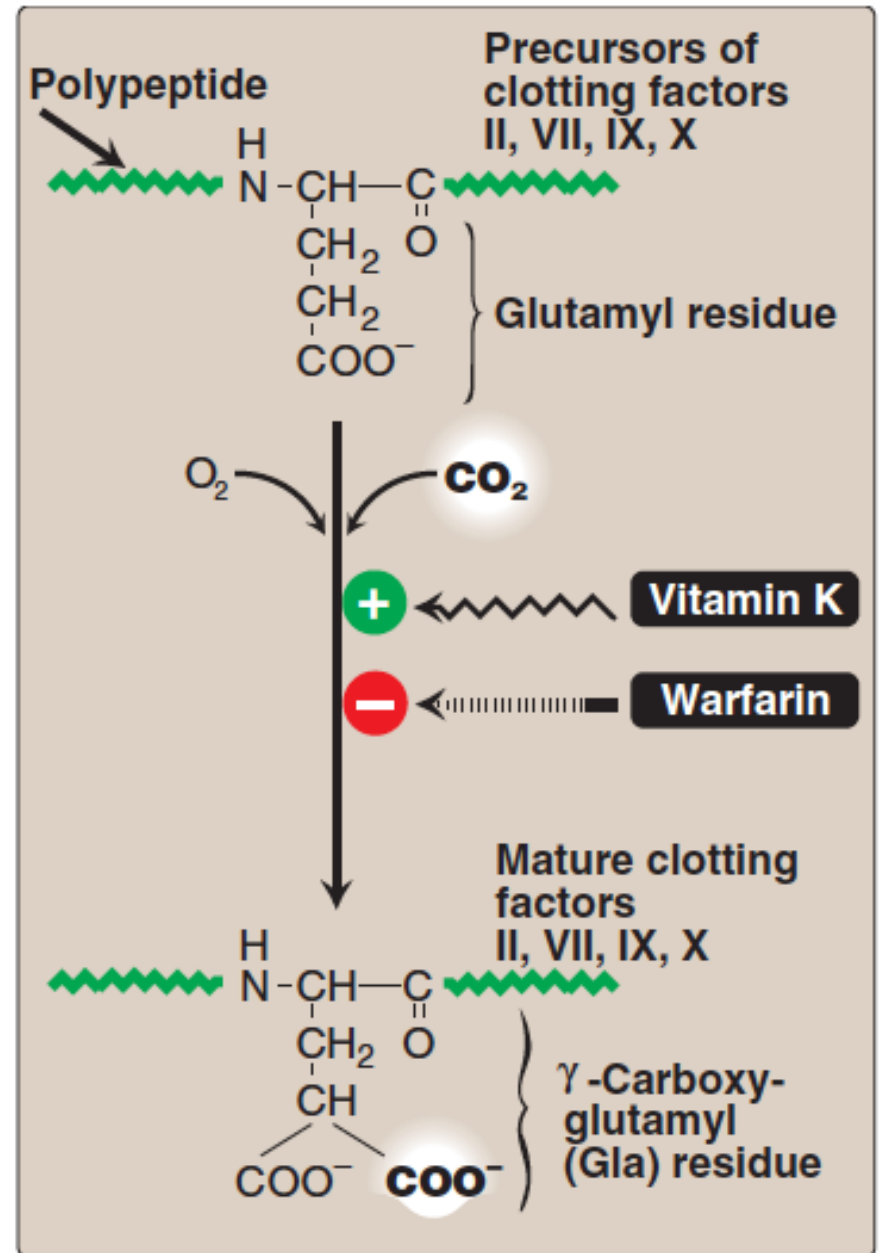


Analogues of Vitamin K



- Anticoagulant drugs: warfarin and dicoumarol
 - Structural analogs of vitamin K
- They inhibit the activation of vitamin K to hydroquinone form (inhibiting the reductase enzyme)
- Prothrombin and clotting factors are not carboxylated
- Hence blood coagulation time increases upon injury

- Carboxylation of glutamate requires vitamin K
- The process is inhibited by **warfarin**

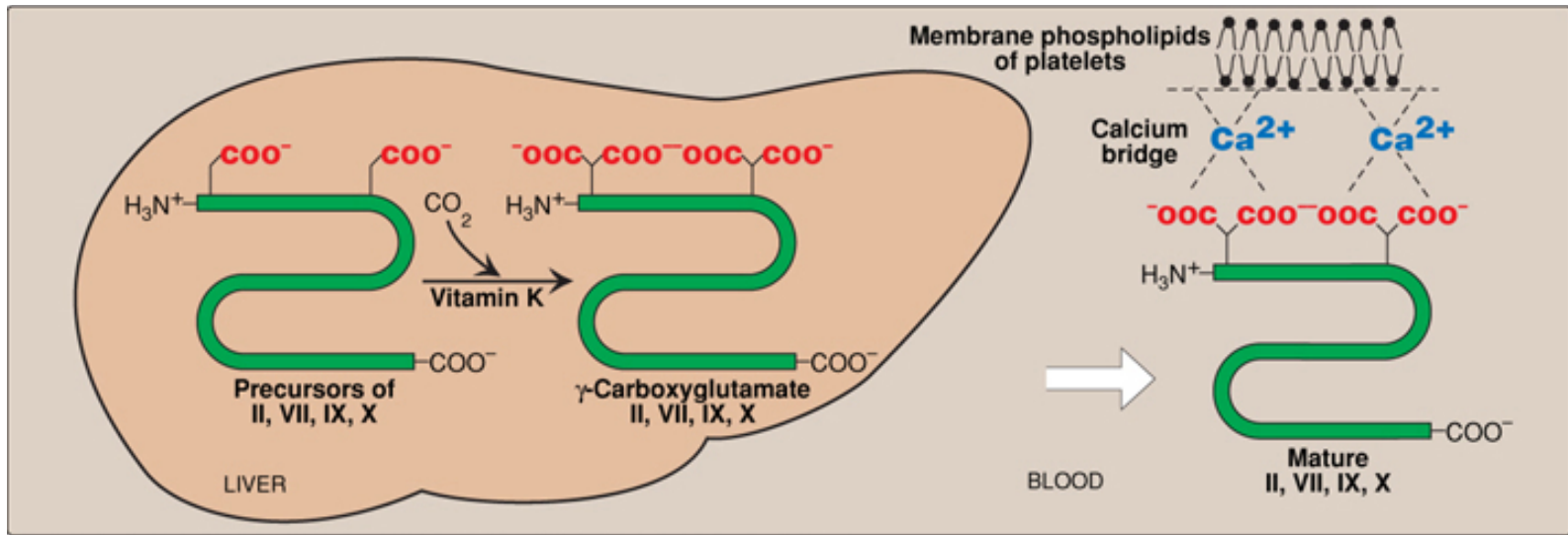


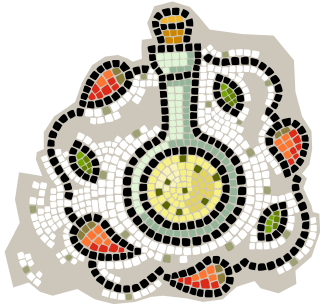
Functions of Vitamin K



- **Prothrombin – platelet interaction**
 - ❑ Carboxylated prothrombin contains two carboxylate groups (COO^-)
 - ❑ These groups bind to Ca^{2+} , forming prothrombin-calcium complex
 - ❑ The complex then binds to phospholipids on the surface of platelets (important for blood clotting)
 - ❑ Converting prothrombin to thrombin and initiating clot formation
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Prothrombin – platelet interaction





Functions of Vitamin K



- **Synthesis of γ -carboxyglutamate in osteocalcin**
 - ❑ Osteocalcin is a bone turnover protein
 - ❑ Also called Bone Gla Protein (BGP)
 - ❑ Involved in bone formation, mineralization and resorption
 - ❑ γ -Carboxyglutamate is required for osteocalcin binding to hydroxyapatite (a calcium mineral) in the bone
 - ❑ The binding mechanism is similar to that of prothrombin-platelet binding

Deficiency of Vitamin K



- Deficiencies are rare: it is synthesized by intestinal bacteria
 - Hypoprothrombinemia: increased blood coagulation time
 - Some second-generation cephalosporin drugs cause this condition due to warfarin-like effects (antibiotics given with vit. K)
 - May affect bone growth and mineralization
 - Lipid malabsorption can lead to vitamin K deficiency
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Deficiency of Vitamin K



- Prolonged antibiotic therapy
 - Especially in marginally malnourished individuals (e.g. debilitated geriatric patients)

 - Gastrointestinal infections with diarrhea

 - Both of the above destroy the bacterial flora leading to vitamin K deficiency
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Deficiency of Vitamin K



- Deficiency most common in newborn infants
 - Newborns lack intestinal flora
 - Human milk can provide only 1/5th vitamin K
 - Supplements are given intramuscularly at birth

Clinical Manifestations of the Deficiency



- Hemorrhagic disease of the newborn
 - Bruising tendency, ecchymotic patches (bleeding underneath the skin)
 - Mucus membrane hemorrhage
 - Post-traumatic bleeding / internal bleeding
 - Prolonged prothrombin time
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Toxicity of Vitamin K



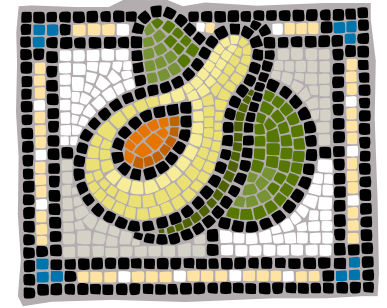
- Prolonged supplementation of large doses of menadione can cause:
 - Hemolytic anemia
 - Jaundice
 - Due to toxic effects on RBC membrane
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Take home message



- Vitamin K is essential for blood coagulation process
 - It mediates the process by γ -carboxylation of glutamic acid residues of prothrombin and coagulation factors
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References



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Chapter 28, pp. 389-391
Richard Harvey and Denise Ferrier
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 - Textbook of Biochemistry with Clinical
Correlations by Thomas M Devlin. 6th Edition
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