



**Important** Doctors slides  
Extra Information **Doctors notes**

# Biochemistry

## Vitamin K

Don't limit your challenges ..  
Challenge your limits



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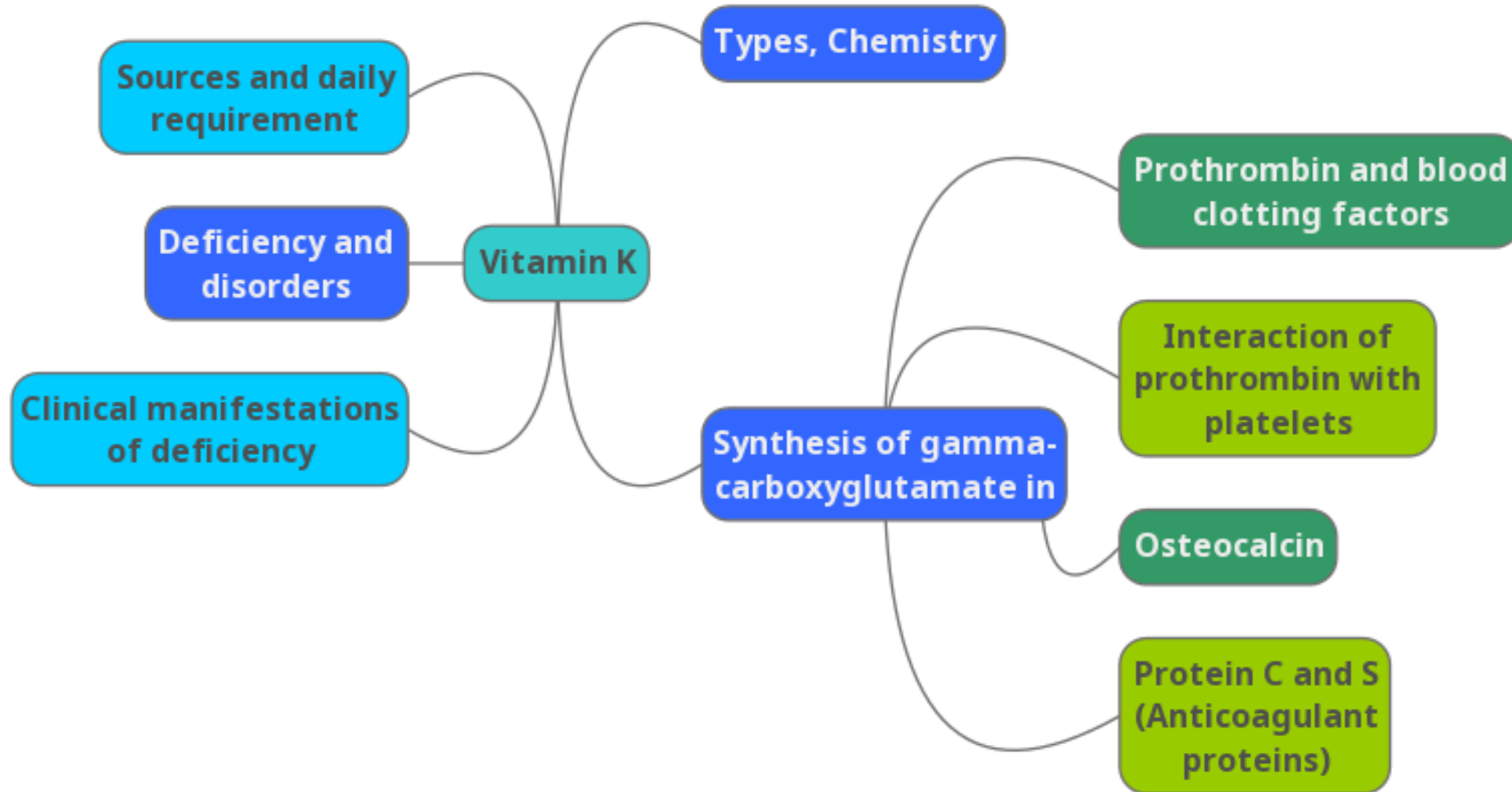
# OBJECTIVES

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  $\gamma$ -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



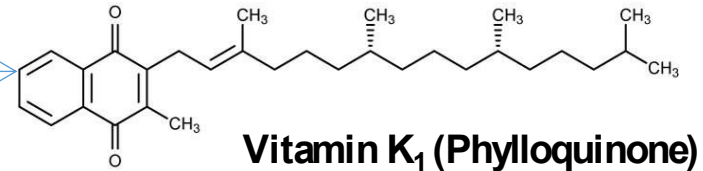
# Lecture overview



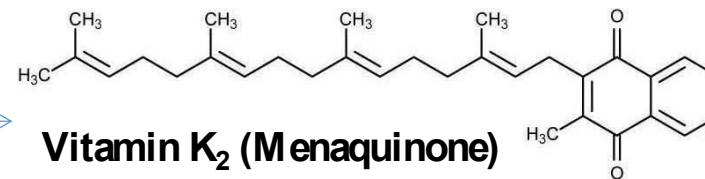
# Types and sources

Occurs in several forms

Vitamin K<sub>1</sub>  
(Phylloquinone)



Vitamin K<sub>2</sub>  
(Menaquinone)



Vitamin K<sub>3</sub>  
(Menadione) –  
synthetic form



## Chemistry

## Dietary sources

Cabbage, kale, spinach, egg yolk, liver



Cabbage



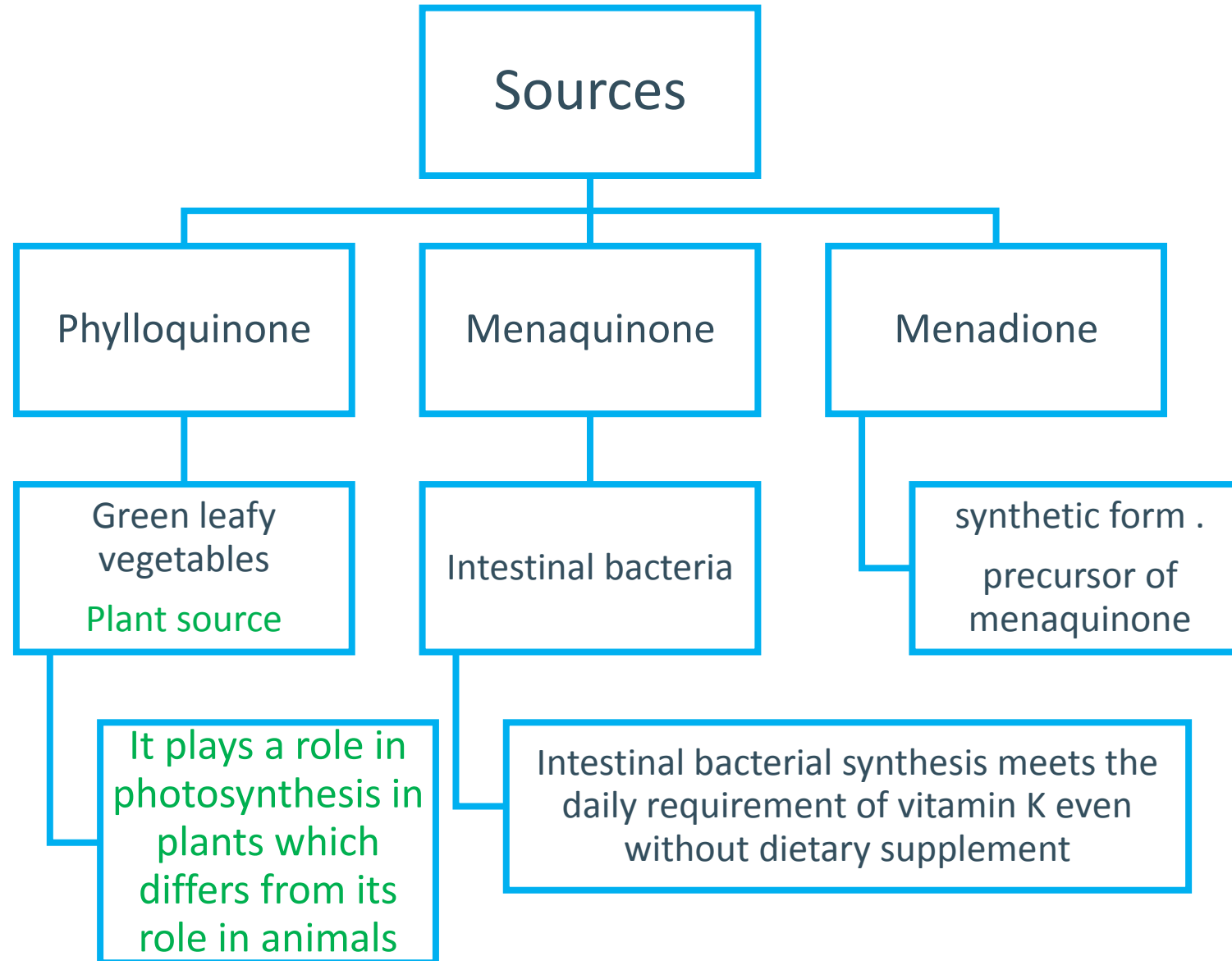
Kale



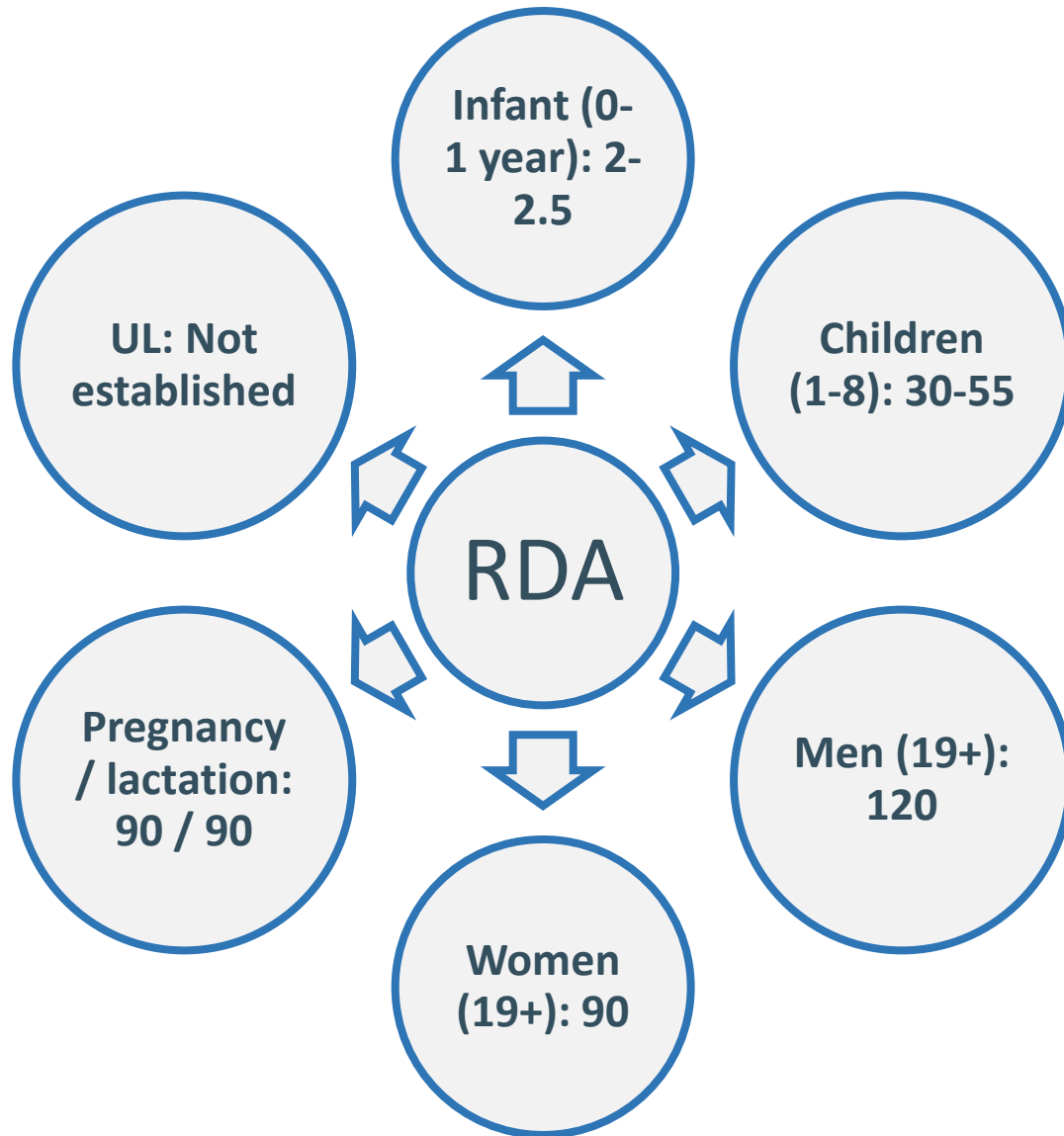
Spinach

Menadione doesn't have chains like vit. K<sub>1</sub> and K<sub>2</sub>, hence it's water soluble to be supplementary type. So, when we take it we can add the chain in our bodies.

# Sources of Vitamin K



# RDA for Vitamin K (micro g/day)



Upper limit is not established because toxicity is rare , although it might happens and it's mentioned at the end of this lecture ..

Note that pregnancy and lactation does not affect the RDA of vitamin K



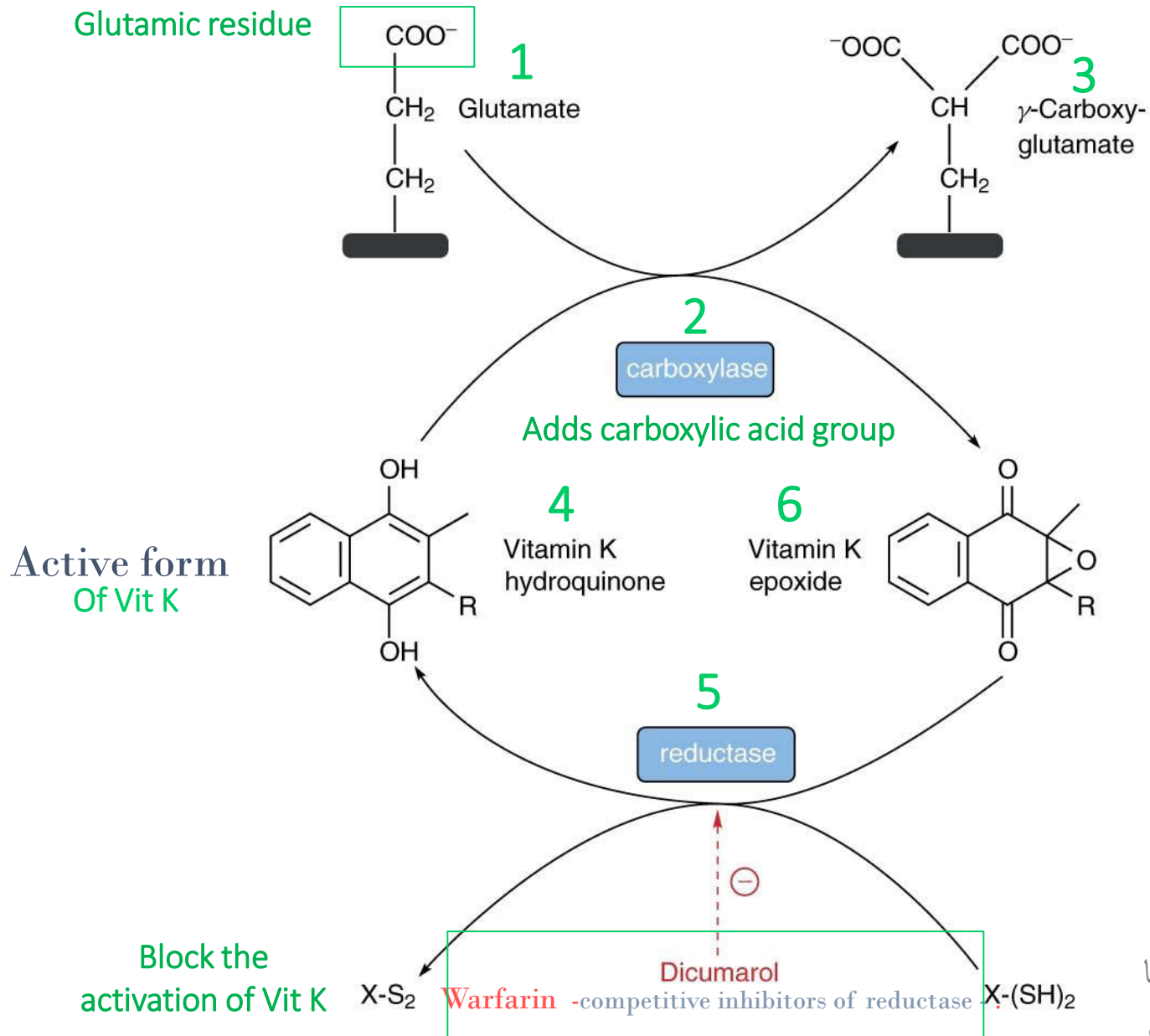
# Functions of Vitamin K:

## ❖ Coenzyme for the synthesis of prothrombin and blood clotting factors in the liver

- Prothrombin and clotting factors are protein in nature
- Synthesis of prothrombin, clotting factors II, VII, IX, X require carboxylation of their glutamic acid (Glu) residue
- Mature prothrombin and clotting factors contain  $\gamma$ -carboxyglutamate (Gla) after carboxylation reaction
- Vitamin K is essential for the carboxylase enzyme involved
- Dihydroquinone form of vitamin K is essential for this reaction

When clotting factors which are proteins are synthesized in the liver they are not active yet .. They have to be activated by carboxylation and the carboxylation step needs vit K as a co-factor to complete it

The carboxylation happens at glutamic acid residues since its one of the amino acids the already have carboxylic acid side chain .. So the other COO- is added during the interaction that is mediated by carboxylase enzyme and that is required for activation of clotting factors



**Figure 28.7. Function of Vitamin K.**

Vit K work as a co-factor for carboxylase converts no.1 into no.3

6: If Vit K is in it's epoxide form and can't get back to it's dihydroquinone form(4) that leads to decrease clotting factors and increase prothrombin time

Quinone form "epoxide" is not active so even vit K needs to get activated by being reduced again into dihydroquinone "active form" with the help of the enzyme reductase

Carboxylase enzyme is also called epoxidase since it turn vit k to epoxide form

هنا مجرد شرح  
 لاشكال فيتامين K  
 الاكتيف والان  
 اكتيف والانزيمات  
 التي ستساعد على  
 تحويل كل منهم وما  
 سيؤدي اليه نقصهم



# Analogues of Vitamin K

- Anticoagulant drugs: warfarin and dicoumarol
  - ✓ Structural analogues 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 (Increasing the coagulation time)

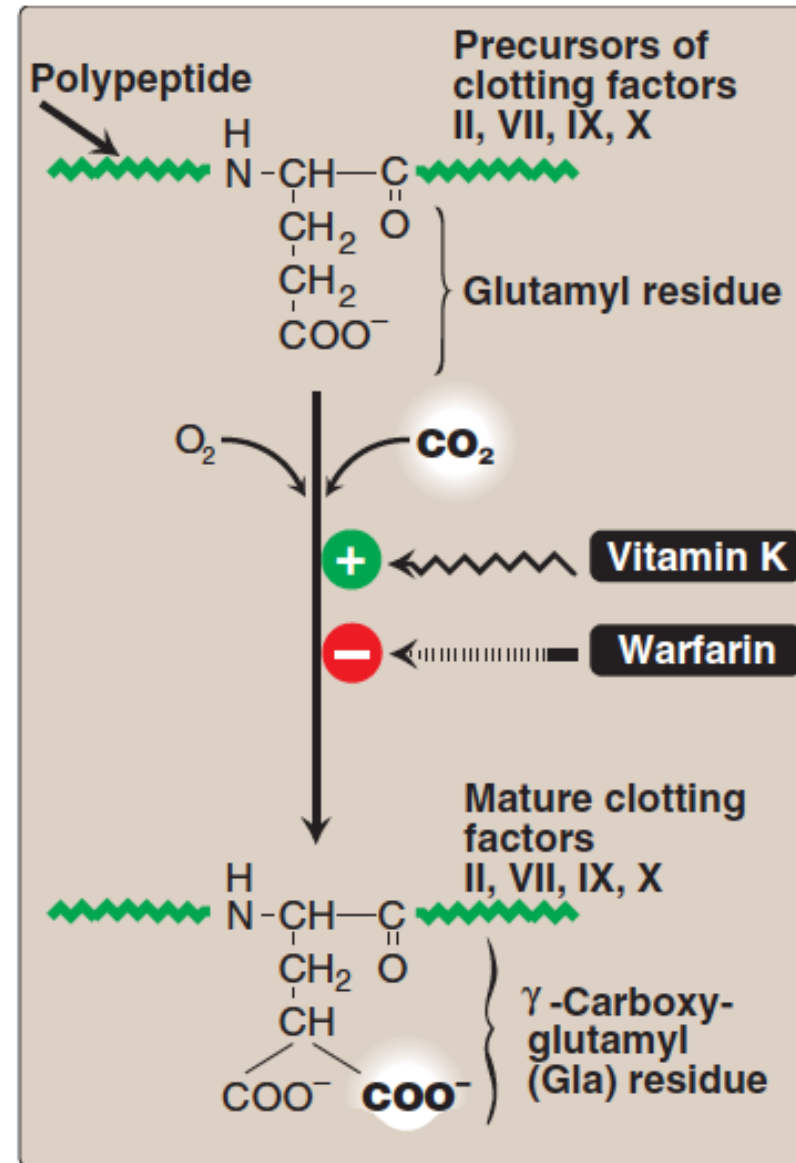
Here vit K can't get back to its Dihydroquinone form and that leads to decrease clotting factors and increase prothrombin time So they work at the reduction step ..

Actually the reduction of epoxide form occurs by two steps but we only mentioned the one that can be inhibited by warfarin dicoumarol .. Hence if warfarin overdose is administered that will block only one pathway so if we want to reverse the action we need to give high doses of vit K to let the other pathway work and complete the cycle ..

# Glutamate

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

This diagram shows that the process of converting glutamic acid residue into gamma-carboxy-glutamate needs oxygen, carbon dioxide and vitamin K while it gets inhibited by warfarin as mentioned before.

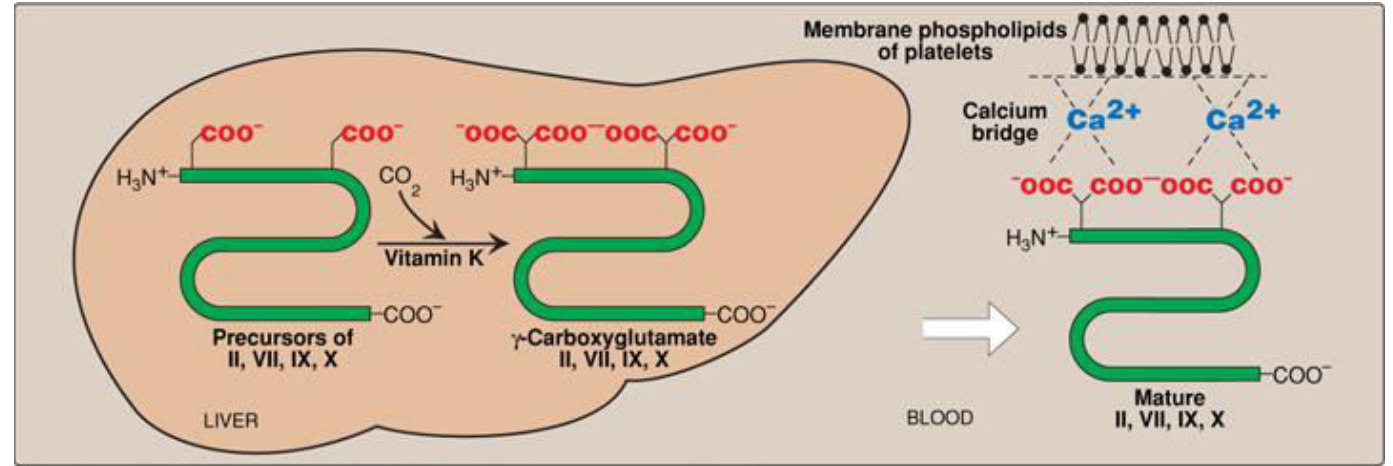


# Functions of vitamin K

## Prothrombin – platelet interaction

- Carboxylated prothrombin contains two carboxylate groups (COO<sup>-</sup>)
- These groups bind to Ca<sup>2+</sup> forming prothrombin-calcium complex
- The complex then binds to phospholipids (Making a bridge) on the surface of platelets (important for blood clotting)
- Converting prothrombin to thrombin and initiating clot formation

## Prothrombin – platelet interaction



نفس السايكل اللي بالصورة اللي بالسلاميد اللي قبل .. فيتامين كي رح يشتغل كوفاكثور ويحول القلوتاميت لقاما كاربوكسي قلوتاميت (بروثرومبين) في الكبد الفرق ان هنا بعد ما تصير هذي السايكل المعتادة راح يطلع المركب الناتج للدم ويسوي جسر مع الكالسيوم باستخدام الكاربوكسيليك اسيدز اللي عنده ويسون كومبليكس موجب الشحنة بسبب الكالسيوم بعدها بيرتبطون مع الدهون اللي موجودة على سطح البليتليتس (سالبة الشحنة) عشان يحصل التخثر

Prothrombin > Thrombin > Clot formation

# Functions of vitamin K

## Synthesis of $\gamma$ -carboxyglutamate in osteocalcin

- ❖ Osteocalcin is a bone turnover protein
  - Also called Bone Gla Protein (BGP)
  - Involved in bone formation, mineralization and resorption
  - $\gamma$ -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

Osteocalcin is another protein that needs similar way of carboxylation and it's the major non-collagenous protein incorporated in bone matrix during bone formation

Exact function is unknown but people who have less amounts of carboxylated osteocalcin are more prone to develop bone fractures

# Deficiency of Vitamin K

Deficiencies are rare: it is synthesized by intestinal bacteria

Prolonged antibiotic therapy  
Especially in marginally malnourished individuals (eg debilitated geriatric patients)

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  
Because absorption of dietary vitamin K from your small intestine depends on normal fat digestion



# Deficiency of Vitamin K

Gastrointestinal infections  
with diarrhea

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

Deficiency most common in newborn infants

1. Newborns lack intestinal flora
2. Human milk can provide only 1/5th vitamin K
3. Supplements are given intramuscularly at birth

New borns are more  
susceptible to develop  
deficiencies because  
their intestine are  
sterile with no vit k  
producing bacteria  
Some times that is  
regulated by giving  
intramuscular vit k  
injections

# Deficiency manifestation and toxicity

## Manifestations

Hemorrhagic disease of the newborn

- Bruising tendency, ecchymotic patches (bleeding underneath the skin) **Purple patches under the skin**

Mucus membrane hemorrhage

Post-traumatic bleeding / internal bleeding

Prolonged prothrombin time

**And also their bones get fractured easier than normal people “osteocalcin”**

## Toxicity

- Prolonged supplementation of large doses of menadione can cause:
- **It is occasionally used as a nutritional supplement because of its vitamin K activity.)**
  1. Hemolytic anemia
  2. Jaundice
- Due to toxic effects on RBC membrane



# Take home messages

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- ✓ Vitamin K is essential for blood coagulation process
- ✓ It mediates the process by  $\gamma$ -carboxylation of glutamic acid residues of prothrombin and coagulation factors





# Summary:

## Types of Vitamin K

K1 (Phylloquinone)

K2 (Menaquinone)

K3 (Menadione)

### RDA:

Infant > Children > Women > Pregnant Women > Men

## Functions of Vitamin K

Coenzyme for the synthesis of proteins in the liver: Prothrombin and Blood clotting factors

by carboxylation of (Glu) into (Gla) which needs dihydroquinone form of Vit K

**Warfarin** inhibits reductase (no dihydroquinone formation)

Carboxylated Prothrombin +  $Ca^{2+}$  phospholipids on surface of platelets:

Important for clotting

Synthesis of (Gla)  $\gamma$ -carboxyglutamate for osteocalcin to bind with hydroxyapatite.

### Deficiencies of Vitamin K:

Lipid malabsorption  
2<sup>nd</sup> Gen cephalosporins  
Malnourished and using antibiotics  
GI infections with diarrhea  
Common antibiotics

### Clinical manifestations:

Hemorrhagic disease of the newborn  
Bruising tendency, ecchymotic patches  
Mucous membrane hemorrhage  
Post-traumatic bleeding / internal bleeding  
Prolonged prothrombin time

### Toxicity:

Prolonged large intake of menadione for a long time > toxic effects on the RBC membrane which leads to Hemolytic anemia  
Jaundice

# QUIZ

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**Q1 :** What factors of Vit K are pro-coagulants ?

- A. I , II & X
- B. II , VII, IX, & X
- C. IX , V & X
- D. None of the above

**Q2 :** Which ONE of the following is synthetic form of Vit k ?

- A. Menaquinone
- B. Menadione
- C. Phylloquinone
- D. Dihydroquinone

**Q3 :** All factors and proteins in blood clotting are synthesized in ?

- A. Pancreas
- B. Kidney
- C. Liver
- D. Spleen

**Q4 :** The form of vitamin K that is required for activation of clotting factors is ?

- A. Menaquinone
- B. Menadione
- C. Phylloquinone
- D. Hydroquinone

**Q5 :** Vitamin K is synthesized in the body by ?

- A. Kidney
- B. Liver
- C. Spleen
- D. Intestinal bacteria

**Q6 :** What group of people need additional Vitamin K ?

- A. Premature newborns
- B. People with bile production abnormalities
- C. Patients with urinary tract infections
- D. Both A and B

# QUIZ

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**Q7 :** Mention the dietary sources of Vitamin K ?

Cabbage, kale, spinach, egg yolk, liver

**Q8 :** Mention two conditions in which an individual is more prone to be Vitamin K deficient ?

Newborns, prolonged use of antibiotics

**Q9 :** Describe briefly the biological action of Vitamin K ?

Carboxylation of non-mature clotting factors into mature, functional ones.

**Q10 :** A patient came with liver cirrhosis and they noticed an increase in prothrombin time. As a prognosis do you suspect the patient to have Vitamin K deficiency and why ?

No, in liver diseases there is an increased prothrombin time due to deficient synthesis of coagulation factors. Further, vitamin K fails to restore Prothrombin time when administered.

*Suggestions and recommendations*

1) B 2) B 3) C 4) D 5) D 6) D



# TEAM MEMBERS



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## TEAM LEADERS

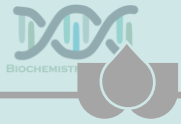


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**THANK  
YOU**

**FOR CHECKING  
OUR WORK**



**PLEASE CONTACT  
US IF YOU HAVE  
ANY ISSUE**



• Lippincott's Illustrated Reviews Biochemistry 6<sup>th</sup> E



Review the notes



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