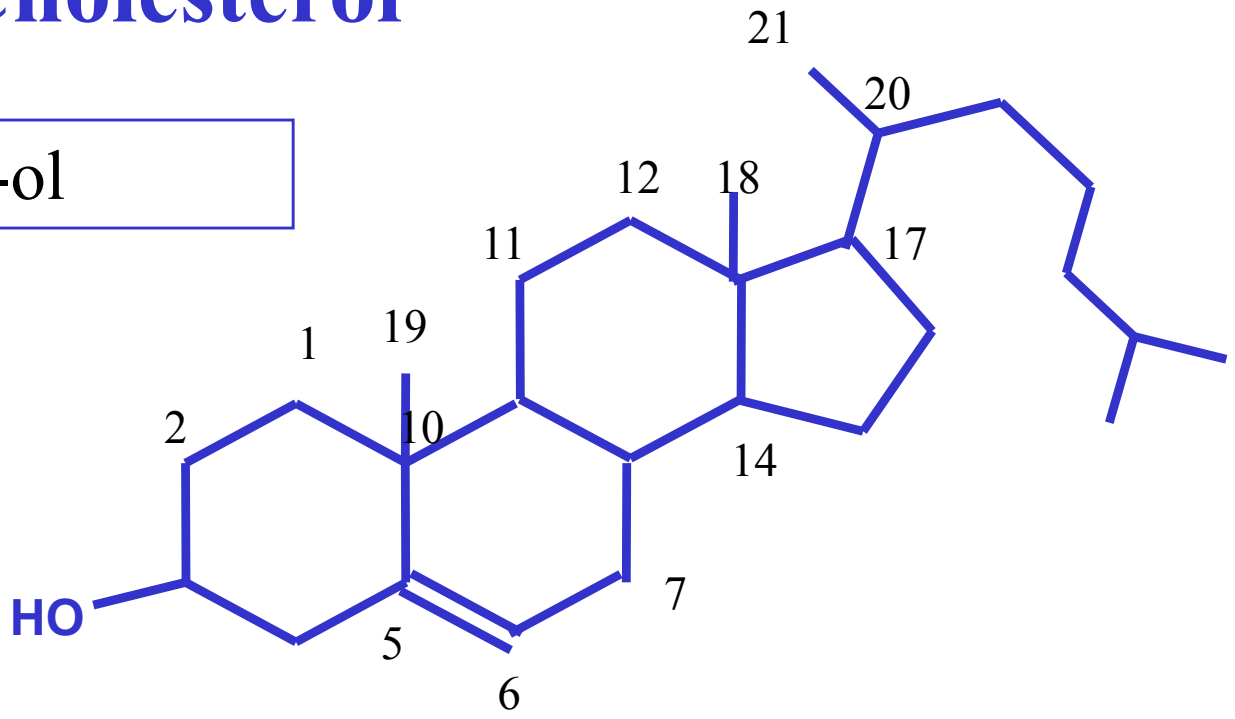
Cholesterol transport and elimination. Bille acids and calciols.

Cholesterol

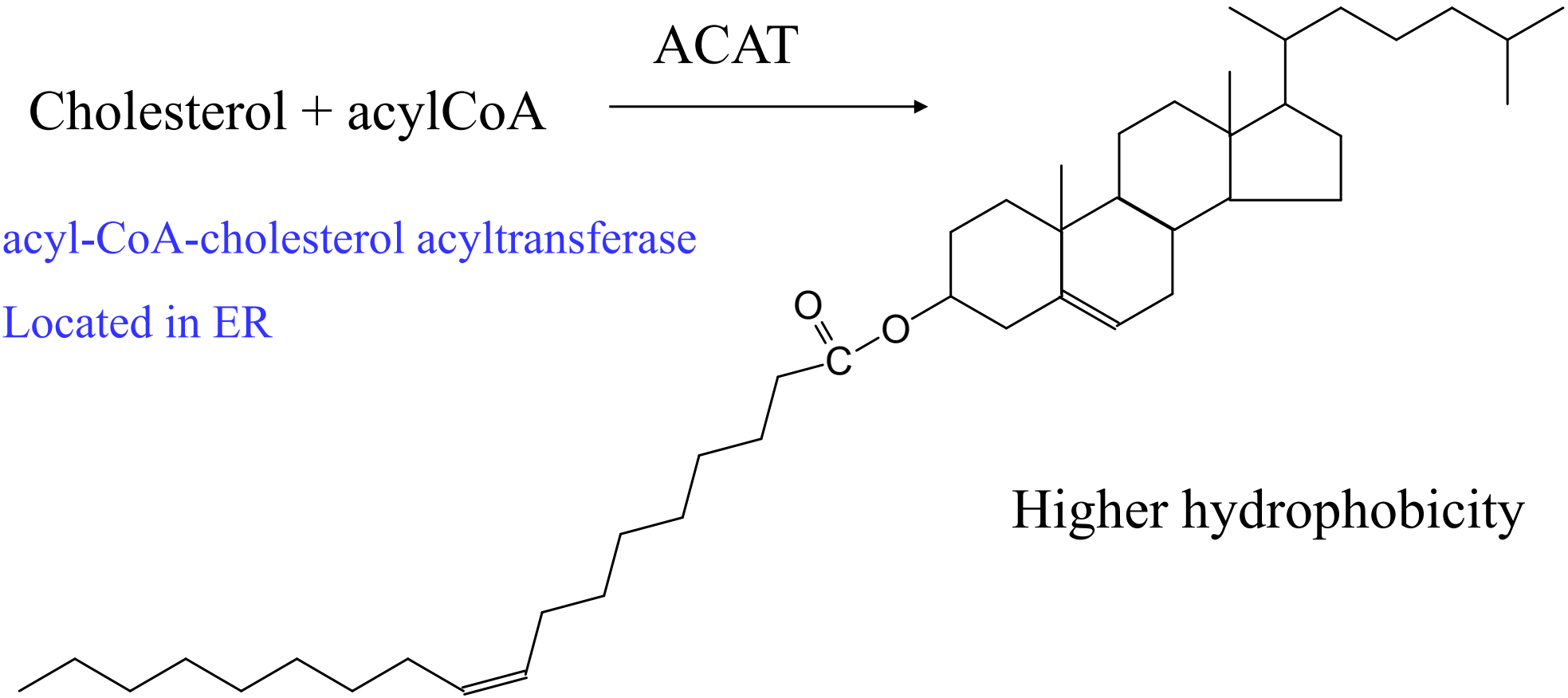
5-cholesten-3β-ol



Essential component of membranes
Source for synthesis of bile acids, steroids and vitamin D3

Esterification of cholesterol

Cholesterol + acylCoA $\xrightarrow{\text{ACAT}}$



acyl-CoA-cholesterol acyltransferase

Located in ER

Higher hydrophobicity

Most often linoleic and linolenic acid

Transport of cholesterol in blood in form of lipoproteins

From liver transported in form of VLDL

Most of VLDL is converted to LDL after the utilization of main part of TG contained in them

LDL transfers cholesterol into the periferal tissues

Reverse transport of cholesterol to the liver - HDL

25-40% - esterified cholesterol

Cholesterol in blood

Recommended value < 5 mmol/l

When the total cholesterol level exceeds 5 mmol/l further investigation of lipid metabolism is necessary, especially the finding of the cholesterol distribution in the lipoprotein fractions

LDL-cholesterol = „bad“ cholesterol

HDL-cholesterol = „good“ cholesterol

A high proportion of serum total cholesterol incorporated in HDL is considered as a sign of the satisfactory ability of an organism to eliminate undesirable excess cholesterol. On the contrary, an increased concentration of LDL-cholesterol represents the high coronary risk involved in hypercholesterolaemia.

See Biochemistry II – 4.semestr

Familiar hypercholesterolemia

Inherited disorder which causes cholesterol levels to be elevated

Lack LDL receptors

High amount of LDL circulates in blood → level of cholesterol is elevated

This causes plaque formation and high risk of coronary artery disease

Charakteristic xantoma on tendons

„Degradation of cholesterol“

• in higher animals steroid nucleus of cholesterol is **neither decomposed** to simple products **nor oxidized** to CO_2 a H_2O

• only liver have ability to eliminate cholesterol

• two ways of cholesterol elimination:

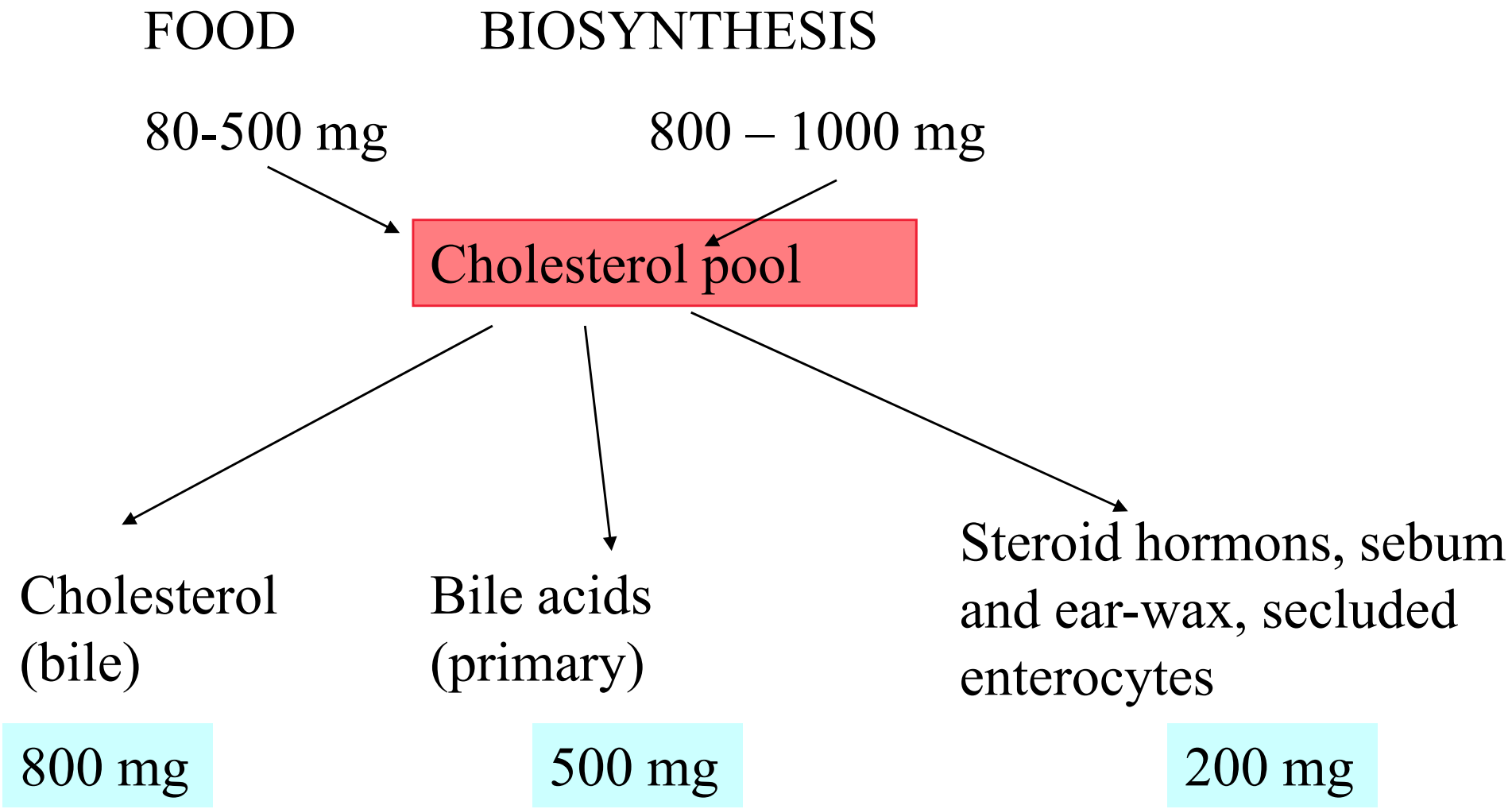
conversion to bile acids and their excretion

excretion of free cholesterol in bile

• small amount is used for synthesis of steroid hormones and vitamin D

• minimum amount of cholesterol is lost by sebum and ear-wax, in secluded enterocytes

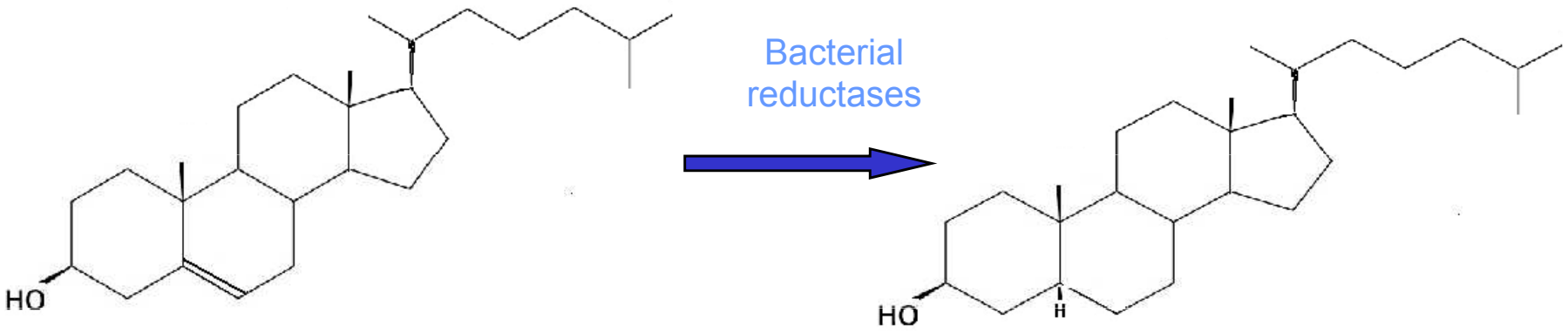
Cholesterol balance per 24 h



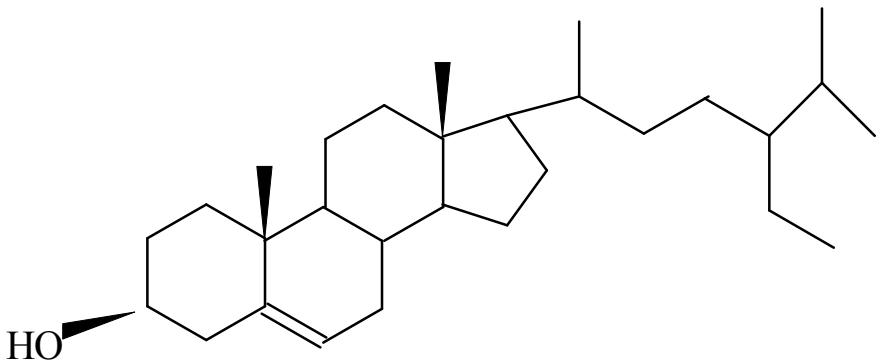
1000-1500 mg/day is excreted

Cholesterol in the gut

- cholesterol that enters gut lumen is mixed with dietary cholesterol
- about 55% of this cholesterol is resorbed by enterocytes
- remainig part is reduced by bacterial enzymes to coprostanol and excreted in feces



Phytosterols - sterols of plant origin



β-sitosterol

Structurally related to cholesterol; only the side chain on C-17 is changed

Consumption of phytosterols reduces the resorption of cholesterol.

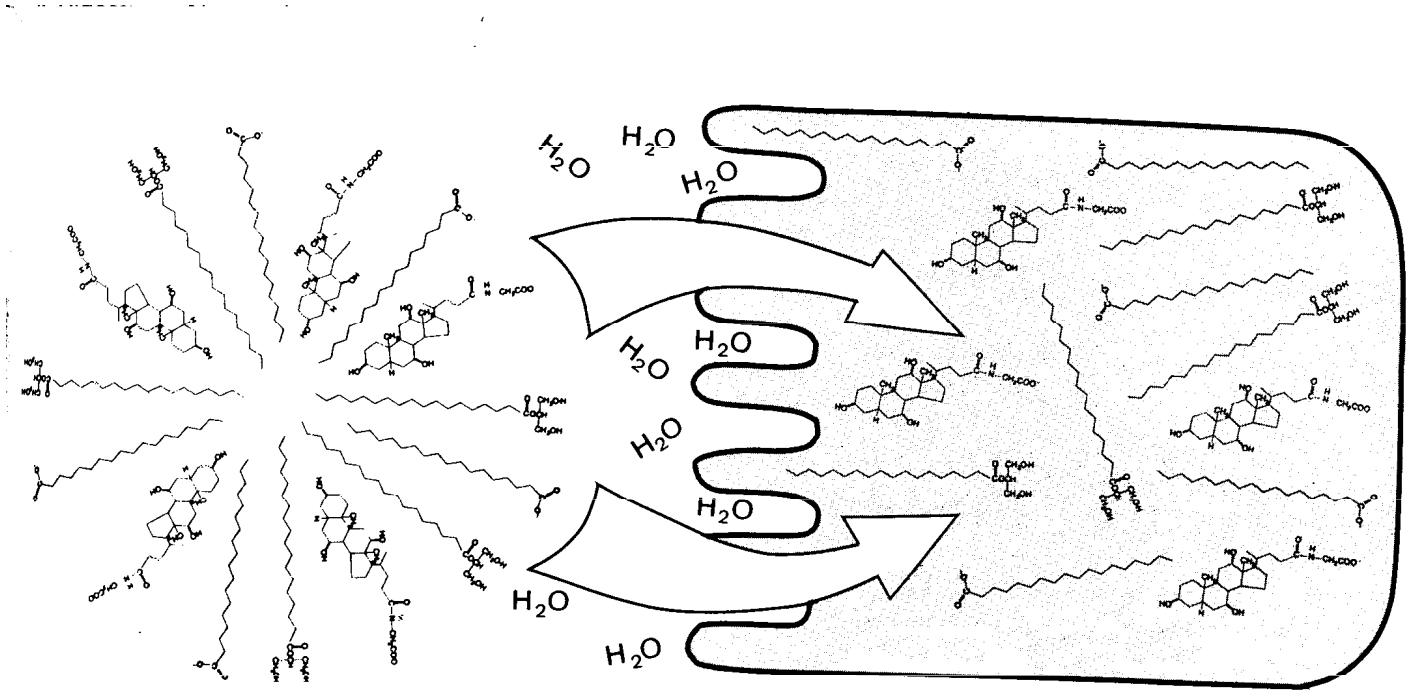
Plant oils (corn, rapeseed, soya, sunflower, walnut) contain up to 0.9 % phytosterols.

Average intake of phytosterols in Czech republic - about 240 mg per day,

Recommended intake for people with increased level of cholesterol - 2g/day

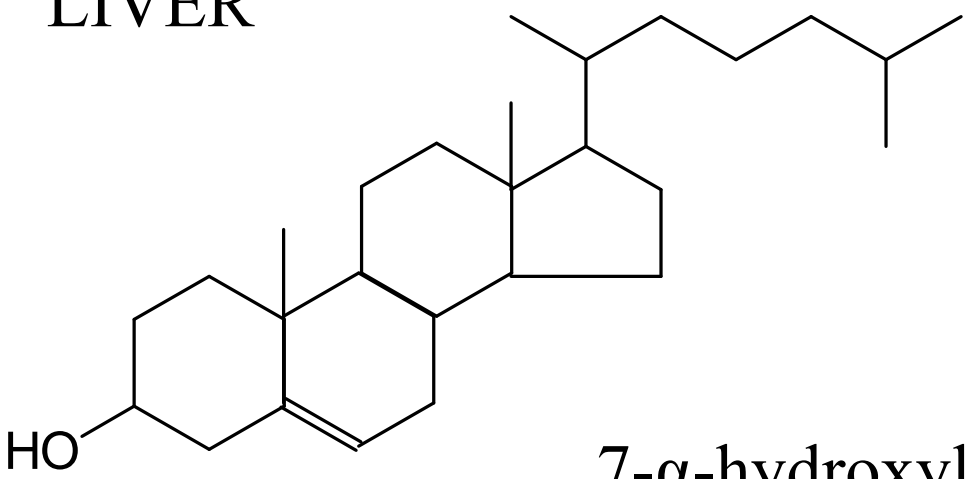
How do phytosterols function?

They penetrate into the mixed micelles that are in contact with intestine mucosa, they compete with cholesterol in resorption into the enterocytes.



Synthesis of bile acids

LIVER

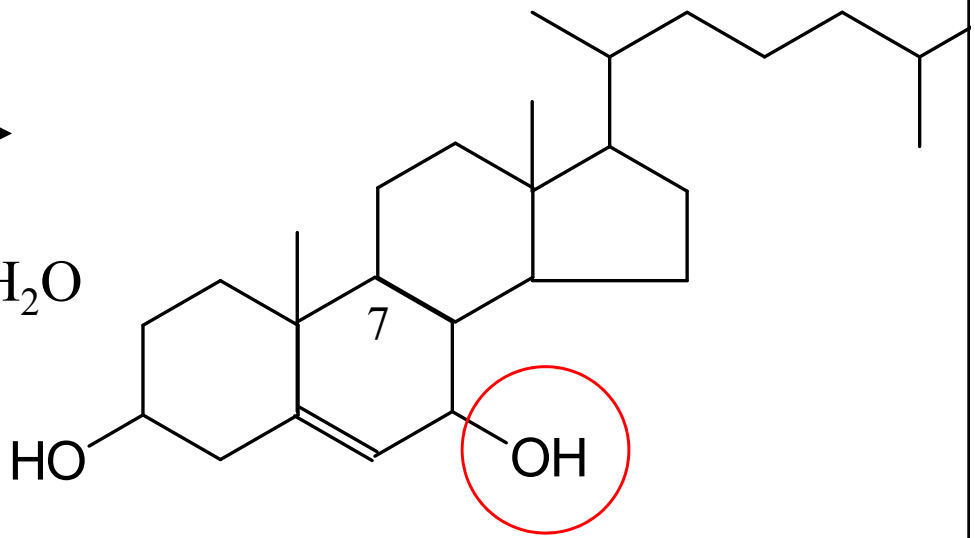


rate-limiting step
in the synthesis

7-α-hydroxylase

cytP450

NADPH, O_2 → $NADP^+$, H_2O



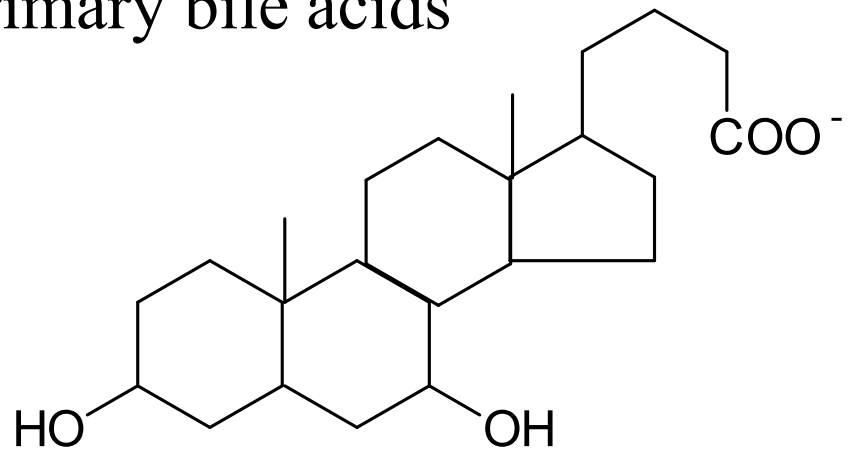
Located in ER (monooxygenase reaction)

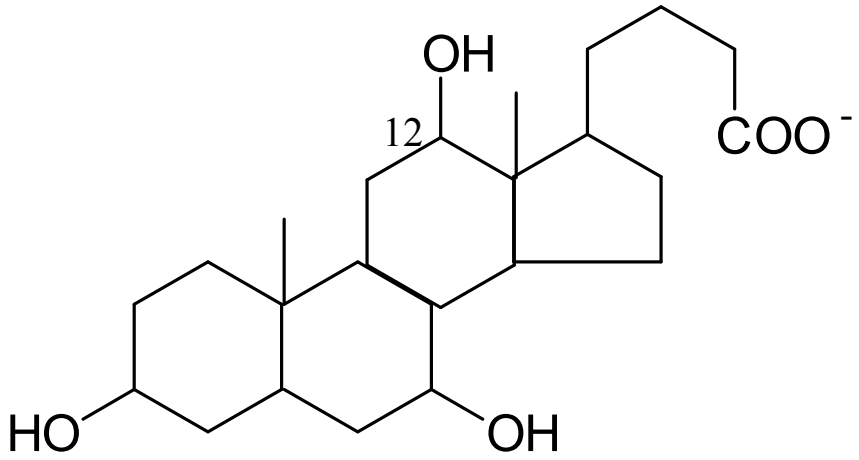
LIVER

In subsequent steps, the double bond in the B ring is reduced and additional hydroxylation may occur. Two different sets of compounds are produced. One set has α-hydroxylgroups at position 3,7, and 12, the second only at positions 3 and 7. Three carbons from the side chain are removed by an oxidation reaction.

24 C

Primary bile acids



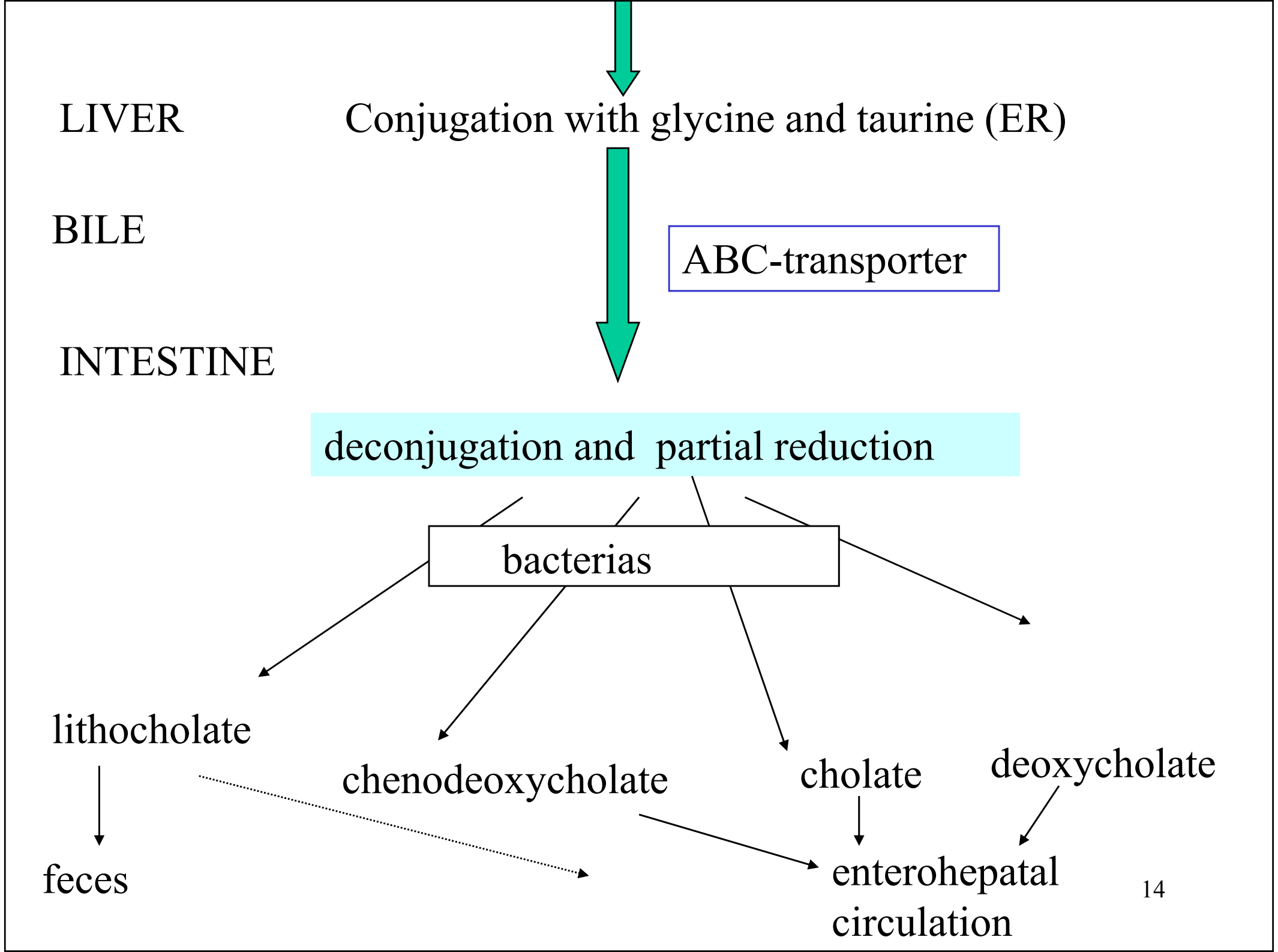


chenodeoxycholate

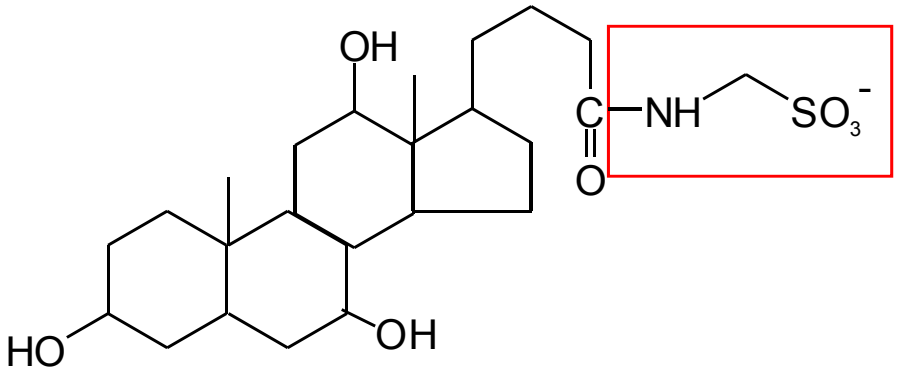
$pK_A \approx 6$

cholate

$pK_A \approx 6$

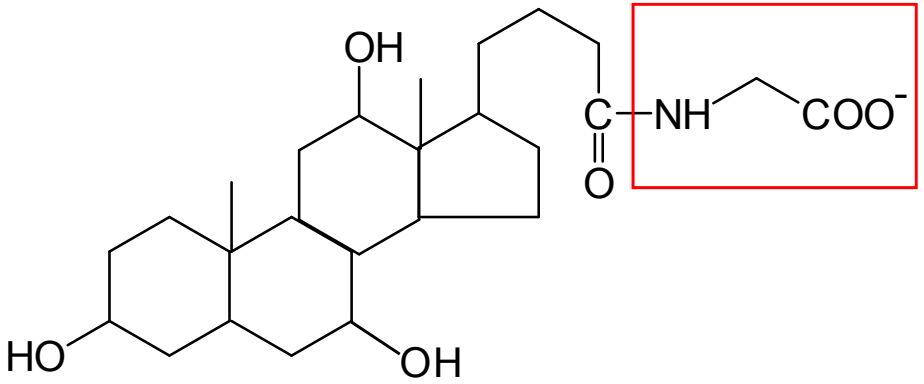

LIVER
Conjugation with glycine and taurine (ER)
BILE
ABC-transporter
INTESTINE
deconjugation and partial reduction
bacterias
lithocholate
chenodeoxycholate
cholate
deoxycholate
feces
enterohepatal circulation

Conjugated bile acids



taurocholic

$pK_A \approx 2$

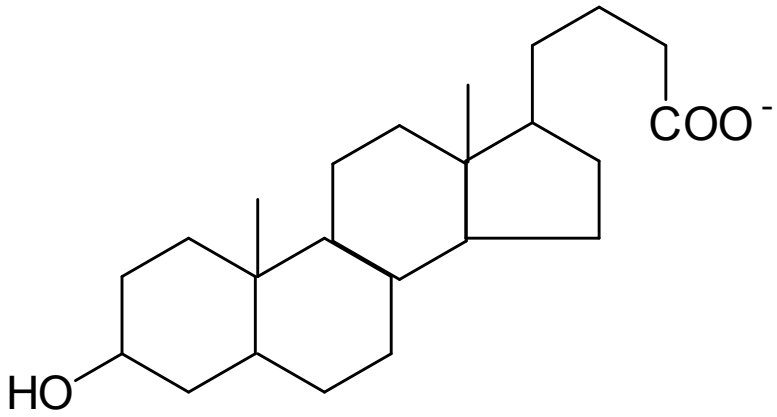


glycocholic

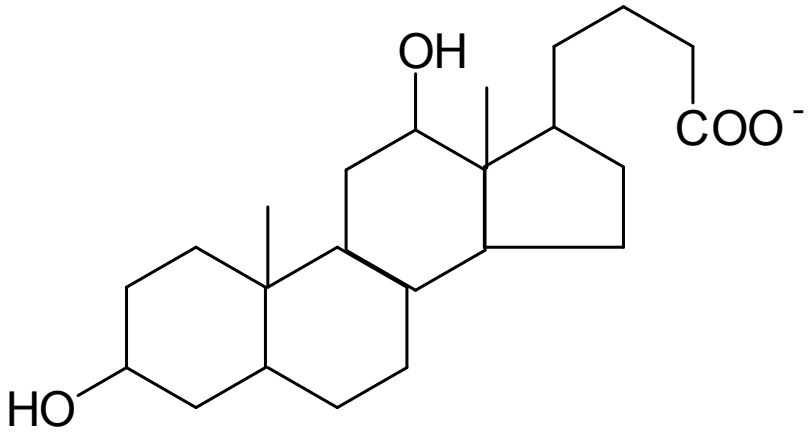
$pK_A \approx 4$

Conjugation increase pK_a values , increases detergent efficiency

Secondary bile acids – do not have OH on C-7



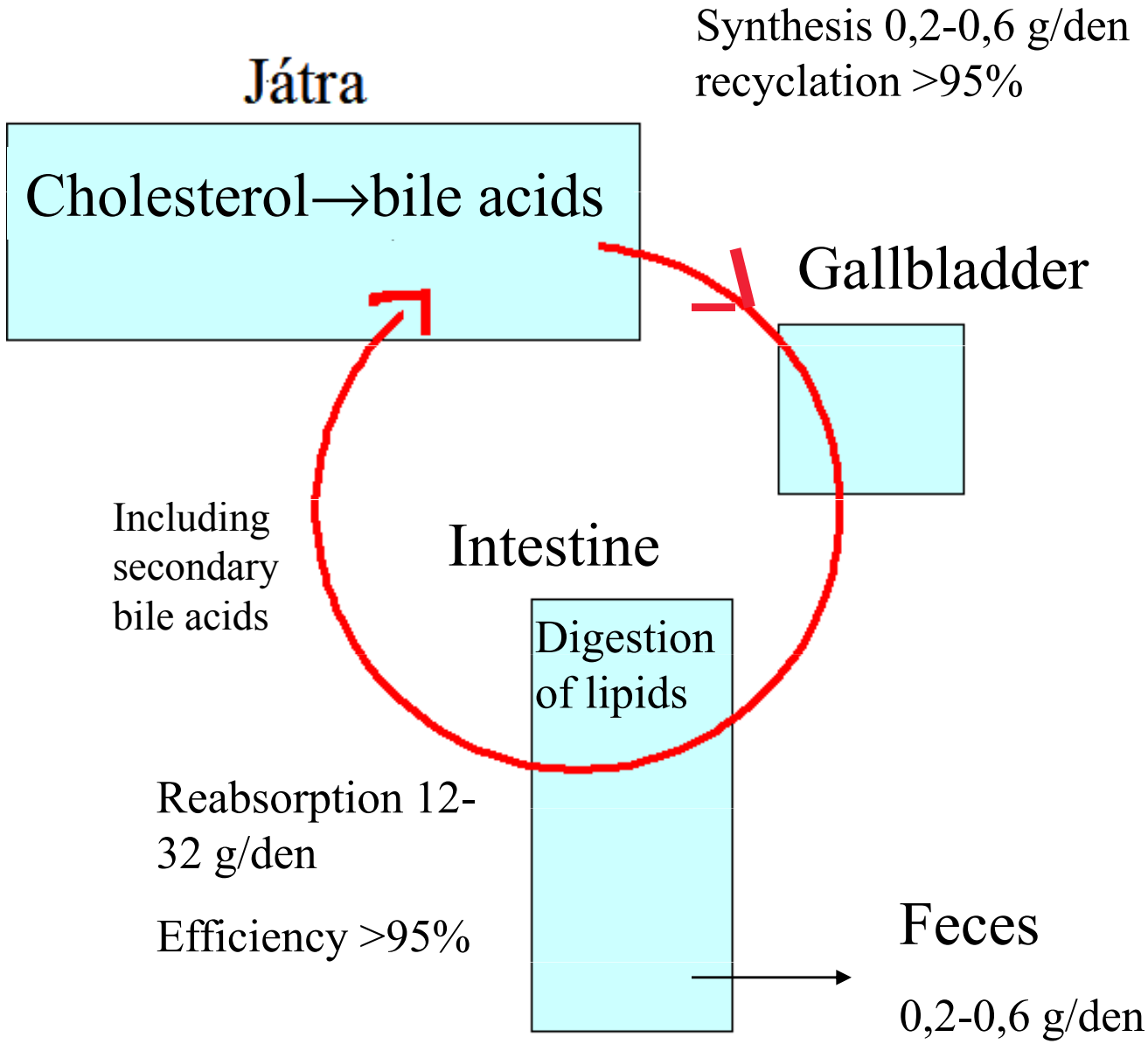
lithocholate



deoxycholate

Less soluble, excreted by feces

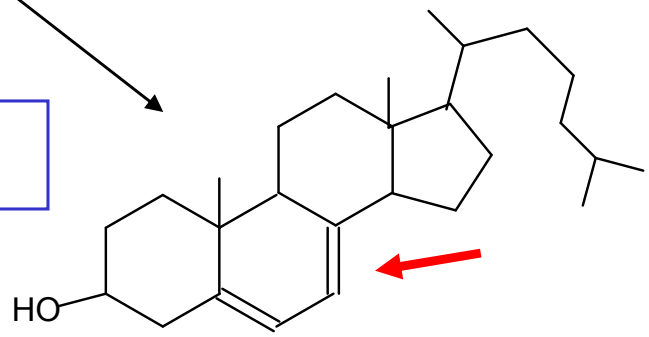
Enterohepatal circulation of bile acids



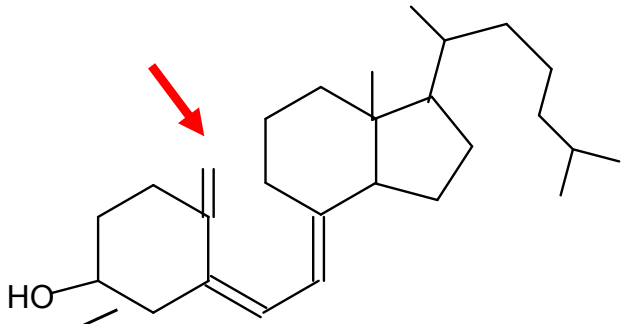
Intake and synthesis of vitamins D

cholesterol

Liver



Skin



7-dehydrocholesterol

cholecalciferol - vitamin D_3

(calciol)

D_3 D_2

Transport in blood into the liver

vit. D_3 – absorption with animal food (fish oils, eggs)

vit.D_2 – absorption with plant food

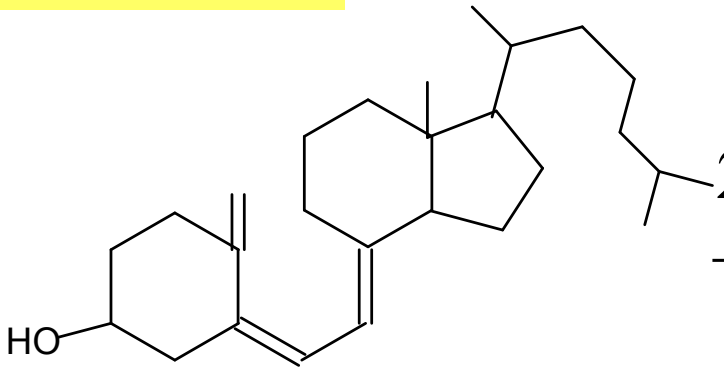
(also supplementations)

Plants

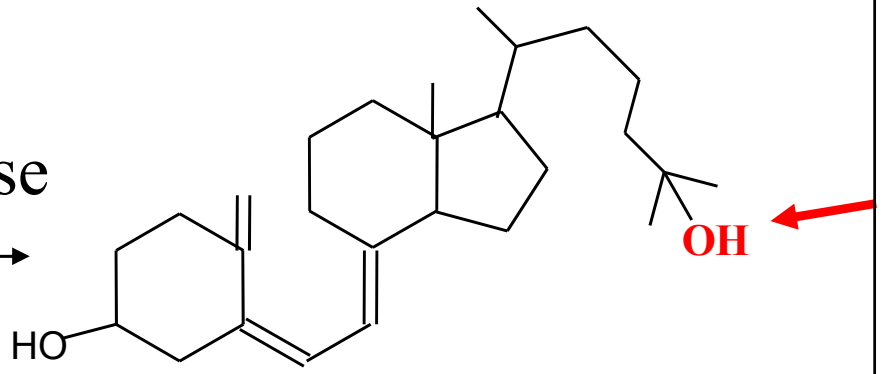
ergosterol → ergocalciferol-vitamin D_2 (ercalciol)

Synthesis of calciols

Liver



25-hydroxylase



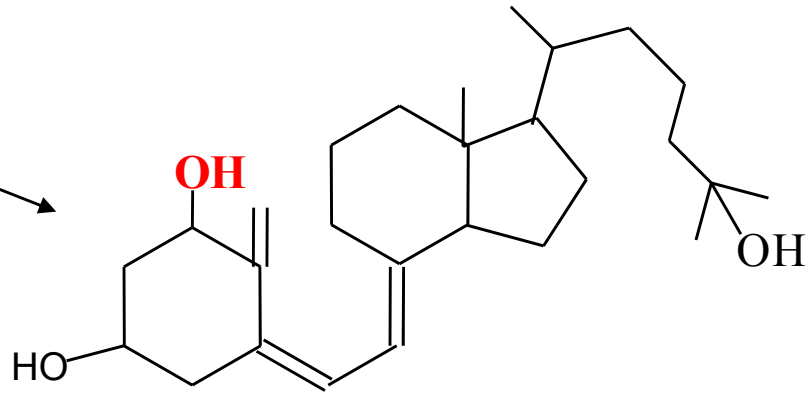
calcidiol

calciol - vitamin D_3

1α-hydroxylase

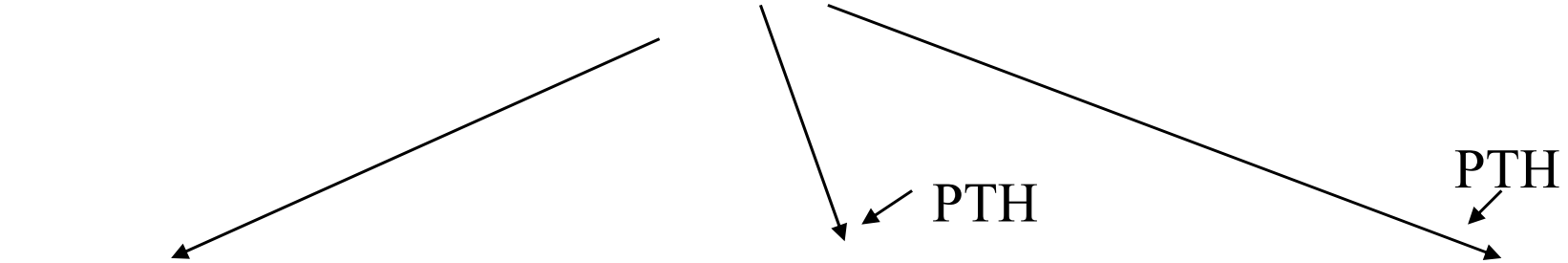
Kidney

Active form – regulation of calcium level



1,25-dihydroxycholecalciferol (calcitriol)

Effects of calcitriol



- intestine

Resorption of Ca^{2+}

- kidney

Resorption of Ca^{2+}

- bone

Regulates resorption and de novo synthesis ob bone tissue