



Cytochrom P 450 : SER. In liver.

reduced and complexed with carbon monoxide  
it exhibited a spectral absorbance maximum at 450 nm.

protein containing heme.

prophyrin ring containing Fe

\* Ferrous  $+2$   $\xrightarrow{\text{oxi}}$  Ferric  $+3$

can bind  $O_2$ . can not

\* Oxidation to get water soluble sub. which make it easily

( $+O, -H$ ) excreted

act as  $e^-$  transport.

carrier.

≠ Drug metabolism reactions can be divided into phase I & phase II

not sufficiently polar may undergo phase II metabolism

oxidation,  $\rightarrow$  most common / oxidase in liver.  
reduction,  
hydroxylation,  
hydrolysis,  
cyclization or decyclization

• Sulfation ( $SO_4-2$ )

• Methylation : convert the amino acid (homocysteine) into a amino acid (methionine),

• Glucuronidation : D-Glucuronic Acid is a sugar acid formed by the oxidation of the C-6 carbon of glucose

• conjugation: conjugation of the metabolite or drug with large molecular groups that further reduced the biological activity of the metabolite (if any) and increase its solubility even further.

Conjugation occurs with :

- glucuronic acid,
- sulfonates,
- glutathione or amino acids.

Functional groups that are often attached to these large molecules include

- carboxyl,
- hydroxyl,
- amino and sulhydryl groups

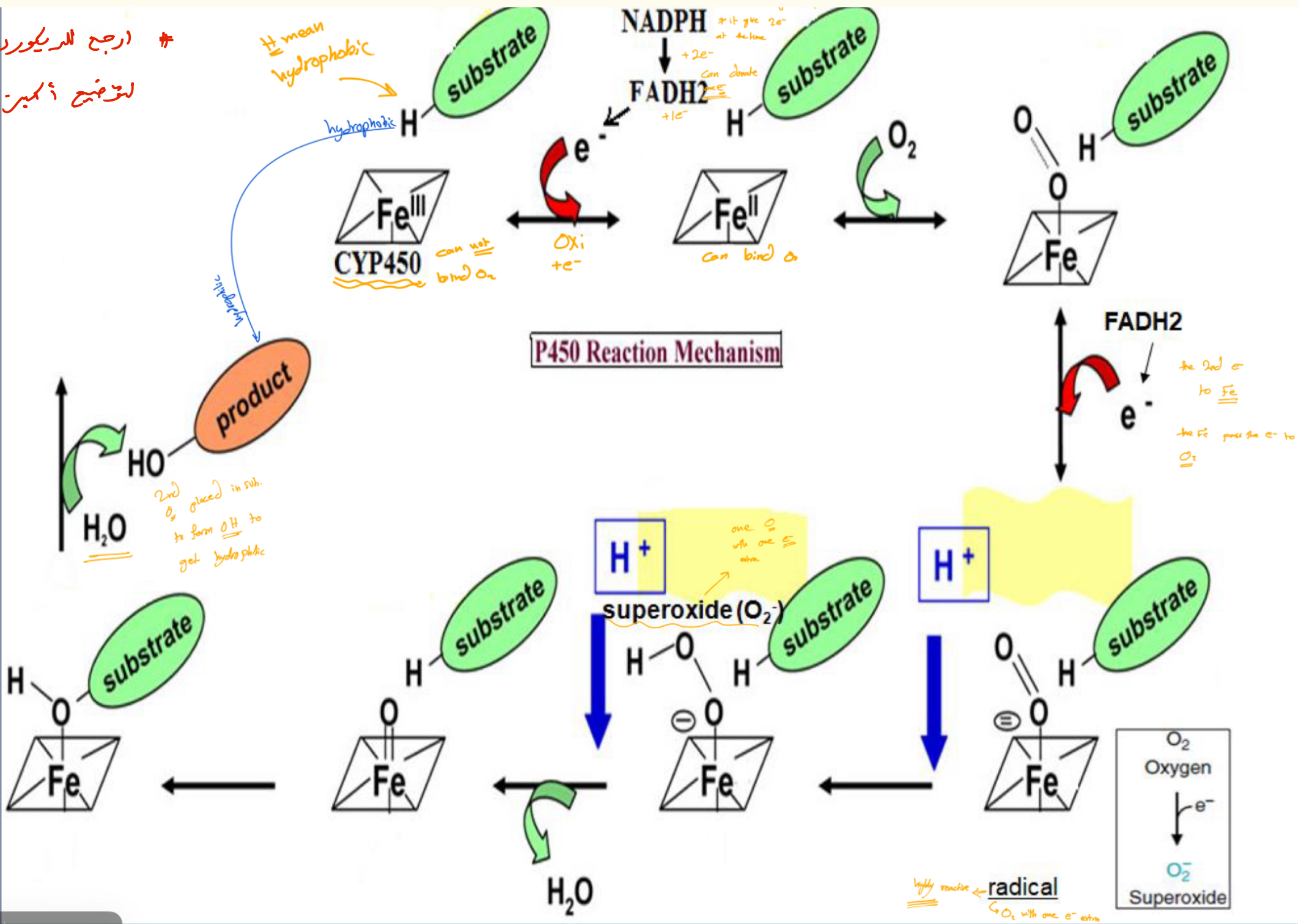
ارجع للريكتور  
لنوضح الامور

H mean hydrophobic

hydrophobic

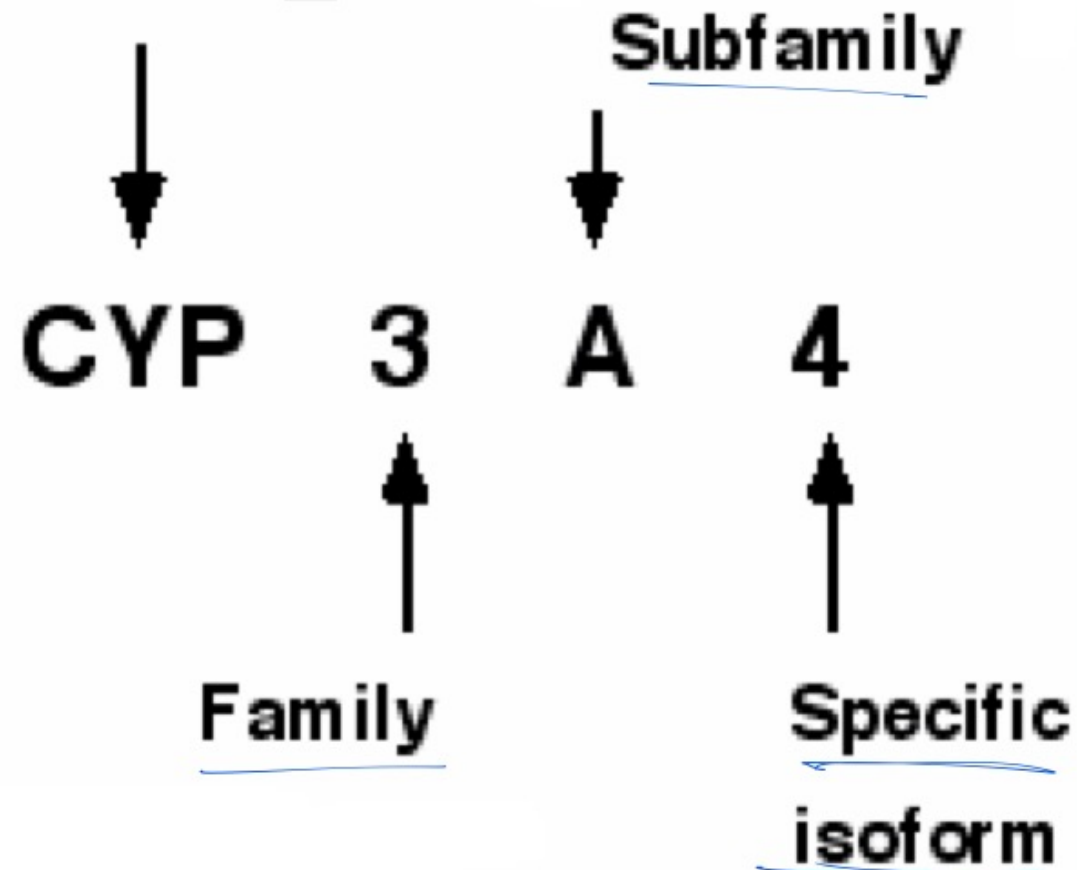
hydrophobic

P450 Reaction Mechanism



# Nomenclature of CYP450

## CYTOCHROME P450



isozyme

(enzymes with different primary structure but catalyze the same reaction)

- Role of cytochromes P- 450 in the metabolism of Steroid hormones

#P450SCC is Cholesterol Side-Chain-Cleavage Enzyme  
#is found in the mitochondria of tissues that synthesize steroids (mainly the adrenal glands and gonads)

#Cholesterol (27 carbons) → Cytochrome P450SCC (Desmolase) → Cleavage of 6-carbon unit from cholesterol side chain → Formation of Pregnenolone (21 carbons)

#Progesterone → P450 family enzymes → Production of other steroid hormones

- Steroid hormones contain 21 or fewer carbon atoms, whereas cholesterol contains 27

.Cholesterol is the precursor of all steroid hormones

- Genetic variation leads to differences in CYP enzyme activity (higher or lower expression).
- This affects drug metabolism, resulting in:
  - Poor drug metabolizers
  - Normal drug metabolizers
  - Ultra drug metabolizers
- Ultra drug metabolizers: Drugs are detoxified too quickly, reducing effectiveness, and toxic intermediates may accumulate, causing toxicity.
- **Some drugs inhibit P450 enzymes to prolong the activity of other drugs.**
- Poor metabolizers: Drugs may stay in the body longer, which can be desirable for certain medications.
- Poor metabolizers of drugs with a narrow therapeutic window may experience overdose.
- CYP enzymes can activate some drugs while making others ineffective.

# Bile

from hepatocyte / promotes the digestion of fats from food emulsifying in S. intestine.

- The emulsifying components of bile mainly consist of **bile acids and bile salts plus free cholesterol**.

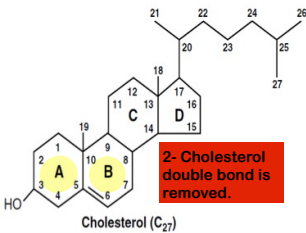
are steroids (cholesterol) consisting of 24 C atoms carrying one carboxyl group and several hydroxyl groups.

They are activated with coenzyme A → Then conjugated with glycine or taurine

an end-product of cysteine metabolism

## Primary Bile Acids

1- The side chain is shortened by three C atoms, and the terminal C atom is oxidized to a carboxylate group (COO<sup>-</sup>)

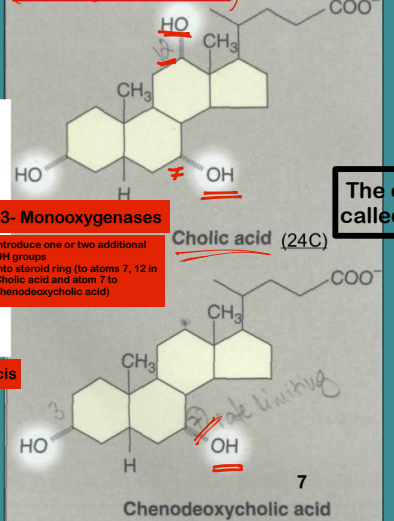


2- Cholesterol double bond is removed.

### 3- Monooxygenases

introduce one or two additional OH groups into steroid ring (to atoms 7, 12 in cholic acid and atom 7 to chenodeoxycholic acid)

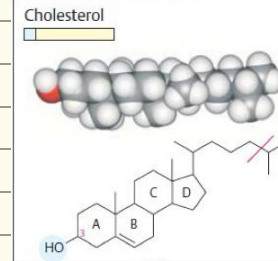
4- A-and- B rings is altered from trans to cis



The cholic acid conjugates with glycine and taurine are called the **conjugated bile acids or bile salts**.

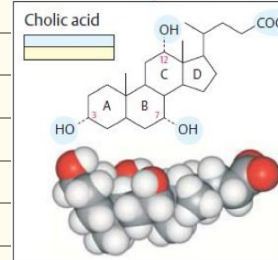
- Bile salts include glycocholic and glycochenodeoxycholic acids, and taurocholic and taurochenodeoxycholic acids
- Bile salts are **more amphipathic** than the primary bile acids
- Bile salts are **more effective** detergents than bile acids because of their enhanced amphipathic nature.
- Therefore, only bile salt are found in the bile

## A. Bile acids and bile salts

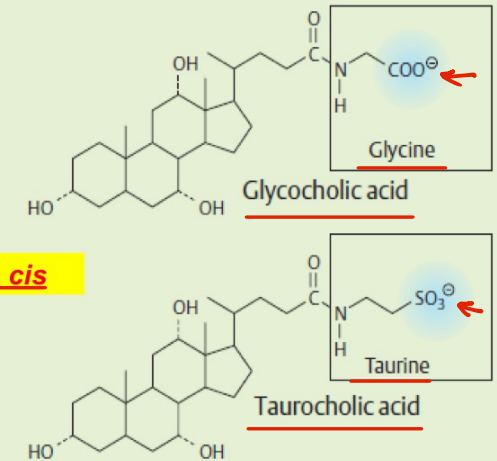


14 steps

**trans to cis**



## Bile salts



Bile salts = conjugated bile acids

so the hydrophilic groups in the bile acids lie on one side of the molecule

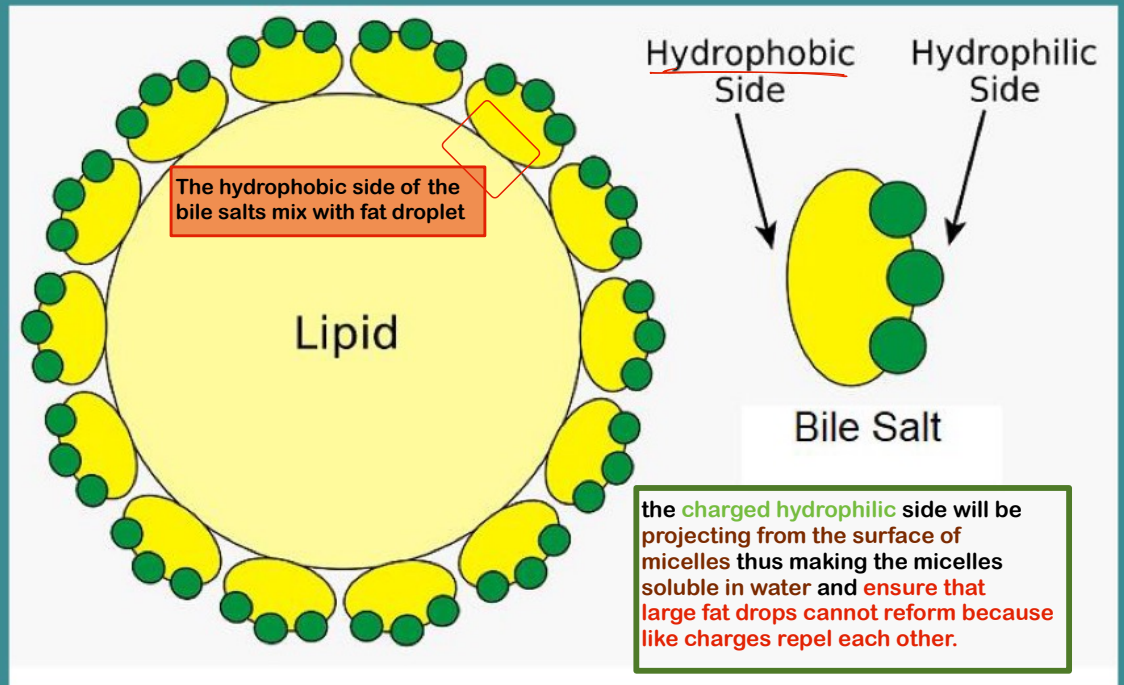
# Action of Bile Salts

#Emulsification: mixes two different substances that normally do not mix together like fat and water through formation of micelles.

Bile salt adsorb **on the surface of fat droplet** broken up by action of the **intestinal muscle** forming micelles

✳ greatly increases the surface area of fat, making it available for digestion by **lipases**.

## Micelles



Pancreatic lipase digest the **fat in micelles**  
 then  
 the **micelles travel through a layer of water** to the **microvilli** on the surface of the **intestinal epithelial cells**, where the **fatty acids, 2-monoacylglycerols, and other dietary lipids are absorbed**,

but the **bile salts** are left behind in the lumen of the gut

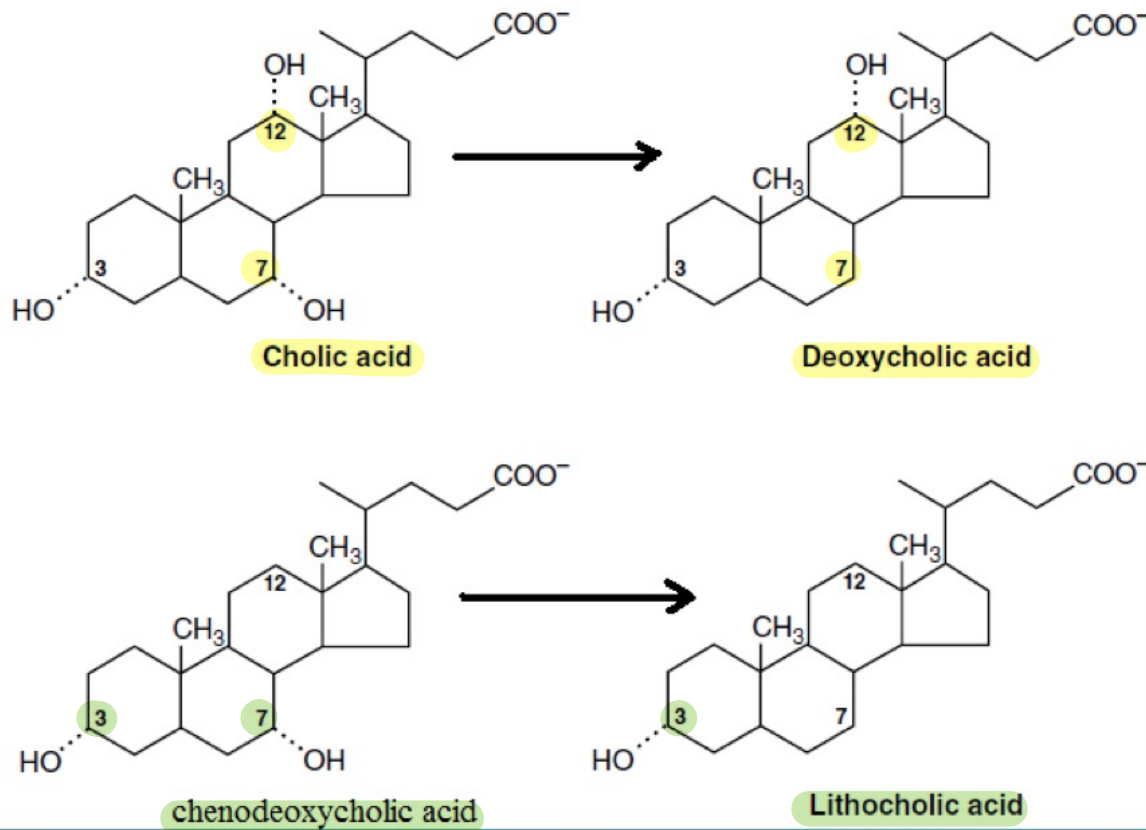
• Fate of bile in intestine

• Intestinal bacteria **deconjugate and dehydroxylate** the bile salts, removing the **glycine and taurine residues** and the **hydroxyl group at position 7** and thus regenerating what is known as **secondary bile acid**

• The bile acids that lack a hydroxyl group at position 7 are called secondary bile acid

### Primary bile acid

### Secondary bile acid



- Greater than 95% of the bile acids are reabsorbed in the **ileum** and return to the liver via the enterohepatic circulation (via the portal vein)

- The bile acids are recycled by the **liver**, which secretes them into the bile.

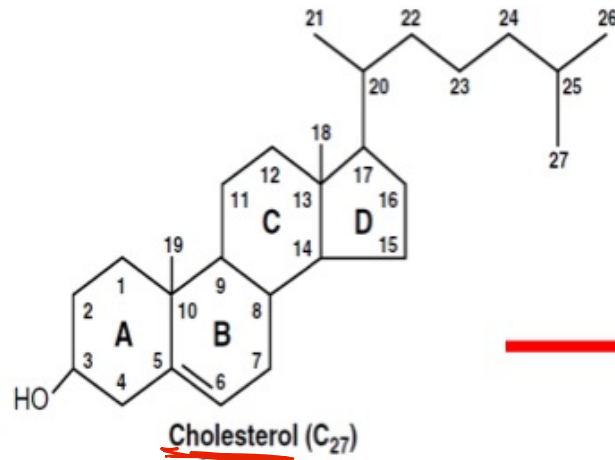
#This enterohepatic recirculation of bile salts is extremely efficient. Less than 5% of the bile acid entering the gut are excreted in the feces each day.

- Because the steroid nucleus cannot be degraded in the body, the excretion of bile acid serves as a major route for removal of the steroid nucleus and, thus, of cholesterol from the body.

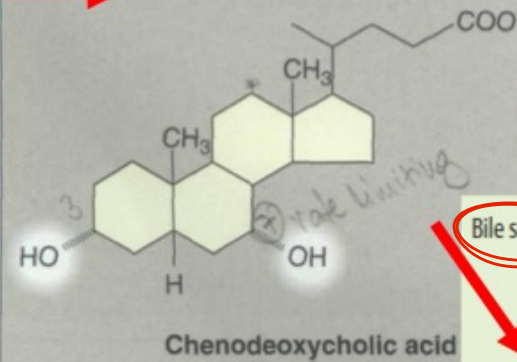
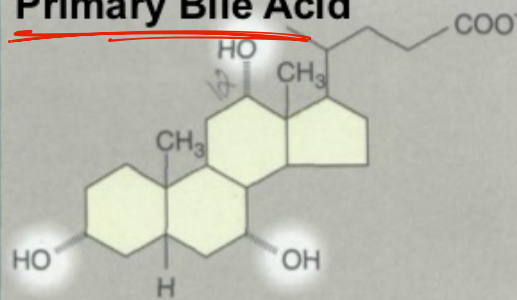
- Lithocholic acid, a secondary bile acid that has a hydroxyl group only at position 3

is the least soluble bile acid.

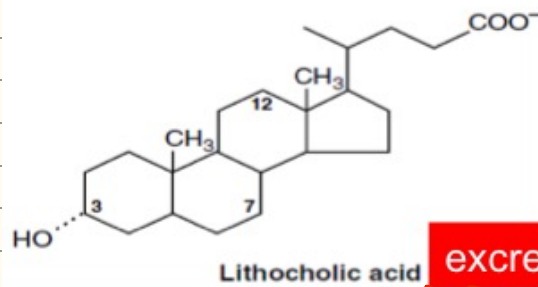
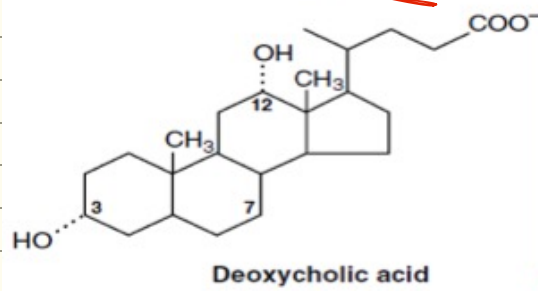
Its major fate is excretion.



## Primary Bile Acid

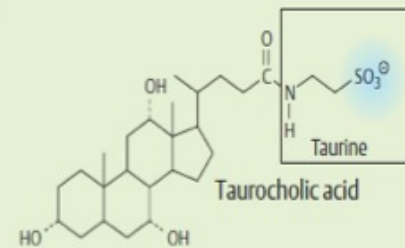
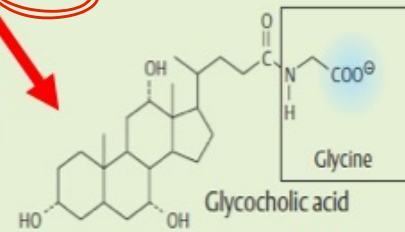


## Secondary bile acid



**excreted**

## Bile salts



**Bile salts = conjugated bile acids**

Best Wishes ♥

Done by : Rayhan Mroyat.