

**AL MUSTAQBAL UNIVERSITY COLLEGE
DEPARTMENT OF PHARMACY
GENERAL TOXICOLOGY
4TH STAGE**

LAB. 4



HEPATOTOXICANTS

QASSIM A ZIGAM

ACETAMINOPHEN

One of the most widely used analgesics.

It is a safe drug when used at therapeutically recommended doses.



ACETAMINOPHEN

However, an overdose can cause severe liver injury and even liver failure in experimental animals and in humans.

Although the toxicity is rare relative to the millions of patients taking the drug daily, APAP mediated liver injury represents a significant clinical problem.

ACETAMINOPHEN

At therapeutic doses, approximately 90% of APAP is conjugated with sulfate or glucuronide and excreted.

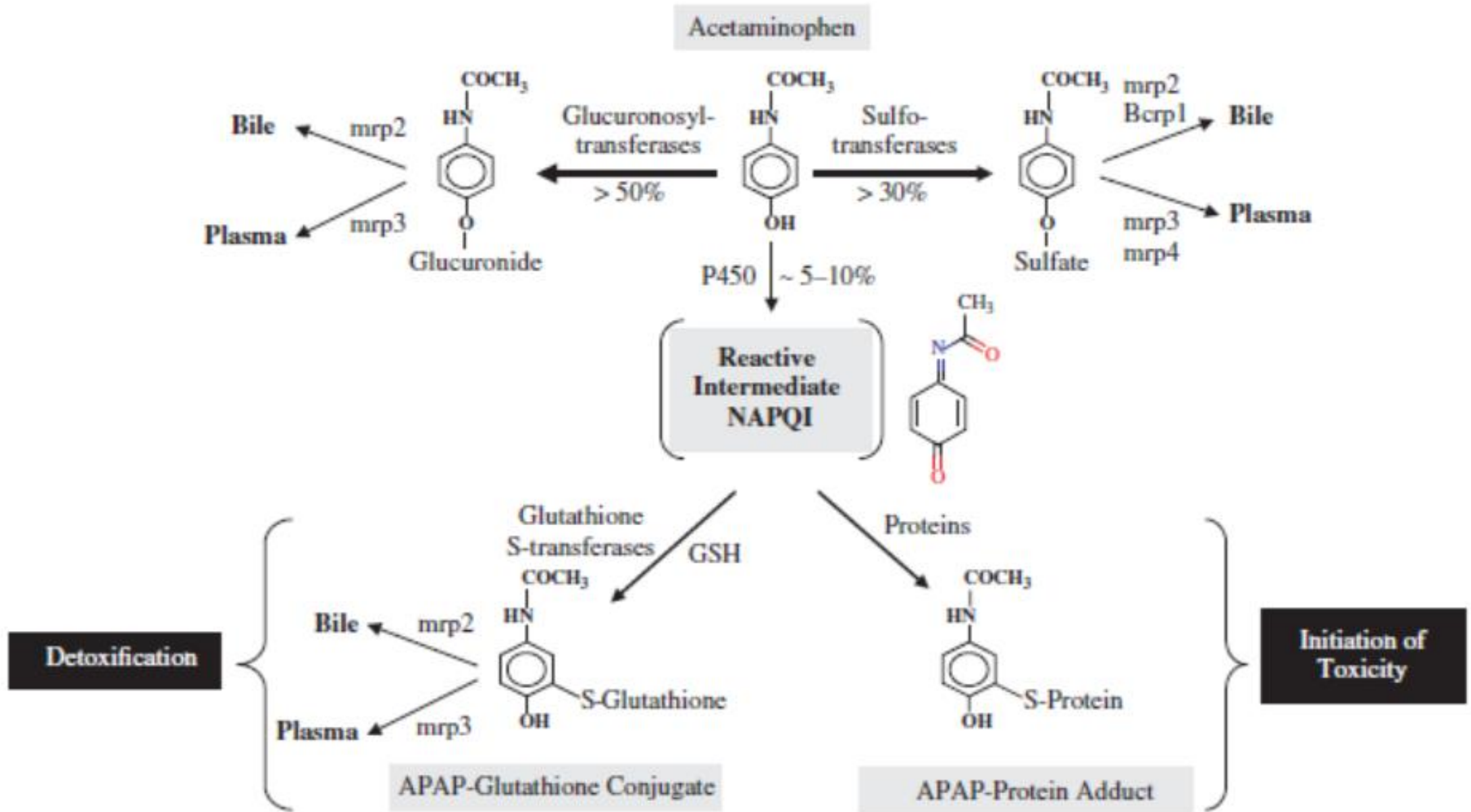
This limits formation by CYPs of a reactive, toxic metabolite, N-acetylbenzoquinone imine (NAPQI).

Most of the NAPQI is detoxified by conjugation with glutathione (GSH), thereby limiting its covalent binding to cellular proteins, which is the initiating event for HPC damage.

ACETAMINOPHEN

After an overdose, overwhelmed sulfate and glucuronide conjugation pathways lead to break-through formation of large amounts of NAPQI, resulting in severe depletion of cellular GSH stores needed for NAPQI inactivation.

Thereby allowing extensive covalent binding of NAPQI to intracellular proteins



ETHANOL

Alcohol abuse is among the major causes of liver disease.

The early stage of ethanol abuse is associated with hepatic lipid accumulation (steatosis).

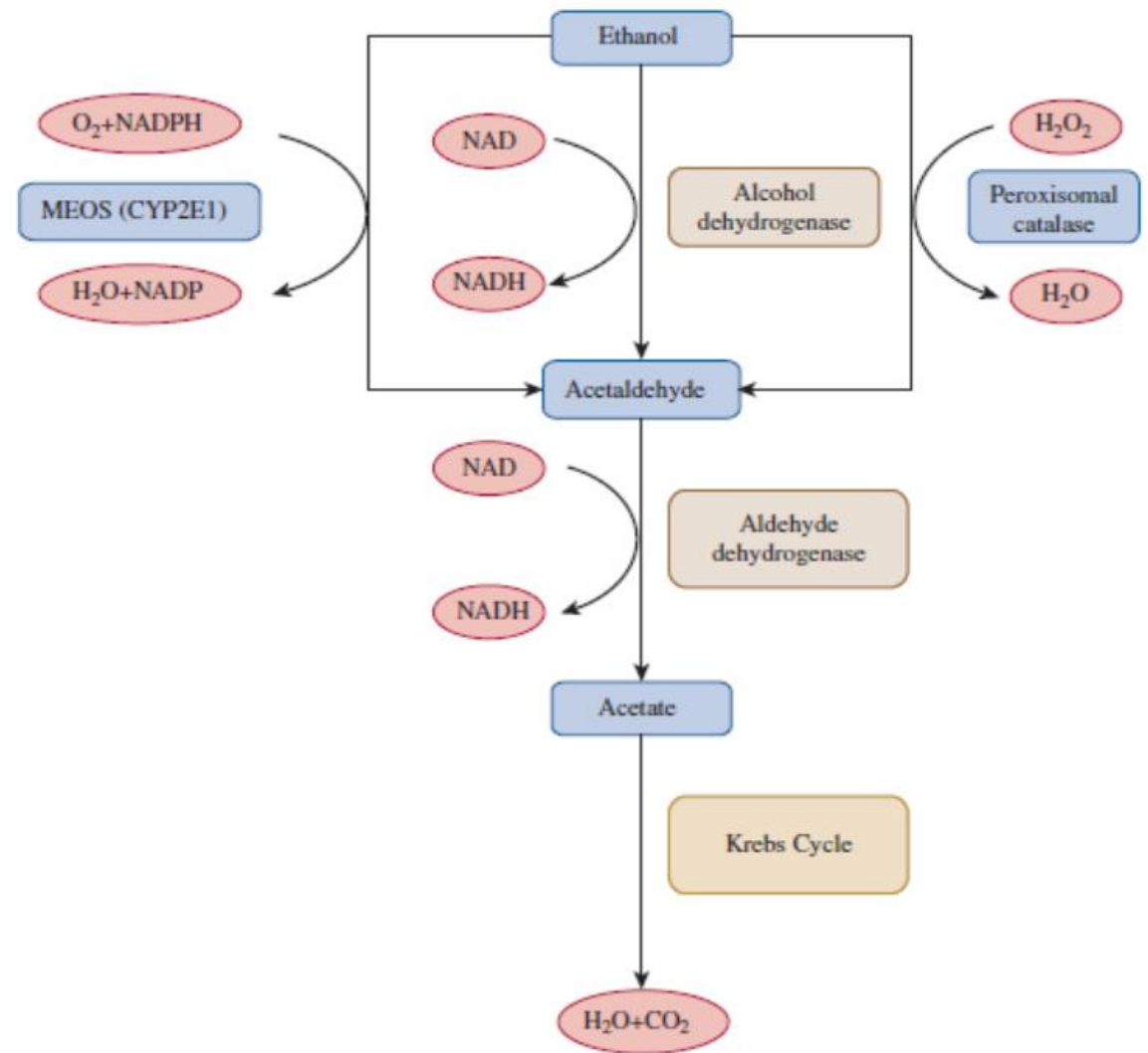
As alcohol-induced liver disease progresses, appreciable cell death occurs alongside increasing hepatic inflammation (i.e. steatohepatitis).

ETHANOL

If left unchecked, these pathologic processes drive replacement of functional liver mass with scar tissue.

This results in impairment of many functions of liver, including a progressive reduction in capacity for biotransformation of drugs.

ETHANOL METABOLISM



ETHANOL

This results in impairment of many functions of liver, including a progressive reduction in capacity for biotransformation of drugs.

People with hepatic cirrhosis due to chronic alcohol abuse frequently become deficient at detoxifying both the ammonia formed by catabolism of amino acids and the bilirubin derived from breakdown of hemoglobin.

ETHANOL

Such hepatic dysfunction combined with defects in synthesis of key proteins, such as albumin and clotting factors.

Which can ultimately drive multiple organ dysfunction and death.

Thus, ethanol provides a highly relevant example of a toxicant to which exposure contributes significantly to liver-related morbidity

CARBON TETRACHLORIDE

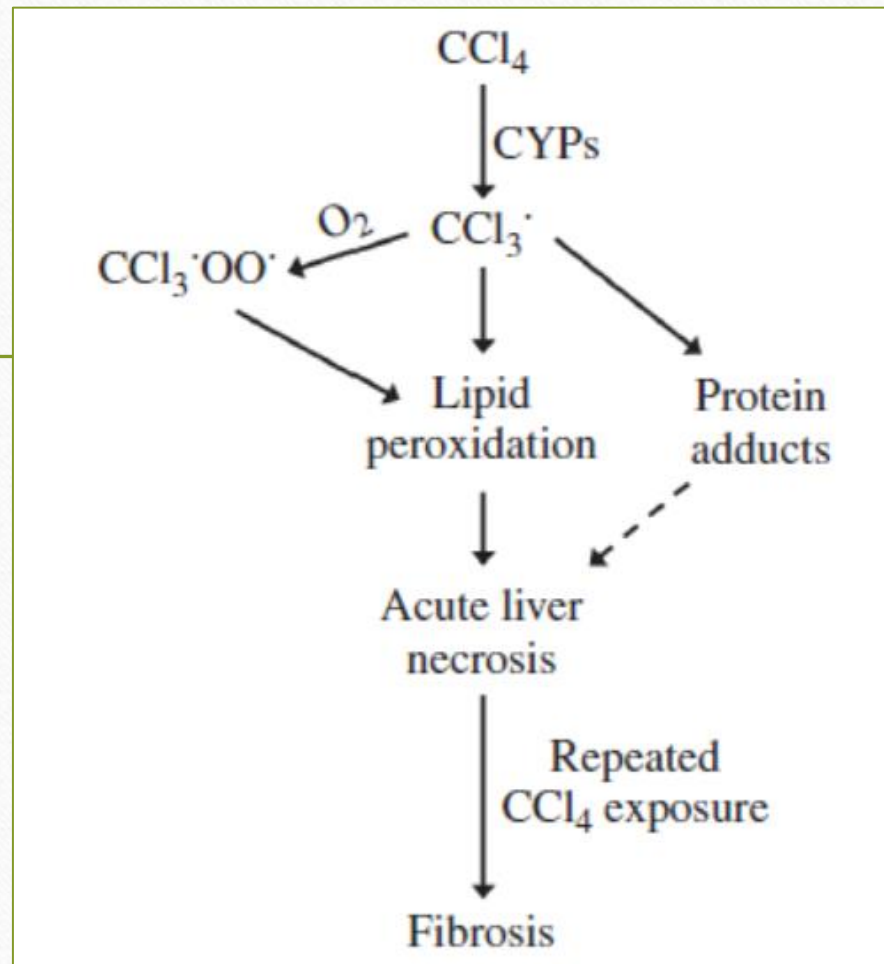
CCl₄ was once a widely used solvent, but human exposure to it has been restricted due to recognition that it is a potent hepatotoxicant.

Acute exposure to CCl₄ causes centrilobular necrosis in animals and humans.

CARBON TETRACHLORIDE

Cytochrome P450-dependent conversion of CCl₄ to trichloromethyl free radical ($\cdot\text{CCl}_3$) and then to the trichloromethyl peroxy radical ($\text{CCl}_3\text{OO}\cdot$) is a classic example of xenobiotic bioactivation to a free radical

This free radical is capable of initiating lipid peroxidation by abstracting hydrogen atoms from polyunsaturated fatty acids in phospholipid membrane



Liver toxicity induced by CCl4

CARBON TETRACHLORIDE

CCl₄-induced lipid peroxidation increases the permeability of the plasma membrane to Ca²⁺, leading to severe disturbances in calcium homeostasis and consequent necrotic cell death.

CCl₄ also induces significant mitochondrial damage, which is dependent on CYP2E-mediated metabolism and lipid peroxidation.

CARBON TETRACHLORIDE

In addition, the $\cdot\text{CCl}_3$ radical can bind directly to tissue macromolecules, as can some of the lipid peroxidation products such as 4-hydroxynonenal, which can form adducts with cellular protein.

Besides the intracellular events, Kupffer cell activation can contribute to liver injury.

Kupffer cells may enhance the injury by oxidant stress or $\text{TNF-}\alpha$ generation, which can lead to apoptosis

ANTIFUNGALS

Ketoconazole and other azoles are associated with an increased risk of hepatotoxicity.

Liver injury generally presents as increased transaminase levels that are usually reversible.

Although the hepatitis pattern is the most common, cholestatic and mixed forms have been observed.

ANTIFUNGALS

Patients on antifungal therapy require careful monitoring, and administration should be abruptly stopped if the liver enzymes become elevated.

Failure to do so can result in severe liver damage, and death.

ANTIMICROBIAL MEDICATIONS

Antibiotic-induced hepatotoxicity is responsible for 25-45% of DILI cases.

Antituberculosis drugs are reported to be hepatotoxic in up to 35% of patients receiving these medications.

Isoniazid (INH) is metabolized in the liver mainly to mono- and diacetylhydrazine and several other compounds.

ANTIMICROBIAL MEDICATIONS

Genetic variations in rates of INH metabolism exist; slow metabolizers are likely to develop high transaminase levels in response to INH administration.

Co-administration of drugs that increase cytochrome p450 activity has an additional effect: rifampin, for example, enhances the toxicity of INH.

Most patients recover in several weeks after discontinuing the drug, while continuing the medication may result in severe hepatotoxicity (potentially leading to acute liver failure).

ANTIMICROBIAL MEDICATIONS

Pirazinamide is generally not toxic, but when administered in combination with other drugs (INH, rifampin, ethambutol or quinolones) the risk of hepatic adverse reaction is significantly increased.

Therefore, rifampin is no longer combined with pyrazinamide for treating latent tuberculosis infections.

THANK YOU FOR YOUR ATTENTION