•Drug interactions in biliary excretion:

1. Drugs are often conjugated and excreted in bile. Some drugs are excreted in bile transformation.

Eg: In humans most water soluble drugs and metabolites of relatively high molecular weight (more than about 450) are excreted largely in the bile.

2. This excretion is mainly via transporters and The possibility exists for drug interaction with concamitant administration.

3 Conjugates such as glucoronides are often excreted in bile and then deconjugated in the intestinal tract and reabsorbed (enterohepatic circulation).

4. Drug interaction in the process of biliary excretion may affect the residence time and AUC of unchanged drug in plasma.

Hepatobiliary drug interaction:

Transporter	Drug	Inhibitor	Result of interaction
P-gp	Digoxin	Quinidine	Decreased biliary excretion
MRP2	SN-38	Probenecid	Decreased biliary excretion Results in increased AUC

1. The co-administration of drugs which inhibit the cotransporter involved in biliary excretion can reduce the biliary excretion of drug which are substrates of the transporter, leading to elevated plasma concentration of drugs.

2 Irinotecan is a component in chemotherapy of advanced colorectal cancer, it is metabolized by carboxylase esterase-2 to SN-38 (active metabolite) which is conjugated by uridine diphosphate glucuronide transferase 1A1 to the SN-38

glucpronide. Probenecid inhibits MRT^2 transporter resulting in decreased biliary excretion and increased plasma drug concentration.

Effect on biliary excretion:

1. Verapamil and cyclosporine are both inhibitors of P-gp but through different mechanism, verapamil is a substrate for P-gp and is a competitive inhibitor of this pump, where as cyclosporin inhibit transport function by interfering with substrate recognition and ATP hydrolysis.

2. Decrease clearance of drug through inhibition of P-gp translates clinically into increased AUC and an increase in toxicity

Examples:

decreased in vincristine clearance in presence of verapamil.