Gut microbes can convert prodrugs into active drugs, (eg, sulfasalazine)

Gut microbe Activation

Direct mechanisms

Intermediate Gut metabolic pathways share steps between host enzymes and those encoded by gut microbes. Intermediate microbial products can lead to pathogenicity; the best known example of this is not a therapeutic drug but a toxin called melamine.

Deactivation Gut microbes can encode enzymes that detoxify drugs, eg, digoxin is inactivated by the gut-residing Actinobacterium Eggerthella lenta

Direct binding Gut microbes can bind directly with drugs, compromising their bioavailability, eg, levodopa is converted to dopamine in the gut, preventing it from reaching the brain.

Intermediate microbial products can lead to pathogenicity; the best known example of this is not a therapeutic drug but a toxin called melamine.

Enterohepatic cycling The liver processes many drugs by adding glucuronic acid, which detaches the drug and tags it for transport to the intestine and elimination. Gut microbes produce an enzyme called beta-glucuronidase, which enables them to scavange the glucuronic acid and reactivate the drug, leading to toxicity, eg, irinotecan.

Altered gene expression Gut microbes alter the hepatic expression of key host enzymes involved in drug metabolism, eg, CYP450, leading to alterations in drug efficacy or toxicity

Altered kinetics Gut microbial metabolites compete with drugs for enzyme-binding sites, leading to alterations in the drug efficacy or toxicity, eg, paracetamol

Source: Journal of Clinical Investigation 2014

Microbiome-host interaction

The gut microbiota consists of approximately 100 trillion microbial cells. The metabolic activities of these microbes expand host metabolic capabilities by activating or inactivating drugs, generating toxic byproducts of drug metabolism, and altering drug metabolism by human cells in both direct and indirect ways.