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A REVIEW ON BENEFICIAL PHARMACOKINETIC INTERACTIONS IN ENHANCING BIOAVAILABILITY OF POORLY PERMEABLE DRUGS

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ABSTRACT

Pharmacokinetic interactions between drugs and other co-administered substances—such as additional drugs or food components—can significantly influence drug absorption, distribution, metabolism, and excretion (ADME). While often viewed as a source of adverse effects or therapeutic failure, certain drug-drug and drug-food interactions can result in beneficial pharmacokinetic outcomes that enhance therapeutic efficacy and safety. These interactions may be harnessed to improve bioavailability, extend plasma half-life, or reduce dosing frequency for drugs with narrow therapeutic windows or poor oral absorption. Beneficial drug-drug interactions can occur when one agent inhibits metabolic enzymes (e.g., cytochrome P450 isoforms) or efflux transporters (e.g., P-glycoprotein), thereby increasing the systemic exposure of a co-administered drug. For anti-retroviral drugs, the drug called ritonavir is used as an pharmacokinetic enhancer. Similarly, drug-food interactions—such as co-administration of high-fat meals with lipophilic drugs (e.g., posaconazole or fenofibrate)—can enhance absorption by improving solubilization and gastrointestinal retention. Citrus fruits like grapefruit inhibit intestinal CYP3A4, potentially increasing drug concentrations of certain statins or calcium channel blockers. Mechanistically, these interactions may involve enzyme inhibition, transporter modulation, or membrane permeability enhancement. When clinically predictable and well-managed, such interactions can be used to reduce drug costs, improve patient adherence, and increase therapeutic response. This shows the positive potential of selected pharmacokinetic drug-drug and drug-food interactions. Understanding these mechanisms allows clinicians and pharmacists to optimize drug therapy through evidence-based use of co-administered agents and dietary strategies.

KEYWORDS: Bioavailability, pharmacokinetics, enzyme inhibition, drug-drug interaction, drug-food interaction, transporter modulation, therapeutic optimization.

INTRODUCTION

In recent years, the simultaneous use of prescribed medications alongside food, dietary supplements, and over-the-counter health products has become increasingly common among patients.[1,2] While often overlooked, this practice can give rise to a range of interactions namely, food-drug, supplement-drug, and even drug-drug interactions.[3,4]

These interactions are frequently complex and unpredictable, but substantial evidence suggests they can significantly influence the pharmacological properties of co-administered drugs.[1–5] Specifically, interactions may affect a drug's pharmacodynamics the biochemical and physiological effects of drugs and their mechanisms of action or its pharmacokinetics, which involves the processes of absorption, distribution, metabolism, and excretion.[1,2,4,5]

Pharmacodynamic interactions typically occur at receptor sites and may result in synergistic or antagonistic effects, sometimes altering physiological conditions. In contrast, pharmacokinetic interactions can modify how drugs or active ingredients in food and supplements are processed by the body, impacting their bioavailability and therapeutic effectiveness.

While many of these interactions have been associated with adverse outcomes, such as increased toxicity or reduced therapeutic effect due to suboptimal drug concentrations, they are not universally negative. In some cases, such interactions may actually enhance the pharmacological efficacy or bioavailability of co-administered drugs.[1,3,4]
Understanding these interactions is crucial for ensuring patient safety and optimizing therapeutic outcomes. As the use of complementary health products continues to rise, both healthcare professionals and patients must be vigilant in monitoring and managing potential interactions to avoid unintended consequences.

Oral bioavailability is a critical determinant of a drug's therapeutic efficacy. However, many drugs exhibit poor oral bioavailability due to several physiological and biochemical barriers. The most significant factors contributing to this challenge include low aqueous solubility, extensive pre-systemic metabolism, limited membrane permeability, and active efflux transport mechanisms such as those mediated by P-glycoprotein (P-gp) (Figure 1A, B).[2,4,6] These limitations collectively reduce the concentration of the drug that ultimately reaches systemic circulation.

To address these issues, researchers have explored the deliberate inhibition of pre-systemic metabolism and efflux transporters as a strategy to improve drug absorption. Specifically, targeting key proteins such as P-glycoprotein (P-gp), cytochrome P450 enzymes (CYP450), and organic anion transporters (OAT) 1 and 3 has shown potential in enhancing the bioavailability and prolonging the half-life of poorly absorbed drugs.[1,4,6] These improvements can lead to less frequent dosing, lower overall dosage requirements, and cost savings, while also enhancing patient adherence to treatment regimens.[1]

MECHANISMS OF PHARMACOKINETIC DRUG INTERACTIONS

Carrier-Mediated Transporters: Gatekeepers of Drug Absorption and Elimination

Carrier-mediated transporters are integral membrane proteins found throughout the body, playing a critical role in regulating cellular uptake and transcellular permeation of a wide range of solutes. These transport processes are either active—requiring energy in the form of ATP—or passive facilitated, which occur along a concentration gradient without ATP input. Despite their differing mechanisms, both types of transporters exhibit saturable kinetics, as each transporter can carry only one molecule at a time.[7–9]

Active transport is further divided into primary-active and secondary-active mechanisms. Primary-active transporters, such as those in the ATP-binding cassette (ABC) superfamily, directly Hydrolyse ATP to translocate substrates across membranes. In contrast, secondary-active transporters (e.g., ion pumps from the solute carrier [SLC] superfamily utilize electrochemical gradients indirectly maintained by ATP. A clinically important subgroup within the SLC family includes the organic anion transporters (OATs), which are essential in drug excretion.[7–9]

Among the ABC superfamily, P-glycoprotein (P-gp)—also known as multidrug resistance protein 1 (MDR1) and encoded by the ABCB1 gene—is the most widely distributed efflux transporter. It is highly expressed in protective tissues such as the liver, kidneys, intestines, testes, and at the blood-brain barrier.[10–12] Other notable members of the ABC transporter family include the cystic fibrosis transmembrane conductance regulator (CFTR), transporter associated with antigen processing (TAP), breast cancer resistance protein (BCRP), and multidrug resistance-associated protein 1 (MRP1)—the latter two often linked to drug resistance in cancerous tissues.[7,10,11]

These transporters play a vital defensive role by outflowing xenobiotic and potentially harmful compounds out of cells. However, many therapeutic agents are also substrates for these proteins. For example, in oncology, anticancer drugs are often expelled from tumour cells, contributing to multidrug resistance and diminished pharmacological efficacy. In the context of oral drug administration, efflux transporters like P-gp actively pump drug molecules back into the intestinal lumen, reducing systemic absorption and consequently lowering bioavailability.[10,11] Therefore, inhibiting ABC transporters has emerged as a promising strategy to enhance the bioavailability and therapeutic response of such substrate drugs.[11,12]

Within the SLC superfamily, the OAT (organic anion transporter) family plays a significant role in renal drug elimination. Key members, OAT1 and OAT3, are located on the basolateral membrane of renal proximal tubule cells, where they mediate the uptake of drugs and metabolites from blood into renal cells, contributing to their tubular secretion and urinary excretion (Figure 1C).[13–15] In contrast, OAT4, located on the apical membrane, facilitates reabsorption of anionic compounds from urine back into circulation.[13,15] As a result, these transporters play a central role in modulating the plasma levels of drugs, particularly those primarily excreted via the kidneys.

Understanding and manipulating the function of carrier-mediated transporters offer opportunities to optimize drug delivery, reduce resistance, and enhance bioavailability, forming a key aspect of modern pharmacokinetic strategies.

Enhancing drug absorption

1. Co-administered fatty meals or oils increase solubility of lipophilic drugs. Fat-soluble vitamins (A, D, E, K), isotretinoin, griseofulvin, etc., show higher absorption with fats via enhanced passive diffusion.
2. Inhibiting Efflux Transporters: Natural supplements like piperine inhibit P-glycoprotein (P-gp), which normally pumps drugs back into the gut lumen. This inhibition allows more drug to passively diffuse into the systemic circulation increasing bioavailability.
3. Avoiding First-pass Metabolism: When drug absorption is rapid and extensive via passive diffusion, it can saturate the liver enzymes, reducing first-pass loss.
4. Improving Lipophilic Prodrugs: Lipid-soluble prodrugs are designed to use passive diffusion efficiently.

Once absorbed, they convert to active drugs, offering higher systemic exposure.

1. Enhancing Uptake of Nutrient-Like Drugs: Drugs structurally similar to nutrients can use these carriers.
   Example: Certain antibiotics and amino acid-based drugs use PEPT1, enhancing absorption.
2. Upregulation of Transporters: Co-administration of some nutrients or herbs may increase expression of transporters.
   Example: Vitamin C upregulates DMT1 (divalent metal transporter) → better iron absorption.
3. Reducing Competition: Some PK strategies involve separating drugs that compete for the same transporter, allowing one to be absorbed more efficiently through facilitated diffusion.
4. Targeted Delivery: Certain drugs are designed to exploit tissue-specific transporters (e.g., OATP in liver) for localized delivery and enhanced effect.

Metabolism

A Key Barrier and Opportunity in Enhancing Drug Bioavailability.

Pre-systemic metabolism represents one of the first major barriers an orally administered drug encounters, occurring primarily in the gastrointestinal tract and the liver before the compound can reach systemic circulation (Figure 1A, B). This process often limits the amount of unchanged drug available for absorption, thereby reducing its bioavailability. However, inhibition of pre-systemic metabolic enzymes can enhance the fraction of unchanged drug reaching the bloodstream, potentially improving therapeutic efficacy.[6]

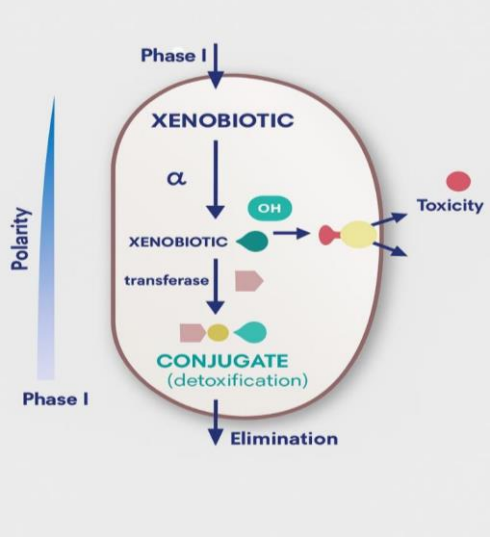
Metabolism in the liver occurs in two distinct phases. Phase 1 metabolism primarily involves oxidation reactions and is predominantly mediated by the cytochrome P450 (CYP450) enzyme family. This superfamily plays a central role in the metabolism of over 60% of clinically used drugs, performing oxidation, reduction, and hydrolysis reactions.[1,4,16,18]. Importantly, the distribution of CYP450 subfamilies varies across tissues. For instance, CYP3A4/5 constitutes approximately 82% of CYP450 enzymes in the small intestine, but only 39% in the liver. In contrast, CYP2C9 accounts for just 13% in the small intestine, but rises to 25% in the liver. Other notable liver-expressed isoforms include CYP2B6 (1%), CYP2D6 (2%), CYP2A6 (6%), CYP2E1 (9%), and CYP1A2 (18%).[4]

Additional enzyme systems contributing to Phase 1 metabolism include flavin-containing monooxygenases (FMOs) and epoxide hydrolases.[17] While CYP450-mediated metabolism typically decreases drug bioavailability, this process is essential for activating prodrugs, in which the metabolite—not the parent compound—is pharmacologically active. Notably, many compounds have been identified as CYP450 inhibitors, which can significantly increase the bioavailability of co-administered drugs that are CYP substrates. Although this may carry a risk of enhanced drug toxicity, it also presents a valuable strategy to improve therapeutic outcomes for drugs that suffer from extensive pre-systemic metabolism.[1,4,16,18]

Following Phase 1, Phase 2 metabolism involves conjugation reactions that increase the water solubility of drug molecules, facilitating their excretion. These reactions include glucuronidation (mediated by uridine 5′-diphospho-glucuronosyltransferases, UGTs), sulfation (by sulfotransferases), methylation (by methyltransferases), N-acetylation (by N-acetyltransferases), and glutathione conjugation (by glutathione-S-transferases).[17]

Among these, UGTs are particularly well-studied and play a central role in the detoxification and elimination of both exogenous compounds and endogenous substances, such as bilirubin, bile acids, and fat-soluble vitamins.[19–22] Many

drugs, as well as dietary phytochemicals, are known substrates for UGT-mediated glucuronidation.[23] Importantly, competitive inhibition of UGT enzymes may lead to increased plasma levels of UGT-metabolized drugs, representing another avenue for beneficial pharmacokinetic interactions and potential improvement in oral bioavailability.



POTENTIAL BENEFICIAL PHARMACOKINETIC INTERACTIONS BETWEEN DRUGS AND OTHER SUBSTANCES

Pharmacokinetic drug interactions often arise from the modulation of specific active transporters and metabolic pathways by co-administered substances. The induction of efflux transporters and metabolic enzymes can lead to reduced plasma concentrations of the affected drug, potentially resulting in sub-therapeutic levels and diminished pharmacological efficacy. Conversely, inhibition of these transporters and enzymes may enhance the bioavailability of the drug, potentially improving therapeutic outcomes—provided that plasma concentrations remain within the therapeutic window. However, excessive inhibition may result in supra-therapeutic plasma levels, increasing the risk of adverse effects and drug toxicity.[24,25] While such interactions are typically unpredictable and may pose significant clinical challenges—including serious or life-threatening outcomes.[4]—they can, under controlled conditions, be strategically employed to optimize therapeutic benefit.

DRUG – DRUG INTERACTIONS

These interactions Increases bioavailability by inhibiting enzymes (CYP3A4) or efflux transporters(P-gp) improving drug absorption that benefits drug to reach blood stream leads to better effect. It also prolongs the half-life by inhibiting metabolism or renal elimination which results in longer duration of action leads to less frequency dosing. This Interactions also benefits by reducing required dose, minimising first pass metabolism and improving drug stability.[26]

1. KETOCONAZOLE AND TACROLIMUS

Ketaconazole plays a crucial role in enhancing the bioavailability of tacrolimus by inhibiting multiple pathways involved in its metabolism and efflux. First, it inhibits intestinal CYP3A4 enzymes located in enterocytes. Under normal conditions, tacrolimus undergoes extensive first-pass metabolism in the intestinal wall via these enzymes, significantly reducing the amount of active drug reaching the blood stream. Ketoconazole acts as a strong competitive inhibitor of CYP3A4 by binding to the haem iron in its active site, forming a reversible coordination complex. This binding prevents the phase 1 oxidation reactions of tacrolimus, such as demethylation and hydroxylation. As a result,

less tacrolimus is metabolised in the intestine, and more of the active drug passes intact into the portal for liver transport.

Secondly, ketoconazole also inhibits hepatic CYP3A4 enzymes, particularly in zone3 hepatocytes of the liver. Normally after absorption, tacrolimus is carried to the liver via portal circulation, where hepatic CYP3A4 enzymes further metabolise it, reducing its systemic availability. By inhibiting these hepatic enzymes, ketoconazole reduces the metabolic clearance of tacrolimus, resulting in less metabolism and higher plasma concentration and prolonged elimination half-life. This leads to a reduced frequency of dosing.

Thirdly, ketoconazole inhibits the activity of intestinal P-glycoprotein (P-gp), an ATP dependent efflux pump located on the apical membrane of intestinal epithelial cells. Under normal conditions, P-gp actively exports tacrolimus from the enterocytes back into the intestinal lumen, thereby reducing net drug absorption. Ketoconazole inhibits P-gp through two main mechanisms: ATPase inhibition mechanism involves blocking the hydrolysis of ATP, which is necessary for P-gp to transport substrates. This halts the transport activity of P-gp. In the confirmational interference mechanism, ketoconazole binds to the transmembrane domains of P-gp, altering its structure and preventing substrate binding or movement. These actions result in more tacrolimus remaining within the enterocytes and enhance its passive diffusion into the portal circulation.[27,28]

2. SAQUINAVIR AND RITONAVIR

Mechanism

Saquinavir, an antiretroviral protease inhibitor used in the treatment of HIV, undergoes extensive first pass metabolism primarily via the hepatic cytochrome P450 3A4 (CYP3A4) enzyme. This extensive metabolism results in a very low oral bioavailability of less than 4%, along with rapid clearance from the body and a short elimination half-life. Consequently, when administered alone, saquinavir achieves sub-therapeutic plasma concentrations, limiting its clinical effectiveness.

To overcome these pharmacokinetic limitations, saquinavir is often co-administered with ritonavir, another protease inhibitor that serves as a potent inhibitor of both CYP3A4 and the efflux transporter P-glycoprotein. Ritonavir's inhibitory action significantly reduces the metabolism and efflux of saquinavir, thereby enhancing its systemic exposure. This combination leads to increased oral bioavailability, prolonged half-life, reduced clearance and higher more sustained concentrations of saquinavir, ultimately improving its therapeutic efficacy in HIV treatment.[29,30]

Parameters	Without ritonavir	With ritonavir
CYP3A4 activity	Normal (active)	Inhibited
Saquinavir clearance	High	Low
Bioavailability	Poor	Significantly improved
Half life	Short(1-2hrs)	Longer(5-7hrs)
Plasma concentration	Low	High

3. CYCLOSPORIN AND DILTIAZEM

Mechanism of Interaction

Cyclosporin is a calcineurin inhibitor used as an immunosuppressant, especially in organ transplantation, and it is primarily metabolized by the hepatic enzyme cytochrome P450 3A4 (CYP3A4). Additionally, it is a known substrate of P-glycoprotein (P-gp), an efflux transporter found in the intestinal epithelium, liver, and kidney that actively pumps

drugs out of cells, thereby reducing their absorption and promoting elimination. Diltiazem, a calcium channel blocker, exhibits potent inhibitory effects on both CYP3A4 and P-gp. When co-administered, diltiazem inhibits the activity of CYP3A4 in the liver, thereby slowing the metabolism of cyclosporin and prolonging its half-life. Simultaneously, by inhibiting intestinal P-gp, diltiazem decreases the efflux of cyclosporin back into the gastrointestinal tract, which enhances its oral bioavailability. These dual inhibitory effects lead to significantly increased systemic exposure of cyclosporin.

As a result, a lower dose of cyclosporin is needed to achieve and maintain therapeutic plasma concentrations, thereby reducing drug costs and minimizing the risk of nephrotoxicity and other dose-related adverse effects. Clinically, this interaction is often intentionally utilized to improve cost-efficiency, especially in long-term transplant therapy, and to achieve better control over immunosuppressive regimens. However, close monitoring of cyclosporin levels is essential to avoid toxicity due to its narrow therapeutic index.[31,32]

4. LOPERAMIDE AND QUINIDINE

Loperamide is an anti-diarrheal agent that functions as a peripheral opioid receptors agonist, primarily acting on the gastrointestinal (GI) tract to reduce intestinal motility. Although it is structurally similar to other opioids, loperamide doesn't typically produce central nervous system effects such as euphoria or respiratory depression. This is because it is a substrate for p-glycoprotein, an efflux transporter highly expressed at the blood-brain barrier. After oral administration and systemic absorption, any loperamide attempting to cross into the CNS is actively pumped back into the circulation by P-gp, there by restricting its action to the periphery.

However, when loperamide is co-administered with quinidine, a class 1 anti-arrhythmic agent and a potent P-gp inhibitor, a significant pharmacokinetic drug-drug interactions occurs. Quinidine inhibits P-gp at the BBB, which allows loperamide to penetrate the CNS more effectively. This can lead to central opioid effects, including the potential for euphoria and respiratory depression, which are not observed with loperamide alone. Additionally, quinidine may also inhibit intestinal P-gp, further increasing the absorption and systemic bioavailability of loperamide. This interaction exemplifies a beneficial pharmacokinetic modulation in certain research or clinical contexts, but it also highlights the potential for serious adverse effects if not properly monitored.[33]

5. PENICILLIN AND PROBENECID

Penicillin is primarily eliminated from the body through renal excretion and undergoes minimal metabolism. Its clearance is mainly facilitated by active tubular secretion in the proximal tubule of the kidney, Involving transport via organic anion transporter 1(OAT1) on the basolateral membrane and either multi drug resistance- associated protein 2(MRP2) or organic anion transporter 4 (OAT4) on the apical membrane. Penicillin enters the renal tubular cells from the blood stream via OAT1 and is then secreted into the urine through MRP2 or OAT4, leading to rapid clearance and a short plasma half-life of approximately 30-60min.

When probenecid, a potent inhibitor of OAT1 and especially OAT3(the main transporter for penicillin), is co-administered, it competitively inhibits these transporters on the basolateral side of the tubular cells. These prevents the uptake of penicillin from the blood into the tubular cells, thereby significantly reducing its secretion into the urine. While glomerular filtration of penicillin still occurs, active tubular secretion accounts for around 80% of its elimination,

so this inhibition substantially decreases renal clearance. As a result, the plasma concentration of penicillin increases, its duration of action is prolonged, and overall therapeutic effectiveness is enhanced.

Pharmacokinetically these interactions lead to increase in the peak plasma concentration, AUC and elimination of life(t1\2) of penicillin. These changes enhance the drug's exposure and efficacy without the need to increase its dosage. Clinically, these beneficial PK drug-drug interaction is purposefully employed to extend the therapeutic duration of penicillin, reduce dosing frequency, and improve treatment outcomes for infections such as gonorrhoea syphilis and streptococcal diseases.it is also used to enhance the duration of intramuscular penicillin formulations such as benzathine penicillin, by co0administation with probenecid.[34,35]

6. LAMOTRIGINE AND VALPROIC ACID

Lamotrigine, an antiepileptic drug commonly used for treating seizures and bipolar disorder, is primarily eliminated from the body through phase II metabolism in the liver via N-glucuronidation. This metabolic process is catalyzed by the enzyme UGT1A4 (Uridine 5'-diphospho-glucuronosyltransferase 1A4), which converts lamotrigine into an inactive glucuronide conjugate that is subsequently excreted by the kidneys. Under normal circumstances, this pathway ensures efficient clearance of lamotrigine from the body.

However, when lamotrigine is co-administered with valproic acid (VPA), a known inhibitor of several UGT enzymes, including UGT1A4 and UGT2B7, a significant pharmacokinetic interaction occurs. Valproic acid acts as a competitive inhibitor by occupying the active site of the UGT enzymes, thereby reducing the metabolism of lamotrigine. This inhibition leads to decreased glucuronidation and, consequently, reduced clearance of lamotrigine from the body.

As a result, lamotrigine accumulates in the plasma, leading to increased plasma concentrations, an elevated area under the concentration–time curve (AUC), and a prolonged elimination half-life—from approximately 25–30 hours to as much as 60 hours. This means lamotrigine remains in the body for a longer duration, enhancing its therapeutic effect. However, due to this interaction, a lower initial dose of lamotrigine is required when it is given alongside valproic acid to avoid potential toxicity. Clinically, this interaction can be beneficial, as it allows therapeutic levels of lamotrigine to be achieved without increasing the dose, making it particularly useful in managing conditions such as partial seizures and bipolar disorder—though careful dose adjustments and monitoring are essential to prevent adverse effects.[36,37]

7. ATAZANAVIR AND COBICISTAT

Atazanavir, an antiretroviral protease inhibitor used in the treatment of HIV, is primarily metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme. Without metabolic inhibition, atazanavir is rapidly broken down, resulting in low oral bioavailability and reduced therapeutic effectiveness. To overcome this limitation, cobicistat—a potent mechanism-based (suicide) inhibitor of CYP3A4—is co-administered. Cobicistat irreversibly binds to the haem group of the CYP3A4 enzyme in hepatocytes, thereby preventing the oxidative metabolism of atazanavir (including reactions like dealkylation and hydroxylation). This inhibition significantly reduces the hepatic clearance of atazanavir, leading to increased plasma concentrations, prolonged half-life, and a higher area under the concentration-time curve (AUC).
In addition to its hepatic effects, cobicistat also acts within the gastrointestinal tract to improve atazanavir absorption. In the enterocytes of the small intestine, atazanavir is subject to first-pass metabolism and efflux by both intestinal CYP3A4 enzymes and P-glycoprotein (P-gp) transporters. Cobicistat inhibits both of these mechanisms—reducing intestinal metabolism and preventing atazanavir from being pumped back into the intestinal lumen. As a result, oral

bioavailability and systemic drug exposure are significantly enhanced. Notably, cobicistat itself possesses no intrinsic antiviral activity, distinguishing it from ritonavir. Its sole purpose is pharmacokinetic enhancement, thereby minimizing the risk of HIV resistance or unwanted interactions with viral targets.[38,39]

8. DIGOXIN AND OMEPRAZOLE

Digoxin, a cardiac glycoside used in the management of heart failure and arrhythmias, is a weak base that is primarily absorbed in the upper small intestine through passive diffusion. Its absorption is significantly influenced by gastric pH. While digoxin remains chemically stable in acidic environments, excessive acidity can lead to increased ionization, which decreases its lipid solubility and limits its ability to cross intestinal membranes. Furthermore, high acidity may upregulate the activity of P-glycoprotein (P-gp), an efflux transporter that reduces digoxin absorption by actively pumping it back into the intestinal lumen.

When co-administered with omeprazole, a proton pump inhibitor that blocks the H^+/K^+ ATPase in gastric parietal cells, gastric acid secretion is reduced, thereby increasing the pH of the stomach. This decrease in acidity reduces the ionization of digoxin, promoting its lipophilic form and enhancing its dissolution and absorption in the intestine. Additionally, omeprazole inhibits intestinal P-gp, either by non-competitive inhibition or downregulation of its expression, further increasing digoxin absorption by limiting its efflux. Although digoxin undergoes minimal hepatic metabolism, omeprazole may also slightly reduce first-pass elimination by inhibiting hepatic transporters or reducing biliary excretion, contributing to a modest rise in systemic drug levels. Overall, these combined effects result in enhanced bioavailability and higher plasma concentrations of digoxin.[40]

9. PIPERINE AND CURCUMIN

Piperine enhances the bioavailability of curcumin through multiple pharmacokinetic mechanism. Firstly, it inhibits key drug-metabolising enzymes, specifically hepatic and intestinal cytochrome P450 enzymes such as CYP3A4 and CYP1A1, which are involved in the phase1 metabolism of curcumin. This inhibition reduces the extent of first pass metabolism, thereby increasing the systemic availability of curcumin. Secondly, piperine interferes with phase2 metabolism by inhibiting UDP-glucuronosyltransferase (UGT) enzymes responsible for converting curcumin into its inactive, water-soluble metabolite, curcumin glucuronide. This slows the elimination of curcumin via bile and urine. Additionally, piperine inhibits the intestinal efflux transporters like P-gp, which normally pump curcumin back into the intestinal lumen, thus allowing for greater absorption. Beyond these metabolic effects, piperine also enhances GI absorption by altering membrane dynamics-specifically by increasing membrane fluidity and intestinal permeability-thereby facilitating greater uptake of curcumin through the intestinal epithelium.[40,41,42]

DRUG FOOD INTERACTIONS

Drug food interactions occur when the presence of food alters the absorption, metabolism, distribution and excretion. These are interactions where food intake positively influences one or more pharmacokinetic processes such as increased absorption of poorly soluble drugs, increased bioavailability by reducing metabolism, increased stability of drug in GI tract and increased plasma drug levels, leading to improved therapeutic response.[43]

1. SAQUINAVIR+HIGH-FAT MEAL

When Saquinavir is taken with a high-fat meal, it significantly enhances the drug's pharmacokinetic profile and therapeutic efficacy. The systemic absorption of Saquinavir increases dramatically, with plasma drug concentrations

rising up to three times higher compared to when taken in a fasting state. This enhanced bioavailability ensures that therapeutic plasma levels are achieved more consistently, thereby improving its effectiveness in suppressing HIV replication. Additionally, food intake reduces intra-patient variability in plasma drug concentrations, making the response to treatment more predictable. The improved absorption may also allow for dose optimization, potentially enabling lower dosages, minimizing adverse effects, and reducing treatment costs. The underlying mechanism involves several factors. Saquinavir is a lipophilic protease inhibitor with poor water solubility, resulting in very low bioavailability (about 4%) when taken on an empty stomach. However, a high-fat meal stimulates the secretion of bile acids from the gallbladder, which emulsify dietary fats and aid in the solubilization of lipophilic drugs like Saquinavir. This results in the formation of colloidal mixed micelles that disperse the drug effectively in the gastrointestinal tract. The fat content also promotes micelle formation, which protects the drug from degradation and facilitates its absorption through intestinal cells via transcellular diffusion. Furthermore, high-fat meals delay gastric emptying, prolonging the drug's residence time in the upper small intestine, the main site of absorption, thereby maximizing its uptake. Finally, fat in the intestine supports the formation of chylomicrons, into which Saquinavir dissolves. These chylomicrons are absorbed through the intestinal lymphatic system, allowing the drug to bypass first-pass metabolism in the liver and enter systemic circulation in higher concentrations.[44]

2. ISOTRETINION+HIGH FAT MEAL

When Isotretinoin is taken with a high-fat meal, its absorption and bioavailability significantly increase, leading to improved therapeutic outcomes, particularly in the treatment of severe acne. The presence of dietary fat enhances systemic exposure to the drug, ensuring more consistent and adequate plasma concentrations. This reduces inter-individual variability and helps maintain therapeutic levels, making the treatment more effective. The mechanism behind this interaction involves several steps. Isotretinoin, a highly lipophilic compound (13-cis-retinoic acid), is poorly soluble in water, and when taken on an empty stomach, its absorption is erratic and often sub therapeutic. A high-fat meal stimulates the gallbladder to release bile acids into the duodenum, which play a crucial role in the solubilization of lipophilic drugs. Bile acids form micelles that encapsulate isotretinoin, increasing its solubility in intestinal fluids. These micelles enhance the drug's surface area and improve its ability to pass through the intestinal mucosa. Once in micellar form, isotretinoin can more easily penetrate the intestinal epithelial membrane via passive diffusion or lipid transport mechanisms, leading to greater absorption in the small intestine. Additionally, high-fat meals delay gastric emptying, allowing isotretinoin to remain longer in the upper gastrointestinal tract, primarily the duodenum and jejunum, where absorption is most efficient. Furthermore, the fat content in the meal promotes the formation of chylomicrons in the intestines. As a lipophilic drug, isotretinoin dissolves into these chylomicrons, which are then absorbed into the lymphatic system. This route bypasses hepatic first-pass metabolism, resulting in enhanced systemic bioavailability.[45]

3. GRISEOFULVIN + FATTY FOOD INTERACTION

When Griseofulvin is administered with a fatty meal, its absorption significantly improves, leading to increased bioavailability and enhanced systemic exposure. This effect is particularly beneficial in treating fungal infections of the skin, nails, and hair, where high tissue concentrations are necessary. By ensuring adequate drug levels in the body, the risk of treatment failure due to sub-therapeutic concentrations is greatly reduced. The underlying mechanism involves several key steps. Griseofulvin is a lipophilic antifungal agent with poor water solubility, which limits its dissolution and absorption in the gastrointestinal tract when taken on an empty stomach. In fasting conditions, the drug's

bioavailability is low and inconsistent. However, ingestion of a fatty meal stimulates bile secretion from the gallbladder. Bile salts aid in the emulsification of dietary fats and also assist in dissolving lipophilic drugs such as Griseofulvin. These bile salts, together with lipids, form micelles that encapsulate the drug, increasing its solubility in intestinal fluids and enhancing its absorption through the gut wall. Furthermore, the fatty environment improves the wetting and dispersion of Griseofulvin particles, creating a greater concentration gradient that facilitates passive diffusion across the intestinal membrane. Fatty meals also slow gastric emptying, allowing more time for the drug to remain in the upper gastrointestinal tract, where absorption is most efficient. Additionally, although to a lesser extent, Griseofulvin may be absorbed into the intestinal lymphatic system through chylomicron formation, thereby partially bypassing first-pass hepatic metabolism and contributing further to its systemic availability.[46]

4. ATOVAQUONE+ FOOD (especially high fat meal)

When Atovaquone is taken with food, especially high-fat meals, its oral bioavailability increases by more than two-fold. This enhancement significantly improves its therapeutic efficacy in treating infections such as Pneumocystis jiroveci pneumonia and malaria, while also reducing the likelihood of treatment failure due to sub-therapeutic drug levels. The mechanism behind this effect is largely due to Atovaquone's extreme lipophilicity and poor water solubility, which make it difficult to absorb when taken on an empty stomach. A high-fat meal stimulates the secretion of bile salts from the gallbladder. These bile salts emulsify dietary fats and aid in dissolving lipophilic drugs like Atovaquone. This leads to the formation of micelles, tiny lipid-bile salt complexes that encapsulate Atovaquone and significantly enhance its solubility in the intestinal fluids. The presence of these micelles increases the concentration of the drug available for absorption and facilitates its passive diffusion across the intestinal epithelium. Additionally, some Atovaquone molecules are absorbed via chylomicron formation into the intestinal lymphatic system. This lymphatic transport route bypasses the hepatic first-pass metabolism, allowing a greater portion of the drug to reach systemic circulation and thus improving its overall bioavailability.[47]

5. FELODIPINE+GRAPE FRUIT JUICE

When Felodipine is taken with grapefruit juice, its plasma concentration significantly increases, leading to an enhanced blood pressure-lowering effect. While this might improve therapeutic outcomes, it also raises the risk of adverse effects such as hypotension, headache, and flushing. This interaction is primarily due to the inhibition of intestinal CYP3A4 enzymes by compounds present in grapefruit juice. Felodipine is extensively metabolized by CYP3A4 enzymes located in the intestinal wall during first-pass metabolism, which substantially reduces its systemic availability. Grapefruit juice contains furanocoumarins, such as bergamottin, which irreversibly inhibit these CYP3A4 enzymes. As a result, the metabolism of Felodipine is significantly reduced, allowing more of the drug to enter systemic circulation. Although this increases its bioavailability and therapeutic efficacy, it also raises the risk of excessive drug levels and associated side effects, making this a clinically important food-drug interaction.[48]

6. CYCLOSPORINE+GRAPE FRUIT JUICE

When Cyclosporine is taken with grapefruit juice, there is a significant increase in its systemic exposure, as reflected by a higher AUC (Area under the Curve). This interaction can be therapeutically beneficial, particularly in transplant patients who require strong immunosuppression. However, due to Cyclosporine's narrow therapeutic index, this effect necessitates careful dose adjustment and monitoring to avoid toxicity. Cyclosporine is a substrate of the enzyme CYP3A4 and undergoes extensive first-pass metabolism in both the intestine and liver, which limits its bioavailability.

Grapefruit juice contains compounds that inhibit intestinal CYP3A4 enzymes, reducing the metabolism of Cyclosporine in the gut wall and thereby increasing the amount of drug that reaches systemic circulation. Additionally, grapefruit juice also inhibits P-glycoprotein (P-gp), an efflux transporter that pumps drugs like Cyclosporine back into the intestinal lumen. Inhibiting P-gp further enhances the net absorption of Cyclosporine. As a result, plasma levels of the drug rise, leading to a stronger immunosuppressive effect. While this can be advantageous if managed properly, it also poses a risk of serious side effects such as nephrotoxicity if not carefully monitored.[49]

7. CARBAMAZEPINE+GRAPE FRUIT JUICE

Carbamazepine undergoes extensive first-pass metabolism by the CYP3A4 enzyme located in both the intestinal wall and liver, which significantly reduces its oral bioavailability. When grapefruit juice is consumed alongside Carbamazepine, a notable interaction occurs due to the presence of furanocoumarins such as bergamottin in the juice. These compounds irreversibly inhibit CYP3A4 enzymes in the intestinal lining. After oral administration, Carbamazepine enters the intestinal lumen, where under normal circumstances, a substantial portion is metabolized by CYP3A4 enzymes in the enterocytes before it can reach systemic circulation. However, when grapefruit juice is present, this enzyme activity is inhibited, resulting in less pre-systemic metabolism of the drug. Consequently, a greater amount of active Carbamazepine enters the portal vein and ultimately reaches the bloodstream. This leads to enhanced bioavailability and increased systemic drug levels, which may improve therapeutic outcomes but also necessitate caution due to the potential for toxicity.[50]

8. LOPINAVIR \ RITONAVIR+HIGH FAT FOOD

Lopinavir, an anti-retroviral drug, has poor oral bioavailability due to its low solubility and extensive first-pass metabolism by the enzyme CYP3A4. To overcome this, it is co-administered with Ritonavir, a potent CYP3A4 inhibitor, which enhances Lopinavir levels in the bloodstream. When taken with a high-fat meal, the absorption of Lopinavir is further improved due to physiological changes in the gastrointestinal tract that favor the uptake of lipid-soluble drugs. A high-fat meal stimulates the secretion of bile salts, which aid in the emulsification of dietary fats and facilitate the formation of micelles. These micelles encapsulate Lopinavir, significantly increasing its solubility and surface area in intestinal fluids. This enhances the drug's dissolution and promotes better absorption through the intestinal lining. Additionally, the presence of food slows gastric emptying, thereby prolonging the drug's exposure to the absorptive surfaces of the small intestine. Meanwhile, Ritonavir plays a crucial role by inhibiting CYP3A4, reducing the first-pass metabolism of Lopinavir. As a result, the combined effects of improved dissolution, prolonged absorption time, and reduced metabolic degradation lead to a substantial increase in the bioavailability of Lopinavir when taken with high-fat food.[51]

9. ITRACONAZOLE CAPSULE+ACIDIC FOOD\COLA

Itraconazole capsules require an acidic environment in the stomach for optimal dissolution, as their solubility is highly pH-dependent. In an acidic gastric pH, the capsule dissolves efficiently, allowing the drug to pass into the duodenum where it is absorbed into the bloodstream. However, in non-acidic conditions, such as when a patient is taking proton pump inhibitors (PPIs) or antacids and the capsule fails to dissolve properly, leading to reduced absorption and decreased therapeutic efficacy. Acidic foods or beverages, such as cola, can lower gastric pH and mimic an acidic environment, thereby enhancing the dissolution of Itraconazole capsules. Once dissolved, the drug is more readily absorbed in the intestines, resulting in higher systemic concentrations. This food-drug interaction significantly

improves the bioavailability of Itraconazole and ensures more consistent therapeutic outcomes, particularly in patients who may otherwise have low stomach acidity.[52]

10. TACROLIMUS+GRAPE FRUIT JUICE

Tacrolimus, an immunosuppressant drug, is a substrate for both the CYP3A4 enzyme and the P-glycoprotein (P-gp) efflux transporter, which together significantly reduce its oral bioavailability. After oral administration, a portion of tacrolimus is metabolized by CYP3A4 in the intestinal lining, while another portion is actively pumped back into the intestinal lumen by P-gp, limiting the amount of drug that reaches systemic circulation. When grapefruit juice is consumed alongside tacrolimus, it inhibits both of these barriers to absorption. The furanocoumarins present in grapefruit juice block intestinal CYP3A4 activity, reducing the metabolic breakdown of tacrolimus in enterocytes. Simultaneously, grapefruit juice inhibits P-gp, decreasing the efflux of the drug back into the gut. As a result, more intact tacrolimus is able to cross the intestinal wall and enter the bloodstream. This dual inhibition significantly increases the drug's plasma concentration and enhances its bioavailability, necessitating careful monitoring to avoid toxicity due to elevated systemic levels.[53]

11. RIBAVIRIN+HIGH FAT MEAL

Ribavirin exhibits low and variable oral bioavailability when taken on an empty stomach, with absorption averaging around 30%. However, its bioavailability significantly increases when administered with a high-fat meal, reaching approximately 70%. This improvement is due to several physiological changes induced by dietary fat that enhance the drug's solubility and absorption. High-fat meals stimulate the secretion of bile acids, which aid in the solubilization of ribavirin in the gastrointestinal tract. Additionally, fat slows gastric emptying, allowing the drug to remain in contact with the absorptive surfaces of the small intestine for a longer duration. High-fat meals also increase intestinal blood flow, which facilitates greater drug uptake into systemic circulation. As a result, more ribavirin is absorbed before undergoing first-pass metabolism, leading to significantly enhanced bioavailability and more consistent therapeutic effects.[54]

12. NITROFURANTOIN+FOOD

Nitrofurantoin is better absorbed when taken with food, particularly when consumed alongside a full meal. Food intake enhances the drug’s dissolution in the gastrointestinal tract and also helps reduce gastrointestinal irritation, which is a common side effect of Nitrofurantoin. The mechanism behind this improvement involves several food-induced physiological changes. Food increases bile flow, which enhances the solubility of the drug. It also slows gastric emptying, allowing Nitrofurantoin to remain longer in the stomach and intestines, thus providing more time for absorption. Additionally, food improves blood flow to the gastrointestinal tract, facilitating more efficient drug uptake. These factors together promote enhanced passive diffusion of Nitrofurantoin across the intestinal wall. As a result, its bioavailability increases by approximately 40–50% when taken with food, leading to more effective therapeutic outcomes.[55]

13. FENOFIBRATE+HIGH FAT MEAL

Fenofibrate is a lipophilic (fat-soluble) drug with poor water solubility, which limits its absorption in the fasting state. This reduced absorption is primarily due to minimal bile salt secretion and the lack of emulsification needed for the dissolution of fat-soluble drugs. However, when taken with a high-fat meal, the bioavailability of fenofibrate significantly improves through several physiological mechanisms. High-fat meals stimulate the secretion of bile acids,

which are essential for solubilizing lipophilic drugs like fenofibrate. These bile acids facilitate the formation of micelles, which encapsulate the drug and enhance its dissolution and absorption in the intestine. Additionally, the digestion of fats promotes lymphatic transport—a route that allows fenofibrate to bypass first-pass hepatic metabolism and enter systemic circulation more efficiently. High-fat meals also increase splanchnic blood flow due to post-meal vasodilation, which further enhances drug uptake from the gastrointestinal tract. It is important to note that the extent of this food effect may vary depending on the formulation of fenofibrate. Older formulations, such as standard or micronized tablets, rely heavily on high-fat meals for optimal absorption. Newer formulations, including nanoparticle-based versions or fenofibrate choline salt, are less dependent on dietary fat but may still experience improved absorption when taken with food. Therefore, co-administration with a high-fat meal is generally recommended to maximize the therapeutic efficacy of fenofibrate, especially with older formulations.[56]

14. DIGOXIN+HIGH FIBER MEAL

When digoxin is taken with a meal rich in dietary fibre . Such as oats, fruits, or vegetables, its absorption profile changes significantly. Soluble fibre, like psyllium, forms a gel-like matrix in the gastrointestinal tract, and some digoxin molecules become adsorbed onto this matrix. This binding action slows the immediate absorption of the drug in the upper intestine, leading to a more gradual and sustained release. Instead of causing a rapid spike in plasma concentration, digoxin is slowly released from the fiber matrix, which helps in preventing peak-level toxicity, particularly important for patients sensitive to fluctuations in digoxin levels. As a result, the peak plasma concentration (Cmax) is reduced, which can be beneficial for long-term therapy by maintaining stable therapeutic levels. This flattening of the pharmacokinetic curve leads to fewer fluctuations in drug levels, reducing the likelihood of side effects such as nausea and visual disturbances, and improving overall patient tolerance. Additionally, consistent intake of dietary fiber with digoxin may offer a protective effect; in cases of accidental overdose or sudden dose increase, fiber can buffer absorption and reduce the risk of toxic plasma spikes. This interaction highlights the role of dietary fiber in modulating drug absorption and maintaining more consistent and safer drug levels over time.[57]

15. POSACONAZOLE+HIGH FAT MEAL

When posaconazole, particularly in its oral suspension form, is taken with a high-fat meal such as one containing cheese, eggs, or butter—its absorption and systemic availability significantly improve. The presence of fat in the meal stimulates the gallbladder to release bile acids, which are essential for the solubilization of lipophilic drugs like posaconazole. These bile acids promote the formation of mixed micelles, which greatly enhance the drug's solubility in the gastrointestinal (GI) tract and create an optimal environment for absorption. Posaconazole, being a lipophilic compound with low water solubility, benefits from this micellar solubilization process. The mixed micelles encapsulate the drug, increasing its dissolution and facilitating better absorption. Additionally, high-fat meals slow gastric emptying, prolonging the retention of the drug in the stomach and duodenum. This extended duration in the upper GI tract-the primary site of posaconazole absorption, allows more time for the drug to dissolve and be absorbed. As a result, intestinal absorption is enhanced, and more posaconazole molecules are able to passively diffuse across the intestinal lining into systemic circulation. This leads to significantly higher plasma concentrations, with the peak concentration (Cmax) increasing up to threefold and the overall drug exposure (AUC) increasing up to fourfold compared to fasting conditions. Such improvements in bioavailability translate into better antifungal efficacy, making the co-administration of posaconazole with a high-fat meal a critical consideration for optimizing therapeutic outcomes.[58]

16. FERROUS SULPHATE+VITAMIN C RICH FOOD

When ferrous sulphate (iron) is taken orally along with vitamin C-rich foods or drinks. Such as citrus fruits, amla, or lemon water, its oral bioavailability is significantly enhanced. This combination leverages the biochemical properties of vitamin C (ascorbic acid) to improve iron absorption in the gastrointestinal tract, ultimately leading to better correction of iron deficiency. Vitamin C plays a key role by acidifying the gastric environment, lowering the stomach's pH. This acidic environment maintains iron in its reduced ferrous (Fe^{2+}) form and prevents its oxidation to the ferric (Fe^{3+}) form, which is poorly absorbed. Additionally, vitamin C acts directly as a reducing agent, converting ferric iron (Fe^{3+}), present in many dietary sources, into the more absorbable ferrous form (Fe^{2+}). Only ferrous iron can be efficiently transported across the intestinal mucosa, making this conversion essential for effective absorption. Moreover, ascorbic acid forms soluble iron-ascorbate complexes with ferrous iron. These complexes remain stable in the acidic conditions of the stomach, prevent precipitation, and enhance solubility in the intestinal lumen. Once in the intestine, these soluble iron complexes or free ferrous ions are absorbed through the apical membrane of enterocytes via the Divalent Metal Transporter 1 (DMT1). As a result, more absorbable ferrous iron enters the bloodstream, leading to increased peak plasma concentrations (Cmax) and overall drug exposure (AUC). This improved bioavailability supports more effective treatment of iron deficiency and anaemia.[59]

17. LOVASTATIN+EVENING MEAL

When lovastatin is taken with an evening meal, its oral bioavailability significantly increases, resulting in improved therapeutic outcomes. Evening administration is particularly beneficial because it aligns with the body's natural peak in cholesterol synthesis, which occurs during night time, thereby enhancing the drug's cholesterol-lowering efficacy. Lovastatin is a pro-drug in its inactive lactone form and requires conversion in the liver to its active β-hydroxy acid form. Therefore, greater absorption ensures that more of the drug reaches the liver for activation. Lovastatin is a highly lipophilic compound with poor water solubility. When taken with food, especially a meal containing moderate fat, bile acid secretion is stimulated. These bile acids aid in solubilizing lovastatin by forming micelles in the gastrointestinal (GI) tract, which significantly enhances its dissolution. Additionally, food slows gastric emptying, increasing the residence time of lovastatin in the upper intestine, which is the primary site for its absorption. This extended contact time allows for more effective dissolution and absorption of the drug. The improved solubility and micelle formation facilitate increased passive diffusion of lovastatin across the intestinal mucosa. As a result, a higher concentration of the pro-drug enters the portal circulation and is transported to the liver. Since lovastatin is mainly activated in the liver, this increased delivery enhances its conversion to the active β-hydroxy acid form. Ultimately, this leads to more effective inhibition of HMG-CoA reductase, the key enzyme in cholesterol synthesis, thereby maximizing the lipid-lowering effect of the drug.[60]

18. VALPROIC ACID+FOOD

When valproic acid is taken with food, particularly high-fat meals, several beneficial pharmacokinetic and tolerability effects occur. Firstly, food delays gastric emptying, which is especially advantageous for delayed-release or enteric-coated formulations. This slower gastric transit allows for more complete dissolution of the drug, leading to steadier plasma concentrations and reducing peak-trough fluctuations. Such stability in drug levels enhances therapeutic consistency and effectiveness. Secondly, valproic acid is a lipophilic compound, and fatty meals may promote the formation of micelles in the gastrointestinal tract. These micelles enhance the solubilization and absorption of the drug, resulting in a slight increase in its bioavailability. Thirdly, food serves as a physical buffer in the stomach, helping to

reduce the gastrointestinal irritation often associated with the acidic nature of valproic acid. This buffering effect improves tolerability and encourages better patient compliance with the medication. Finally, for extended-release or enteric-coated valproate formulations, food-induced delay in gastrointestinal transit provides additional time for the drug to be released and absorbed effectively. This contributes to more sustained drug levels over time, ensuring more consistent therapeutic outcomes and minimizing fluctuations in plasma drug concentration.[61]

CONCLUSION

The exploration of beneficial pharmacokinetic (PK) interactions between drugs and with food represents an evolving frontier in therapeutic optimization. While drug interactions are often viewed with caution due to their potential for toxicity or therapeutic failure, emerging evidence demonstrates that under controlled conditions, certain interactions can significantly improve drug absorption, prolong systemic exposure, and enhance overall clinical efficacy. These advantageous outcomes arise from deliberate manipulation of pharmacokinetic parameters—absorption, distribution, metabolism, and excretion (ADME) through co-administration with specific drugs, foods, or supplements.

Several mechanisms underlie these beneficial effects. Inhibition of metabolic enzymes like cytochrome P450 isoforms (CYP3A4, CYP2C9) and Phase II enzymes such as UGTs leads to reduced pre-systemic and hepatic metabolism, allowing a higher proportion of the active drug to reach systemic circulation. Co-administration of enzyme inhibitors (e.g., ritonavir, cobicistat, ketoconazole) is a well-established strategy in antiretroviral and immunosuppressive therapy. Similarly, inhibition of efflux transporters like P-glycoprotein (P-gp), which would otherwise pump drugs out of enterocytes or across the blood-brain barrier, enhances net drug absorption. Natural bioenhancers such as piperine and grapefruit juice exemplify this approach in both herbal and pharmaceutical practice.

Drug–food interactions, particularly with high-fat meals, play a central role in improving the solubility and absorption of lipophilic, poorly water-soluble drugs. Enhanced bile secretion, delayed gastric emptying, micelle formation, and lymphatic transport collectively contribute to increased bioavailability. Examples include isotretinoin, griseofulvin, atovaquone, and saquinavir, all of which show significantly improved pharmacokinetic profiles when administered with fatty meals. In many cases, these interactions also reduce pharmacokinetic variability and improve patient adherence through more predictable responses and longer dosing intervals.

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