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To Study Food Drug Interaction: Mechanisms, Challenges And Solutions

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ABSTRACT

Medications are essential for treating various health issues, but their efficacy and safety can be influenced through drug-food interactions. The pharmacokinetics of drugs may be changed by these reactions. (absorption, distribution, metabolism, and elimination) and pharmacodynamics, posing risks of adverse effects or diminished therapeutic outcomes. Factors such as age, gender, medical conditions, and polypharmacy increase the likelihood of such interactions. Grapefruit, oranges, berries, and other foods are known to modify enzymes like cytochrome P450, impacting drug metabolism. The document emphasizes the importance of raising awareness among healthcare professionals regarding these interactions to optimize therapeutic outcomes. It also discusses the role of healthcare professionals in managing drug-food interactions effectively through patient education and improved clinical practices.

Keywords – Food Drug Interaction, Adverse Effect, Pharmacokinetics,Pharmacodynamics,Cytochrome P450 Enzymes,Medication.

INTRODUCTION

Medications can be employed to manage and resolve a wide range of health concerns. They must be taken exactly as prescribed in order to ensure their safety and effectiveness. Drugs should have highly precise effects, be consistent for all patients, be constant in efficacy, be fully not harmful at whatever dosage, be unaffected by diet or other prescriptions, and only require one dose to provide a long-lasting cure.

A lot of medications contain potent components that have various effects on the body. Lifestyle choices and diet can occasionally have a big influence on drug use. (1) An interaction that results from a biological, chemical, physiological, or pathophysiologic connection between a drug and one or more nutrients, food in general, or dietary intake is another way to define a medication-nutrient interaction. A food-drug interaction can make a medication not perform as intended or can make a medication side effect worse or better. It may also result in a new adverse consequence. (2)

Pharmacokinetics (absorption, distribution, metabolism, and excretion and pharmacodynamics are associated with the most detailed food-drug interactions. These reactions can include, among other things, modifications to transporters like P-glycoprotein, enzymatic activation or inhibition in drug metabolization (such as cytochrome P450), and variations in absorption and bioavailability throughout the gastrointestinal tract. A number of publications stressed the significance of raising stakeholder awareness regarding this health concern, as food-drug interactions provide a significant risk of unpleasant reactions. It has been determined and explained that the interactions between food and drugs, as well as those between drugs and nutrients and herbs, are essential components of risk management. Patients who take multiple dietary supplements and medications at the same time, frequently with comorbidities, provide these interactions new dimensions and complexity. (3)

Recent studies have demonstrated that a number found in berries and fruits that change the enzymes involved in the metabolism of drugs. (1) The most famous example is the grapefruit, although orange, pomelo, and star fruit are all examples of foods that suppress the enzyme cytochrome P450. The most

important enzyme for drug metabolism is 3A4 (CYP3A4). Given that many individuals today feel that leading a healthy lifestyle is essential, fruit juices have lately gained attention as a unique class of functional beverages because they are promising transporters of physiologically active substances from a variety of other dietary sources. Specifically, consumers looking for a well-balanced diet can now benefit from even greater nutritional and health benefits from fruit juices thanks to recent advancements in food biotechnology. (4) Health care professionals, including doctors, pharmacists, nurses, and dietitians, must understand significant drug-food interactions to maximize the therapeutic benefits of both prescription and over-the-counter medications. Here, we examine some of the most popular fruits and vegetables to alert medical professionals to potential drug-nutrient interactions and their prospective clinical implications. (5)
Numerous factors, such as gender, age, body composition, nutritional status, medical concurrent illnesses, and the use of multiple drugs can influence the risk of food-drug interactions. (6)

ABSORPTION, DISTRIBUTION, METABOLISM, ELIMINATION

The pharmacokinetics of a medicine, which includes Absorption, Distribution, Metabolism, and Elimination (ADME), can be greatly impacted by food-drug interactions. Food can either support or obstruct each of these processes, which dictate how a medicine acts in the body. (7)
The term "absorption" describes how a medication enters the bloodstream following administration. Food can change how medications are absorbed in a number of ways:
Food slows down the stomach's emptying process, which delays the absorption of medications. This is typical of meals that are high in fat or fibre. Drug Binding: Some foods, such as calcium-rich dairy items, can bind to medications like tetracycline and decrease their absorption. Food can change the pH of the stomach, which can have an impact on medications like ketoconazole that need an acidic environment to be absorbed. Greater Absorption: Because of their increased solubility in fat, several medications (such as griseofulvin) have greater absorption when consumed with fatty meals.

Important physiological characteristics affecting the area of the absorption surface:

Absorption is maximized by larger surface areas, such as those found in the alveoli or small intestine. The small intestine's microvilli, for instance, greatly increase the surface area that can be used to absorb nutrients.
Permeability of Membranes: Small, nonpolar, or lipophilic molecules (like carbon dioxide and oxygen) and lipids) can more readily flow through the selectively permeable lipid bilayer of cells. Certain transport systems, including as ion channels and carrier proteins, are necessary for polar or charged compounds.
Concentration Gradient: Diffusion is the tendency of substances to flow from areas of greater quantities to areas of smaller quantities.
Passive absorption is driven by this gradient.
When active transport takes place, materials are moved against the gradient using energy.

Molecular-Dimensions:

Compared to large molecules, small molecules are more easily absorbed. For example, monosaccharides and amino acids are better absorbed in the colon than proteins or polysaccharides.
Solubility: Hydrophilic chemicals might need aqueous channels or active transport, whereas lipophilic molecules dissolve in lipid membranes and disperse readily.
Flow of Blood: By preserving a concentration gradient, increased blood flow to a region (such as the intestinal villi during digestion) improves absorption.

Theories of Absorption:

Passive Diffusion: Without requiring energy, substances flow over membranes along their concentration gradient. This procedure is necessary for the majority of gases (such as carbon dioxide and oxygen) and lipid-soluble medications.
Promoted-Diffusion: Movement involves a carrier protein or channel and happens along the concentration gradient. Glucose transfer by GLUT transporters is one example.
Transport in Action: In this process, chemicals are moved against their concentration gradient using energy (ATP). For instance, the small intestine's absorption of amino acids and sodium-potassium pumps.
Pinocytosis and endocytosis: Vesicles are formed when the cell membrane engulfs large molecules or particles. This is crucial for macromolecules like antibodies that are absorbed by neonatal gut cells.
Paracellular Transport/Solvent Drag: Dissolved materials are transported by water when it passes through paracellular channels, which frequently happens in leaky epithelia.
For instance, grapefruit juice may improve the absorption of some medications, including statins, by blocking specific intestinal transporters. **(4,7)**

Distribution is the process by which a medication is delivered to tissues following absorption. Food has an indirect impact on the delivery of drugs by: Drug binding may be changed by plasma protein levels, such as albumin, which are influenced by high-protein diets. The only active medication is the free (unbound) form. The distribution of lipophilic medications, such as benzodiazepines, into fatty tissues can be improved by a high-fat diet.

Physiological Properties of Distribution

Blood Flow to Tissues: Substances enter highly perfused tissues (liver, kidneys, brain, and heart) more rapidly and in larger quantities than they do in less perfused tissues (fat or cartilage). For instance, the brain is a crucial location for the quick delivery of lipid-soluble medications since it receives 15–25% of cardiac output.

Protein Binding in Plasma: Alpha-1-acid glycoprotein (for basic medications) and albumin (for acidic drugs) are two examples of the plasma proteins that many chemicals bind to. The only fraction that can be distributed and used for biological activity is the unbound (free) fraction.

Distribution is restricted by high protein binding because the bound fraction is unable to pass through cell membranes.

Solubility of Lipids: Substances that are lipophilic (fat-soluble) readily penetrate cell membranes and gather in adipose tissues or membranes. The majority of hydrophilic (water-soluble) materials, like plasma and interstitial fluid, stay in the aqueous compartments.

Permeability of Membranes: Distribution is influenced by the permeability of cell membranes and capillary walls. For example, Due to its close connections, the blood-brain barrier (BBB) restricts the flow of several substances to the brain.

Tissue Attachment: Certain chemicals accumulate selectively because of their high affinity for particular tissues. For instance, calcium builds up in bones, but iodine concentrates in the thyroid.

Distribution Volume (Vd): This is a theoretical number that indicates how widely a chemical is distributed throughout the body in relation to its plasma concentration.

Low Vd substances stay in the plasma, but high Vd substances spread widely throughout tissues.

Principles and Mechanisms Controlling Distribution

Passive Diffusion: Chemicals enter tissues along their concentration gradient. This method works best with lipophilic compounds.

Transport in Action: Energy-dependent transport systems are necessary for some substances, such as glucose or amino acids, to pass through cell membranes.

Bulk Flow: The body uses lymphatic and blood circulation to deliver substances.

Redistributing: Certain anaesthetics, such as thiopental, are examples of lipophilic chemicals that may first collect in organs with high blood flow, like the brain, before redistributing to tissues with lower blood flow, like fat.

Models of Compartments: One or more compartments (central, peripheral, etc.) are frequently used to model the body. Organs with high perfusion and plasma are located in the central compartment. Tissues having a slower distribution are found in the peripheral compartment.

Distribution-Related Factors

Physiological Barriers: Large or polar molecules are restricted by the blood-brain barrier (BBB). Although the placental barrier offers some protection, some chemicals, such as tiny lipophilic medicines, can get through to the foetus.

Age: New-borns' distribution is impacted by their immature liver enzymes, lower plasma protein levels, and increased body water content. Elderly people may have changed tissue composition (fatter, for example) and decreased blood flow.

Pathophysiology: Distribution can be greatly impacted by conditions such as cardiovascular problems (which decrease blood flow) or liver disease (which reduces plasma proteins). For instance, medications that rely on fat or plasma proteins for distribution may have altered distribution patterns as a result of malnutrition or high-fat diets**.** (4,7)

The term "metabolism" describes the chemical changes that a drug undergoes in the body, mostly in the liver.

Physical Characteristics of Metabolism

1. Two Metabolism Phases:
    a. Catabolism is the process by which complex molecules (such proteins, lipids, and carbohydrates) are broken down into simpler one's releases ATP, which is the energy that is stored.
    b. Anabolism is the transformation of smaller molecules into more complicated ones, including lipids, proteins and nucleic acids. It needs energy to function, usually from ATP.
2. Metabolic Routes:

Glycolysis is the process by which glucose is converted to pyruvate, it produces ATP and NADH.

The Krebs Cycle (TCA Cycle), which produces ATP, NADH, and $FADH_2$ in the mitochondria, is essential

to energy metabolism. In the mitochondria, oxidative phosphorylation produces ATP by using oxygen. Fatty acid breakdown for energy production is known as beta-oxidation.

3. Amino Acid Metabolism: Energy-producing or biosynthesis-related deamination and transamination activities.
4. The Liver as the Center of Metabolism:
    The main location for drug and toxin detoxification is the liver. Storage and release of glycogen. Lipoprotein, cholesterol, and plasma protein synthesis. Ammonia is transformed into urea for excretion.
5. Activity of Enzymes:
    Metabolic reactions are catalyzed by enzymes, frequently in tightly controlled pathways.
    Enzyme specificity guarantees that only specific substrates are digested, averting unwanted reactions.
    Homeostasis of Energy: balancing the consumption, storage, and use of energy.

Insulin and glucagon are two important hormones that control metabolism.

Metabolism of Xenobiotics (Drugs/Toxins):

- Phase I Reactions (Modification):
    Functional groups are added or exposed by enzymes (like cytochrome P450) through processes like hydroxylation and oxidation. Changes lipophilic materials into more polar forms so that processing can proceed more easily.
- Phase II Conjugation Reactions:
    Hydrophilic compounds, such as glutathione, glucuronic acid, or sulphate, are conjugated with substances to increase their water solubility for excretion.
- Transport Phase III:
    Efflux transporters, such P-glycoproteins, transfer materials from cells, frequently into urine or bile.

Metabolism Factors:

Age: Because of their undeveloped liver enzyme systems, newborns have trouble metabolizing drugs and toxins. Enzyme activity and metabolic rates may be lower in older persons.

Genetics: The rate of metabolism can be changed by genetic variations in enzymes (like cytochrome P450). For instance, some medications are metabolized more slowly by slow acetylators.

Sexual: Different hormones can have an impact on metabolism rates. Women may metabolize alcohol differently than men, for instance.

Status of Nutrition: Enzyme function can be hampered by malnutrition or cofactor deficits (such as those in vitamins or minerals).

Medical Conditions: Hepatitis and liver cirrhosis are two conditions that can significantly impair metabolic capability.

Interactions between Food and Drugs or Drugs: Drug metabolism can be changed by some chemicals that either block or activate metabolic enzymes. For instance, grapefruit juice affects medication breakdown by inhibiting CYP3A4.

Meals can affect metabolism in the following ways:

Enzyme Induction or Inhibition: Cytochrome P450 enzymes, which break down a variety of medications, are influenced by food. Dishes that speed up drug metabolism, such as cruciferous vegetables and dishes cooked with charcoal, may lessen the effectiveness of drugs. Grapefruit juice is one example of an inhibitor that slows metabolism, raising medication levels and perhaps increasing toxicity.

First-Pass Effect: Certain foods change the bioavailability of medications by increasing or decreasing first-pass metabolism. (4,7)

Drugs are eliminated by excretion in the form of urine, feces, or bile. Food can affect how well drugs are eliminated by:

Urinary pH Alteration: Some meals, including cranberry juice, cause the urine to become more acidic, which can impact the kidneys' ability to excrete medications like amphetamines and methotrexate

Biliary Excretion: Eating foods high in fat may help the biliary system get rid of medications that are lipophilic.

Kidney Function: Diets high in sodium may have an impact on how well medications like lithium are cleared by the kidneys.

Important Physiological Features of Elimination Pathways:

1. Routes of Elimination
   Kidneys and Renal Excretion: The kidneys filter blood plasma, eliminating drug metabolites and water-soluble waste products such creatinine and urea through urine.
   Hepatic Elimination (Liver): After being broken down into more polar compounds, substances are expelled as bile, which travels to the gastrointestinal tract and is thereafter expelled as feces.
   Gases and volatile chemicals (such as carbon dioxide and anaesthetic drugs) are expelled by expiration in the lungs.
   Other Routes: Some toxins can be mildly eliminated by the use of sweat, saliva, tears, and breast milk.
2. Function of the Organ:
   Kidneys: Nephrons that are able to filter, reabsorb, and secrete are necessary for effective elimination.
   Liver: The enzymatic pathways in the liver, such as cytochrome P450, are essential for changing chemicals into forms that are easier to eliminate.
   Lungs: The partial pressure gradient of gases determines excretion through the lungs.
3. Solubility:
   The kidneys are largely responsible for the elimination of water-soluble substances. Prior to excretion, lipophilic (fat-soluble) substances undergo hydrophilic form metabolism, frequently through hepatic routes.
4. Half-Life:
   The effectiveness of elimination is indicated by how long it takes for a substance's body concentration to decrease by half. While substances with long half-lives tend to collect more readily, those with short half-lives are removed quickly.
5. Clearance:
   The amount of plasma that is removed from a drug in a given amount of time (e.g., renal clearance, hepatic clearance). Effective elimination is indicated by high clearance rates.
6. The binding of proteins:
   A medication or molecule can only be eliminated in its unbound (free) component. The removal of substances that are strongly attached to plasma proteins may be delayed.
7. Dependency on pH:
   Renal excretion is impacted by substance ionization. Weak bases are more excretable in acidic urine, whereas weak acids (like aspirin) are more easily eliminated in alkaline urine.

Elements Affecting Elimination

Age: Elimination is delayed in newborns due to their undeveloped kidney and liver function.

Hepatic enzyme activity and renal function may decline in older persons.

Conditions of Disease: Reduced clearance of chemicals expelled by urine is a result of renal impairment.

Liver disease: Affects biliary excretion and medication metabolism.

Cardiovascular disorders: Impact the flow of blood to the organs that eliminate waste.

Variations in Genetics: Metabolic enzyme polymorphisms can change how quickly biotransformation and elimination occur.

Drug Reactions: Elimination rates can be changed by substances that stimulate or inhibit transport proteins or metabolic enzymes (like CYP450). For instance, rifampin increases the clearance of co-administered medications via inducing CYP450 enzymes.

Properties of Substances: The path and rate of elimination are influenced by molecular size, solubility, and ionization state.

Status of Hydration: The best renal clearance is ensured by adequate hydration.

Theories and Models of Elimination:

First-Order Kinetics: The majority of chemicals are removed from the body at a pace that corresponds to their plasma concentration. For every unit of time, a constant fraction is eliminated.

Zero-order kinetics: Regardless of plasma concentration, elimination proceeds at a steady pace. Observed when the elimination channels are saturated with drugs such as alcohol.

Models of Compartments: The distribution and removal of chemicals from various tissues are described using single-compartment and multi-compartment models.

Diets high in protein, for instance, may increase the renal clearance of several medications, decreasing their therapeutic benefits. (4,7)

Function of Cytochrome P450 Enzymes in Drug Interactions

The CYP450 enzymes are a class of enzymes found mostly in the liver and intestines that are responsible for the metabolism of about 70-90% of all medications. Phase I of drug metabolism, which includes reduction, oxidation, or hydrolyzed to make medications more hydrophilic and readier for excretion, is where they play a significant role. (4,7)

Drug transporters have a role in drug interactions.

Drug transporters are membrane proteins that facilitate drug uptake or efflux across cellular membranes, regulating absorption, distribution, and elimination. The most extensively researched transporters are (P-gp), (OATs), and (OCTs). (8)

Drug Interaction Mechanisms: Transporter Inhibition: Inhibitors can inhibit drug transport, affecting absorption and clearance.

Grapefruit juice inhibits P-gp in the intestine, leading to increased absorption of medicines such as digoxin. (8)

Introducing the Transporters: Inducers decrease drug absorption or promote clearance by raising transporter expression or function. For instance, rifampin causes P-gp, which lowers the bioavailability of medications such as tacrolimus. (7)

Competition of Substrates: Drug levels may change as a result of competition between several medications that use the same transporter. For instance, probenecid prolongs the half-life of penicillin by inhibiting OATs, which lowers renal clearance of the antibiotic. (4)

Effects Specific to Tissue: Drug distribution and excretion are controlled by transporters in certain tissues, such as kidneys, intestines, and blood-brain barrier. For instance, P-gp at the blood-brain barrier prevents central opioid effects by limiting the CNS penetration of medications like loperamide. (4)

Clinical Importance of Transporters and CYP450 in Drug Interactions

Forecasting Interactions Between Drugs: Comprehending the substrates, inducers, and inhibitors of enzymes and transporters aids in dosage adjustments and possible interaction prediction. Genetic testing for CYP polymorphisms (such as CYP2D6 and CYP2C19) helps customize treatment for the best possible pharmacological efficacy and safety in personalized medicine.

Steer clear of drug-food interactions: Understanding the presence of transporter and enzyme inhibitors in meals (such as grapefruit juice and herbal supplements) can help avert negative consequences. Enhancing Drug Design: By reducing transporter-related variability or metabolism, new medications can be created with a higher safety profile. (4,7,8)

Pharmacokinetic Interactions

Common Fruit Juice Interactions with Drugs

Although fruit juices are sometimes regarded as healthy, they can have a major effect on how well drugs are absorbed, metabolized, and eliminated. These effects are mostly brought about by interactions with drug transporters (like P-glycoprotein) and enzymes (like cytochrome P450 enzymes). An outline of medication interactions with typical fruit juices is provided below: (1,4)

1.Grapefruit Juice Interaction Mechanism:

Furanocoumarins included in grapefruit juice increase the bioavailability of drugs by inhibiting the intestinal wall's CYP3A4 enzyme. Drug efflux into the intestinal lumen is decreased by P-glycoprotein (P-gp).

Frequently Affected Substances:

Statins: Simvastatin and Atorvastatin → Enhanced risk of rhabdomyolysis, or muscular poisoning. Amlodipine and nifedipine, calcium channel blockers, have more hypotensive effects. Tacrolimus and cyclosporine are immunosuppressants that increase the risk of harm

Midazolam and Triazolam are benzodiazepines that cause increased sedation.

Antiarrhythmics: Amiodarone → Potential for toxicity or arrhythmia. (1,4,9)

Grapefruit juice Lovastatin Grapefruit juice

Mediated inhibition of Human CYP 3A4 Activity

Fig no 1. This Figure indicates the dangerous interactions of grape fruit/juice with the lovastatin drug of statin group which shows the inhibition of human CYP 3A4 activity in the intestinal tract.

2. Orange Juice Interaction Mechanism:

Some orange juices, particularly those from Seville oranges, have the ability to: Reduce medication absorption by inhibiting organic anion-transporting polypeptides (OATPs).

Frequently Affected Substances:

Fexofenadine, an antihistamine, has less effectiveness because of its lower absorption.

Atenolol → Diminished therapeutic efficacy in beta blockers. Fluoroquinolone Ciprofloxacin is an antibiotic with somewhat decreased absorption. (1,4,9)

3. Apple Juice's Interaction Mechanism:

OATPs are inhibited by apple juice, which reduces medication absorption.

Frequently Affected Substances:

Fexofenadine, an antihistamine, has a lower bioavailability.

Antibiotics: Levofloxacin and Ciprofloxacin ⇒ Decreased effectiveness.

ACE Inhibitors: Aliskiren Reduces Blood Pressure Control by Lowering Drug Absorption (9)

4. The Mechanism of Interaction of Cranberry Juice:

Reduces the metabolism of several medications by inhibiting the CYP2C9 enzyme.

changes the pH of the urine, which has an impact on how some drugs are excreted.

Frequently Affected Substances:

Warfarin: Lowers metabolism, increasing bleeding risk.

NSAIDs: Modified urine excretion, heightened toxicity or effects of the drug.

Methotrexate: Modifications in renal clearance may cause toxicity. (9)

5. Pomegranate Juice Interaction Mechanism:

CYP2D6 and CYP3A4 inhibition modifies drug metabolism.

Frequently Affected Substances:

Antihypertensives: ACE inhibitors (such captopril) have stronger impact on lowering blood pressure. Warfarin is one anticoagulant that increases the risk of bleeding

Metoprolol and propranolol are beta blockers that alter metabolism and increase the risk of toxicity. (9)

FRUIT JUICE	ENZYMES/ TRANSPORTERS AFFECTED	DRUGS	EFFECT	RECOMMENDATION
Grapefruit Juice	CYP3A4	Statins(lovastatin), Calcium Channel Blockers	Increased Risk of toxicity	Avoid juice during the treatment
Orange Juice	OATPs	Anti -histamines, Beta-blockers (atenolol)	Decreased pharmacological Effectiveness due to lower absorption	Avoid juice within four hours of dosage
Apple Juice	OATPs	Beta-blocker (atenolol) Anti- hypertensive Agent (Aliskiren)	Decreased drug efficiency due to lower absorption	Avoid juice within four hours of dosage
Cranberry Juice	CYP2C9	Warfarin, NSAIDs	Increased bleeding risk	If routinely consumed, Closely monitor

Pomegranate Juice	CYP3A4	Beta – blockers, warfarin	Increased risk of toxicity	Avoid juice during treatment

Table no 1. Examples of Fruit Juices and their potential Drug Interactions

Alcoholic Beverages

Moderate drinking of alcohol has been promoted as a component of a healthy lifestyle due to mounting evidence of the cardio-protective benefits of alcoholic beverages. Flavonoids and other polyphenols, which are abundant in alcoholic beverages like beer and wine, have antioxidant properties and can affect CYP activity through mechanisms unrelated to ethanol. (11) However, there is little proof that teas and alcoholic beverages (such as wine and beer) inhibit enteric CYP3A, and their therapeutic significance has not yet been established.

1.BEER Beer is an alcoholic beverage with specific features due to its mix of hops, barley, and micronutrients, while sharing typical pharmacokinetic interactions with alcohol.

Mechanisms of Interaction:

- Ethanol Content:
  Beer contains ethanol, which affects medication absorption, metabolism, and excretion. Acute ethanol consumption inhibits liver enzymes, however chronic use increases enzymes such as CYP2E1.Beer's moderate alcohol concentration may increase gastrointestinal permeability, affecting medication absorption.
- Impact on gastric pH:
  Beer stimulates gastric acid secretion, which may affect the solubility and absorption of pH-sensitive medicines (such as proton pump inhibitors and certain antibiotics).
- Nutritional Components:
  Beer contains vitamins and minerals which may interfere with medications by competing for absorption pathways.

Examples of Drug Interactions

- Sedatives (e.g., benzodiazepines): Due to its ethanol level, beer can exacerbate CNS depression.
- Iron Supplements: Because of its high phytate content, beer may reduce iron absorption.
- Metronidazole with Disulfiram-related reactions: Combining alcohol with medications such as metronidazole can cause nausea, vomiting, and flushing. (10)

2.Wine

Wine, particularly red wine, contains not only ethanol but also polyphenols, tannins, and resveratrol, which can add complexity to its interactions with drugs and supplements.

Mechanisms of Interaction

- Ethanol Content:
  Similar to beer, ethanol in wine affects enzyme activity (e.g., CYP2E1 induction or inhibition).
- Polyphenols:
  Compounds like flavonoids and resveratrol can inhibit drug-metabolizing enzymes such as CYP3A4 and affect P-glycoprotein, altering the bioavailability of drugs like statins and calcium channel blockers.
- Tannin and Iron Absorption:
  Tannins in wine can limit the absorption of non-heme iron, potentially decreasing the efficacy of iron supplementation.
- Antioxidant Effects:
  Polyphenols may interfere with oxidative pathways, influencing medication metabolism or increasing the effectiveness of antioxidant supplements.

Examples of Drug Interactions

Statins (e.g., atorvastatin): Red wine can raise plasma levels by inhibiting CYP3A4 with ethanol and polyphenols.

Anticoagulants (e.g., warfarin): Wine increases bleeding risk due to its alcohol level and platelet-inhibitory effects from polyphenols.

Wine may cause sedation or harmful effects when coupled with some antidepressants, such as MAO inhibitors. (10)

3.TEA

Tea, a non-alcoholic beverage, contains bioactive components such caffeine, catechins, tannins, and theanine, which can affect drug pharmacokinetics.

Mechanism of Interaction:

- Caffeine Content: Black and green teas contain caffeine, which is processed by CYP1A2. Drugs that inhibit CYP1A2 (for example, fluvoxamine) might raise caffeine levels, resulting in adverse effects such as sleeplessness or tachycardia.
- Polyphenols (catechins): Green and black teas contain catechins, which can bind to medicines in the gastrointestinal tract, limiting absorption (for example, iron or bisphosphonates). Catechins can block drug-metabolizing enzymes, potentially affecting the metabolism of statins.
- Tannins: Tannins can bind minerals (such as iron) and decrease their absorption, which is important for anaemic people.
- Theanine: Theanine may have a synergistic impact with sedative medications, improving relaxation while potentially increasing sedation.

Examples of Drug Interactions

Antibiotics (such as ciprofloxacin): Caffeine in tea may raise the likelihood of adverse effects such as agitation or tremors due to impaired caffeine metabolism.

Tannins in tea limit iron absorption, particularly when drunk with food or supplements.

Warfarin: Green tea's high vitamin K content may counteract warfarin's anticoagulant effects. (10)

Drug Class	Example Drug(s)	Food Involved	Mechanism of Interaction	Effect on Drug/Patient
CNS Stimulants	Methylphenidate	Caffeine	Synergistic stimulant effects	Nervousness, tachycardia
Antivirals	Ritonavir	Fatty meals	Increased drug absorption	Enhanced efficacy, toxicity risk
Antifungals	Ketoconazole	Acidic foods (orange juice)	Enhanced drug absorption	Improved therapeutic effect
Thyroid Drugs	Levothyroxine	Soy products, fiber, calcium	Reduced drug absorption	Hypothyroidism symptoms
Diuretics	Furosemide	Licorice	Increased sodium retention	Reduced drug efficacy
Immunosuppressants	Cyclosporine	Grapefruit juice	CYP3A4 inhibition	Increased drug toxicity
Anti-Parkinson's Drugs	Levodopa	High-protein foods	Competition for transport across gut	Reduced drug absorption, efficacy
Analgesics	NSAIDs (Ibuprofen)	Food (general)	Delayed drug absorption	Reduced peak effect, less irritation
Analgesics	Paracetamol (Acetaminophen)	Alcohol	Increased liver toxicity	Risk of liver damage
Antidepressants	SSRIs (Fluoxetine)	Caffeine	Increased CNS stimulation	Anxiety, palpitations
Antidepressants	MAO Inhibitors (Phenelzine)	Tyramine-containing foods (cheese)	Inhibition of tyramine breakdown	Hypertensive crisis
Statins	Atorvastatin, Simvastatin	Grapefruit juice	CYP3A4 inhibition	Increased drug levels (toxicity)
Antidiabetics	Insulin	Irregular food intake	Delayed glucose absorption	Hypoglycemia or hyperglycaemia
Antidiabetics	Sulfonylureas (Glipizide)	Alcohol	Potentiates hypoglycemia	Increased risk of low blood sugar
Antidiabetics	Metformin	High-fiber foods	Delayed drug absorption	Reduced blood glucose control

Anticoagulants	Dabigatran	Fatty meals	Delayed drug absorption	Reduced immediate therapeutic effect
Anticoagulants	Warfarin	Leafy greens (spinach, kale)	Vitamin K counteracts drug action	Decreased drug effectiveness (clotting)
Antihypertensives	Beta-blockers (Metoprolol)	High-sodium foods	Reduced drug efficacy	Poor blood pressure control
Antihypertensives	Calcium Channel Blockers	Grapefruit juice	Inhibition of CYP3A4 enzyme	Increased drug levels (toxicity)
Antihypertensives	ACE Inhibitors (Lisinopril)	High-potassium foods (bananas)	Increased potassium levels	Risk of hyperkalaemia (heart issues)
Antibiotics	Metronidazole	Alcohol	Inhibition of alcohol metabolism	Severe nausea, vomiting, headache
Antibiotics	Erythromycin	Acidic foods (citrus, soda)	Drug stability affected	Decreased drug effectiveness
Antibiotics	Tetracycline, Ciprofloxacin	Dairy products (milk, cheese)	Calcium binds to the drug	Reduced drug absorption, efficacy

Table no 2. Food-drug interactions, drug class, example drugs, food involved, interaction mechanism, and effect.

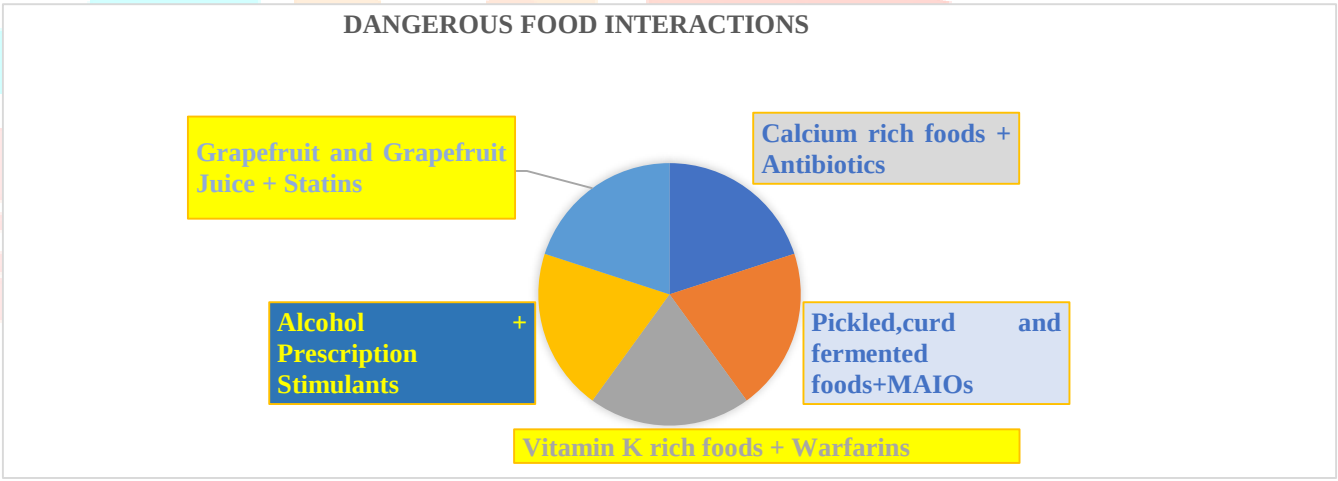

Fig.no.:2 This chart summarizes the dangerous food drug interactions as the drug we take might interact with the food we eat, i.e. Grape fruit/juice interact with statins in GIT, calcium rich foods interact with antibiotics in stomach and upper small intestine, Pickled/ Curd/Fermented Foods interact MAIOs increases the blood pressure, Vitamin K-Rich Foods interacts with Warfarin which can antagonize the anticoagulant effect and prevent the drug from working, and Alcohol interacts with Prescription Stimulants intoxicates the person's body.

The formulation's role in food-drug interactions

Consuming food causes dynamic changes in the quantity and composition of luminal fluids as well as GI motility patterns, all of which have an impact on how oral medication formulations behave. The previous sections of this paper provide a thorough description of the primary alterations brought about by food consumption; however, the primary methods for overcoming dietary impacts through formulation will be covered here. Because food impacts can have complicated and troublesome effects, a therapeutic product taken orally should ideally have the same bioavailability whether it is fed or fasted.

When dietary impacts are detected, regulatory scientists or drug development professionals can often use three strategies to counteract them, including:

1. To consider a different lead drug molecule that won't exhibit a food impact; nevertheless, this approach is time-consuming, costly, and may cause delays in the drug development process
2. To use detailed instructions on how to take a medication in relation to meals, even though this is restricted and could disrupt the patient's daily routine
3. To create a formulation that circumvents the overall food effect. The latter is thought to be the most workable way to get over possible dietary impacts when compared to the other options.

Drug bioavailability may be reduced by adverse dietary effects caused by food-drug interactions. The direct physicochemical interactions between medications (or drug products) and food are the most frequent reasons for decreased bioavailability in the fed state. The decreased drug diffusivity in the fluid postprandial upper GI tract is one possible explanation for this effect. Increased viscosity can either restrict a formulation's breakdown, preventing drug release, or impede the drug's diffusion to the GI tract's absorptive membranes. This can be troublesome for medications that are poorly permeable, especially those with narrow absorption windows, because absorption will be diminished by the time the absorption window has been transited and viscosity has decreased in the distal gut.

The binding of drugs with food components is a second direct way that food can prevent drug absorption. The drug product can be designed to release lower down the GI tract to minimize the interaction of the medicine with the consumed meal, hence overcoming adverse food effects. The use of modified release formulations, especially delayed release (such as enteric coated) systems, is part of this strategy. However, these formulations may also have the potential for dosage dumping and are susceptible to dietary effects related to delayed stomach emptying. (7)

Advice and Counselling Regarding Drug-Food Interactions

- When giving out medication, patients can be informed about the following. (12-14)
- Examine the container's prescription label. If you feel that you need additional information or have any questions, speak with your pharmacist or doctor.
- Examine all drug labels and package inserts for instructions, warnings, and precautions against interactions. Even over-the-counter drugs have the potential to be problematic.
- Drink a full glass of water before taking any medications. Unless your doctor instructs you otherwise, do not break up capsules or mix medication into food. This could affect how effective the medication
- Avoid using vitamin supplements concurrently with prescription drugs. Certain medications may interact with vitamins and minerals.
- Avoid mixing medications with hot beverages as the heat from the beverage may reduce the medication's potency.
- Alcohol and medication should never be consumed together.
- Be sure to disclose all of your medications, including prescription and over-the-counter, to your doctor and pharmacist.
- Consult the pharmacist about the potential effects of certain drugs taken with food.

Safety measures to be taken

- It is necessary to take medications at separate times than meals
- If health issues continue, see a doctor.
- Before taking any drug while pregnant or nursing, always get advice from a doctor or pharmacist. The infant may be impacted by the mother's drug use.
- Consult a physician or pharmacist about the best time and method to take your medications.

Regulatory considerations in real-world dosage scenarios

The process used to manufacture information's user instructions, a drug material into a drug product may have an impact on the degree of food-drug interactions. In the product information, user instructions (warnings or recommendations) may therefore be product-specific or drug substance-specific. Additionally, there are a variety of justifications for the cautions about food-drug interactions in the product ranging from rather severe to gentle. For instance, there is a well-known and stringent warning that the product should not be used with specific foods. (16)

For Example, the iron supplement ferrous fumarate states that milk, tea, or coffee should not be consumed within two to three hours of consumption because this decreases absorption. For the calcium antagonist nifedipine, a less stringent warning is provided, stating that grapefruit juice should not be consumed concurrently with nifedipine due to the extended impact and elevated plasma levels. A milder warning is added for levothyroxine, noting that foods high in soy and fiber may reduce absorption from the intestine

and that dose changes may be necessary, particularly when beginning or stopping soy-containing products. (16)

The product should be used as directed by the user instructions. be consumed with food or beverages, which essentially suggests a directive. Usually, this is done to purposefully change absorption or to lessen adverse effects. Non-steroidal anti-inflammatory drugs, for instance, to lower the risk of gastric reflux, medications such diclofenac or the antibiotic amoxicillin/clavulanic acid should be administered before or during meals.

Another medication that needs to be taken with food is acamprosate, which is used in alcohol treatment therapy. Many patients and medical professionals believe that there isn't a warning or recommendation regarding the use of a drug product with food or drink in real-world situations. Based on this understanding, they typically believe that mixing a medication product with a full glass of any beverage other than water or with (semi-solid) food or drink on a spoon is not problematic. Similarly, it is frequently not regarded as an issue to alter the product initially, such as breaking tablets or opening capsules. All of these administration techniques are frequently used to facilitate or guarantee safe ingestion. (18) For instance, in young toddlers, individuals with severe illnesses, or patients dealing with cognitive issues like dementia. These techniques are also frequently employed to enhance taste in children, however this is less significant in (older) adults. Patients and medical professionals frequently fail to consider that mixing should only be done in situations where co-administration is not an option because there is a chance that the patient won't swallow the entire meal or drink the entire glass, which could result in their not taking the entire dosage. Additionally, when the entire meal's flavour is impacted rather than just a single spoonful of food or drink, patients are more likely to grow resentful of the dish. (17) Companies may acknowledge that it is occasionally inevitable in real-world situations for a drug product to be used alongside food or beverages. Pharmaceutical firms should therefore try to think about developing new drug products with food co-administration in mind, especially for use in youngsters or the elderly population. (15)

Conclusion

Food-drug interactions significantly influence the safety, efficacy, and nutritional outcomes of medication therapy. These interactions can alter drug absorption, metabolism, distribution, and elimination, leading to diminished therapeutic effects or potential adverse reactions. Proper management of these interactions often involves timing medications appropriately with respect to meals or modifying dietary habits to minimize interference. Healthcare professionals, particularly pharmacists, play a critical role in identifying potential interactions and educating patients on foods and beverages to avoid while on specific medications. Despite the knowledge available, food-drug interactions remain under-researched, particularly regarding their personalized impacts on individuals. Expanding research efforts in this area is essential to optimize therapeutic outcomes and improve patient care. Increased awareness among healthcare providers and patients, combined with tailored advice and strategies, is vital for enhancing the effectiveness of drug therapies and ensuring patient safety.

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