



REVIEW ARTICLE



Interactions- Readdressing the Issue

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Abstract

Broadly drugs include all the chemical substances excluding food that affect the bodily processes. The drug is considered to be a medicine if it benefits the body. Whereas, if the drug is injurious to the body, it's considered as a poison. Therefore, the same chemical can be a boon or curse with respect to the situation, condition of use, dosage and the individual using it. In this contemporary healthcare era, a huge number of medications are formulated each year and new interactions between drugs are reported every now and then. As a result, it is no more practical for doctors to be dependent on the memory alone to avoid possible drug interactions. Changes in absorption, distribution, metabolism or elimination of drugs are referred to as pharmacokinetic interactions, resulting in alteration in the level of drugs and its metabolites. The effect of drug changes from person to person than expected because it causes different reaction when a drug reacts with the food or dietary supplements they take (drug -food interaction). So, the effect of the drug is altered by means of increasing, decreasing, or producing a new effect which cannot be produced on its own the effect caused by food or dietary supplements. These interactions may occur due to accidental misuse or due to other factors such as lack of knowledge about it. This review provides a comprehensive literature review on various drug interaction. Generally, drug food interactions are neglected and not well defined but it can cause mild to serious effects. However, all clinicians, pharmacists and nurses should be aware of drug interaction to avoid the consequences caused by drug interactions.

Keywords: Drug interaction, Pharmacokinetic, Pharmacodynamic, Drug food interaction, Drug herb interaction.

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1 | INTRODUCTION

Broadly drugs include all the chemical substances excluding food that affect the bodily processes. The drug is considered to be a medicine if it benefits the body. Whereas, if the drug is injurious to the body, it's considered as a poison. Therefore, the same chemical can be a boon or curse with respect to the situation, condition of use, dosage and the individual using it. ¹In this contemporary healthcare era, a huge number of medications are formulated each year and new interactions between drugs are reported every now and then. As a result, it is no more practical for doctors to be dependent on the memory alone to avoid possible drug interactions.²

The change in efficiency and toxicity of certain drugs in the presence of some other drugs is referred to as drug- drug interactions (DDIs).³During a drug- drug interaction, a drug hampers with pharmacodynamics, pharmacokinetic or any pharmaceutical properties of some other drug which subsequently change the net effect of one or both the medication.⁴Apart from the type of drug used, there are certain other factors responsible for an increased incidence rate of DDIs, which includes the number of drugs prescribed, age of the patients and presence of any comorbid conditions in a patient.⁵

10-20% of adverse drug reactions is caused as a result of harmful DDIs and requires hospitalization. Especially, the geriatric patients are more susceptible to DDIs with their increasing age, decreased metabolism and the number of medications prescribed.⁶To avoid these DDIs clinical pharmacists contribute significantly to the safety and efficacy of the drug use, and generally they are the first being approached by the patients for medical guidance. Clinical pharmacists are accountable for reviewing the drugs and also, more importantly counselling the patients. Therefore, pharmacist's knowledge of DDIs is important for proper patient's education, improvement in treatment efficiency and avoiding some serious side effects.⁷

The possibility of interaction increases, when multiple medications are administered concurrently, such that one drug might affect the other. There might be a

positive or negative effect of DDIs on the predictable therapeutic results. A negative effect may deteriorate a patient's state of illness or lead to higher healthcare expenses.⁸DDIs can be classified into:

- Pharmacokinetic interactions involving absorption, distribution, metabolism and excretion (ADME), all of which are accompanied to toxicity and management failure.
- Pharmacodynamic interactions are further classified into: (i) directly effecting the receptor functioning, (ii) interfering with physiological and biological control processes and (iii) additive or opposite pharmacological effect.⁹

2 | WHAT IS FOOD INTERACTION?

The most common unknown problem observed by a clinical practitioner is the interaction between a natural substance and a drug. These interactions are based on similar pharmacokinetic and pharmacodynamics principles as DDIs. Recently numerous fruits and berries have shown to comprise of agents that are known to affect the drug-metabolizing enzymes. An eminent example is grapefruit, seville orange, star fruits and pomegranate, known to have agents inhibiting the most significant enzyme in drug metabolism, that is cytochrome P450 3A4 (CYP3A4).¹⁰ Food interactions are classified into-

- Food-drug interactions
- Drug-food interactions

Food interactions that cause delay in absorption is unusual and typically take place with metal ion

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chelate complex drugs like some cytotoxic agents, oxiquinolones and tetracyclines. On the other hand, another subsequent interaction comprises of circumstances where prolonged management prompts harmful physiological and sometimes pathological changes. Antidiabetic drugs, antipsychotics, corticosteroids and antidepressants can possibly increase appetite which leads to weight gain while drugs like opioids causing nausea have an opposite action. Whereas in some cases the uptake of vitamin K Folic acid absorption is decreased by phenytoin and the mucosal function gets disturbed by antibiotic agents.¹¹

3 | METHODOLOGY:

Usually drug-drug interactions are well-defined as change in the outcome of one drug after it is being consumed with a different drug. During drug-drug interactions various mechanisms are involved which may cause an increase in the mechanism of any of the drug, an interruption in absorption of either of the drug, reduction in efficiency of drug or an unpredicted adverse drug reaction. The occurrence of interaction escalates when the concurrent use of different drugs become common.¹²

There might be positive, lethal or no pharmacological effects between drugs during interaction. Drug-drug interactions can be casually categorized on the basis of physicochemical incompatibility as pharmacokinetic or pharmacodynamics or combination of both.¹³

4 | PHARMACOKINETIC DRUG-DRUG INTERACTION

When a drug modifies the absorption, distribution and elimination of another drug (co-administered drug) is referred to as pharmacokinetic drug-drug interactions. Due to these interactions the plasma concentrations may be increased or decreased. These changes can be of variable intensity, but can also results in contraindication of co administration. The

several pharmacokinetic interactions include drug transporters, orphan nuclear receptors, drug metabolizing enzyme, controlling the expression of transporters and enzymes at the transcriptional level. When the plasma concentration of drug increases, it is usually related to drug transport inhibition or / and inhibition of enzyme. Similarly, when the plasma concentration of drug decreases, it is as a result of actuation of orphan nuclear receptors with the help of inducers leading to the escalation of drug transporters and enzymes. Induction of drug transport or metabolism takes 7-10 days, whereas the inhibition of drug transport and metabolism is instant, and takes 24-48h. Drugs like rifampin or ritonavir which is both inducers and inhibitors, can cause an increase or decrease in the exposure of co-administered agent (in subject to duration of association).¹⁴

The drug plasma level and its ability to bind to their desired receptors predicts the intensity and duration of drug action. Also, along with the dosage form, the plasma drug concentration is controlled by the rate of absorption, distribution, metabolism and elimination of drugTable 1 .¹⁵

5 | PHARMACODYNAMICS DRUG-DRUG INTERACTION

The formation of a complex is necessary by the drug with its intended receptor or unintended receptor to affect the target or non-target tissues. The effect produced may be intended or unintended. The effect is as a result of the plasma level concentration of a given drug or may be due to the presence of another drug or prolonged usage of one or more drug that led to (a) physiological, (b) pharmacological, or lead to (c) variations in the number of existing receptors or their capability to react, (d) chemical drug interactions, which in turn can be of therapeutic significance.Table 2¹⁵

6 | HERB DRUG INTERACTION:

Herbal medicines require Food and Drug Administration (FDA) approval but are not as strict as of

TABLE 1: Types of pharmacokinetic drug-drug interaction

Types	Mechanism	Example
ABSORP	When Drug A interacts to form chelates or insoluble complexes with Drug B and inhibits its absorption.	Tetracycline, ciprofloxacin form insoluble chelates with calcium, iron and aluminium resulting in decreased antibacterial effects.
	When Drug A elevates gastric pH or neutralizes gastric acid and inhibits the absorption of Drug B.	Gastrointestinal alkalization of by omeprazole may decrease absorption of ketoconazole.
	When Drug A delays stomach –emptying and systemic absorption of Drug B as most of them are absorbed in small intestine.	Increased Gastro intestinal motility caused by mecloramide may decrease cefprozil absorption.
	When Drug A causes vasoconstriction at the site of absorption and inhibits the systemic absorption of Drug B (administered at the same site).	Local analgesics cause vasoconstriction at the site of administration and interfere with the absorption of epinephrine.
DISTRIBI	When Drug A competes with Drug B for plasma protein binding, increasing its plasma level.	Displacement of methotrexate from plasma protein by NSAID may increase risk of methotrexate toxicity.
	When Drug A inhibits the transport of Drug B into hepatocytes and increases its plasma level.	Efflux transporter inhibitors like quinidine with digoxin shows significant clearance changes. ¹⁶
	When Drug A blocks the transport of Drug B into the intestinal lumen and increases its plasma concentration.	Verapamil inhibits efflux transporters (P-glycoprotein) increasing plasma concentration of substrates like cyclosporine and digoxin.
METABOLISM	When Drug A induces a CYP450 isoenzyme which is responsible for the stimulation of metabolism of Drug B.	Phenobarbital increases the rate of metabolism of warfarin resulting in decrease anticoagulant activity.
	When Drug A induces a CYP450 isoenzyme which is responsible for the inhibition of metabolism of Drug B.	Erythromycin strongly inhibits CYP3A4, major enzyme responsible for sildenafil metabolism.
	When Drug A inhibits CYP450-independent oxidation and causes accumulation of toxic intermediary metabolites of Drug B.	Sunitinib when concomitantly used with CYP3A4 inhibitors (clarithromycin, erythromycin) results in risk of dermatological toxicities, due to decreased metabolism of sunitinib. ¹⁷
RE-NAL CLEAR-ANCE	When Drug A competes for renal transport with Drug B and increases its elimination half-life.	By causing sodium loss, diuretics can reduce the renal clearance of lithium, and increase lithium retention, with potential toxicity.

CYP450; Cytochrome P 450

TABLE 2: Types of pharmacodynamic drug-drug interaction

Types	Mechanism	Examples
RECEPT ALTERA'	When Drug A is administered chronically, it reduces the number of its own receptors and/or modifies the adaptability of receptors to physical events.	The decrease in number of insulin receptor during a extended exposure to insulin. The surface receptors for insulin gradually decreases by receptor internalization and degradation brought about by increased hormonal binding. ¹⁸
	When Drug A is administered chronically, it increases the number of its own receptors and/or modifies the adaptability of receptors to physical events.	The increase in number of receptors for nicotine upon chronic exposure to nicotine, despite nicotine being an agonist. ¹⁸
PHAR-MA-CO-LOG-ICAL	When an antagonist (Drug A) and an agonist (Drug B) compete for the similar receptor site and as a result of their respective concentration, they either produce (agonist) or prevent (antagonist) an effect.	Concurrent use of epinephrine and β 1-adrenergic receptors: Subsequently the β 1-adrenergic receptors are blocked; unopposed α 1-adrenergic receptor activation by epinephrine possibly can cause hypertensive reaction.
PHYSIOLOGICAL	When Drug A and Drug B interact with different receptors and improve each other's actions through different cellular mechanism.	Alcohol enhances analgesic activity of aspirin
	When Drug A and Drug B interact with different receptors and produce opposite effects through different cellular mechanism.	Salicylates decreases the ability of platelets to aggregate thus impairing the Homeostasis if warfarin induced bleeding occurs.
CHEM-ICAL	When Drug A interacts with Drug B and averts Drug B from interacting with its intended receptor.	When ethanol interacts with sedatives, ethanol averts sedative from interacting with its intended receptor.

other new chemical drugs. These products are categorized as dietary supplements with pharmacological properties, yet have potential to cause harmful side effects. The term ‘Herbal products’ commonly involves preparations obtained from herbs, roots, leaves, spices, stems and other materials of natural source. These include products prescribed therapeutically or OTC (over- the- counter) medications or used as cosmetics or applied topically.¹⁹

It has turned out to be challenging to identify the probability of herb drug interaction, due to the following reasons:

- Mixture of multiple ingredients of numerous pharmacological significance
- Ease of access and obtainability of various herbal products in market place

- Absence of proper data on mechanism of interaction and pharmacological properties of herbal products
- Herbs with lower possibility of adverse effects
- Dishonest information on the labels of herbal products.^{20,21}

7 | MECHANISM INVOLVED IN HERB-DRUG INTERACTION

- Pharmacokinetic Interactions:

Changes in absorption, distribution, metabolism or elimination of drugs are referred to as pharmacokinetic interactions, resulting in alteration in the level of drugs and its metabolites.

- Herb-Drug Interaction at Absorption Level:
- Herbs Interactions on Efflux transporters: Efflux of herbal drugs in contrary to a sharp concentration gradient is mediated by ABC (ATP binding cassette) transporters, typically sited in the canalicular membrane of intestinal epithelium, kidney, liver or endothelial cells of blood capillaries of brain.¹¹ These transporters are comparatively easily modified by factors like drugs and herbal medications, foods and drinks. The efflux transporters also play a vital role in restraining the influx of xenobiotics, hence inhibiting the intracellular build-up of their substrates. The interaction of herbs and the activity of efflux transporters may be avoided by competitive and/or non-competitive mechanisms, which eventually leads to potential toxic blood plasma concentration of the substrates. Also, it may lead to treatment failure through induction of efflux transporters by the herbal substrates.²³

The examples are-

P- Glycoprotein (P-gp): P-glycoprotein play a vital role in oral drug absorption and reduces the bioavailability due to intact drug molecules are driven back to the gastrointestinal tract lumen and are exposed several times to enterocyte metabolism using Adenosine Triphosphate as an energy source.¹³ P-gp plays a significant part in regulation of absorption, distribution, elimination and reabsorption of clinically active therapeutic agents. Therefore, variation in P-gp by herbal products involves direct interaction with one or more binding site on P-gp molecules.²⁵

For example: Grapefruit juice inhibits P-gp rhodamine-123 efflux in-vivo in healthy individuals and in-vitro in Caco-2 cells. It was observed that the bioavailability of nifedipine increases in-vivo in rats and talinolol in-vitro in Caco-2 cells.²⁶

Multi- Drug Resistance- Associated Protein-2 (MRP2): The expression of MRP2 is relatively high in proximal and very little in distal region of human intestines. It is found in several cancer cells and tumors. It is also responsible for biliary secretion of organic anions like campyothecin

and acetaminophen glucuronide.²⁷ Breast Cancer Resistance Protein (BCRP): BCRP is also known as mitoxantrone resistance gene, found in several tumor cells and also in normal human tissues. It causes resistance to few narrow spectrum anticancer drugs.²⁸

For example: Flavonoids such as biochaninA, apigenin, kaempferol from *Silybummarianum* increases the buildup of mitoxantrone by inhibiting BCRP.²⁹

Uptake Carrier Proteins: The solute carrier transporters like Organic Cation Transporters (OCTs), Organic Anion Transporters (OATs) and Organic Anion Transporting polypeptides (OATPs), specially mediate the uptake of substrates into cells.³⁰

For example: OATP1 and OATP3 is inhibited by components of Seville orange and apple juices, decreasing uptake and leading to sub-therapeutic in-vivo and in-vitro concentrations.³⁰

- Herb Interactions on Gastrointestinal Motility:

On consumption of herbal products may lead to altered gastrointestinal motility, which eventually create a severe impact on therapeutic outcomes of herbal drugs. Herb induced diarrhoea, resulting in short transit time of herbs lateral to gastrointestinal tract, decreases contact time with gastrointestinal epithelial cells and hence, leading to decreased drug absorption.³¹

For example: Leaf extract of *Ginkgo biloba* contains flavonoids and terpenoids which increases gastrointestinal motility.³²

- Herb Interaction through Complex Formation:

Reduction in the bioavailability of co-administered drugs takes place as a result of formation of insoluble herb-drug complex in gastrointestinal (GI) tract.³³

For example: Fibres like psyllium and alginates form chelate with iron and other drugs like metformin.³³

- Herb- Drug interactions at Distribution Level:

Herbs like black willow and meadowsweet (containing pain-reducing salicylates), displaces highly protein bound drugs like carbamazepine and increases its adverse effects. Concurrent use of these products should be avoided.³⁴

- Herb- Drug interactions at Metabolism Level:

Inhibition or induction of drug metabolic enzymes by simultaneously used herbal drugs, results in pharmacokinetic herb- drug interactions.³⁵

1. Example of Enzyme Induction: Hypericum perforatum induces CYP3A4 and CYP2B6 enzymes, which results in reduction in plasma concentrations of some chemotherapeutic agents like irinotecan and imatinib.³⁶
2. Example of Enzyme inhibition: Furanocoumarins and *C. sinensis* increases the plasma levels of numerous medicines like cyclosporine, midazolam and terfenadine through mechanism-based inhibition of CYP3A4 isoenzyme in humans.³⁷
3. Herb- Drug interactions at Elimination Level:

8 | KIDNEY AND BILE REMAIN THE TWO MAJOR ROUTE OF ELIMINATION OF DRUGS. THERE IS NO IMPORTANT DRUG INTERACTION THROUGH BILE EXCRETION BUT DRUGS, PRIMARILY EXCRETED THROUGH KIDNEY INVOLVES HERBS-DRUG INTERACTION THROUGH SEVERAL MECHANISMS LIKE ACTIVE TRANSPORT SITES COMPETITION, ALTERED GLOMERULAR FILTRATION RATES, ACTIVE SECRETION, PASSIVE RENAL REABSORPTION OR PH OF URINE.³⁸

For example: *Callilepis laureola* was found to damage the Loop of Henle and proximal convoluted tubules, hence hepatotoxic. Goldenrod, asparagus roots, alfalfa constitute diuretic properties and increases renal elimination of some medicines.³⁹

- Pharmacodynamic Interactions:

These interactions involve the pharmacological responses like mechanism of action and altered physiological responses of drugs on body and changes

in relation of concentration of drug-to-drug action. Herb- drug pharmacodynamics interactions involve pharmacological changes of drugs through synergistic, antagonistic or additive effects.⁴⁰

Any herbal medicine may be a mixture of several ingredients with unknown biological mechanisms, thus an herbal preparation can possibly increase, decrease or mimic the pharmacological effects of co-administered drugs by effecting on similar drug targets.⁴¹ Undesirable effects may cause drug target toxicity, if the drug used concurrently with herbal drug is increased synergistically or additively.

For example: Herbal medicines like ginger, garlic chamomile may increase the anticoagulant activity of warfarin.⁴²

9 | DRUG FOOD INTERACTION

The effect of drug changes from person to person than expected because it causes different reaction when a drug reacts with the food or dietary supplements they take (drug -food interaction). So, the effect of the drug is altered by means of increasing, decreasing, or producing a new effect which cannot be produced on its own the effect caused by food or dietary supplements. These interactions may occur due to accidental misuse or due to other factors such as lack of knowledge about it. Food-drug interactions occur when drugs or food when taken simultaneously can cause change in the mechanism of the body to metabolize or utilize a food or drug and can cause side effects. Changes in the pharmacodynamic, pharmacokinetic or on pharmaceutical factors are the ones which products clinically significant drug interactions. They can cause benefit or cause adverse drug reactions.⁴³

10 | MECHANISM OF FOOD-DRUG INTERACTION ON

Absorption

Absorption, that is, by concentration gradients or through transporters, can happen both passively and actively. A wide number of transporters and enzymes

are used in order to ingest or metabolise enterocytes. Drug molecules can use similar mechanisms of food-drug interactions in order to access the systemic circulation.⁴⁴

Interaction with uptake and efflux transporters

The nutrient molecules vying for the same transport route communicate with the drug molecules, triggering drug food interactions, to list, absorption and efflux transporters in the human intestine (and other organs).⁴⁵

1.1.2 Organic anion transporting polypeptides (OATP)

They belong to the transporter family of protein uptake, situated in both the liver and the intestine. It is suspected that OATP2B1, which is found in the apical membrane of intestinal enterocytes, plays a significant role in the digestion of nutrients and drugs. The mechanism, like bile acids, thyroid, etc, is said to be involved in the conversion of endogenous substrates.

For e.g., statins, protease inhibitors, fexofenadine, midazolam, montelukast, aliskiren, and talinolol are common drug substrates that are said to interfere with food substrates such as grapefruit, orange, and apple juices by decreasing intestinal absorption.⁴⁶

1.1.3 Oligopeptide transporter (PEPT1)

They are predominantly located in intestinal epithelial cells' apical membranes. The most popular drug substrates include β -lactam antibiotics, cephalosporins, l-dopa prodrugs and certain ACE inhibitors. Where an oligopeptide competes with a peptidomimetic drug, an association could occur, observed that Parkinson patients could be on a low-protein diet relative to a high-protein diet.⁴⁷

1.1.4 P-glycoprotein (P-gp)

It can be found in a vast variety of tissues, too. ATP hydrolysis, while not fully understood, is considered to be involved. P-gp inhibitors are thought to be substrates such as antiarrhythmics, antihypertensive medications, cyclosporine, tacrolimus and morphine (Furanocoumarins and flavonoids found in a wide range of fruits and vegetables). For example, when mixed with a fruit juice inducing OATP inhibition compared to P-gp, the bioavailability of fexofenadine is decreased.⁴⁸

1.1.5 Other efflux transporters

Other efflux transporters present in the apical membrane of intestinal cells are multidrug resistance associated proteins (MRPs) and Breast Cancer Resistance Protein (BCRP). In general, MRP effluxes conjugate metabolites including glutathione, enterocyte adducts of glucuronides. Flavonoids are popular inhibitors. Conjugated statins, steroid receptors, folic acids and B2 vitamins are the substrates of BCRPs.

1.1.6 Interaction with intestinal monolayer: membrane fluidity

Those that increase the fluidity of the intestinal monolayer change the absorption of drugs due to the fact that increasing fluidity raises the rate of diffusion of such drugs. Flavonoids, cholesterol and α -tocopherol are primarily compounds that indicate differentiation into cell membranes.

1.3 Interaction with intestinal drug-metabolising enzymes

CYP3A and CYP2C9 are the major enzymes that induce an immense rise in overall CYP content, but along the small intestine it can be varies differently. The levels can vary greatly across the small intestine and the liver.

2 Food effects on drug distribution

Food may modify the path of drug delivery from the stomach to the circulation of the blood (lymph vs. portal vein), as well as the transfer of drugs to organs and tissues, including target and off-target locations, and elimination organs.

2.1 Lymphatic drug transport

After ingestion, drugs are transferred from the stomach to the blood through the mesenteric capillaries and veins. They then penetrate the liver via the portal vein. Based on the lipid content in consumed foods, the intestinal lymphatic transport of strongly lipophilic drugs shifts. Improving the bioavailability of medications would decrease the metabolism that induces medicinal results

2.2. Binding to lipoproteins

Lipoproteins are macromolecular carriers that allow medications such as halofantrine, cyclosporine A, clozapine, haloperidol, paclitaxel, etc. to carry lipids and lipophilic molecules into the aqueous atmo-

sphere of the blood circulation and lymphatic system. The delivery of lipids and the metabolism and tissue uptake of lipoprotein lipids is altered after a meal. Changes in the binding of plasma protein adversely affect those with a small clinical window where clearance is high and hence changes in free plasma concentration.

2.3 Plasma Protein Binding

Albumin is the most abundant plasma protein (3.5-5 g/dL concentration) and the most common protein to which plasma drugs bind. While present in far lower amounts than albumin (0.04-0.1 g/dL), alpha-1 acidic glycoprotein (AAG) is the second major plasma protein that binds to narcotics. For some endogenous compounds, some other proteins have particular affinities and can bind to specific drugs. There are two key albumin drug binding sites, site I (also known as the warfarin binding site) and site II (the benzodiazepine binding site). Albumin and AAG concentrations can be affected by changes in diet status. Albumin and AAG concentrations may be decreased by starvation and cachexia, whereas a high protein diet may increase plasma protein concentrations. Dietary components and metabolites can also have a possible effect on drug binding to plasma proteins. For starters, fatty acids are strongly bound to albumin, and the binding of drugs to albumin will allosterically modulate changes in fatty acid concentration.

3 Food effects on metabolism

The effect of drug-metabolising enzymes and drug transporters may be altered by food components. The most well-known example is that grapefruit juice inhibits the metabolism of CYP3A substrates. CYP3A enzyme inducers may also activate essential food intake interactions.

4 Food effects on elimination

In addition, nutrition will modify the end by modifying urinary pH alkalization processes due to drain admissions, vegan calories count or due to fermentation caused by a very rich protein diet. The changes in pee pH can contribute to a difference in the pharmacokinetics of medications disposed of by the kidneys when the non-ionized shape is reabsorbed during glomerular filtration or discharge. For

example, it is recommended that calorie count should be maintained relentlessly in memantine administration as its pharmacokinetic profile is fundamentally impaired by pH.

Does drug food interaction be considered serious?

Food-drug reactions may have detrimental impacts on the efficacy and effectiveness of drug treatment, as well as on the patient's nutritional status. Generally speaking, medication reactions, owing to the risk of bad or unexpected effects, should be discouraged. Like food, via the lining of the stomach or the small intestine, medicines ingested by mouth must be swallowed. Consequently, absorption of a drug may be decreased by the presence of food in the digestive tract. Sometimes, by taking the medication 1 hour before or 2 hours after feeding, such interactions can be prevented. Like medications, foods are not checked as closely enough that they can compete with prescription or over-the-counter medicines.⁴⁹

Drug-food interactions can result in decreased drug effectiveness or increased drug toxicity in hospitalised patients. The increasing complexity of drug therapy regimens has raised the possibility for drug-food reactions to arise, highlighting the need to improve strategies to reduce drug-food interactions of therapeutic importance.

Until choosing the best approach, medications with the potential for clinically relevant reactions with food must be defined in terms of viability of adoption and efficient result.⁵⁰

Drug Alcohol Interaction

Ethanol and drugs can influence each other's assimilation, dispersion, digestion system, and excretion. When ingested together, ethanol can increment medicate retention by improving the gastric solvency of drugs and by expanding gastrointestinal blood stream. In any case, tall concentrations of ethanol actuate gastric bothering causing a pyloric fit which in turn may delay medicate retention and/or decrease bioavailability. The 'quality' of the alcoholic refreshment, autonomous of its ethanol substance, can contribute to changed retention of a medicate.

Ethanol is not deeply bound to plasma proteins sufficiently to change the delivery of drugs. Serum albumin levels can, however, be abnormally low in

chronic alcoholics, so that certain medications, such as diazepam, have an increased delivery rate.

In addition to the consumed volume, ethanol has an effect on the metabolism of the medication on the duration of its daily intake. Acute ethanol intake prevents the metabolism of many medications, but high-level ethanol intake over the long term (> 200g of pure ethanol per day) will cause liver enzymes to more effectively metabolise drugs. There are actually no reliable methods, with the potential exception of liver biopsy, of scientifically predicting the ability of alcoholics to use metabolic drugs. Several medications can inhibit the metabolism of ethanol at the stage of alcohol dehydrogenase. The magnitude of this drug-ethanol reaction is determined by human predisposition.

Ethanol prevents antidiuretic hormone production during the ingestion process and is also capable of causing accelerated excretion of a drug through the kidneys. However, chronic alcoholics with water accumulation may have decreased opioid excretion through this method.

At the pharmacodynamic stage, ethanol will intensify the deleterious effects on efficiency of sedatives, some anxiolytics, sedative antidepressants and antipsychotics, and anticholinergic agents.

There is a lack of knowledge mechanism of lethal associations between mild and overdose ethanol / opioid / sedation. Any peptides, 'unspecific' stimulants, dopaminergic agents and opiate antagonists, on the other hand, can substantially antagonise alcohol-induced intoxication.⁵¹

The acute high dose of rapidly administered alcohol reduces the metabolism of microsomal drugs and thus increases opioid effects. The synthesis of Cytochrome P-450 isoenzyme P-450 II E1 typically results with chronic alcohol administration, thereby accelerating the metabolism of the organism and of different drugs depending of circumstances. The agents will then reduce their actions. When a drug (eg. paracetamol) is poisonous, it will paradoxically decrease the drug effect, whereas chronic consumption of alcohol is increased by development of active metabolites.

The induction by alcohol of hepatic enzymes may influence the turnover of endogenous vitamins and

hormones or even the development of carcinogenic agents.

The drug classes that associate substantially with ethanol include:

1. Depressants of the central nervous system (hypnotics, antidepressants, psychotropic medications, H1-antihistamines, anticonvulsants), the cumulative effects of which are often additive and without any substantial pharmacokinetic component;
2. Antabuse-provoking reaction agents (disulfiram, carbimide, etc.);
3. Vasodilating agents, which can result in an abrupt breakdown;
4. Anti-diabetic pharmaceutical products (poor diabetes control; antabuse reaction);
5. Anticoagulants with coumarin (instable kinetics during drinking spells);
6. Non-steroidal (gastrointestinal toxicity, core associations possible) anti-inflammatory drugs;

The collective activities of groups 1 and 2 impact the nervous system.⁵²

COMMON FOOD INTERACTIONS WITH OTC MEDICATIONS:

The drug which are available without prescriptions are called as Over-the-counter (OTC) medications. In India, which medicines are mentioned under various schedules in the Drugs and Cosmetics (D&C) Act and Drugs and Cosmetics (D&C) Rule. Drugs that are listed in Schedules X, H and H1 should bear a label by stating that these drugs are should be sold by retailer only on prescription of a registered medical practitioner, and the drugs mentioned in Schedule G (most of them are antihistamines) should have a mandatory text on the label saying, "Warning/Caution: this is unsafe to take this medication without medical supervision." shockingly, certain significant drug categories such as aminosalicylates and diuretics (mesalamie, sulfasalazine) are not included under any drug schedule, hence it is creating a confusion among pharmacists whether to sell these drugs prescription or OTC medicines. Many OTC medications interact with Food and drugs, also have adverse reactions. So, it is important to avoid those inappropriate OTC dispensing which is the main

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cause for food-drug interactions by properly advising and counselling the patients.⁵³

Interactions between food and drugs may unintentionally increase or decrease the effect of drug. Most common food includes some herbs, fruits as well as alcohol which may cause unsuccessful therapy and some severe alteration in the health of the patient. Most of the clinically related food-drug interactions are caused by food-induced alterations in the drug's bioavailability. Table 3 Table 4⁵⁴

TABLE 3: Shows some common interactions between food and OTC drugs.

OTC Drugs	Foods	Mechanism
Acetaminophen	Pectin	Delays the absorption and onset of action.
NSAID'S	Alcohol Beverages	May increase risk of liver damage and stomach bleeding
Antibiotics	With milk products (cheese, curd, yogurt)	Form complexes and prevent the absorption and reduce bioavailability
Multivitamins	Milk and other dairy products (cheese, yogurt)	Decreases the absorption of certain ingredients present in the multivitamins
Iron supplements	Milk and other beverages including tea	Inhibits the iron absorption
Insulin	Sugary drinks, Alcohol	Sugary drinks spike the insulin levels. Alcohol alters glucose effect of insulin.
Cimetidine, Ranitidine	With food (any type)	Increases bioavailability
Antihistamines	Grape fruit juice	Increases drug toxicity ⁵⁵

INTERACTIONS- READDRESSING THE ISSUE

TABLE 4: Newly reported Drug-Druginteraction

Sl.No	DRUG NAME	BRAND NAMES	CLASS	INDICATION	SEVERITY OF INTER-ACTION	INTERACTION	MECHANISM OF INTERACTION AND EFFECTS
•	Lonafarnib	Zokinvy	Farnesyl transferase (FTase) inhibitor (FTI)	Hutchinson-Gilford Progeria syndrome (HGPS)	Major	The plasma concentration of Lonafarnib may be increased by grape juice	Certain compounds of grapefruit juice inhibit the CYP450 3A4 mediated first pass metabolism in the gut wall. ⁵⁶
•	Remdesivir	Veklury, Remdac	Antiviral (anticoronaviral)	COVID-19	Moderate	Alcohol presents a moderate drug interaction with Remdesivir. As Remdesivir can cause liver problems, its use alongside other medications that can also affect the liver such as ethanol may increase that risk	Clinical manifestations that may appear due to this interaction is symptomatic of liver problems including: fever, chills, joint pain or swelling, nausea, vomiting, abdominal pain, unusual bleeding or bruising, skin rash, itching, loss of appetite, fatigue, dark urine, pale stools, and/or yellowing of the skin or eyes. ⁵⁷

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Table 4 continued

•	Pralsetinib	Garvito	Kinase inhibitors (phosphotransferase inhibitors)	Metastatic RET fusion-positive non-small cell lung cancer (NSCLC) in adults	Major	Pralsetinib should be taken on an empty stomach, at least 2 hours before or 1 hour after a meal. Do not consume grapefruit, grapefruit juice, or any supplements that contain grapefruit extract during treatment with pralsetinib unless directed otherwise by your doctor	Grapefruit juice can increase the blood levels of pralsetinib. This may increase the risk and/or severity of serious side effects such as lung problems, high blood pressure, liver problems, bleeding, fatigue, muscle pains, or constipation. ⁵⁸
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Table 4 continued

••	Osilodrostat Isturisa	Cortisol synthesis inhibitors	Cushing's disease (In adults who cannot have pituitary surgery)	Moderate	Interaction with caffeine	Osilodrostat may increase the blood levels and effects of caffeine. You may need a dose adjustment or more frequent monitoring by your doctor to safely use both medications. ⁵⁹
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Table 4 continued

•	Ozanimod	Zeposia	Sphingosine 1- phosphate receptor modula- tors	Multiple Sclerosis (MS), to include clinically isolated syn- drome, relapsing- remitting disease, and active secondary pro- gressive disease, in adults	Major	While taking ozanimod, one must not eat or drink certain foods and beverages that are high in tyramine.	Eating tyramine rich foods while taking ozanimod can raise blood pressure to dangerous levels leading to life threatening symptoms such as sudden and severe headache, confusion, blurred vision, problems with speech or balance, nausea, vomiting, chest pain, seizures and sudden numbness or weakness (especially on one side of the body). ⁶⁰
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Table 4 continued

••	Oliceridine	Olinvyk	G protein pathway selective modulator (μ GPS) to the mu-opioid receptor	Spinal cord stimulators in acute and chronic pain conditions	Major	oliceridine with alcohol & with grapefruit	Alcohol may potentiate the central nervous system (CNS) depressant effects of opioid analgesics including oliceridine. Concomitant use may result in additive CNS depression and impairment of judgment, thinking, and psychomotor skills. Grapefruit or grapefruit juice may increase the plasma concentrations of oliceridine by inhibiting the CYP450 3A4-mediated metabolism of oliceridine. ⁶¹
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Table 4 continued

••	Pemigatinib Pemazyre	Kinase inhibitors	Unresectable locally advanced or metastatic cholangiocarcinoma in previously-treated adult patients with a fibroblast growth factor receptor 2 (FGFR2) fusion	Major	Do not consume grapefruit, grapefruit juice, or any supplements that contain grapefruit extract during treatment with pemigatinib unless directed otherwise by your doctor	Grapefruit juice can increase the blood levels of pemigatinib. This may increase the frequency and severity of serious side effects such as abdominal pain, kidney injury, inflammation and infection of the bile duct system, diarrhea, failure to thrive, blood calcium levels above normal, blood sodium levels below normal, fluid buildup between tissues that line the lungs and chest, fever, small intestinal obstruction, and urinary tract infection. ⁶²
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Table 4 continued

••	Semaglutide Ozempic, rybelsus	Incretin Mimetics	Type 2 Diabetes Mellitus	Moderate	Interaction with alcohol	Alcohol may affect blood glucose levels in patients with diabetes. Both hypoglycemia (low blood sugar) and hyperglycemia (high blood sugar) may occur, depending on the level of alcohol consumption. ⁶³
••	Lurbinectedin Zepzelca	Alkylating agents (antineoplastics)	Metastatic small cell lung cancer (SCLC) in adults	Moderate	Do not consume grapefruit, grapefruit juice, or any supplements that contain grapefruit extract during treatment with lurbinectedin unless directed otherwise by your doctor	Grapefruit juice may increase the blood levels of lurbinectedin. This may increase side effects such as liver problems and impaired bone marrow function resulting in low numbers of different types of blood cells. ⁶⁴

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Table 4 continued

••	Nifurtimox	Lampit	Nitrofurantoin antiprotozoal	Chagas disease (American Trypanosomiasis) in children and sleeping sickness.	Major	Consumption of alcoholic beverages or products containing alcohol during treatment with nifurtimox is not recommended.	Interaction of alcoholic beverages or products containing alcohol during treatment with nifurtimox may occasionally trigger a reaction in some patients similar to the disulfiram reaction, which includes unpleasant effects such as flushing, throbbing in head and neck, throbbing headache, difficulty breathing, nausea, vomiting, sweating, thirst, chest pain, rapid heartbeat, palpitation, low blood pressure, dizziness, lightheadedness, blurred vision, and confusion. ⁶⁵
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MOST DANGEROUS FOOD-DRUG (PRESCRIBED) INTERACTIONS: Table 5**PREVENTIVE STRATEGIES TO AVOID FOOD-DRUG INTERACTIONS BY CLINICAL PHARMACIST**

Avoidance of adverse effects from food-drug-herb interactions may require clinical monitoring in high-risk regimens and populations especially in geriatrics. Both diet history and drug history required for counselling the patients to avoid food-drug interactions.⁶⁷

Conventionally, food and drug interactions are recognized when a food or nutrient interferes/alters the action of a drug, especially in the inpatient where monitoring results in rapid diagnosis of therapeutic failure. The reverse situation that is when a drug interferes with nutritional status, it is not easy to be diagnosed, recognized or monitored. Diagnosis of food-drug interactions may even more slowly in the outpatient for several reasons.⁶⁸

Above 30% of all the drugs with prescription are found to be taken by Geriatrics.⁶⁹ Use of over-the-counter (OTC) drugs is also highest in Geriatrics.⁷⁰ Malnutrition status can also hinder with effectiveness of drug or drug release leading to a great risk of drug toxicity.⁷¹

Clinical pharmacists need to be attentive and cautious in observing for possible drug-food interactions and counselling patients regarding their foods or beverages that should avoid when taking certain medications. It is essential for clinical pharmacists to keep up to-date knowledge on possible drug-food interactions of medications. In providing drug information to patients, clinical pharmacists should discuss possible side effects and the way to take medication.⁷²

It is essential to give information to patients on their medications with related to intake of food. Major consequences of food-drug interactions include decreased, increased or delayed absorption of the drug. Food may also affect the pharmacokinetics (bioavailability, metabolism and excretion) of many drugs. The patient also experiences toxicity or an adverse side effect and may not receive the complete therapeutic benefit of the medications. The Joint

Commission on the Accreditation of Healthcare Organizations (JCAHO) needs that a patient's drug profile include possible drug-food interactions, that the clinical pharmacist can call the prescriber whenever there is possibility of a food-drug interactions and document the same and follow-up action should be taken on the prescription, after that patients should be given with instructions and counselling regarding the possibility of food-drug interactions before their discharge from the hospital.⁷³

Geriatric patients may be at a higher risk of developing food-drug interactions because of their typically consumption of more drugs for their chronic medical conditions/illness. A study "Drug-nutrient interactions in long-term care facilities" found a major relationship between the number of medications a patient consumed and the number of drug-nutrient interactions for which a patient was at risk.⁷⁴

Guidance and Counselling to minimize Food-Drug Interactions

The below mentioned information can be given to the patients while dispensing the medicine.

- Read the label of prescription on the container. If you do not understand or you need more information about your medication, ask your pharmacist or physician.
- Read warnings, directions and interaction precautions printed on all medication labels and package inserts carefully. Even over-the-counter (OTC) medications can cause problems.
- Take your medication with a full glass of water to avoid GI irritations.
- Do not stir your medication into your food and do not take capsules apart (unless directed by your physician). Doing this may affect the efficacy of the medication.
- Do not take vitamin pills/multivitamin tablets or capsules at the same time you take medication. Vitamins and minerals also interact with some medications.

TABLE 5: Commonly reported Drug-Food interaction

Drugs	Foods	Mechanism
Theophylline	High fat meal and grape fruit juice.	Increased in bioavailability.
Warfarin	Caffeine.	Increases toxicity of drug.
	Vegetables containing vitamin K	Alters the effectiveness and safety of warfarin therapy
	Cooked onions	Increases activity of warfarin
	High-protein diet	Decreases warfarin activity and increases serum albumin levels
	Green leafy vegetables	Thromboembolic complications.
Monoamine oxidases	Tyramine containing food	Hypertensive crisis
Propranolol	Protein rich food	Increases serum level
Celiprolol	Orange juice	Inhibits intestinal absorption
ACE inhibitors	Empty stomach	Increased absorption
Calcium channel blockers	Grape fruit juice	Increased bioavailability
Isoniazide	Medicinal herbs	Synergism effect
Cycloserine	High fat meals	Reduces serum concentration
Glimepride	With breakfast	Absolute bioavailability
Mercaptopurine	Cow milk	decreases bioavailability
Tamoxifen	Sesame seeds	Beneficially interacts with tamoxifen on bone in ovariectomized athymic mice but negatively interferes with tamoxifen by inducing regression of recognized mcf-7 tumour size.
Levothyroxine	Grape fruit juice	Delay the absorption
Statins	Grape fruit juice	Increases medication potency
Prescription stimulants (dextroamphetamine, methylphenidate)	Alcohol	Drug toxicity ⁶⁶

- Do not mix or stir your medication into hot drinks because the heat from the drink may destroy the effectiveness of the drug and also it causes some adverse effects.
 - Never take any of your medication with alcoholic drinks. It causes some serious unwanted and harmful reactions.
 - Don not forgets to tell your pharmacist and physician about all medications that you are taking, both prescribed and over-the-counter (OTC).
1. Talk with the pharmacist about how food can affect specific medications taken with the food.75

Conclusion:

This review provides a comprehensive literature review on various drug interaction. Generally, drug food interactions are neglected and not well defined but it can cause mild to serious effects. However, all clinicians, pharmacists and nurses should be aware of drug interaction to avoid the consequences caused by drug interactions.

Abbreviation:

- DDIs- Drug- Drug Interactions
- CYP450- Cytochrome P 450
- FDA- Food and Drug Administration
- P gp- P- Glycoprotein
- MRP2- Multi- Drug Resistance- Associated Protein- 2
- OTC - Over-the-counter
- JCAHO - Joint Commission on the Accreditation of Healthcare Organizations

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