Review on Preclinical and Clinical Evidence of Food (Beverages, Fruits and Vegetables) and Drug Interactions: Mechanism and Safety

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Abstract: Background: The therapeutic potency and efficacy of drugs can be affected by a patient’s dietary habit. The food composition and their nutritional value interact with drugs that lead to alteration of the therapeutic response of drugs in patients.

Objective: This present review is an attempt to illustrate clinical reports of food-drug interaction. Further, it also highlights specific interaction mechanism(s) and the safety thereof.

Methods: Through the search engine “Scopus”; literature on recent advances in food and drug interactions includes almost all therapeutic categories such as antimicrobials, antiviral, antifungal, antihistamines, anticoagulants, non-steroidal anti-inflammatory drugs, and drugs acting on the central nervous system and cardiovascular system.

Results: Preclinical and clinical studies that have been conducted by various researchers affirm significant drug-food interactions across the various therapeutic categories of drugs. Preclinical studies have documented the effects of food, milk products, alcohols, fruit and vegetables on the drug absorption, metabolizing enzymes and drug transporters. The clinical studies on food/vegetables and drugs interactions report significant alteration in therapeutic response.

Conclusion: Based on the preclinical and clinical reports, it can be concluded that the interaction of food with drug(s) significantly alters their therapeutic potential. The inputs from clinical practitioners to elucidate potential risk of food-drug interaction need to be intensified in order to prevent adverse clinical consequences.

Keywords: Preclinical reports, clinical study, food, drugs, interaction, therapeutic.

1. INTRODUCTION

Drugs are used to treat acute and chronic diseases or disorders. Newer drugs and dosage forms are being developed to improve health via novel research technology [1]. Drugs have specific physicochemical properties and have specific predictable effects and side effect(s) and are deemed not to be affected by concomitant food or other medications [2]. However, many drug-food interactions tend to occur due to the concomitant use of drugs and broad variability in nutrition status, dietary habits, food composition, and dietary supplement [3]. Food and drug interactions are defined as an alteration in pharmacokinetics or pharmacodynamics of a drug or nutritional element or as a compromise in nutritional status of food as a result of drug’s presence [4, 5]. Pharmacokinetics refers to the quantitative description of drug disposition, which includes absorption, distribution, metabolism, and excretion while pharmacodynamics refers to the physiologic or clinical effects of a drug [6].

Bobroff et al. reported that food-drug interactions are frequently caused by chelating with food element that may affect the bioavailability of certain drugs [7]. Chan et al. (2006) also reported that food-drug interactions can result in two main clinical effects: either a decreased bioavailability of a drug, which predisposes to treatment failure, or an increased bioavailability, which increases the risk of adverse effect and may even induce toxicities. Patient populations who have increased risks of suffering from adverse effects associated with drug-nutrient interactions are elderly patients, cancer patients, malnutrition patients, gastrointestinal tract dysfunctions, acquired immunodeficiency syndrome, those receiving enteral nutrition and transplant recipients. Elderly patients are particularly at high risk because more than 30% of all the prescription drugs are taken by this population [8]. Reports the high risk of treatment failure arising due to significantly altered bioavailability of drug have been documented in the literature. The alteration may lead to se-
vere adverse effects in geriatric patients during treatment of major disorders.

With the background of previous studies of food-drug interaction, this review is an attempt to compile preclinical and clinical evidence of food (beverages, fruits and vegetables) and drug interactions: mechanism and safety, primarily in the past two decades.

2. FACTORS AFFECTING FOOD AND DRUG INTERACTION

The physical and chemical properties of a drug and food are important factors for their interaction potential. The impact of food and drug interactions depends on a variety of factors including the drug’s composition, dosage form and clinical factors like sex, age of the patient, family history of the patient, state of health and time of the drug taken. It is well documented that drug composition and the dosage form of drug interact with food and can significantly alter the drug response. Apart from these, the time of food and drug taken also has a significant role in food and drug interaction. It can be solved by maintaining sufficient gap between diet and drug taken [9]. For example, tetracycline and dairy product(s) should be taken at a different time to avoid food-drug interaction. Food affects absorption, distribution, metabolism or elimination of a drug which is termed as pharmacokinetic interaction of drug. When food or food derivatives affect the drug action at receptor level, it is called pharmacodynamic interaction (Fig. 1). There are only a few examples of pharmacodynamic interactions [10].

3. TYPES OF FOOD AND DRUG INTERACTIONS

3.1. Pharmacokinetic Interactions

The food and drug interactions can quantitatively alter the pharmacokinetics of drugs which is detailed as follows.

3.1.1. Drug Absorption

Food can affect drug’s absorption in the gastrointestinal tract by changing gastric pH, secretion, dissolution of drugs, chelation with food elements, gastric motility and transit time. This may result in the change of rate of absorption or extent of absorption of a drug or both [11, 12]. Jong and Chang reported that food products may chemically bind to the drugs, thus make insoluble salt which is not easily absorbed due to altered pharmacokinetics of the drug. For example, proteins in the food would bind to the antiepileptic agent, phenytoin, resulting in reduced phenytoin absorption and potentially inadequate seizure control [13]. Some tetracycline and fluoroquinolones can bind to calcium ions of dairy products resulting in a significant reduction in drug absorption leading to treatment failure [14]. Fat rich foods can enhance drug absorption by increasing the solubility of lipid soluble drugs like antiretroviral protease inhibitors e.g., saquinavir and atazanavir [15].

Primarily food dilutes the drug concentration and retards absorption. Various mechanisms by which food affects the bioavailability of drugs are discussed below [16]:

1. **Increase in viscosity of gastrointestinal contents:**
   An increase in the viscosity of gastrointestinal tract

Fig. (1). Flow diagram of food and drugs interactions.
i. Acetaminophen

Acetaminophen is used for the treatment of headache, muscle aches, arthritis, backache, toothaches, colds, and fevers. James et al. reported that the apparent inhibition of acetaminophen absorption by carbohydrate meals could be partially attributed to interaction with pectin in some cases [17]. Acetaminophen should be avoided with high-protein foods because these act as an adsorbent in its absorption [18].

ii. Digoxin

Digoxin helps to increase the contraction force of myocardial muscle and with a regular rhythm and is used to treat heart failure. If digoxin is taken with a high-fiber meal, a decrease in its bioavailability by almost 20% is reported. Fiber can sequester up to 45% of the drug, when given orally. Patients should be advised to maintain a regular diet without significant fluctuation in fiber intake while digoxin is being titrated [19-21].

iii. Levodopa

It is used alone or in combination with carbidopa for the treatment of Parkinson’s disease. Administration of levodopa (L-dopa) with high protein diet has shown that high protein food can interfere with the absorption and also that the high blood levels of protein interfere with the transport of levodopa from the blood into the brain. Therefore patients are advised to avoid high protein diet during levodopa treatment [22-26].

iv. Glipizide

Glipizide should be taken 30 min before meals because it delays the carbohydrate absorption by inhibiting the enzyme alpha-glycosidase, if taken with meals [27].

v. Quinidine

It is used to treat or prevent many types of irregular heartbeats such as atrial fibrillation. Food intake does not affect the bioavailability of quinidine sulfate, but it slows the absorption rate [28, 29].

vi. Methyldopa

Methyldopa should be avoided with concurrent administration of iron-containing products because it significantly decreases oral bioavailability and pharmacological effects. The proposed mechanism is chelation of methyldopa by the iron cation, forming an insoluble complex that is poorly absorbed from the gastrointestinal tract [30, 31]. Authors have also reported that methyldopa should be avoided with high protein food because it decreases the absorption of methyldopa due to competitive inhibition.

vii. Sulphonamide

Sulphonamide taken with meals may prolong gastric emptying. Sulfamethoxazole-trimethoprim administered after consuming beer results in flushing, heart palpitations, dyspnea, headache, and nausea (disulfiram-alcohol type reactions). The proposed mechanism is the inhibition of acetaldehyde dehydrogenase resulting in acetaldehyde accumulation. Patients should be alerted about the potential for this interaction and advised to avoid alcohol while taking sulfamethoxazole-trimethoprim [32].

viii. Tetracycline

Tetracycline should be taken one hour before meals and two hours after meals and not with milk. It binds with calcium ions and iron salts forming insoluble chelates [33].

3.1.1.2. Food Drug Interactions that Accelerate the Absorption of Drugs

i. Griseofulvin

Ingestion of alcohol during griseofulvin therapy may induce disulfiram-like reactions, flushing, tachycardia, or increased effects of alcohol. The mechanism is unknown [34].

ii. Propranolol

It is used to treat hypertension, heart rhythm, angina and other heart or circulatory conditions. Multivitamin with minerals may decrease the therapeutic effects of the drug. However, food increases absorption of propranolol, hence it should be taken with or immediately following meals. During treatment with propranolol, alcohol should be avoided as it could increase drowsiness and dizziness in patients [35].
3.1.2. Drug Metabolism

Various enzymes are involved in drug metabolism; and food may alter the hepatic metabolism of some drugs. Previous studies have reported that calcium channel blockers; felodipine administered concurrently with concentrated grapefruit juice results in significantly increased bioavailability of felodipine (284 %). This may be due to the inhibition of cytochrome P-450 metabolism of felodipine. This causes lowering of diastolic blood pressure and adverse effects like headache, facial flushing has been observed after ingestion of 250 ml (100 % v/v) of grapefruit juice. However, the bioavailability of nifedipine with grape juice is increased by 108-169 % but orange juice does not increase the bioavailability of nifedipine. In view of modulation in efficacy and toxic potential, patients consuming calcium channel blockers should be advised to avoid grapefruit juice concurrently with these drugs [36, 37].

The antidiabetic drug, troglitazone, when administered after meal results in an increase in its bioavailability by 59% enhanced insulin action [38]. Foods containing tyramine are normally inactivated by the enzyme monoamine oxidase (MAO) as they prevent tyramine from accumulating in the body. Monoamine oxidase inhibitors (MAOIs) can present potentially dangerous interactions with certain foods and beverages. So the physician advises to avoid foods containing high levels of tyramine such as aged cheese, sauerkraut, cured meats, draft beer and fermented soy products. The interaction of tyramine with MAOIs can cause high blood pressure [39].

3.1.3. Drug Excretion

Foods can alter the urinary pH, which may affect the therapeutic response of some drugs. The duration of action of some medications may be significantly changed by alterations in urinary pH due to altered half-life of drugs. Thus the half-life of acidic drugs is enhanced in acidic urine because its unionized form in the acidic medium is excreted slowly whereas the half-life of acidic drugs in alkaline urine medium is reduced as it will be in an ionized form and excreted fast. Lithium and sodium compete for tubular reabsorption in the renal tubule. A high-salt containing food causes more lithium to be excreted, whereas a low-salt containing food causes decreased renal excretion of lithium and increased lithium levels in serum [40]. The bioavailability of furosemide is reduced from 16 to 45% due to decreased absorption rate when taken with food, but food-drug interaction is absent in case of bumetamide [41-44]. A high intake of potassium-rich foods like bananas and spinach along with potassium-sparing diuretics may result in hyperkalemia [45].

3.2. Pharmacodynamic Interactions

Foods may react with drugs by altering their pharmacological actions called pharmacodynamics interactions. High vitamin K diets can be antagonized with warfarin and the therapeutic response of latter may be decreased hence, excessive intake of vitamin K with warfarin should be avoided [46, 47]. Some examples of vitamin K containing foods are pork and beef liver, green tea, turnip greens, spinach, broccoli, Brussels sprouts and cauliflower. Alcoholic beverages can enhance the sedative actions of narcotics, benzodiazepines, antipsychotics, antihistamines, and muscle relaxants [48]. Caffeine has mild bronchodilator effects and it may enhance the effects of theophylline. It may enhance the effects of theophylline due to increases serum theophylline levels by 20–30% and also enhances the half-life of theophylline by decreasing its clearance. Patients may complain of nervousness, tremor or insomnia due to enhanced dose of theophylline. A lower dosage of theophylline is advisable for those patients who consume excessive quantities of coffee.

4. SAFETY FROM VARIOUS KINDS OF FOOD AND DRUG INTERACTION

4.1. Drugs Recommended After a Meal

Inadvertently, most of the drugs are advised to be taken after meal to avoid GIT problems but some drugs should be

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Patient Counseling</th>
<th>Proposed Mechanism</th>
<th>Effect</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albenazole</td>
<td>After fatty meal</td>
<td>Increase dissolution with fat intake</td>
<td>Increased bioavailability</td>
<td>[49]</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>After a fatty meal</td>
<td>Increased solubility with fat intake</td>
<td>Increased target concentrations against Pneumocystis pneumonia infection</td>
<td>[50-53]</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>After meal</td>
<td>Unknown</td>
<td>Quick achievement of therapeutic level</td>
<td>[54]</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>After fatty meal</td>
<td>Absorption favoured by bile secretion</td>
<td>Suitability in treatment</td>
<td>[55-58]</td>
</tr>
<tr>
<td>Itraconozole capsules</td>
<td>After meal</td>
<td>Dependent on gastric acid for solubility</td>
<td>Improved clinical response</td>
<td>[59-63]</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Meal with low fibre</td>
<td>Increased solubility with fat intake</td>
<td>A high fibre diet leads treatment failure</td>
<td>[64, 65]</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>After food</td>
<td>Reduced absorption rate</td>
<td>Reduced risk of systemic adverse effect</td>
<td>[66, 67]</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>After food</td>
<td>Reduced absorption rate</td>
<td>Reduced risk of adverse effect</td>
<td>[68-72]</td>
</tr>
<tr>
<td>Quinidine sulfate</td>
<td>After food</td>
<td>Reduced absorption rate</td>
<td>Reduced risk of adverse effect</td>
<td>[73]</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>After a meal</td>
<td>Increased dissolution</td>
<td>High risk of treatment failure</td>
<td>[74, 75]</td>
</tr>
</tbody>
</table>

Table 1. A cross section of drugs recommended with meal, proposed mechanism and effect.
taken with meal because it enhances bioavailability, causes quick achievement of therapeutic levels and improved clinical response. Cross sections of such examples are listed in Table 1.

4.2. Drugs Recommended without Meal

Some drugs are advised to be take without meal because drugs may interact with food resulting in increased risk of treatment failure. Some drugs taken with food may result in severe toxicity because their absorption is favoured by bile secretion e.g. halofantrine. Thus, for reducing toxicity, these should be take before/after meals. Table 2 enlists examples of the drugs to be taken without meal.

4.3. Dairy Products and Drugs

When tetracycline or fluoroquinolones like ciprofloxacin, alendronic acid, etidronic acid, penicillamine, norfloxacin or bisphosphonates are taken with dietary products like milk, yoghurt and cheese, containing calcium, they react to form insoluble chelates causing reduced absorption and therapeutic efficacy of the drugs [115-124]. To avoid such interaction; calcium-rich dairy products should be taken two hours before or six hours after the administration of such drugs.

4.4. Potassium Rich Food

Potassium-rich foods such as banana, spinach, apple, grapes, and tomato react with ACEIs (lisinopril) or ARBs (losartan) or potassium-sparing diuretic (spironolactone) and induce hyperkalemia due to lowering of aldosterone levels and increase in potassium retention [125, 126]. The therapeutic activity of digoxin is decreased when administered with potassium-rich foods due to increased potassium levels. It is best to avoid potassium-rich foods when patients are taking above mentioned drugs [127, 128].

4.5. Tyramine-rich Food and Non-selective MAO Inhibitors

Tyramine is amino acid found in strong or aged cheeses, cured meats, smoked or processed meats, pickled or fermented foods, sauces, soybeans, snow peas, broad beans (fava beans), dried or overripe fruits, yeast extract spreads and alcoholic beverages. It helps regulate blood pressure and is found naturally in the body and also certain foods. MAOIs block monoamine oxidase that helps relieve depression but it also breaks down excess tyramine in the body. Thus when on MAOI therapy, high-tyramine foods can cause tyramine to quickly reach dangerous levels. This can cause a serious blood pressure rise and may require emergency treatment [129, 130]. Avoidance of tyramine-rich foods is recommended with MAOI therapy. Patients may need to continue following a low-tyramine diet for a few weeks after they stop the medication.

4.6. Omega-3 Fatty Acid

It is found in mackerel, tuna, salmon, mullet and bluefish. Omega-3 fatty acid reacts with anticoagulant agents, increasing the risk of bleeding. Avoidance of food containing omega-3 fatty acid is recommended. When a patient takes such food and feels unusual bleeding or swelling, blood in

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proposed Mechanism</th>
<th>Effect</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin</td>
<td>Favoureted by bile secretion</td>
<td>Possible increase in drug effect</td>
<td>[76]</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Acid lability</td>
<td>Risk of treatment failure</td>
<td>[77-80]</td>
</tr>
<tr>
<td>Azithromycin capsules</td>
<td>Acid lability</td>
<td>Risk of treatment failure</td>
<td>[81]</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Acid lability</td>
<td>Risk of treatment failure</td>
<td>[82, 83]</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Acid lability</td>
<td>Risk of treatment failure</td>
<td>[84-86]</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>Absorption favored by bile secretion</td>
<td>May result in severe toxicity</td>
<td>[87]</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Food may cause precipitation</td>
<td>Risk of treatment failure</td>
<td>[88]</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Acid labiality</td>
<td>Risk of treatment failure</td>
<td>[89-93]</td>
</tr>
<tr>
<td>Itraconazole solution</td>
<td>Food increases first-pass metabolism</td>
<td>Advantageous in anorexic patient</td>
<td>[94]</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Interaction with food components</td>
<td>Risk of insufficient drug response</td>
<td>[95-99]</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Interaction with food components</td>
<td>Risk of treatment failure</td>
<td>[100-102]</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Oxidized by food into inactive metabolites</td>
<td>Risk of treatment failure</td>
<td>[103-105]</td>
</tr>
<tr>
<td>Phenoxy methyl penicillin</td>
<td>Acid labiality</td>
<td>Treatment failure</td>
<td>[106-108]</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Food inhibits conversion into active metabolite</td>
<td>Significant decrease in ACE inhibition</td>
<td>[109]</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Food increases first-pass metabolism</td>
<td>Treatment failure</td>
<td>[110-114]</td>
</tr>
</tbody>
</table>
Clinical Aspects of Drug Food Interaction

4.7. Protein-rich Food

Protein-rich foods like fish, chicken, eggs, beans and nuts interact with beta-blocker such as metoprolol and propranolol causing enhanced absorption as well as bioavailability leading to bradycardia, hypotension, and bronchoconstriction in patients. However, protein-rich foods react with carbidopa, levodopa and theophylline causing decreased bioavailability leading to insufficient drug response. Patients are advised to avoid high protein rich food during intake of above mentioned drugs and also should not abruptly stop taking beta-blocker because the patient may experience sudden chest pain, irregular heartbeat or a heart attack. Physicians may decrease the dose of beta-blocker gradually.

4.8. Alcohol

Alcohol interacts with almost all drugs. Specially antidepressants and other drugs which affect the central nervous system. The examples are depicted in Table 3. The patient should avoid alcohol while taking any of these drugs.

4.9. Caffeine

It is present in coffee, tea, and soft drinks. Many drugs interact with caffeine and induce various adverse effects as mentioned in Table 4. Patients are advised to avoid caffeine-rich food or drink during treatment of the above drugs.

Table 3. Effects of alcohol on drug action. The patient needs to be counseled for avoidance of alcohol.

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>Proposed Mechanism</th>
<th>Effects</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>Inhibit alcohol dehydrogenase</td>
<td>Precipitate disulfiram-like reaction Flushing, headache, palpitation, nausea and vomiting</td>
<td>[131-133]</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Inhibition of prostaglandins</td>
<td>Increases risk of liver toxicity and stomach bleeding</td>
<td>[134]</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Decreases / Increases warfarin metabolism</td>
<td>Increase the risk for a hemorrhage activity / increasing the risk of clot formation</td>
<td>[136, 137]</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihistamine Diphenhydramine</td>
<td>Synergistic effect</td>
<td>Increased drowsiness</td>
<td>[135]</td>
</tr>
<tr>
<td>Anticoagulants Warfarin with acute/ chronic alcohol consumption</td>
<td>Decreases / Increases warfarin metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Exacerbate adverse effects.</td>
<td>Disulfiram-like reactions Increase the risk of liver disease.</td>
<td>[138, 139]</td>
</tr>
<tr>
<td>β-lactam antibiotics, metronidazole sulfamethoxazole/ trimethoprim</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidiabetic agents</td>
<td>Alcohol suppresses gluconeogenesis</td>
<td>Hypoglycemia Disulfiram-like activity Increased levels of lactic acid</td>
<td>[140-141]</td>
</tr>
<tr>
<td>Glipizide &amp; Glyburide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolbutamide glyburide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide Tolbutamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Increased metabolism and decreased effectiveness</td>
<td>Enhanced orthostatic hypotension/ prolonged intoxication</td>
<td>[142]</td>
</tr>
<tr>
<td>Nitrates, Hydralazine, and Nitroglycerin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbiturates Phenobarbital</td>
<td>Synergism</td>
<td>Enhances the sedative and hypnotic effects on the CNS.</td>
<td>[143]</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Synergism</td>
<td>Alcohol enhances the effects of these agents on the CNS, such as drowsiness, sedation, and decreased motor skills</td>
<td>[144]</td>
</tr>
<tr>
<td>Immune modulators Methotrexate</td>
<td>Exact mechanism of interaction is not known but may be due to additive hepatotoxicity</td>
<td>risk of liver damage</td>
<td>[145]</td>
</tr>
<tr>
<td>Muscle relaxants Cyclobenzaprine Carisoprodol</td>
<td>Narcotic-like reaction</td>
<td>Enhances impairment of physical abilities like driving and increases sedation</td>
<td>[146]</td>
</tr>
<tr>
<td>Tricyclic antidepressant</td>
<td>Unclear</td>
<td>increases the risk of sedation and orthostatic hypotension</td>
<td>[147, 148]</td>
</tr>
</tbody>
</table>
Table 4. Effect of caffeine on drug action.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>both stimulant drugs</td>
<td>serious side effects and heart problems</td>
<td>[149]</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Caffeine might block the effects of adenosine</td>
<td>Effect cardiac stress test</td>
<td>[150]</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Caffeine inhibits theophylline metabolism</td>
<td>increase the effects and side effects of theophylline</td>
<td>[151]</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Decrease breaks down caffeine</td>
<td>increase the risk of side effects</td>
<td>[152, 153]</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Caffeine changes activity of bronchodilators</td>
<td>Excitability, nervousness, rapid heart beat</td>
<td>[154, 155]</td>
</tr>
<tr>
<td>Oral contraceptive, prednisone</td>
<td>Increase effect of caffeine due to it inhibited metabolism by these drugs</td>
<td>Cardiac arrhythmia</td>
<td>[156, 157]</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Decrease breaks down caffeine</td>
<td>Increase the risk of side effects like jitteriness, headache, and increased heart rate</td>
<td>[158]</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Increase effect of caffeine due to it</td>
<td>increase the effects and side effects of caffeine</td>
<td>[159]</td>
</tr>
</tbody>
</table>

4.10. Fruit Juices

In view of the physicochemical properties, fruit juices have the tendency to interact with many drugs and cause treatment failure. The following text describes the interaction of juices with various drugs.

4.10.1. Grapefruit (Citrus paradisi) Juice

Grapefruit juice and food interactions have been well documented by various authors in the past two decades [160]. Studies have reported a pronounced effect of grapefruit juice on intestinal cytochromes P450 (CYPs) system and less effect at the hepatic level [161]. Grapefruit and their components can affect CYP450 drug oxidation and transportation [162-164] and also inhibit cytochrome P-450 3A4 (CYP3A4) in the small intestine causing significantly decreased first-pass metabolism which results in increased drug absorption and systemic drug bioavailability [165-168]. In vitro studies have reported a significant inhibition of the organic anion-transporting polypeptide B (OATP-B) function by grapefruit juice [169]. Grapefruit juice should be avoided when a patient is treated with the drugs listed in Table 5.

4.10.2. Orange (Citrus sinensis)

Orange juice does not alter CYP3A4 activity but can alter the pharmacokinetic parameters of CYP3A4 substrates [182]. Previous findings have shown that when 240 mL Sevilla orange juice was taken, 76% increase in felodipine bioavailability was observed when compared to grapefruit juice consumption [183]. The effect is attributable to a significant concentration of flavonoids, mainly bergamottin and 6,7-dihydroxybergamottin in orange juice that exerts inhibitory effects on P-glycoprotein (P-gp)-mediated drug efflux [184]. Furthermore, in vitro studies reported that the naringin components of orange juice are inhibitors of OATP transport activity [185] and Dresser et al., reported that orange juice inhibits the function of human OATP-A (OATP1A2, gene symbol SLC21A3/SLCO1A2) [186]. In view of various findings, it can be concluded that a significantly increased bioavailability of calcium channel blocker like felodipine is due to the inhibition of P-glycoprotein, OATP-A function and intestinal absorption of substrates of OATP-B. Likewise, oral coadministration of fexofenadine with orange juice reported a significant decrease in fexofenadine bioavailability due to reduced intestinal OATP activity. Thus it is best to avoid oral coadministration of orange juice with these drugs to ensure therapeutic efficacy and potency.

4.10.3. Cranberry (Vaccinium macrocarpon)

Cranberry is a native American fruit and is used as a prophylactic treatment of urinary tract infections. Cranberry juice is rich in flavonol glycosides, anthocyanins, proanthocyanidins, and organic and phenolic acids which interact with drugs. Izzo reported various cases of interaction between cranberry juice and warfarin leading to bleeding in patients due to the inhibition of warfarin metabolism [187, 188].

4.10.4. Pomegranate (Punica granatum)

Pomegranate contains organic acids, phenolic compounds, sugar, water-soluble vitamins and is a good source of bioactive compounds such as phenolics, flavonoids, ellagitannins and proanthocyanidin compounds [189]. Findings have shown that it has antioxidant, antiatherosclerotic, hypolipidemic, antibacterial, anti-inflammatory, antiviral, and anticarcinogenic activities [190]. However, it has been reported that pomegranate juice alters pharmacokinetic parameters of carbamazepine by inhibiting CYP3A activity [191]. Nagata et al. reported that pomegranate juice increased tolbutamide bioavailability in rats by inhibiting human cytochrome P450 2C9 (CYP2C9) activity [192]. This may have occurred probably due to punicalagin, a constituent of pomegranate juice, which can impair the metabolic functions (specifically sulfonation) of the intestine [193].

4.10.5. Papaya (Carica papaya L.)

Papaya contains carotenoids, polyphenols, benzyl isothiocyanates, benzyl glucosinates and cyanogenic substance prunasin [194-196]. It is used for the treatment of various diseases, including malaria, diabetes, obesity, infections, abdominal discomfort, oral drug poisoning and pain [197,
Table 5. Effect of grapefruit juice on drug action.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel antagonists</td>
<td>Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein and increased bioavailability</td>
</tr>
<tr>
<td>CNS modulators</td>
<td>Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein and increased bioavailability</td>
</tr>
<tr>
<td>Statins</td>
<td>Furanocoumarins of grapefruit juice inhibit metabolism of statins</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein and increased bioavailability</td>
</tr>
<tr>
<td>Antivirals</td>
<td>Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein and increased bioavailability</td>
</tr>
<tr>
<td>Phosphodiesterases-5 inhibitors</td>
<td>Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein and increased bioavailability</td>
</tr>
<tr>
<td>Antihistamines, Terfenadine, fexofenadine</td>
<td>Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein and increased bioavailability</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein and increased bioavailability</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein and increased bioavailability</td>
</tr>
<tr>
<td>Oral contraceptives Ethinylestradiol</td>
<td>Inhibit metabolism</td>
</tr>
<tr>
<td>Opioids Oxycodone, fentanyl</td>
<td>Inhibits the CYP3A4</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Inhibit benzodiazapine metabolism</td>
</tr>
</tbody>
</table>

198]. Hidaka et al. reported that papaya inhibited CYP3A activity in human microsomes [199]. In vivo study did not confirm the inhibition of CYP3A but the alteration in pharmacokinetics property of drugs has been reported.

4.10.6. Apple (Malus domestica)

Apple is rich in antioxidants, flavonoids, and dietary fiber including high amounts of polyphenols (epicatechin and procyanidins), flavonoids (catechins, flavanols, and quercetin) [200] which may contribute to be beneficial to health as protective in many diseases [201]. Previous findings reported that apple juice extract inhibits CYP1A1 messenger RNA (mRNA), protein and enzymatic activity, and transporter family activity of OATP-1, OATP-3 and NTCP (sodium taurocholate co-transporting polypeptide) [202]. For example, apple juice interacts with fexofenadine, cyclosporine and Aliskiren inhibit OAPT, resulting in decreased bioavailability as well as therapeutic efficacy of drugs.

4.10.7. Raspberry (Rubus coreanus)

Raspberry has a protective effect on several chronic disorders like cardiovascular diseases, obesity, cancer, and neurodegenerative diseases [203, 204]. It has a high level of various phenol compounds and flavonoids which are antioxidant, anti-inflammatory and inhibit cancer cell growth [205, 206]. It has been found that black raspberries inhibit human CYP3A-catalyzed (midazolam 1-hydroxylation) activity in the liver and OATP-B. This leads to altered therapeutic potential and efficacy of drugs.

4.10.8. Guava (Psidium guajava L.)

Psidium guajava has various chemical constituents such as phenolics, flavonoids, carotenoid, terpenoid and triterpene that confer good medicinal value [207]. Findings have reported that the extract of guava fruit inhibits efflux transport from serosal to mucosal surfaces in the rat ileum [208] and affects P-gp mediated efflux in Caco-2 cells. Hence, guava should be avoided when on therapy with drugs like digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, and paclitaxel because it decreases absorption in small intestine.

4.10.9. Mango (Mangifera indica)

The phytochemical constituents of mango include quercetin and glycosylated xanthones such as mangiferin [209]. It is used as an anti-inflammatory, antimicrobial, antitumor, antihypertensive and antiatherosclerosis product [210, 211].
4.11. Vegetables

Vegetables contain antioxidants, vitamins, flavonoids, and polyphenols [215]. Phenol compounds may be protected in the gastrointestinal tract against damage by free radicals within the stomach and intestines. So, they are useful for gut health and polyphenols [215]. Phenol compounds may be protected from free radical damages but should be avoided with medication because flavonoids interact with drug(s) resulting in the enhancement of drug toxicity or a decline in their therapeutic effect due to modulation of the pharmacokinetics of certain drugs [217]. The impact of coadministration of flavonoids with drug(s) is depicted in Table 6.

<table>
<thead>
<tr>
<th>Source</th>
<th>Phytochemical</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broccoli (Brassica oleracea)</td>
<td>Isothiocyanate sulforaphane</td>
<td>Decreases the enzyme activities in hepatocytes and expression CYP3A4, &amp; CYP</td>
<td>Decreases metabolism of drugs, excessive adverse effects</td>
<td>[218-221]</td>
</tr>
<tr>
<td>Watercress (Nasturtium officinale)</td>
<td>β-phenylethyl isothiocyanate</td>
<td>Inhibit phase I enzymes and/or activate phase II enzymes</td>
<td>Excessive adverse effects</td>
<td>[222]</td>
</tr>
<tr>
<td>Spinach (Spinacia oleracea)</td>
<td>Isothiocyanate and flavonoid</td>
<td>by interaction with CYP1A2</td>
<td>Decreases metabolism of drugs, Excessive adverse effects</td>
<td>[223]</td>
</tr>
<tr>
<td>Tomatoes (Lycopersicon esculentum)</td>
<td>Lycopene</td>
<td>Inhibits CYP1A1 and CYP1B1</td>
<td>Increased risk of adverse effects</td>
<td>[223]</td>
</tr>
<tr>
<td>Carrots (Daucus carota)</td>
<td>β-carotene and panaxynol</td>
<td>Decrease CYP1A2 activity.</td>
<td>Increased risk of adverse effects</td>
<td>[224, 225]</td>
</tr>
<tr>
<td>Avocado (Persea americana)</td>
<td>Mono-unsaturated fatty acids and sterols</td>
<td>Unknown cause</td>
<td>Inhibit the effect of warfarin</td>
<td>[226, 227]</td>
</tr>
<tr>
<td>Red pepper (Capsicum annuum L.)</td>
<td>Capsaicinoids, dihydrocapsaic, capsaicin</td>
<td>Affected the metabolic pathway of xanthine oxidase</td>
<td>Altered pharmacokinetic parameters</td>
<td>[228]</td>
</tr>
<tr>
<td>Apiaceous vegetables (dill weed, celery, parsley)</td>
<td>Furanocumarins</td>
<td>Inhibitory effects on CYP1A2</td>
<td>Increased risk of adverse effect of drugs</td>
<td>[229, 230]</td>
</tr>
<tr>
<td>Cabbage, celery, Onion and Parsley</td>
<td>High content of polyphenols</td>
<td>Direct inhibition of phase I &amp; modulate phase II metabolism II enzymes and interactions with regulatory cascades</td>
<td>Increased risk of adverse effect of drugs</td>
<td>[231]</td>
</tr>
</tbody>
</table>

Studies have reported that mango and its components like polyphenols inhibit the major human P450 enzymes involved in drug metabolism and some transporters [212, 213]. Findings have documented that mango and its components inhibit the major human P450 enzyme which is involved in drug metabolism and some transporters indicating significant drug interaction(s) [214].

4.12. Chocolate

MAO inhibitors drugs should be avoided when excessive amount of chocolate is consumed because caffeine in chocolate may interact with stimulant drugs such as methylphenidate, and significantly increase their therapeutic effect. However, it decreases the sedative-hypnotic effect of drugs like zolpidem [232]. Chocolate also contains xanthenes, which may increase the risk of theophylline toxicity [233].

CONCLUSION

Food-drug interactions are associated with a high risk of treatment failure due to significantly reduced bioavailability of drugs. However, some food-drug interactions can increase drug bioavailability and produce toxic effects. Drug-grapefruit juice interactions develop severe adverse effects and may even cause death. Not necessarily, the drug-food interaction is detrimental; in some cases, it may prove beneficial. The pharmacist can play a significant role in creating awareness in this context. The information on food-drug interaction may improve the patient’s compliance and enhance therapeutic effectiveness. The physician also needs to patient should consult a physician before taking licorice. On the other hand, licorice enhances some of the adverse effects of insulin. For women taking birth control medications like oral contraceptives, licorice should be avoided especially when subjects are suffering from high blood pressure. On the positive note, animal studies have suggested that licorice may reduce stomach irritation as well as the risk of stomach ulcers associated with aspirin.
be aware of potential food-drug interactions and both the physician and pharmacist need to continuously update their knowledge on food-drug interactions for better treatment of patients.

CONSENT FOR PUBLICATION
Not applicable.

CONFLICT OF INTEREST
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