## Review Article

# Food-drug Interactions : Clinical Significance and Management

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The type of food consumed and the time interval between food and oral drug intake are both crucial in the genesis of some significant Food-drug Interactions (FDIs). Such interactions (usually detrimental but sometimes advantageous) are on the rise because of an increasingly elderly population in which they are more frequent. This article presents a review of the literature focussing on various clinically relevant FDIs. Emphasising on the prescriber's perspective, prevention and management have been highlighted. [*J Indian Med Assoc* 2025; **123(1):** 63-5]

***Key words*** **: Food-drug Interactions, Bio-availability, Pharmacokinetics, Pharmacodynamics.**

Healthcare Providers need to be very wary of the type (and timing) of food the patient may be consuming (regularly or intermittently) when prescribing oral medication. There are common pathways between food and oral drugs with regard to utilisation by the body and this may lead to interactions in several ways.

### Pathophysiology and Pharmacological Basis :

FDIs may be Pharmacokinetic (involving drug absorption, distribution, metabolism and elimination) or Pharmacodynamic (involving drug effects at the action-site)[1] or a combination of both, different outcomes may thus be expected in terms of drug effectiveness and toxicity[2,3]. Pharmacokinetic interactions may involve interference with metabolising enzymes and transporters. CYP3A4 is part of the metabolising enzyme superfamily Cytochrome P450 which destroys drugs pre-systemically. Transporters in the Gastrointestinal enterocytes include the efflux transporter P-glycoprotein (P-gp) which extrudes unknown substances and the influx transporters Organic Anion Transporting Polypeptides (OATPs) which facilitate uptake of drugs[4]. These interactions may raise or lower drug blood levels and consequently their effects and toxicities. Increased absorption is particularly concerning in drugs with a narrow therapeutic index.

Physicochemical properties of food such as protein, fat, carbohydrate or fibre content are important pharmacokinetically[4]. Common parameters altered are area under the concentration-time curve, Bioavailability and the Maximum plasma concentration[2]. FDIs are of particular concern in elderly patients because of age-related changes in Pharmacokinetic function, diminished drug binding to Plasma Proteins and diminished Renal and Hepatic function and also because they are commonly on multiple medications for chronic co-morbidities[5]. FDI effects cannot be generalised because of unknown phytochemicals in some food items and inter-personal differences among individuals[6]. The hepatic metabolism of several drugs is accelerated by High Protein, Low Carbohydrate Diets.

***Editor's Comment :***

- Food-drug interactions are a distinct possibility in clinical practice. They may significantly impact the desired outcome.
- Specific advice regarding their avoidance and prevention must be given when prescribing.

### Practical Examples and Clinical Significance :

From the prescriber's perspective, several food items such as Fruits, Fruit Juices, Dairy Products, Fermented Foods, Aged Cheeses, Alcoholic Beverages and Caffeine based beverages can potentially interact with many drugs Pharmaco-kinetically. The nutritious Grapefruit is rich in flavonoids which have many health benefits[7]. However, Grapefruit Juice (GFJ) is notorious for causing FDIs by significantly decreasing intestinal metabolism (and hence significantly increasing bioavalability) of drugs which are substrates of the CYP3A enzyme[8]. GFJ may also affect the activity of OATP and P-gp transporters[9]. GFJ has been shown to significantly diminish the bio-availability of fexofenadine (a widely used anti-allergic antihistamine) likely by direct inhibition of intestinal OATP-A[10]. This may be relevant to Apple and Orange Juices also. GFJ increases the bio-availability of some drugs such as the immuno-suppressant cyclosporine and the antimalarial artemether. This is a 'drug sparing' effect allowing lowering of drug doses thereby minimising side effects. Oral nitrofurantoin, cefuroxime, itraconazole and griseofulvin are increasingly absorbed when taken along with food. This beneficial interaction may be utilized judiciously. Conversely, concomitant

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intake of food diminishes absorption of azithromycin, isoniazid, amoxicillin, levothyroxine and ketoconazole. This is particularly significant in case of tetracyclines and fluoro-quinolones interacting with dietary Calcium and Iron. There is complete non-absorption of oral bisphosphonates when given along with food. A high protein diet raises serum albumin levels with increased binding (and decreased efficacy) of Warfarin[11].

Pharmacodynamically, the action of the anticoagulant Warfarin may be opposed by vegetables rich in Vitamin K (such as spinach, broccoli and asparagus) and summative hyperkalaemia may occur with hyperkalaemia causing drugs like the antihyperensives telmisartan and ramipril when potassium rich foods like bananas and oranges are consumed alongwith. Tyramine (a precursor of catecholamines) is a migraine trigger and may cause hypertensive crisis when a patient on MAOIs (Mono Amine Oxidase Inhibitors) consumes tyramine rich foods[4]. MAOIs include the anti-depressants moclobemide, phenelzine and tranylcypromine, the antibacterial linezolid and the anti-tuberculosis agent isoniazid. Fermented and smoked foods, aged and mature cheeses, cured meats (such as pepperoni and salami), fermented cabbage (such as sauerkraut and kimchee) and soy sauce may contain significant amounts of tyramine[12].

## Clinico-pharmacological Correlation : Clinical Situations

Clinical manifestations result from decreased therapeutic effect, increased drug toxicity or the appearance of an unexpected adverse effect. Many anti-neoplastic agents suppress appetite causing diminished food intake and nutritional compromise[13].

Reduced antimicrobial absorption may lead to sub-therapeutic blood levels with potential therapeutic failure and subsequent bacterial resistance.

Bradycardia, hypotension and bronchoconstriction may result from the increased bio-availability of the non-selective beta-blocker propranolol when taken with a high protein diet. Such a diet can, however, decrease the concentration and efficacy of carbidopa/levodopa and theophylline. Jitteriness, Insomnia and Cardiac arrhythmias may present as adverse theophylline related effects when taken along with Caffeine containing Beverages[14]. Conversely, ciprofloxacin which affects liver function may increase blood caffeine levels when taken with such beverages[12].

Summative hyperkalaemia as an FDI may cause Nausea, Vomiting or even Cardiac Arrest. Intake of alcohol can increase or decrease the effects of many drugs[12]. Facial flushing and Vomiting (a 'disulfiram reaction') may occur when Alcohol is taken concomitantly with metronidazole or isoniazid[14].

Sudden rise of blood tyramine as an FDI may cause hypertensive crisis with headache, nausea, sweating, chest pain, breathlessness and cardiovascular events.

GFJ can lead to increased absorption (and accentuated toxicity) of some statins (like simvastatin and atorvastatin), some antihypertensives like nifedipine and some antiarrhythmics such as amiodarone. Interestingly, not all the drugs in a given class of drugs are affected. Statin related side effects may be myalgia, myopathy or rhabdomyolysis[14].

The bio-availability of the anti-neoplastic drug mercaptopurine (a purine analogue inactivated by xanthine oxidase) may be reduced by concurrent intake of cow's milk which contains Xanthine Oxidase[15]. Concomitant use of Pomegranate fruit juice (rich in flavonoids) and sildenafil (a drug used for erectile dysfunction) has been reported to cause acute painful priapism (which is an emergency and may cause impotence).

## Diagnosis :

A carefully taken history is the most important pointer to the diagnosis. The age, gender, Body Mass Index, cognitive function, presence of other co-morbidities, full list of regular medications, typical daily meal plan, appetite, preponderance of fats or proteins in the diet, awareness regarding timing of medications with regard to food intake, awareness regarding which food items to avoid and whether there is a competent carer are all important determinants of FDIs. Specific symptoms and signs attributable to known side effects of (and treatment failure of) commonly used drugs are additionally important.

When not confirmed by history alone, blood levels of the drug in question may lead to the diagnosis.

## Awareness and Prevention :

Health Education and counselling of the patient (and carers) is the key in raising awareness. Medication labels and package inserts must be checked particularly for interaction warnings. The physician and the pharmacist must be consulted if there is a concern regarding taking a particular food or beverage whenever one is on long term medication[12].

## Management : The Presciber's Perspective

FDIs have to be avoided and prevented. Once they do happen, the immediate management will depend on the type of interaction. Therapeutic failure of an important drug like Warfarin, levothyroxine or fexofenadine would necessitate temporary dose increment. Drug toxicity like hypertensive crisis, cardiac arrhythmias and Orthostatic Hypotension have to be treated in their own right. Ultimately, however, management hinges on preventive measures to avoid further episodes.

Even seemingly simple dietary manipulations can improve the therapeutic outcome with several drugs.

Avoiding dietary fibre can improve the absorption of digoxin. Metformin absorption is decreased with large amounts of dietary fibre and high sodium intake can lower Lithium blood levels[5]. Fat-rich foods improve the absorption of lipid-soluble drugs such as some antiretrovirals like saquinavir and atazanivir and also of griseofulvin. Presence of food in the digestive tract may reduce absorption of many drugs and this may be avoided by taking the drug 1 hour before or 2 hours after food intake[11]. NSAIDs (Non Steroidal Anti Inflammatory Drugs) like ibuprofen, naproxen and ketoprofen, however, can cause gastric irritation and should be taken with food or milk. The main absorption site of drugs and food components may be separated by using enteric coated tablets which disintegrate in the lower part of the small intestine.

It is prudent to limit drug prescription to only essential medications for as short a duration as possible with periodic reviews[16].

## Clinically Significant Newer Frontiers :

For mitigating FDIs, New Chemical Entities (NCEs) are now assessed for the bio-pharmaceutical performance risk for Food Effect (FE) by experimental models (in vitro and in vivo). The ability of these tools to predict human FE depends on building an in vitro in vivo relationship (IVIVR). Fed/fasted dissolution studies show a reasonable correlation to human FE making them useful tools in flagging (and preventing) high risk NCEs entering clinical development. In silico (computer) modelling can also enable studying FE mechanism[17]. Software vendors and knowledge providers play an important part in providing interaction alerts (which should be difficult to override)[18].

## Discussion and Key Practice Points :

Drug interactions may often be merely theoretical but are sometimes clinically very relevant.

Factors to be considered while advising the timing of drug administration with regard to meal timing include drug Pharmacokinetics, optimizing drug efficacy and minimizing Gastrointestinal (GI) intolerance[19]. Nitrofurantoin causes adverse GI effects and should be taken after meals. Erythromycin absorption is less affected by food and it may be given with low fat meals if GI upset occurs. Food may alter absorption and may also improve gastric tolerance. Proper understanding of Pharmacokinetic and Pharmacodynamic properties and their judicious clinical utilization is essential for obtaining optimal clinical benefit[20].

It is the prescriber's responsibility to ensure

(1) Avoidance of known and possible FDIs

(2) Awareness of FDIs among patients and their carers

(3) That the patient's nutritional status is not hampered by FDIs and

(4) Regular review of prescription and over the counter medicines in relation to the patient's dietary habits.

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