Interactions of herbs and food products with drugs
Grapefruit juice as an example

Inder Pal Singh*, Sandip B Bharate and K K Bhutani
Department of Natural Products, National Institute of Pharmaceutical Education and Research (NIPER)
Sector-67, SAS Nagar-160 062, Punjab, India
*Correspondent author, E-mail: ipsingh@niper.ac.in

Abstract

Plants have been used throughout human history for their medicinal properties and herbal medicines are popular worldwide. Since, all herbal medicines are mixtures of more than one active ingredient, such combinations of many substances obviously increase the likelihood of interactions taking place. Although herbal medicines have been used as remedies for number of illnesses, many of them have shown interactions with the synthetic drugs and also exhibited adverse effects. These herb-drug interactions may be adverse as well as beneficial. Herb-drug interactions are discussed in this article with an example of Grapefruit (Citrus paradisi Macf.) juice-drug interaction. The oral bioavailability of many drugs was found to be increased when these are consumed along with grapefruit juice.

Keywords: Herb-drug interactions, Grapefruit juice, Citrus paradisi, Furanocoumarin.

IPC code: Int. cl.7— A61K 35/78, A23L 2/06

Introduction

There is a global resurgence in the use of herbal medicines. An estimated one third of adults in the Western world use alternative therapies, including herbs1,2. These herbs may be used either in their primary forms or combined into mixtures. In contrast to chemical drugs, herbs are generally claimed to be non-toxic, because of their natural origin and long-term use as folk medicines. However, problems arising due to intrinsic toxicity, adulteration, substitution, contamination, misidentification, drug-herb interactions, and lack of standardization are generally overlooked5,4. Herbs may increase or decrease the effects of some medications when taken together. There are increasing reports on adverse drug reactions and poisonings associated with the use of herbal medicines as well as dietary supplements and food products5,7.

Herb-drug Interactions

All herbal medicines are mixtures of more than one active ingredient; there is a likelihood of interactions between combinations of these substances. It is often difficult to analyze these interactions as these herbal remedies contain many substances and mostly are of variable and undefined composition. Herbal drugs show interaction with drugs and such interactions may often be serious or even life threatening, for example, Ginkgo biloba Linn. raised blood pressure when combined with Thiazide and cause coma when combined with Trazodone6. On the other hand these interactions may also be beneficial in some cases7. Importantly, majority of people who use herbal medicines concurrently with prescribed or over the counter medicines do not
reveal this use to their physician or pharmacist, thereby greatly increasing the risk of side effects from the interactions between herbal components and concurrent pharmacotherapy. Moreover, because most herbal product purchases occur outside the pharmacy, concurrent use of herbal products and prescription drugs often evades the attention of the pharmacist and physician. As such, the use of herbal products often escapes standard mechanisms for protecting persons from harmful effects of drugs and drug interactions.

St. John’s wort (Hypericum perforatum Linn.) is extremely popular in US and Europe and is used to treat wounds, gastritis, kidney and lung disorders, insomnia and depression. However, recent data have revealed dangerous interactions of St. John’s wort with several drugs such as Indinavir and Cyclosporin. Blood levels of Indinavir, a drug prescribed to treat HIV infection, decrease to such low levels (81%) when taken together with the herb that the drug no longer remains effective. Similarly, Cyclosporin given to heart transplant patients to prevent their immune system from rejecting transplant organs, when taken together with the herb falls to subtherapeutic level prompting episodes of rejection. However, Cyclosporin concentration returned to therapeutic levels with discontinuation of St. John’s wort. St John’s wort also lowers blood concentration of Amitryptyline, Digoxin, Warfarin and Theophylline. It causes intermenstrual bleeding when used with oral contraceptives (ethinyl estradiol) and delirium when used together with selective serotonin re-uptake inhibitors. St. John’s

<table>
<thead>
<tr>
<th>Herb</th>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe vera</td>
<td>Digoxin and Thiazide</td>
<td>Increase cardiac toxicity</td>
</tr>
<tr>
<td>Bitter melon</td>
<td>Hypoglycaemics</td>
<td>May affect blood glucose levels</td>
</tr>
<tr>
<td>Capsicum</td>
<td>Aspirin</td>
<td>Protects against stomach irritation</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Corticosteroids</td>
<td>May increase cough</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Warfarin</td>
<td>May increase absorption</td>
</tr>
<tr>
<td>Ephedra</td>
<td>Anticonvulsants</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>Ephedra</td>
<td>Caffeine</td>
<td>Decrease Warfarin metabolism</td>
</tr>
<tr>
<td>Garlic</td>
<td>Hypoglycaemics</td>
<td>Herb may cause seizures</td>
</tr>
<tr>
<td>Garlic</td>
<td>Antihypertensive drugs</td>
<td>Herb may increase nervousness</td>
</tr>
<tr>
<td>Garlic</td>
<td>Warfarin</td>
<td>Herb may cause hyperglycaemia</td>
</tr>
<tr>
<td>Garlic</td>
<td>Aspirin/Warfarin</td>
<td>Irreversible inhibition of Platelet aggregation</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Acetaminofen</td>
<td>Subarachnoid haemorrhage</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Anticonvulsants/TCA</td>
<td>Increase seizures</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Thiazides</td>
<td>May lead to hypertension</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>Calcium channel blockers and many drugs</td>
<td>Increases oral bioavailability</td>
</tr>
<tr>
<td>Licorice</td>
<td>Antihypertensives, Digoxin</td>
<td>Herb may cause hypokalemia</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Loop diuretics</td>
<td>Sodium and fluid retention</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Antihypertensives</td>
<td>May increase BP</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Barbiturates</td>
<td>May decrease barbiturate-induced sleeping time</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Cyclosporin/Digoxin</td>
<td>Herb may decrease levels of these drugs via metabolism</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>5-HT reuptake inhibitors</td>
<td>Additive effect</td>
</tr>
</tbody>
</table>
wort is known to increase cytochrome P 450 isozymes that are responsible for metabolism and elimination of many drugs. Ginseng (Panax ginseng Mey.) lowers blood concentration of alcohol and Warfarin and induces mania if used together with Phenelzine. Similarly, Ayurvedic formulation Shankhpushpi leads to decreased blood concentrations of Phenytoin. Some other herb-drug interactions are enlisted in the Table 1 to highlight the risks associated with concurrent use of herbal remedies and prescription drugs.

There are following possible ways in which herb-drug interaction may occur.

1. Decrease in the bioavailability of the drug — This may occur by (i) reduction of the absorption of the drug [Amorphophallus konjac K. Koch, tea [Camellia sinensis (Linn.) O. Kuntze], guar gum [Cyamopsis tetragonolobus (Linn.) Taub.] and Plantago spp.]; (ii) enhancement of metabolism (mustard); or (iii) enhancement of elimination (coffee).

2. Increase in the bioavailability of the drug — The bioavailability of drug can be enhanced by (i) increase of the absorption of the drug as with cayenne pepper (Capsicum spp.) or black pepper (Piper nigrum Linn.), or (ii) reduction in the metabolism (as with citrus and licorice). The oral drug absorption can be increased by Zingiber officinale Rosc. Piperine, which is a known bioavailability enhancer increases absorption of Phenytoin and Propranolol and slows down the elimination of both drugs.

3. Protection from adverse effects — Several herbs such as cayenne pepper, licorice, milk thistle (Silybum marianum Gaertn.) and Zingiber officinale Rosc. may provide protection against the adverse effects of drugs. Prior administration of ginger acetone extract can prevent cyclophosphamide induced vomiting.

4. Enhancement of drug effect — The effects of drugs may be enhanced by a mechanism dissimilar from that of the drug, for example, by bromelian [Ananas comosus (Linn.) Merrill]. Hypokalemia resulting from a long-term use of stimulant laxative herb potentiates the effect of cardiotonic and anti-arrhythmic drugs like Quinidine.

5. Additive effect — Similar activities of the herb and the drug lead to an additive effect. Some examples are Aloe, betelnut (Areca catechu Linn.), gingko, licorice, gurmar (Gymnema sylvestre R. Br., leaves), bitter melon (Momordica charantia Linn., fruit and juices), and kava (Piper methysticum G. Forst.). The hypoglycaemic effect of an oral antidiabetic drug was increased when associated with gurmar in human clinical trial. The gurmar is used as antidiabetic remedy in Chinese traditional medicine. The low absorption of dietary carbohydrates can lead to the reduction of insulin dose in insulin-dependant patients.

6. Antagonistic effect — Antagonism or incompatibility may occur with betelnut, mustard, and papaya (Carica papaya Linn.). In human case report (per os) the antiparkinsonian effect of phenothiazines such as Flupenthixol and Fluphenazine and anticholinergic effect of Procyclidine are reduced when administered with Arecoline and that could be due to the Cholinergic effect of the later.

Grapefruit juice—Drug interactions

Foods are intended to be safe for human consumption, but at the same time, few foods can produce an interaction with drugs by altering their pharmacokinetics and subsequent clinical response. For example, grapefruit juice has been shown to increase the oral bioavailability of more than 20 drugs from a diverse range of therapeutic categories (Table 2).

Grapefruit, botanically named as Citrus paradisi Macf. (Hindi — Chakotra) of Rutaceae family, is indigenous to West-Indies (Jamaica) and cultivated in India both in subtropical and tropical areas, mostly in Punjab, the western parts of Uttar Pradesh and to places around Pune in Maharashtra. ‘Duncan’ variety is being grown commercially in India. In view of the consumption of grapefruit juice in India, it is important that people should be aware of potential risks associated with concurrent use of grapefruit juice and drugs.

Grapefruits are high in pectin and lycopene that help lower blood cholesterol and the risk of cancer, respectively. However, it also inhibits cytochrome P450 3A4 (CYP3A4), an enzyme that is responsible for metabolism and absorption of many drugs. This inhibition
causes blood levels of these medications to increase, which can lead to toxic side effects from these medications. Substances in grapefruit juice appear to be metabolized to chemically reactive intermediates that covalently bind to CYP3A4, resulting in irreversible enzyme inactivation, a process termed suicide or mechanism-based inhibition.17

It was an accidental discovery when grapefruit juice used to mask the taste of ethanol in a study involving the calcium channel blocker Felodipine, was found to increase its oral availability.18 Since then, grapefruit juice has been shown to enhance oral availability of more than a dozen different drugs.19 These include antihistamines (Terfenadine), cholesterol lowering drugs (Statins), psychiatric medications (Triazolam, Diazepam), calcium channel blockers (Felodipine) and immunosuppressant drugs (Cyclosporine).20 Some drugs such as Terfenadine require 100% breakdown by ‘first-pass’ metabolic pathway to convert it to its active and less toxic metabolite. Any drug or food such as grapefruit, which inhibits CYP3A4 will block this metabolic pathway resulting in absorption of unmetabolized Terfenadine, that may result in cardiac arrest and death.20

Most of the drugs affected by grapefruit juice have poor and highly variable oral bioavailability. Additionally, most of these drugs are mainly metabolized in the body by CYP3A4, an enzyme present in the liver and intestine. The major effect of grapefruit juice appears to be to reduce ‘first-pass’ metabolism by reducing CYP3A4 activity. Because grapefruit juice does not generally affect the systemic clearance of affected drugs, it seems that grapefruit juice may selectively reduce intestinal CYP3A4 activity while having little effect on liver CYP3A4. Although a variety of juice components have been implicated, the major active ingredients appear to be furanocoumarins. The most abundant and probably the most important single furanocoumarin is 6′, 7′-dihydroxy-bergamottin (DHB). DHB and other furanocoumarins appear to reduce CYP3A4 activity by three related but distinct mechanisms: (1) competitive or reversible inhibition, (2) mechanism-based inactivation, and (3) actual loss of CYP3A4 enzyme. In the future it would be possible to use grapefruit-derived furanocoumarins as additives to certain drugs to improve the oral delivery of some drugs.17

Role of Bergamottin in grapefruit juice effect

Although grapefruit juice contains a number of diverse components, accumulating evidence indicates that furanocoumarins are important CYP3A4 inhibitors. Accordingly, furanocoumarins have been proposed as the primary components responsible for grapefruit juice-drug interactions. The two most abundant furanocoumarins present in the juice are bergamottin and 6′, 7′-dihydroxy-bergamottin (DHB). Bergamottin is the parent furanocoumarin and has been shown to be both a reversible and a mechanism-based inhibitor of CYP3A4. The reactive metabolites of bergamottin are not known, but it may undergo oxidation to form a reactive furanooxide that covalently binds to CYP3A4. DHB, as its name implies, is a
Article

dihydroxy derivative of bergamottin and has also been shown to be a reversible and mechanism-based inhibitor of the enzyme. An ether dimer of two DHB molecules, termed GFI-1 (or FC726), and an ether dimer of a bergamottin and a DHB molecule, termed GFI-4, represent two other furanocoumarins in the juice. Although these dimers are generally present at much lower concentrations relative to the parent compounds (0.1-0.6 mol/L versus 1-40 mol/L), they appear to be considerably more potent CYP3A4 inhibitors compared with bergamottin or DHB.

Conclusion

In conclusion, herb-drug interactions pose serious threat to human health and represent an important issue to be tackled. It is necessary that healthcare professionals as well as patients are aware of potential herb-drug interactions and researchers should strive to fill the numerous gaps in our present understanding of this problem. On the other hand, positive herb-drug interactions having beneficial effects also need to be elucidated, where it should be possible to exploit the increased bioavailability of the drugs for reducing the dosage.

References

5. Izzo AA and Ernst E, Interactions between herbal medicines and prescribed drugs: a systematic review, Drugs, 2001, 61, 2163-2175.


