Review

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Food and Drug Interaction–a Growing Concern

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Abstract. Food and drug are taken for the survival and well-being of human race. Food-drug interaction occurs when food including beverages taken orally affects the properties of intestinal enzymes (P450), which alters pharmacokinetics, bioavailability and pharmacodynamics of the drug. The bioavailability of a drug determines its therapeutic value. An increase in the amount of a drug would produce undesired toxic effects; whereas a reduced amount would result in serious complications that could be termed as therapeutic failure. Such health hazards are more pronounced in elderly persons and those who are taking potent drugs to control/treat chronic diseases. Also, the severity of adverse effect depends on the therapeutic index of a drug, more pronounced for a drug with low therapeutic index. The food (nutrient)-drug interaction has been recognized as a major health issue in western countries. Popular health magazines, newspapers etc. often summarize researches published in scientific journals, proceedings of conferences in simple to understand language to educate and warn readers on the consequences of food (nutrient)- drug interaction etc. Several national health agencies are also involved in conducting surveys and devising policies to minimize food-drug interactions.

Keywords: food-drug interaction, foods, drugs

Introduction

Both food and drugs (medicine) are essential for a good, healthy and productive life. Food consists of nutrients (*macro*: carbohydrates, fats, proteins, minerals such as calcium, potassium, sodium; *micro*: vitamins, trace minerals such as (copper, iodine, iron, selenium, zinc...) that are the source of energy and other materials necessary for sustenance, whereas drugs prevent and cure illnesses. Food and drugs are taken mainly orally (by mouth) and follow processes before imparting desired benefits. On consumption of food, nutrients are digested and absorbed from the intestine.

When a drug is taken orally, it is absorbed from the intestine, distributed as is or after metabolism and finally excreted (pharmacokinetic step). The effect of a drug to the body is referred to as pharmacodynamic. Another often used term in drug efficacy is its therapeutic index. A drug with higher therapeutic index provides a greater degree of safety compared to the one with low value i.e., toxic dose and effective dose are very close. In order to be effective, a drug must be bioavailable at the site i.e., it is absorbed from the intestine (before and/or after enzymatic reactions mainly by P450) and transported by P-glycoprotein (P-GP). Both P450 and P-glycoprotein are in high concentration in the human liver and small intestine.

Since both food and drug are integral part of human health and a productive lifestyle, they should be compatible with each other for wellness as well. Unfortunately, this is not always the case. The individual's age, weight, body-mass index (BMI) and general health as well as the food composition and time of intake may have significant impact on the absorption, distribution and bioavailability of pharmaceuticals (drugs). Such impact is often referred to as food-drug interaction. After World War II, and since the 1980s, there have been considerable changes in travel, migration, eating, cooking habits and tastes. This is more common among the more affluent middle to older generations because of financial independence. With advancing age, the adult population is also prone to several health related issues including chronic diseases. This group also uses more herbal supplements in addition to prescription drugs, often without the knowledge of medical practitioners, mainly to manage aches and pains. Thus, this group is the most affected by food-drug interactions and has raised serious health concerns**.**

A recent survey done in Canada reported that 47% of those who use prescription drugs and natural health products simultaneously encountered adverse effects, which could range from mild to severe rashes to headaches and serious effects for those using prescription drugs such as blood thinner, insulin. These authors concluded that the use of natural drugs with prescription drugs should be treated with respect (Charrois *et al*., 2007). Natural products commonly referred to are vitamins, herbal supplements (garlic, carrot and others), trace minerals etc. The aim of this article is to review current popular health magazines and scientific literature on the interaction of food and drug to enlighten public, healthcare practitioners, scientific communities and those interested in

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self-health management programme on the hazards of some foods including supplements taken routinely, most importantly with life saving drugs.

What are the issues? Modern day consumers worldwide want food that not only provides basic energy, but contributes to enjoyment, productivity, fun and a lifestyle that is free from diseases (infirmity) i.e., food should contribute to health and wellness and support:

"Let food be your medicine and medicine be your food" (Hippocrates)

Health and wellness (in some circles it is also referred to as fitness and wellness) is routinely referred in the developed countries to describe a productive, healthy and happy lifestyle. We all understand health means fit, but wellness has evolved and continues to evolve to describe a lifestyle with good physique (good and attractive body), stable mental capacity, longevity, free from disability (infirmity). Wellness is a holistic approach for taking control and making a commitment where body, soul and mind are in harmony for an enjoyable lifestyle. This requires managing proper food intake as part of a regular diet that not only provides energy but also contributes to improving other physiological benefits. Hence food in this overview refers to substances that provide not only the basics for sustained living, but also beverages and other natural products with healthy benefits, commonly referred to as natural health products (NHP). The Ayurvedic, Chinese Traditional medicine, Unani-Tibbi (also referred to as Islamic medicine that has been practiced for over 800 years and promotes nutrition management for a healthy lifestyle) and native medicines in the Americas, Australia and other countries are still the first line of health care. Even in the 21st century, about 70% of the world population rely on alternatives to conventional medicine (western medicine). In the developed countries, they are called by a variety of names such as folk medicine, complementary and alternative medicine/therapy (CAM/T).

How do we achieve health and wellness? Health and wellness are a pre-occupation with modern day consumers, especially in the developed countries. Recent studies have clearly established a link between health and diet. Consumers want to take control and manage their own health. They are influenced by constant bombardment through the media on the benefits of green tea, garlic, tomato and spices e.g., turmeric (Daniells, 2006). This has resulted in marked increase in the use of herbal products as supplements and complementary alternative medicine (CAM), mainly as the booster of immune system (health benefits) (Ness *et al*., 1999). There are serious demands for new products with physiological benefits along with better information. Literature and anecdotal reports for concomitant oral intake of natural products and therapeutic drugs affect drug metabolism and have significantly increased risks with serious clinical adverse events (safety issue). However, the effect of concomitant administration of the 42,000 or so herbal products on the safety and efficacy of conventional drugs has not been unequivocally established.

Examples of food-drug interaction. Many patients take a wide range of NHP in addition to their western medicine (Eisenberg *et al*., 1998). The effect of concomitant administration of herb and/or herbal medicine on the safety and efficacy of conventional drugs has not been fully determined (Anastasio *et al*., 1997; Kozryskyj, 1997; De Smet, 1995). Literature and anecdotal report suggests that concomitant oral adminis-tration of natural products and therapeutic drugs may affect human drug metabolism and significantly increase the risk of serious clinical adverse events (Foster *et al*., 2002, 1999; Ameer and Weintraub, 1997). In recent years several excellent reviews and analysis reports have appeared on the interaction of natural health products with therapeutic drugs including antiretroviral agents (Lee 2006; Foster *et al*., 2005; Haddad *et al*., 2005; Guo and Yamazoe, 2004; Bailey and Dresser, 2004; Raucy, 2003). One of the most popular over-the-counter herbal products to treat depression and other mental disorders is St. John's Wort. It has been implicated in several drug interactions (Boullata, 2005; Markowitz *et al*., 2003; Izzo and Ernst, 2001). It is recommended that St. John's Wort should not be taken concurrently with most of the drugs, especially digoxin (digitalis), immunosuppressive medications, protease inhibitors (drugs for HIV/AID treatment) loperamide, oral contraceptives, reserprine (used in high blood treatment) and Warfarin (anticoagulant) (National Centre for Complementary and Alternative Medicines (NCCAM): http://nccam.nih. gov/health/stjohnswort/#cautions). Similarly, garlic is used in cooking as herb, and as supplement to control cholesterol level, high blood pressure, to reduce blood sugar levels and as antifungal agent among others. On the other hand, there is concern that use of garlic would be detrimental when taking blood clotting drugs such as Warfarin, Plavix and Aspirin and antiretroviral drugs (Mills *et al*., 2005). An interaction between garlic and chlorpropamide caused hypoglycemia in a diabetic Pakistani woman, who consumed a curry dish that consisted of karela (*Momordica charantia*, also known as bitter gourd) and garlic (*Allium sativum*) (Aslam and Stockley, 1979). Foster *et al*. (1998) reported that garlic extracts interfered with CYP3A4-mediated metabolism, which may have been responsible for observed interaction of garlic in diets.

During the In last 20 years or so, numerous articles have appeared in medical journals as well in the popular magazines including lay press that describe incidences of adverse drug reaction. Interactions between foods and drugs can have profound influence on the success and failure (side effects) of many drugs (Medical University of South Carolina Health Topic Library, 2008; McLachlan and Ramzan , 2006; Ayo *et al*., 2005; Bland, 1998). A careful review of literature showed that incidences are more frequent among senior citizens because of multiple medication usage and several age-related physiological changes that affect drug absorption, distribution, metabolism and excretion. Frequent and serious incidences of food drug interactions among seniors often lead to hospitalization, significant morbidity and even death. Recent studies predict the population of seniors (over 60 years of age) to reach about 22% of the total globle population including the North America by 2050. But two Asian countries, South Korea (37.3%) and Japan (36.5%), are expected to lead the pack, followed closely by Italy (34.4%) and other European countries (>27%) (United Nations, 2007; SCIN, 2005). Increase in health care costs in most of the major developed countries is already out-pacing the revenue growth, and with the projected increase in number of seniors, the burden on treasury would increase substantially. Food/ supplements (herbs)-drug interactions are becoming important and major public health issues due to their impact on fitness, productive and enjoyable lifestyle and of course on health care cost (Cheng, 2006; Health Canada, 2006; Boullata and Armaenti, 2004; Leibovitch *et al*., 2004; McCabe *et al*., 2003; University of Florida, 2003; Thomas and Burns, 1998).

How does food-drug interaction occur (mechanism of action)? The "food-drug interaction" initially suggests a chemical interaction between food and a drug that produces toxic substance(s). It is far from the truth. It refers to the effect of natural products including some foods that enhances or inhibits the activities of major metabolizing enzymes located in the human intestine. The efficiencies of these enzymes can alter pharmacokinetics and of course the pharmacodynamics of a drug by either increasing or decreasing the amount of a drug in the blood stream.

In order for a drug to be effective, it must be absorbed (most often unchanged), distributed and localized to the site, metabolized and excreted from the body. Any deviation in the process has the potential for side effects, the degree of which is highly dependent on the potency of the drug (therapeutic index) i.e., a drug with lower therapeutic index has greater possibility of toxic effects.

A drug is administered orally, subcutaneously or intravenously, but it is the orally administrated drug that interacts with foods including beverages that often cause side effects. Orally a drug can be taken with water (highly recommended), with food or in empty stomach. In all cases the purpose is to deliver the drug at the site for maximum action. An orally taken drug must follow the following steps: absorption, distribution, metabolism and excretion in timely fashion for both benefits and avoidance of toxic side effects. In simple terms a drug must be bioavailable in right quantity at the right cell in timely fashion. The absorption and the bioavailability of a drug could easily be altered by the type, quantity and composition of food and beverages, which is highly dependent on several factors such as (i) dosages of the drug (medication); (ii) patient's age, size (BMI), state of health; (iii) the relationship between drug and food intake. A drug is of clinical significance only if it is bioavailable and reaches the target, most often in the unchanged state.

The effectiveness of a drug is measured by its desired therapeutic outcome. Natural products are known to interfere with drugs used for some chronic diseases such as neuroendrochrine (e.g., sedative, MAO inhibitors); cardiovascular e.g., hypotensive and hypertensive; hematological (high vitamin K containing products); metabolic (hyper/hypoglycemic); immune (immune modifier, salicylate containing compounds) (Dharmananda, 2003). Hence the choice of carrier (mode of administration) for drug is very important and advice should be based on the nature and chemistry of drug under consideration. Food can either retard or accelerate absorption of a drug depending on its chemistry and its effect on CYP 450. For example, Coumadin, Warfarin (anticoagulant) when taken concomitantly with foods with high vitamin K content (found mainly in kale, spinach, turnip greens, collards, Swiss chard, parsley, mustard greens, the cabbage or cruciferous type vegetables such as broccoli, cauliflowers and lettuce) can be less effective due to low bioavailability. It is a cause of concern for therapeutic failure and in certain instances may result in death. Similarly, high-protein, low carbohydrate diets can accelerate hepatic metabolism of a number of major drugs resulting in therapeutic failure with serious consequences (Leibovitch *et al*., 2004; Hansten and Horn, 2003; Singh, 1999; Winstanely and Orme, 1989).

Food/beverages. The extent of absorption of a drug is highly dependent on its chemistry, timing and composition of the foods/beverages. A physician when prescribing a drug and its mode of administration takes into consideration the health and age of the patient and the timing and type of food intake. The food factors that influence absorption as well as the bioavailability include (i) chelation, (ii) poor acid stability,

(iii) acid dependency; (iv) bile acid or fat enhanced drugs dissolution, (v) physical binding/adsorption (vi) reduced gastric emptying (McLachlan and Ramzan, 2006):

Aging causes following significant changes: (Thomas and Burns, 1998):

a) Absorption: Gastrointestinal (GI) system (i.e., increased gastric pH; decreased GI tract blood flow; increased gastric emptying system);
b) Distribution: Body composition (BMI factor (i.e., decreased lean body mass; increased fatty tissue; decreased total body water, decreased plasma protein i.e., albumin);
c) Metabolism: Hepatic system influences metabolism (decreased liver size, decreased microsomal enzyme activities, decreased hepatic blood flow; increased incidences of drug-induced hepatitis);
d) Excretion: Renal changes (i.e., decreased creatinine level; decreased renal size; decreased renal blood flow; reduced kidney function e.g., decreased glomerular filtration rate (GFR) and number of functioning glomerulli).

Effect of foods/beverages on human Cytochrome P450 (CYP450). Aging causes change in hepatic systems, whereas xenobiotics including foods/beverages affect the enzymatic activities: neutral, enhance or retard. For food and beverages, it is the changes in the intestinal enzymatic activities that influence the absorption/ bioavailability of a drug. A therapeutic failure would result if the drug is degraded by enhanced metabolizing activity of the enzymes, where a toxic effect is expected when retardation of enzymatic activities allows more drugs in the system. In both cases there are health issues. Food and drugs when consumed affect mainly the P450 enzymes located in the human intestine. Human P450 consists of two major classes of enzymes, but only isozymes CYP1, CYP2, CYP3 and CYP4 are involved in the metabolism of pharmaceuticals (medicine).CYP3A is responsible for hepatic metabolism (breakdown) of approximately 60% of currently available human medicines, whereas CYP2, CYP1 are estimated for 20 and 15%, respectively (Chen and Raymond, 2006; Christians, 2004; Dahan and Altman, 2004; Kivisto *et al*., 2004), but specifically CYP3A4 and P-glycoprotein (PGP) in the intestine. PGP transports many drugs from the intestine into the blood (Sharom *et al*., 2005).

Beverages. Juices are highly recommended as functional food because of their physiologically active components e.g. vitamins, fibre, bioavailability of certain drugs etc. The most often recommended is apple, grapefruit or orange juice. Bailey *et al*. (1991) reported a pharmacokinetic interaction of grapefruit juice with the calcium-channel blockers felodipine and nifedipine. These researchers gave 5 mg of felodipine to six men with borderline hypertension with water, grapefruit juice or orange juice. The mean bioavailability of the drug was 284% (range 164-469%) with grapefruit compared to that when taken with water. Similarly the availability of 10 mg of nifedipine to male adult was 134% (range 108-169%) of that of water when taken with orange juice. Further, it generated considerable interest in this area globally. This group later showed that grapefruit juice mediated inhibition of CYP3A4 in the intestine was responsible for increased bioavailability of felodipine- an increased felodipine concentration in plasma (Bailey *et al*., 1988). These are landmark studies on the food/ beverage interaction with therapeutic drugs, which were responsible for considerable research in food and drug research globally. A group of researchers (Paine *et al*., 2006) fifteen years later reported that felodipine plasma concentration did not increase when adults were given furanocoumarin-free grapefruit juice (but contained other flavonoids). They also observed that the maximum concentration of felodipine in plasma was similar to that of orange juice, but considerably lower than regular grapefruit juice that contained furanocoumarins, most abundant are 6',7'-dihydroxy bergamottin and bergamottins, derived from psoralen following metabolism (structures in Fig. 1). Thus, these authors concluded that furanocoumarins are the active ingredients for observed increased bioavailability of felodipine. It should be mentioned here that there has been no reported incidence of interaction of apple juice with a drug. However, most recently, Bailey (2008) reviewed his pioneering work with grapefruit juice at the American Chemical Society Meeting. He also reported that patients who took an antihistamine with grapefruit juice absorbed only half the drug compound compared to those who took the pill with water. He also suggested inhibitory effects of other juices including apple, orange, and the whole fruits.

Collectively, the vast numbers of published studies with grapefruit juice have resulted in the most drug regulatory authorities advising consumers and patients to avoid or greatly limit their intake of grapefruit products. A recent article in Ladies Home Journal, compiled by Wagle (2008) reproduced from Karch (2004) a complete list of drugs that included several anthelmintic, antileptic, calcium-channel blockers, hormone replacements, which interact with grapefruit juice. The article advocated "to avoid grapefruit juice within a few hours of taking medication, or perhaps even at all". Recently, an interesting article titled "The grapefruit challenge: the juice inhibits a crucial enzyme, with possibility fatal consequences" was posted at the Mayo clinic site (Jan 23, 2007).

Such advisories will have serious negative impact on grapefruit growers and processing industries. Psoralen derivatives

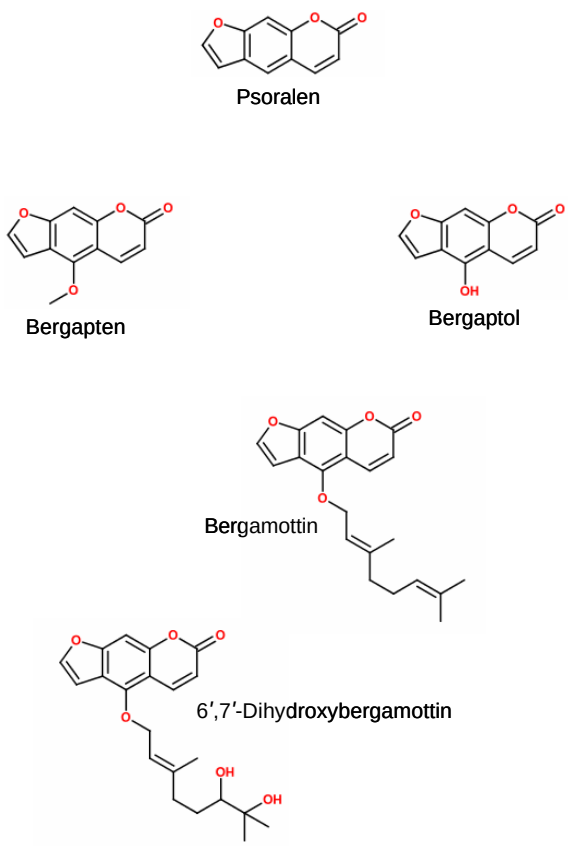

Fig. 1. Chemical structures of major furanocoumarins (Psoralen based) in foods/beverages.

are also present in many foods including, but not limited to, peas, beans, figs, jackfruit, carrot, celery, dill, fennel, parsnip, Baizhi (*Angelica dahurica* root), Hamaudo (*Angelica japonica*), Qianghuo (*Notopterygium incisum*), and Fangfeng (*Saposhnikovia divaricata*) (Guo and Yamazoe, 2004). Many but not all of the psoralen derivatives can cause mechanism-based inactivation; hence foods with lower levels of the active derivatives would be useful and provide a market advantage. A recent article reviews the literature on mechanism, extent and relevance of drug interactions with grapefruit juice and concludes that the predominant mechanism for this interaction is the inhibition of cytochrome P450 3A4 in the small intestine resulting in a significant reduction of drug presystemic metabolism (Dahan and Altman, 2004).

Reported incidences of food, including beverages, and drug interactions have directed researchers to look into the behaviour of other commonly used beverages that are promoted for health benefits. The unexpected observation of grapefruit juice resulted in investigation of other juices. A study by Malhotra *et al*. (2001) also identified Seville orange juice to interact with felodipine by a common mechanism-based inactivation of intestinal CYP3A4.

Pomegranate juice, derived from a fruit that has been prescribed as medicine (complementary medicine) in Eastern and Mediterranean cultures from pre-historic times, is a new addition as beverage in the west, and is promoted in lay magazines and newspapers for its health benefits (Bowden, 2008; Underwood, 2005). Most of the health benefits in pomegranate have been associated to its rich antioxidant polyphenol compounds that may have more activity than highly touted red wine and green teas (Malik *et al*., 2005). However, some studies (Summer, 2006; Hidaka *et al*., 2005) have also reported inhibition of CYP450 by pomegranate juice similar to that of grapefruit juice in rats.

Cranberry juice is a popular addition to beverages for its antioxidant properties. However, concerns have been raised for its interaction with Warfarin, a most often prescribed drug for anticoagulation therapy (Suvarna *et al*., 2003). But a review of published research could not support this hypothesis because the two clinical studies with patients taking Warfarin and cranberry juice did not conclusively show cranberry as the sole source for observed increase in the international normalized ratio (Pham and Pham, 2007).

Star fruit (*Averrhoa carambola*) another delicious fruit found, grown and eaten in many tropical countries – has now been introduced in the west. It has also shown to inhibit human cytochrome P450 3A (Hidaka *et al*., 2004).

To date there has been no report of verifiable actual incidence of interaction of any other juice and star fruit with any life saving drug. There is no information in the published literature on the nature of bioactives substances in pomegranate and star fruit.

As a general rule, drugs such as Lipitor, Toprol XL, Vytorin Lexapro, Synthroid, Prevacid, Norvasc taken to control high cholesterol level, high blood pressure, depression should not be taken with food and/drug to avoid and/or minimize therapeutic failure or side effects. Most often it is better to take these drugs with water.

Herbs in food. A large population of senior citizens often also use herbal supplements in combination with prescription medications; most often they do not inform their physicians. A few of these herbs and supplements are also used regularly in diets as flavouring agents or as vegetables. Not unexpectedly, there are many reported incidences of herb-drug interactions which require separate detailed studies. Garlic and carrot have been used both as food and herbal supplements for their antioxidative properties. Garlic is used for flavor in many Asian and Mediterranean diets, especially after frying in oil until golden brown for aroma. It is also used as supplement to control cholesterol level, high blood pressure and as disinfec-

tant among others. However, there is also some concern that the use of garlic would be detrimental when taken in conjunction with blood clotting drugs such as Warfarin, Plavix and aspirin; or antiretroviral drugs (to treat HIV/AIDS patients). A survey revealed that the use of herbal drinks/supplements is considerably higher in persons with AIDS/HIV who also take antiretroviral and other prescribed medicines (Fairfield *et al*., 1998). It has been reported that HIV-infected patients have carotene deficiency most likely caused by general malabsorption, fat malabsorption or altered metabolism– a cause of concern for increased oxidative stress (Keating *et al*., 1995; Pace and Leaf, 1995). For this reason HIV/AID patients often take beta-carotene supplements in combination with prescription drugs such as nelfinavir (NLF, a protease inhibitor recommended for use by HIV/AID patients). Several studies were undertaken to assess the interaction of beta-carotene with CYP 3A4 and P-glycoprotein in vitro (Chauhan *et al*., 2005; Foster *et al*., 2002). This was extended to an *in vitro*-study on the effect of beta carotene on the pharmacokinetics of NLF or its major metabolite, commonly referred to as M8, which indicated no potential for significant interaction (van Heeswijk *et al*., 2004). In order to assess the benefit of beta-carotene supplements on the absorption of NLF, the team conducted clinical trials on 24 persons with AIDS. Data suggested that beta-carotene given twice daily at a dose of 25000 IU with regular dose of NLF for more than 2-week did not significantly alter the steady-state pharmacokinetic of NLF and M8, though it delayed NLP absorption, and is safe (Sheehan *et al*., 2005; 2008).

Foster *et al*. (2003) studied *in vitro* inhibition of human P450-mediated metabolism of marker substrates by natural products. The products studied included several routinely used spices, herbal and black teas and soybeans and investigated their capacity to inhibit metabolism of drug marker substrates by human cytochrome P450 (CYP) isoforms (CYP3A4). Products were purchased from local markets: 6 spices (clover, ginger, oregano, sage, thyme leaves, turmeric), 20 teas: single-entity herbal teas (Cat's claw bark, Chamomile herb, Feverfew leaf, Goldseal Herb, Gotu Kola herb; Kava kava, Siberian ginseng, St. John's Wort; Black tea: (Darjeeling tea, Earl Grey, English Breakfast, Irish Breakfast, Orange Pekoe) and Herbal mixture (Echinacea plus; Echinacea Special, Echinacea and Goldenseal, Ginger mix, Ginko biloba Special, Green tea with Kombucha and Chinese herbs; and Green tea with Triple Echinacea and Kombucha), 7 soybean varieties and 4 pure soy isoflavones. Data showed that all products including spices had significant varied inhibition of P450 metabolism of the substrates. Further, the conducted screening clearly demonstrated the potential of these products to interfere with human CYP mediated drug metabolism. Surprisingly, the single-entity herbal teas exhibited lower inhibition than other categories. Also, soybean extracts also inhibited CYP, which is in agreement with previously reported inhibition of pure major isoflavones.

Conclusion

Food-drug interaction occurs regularly, but is poorly reported to the appropriate authorities. Recent activities including research reports, articles in lay magazines and surveys of various stakeholders highlight the growing health concern among health care professionals. Now more and more people, especially the senior citizens –who have the financial resources to travel to many exotic places and try a variety of foods including exotic foods and fruits and juices –without having knowledge of ingredients that may interact with prescription drugs, fall victims to such reactions. In addition, a lot of exotic fruits, beverages are now found at local groceries in many parts of the developed countries. It is highly advisable that high risk patients taking regular prescription drugs consult their physicians before they venture out in tasty, delicious fruits and foods that may not be good for health, and may become fatal. Although, the food-drug interactions most often are seen in negative context, a recent presentation by Reddy *et al*. (2007) reported the bioavailability of very expensive breast cancer drug lapatinib (Tykerb, approved by the US Food and Drug Administration on March 13, 2007 to be taken in empty stomach- fasting) is greatly increased by food, especially a high-fat meal. In a commentary Ratain and Cohen (2007) estimated a cost saving of 60% or $1740 per month if lapatinib is taken with food instead of in empty stomach. They also recommend marketing of a 500 mg formulation of the drug to be taken with food instead of currently recommended 1250 mg formulation. The estimates and recommendation may appear very simple, but one should be mindful of various competing factors that come into play for delivery and efficacy of a drug. This suggests comprehensive studies of the use of food for delivery of expensive drugs at reduced dosages for the maximum benefits.

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References

Ameer, B., Weintraub, R. 1997. Drug interaction with grapefruits juice. *Clin. Pharmacokinetic* **33:** 103-121. http://pharmacokinetics.adisonline.com/pt/re/cpk/home.htm

Anastasio, G.D., Cornell, K.O., Menscer, D. 1997. Drug interac-

tions: Keeping it straight American. *Am. Fam. Physician* **56:** 883-895. http://www.aafp.org/online/en/home/publications/journals/afp.html

Aslam, M., Stockley, I.H. 1979. Interaction between curry ingredient (karela) and drug (chlorpropamide). *Lancet* **1:** 607. http://dx.doi.org/10.1016/S0140-6736(79)91028-6

Ayo, J.A., Agu, H., Madaki, I. 2005. Food and drug interactions: its side effects. *Nutrition & Food Science* **35:** 243-252. http://www.emeraldinsight.com/Insight/viewContent Item. do; jsessionid=5BE61A7A95B08A6D564B65285C9C8390? content Type=Article & contentId=1509894.

Bailey, D.G. 2008. Grapefruit: A food that potently impairs intestinal drug metabolism and uptake transport clinically. In: *Session Toxi-30, The 236th ACS National meeting*, Philadelphia, PA, USA (Abstr. No. 30).

Bailey, D.G., Dresser, G.K. 2004. Natural products and adverse drug reaction. *Can. Med. Assoc. J.* **170:** 1531-1532. http://dx.doi.org/10.1503/cmaj.1031558

Bailey, D.G., Spence, J.D., Munoz, C., Arnold, C.M. 1991. Interaction of citrus juices with felodipine and nifedipine. *Lancet* **337:** 268-269. http://www.ncbi.nlm.nih.gov/pubmed/1671113

Bailey, D.G., Arnold, J.M.O., Spence, J.D. 1988. Grapefruit juice-drug interaction. *Br. J. Clin. Pharmacol*. **46:** 101-110. http://dx.doi.org/10.1046/j.1365-2125.1998.00764.x

Bland, S.E. 1998. Drug-Food Interactions. *J. Pharmacy Soc*. Wisconsin Nov/Dec. http://www. pswi.org/professional/pharmaco/druginteractions.pdf

Boullata, J. 2005. Natural health product interactions with medication. *Nutr. Clini. Pract.* **20:** 33-51. http://ncp.aspenjournals.org/cgi/content/abstract/20/1/33

Boullata, J.I., Armaenti, V.T. (eds.), 2004. Handbook of drug-nutrient interactions. Humana Press, Totowa, New Jersy, USA. http://www. springer.com/humana+press/book/978-1-58829-249-0

Bowden, J. 2008. The 10 best foods You aren't eating. Men's Health Nutrition: Food for fitness. http://health. msn.com/fitness/articlepage.aspx?cp-documentid=100168050

Chauhan, B.M., van Heeswijk, R., Borbeau, Akhtar, H., Singhal, N., Cameron, B., Foster, B.C. 2005. The effect of beta-carotene on P-glycoprotein and CYP3A4 activity *in vitro*. 14th Annual Canadian Conference on HIV/AIDS (CAHR). *Can. J. Inf. Dis. & Med. Microbiol*. Abstract 254.

Charrois, T.L., Hill, R.L., Vu, Duc., Foster, B.C., Boon, H.S., Cramer, K., Vohra, S. 2007. Community identification of natural health product-drug interactions. *Ann. Pharmacother*. **41:** 1124-1129. www.theannals.com/cgi/content/abstract/41/7/1124

Chen, J., Raymond, K. 2006. The role of CYP3A4 and P-glycoprotein in food-drug and herb-drug interactions. *Pharmacist* **25:** 732-737. http://www.psa.org.au/site.php?id=745

Cheng, T.O. 2006. Food-drug interaction. Letter to Editor. *Int. J. Cardiol.* **106:** 392-393. http://dx.doi. org/10.1016/j.ijcard.2004.12.083

Christians, U. 2004. Transport proteins and intestinal metabolism: P-glycoprotein and cytochrom P4503A. *Ther. Drug Monit.* **26:** 104-106. http://www.drug-monitoring. com/pt/re/tdm/fulltext.00007691-200404000-00002.htm

Dahan, A., Altman, H. 2004. Food-drug interaction: grapefruit juice augments drug bioavailability -mechanism, extent and relevance. *Eur. J. Clin. Nutr.* **58:** 1-9. http://www.nature.com/ejcn/journal/v58/n1/pdf/1601736a.pdf

Daniells, S. 2006. Curry spice may have anti-arthritis potential. NutraIngredient-europe, October 30. http://www.nutraingredients.com/news/ng.asp?id=71667

De Smet, P.A.G.M. 1995. Health risks of herbal remedies. *Drug Saf.* **13:** 81-93. http://md1.csa.com/partners/viewrecord.php? requester=gs&collection=ENV&recid=3804379

Dharmananda, S. 2003. Checking for possible herb-drug interactions. www.itmonline.org/arts/herbdrug2.html

Eisenberg, D.M., Davis, R.B., Ettner, S.L., Appel, S., Wilkey, S., Van Rompay, M., Kessler, R.C. 1998. Trends in the alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *J. Am. Med. Assoc*. **280:** 1569-1575. http://jama.ama-assn.org/cgi/content/abstract/280/18/1569

Fairfield, K.M., Eisenberg, D.M., Davis, R.B., Libman, H., Philips, R.S. 1998. Patterns of use, expenditures, and perceived efficacy of complementary and alternative therapies in HIV-infected patients. *Arch. Intern. Med*. **158:** 2257-2264. http://archinte.highwire.org/cgi/content/abstract/158/20/2257

Foster, B.C., Arnason, J.T., Briggs, C.J. 2005. Natural health products and drug disposition. *Annu. Rev. Pharmacol. Toxicol*. **45:** 203-226. http://dx.doi.org/10.1146/annurev.pharmtox.45.120403.095950

Foster, B.C., Vandenhoek, S., Hana, J., Krantis, A., Akhtar, M.H., Bryan, M., Budzinski, J.W., Ramputh, A., Arnason, J.T. 2003. *In vitro* inhibition of human cytochrome P450-medicated metabolism of marker substrates by natural product. *Phytomed.* **10:** 334-342. http://dx.doi.org/10.1078/094471103322004839

Foster, B.C., Vandenhoek, S., Li, K.Y., Tang, R., Budzinski, J.W., Krantis, A., Li, K.Y. 2002. Effect of several Chinese naturalhealth products on human cytochrome P450 metabolism. *J. Pharm. Pharm. Sci.* **5:** 185-189. http://epe.

lac-bac. gc.ca/100/201/300/jrn_pharmacy/1998-2002/v05n02/B.Foster/cytochrome.htm

Foster, B.C., Vandenhoek, S., Hanna, J., Akhtar, M.H., Krantis, A. 1999. Effects of natural health products on cytochrome P-450 drug metabolism. *Can. J. Infect. Dis. Supp*. **10(B):** 18. http://www.pulsus.com/Infdis/home.htm

Foster, B.C., Gallicano., K., Cameron, W., Chaudri, S. 1998. Constituents of garlic inhibit cytochrome CYP450 3A4 mediated metabolism. Abstr. No. 472P. *Can. J. Supp. Infect. Dis*. **9(B):** 472. http://www.pulsus.com/Infdis/home.htm

Guo, L.Q., Yamazoe, Y. 2004. Inhibition of cytochrome P450 by furanocoumarins in grapefruit juice and herbal medicines. *Acta Pharmacol. Sin*. **25:** 129-136. http://www.chinaphar.com/1671-4083/25/129.pdf

Haddad, P.S., Azar, G.A., Groom, S., Boivin, M. 2005. Natural health product, modulation of immune function and prevention of chronic diseases. *eCAM* (*Evidence-based Compl. and Alt. Medicines*) **2:** 513-520. http://ecam.oxfordjournals.org/cgi/content/full/2/4/513

Hansten, P.D., Horn, J.R. (eds.), 2003. The top 100 Drug interactions: A guide to patient management. Edmonds, WA,H&H Publ. USA, http://pmj.bmj.com/cgi/content/extract/80/940/123

Health Canada, 2006. In: *Proc. Int. Symp. Drug, Food and Natural Health Products Interactions*, February 9-10, Aylmer, Quebec, Canada. http://www.hc-sc.gc.ca/dhp-mps/pubs/drug-medic/interaction_symposium_rop_crd_e.html

Hidaka, M., Okumura, M., Fujita, K., Ogikubo, T., Yamasaki, K., Iwakiri, T., Setoguchi, N., Arimori, K. 2005. Effects of pomegranate juice on human cytochrome P450 3A (CYP3A) and carbamazepine pharmacokinetics in rats. *Drug Metab. Dispos*. **33:** 644- 648. http://dmd.aspetjournals.org/cgi/reprint/33/5/644.pdf

Hidaka, M., Fujita, K-i., Ogikubo, T., Yamasaki, K., Iwakiri, T., Okumura, M., Kodama, H., Arimori, K. 2004. Potent inhibition by star fruit of human cytochrome P 450 3A (CYP3A) activity. *Drug Metab. Dispos*. **32:** 581-3. http://dmd.aspetjournals.org/cgi/content/abstract/32/6/581

Izzo, A.A., Ernst, E. 2001. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* **15:** 2163-2175. http://www.drugs.adisonline.com/pt/re/drugs/abstract.00003495-200161150-00002.htm

Karch, A.M. 2004. The grapefruit challenge: the juice inhibits a crucial enzyme, with possibly fatal consequences. *Am. J. Nurs.* **104:** 33-35. http://www.ajnonline.com/pt/re/ajn/fulltext.00000446-200412000-00020.htm

Keating, J., Bjarnason, I., Somasundaram, S., Macpherson, A., Francis, N., Price, A.B., Sharpstone, D., Smithson, J., Menzies, I.S., Gazzard, B.G. 1995. Intestinal absorptive capacity, intestinal permeability and jejunal histology in HIV and their relation to diarrhoea. *Gut.* **37:** 623-629. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1382865

Kivistö, K.T., Niemi, M., Fromm, M.F. 2004. Functional interaction of intestinal CYP3A4 and P-glycoprotein. *Fundam. Clin. Pharmacol*. **18:** 621-626. http://dx.doi.org/10.1111/j.1472-8206.2004.00291.x

Kozyrskyj, A. 1997. Herbal products in Canada. How safe are they? *Can. Fam. Physician* **43:** 697- 702. http://www.cfp.ca

Lee, L.S., Andrade, A.S., Flexner, C. 2006. Interations between natural health products and antiretroviral drugs: Pharmacokinetic and Pharmacodynamic effects. *Clin. Infect. Dis*. **43:** 1052-1059. http://dx.doi.org/10.1086/507894

Leibovitch, E.R., Deamer, R.L., Sanderson, L.A. 2004. Food-drug Interactions: Careful drug selection and patient counseling can reduce the risk in older patients. *Geriatrics* **59:** 19-33. http://geriatrics. modernmedicine.com/geriatrics/data/articlestandard//geriatrics/112004/87937/article.pdf

Malhotra, S., Bailey, D.G., Paine, MF., Watkins, P.B. 2001. Seville orange juice-felodipine interaction: Comparison with dilute grapefruit juice and involvement of furanocoumarins. *Clin. Pharmacol. Ther.* **69:** 14-23. http://dx.doi.org/10.1067/mcp.2001.113185

Malik, A., Afaq, F., Sarfraz, S., Adhami, V.M., Syed, D.N., Mukhtar, H. 2005. Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer. *Proc. Natl. Acad. Sci. USA* **102:** 141813-141818. http://www.pnas.org/cgi/reprint/0505870102v1.pdf

Markowitz, J.S., Donovan, J.L., DeVane, C.L., Taylor, R.M., Ruan, Y., Wang, J.S., Chavin, K.D. 2003. Effects of St. John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *J. Am. Med. Assoc*. **290:** 1500-1504. http://jama.ama-assn.org/cgi/content/abstract/290/11/1500

Mayo Clinic: Zeratsky, K. website under (Jan 23, 2007). Grapefruit juice: Can it cause drug interactions? www.mayoclinic.com/health/food-and-nutrition/AN00413

McCabe, B.J., Frankel, E.H., Wolfe, J.J. (eds.), 2003. Handbook of Food-Drug Interactions. CRC Press Boca Raton, Flourida, =Mens Health & USA Channel. http://www.crcpress. com/shopping_cart/products/product_detail.asp? sku=1531&isbn=9780849315312&parent_id=&pc=

McLachlan, A., Ramzan, I. 2006. Meals and Medicine. *Australian Prescriber* **29:** 40-42. http://www.australianprescriber.com/upload/pdf/articles/791.pdf

Medical University of South Carolina –Health Topic Library (January 2008). Food-drug interactions: What happens during a food-drug interaction? http://www.muschealth.com/gs/HealthTopic. aspx?action=showpage&pageid=P00838

Mills, E., Montori, V., Perri, D., Phillips, E., Koren, G. 2005. Natural health product-HIV drug interactions: a systematic review. *Int. J. STD. AIDS* **16:** 181-186. http://www.saberviver.org.br/pdf/Natural_Health.pdf

Nagata, M., Hidaka, M., Sekiya, H., Kawano, Y., Yamasaki, K., Okumura, M., Fujita, K., Ogikubo, T., Ya Masaki, K., Iwakiri, T., Setoguchi, N., Arimori, K. 2005. Effects of pomegranate juice on human cytochrome P450 2C9 and tolbutamide pharmacokinetics in rats (CYP3A) and carbamazepine pharmacokinetics in rats. *Drug Metab. Dispos*. **33:** 644-648. http://dx.doi.org/10.1124/dmd.106.011718

Ness, J., Sherman, F.T., Pan, C.X. 1999. Alternative medicine: What the data say about common herbal therapies. *Geriatrics* **54:** 33-38. http://geriatrics.modernmedicine.com

Pace, G.W., Leaf, C.D. 1995. The role of oxidative stress in HIV disease. *Free Radic. Biol. Med*. **19:** 523-528. http://www.ncbi.nlm.nih.gov/pubmed/7590404

Sheehan, N.L., van Heeswijk, R., Foster, B.C., Akhtar, M.H., Singhal, N., Seguin, I., DelBalso, L., Bourbeau, M., Chauhan, B.M., Boulassel, M.R., Burger, D.M., Lalonde, R.G., Cameron, D.W. 2008. The effect of beta-carotene supplementation on the pharmacokinetics of nelfinavir and its active metabolite M8 in HIV-1 infected patients" [Private communication]. *Antimicrobial Agents and Chemotherapy* (under review).

Singh, B.N. 1999. Effects of food on clinical pharmacokinetics. *Clin. Pharmacokinet*. **37:** 213-255. http://www.ingentaconnect.com/content/adis/cpk/1999/00000037/00000003/art00003

Summer, K.M. 2006. Letter to the editor. Potential drug-food interactions with pomegranate juice. *Ann. Pharmacother.* **40:** 1472-1473. http://www.thearnnals.com/cgi/reprint/40/7/1472/pdf

Paine, M.F., Wilbur, W.W., Hart, H.L., Pusek, S.N., Beavers, K.L., Criss, A.B., Brown, S.S., Thomas, B.F., Watkins, P.B. 2006. A furanocoumarin-free grapefruit juice establishes furanocoumarins as the mediators of the grapefruit juice-felodipine interaction. *Am. J. Clin. Nutr.* **83:** 1097-1105. http://www.ajcn.org/cgi/content/full/83/5/1097

Pham, D.Q., Pham, A.Q. 2007. Interaction potential between cranberry juice and warfarin. *Am. J. Health Syst. Pharm.* **64:** 490-494. http://pt.wkhealth.com/pt/re/ajhp/abstract.00043627-200703010-00013.htm

Ratain, M.J., Cohen, E.E. 2007. The value meal: How to save $1700 per month or more on lapatinib. *J. Clin. Oncol*. **25:** 3397-3398. http://dx.doi.org/10.1200/JCO.2007.12.0758

Raucy, J.L. 2003. Regulation of CYP3A4 expression in human hepatocytes by pharmaceuticals and natural products. *Drug Metab. Dispos*. **31:** 533-539. http://dmd. aspetjournals.org/cgi/content/full/31/5/533

Reddy, N., Cohen, R., Whitehead, B. 2007. A phase I, open-label, three period, randomized crossover study to evaluate the effect of food on the pharmacokinetics of lapatinib in cancer patients. *Clin. Phramacol. Ther*. **81:** S16-S17. http://www.cancer.dartmouth.edu/media/release/072307.html

Senior Citizens Information and News (SCIN) 2005. S. Korea expects to lead by 2050 in World senior citizen population boom, beats Japan, Italy, U.S. *Senior Journal*, (May 23, 2005). http://seniorjournal.com/NEWS/SeniorStats/5-05-23KoreaSeniorBoom.htm

Sharom, F.J., Lugo, M.R., Eckford, P.D. 2005. New insights into the drug binding, transport and lipid flippase activities activities of the p-glycoprotein multidrug transporters. *J. Bioenerg. Biomembr*. **37:** 481-487. http://www. springerlink.com/index/C74287P4U6682J67.pdf

Sheehan, N.L., Bourbeau, M., Foster, B.C., Seguin, I., Akhtar, H., Singhal, N., Boulassel, M.R., DelBalso, L.D., Lalonde, R.G., van Heeswijk, R., Cameron, D.W. 2005. The effect of beta-carotene on the steady-state pharmacokinetics (PK) of nelfinavir (NFV) and its M8 metabolite. In: *6th International Workshop on Clinical Pharmacology of HIV Therapy*, April 28-30, Quebec, Canada.

Suvarna, R., Pirmohamed, M., Henderson, L. 2003. Possible interaction between warfarin and cranberry juice. *Br. Med. J.* **327:** 1454. http://dx.doi.org/10.1136/bmj.327.7429.1454

The University of Florida Center for Food-Drug Interaction Research and Education (2003). http://www. drug interactioncenter.org

Thomas, J.A., Burns, R.A. 1998. Important drug-nutrient interactions in the elderly. *Drugs & Aging* **13:** 199-210. aging.adisonline.com/pt/re/dra/toc. 00002512-199813030

Underwood, A. 2005. The new superfoods. *Newsweek* Oct. 24; **146:** 79-80. www. newsweek. com/id/50703).

United Nations, 2007. Department of Economic and Social Affairs. Population Division. *World Population Ageing* 2007, United Nations, New York, USA.

van Heeswijk, R., Bourbeau, M., Foster, B., Seguin, I., Akhtar, H., Singhal, N., Cameron, B. 2004. The effect of beta-carotene on the pharmacokinetics of nelfinavir and M8. *The OTN (Ontario HIV Treatment Network) Annual Research*

Conference, Toronto, Canada, Nov. 24-25. http://www.ohtn.on.ca/documents/poster_abstracts%5CTreatment%5CA211.pdf

Wagla, S. 2008. A complete list of drugs that interacts with grapefruit juice. *Ladie's Home Journal® Magazine*. http://www.lhj.com/lhj/story.jhtml?storyid=/templatedata/lhj/story/data/DrugGrapefruitJuice_03292005.xml

Winstanley, P.A., Orme, M.L. 1989. The effects of food on drug bioavailability. *Br. J. Clin. Pharmacol*. **28:** 621-628. http://www.blackwell-synergy.com/loi/BCP