Review Article

Natural product and drugs interactions, its clinical implication in drug therapy management

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ABSTRACT

يعتبر تفاعل المنتج الطبيعي والأدوية مشكلة خفية شائعة يتم مواجهتها في الممارسة السريرية. التفاعلات بين المنتجات الطبيعية والأدوية مبنية على نفس مبادئ حركيات الدواء وفعالية العقاقير كتفاعلات الدواء الى الدواء. تظهر التفاعلات السريرية المهمة في تدخل التأثيرات على إستقلابات الدواء مقابل إنزيمات إسويات الصبغ الخلوي P-450 وقصور وظيفة الكبد أو الكلى والآليات المحتملة الأخرى. للمشورة المرضى الفعالة حول التفاعلات المتعلقة بالمنتجات الطبيعية يجب أن يكون الطبيب والصيدلاني ملمان بالمنتجات شائعة الاستعمال والتي تدخل في تكوين الكثير من المنتجات الغامضة. في هذه المراجعة تم شرح تفاصيل تفاعلات الأدوية مع المنتجات الطبيعية وأثرها على المعالجة بالأدوية.

The interaction of natural products and drugs is a common hidden problem encountered in clinical practice. The interactions between natural products and drugs are based on the same pharmacokinetic and pharmacodynamic principles as drug-drug interactions. Clinically important interactions appear to involve effects on drug metabolism via cytochrome P-450 isoenzymes, impairment of hepatic or renal function, and other possible mechanisms. To effectively counsel patients on interactions involving natural products, physicians, and pharmacists should be familiar with the most commonly used products, and have access to information on more obscure products. In this review, we describe details of drugs interaction with natural products and its impact on drug therapy management.

Saudi Med J 2008; Vol. 29 (3): 333-339

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The public generally considers natural products as "health foods" and herbal remedies as safe and beneficial. These substances are largely unregulated and hence contribute to the misconception that they are innocuous. Patients do not feel the need to tell their physicians that they are using some herbs or natural products, and physicians also do not routinely ask the patients.[1] Natural products and drug interactions are among the significant problems in clinical practice, since it interacts with various pharmacokinetic processes. Interactions between natural products and drugs can unintentionally reduce or increase the effect of the drug, resulting in therapeutic failure, or increase toxicity.[2] When drugs and natural products are taken simultaneously they can interact in ways that diminish the effectiveness of the ingested drug or reduce the absorption of ingredient of the natural product. Additionally, vitamin and herbal supplements taken with prescribed medication can result in adverse reactions.[3] The interactions can occur when the food intake affects the ingredients in a medication, preventing the medicine from working the way it should. Some constituents of the natural products can affect the way of metabolizing certain drugs by binding with drug ingredients, thus reducing their absorption or speeding their elimination. For example, the acidity of the fruit juice may decrease the effectiveness of antibiotics such as penicillin. Natural products and drug interactions can lead to increase, decrease, or no change in the action of a drug. Increase in action leads to toxicity, and a decrease in action leads to therapeutic failure of the drug. This may lead to a) prolongation of the stay in the hospital, b) increased morbidity and mortality, c) increase in economic burden on a country. There are certain natural products that are beneficial for the body and their interaction with some concurrent medication may be beneficial or harmful. So, there is need for strategies to identify and prevent the development of such harmful natural products and drug interactions. Natural products can "interact" with drugs by affecting the biological processes that regulate their metabolism and elimination. Cytochrome P450 is the system of enzymes that are abundantly involved

in the metabolism of many drugs. Cytochromes are present in the liver and also expressed throughout the gastrointestinal tract, but minimal amounts in lung, kidney, and even in the central nervous system. The CYP3A4 is the most abundantly expressed and involved in the metabolism of approximately 50% of clinically used drugs. There are various natural products, which are either inhibitors, or inducers of these enzymes and thus readily affect the metabolism of many orally administered drugs.[1] The cytochrome P450 enzymes are a super-family of heme-thiolate proteins widely distributed across all living kingdoms. The enzymes are involved in the metabolism of a plethora of chemically diverse, endogenous, and exogenous compounds, including drugs, environmental chemicals, and other xenobiotics.[5] Many people have the mistaken notion that, being natural, all herbs and foods are safe. This is not so. Most of the time, herbs and foods may interact with medications normally taken that may result in serious side effects. It is always good practice to tell the doctor or health practitioners what patients are taking so that physicians can advice the patients regarding possible complications, if there are any. One should also watch for unusual symptoms. Very often, this may foretell the symptoms of a drug interaction. Experts suggest that natural does not mean it is completely safe. Everything has the potential to interact with something else. So, when a drug is mixed with food or another herb, each can alter the way the body metabolizes the other. Some drugs interfere with the body's ability to absorb nutrients. Similarly, some herbs and foods can lessen or increase the impact of a drug.[3] Basically the nature of herb-drug interaction is not a chemical interaction between the drug and herb component to produce toxic effect. Instead, the interaction may involve an herb component causing either an increase or decrease in the amount of drug in the blood stream. A decrease in the amount of drug could occur by herb components binding up the drug and preventing it from getting into the blood stream from the gastrointestinal tract, or by stimulating the production and activity of enzymes that degrade the drug and prepare it for elimination from the body. Similarly, an increase can occur by aiding absorption of the drug or by inhibiting the enzymes that break down the drug. Actually, herbal medicines either mimic, or increase, or decrease the action of prescribed drugs. This can be especially important for drugs with narrow therapeutic windows and in sensitive patient populations such as older adults, the chronically ill, and those with compromised immune systems.[6] It is hard to warn the public of the potential of dangerous interactions between number of drugs and natural products. This problem is different from drug-drug interaction where a pharmacist should take a drug history before dispensing the 2 drugs, for example, erythromycin or ketoconazole.

There is some concern regarding whose responsibility it is to warn the public? Is it the responsibility of the practicing physician or the regulating agencies or the manufacturers? Are there other groups with responsibility, such as medical journals or journalists in the lay press that specialize in medical reporting? Should scientific associations bear responsibility? If it is so then how the public should be notified and made concerned regarding what is the reasonable delay? What constitutes adequate evidence to justify a warning? When should the public be warned? If the interaction is very unlikely to occur, is likely to be prevented by monitoring programs in place (such as pharmacist intervention). If it is likely to be clinically unimportant, then no public warning would likely be needed. How should the public be warned? News reports in the print and electronic media, editorial advertisements in medical journals, and letters to physicians from manufacturers and regulatory agencies, warning labels on drug products and food packaging, warning in the product monograph and package insert of affected products. Notices should be pasted in pharmacies on the counters at which affected over the counter preparations are sold. Warnings on the grocery counters should be displayed where grape fruit juice and other food products are sold.

Suggested approaches. There can be several approaches to check these interactions. Scientific organizations should develop a standing committee on communication with the public to provide drug information. It should include information on appropriate drug use, including warnings about important new drug-drug and drug-food interactions. The urgency of warnings would be determined by how likely they are to occur, how controlled monitoring the dispensing would be, and how dangerous the interactions are. The Federal Drug Association and other regulatory agencies need to recognize the various drug and natural product interactions and should take appropriate steps to minimize these interactions by producing awareness in common people. Manufacturers need to be more aware of the risk to the company, as well as to the public, of failing to provide adequate warning and they need to put in place mechanisms for earlier awareness of such risks and for ways to deal with them. A condition that is somewhat more worrisome is the interaction between grape fruit juice and felodipine, where the average increase is 284%, with a range up to 600% and Nisoldipine, where the increase is 500-900%.[8] In such circumstances an interaction is likely to cause adverse consequences, ranging from facial flushing and ankle edema to faintness and provocation of myocardial ischemia. In such situations, it would seem to be reasonable to

warn the physicians and pharmacists. It would also be prudent for physicians prescribing the affected drugs and for pharmacists dispensing them, to warn patients not to take them with grape fruit juice. Package inserts should also provide warnings. If, on the other hand, the interaction is likely to be unmonitored, is likely to have a large effect, is potentially dangerous, and is likely to occur, then it would seem to be reasonable to warn the public directly. Some examples are terfenadine, and grape fruit juice, itraconazole-lovastatin also with grape fruit juice, cisapride causes QTc prolongation. Grape fruit juice enhances the effect of some commonly used medications by increasing their function by selective down regulation of the specific super family of the cytochrome P450 enzyme system in the small intestine. Its interaction has potential clinical importance as it is often consumed at breakfast time when drugs are also taken. Grape fruit juice inhibits hepatic cytochrome P450 isoenzymes (CYP3A4 subfamily) and interacts with compounds such as cyclosporine and the calcium entry blocking dihydropyridines, both of which are metabolized via CYP3A4. This interaction may take place during the first pass of the drugs concerned. It has been attributed to certain active aglycones (naringenin, quercetin, kaempferol) formed in the gut from the corresponding bioflavonoid glycosides in grape fruit juice. However, the overall inhibitory effect of grape fruit juice on cytochrome isoenzymes may also include CYP1A2. The concentration of the flavonoids in juice can vary quantitatively and qualitatively (chiral isomers), presumably due to different kinds of grape fruit, the method of juice extraction from the fruits and perhaps on the subsequent processing of juice to branded consumer products.[9] There are considerable inter-individual differences in the amount of intestinal and hepatic CYP3A4, which could modify drug interactions with this enzyme. The unique components in grape fruit juice that are responsible for the drug interactions include the furanocoumarin 6',7'- dihydroxy bergamottin, quercetin (also in strawberries), kaempferol and naringenin. These compounds are primarily responsible for the inhibitory effects of grape fruit juice on CYP3A4 activity. The flavonoids are present in the juice as glycosides that are hydrolyzed in the intestine.[9]

Grape fruit juice and drug interactions. The magnitude and the mechanism of the interaction between grape fruit juice and low bioavailability drugs metabolized by grape fruit juice and low bioavailability drugs metabolized by gut wall CYP3A4 appears to be very similar to that observed with erythromycin; both erythromycin and grape fruit juice increase felodipine levels nearly 3 folds. It is now known that grape fruit juice on average increases felodipine area under the curve by 204% with a range up to 600%, and increases nisoldipine peak plasma concentration on average 5 fold, with a range up to 9 fold (900%), and cyclosporine levels (3 fold). Grape fruit juice increases the proportion of patients with detectable levels of parent terfenadine 7 fold to 10 fold. Importantly the rise in blood levels of felodipine in patients with hypertension was associated with a doubling of both blood pressure and heart rate.[10] The adverse effects were also increased. Excessive ingestion of grape fruit juice increases the bioavailability of lovastatin by 1400%, atorvastatin by 200%, and simvastatin by 1500%, by inhibiting their first pass metabolism. This may lead to drug accumulation and possible development of adverse effects.[11-13] Significant inhibition of CYP3A4 leads to altered levels of dihydropyridines, hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, cisapride, midazolam, terfenadine, and cyclosporine.[14] Significant inhibition of CYP1A2 leads to reduced metabolism of warfarin, caffeine, theophylline, and imipramine, and so forth. It also appears that interaction between terfenadine[15] and erythromycin- ketoconazole with the potential to cause fatal arrhythmias associated with torsades de pointes will also occur with grape fruit juice.[16,17] Astemizole is not affected to a significant extent by grape juice, because it is not metabolized by several isozymes of P450. Natural diary products like milk, vitamins, minerals containing iron and antacids decreases fluoroquinolone drug concentration. Milk interferes with digoxin absorption. So, milk should not be mixed with laxatives containing bisacodyl and also large amounts of oatmeal and other high fiber cereals should not be eaten when taking digoxin. The fibers can interfere with the absorption of the drug making the act of swallowing the pill a waste of time. Green leafy vegetables (for example, spinach) have high concentrations of vitamin K. Spinach should not be taken in great quantities while taking Coumadin. It can totally negate the affects of the drug and cause blood clotting. Turnips contain 2 goitrogens, progoitrin, and gluconasturtin, which can interfere with thyroid function. They can only promote goiter in persons with thyroid disease, not in normal persons so the patients with hypothyroidism should not eat turnips. Tomatoes, garlic, turmeric, and so forth, are among the main constituents of the daily meal. Tomatoes contain a small quantity of a toxic substance known as Solamine that may trigger headaches in susceptible persons. Turmeric should be avoided in persons with gallstones. Strawberries, raspberries, spinach, and rhubarb, contains oxalic acid, which causes stones in the kidney and decreases the absorption of iron and calcium.[3] It is well known that turmeric has antibacterial, anti-inflammatory, antiviral, antifungal, antitumor, antispasmodic, and hepatoprotective properties, but still should be avoided in persons with gall stones, gastric ulcer, or hyperacidity.[18]

Cardiovascular disorders. Highly used drug therapies in developed as well as developing countries are related to the cardiovascular system. There are numerous medications used to treat cardiovascular disorders such as high blood pressure, angina, irregular heart beat, and high cholesterol. Among them hypertension is the most common. The prevalence of hypertension increases with advancing age, for example, approximately 50% of people between the ages of 60-69 years old have hypertension, and the prevalence is further increased beyond age 70. Thus, the third National Health and Nutrition Examination survey (NHANES III), conducted from 1992 to 1994, found that 27% of the American adult population had hypertension.[20] People have the habit of taking herbal medicines or other natural products in their daily life. Various herbs like black cohosh, ginseng, licorice, and yohimbe should not be used in combination with antihypertensive drugs. If it is necessary to use the herbs with the therapy then one should monitor blood pressure very closely during the treatment, for example, Coenzyme Q-10, ginger, ginkgo biloba, ginseng, hawthorn, grape fruit juice, peppermint oil. Ginseng inhibits the metabolism of nifedipine by 53%, while yohimbe antagonizes the effect of clonidine. Grape fruit juice increases the bioavailability of calcium channel blockers. Peppermint oil, which is used daily can also inhibit the metabolism of nifedipine in human liver microsomes. Licorice is used as demulcent and large amounts can cause sodium and water retention leading to hypertension and decreased efficacy of antihypertensive drugs and also causes depletion of potassium. If licorice is combined with digoxin and furosemide, the symptoms of heart failure develop in many cases so one should avoid the concomitant use of licorice and digoxin. Actually, the various classes of drugs are often used in combination to enhance their effectiveness. Some classes of drugs can treat several conditions. For example, beta-blockers can be used to treat high blood pressure, angina, and irregular heartbeats. The effect of various natural products on these medications produce very severe effects if occurred unnoticed. So, one should be aware of these interactions while taking the medication. Some diuretics cause loss of potassium, calcium, and magnesium. Triamterene, on the other hand, is known as a "potassium sparing" diuretic. It blocks the kidneys' excretion of potassium, which can cause hyperkalemia. Excess potassium may result in irregular heartbeat and palpitations. Avoid eating large amounts of potassium-rich foods such as bananas, oranges, and green leafy vegetables, or salt substitutes that contain potassium.[21] Ephedrine-containing herbal products have been associated with adverse cardiovascular events, seizures, and even death.[22] Foods high in fiber, such as oatmeal, and soluble fiber cereal decrease the absorption of lovastatin, resulting in a substantially higher level of low density lipoprotein cholesterol.[23]

Anticoagulants. Millions of people regularly take blood-thinning drugs such as warfarin, and even more take aspirin and similar medications to prevent heart attacks and strokes. At the same time, most of the people do not inform their physician of the use of herbs or vitamin supplements. Anticoagulants help to prevent the formation of blood clots, for example, warfarin/ Coumadin. Intake of a regular meal does not affect the bioavailability of warfarin.[24] A single excessive intake of vitamin K rich food has no clinically significant impact on the anticoagulant effect of warfarin; however, a continuous daily ingestion of high amounts of vitamin K rich food for one week may lead to warfarin requiring dosage adjustments.[25,26] For example, broccoli, spinach, kale, turnip, cauliflower, brussel sprouts, and so forth. Various herbs, which should be used with caution during the anticoagulant therapy are chondroitin sulphate and glucosamine, which enhance the action of warfarin. The monitoring of signs and symptoms of bleeding are necessary while taking various compounds like Cod liver oil, Evening primrose oil, feverfew, garlic, ginger, ginkgo biloba, ginseng, green tea, saw palmetto, and bilberry. There are many other herbs, which increase the risk of bleeding and thus increase the efficacy of warfarin for example, ginseng, licorice, and the very famous St. John's wort, soy, and the highly used food component turmeric (high dose only) and so forth.[27] Therefore, the physician should give a list of daily use as well as other concurrent use of herbal medicines that should not be used during treatment and also encourage the patient to have a daily check on the prothrombin time and international normalized ratio, so, that further complications of the disease can be controlled.

Non steroidal anti-inflammatory drugs (NSAIDs). Medicines can treat and cure many health problems. However, they must be taken properly to ensure that they are safe and effective. Many medicines have powerful ingredients. The physician or the pharmacist should know of every drug the patient is taking, including nonprescription drugs and any dietary supplements such as vitamins, minerals, and herbals. Some drugs like NSAIDs are among the most prominently used over the counter drugs, and the patient does not require any prescription from the physician for taking NSAIDs. Many over the counter cold remedies contain aspirin in combination with other active ingredients. The NSAIDs reduce pain, fever, and inflammation. So, the chances of interactions of various natural products with these drugs are very common. These medications can irritate the stomach, it is best to take them with food or milk. Avoid or limit the use of alcohol because chronic

use of alcohol can increase the risk of liver damage or stomach bleeding. The NSAIDs used to increase the absorption of an element known as chromium and cause its retention. This may lead to increase risk of adverse reactions from chromium consumption (for example, anemia, thrombocytopenia, hepatic dysfunction). So, the patients should use this combination with caution, especially at higher doses (600-2400 mg/day). Similarly, evening primrose oil may predispose patients to more severe adverse effects of NSAIDs. So one should avoid their concomitant use. The NSAIDs, particularly aspirin, have the potential to interact with herbal supplements that are known to cause antiplatelet activity (ginkgo, garlic, ginger, bilberry, dong quai, feverfew, ginseng, turmeric, meadowsweets and willow), with those containing coumarin (for example, chamomile, mother wort, horse chestnut, fenugreek and red clover) and with tamarind, accelerate the risk of bleeding. Acetaminophen may also interact with ginkgo and possibly with at least some of the above herbs to increase the risk of bleeding. The anti platelet activity of ginkgo is high enough that it can cause bleeding complications of its own. At least 3 cases of brain hemorrhage have been blamed on ginkgos. Garlic, an important ingredient of a normal spicy meal also reduces platelet aggregation and increases fibrinolytic activity. Ginkgo biloba also inhibits platelet aggregation. So avoid its use in patients on anti platelet (aspirin, dipyridamole, ticlopidine) or anticoagulant (warfarin) therapy. Monitor bleeding time and prothrombin time if the patient is taking ginkgo concurrently with antiplatelet or anticoagulant drugs.

Central nervous system (CNS). Drugs acting in the CNS were among the first to be discovered by primitive humans and are still the most widely used group of pharmacologic agents. In addition to their therapy, many drugs acting on the CNS are used without prescription to increase one's sense of well-being. The uses of herbs in various CNS disorders are very common. People also used to take magic remedies for the treatment of CNS disorders. Epilepsy is the disorder of brain function characterized by the periodic and unpredictable occurrence of seizures. The epilepsies are a common and frequently devastating disorder, affecting approximately 2.5 million people in the United States alone.[5] The various herbs like Evening primrose oil and ginkgo biloba should be used with caution as they increase the risk of seizures in high doses. One case report also describes hypomania in a patient receiving ginkgo in combination with fluoxetine, St. John's wort, melatonin, and buspirone. Trazodone is associated with coma. So, use of ginkgo might lead to complications in patients being treated with fluoxetine and buspirone. It may also increase the activity/toxicity of monoamine oxidase (MAO) inhibitors. St. John's Wort and S-adenosyl methionine, used along with tricyclic antidepressants, selective serotonin reuptake inhibitors, and MAOI may lead to an increase in serotonergic effects (for example, serotonin syndrome). It may effect the serum concentration of antiepileptics and cause either an increased risk of adverse effects or a decrease in efficacy. So, concomitant use should be avoided. Physicians should wait at-least 2 weeks after stopping St. John's wort to initiate therapy with a serotonergic agent and at least 5 half lives of a serotonergic before starting the herb. Kava is another herb, which may increase the risk of drowsiness and motor reflex depression with CNS depressants (for example, alcohol, benzodiazepines, muscle relaxants, phenobarbital, opioids) and also oppose various dopaminergic effects of dopamine agonists (for example, levodopa). Therefore, it should not be used in Parkinsonism and with CNS depressants. If kava is being taken by the patient, then they should be advised against operating heavy machinery and driving. Green tea, which is normally used by every individual contains caffeine and may have additive CNS effects with amphetamine and can also precipitate hypertensive crises with MAO inhibitors. So the use of green tea within several weeks of taking a MAO inhibitors should be avoided.[27] Licorice, an important ingredient of herbal cough treatments also has an inhibitory action on MAO. So it should not be used in combination due to increased risk of toxicity. Sarsaparilla roots were used in rheumatism and various skin diseases can also accelerate elimination of hypnotics. So it should be used with caution.[28] Valerian also known as Jatamansi has antispasmodic and depressant action on the CNS.[28] Concomitant use with other CNS depressants should be avoided, or precaution should be given to patients to avoid driving or operating machinery during the treatment. Its use with loperamide may result in delirium with symptoms of confusion, agitation, and disorientation. Yohimbe, a constituent of the commonly used herb Sarpagandha has an MAO inhibiting property, and it should be avoided in combination with other MAO inhibitors to avoid the risk of hypertensive crises. Various food items like cheese and wine should not to be taken during treatment.[31]

Chemotherapeutic agents. These include antimicrobials, non-nucleoside reverse transcriptase inhibitors (NNRTIs), and immunosuppressants like cyclosporine, and corticosteroids. The absorption of several antimicrobial agents such as tetracyclines and certain fluoroquinolones, may be decreased by chelation with dietary cations (calcium and magnesium), found in milk and other dairy products.[29] Cyclosporine, nevirapine, saquinavir, most of the statins, tacrolimus, benzodiazepines, azole antifungals

and various other antimicrobials are metabolized by the CYP3A4 system of enzymes. Various natural products like Echinacea, which inhibits CYP3A4 in vitro, may lead to increased serum drug concentration of these drugs. Moreover, immunostimulants effect like ginseng, can interfere with immunosuppressant agents including corticosteroids, so, concomitant use should be avoided. St. John's wort induces CYP3A4, and thus leads to decrease in the concentration of drugs that are substrates of CYP3A4 like cyclosporine, certain chemotherapeutic agents and NNRTIs.[30] Garlic, which is used as carminative, expectorant, and disinfectant in the treatment of pulmonary conditions induces the CYP3A4 system leading to decreased concentration of drugs metabolized by this system. Kava-Kava is found to be useful for nervousness, anxiety, or restlessness, and it is also a muscle relaxant. It also significantly inhibits the above mentioned enzyme system and increases the concentration of statins and azole antifungals. So precautions should be taken while combining kava with these agents.[27] Licorice used as an expectorant and demulcent in daily use can prolong the duration of action of corticosteroids, and thus monitoring of dose is required. Grape fruit juice and St. John's Wort are already known to have interaction with the drugs metabolized by the CYP3A4 system.[27]

Antidiabetic agents. Diabetes mellitus is among one of the most common diseases of the developed as well as developing countries. There are trends that people used to prefer herbal medicines than the allopathic treatment. Various natural products interfere with the blood glucose concentration in the body. So, monitoring of blood glucose concentration and signs of hyperglycemia or hypoglycemia are necessary during the treatment of diabetes mellitus with any of the drugs. The concomitant use of many herbs should be avoided or should be used with caution. Chromium is a metal ion, which decreases fasting blood glucose. Therefore, it may increase the risk of hypoglycemia.[27] Ginkgo biloba that is used for increasing blood circulation and oxygenation as well as for improving memory and mental alertness may affect blood glucose; alters insulin secretion and metabolism. So monitoring of blood glucose is required very frequently. Ginseng which increases physical stamina and mental concentration has also been shown to have hypoglycemic effects. So, concomitant use should be avoided. Caffeine in green tea may interfere with blood glucose control and should be used with caution. Licorice, which is mostly used in traditional medicines, may cause hyperglycemia. Ginger is used for reducing nausea, vomiting, and vertigo and also has theoretical interaction with anti-diabetics due to its hypoglycemic effect.

Miscellaneous hormonal preparation. Garlic is used for lowering blood cholesterol, triglyceride levels, and blood pressure by various women. It has been found that garlic has variable effect (may decrease or have no change in effectiveness of oral contraceptives (OC) as a result of changes in drug serum concentrations). Similarly licorice can also reduce the effectiveness of OC's or hormone therapy. Black cohosh is another herb, which has potential estrogenic effect and may cause additive effects with estrogen products, and concomitant use should be avoided. Ginseng may have estrogenic activity, leading to symptoms of estrogen excess when combined with hormone therapy. Therefore, physicians should avoid ginseng in patients with breast cancer, abnormal vaginal bleeding, or thromboembolic disorders, or in pregnant women. Milk thistle may increase the clearance of estrogen by inhibiting beta glucuronidase. So, concomitant use should be avoided. Saw palmetto is an herb that is used for enlarged prostate and urinary inflammations. It also has anti-estrogenic effects and thus may interfere with hormone therapy. St. John's wort can decrease steroid concentration causing breakthrough bleeding, irregular menses, or unplanned pregnancy. So back up birth control should be used if agents are combined. Soy has estrogen like activity so combined use with hormonal agents may result in either additive or antagonistic effects. Patients receiving these drugs should be advised to speak with their oncologist prior to taking soy in amounts greater than normally found in the diet.[27] Tribulus may increase follicle stimulating hormone in women, which in turn increases the levels of estrogen. So this herb may be a gastro irritant. It is contraindicated in gallstones patients, and should be used only after consulting the physician.

In conclusion, many disease states can affect both the magnitude and the incidence of normal actions of natural products in the body, as ageing, hepatic dysfunction, and other pathophysiologic factors can also have an impact of natural product and drug interactions. Therefore, clinicians need to review the complete patient profile in order to make the most appropriate therapeutic recommendations. The clinical relevance of natural product interaction with drugs depends on the magnitude of change in the pharmacokinetic profile of the drug, the drug concentration-response relationships and the patient. Since the current information indicates that the interactions are variable and unpredictable. Therefore, it appears reasonable to caution patients not to take anything at the same time as they are on medication. The patient should tell the physician everything about his natural eating habits, so they can guide him on the further consequences. It is not only the responsibility of patients, the physician should ask every patient about their daily routine. Furthermore,

physicians should be aware of all the current interactions of drugs with natural products and should apply this to their routine prescriptions to minimize the hazard of drug interactions, by at least some extent. The regulatory and scientific organizations should also organize programs to increase awareness of the effects of natural products on the prescribed drugs. The chemical constituents of all natural products can interfere with the normal mechanism of action of prescribed drugs. Therefore, physicians should be aware of current findings.

Acknowledgment. *We are very thankful to Dr. Sujata Upadhyay, Lecturer, Department of Physiology, Punjab University, Chandigarh, Dr. Deonis Xess, Senior Resident, Department of Internal Medicine, PGIMER, and Dr. S. K. Garg, Professor in Pharmacology (Rt), PGIMER, Chandigarh, India for their valuable contribution while preparing this manuscrip*t.

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