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HERB-DRUG INTERACTION: A SYSTEMATIC: A REVIEW

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ABSTRACT
Presently many individuals have the mistaken notion that all herbs are safe, due to the fact that they are of natural origin. This is an inaccurate perception. In fact, herbs may interact with many routinely used medications, which may result in serious adverse reactions. It is always a good practice for patients to inform their doctor or health practitioner about which medication they are currently taking, so that any potential complications are averted. The patient should also point out for unusual symptoms. Very often, this may foretell the symptoms of a herbal drug interaction.

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1. INTRODUCTION

The issue of herb-drug interactions looms over the practice of herbal medicine. Up until now, there have been a small number of incidents recorded of herb-drug interactions, but since the first such report emerged, a concern has been raised: we know so little about herbs and their potential for interaction with drugs, that these incidents could be just the "tip of the iceberg". Virtually all medical writers who review the literature acknowledge the small number of reports, but they conclude that the issue of herb-drug interactions is a serious one that must be pursued. In a few instances, the interactions may have been responsible for severe consequences. [1] The nature of herb-drug interactions is not necessarily a chemical interaction between a drug and a herb component to produce a toxic reaction. Instead, the interaction may involve having a herb component cause 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 being absorbed into the blood stream from the gastrointestinal tract, or by stimulating the production and activity of enzymes that metabolize the drug to form inactive products. An increase in the drug dosage could occur when a herb component aids absorption of the drug, or inhibits the enzymes that break down the drug and prepare it for elimination. A decrease in drug dosage by virtue of an interaction could make the drug ineffective; an increase in drug dosage could make it produce adverse effects. Alternatively, a herb might produce an effect which is contrary to the effect desired for the drug, thereby reducing effect of the

drug; or a herb might produce the same kind of effect as the drug and cause an increase in the drug effect (synergism). [1, 2] A better understanding of the herbal-drug interactions can be achieved by discussing a few incidences of the impact of these interactions.

2. CASES

CASE.1 – A female patient has moderate asthma and uses two inhalations of budesonide 400 mcg morning and night, among other medications. The patient has just been discharged from the hospital after a severe asthma attack. One morning she could not breathe and became very frightened and thought that she was going to die. She tells the pharmacist that the attack happened soon after she started taking a complementary product containing Echinacea, vitamin E and zinc to help stimulate her resistance to airborne pollens and pollutants. Did the immune stimulating effects of these complementary medicines offset the immunosuppressive effects of the corticosteroids to precipitate a severe attack? Or was it a problem of not having an adequate asthma management plan? Or a problem of compliance?

CASE 2 – A male patient that has been on oral hypoglycaemics (gliclazide and metformin) for years without problems is pulled over by the police for driving erratically. When asked to get out of the car, he is shaking, sweating, and complaining of palpitations. Severe anxiety regarding the proximity of other drivers had caused with to swerve away from them. He regularly takes ginseng as a stress-buster. It just so happens that tremendous content variation has been reported among products reported as containing ginseng. Furthermore, panax-type ginsenosides in Asian or Korean ginseng have been reported to have a hypoglycaemic effect, but not Eleutherococcus senticosus in Siberian ginseng. [3] Was this man's hypoglycaemic attack due to a change in the type of ginseng he bought? Or did he double up on his tablets by mistake? Or did he forget to eat properly? Could he have been affected by variations in the potency of the ginseng preparation he always buys?

CASE 3 – An elderly patient comes into the pharmacy with his wife for repeats of his cardiovascular medications (isosorbid mononitrate, aspirin and lisinopril). In the course of talking to them, his wife tells you that the patient is complying with his medications although he complains of bruising, mild bleeding and dizziness. You ask if there are any other medications he is currently on. She says that he has taken some gingko to help him remember things and some "tablets" containing garlic and vitamin C for his mild hay fever. Should you be worried about possible interactions? The important question is, can the scientific literature confirm that the above scenarios are of concern, and that we as

3. WHY ARE HERB-DRUG INTERACTIONS DIFFICULT TO ASSESS?

Herbal preparations vary in contents. For example, in a review of feverfew (Tanacetum parthenium), a preparation used to treat recurrent migraines, fever, menstrual disorders and arthritic conditions, a high variation in the active ingredient (parthenolides) was found in 21 commercial products purchased at pharmacies, retail stores and herbal websites. If a person consumed the daily dose recommended on the label, intake of dried feverfew leaf would have varied tenfold, while intake of parthenolide would have varied 160-fold. Wide variations have also been reported for dehydroepiandrosterone (DHEA), kava and ginseng.[4] This is particularly worrying for feverfew because parthenolide content has been found to be correlated with inhibition of cyclooxygenase and phospholipase A2. Hence, feverfew products may interact with warfarin and potentiate the antiplatelet effects of aspirin in a variable manner.[5] Herbal preparations may contain incorrectly identified botanical ingredients and/or ingredients contaminated with metals or nonherbal drug substances.[6] In general, most drug-interactions are dependent on dose and frequency, and the heterogeneity of dosing recommendations can make it difficult to assess the clinical significance for particular combinations.[6] The enormous number of different types of herbal and

complementary medicines containing a variety of different ingredients to treat the same condition makes interpretation of clinical interactions very difficult. For instance, more than 100 different complementary therapies have been recommended for asthma, although it should be noted that systematic reviews have failed to back up a single treatment for this condition.[7] In many cases there have been no systematic investigations of the potential interaction. Reports may have come from indirect evidence based on a mechanistic understanding of a herb. For example, it seems reasonable to assume that the sedative properties of valerian may potentiate the effects of benzodiazepines, opiates and alcohol. Other reports of interaction may be based on poorly designed studies with an inappropriately small number of patients. In the case of kava, a preparation used as an anxiolytic and sedative, interaction has been reported with anxiolytics (e.g. benzodiazepines).[8] However, this was based on a single case report of a 54-year-old man who was hospitalized in a lethargic and disorientated state where the combination of kava with alprazolam was identified as the cause.[3] The data was then scored for interaction probability. A total of 108 cases of suspected interactions were identified. Almost 70% did not contain sufficient information to evaluate the likelihood of an interaction. Only 13% were classified as well documented. Warfarin was the most common drug involved, and the St John's wort was the most commonly implicated herb.[1]

5. RECOMMENDATIONS

Copious information including tables of herb-drug interactions are available, yet we are unsure about the importance of these reported interactions. Perhaps we should focus on the areas of most concern, and only act if we suspect a problem. For example, if a patient is having trouble stabilizing their International Normalised Ratio (INR), are they taking bilberry, chamomile, devils claw, dong quai, feverfew, gingko, garlic, ginseng or goldenseal? Since this is not an exhaustive list, it would appear that the combination of warfarin and complementaries should be avoided altogether. If your patient is bruising excessively, could it be gingko, which is one of many agents that may have an additive effect in reducing platelet aggregation? If your patient is taking digoxin, a drug with a narrow therapeutic window, should we be vigilant for ginseng or St John's wort, which have been reported to respectively raise or lower digoxin's serum concentration? If your diabetic patient is having trouble stabilizing their blood sugar, could they be taking fenugreek, garlic, ginger, ginseng (hypoglycemia), devils claw,
or ma huang (hyperglycemia)? Finally, if your patient is on an anti-depressant and they have been feeling strange (agitation, tremor, unsteadiness, mental state changes – that is, symptoms of
serotonin syndrome), could they been taking St John's wort?

4. DO HERB-DRUG INTERACTIONS ACTUALLY OCCUR?

In a review and assessment of report reliability, four electronic databases were searched from their inception to the end of 2000 for case reports, case series or clinical trials of such interactions. St John's wort has been reported to interact with antidepressants to cause serotonin syndrome, and with digoxin, cyclosporine and indinavir to reduce their concentrations. The former is thought to occur because St John's wort has an inducing effect on CYP3A4 as well as interacting with P-glycoprotein, which is involve0d in pumping drugs out of cells, thus decreasing their intracellular concentrations. The conclusion reached is that herb-drug interactions occur but are under-researched. In many cases there is no plausible mechanism to explain the observed phenomena and causality is uncertain. Patients taking St John's wort or anticoagulants were reported to be at the highest risk of an interaction.[1] In another study, patients enrolled in a geriatric clinic were surveyed starting from November 2000 for a duration of five months. They were asked to provide information about their use of common dietary supplements. A list of their current prescription interactions was

investigated. Of the patients who completed the survey (47% of 285 patients), 23% were taking dietary supplements. Of these 28 patients, garlic and glucosamine were the most commonly used dietary supplements. Some of the other supplements were gingko, saw palmetto, chondroitin, coenzyme Q10, echinacea, melatonin and ginseng.[9] After review, it was found that 15 patients (54%) were taking at least one combination that could cause an interaction. A total of 45 potential and possible interactions were found, the most important being between gingko and aspirin (gingko reduces platelet aggregation and may add to the risk of bleeding) and between garlic and warfarin (additive anticoagulant effect). None of these interactions were confirmed by chart review to have occurred [9]

6. Examples of Herb drug Interactions

Sr.No	Name of Phytoconstituent	Interaction With	Effect
1	Karela or bitter melon (*Momordica charantia*)	Clorpropamide	Less glycosuria[10]
2	Liquorice (*Glycyrrhiza glabra*)	Pregnisolone	Glycyrrhizin decreases plasma clearance, increases AUC,36 increases plasma concentrations prednisolone[11]
		Hydrocortisone	Glycyrrhetinic acid potentiates of cutaneous vasoconstrictor response[12]
		Oral contraceptives	Hypertension, oedema, hypokalaemia
3	Papaya (*Carica papaya*)	Warferin	Increased INR[13]
4	Psyllium (*Plantago ovata*)	Lithium	Decreased lithium concentrations[14]
5	St John's wort (*Hypericum perforatum*)	Praoxetin	Lethargy/incoherence[15]
		Trazodone	Mild serotonin syndrome[16]
		Sertaline	Mild serotonin syndrome[17]
		Nefazodone	Mild serotonin syndrome[18]
		Theophyllin	Decreased Theophylline concentrations[19]
		Digoxin	Decreased AUC, decreased peak and trough concentrations[20]
		Combined oral conatrceptives	Course through Bleeding
6	Saiboku-to (Asian herbal mixture)	Predinisolone	Increased prednisolone AUC[21]
7	Shankhapushpi (Ayurvedic mixed-herb syrup)	Phenytoin	Decresed phenytoin concentration loss of control of seizures[22]

8	Betel nut (*Areca catechu*)	Flupenthixol and procyclidine	Rigidity, bradykinesia, jaw tremor[23]
		Prednisone and salbutamol	Inadequate control of asthma
9	Chilli pepper (*Capsicum* spp)	ACE Inhibiters	Cough[24]
		Theophylline	Increased absorption and bioavailability[25]

Sr.No	Phytoconstituent	Interaction With	Effect
10	Ginko Biloba	Aspirin	Spontaneous Hypema[26]
		Paracetamol	Bilateral subdural heamatoma[27]
		Warferine	Intracerebral Heamorrahge[28]
11	Ginseng(*Panex Ginseng)*	Warferine	Decresed INR[29]
		Phenalzine	Headeach tremors, mania[30]
		Alcohol	Incresed alcohol clearance[31]
12	Gaur gum	Metformine	Decresed Absorption[32]
		Glibencamide	Decresed Absorption[32]
		Phenoxy methyl Penicilin	Decresed Absorption[32]
13	Garlic(*Allium Sativum*)	Warferine	Incresed INR
14	Yohimbine (*Pausinystalia yohimbe*)	Clomipramine	Hypertension[34]

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