Natural health product–drug interaction tool: A scoping review

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Introduction

Natural health products (NHPs), such as herbal medicines, probiotics, vitamins and minerals, are used regularly by 73% of Canadians.¹ Many consumers believe that NHPs derived from plants (such as herbal medicines) are safe because they are “natural.”¹ However, some plant-derived NHPs can interact with pharmaceutical medications, potentially resulting in serious harm for patients.² A recent active surveillance study found that approximately 45% of consumers presenting to a Canadian pharmacy report using NHPs and prescription drugs concomitantly, with 7.4% describing an adverse event.³

It is important for clinicians to initiate patient communication about NHP use and be knowledgeable about the potential risks to ensure patient safety. Unless clinicians ask, they may be unaware of patient NHP use. Most NHPs can be purchased from many sources without involvement of a health professional, and many patients do not disclose NHP use to clinicians.⁴ However, education about NHP interactions is not always included within medical and pharmacy curricula,⁵ and new evidence on NHP–drug interactions is constantly emerging. In addition, a quick search of the medical literature might identify contradictory information or poor-quality reports that are challenging to interpret. Clinicians could benefit from effective knowledge translation tools to identify and prevent potential NHP–drug interactions in their patients. As pharmacists have confirmed the utility of a NHP–drug interaction grid⁶ as an effective knowledge translation tool,⁷ we undertook a scoping review to identify and incorporate new NHP–drug interactions.

Data sources

We started with our team’s prior work in this area,⁶ which includes 29 plant-derived NHPs cross-referenced with 27 drug classes, and identified NHPs that have documented nephrotoxic and/or hepatotoxic effects. The process for selecting plant-derived NHPs included on the tool has been described previously.⁶

Medical databases (MEDLINE, EMBASE and International Pharmaceutical Abstracts) were searched from January 2007 to December 2012. Search terms included medical subject headings/key words for each of the NHPs, combined with the terms *clinical trials*, *case studies* and *case reports*.

Study selection

One reviewer screened titles and abstracts of identified publications for select NHPs and pharmaceutical drugs. Inclusion criteria included 1) English language; 2) studies containing original data; 3) clinical, animal studies or in vitro studies; 4) studies that could potentially describe an interaction (theoretical or actual) of a single ingredient NHP with a pharmaceutical drug or a hepatotoxic or nephrotoxic reaction (Figure 1).

Additional records were identified from reference lists of review articles, the Natural Medicines Database⁸ (formerly known as Natural Medicines Comprehensive Database), *Stockley’s Herbal Medicines Interactions*⁹ and a textbook titled *Herb, Nutrient and Drug Interactions*.¹⁰ Full-text articles of included publications were retrieved.

Data were collected in a standardized fashion, including (if appropriate) reason for exclusion, and if included: 1) NHP involved, 2) drug class/drug involved, 3) colour assignment as per the

FIGURE 1 PRISMA flow diagram

level of evidence and 4) brief description of the documented interaction.

We defined 6 levels of evidence:

- I. **Purple square:** Clinical evidence describes an NHP–drug interaction in humans, based on randomized clinical trials or case reports.
- II. **Purple dot:** Clinical evidence describes an NHP–drug interaction, but we had

reservations about the available data, for reasons such as

- a. insufficient details provided in reporting,
- b. instances of product misuse (for example, patient overdose),
- c. adulteration or contamination of the NHP and/or poor manufacturing processes provide alternative explanations for the adverse event,

FIGURE 2 Natural health product–drug interaction tool

	Gastrointestinal system				Cardiovascular system							Respi- ratory system	Central nervous system					Endocrine system				Anti- infectives							
	Laxative agents	Anti-ulcer agents	Antacid agents	Antidiarrheal agents	Antiplatelet / Anticoagulant agents	Lipid-lowering agents	Antihypertensive agents	Beta-blockers	Diuretic agents	Cardiac glycosides	Antiarrhythmic agents	Antiasthmatic agents	Anti-allergy agents	Antiparkinson agents	Analgesic agents	Antipsychotic agents	Antiepileptic agents	Antidepressant agents	Sedative agents	Sex hormones	Corticosteroids	Hyperthyroid agents	Hypothyroid agents	Antidiabetic agents	Antifungal agents	Antibiotic agents	Anti(RETRO)viral agents	Nephrotoxic*	Hepatotoxic*
Alfalfa						1																		2					
Aloe vera																						3	4	5					6
Angelica (Dong Quai)					7																								
Black cohosh																													8
German chamomile					9																								
Chaste tree (Vitex)																													
Cranberry					10	11													12										
Devil's claw															13														
Echinacea					14					15									16										17
Ephedra (Ma Huang)						18	19			20	21					22	23				24	25	26	27					28
Evening primrose							29									30	31												
Feverfew																													
Garlic					32	33	34								35									36			37		
Ginger					38																								
Ginkgo		39			40		41	42	43						44	45	46	47	48					49			50		
Asian ginseng					51	52		53			54													55		56			
Hawthorn							57																						
Horse chestnut																													
Kava													58					59	60										61
Licorice							62		63	64											65	66			67		68		
Milk thistle						69		70																71		72	73		
Peppermint							74																						
Saw palmetto							75																						76
St. John's wort		77			78	79	80				81	82	83			84	85	86	87	88		89	90	91	92		93		
Tea tree oil																													
Thyme																													94
Valerian																		95											96
Wild yam																													
Willow					97										98														

*Nephrotoxic/hepatotoxic: Herbs that potentially influence kidneys and/or liver also potentially influence drug metabolism and can therefore cause general interactions.

Numbers on this chart refer to interaction details described on the next page. The references cited on next page are available online at www.cpjjournal.ca.

Disclaimer: To the best of our knowledge, the data in the chart are an accurate summary of the published data up to December 2012. See full disclaimer at end of article.

- Clinical evidence describes an NHP–drug interaction in humans, based on randomized clinical trials (RCTs) or case reports.
- Clinical evidence describes an NHP–drug interaction, but we had reservations about the available data.
- Evidence describes an interaction postulated in theory, but not yet reported in practice.
- Interactions based on pre-clinical studies (animal studies or in vitro) for which the clinical significance is unknown.
- No reported interactions or theoretical interactions identified from the literature.
- Clinical evidence documenting the lack of interaction after concurrent use.

Interaction details

- 1) Alfalfa may produce a theoretical additive effect when taken concurrently with lipid-lowering drugs, since decreased cholesterol concentrations have been associated with alfalfa use (clinical trial).¹
- 2) Alfalfa may cause an additive effect with hypoglycemic agents (case report, animal studies).^{2,3}
- 3) Aloe vera has been reported to cause thyroid dysfunction (case report).⁴
- 4) Aloe vera has been reported to cause thyroid dysfunction (case report).⁴
- 5) Oral aloe vera gel can cause additive glycemic-lowering effects when taken concurrently with a hypoglycemic agent (glibenclamide) (clinical study).⁵
- 6) Oral aloe vera supplements have been reported to cause liver damage (case reports).^{6,7}
- 7) Angelica (dong quai/dang gui) was associated with enhanced anticoagulant effects when taken concurrently with warfarin (case reports).^{8,9}
- 8) Black cohosh has been reported to cause hepatotoxicity (case reports).¹⁰
- 9) Chamomile can alter INR values in patients taking warfarin (case report).¹¹
- 10) There is conflicting evidence regarding a possible interaction between warfarin and cranberry (case reports)¹²; clinical trials have reported mixed reports on the clinical impact on INR values with the use of cranberry and warfarin concurrently (clinical trials).^{13,14} Caution is warranted until further research is available.
- 11) Diabetic patients on glucose-lowering drugs and cranberry had decrease in lipid profiles (clinical trial).¹⁵
- 12) Cranberry juice increases the concentrations of midazolam (clinical trial).^{16,17}
- 13) Devil's claw may produce a theoretical additive effect when taken concurrently with analgesics, since devil's claw has been associated with reduced pain levels (clinical trials).¹⁸
- 14) Echinacea increases the clearance of warfarin, but had no effect on INR values (clinical trial).¹⁹
- 15) Clinical evidence of no interaction between echinacea and digoxin (small clinical trial).^{20,21}
- 16) Echinacea increases the metabolism of midazolam in healthy individuals; clinical significance is unknown.^{22,23}
- 17) Echinacea has been reported to cause hepatotoxicity, however, product quality was not assessed and clinical significance remains unclear (case report).²⁴
- 18) Increased blood pressure and prolonged blood pressure elevation has been found with the concurrent use of ephedrine and clonidine (clinical trial).²⁵
- 19) Ephedra alkaloids have been reported to cause negative cardiovascular symptoms and thus should be used with caution in patients taking beta blockers (multiple case reports).²⁶
- 20) Ephedra alkaloids have been reported to cause negative cardiovascular symptoms and thus should be used with caution in patients taking cardiac glycosides (multiple case reports).²⁶
- 21) Ephedra alkaloids have been reported to cause negative cardiovascular symptoms and thus should be used with caution in patients taking an antiarrhythmic agent (multiple case reports).²⁷
- 22) Ephedra may produce a theoretical decreased effect of antipsychotics when taken concurrently, since psychotic episodes have been reported with ephedra use (case reports).^{28,29}
- 23) Ephedra may produce a theoretical decreased effect of anti-epileptics, since seizures have been reported with ephedra use (and may be more likely when it is combined with caffeine) (case reports).³⁰
- 24) Ephedrine may increase the clearance of corticosteroids (clinical trial).³¹
- 25) Ephedrine has been shown to slightly increase then decrease the T3/T4 ratio, significance unknown (clinical trial).³²
- 26) Ephedrine has been shown to slightly increase then decrease the T3/T4 ratio, significance unknown (clinical trial).³¹
- 27) Ephedrine may increase blood glucose concentrations especially when combined with caffeine (several clinical trials).^{27,33}
- 28) Ephedra has been reported to cause hepatitis (case reports).^{34,37}
- 29) Gamma-linolenic acid of evening primrose oil may decrease blood pressure in some patients (conflicting evidence) and thus may have an additive effect with antihypertensive agents (clinical significance unknown) (clinical trial, animal studies).^{38,41}
- 30) Seizures have been reported with the concurrent use of phenothiazine antipsychotics and evening primrose oil (case reports).⁴¹
- 31) Evening primrose oil may reduce the seizure threshold in antiepileptic patients (case study).⁴²
- 32) Isolated case reports indicate that garlic extracts may increase or decrease the anticoagulant effects of warfarin and fluidione, respectively.^{43,44} though effects on warfarin have not been observed in clinical trials.^{45,46} Garlic may have antiplatelet effects and may increase the risk of bleeding with antiplatelet agents.^{47,48}
- 33) Garlic may produce a theoretical additive effect when taken concurrently with lipid-lowering drugs, since decreased lipid concentrations have been associated with garlic use (several clinical trials).^{49,52}
- 34) Garlic lowers raised systolic blood pressure, thus it may have additive effects if used with other antihypertensive agents (>10 clinical trials).^{53,54}
- 35) Aged garlic extract has no clinically significant effect on the metabolism of single-dose (1 g) paracetamol.⁵⁵ Garlic may have antiplatelet effects and may increase the risk of bleeding with antiplatelet agents, such as NSAIDs.^{47,48}
- 36) Garlic may produce a theoretical additive effect when taken concurrently with antihyperglycemic drugs, since changes in glucose concentrations (usually decreased) has been associated with garlic use; clinical significance is unclear (clinical trials and case reports).^{56,58}
- 37) Garlic decreases plasma concentrations of saquinavir (protease inhibitor) (clinical study).⁵⁹
- 38) Concurrent use of ginger and coumarin anticoagulants was associated with an increased risk of bleeding (case reports, uncontrolled, longitudinal study).⁶⁰⁻⁶²
- 39) Ginkgo decreases the concentrations of omeprazole (clinical trial).⁶³
- 40) Ginkgo can potentiate bleeding time when taken concurrently with cilostazol (mixed clinical studies)⁶⁴; no interaction found between ginkgo and warfarin⁶⁵; ginkgo produces no effect on INR values or platelet aggregation (clinical studies).⁶⁶
- 41) Ginkgo has been reported to cause antihypertensive effects (2 clinical trials).^{67,68}
- 42) Ginkgo biloba extract increases the serum concentrations of talinolol in healthy individuals (clinical trial); clinical significance unknown.⁶⁹
- 43) Paradoxical hypertension has been reported with the concurrent use of ginkgo and a thiazide diuretic (case report).^{70,71}
- 44) Increased bleeding has been reported with the concurrent use of ginkgo and NSAIDs (case reports).^{72,73}
- 45) Risk of priapism is possible with the concurrent use of ginkgo and risperidone (case report)⁷⁴; ginkgo may increase the effect of haloperidol and decrease the side effects when taken concurrently (clinical trial)⁷⁵; ginkgo has not been associated with any effect on clozapine when taken concurrently (clinical trial).⁷⁶
- 46) Ginkgo may theoretically decrease phenytoin and valproate concentrations, based on its hypothesized mechanism of action.⁶³
- 47) Coma has been reported with concurrent use of ginkgo and trazodone (case report)⁷⁷; ginkgo may produce a theoretical additive effect with MAO-A or -B inhibitors, since ginkgo has been shown to have MAO-A and -B inhibitory activity (in vitro study).⁷⁸
- 48) Ginkgo may decrease concentrations of midazolam in healthy volunteers; clinical significance is unknown (clinical trials).⁷⁹
- 49) Ginkgo may increase insulin serum concentration in healthy volunteers, but decrease it in patients with type 2 diabetes (several clinical trials).^{87,80,81}
- 50) Serum ritonavir concentrations lowered in healthy volunteers with concurrent administration of ginkgo (clinical trial)⁸²; decreased efavirenz concentrations and increased viral load in a patient with HIV infection who began taking ginkgo (case report).⁸²
- 51) Conflicting studies exist regarding whether ginseng may interact with anticoagulants; clinical significance seems unlikely based on current evidence.^{83,86}
- 52) Asian ginseng has been reported to lower lipid concentrations (clinical trial) and thus may have an additive effect with lipid-lowering agents; clinical significance unknown.⁸⁷
- 53) Ginseng may increase QTc interval. Use caution with cardiac medications (clinical trial).⁸⁸
- 54) Ginseng may increase QTc interval. Use caution with cardiac medications (clinical trial).⁸⁸
- 55) Ginseng may improve glucose and insulin regulation and thus may impact doses needed of hypoglycemic agents (several clinical trials).^{89,91}
- 56) Ginseng may increase the effect of antibiotics (clinical trial).⁹²
- 57) Hawthorn may have an additive effect with antihypertensives (clinical trials).⁹³
- 58) Kava has been reported to decrease the efficacy of Parkinsonism agents (levodopa) (case report).^{94,95}
- 59) Kava appears to have antidepressant activity and thus may have an additive effect with antidepressants (clinical trial).⁹⁶
- 60) Kava has been reported to have sedative activity and thus may have additive effects when taken concurrently with other sedatives.⁹⁷
- 61) There is conflicting evidence regarding the relationship of kava intake and hepatotoxicity; caution is warranted until further research is available (case reports).⁹⁸⁻¹⁰⁰
- 62) Licorice has been reported to cause hypertensive effects and may reduce the effects of antihypertensives (clinical trials in healthy volunteers).¹⁰¹
- 63) Hypokalemia has been reported with the concurrent use of licorice or glycyrrhizic acid (a constituent of licorice) and certain diuretics (furosemide, hydrochlorothiazide), (clinical trial and case reports).¹⁰²⁻¹⁰⁵ Licorice or glycyrrhizic acid reduces the adverse effects of spironolactone (volume depletion, hypotension) in women with polycystic ovary syndrome (clinical trial).¹⁰⁶
- 64) Licorice has been reported to decrease potassium serum concentrations and may increase the toxicity of digoxin (case report).¹⁰⁷
- 65) Chronic ingestion of licorice, when taken concurrently with an oral contraceptive pill, has been reported to cause headache, weakness, edema and generalised convulsive seizure (case report).¹⁰⁸
- 66) Licorice may increase the likelihood of adverse effects, including hypokalemia, of certain corticosteroids.¹⁰⁹⁻¹¹⁴
- 67) Intravenous glycyrrhizin (a constituent of licorice) has been reported to cause hypokalemia in diabetic patients with chronic hepatitis taking concurrent insulin (case reports).¹¹⁵
- 68) De-glycyrrhized licorice increased urinary excretion of nitrofurantoin in patients with urinary tract infections (clinical trial); clinical significance unclear.¹¹⁶
- 69) Milk thistle may decrease the effectiveness of antihypertensives, but clinical significance is unclear (clinical trial).¹¹⁷
- 70) Milk thistle may increase the concentrations of talinolol in healthy volunteers (clinical trial); clinical significance is unclear.¹¹⁸
- 71) Concurrent use of silymarin and antidiabetic agents has been shown to improve glycemic control and decreased need for antidiabetic medication (both insulin and oral agents) (clinical trials).¹¹⁹
- 72) Milk thistle may decrease the effectiveness of antibiotics such as metronidazole, clinical significance is unclear (clinical trial).¹²⁰
- 73) There is conflicting evidence regarding whether milk thistle may impact the effectiveness of anti-retrovirals; caution is warranted until further research is available (clinical trials).¹²¹
- 74) Peppermint increases the bioavailability of felodipine (clinical study).¹²²
- 75) Saw palmetto may cause hypertension (several clinical trials).¹²³
- 76) Saw palmetto has been reported to cause hepatotoxicity (case reports).¹²⁴
- 77) Hypericin (a constituent of St. John's wort, or SJW) concentrations increase marginally with concurrent administration of cimetidine (clinical trial)¹²⁵; SJW decreases omeprazole concentrations (clinical trial).¹²⁶
- 78) SJW increases the clearance of warfarin (clinical trials).^{127,128}
- 79) SJW decreases the concentrations of simvastatin and atorvastatin (clinical trials).¹²⁹⁻¹³¹
- 80) SJW has been reported to cause cardiovascular collapse during general anesthesia (case report)¹³²; SJW decreases the concentrations of ivabradine (clinical trial).¹³³
- 81) SJW decreases the concentration of digoxin (clinical trials, case reports).¹³⁴⁻¹³⁷
- 82) SJW has been reported to decrease the concentrations of theophylline (case report).¹³⁸
- 83) SJW decreases the maximum serum concentrations of fexofenadine (clinical studies).¹³⁹⁻¹⁴¹
- 84) SJW has been reported to decrease the effect of antipsychotics (clinical trial and case reports).^{142,143}
- 85) SJW increases the metabolism of mephenytoin (a CYP2C19 substrate) in extensive metabolisers, SJW could theoretically interact with drugs that are substrates for CYP2C19 isoenzymes, including phenytoin (clinical trial)¹⁴⁰; pseudohypericin, but not hypericin (constituents of SJW) concentrations decreased marginally with concurrent administration of carbamazepine (clinical trial).¹²⁵
- 86) SJW: Reduced concentration of tricyclic antidepressants (amitriptyline, nortriptyline)¹⁴⁴; orofacial dystonia reported with concurrent use of SJW and bupropion (case reports)¹⁴⁵; mechanistic evidence of no interaction between SJW and MAO-A inhibitors (clinical trial).¹⁴⁶
- 87) SJW decreases the concentration of midazolam (clinical study).¹⁴¹
- 88) SJW decreases the concentration of oral contraceptives, possibly leading to unintended pregnancies and breakthrough bleedings (case report, clinical trial).^{147,148}
- 89) In a case report study, there was an association between SJW and elevated TSH.¹⁴⁹
- 90) In a case report study, there was an association between SJW and elevated TSH.¹⁴⁹
- 91) SJW increases the clearance of glimepiride (clinical trial)¹⁵⁰; SJW had no effect on the pharmacokinetics or pharmacodynamics of repaglinide (clinical trial in healthy volunteers).¹⁵¹
- 92) SJW increases the concentrations of voriconazole with single-dose administration and decreases its concentrations with repeated voriconazole administration (clinical trial).¹⁵⁰
- 93) SJW is associated with decreased concentrations of indinavir, lamivudine and nevirapine (clinical trials).¹⁵³⁻¹⁵⁶
- 94) Toxic hepatitis was reported following the oral ingestion of a substantial quantity of concentrated thyme (*Thymus vulgaris*) oil (case report).¹⁵⁷
- 95) Psychiatric episode (delirium-like state resulting in self-harm) in an alcohol-dependent patient taking fluoxetine for alcohol-induced mood disorder and who began treatment with valerian (case report).¹⁵⁸
- 96) Valerian has been reported to cause hepatotoxicity (case report).¹⁵⁹
- 97) Salicin, a constituent of willow bark extract, has antiplatelet effects¹⁶⁰; the potential for willow bark extract to interact with anticoagulants when used concurrently is not known; concurrent use should probably be avoided until further information is available. Concurrent use of willow and warfarin was associated with an increased risk of bleeding (uncontrolled, longitudinal study).⁶²
- 98) Willow bark extract has effects on platelet aggregation that are similar to those of aspirin, but which are less pronounced (clinical trial).¹⁶⁰

- d. the intervention was an isolated constituent(s) of the NHP rather than the plant extract and used in a way that was inconsistent with clinical use, and
 - e. conflicting (contradictory) clinical evidence.
- III. **Orange square:** Evidence describes an interaction postulated in theory but not yet reported in practice.
 - IV. **Yellow square:** Interactions based on preclinical studies (animal studies or in vitro) for which the clinical significance is unknown.
 - V. **Blue square:** No reported interactions or theoretical interactions identified from the literature.
 - VI. **White dot:** Clinical evidence documenting the lack of interaction after concurrent use.

Representative papers describing the strongest level of evidence of interaction for each NHP-drug combination and supporting documentation underwent an independent second review to confirm the classification and to finalize interaction details. Disagreements were decided by group discussion to reach consensus. All remaining interactions coded red and orange on our earlier tool⁶ were confirmed from reference lists and secondary sources. Interactions previously coded yellow⁶ for which there were no new literature reports were transferred without review. Interaction details were developed for each clinical interaction, with relevant citations identified. For interactions documented in multiple papers, a review paper was cited.

The results were synthesized into a colour-coded NHP-drug interaction grid for clinicians.

Results

The updated NHP-drug interaction tool is shown in Figure 2. It includes 23 interactions coded purple, 37 interactions coded purple dot, 36 interactions coded orange, 123 interactions coded yellow and 2 interactions coded white dot. NHP-drug interactions documented in in vitro or animal studies that are new to this tool from the previous tool are summarized in Table 1.

Of the 29 NHPs, 27 had interactions with multiple drug categories cited in the medical literature—22 had interactions documented in

clinical studies, 6 had only theoretical interactions, and 1 had no interactions.

Interpretation

Our NHP-drug interaction tool is comprehensive for 29 plant-derived NHPs. However, caution must be applied, as evidence in this field is constantly emerging (for example, we identified 97 clinically documented interactions compared with 59 in the first version).

There are many published studies regarding NHP-drug interactions; however, our study's strengths are 1) it captures a large amount of clinically relevant information, including 29 popular plant-derived NHPs and 27 drug classes, including nephrotoxicity and hepatotoxicity; 2) it is categorized and colour coded for ease of use; 3) it has succinct details for rapid clinical interpretation; and 4) it cites original data documented in medical literature.

This tool has many differences from our first version. First, the classification system was updated, to allow for more nuanced interpretation. We avoided the colours red and green, as these can be interpreted as “bad (unsafe)” or “good (safe),” when reality is more complex. A known interaction can be used to promote favourable outcomes. For example, extract of milk thistle (silymarin) in combination with antidiabetic agents can improve glycemic control and reduce the need for antidiabetic medication (both insulin and oral agents).²² However, safe concurrent use requires clinical knowledge and close monitoring of the patient to confirm there are no adverse reactions and that the desired clinical effect is achieved. Whether or not concurrent use of products is desirable depends on the patient's clinical condition and the goals of treatment. As such, we chose a neutral colour (purple), so that the inference of safe/unsafe is removed, prompting clinicians to use the interaction details and their clinical judgment to determine if concurrent use is advisable or acceptable for their patients.

We decided to include an option for when evidence was emerging but not yet conclusive (i.e., a dot vs a fully shaded square). Typically, emerging harms are reported as case reports; these can vary considerably in terms of quality of reporting.²³ The same issues were described in Fugh-Berman and Ernst²⁴—that it was not always possible to ascribe causality in case reports to a particular NHP-drug interaction, often because

TABLE 1 Plant-derived natural health product (NHP)–drug interactions documented in in vitro or animal studies*

NHP	Drug categories
Black cohosh	Antihypertensive agents ¹¹
Chaste tree (Vitex)	Analgesic agents ¹²
Devil's claw	Beta-blockers, ¹³ cardiac glycosides ¹³
Garlic	Antibiotic agents ¹⁴
Ginger	Antibiotic agents ¹⁵
Ginkgo biloba	Antibiotic agents ¹⁶
Asian ginseng	Cardiac glycosides, ¹⁷ antihypertensive agents, ¹⁸ antidepressant agents ^{19,20}
Licorice	Antidepressant agents ²¹

*Coded yellow in Figure 2

of a lack of full reporting. Often, NHPs are not well described in documentations in terms of species name, manufacturer or quality, leading to questions about the reproducibility of an interaction. In addition, if information such as the specific plant part used (e.g., leaves, roots) and type of preparation is lacking, the product's chemical profile is unknown, since the profile of chemical constituents is not uniform throughout a plant. In addition, our team was not comfortable attributing the effect of a highly concentrated component of a plant-derived NHP (such as glycyrrhizin isolated from licorice) to that of the whole plant-derived extract, recognizing that plant-derived NHPs are often large and complex substances with many active bioingredients, some of which may work synergistically to provide a clinical effect. Their absorption, distribution, metabolism and excretion is often not well understood. We differentiate between adverse events that have been documented in humans rather than postulated in theory or seen in animal models for this reason. A recent literature review revealed that in some cases, preclinical studies have been shown to predict clinical reactions and in some cases they do not; for example, CYP3A4-mediated interactions documented in vitro were predictive for clinical interactions seen in St. John's wort but not for milk thistle or *Panax ginseng*.²⁵ However, these interactions can alert clinicians to the possibility of a clinical interaction and promote clinical vigilance.

Limitations

Our study has several limitations. Given the scope of the work undertaken, we took a scoping

review approach, rather than a full systematic review for all NHPs and drugs of interest. As our primary interest was to inform clinicians of clinically relevant interactions, our search strategy underrepresents preclinical data. Many studies of cytochrome P450 (CYP) enzyme inhibition/induction are conducted in in vitro/animal settings and thus are also underrepresented based on the search strategy. The absence of interactions (coded white dot) is also underreported, as this was not the focus of our searches.

Finally, our study was also limited by the quality of available data. As the current risk-of-bias tool used by the Cochrane Collaboration²⁶ is more appropriate when assessing studies of effectiveness, rather than adverse events,²⁷ we did not formally assess risk of bias. Instead, we assessed reports for causality and used expert judgment to identify which were less consistent with how products are typically used in clinical practice. Since we classified drugs by their clinical effect rather than their pharmacologic class, we added as much clarity as possible in the interaction details.

Future directions for NHP–drug interaction research are many and varied. More primary research is needed. For several reasons, adverse reactions associated with NHP–drug interactions may not be reported.^{3,28–32} Most national pharmacovigilance strategies are based on a passive surveillance system for reporting of suspected adverse drug reactions; this approach is well known to suffer from underreporting (both the quantity and quality of reported adverse reactions are often insufficient for meaningful interpretation).^{31,33} Active surveillance is a strategy to identify NHP–drug interactions at a faster rate than

passive reporting of adverse events or by developing case studies, as described in Necyk.³ All new evidence must be weighed against previous evidence to determine the clinical significance of the interaction in question. Future updates of our knowledge translation tool would also benefit from a larger scope, for example, the inclusion of more instances in which products have been taken concurrently with no documented interactions, adding interaction details to preclinical interactions and adding literature search terms relating to cytochrome P450. Knowledge translation tools are most helpful when they are up to date, and given the volume of relevant publications in this field, we are working to develop an app that can be more easily updated.

Conclusion

The NHP-drug interaction tool that has been developed can help clinicians determine if their patient is at risk. We urge clinicians to inquire about NHP use at every patient encounter and

to report all suspected NHP-drug interactions to their respective national pharmacovigilance center (e.g., Marketed Health Products Directorate, Health Canada).

Disclaimer

To the best of our knowledge, the data in the chart are an accurate summary of the published data up to December 2012. The data have been reviewed by a panel of researchers and clinicians. Rare or currently undocumented interactions are always possible. Remember that the likelihood that a drug interaction may occur will also vary depending on a patient's individual characteristics, as well as on the quality of the plant-derived NHP, the part of the plant used, how a specific product is manufactured and what NHPs are combined together. Some of the common names listed here (e.g., Asian ginseng) refer to several different species or subspecies. We caution that all interactions are underreported and evidence is still emerging. ■

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