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Published in:
Australian Prescriber

DOI:
[10.18773/austprescr.2010.084](https://doi.org/10.18773/austprescr.2010.084)

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Recommended citation(APA):
Moses, G. M., & McGuire, T. M. (2010). Drug interactions with complementary medicines. *Australian Prescriber*, 33(6), 177-180. <https://doi.org/10.18773/austprescr.2010.084>

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Drug interactions with complementary medicines

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Summary

Health professionals are expected to be familiar with common and clinically significant complementary medicine interactions or at least know where to look them up. Knowing the dynamic and kinetic interactions associated with commonly used complementary medicines helps to identify the risk of drug interactions. Although information on complementary medicine interactions is not readily provided by the manufacturers, evidence is available by way of case reports, independent research and web-based resources, which have increased in recent years. Collectively, these data make interactions with complementary medicines largely predictable and therefore preventable.

Key words: drug interactions, St John's wort.

(Aust Prescr 2010;33:177–80)

Introduction

The Therapeutic Goods Administration refers to complementary medicines as 'medicinal products containing herbs, vitamins, minerals, nutritional supplements, homoeopathic medicines, traditional medicines and certain aromatherapy products'.¹ In Australia, complementary medicines are largely regulated as unscheduled medicines, and are usually self-selected.

Complementary medicines are very popular among Australians, with surveys indicating that up to 60% of people use at least one complementary medicine on a regular basis. However, about 50% of consumers also report using a conventional medicine on the same day as their complementary medicine.^{2,3} It is not surprising, therefore, that healthcare professionals and consumers alike are concerned about the potential for drug interactions between these medicines.

As so many Australians use complementary medicines, including children, the elderly, patients with chronic disease, mental health disorders and cancer, it is important that prescribers always ask what complementary products their patients are taking in addition to any conventional medicines. Knowing this, and

extrapolating reported pharmacodynamic and pharmacokinetic outcomes, can help predict potential drug interactions.

Polypharmacy

Complementary medicines are frequently used in the context of polypharmacy. A study of 3070 elderly people found that 74.2% took at least one prescription drug and one complementary medicine, with 32.5% of them using three or more prescription medicines with three or more complementary medicines.⁴ This translates to an increased risk of drug interactions. In a study of 458 US Veterans' Administration patients, 197 of them reported taking complementary medicines combined with prescription medicines. Of these patients, 45% had potential for interactions, which was rated as serious in 6% of patients.⁵ In another study which interviewed 3000 people (aged 57–85) about prescription, over-the-counter and complementary medicine use, 4% of them were potentially at risk of a major drug–drug interaction.⁶ It has been suggested that once a patient is on eight or more medicines, regardless of origin, there is a 100% chance of a drug interaction occurring.⁷

Drug interactions

As with other drugs, complementary medicine interactions can be broadly classified by their mechanism, that is, pharmacodynamic and pharmacokinetic. The former are due to overlap of pharmacological actions, while the latter result from changes in absorption, distribution, metabolism or excretion.

Risk factors for significant complementary medicine interactions are the same as for conventional medicines. These include patient characteristics (such as extremes of age, frailty, female gender, cognition, comorbidities and genetic disposition) and medication factors (such as high medication burden, recent changes in medicines, drugs with a low therapeutic index and limited elimination pathways).

Due to their complex chemical structure, herbal medicines are prone to interactions via the oxidative cytochrome P450 system or the efflux drug transporter P-glycoprotein.^{8,9} *In vitro* assays, using human tissue or cell lines, are frequently used to determine whether a herb affects these enzymes.¹⁰ However, *in vitro* findings do not necessarily correlate with what happens in the human body. As several herbal medicines and many prescription drugs are substrates, inducers or inhibitors of CYP isoenzymes or P-glycoprotein, interactions can ensue when they

are used concomitantly.⁹ A classic example is St John's wort, which has kinetic interactions with a wide range of drugs via the induction of CYP1A2, CYP3A4, CYP2C9 and P-glycoprotein.¹¹ This lowers the concentration of the concomitant drug.

Table 1 shows selected documented interactions which have been chosen based on a composite of:

- the most frequently used complementary medicines in Australia, from survey and sales data¹²
- interactions with serious or clinically significant outcomes.

Table 1 categorises interactions by their possible outcome, severity, supporting evidence and proposed mechanism. Generic guidance on interaction management is given in the key, within the definitions of severity (major, moderate, minor). Certain therapeutic drug classes appear repeatedly in the table such as antiplatelet drugs, anticoagulants, antidepressants, antihypertensives, hypoglycaemics, immunosuppressants, antiretrovirals and hormones. Health professionals should monitor patients closely when a complementary medicine is taken concomitantly with these drugs.

Table 1

Evidence-based complementary medicine interactions^{8,11,13,14}

This table shows complementary medicines with at least one 'major' interaction. For the full version of this table, see this article online at www.australianprescriber.com

Complementary medicine	Interacting drug	Possible outcome	Severity and level of evidence*	Proposed mechanisms/comment
Evening primrose oil	Antiplatelet drugs, warfarin	↑ drug effect	Major , level B	Contains gamma-linolenic acid, probable anticoagulant
Garlic	Contraceptives, oral	↓ drug effect	Moderate, level D	Induces CYP3A4
	Saquinavir/non-nucleoside reverse transcriptase inhibitors	↓ drug levels and effect	Major , level B	Induces CYP3A4
	Antiplatelet drugs, warfarin	↑ bleeding risk	Moderate, level D	Theoretical antiplatelet activity
Ginkgo	Anticonvulsants	↑ seizure risk	Moderate, level D	Large amounts of ginkgotoxin can cause neurotoxicity
	Warfarin, antiplatelet drugs	↑ bleeding risk	Major , level D	Antiplatelet activity after several weeks
	CYP2C9 substrates e.g. glipizide, warfarin, celecoxib	↑ substrate levels	Moderate, level D	Inhibits CYP2C9 activity
	CYP1A2, CYP2C19, CYP2D6 and CYP3A4 substrates	↑ substrate levels	Moderate, level B	Potentially inhibits these enzymes
	Hypoglycaemic drugs	↑ ↓ drug effect	Moderate, level B	Variably affects blood glucose concentrations
Glucosamine	Warfarin	↑ bleeding risk	Major , level D	Several case reports of increased INR
Hawthorn	Calcium channel blockers, nitrates, phosphodiesterase inhibitors	↑ drug effect	Major , level D	Additive vasodilator effects
	Digoxin, beta blockers	↑ drug effect	Major , level D	Additive effects on heart rate and/or blood pressure. Hawthorn has cardiotoxic effects.
Kava	CNS depressants	↑ drug effect	Major , level A	Additive somnolence Kava potentially inhibits these enzymes
	CYP1A2, CYP2D6, CYP2C9, CYP2E1, CYP3A4 substrates	↑ substrate levels	Moderate, level B	
	P-glycoprotein substrates	↑ substrate levels	Moderate, level D	
St John's wort	Alprazolam	↓ drug levels and effect	Major , level B	Increased clearance; half-life reduced by 50% Increased risk of serotonin syndrome
	Amitriptyline	↑ drug effect	Major , level B	
	Antidepressants, tramadol	↑ drug effect	Major , level D	
	Pethidine	↑ drug effect	Major , level D	
	Triptans	↑ drug effect	Moderate, level D	

Table continued...

...Table continued

Complementary medicine	Interacting drug	Possible outcome	Severity and level of evidence*	Proposed mechanisms/comment
	Clopidogrel	↑ bleeding risk	Moderate, level B	Increased conversion to active metabolite
	CYP1A2, CYP2C9, CYP3A4 substrates e.g. imatinib, indinavir, tacrolimus, carbamazepine, phenytoin	↓ drug levels and effect	CYP3A4 = Major , level B CYP1A2, CYP2C9 = Moderate, level B	Induces CYP enzymes
	Non-nucleoside reverse transcriptase inhibitors, protease inhibitors	↓ drug levels and effect	Major , level B	Induces CYP3A4
	Oral contraceptives	↓ drug levels	Major , level B	Risk of breakthrough bleeding/contraceptive failure
	P-glycoprotein substrates e.g. digoxin, fexofenadine, irinotecan	↓ drug levels and effect	Major , level B	Induces intestinal P-glycoprotein
	Simvastatin	↓ drug levels	Moderate, level B	Statin levels reduced by up to 28%
	Warfarin	↓ drug effect	Major , level B	Induces CYP1A2, CYP2C9 and CYP3A4
Valerian	Alprazolam	↑ drug levels	Major , level B	CYP3A4 inhibitor. Alprazolam increased by 19% in one study.
	CNS depressants	↑ drug effect	Major , level D	Pharmacodynamic effect
	CYP3A4 substrates	↑ substrate effect	Moderate, level D	

CYP cytochrome P450

INR international normalised ratio

CNS central nervous system

* Interaction rating adapted from Natural Medicines Comprehensive Database.¹¹ The level of severity (major, moderate, minor) has been calculated using the evidence and probability of harm. This rating is linked with a generic recommendation for management.

Major Strongly discourage patients from using this combination as a serious adverse outcome could occur. If used, patient should be monitored closely for potential adverse outcomes.

Moderate Use cautiously or avoid combination as a significant adverse outcome could occur. If used, monitor for potential adverse outcomes.

Minor Be aware that there is a chance of an interaction. Advise patients of symptoms that may occur and an action plan to follow.

Level of evidence ratings:

A High-quality randomised controlled trial or meta-analysis

B Non-randomised clinical trial, literature review, clinical cohort or case-control study, historical control or epidemiologic study

C Consensus or expert opinion

D Anecdotal evidence; *in vitro* or animal study or theoretical based on pharmacology

Finding information about complementary medicine interactions

Most complementary medicines are listed (AUST L) medicines, which are not subjected to the same rigorous premarketing safety and efficacy trials as registered (AUST R) medicines. Thus evidence of their interaction potential is often not available. In addition, manufacturers are not obliged to provide a consumer medicine information leaflet with advice or warnings regarding complementary medicine interactions.

Despite the lack of hard data, health professionals still need to make reasonable recommendations to patients about potential interactions. With a view to helping Australians make more informed decisions about using complementary medicines, an independent consortium from Mater Health Services Brisbane, Bond University and University of Queensland, with funding from the National Prescribing Service, evaluated complementary medicines information resources in 2008.¹² Specific criteria were used to identify 52 resources – 26 of these

were shortlisted and assessed for technical quality, content and clinical utility. The quality of drug interaction information was also assessed in the review, specifically whether mechanisms were outlined, degree of severity was stated, and whether the absence of known drug interactions was disclosed.

While many resources (free or subscription) had technical strengths, few had comprehensive interaction coverage. Those with some detail are included for further reading. Two of the highest ranked resources were online subscription databases, both of which contained reasonably comprehensive complementary medicine–drug interaction checkers. These were:

- Natural Standard (www.naturalstandard.com), which provides detailed monographs and brief summaries ('bottom line')
- Natural Medicines Comprehensive Database (www.naturaldatabase.com).

Conclusion

Consumers frequently use complementary medicines in combination with conventional medicines. For this reason, health professionals should always consider the potential for pharmacodynamic and pharmacokinetic interactions between them. High quality evidence is increasingly available for identification and prevention of these interactions.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 198)

3. St John's wort can decrease phenytoin concentrations via its induction of cytochrome P450 3A4.
4. Ginkgo can increase the bleeding risk when given with warfarin.