Interactions between complementary medicines and drugs used in primary care and oral COVID-19 antiviral drugs

CPD

Jennifer Hunter, Joanna E Harnett

Background
Patient harm resulting from drug interactions between conventional and traditional or complementary medicines (CM) are avoidable.

Objective
To provide a clinical overview of a selection of CM interactions with drugs commonly used in Australian general practice or in the management of COVID-19.

Discussion
Many herb constituents are substrates for cytochrome P450 enzymes, and inducers and/or inhibitors of transporters such as P-glycoprotein. *Hypericum perforatum* (St John's Wort), *Hydrastis canadensis* (golden seal), *Ginkgo biloba* (ginkgo) and *Allium sativum* (garlic) are reported to interact with many drugs. Simultaneous administration of certain anti-viral drugs with zinc compounds and several herbs should also be avoided. Preventing and identifying unwanted CM–drug interactions in primary care requires vigilance, access to CM–drug interaction checkers and excellent communication skills. Potential risks from interactions should be balanced against the potential benefits of continuing the drug and/or CM and involve shared decision making.

UNWANTED DRUG INTERACTIONS with complementary medicines (CMs) can be avoided by being aware of the risks and discussing them with patients.[1] CMs contain nutritional and herbal ingredients that are complex, multiconstituent compounds with demonstrable pharmacological actions.[2] As such, the use of CMs is associated with potential benefits and harms, including harm from CM–drug interactions.[3]

Approximately 50% of adults living in Australia reportedly use CM products. Of these, 80% also use prescription and over-the-counter drugs, and 73% have chronic conditions that further increase their risk of unwanted drug interactions due to polypharmacy.[4,5]

Aim

This narrative review provides an overview of selected CM–drug interactions reported in human studies that may occur when CMs are used with drugs that are commonly prescribed in Australian general practice and reviews potential interactions between CMs marketed for respiratory tract infections or immune support in Australia and drugs used to treat COVID-19.

Methods

This review article summarises the findings from systematic reviews and comprehensive narrative reviews and other primary studies known to the authors. Interactions between CMs and medicines typically only prescribed in secondary care settings are not reported. Given the emerging evidence for interactions between CMs and drugs used to treat COVID-19, product information documents for drugs and reputable interaction checkers listed in Table 1 were also used to identify interactions.

Mechanisms of drug interactions

Drug interactions can occur when two or more compounds taken within a certain period of time alter the pharmacokinetics or pharmacodynamics of either compound. Both are implicated in an increased or decreased clinical effect that is not observed when either compound is used alone.[6]

Pharmacokinetic interactions change the systemic concentration of a compound and/or its active metabolites by altering absorption, distribution, metabolism or excretion.[6] Most CM–drug pharmacokinetic interactions are associated with the induction or inhibition of cytochrome P450 (CYP) enzymes or transporters such as P-glycoprotein and organic anion transporting polypeptides.[4] Approximately 80% of drugs used in clinical practice are metabolised by CYP enzymes.[7]

Pharmacodynamic interactions occur when the compounds have negative, additive or synergistic effects on drug targets.[8]

Determining clinically important interactions

Preclinical studies, such as in vitro and animal studies, are useful for identifying potential CM–drug interactions and the mechanisms by which they occur. Human studies are still required to determine the clinical relevance of any such interactions.[6] As such, for the purpose of the present narrative review, our focus is on human studies.

Many of the CM–drug interactions flagged by interaction checkers or in the drug product information or CM monographs are theoretical and based on knowledge of shared mechanisms of action and/or shared metabolism. Sometimes, they are inferred from the findings of studies evaluating other drugs with similar pharmacological properties or in vitro and animal studies.[6] However, there are a growing number of case reports, case series and controlled trials reporting clinically important CM–drug interactions.[9]

Collectively, this evidence warrants attention, especially for drugs that have a narrow therapeutic index or when there are potentially serious consequences.[6] These include drugs used for contraception, mental health, epilepsy, cancer, immunosuppression, infections, diabetes and cardiovascular conditions.[6]

However, not all CM–drug interactions are necessarily unwanted or undesirable, and some could improve clinical outcomes (eg by augmenting the clinical effects of the drug, increasing drug concentrations or reducing side effects).[9]

CM–drug interactions relevant to general practice

Table 2 summarises some of the clinical research on CM–drug interactions relevant to general practice. Notable in

Table 1. Complementary medicine–drug interaction resources

Name	Website	Comments
Most comprehensive for CM–drug interactions		
IMgateway[A,B]	www.imgateway.net	Only CM–drug interaction checker Search research database/monographs according to conditions, treatment options, nutrient depletion risk from drugs
Natural Medicines[A]	https://naturalmedicines.therapeuticresearch.com	Only CM–drug interaction checker Check for effectiveness, nutrient depletion from drugs, use during pregnancy and lactation, and adverse events
MedicinesComplete Stockley's interactions checker[A,C]	https://about.medicinescomplete.com	Both CM–drug and drug–drug interaction checker Herb interaction monographs[D]
Only some CM–drug interactions are listed		
MIMS Integrated[A]	www.mims.com.au	Interaction checker for all registered medicines and some listed CMs in Australia Integrates with clinical practice software common in Australia
University of Liverpool drug–drug interaction resources	www.druginteractions.org	Specific HIV, hepatitis, cancer and COVID-19 drug interactions checkers; includes some CM ingredients
DynaMed/Micromedex[A]	www.dynamed.com	Drug interaction checker, FDA-approved drugs, includes some CM ingredients and products available in the US, missing many known CM–drug interactions

[A]Subscription is required for access.

[B]Available as an eMIMS Australia add-on module.

[C]Available via John Murtagh Library for members of The Royal Australian College of General Practitioners.

[D]Monographs are in Stockley's Herbal Medicines Interactions.

CM, complementary medicine; FDA, US Food and Drug Administration.

some reports, altered plasma or serum concentrations of a drug were not always associated with altered clinical effects. For example, *Echinacea purpura* was found to lower warfarin levels, yet there was no significant change in INR.[10]

Given this review is not comprehensive, practitioners should also refer to interaction checker databases to identify other potentially important interactions (Table 1).

Table 2 lists numerous examples when a CM altered the plasma or serum concentrations of a drug, yet it is unknown whether these changes are clinically important. Clinical importance cannot be assumed; for example, *Echinacea purpurea* (with or without *Echinacea angustifolia*) lowered warfarin levels, yet this did not appear to affect the international normalised ratio of prothrombin time (INR).[9,10,14] Similarly, it was unclear whether the small increase in digoxin levels from coadministration with *Hydrastis canadensis* (goldenseal) was clinically important.[14,18]

There were quite a few instances where the clinical outcomes from a CM–drug interaction could be favourable. Many of these interactions were due to the additive hypoglycaemic effects of the CM, which improved glycaemic control when coadministered with a hypoglycaemic drug.[12,13] Depending on the clinical circumstances, close monitoring may still be advisable to reduce the risk of a hypoglycaemic event. Other examples include specific species and strains of probiotic bacteria that may

Table 2. Clinical interactions[A] between ingredients of complementary medicines and primary care drugs available in Australia

CM ingredient (common name)	Risk[B]	Drug investigated	PD and/or PK enzyme transporter involved	Observed effects on drug concentrations and/or clinical effects
Ascorbic acid (vitamin C)	✕✕	Warfarin[10,11]	Unclear mechanism decreased anticoagulant effect[D]	↓ Anticoagulant–warfarin resistance[11] ↔ ≤1,000 mg/day[10]
Allium sativum (garlic)	✕✕	Metformin[12,13]	Additive PD effect[D] Unclear PK mechanism	Improved glycaemic control ↑ Metformin
	✕	Alprazolam[14]	CYP3A4	↔ Alprazolam
	✕	Dextromethorphan[14]	CYP3A4	↔ Dextromethorphan
	✕✕	Ritonavir[14,15]	CYP3A4	↔ Ritonavir ↓ (non-significant) Ritonavir concentrations
	✕✕	Warfarin[10,16]	Additive PD effect[D]	↓ ADP-induced platelet aggregation
Aloe barbadensis Miller (aloe vera)	✕✕	Glibenclamide[12,13]	Additive PD effect[D]	Improved glycaemic control
Curcuma longa (turmeric)	✕✕	Glibenclamide[12]	CYP3A4, CYP2C19	↑ Glibenclamide Improved glycaemic control
Crocus sativus (saffron)	✕	Fluoxetine[9]	Unclear	↓ Sexual dysfunction ↔ Depression
Echinacea angustifolia and *Echinacea purpurea*	✕✕	Warfarin[9,14]	CYP2C9	↓ Warfarin ↔ INR
Echinacea purpurea	✕	Ritonavir[14]	CYP3A4	↔ Ritonavir
	✕✕	Warfarin[10]	CYP3A4	↓ Warfarin ↔ INR
Eurycoma longifolia (longjack)	✕✕	Propranolol[9]	↓ Absorption	↓ Propranolol
Folic acid	✕✕	Warfarin[10]	↑ Clearance of (*S*)-7-hydroxywarfarin	↔ INR ↔ Anticoagulation (Unclear risk for >5 mg)

Table continued on the next page.

improve vaccine efficacy and duration of protection.[29]

Coincidentally, except for *Hypericum perforatum* (St John's wort), the common name for many of the CMs commonly implicated in clinically important drug interactions begins with the letter 'G': *Allium sativum* (garlic), *Zingiber officinale* (ginger), *Ginkgo biloba* (ginkgo), *Hydrastis canadensis* (goldenseal), *Camellia sinensis* (green tea), *Gymnema sylvestre* (gymnema), *Panax quinquefolius* (American panax ginseng), *Panax notoginseng* (Korean/Chinese ginseng) and *Eleutherococcus senticosus* (Siberian ginseng) and glucosamine. Clinically important drug interactions are summarised below.

Pharmacokinetic interactions

Interactions of P-glycoprotein and CYP enzymes with several herbs are relatively common. It is well established that *Hypericum perforatum* (St John's Wort) and one of its bioactive constituents, hyperforin, are potent inducers of intestinal P-glycoprotein and several CYP enzymes, specifically cytochrome P450 family 3 subfamily A member 4 (CYP3A4), which is involved in the metabolism of over 50% of commonly prescribed drugs.[30] Extracts with hyperforin doses over 0.3 mg have a substantially increased risk of a drug interaction.[30,31] Consequently, some *Hypericum perforatum* (St John's wort) products standardise both the hypericin and hyperforin content.

Clinical studies have confirmed that *Hypericum perforatum* (St John's Wort) alters the expected pharmacokinetics of

Table 2. Clinical interactions[A] between ingredients of complementary medicines and primary care drugs available in Australia (Cont'd)

CM ingredient (common name)	Risk[B]	Drug investigated	PD and/or PK enzyme transporter involved	Observed effects on drug concentrations and/or clinical effects
Ginkgo biloba	××	Alprazolam[14]	CYP3A4	↓ Alprazolam
	××	Atorvastatin[14]	Unclear	↓ Atorvastatin
	××	Metformin[12]	Unclear	↓ Metformin ↓ Glycaemic control
	××	Simvastatin[9,14]	OATP1B1, CYP3A4, BCRP	↓ Simvastatin ↔ On simvastatin acid (active metabolite)
	××	Tolbutamide[12]	CYP2C9, CYP3A4	↓ Tolbutamide ↓ Glycaemic control
	×	Bupropion[14]	CYP2B6	↔ Bupropion
	×	Dextromethorphan[14]	CYP3A4	↔ Dextromethorphan
	×	Diazepam[14]	CYP2C19	↔ Diazepam
	×	Omeprazole[14]	CYP2C19	↓ Omeprazole
	××	Warfarin[10,14]	CYP2C9, ↓ PAF	↔ Warfarin ↔ INR ↑ Increased risk of bleeding in some patients
Camellia sinensis (green tea)	××	Simvastatin[17]	CYP3A4, P-gp	↑ Simvastatin
	××	Rosuvastatin[17]	OATP1A2, OATP2B1	↓ Rosuvastatin
	××	Sildenafil[17]	CYP3A	↑ Sildenafil
Hydrastis canadensis (goldenseal)	××	Digoxin[14,18]	CYP3A	Small ↑ digoxin, may not be clinically important
	××	Midazolam[19]	CYP3A	↑ Midazolam

Table continued on the next page.

Table 2. Clinical interactions[A] between ingredients of complementary medicines and primary care drugs available in Australia (Cont'd)

CM ingredient (common name)	Risk[B]	Drug investigated	PD and/or PK enzyme transporter involved	Observed effects on drug concentrations and/or clinical effects
Hypericum perforatum (St John's wort)	××	Amitriptyline[14]	CYP3A5, P-gp	↓ Amitriptyline
	××	Digoxin[9,20]	CYP3A4, P-gp	↓ Digoxin
	××	Gliclazide[14]	CYP2C9	↓ Gliclazide
	××	Nifedipine[14]	CYP3A4	↓ Nifedipine
	××	Nortriptyline[14]	CYP3A5, P-gp	↓ Nortriptyline
	×××	OCP: ethinyl oestradiol and norethindrone[14,21]	CYP3A4/5	↓ Ethinyl oestradiol ↓ Norethindrone ↑ Breakthrough bleeding ↑ Ovarian follicles >30 cm
	××	Omeprazole[9,14]	CYP2C19	↓ Omeprazole
	××	Oxycodone[9,22]	CYP3A	↓ Oxycodone ↓ Analgesia
	××	Simvastatin[14]	CYP3A4	↓ Simvastatin
	××	Verapamil[14]	CYP3A4/5	↓ Verapamil
	×××	Warfarin[9,14]	CYP1A2, CYP3A4	↓ Warfarin ↓ INR
	××	Zolpidem[14]	CYP3A4	↓ Zolpidem
	××	Metformin[13,14]	↓ Renal clearance ↑ Insulin secretion[D]	↔ Metformin ↑ Glycaemic control
	×	Pravastatin[14]	CYP3A	↔ Pravastatin
	×	Repaglinide[13,14]	CYP3A4	↔ Repaglinide ↔ Glycaemic control
Momordica charantia (bitter gourd/melon, karela)	××	Glibenclamide[12,13]	Additive PD effect, CYP3A4[D]	Improved glycaemic control
	××	Metformin[12,13]	Additive PD effect[D]	Improved glycaemic control
Panax ginseng (Korean ginseng)	×	Warfarin[10]	Additive PD effect[D]	↔ INR ↔ anticoagulation
Panax quinquefolius (American ginseng)	×××	Warfarin[9,10]	Additive PD effect	↓ Warfarin ↑ TT ↑ aPTT ↓ INR
Omega-3 fatty acids (fish oil)	××	Warfarin[10]	Additive PD effect	↓ Factor V ↓ Factor VII ↑ or ↔ Anticoagulant effect (conflicting clinical results)
Psyllium hydrophilic mucilloid	×	Warfarin[10]	↓ Absorption[D]	↔ INR ↔ Anticoagulation

Table continued on the next page.

Table 2. Clinical interactions[A] between ingredients of complementary medicines and primary care drugs available in Australia (Cont'd)

CM ingredient (common name)	Risk[B]	Drug investigated	PD and/or PK enzyme transporter involved	Observed effects on drug concentrations and/or clinical effects
Policosanol	×	Warfarin[10]	Additive PD effect[D]	↔ INR ↔ Anticoagulation
Rhodiola rosea	××	Losartan[23]	CYP2C9	↓ Losartan
Salvia miltiorrhiza (danshen)	×××	Warfarin[10]	Additive PD effect[D]	↑ Anticoagulant effect
Silybum marianum (St Mary's thistle, silymarin, milk thistle)	××	Losartan[14]	CYP2C9*1/*1 genotype[E]	↑ Losartan
	×	Losartan[14]	CYP2C9*1/*1 genotype[E]	↔ Losartan
Scutellaria baicalensis	××	Rosuvastatin[9]	↑ CYP2C9*1/*1 genotypes[E]	↓ Rosuvastatin
Ubiquinone (coenzyme Q10)	×××	Warfarin[10,24,25]	Unclear	↑ ↓ Anticoagulation
Vaccinium macrocarpon (cranberry)	×××	Warfarin[9,10,26]	CYP2C9, CYP3A4, BRCP	↑ ↓ Warfarin Unstable INR (depending on timing of coadministration)
Vitamin E	×××	Warfarin[10]	Additive PD effect[D]	↔ INR ↑ Risk of bleeding
Vitamin K	×××	Warfarin[10]	Antagonistic PD effect	↓ Anticoagulant effect
Yin Zhi Huang formula[C]	××	Omeprazole[9]	CYP3A4, CYP2C19	↓ Omeprazole
Zinc	××	Tetracycline antibiotics[27]	↓ Absorption	↓ Tetracycline antibiotics if simultaneously coadministered
	××	Quinolone antibiotics[28]	↓ Absorption	↓ Quinolone antibiotics if simultaneously coadministered

[A]Interaction confirmed in at least one controlled trial involving humans with or without preclinical studies that was reported in one or more systematic or comprehensive narrative review.

[B]Risk is categorised as follows: (×), lower risk (of unwanted interaction or theoretical risk; monitor); (××), moderate risk (interaction probable; monitor, adjust dose or avoid); and (×××), higher risk (of serious adverse event from interaction; avoid).

[C]Yin Zhi Huang formula: *Artemisia scoparia*, *Gardeniae fructus*, *Scutellaria baicalensis* Georgi and *Lonicerae japonicae flos*.

[D]The mechanism of potential interaction is either yet to be confirmed and/or is only theoretical.

[E]The interaction is likely to only occur in people with CYP2C9*1/*1 genotype.

aPTT, activated partial thromboplastin time; BCRP, breast cancer resistance protein; CMs, complementary medicine products; CYP, cytochrome P450; INR, international normalised ratio of prothrombin time; OATP, organic anion transporting polypeptide; OCP, oral contraceptive pill; PAF, platelet-activating factor; PD, pharmacodynamic; P-gp, P-glycoprotein transporter; PK, pharmacokinetic; TT, thrombin time.

drugs commonly used for the prevention and treatment of cardiovascular disease, diabetes and contraception (Table 2).[32] In addition, the product information for numerous other drugs often includes an interaction warning for *Hypericum perforatum* (St John's wort) when it has been shown to dramatically alter the pharmacokinetics of another drug with similar pharmacokinetic properties.[33]

Allium sativum (garlic) is known to substantially increase the intestinal expression of P-glycoprotein and inhibits several CYP enzymes. Thus, there is a risk of pharmacokinetic interactions between garlic and numerous drugs (Table 2).[34] The risks may be higher with *Allium sativum* (garlic) products that have a high allicin content (Table 2).[35]

Hydrastis canadensis (goldenseal) and its main bioactive constituents berberine and hydrastine inhibit cytochrome P450 family 2 subfamily D member 6 (CYP2D6), CYP3A and P-glycoprotein.[14,36] The clinical importance of this is uncertain given the results of one clinical trial in which digoxin concentrations were only slightly increased by goldenseal (Table 2).[18]

Interactions between *Camellia sinensis* (green tea/green tea supplements) and cardiovascular drugs that are metabolised by CYP3A or transported by P-glycoprotein, organic anion transporting polypeptide (OATP) 1A1 or OATP1A2 are another potential risk, although the clinical significance of some of these interactions is yet to be determined (Table 2).[17]

Zinc is a common ingredient in CM used to support immune function and

Wonca 2023

Bringing your RACGP annual conference to WONCA 2023

Recovery, reconnection and revival: A celebration of primary care

26 to 29 October 2023,
International Convention Centre (ICC), Sydney

WONCA 2023 will incorporate our annual GP conference (GP23) this year. This means that everything you love about your RACGP annual conference will be a part of the WONCA Sydney 2023 conference, plus you will get a chance to make some new local and international connections.

WONCA 2023 offers a dynamic program of accredited activities including pre-conference workshops, clinical skills updates, CPR workshops and targeted sessions for practice owners. The program includes a mix of informative and interactive presentations that will showcase the latest primary care research and help you improve your practice.

Presenter details and early bird registrations:
wonca2023.com.au

Keynote presenters

Professor Michael Kidd AM

Dr Anna Stavdal

Professor Enrique Falceto de Barros

RACGP | Wonca

GP23 Bringing your RACGP annual conference to WONCA

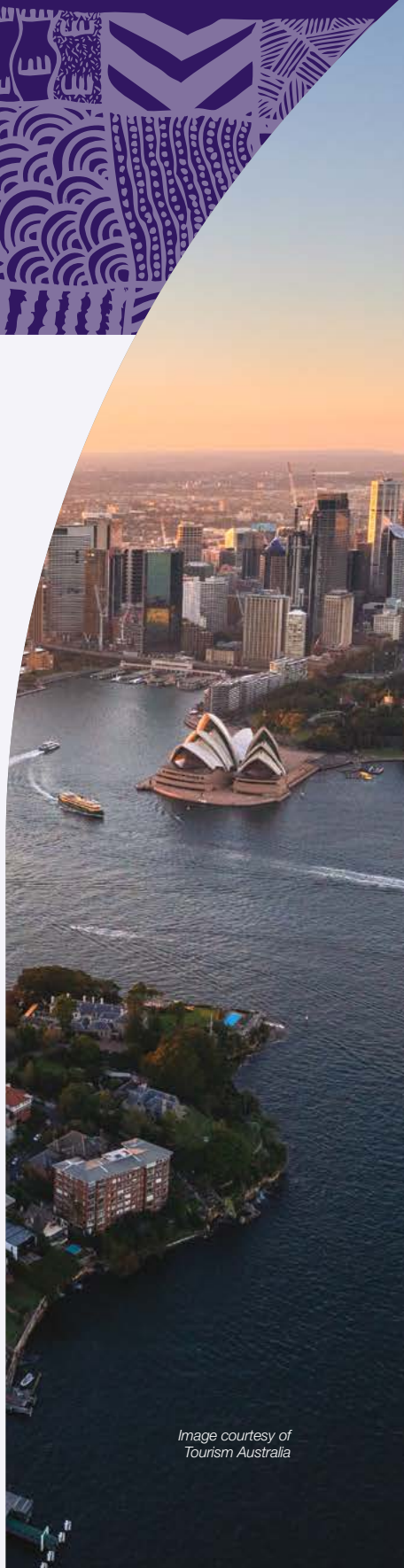

Image courtesy of Tourism Australia

2023 RACGP Awards

Recognising excellence in general practice

It's time to recognise and celebrate the hard work of GPs and their teams in caring for their communities. We want to hear about exceptional people in Australian general practice and their outstanding achievements.

Nominations are now open for the 2023 RACGP Awards.

If you know a GP, supervisor or GP in training who has gone above and beyond to improve the health of their community, nominate them for the RACGP Awards.

Nominations can be made online until 16 July 2023.

Find out more, including a full list of award categories, at racgpawards.org.au

RACGP

Table 3. Interactions between oral COVID-19 antiviral drugs and complementary medicines marketed for respiratory tract infections or immune support[A]

Interaction risk	Complementary medicine	COVID-19 antiviral drug	Mechanism and effect on plasma concentrations of antiviral drug
Clinically important interaction possible	Zinc sulfate[B]	Paxlovid® (ritonavir + nirmatrelvir)	Lower plasma concentration from zinc chelation of ritonavir in the gut (one RCT)[48]
Interaction possible, clinical risk uncertain	Zinc compounds[B] *Althaea officinalis*[B] (marshmallow)	Paxlovid® (ritonavir + nirmatrelvir) Veklury® (remdesivir) Lagevrio® (molnupiravir)	Lower plasma level from zinc chelation in the gut (human studies of other drugs) Lower plasma level from marshmallow reducing absorption in gut (theoretical risk)
	Allium sativum (garlic) *Echinacea purpurea*	Veklury® (remdesivir)	Lower plasma level from CYP3A induction (conflicting results from human studies of other drugs)
	Allium sativum (garlic), with high allicin content	Paxlovid® (ritonavir + nirmatrelvir)	Gastrointestinal adverse effects from complex interaction of CYP enzymes induction/inhibition and/or P-glycoprotein induction (two case reports)[49]
	Glycyrrhiza uralensis and *Glycyrrhiza glabra* (licorice, gan cao) *Schizonepeta tenuifolia* (jing jie) Honey Propolis	Paxlovid® (ritonavir + nirmatrelvir) Veklury® (remdesivir)	Lower plasma concentration from CYP3A induction (conflicting results from human studies of other drugs, or only preclinical studies)
	Schisandra chinensis (wu wei zi)	Paxlovid® (ritonavir + nirmatrelvir) Veklury® (remdesivir)	Higher plasma concentration from CYP3A4 inhibition (human studies of other drugs)
	Eucalyptus oil	Paxlovid® (ritonavir + nirmatrelvir) Veklury® (remdesivir)	Higher plasma concentration from CYP3A4 inhibition (preclinical studies)
Interaction unlikely	*Allium sativum* (garlic), with low allicin content	Paxlovid® (ritonavir + nirmatrelvir)	Non-significant lower ritonavir plasma concentration from CYP enzymes and/or P-glycoprotein induction (one RCT)[50]
	Echinacea purpurea	Paxlovid® (ritonavir + nirmatrelvir)	No effect on plasma concentration despite potential CYP3A induction (one RCT)[51]

Table continued on the next page.

reduce the symptoms and duration of the common cold and flu.[37] Of clinical importance to general practitioners prescribing tetracycline and quinolone antibiotics is the potential for zinc to reduce the intestinal absorption of these antibiotics.[27,28]

Pharmacodynamic interactions

Along with pharmacokinetic interactions, there is also the potential risk of serotonin syndrome when *Hypercium perforatum* (St John's wort) is combined with another drug that has a serotonergic effect.[38] It is therefore recommended that this combination is avoided.[39]

Interactions that increase the risk of bleeding from antithrombotic or non-steroidal anti-inflammatory drugs are predominantly due to the additive anticoagulant and/or platelet aggregation inhibitory effects of CMs and/or an increase in the plasma concentrations of the drugs. The commonly used herbs, *Allium sativum* (garlic), *Zingiber officinalis* (ginger) and *Ginkgo biloba* (ginkgo) all have antiplatelet and anticoagulant properties.[40] Consequently, despite the inconsistent clinical evidence of an increased risk (Table 1), coadministration of these herbs with antithrombotic drugs is generally not recommended.[10] Glucosamine supplements should also be avoided in patients taking warfarin. A case series reported an increased INR associated with the concurrent use of glucosamine supplements and warfarin, in which 17 of 21 cases resolved after discontinuation of the glucosamine supplements.[41] Coadministration of *P. quinquefolius* (American ginseng) and warfarin can lower INR levels. Changes in

Table 3. Interactions between oral COVID-19 antiviral drugs and complementary medicines marketed for respiratory tract infections or immune support[A] (Cont'd)

Interaction risk	Complementary medicine	COVID-19 antiviral drug	Mechanism and effect on plasma concentrations of antiviral drug
No interactions expected based on PK and PD data	*Andrographis paniculata*		
	Armoracia rusticana (horseradish)		
	Astragalus membranaceus (huang qi)		
	Codonopsis pilosula		
	Eleutherococcus senticosus (Siberian ginseng, ci wu jia)		
	Forsythia suspensa (lian qiao)		
	Ganoderma lucidum (reishi mushroom, ling zhi)		
	Hedera helix (ivy leaf)		
	Inula helenium (xuan fu hua)		
	Isatis tinctoria (banlangen)		
	Ligustrum lucidum (privet, mi zhen zi)		
	Lonicera japonica (honeysuckle, ren dong teng)		
	Magnolia liliiflora (xin yi hua)		
	Olea europaea (olive leaf)		
	Platycodon grandiflorus (balloon flower, jie geng)		
	Salvia officinalis (sage)		
	Sambucus nigra (elderberry)		
	Thymus vulgaris (thyme)		
	Trigonella foenum-graecum (fenugreek)		
	Verbascum thapsus (mullein)		
	Vitamin C		
	Vitamin D_3		

[A]Common ingredients in Therapeutic Goods Administration Listed Medicines[58] that are marketed for respiratory tract infection or immune support.

[B]Either avoid coadministration or administer the antiviral drugs at least two hours before or six hours after ingesting the complementary medicine.[33]

CYP, cytochrome P450; PD, pharmacodynamic; PK, pharmacokinetic; RCT, randomised controlled trial.

Sources: Natural Medicines (https://naturalmedicines.therapeuticresearch.com/), University of Liverpool drug–drug interaction resources (www.druginteractions.org/) or IMgateway interaction database (www.imgateway.net/).

the dose, batch or brand of ginseng may destabilise a patient's INR and increase the risk of bleeding or clotting.[9,10]

Interactions can also occur between antihypertensive drugs and several CMs, most notably with *Allium sativum* (garlic). Garlic formulations containing higher amounts of the bioactive sulfur compound allicin have demonstrated additive hypotensive effects.[42]

Interactions between glycaemic drugs and *Allium sativum* (garlic),[43] *Ginkgo biloba* (ginkgo),[44] *P. quinquefolius* (American ginseng),[45] *Hydrastis canadensis* (goldenseal)[46] and *Gymnema sylvestre* (gymnema)[12] could also occur. Clinical monitoring is recommended because of potential additive hypoglycaemic effects or unstable glycaemic control due to pharmacodynamic and/or pharmacokinetic interactions.[12,13,43–45,47]

Interactions between CMs and oral COVID-19 antiviral drugs

Of the three oral COVID-19 antiviral drugs provisionally registered by the Therapeutic Goods Administration in Australia, only ritonavir plus nirmatrelvir has an interaction warning for a CM (St John's wort). However, there are other CMs that could potentially interact with drugs that patients might be taking to prevent or treat COVID-19 infections (Table 3).

The gastrointestinal absorption of the three oral antiviral COVID-19 drugs may be reduced by zinc compounds or *Althaea officinalis* (Marshmallow root). Zinc sulfate has been shown to lower plasma concentrations of ritonavir through chelation in the gut.[48] It is possible that other zinc compounds could also have chelating properties. However, it should be noted that at the time of writing this review, the University of Liverpool's COVID-19 drug interaction checker (www.covid19-druginteractions.org/checker) does not mention the study of Moyle et al[48] and only considers whether zinc is likely to affect the metabolism of ritonavir. Coadministration of marshmallow (*A. officinalis*) root may also reduce the absorption of any three oral antiviral COVID-19 drugs due to the mucilage content of marshmallow root.

As a precaution, patients should avoid CMs with either ingredient, or take the antiviral drugs at least two hours before or six hours after ingestion of the CM.[48]

CMs that induce or inhibit CYP3A4 and/or P-glycoprotein can potentially interact with remdesivir, ritonavir or nirmatrelvir. Pharmacokinetic interactions with molnupiravir are unlikely because it is not metabolised by CYP enzymes or renally excreted.[52]

Taking *Hypericum perforatum* (St John's wort) with ritonavir plus nirmatrelvir should be avoided because there is a theoretical risk that the CM may reduce the plasma concentrations of either drug because of its induction of CYP3A4 and P-glycoprotein, an effect that may take up to two weeks to wear off. Based on this theoretical risk, there is also the potential for a weak interaction between *Hypericum perforatum* (St John's wort) and remdesivir. According to the University of Liverpool's COVID-19 drug interaction checker, strong inducers of CYP3A4 are likely to have a clinically unimportant effect on remdesivir concentrations (~15–30% reduction) and, as such, dose adjustments are not recommended. However, other interaction checkers such as Natural Medicines (https://naturalmedicines.therapeuticresearch.com) take a more cautious approach and recommend against coadministration. Given the limited evidence for molnupiravir,[53] it may still be preferable to prescribe remdesivir despite the theoretical risk of reduced efficacy and, of course, stop *Hypericum perforatum* (St John's wort), at least temporarily.

A controlled trial evaluated the effects of two weeks of *Echinacea purpurea*[51] on ritonavir and another study evaluated the effects of four days of a *Allium sativum* (garlic) product with a low allicin content.[50] Neither of the CMs reduced ritonavir plasma concentrations.[35,36] This might be attributed to ritonavir's potent inhibition of CYP3A4 and P-glycoprotein, which potentially counteracted any induction effects from the CMs.[51]

A pharmacokinetic study of a *Allium sativum* (garlic) product with a high allicin content revealed reduced plasma concentrations of saquinavir, another protease inhibitor,[35] and another case study reported that approximately six stir-fried garlic cloves three times per week reduced serum concentrations of atazanavir, as well as its clinical effectiveness.[54]

Most patients using prescription drugs for COVID-19 are at a high risk of complications. Ensuring optimum drug concentrations is likely to be a priority for these patients, including those who are strong proponents of CM. Therefore, the potential interactions between CMs and drugs prescribed for COVID-19 listed in Table 3 should be discussed with all patients.

Reducing the risk of CM–drug interactions

There is a real opportunity for healthcare professionals to engage in informed conversations that promote the safe and appropriate use of CMs (Table 4).

A CM–drug interaction should be suspected when the clinical presentation correlates with the drug's clinical effects or a known adverse effect. Polypharmacy (five or more medicines) also increases the risk of drug interactions.[5] People living with chronic health conditions are more likely to use CMs alongside multiple over-the-counter and prescription drugs.[4]

Pharmacodynamic interactions are easier to predict because they correlate with the anticipated clinical effects of the compounds. Although the scientific evidence of clinical efficacy is limited for many CMs, these types of interactions should still be considered, even though some may be welcomed, such as improved glycaemic control (Table 3), which may still require the monitoring of blood glucose.

Predicting pharmacokinetic interactions is more difficult. Clinically important interactions with drugs are more likely when there is a narrow therapeutic index and with CMs that are known perpetrators. The risks are also higher with larger doses of constituents known to cause CM–drug interactions. However, the formulation or minimum dose required for an interaction to occur are not always clear from the available research.

Identifying CM–drug interactions is further complicated by the wide variations in CM quality (especially for raw herbs and products purchased outside of Australia) and their different constituent profiles, formulations and doses.[6] CM products, especially herbs when used in a traditional context, often have multiple ingredients that may also interact with each other.[55] Therefore, a CM–drug interaction may be triggered by changing the CM product batch or brand. Unclear labelling and low health literacy can exacerbate these risks; for example, the American, Korean/Chinese and Siberian ginsengs vary in their pharmacological effects and interaction risks. Patients may not realise this and unwittingly switch between CM products containing 'ginseng', and therefore tell their healthcare practitioner that there have been no changes in their CM use.

Close monitoring of CM use or avoidance is warranted when the drug has a narrow therapeutic index or the consequences of an interaction are serious.[56] However, there will be other instances when the benefits of a CM warrant its continuation and other management options should be implemented, such as monitoring clinical outcomes or prescribing another drug with equivalent effectiveness that is unlikely to interact with the CM. Decisions about medicine use, dose adjustments and cessation must also consider patient preferences, including any observed or perceived benefits that are motivators for ongoing use.[37] Shared decision making may improve treatment compliance (Table 4).[57]

Conclusion

Vigilance, an understanding of clinical pharmacology and the nuances of CMs, and effective communication skills are required to prevent and identify unwanted CM–drug interactions.

Key points

- Most Australians who use CMs are also using prescription and over-the-counter medicines.
- Pharmacokinetic CM–drug interactions can alter the absorption, distribution, metabolism and elimination of a drug.
- Pharmacodynamic CM–drug interactions can negate or add to a drug's clinical effects.

Table 4. Identifying and discussing complementary medicine–drug interactions in the context of shared decision making

- Take a full medication history for prescription, over-the-counter and complementary medicines

  Tip: Use non-technical terms that are culturally appropriate and non-judgemental. Explain why you need this information; for example, 'People often use natural therapies, vitamins, herbs, teas, super-foods, and traditional remedies and report benefits. Some can interfere with your medicines, so it's important we talk about them'

- Suspect interactions when there is polypharmacy or the clinical presentation correlates with known pharmacological effects or toxicities of the drug or CM

  Tip: Ask about CM brand changes or starting a new bottle. Explain that herbal constituents can differ between brands and batches

- Use an interaction checker to screen for potential CM–drug interactions

  Tip: Only trust a 'no interaction risk' when searching a comprehensive CM database (Table 1)

- Explain potential risks or benefits from the interaction and whether they are theoretical or proven. Provide consumer information

  Tip: Patients can be sceptical about medical doctors' CM expertise. Be clear about uncertainties, including your information sources. Offer to do more research or follow-up with an expert

- Ask and actively listen to understand reasons for CM/drug choices, preferences/values, risk thresholds

  Tip: Use open-ended questions, be respectful, find out what matters the most and what information sources and opinions influence decisions

- Engage in shared decision making: affirm there are choices, discuss the options (eg stop/adjust drug or CM, use an alternative, monitor), discuss the pros and cons, check understanding, elicit preferences, allow time for deliberation, remain respectful of patient preferences and decisions

  Tip: When making recommendations, acknowledge whether these align with the patient's preferences and any perceived or observed benefits from using the CM. When relevant, involve caregivers (or other key people) in the decision-making process

- Document the discussion, any recommendations and decisions made, and plans to monitor and follow-up

  Tip: Provide written information about key facts, print a copy or excerpt of the consultation notes

CM, complementary medicine.

- Clinically important CM–drug interactions are more likely when there is a narrow therapeutic index, polypharmacy or changes in CM brands and batches.
- The quality use of medicines includes asking patients about CM use and engaging in informed discussions about CM–drug interactions.

Authors

Jennifer Hunter BMed, MScPH, PhD, General Practitioner and Adjunct Associate Professor, The University of Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Camperdown, NSW; Director of Health Research Group Pty Ltd, Sydney, NSW

Joanna E Harnett BHSc, MHSc, PhD, Senior Lecturer, The University of Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, Camperdown, NSW

Competing interests: Both authors have separately received payments for providing expert advice about traditional, complementary and integrative medicine, including nutraceuticals, to industry, government bodies and non-government organisations, and have spoken at workshops, seminars and conferences for which registration, travel and/or accommodation has been paid for by the organisers. JH has received funding from industry to conduct clinical research into the potential role of the microbiome, probiotics and prebiotics in specific conditions.

Funding: None.

Provenance and peer review: Commissioned, externally peer reviewed.

Correspondence to:
joanna.harnett@sydney.edu.au

Acknowledgements

The authors thank Keiran Cooley and Jocelin Chan for their expert advice, and UnityHealth Pty Ltd for providing access to the Integrative Medicine Gateway during the preparation of this manuscript.

References

1. World Health Organization (WHO). Key technical issues of herbal medicines with reference to interaction with other medicines. Geneva, WHO, 2021. Available at www.who.int/publications/i/item/9789240019140 [Accessed 23 March 2023].
2. Barnes J. Quality, efficacy and safety of complementary medicines: Fashions, facts and the future. Efficacy and Safety. Perspectives on complementary and alternative medicine. Routledge, 2019; p. 306–18.
3. Parvez MK, Rishi V. Herb-drug interactions and hepatotoxicity. Curr Drug Metab 2019;20(4):275–82. doi: 10.2174/1389200220666190325141422.
4. Harnett JE, McIntyre E, Steel A, Foley H, Sibbritt D, Adams J. Use of complementary medicine products: A nationally representative cross-sectional survey of 2019 Australian adults. BMJ Open 2019;9(7):e024198.
5. Li Y, Zhang X, Yang L, et al. Association between polypharmacy and mortality in the older adults: A systematic review and meta-analysis. Arch Gerontol Geriatr 2022;100:104630.
6. Coxeter P, McLachlan AJ, Duke C, Roufogalis B. Herb–drug interactions: An evidence based approach. Curr Med Chem 2004;11(11):1513–25.
7. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther 2013;138(1):103–41.
8. Niu J, Straubinger RM, Mager DE. Pharmacodynamic drug-drug interactions. Clin Pharmacol Ther 2019;105(6):1395–1406. doi: 10.1002/cpt.1434.
9. Zhang XL, Chen M, Zhu LL, Zhou Q. Therapeutic risk and benefits of concomitantly using herbal medicines and conventional medicines: From the perspectives of evidence based on randomized controlled trials and clinical risk management. Evid Based Complement Alternat Med 2017;2017:9296404.
10. Tan CSS, Lee SWH. Warfarin and food, herbal or dietary supplement interactions: A systematic review. Br J Clin Pharmacol 2021;87(2):352–74.
11. Sattar A, Willman JE, Kolluri R. Possible warfarin resistance due to interaction with ascorbic acid: Case report and literature review. Am J Health Syst Pharm 2013;70(9):782–86.
12. Thikekar AK, Thomas AB, Chitlange SS. Herb–drug interactions in diabetes mellitus: A review based on pre-clinical and clinical data. Phytother Res 2021;35(9):4763–81.
13. Gupta RC, Chang D, Nammi S, Bensoussan A, Bilinski K, Roufogalis BD. Interactions between antidiabetic drugs and herbs: An overview of mechanisms of action and clinical implications. Diabetol Metab Syndr 2017;9:59.
14. Rombolà L, Scuteri D, Marilisa S, et al. Pharmacokinetic interactions between herbal medicines and drugs: Their mechanisms and clinical relevance. Life (Basel) 2020;10(7):106.
15. Gallicano K, Foster B, Choudhri S. Effect of short-term administration of garlic supplements

on single-dose ritonavir pharmacokinetics in healthy volunteers. Br J Clin Pharmacol 2003;55(2):199–202.
16. Rahman K, Billington D. Dietary supplementation with aged garlic extract inhibits ADP-induced platelet aggregation in humans. J Nutr 2000;130(11):2662–65.
17. Werba JP, Misaka S, Giroli MG, et al. Update of green tea interactions with cardiovascular drugs and putative mechanisms. J Food Drug Anal 2018;26 Suppl 2:S72–77.
18. Gurley BJ, Swain A, Barone GW, et al. Effect of goldenseal (*Hydrastis canadensis*) and kava kava (*Piper methysticum*) supplementation on digoxin pharmacokinetics in humans. Drug Metab Dispos 2007;35(2):240–45.
19. Gurley BJ, Swain A, Hubbard MA, et al. Supplementation with goldenseal (*Hydrastis canadensis*), but not kava kava (*Piper methysticum*), inhibits human CYP3A activity in vivo. Clin Pharmacol Ther 2008;83(1):61–69.
20. Johne A, Brockmöller J, Bauer S, Maurer A, Langheinrich M, Roots I. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). Clin Pharmacol Ther 1999;66(4):338–45.
21. Berry-Bibee EN, Kim MJ, Tepper NK, Riley HE, Curtis KM. Co-administration of St. John's wort and hormonal contraceptives: A systematic review. Contraception 2016;94(6):668–77.
22. Nieminen TH, Hagelberg NM, Saari TI, et al. St John's wort greatly reduces the concentrations of oral oxycodone. Eur J Pain 2010;14(8):854–59.
23. Thu OK, Spigset O, Nilsen OG, Hellum B. Effect of commercial *Rhodiola rosea* on CYP enzyme activity in humans. Eur J Clin Pharmacol 2016;72(3):295–300.
24. Spigset O. Reduced effect of warfarin caused by ubidecarenone. Lancet 1994;344(8933):1372–73.
25. Shalansky S, Lynd L, Richardson K, Ingaszewski A, Kerr C. Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: A longitudinal analysis. Pharmacotherapy 2007;27(9):1237–47.
26. Yu C-P, Yang M-S, Hsu P-W, Lin S-P, Hou Y-C. Bidirectional influences of cranberry on the pharmacokinetics and pharmacodynamics of warfarin with mechanism elucidation. Nutrients 2021;13(9):3219.
27. Penttilä O, Hurme H, Neuvonen P. Effect of zinc sulphate on the absorption of tetracycline and doxycycline in man. Eur Clin Pharmacol 1975;9:131–34.
28. Campbell NR, Kara M, Hasinoff BB, Haddara WM, McKay DW. Norfloxacin interaction with antacids and minerals. Br J Clin Pharmacol 1992;33(1):115–16.
29. Zimmermann P, Curtis N. The influence of probiotics on vaccine responses – a systematic review. Vaccine 2018;36(2):207–13.
30. Chrubasik-Hausmann S, Vlachojannis J, McLachlan AJ. Understanding drug interactions with St John's wort (*Hypericum perforatum* L.): Impact of hyperforin content. J Pharm Pharmacol 2019;71(1):129–38.
31. Mueller SC, Uehleke B, Woehling H, et al. Effect of St John's wort dose and preparations on the pharmacokinetics of digoxin. Clin Pharmacol Ther 2004;75(6):546–57.
32. Nicolussi S, Drewe J, Butterweck V, Meyer zu Schwabedissen HE. Clinical relevance of St. John's wort drug interactions revisited. Br J Clin Pharmacol 2020;177(6):1212–26.
33. Adiwidjaja J, Boddy AV, McLachlan AJ. Physiologically based pharmacokinetic modelling of hyperforin to predict drug interactions with St John's Wort. Clin Pharmacokinet 2019;58(7):911–26. doi: 10.1007/s40262-019-00736-6.
34. Foster BC, Foster MS, Vandenhoek S, et al. An in vitro evaluation of human cytochrome P450 3A4 and P-glycoprotein inhibition by garlic. J Pharm Pharm Sci 2001;4(2):176–84.
35. Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. Clin Infect Dis 2002;34(2):234–38.
36. Asher GN, Corbett AH, Hawke RL. Common herbal dietary supplement–drug interactions. Am Fam Physician 2017;96(2):101–7.
37. Arentz S, Hunter J, Deed G. Integrating traditional and complementary medicine recommendations into clinical practice guidelines for people with diabetes in need of palliative and end-of-life care: A scoping review. J Altern Complement Med 2020;26(7):571–91.
38. Bonetto N, Santelli L, Battistin L, Cagnin A. Serotonin syndrome and rhabdomyolysis induced by concomitant use of triptans, fluoxetine and hypericum. Cephalalgia 2007;27(12):1421–23.
39. Canenguez Benitez JS, Hernandez TE, Sundararajan R, et al. Advantages and disadvantages of using St. John's Wort as a treatment for depression. Cureus 2022;14(9):e29468. doi: 10.7759/cureus.29468.
40. Lippert A, Renner B. Herb–drug interaction in inflammatory diseases: Review of phytomedicine and herbal supplements. J Clin Med 2022;11(6):1567.
41. Knudsen JF, Sokol GH. Potential glucosamine–warfarin interaction resulting in increased international normalized ratio: Case report and review of the literature and MedWatch database. Pharmacotherapy 2008;28(4):540–48.
42. Chan W-JJ, McLachlan AJ, Luca EJ, Harnett JE. Garlic (*Allium sativum* L.) in the management of hypertension and dyslipidemia – a systematic review. J Herb Med 2020;19:100292.
43. Han D-G, Cho S-S, Kwak J-H, Yoon I-S. Medicinal plants and phytochemicals for diabetes mellitus: Pharmacokinetic characteristics and herb–drug interactions. J Pharm Investig 2019;49(6):603–12.
44. Kudolo GB. The effect of 3-month ingestion of *Ginkgo biloba* extract (EGb 761) on pancreatic βcell function in response to glucose loading in individuals with non-insulin-dependent diabetes mellitus. J Clin Pharmacol 2001;41(6):600–11.
45. Vuksan V, Stavro MP, Sievenpiper JL, et al. Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. Diabetes Care 2000;23(9):1221–26.
46. Nguyen JT, Tian D-D, Tanna RS, et al. Assessing transporter-mediated natural product–drug interactions via in vitro–in vivo extrapolation: Clinical evaluation with a probe cocktail. Clin Pharmacol Ther 2021;109(5):1342–52.
47. Devangan S, Varghese B, Johny E, Gurram S, Adela R. The effect of *Gymnema sylvestre* supplementation on glycemic control in type 2 diabetes patients: A systematic review and meta-analysis. Phytother Res 2021;35(12):6802–12.
48. Moyle G, Else L, Jackson A, et al. Coadministration of atazanavir–ritonavir and zinc sulfate: Impact on hyperbilirubinemia and pharmacokinetics. Antimicrob Agents Chemother 2013;57(8):3640–44.
49. Laroche M, Choudhri S, Gallicano K, Foster B. Severe gastrointestinal toxicity with concomitant ingestion of ritonavir and garlic. Can J Infect Dis 1998;9 Suppl A:471P.
50. Gallicano K, Foster B, Choudhri S. Effect of short-term administration of garlic supplements on single-dose ritonavir pharmacokinetics in healthy volunteers. Br J Clin Pharmacol 2003;55(2):199–202.
51. Penzak SR, Robertson SM, Hunt JD, et al. *Echinacea purpurea* significantly induces cytochrome P450 3A activity but does not alter lopinavir–ritonavir exposure in healthy subjects. Pharmacotherapy 2010;30(8):797–805.
52. Atmar RL, Finch N. New perspectives on antimicrobial agents: Molnupiravir and nirmatrelvir/ritonavir for treatment of COVID-19. Antimicrob Agents Chemother 2022;66(8):e0240421. doi: 10.1128/aac.02404-21.
53. Focosi D. Molnupiravir: From hope to epic fail? Viruses 2022;14(11):2560.
54. Duncan A, Mills J. An unusual case of HIV virologic failure during treatment with boosted atazanavir. AIDS 2013; 27(8):1361–62.
55. Gurley BJ, Tonsing-Carter A, Thomas SL, Fifer EK. Clinically relevant herb–micronutrient interactions: When botanicals, minerals, and vitamins collide. Adv Nutr 2018;9(4):524s–32s.
56. Cohen M, Hunter J. Complementary medicine products: Interpreting the evidence base. Intern Med J 2017;47(9):992–98.
57. Deniz S, Akbolat M, Çimen M, Ünal Ö. The mediating role of shared decision-making in the effect of the patient–physician relationship on compliance with treatment. J Patient Exp 2021;8:23743735211018066.
58. Australian Department of Health. Australian Register of Therapeutic Goods. 2023. Available at https://compliance.health.gov.au/artg/ [Accessed 31 March 2023].

correspondence **ajgp@racgp.org.au**