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Herb–drug interactions: an overview of systematic reviews

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OBJECTIVES
The aim of this overview of systematic reviews (SRs) is to evaluate critically the evidence regarding interactions between herbal medicinal products (HMPs) and synthetic drugs.

METHODS
Four electronic databases were searched to identify relevant SRs.

RESULTS
Forty-six SRs of 46 different HMPs met our inclusion criteria. The vast majority of SRs were of poor methodological quality. The majority of these HMPs were not associated with severe herb–drug interactions. Serious herb–drug interactions were noted for *Hypericum perforatum* and *Viscum album*. The most severe interactions resulted in transplant rejection, delayed emergence from anaesthesia, cardiovascular collapse, renal and liver toxicity, cardiotoxicity, bradycardia, hypovolaemic shock, inflammatory reactions with organ fibrosis and death. Moderately severe interactions were noted for *Ginkgo biloba, Panax ginseng, Piper methysticum, Serenoa repens* and *Camellia sinensis*. The most commonly interacting drugs were antiplatelet agents and anticoagulants.

CONCLUSION
The majority of the HMPs evaluated in SRs were not associated with drug interactions with serious consequences. However, the poor quality and the scarcity of the primary data prevent firm conclusions.

Introduction

The prevalence of use of herbal medicinal products (HMPs) is high and continues to increase. This applies to the UK [1] as well as other parts of the world [2]. It is therefore important to be aware of the safety issues associated with the administration of HMPs [3–5]. HMPs contain pharmacologically active ingredients, some of which might interact with synthetic drugs [4] which, in turn, could endanger the health of patients [5–7].

The aim of this article is to provide an overview and critical evaluation of the evidence from systematic reviews (SRs) of herb–drug interactions.

Methods

Electronic literature searches were conducted in January 2012 to identify SRs of herb–drug interactions. The following electronic databases were used: MEDLINE and EMBASE (via OVID), AMED and CINHAL (via EBSCO) and Cochrane Database. Search terms were constructed using 'herbal medicine' and 'adverse events' terms and their derivatives and MeSH terms, and 'review' in the title of the article (details of the search strategy are presented in the appendix). Our own extensive departmental files were hand-searched.

No restrictions of language or time of publication were imposed. Abstracts of reviews thus located were inspected

and those appearing to meet the inclusion criteria were retrieved for further evaluation by both authors. Systematic reviews were defined as articles that included an explicit and repeatable methodology. To get included, SRs had to focus on herb–drug interactions. If, for one specific HMP, multiply SRs were found, the most up-to-date, methodologically sound and independent one was included. Reviews of mixtures of more than one HMP and SRs of polyherbals were excluded. Non-systematic reviews and/or reviews pertaining to the effectiveness of HMPs were also excluded. The methodological quality of all SRs was assessed using the modified Oxman score [8]. This is a validated tool that applies the following criteria for assessing the methodological quality of review articles: reporting of search methods and their comprehensiveness, repeatability of eligibility criteria, avoidance of selection bias and reliability of conclusions. These domains were scored as follows: 1 (fulfilled), 0 (partially fulfilled) or −1 (not fulfilled). A final result of 0 or below means the review has major flaws, 1–2 minor flaws and 3–5 minimal or no flaws.

Results

Our searches generated 4366 articles, of which 4320 had to be excluded (Figure 1). Thus 46 SRs met our inclusion criteria (Table 1) [9–54]. The following herbs were considered to interact with synthetic drugs: *Aloe vera, Boswellia serrata, Calendula officinalis, Camellia sinensis, Cassia senna, Calophyllum thalictroides, Cinnamomum spp., Cimicifuga racemosa, Cnicus benedictus, Commifora mukul, Crataegus spp., Crocus sativus, Curcuma longa, Echinacea spp.,*

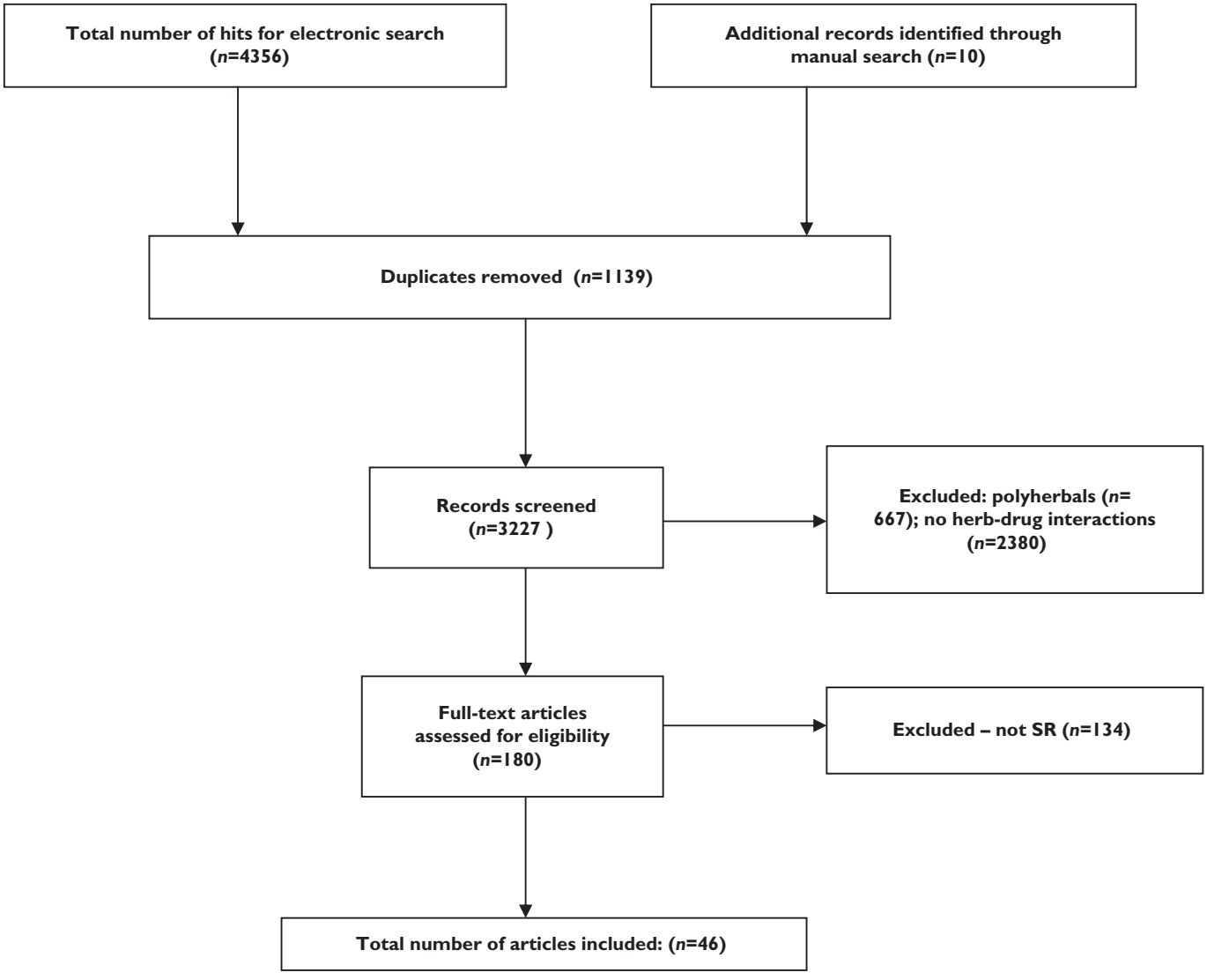

Figure 1
Flow diagram

Table 1

Key data from the included SRs

First author (year) Country [Ref]	Type of primary data	* (*n*)	HMPs evaluated	Drugs that interact	Type of interactions	Clinical outcomes	Mechanism of action	Overall judgment	Quality of SR	Comment
Armbruer (2012) USA [40]	RCTs, NRCT, CCT, SRs, MAs, CR, CS, AS, *in vitro*	<100	Cinnamon (*Cinnamomum spp.*)	1. Antibiotics 2. Anticoagulants or antiplatelets 3. Antidiabetics 4. Antifungals 5. Antilipaemics 6. Antineoplastic agents 7. Antiretroviral agents 8. Cytochrome P450 metabolized agents 9. Anxiolytics 10. Oestrogens 11. Hepatotoxic agents 12. Immunosuppressants 13. Sympathomimetics	Synergism with 1†, 2†, 3†and‡, 4, 5‡, 6†and‡,7, 9‡, 10†, 11‡, 12†and‡, 13‡,	Increased risk of hypoglycaemia, bleeding (theoretical)	Inhibited arachidonic acid release and thromboxane B_2 formation; inhibition of HMG-CoA activity, inhibition of aminopyrine N-demethylation	Only minor concerns	–4	Most interactions were theoretical, limited evidence in humans. Caution for patients with diabetes, autoimmune diseases, liver damage, and for patients using antiarrhythmic agents, antilipemics and anticoagulant or antiplatelet agents.
Barrette (2012) USA [41]	RCTs, CCT, SRs, CR, CS, AS, *in vitro*	<100	Black cohosh (*Cimicifuga racemosa*)	1. Antihistamines 2. Antihypertensives 3. Antilipemic agents 4. Antineoplastic agents 5. Antiseizures 6. OEstrogens 7. Hepatotoxic agents 8. Oral agents 9. Tamoxifen, raloxifene	Inhibition of 1†, 8, synergism with 2, 3†, 4,	GI upset	It is not clear how (or if) black cohosh interacts with estrogens/estrogen receptors and/or progestins	Only minor concerns	–4	Interaction data in this area were lacking. Caution for patients with known estrogen sensitive conditions, such as breast cancer, uterine cancer or endometriosis; in patients on hormone replacement therapy, including tamoxifen or raloxifene; in epileptic patients; in patients on antihypertensive medications; and in patients with liver disease.
Basch (2003) USA [9]	CCTs, CRs	<10	Bitter melon (*Momordica charantia*)	1. Hypoglycaemics	Synergism with 1	Lowered blood glucose concentrations	Decreased hepatic gluconeogenesis, increased hepatic glycogen synthesis; increased pancreatic insulin secretion.	Only minor concerns	–4	Low quality and quantity of the available evidence regarding interactions. Caution for patients with diabetes
Basch (2003) USA [10]	CS, CR	<10	Alfalfa (*Medicago sativa*)	1. Hypoglycaemics 2. Cholesterol lowering agents 3. Chlorpromazine	Synergism with 1 and 2	Increased drug-induced photosensitivity, lowered blood glucose, total cholesterol or LDL	Saponins may reduce cholesterol absorption	Only minor concerns	2	Chlorpromazine was reported to increase drug-induced photosensitivity when taken in combination with alfalfa
Basch (2004) USA [11]	RCT, SRS	<10	Thyme (*Thymus vulgaris*)	1. 5-fluorouracil	Synergism with 1	n.k.	Thymol increases the stratum corneum lipids fluidity and perturbing the barrier integrity of the epidermis	Only minor concerns	–4	Thyme may decrease concentrations of thyroid hormone; caution for patients taking hepatotoxic agents
Basch (2005) USA [42]	RCTs, NRCT, CCT, SRs, MAs, OS, CR, CS, AS, *in vitro*	<100	*Echinacea spp.*	1. Amoxicillin 2. Antineoplastic agents 3. Cytochrome P450-metabolized agents 4. Hepatotoxic agents 5. Hydrophilic agents	Synergism with 2†, 3, 4, 5‡ and inhibition of 3	Rhabdomyolysis, shock, and death (causality questioned)	Selective modulation of the catalytic activity of CYP3A at hepatic and intestinal sites	Only minor concerns	–4	Use cautiously in patients using cytochrome P450-metabolized agents or hepatotoxic drugs

Table 1

Continued

First author (year) Country [Ref]	Type of primary data	* (*n*)	HMPs evaluated	Drugs that interact	Type of interactions	Clinical outcomes	Mechanism of action	Overall judgment	Quality of SR	Comment
Basch (2006) USA [12]	RCTs, CS, comparison study, AS	<10	Calendula (*Calendula officinalis*)	1. Sedatives 2. Antihypertensives	Synergism with 1 and 2‡	n.k.	Insufficient evidence to determine pharmacodynamics/kinetics	Only minor concerns	0	Systemic effects in humans were not clear; caution for patients taking sedatives
Basch (2004) USA [13]	RCTs, NRCT,CS, AS	<10	Lavender (*Lavandula angustifolia Miller*)	1. Sedatives, 2. Anticoagulants, NSAIDs, anti-platelet agents, 3. Anti-seizures 4. Cholesterol lowering agents‡	Synergism with 1, 2, 3 and 4‡	n.k.	Linalool binds to glutamate and increases GABA concentrations‡	Only minor concerns	–4	Use cautiously in patients taking sedatives, anticoagulants, antiplatelet agents and anti-epileptic drugs
Basch (2004) USA [14]	RCTs, NRCTs, SR, comparison study, *in vitro*	<100	Boswellia (*Boswellia serrata*)	1. Leukotriene inhibitors 2. Anti-neoplastic agents†	Inhibition of 1 and synergism with 2†	n.k.	Inhibition of lipoxygenase to produce 5-HETE, LTB4 and HLE†	Only minor concerns	–4	Use cautiously in patients taking leukotriene inhibitors
Basch (2012) USA [43]	RCTs, NRCT, CCT, SRs, OS, cohort study, CR, CS, CCS, AS, *in vitro*	<100	Mistletoe (*Viscum album*)	1. Antidiabetic agents 2. Antihypertensives 3. Antineoplastic agents 4. Cholinergic agents 5. CNS depressants 6. Diuretics 7. Immunosuppressants 8. Thyroid hormones	Synergism with 1†, 2, 3†and‡, 4, 5, 6, inhibition of 7†	Organ fibrosis and death, cardiotoxicity, bradycardia, hypovolaemic shock and CVD collapse, inflammatory reaction	Mistletoe lectins agglutinate human erythrocytes and react with immunoglobulins	Serious concerns	–4	Use cautiously in patients with cardiovascular disease, uncontrolled hyperthyroidism, seizures, glaucoma and diabetics.
Basch (2012) USA [44]	RCTs, NRCT, CCT, SRs, MA, CR, AS, *in vitro*	<100	Hawthorn (*Crataegus spp.*)	1. Alpha agonists 2. Anticoagulants and antiplatelets 3. Antihypertensives 4. Antilipaemic agents 5. β-adrenoceptor blockers 6. Digoxin, digitoxin 7. Phosphodiesterase inhibitors 8. Vasodilators	Inhibition of 1†and‡, 2†, synergism with 3†and‡, 4†and‡, 5‡, 6‡, 7‡, 8‡	Increased risk of bleeding†	Inhibition of thromboxane A_2 biosynthesis†	Only minor concerns	–4	Although possible safe co-administration of hawthorn and cardiac glycosides has been suggested, close monitoring during dose titration is warranted.
Basch (2012) USA [45]	RCTs, CCT, SRs, MAs, CR, AS, *in vitro*	<100	Green tea (*Camellia sinensis*)	1. Analgesics 2. Antiandrogens 3. Antiarthritics 4. Anticoagulants and antiplatelets 5. Antidepressants 6. Antilipaemics 7. Antivirals 8. Cytochrome P450metabolized agents 9. Hepatotoxic agents 10. Oestrogen 11. Hypertensives 12. Hypoglycaemics 13. Sedatives 14. P-glycoprotein modulators 15. Antiseizures 16. β–adrenoceptor agonists	Synergism with 1, 4† and ‡, 6, 7, 9, 15, 16 inhibition of 2, 8, 10, 13, 14†,	Increased risk of toxic effects, hypertensive crisis;, impaired iron metabolism and microcytic anaemia, increased blood pressure; ischaemic stroke	EGCG inhibits the IL-1 beta-induced activity and expression of cyclooxygenase-2 and nitric oxide synthase-2; caffeine acts via blockade of adenosine receptors, and theoretically, may antagonize the effects of adenosine	Some concerns	–4	Use cautiously in patients taking analgesics, antilipaemics, antiseizures, antivirals, β-adrenoceptor blockers, cytochrome P450-metabolized agents, hepatotoxic agents, hormonal agents and sedatives.

Brendler (2006) Germany [15]	RCTs, CS, AS	<100	Devil's claw (*Harpagophytum procumbens*)	1. Anti-arrhythmic agents 2. Inotropic agents 3. Anticoagulant/antiplatelet agents	Synergism with 1‡, inhibition of 2‡	Decreased HR ‡	Release of inflammatory mediators†; inhibition of arachidonic acid metabolism pathways†	Only minor concerns	0 Use with anticoagulant and antiplatelet agents should be approached with caution
Brendler (2012) Germany [46]	RCTs, AS, *in vitro*	<100	Noni (*Morinda citrifolia*)	1. Anti-angiogenic drugs 2. Antibiotics 3. Anticoagulants 4. Antihypertensives 5. Anti-inflammatory agents 6. Hepatotoxic agents 7. Immunosuppressants	Synergism with 1†, 2†, 3‡, 5‡, 6, inhibition of 3, 7‡	Decreased gastric transit time‡, increased risk of hyperkalemia,	Inhibition of copper-induced LDL oxidation; of Ras oncogene function, cell transformation; of the tumour-promoting effect of TNF-a, and activator protein-1 transactivation.	Only minor concerns	–4 Use cautiously in patients using warfarin or other anticoagulants, antihypertensives or ACE inhibitors.
Ceurvels, (2012) USA [47]	CR, AS	<10	Blue cohosh (*Caulophyllum thalictroides*)	1. Antidiabetic agents 2. Cardiovascular drugs 3. Nicotine 4. Oxytocin 5. Cocaine	Synergism with 3 and 5	Coronary vasoconstriction, tachycardia, increase in blood pressure, diaphoresis, abdominal pain, vomiting and muscle weakness	caulosaponin and caulophyllosaponin, have been shown to have labour induction properties	Only minor concerns	–4 Use cautiously in patients who are pregnant or breast-feeding; in patients who smoke or are quitting smoking due to possible nicotine toxicity; and in patients with diabetes
Ernst (2005) UK [16]	CRs	<100	*Ginkgo biloba*	1. Paracetamol (acetaminophen) 2. lisinopril 3. anaesthetics 4. aspirin 5. warfarin 6. ibuprofen	Inhibition of 1, 3, 4, 6	Haemorrhage, bleeding, apraxia, death, haematoma, hyphaema, permanent neurological deficit	Inhibition of platelet aggregation	Some concerns	5 Use cautiously in patients taking anaesthetics, analgesics, anticoagulants and antiplatelet agents
Giles (2005) USA [17]	RCT, OLS, SR	<100	Butterbur (*Petasites hybridus*)	1. Anticholinergics	Synergism with 1	Increased liver enzyme levels	Reduction of smooth muscle spasm; inhibition of lipoxygenase activity and down-regulation of leukotriene synthesis‡	Only minor concerns	1 Administration of butterbur with anticholinergics may not be advisable
Keifer (2007) USA [48]	RCTs, AS, *in vitro*	<10	Peppermint (*Mentha piperita*)	1. Antibiotics 2. Benzoic acid 3. Calcium channel blockers 4. Ciclosporin 5. Cytochrome P450 metabolized agents 6. Oxytetracycline	Synergism with 1,†3,† 6,† and inhibition of 2,† 4,‡ 5†and ‡	n.k.	Menthol and menthyl acetate may inhibit CYP3A4-mediated nifedipine metabolism and increase felodopine concentrations	Only minor concerns	2 No documented interactions in humans.
Nelsen (2002) USA [18]	RCTs, CS, *in vitro*	<100	Red clover (*Trifolium pratense*)	1. Cytochrome P450-metabolized agents 2. HRT and OCPs	Inhibition of 1†, 2 and synergism with 2	Alleviated GrRH, FSH and LH concentrations	Binding to estradiol receptors (estradiol-α and estradiol-β)	Only minor concerns	1 Red clover may have synergistic effects with anticoagulants or antiplatelet agents; use cautiously in patients taking hormonal agents
Sweeney (2005) USA [19]	Case series, *in vitro*, AS	<10	Dandelion *(Taraxacum officinale)*	1. Ciprofloxacin 2. Hypoglycaemic drugs 3. Anticoagulants 4. Cytochrome P450 1A2 and 2E metabolized agents	Inhibition of 1‡, synergism with 3†, 4‡	Inhibition of platelet aggregation†	Sesquiterpenes lactones may act as anti-inflammatory agents; lactones may increase gastric acid secretion; increased bile production and release; inulin may act to buffer blood glucose concentrations	Only minor concerns	–4 Patients using antihypertensive and/or antidiabetic agents or insulin should be monitored closely while using dandelion.

Table 1

Continued

First author (year) Country [Ref]	Type of primary data	* (*n*)	HMPs evaluated	Drugs that interact	Type of interactions	Clinical outcomes	Mechanism of action	Overall judgment	Quality of SR	Comment
Tiffany (2002) USA [20]	RCTs, SR, OS, AS	<100	Horse chestnut seed extract (*Hippocastanaceae*)	1. Hypoglycaemic agents	Synergism with 1‡	n.k.	Inhibition of the normal increase of serum glucose concentrations	Only minor concerns	1	No documented interactions in humans.
Ulbricht (2003) USA [21]	CR, AS	<100	Chaparral (*Larrea tridentate*)	1. Cytochrome P450 metabolized agents	Inhibition of 1‡	Increased renal and liver toxicity (theoretically)	Diminished platelet aggregation; decrease plasma glucose concentrations; blocked cellular respiration and exerted antioxidant effects; inhibited induction of ornithine decarboxylase† and ‡	Only minor concerns	2	Chaparral should be avoided in combination with potentially hepatotoxic agents
Ulbricht (2004) USA [22] [22]	RCTs, NRCT, OS, AS	<100	Belladonna (*Herbae pulvis standardisatus*)	1. Cisapride 2. Tacrine	Inhibition of 1, 2‡	Delayed gastrointestinal transit time	Inhibition of the muscarinic actions of acetylcholine	Only minor concerns	–4	Avoid concomitant use with alcohol, anti-arrhythmics,antidepressants, anticholinergic and drugs that interact with atropine
Ulbricht (2005) USA [23]	RCT, CS, AS	<100	Lemon balm (*Melissa officinalis*)	1. Barbiturates 2. Sedatives 3. Nicotine and scopolamine 4. SSRIs	Synergism with 1‡, 2, inhibition of 4†	Hypnosis‡, sedation	Reduced pituitary and serum TSH concentrations‡	Only minor concerns	0	Use cautiously in patients taking hormonal agents and sedatives
Ulbricht (2005) USA [24]	RCTs, CS, AS	<100	Guggul (*Commifora mukul*)	1. Propranolol 2. Diltiazem 3. Thyroid agents 4. Lipid-lowering agents 5. Anticoagulants, antiplatelet agents	Inhibition of 1, 2, synergism with 3‡, 5	Increased risk of bleeding (theoretical)	Guggulsterones have been reported to function as antagonists of the farsenoid X receptor	Only minor concerns	1	Guggulipid should be used with caution in patients taking thyroid drugs.
Ulbricht (2005) USA [25]	RCTs CRs, *in vitro*	<100	Kava (*Piper methysticum*)	1. Cytochrome P450 substrates 2. Dopamine agonists and antagonists 3. Monoamine oxidase inhibitors 4. Antiplatelet agents 5. Sedatives/CNS depressants	Inhibition of 1†, 2, 3†, and synergism with 5	Coma, sedation, lethargy, drowsiness	Kavalactones or kavapyrones may alter central GABA transmission, blocking ion channels; inhibition of thromboxane synthesis and cyclooxygenase.	Some concerns	3	Anesthesiologists recommend stop taking kava 2–3 weeks prior to surgery; patients with Parkinson's disease should avoid kava. Avoid combining kava with hepatotoxic agents.
Ulbricht (2006) USA [49]	RCTs, SRs, CR, CS, AS, *in vitro*	<100	Saw palmetto (*Serenoa repens*)	1. Androgenic drugs 2. Anti-androgenic drugs 3. Anticoagulants and antiplatelets 4. Antibiotics 5. Antihypertensives 6. Anti inflammatory agents 7. Cytochrome P450 metabolized agents 8. Metronidazole or disulfiram 9. Hormonal agents 10. Immunomodulators	Inhibition of 1, synergism with 2, 3, 4, 6 and 10	Severe intra-operative and cerebral haemorrhage, hypertension, nausea or vomiting	Inhibition of lipooxygenase and cyclooxygenase; exerted activity on estrogen receptors; stimulation of macrophage phagocytosis and NK cell synthesis of interferon-gamma†	Some concerns	–4	Use cautiously in patients with hypertension, hormone-sensitive conditions and bleeding disorders

Ulbricht (2007) USA [27]	RCTs, NRCT, CCT, SRs, MA, CRs, CS, AS	<10	Fenugreek (*Trigonella foenum-graecum*)	1. Anti-arrhythmic agents/cardiac glicosides/potassium depletings 2. Antidiabetic agents 3. Anticoagulants and antiplatelets 4. Antilipaemic agents 5. Laxatives	Synergism with 2, 5 inhibition of 3‡	Increased INR, reduced potassium levels, lowered LDL, TG, and total cholesterol ‡ and †, improved insulin resistance‡	Modulation of beta-glucuronidase and mucinase activities, DNA fragmentation by protodiosgenin; phosphorylation of insulin receptor, or activation of insulin signalling pathway	Only minor concerns	2	Use cautiously in patients taking antidiabetics and antilipemics
Ulbricht (2007) USA [28]	RCT, AS	<10	Banaba (*Lagerstroemia speciosa*)	1. Hypoglycaemic agents	Synergism with 1‡	n.k.	Increase the rate of glucose uptake and decrease the isoprenaline-induced glycerol release	Only minor concerns	1	Lagerstroemin may activate insulin receptors, use cautiously in diabetic patients
Ulbricht (2007) USA [50]	RCTs, CR, AS, *in vitro*	<100	*Aloe vera*	1. Insulin 2. Oral hypoglycemic agents 3. Laxatives 4. Sevoflurane 5. Thyroid hormones 6. Topical hydrocortisone 7. Zidovudine	Synergism with 1, 6 and 7	Potassium depletion, hypokalaemia, increased hypoglycaemic effect	Anthraquinone glycosides act as laxatives; stimulation of β cells	Only minor concerns	2	Use cautiously in patients with diabetes or glucose intolerance. Avoid oral aloe latex in patients with renal insufficiency, cardiac disease, or electrolyte abnormalities
Ulbricht (2008) USA [39]	AS, *in vitro*	<100	Blessed thistle (*Cnicus benedictus*)	1. Antibiotics 2. Anticoagulant and antiplatelet agents 3. Antineoplastic agents	Synergism with 1†, 2†, 3† and ‡	Increasing bleeding risk (theoretical)	Cnicin and arctigenin have exhibited cytotoxic activity against some tumor cells via inhibition of cellular DNA, RNA or protein synthesis†	Only minor concerns	–4	Limited evidence in humans
Ulbricht (2009) USA [29]	RCTs, AS	<10	Chia (*Salvia hispanica*)	1. Anticoagulants and antiplatelets 2. Antihypertensives 3. Antioxidants 4. Cytochrome P450-metabolized agents	Synergism with 1‡, 2,3	Lowered blood pressure	Increased levels of alphalinolenic acid, fibre, protein and magnesium	Only minor concerns	0	Caution is advised as high doses of omega-3 fatty acids in Chia are known to increase the risk of bleeding, use cautiously in patients taking antioxidants
Ulbricht (2009) USA [26]	RCTs, CR	>100	Ginseng (*Panax ginseng*)	1. DHT 2. anticoagulant 3. antidepressants 4. antidiabetics 5. antilipaemics 6. calcium channel blockers 7. digoxin 8. diuretics	Synergism with 1, 4, 5,7 inhibition of 2, 7, 8	Mania, headache, tremor, and insomnia, reduced blood glucose, HbA1c, plasma cholesterol, triglyceride, LDL, and NEFA; elevated HDL, LH, FSH; altered BP	Inhibition of platelet aggregation and CYP2D6	Some concerns	–4	Caution is advised about concomitant use with warfarin, oral hypoglycaemic agents, insulin, antilipaemics anti-arrhythmias hormonal agents diuretics
Ulbricht (2009) USA [35]	RCTs, SR, CRs, AS, *in vitro*,	<100	Green-lipped mussel (*Perna canaliculus*)	1. Anti-inflammatory agents and corticosteroids 2. Leukotriene receptor antagonists	Synergism with 1† and ‡, 2‡	n.k.	Inhibition of lipoxygenase	Only minor concerns	–4	Limited evidence in humans
Ulbricht (2009) USA [51]	Review, NRCT, CS, AS, *in vitro*	<100	Maitake mushroom (*Grifola frondosa*)	1. Antidiabetic agents 2. Antineoplastic agents 3. Antiviral agents 4. Immunosuppressants	Synergism with 2†and‡ 3	n.k.	Beta-glucans are distributed to the liver and spleen with a prolonged half-life	Only minor concerns	–4	Use cautiously in patients using antihypertensives, antidiabetic agents and immunomodulators.

Table 1

Continued

First author (year) Country [Ref]	Type of primary data	* (*n*)	HMPs evaluated	Drugs that interact	Type of interactions	Clinical outcomes	Mechanism of action	Overall judgment	Quality of SR	Comment
Ulbricht (2010) USA [52]	RCTs, CCT, CS, AS, *in vitro*	<100	Reishi mushroom (*Ganoderma lucidum*)	1. Antibiotics 2. Anticoagulant and antiplatelets 3. NSAIDs 4. Antidiabetics 5. Antineoplastic agents 6. Antiviral agents 7. Cardiovascular agents 8. Neurologic agents	Synergism with 1†, 2, 3, 5†and‡, 6† and inhibition of 8	Increased risk of bleeding (theoretical)	Inhibitory activity on angiotensin converting enzyme†	Only minor concerns	–4	Use cautiously in patients using anti-inflamatory agents anticoagulants and antiplatelet agents
Ulbricht (2010) USA [30]	RCTs, CCTs, AS	<10	Stevia (*Stevia rebaudiana*)	1. Sodium monoketocholate 2. Vasodilators 3. Diuretics 4. Calcium channel blockers	Synergism with 1, 2, 3, 4‡	Decreased glucose levels and blood pressure, inhibition of rotavirus	Inhibition of oxidative phosphorylation, ATPase activity, NADH-oxidase activity, succinate-oxidase activity, succinate dehydrogenase, and L-glutamate dehydrogenase†; inhibition of ketogenesis and [14C] CO_2 production from [1-14C] palmitate‡	Only minor concerns	0	Use cautiously in patients using diuretics and antihypertensives
Ulbricht (2010)USA [37]	RCTs, OS, CRs, in vitro	<100	Umckaloabo (*Pelargonium sidoides*)	1. Anticoagulant and antiplatelet agents 2. Cardiovascular agents 3. Hepatotoxic agents 4. Laxatives 5. Immunosuppressants	Synergism with 1†, 3, 4; inhibition of 5†	Cardiovascular complications, hepatotoxicity, increased risk of bleeding (theoretical), laxative effect	Gallic acid may stimulate a release of TNF, stimulate interferon activity and increase NK activity	Only minor concerns	–4	Use cautiously in patients using anticoagulants or antiplatelet agents
Ulbricht (2010)USA [34]	RCTs, CRs, AS, *in vitro*	<100	Rosemary (*Rosmarinus officinalis*)	1. Immunosupressants 2. Cytochrome P450-metabolized agents 3. Anxiolytics 4. Antibiotics 5. Anticoagulants or antiplatelets	Synergism with 3, 4, 5† and ‡	Increased risk of bleeding, hypotension	Inhibition of ACE, and platelets aggregation‡, decreased fibronectin and fibrin‡	Only minor concerns	–4	Use cautiously in patients using salicylates, cytochrome P450 metabolized drugs and anti-diabetic agents
Ulbricht (2010) USA [32]	RCTs, NRCTs, *in vitro*, AS	<100	Spearmint (*Mentha spicata*, *Mentha viridis*)	1. Nephrotoxic agents 2. Hepatotoxic agents 3. Cytochrome P450-metabolized agents	Synergism with 1‡, 2‡, inhibition of 3‡	n.k.	Decreased expression of cytochrome P450scc and cytochrome P450C17 enzymes	Only minor concerns	–4	Interactions in humans are hypothetical
Ulbricht (2011) USA [33]	RCTs, SR, ET, OLS, CS	<100	Saffron (*Crocus sativus*)	1. SSRIs 2. MAOIs 3. Fertility agents 4. Alzheimer's agents 5. Anti hypertensives 6. Anticoagulants or antiplatelets	Synergism with 1, 2, 3, 4, 5 and inhibition of 6† and ‡	n.k.	Trans-crocin-4 may inhibit Abeta fibrillogenesis and platelet aggregation‡	Only minor concerns	–4	Use cautiously in patients using anticoagulants or antiplatelet agents, hormonal agents, antidepressants and antihypertensives
Ulbricht (2011) USA [36]	RCTs, SRs, CCTs,	<100	Senna (*Cassia senna*)	1. Digoxin 2. Anticoagulant and antiplatelet agents 3. Antibiotics 4. Antineoplastics	Synergism with 1†, 2, 3†, 4†	Lowered serum estrogen concentrations and potassium levels; increased risk of excessive bleeding and gallstones	Decreased deoxycholic acid and biliary cholesterol saturation	Only minor concerns	–4	Use cautiously in patients using anticoagulant and antiplatelet agents

Ulbricht (2011) USA [38]	RCT, CCTs, CS, AS	<100	Gymnema (*Gymnema sylvestre*)	1. Antidiabetic agents 2. antilipaemic agents	Synergism with 1, 2	Hypoglycemia	Reductions of serum TG, total cholesterol, VLDL and LDL	Only minor concerns	–4 Supervision is needed in diabetic patients
Ulbricht (2011) USA [53]	RCTs,SRs, CCT, CS, CR	<100	Turmeric (*Curcuma longa*)	1. Paracetamol (acetaminophen) 2. acetylcholinesterase inhibitors 3. amiloride 4. antibiotics 5. anticoagulants and antiplatelets 6. antidiabetic agents 7. antihypertensives 8. Anti-inflammatory agents 9. Antilipemic agents 10. Antineoplastic agents 11. Celecoxib 12. Cytochrome P450-metabolized agents 13. Erythromycin 14. Erythropoietin 15. Hormonal agents 16. NSAIDs 17. Norfloxacin 18. Oxaliplatin 19. P-glycoprotein-regulated drugs 20. Retinol 21. Talinolol 22. Taxol 23. Warfarin	Inhibition of 1†, 12†and‡, 15†, 19, 21 synergism with 2‡, 3†, 4‡, 5† and‡, 6, 8†and‡, 9‡, 10†and‡, 11†and‡, 13†, 14‡, 15‡, 17‡, 18†, 19, 20†, 21†, 23	Increased risk of bleeding, transient hypotension, bradycardia, and vasodilation	Diferuloylmethane is believed to be the principal pharmacological agent responsible for all interactions	Only minor concerns	–4 Use cautiously in patients using beta blockers or those with metabolic syndrome or increased risk of bleeding.
Vora (2012) USA[54]	RCT	<10	Chasteberry (*Vitex agnus-castus*)	1. Prolactin	Synergism with 1 (low doses)	n.k.	Constituents of chasteberry bind to dopamine-2 receptors in the pituitary, thereby inhibiting prolactin secretion†	Only minor concerns	–4 Use cautiously in patients taking oral contraceptives or HRT or in patients taking dopamine agonists or antagonists. Avoid using in patients with hormone sensitive cancers or conditions, in patients who are pregnant or breastfeeding or in women undergoing *in vitro* fertilization.
Whitten (2006) Australia [31]	RCTs	<100	St John's wort (*Hypericum perforatum*)	1. Immunosupressants 2. Antiretrovirals 3. Hormonal therapy 4. CVD drugs 5. Anicancer drugs 6. CNS drugs 7. Antimicrobals	Inhibition of 1, 2, 4, 5, 6 and 7	Transplant rejection, unwanted pregnancy, mania, orofacial dystonia, delayed emergence from anaesthesia, CVD collapse	Induction of CYP3A enzymes and/or intestinal P-glycoprotein	Serious concerns	5 High doses of this HMP cause significant changes in pharmacokinetic measurements consistent with CYP3A induction. Avoid in transplant patients or those requiring anaesthesia.

*Range of primary data. †Based on *in vitro* studies. ‡Based on animal studies.

ACE, angiotensin-converting enzyme; AS, animal study; ATP, Adenosine triphosphate; BP, blood pressure; CAM, complementary and alternative medicine; CCS, case control study; CCT, controlled clinical trial; CNS, central nervous system; CR, case report; CS, case series; CVD, cardiovascular; CYP2D6, cytochrome CYP 2D6; DHT, dihydrotestosterone; EGSG, epigallocatechin gallate; ET, equivalence trial; FSH, follicle stimulating hormone; GABA, gamma-aminobutyric acid; GrRH, gonadotropin releasing hormone; HbA1c, haemoglobin A1c; HLE, human leucocyte elastase; HMG, CoA-hepatic 3-hydroxy-3-methylglutaryl reductase; HDL, high-density lipoprotein; HRT, hormone replacement therapy; INR, International Normalized Ratio; LH, luteinizing hormone; LDL, low-density lipoprotein; LTB_4, leukotriene B_4; MOAI, monoamine oxidase inhibitors**;** NADH, dehydrogenase; NEFA, non-esterified fatty acid; NK, natural killer cells; n.m., not mentioned; n.k., not known; NRCT, non-randomized controlled trial; OCPs, Oral contraceptives; OS, observational study; OLS, open label study; RCT, randomized controlled trial; RRC, retrospective review of cases; SSRIs, Selective serotonin re-uptake inhibitors; SR, systematic review; SRS, spontaneous reporting scheme; TG, triglicerides; TNF, tumour necrosis factor; TSH, Thyroid stimulating hormone; UCT, uncontrolled trial; VLDL, very low density lipoprotein; 5-HETE, 5-hydroxyeicosatetraenoic.

Table 2

The found herb–drug interactions for each class of medication

Class of medication	Herb	Type of interaction Synergism	Antagonism
Alzheimer's agents	Saffron (*Crocus sativus*)	x	
Anaesthetics	Ginkgo (*Ginkgo biloba*)		x
Analgesics	Ginkgo (*Ginkgo biloba*)		x
	Green tea (*Camellia sinensis*)	x	
Anti-arrhythmias	Ginseng (*Panax ginseng*)	x	x
Antibiotics	Rosemary (*Rosmarinus officinalis*)	x	
	Saw palmetto (*Serenoa repens*)	x	
	St John's wort (*Hypericum perforatum*)		x
Anticoagulants and antiplatelet agents	Ginkgo (*Ginkgo biloba*)		x
	Ginseng (*Panax ginseng*)		x
	Guggul (*Commifora mukul*)	x	
	Lavender (*Lavandula angustifolia Miller*)	x	
	Noni (*Morinda citrifolia*)		x
	Reishi mushroom (*Ganoderma lucidum*)	x	
	Saw palmetto (*Serenoa repens*)	x	
	Senna (*Cassia senna*)	x	
	Turmeric (*Curcuma longa*)	x	
Antidiabetics	Aloe (*Aloe vera*)	x	
	Cinnamon (*Cinnamomum spp.*)	x	
	Fenugreek (*Trigonella foenum-graecum*)	x	
	Ginseng (*Panax ginseng*)	x	
	Gymnema (*Gymnema sylvestre*)	x	
	Turmeric (*Curcuma longa*)	x	
Antihypertensives	Black cohosh (*Cimicifuga racemosa*)	x	
	Chia (*Salvia hispanica*)	x	
	Mistletoe (*Viscum album*)	x	
	Saffron (*Crocus sativus*)	x	
	Stevia (*Stevia rebaudiana*)	x	
Anti-inflamatory agents	Aloe (*Aloe vera*)	x	
	Saw palmetto (*Serenoa repens*)	x	
	Reishi mushroom (*Ganoderma lucidum*)	x	
Antilipaemics	Alfalfa (*Medicago sativa*)	x	
	Fenugreek (*Trigonella foenum-graecum*)	x	
	Ginseng (*Panax ginseng*)	x	
	Green tea (*Camellia sinensis*)	x	
	Gymnema (*Gymnema sylvestre*)	x	
Antineoplastics	Black cohosh (*Cimicifuga racemosa*)	x	
	St John's wort (*Hypericum perforatum*)		x
	Thyme (*Thymus vulgaris*)	x	
Anti-oxidants	Chia (*Salvia hispanica*)	x	
Antiseizures	Green tea (*Camellia sinensis*)	x	
	Lavender (*Lavandula angustifolia Miller*)	x	
Antivirals	Aloe (*Aloe vera*)	x	
	Green tea (*Camellia sinensis*)	x	
	Maitake mushroom (*Grifola frondosa*)	x	
	St John's wort (*Hypericum perforatum*)		x
Anxiolytics	Rosemary (*Rosmarinus officinalis*)	x	
β-adrenoceptor blockers	Green tea (*Camellia sinensis*)	x	
	Guggul (*Commifora mukul*)		x
	Turmeric (*Curcuma longa*)		x
Cholinergic agents	Butterbur (*Petasites hybridus*)	x	
	Mistletoe (*Viscum album*)	x	
CNS depressants	**Kava (*Piper methysticum*)**	x	
	Mistletoe (*Viscum album*)	x	
Cytochrome P450-metabolized agents	*Echinacea spp.*	x	x
	Green tea (*Camellia sinensis*)		x
	St John's wort (*Hypericum perforatum*)		x
Dopamine agonists and antagonists	**Kava (*Piper methysticum*)**		x
Diuretics	Ginseng (*Panax ginseng*)		x
	Mistletoe (*Viscum album*)	x	
	Stevia (*Stevia rebaudiana*)	x	
Gastroprotective agents	Belladonna (*Herbae pulvis standardisatus*)		x
Hepatotoxic agents	*Echinacea spp.*	x	
	Green tea (*Camellia sinensis*)	x	
	Noni (*Morinda citrifolia*)	x	
	Umckaloabo (*Pelargonium sidoides*)	x	

Table 2
Continued

Class of medication	Herb	Type of interaction Synergism	Antagonism
Hormonal agents	Chasteberry (*Vitex agnus-castus*)	x	
	Ginseng (*Panax ginseng*)	x	
	Green tea (*Camellia sinensis*)		x
	Red clover (*Trifolium pratense*)	x	x
	Saffron (*Crocus sativus*)	x	
	Saw palmetto (*Serenoa repens*)	x	x
Hypoglycaemics	Alfalfa (*Medicago sativa*)	x	
	Bitter melon (*Momordica charantia*)	x	
Immunomodulators	Saw palmetto (*Serenoa repens*)	x	
	St John's wort (*Hypericum perforatum*)		x
Laxatives	Umckaloabo (*Pelargonium sidoides*)	x	
Leukotriene inhibitors	Boswellia (*Boswellia serrata*)		x
Monoamine oxidase inhibitors	Saffron (*Crocus sativus*)	x	
Sedatives	Calendula (*Calendula officinalis*)	x	
	Green tea (*Camellia sinensis*)		x
	Lavender (*Lavandula angustifolia Miller*)	x	
	Lemon balm (*Melissa officinalis*)	x	
Selective serotonin re-uptake inhibitors	Saffron (*Crocus sativus*)	x	

CNS, central nervous system.

Ganoderma lucidum, Ginkgo biloba, Grifola frondosa, Gymnema sylvestre, Harpagophytum procumbens, Herbae pulvis standardisatus, Hippocastanaceae, Hypericum perforatum, Lagerstroemia speciosa, Larrea tridentate, Lavandula angustifolia miller, Medicago sativa, Melissa officinalis, Mentha piperita, Mentha spicata/Mentha viridis, Momordica charantia, Morinda citrifolia, Panax ginseng, Piper methysticum, Pelargonium sidoides, Perna canaliculus, Petasites hybridus, Rosmarinus officinalis, Serenoa repens, Salvia hispanica, Stevia rebaudiana, Taraxacum officinale, Thymus vulgaris, Trifolium pretense, Trigonella foenum-graecum, Viscum album and *Vitex agnus-castus*.

The following drugs interacted with HMPs (Table 2): anaesthetics [16], anti-arrhythmic agents [15, 27], antibiotics [19, 34, 36, 39, 40, 42, 46, 48, 49, 52, 53], anticoagulants [13, 15, 16, 18, 24, 26, 27, 29, 33, 34, 36, 37, 39, 40, 44–46, 49, 50, 52, 53], anticholinergics [17, 22], antidepressants [25, 26, 33, 45], antidiabetics [26, 27, 38, 40, 43, 47, 50–53], antihypertensives [16, 29, 33, 41, 43–46, 49, 53], anti-inflammatory agents [13, 16, 35, 46, 52, 53], antimicrobials [31], antineoplastics [11, 14, 31, 36, 39–43, 51–53], antiplatelet agents [13, 15, 24, 25, 27, 29, 33, 34, 36, 37, 39, 40, 44, 45, 49, 50, 52, 53], anti-epileptic drugs [13, 41, 45], antivirals [31, 40, 45, 51, 52], calcium channel blockers [24, 26, 30], cholesterol lowering agents [10, 13, 24, 26, 27, 40, 41, 44, 45, 50, 53], CYP-450 metabolized agents [18, 21, 25, 29, 32, 34, 40, 42, 45, 48, 49, 53], diuretics [26, 30, 43], hormonal agents [18, 24, 26, 31, 40, 41, 43, 45, 49, 53, 54], hypoglycaemics [9, 10, 19, 20, 28], immunnosupressants [31, 34, 37, 40, 43, 46, 48] laxatives [27, 37, 50], leukotriene inhibitors [14], sedatives [12, 13, 23, 25, 45], selective serotonin re-uptake inhibitors [23, 33] and vasolidators [30, 44].

These interactions were thought to cause a wide variety of clinical outcomes such as altered hormone concentrations [18], apraxia, death, haematoma, hyphaema, permanent neurological deficit [16], bradycardia and vasodilation [53], cardiovascular complications, hepatotoxicity [37], coma, sedation, lethargy, drowsiness [25], coronary vasoconstriction, tachycardia, diaphoresis, abdominal pain, muscle weakness [47], gastrointestinal upset [41], haemorrhage, bleeding [34], increased body weight, diarrhoea, decreased blood haemoglobin and altered calcium serum concentrations, hypoglycaemia [10, 38], increased liver enzyme levels [17], mania, headache, tremor and insomnia [26], microcytic anaemia, ischaemic stroke [45], organ fibrosis and death, cardiotoxicity, hypovolaemic shock, inflammatory reaction [43], potassium depletion, hypokalaemia [50], rhabdomyolysis, shock and death [42], severe intra-operative and cerebral haemorrhage, hypertension, nausea or vomiting [49], transplant rejection, unwanted pregnancy, mania, orofacial dystonia, delayed emergence from anaesthesia, cardiovascular collapse [31].

Thirteen SRs were based on less than 10 primary reports [9–13, 19, 27–30, 47, 48, 54], 32 were based on less than 100 primary reports [14–18, 20–25, 31–46, 49–53] and one SR was based on more than 100 primary reports [26]. The SRs included human studies [9–11, 16–18, 23–27, 29, 31, 33, 34, 36–38, 40–47, 49–54], animal studies [12, 13, 15, 19–24, 27–30, 32–35, 39, 40, 42–46, 48, 51–53] or *in vitro* experiments [14, 18, 19, 23, 25, 33–37, 39–46, 48, 51–53]. Some HMPs acted as inhibitors/antagonists [16, 21, 22, 31] while others acted as agonists/synergists [9–13, 17, 20, 28–30, 34–36, 38–40, 47, 50, 51, 54]. In nine

Table 3

Quality ratings for included systematic reviews of HMPs

Study (year) [ref]	Search methods? (a)	Search comprehensive? (b)	Inclusion criteria? (c)	Bias avoided? (d)	Conclusions supported? (e)	Sum
Armbruer (2012) [40]	–1	–1	–1	–1	0	–4
Barrette (2012) [41]	–1	–1	–1	–1	0	–4
Basch (2003) [9]	–1	–1	–1	–1	0	–4
Basch (2003) [10]	1	1	0	–1	1	2
Basch (2004) [11]	–1	–1	–1	–1	0	–4
Basch (2006) [12]	0	1	0	–1	0	0
Basch (2004) [13]	–1	–1	–1	–1	0	–4
Basch (2004) [14]	–1	–1	–1	–1	0	–4
Basch (2005) [42]	–1	–1	–1	–1	0	–4
Basch (2012) [43]	–1	–1	–1	–1	0	–4
Basch (2012) [44]	–1	–1	–1	–1	0	–4
Basch (2012) [45]	–1	–1	–1	–1	0	–4
Brendler (2006) [15]	0	1	0	–1	0	0
Brendler (2012) [46]	–1	–1	–1	–1	0	–4
Ceurvels (2012) [47]	–1	–1	–1	–1	0	–4
Ernst (2005) [16]	1	1	1	1	1	5
Giles (2005) [17]	0	1	0	–1	1	1
Keifer (2007) [48]	1	1	0	–1	1	2
Nelsen (2002) [18]	1	1	–1	–1	1	1
Sweeney (2005) [19]	–1	–1	–1	–1	1	–4
Tiffany (2002) [20]	1	1	0	–1	0	1
Ulbricht (2003) [21]	1	1	0	–1	1	2
Ulbricht (2004) [22]	–1	–1	–1	–1	1	–4
Ulbricht (2005) [23]	0	1	0	–1	0	0
Ulbricht (2005) [24]	0	1	0	–1	1	1
Ulbricht (2005) [25]	1	1	1	–1	1	3
Ulbricht (2006) [49]	–1	–1	–1	–1	1	–4
Ulbricht (2007) [27]	1	1	0	–1	1	2
Ulbricht (2007) [28]	1	1	0	–1	0	1
Ulbricht (2007) [50]	1	1	0	–1	1	2
Ulbricht (2008) [39]	–1	–1	–1	–1	0	–4
Ulbricht (2009) [29]	0	1	0	–1	0	0
Ulbricht (2009) [35]	–1	–1	–1	–1	0	–4
Ulbricht (2009) [26]	–1	–1	–1	–1	0	–4
Ulbricht (2009) [51]	–1	–1	–1	–1	0	–4
Ulbricht (2010) [52]	–1	–1	–1	–1	0	–4
Ulbricht (2010) [30]	0	1	0	–1	0	0
Ulbricht (2010) [37]	–1	–1	–1	–1	0	–4
Ulbricht (2010) [34]	–1	–1	–1	–1	0	–4
Ulbricht (2010) [32]	–1	–1	–1	–1	0	–4
Ulbricht (2011) [33]	–1	–1	–1	–1	0	–4
Ulbricht (2011) [36]	–1	–1	–1	–1	0	–4
Ulbricht (2011) [38]	–1	–1	–1	–1	0	–4
Ulbricht (2011) [53]	–1	–1	–1	–1	0	–4
Vora (2012) [54]	–1	–1	–1	–1	0	–4
Whitten (2006) [31]	1	1	1	1	1	5

Scoring: each question is scored as 1, 0 or –1; A score of 0 or below means the review has major flaws, 1–2 minor flaws and 3–5 minimal or no flaws.

1 means that: (a) the review states the databases used, date of most recent searches and some mention of search terms; (b) the review searches at least 2 databases and looks at other sources; (c) the review states the criteria used for deciding which studies to include in the overview; (d) the review reports how many studies were identified by searches, numbers excluded and appropriate reasons for excluding them; (e) the conclusions made by the author(s) are supported by the data and/or analysis reported in the review.

0 means that the above mentioned criteria were partially fulfilled.

–1 means that none of the above criteria was fulfilled.

This is an operationalization of the Oxman criteria [8], adapted from reference [55].

Table 4
The most clinically important herb–drug interactions

HMP	Synthetic drug	Clinical outcome
Ginkgo	Anticoagulants, anti-inflammatory agents, antihypertensives, anaesthetics	Haemorrhage, apraxia, haematoma, hyphaema, permanent neurological deficit, death
Ginseng	Antidepressants, antidiabetics, anticoagulants, calcium channel blockers, cholesterol lowering agents, diuretics, hormonal agents	Inhibition of platelet aggregation, reduced platelet adhesiveness, hypoglycaemia, changes in blood pressure and heart rate, mania, headache, tremor, insomnia
Kava	Antidepressants, antiplatelets, CYP-450 metabolized agents, sedatives	Coma, sedation, lethargy, drowsiness
St John's wort	Antineoplastics, antimicrobials, antiretrovirals, hormonal agents, immunnosupressants	Transplant rejection, unwanted pregnancy, delayed emergence from anaesthesia, CVD collapse

SRs, HMPs acted both as inhibitors and synergists [14, 15, 18, 19, 23–27, 32, 33, 37, 41–46, 48, 49, 52, 53]. For 39 HMPs, only minor concerns were raised regarding interactions [9–15, 17–24, 27–30, 32–42, 44, 46–48, 50–54], five raised some concerns [16, 25, 26, 45, 49] and two raised serious concerns [31, 43].

Only three SRs were of excellent methodological quality [16, 25, 31], 10 had minor deficits [10, 17, 18, 20, 21, 24, 27, 28, 48, 50] and 20 had major methodological flaws [9, 11–15, 19, 22, 23, 26, 29, 30, 32–47, 49, 51–54] (Table 3). Conflicts of interest of the authors were mentioned in only one SR [31]. The source of funding was mentioned in only two SRs [20, 21].

Discussion

This article was aimed at providing an overview of SRs of herb–drug interactions. Forty-six SRs could be included. Thirty-nine of the HMPs submitted to SRs did not interact with drugs [9–20, 22–24, 27–30, 32–42, 44, 46–48, 50–54]. Eight HMPs had the potential for such interactions [21, 25, 26, 31, 43, 45, 49]. The interactions caused mostly mild to severe adverse effects (AEs). The HMPs implicated were ginkgo, ginseng, green tea, kava, mistletoe, saw palmetto and St John's wort (Tables 1, 2 and 4).

The most common interacting drugs were anticoagulants [13, 15, 16, 18, 24, 26, 27, 29, 33, 34, 36, 37, 39, 40, 44–46, 49, 50, 52, 53] and antiplatelet agents [13, 15, 24, 25, 27, 29, 33, 34, 36, 37, 39, 40, 44, 45, 49, 50, 52, 53]. The most probable mechanisms of these interactions involve an inhibition of thromboxane synthesis and cyclooxygenase. Some herbs acted as inhibitors/antagonists of drugs [16, 21, 22, 31] whereas others acted as agonists/synergists [9–13, 17, 20, 28–30, 34–36, 38–40, 47, 50, 51, 54]. In nine SRs, there was a bimodal mode of action causing both antagonism and synergism [14, 15, 18, 19, 23–27, 32, 33, 37, 41–46, 48, 49, 52, 53].

The methodological quality of the included SRs was frequently inadequate (Table 3). Many of the articles that scored poorly on our quality rating were monograph-type publications which are not designed as typical systematic reviews. As these articles do contribute relevant information and are relatively frequent in the literature about herbal medicine, we decided to include them in our overview.

Thirty-nine HMPs were reported not to interact with synthetic drugs. However, this information may be unreliable because of the frequently poor quality of the primary data that missed detection of herb–drug interactions and subsequent AEs. In 10 SRs, herb–drug interactions were hypothetical as the primary research was based on *in vitro* and/or animal studies. This overview suggests that the quality of research on herb–drug interactions is often wanting. It also reveals that there is still paucity of such investigations. As a consequence, therapeutic decisions can be hampered. To make progress in this area, we need more effective monitoring systems, better implementation of existing regulations, better quality of reporting and more reliable SRs.

The present analysis has several limitations. Although comprehensive searches were conducted, there is no guarantee that all relevant SRs were located. Furthermore, any overview of SRs is susceptible to publication bias. As we only included SRs, our overview cannot provide information on HMPs for which no SR is available.

Conclusion

In conclusion, the majority of SRs revealed moderately severe or minor interactions between HMPs and drugs. Some HMPs, however, do interact with drugs posing severe health threats. Due to the limited quality and scarcity of the primary data, these conclusions should be treated with caution.

Competing Interests

There are no competing interests to declare.

Appendix 1 Search strategy for MEDLINE

1	(herb$ adj3 (caplet$ or capsule$ or compound$ or cream$ or decoction$ or drug$ or essence$ or extract$ or formul$ or heal$ or Infus$ or juice$ or medic$ or mixture$ or powder$ or prepar$ or prescri$ or product or products or remed$ or supplement$ or tablet$ or tea or teas or therap$ or tincture$ or tisane$ or treatment$)).ti,ab.
2	Herbal$.ti,ab.
3	(plant$ adj3 (caplet$ or capsule$ or compound$ or cream$ or decoction$ or drug$ or essence$ or extract$ or formul$ or heal$ or herb$ or Infus$ or juice$ or medic$ or mixture$ or powder$ or prepar$ or prescri$ or product or products or remed$ or supplement$ or tablet$ or tea or teas or therap$ or tincture$ or tisane$ or treatment$)).ti,ab.
4	(phytodrug$ or phytomed$ or phytopharmac$ or phytother$ or phytochemical$).ti,ab.
5	((natural$ or naturo$) adj3 (caplet$ or capsule$ or compound$ or cream$ or decoction$ or drug$ or essence$ or extract$ or formul$ or herb$ or Infus$ or juice$ or medic$ or mixture$ or powder$ or prepar$ or prescri$ or product or products or remed$ or supplement$ or tablet$ or tea or teas or therap$ or tincture$ or tisane$ or treatment$)).ti,ab.
6	(botanical$ adj3 (caplet$ or capsule$ or compound$ or cream$ or decoction$ or drug$ or essence$ or extract$ or formul$ or heal$ or herb$ or Infus$ or juice$ or medic$ or mixture$ or powder$ or prepar$ or prescri$ or product or products or remed$ or supplement$ or tablet$ or tea or teas or therap$ or tincture$ or tisane$ or treatment$)).ti,ab.
7	(traditional adj3 (caplet$ or capsule$ or compound$ or cream$ or decoction$ or drug$ or essence$ or extract$ or formul$ or herb$ or Infus$ or juice$ or medic$ or mixture$ or powder$ or prepar$ or prescri$ or product or products or remed$ or supplement$ or tablet$ or tea or teas or tincture$ or tisane$)).ti,ab.
8	(Chinese adj3 (caplet$ or capsule$ or compound$ or cream$ or decoction$ or drug$ or essence$ or extract$ or formul$ or herb$ or Infus$ or juice$ or medic$ or mixture$ or powder$ or prepar$ or prescri$ or product or products or remed$ or supplement$ or tablet$ or tea or teas or tincture$ or tisane$)).ti,ab.
9	(Ethnobotan$ or pharmacogno$ or Ethnopharmaco$ or ethnomedic$).ti,ab.
10	(Ayur ved$ or Ayurved$ or kampo or siddha or unani).ti,ab.
11	(folk adj3 (caplet$ or capsule$ or compound$ or cream$ or decoction$ or drug$ or essence$ or extract$ or formul$ or herb$ or Infus$ or juice$ or medic$ or mixture$ or powder$ or prepar$ or prescri$ or product or products or remed$ or supplement$ or tablet$ or tea or teas or tincture$ or tisane$)).ti,ab.
12	exp Ethnobotany/
13	exp Phytotherapy/
14	exp Plants, Medicinal/
15	exp Herb–Drug Interactions/
16	exp Plant Exudates/
17	exp Materia Medica/
18	exp Herbal Medicine/
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	complicat$.ti,ab.
21	(safe or safety or risk$).ti,ab.
22	Side effect$.ti,ab.
23	(tolerate or tolerability or tolerance or hypersensativ$ or aggravat$).ti,ab.
24	(Adverse adj3 (effect$ or event$ or Interaction$ or outcome$ or Reaction$ or response$)).ti,ab.
25	(Uninten$ adj3 (effect$ or event$ or Interaction$ or outcome$ or Reaction$ or response$)).ti,ab.
26	(Unwanted adj3 (effect$ or event$ or Interaction$ or outcome$ or Reaction$ or response$)).ti,ab.
27	(Unexpected adj3 (effect$ or event$ or Interaction$ or outcome$ or Reaction$ or response$)).ti,ab.
28	(Undesir$ adj3 (effect$ or event$ or Interaction$ or outcome$ or Reaction$ or response$)).ti,ab.
29	(harm$ adj3 (effect$ or event$ or Interaction$ or outcome$ or Reaction$ or response$)).ti,ab.
30	(Toxic$ or Adulterat$ or Contaminat$ or Poison$ or hepatotoxic$).ti,ab.
31	(Aftereffect or after effect).ti,ab.
32	exp Drug Toxicity/
33	exp Drug Contamination/
34	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	Review$.ti.
36	19 and 34 and 35

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