Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review

H.-H. Tsai,¹,² H.-W. Lin,¹,²,³ A. Simon Pickard,³,⁴,⁵ H.-Y. Tsai,¹,² G. B. Mahady⁵

SUMMARY

Background and Aims: The use of herbs and dietary supplements (HDS) alone or concomitantly with medications can potentially increase the risk of adverse events experienced by the patients. This review aims to evaluate the documented HDS-drug interactions and contraindications. Methods: A structured literature review was conducted on PubMed, EMBASE, Cochrane Library, tertiary literature, and Internet. Results: While 85 primary literatures, six books and two web sites were reviewed for a total of 1,491 unique pairs of HDS-drug interactions, 213 HDS entities and 509 medications were involved. HDS products containing St. John’s Wort, magnesium, calcium, iron, and ginkgo had the greatest number of documented interactions with medications. Warfarin, insulin, aspirin, digoxin, and ticlopidine had the greatest number of reported interactions with HDS. Medications affecting the central nervous system or cardiovascular system had more documented interactions with HDS. Of the 882 HDS-drug interactions being described its mechanism and severity, 42.3% were due to altered pharmacokinetics and 240 were described as major interactions. Of the 152 identified HDS contraindications, the most frequent involved gastrointestinal (16.4%), neurological (14.5%), and renal/genitourinary diseases (12.5%). Flaxseed, echinacea, and yohimbine had the largest number of documented contraindications. Conclusions: Although HDS-drug interactions and contraindications primarily concerned a relatively small subset of commonly used medications and HDS entities, this review provides the summary to identify patients, HDS products, and medications that are more susceptible to HDS-drug interactions and contraindications. The findings would facilitate the health-care professionals to communicate these documented interactions and contraindications to their patients and/or caregivers thereby preventing serious adverse events and improving desired therapeutic outcomes.

Introduction

The marketing and consumer use of herbs and dietary supplements (HDS) has risen dramatically in the USA over the past two decades (1,2). It is estimated that > 50% of patients with chronic diseases or cancers ever use HDS (3), and nearly one-fifth of patients take HDS products concomitantly with prescription medications (4,5). Despite their widespread use, the potential risks associated with combining HDS with other medications are poorly understood by these consumers. Although many HDS users believe that HDS are safe (6), HDS products have been reported to be associated with mild-to-severe adverse effects such as heart problems, chest pain, abdominal pain and headache (2,7,8). Because a majority of patients often fail to disclose that they have taken HDS products to their healthcare providers, e.g. one study estimated only 30% disclosure (9), patient-provider communication concerning the risks and benefits of HDS is critically important.

A major challenge for healthcare providers in counselling patients about HDS is that the available clinical evidence may be ambiguous and sometimes conflicting for HDS adverse events and drug interactions (10,11). Also, there are often practice-based barriers to identifying the evidence on HDS–drug interactions (12), including lack of familiarity or access to HDS-related textbooks and databases (13,14). In general, fewer and less rigorous studies
are available for HDS than that of prescription drugs, particularly with respect to randomised controlled clinical trials (15). Many available references for HDS list numerous ‘potential HDS–drug interactions’ with little clinical significance or risk. Many reference books are replete with errors that serve only to confuse healthcare practitioners or consumers. The aim of this review was to provide healthcare professionals with a resource that concisely summarises the scientific evidence for HDS–drug interactions and contraindications from 2000 to 2010.

Methods

Evidence resources and literature search
This review of HDS–drug interactions and contraindications focused on the evidence in the primary literature and tertiary literature (i.e. textbooks) related to HDS or drug interactions (16–21). Important online resources about HDS, including the website of National Center for Complementary and Alternative Medicine (NCCAM) (22), and Office of Dietary Supplements (23) were also included. The definition of HDS used for this study was the official definition of dietary supplements as stated in the Dietary Supplement Health and Education Act of 1994 (DSHEA) (24). HDS refers to any herbal product or dietary supplement product containing one of the following ingredients: vitamin, mineral, other botanical, amino acid, or other dietary substance. Thus, traditional foods or fruit products, not listed in the definition (e.g. avocado, grapefruit, and onion, etc.), were not included in this review.

The primary literature was obtained by searching databases, i.e. MEDLINE (via PubMed), EMBASE and Cochrane Library. Search terms included, but were not limited to the medical subject headings (MeSH terms) or key words that encompassed ‘herb drug interactions’, ‘dietary supplements’ OR ‘vitamins’ OR ‘minerals’ OR ‘amino acids’ OR ‘botanical’ OR ‘herbal medicine’ OR ‘phytotherapy’ combined with ‘contraindications’ OR ‘drug interactions’. The searches were performed in English only for the period of January 2000 to December 2010. The articles were selected based on the titles and abstracts and reviewed independently by two authors (HHT, HWL). Literature without related information, including studies regarding efficacy of HDS, regulation of HDS or methods of assay, was excluded. All relevant articles were selected without restriction for animal studies, clinical trials, observational studies (including case reports) or review articles.

Data extraction and synthesis
Two standardised data abstraction checklists were developed and used to perform the review (one for the HDS–medication interactions and the other for HDS contraindications). All pairs of HDS–drug interactions documented in the retrieved literature sources (except for those interaction pairs with consequences that may benefit to users) were extracted. Because most HDS products or ingredients are not recommended for use during pregnancy or lactation (25), documented contraindications for these conditions were not further reviewed. All relevant data were extracted, compiled and classified all by one qualified reviewer, and then validated by another. Any disagreements related to the abstraction of data were resolved by consensus.

We grouped HDS products/ingredients into three categories: herb/botanical, vitamin/mineral/amino acid (VMA) and others. The most common drugs were grouped according to the Anatomical Therapeutic Chemical (ATC) classification system (26). Possible mechanisms and the severity ratings of each pair of interactions were retrieved using the Interactions database in MicroMedex® (27) and ‘Natural Product/Drug Interaction Checker’ in Natural Medicines Comprehensive Database® (NMCD®) (28). We categorised the mechanisms for pairs of interactions into four types: pharmacokinetics, pharmacodynamics, both (pharmacokinetics plus pharmacodynamics) and unknown. The severity of each documented interaction was categorised as contraindicated, major, moderate and minor based upon MicroMedex®, and major, moderate and minor based upon NMCD®, respectively. The definitions of ‘major’, ‘moderate’ and ‘minor’ were similar in these two databases. For instance, a major interaction may cause life-threatening damage and/or serious adverse effect(s), and a minor interaction would result in a negligible effect(s). However, contraindicated interactions were rated as ‘major’ severity in NMCD®. The types of contraindications were categorised based on Goldman: Cecil Medicine® (29). All data were compiled and managed using an Excel spreadsheet. Descriptive analyses to define the frequency or proportion of the evidence associated with the interaction pairs, the corresponding mechanisms and severity ratings of interactions and the types of contraindications for certain populations or patients was performed.

Results

Literature search
Finally, 461 articles of primary literature were initially identified. Eighty-five articles with full text, including 54 review articles, other than the 6 books and 2 web sites were selected for further review (Figure 1). The summaries of the animal studies, observational studies and clinical trials to retrieve
information about HDS–drug interactions and contraindications for the original studies are listed in Tables 1–3, respectively. The summaries of the retrieved books and reviewed articles to retrieve information about HDS–drug interactions and contraindications were listed in Appendices 1 and 2, respectively. Among the original studies (n = 31), more than half (n = 16) were clinical trials. All of these articles contained information about HDS–drug interactions (12,30–113), but only five articles provided descriptive information about HDS contraindications (55–57,59,102).

Quantity of retrieved evidence
After excluding the evidence regarding HDS not recommended for human use (i.e. anvirzel, belladonna, chaparral, comfrey, ephedra and pennyroyal) (16,19,21–23) and the duplicates, a total of 1491 unique pairs of documented interactions between HDS and individual drugs were identified. Among these pairs, 814 pairs (54.6%) were retrieved from the primary literature, 1018 pairs (68.3%) from books and only 23 pairs of interactions were identified in the two reviewed web sites. Among these interactions, the corresponding mechanism and severity was determined for 507 pairs (34.0%) using MicroMedex® and 763 pairs (51.2%) in the NMCD® online database. In total, 882 pairs (59.2%) of documented HDS–drug interactions were identified for their potential mechanism and severity. In terms of contraindications, there were 128, 15 and 9 documented HDS contraindications retrieved from books, primary articles and web sites, respectively, for a total of 152.

HDS–drug interactions
Among all included interactions between HDS and individual drugs, 166 different herbs/botanical products, 28 VMA and 19 other supplements accounted for 890 pairs (59.7%), 529 pairs (35.5%) and 72 pairs (4.8%) of documented interactions, respectively (Figure 2). The top five herbs/botanical products, which were documented to have the most interactions with individual medications, were St John’s Wort (Hypericum perforatum), ginkgo (Ginkgo biloba), kava (Piper methysticum), digitalis (Digitalis purpurea) and willow (Salix alba). For example, St John’s Wort, magnesium, calcium, iron and ginkgo have been documented to interact with 147, 102, 75, 71 and 51 individual medications, respectively. Furthermore, a total of 509 unique drugs contributed to the 1491 documented pairs of interactions with HDS. The majority of these medications (n = 100) were categorised as treatment for central nervous system (CNS), second were those medications affecting the cardiovascular system and then systemic anti-infective drugs (n = 90 and 75, respectively).
### Table 1 Summary of the included animal studies to retrieve information about HDS–drug interactions

| Reference         | HDS                                                                 | Medication                        | Animal model (number)          | Study design                  | Outcome measures     | Dose dependent | Major findings                                                                 |
|-------------------|----------------------------------------------------------------------|-----------------------------------|--------------------------------|------------------------------|----------------------|----------------|--------------------------------------------------------------------------------|
| Chiang et al. (61) | Water extract of crude *Pueraria lobata* (oral)                      | Methotrexate (oral and intravenous) | Rats (7 in each group)         | Parallel design              | Pharmacokinetic parameters | Yes            | *Pueraria lobata* significantly decreased the elimination of methotrexate       |
| Jan et al. (67)    | 1. Extract of dry *Evodia rutaecarpa* (Wu-Chu-Yu) 2. Commercial herbal extract preparation of Wu-Chu-Yu-Tang (gastrogavage). | Theophylline (intravenous)        | Rats (6 in each group)         | Randomised parallel design   | Pharmacokinetic parameters | Yes            | Theophylline level was significantly decreased                               |
| Tang et al. (83)   | Commercial extract of *Ginkgo biloba* (oral)                         | Theophylline (oral and intravenous) | Rats (6 in each group)         | Randomised parallel design   | Pharmacokinetic parameters | Yes            | Ginkgo significantly increased the total clearance, and significantly reduced the AUC of theophylline |
| Okonta et al. (94) | Extract of fresh ginger (oral)                                      | Metronidazole (oral)              | Rabbit (5)                     | Crossover study              | Pharmacokinetic parameters | No data         | Ginger significantly increased the absorption and plasma half-life, and significantly decreased the elimination rate constant and clearance of metronidazole |
| Chang et al. (100) | Silymarin, silibinin dissolved in ethanol and PEG2000 (oral)         | Trazodone (intravenous)           | Rats (6 in each group)         | Randomised parallel design   | Pharmacokinetic parameters | Biliary excretion | No marked effects of silymarin and silibinin on the pharmacokinetics of trazodone under normal daily doses |
| Chien et al. (109) | Extract of crude *Andrographis paniculata* and major components (oral) | Theophylline (intravenous)        | Rats (9 in control group and 6 in each studied group) | Randomised parallel design | Pharmacokinetic parameters | Major component of HDS. | *Andrographis paniculata* increased elimination of theophylline, and chronic use of *A. paniculata* could elevate the concentration of theophylline |

HDS, herbs and dietary supplements; AUC, area under concentration curve.
| Reference      | HDS                      | Medication          | Study design       | Population (number of participants) | Outcome measures                                                                 | Evidence resources of interactions                                                                 | Results related to HDS–drug interactions                                                                 |
|----------------|--------------------------|---------------------|--------------------|-------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Barone et al. (34) | St John’s wort            | Cyclosporine        | Case report        | Transplant recipients \(n = 2\)    | No mention                                                                      | Cyclosporin concentrations were consistently subtherapeutic                                          | Six patients were identified at risk for seven known herb–drug interactions                             |
| Rogers et al. (38)  | Herbs                    | General             | Survey             | Emergency department patients with heart disease, diabetes, psychiatric disorders and/or hypertension \(n = 944\) | Prevalence and occurrence of severe herb–drug interactions                       | No mention                                                                                         | Six patients were identified at risk for seven known herb–drug interactions                             |
| Dergal et al. (40)  | Herbal medicines         | Prescription and over-the-counter drugs | Survey             | Older adults \( \geq 65\) attending a memory clinic \(n = 195\) | The frequency of potential interactions between herbal medicines and conventional drug therapies | Book, medical literature identified in MEDLINE                                                       | There were 11 potential herb–drug interactions in nine patients                                         |
| Ly et al. (41)      | Dietary supplements       | Prescription drugs  | Survey             | Veterans \( \geq 65\) \(n = 285\) | The frequency of dietary supplement use and to identify potential interactions    | Tertiary references, newsletters, textbooks, internet web pages and medical literature                   | There were 15 patients taking at least one combination that could cause an interaction                 |
| Peng et al. (52)    | Dietary supplements       | Prescription drugs  | Survey             | Veteran outpatients \(n = 458\)   | The incidence and severity of potential interactions between prescription medications and dietary supplements | Tertiary references, newsletters, textbooks, internet web pages and medical literature                   | There were 89 patients who had a potential for drug–dietary supplement interactions                  |
| Sood et al. (96)    | Dietary supplements       | Prescription drugs  | Cross-sectional, point-of-care survey | Patients in 6 different specialty clinics \(n = 1818\)  | The frequency of clinically significant interactions between dietary supplements and prescription medications | MEDLINE database, Natural Medicines Comprehensive Database, published textbook                       | There were 107 interactions with potential clinical significance identified                              |
| Goldman et al. (101) | Vitamins                 | Prescribed or over-the-counter medications | Cross-sectional study (survey) | Children aged 0–18 years \(n = 1804\) | The frequency and types of potential interactions between vitamins and medications | PubMed database, MEDLINE Plus, Drug digest and the database of the University of Maryland Medical Center | There were 193 children with a potential vitamin–drug interaction identified                           |
| Lapi et al. (104)   | Herbal drugs and dietary supplements | Synthetic drugs    | Cross-sectional study (survey) | Patients during preoperative anaesthesiological visit \(n = 478\) | The predictors of potential interactions among drugs, HDS and/or other CAM medications | No mention                                                                                         | There were 88 patients detectable for potential interactions evaluation                                 |
| Simmons and Schneir (113) | Commercial supplement products (Atrophex<sup>®</sup>) | Phenoxyline        | Case report        | 24-Year-old male with hypertension \(n = 1\) | No mention                                                                      | Hypertensive crisis associated with an MAOI interaction with beta-phenylethylamine                      |                                                                                                        |

HDS, herbs and dietary supplements; CAM, complementary and alternative medicine; MAOI, monoamine oxidase inhibitors.
Table 3 Summary of the included clinical trials to retrieve information about HDS–drug interactions

| Reference       | HDS                                               | Dose schedule of HDS | Medication                                                                 | Study design                          | Country     | Population (number of participants) | Outcome measures                                                  |
|-----------------|---------------------------------------------------|----------------------|-----------------------------------------------------------------------------|---------------------------------------|-------------|-------------------------------------|-------------------------------------------------------------------|
| Wang et al.     | Commercial product of St John's wort (oral)      | Single dose and long term for 14–15 days | Fexofenadine (oral)                                                        | Open-label, fixed-schedule study     | USA         | Healthy subjects (n = 12)           | Pharmacokinetics ($C_{max}, T_{max}$)                              |
| Gurley et al.   | Commercial products of Citrus aurantium, Echinacea purpurea, Milk thistle, Saw palmetto (oral) | 28 days              | Midazolam, caffeine, chlorzoxazone, debrisoquin (oral)                     | Randomised open-label study           | USA         | Healthy subjects (n = 12)           | Phenotypic ratio                                                   |
| Yin et al.      | Commercial Ginkgo biloba product (oral)           | 12 days              | Omeprazole (oral)                                                          | Open-label sequential study           | Hong Kong   | Healthy subjects genotyped for CYP2C19 (n = 18) | Pharmacokinetics ($C_{max}, T_{max}$)                              |
| Yoshioka et al. | Commercial product of Ginkgo biloba (oral)        | Single dose          | Nifedipine (oral)                                                          | Randomised crossover study            | Japan       | Healthy subjects (n = 8)            | Pharmacokinetics ($C_{max}, T_{max}$), Pharmacodynamics (blood pressure), Phentypic metabolic ratios, serum concentration |
| Gurley et al.   | Commercial products of St John's wort, garlic oil, Panax ginseng and Ginkgo biloba (oral) | 28 days              | Midazolam, caffeine, chlorzoxazone and debrisoquine (oral)                | Randomised open-label study           | USA         | Healthy older subjects who were extensive metabolisers of CYP2D6 (n = 12) | Pharmacokinetics (CYP2D6)                                         |
| Gurley et al.   | Commercial products of goldenseal, kava kava, black cohosh and valerian (oral) | 28 days              | Caffeine, midazolam, chlorzoxazone, debrisoquin (oral)                     | Randomised open-label study           | USA         | Healthy subjects who were extensive metabolisers of CYP2D6 (n = 12) | Pharmacokinetics (CYP2D6)                                         |
| Gurley et al.   | Commercial products of milk thistle, black cohosh (oral) | 14 days              | Digoxin (oral)                                                             | Randomised open-label study           | USA         | Healthy young adults (n = 16)       | Pharmacokinetic analysis, ABCB1 (MDR1) genotyping                   |
| Jiang et al.    | Commercial products of St John's wort, Asian ginseng, Ginkgo biloba or ginger (oral) | 7 or 14 days         | Warfarin (oral)                                                            | Two randomised, open-label, controlled, crossover studies | Australia   | Healthy subjects (n = 24)            | Population pharmacokinetic and pharmacodynamic parameter          |
| Gurley et al.   | Commercial products of goldenseal, kava kava (oral) | 14 days              | Digoxin (oral)                                                             | Randomised open-label study           | USA         | Healthy subjects (n = 20)           | Pharmacokinetic analysis, phytochemical analyses                   |
| Fan et al.      | Commercial product of baicalin (oral)             | 14 days              | Rosuvastatin (oral)                                                        | Randomised crossover study            | China       | Healthy subjects who were CYP2C9*1/*1 with different OATP1B1 haplotypes (n = 18) | Plasma concentration and pharmacokinetic parameters                |
Table 3

| Reference          | HDS                          | Dose schedule of HDS | Medication     | Study design                  | Country | Population (number of participants) | Outcome measures                                      |
|--------------------|-------------------------------|----------------------|----------------|-------------------------------|---------|-------------------------------------|-------------------------------------------------------|
| Gurley et al.      | Commercial products of goldenseal, kava kava (oral) | 14 days             | Midazolam (oral) | Randomised open-label study   | USA     | Healthy subjects (n = 16)           | Pharmacokinetic parameters, phenotypic ratios          |
| (88)               |                               |                      |                |                               |         |                                     | Phenotypic ratios, phytochemical analysis and disintegration times |
| Gurley et al.      | Commercial products of black cohosh, echinacea, goldenseal, kava kava, milk thistle and St John's wort (oral) | 14 days             | Debrisoquine (oral) | Randomised open-label design  | USA     | Healthy subjects who were extensive metabolisers of CYP2D6 (n = 16) | Pharmacokinetic parameters, phenotypic ratios, phytochemical analysis and disintegration times |
| (89)               |                               |                      |                |                               |         |                                     |                                                        |
| Gurley et al.      | Commercial products of St John's wort, echinacea (oral) | 14 days             | Digoxin (oral)  | Randomised open-label study   | USA     | Healthy young adults (n = 18)       | Pharmacokinetic parameters, phytochemical analysis and disintegration times |
| (90)               |                               |                      |                |                               |         |                                     |                                                        |
| Mohammed Abdul et al. | Commercial products of garlic, cranberry (oral) | 14 days             | Warfarin (oral) | Randomised open-label crossover study | Australia | Healthy subjects of known CYP2C9 and VKORC1 genotype (n = 12) | Pharmacokinetic parameters, pharmacodynamics (INR) |
| (91)               |                               |                      |                |                               |         |                                     |                                                        |
| Kim et al.         | Commercial product of Ginkgo biloba (oral) | Single dose         | Ticlopidine (oral) | Randomised open-label, crossover study | Korea   | Healthy subjects (n = 24)           | Pharmacokinetic parameters, pharmacodynamics (bleeding times) |
| (110)              |                               |                      |                |                               |         |                                     |                                                        |
| Nieminen et al.    | Commercial product of St John's wort (oral) | 15 days             | Oxycodone (oral) | Randomised, balanced, placebo-controlled, crossover study | Finland | Healthy subjects (n = 12)           | Pharmacokinetic parameters, pharmacodynamics (behavioural and analgesic effects); adverse effects |
| (111)              |                               |                      |                |                               |         |                                     |                                                        |

HDS, herbs and dietary supplements; C<sub>max</sub>, maximum plasma concentration; T<sub>max</sub>, time to reach C<sub>max</sub>; CYP, Cytochrome P450; VKORC1, vitamin K epoxide reductase subunit 1; INR, international normalised ratio.
The medications that most contributed to documented interactions with HDS were warfarin, insulin, aspirin, digoxin and ticlopidine. Not surprisingly, warfarin was documented to have interactions with over 100 HDS entities (Figure 4).

Among 882 pairs of interactions with identified mechanisms, a total of 373 pairs (42.3%) were attributable to pharmacokinetic-related mechanisms, i.e. affected the absorption, distribution, metabolism or excretion of the HDS/drug. Approximately 40.1% of all interaction pairs accounted for pharmacodynamic-related mechanisms, and 8.5% were attributed to a combination of both mechanisms. No mechanism was identifiable for the remaining 9.1% of pairs. Among the 373 documented HDS interaction pairs that were pharmacokinetic-related, 87 pairs were associated with St John’s Wort (23.3%), whereas calcium supplements were involved in 47 pairs of documented interactions (12.6%), and iron was involved in 42 pairs of interactions (11.3%). St John’s Wort was documented to reduce the effectiveness of alprazolam, amitriptyline, imatinib, midazolam, nifedipine and

(Figure 3). The medications that most contributed to documented interactions with HDS were warfarin, insulin, aspirin, digoxin and ticlopidine. Not surprisingly, warfarin was documented to have interactions with over 100 HDS entities (Figure 4).

Among 882 pairs of interactions with identified mechanisms, a total of 373 pairs (42.3%) were attributable to pharmacokinetic-related mechanisms, i.e. affected the absorption, distribution, metabolism or excretion of the HDS/drug. Approximately 40.1% of all interaction pairs accounted for pharmacodynamic-related mechanisms, and 8.5% were attributed to a combination of both mechanisms. No mechanism was identifiable for the remaining 9.1% of pairs. Among the 373 documented HDS interaction pairs that were pharmacokinetic-related, 87 pairs were associated with St John’s Wort (23.3%), whereas calcium supplements were involved in 47 pairs of documented interactions (12.6%), and iron was involved in 42 pairs of interactions (11.3%). St John’s Wort was documented to reduce the effectiveness of alprazolam, amitriptyline, imatinib, midazolam, nifedipine and

(Figure 3). The medications that most contributed to documented interactions with HDS were warfarin, insulin, aspirin, digoxin and ticlopidine. Not surprisingly, warfarin was documented to have interactions with over 100 HDS entities (Figure 4).

Among 882 pairs of interactions with identified mechanisms, a total of 373 pairs (42.3%) were attributable to pharmacokinetic-related mechanisms, i.e. affected the absorption, distribution, metabolism or excretion of the HDS/drug. Approximately 40.1% of all interaction pairs accounted for pharmacodynamic-related mechanisms, and 8.5% were attributed to a combination of both mechanisms. No mechanism was identifiable for the remaining 9.1% of pairs. Among the 373 documented HDS interaction pairs that were pharmacokinetic-related, 87 pairs were associated with St John’s Wort (23.3%), whereas calcium supplements were involved in 47 pairs of documented interactions (12.6%), and iron was involved in 42 pairs of interactions (11.3%). St John’s Wort was documented to reduce the effectiveness of alprazolam, amitriptyline, imatinib, midazolam, nifedipine and

(Figure 3). The medications that most contributed to documented interactions with HDS were warfarin, insulin, aspirin, digoxin and ticlopidine. Not surprisingly, warfarin was documented to have interactions with over 100 HDS entities (Figure 4).

Among 882 pairs of interactions with identified mechanisms, a total of 373 pairs (42.3%) were attributable to pharmacokinetic-related mechanisms, i.e. affected the absorption, distribution, metabolism or excretion of the HDS/drug. Approximately 40.1% of all interaction pairs accounted for pharmacodynamic-related mechanisms, and 8.5% were attributed to a combination of both mechanisms. No mechanism was identifiable for the remaining 9.1% of pairs. Among the 373 documented HDS interaction pairs that were pharmacokinetic-related, 87 pairs were associated with St John’s Wort (23.3%), whereas calcium supplements were involved in 47 pairs of documented interactions (12.6%), and iron was involved in 42 pairs of interactions (11.3%). St John’s Wort was documented to reduce the effectiveness of alprazolam, amitriptyline, imatinib, midazolam, nifedipine and
verapamil via the CYP (Cytochrome P450) 3A4 pathway, and the plasma levels of fexofenadine and digoxin via PgP (p-glycoprotein) pathway. Some drugs (i.e. atorvastatin, cyclosporin, indinavir, nevirapine and simvastatin) were documented to interact with St John’s Wort through both pathways (37,99).

Among the 354 documented interactions that were pharmacodynamic-related, kava accounted for 4.8% pairs of interactions (17 pairs). St John’s Wort and ginkgo were both involved in 15 pairs of interactions (4.2%). Risk of additive serotonergic effects were increased when St John’s Wort was used concurrently with monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI), or tryptamine-based drugs causing symptoms of anxiety, dizziness, restlessness, nausea and vomiting (16–18,20). As a result of their pharmacological actions on the GABA receptor, synergism in CNS adverse events may result from taking barbiturates or benzodiazepines in combination with kava (16,20,98). Furthermore, kava may worsen the extrapyramidal effects associated with the use of droperidol, haloperidol, metoclopramide or risperidone because of a dopamine (21,98).

Among the 507 documented interaction pairs identified with a severity rating in MicroMedex®, 69.4% were categorised as the moderate interactions, 17.2% as major interactions, 10.3% as minor interactions and 3.1% were attributable to the contraindications. As for the 763 pairs of documented interactions being identified with the severity rating based on the NMCD®, the majority documented interaction pairs were categorised as moderate (69.2%), major (26.5%) and minor (4.3%). Approximately, 240 documented HDS–drug interactions were categorised as major severity in either database (Tables 4 and 5). For example, the following pairs of interactions were considered as being contraindicated for concurrent use in MicroMedex®: L-Tryptophan vs. MAOI (i.e. isocarboxazid, phenelzine and tranylcypromine) or venlafaxine and St John’s wort vs. protease inhibitors (i.e. amprenavir, fosamprenavir and indinavir), irinotecan, rasagiline or voriconazole, respectively. Among the 390 documented interaction pairs having severity ratings in both databases, 41.3% were inconsistent. For example, the combination of alfalfa (Medicago sativa) and warfarin were considered as the minor interaction in MicroMedex®; however, it was rated as the major interaction in NMCD®. The combination of St John’s Wort with quetiapine, quinidine, risperidone or sildenafil gave severity ratings major according to NMCD®, and no interaction was reported in MicroMedex®.

HDS contraindications

Fifty-nine HDS from 152 reports were contraindicated for use among patients with specific disease states. The reports were classified into 19 disease states, including gastrointestinal diseases, neurologic disorders, renal/genitourinary diseases, neoplastic disorders, diseases of the liver/gallbladder/bile ducts
| HDS Drugs | Potential consequences/reactions |
|-----------|---------------------------------|
| Fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine (17) | ↑Risk of serotonin syndrome |
| Amoxicillin (98) | ↓Absorption of amoxicillin |
| Warfarin (21,33,43,75) | ↓The effect of warfarin |
| Digenoxin (16,21,33,45) | ↑Digenox toxicity |
| Warfarin (17,60,75) | ↓The effect of warfarin |
| Enalapril, nitroglycerin (21) | ↑Hypotensive effects |
| Spironolactone (21) | ↑Risk of hyperkalemia |
| Phenelzine (22,98) | ↑Risk of hypertensive crisis |
| Methyldopa (98) | ↑Hypotensive effects |
| Digoxin (17) | ↑Risk of bleeding |
| Warfarin (16–19,31,33,35,36,41,43,47,51,52,64–66,68,75,77,81,85,87,96,98) | ↑Risk of bleeding |
| Aspirin, ticlopidine, warfarin (12,16–20,30,31,33–36,38,40,47,51,52,55,60,64–66,68,75,77,80,81,85,87,98,103,105,110) | ↑Risk of bleeding |
| Ephedrine (17,21) | ↑Risk of sertraline adverse effects |
| Ephedrine (16) | ↑Risk of bleeding |
| Ephedrine (17,21,33,38) | ↑Risk of stimulatory adverse effects |
| Ephedrine (16) | ↑Risk of stimulatory adverse effects |
| Dapsone, sulfamethoxazole (17,20) | ↑Risk of anticholinergic side effects |
| Alprazolam, chloridiazepoxide, clonazepam, diazepam, estazolam, flurazepam, lormazepam, midazolam, morphine, oxazepam, henobarbital, quazepam, temazepam, triazolam (16–20,30,35,36,42,57,64,65,69,72,80,81,85,103) | ↑Central nervous system depression |
| Warfarin (16,43,68,75) | ↑Risk of bleeding |
| Citalopram, duloxetine, fluoxetine, fluvoxamine, isocarboxazid, paroxetine, phenelzine, selegiline, sertraline, sibutramine, tranylcypromine, venlafaxine (17,20,51) | ↑Risk of serotonin syndrome |
| Zolpidem (17) | ↑Zolpidem-induced sedative effects |
| Zolpidem (21) | ↑Sedative effects |
| Nitroglycerin (17) | ↑Severe hypotension, intolerable headaches |
| Atorvastatin, cerivastatin, lovastatin, rosuvastatin, simvastatin (19,20,82,84,112) | ↑Risk of myopathy or rhabdomyolysis |
| Dapsone, sulfamethoxazole (17,20) | ↓Antibacterial effects |
| Digenoxin (17) | ↑Digenox toxicity |
| Amiloride, benazepril, captopril, enalapril, fosinopril, indomethacin, lisinopril, moexipril, quinapril, ramipril, spironolactone, trandolapril, triamterene (17,19,20,52,82) | ↑Risk of hyperkalemia |
| Cyclosporin (21,65,98) | ↑Creatine phosphokinase values |
| Clomipramine (16) | ↑Risk of serotonin syndrome |
| Haloperidol (98) | ↑The potential toxicity |
| Phenerzine (17) | ↑Risk of hypertensive crisis |
| Alprazolam, phenobarbital (16,20,42) | ↑Central nervous system depression |
| Aclitretin, bexarotene, etretinate, isotretinoin, tretinoin (17,19,51,82,84,101,112) | ↑Risk of vitamin A toxicity |
| Altretamine (84) | ↓Response to altretamine |
Table 4 Continued

| HDS       | Drugs                                      | Potential consequences/reactions† |
|-----------|--------------------------------------------|-----------------------------------|
| Vitamin E | Dicumarol (84)                             | †Risk of bleeding                  |
| Vitamin K | Warfarin (17, 19, 20, 23, 43, 47, 75, 82, 84, 112) | ↓Effect of warfarin                |
| Willow    | Diclofenac, ibuprofen, naproxen, ticlopidine, warfarin (16, 17, 47, 68, 75) | †Risk of bleeding                  |

*Any HDS–drug interactions with severity rated as contraindicated or major in either database of Micromedex® or NMCD® were included in this table.
†Potential consequences or reactions were documented according to either aforementioned database with severity rating as major or contraindicated. †, increasing; ↓, decreasing.

and cardiovascular diseases (Figure 5). Flaxseed (*Linum usitatissimum*), echinacea (*Echinacea purpurea*) and yohimbe (*Pausinystalia yohimbe*) had the highest number of documented contraindications. For example, flaxseed was documented to have contraindications associated with gastrointestinal disorders such as acute or chronic diarrhoea, oesophageal stricture, inflammatory bowel disease, hypertriglyceridaemia and prostate cancer (21). Echinacea was contraindicated for use among patients with rheumatoid arthritis, systemic lupus erythematosus, leukosis, multiple sclerosis, tuberculosis and HIV infection (16,18). Yohimbe was contraindicated in patients with anxiety, bipolar disorder, depression, mania and schizophrenia, as well as benign prostate hypertrophy and kidney disease (21,22).

**Discussion**

In this study, we summarised the evidence of HDS-drug interactions and contraindications that have been reported in the primary and tertiary literature. The existing evidence suggests that some HDS products/ingredients have potentially harmful drug interactions that are predominately moderate in their severity. HDS products containing St John’s Wort, magnesium, calcium, iron, and ginkgo had the greatest number of documented interactions with drugs. Medications affecting the CNS and cardiovascular system tended to have more documented interactions with these HDS. Of all listed medications, warfarin was documented to have the greatest number of HDS interactions. HDS products containing herbal remedies were more likely to have documented interactions with medications and the contraindications than vitamins, minerals and other types of dietary supplements.

Some of the commonly used herbal remedies such as echinacea, flaxseed, ginkgo and St John’s Wort have featured more prominently in industry or government sponsored clinical trials, academic studies and official monographs (114,115). Some of these HDS entities have undergone more rigorous scientific evaluations. The clinical evidences for HDS are often mixed in terms of their support for efficacy and/or effectiveness. The benefits of HDS treatment must be balanced against the potential harmful effects including adverse events, and the potential for drug interactions or disease state contraindications. Furthermore, there often may be just a self-medicating ‘indication creep’, where patients who have a certain disease or condition unrelated to the supportive therapy with these HDS. For example, WHO monographs listed that echinacea products could be used in supportive therapy of colds and infections but were contraindicated for patients with autoimmune diseases (116). Even though the evidence to support the immunological effects of echinacea was still controversial (117), 6.4% of patients with arthritis/lupus reportedly used echinacea in the 2002 NHIS (4). Thus, patients need to understand that advantages of using echinacea products are outweighed by the potential harm if they have a specific disease state.

Patients using medications that have a narrow therapeutic range (i.e. warfarin, digoxin) were at greater risk for adverse outcomes because of HDS–drug interactions (20). This was particularly important for patients on anticoagulants (i.e. warfarin) who concomitantly took HDS products that had antiplatelet or anticoagulant effects (e.g. danshen, dong quai, garlic, ginger and ginkgo) (70,75). In particular, HDS products that contained vitamin K or metabolites related to vitamin K (e.g. coenzyme Q10) had the potential to reduce the effects of warfarin (75). However, some conflicting information regarding warfarin–HDS interactions was observed when the evidence was retrieved from different literature sources. For instance, in a case study, the international normalised ratio (INR) decreased in patients when ginseng was administered with warfarin in some case reports (12,66,118), but other *in vitro* studies demonstrated that several components of *Panax ginseng* had anticoagulant effects (12). Furthermore, a controlled clinical trial of healthy
| Table 5  The St John’s Wort-drug interactions with major severity* |
|-----------------------------------------------|
| **HDS** | **Drugs** | **Potential consequences/reactions†** |
|-----------------------------------------------|
| St John’s wort | Amiodarone (20,37) | ↓Effect of amiodarone |
| | Benzodiazepine: alprazolam, clonazepam, diazepam, midazolam, triazolam (20,36,37,49,59,62,64,65,76,77,80,81,87,93,97,99,103) | ↓Benzodiazepine effectiveness |
| | Bupropion, buspirone, eletriptan, meperidine, trazodone (17,31,37,39,62,64,65,76,77,80,81,87,93,97,99,103) | ↑Risk of serotonin syndrome |
| | MAOI: isocarboxazid, phenelzine, tranylcypromine (17,33) | |
| | SSRI: citalopram, duloxetine, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, venlafaxine (12,16–18,20,31,32,35–37,47,52,59,64,65,69,72,76,77,80,81,87,93,97,99,103) | |
| | Busulfan (39) | ↓Effect of busulfan |
| | Calcium channel blockers: diltiazem, felodipine, nicardipine, nifedipine, nitrendipine, verapamil (16,20,37,59,65,76,79–81,99,102,103) | ↓Effect of calcium channel blockers |
| | Carbamazepine (32,37,99) | ↓Effect of carbamazepine |
| | Cyclophosphamide (16,37,93) | ↓Effect of cyclophosphamide |
| | Cyclosporin (12,16–18,20–22,30–32,34–37,49–51,59,64,65,69,72,76,77,79–81,92,93,97,99,102,103) | ↓Effect of cyclosporine |
| | Dapson (37) | ↓Effect of Dapsone |
| | Dexamethasone (39) | ↓Effect of dexamethasone |
| | Digoxin (12,16–18,20,22,30–32,34,36,37,47,51,59,64–66,69,72,76,77,79–81,87,90,92,93,97,99,102,103) | ↓Effect of digoxin |
| | Docetaxel (39,74) | ↓Effect of docetaxel |
| | Dolasetron (39) | ↓Effect of dolasetron |
| | Doxorubicin (39,81) | ↓Effect of doxorubicin |
| | Erlotinib (20) | ↓Effect of erlotinib |
| | Erythromycin (103) | ↓Effect of erythromycin |
| | Estragens/progestogens: estradiol, gestodene, levonorgestrel, norethindrone (37,39,50,72) | ↓Effect of contraceptive |
| | Etoposide (39,81) | ↓Effect of etoposide |
| | Exemestane (20) | ↓Effect of exemestane |
| | Fentanyl, Morphine, Oxycodone (21,37,99,111) | ↑Sedation |
| | Fexofenadine (20,44,59,64,65,67,76,77,79,80,93,97,99,103) | ↓Effect of fexofenadine |
| | Finasteride (39) | ↓Effect of finasteride |
| | Flutamide (32,39) | ↓Effect of flutamide |
| | Gliclazide (103) | ↓Effect of gliclazide |
| | Haloperidol (37) | ↓Effect of haloperidol |
| | Ifosfamide (39) | ↓Effect of ifosfamide |
| | Imatinib (20,59,76,77,79,80,97,99,103) | ↓Effect of imatinib |
| | Irinotecan (12,16,20–22,49,59,64,65,76,77,80,81,97,103) | ↓Effect of irinotecan |
| | Ivabradine (103) | ↓Effect of ivabradine |
| | Ixabepilone (20) | ↓Effect of ixabepilone |
| | Lapatinib (20) | ↓Effect of lapatinib |
| | Lidocaine (37) | ↑Risk of cardiovascular collapse |
| | Loperamide (21,30,35,36,64,77,99,103) | ↓Effect of loperamide |
| | Maraviroc (20) | ↓Effect of maraviroc |
| | Mephenytoin (76,97,99,103) | ↓Effect of mephenytoin |
| | Methadone (20,21,37,64,65,77,92,93,99,103) | ↓Effect of methadone |
| | NNRTI: delavirdine, efavirenz, nevirapine (16,18,20,32,37,69,76,77,80,99,103) | ↓NNRTI concentrations |
| | Omeprazole (17,20,65,76,77,80,92,93,103) | ↓Effect of omeprazole |
| | Ondansetron (39) | ↓Effect of ondansetron |
| | Paclitaxel (37,39) | ↓Effect of paclitaxel |
subjects revealed that there was no significant interaction when ginseng was administered with warfarin (12,17,20,31,64). This discrepancy may be attributed to the fact that there are several different species of ginseng on the market [i.e. Asian ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius*), Siberian ginseng (*Eleutherococcus senticosus*)], different extract types and different doses used. Another interesting example is the concomitant use of warfarin with green tea. Some studies suggested that green tea may enhance the anticoagulant effects of warfarin (19,75). However, much of the literature suggested that the content of vitamin K in green tea might antagonise the effect of warfarin (16,17,68,70,75). Regardless, it is important to regularly monitor the INR levels of warfarin users who also use HDS products that might influence the anticoagulation effect.

In addition, patients on a digoxin regime who have been taking an HDS should check to ensure that their plasma concentration of digoxin is indeed within the therapeutic ranges. If this is not the case, then the pharmacist usually should recommend to their patients to stop taking these HDS or have their digoxin dose adjusted by their healthcare providers; for example, as digoxin serum concentrations are usually measured by fluorescence polarisation immunoassay or microparticle enzyme immunoassay, which may be influenced by ginseng and danshen (*Salvia miltiorrhiza*) (20,58). False digoxin levels may confuse laboratory results and result in inappropriate patient management. Furthermore, *Aloe barbadensis*, buckthorn (*Rhamnus cathartica*), cascara (*Rhamnus purshiana*), licorice (*Glycyrrhiza glabra*) and senna (*Cassia senna*) may cause hypokalaemia and result in digoxin toxicity (16,17,33,47). As a result, digoxin users should be told to avoid taking the aforementioned herbal remedies.

In this study, the documented evidence of HDS–drug interactions and contraindications were systematically reviewed from the published literature. This was done because healthcare professionals, in general, use only textbooks, journal and review articles, as

### Table 5 Continued

| HDS                          | Drugs | Potential consequences/reactions† |
|------------------------------|-------|-----------------------------------|
|                               |       |                                   |
| Phenprocoumon (12,18,31,35–37,47,65,66,77,80,81,97,103) | ↓Effect of phenprocoumon |
| Phenytoin (32)                | ↓Effect of phenytoin |
| Piroxicam, rasagiline, risperidone, tetracycline, tolbutamide, tretinoin (20,37,39,77,102,103) | ↑Photosensitivity reactions |
| Propofol, sevoflurane (20,99,103) | ↑Risk of cardiovascular collapse |
| Protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir (12,16–22,32,34,36,37,47,49,51,64,65,69,72,76,77,79–81,93,97,103) | ↓Effect of protease inhibitor |
| Quetiapine (37)               |       |                                   |
| Quinidine (37)                | ↓Effect of Quetiapine |
| Sildenafil (37,50,93)          | ↓Effect of Quinidine |
| Sirolimus (20)                | ↓Effect of Sirolimus |
| Sunitinib (20)                | ↓Effect of sunitinib |
| Tacrolimus (12,16,20,37,59,64,65,76,77,79–81,92,93,97,99,103) | ↓Effect of tacrolimus |
| Tamoxifen (16,37,39)          | ↓Effect of tamoxifen |
| Temsirolimus (20)             | ↓Effect of sirolimus, the active metabolite of temsirolimus |
| Teniposide (39)               | ↓Effect of teniposide |
| Tramadol (96)                 | ↓Effect of tramadol |
| Vinblastin (37,39,81)         | ↓Effect of vinblastin |
| Vincristine (39)              | ↓Effect of vincristine |
| Voriconazole (20,76,77,99,103) | ↓Effect of voriconazole |
| Warfarin (16–18,20,22,32,35–37,43,47,51,59,64–66,69,70,72,73,75–77,79–81,85,87,97,99,102,103) | ↓Effect of warfarin |

*Any HDS–drug interactions with severity rated as contraindicated or major in either database of MicroMedex® or NMCD® were included in this table. †Potential consequences or reactions were documented according to either aforementioned database with severity rating as major or contraindicated. ↑, increasing; ↓, decreasing. MAOI, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; NNRTI, non-nucleoside reverse transcriptase inhibitors.*
well as Internet as their major information source for HDS (119). Although the NCCAM and Office of Dietary Supplements are the two most commonly used, free online resources about HDS (120), only limited information is available related to HDS interactions and contraindications on these sites. Furthermore, only 59% of documented HDS–drug interactions could be identified with either their mechanisms and/or severity in either of the two common drug interaction resources (i.e. MicroMe- dex® and NMCD®). Among them, over 40% of the interactions differed in their severity rating, which is likely to create confusion among healthcare providers about the potential harmful effects associated with a given HDS–drug interactions. Concerns about disagreements across literature resources and databases for drug interactions have been raised before (121), and these increase the difficulty in implementing an evidence-based clinical practice for HDS products in clinical care. The intention of this review was to evaluate the evidence of HDS interactions and contraindications and to assist clinical practitioners in identifying patients with specific disease states and drug regimens that are more susceptible to these HDS–drug interactions and contraindications.

One of the limitations of this review was that it included all relevant information identified in the literature, regardless of the evidence types or quality...

---

**Figure 5** Common contraindications for HDS use. *Other contraindications of gastrointestinal diseases included fecal impaction for aloe vera and oesophageal stricture for flaxseed. †Other contraindications of neurologic disorders included multiple sclerosis for echinacea and posttraumatic stress disorder for yohimbe. HDS, herbs and dietary supplements.
of the studies. Although some HDS–drug interactions with little or no clinical significance were included in this study, their severity grading was based upon the available version of MicroMedex® and NMCD®. In order to reduce any personal bias, only those pairs of interactions with evidence retrieved from the aforementioned two databases were included to categorise the corresponding mechanisms and the severity rating. Consequently, we were unable to evaluate 41% of the interaction pairs for the corresponding mechanisms and severity in this study. Another limitation was the concern of publication bias, which might arise as only HDS products and medications that have been published in the literature on the basis of evidence-based medicine. Therefore, there are many potential HDS–drug or disease interactions that may exist but are simply without documented outcomes. Lastly, only reports, books or articles published in English were included in this review. Those evidence regarding traditional herbal medicine or folk therapies, which were published in other languages (e.g. Chinese, Japanese), might be missing. Thus, it is very likely that the amount of documented HDS–drug interactions and/or contraindications in this review might be under-reported.

Conclusions
This review provides a structured summary of the evidence of the most widely documented HDS interactions and contraindications with medications. Although our findings primarily concern with a relatively small subset of commonly used medications and HDS entities, it is recommended that healthcare professionals should be paid more attention towards those pairs of interactions between any HDS products that contain St John’s Wort, magnesium, calcium, iron and ginkgo, and medications that affect the CNS or the cardiovascular system. These findings should be helpful for healthcare professionals to identify the priority areas where communication regarding HDS usages has the greatest potential to prevent adverse events and to improve patient’s therapeutic outcomes.

Acknowledgements
The authors express their gratitude to Jun-Fon Wang, Yi-Ling Chen, Ying-Hung Lu, Po-Ming Hung, Tang-Ping Shih, Chung-Hui Ku, Shan-Chieh Wu and Yi-Zhu Chen for their help on data management, and Dr Chao-Ling (David) Chen, Daniel Lee, Vincent Lee and Matthias C. Lu for their insights and comments for the manuscript. This work was partially supported by the National Science Council (NSC 99-2320-B-039-031-MY3), China Medical University Hospital (DMR-99-140) and Committee on Chinese Medicine and Pharmacy, Department of Health, Executive Yuan, Taiwan, R.O.C. (CCMP99RD-016).

Author contributions
HHT, HWL and ASP participated in designing the review. HHT and HWL searched databases and retrieved the articles. HHT extracted and managed the data, while HWL validated it. HYT helped to resolve the disagreements in evidence abstraction. HHT wrote the manuscript, HWL, ASP, HYT and GBM reviewed and revised the manuscript. All authors read and approved the final manuscript.

References
1 Radimer K, Binewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999–2000. Am J Epidemiol 2004; 160: 339–49.
2 Timbo BB, Ross MP, McCarthy PV, Lin CT. Dietary supplements in a national survey: prevalence of use and reports of adverse events. J Am Diet Assoc 2006; 106: 1966–74.
3 Miller MF, Bellizzi KM, Sufian M, Ambs AH, Goldstein MS, Ballard-Barbash R. Dietary supplement use in individuals living with cancer and other chronic conditions: a population-based study. J Am Diet Assoc 2008; 108: 483–94.
4 Gardiner P, Graham RE, Legedza AT, Eisenberg DM, Phillips RS. Factors associated with dietary supplement use among prescription medication users. Arch Intern Med 2006; 166: 1968–74.
5 Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA 2002; 287: 337–44.
6 Blendon RJ, DesRoches CM, Benson JM, Brodie M, Altman DE. Americans’ views on the use and regulation of dietary supplements. Arch Intern Med 2001; 161: 805–10.
7 Palmer ME, Haller C, McKinney PE et al. Adverse events associated with dietary supplements: an observational study. Lancet 2003; 361: 101–6.
8 Shahansky 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: 1237–47.
9 Mehta DH, Gardiner PM, Phillips RS, McCarthy EP. Herbal and dietary supplement disclosure to health care providers by individuals with chronic conditions. J Altern Complement Med 2008; 14: 1263–9.
10 Kemper KJ, Amata-Kynvi A, Dvorkin L et al. Herbs and other dietary supplements: healthcare professionals’ knowledge, attitudes, and practices. Altern Ther Health Med 2003; 9: 42–9.
11 Suchard JR, Suchard MA, Steinfeld J. Physician knowledge of herbal toxicities and adverse herb-drug interactions. Eur J Emerg Med 2004; 11: 193–7.
12 Coxeter PD, McLachlan AJ, Duke CC, Reufogalis BD. Herb-drug interactions: an evidence based approach. Curr Med Chem 2004; 11: 1513–25.
13 Silverstein DD, Spiegel AD. Are physicians aware of the risks of alternative medicine? J Community Health 2001; 26: 159–74.
14 Zeolla MM, Cerulli J. Use of and familiarity with dietary supplement information references by practicing pharmacists. J Am Pharm Assoc 2008; 48: 401–4.
1072 Evidence evaluation of drugs with herbs and dietary supplements

72 Haller CA. Clinical approach to adverse events and interactions related to herbal and dietary supplements. Clin Toxicol (Phila) 2006; 44: 605–10.

73 Jiang X, Blair EY, McLachlan AI. Investigation of the effects of herbal medicines on warfarin response in healthy subjects: a population pharmacokinetic-pharmacodynamic modeling approach. J Clin Pharmacol 2006; 46: 1370–8.

74 Meijerman I, Beijnen JH, Schellens JH. Herb-drug interactions in oncology: focus on mechanisms of induction. Oncology 2006; 11: 742–52.

75 Natescu EA, Shapiro NL, Ibrahim S, West P. Warfarin and its interactions with foods, herbs and other dietary supplements. Expert Opin Drug Saf 2006; 5: 433–51.

76 Venkataramanan R, Komoroski B, Strom S. In vitro and in vivo assessment of herb-drug interactions. Life Sci 2006; 78: 2105–15.

77 Yang XX, Hu ZP, Duan W, Zhu YZ, Zhou SF. The pharmacokinetic-pharmacodynamic modeling approach. J Clin Pharmacol 2006; 46: 1379–90.

78 Gurley BJ, Swain A, Barone GW et al. Pharmacodynamic interaction of warfarin with cranberry but not with garlic in healthy subjects. Br J Pharmaco 2008; 154: 1691–700.

79 Nowack R. Herb-drug interactions in nephrology: documented and theoretical. Clin Nephrol 2008; 69: 319–25.

80 Nowack R. Review article: cytochrome P450 enzyme, and transport protein mediated herb-drug interactions in renal transplant patients: grapefruit juice, St John’s Wort – and beyond! Nephrology (Carlton) 2008; 13: 357–62.

81 Okonta JM, Uboh M, Obonga WO. Herb-drug interaction: a case study of effect of ginger on the pharmacokinetic of metronidazole in rabbit. Indian J Pharm Sci 2008; 70: 230–2.

82 Samuels N, Finkelstein Y, Singer SR, Oberbaum M. Herbal medicine and epilepsy: proconvulsive effects and interactions with antiepileptic drugs. Epilepsia 2008; 49: 173–80.

83 Sood A, Sood R, Brinker FJ, Mann R, Loehrle LL, Wahner-Roedler DL. Potential for interactions between dietary supplements and prescription medications. Am J Med 2008; 121: 207–11.

84 Tomlinson B, Hu M, Lee VW. In vivo assessment of herb-drug interactions: possible utility of a pharmacogenetic approach? Mol Nutr Food Res 2008; 52: 799–809.

85 Ulbricht C, Chao W, Costa D, Rusie-Seamon E, Kaiser AM. Herb-drug interactions: a systematic review by the natural standard research collaboration. Curr Drug Metab 2008; 9: 1063–120.

86 Borrelli F, Izzo AA. Herb-drug interactions with St John’s wort (Hypericum perforatum): an update on clinical observations. AAPS J 2009; 11: 710–27.

87 Chang JC, Wu YT, Lee WC, Lin LC, Tsai TH. Herb-drug interaction of silymarin or silibinin on the pharmacokinetics of trazodone in rats. Chem Biol Interact 2009; 182: 227–32.

88 Goldman RD, Vohra S, Rogovik AL. Potential vitamin-drug interactions in children: a pediatric emergency department. Paediatr Drugs 2009; 11: 251–7.

89 Holcomb SS. Common herb-drug interactions: what you should know. Nurse Pract 2009; 34: 21–9.

90 Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs 2009; 69: 1777–98.

91 Lapi F, Vietri M, Moschini M et al. Definition of potential interactions between synthetic drugs, herbal drugs and dietary supplements during preoperative anaesthesiological assessment: a cross-sectional study in Tuscan County, Italy. Drug Saf 2009; 32: 982.

92 Shord SS, Shah K, Lukose A. Drug-herbal interactions: a review of the laboratory, animal, and human data for 8 common botanicals. Integr Cancer Ther 2009; 8: 208–27.

93 Toselli F, Matthias A, Gilliam EM. Echinacea metabolism and drug interactions: the case for standardization of a complementary medicine. Life Sci 2009; 85: 97–106.

94 Abad MJ, Bedoya LM, Bermejo P. An update on drug interactions with the herbal medicine Ginkgo biloba. Curr Drug Metab 2010; 11: 171–81.

95 Cheng CW, Fan W, Ko SG, Song L, Bian ZX. Evi- dence-based management of herb-drug interaction in cancer chemotherapy. Explore (NY) 2010; 6: 324–9.

96 Chiin CF, Wu YT, Lee WC, Lin LC, Tsai TH. Herb-drug interaction of Andrographis paniculata extract and andrographolide on the pharmacokinetics of theophylline in rats. Chem Biol Interact 2010; 184: 458–65.

97 Kim BH, Kim KP, Lim KS et al. Influence of Ginkgo biloba extract on the pharmacodynamic effects and pharmacokinetic properties of ticlopi- dine: an open-label, randomized, two-period, two-treatment, two-sequence, single-dose crossover study in healthy Korean male volunteers. Clin Ther 2010; 32: 380–90.

98 Nieminen TH, Hagelberg NM, Saari TI et al. St John’s wort greatly reduces the concentrations of oral oxycodone. Eur J Pain 2010; 14: 854–9.

99 Rogovik AL, Vohra S, Goldman RD. Safety consid- erations and potential interactions of vitamins: should vitamins be considered drugs? Ann Pharma- macother 2010; 44: 311–24.

100 Simmons T, Schneir AB. Hypertensive crisis from a MAOI/Supplement interaction leading to myo- cardiac infarction and acute heart failure. Clin Tox- icol 2010; 48: 631.

101 Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. Adv Data 2004; 343: 1–19.

102 Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. Natl Health Stat Report 2008; 12: 1–23.

103 World Health Organization. WHO Monographs on Selected Medicinal Plants. Vol. 1. Geneva http://whoilibdoc.who.int/publications/1999/9241545178.pdf (accessed January 2012)

104 Barnes J, Anderson LA, Gibbons S, Phillipsion JD. Echinacea species (Echinacea angustifolia (DC.) Hell., Echinacea pallida (Nutt.) Nutt., Echinacea purpurea (L.) Moench): a review of their chemis- try, pharmacology and clinical properties. J Pharm Pharmacol 2005; 57: 929–54.

105 Sparreboom A, Cox MC, Acharya MR, Figg WD. Herbal remedies in the United States: potential adverse interactions with anticancer agents. J Clin Oncol 2004; 22: 2489–303.

106 Howard N, Tsourounis C, Kapusnik-Uner J. Die- tary supplement survey of pharmacists: personal and professional practices. J Altern Complement Med 2001; 7: 667–80.

107 McHughes M, Timmermann BN. A review of the use of CAM therapy and the sources of accurate and reliable information. J Manag Care Pharm 2005; 11: 695–703.

108 Vitry AI. Comparative assessment of four drug interaction compendia. Br J Clin Pharmacol 2007; 63: 709–14.

Paper received May 2012, accepted July 2012
Appendix 1 Summary of included books to retrieve information about HDS–drug interactions and contraindications.

| Reference  | Year | HDS–drug interactions | Medication          | Format             | Severity rating of interactions | Contraindications | HDS                                                                 | Cited references | Website |
|------------|------|-----------------------|---------------------|--------------------|-------------------------------|------------------|----------------------------------------------------------------------|------------------|---------|
| Cassileth (16) | 2003 | Yes                   | Drug class or individual drug | By HDS            | No                            | Yes              | Herbal remedies, other dietary supplements and non-mainstream products promoted as cancer treatments | Yes              | Yes     |
| Gaby (17)   | 2006 | Yes                   | Individual drug     | By drug and by HDS | No                            | No               | Herbs, dietary supplements, foods and alcohol                        | Accessed online  | Yes     |
| Mahady (18) | 2001 | Yes                   | Drug class or individual drug | By HDS            | No                            | Yes              | Herbs                                                                | Yes              | No      |
| Mason (19)  | 2001 | Yes                   | Drug class and/or individual drug | By HDS            | No                            | Yes              | Vitamins, minerals and natural oils, natural substances, enzymes, amino acid | Yes              | No      |
| Tatro (20)  | 2010 | Yes                   | Drug class with individual drug | By drug           | Yes                            | No               | Vitamins, electrolytes and few common used herbs                     | Yes              | Yes     |
| Ulbricht (21) | 2005 | Yes                   | Drug class or individual drug | By HDS            | No                            | Yes              | Herbs and supplements                                                  | Yes              | Yes     |

HDS, herbs and dietary supplements.
| Reference | Review type | HDS | Medications | Databases | Searching period |
|-----------|-------------|-----|-------------|-----------|-----------------|
| Coxeter et al. (12) | Narrative review | Herbs | General | No mention | No mention |
| Ernst (30) | Narrative review | Herbs | Conventional drugs | No mention | No mention |
| Fugh-Berman (31) | Narrative review | Herbs | General | MEDLINE; EMBASE | MEDLINE: 1966–1998; EMBASE: 1994–1999 |
| McIntyre (32) | Narrative review | St John’s wort | General | No mention | No mention |
| Semaan (33) | Narrative review | Herbal medicine | General | No mention | No mention |
| Fugh-Berman and Ernst (35) | Systematic review | Herbs | Conventional drugs | MEDLINE (via PubMed), EMBASE, the Cochrane Library, CISCOM | Their inception to 2000 |
| Izzo and Ernst (36) | Systematic review | Herbal medicines | Prescribed drugs | MEDLINE (via PubMed), EMBASE, Cochrane Library and Phytobase | Their inception to 2000 |
| Markowitz and DeVane (37) | Narrative review | St John’s wort | General | MEDLINE, Current contents and PSYCINFO | 1966–2000 |
| Block and Gyllenhaal (39) | Narrative review | Natural inhibitors and inducers of CYP450 | Cancer chemotherapy drugs, adjunctive drugs | No mention | No mention |
| Lyons (42) | Narrative review | Herbal medicine | Drugs used in anaesthesia | No mention | No mention |
| Myers (43) | Narrative review | Complementary medicines | Warfarin | No mention | No mention |
| Buehler (45) | Narrative review | Herbal products | Conventional medicines | No mention | No mention |
| Chavez et al. (46) | Narrative review | Herbs | General | No mention | No mention |
| Williamson (47) | Narrative review | Herbs | Prescription medicines | EMBASE, MEDLINE | EMBASE: 1980–2003; MEDLINE: 1966–2003 |
| Zhou et al. (48) | Narrative review | Herbs | Substrates of CYP enzymes | No mention | No mention |
| Huang and Lesko (50) | Narrative review | Dietary supplements | General | No mention | No mention |
| Ohnishi and Yokoyama (51) | Narrative review | Dietary supplements | General | No mention | No mention |
| Bartlett and Eperjesi (55) | Narrative review | Ocular nutritional supplements | General | PubMed, Web of Science | 1980–2004 |
| Bressler (56) | Narrative review | Saw palmetto | Prescription medications | No mention | No mention |
| Bressler (57) | Narrative review | Kava | Prescription medications | No mention | No mention |
| Bressler (58) | Narrative review | Ginseng | Prescription medications | No mention | No mention |
| Bressler (59) | Narrative review | St John’s wort | Prescription medications | No mention | No mention |
| Bressler (60) | Narrative review | Ginkgo biloba | General (prescription drugs) | No mention | No mention |
| Hu et al. (64) | Narrative review | Herbal medicines | General (prescription drugs) | MEDLINE, Biological Abstracts, Cochrane Library, AMED, Biosis Previews and EMBASE | Their inception to 2005 |
| Izzo (65) | Narrative review | Herbal remedies | General (prescription drugs) | No mention | No mention |
| Izzo et al. (66) | Systematic review | Herbal medicines | Cardiovascular drugs | MEDLINE | 1966–2003 |
| Marder (68) | Narrative review | Dietary supplements | Antithrombotic agents | No mention | No mention |
| Singh (69) | Narrative review | Kava and St John’s wort | General (prescription drugs) | No mention | No mention |
| Reference | Review type | HDS                          | Medications                                                      | Databases                        | Searching period |
|-----------|-------------|------------------------------|-----------------------------------------------------------------|----------------------------------|------------------|
| Daughtery and Smith (70) | Narrative review | Dietary supplements          | Warfarin                                                        | No mention         | No mention       |
| Haller (72) | Narrative review | Herbal and dietary supplements | General                                                         | No mention         | No mention       |
| Meijerman et al. (74) | Narrative review | Herbs                        | Anticancer drug                                                  | No mention         | No mention       |
| Nutescu et al. (75) | Narrative review | Herbal and dietary supplements | Warfarin                                                        | No mention         | No mention       |
| Venkataramanan et al. (76) | Narrative review | Herbs                        | General                                                         | No mention         | No mention       |
| Yang et al. (77) | Narrative review | Herbs                        | General                                                         | No mention         | No mention       |
| Marchetti et al. (79) | Narrative review | P-gp modulators              | ABCB1 substrates, e.g. digoxin, cyclosporin A, tacrolimus      | No mention         | No mention       |
| Nekvindova and Anzenbacher (80) | Narrative review | Dietary constituents affecting CYPs | CYP substrates                                                  | No mention         | No mention       |
| Skalli et al. (81) | Systematic review | Common herbal                | General                                                         | MEDLINE via PubMed, Allied and Complementary, Medicine Database, Healthstar, AMBASE, CINAHL, Cochrane Library | 1966–2006       |
| Sulli and Ezzo (82) | Narrative review | Vitamins and minerals        | General                                                         | No mention         | No mention       |
| Yetley (84) | Narrative review | Multivitamin and multimineral dietary supplements | General                                                        | No mention         | No mention       |
| Cranwell-Bruce (85) | Narrative review | Herbs                        | General, Anticoagulants, cardiovascular medications, psychiatric medications, laxatives, diabetes medications or medications for human immunodeficiency virus (HIV) infection | No mention         | No mention       |
| Gardiner et al. (87) | Narrative review | Herbs, vitamins              | General                                                         | No mention         | No mention       |
| Nowack (92) | Narrative review | Herbs                        | CYP3A4 and transport-protein dependent drug, anticoagulants or antiplatelets, antidiabetics, antihypertensive agents | No mention         | No mention       |
| Nowack (93) | Narrative review | Herbs                        | Immunosuppressive drugs                                         | No mention         | No mention       |
| Samuels et al. (95) | Narrative review | Herbal medicine              | Antiepileptic drug                                               | No mention         | No mention       |
| Tomlinson et al. (97) | Narrative review | Herbs                        | CYP3A4/P-gp substrates                                           | No mention         | No mention       |
| Ulbricht et al. (98) | Systematic review | Herbs                        | General                                                         | MEDLINE, EMBASE, the Cochrane Library, CINAHL, Napalert, International Pharmaceutical Abstracts, CANCERLIT, CISCOM, HERBMED | No mention       |
| Borrelli and Izzo (99) | Narrative review | St John's wort               | General                                                         | No mention         | No mention       |
| Holcomb (102) | Narrative review | Herbs                        | General                                                         | No mention         | No mention       |
| Reference          | Review type  | HDS          | Medications      | Databases                                                                 | Searching period          |
|-------------------|--------------|--------------|------------------|---------------------------------------------------------------------------|---------------------------|
| Izzo and Ernst (103) | Systematic review | Herbs       | General         | MEDLINE (via PubMed), EMBASE and Cochrane Library                         | Their inception to 2009   |
| Shord et al. (105) | Narrative review | Herbs       | General         | No mention                                                               | No mention                |
| Toselli et al. (106) | Narrative review | Echinacea  | CYP450 substrate | No mention                                                               | No mention                |
| Abad et al. (107)  | Narrative review | Ginkgo biloba | General         | No mention                                                               | No mention                |
| Cheng et al. (108) | Narrative review | Herbs       | Anticancer drugs | MEDLINE/OLDMEDLINE, Ovid MEDLINE, Excerpta Medica Database (EMBASE), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CCRT), Health Technol | Until November 2009        |
| Rogovik et al. (112) | Narrative review | Vitamins     | General         | MEDLINE/PubMed, MEDLINE Plus, Drug Digest, Natural Medicine Comprehensive Database and the database of the University of Maryland | 1966–2009                 |

HDS, herbs and dietary supplements; CYP, Cytochrome P450; P-gp, P-glycoprotein.
### Appendix 3 PRISMA checklist.

| Section/topic         | No. | Checklist item                                                                                   | Reported on page no. |
|-----------------------|-----|--------------------------------------------------------------------------------------------------|----------------------|
| Title                 | 1   | Identify the report as a systematic review, meta-analysis or both.                               | P1                   |
| Title                 | 1   | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number | P2                   |
| Introduction          | 2   | Rationale for the review in the context of what is already known                                 | P4                   |
| Objectives            | 3   | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS) | P4                   |
| Methods               | 4   | Indicate if a review protocol exists, if and where it can be accessed (e.g. Web address), and, if available, provide registration information including registration number | N/A                  |
| Protocol and registration | 5   | Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale | P5                   |
| Eligibility criteria  | 6   | Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched | P5                   |
| Information sources   | 7   | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated | P5                   |
| Search                | 8   | State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis) | P5                   |
| Study selection       | 9   | Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators | P6                   |
| Data collection process | 10  | List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made | P6                   |
| Data items            | 11  | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis | N/A                  |
| Summary measures      | 12  | State the principal summary measures (e.g. risk ratio, difference in means)                      | N/A                  |
| Synthesis of results  | 13  | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. i²) for each meta-analysis | N/A                  |
| Risk of bias across studies | 14 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies) | N/A                  |
| Risk of bias across studies | 15 | Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified | N/A                  |
| Additional analyses   | 16  | Study selection                                                                                   | P7, P48 (Figure 1)   |
| Study characteristics  | 17  | For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations | P28–37 (Table 1–3); P53–62 (Appendix 1–2) |
| Risk of bias within studies | 18  | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12) | N/A                  |
| Section/topic                  | No. | Checklist item                                                                                                                                                                                                 | Reported on page no. |
|-------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Results of individual studies | 20  | For all outcomes considered (benefits or harms), present, for each study; (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot          | N/A                 |
| Synthesis of results          | 21  | Present results of each meta-analysis done, including confidence intervals and measures of consistency                                                                                                     | N/A                 |
| Risk of bias across studies   | 22  | Present results of any assessment of risk of bias across studies (see Item 15)                                                                                                                                   | N/A                 |
| Additional analysis           | 23  | Give results of additional analyses, if done [e.g. sensitivity or subgroup analyses, meta-regression (see Item 16)]                                                                                              | N/A                 |
| Discussion                    |     | Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. healthcare providers, users and policy makers)                                      | P11–14              |
| Limitations                   | 25  | Discuss limitations at study and outcome level (e.g. risk of bias), and at review level (e.g. incomplete retrieval of identified research, reporting bias)                                                   | P14                 |
| Conclusions                   | 26  | Provide a general interpretation of the results in the context of other evidence, and implications for future research                                                                                       | P14–15              |
| Funding                       |     | Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review                                                                     | P15                 |