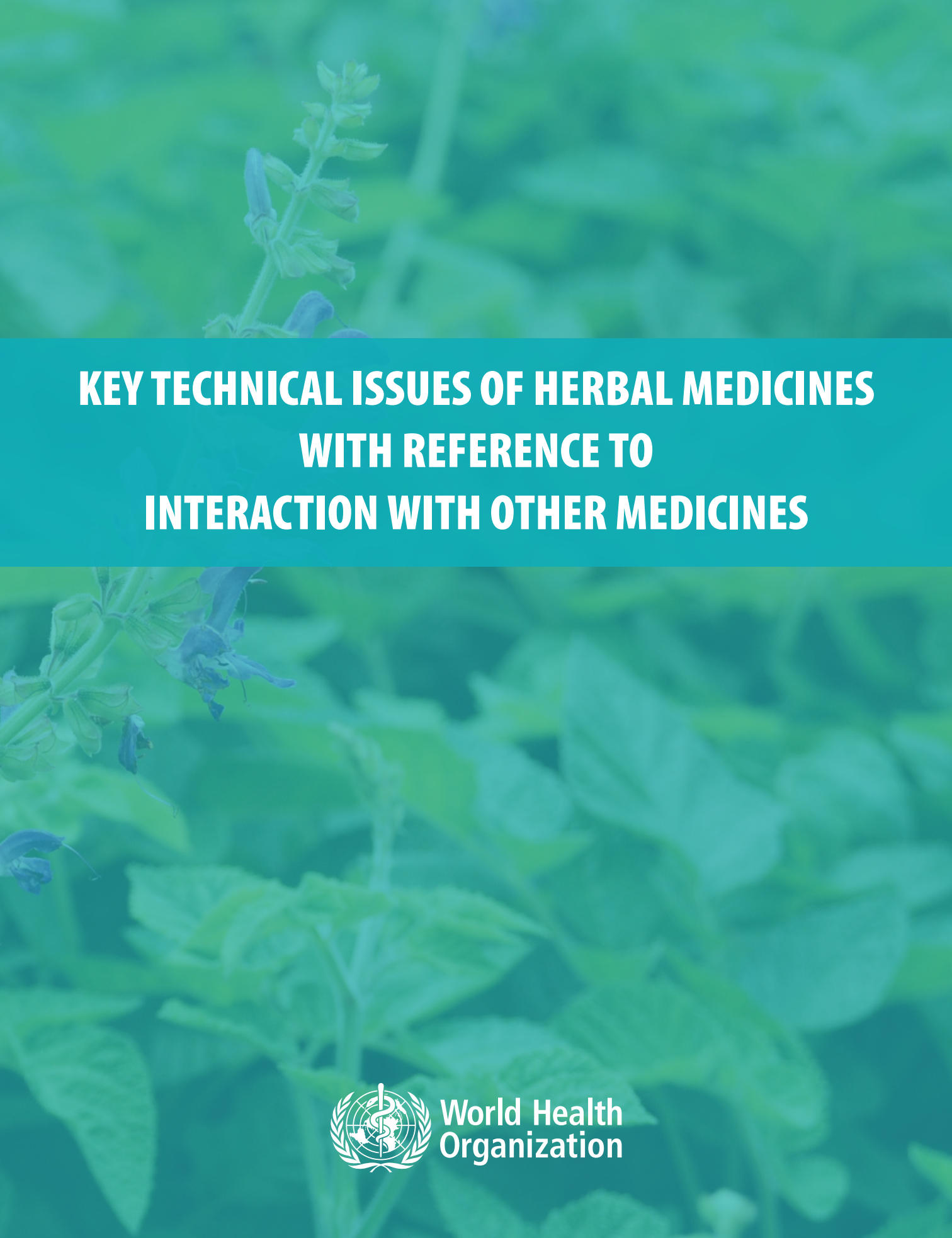

KEY TECHNICAL ISSUES OF HERBAL MEDICINES WITH REFERENCE TO INTERACTION WITH OTHER MEDICINES

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Foreword

Many countries are seeking to expand coverage of essential health services, including essential medicines, at a time when the unique health challenges of the twenty-first century are emerging, such as rising consumer expectations for care, soaring costs, and stagnant or reduced budgets. One important part of the efforts to address these challenges is using the resources of traditional and complementary medicine. According to the WHO Global Report on Traditional and Complementary Medicine 2019 (WHO, 2019a), traditional and complementary medicine practices are recognized by the health authorities in 170 World Health Organization (WHO) Member States. The Global Report also shows the growing trend in numbers of countries where policies and regulations on traditional and complementary medicine have been developed and implemented over the past two decades.

Combining the use of traditional and complementary medicine with conventional medicine has increased significantly in recent years worldwide, in particular the combined use of herbal and conventional medicines. Interactions between medicines can possibly result in therapeutic failure or adverse events during treatment, and can also affect the outcome of clinical trials if not controlled. Despite increasing recognition of herb–drug interactions (HDIs), there is no standard system for prediction and evaluation – and WHO is receiving increasing numbers of requests from Member States to provide technical and policy support in this area.

It is a priority for WHO to enhance the safety, quality and effectiveness of traditional and complementary medicines in achieving the goal of universal health coverage, as documented in the WHO Traditional Medicine Strategy: 2014–2023 (WHO, 2013). In response to the request from Member States, and in implementing the WHO strategy, WHO initiated the development of a technical document on interaction of herbal medicines with other medicines.

This document provides information on the critical technical issues related to interactions between herbal medicines and other medicines for health-care professionals, regulators, researchers, pharmacovigilance centres, manufacturers and consumers. WHO encourages Member States to strengthen research, education, international cooperation and pharmacovigilance on HDIs to maximize the benefits and minimize the harmful effects of using herbal medicines, reduce risks, and support health professionals, patients and consumers in making informed and safe decisions.

This document will be helpful in promoting the safety, quality and effectiveness of traditional, complementary and integrative medicines and in appropriate integration of traditional and complementary medicines into national health systems. It will also support the implementation of the WHO 13th Programme of Work, in particular integrated, people-centred health services for achieving the goal of universal health coverage.

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WHO is grateful to all participants in the two working group meetings and the consultative meeting for their work in reviewing the draft document; participants are listed in Annex 2. Thanks are also given to the more than 100 experts in over 30 countries, including WHO Collaborating Centres for Traditional Medicine, and members of the WHO Expert Advisory Panel on Traditional Medicine, who reviewed and provided comments and advice on the draft document.

Abbreviations

CAR	constitutive active/and rostane receptor
CYP	cytochrome P450
HDI	herb–drug interaction
HIV	human immunodeficiency virus
INR	international normalized ratio
P-gp	permeability glycoprotein
PXR	pregnane X receptor
WHO	World Health Organization

Glossary

Active pharmaceutical ingredient – Substance used in a finished pharmaceutical product intended to furnish pharmacological activity or to otherwise have a direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have a direct effect in restoring, correcting or modifying physiological functions in humans (WHO, 2011a). Some active pharmaceutical ingredients contain more than one active component responsible for their effects, for example herbal products.

Adverse event/experience – Any untoward medical occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with this treatment (WHO, 2004a). A serious adverse event is any untoward medical occurrence that, at any dose, results in death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, or is life-threatening.

Adverse reaction – Response to a pharmaceutical product that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis or treatment, or for the modification of physiological function (WHO, 2004a).

Complementary medicine – Broad set of health-care practices that are not part of that country's own traditional or conventional medicine and not fully integrated into the dominant health-care system. The term "complementary medicine" is used interchangeably with "traditional medicine" in some countries (WHO, 2013).

Cytochrome P450 (CYP) – Group of enzymes involved in food and drug metabolism and found in high levels in the liver. This class consists of more than 50 enzymes, three of the most significant being CYP3A4, CYP2D6 and CYP2C9.

Dosage form – Form of the completed pharmaceutical product, such as tablet, capsule, injection, elixir or suppository (WHO, 2011b).

Drug/medicine – Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient (WHO, 2011b).

Excipient – Any component of a medicine other than the claimed therapeutic ingredient or ingredients (WHO, 2011b).

Finished herbal product – Herbal preparation made from one or more herbs (i.e. different herbal preparations from the same herb, or herbal preparations from different plants). Products containing different herbal materials are called "mixture herbal products". Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients (WHO, 2017).

Herb – Crude plant material that may be entire, fragmented or powdered. Herbs include the entire aerial part, leaves, flowers, fruits, seeds, roots, bark, trees (stem or root), tubers, rhizomes and other plant parts (WHO, 2017).

Herbal material – Includes, in addition to herbs, other crude plant materials, such as gums, resins, balsams and exudates (WHO, 2017).

Herbal medicine – May include herbs, herbal materials, herbal preparations and finished herbal products in a form suitable for administration to humans (WHO, 2017). In some countries, herbal medicines may also contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal or mineral materials).

Herbal preparation – Preparation produced from herbal materials by physical or biological processes, such as extraction (with water, alcohol or supercritical carbon dioxide), fractionation, purification, concentration, fermentation, processing with a natural vehicle, or steeping or heating in alcoholic beverages, honey or other materials. The resulting herbal preparations include comminuted (fragmented) or powdered herbal materials, extracts, tinctures, fatty (fixed) or essential oils, expressed plant juices, decocts, and cold and hot infusions (WHO, 2017).

Herbal product – Broad term encompassing herbal medicines and related products. Other terms used include botanical drugs, herbal dietary supplements, herbal drugs, herbal food supplements, herbal functional foods, herbal nutraceuticals, natural health products, phytomedicines, phytopharmaceuticals and phytotherapics. These terms vary widely according to regional and national legislation.

Herb-drug interaction (HDI) – Interaction involving a herbal medicine, as defined above, and another medicine. This may be a herb–drug interaction (involving a conventional medicine) or a herb–herb interaction (involving two or more herbal medicines).

P-glycoprotein – Multidrug-resistance protein in the cell membrane that pumps many medicines out of cells, reducing their bioavailability.

Pharmaceutical interaction/incompatibility Includes complex formation, such as that between proteins and polyphenols or metals, which may reduce solubility of the drug or herbal constituent(s), thus delaying or preventing absorption. It may also involve chemical degradation and render either or both medicines ineffective or toxic.

Pharmaceutical product – Any preparation for human or veterinary use that is intended to modify physiological or pathological states for the benefit of the recipient (WHO, 2011b). In the context of this document, pharmaceutical products also include herbal medicinal products.

Pharmacodynamic interaction – Occurs when two drugs or more interact as a result of their intrinsic pharmacological effects. The interaction may involve receptor binding and post-receptor effects, resulting in synergistic or antagonistic outcomes.

Pharmacogenetics – Study of single or multiple related drug–gene interactions.

Pharmacogenomics – Study of genetic variations that influence the response to drugs, encompassing genomics and epigenetics and the effects of multiple genes.

Pharmacokinetic interaction –Occurs due to differences in the absorption, distribution, metabolism or excretion of a drug when taken in combination with another drug, compared with the predicted behaviour when taken individually. These differences may cause changes in the concentration of one or both drugs, which may affect treatment outcomes or increase toxicity.

Pharmacovigilance–Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related issue (WHO, 2004a).

Polymorphism – Presence of genetic variations, for example changes in cytochrome P450 enzyme and transporter expression profiles, which affects the capacity of an individual to metabolize drugs.

Side-effect – Unintended effect of a pharmaceutical product occurring at doses normally used in humans that is related to the pharmacological properties of the drug (WHO, 2004a).

Traditional and complementary medicine – Merges the terms "traditional medicine" and "complementary medicine", encompassing practices, practitioners and products (WHO, 2013).

Traditional medicine – Sum total of the knowledge, skill and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health and the prevention, diagnosis, improvement or treatment of physical or mental illness (WHO, 2013).

Executive summary

Although there are few sources of reliable data on the number of people taking conventional medicines and traditional or complementary medicines concurrently, the practice of using combinations of herbal medicines and conventional medicines to improve therapeutic outcomes is widespread. Evaluation of herb–drug interaction (HDI) liability is challenging due to variability in herbal product composition, uncertainty of the causative constituents, and often scant knowledge of constituent pharmacokinetics. These limitations are confounded further by the varying perspectives concerning herbal product regulation. Many Member States have requested that the World Health Organization (WHO) provide technical support on how to deal with HDIs correctly.

This document is part of a more comprehensive series of documents that provide greater context about the safe and effective use of herbal medicines. The document was initiated in 2011 in Milan, Italy, when the first working group meeting was organized. The document was drafted in May 2015, and then discussed in the second working group meeting in 2016 in Mississippi, United States of America. The first and second global peer reviews were conducted in October 2018 and February 2019, respectively. The final consensus was reached in a WHO consultation meeting in Beijing, China, on 16–18 October 2019. Based on this consensus, the draft was further updated and finalized by a small peer-review group in November 2019.

The concepts of beneficial and harmful HDIs are introduced, with documented examples from the published literature. Types of HDI and their mechanisms are outlined, and the relevance of in vitro, general screening and in vivo tests is included. Challenges faced in evaluating and monitoring HDIs, data collection, assessment and dissemination of information are briefly discussed. The education and training of health professionals and consumers are addressed, together with potential research strategies for further investigation of the mechanisms, incidence, monitoring and management of HDIs.

The intention of this document is to provide as much concise information as possible, and to give direction and guidance on capitalizing resources to support informed decision-making and maximize the safe concurrent use of herbal medicines and other medicines. It is not the objective of this document to address complex toxicological issues or to act as a guideline for clinical treatment or the use of fixed combinations of herbal medicines. Interactions with diagnostic procedures and with nonpharmaceutical interventions such as surgery are beyond the scope of this report and are not addressed.

A selection of reports and case histories of HDIs involving well-documented herbs is collated in Annex 1. An evaluation of the available evidence is provided, and the entries have been reviewed by expert panels over several global reviews.

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1. Introduction

1.1 The herbal medicines/products market and consumption and concomitant use of traditional and complementary medicines with conventional medicines

Increasing numbers of people use traditional, complementary and integrative medicine in Africa, Asia, Oceania and the Americas (WHO, 2013). Many traditional, complementary and integrative medicine modalities include the use of herbal medicines, although the results from studies on the frequency of herbal medicines use vary too widely to be meaningful due to the survey methods used, vague definitions of "herbal medicines" or "food supplements", and the notoriously poor response rates achievable with such studies. It can be agreed, however, that the use of herbal medicines is high, increasing, and predominant in certain types of patient, culture and disease states.

A 2014 study estimated that 18.8% of respondents were using at least one "plant-based supplement" in Europe (Garcia-Alvarez et al., 2014). In South Africa, over 27 million people have been reported to use herbal medicines and there are an estimated 200 000 traditional healers (Abdullahi, 2011). Up to 60% of South Africans consult these healers, usually in addition to using modern biomedical services (Van Wyk et al., 2009). In Japan, according to a survey in 2011, 89% of doctors prescribe Kampo products in their daily practice (Arai and Kawahara, 2019). Popular use of herbal medicines in Brazil is often due to poor medical and pharmaceutical assistance and the high cost of treatment with conventional medicines (Mazzari and Prieto, 2014).

Another indicator of herbal medicines use is the expanding commercial market over the past 50 years. Sales of herbal dietary supplements in the United States of America surpassed US$ 8.8 billion in 2017, an increase of 9.4% from 2017 and the strongest growth since 1998 (Smith et al., 2019). In China, the herbal medicines market was worth US$ 100–120 billion in the period 2014–2016, representing about 30% of the pharmaceutical industry (Dang et al., 2016). Sales of herbal medicines in Brazil in 2014 reached US$ 343.7 million (Carvalho et al., 2018). In South Africa, the herbal product trade has been estimated to contribute over US$ 200 million to the economy (Abdullahi, 2011).

Along with the dramatic global rise in herbal medicine use and sales, there has been a parallel increase in the number of people taking conventional medicines and traditional or complementary medicinal products concurrently. Although there are few sources of reliable data on the number of people using combinations of herbal medicines and conventional medicines to improve therapeutic outcomes, it is reasonable to assume this is widespread.

Although there are limited data on the number of people taking conventional medicines and traditional or complementary medicines concurrently, the increasing consumption and concomitant expansion of the herbal products market have raised concern among health-care professionals, researchers, regulatory authorities and consumers regarding herb–drug interactions (HDIs). The practice of using combinations of herbal medicines and conventional medicines, whether prescribed or bought over-the-counter, to improve therapeutic

outcomes, maintain general health, prevent diseases, and treat chronic and refractory diseases such as mental health issues, cardiovascular and cerebrovascular diseases, and tumours, is widespread. According to a British study, the prevalence of taking herbs or dietary supplements concurrently with prescription medicines in elderly people was 33.6% (Agbabiaka et al., 2017). People frequently fail to tell their doctors, and doctors often fail to ask their patients, about use of herbal medicines. The concurrent use of herbal medicines with other medicines can result in therapeutic failure or adverse events, and can also affect the outcomes of clinical trials if not appropriately controlled. Systematic evaluation of HDI liability, as is routine for new medicines under development, necessitates identifying individual chemical constituents of herbal products and characterizing their interaction potential.

Despite increasing recognition of HDIs, there is no standard system for prediction and evaluation. Evaluation of HDI liability is challenging due to variability in herbal product composition, uncertainty of the causative constituents, and often scant knowledge of constituent pharmacokinetics. These limitations are confounded by the varying perspectives concerning herbal product regulation.

1.2 Objectives, aims and scope

1.2.1 Objectives

The primary objective of this document is to provide information for health-care professionals, regulators, researchers and other stakeholders on key technical issues related to HDIs in order to support health professionals, patients and consumers in making informed decisions to maximize beneficial applications and minimize side-effects of herbal medicines and products.

A second objective seeks to encourage health professionals to engage in their jurisdictional pharmacovigilance system, because reporting interactions makes herbal medicines usage safer for all patients; regulators and policy-makers to ensure traditional, complementary and integrative medicine is effectively incorporated into pharmacovigilance systems; and researchers and academics to become familiar with this topic and contribute to the body of scientific knowledge needed to advance the understanding of this important field.

It is not the objective of this document to address complex toxicological issues or to provide guidelines for clinical treatment. Interactions with diagnostic procedures and with nonpharmaceutical interventions such as surgery are beyond the scope of this report and are not addressed.

1.2.2 Aims

- To summarize the issues surrounding HDIs regarding their incidence, and the mechanisms and pharmacokinetic and pharmacodynamic principles involved in HDIs.
- To discuss the challenges in evaluating and monitoring HDIs resulting from issues specific to herbal medicines, such as their complexity, variability in sources and

production methods (as detailed in other WHO guidelines), and in terms of consumer behaviour.

- To outline strategies for increasing awareness and educating health-care professionals and consumers.
- To create awareness about reporting of HDIs.
- To promote and facilitate research on HDIs.

1.2.3 Scope

There are many examples of combinations of herbs that should or should not be taken together based on empirical knowledge and centuries of observation, but the scientific information available about HDIs is rare. These points are addressed in the individual WHO benchmarks for training in traditional, complementary and integrative medicine publications. For example, Benchmarks for Training in Traditional Chinese Medicine includes a list of combinations that should not be used, except by specialists under "extreme caution" (WHO, 2010a). Benchmarks for Training in Ayurveda explains antagonistic combinations of herbs and foods in terms of their Ayurvedic properties, but interactions between specific herbs are not detailed (WHO, 2010b). In Benchmarks for Training in Unani Medicine, although no specific herbal combinations are given, the importance of recognizing herbal interactions is emphasized (WHO, 2010c). Naturopathy training requires competence in botanical medicines; Benchmarks for Training in Naturopathy states that practitioners should be aware of "the potential interactions between herbal remedies, pharmaceutical products or foods" (WHO, 2010d).

2. Therapeutic aspects of herb–drug interactions

Examples from the current literature related to HDIs are shown in Table 1 and Annex 1. Harmful HDIs are the priority in terms of public health and safety; however, herbal medicines may be taken alongside other products not only as part of integrated treatment but also to deliberately exploit beneficial herbal interactions – for example, to improve the bioavailability of a medicine. Research into HDIs is a relatively new field of clinical study, and it is important to acknowledge that not all HDIs are harmful and some can result in positive effects.

2.1 Beneficial and harmful interactions

2.1.1 Beneficial interactions

Herb–drug interactions

The use of herbal formulae and their positive effects on people receiving chemotherapy was reviewed by Qi et al. (2015). In Japan, many doctors prescribe Kampo medicines to manage cancer-related symptoms and outcomes (Amitani et al., 2015). Chinese herbal medicines have been used successfully in the treatment of various diseases, including drug-resistant enterobacteria infection (Cai et al., 2017). *Schisandra sphenanthera* Rehder & E.H. Wilson is used in traditional Chinese medicine as a hepatoprotective agent in people undergoing liver transplant who are also being treated with the immunosuppressant tacrolimus. This combination has been shown to reduce diarrhoea and agitation associated with the use of tacrolimus, to increase the oral bioavailability of tacrolimus, and to improve liver function (Jiang et al.2010), and further studies are warranted.

Herb–herb interactions

The therapeutic efficacy of certain herbal medicines can be augmented by the administration of other herbs through synergistic, additive, chemical or metabolic mechanisms, including increasing biological effects through more than one mechanism or altering absorption and bioavailability. Alternatively, a herbal medicine may reduce the toxicity of another herb, for example by reducing the bioavailability of a specific component.

An example of the augmentation of effects is shown by a double-blind, placebo-controlled study on the cognitive performance of healthy adults following administration of *Ginkgo biloba* L. or *Panax ginseng* C.A. Mey. or their combination. A sustained improvement of test responses following treatment with the ginkgo–ginseng combination was observed compared with use of the individual herbs (Scholey and Kennedy, 2002), although no mechanism for this synergistic effect was postulated.

Black pepper (*Piper nigrum* L.) is a component of many Ayurvedic formulae such as Trikatu. The constituent piperine enhances the absorption and bioavailability of herbal and conventional medicines, partly by modulating p-glycoprotein and metabolic enzymes (Meghwal and Goswami, 2013).

The use of specific combinations to attenuate toxicity is documented in ancient classical traditional Chinese medicine texts and was established over many years of observation and empirical evidence from clinical practice. They are known as principles of "mutual detoxification" and "mutual restraint" and refer to the action of removing or restraining (weakening) the toxicity of one ingredient by another ingredient; for example, liquorice rhizome and astragalus root have been used to attenuate the toxicity of Aconiti Praeparata Radix (Liu et al., 2014).

There are few human studies comparing combinations with individual herbs in reducing toxicity, but animal studies support the principle. The combination of Ku Shen (*Sophora flavescens* Aiton) with Gan Cao (*Glycyrrhiza uralensis* Fisch.) is an established traditional Chinese medicine formula. A study in rats has shown that the absorption of glycyrrhetinic (or glycyrrhetic) acid is reduced and its metabolism increased compared with Gan Cao alone; thus reduced in vivo accumulation of glycyrrhetinic acid may be a mechanism for reducing the sodium- and water-retentive effects of Gan Cao (Shi et al., 2015).

2.1.2 Harmful interactions

Herb-drug interactions

St John's wort (*Hypericum perforatum* L.) was one of the first herbs to be implicated in case reports of drug interactions, and it remains the most commonly cited. The concomitant use of St John's wort with the anticoagulant warfarin, immunosuppressants (e.g. ciclosporin), antiretrovirals (e.g. indinavir, nevirapine), inotropics (e.g. digoxin) or antineoplastics (e.g. imatinib, irinotecan) may result in reduced plasma concentrations and reduced efficacy of these medicines (Russo et al., 2014). Other herbs have since been reported to be involved in HDIs, but the evidence for many is inconclusive; some examples are given in Table 1.

Herb–herb interactions

The overall clinical effects of herbal combinations are expected and intended to be the result of complex interactions between components of the mixture. To avoid harmful interactions, multi-herb and fixed formulae are usually produced according to strict rules governing appropriate combinations based on traditional properties (e.g. Tridosha attributes in Ayurveda). In traditional Chinese medicine, specific combinations of herbs have been claimed to be detrimental when taken together; these are described as the "18 incompatible medicaments", reported to cause adverse reactions when used in combination (see Table 2). Bioavailability enhancers may enhance the effects of other toxic compounds taken at the same time, whether in the same herbal medicine or in a different product, and may need to be considered.

Table 1. Examples of reported herb–drug interactions [1,2,3]

Plant species name and part used	Common name	Prescribed medicine	Reported result of interaction
Allium sativum L., bulb	Garlic	Chlorzoxazone	Increased plasma concentration of chlorzoxazone
		Paracetamol	Changes in paracetamol pharmacokinetics
		Saquinavir	Decreased saquinavir blood concentration
Angelica sinensis (Oliv.) Diels, root	Danggui, Dong quai	Warfarin	Increased anticoagulant effect
Areca catechu L., seed	Betel nut	Procyclidine	Rigidity, bradykinesia, jaw tremors
Camellia sinensis (L.) Kuntze, leaf	Green tea	Folic acid	Decreased folate blood concentration
Ginkgo biloba L., leaf	Ginkgo leave, Yinxingye	Omeprazole	Decreased omeprazole blood concentration
		Tolbutamide	Decreased tolbutamide blood concentration
		Talinolol	Increased talinolol blood concentration
Hibiscus sabdariffa L., flower	Hibiscus (roselle)	Chloroquine	Reduced blood concentration of chloroquine
		Paracetamol	Changes in paracetamol pharmacokinetics
Hydrastis canadensis L., root	Goldenseal	Debrisoquine	Decreased debrisoquine urinary recovery ratio
Lycium barbarum L., fruit	Goji berry, Chinese wolfberry	Warfarin	Increased anticoagulant effect
Mentha piperita L., essential oil	Peppermint	Felodipine	Increased felodipine blood concentration
Oenothera biennis L., seed oil	Evening primrose	Fluphenazine	Seizures
Panax ginseng C.A. Mey., root and rhizome	Ginseng, red or Korean	Phenelzine	Sleeplessness, tremor, headache
Panax quinquefolius L., root	Ginseng, American	Warfarin	Reduced warfarin concentration and anticoagulation effect
Piper methysticum G. Forst., root	Kava	Chlorzoxazone	Decreased metabolite/chlorzoxazone serum ratio
Salvia miltiorrhiza Bunge, root and rhizome	Dan Shen, red sage	Warfarin	Increased anticoagulant effect
Schisandra chinensis (Turcz.) Baill., fruit	Magnolia vine fruit	Talinolol	Increased talinolol blood concentration
Silybum marianum (L.) Gaertn., seed	Milk thistle	Metronidazole	Decreased metronidazole blood concentration

1 Table reprinted with permission from Izzo AA, Kim SH, Radhakrishnan R, Williamson EM (2016). A critical approach to evaluating clinical efficacy, adverse events and drug interactions of commonly used herbal remedies. Phytother Res. 30(5):691–700.

2 Data extracted from Izzo AA (2012). Interactions between herbs and conventional drugs: overview of the clinical data. Med Princ Prac. 21:404–28.

3 Well-documented interactions are those revealed by a well-documented case report or multiple case reports and case series (level of evidence 3 out of 5); pharmacokinetic trials in patients or healthy volunteers (level of evidence 4 out of 5); or case report(s) and confirmed by clinical pharmacokinetic trials (level of evidence 5 out of 5) (Izzo 2012).

Table 2. The 18 incompatible medicaments in traditional Chinese medicine[1]

Herb				Incompatible with			
Pharmaceutical/ pharmacopoeial name	**Plant species name**	**Chinese name (Pinyin)**	**Common names**	**Pharmaceutical/ pharmacopoeial name**	**Plant species name**	**Chinese name (Pinyin)**	**Common names**
Aconiti Radix	*Aconitum carmichaeli* Debeaux	Wutou	Wolfbane, aconite	Fritillariae Bulbus	*Fritillaria cirrhosa* D. Don.	Beimu	Fritillary
				Trichosanthis Fructus	*Trichosanthes kirilowii* Maxim.; *Trichosanthes rosthornii* Harms	Gualou	Mongolian snakegourd
				Pinelliae Rhizoma	*Pinellia ternata* (Thunb.) Breit.	Banxia	Ternate pinellia
				Ampelopsis Radix	*Ampelopsis japonica* (Thunb.) Makino	Bailian	Japanese ampelopsis tuber
				Bletillae Rhizoma	*Bletilla striata* (Thunb.) Reichb. f.	Baiji	Common bletilla tuber
Glycyrrhizae Radix et Rhizoma	*Glycyrrhiza uralensis* Fisch.; *Glycyrrhiza glabra* L.; *Glycyrrhiza inflata* Batalin	Gan Cao	Liquorice, licorice, sweet grass	Euphorbiae Pekinensis Radix	*Euphorbia pekinensis* Rupr.	Daji	Peking spurge
				Genkwa Flos	*Daphne genkwa* Siebold & Zucc.	Yuanhua	Lilac daphne flower bud
				Kansui Radix	*Euphorbia kansui* S.L. Liou ex S.B. Ho	Gansui	Gansui, Kansui root
				Sargassi Thallus	*Sargassum pallidum* (Turner) C. Agardh; *Sargassum fusiforme* (Harvey) Setchell	Haizao	Seaweed, sargassum
Veratri Nigri Radix et rhizoma	*Veratrum nigrum* L.	Lilu	False hellebore root and rhizome	Ginseng Radix et rhizoma	*Panax ginseng* C.A. Mey.	Ren Shen	Ginseng
				Salvia Miltiorrhizae Radix	*Salvia miltiorrhiza* Bunge	Dan Shen	Red root sage
				Adenophorae Radix	*Adenophora stricta* Miq.; *Adenophora triphylla* (Thunb.) A.DC.; *Adenophora tetraphylla* (Thunb). Fisch.	Sha Shen	Ladybells root
				Sophorae Flavescentis Radix	*Sophora flavescens* Ait.	Ku Shen	Light yellow sophora root
				Asari Radix et rhizoma	*Asarum sieboldii* Miq.	Xixin	Manchurian wild ginger
				Paeoniae Radix	*Paeonia lactiflora* Pall.; *P. veitchii* Lynch	Shaoyao	Chinese peony

1 Adapted from Liu XM, Wang Q, Song G, Zhang G, Ye Z, Williamson EM (2014). The classification and application of toxic Chinese materia medica. Phytother Res. 28(3):334–47.

2.2 Types and mechanisms of herb–drug interaction

HDIs occur when known or unknown constituents alter the activity of another medicine administered at the same time or within a short timeframe. This action may be synergistic (increased effect) or antagonistic (decreased effect), or a new effect may be produced that would not be expected from use of either medicine alone. The mechanisms of HDIs are defined below; for more information, see European Medicines Agency (2012). HDIs can have a pharmaceutical, pharmacokinetic or pharmacodynamic basis; they can occur during any pharmacokinetic processes or at the site of action.

HDIs may interact by more than one mechanism. Figure 1 summarizes the main route by which all drug interactions, including HDIs, occur. A herbal medicine may interact by more than one mechanism; for example, *Hypericum perforatum* L. may interact with other antidepressants by pharmacodynamic mechanisms to produce a toxic serotonergic syndrome, and by pharmacokinetic processes with ciclosporin to cause transplanted organ rejection by reducing blood levels of the immunosuppressant (Colombo et al., 2014).

2.2.1 Pharmaceutical interactions

Pharmaceutical interactions, or incompatibilities, occur when two or more preparations, mixed before administration (e.g. in a liquid medicine), react. This is usually a chemical interaction, such as complex formation between proteins and polyphenols or metals, causing reduced solubility or chemical degradation of the medicine or herbal constituents, and thus may be predictable. Theoretically, the consumption of herbal medicines with probiotics may render the probiotics inactive. The results may be visible in the medicine as colour changes or flocculent precipitates; with herbal medicines, however, colour changes may be masked by natural pigments.

2.2.2 Pharmacokinetic interactions

Pharmacokinetic interactions occur when a medicine's absorption, distribution, metabolism or elimination is altered by the administration of another medicine or herb; they include metabolism-mediated and transporter-mediated interactions. Changes in the gut microflora may alter the bioavailability of orally administered medicines.

Absorption interactions

Herbal medicines may influence transit time through the gut, which may affect the absorption of a drug.

Chemical reactions or complexation may occur in the stomach when two medicines are taken together, which may interfere with the absorption of one or both medicines.

Some medicines exist in either ionized or non-ionized form, depending on the pH of the gut and the acid–base dissociation constant (pKa) of the medicine. Non-ionized forms are more lipophilic and more easily absorbed. The regulation of gut pH is important in this context. Smaller, neutral molecules can undergo passive diffusion.

The absorption of some medicines is altered if administered together with substances with a high fat content. Some traditional medicines are formulated in an oil base, such as Ayurvedic formulations containing ghee or clarified butter.

Distribution interactions

Transporter- and metabolic enzyme-mediated interactions include modulating active uptake or efflux of a medicine, and competition for plasma protein binding, thus altering drug transport and bioavailability.

P-glycoprotein is a multidrug-resistance protein distributed extensively in the intestinal epithelium, liver, kidney and blood–brain barrier. P-glycoprotein transports many medicines, including tacrolimus, doxorubicin, vinblastine and some protease and reverse transcriptase inhibitors. Activation of P-glycoprotein reduces the bioavailability of these medicines, while inhibition of P-glycoprotein may enhance their bioavailability.

Competition for plasma protein transport may alter bioavailability, with consequent transient changes in concentrations of medicines.

Metabolic interactions

Cytochrome P450 (CYP) enzymes are found in the membranes of the endoplasmic reticulum (microsomes) and mitochondria, hepatocytes and other cell types. About 70–80% of prescribed medicines are metabolized by cytochrome P450 enzymes (Cho and Yoon, 2015). More than 50 isozymes are known, but only 6 are responsible for the metabolism of most drugs, the 3 most significant being CYP3A4, CYP2D6 and CYP2C9. If cytochrome P450 enzyme activity is increased due to increased microsomal enzyme synthesis, the metabolism of other medicines that are substrates for the same enzyme will be increased, leading to reduced therapeutic levels of the first medicine and possible treatment failure. If enzyme activity is reduced, the metabolism of other medicines that are substrates for the same enzyme will be decreased, leading to increased plasma levels of the first medicine and possible induction of toxicity. The outcome of cytochrome P450 inhibition or induction may be more complex than a simple change in plasma levels; for example, unexpected effects may be seen if an active metabolite is produced.

Phase II metabolic enzymes include uridine diphosphate-glucuronosyltransferases, sulfotransferases, *N*-acetyltransferases and glutathione S-transferases. These enzymes facilitate the attachment of polar and ionizable groups to metabolites generated by phase I metabolism and thereby increase their elimination rate. Phase II enzymes are present in the liver and intestine and may be induced or inhibited. Several herbal extracts and compounds have been shown to induce or inhibit phase II enzymes (Mohamed and Frye, 2011), but no clinical cases of interaction have been reported.

The constitutive active/and rostane receptor (CAR) and the pregnane X receptor (PXR) are the two major nuclear receptors involved in the regulation of metabolism, distribution and elimination of xenobiotics (Urquhart et al., 2007; Tolson and Wang, 2010). Both play a crucial role in drug interactions and regulate the expression of a wide range of cytochrome P450 enzymes, uridine diphosphate-glucuronosyltransferases and glutathione S-transferases. Some efflux transporters (e.g. P-glycoprotein) and influx transporters (e.g. organic anion-transporting polypeptide 1A2, OAT P1A2) are also regulated by PXR or CAR (Chen et al., 2012;

Liu and Li, 2012). Several herbal medicines have now been identified as regulators of PXR (Chang, 2009; Yu et al., 2011).

Elimination interactions

Renal excretion of drugs comprises three major physiological processes in the kidney: glomerular filtration, tubular secretion and tubular reabsorption. Medicines and metabolites that are tightly bound to plasma proteins are not available for glomerular filtration and are not easily eliminated by this process, but protein binding is not an impediment to medicines that are renally excreted via tubular secretion.

In biliary excretion, drugs and their metabolites are transferred to the bile by hepatocytes, delivered via the gallbladder to the intestine, and excreted via the stool. The active drug may also be reabsorbed; this is the enterohepatic cycle. The intestinal flora may hydrolyse conjugated metabolites and free the active drug, allowing it to be reabsorbed. Active transportation is the major mechanism in biliary excretion, and therefore interaction is more likely to be caused by inhibitors or inducers of transporters.

2.2.3 Pharmacodynamic interactions

Pharmacodynamic interactions occur when two medicines interact due to their intrinsic pharmacological effects. Many medicines, especially herbal medicines, produce their effects via more than one mechanism and regardless of the route of administration.

It is important not to overgeneralize or speculate on interactions based purely on the chemical structures of components of herbal extracts. For example, many case reports cite the coumarin content as a logical reason for an observed cardiovascular interaction. Coumarins are distributed widely in plants, however, and most lack the structural features necessary to inhibit coagulation by depleting vitamin K, as with dicoumarol.

Receptor interactions

A drug agonist combines with receptors to elicit a pharmacological response, whereas an antagonist blocks this response. A full agonist binds to and activates a receptor to its maximum response. A partial agonist has different affinities for different states of the same receptor or isoforms of the receptor, producing a similar but weaker effect. A drug can act as a full agonist in some tissues and as a partial agonist in other tissues. The outcome of combining two drugs with agonist activity will depend on the doses used, the receptor density, and the relative binding affinity of each drug.

An inverse agonist binds to the same receptor as an agonist but dislocates the receptor to its inactive state, thus reducing its intrinsic activity. An inverse agonist thus has opposite actions to those of an agonist – but the effects of both can be blocked by antagonists.

Pure antagonists are devoid of action themselves but bind to the receptor, blocking the action of an agonist. They are classified into reversible and non-reversible antagonists. Reversible antagonism can be overcome by increasing the concentration of agonist. Many drugs initially characterized as antagonists are now known to have inverse agonist activity.

Organ and system interactions

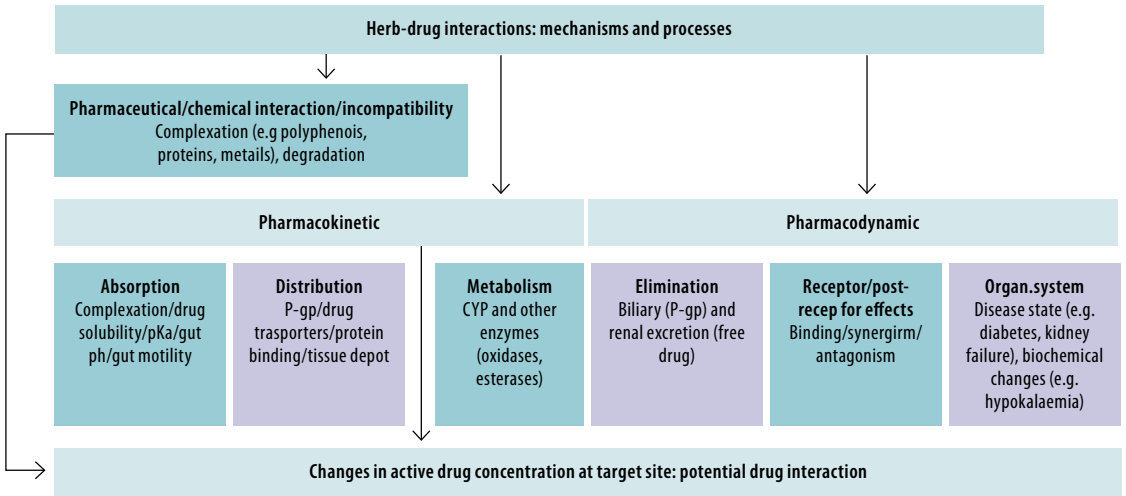
With certain drug combinations, the interaction results in metabolic processes that eventually cause clinical symptoms, some of which are serious. For example, diuretics or strong laxatives such as senna may cause potassium depletion; under such physiological conditions, the toxicity of digoxin is elevated (Wang et al., 2011).

2.2.4 Pharmacogenomics and pharmacogenetics

Knowing whether a person has specific genetic variations can help to individualize therapy, reducing the chances of adverse drug events and increasing efficacy, an approach termed "personalized medicine" (Pirmohammed, 2001; WHO, 2002; Scott, 2011; Johnson 2013). The cytochrome P450 enzyme expression profile, including specific genetic variants, influences drug interactions and susceptibility to the drug itself (WHO, 2005; Samer et al., 2013).

Pharmacogenomics and pharmacogenetic mechanisms should not be confused with pharmaceutical interactions or chemical incompatibilities, which can be dealt with by a revised system of administration. Mechanisms of HDIs have been well reviewed (e.g. Butterweck and Nahrstedt, 2012; Fasinu et al., 2012; Gurley, 2012; Gurley et al., 2012; Hermann and von Richter, 2012; Posadzki et al., 2013; Chan, 2014; Cho and Yoon, 2015).

Figure 1. Possible herb–drug interactions: mechanisms and processes



CYP, cytochrome P450; P-gp, P-glycoprotein.

2.3 Application of in vitro testing to evaluate herb–drug interactions

The same principles for testing the effects of drug-metabolizing enzymes and drug transporter activity apply to herbal medicines as for any other medicines, and the same rigour should be applied when assessing them. The complexity of some herbal medicines, however, means that the overall effects may be difficult to predict. The usual factors that

influence an individual's response to any medicine apply to herbal medicines, but variability in the quality and the chemical constituents of the products must also be considered.

There are so many confounding factors associated with screening herbal medicines that some in vitro tests may not be clinically meaningful. In vitro evidence should also include considerations of single-component versus whole-extract effects, intestinal absorption, genetic diversity, enzyme-inducing and enzyme-inhibiting effects offsetting each other, quantitative concentration–response relationships, and metabolic activation issues. Ingested materials are exposed to stomach acid and digestive enzymes, the microbiome, and substantial hepatic first-pass effects that cannot be predicted from in vitro screening tests. Several studies have been criticized for using doses too high to be clinically relevant – for example, at millimolar rather than nanomolar or picomolar levels (Butterweck and Nahrstedt, 2012; Markowitz and Zhu, 2012) – and to date there are no validated approaches to translating in vitro to in vivo extrapolation for HDIs.

A medicine may interact with more than one cytochrome P450 or other enzyme and with P-glycoprotein and other drug transporters. Table 3 shows the cytochrome P450, P-glycoprotein and other transporter activity profiles of some commonly used medicinal plants and reports of their clinical interactions. These herbs were selected due to the range of tests that have been performed on their extracts, for comparison with their clinical records of interaction and to illustrate the relevance of the evidence available. They are important for clinically different reasons. Several are used in vulnerable groups of people, such as older people (*Ginkgo biloba* L., *Panax ginseng* C.A. Mey.), or for self-medication for minor issues (*Valeriana officinalis* L. as a sleep aid); others are widely consumed foods and nutritional supplements for health maintenance (*Allium sativum* L., garlic; *Zingiber officinale* Roscoe, ginger). Echinacea merits attention as it is often administered to children as an immunostimulant.

As shown in Table 3, in vitro evidence frequently does not predict documentable clinical interaction. St John's wort is the only herb in the list with a battery of preclinical results that would predict an interaction; it potently induces many cytochrome P450 enzymes and strongly induces P-glycoprotein. Conversely, for garlic and ginger, both widely eaten and taken as herbal medicines, the reported cytochrome P450 inhibition does not seem to be detrimental to health – in fact, it is part of their chemopreventive effects – illustrating that cytochrome P450 enzyme induction, especially when combined with P-glycoprotein induction, is so far the best predictor of HDIs.

The primary genetic polymorphisms involve CYP2D6, CYP2C19 and CYP2C9. In people who are ultrarapid metabolizers, high activity of polymorphic enzymes may result in treatment failure due to subtherapeutic plasma levels; in people who are poor metabolizers, reduced clearance may lead to overt toxicity (Samer et al., 2013). Thus far, the study of polymorphism has barely been explored in HDIs.

Table 3. Cytochrome P450 (CYP) and P-glycoprotein (P-gp) activity of some commonly used herbal medicines, and their interaction reports

Plant species name and part used	Common name	Major constituents	CYP involvement	P-gp and other transporter effects	Clinical interaction reports	References
Allium sativum L., bulb	Garlic	Sulphides (alliin, allicin, ajoene, allyl disulphides), steroidal glycosides, flavonoids	Inhibition of CYP 2C19, 3A4, 3A5 and 3A7 in human and some animal studies	Conflicting results (3 studies)	Several recorded; causality often not proven; widely used food item; may add to cardiovascular (antiplatelet) effects	Hermann and von Richter (2012) Ge et al. (2014) Cho and Yoon (2015)
Echinacea spp., root, herb, juice	Echinacea	Alkylamides (root), caffeic acid derivatives, polysaccharides; some differences between species	No significant inhibition of CYP2D6 or CYP1A2; weak induction of CYP3AA4	Induction of P-gp via PXR activation	No clinical reports; in vivo studies show relative lack of interaction potential	Awortwe et al. (2015) Ardjomand and Bauer (2016)
Ginkgo biloba L., leaf	Ginkgo	Diterpene lactones, ginkgolides, bilobalide; biflavone glycosides (ginkgetin, bilobaletin)	Inhibition of CYP1A2, CYP2C9 and CYP2E1 (extract); induction of CYP3A4 (human in vitro studies)	Induction of P-gp	Several; causality often not proven (vulnerable people); may add to cardiovascular (antiplatelet) effects	Ge et al. (2014) Cho and Yoon (2015)
Hypericum perforatum L., herb	St John's wort	Naphthodianthrones (hypericins); phloroglucinols (hyperforins), flavonols (hyperoside)	Potent induction of CYP3A4, CYP2C9, CYP2C19 and CYP2E1; extracts and hyperforin induce PXR	Strong Induction of P-gp via PXR	High; many recorded events supported by clinical and mechanistic evidence	Ge et al. (2014) Russo et al. (2014)
Salvia miltiorrhiza Bunge, root	Dan Shen	Diterpenoid quinones (tanshinones), phenolic acids (salvianolic acids)	Inhibition of CYP2C19, CYP2C9, CYP3A2 and CYP3A4 and carboxylesterase	Inhibition of P-gp, OAT1 and OAT3	Compound Dan Shen tablets had little influence on pharmacokinetic and pharmacodynamic profiles of warfarin in most people; potential for interaction with warfarin and with ester prodrugs suggested by animal studies, but no clinical reports	Wang and Yeung (2011) Ge et al. (2014) Chua et al. (2015) Lv et al. (2017)
Valeriana officinalis L., root	Valerian	Sesquiterpenes (valerenic acids), monoterpenes, iridoids (valepotriates) in herb but not most extracts	No effect on CYP1A2 or CYP2E1; induction of CYP2D6 and CYP3A4 in vitro but not in vivo	Weak induction of P-gp and UGT 1A1 and 2B7	Review suggests no pharmacokinetic interaction, but may add to sedative effects	Kelber et al. (2014)
Zingiber officinale Roscoe, rhizome	Ginger	Phenolic gingerols (dehydrate to shogaols), essential oil (mono- and sesquiterpenes)	Individual gingerols inhibit CYP; total extract does not	Weak inhibition of P-gp (only 6-gingerol)	Few recorded; causality often not proven; in vivo studies suggest low interaction profile	Jiang et al. (2005) Young et al. (2006) Mukkavilli et al. (2015)

OAT, organic anion transporter; PXR, pregnane X receptor; UGT, uridine diphosphate-glucuronosyltransferase.

2.4 Challenges for evaluating and monitoring herb–drug interactions

Over the past 20 years, case reports, case series, and human and animal pharmacokinetic studies have clearly shown that herbal medicines can interact with other medicines, whether prescribed conventional medicines or other herbal medicines. Much of the evidence is of poor quality, however, often with relevant information missing (Izzo et al., 2016). Even with well-documented interaction reports, it may not be possible to establish a causal relationship without further exploratory investigation. Unlike clinical trials accorded to efficacy studies, it is unethical to subject people to a study with potentially harmful interventions and no expected beneficial therapeutic outcome. Therefore, case reports coupled with pharmacokinetic trials usually constitute the highest level of evidence available for HDIs (Izzo, 2012; Posadzki et al., 2013). Many in vivo and in vitro interactions seen under experimental conditions are unlikely to lead to serious clinical consequences, but they must be evaluated in a mechanistic context (Hermann and von Richter, 2012).

2.4.1 Factors associated with increased risk of herb–drug interactions

For an HDI to be clinically significant, the therapeutic range of the medicine must be narrow, meaning that a small reduction in pharmacological effect will lead to loss of efficacy or a small increase in pharmacological effect will lead to toxicity. A herbal medicine is unlikely to have these properties, and so the main impact of interaction is on the effects of conventional medicines. For an interaction to be significant, the dose–response curve of the medicine must be steep, such that a small change in plasma concentration leads to a significant change in clinical effect.

For many medicines, these conditions are not met because there is an adequate safety margin between effective and toxic plasma levels; this applies to an even greater extent to herbal medicines. Medicines that do meet these conditions, however, such as some antiarrhythmic, antiepileptic, antineoplastic, antithrombotic and immunosuppressant medicines, are susceptible to interactions, and people taking these medicines are usually monitored closely. However, if an individual on any of these medicines presents suddenly with toxic symptoms having previously being stable, it is worthwhile asking whether they have taken any herbal medicines, dietary supplements, or traditional or complementary medicine products recently.

Some of the factors associated with an increased risk of interaction are summarized in Table 4. Additional risks are posed by herbal medicines, such as the potential for lifetime exposure and unsupervised consumption (Shipkowski et al., 2018).

Table 4. Factors associated with increased risk of herb–drug interaction[1]

Steep dose–response curve
Narrow therapeutic index
Route of administration
Problematic disposition or pharmacokinetic properties
Enzyme inducers or inhibitors used for long-term treatment
P-glycoprotein and cytochrome P450 induction or inhibition
Susceptibility to genetic polymorphism
Simultaneous prescribing by several practitioners
Inappropriate self-medication

1 Modified from Chan K (2014). Understanding interactions between Chinese medicines and pharmaceutical drugs in integrated healthcare. Chin J Integr Med. 21(2):83–9.

2.4.2 Complexity of herbal medicines

Many conventional medicines are intended to elicit a specific response in the body, based on a single target. Conversely, most herbal medicines are complex mixtures of active and inactive compounds or ingredients and act multisystemically. The pharmacokinetics of herbal medicines are often not known, and there may be constituents that affect the transport and bioavailability of other herbal compounds or conventional medicines. Standards and techniques for monitoring drug–drug interactions may not be suitable for investigating HDIs. Furthermore, the evidence regarding the interaction potentials of mixed herbal formulae is almost nonexistent, although manufacturers are now beginning to assess these products.

Herbal medicines are rarely produced to the same standards as licensed medicines, unless they are registered as medicines, and the composition of herbal medicines, both qualitatively and quantitatively, is subject to wide variations.

2.4.3 Quality of herbal medicines

Herbal medicines are affected by a complex range of factors, leading to variability in their chemical composition and thus their quality, safety and efficacy. Quality improvement may be achieved by implementing control measures for medicinal plant procurement under good agricultural and field collection practices, processing and manufacture of standardized finished herbal medicinal products under good manufacturing practices, and the adoption and implementation of regulatory standards by member states.

WHO guidelines and monographs provide helpful information on quality-control measures for herbal medicines (WHO, 1999; WHO, 2003; WHO, 2004c; WHO, 2007a; WHO, 2007b; WHO, 2007c; WHO, 2009; WHO, 2010e; WHO, 2011c; WHO, 2017; WHO, 2018).

Botanical sourcing and quality issues

The composition of herbal medicines, qualitatively and quantitatively, can vary widely due to intrinsic and extrinsic factors. Intrinsically, species differences and genetic variations, plant organ specificity, ontogeny (stage of development), and diurnal and seasonal variations

affect the accumulation of active constituents. Extrinsic factors include environmental factors (e.g. geographical origin, soil), methods of cultivation and field collection (e.g. harvest and post-harvest treatments, drying, transport and storage, preservation, processing and manufacturing processes), inadvertent contamination or substitution, and intentional adulteration. These factors contribute to the quality of botanical materials and the herbal medicinal products prepared from them. Label claims may need to be independently verified for phytochemical content, especially for certain types of product such as those for weight loss, muscle development, and ergogenic and sexual enhancement, where adulteration is particularly rife (Gurley et al., 2018).

Processing

Before use as a medicine or for the production of finished herbal medicinal products, the harvested plant material first undergoes primary processing to remove soil, foreign materials and unwanted plant parts. The desired plant part may be subjected to only a few simple processing steps, such as cleaning and drying, or it may undergo a series of more complex steps, such as fermenting, roasting, frying, steaming or boiling. The primary purposes of secondary processing are ensuring quality and safety, including the neutralization of toxicity and diminishing side-effects, modification of therapeutic properties, and enhancing efficacy. Examples of herbal materials requiring specific detoxification processing include aconite root (*Aconitum* sp.), nux-vomica seed (*Strychnos nux-vomica* L.), gansui root (*Euphorbia kansui* S.L. Liou ex S.B. Ho), *Euphorbia pekinensis* Rupr.) and corydalis rhizome (*Corydalis yanhusuo* (Y.H. Chou & Chun C. Hsu) W.T. Wang ex Z.Y. Su & C.Y. Wu) (Zhao et al., 2010). Processed materials can serve as herbal medicines or as starting materials for manufacturing other herbal products. For further information, see WHO (2018).

2.4.4 Patient susceptibility

Genetic factors

Different ethnic groups and individual genetic differences among people from the same ethnic origin have genotypic variations that can alter the activity of drug-metabolizing enzymes and increase the likelihood of interactions (see Section 2.2.4).

Age and gender

Herbal products are used widely by older people (Alsanad et al., 2014; Agabiaka et al. 2017). Metabolic function of the liver and kidney decreases with age, leading to reduced plasma clearance of drugs. Neonates do not have the same range or activity of enzymes for metabolizing drugs; this develops at different rates in individuals over the first two years of life (Lu and Rosenbaum, 2014). These groups of people may be more susceptible to herbal interactions.

The influence of gender-related factors means that men and women may experience different HDIs. For instance, during pregnancy or while breastfeeding, women are often discouraged by conventional medical practitioners from taking all but essential medicines (e.g. for epilepsy). However, conventional practitioners may be unaware that some herbs are used explicitly at these times by local tradition, such as raspberry leaf tea (*Rubus idaeus* L.) during pregnancy, and fenugreek (*Trigonella foenum-graecum* L.) and fennel (*Foeniculum vulgare* Mill.) to enhance lactation. There are no known reports of drug interactions or toxicity involving these herbs that have been published to date, and most have "generally recognized as safe" (https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/) or "qualified presumption of safety" (https://www.efsa.europa.eu/en/topics/topic/qualified-presumption-safety-qps) status, but their use should be closely monitored.

Comorbidities

The blood concentrations of herbal products and drugs metabolized in the liver or eliminated by the kidneys may be altered if the functioning of these organs is impaired. The most common result is an increase in blood levels, leading to enhanced toxicity and potential for HDIs.

People living with cancer are more likely than the general population to take herbal medicines (Alsanad et al., 2014; Poonthananiwatkul et al., 2015). These people are already in a state of impaired health, and so interactions may have severe consequences. In addition, many of the drugs used in chemotherapy have toxic effects even at their usual clinical doses and have a narrow therapeutic index.

Many people with cardiovascular disease take warfarin, which has a high potential for interaction with all drugs. People taking warfarin are monitored for anticoagulant effects at regular intervals, depending on their international normalized ratio (INR), a measure of blood clotting time. This has probably reduced the impact of warfarin interactions with herbal medicines. In addition to anticoagulation, many people with cardiovascular disease also take drugs for conditions such as hypertension, arrhythmias, hyperlipidaemia, hypercholesterolaemia or electrolyte imbalance.

Many central nervous system drugs are associated with side-effects and the potential for interaction with other medicines. People taking these medicines may not know the possible consequences of taking herbal medicines at the same time as neuroleptics and antidepressants. *Hypericum perforatum* L. is commonly indicated to treat low mood conditions and has a high interaction potential; people with depression should be asked specifically whether they are considering taking it (Russo et al., 2014).

Drug interactions are a common and recurring problem in immunocompromised people (Devanathan et al., 2019), including people living with human immunodeficiency virus (HIV), people living with cancer, and people undergoing transplant and taking certain immunosuppressants. People living with HIV may use herbal remedies and dietary supplements alongside conventional treatments; pharmacokinetic interactions between herbal medicines and antiretroviral drugs may increase the risk of toxicity or antiretroviral treatment failure (Stolbach et al., 2015).

2.4.5 Practitioner competence and training

Conventionally trained health-care providers should be familiar with the herbal medicines being taken by their patients and the literature describing their known mechanisms of action, therapeutic use, safety and potential for drug interactions. Similarly, traditional or complementary medicine practitioners should have adequate training (WHO, 2010a; WHO, 2010b; WHO, 2010c) and be familiar with the conventional medicines being taken by their patients. Most importantly, both types of practitioner should be able to counsel their patients with regard to the use of herbal medicines alongside conventional medicines and serve as reference sources for all providers.

3. Data collection, assessment and dissemination of herb–drug interactions

This section contains suggestions for regulators, researchers, clinicians, adverse drug reaction monitors, manufacturers, and other stakeholders concerned with the collection, assessment and dissemination of information on HDIs. The section outlines best current practice for undertaking data collection. The approach is consistent with general pharmacovigilance recommendations for medicines, with additional information required explicitly for herbal medicines.

3.1 Herb–drug interaction reports

There is increasing awareness by conventional practitioners that their patients may use herbal and other natural remedies, but globally such awareness is highly variable. Therefore, there is inconsistent documentation in patient records regarding their use of herbal medicines. As a result, HDIs may be missed, information not collated, and no overall reliable statistics for the incidence of clinical HDIs be available. Regulatory authorities should inform health professionals and consumers about safety issues as they arise; in turn, health professionals, consumers, and herbal medicines manufacturers and sponsors should report any suspected potential herbal interactions to the designated authority (see Section 3.2). The type of reporting will vary in different jurisdictional settings.

Underreporting of herbal medicines use is exacerbated by the inconsistent classification of herbal medicines in different jurisdictions and countries. Herbal medicines may be classified as herbal or botanical drugs, phytomedicines, therapeutic goods, traditional medicines, complementary medicines, natural health products, functional foods, dietary supplements, biologicals, cosmetics and medical devices, but many herbal medicines are not regulated at all. Some herbal medicines can be purchased directly by consumers without expert counselling on their safe use. The same plant product may be regulated differently within one country (e.g. as a food supplement and as a herbal medicine). These different regulatory approaches affect the identification of interactions and the selection of agency to report to. Consequently, the subsequent action(s), if any, taken by the regulatory and enforcement agencies or jurisdictions may be inconsistent, even if the inherent risks are unchanged.

3.2 Pharmacovigilance systems

The WHO Guidelines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems (WHO, 2004a) were prepared in the context of the WHO International Drug Monitoring Programme to strengthen national pharmacovigilance capacity regarding herbal medicines. The aim of the Guidelines is to provide technical guidance within existing national drug safety monitoring systems, or, if these systems are not in place, to facilitate their establishment. The Guidelines also provide standard definitions of terms relating to pharmacovigilance and safety monitoring of herbal medicines in order to promote

internationally coordinated information exchange. The Guidelines identify challenges posed in the safety monitoring of herbal medicines and propose approaches for overcoming these. Special attention is given to the reporting system for adverse reactions and the analysis of their causes. Currently, the majority of reported adverse events related to the use of herbal medicines are attributable either to poor product quality or to improper use (WHO, 2004a).

Although pharmacovigilance systems for monitoring herbal medicines are not in place in many countries, the WHO Collaborating Centre for International Drug Monitoring in Uppsala has been collating reports of adverse events involving herbal medicines from around the world (http://www.who-umc.org/); for example, the pharmacovigilance centre in Morocco reported over 4800 individual herbal case safety reports between 2004 and 2008.

In Africa, a survey of 39 countries identified several voluntary and compulsory pharmacovigilance systems (Skalli and Bencheikh, 2015). In Mali, a programme establishing *médicaments traditionnels améliorés* ("improved traditional medicines") requires standardization and quality control of the herbal medicines, and submission of a dossier of safety and efficacy, in order to obtain marketing authorization (Wilcox et al., 2012).

In Brazil, regulation of herbal medicines, including pharmacovigilance, is established, but only a few reports of herbal interactions have been collected to date. Considering the widespread use of herbal medicines in Brazil, if HDIs occur, they remain unrecognized and unreported (Mazzari and Prieto, 2014).

In China, over 310 000 registered reporters, including from hospitals, clinics and pharmaceutical companies, form a network for monitoring and reporting adverse drug reactions for conventional and herbal drugs (National Center for ADR Monitoring, China, 2016).

In the European Union, the European Association of Poisons Centres and Clinical Toxicologists collaborates with other agencies (https://www.eapcct.org/).

In Indonesia, the National Agency of Drug and Food Control of the Republic of Indonesia has a role in post-marketing surveillance and pre-market evaluation of herbal products. The manufacturer is required to submit a dossier with details of labelling and advice for consumers, including side-effects and possible interactions (WHO, 2019b).

In Thailand, there is a list of registered herbal medicines used in hospitals for intensive safety monitoring (Saokaew et al., 2011).

In India, pharmacovigilance is covered under the auspices of Ayurveda, Siddha, Unani and homoeopathy (https://www.ayushsuraksha.com/).

3.3 Types and relevance of herb–drug interaction reporting

Table 5 summarizes the types of HDI report available and their relevance. Reports for some of the most important herbal medicines are presented in Annex 1 to show how experimental,

mechanistic and clinical evidence can be interpreted together to aid clinical decision-making through published literature.

Although good clinical studies and case reports form the basis of herbal interaction evidence, animal and in vitro studies may be needed to determine causality of the interaction or to support a mechanism. Animal and in vitro results can be useful for interpreting clinical findings and explaining mechanisms of action, and perhaps predicting potential interactions. However, it is important to consider any metabolic transformations that may occur, and the drug and herb concentrations used experimentally, for their relevance to human clinical doses.

The example of *Hypericum perforatum* L. (Table 3) suggests that for well-documented clinical interactions, experimental studies usually provide supporting evidence that more than one mechanism is involved; where these reinforce each other, such as strong induction of cytochrome P450 enzymes coupled with strong induction of P-glycoprotein, it may result in reduced blood levels of many drugs, causing treatment failure. Collating the evidence of reported HDIs also highlights where research may be focused.

Current published evidence mainly concerns herbs of high economic or therapeutic importance, from countries and areas with a more developed tradition and industry (China, European Union, United States). Meta-analyses, which are ideal for evaluating the overall conclusions of several studies, are rarely possible for HDIs because the data sets must be the same to pool the acquired data. The composition (qualitative and quantitative chemical content), formulation and dosage of the herbal medicines being administered in different studies is rarely comparable. A systematic review is therefore usually more appropriate – but this requires a reasonable number of reports to analyse, which is unusual for herbal medicines, and so subjecting such reports to a higher evaluation process is rarely possible. It is even more challenging to assess interactions involving poly-herbal formulae, although an evaluation of the component herbs may allow a tentative identification of the herb causing the interaction. Negative results from clinical studies and in vivo and in vitro tests, which suggest a lack of potential interaction, should always be considered and included in evaluation of a specific herb.

Table 5. Types and relevance of herb–drug interaction reporting

Type of report		Relevance
Human, clinical	Clinical interaction report confirmed (e.g. by repeated challenge)	Highest
	Clinical report unconfirmed but likely on mechanistic grounds	Medium
	Experimental using human healthy volunteers	High
Animal	In vivo using probe drugs	Medium; animal and human cytochrome P450 expression are different
	Ex vivo using isolated tissue or cells	Low; may not consider metabolic transformation
In vitro	Cell culture, e.g. using human or animal cell lines or microsomal preparations	Low; may not consider metabolic transformation or variations in animal and human cytochrome P450 expression

3.4 Assessing clinical reports and human case studies

Causality assessment methods were developed for conventional medicines and may be difficult to apply to herbal medicines and HDIs. The basic information required for clinical reports is the same as for all medicines, with additional information specific for herbal medicines.

In many published reports, information regarding a herbal medicine is incomplete, with the scientific name of the plant material, the parts used, the extraction type or the dosage regimen not stated.

The validity of any report relies on accurate identification of the product or herb, which may be difficult when different common names are used. For example, "ginseng" may refer to several plant species, including *Panax ginseng* C.A. Mey. (Chinese or Korean ginseng), *Panax quinquefolius* L., (American ginseng), *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Siberian ginseng), or *Withania somnifera* (L.) Dunal (Indian ginseng) (Shaw et al., 2012). To avoid confusion, the binomial Latin plant name and botanical authority must be cited where known (Chan et al., 2012).

Table 6 presents the WHO guidelines on pharmacovigilance for herbal medicines (WHO, 2004a).

Table 6. World Health Organization guidelines on information requested for herb–drug interactions[1]

Where permitted by health information privacy codes, and with appropriate confidentiality, some identification of the patient or consumer in order to avoid duplications and facilitate follow-up
Age, sex and brief medical history of the patient or consumer (when relevant); in some countries, ethnicity may need to be specified
Details of suspected herbal product if known: species name (Latin binomial and common names of plant), part of the plant used (e.g. herb, root), preparation method, brand or ingredient name, manufacturer, country of origin, batch number, expiry date and provider (supplier or prescriber)
Administration details: dose and quantity supplied, dosage form, route, frequency, start and stop dates
Indication or reason for use
Adverse reaction data: date of onset, including duration from first administration to event, description with symptoms and signs, severity and seriousness, results of clinical investigations and tests, course and outcome, re-challenge with same products where appropriate
All other medicines used concurrently or recently (including self-medication), with administration details as above
Risk factors where known, e.g. age, impaired renal or hepatic function, previous exposure to herbal medicines concerned, previous allergies, misuse of medicines, social use of drugs
Country where report was made and status of reporter (doctor, pharmacist, nurse, other health-care professional, other non-health-care professional)
Name and address of reporter (to be considered confidential and to be used only for data verification, completion and case follow-up)

1 Based on WHO (2004). WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. Geneva: World Health Organization (http://apps.who.int/medicinedocs/en/m/abstract/Js7148e/).

If an HDI is suspected, as much data as possible must be recorded so the assessment can be revisited when needed, such as in the light of new information or suspected error in the evaluation. The determination of causality of HDIs should be carried out by qualified individuals experienced in clinical pharmacology and pharmacokinetics, and experts in phytochemistry and pharmacognosy should be recruited to investigate specific aspects of the herbal medicines.

3.5 Information retrieval

Many resources are available, including research papers, conference reports, books, review articles and document collections from credible sources. These reports can be identified through systematic surveillance of literature sources, such as the WHO database, international English-language electronic databases (e.g. AMED, CINAHL, IPA, Medicines Complete, NMCD, PubMed), Chinese electronic databases (e.g. CBM, CMCC, CNKI, TCMDS, Wanfang), and other national databases. There are also databases for specific disease targets, such as HIV (http://www.hiv-druginteractions.org) and hepatitis (http://www.hep-druginteractions.org).

Reports of HDIs should be viewed with caution. Speculation based on extrapolation from data associated with an individual constituent of a complex herbal medicine, or those based on large scale in vitro screening exercises or purported mechanisms of action, may not necessarily have clinical significance. The data collected should be evaluated for quality, applicability and clinical relevance in accordance with reporting recommendations for safety monitoring of herbal medicines (WHO, 2004a).

3.6 Dissemination of information

The provision of valid and validated information on HDIs to decision-makers is essential for the safe use of herbal medicines or concomitant use of herbal and conventional medicines. These stakeholders include national, provincial, state and local health authorities and regulatory agencies, pharmacovigilance centres, poison centres, health professional organizations, health-care providers, other health-care professionals, manufacturers, and patients and consumers.

Although it is important that practitioners receive accurate information about HDIs, its dissemination may encounter obstacles similar to those for pharmacovigilance of herbal products (WHO, 2004a). These may include a lack of interest by professional societies and the journals on which practitioners rely for information regarding traditional medicine practices; lack of activity by relevant authorities and health-care professionals regarding reports of herbal interactions; failure to communicate these to patients, consumers, manufacturers and suppliers; conflicts of interest; and inaccurate reporting by media outlets.

Communication strategies should be established to effectively reach, or be easily accessible to, all relevant stakeholders (WHO, 2004a). Methods of communication recommended for the safety monitoring of herbal medicines by the WHO (2004a) guidelines include posting on websites, direct mass mailing to providers of herbal medicines and health professionals, briefings to the mass media and patient and consumer associations, education sessions at health professional society meetings, and continuing education of health-care providers.

4. Managing herb–drug interactions

There are few strategies available for managing HDIs. When health professionals and regulators establish guidelines, the following issues should be considered.

4.1 Education and training of health professionals

4.1.1 Raising awareness

Although an increasing number of people consult their health-care professionals before taking herbal medicines, many do not. Before prescribing any medicines that may result in the manifestation of a harmful HDI, health-care professionals are encouraged to ask their patients for full disclosure of all medicines taken, usual diet, recent changes in diet, and conventional and herbal products they may have taken or intend to take.

4.1.2 Basic and continuing education

Few, if any, courses on herbal medicines are included in the medical curriculum of conventional health-care practitioners, although in countries with a strong tradition of using herbal medicines, such as China and India, training in herbal medicine should be included in medical universities. In Japan, basic instruction in Kampo medicine is included in the medical and pharmaceutical curriculum; for a health-care professional to prescribe or practise Kampo medicine, they must have completed conventional medicine or pharmacy education.

A framework for training traditional medicine practitioners is included in the WHO benchmarks for training herbal practitioners (WHO, 2010a; WHO, 2010b; WHO, 2010c). For health professionals, a curriculum developed by WHO and the International Society for Pharmacovigilance is available to aid planning and conduct training courses in pharmacovigilance (http://isoponline.org/training/pv-curriculum/).

4.1.3 Overview of reporting suspected herb–drug interactions

The safety of medicines is usually monitored through spontaneous reporting pharmacovigilance systems. These systems can be used to report suspected adverse reactions to herbal medicines, including HDIs (WHO, 2004a). Standard forms are available for reporting to designated authorities (e.g. pharmacovigilance centres, regulatory authorities, poison centres) by manufacturers of herbal medicines, doctors, pharmacists, nurses and other health professionals and, in some countries, by patients.

Many countries (e.g. Australia, Canada, China, Japan, Malaysia, Morocco, New Zealand, Philippines, South Africa, Thailand, United Kingdom, United States) have a reporting system for HDIs. In the United States, health professionals and consumers can report suspected adverse drug reactions of herbal medicines (marketed and consumed as

dietary supplements) to the Food and Drug Administration MedWatch scheme. In the United Kingdom, the spontaneous reporting system is referred to as the "yellow card scheme" (because the hard copy of the form is yellow); the Medicines and Healthcare Products Regulatory Agency receives approximately 20 000 yellow card reports every year, of which about 100 concern herbal products (Shaw et al., 2012). Australia has a similar "blue card scheme".

In some countries, such as European Union countries and the United States, poisons control centres, drug information centres and selected consumer organizations can also serve as intake facilities for enquiries on product safety or suspected poisonings, including herbal medicines, and can be useful sources of information on HDIs. The value of these alternative centres in public safety monitoring has been shown in Morocco, for example, where 62% of reports in the poisons control database concerned herbal medicines (Skalli and Bencheikh, 2012).

In reporting a suspected HDI, the reporter does not need to confirm any association between the drug and the effect. WHO (2004a, p.23) describes how the degree of certainty of a causal relationship is assigned to one of six categories by the Uppsala Monitoring Centre (Table 7). These criteria were developed with the aim of providing a structured approach to determining the strength of the relationship between a reported event and suspected product. This is a combined assessment that considers the clinical and pharmacological aspects of the case history and the quality of the data reported.

Table 7. Causality categories described by the Uppsala Monitoring Centre[1]

1	Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to medicine administration, and that cannot be explained by concurrent disease or other medicines or chemicals. The response to withdrawal of the medicine (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary
2	Probable/likely	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the medicine, unlikely to be attributed to concurrent disease or other medicines or chemicals, and that follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition
3	Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the medicine, but that could also be explained by concurrent disease or other medicines or chemicals. Information on medicine withdrawal may be lacking or unclear
4	Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to medicine administration that makes a causal relationship improbable, and in which other medicine, chemicals or underlying disease provide plausible explanations
5	Conditional/ unclassified	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment, or the additional data are under examination
6	Unassessable/ unclassifiable	A report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory, and that cannot be supplemented or verified

[1] Source: UMC (2000). Safety monitoring of medicinal products. Uppsala: Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring (https://www.who-umc.org/media/1703/24747.pdf).

As a step towards harmonization in medicine regulation in the European Union, three causality categories were proposed by the European Union pharmacovigilance working parties (Table 8).

Table 8. Causality categories proposed by the European Union pharmacovigilance working parties[1]

Category A	Reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable
Category B	Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain and may even be doubtful, e.g. because of missing data, insufficient evidence or the possibility of another explanation
Category C	Reports where causality is, for one or another reason, not assessable, e.g. because of missing or conflicting data

1 Source: WHO (2019b). Essential medicines and health products information portal. Geneva: World Health Organization (http://apps.who.int/medicinedocs/en/d/Jh2934e/15.html).

National pharmacovigilance centres, poison control centres and other designated bodies collecting HDI reports use statistical methods to detect and analyse signals of adverse events for further study or for regulatory action. Usually, a series of similar events rather than a single report is required to generate a signal. The significance of a given signal is dependent upon the seriousness of the event, geographical occurrence (local, national, regional, global), and the quality of the information (WHO, 2002).

Published reports documenting HDIs are available from several online databases provided by professional, commercial and nongovernmental organizations and from governmental agencies (e.g. https://nccih.nih.gov/health/providers/digest/herb-drug, https://medlineplus.gov/druginfo/herb_All.html). The Uppsala Monitoring Centre manages the global WHO database for international drug monitoring (http:/www.who-umc.org/).

When an HDI is suspected or confirmed, there should be an expected protocol to be followed by both conventional and traditional practitioners in accordance with the regulation of that country.

4.2 Consumer information and education

People may not associate their signs and symptoms with the use of herbal medicines, or may not be aware of the importance of reporting adverse effects. Therefore, individuals should be educated and encouraged to be open with their clinicians about their use of all medicines and supplements. Although the prescriber should report the suspected case, individuals can also report suspected adverse effects in many countries (e.g. Australia, China, European Union countries, India, Indonesia, Morocco). The WHO (2004b) Guidelines suggest that "because of the limited knowledge about interactions between conventional medicines and herbal medicines, this is an area that needs further study". The Guidelines provide a reference for guiding consumers in choosing a traditional and complementary medicine therapy that is safe and effective. They state that "consumers need to be informed about any potential interactions involved in their therapy". Relevant information should be provided in a patient information leaflet, which is a requirement in some regions (e.g. Brazil, European Union, Indonesia) but is not mandatory in others.

Patient information leaflets and other resources for consumer advice such as websites should include the following, in addition to the usual information concerning indications, contraindications and dosage:

- If you are feeling unwell, please tell your doctor or another health-care professional that you are taking a herbal medicine with other medicines.
- Show this leaflet to your doctor or pharmacist so they know what you are taking.
- Ask whether a report about your case will be made.
- You can make a report yourself if you think it is important. Consult the authorized website for guidance.

4.3 Research strategies for herb–drug interactions

4.3.1 Research methods

Producing evidence to support HDIs would ideally be accomplished by studying the interaction between the herbal medicine as the active pharmaceutical ingredient and the interacting drug. As each herbal product contains hundreds of constituent molecules, and these may vary between batches of the herb, delineating HDIs using standard in vitro and in vivo methods is usually unfeasible.

In vivo methods may offer better models than in vitro methods for studying complex mixtures of chemicals, but metabolic differences between animals and humans complicate the interpretation of results. No standard methods are currently available for the study of HDIs, but new methods are being researched (Jackson et al., 2017; Pelkonen et al., 2017). Ethical issues often make human clinical intervention trials difficult to justify, and thus individual case reports and clinical observational studies remain the primary source data for identification of new HDIs and confirming suspected risks.

As standard research methods are not available to study HDIs, social science and public health research methods can be used to help understand consumer behaviour and attitudes to assist health regulators and providers in policy development.

An emerging strategy for targeting experiments and clinical interventions for herbal medicine research is combining pharmacoepidemiological methods with case–control and cohort studies (Shaw et al., 2012). If herbal interaction signals are detected from spontaneous pharmacovigilance reports (evaluated per pharmacovigilance guidelines; WHO, 2004a), they may serve as a rationale for conducting a case–control study. Clinical studies in tandem with chemical characterization using metabolomics can be applied to identify compounds present in herbal medicines that are responsible for the effect.

4.3.2 Correlation of preclinical studies with clinical outcomes

Recent reviews have suggested that although in vitro screening of plant extracts against enzymes responsible for drug metabolism may offer only limited evidence to correlate

preclinical results with clinical outcomes, it may provide preliminary data for more in-depth investigations (Brewer and Williams, 2012; Fasinu et al., 2012; Gurley et al., 2012; Izzo, 2012).

Table 3 contains a summary of preclinical and experimental tests on specific herbs and the reported clinical interactions for these herbs. It shows that certain in vitro effects are likely to be related to significant interactions. To further understand these interactions, it is important to consider the processes of preparation of the herbal medicine and potential changes in its chemistry. All extracts should be chemically characterized before testing.

4.3.3 Identification of interactive constituent(s)

A chemical analysis should be undertaken to identify, if possible, the constituent(s) responsible for the interaction(s). These component(s) may or may not be the same as the active constituents, and bioassays may be useful in assessing the role of the constituent(s) in the interaction.

In the event that compounds responsible for the HDI are not necessary for therapeutic activity, then they could be removed. For instance, *Hypericum perforatum* L. contains hyperforin; this is the main interacting compound but is also an active component (in addition to the hypericins and flavonoids). A hyperforin-free product has been shown to be efficacious (Russo et al., 2014). There are no other well-documented examples of constituents being removed to reduce HDIs.

4.3.4 Combination herbal medicines

In addition to investigating the safety of single herbs or medicines, chemical and pharmacological research on herbal formulation is required: in most traditional and complementary medicine systems, mixtures of herbs are used more commonly than single herbs or chemical compounds. The contribution of individual herbs to the overall effect is complex and may involve pharmacodynamic or pharmacokinetic effects. The herbal mixture may be treated as the active pharmaceutical ingredient and tested as an entity. In cases where a component herb is suspected to be the one that causes an HDI, that individual herb must be tested. Fingerprint chemical profiles of the active pharmaceutical ingredient should be recorded and analysed in accordance with WHO guidelines and other pharmacopoeial and relevant standards.

4.3.5 Overview of research strategies

Currently, limited guidance or useful information is available for rapid reference on HDIs. Herbal medicines are included in the drug–drug interaction guideline of the European Medicines Agency (2012), but specific guidelines for HDIs have not been developed. There is also a lack of evidence regarding the incidence and severity of herbal interactions. To address these concerns, rigorous research is required to provide support for evaluating clinical reports and making decisions.

Most of the research on HDIs has been performed in a limited number of countries. It is crucial to expand research in regions where herbal medicines are used routinely alongside conventional medicines in order to harness knowledge and experience.

Although no uniform approach is taken globally, many countries have already established, or even integrated into national health-care systems, regulatory and monitoring programmes to safeguard the use of traditional and complementary medicines in line with national and regional needs. When formulating these initiatives, WHO policies and guidelines should be considered, and existing resources and monitoring schemes exploited. Key areas for attention can be found in the WHO Traditional Medicine Strategy: 2014–2023 (WHO, 2013), which recommends that Member States ensure high-quality traditional medicine products, establish appropriate regulatory frameworks for practitioners and products, and improve the education of practitioners and their patients. Regulatory frameworks and approaches on HDIs should be established by Member States according to their individual circumstances and needs.

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Annex 1. Summary of interaction reports for well-documented herbs

Introduction

A selection of 110 reports and case histories has been collected in this annex to show how a varied body of evidence can be established to support herb–drug interactions (HDIs), with examples from the most common herbal medicines used today. It is not intended to be a comprehensive account of all interactions reported for each herb, nor should it report all pharmacokinetic experiments that support an interaction or reports of other adverse drug reactions. It is intended simply to illustrate how experimental and clinical evidence can be interpreted together to decide upon the likelihood or causality of an interaction.

The herbs were chosen based on a preliminary search to identify the most cited herbs in HDI studies, but the number of citations does not necessarily reflect the likelihood or seriousness of an interaction, since "negative" or "lack of interaction" studies are also included. Further review references are provided for certain herbs where the entries have been truncated.

The reports cited in the annex were selected as examples for different medicines involved in the interaction and subjected to a critical evaluation, but inevitably some important studies have been omitted purely due to space constraints. In vitro or in vivo animal studies are included only if they support a mechanism of interaction for a human study. Multi-ingredient herbal formulae, although crucial in the application of most forms of traditional medicine, are not included due to difficulties in ascribing causality to a specific component. The mechanism(s) ascribed to an interaction may have been updated since the earlier reports; our citations are those of the conclusions of the original study.

Empty cells in the tables denote that information may have been insufficient or of poor quality or would not meet the purpose of this document, rather than a negative effect.

Strategy for search

Searches using the keywords "herb–drug interaction" and "herbal interaction" were carried out using PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Science Direct (http://www.sciencedirect.com/), Google Scholar (https://scholar.google.com/) and NAPRALERT (https://www.napralert.org).The Chinese literature and databases were also searched without restriction on the study design. After removing duplicates, papers retrieved were reviewed for additional relevant citations. Studies where the full paper was unavailable were excluded as they could not be evaluated properly.

A selection of examples of HDI reports in line with the purposes of this document was compiled and reviewed by expert panels in two global reviews. Additional reports suggested by experts during the review process were then added where appropriate. These are summarized in Table A1.1.

Table A1.1. Summary of studies included in Annex[1]

Annex table	Herb	Number of studies cited			
		Total	Human [1]	Animal	In vitro
A1.2	*Astragalus* spp. (milk vetch)	4	1	3	
A1.3	*Curcuma longa* L. (turmeric)	8	3	3	2
A1.4	*Echinacea* spp. (coneflower)	8	8		
A1.5	*Ginkgo biloba* L. (maidenhair tree)	19	13	4	2
A1.6	*Glycyrrhiza* spp. (liquorice)	4		4	1
A1.7	*Hypericum perforatum* L. (St John's wort)	26	26		
A1.8	*Panax ginseng* C.A. Mey. (ginseng)	10	8	2	
A1.9	*Salvia miltiorrhiza* Bunge (Dan Shen)	11	3	5	3
A1.10	*Schisandra* spp. (magnolia vine)	11	3	7	1
A1.11	*Silybum marianum* (L.) Gaertn. (milk thistle)	6	5		1
A1.12	*Zingiber officinale* Roscoe (ginger)	3	2		1
	Total	*110*			

1 Human studies contain both case reports/series and clinical trials.

Table A1.2. Astragalus: Astragalus mongholicus Bunge/Astragalus propinquus Schischkin [= Astragalus membranaceus (Fisch.) Bunge] (Leguminosae); milk vetch – four studies

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Docetaxel	35 mg/ m^2/ week for 3 weeks	*Astragalus mongholicus* (Jinfukang)	Multiherb formula containing Astragalus	75 ml/m^2/day	20 people living with lung cancer			No effect	N/A	No interaction	Cassileth et al. (2009)
Pioglitazone	1.5 mg/ kg single dose	10 : 1 ratio decoction from granules	Not stated	2.8 g/kg/day for 7 days		Rat, type 2 diabetes		No effect	N/A	No interaction	Yuan et al. (2012)
Theophylline	15 mg/kg	Astragaloside IV (AG-IV)	Pure AG-IV	3 mg/kg IV for 7 days		Rat		Reduced clearance of theophylline	Inhibition of CYP1A2	Potential interaction: increased toxicity of theophylline	Zhang et al. (2013)
Midazolam	15 mg/kg	Extract	Not stated	10 mg/kg		Rat		Increase in Cmax and AUC	Inhibition of CYP3A4	Potential interaction: increased effect of midazolam	Pao et al. (2012)

AUC, area under concentration–time curve; Cmax, maximum plasma concentration; CYP, cytochrome P450; IV, intravenous; N/A, not applicable.

Cassileth BR, Rizvi N, Deng G, Yeung KS, Vickers A, Guillen S, et al. (2009). Safety and pharmacokinetic trial of docetaxel plus an Astragalus-based herbal formula for non-small cell lung cancer patients. Cancer Chemother Pharmacol. 65(1):67–71.

Pao LH, Hu OY, Fan HY, Lin CC, Liu LC, Huang PW (2012). Herb–drug interaction of 50 Chinese herbal medicines on CYP3A4 activity in vitro and in vivo. Am J Chin Med. 40(1):57–73.

Yuan YM, Gao JW, Shi Z, Huang P, Lu YS, Yao MC, Huang M (2012). Herb–drug pharmacokinetic interaction between radix astragali and pioglitazone in rats. J Ethnopharmacol. 144(2):300–304.

Zhang YH, Zhang YJ, Guo YL, Li WJ, Yu C (2013). Astragaloside IV inhibited the activity of CYP1A2 in liver microsomes and influenced theophylline pharmacokinetics in rats. J Pharm Pharmacol. 65(1):149–55.

Table A1.3. Curcuma longa L. (Curcuma domestica Val.) (Zingiberaceae); turmeric – eight studies[1]

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Carboplatin, etoposide, vincristine	Carboplatin, etoposide and vincristine as probe drugs	Curcumin	Curcumin	N/A			Human retinoblastoma cells	Synergistic cytotoxic effect	Not stated	Potential interaction: may enhance cytotoxicity	Sreenivasan et al. (2015)
Clopidogrel, warfarin	Clopidogrel and warfarin as probe drugs	Curcumin	Curcumin	25, 50 or 100 mg/kg for 7 days		Rat		Competitive inhibition of CYP2C19; negligible effect on other CYP enzymes	Inhibition of CYP2C19	Unclear	Liu et. (2013)
Dextromethorphan	30 mg single dose	Turmeric powder, ethanolic extract	N/A	Not stated	6 males			Increase in urine metabolic ratio of dextromethorphan/ dextrorphan	Inhibition of CYP2D6	Unclear	Al-Jenoobi et al. (2015)
	100 µg/ml		N/A				Human liver microsomes	Inhibition of O- and N-demethylation of dextromethorphan			
Everolimus	0.5 mg/kg	Curcumin	Curcumin	50–100 mg/kg		Rat		Decrease in AUC and Cmax of everolimus with lower bioavailability	Induction of CP3A4; inhibition of P-gp	Interaction: reduced efficacy of everolimus	Hseih et al. (2014)
Fluindione	Not stated	Turmeric powder infusion	Not stated	2.5 g/day for 5 days	1 woman aged 56 years			Elevation of INR	Not stated	Interaction: increased risk of bleeding	Daveluy et al. (2014)
Losartan	10 mg/kg gavage	Curcumin	Curcumin	100 mg/kg for 7 days		Rat		Increased plasma concentrations of losartan and its metabolites	Inhibition of P-gp, inhibition of CYP3A4	Unclear	Liu et al. (2012)

Table A1.3. Curcuma longa L. (Curcuma domestica Val.) (Zingiberaceae); turmeric – eight studies[1] (Con't.)

Drug details		Herb and product details			Study details						
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/ human	In vivo	In vitro	Symptoms/ outcomes	Hypothesized mechanism	Evaluation	Reference
Sulfasalazine	2 g	Curcumin capsules	Curcumin	2 g	8 males			Increased plasma levels of sulfasalazine	Inhibition of P-gp	Interaction: increased bioavailability of sulfasalazine	Kusuhara et al. (2012)

AUC, area under concentration–time curve; Cmax, maximum plasma concentration; CYP, cytochrome P450; INR, international normalized ratio; N/A, not applicable; P-gp, P-glycoprotein.

1 For further details of the complex pharmacokinetics of the curcuminoids, see Bahramsoltani R, Rahimi R, Farzaei MH (2017). Pharmacokinetic interactions of curcuminoids with conventional drugs: a review. J Ethnopharmacol. 209:1–12.

Al-Jenoobi FI, Al-Thukair AA, Alam MA, Abbas FA, Al-Mohizea AM, Alkharfy KM, Al-Suwayeh SA (2015). Effect of Curcuma longa on CYP2D6- and CYP3A4-mediated metabolism of dextromethorphan in human liver microsomes and healthy human subjects. Eur J Drug Metab Pharmacokinet. 40(1):61–6.

Daveluy A, Géniaux H, Thibaud L, Mallaret M, Miremont-Salamé G, Haramburu F (2014). Probable interaction between an oral vitamin K antagonist and turmeric (Curcuma longa). Therapie. 69(6):519–20.

Hsieh YW, Huang CY, Yang SY, Peng YH, Yu CP, Chao PD, Hou YC (2014). Oral intake of curcumin markedly activated CYP 3A4: in vivo and ex-vivo studies. Sci Rep. 4:6587.

Kusuhara H, Furuie H, Inano A, Sunagawa A, Yamada S, Wu C, et al. (2012). Pharmacokinetic interaction study of sulfasalazine in healthy subjects and the impact of curcumin as an in vivo inhibitor of BCRP. Br J Pharmacol. 166:793–803.

Liu AC, Zhao LX, Lou HX (2013). Curcumin alters the pharmacokinetics of warfarin and clopidogrel in Wistar rats but has no effect on anticoagulation or antiplatelet aggregation. Planta Med. 79(11):971–7.

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Table A1.4. Echinacea: Echinacea purpurea (L.) Moench./Echinacea angustifolia DC./Echinacea pallida (Nutt.) Nutt. (Asteraceae); purple coneflower, narrow-leaved coneflower, pale coneflower – eight studies[1]

Drug details		Herb and product details			Study details					
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/human	In vivo	In vitro	Symptoms/outcomes	Hypothesized mechanism	Evaluation	Reference
Caffeine, midazolam	Caffeine 200 mg, midazolam 0.05 mg/kg IV	Root extract *Echinacea purpurea* (Nature's Bounty)	Not stated	400 mg 4 times/day for 8 days	12 people (6 female)			Increased systemic clearance of oral caffeine and IV midazolam	Induction of CYP1A2 and CYP3A4; no effect on other enzymes	Potential interaction with caffeine and midazolam	Gorski et al. (2004)
Darunavir, ritonavir	Darunavir 600 mg/ritonavir 100 mg 2 times/day for 4 weeks	Root extract *Echinacea purpurea* (Arkopharma)	Not stated	500 mg every 6 h on days 1–14	15 people living with HIV			Little overall effect on darunavir pharmacokinetics, but some individuals showed decrease in AUC; no effect on ritonavir	Induction of CYP3A4	Potential interaction with darunavir in some people; no interaction with ritonavir	Moltó et al. (2011)
Digoxin	0.25 mg	Extract of *Echinacea purpurea* all parts, and *Echinacea augustifolia* root	Standardized 2.2 mg isobutylamides	1 capsule 3 times/day for 14 days	18 people (9 female)			No change in pharmacokinetics of digoxin	N/A	No interaction	Gurley et al. (2008)
Docetaxel	135 mg as 60 min IV infusion before echinacea	Drops containing 95% aerial parts and 5% root *Echinacea purpurea*	Not stated	20 drops 3 times/day	10 people living with cancer			No change in pharmacokinetics of paclitaxel	N/A	No interaction	Goey et al. (2013)
Etoposide	50 mg/m^2 on days 1–5 of each cycle	Not stated	Not stated	Not stated	1 male living with lung cancer			Thrombocytopenia requiring platelet transfusion	Not stated	Potential drug interaction: increase in toxicity of etoposide	Bossaer et al. (2012)
Etravirine	400 mg/day	Extract of root of *Echinacea purpurea*	Not stated	500 mg every 8 h for 14 days	15 people living with HIV			No change in any pharmacokinetic parameters	N/A	No interaction	Moltó et al. (2012)

Table A1.4. Echinacea: Echinacea purpurea (L.) Moench./Echinacea angustifolia DC./Echinacea pallida (Nutt.) Nutt. (Asteraceae); purple coneflower, narrow-leaved coneflower, pale coneflower – eight studies[1] (Con't.)

Drug details		Herb and product details			Study details					
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/human	In vivo	In vitro	Symptoms/outcomes	Hypothesized mechanism	Evaluation	Reference
Lopinavir, ritonavir	Lopinavir 400 mg or ritonavir 100 mg 2 times/day for 29.5 days	Fresh liquid extract 8 : 1 *Echinacea purpurea* herb soft-gel capsules 250 mg	Standardized alkylamides, polysaccharides, cichoric acid	500 mg 3 times/day on days 16–28	13 people (5 female)			No effect on concentrations of lopinavir or ritonavir	Possible induction of CYP3A4 by echinacea counteracted by inhibition by ritonavir	No interaction	Penzak et al. (2010)
Warfarin	25 mg	Extract of *Echinacea purpurea* and *Echinacea angustifolia* root (MediHerb)	Standardized 75 mg total alkamides	1275 mg 4 times/day	12 males			No pharmacodynamic, platelet aggregation or baseline clotting changes; small increase in clearance of *S*-warfarin	N/A	No interaction	Abdul et al. (2010)

AUC, area under concentration–time curve; CYP, cytochrome P450; HIV, human immunodeficiency virus; IV, intravenous; N/A, not applicable.

1 For a review of echinacea interactions, see Gurley BJ, Fifer EK, Gardner Z (2012). Pharmacokinetic herb–drug interactions (part 2): drug interactions involving popular botanical dietary supplements and their clinical relevance. Planta Med. 78(13):1490–514.

Abdul MI, Jiang X, Williams KM, Day RO, Roufogalis BD, Liauw WS, et al. (2010). Pharmacokinetic and pharmacodynamic interactions of echinacea and policosanol with warfarin in healthy subjects. Br J Clin Pharmacol. 69(5):508–15.

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Goey AK, Meijerman I, Rosing H, Burgers JA, Mergui-Roelvink M, Keessen M, et al. (2013). The effect of Echinacea purpurea on the pharmacokinetics of docetaxel. Br J Clin Pharmacol. 76(3):467–74.

Gorski JC, Huang SM, Pinto A, Hamman MA, Hilligoss JK, Zaheer NA, et al. (2004). The effect of echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo. Clin Pharmacol Ther. 75(1):89–100.

Gurley BJ, Swain A, Williams DK, Barone G, Battu SK (2008). Gauging the clinical significance of P-glycoprotein-mediated herb-drug interactions: comparative effects of St John's wort, echinacea, clarithromycin, and rifampin on digoxin pharmacokinetics. Mol Nutr Food Res. 52(7):772–9.

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Moltó J, Valle M, Miranda C, Cedeño S, Negredo E, Barbanoj MJ, Clotet B (2011). Herb–drug interaction between Echinacea purpurea and darunavir–ritonavir in HIV-infected patients. Antimicrob Agents Chemother. 55(1):326–330.

Penzak SR, Robertson SM, Hunt JD, Chairez C, Malati CY, Alfaro RM, et al. (2010). Echinacea purpurea significantly induces cytochrome P450 3A activity but does not alter lopinavir–ritonavir exposure in healthy subjects. Pharmacotherapy. 30(8):797–805.

Table A1.5. Ginkgo biloba L.; (Ginkgoaceae); maidenhair tree, fossil tree – 18 studies

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Amlodipine	1 mg/kg before and after extract (GBE)	Extract, tablets	Standardized: ginkgolide (GKL) A 1.9%, GKL B 4.6%, bilobalide 3.8%	100 mg/ kg/day for 10 days		Rat		Cmax, AUC and elimination increased by extract, GKL B, bilobalide	Inhibition of CYP3A4	Unclear	Wang et al. (2016)
Antihormone therapy	Anastrozole, letrozole, tamoxifen; usual treatment	Extract (EGB 761) tablet 120 mg	Standardized: 24% flavones, 6% terpene lactones	120 mg 2 times/day for 3 weeks	Open-label crossover study: 60 women, n = 20 per group			No difference for any drugs; 31/60 reported no side-effects; others cited nausea, diarrhoea or headache	N/A	No interaction	Vardy et al. (2013)
Aspirin	325 mg/day	Extract (EGB 761) tablet 300 mg	Standardized: 24% flavones, 6% terpene lactones	300 mg/ day versus placebo	Double-blind RCT: 55 people aged ≥ 69 years with risk factors for cardiovascular disease			No detectable impact on coagulation over 4 weeks	N/A	No interaction	Gardner et al. (2007)
Atorvastatin	40 mg single dose before and after extract	Extract tablet 120 mg	Standardized (not stated)	360 mg/day for 14 days	16 males			AUC and Cmax reduced; no effect on markers of cholesterol synthesis/absorption	N/A	No interaction	Guo et al. (2012)
Cilostazol	100 mg 2 times/ day	Extract (Ginexin)	Not stated	80 mg 2 times/day for 7 days	RCT crossover: 34 males			No changes in bleeding times or adverse events	No effect on CYP3A4 or CYP2C19	No interaction	Kim et al. (2014)

Table A1.5. Ginkgo biloba L.; (Ginkgoaceae); maidenhair tree, fossil tree – 18 studies (Con't.)

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Clopidogrel	7.5 mg/kg on day 15	Extract (EGB 761)	Standardized: 24% flavones, 6% terpene lactones	4, 20 or 100 mg/kg		Rat		Dose-dependent increase in Cmax and AUC of clopidogrel active metabolite	Activation of PXR, inhibition of P-gp, induction of multiple CYP enzymes	Unclear	Deng et al. (2016)
	10 µM						Rat liver microsomes				
Donepezil	1.5 mg/kg/day for 14 days	Extract (EGB 761)	Standardized: 22–27% flavones, 5–7% terpene lactones	100 mg/kg/day for 14 days		Rat		Acetylcholinesterase, choline acetyl transferase, choline uptake unaffected	N/A	No interaction	Stein et al. (2015)
Efavirenz	Usual regimen (> 10 years)	Extract tablet	Not stated	300 mg/day for 2 months	Man aged 41 years living with HIV			Treatment failure	Induction of CYP2B6	One case; potential interaction	Naccarato et al. (2012)
Ibuprofen	600 mg/day	Extract (Gingium, Biocur)	Not stated	40 mg 2 times/day	Man aged 71 years			Death due to cerebral haemorrhage	Inhibition of platelet aggregation	One case; potential interaction	Meisel et al. (2003)
Omeprazole	40 mg before and after treatment	Extract tablet 70 mg	Standardized: 22.9% flavones, 6.8% terpene lactones	140 mg 2 times/day for 12 days	18 males genotyped for CYP2C19			Decrease in ratio of AUC omeprazole to 5-hydroxy-omeprazole	Induction of CYP2C19	Reduced plasma omeprazole in poor metabolizers	Yin et al. (2004)
Paclitaxel	3.5 µM	Hydrolysed extract	Quantified for GKL, bilobalide and flavones	10–100 mM terpene lactones			Human hepatocytes	Dose-dependent inhibition of 6α-hydroxylation of paclitaxel	Inhibition of CYP2C8	May result in increased blood levels of paclitaxel	Etheridge et al. (2009)

Table A1.5. Ginkgo biloba L.; (Ginkgoaceae); maidenhair tree, fossil tree – 18 studies (Con't.)

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Phenytoin	Person's usual regime	Extract; also other herbal medicines	Not known	Not known	Man aged 55 years			Fatal seizure associated with subtherapeutic plasma levels of phenytoin	Induction of CYP2C19	Interaction: reduced plasma levels of phenytoin	Kupiec and Raj (2005)
Simvastatin	40 mg/day with and without GBE	Extract tablet 120 mg	Standardized: 24% flavones, 6% terpene lactones	120 mg 2 times/day for 14 days, repeated	RCT crossover: 14 males			Reduced AUC and Cmax of simvastatin, but no other effect on pharmacokinetics or cholesterol levels	Possible pharmacodynamic effects at high dose	Unclear	Dai et al. (2013)
Talinolol	100 mg before and after GBE treatment	Extract tablet 120 mg	Standardized (not stated)	Single dose of 120 or 360 mg/day for 14 days	10 males, 3-stage sequential study			No effect of single dose; 14-day treatment increased AUC of talinolol by 33%	Inhibition of P-gp	Unclear	Fan et al. (2009)
Valproate	Person's usual regime	Extract, with other herbal medicines	Not known	Not known	Man aged 55 years			Fatal seizure associated with subtherapeutic plasma levels of valproate	Induction of CYP2C19	Interaction: reduced plasma levels of valproate	Kupiec and Raj (2005)
Warfarin	Person's usual regimen	Person's usual dose	Various, mainly not stated	N/A	Literature review with statistical processing			Increased risk of bleeding	Not investigated	Interaction: increase in warfarin levels	Stoddard et al. (2015)
	1.5 mg/kg on days 3–5	Extract, GKL B, bilobalide	Standardized:24.9% flavones, 6.4% GKL, 4.2% bilobalide	Extract 1 g; GKL B 140 mg; bilobalide 10 mg/kg for 5 days		Mouse		Extract/GKL B did not cause bleeding; extract reduced warfarin effects	Induction of multiple CYP enzymes by bilobalide	Reduced effect with high levels of bilobalide	Taki et al. (2012)
	25 mg	Extract (EGB 761) tablet 300 mg	Standardized:22–27% flavones, 5–7% terpene lactones	300 mg 3 times/day for 7 days	12 males			No effect on distribution or protein binding of *S*- or *R*-warfarin	None	No interaction	Jiang et al. (2005)

Table A1.5. Ginkgo biloba L.; (Ginkgoaceae); maidenhair tree, fossil tree – 18 studies (Con't.)

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypo-thesized mecha-nism**	**Evalua-tion**	**Refer-ence**
Drug probe cocktail	Caffeine, omeprazole midazolam, tolbutamide	Extract EGB 761	Standardi-zed:22–27% flavones, 5–7% terpene lactones	240 mg/day for 8 days	RCT crossover: 18 people			No significant effect, no clinical symptoms	N/A	No interaction	Zadoyan et al. (2012)

AUC, area under concentration–time curve; Cmax, maximum plasma concentration; CYP, cytochrome P450; N/A, not applicable; P-gp, P-glycoprotein; PXR, pregnane X receptor; RCT, randomized controlled trial.

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Table A1.6. Glycyrrhiza: Glycyrrhiza glabra L., Glycyrrhiza uralensis Fisch. ex DC., Glycyrrhiza inflata Batalin (Leguminosae); liquorice, licorice – four studies[1]

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Ciclosporin	2.5 mg/kg	Extract	Extract and glycyrrhizin	150 mg/kg once, or once a day for 7 days		Rat		Decreased ciclosporin blood levels	Induction of P-gp and CYP3A4	Interaction: reduced blood levels of ciclosporin	Hou et al. (2012)
Kansui	Dried herb *Euphorbia kansui* S.L. Liou ex S.B. Ho	Decoction of *Glycyrrhiza uralensis* Fisch. (GU)	Not stated	Varying ratios		Rat		Reduced efficacy, increased toxicity	Inhibition of CYP2C19 and increased solubility of kansui diterpenes	Interaction: may reduce efficacy and increase toxicity of kansui	Shen et al. (2016)
Methotrexate	5 mg/kg	Decoction of GU and glycyrrhizin (GZ)	Characterized for GZ	75 or 150 mg/kg of GZ or liquorice decoction (containing 75 or 150 mg/kg of GZ) once a day for 7 days		Rat		AUC and mean residence time of methotrexate increased by GZ and liquorice decoction	Inhibition of breast cancer resistance protein (BCRP) and multidrug resistance proteins (MRP2)	Interaction: increased toxicity of methotrexate	Lin et al. (2009)
Peony root	Decoction of *Paeonia lactiflora* Pall. root (PR)	Decoction of GU, dose ratio varying	Characterized for GZ			Rat		Decreased bioavailability of paeoniflorin	Activation of P-gp and CYP3A4; ratio between PR and GU critical for effect	Unclear	Xu et al. (2013)

AUC, area under concentration–time curve; CYP, cytochrome P450; P-gp, P-glycoprotein.

1 Liquorice and glycyrrhizin are known to cause hypertension and hypokalaemia and may therefore interact with other potassium-depleting drugs, such as diuretics, and increase the risk of digoxin toxicity. For further details of the highly complex interactions of liquorice and its constituents, and its use in traditional formulae to modify the effects of other herbs, see Nazari, S, Rameshrad M, Hosseinzadeh H (2017). Toxicological effects of Glycyrrhiza glabra (licorice): a review. Phytother Res. 31:1635–50; and Wang X, Zhang H, Chen L, Shan L, Fan G, Gao X (2013). Liquorice: a unique "guide drug" of traditional Chinese medicine – a review of its role in drug interactions. J Ethnopharmacol. 150(3):781-90.

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Table A1.7. Hypericum perforatum L., (Clusiaceae); St John's wort – 26 studies[1,2]

Drug details		Herb and product details			Study details					
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/ human	In vivo	In vitro	Symptoms/ outcomes	Hypo-thesized mechanism	Evaluation	Reference
Atorvastatin	10–40 mg/day	Extract (Movina) tablet 300 mg	Not stated	600 mg/ day	16 people with hyper-choleste-rolaemia (6 female)			Higher blood levels of LDL and total cholesterol	Induction of CYP and P-gp	Interaction: reduced effect of atorvastatin	Andrén et al. (2007)
Carbamazepine	100 mg 2 times/ day for 3 days, then 200 mg 2 times/day for 3 days, then 400 mg/day for 14 days	Extract tablet	Standardized: 0.3% hypericin	300 mg 3 times/ day	8 people (3 female)			No difference in any phar-macokinetic parameters	N/A	No interaction	Burstein et al. (2000)
Ciclosporin	125–150 mg/day	Herbal tea	Not known	"Regularly" (not stated)	1 male			Reduced plasma levels of ciclosporin	Induction of CYP and P-gp	Interaction: risk of organ rejection even at subtherapeu-tic doses of St John's wort	Alscher and Klotz (2003)
	Person's prescri-bed dose	Extract (Jarsin) tablet 300 mg	Standardized:0.3% hypericin, 3–5% hyperforin	600 mg/ day	11 people under-going renal transplant			Significant decrease in blood levels of ciclosporin			Bauer et al. (2003)
	125 mg twice daily	Extract (Jarsin) tablet 300 mg	Standardized:0.3% hypericin, 3–5% hyperforin	900 mg/ day	2 people under-going heart transplant			Acute organ rejection			Ruschitzka et al. (2000)
Clozapine	Person's usual dose	Extract tablet 300 mg	Standardi-zed:0.36–0.84 mg hypericin, ≥ 9 mg hyperforin	900 mg/ day	Woman aged 41 years			Reduced plasma levels of clozapine	Induction of CYP and P-gp	Interaction: psychiatric deterioration	Van Strater et al. (2012)
Docetaxel	135 mg IV over 60 min before and after St John's wort	Extract (Hyperi-plant) tablet 300 mg	Standardi-zed:0.36–0.84 mg hypericin, 9–19 mg hyperforin	300 mg 3 times/day for 14 days	10 people living with cancer			Decreased docetaxel plasma levels	Induction of CYP and P-gp	Interaction: reduced plasma levels of docetaxel	Goey et al. (2014)

Table A1.7. Hypericum perforatum L., (Clusiaceae); St John's wort – 26 studies[1,2] (Con't.)

Drug details		Herb and product details			Study details					
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/ human	In vivo	In vitro	Symptoms/ outcomes	Hypo-thesized mechanism	Evaluation	Reference
Oral (hormonal) contraceptives	Systematic review of published studies before 2016: 48 articles identified; 4 studies met inclusion criteria				Women taking oral contraceptives			Increased risk of breakthrough bleeding	Induction of CYP3A4 and CYP2C9	Interaction: reduced plasma levels of hormones, leading to contraceptive failure	Berry-Bibee et al. (2016)
	Ethinyl oestradiol/ dienogesterol	Extract (Helarium 425) tablet	Not stated	1700 mg/ day for 3 months	Woman aged 36 years			Pregnancy	Not stated		Schwarz et al. (2003)
	Ethinyl estradiol/3-keto-desogestrel	Extract Ze 117) tablet 300 mg	Standardized: hypericin 0.2%, hyperforin ≤ 0.2%	250 mg 2 times/day for 14 days from day 7	16 females			No effect on pharmacokinetics of hormonal components	N/A	No interaction with low hyperforin extract	Will-Shahab et al. (2009)
Ibuprofen	400 mg before and after St John's wort	Extract tablet 300 mg	Standardized:0.3% hypericin	300 mg 3 times/day for 3 weeks	8 males			Minimal effects on ibuprofen pharmacokinetics	N/A	No interaction	Bell et al. (2007a)
Imatinib	400 mg before and after St John's wort	Extract (Kira) tablet 300 mg	Standardized:0.3% hypericin	300 mg 3 times/day for 2 weeks	12 people (6 female)			Reduced blood levels of imatinib	Induction of CYP3A4	Interaction: reduced plasma levels of imatinib	Frye et al. (2004)
	400 mg before and after St John's wort	Extract (form not stated)	Not stated	300 mg 3 times/day for 2 weeks	10 people			Mean imatinib AUC decreased by 32%			Smith et al. (2004)

Table A1.7. Hypericum perforatum L., (Clusiaceae); St John's wort – 26 studies[1,2] (Con't.)

Drug details		Herb and product details			Study details					
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/ human	In vivo	In vitro	Symptoms/ outcomes	Hypo-thesized mechanism	Evaluation	Reference
Indinavir	800 mg every 8 h for 3 doses before and after St John's wort	Extract tablet 300 mg	Standardized:0.3% hypericin	300 mg 3 times/day for 2 weeks	8 people (2 female)			Mean indinavir AUC decreased by 57%; mean Cmax decreased; Tmax unaltered	Induction of CYP3A4	Interaction: reduced plasma levels of indinavir	Piscitelli et al. (2000)
Irinotecan	350 mg/m^2 IV with and without St John's wort	Extract tablet 300 mg	Not stated	300 mg 3 times/day for 18 days	5 people living with cancer (3 female)			Reduction in irinotecan concentration	Induction of CYP3A4	Interaction: reduced plasma levels of irinotecan	Mathijssen et al. (2002)
Metformin	1 g 2 times/day for 1 week with and without St John's wort	Extract capsule 240–294 mg	Standardized:900 µg hypericin	240–294 mg 2 times/day for 21 days	20 males			Improved glucose tolerance by enhancing insulin secretion	Decreased renal clearance	Potential interaction: increased effect of metformin	Stage et al. (2015)
Oxycodone	15 mg on day 14	Extract (Jarsin) tablet 300 mg	0.3% hypericin, 3–5% hyperforin Standardized: 0.3% hypericin, 3-5% hyperforin	300 mg 3 times/day for 14 days	12 people (6 female)			Reduced levels of oxycodone; reduced cold pain threshold	Induction of CYP3A4	Interaction: reduced blood levels of oxycodone	Nieminen et al. (2010)
Prednisone	20 mg before and after St John's wort	Extract tablet 300 mg	Standardized:0.3% hypericin	300 mg 3 times/day for 28 days	8 males			No effect on pharmacokinetics of prednisone or its reversible metabolite prednisolone	N/A	No interaction	Bell et al. (2007b)
Repaglinide	1 mg before and after St John's wort	Extract tablet 325 mg	Not stated	325 mg 3 times/day for 14 days	15 people			No effect on PXR or pharmacokinetics of repaglinide	N/A	No interaction	Fan (et al.) 2011

Table A1.7. Hypericum perforatum L., (Clusiaceae); St John's wort – 26 studies[1,2] (Con't.)

Drug details		Herb and product details			Study details					
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/ human	In vivo	In vitro	Symptoms/ outcomes	Hypo-thesized mechanism	Evaluation	Reference
Simvastatin	10–40 mg/day	Extract (Movina) tablet 300 mg	Not stated	300 mg 2 times/ day	24 people with hyper-cholestero-laemia (10 female)			Higher blood levels of LDL and total cho-lesterol with St John's wort	Not stated	Interaction: reduced effect of simvastatin	Eggertsen et al. (2007)
	10 mg/day	Extract caplet 300 mg	Standardized:0.3% hypericin	300 mg 3 times/ day	8 healthy people			Lower plasma simvastatin concentration	Induction of CYP enzymes and P-gp	Interaction: reduced plasma level of simvastatin	Sugimoto et al. (2001)
Tacrolimus	0.1 mg/kg before and after St John's wort	Extract tablet 300 mg	St John's wort tablet (300 mg/tablet, containing 440.0 µg hypericin)	300 mg 3 times/day for 18 days	10 people (8 female)			Average decrease of 34% for tacroli-mus AUC	Induction of CYP3A4 and P-gp	Interaction: reduced plasma levels of tacrolimus	Hebert et al. (2004)
Tacrolimus–mycophenolate	Person's usual dose	Extract (Jarsin) tablet 300 mg	0.3% hypericin, 3–5% hyperforin Standardized: 0.3% hypericin, 3–5% hyperforin	300 mg 2 times/day for 14 days	10 people under-going renal transplant (4 female)			Significant decrease in AUC tacro-limus; no effect on mycophenolate	Induction of CYP3A4 and P-gp	Interaction with tacrolimus: reduced plasma levels No interac-tion with mycophenolate	Mai et al. (2003)
Verapamil	24 mg over 100 min by jejunal perfusion	Extract (Movina) tablet 300 mg	3–6% hyperforin Standardized: 3–6% hyperforin	300 mg 3 times/day for 14 days	8 males			Decrease in bioavailabi-lity of *R*- and *S*-verapamil	Induction of first-pass CYP3A4 meta-bolism	Interaction: reduced plasma levels of verapamil	Tannergren et al. (2004)

Table A1.7. Hypericum perforatum L., (Clusiaceae); St John's wort – 26 studies[1,2] (Con't.)

Drug details		Herb and product details			Study details						
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/ human	In vivo	In vitro	Symptoms/ outcomes	Hypo-thesized mechanism	Evaluation	Reference
Warfarin	25 mg	Extract (Bio-glan) tablet equivalent to 1 g herb	Standardized: 0.825 mg hypericin, 12.5 mg hyperforin	1 tablet 3 times/day for 2 weeks	12 males			Increased metabolism of *R*- and *S*-warfarin, reduced INR	Induction of CYP1A2 and CYP3A4 (*R*-warfarin), and CYP2C9 (*S*-warfarin)	Interaction: reduced plasma levels of warfarin	Jiang et al. (2004)
Zolpidem	10 mg following St John's wort on day 1 and then 10 mg with St John's wort at 14 days	Extract (LI16) tablet 300 mg	Standardized: 0.3% hypericin, 3–5% hyperforin	300 mg 3 times/ day	14 males			Decreased plasma con-centration of zolpidem	Induction of CYP3A4	Interaction: reduced plasma levels of zolpidem	Hojo et al. (2011)

AUC, area under concentration–time curve; Cmax, maximum plasma concentration; CYP, cytochrome P450; INR, international normalized ratio; IV, intravenous; LDL, low-density lipoprotein; N/A, not applicable; P-gp, P-glycoprotein; PXR, pregnane X receptor; Tmax, time to maximum plasma concentration.

1 The studies cited cover only a selection of drugs affected by St John's wort and are not intended to form a comprehensive review. For further reports, see Russo E, Scicchitano F, Whalley BJ, Mazzitello C, Ciriaco M, Esposito S, et al. (2014). Hypericum perforatum: pharmacokinetics, mechanism of action, tolerability, and clinical drug–drug interactions. Phytother Res. 28:643–55.

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Table A1.8. Panax ginseng C.A. Mey., (Araliaceae) Ginseng; Korean/Chinese/oriental ginseng – 10 studies[1]

Drug details		Herb and product details			Study details					
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/human	In vivo	In vitro	Symptoms/outcomes	Hypothesized mechanism	Evaluation	Reference
Amlodipine	10 mg/kg orally after ginseng treatment	Steamed ginseng root	Not stated	0.5, 1 and 2 g/kg/day orally for 2 weeks		Rat		Increased Tmax; decreased Cmax; no change in AUC No change if amlodipine administered IV	None specified	No interaction	Ryu et al. (2014)
Imatinib	400 mg/day for 7 years	Extract in "energy drinks"	Not stated	Taken over 4 months before event	1 man aged 26 years			Acute lobular hepatitis	CYP3A4 inhibition	Interaction: imatinib-induced hepatotoxicity	Bilgi et al. (2010)
Lamotrigine	150 mg 2 times/day	Ginseng/deer antler velvet extract	Not stated	Taken over 4 months before event	1 man aged 44 years			DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome	Inhibition of UGT 2B7	Interaction: increased toxicity of lamotrigine	Myers et al. (2015)
Lopinavir/ritonavir	400 mg/100 mg 2 times/day for 29.5 days	Root extract capsules	Standardized to 5% ginsenoside	500 mg 2 times/day from day 16 for 2 weeks	13 people			No change in pharmacokinetic parameters for either drug	N/A	No interaction	Calderón et al. (2014)

Table A1.8. Panax ginseng C.A. Mey., (Araliaceae) Ginseng; Korean/Chinese/oriental ginseng – 10 studies[1] (Con't.)

Drug details		Herb and product details			Study details						
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/human	In vivo	In vitro	Symptoms/outcomes	Hypothesized mechanism	Evaluation	Reference
Losartan	10 mg/kg	Red ginseng root	Not stated	0.5, 1 and 2 g/kg/day for 2 weeks		Rat		Negligible influence on losartan pharmacokinetics	N/A	No interaction	Ryu et al. (2015)
Midazolam–fexofenadine	Midazolam 8 mg and fexofenadine 120 mg before/after ginseng treatment	Powdered root extract capsules	Standardized to 5% ginsenoside	500 mg 2 times/day for 28 days	12 people, (4 female)			Decrease in Cmax and AUC of midazolam; no effect on fexofenadine	Induction of CYP3A4	Possible interaction: reduced effect of midazolam	Malati et al. (2012)
Raltegravir	Raltegravir/lopinavir ritonavir 400 mg/400 mg/100 mg 2 times/day	Lyophilized root extract lozenges 1000 mg	Not stated	Not given	1 male living with HIV			Acute elevation of liver enzymes; jaundice; weight loss	Induction of CYP3A4	Possible interaction: increase in raltegravir toxicity	Mateo-Carrasco et al. (2012)

Table A1.8. Panax ginseng C.A. Mey., (Araliaceae) Ginseng; Korean/Chinese/oriental ginseng – 10 studies[1] (Con't.)

Drug details		Herb and product details			Study details					
Drug	Dosage regimen	Form	Chemical constituents	Dosage regimen	Clinical/human	In vivo	In vitro	Symptoms/outcomes	Hypothesized mechanism	Evaluation	Reference
Warfarin	2–5 mg	Root extract	Not stated	500 mg 3 times/day	RCT: 25 people with ischaemic stroke			Increased warfarin INR, PT and AUC, but no statistical difference	N/A	No interaction	Lee et al. (2008)
	Usual dose	Korean red ginseng root	Not stated	1 g/day	RCT: 25 people with cardiac valve replacement (21 female)			No significant difference in INR	N/A		Lee et al. (2010)
	25 mg with or without 7 days of pretreatment	Extract of Korean ginseng root equivalent to 0.5 g, capsule	Standardized to 8.93 mg ginsenosideas Rg1	2 capsules 3 times/day for 1 week	12 males			No effect on pharmacodynamics or pharmacokinetics of *S*- or *R*-warfarin	N/A		Jiang et al. (2004)

AUC, area under concentration–time curve; Cmax, maximum plasma concentration; CYP, cytochrome P450; INR, international normalized ratio; IV, intravenous; LDL, low-density lipoprotein; N/A, not applicable; P-gp, P-glycoprotein; PT, prothrombin (bleeding) time; PXR, pregnane X receptor; RCT, randomized controlled trial; Tmax, time to maximum plasma concentration; UGT, uridine diphosphate-glucuronosyltransferase.

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Table A1.9. Salvia miltiorrhiza Bunge. (Lamiaceae); red sage, Chinese sage – 10 studies[1]

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Clopidogrel	300 mg orally before and after treatment	Extract capsules	Standardized tanshinones	4 capsules 3 times/day for 7 days	20 males			Reduced plasma levels clopidogrel	Induction of P-gp and CYP3A4	Potential interaction	Zhou et al. (2018)
	30 mg/kg orally	Water extract capsules	Not stated	400 mg/kg		Rat		No effect	N/A	No interaction	Lee et al. (2011)
Docetaxel	5 mg/kg IV; 30 mg/kg orally	Water extract capsules	Not stated	400 mg/kg		Rat		No effect	N/A	No interaction	
Fexofenadine	60 mg before and after treatment	Ethanol extract	Standardized tanshinones	1 g 3 times/ day for 10 days	12 males			Increased oral clearance	Induction of P-gp	Interaction: reduced fexofenadine plasma levels	Qiu et al. (2014)
Midazolam	10 mg/kg IV	Extract capsules	Danshensu	Acute 50–200 mg/ kg intraperitoneally for 3 days		Rat		Hypnotic efficacy prolonged	Inhibition of CYP3A	Unclear	Wang et al. (2010)
Irinotecan	Drug probe	Extract; isolated compounds	Standardized tanshinones	N/A			Enzyme, cell growth assays	Reduced hydrolysis of esterified drugs	Inhibition of carboxylesterases	Unclear	Hatfield et al. (2013)
Propofol	Drug probe	Dihydrotanshinone I/cryptotanshinone	N/A	N/A			Human liver microsomes	Inhibition of glucuronidation	Inhibition of UGT	Unclear	Cong et al. (2013)
Rosuvastatin	100 mg/kg	Danshensu	Danshensu	46 mg/kg		Rat		Plasma clearance of rosuvastatin reduced by > 57%	Inhibition of transporter proteins or CYP	Potential interaction: may increase toxicity of rosuvastatin	Wen and Xiong (2011)

Table A1.9. Salvia miltiorrhiza Bunge. (Lamiaceae); red sage, Chinese sage – 10 studies[1] (Con't.)

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Theophylline	100 mg on days 1 and 15	Extract tablet equivalent 1 g root	Standardized tanshinones, miltirone	4 tablets 3 times/day for 14 days	12 people			No significant effect on plasma theophylline	N/A	No interaction	Qiu et al. (2008)
Warfarin	4 mg	Tanshinone IIA	N/A	4 mg		Rat		Significant decrease in Cmax and prolonged Tmax of warfarin	Inhibition of CYP1A1, CYP2C6 and CYP2C11	Interaction: increase in levels of free warfarin	Liu et al. (2008)
	1 mM	Extract	Standardized tanshinone II, salvianolic acids	0.1 mM			HSA binding	Increased free drug concentration	Decreased binding to HSA site I		Shao et al. (2016)

Cmax, maximum plasma concentration; CYP, cytochrome P450; HSA, human serum albumin; IV, intravenous; N/A, not applicable; P-gp, P-glycoprotein; Tmax, time to maximum plasma concentration; UGT, uridine diphosphate-glucuronosyltransferase.

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Table A1.10. Schisandra: Schisandra chinensis (Turcz.) Baill./Schisandra sphenanthera Rehder & E.H. Wilson (Schisandraceae); magnolia vine, southern magnolia vine – 11 studies[1]

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Ciclosporin	37.8 or 1.89 mg/kg	Extract of *Schisandra sphenanthera*	Standardized Schisantherin A 7.5 mg	0.25 g/kg		Rat		Increased ciclosporin blood levels with low-dose *Schisandra sphenanthera* extract	Inhibition of CYP3A and P-gp	Interaction: increased plasma levels of ciclosporin	Xue et al. (2013)
	25 mg/kg	Extract of *Schisandra chinensis*	Standardized 37.30 mg/g total lignans	54–216 mg/kg		Rat		Increased blood concentration and longer half-life of ciclosporin			Lai et al. (2015)
Digoxin and vincristine	Digoxin 0.5 mg/kg, vincristine 1.0 mg/kg	Lignan extract	Standardized Schizandrol A, B; Schisantherin A, B; Schizandrin B	500 mg/kg single dose or for 10 days		Rat		Increased digoxin and vincristine AUC	Inhibition of P-gp	Interaction: increased blood levels of digoxin and vincristine	Liang et al. (2013)
	Digoxin 5 µM, vincristine 5 µM			0.5, 2.0 or 10.0 g/ml			Caco-2 cells	Increased intracellular concentration of digoxin and vincristine			
Fenofibrate	0.1% supplement	Extract of *Schisandra chinensis*	Not stated	1 g/kg		Mouse		Increased hepatic lipid- and glucose-lowering effects of fenofibrate	Not stated	Interaction: increased effect of fenofibrate	Zhu et al. (2015)
Midazolam	15 mg single dose	Extract of *Schisandra sphenanthera* capsule	Standardized 11.25 mg deoxyschizandrin	3 capsules 2 times/day for 7 days	12 males			Increased oral bioavailability of midazolam	Inhibition of CYP3A4	Interaction: increased effect of midazolam	Xin et al. (2009)
Paclitaxel	30 mg/kg orally, or 0.5 mg/kg IV	Extract of *Schisandra sphenanthera*	Standardized Schisantherin A	0.25 g/kg		Mouse		Paclitaxel exposure increased, but no central nervous system toxicity or other side-effects	Inhibition of P-gp or CYP	Interaction: increased bioavailability of paclitaxel	Jin et al. (2011)

Table A1.10. Schisandra: Schisandra chinensis (Turcz.) Baill./Schisandra sphenanthera Rehder & E.H. Wilson (Schisandraceae); magnolia vine, southern magnolia vine – 11 studies[1] (Con't.)

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Tacrolimus	2 mg on days 1 and 15	Extract of *Schisandra sphenanthera*	Standardized 11.25 mg deoxyschizandrin	3 capsules 2 times/day for 13 days	12 males			Increased AUC and Cmax of tacrolimus	Inhibition of CYP 3A4 or P-gp	Interaction: increased plasma levels of tacrolimus	Xin et al. (2007)
	1.2 mg/kg	Extract of *Schisandra sphenanthera* capsule	Standardized 11.2 mg deoxyschizandrin	150 mg/kg single dose, or multiple doses 25–1250 mg/kg		Rat		Increased plasma concentration of tacrolimus for single and multiple doses; effect is dose-dependent up to 450 mg/kg	Inhibition of P-gp or CYP3A		Wei et al. (2013)
Talinolol	100 mg with or without *Schisandra chinensis*	Extract of *Schisandra chinensis* tablet	Standardized 16.85 mg deoxyschizandrin	300 mg 2 times/day	12 males			*Schisandra chinensis* increased AUC of talinolol by 47%	Inhibition of P-gp	Potential interaction: may increase plasma levels	Fan et al. (2009)
Warfarin	2 mg/kg IV	Extract of *Schisandra chinensis* and isolated compounds	Schizandrols, schizandrins	500 mg/kg		Rat		Increased warfarin clearance	Activation of PXR by Schizandrol B, Schizandrins A and B	Potential interaction: may reduce plasma levels	Mu et al. (2006)

AUC, area under concentration–time curve; Cmax, maximum plasma concentration; CYP, cytochrome P450; HSA, human serum albumin; IV, intravenous; N/A, not applicable; P-gp, P-glycoprotein; PXR, pregnane X receptor; Tmax, time to maximum plasma concentration; UGT, uridine diphosphate-glucuronosyltransferase.

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Table A1.11. Silybum marianum (L.) Gaertn., (Asteraceae); milk thistle, St Mary's thistle – six studies[1]

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypothesized mechanism**	**Evaluation**	**Reference**
Indinavir	800 mg every 8 h for 4 doses	Extract tablet 300 mg	Standardized silymarin 153 mg	175 mg 3 times/day for 3 weeks	10 people (6 male)			No change in overall exposure of indinavir	N/A	No interaction	Piscitelli et al. (2002)
	800 mg every 8 h	Extract capsules 456 mg	Standardized silymarin	456 mg 3 times/day on days 2–30	16 people			No significant changes	N/A		Mills et al. (2005)
	800 mg 3 times/day on days 1, 2, 16 and 17	Silymarin	Standardized refined extract	160 mg 3 times/day on days 3–17	10 people			No change in overall exposure of indinavir	N/A		DiCenzo et al. (2003)
Midazolam/ caffeine/tolbutamide/ dextromethorphan	Midazolam 10 mg, caffeine 200 mg, tolbutamide 500 mg, dextromethorphan 30 mg, probe drugs	Extract (Legalon 140) capsules 175 mg	Standardized 140 mg silymarin	1 capsule 3 times/day	12 people			No relevant effect on major CYP activity	N/A	No interaction with probe drugs	Kawaguchi-Suzuki et al. (2014)
Midazolam	Midazolam 4 mM	Extract silymarin	Silybin A, B; isosilybin A, B	N/A			Human microsomes	Increased midazolam Cmax and AUC	Inhibition of CYP3A4	Possible: increased effect of midazolam	Brantley et al. (2012)
Nifedipine	10 mg, 2 doses	Fruit extract capsules	Standardized 140 mg silymarin	280 mg 10 h and 1.5 h before nifedipine	16 males			No meaningful effect on haemodynamic parameters	N/A	No significant interaction	Fuhr et al. (2007)

AUC, area under concentration–time curve; Cmax, maximum plasma concentration; CYP, cytochrome P450; N/A, not applicable.

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Table A1.12. Zingiber officinale Roscoe (Zingiberaceae); ginger – three studies

Drug details		Herb and product details			Study details						
Drug	**Dosage regimen**	**Form**	**Chemical constituents**	**Dosage regimen**	**Clinical/ human**	**In vivo**	**In vitro**	**Symptoms/ outcomes**	**Hypo-thesized mechanism**	**Evaluation**	**Reference**
Phenacetin, diclofenac, bupropion	Drug probe mixture	Ginger extract 6-, 8-, 10-gingerols, 6-shogaol	Standardized	500 µg/ml ginger extract, 6-, 8-, 10-gingerols, 6-shogaol			Human liver microsomes, Caco-2 cells	No significant effect on CYP	N/A	No interaction via CYP	Mukkavilli et al. (2014)
Nifedipine	10 mg/day	Dried rhizome	Not stated	1 g/day for 1 week	10 people without and 10 people with hypertension			Potentiation of antiplatelet effects of nifedipine	Not stated	Potential interaction: enhanced effects of nifedipine	Young et al. (2006)
Warfarin	25 mg	Extract dried rhizome capsules equivalent to 0.4 g rhizome	Not stated	3 capsules 3 times/day for 7 days	12 males			No effect on distribution or protein binding of *S*- or *R*-warfarin	None	No interaction	Jiang et al. (2005)

CYP, cytochrome P450; N/A, not applicable.

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Annex 2. Participants

First World Health Organization working group meeting on key technical issues for herbal medicines with reference to interaction with other medicines, Milan, Italy, 23–25 June 2011

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- Dr Michael J. Smith, Member of WHO Expert Advisory Panel on Traditional Medicine, Adjunct Professor, National Center for Natural Product Research, School of Pharmacy, University of Mississippi, University, MS, United States of America
- Dr Duc Vu, Director, Marketed Biologicals, Biotechnology and Natural Health Products Bureau, Marketed Health Products Directorate, Health Products and Food Branch, Health Canada, Ottawa, Canada
- Professor Wang Xinhua, Vice President, Guangzhou University of Chinese Medicine, Guangzhou, China
- Dr Zhang Qi, Coordinator, Traditional Medicine, Department for Health System Governance and Service Delivery, World Health Organization, Geneva, Switzerland
- Dr Zheng Linyun, Deputy Director, WHO Collaborating Centre for Traditional Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Second World Health Organization working group meeting on key technical issues for herbal medicines with reference to interaction with other Medicines, Oxford, Mississippi, United States of America, 12–14 July 2016

- Professor Ichiro Arai, Department of Kampo Medicine, Nihon Pharmaceutical University, Saitama, Japan
- Dr Mohammad K. Ashfaq, Principal Scientist, National Center for Natural Product Research, School of Pharmacy, University of Mississippi, University, MS, United States of America
- Dr Ana Cecilia Bezerra Carvalho, Coordinator, Herbal and Homeopathic Medicines, General Office of Drugs, Brazilian Health Surveillance Agency, Brasilia, Brazil
- Professor Heather Boon, Dean, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada
- Dr Amar Gopal Chittiboyina, Senior Research Scientist, National Center for Natural Product Research, School of Pharmacy, University of Mississippi, University, MS, United States of America
- Mr Kelvin Cheung, WHO Collaborating Centre for Traditional Medicine, Chinese Medicine Division, Department of Health, Hong Kong Special Administrative Region, China
- Dr Amanda H. Corbett, Clinical Associate Professor, University of North Carolina at Chapel Hill, Eshelman School of Pharmacy, Chapel Hill, NC, United States of America
- Dr Hubertus Cranz, Director General, Association of the European Self-Medication Industry, Brussels, Belgium
- Dr Jinhui Dou, Pharmacologist and Pharmacognosist, Botanical Review Team, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, United States of America
- Professor Harry Fong, Member of WHO Expert Panel on Traditional Medicine and Professor emeritus, University of Illinois at Chicago, Chicago, IL, United States of America
- Dr Goh Cheng Soon, Director, Traditional and Complementary Medicine Division, Ministry of Health Malaysia, Kuala Lumpur, Malaysia
- Dr Hakim Abdul Hannan, Vice Chancellor, Hamdard University, Karachi, Pakistan
- Dr Michiho Ito, Associate Professor, Department of Pharmacognosy, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan
- Dr Ikhlas Khan, Assistant Director, National Center for Natural Product Research, School of Pharmacy, University of Mississippi, University, MS, United States of America
- Dr Shabana Khan, Principal Scientist, National Center for Natural Product Research, School of Pharmacy, University of Mississippi, University, MS, United States of America
- Professor Yoshinori Kobayashi, Vice-Director General, WHO Collaborating Centre for Traditional Medicine, Oriental Medicine Research Centre, Kitasato University, Tokyo, Japan
- Professor Liu Xinmin, Member of WHO Expert Advisory Panel on Traditional Medicine, Pharmacology and Toxicology Centre, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, WHO Collaborating Centre for traditional medicine, Beijing, China

- Dr Vamshi Manda, Research Scientist, National Center for Natural Product Research, School of Pharmacy, University of Mississippi, University, M S, United States of America
- Professor Stephen Myers, Director, NatMed Research Unit, Division of Research, Southern Cross University, Lismore, Australia
- Ms Teresa Ngan, Senior Pharmacist, Department of Health, Hong Kong Special Administrative Region, China
- Professor Tamás Paál, Member of WHO Expert Advisory Panel on Pharmaceutical Preparations, Professor Emeritus, Institute of Drug Regulatory Affairs, University of Szeged; and External Senior Advisor to the National Institute of Pharmacy and Nutrition, Budapest, Hungary
- Dr Shanthi Pal, Group Lead, Medicines Safety, Safety and Vigilance Team, Department of Essential Medicines and Health Products, World Health Organization, Geneva, Switzerland
- Professor Olavi Pelkonen, Head of Unit, Department of Pharmacology and Toxicology, University of Oulu, Oulu, Finland
- Dr Mauizzati Purba, Director, Indonesian Herbal Medicines, National Agency for Drug and Food Control, Jakarta, Indonesia
- Dr Ravindra Singh, Assistant Director (Chemistry), Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, New Delhi, India
- Dr Souad Skalli, WHO Collaborating Centre for Strengthening Pharmacovigilance Practices, Pharmacovigilance of Herbal Medicines, Centre Anti Poison et de Pharmacovigilance du Maroc, Rabat, Morocco
- Dr Michael J. Smith, Member of WHO Expert Advisory Panel on Traditional Medicine; and Adjunct Professor, National Center for Natural Product Research, School of Pharmacy, University of Mississippi, University, M S, United States of America
- Professor Tran Quoc Binh, Director, WHO Collaborating Centre for Traditional Medicine, National Hospital of Traditional Medicine, Hanoi, Viet Nam
- Dr Ta Thu Thuy, WHO Collaborating Centre for Traditional Medicine, National Hospital of Traditional Medicine, Hanoi, Viet Nam
- Dr Larry Walker, Director, National Center for Natural Products Research, School of Pharmacy, University of Mississippi, University, Mississippi, MS, United States of America
- Ms Rizka Ayu Kusuma Widjanarko, Indonesian Herbal Medicines, National Agency for Drug and Food Control, Jakarta, Indonesia
- Professor Elizabeth Williamson, School of Pharmacy, University of Reading, Reading, United Kingdom of Great Britain and Northern Ireland
- Dr Charles Wu, Pharmacologist, Botanical Review Team, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, United States of America
- Dr Zhang Qi, Coordinator, Traditional and Complementary Medicine, Service Delivery and Safety Department, World Health Organization, Geneva, Switzerland

World Health Organization consultation meeting on key technical issues for herbal medicines with reference to interaction with other medicines, Beijing, China, 16–18 October 2019

- Professor Rabi Narayan Acharya, Head, Department of Dravya Guna, Institute of Postgraduate Teaching and Research in Ayurveda, Gujarat Ayurveda University, Jamnagar, India
- Professor Ahmad Alkofahi, Member of WHO Expert Advisory Panel on Traditional Medicine, Department of Medicinal Chemistry and Pharmacognosy, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan
- Dr Aditi Bana, Technical Officer, Traditional, Complementary and Integrative medicine, Department of Integrated Health Services, World Health Organization, Geneva, Switzerland
- Peter Chan, Director General, Health Evaluation Directorate, Pest Management Regulatory Agency, Health Canada, Ottawa, Canada
- Professor Chun-Tao Che, Director, WHO Collaboration Centre on Traditional Medicine, University of Illinois at Chicago, Chicago, IL, United States of America
- Professor Elaine Elisabetsky, Member of the WHO Expert Advisory Panel on Traditional Medicine, Departamento de Bioquímica, University, São Paulo, Brazil
- Professor Harry HS Fong, Member of the WHO Expert Advisory Panel on Traditional Medicine, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL, United States of America
- Dr Neil Travis Gower, Senior Lecturer, Department of Homoeopathy, University of Johannesburg, Germiston, South Africa
- Professor Yoshinori Kobayashi, Vice-Director General, WHO Collaborating Centre for Traditional Medicine, Oriental Medicine Research Centre, Kitasato University, Tokyo, Japan
- Professor Liao Yonghong, Director, WHO Collaborating Centre for Traditional Medicine, Department of Pharmaceutical, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Beijing, China
- Professor Liu Chenghai, Institute of Liver Diseases, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China
- Professor Liu Jianxun, Xi Yuan Hospital, China Academy of Chinese Medicinal Sciences, Beijing, China
- Professor Liu Xinmin, Consultant, Traditional, Complementary and Integrative medicine, Department of Integrated Health Services, World Health Organization, Geneva, Switzerland
- Ms Lu Jianxian, Zhejiang Provincial Institutes for Food and Drug Control, Hangzhou City, China
- Professor Pulok K. Mukherjee, Director, School of Natural Product Studies, Jadavpur University, Kolkata, India
- Dr Dal-Seok Oh, East–West Medical Research Institute, Kyung Hee University, WHO Collaborating Centre for Traditional Medicine, Seoul, Republic of Korea
- Professor Dr Suwijiyo Pramono, Member of the WHO Expert Advisory Panel on Traditional Medicine, Faculty of Pharmacy, Gadjah Mada University, Jogjakarta, Indonesia

- Professor Rajan Radhakrishnan, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai Health Care City, Dubai, United Arab Emirates
- Professor Rokia Sanogo, Chief, Department of Traditional Medicine, Faculté de Pharmacie, Université de Sciences des Techniques et des Technologies de Bamako, Bamako, Mali
- Dr Fabio Scano, Officer in Charge, WHO China Office, Beijing, China
- Professor Shi Shangmei, Director, Division of Chinese Herbal Medicine, China National Pharmacopeia Commission, Beijing, China
- Professor Souad Skalli, Centre de Recherche Biotechnologies Végétales et Microbiennes, Biodiversité et Environnement, Faculty of Sciences, University Mohammed V, Rabat, Morocco
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- Ms Manmas Vannabhum, Center for Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
- Professor Wei Jianhe, Deputy Director, WHO Collaborating Centre for Traditional Medicine, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Beijing, China
- Professor Elizabeth Williamson, School of Pharmacy, University of Reading, Reading, United Kingdom of Great Britain and Northern Ireland
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