PHYTOTHERAPY RESEARCH
Phytother. Res. **30**: 691–700 (2016)
Published online 17 February 2016 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/ptr.5591

REVIEW

A Critical Approach to Evaluating Clinical Efficacy, Adverse Events and Drug Interactions of Herbal Remedies

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Systematic reviews and meta-analyses represent the uppermost ladders in the hierarchy of evidence. Systematic reviews/meta-analyses suggest preliminary or satisfactory clinical evidence for agnus castus (*Vitex agnus castus*) for premenstrual complaints, flaxseed (*Linum usitatissimum*) for hypertension, feverfew (*Tanacetum partenium*) for migraine prevention, ginger (*Zingiber officinalis*) for pregnancy-induced nausea, ginseng (*Panax ginseng*) for improving fasting glucose levels as well as phytoestrogens and St John's wort (*Hypericum perforatum*) for the relief of some symptoms in menopause. However, firm conclusions of efficacy cannot be generally drawn. On the other hand, inconclusive evidence of efficacy or contradictory results have been reported for *Aloe vera* in the treatment of psoriasis, cranberry (*Vaccinium macrocarpon*) in cystitis prevention, ginkgo (*Ginkgo biloba*) for tinnitus and intermittent claudication, echinacea (*Echinacea* spp.) for the prevention of common cold and pomegranate (*Punica granatum*) for the prevention/treatment of cardiovascular diseases. A critical evaluation of the clinical data regarding the adverse effects has shown that herbal remedies are generally better tolerated than synthetic medications. Nevertheless, potentially serious adverse events, including herb–drug interactions, have been described. This suggests the need to be vigilant when using herbal remedies, particularly in specific conditions, such as during pregnancy and in the paediatric population. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: dietary supplements; systematic review; herb–drug interaction; pregnancy; safety; elderly subjects; nutraceuticals.

INTRODUCTION

Herbal remedies continue to be an accepted complementary medical option both in Europe and in the USA. Sales of herbal dietary supplements in the USA increased by 6.8% in 2014, reaching an estimated total of more than $6.4 billion and marking the 11th consecutive year of growth (Smith *et al.*, 2015). Table 1 lists the ten top-selling herbal supplements in the US mainstream multi-outlet channel in 2014, according to the American Botanical Council (Smith *et al.*, 2015). Herbal remedies are popular in Europe as well: a recent study reported an estimated 18.8% of screened survey respondents using at least one plant supplement (Garcia-Alvarez *et al.*, 2014). Because of this great popularity, it is incumbent to have updated information on the risk–benefit profile of herbal remedies.

The primary aim of this review is to provide an overview on the efficacy and safety, including drug interactions, based on recently published systematic reviews or meta-analyses of clinical data, of herbal remedies mainly used in Western countries, as these are likely taken in the form of single-herb products for self-medication. The use of herbal medicines during pregnancy as well as in paediatric and geriatric populations is also discussed. A secondary purpose of this brief review is to provide basic concepts in the clinical pharmacology of herbal products, in order to help researchers in their first approach to the phytotherapy field.

THE CLINICAL EFFICACY OF HERBAL REMEDIES

Similar to conventional drugs, clinical evidence on herbal medicine comes primarily from case reports, uncontrolled clinical trials and randomized controlled trials (RCTs). Randomized controlled trials, especially if double blind, are considered as the most rigorous system for evaluating the efficacy of drugs. However, it may happen that diverse, even rigorous, clinical trials do not always yield the same conclusion. Hence, only the totality of the available data, which can be collected in a systematic review, offers the most reliable evidence of efficacy. Systematic reviews and meta-analyses are at the top of the pyramid of the clinical evidence (Fig. 1) (Ho *et al.*, 2008; Rosner, 2012; Elamin and Montori, 2012; Varoni *et al.*, 2014). For this reason, although traditional, narrative review articles on the efficacy and the safety of herbal medicine continue to be published

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Received 27 October 2015
Revised 17 December 2015
Accepted 21 January 2016

Table 1. The ten best-selling herbal dietary supplements in the US mainstream multi-outlet channel in 2014

Rank	Herbal supplement (common name)	Latin name	Retail sales[a]	% Change 2013
1	Horehound	*Marrubium vulgare*	106	−1
2	Cranberry	*Vaccinium macrocarpon*	56	+16
3	Echinacea	*Echinacea* spp.	51	+79
4	Black cohosh	*Actaea* (*Cimicifuga*) *racemosa*	42	−8
5	Flaxseed and/or oil	*Linum usitatissimum*	26	−10
6	Valerian	*Valeriana officinalis*	23	−1
7	Yohimbe	*Pausinystalia yohimbe*	20	−11
8	Bioflavonoid complex	*Citrus* spp.	20	+21
9	Saw palmetto	*Serenoa repens*	18	−17
10	Ginger	*Zingiber officinalis*	18	+8

[a]Million US dollars in rounded figures (from the American Botanical Council, Smith *et al.*, 2015).

(for example, Bella and Shamloul, 2014;Gulati, 2014; Pagano *et al.*, 2014; Stohs, 2014a; Stohs, 2014b; Chingwaru *et al.*, 2015; Gulati, 2015; Stohs and Hartman, 2015), systematic reviews increasingly are replacing them.

Historically, systematic reviews and meta-analyses of herbal medicinal products came emphatically on the scene in the middle of the 1990s when the *British Medical Journal* published a meta-analysis on St John's wort (*Hypericum perforatum*) (Linde *et al.*, 1996). In this work, Linde and colleagues, by evaluating 23 randomized trials including a total of 1757 outpatients, provided evidence that extracts of St John's wort were more effective than placebo in the treatment of mild-to-moderate depression (Linde *et al.*, 1996). Previously, a meta-analysis highlighted the efficacy of garlic as a lipid-lowering agent (Silagy and Neil, 1994).

In the past 3 years, a discrete number of systematic reviews/meta-analyses concerning the clinical efficacy of herbal extracts used mainly in western countries have been published (Miroddi *et al.*, 2015; Zheng *et al.*, 2014; Van Die *et al.*, 2013;Howell, 2013; Wang *et al.*, 2012; Khalesi *et al.*, 2015; Ursoniu *et al.*, 2015; Xiong *et al.*, 2015; Rohner *et al.*, 2015; Jepson *et al.*, 2013; Lissiman *et al.*, 2014; Wider *et al.*, 2015; Viljoen *et al.*, 2014; Nicolaï *et al.*, 2013; Chen *et al.*, 2015b; Hilton *et al.*, 2013; Yang *et al.*, 2016; Shergis *et al.*, 2013; Shishtar *et al.*, 2014; Karsch-Völk *et al.*, 2014, 2015; Liu *et al.*, 2014a; Wang *et al.*, 2016). Key information of some of them, published in the 2013–2015 years, are summarized in Table 2. Furthermore, other recently published systematic reviews provided evidence of efficacy for black cohosh (*Cimicifuga racemosa*) in menopausal women (Ulbricht and Windsor, 2014), Dang Shen (*Codonopsis pilosula*) for chronic obstructive pulmonary disease and some botanical preparations for dermatological conditions (Fisk *et al.*, 2014; Fisk *et al.*, 2015) but failed to show clear beneficial effects for pomegranate (*Punica granatum*) in the prevention and treatment of cardiovascular diseases (Vlachojannis *et al.*, 2015), for *Hibiscus sabdariffa* in lowering serum lipids (Aziz *et al.*, 2013) and for saw palmetto (*Serenoa repens*) in patients with benign prostatic hyperplasia (Tacklind *et al.*, 2012). In several instances, the available evidence is limited by the poor methodological quality and risk of bias of the included studies, so claims of effectiveness appear to rely largely on poor-quality evidence and firm conclusions cannot be drawn.

Clearly, systematic reviews are not devoid of limitations, particularly in the field of herbal medicine. For example, systematic reviews strongly rely on the quality and quantity of primary data (clinical trials), which is low in the field of herbal medicine; furthermore, herbal extracts, because of the different methods of preparation and different part of plant used, may be not

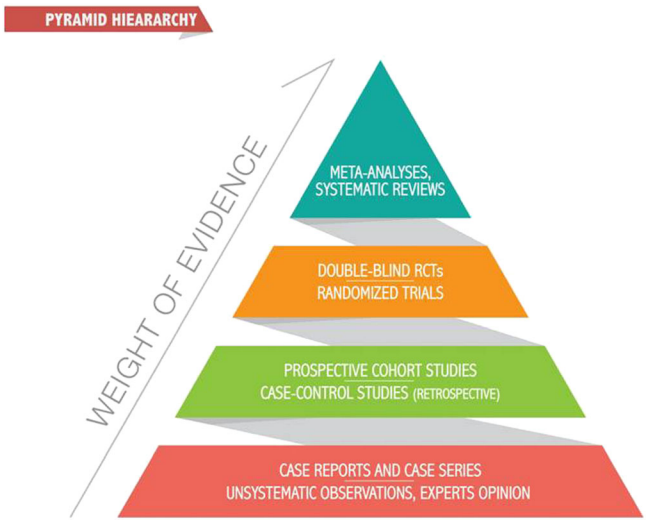

Figure 1. The hierarchy of clinical evidence.

Table 2. Examples of recently published (2013–2015 years) systematic reviews on the efficacy of herbal medicines

Herbal drug	Condition treated	No patients (trials)	Type of trial	Quality of trials	Main results	Adverse effects	Reference
Agnus castus *Vitex agnus castus*	Female reproductive disorders	1280 (12)	RCT	Risk bias predominantly low or unclear	Benefits in premenstrual syndrome, premenstrual dysphoria and latent hyperprolactinaemia.	Mild and similar to placebo	Van Die *et al.*, 2013
Aloe vera *Aloe* spp.	Psoriasis	194 (4)	RCT and DB	Discrete	Contradictory results on mild to moderate plaque psoriasis	No report of serious side effects	Miroddi *et al.*, 2015
	Infusion phlebitis	7465 (43)	RCT	High risk of bias	Effective, although the evidence is not strong	No side effects reported	Zheng *et al.*, 2014
Cranberry *Vaccinium macrocarpon*	Urinary tract infection (prevention)	4473 (24)	RCT	Predominantly a low risk of bias	Small evidence of benefit. Not to be recommended	Similar to placebo	Jepson *et al.*, 2012
Echinacea *Echinacea* spp.	Common cold	4631 (24)	RCT, DB and PC	Variable	Positive trends of questionable clinical relevance for some products	No difference between treatment and placebo	Karsch-Völk *et al.*, 2014
Flaxseed *Linum usitatissimum*	Hypertension	1004 (12)	RCT	All studies had Rosendal score >50%.	Flaxseed consumption (as a whole seed) may lower blood pressure.	Side effects not reported	Khalesi *et al.*, 2015
Feverfew *Tanacetum parthenium*	Migraine prevention	561 (6)	RCT and DB	Good methodological quality	Some evidence of efficacy	Mild and transient, mouth ulcer and gastrointestinal	Wider *et al.*, 2015
Garlic *Allium sativum*	Common cold	146 (1)	RCT	Reasonable quality	Preliminary positive evidence	Odour and skin rash	Lissiman *et al.*, 2014
	Hypertension	391 (7)	RCT and PC	Excellent in three studies	Significant lowering of both systolic and diastolic blood pressure	No serious AEs were reported.	Xiong *et al.*, 2015
	Arterial occlusion	78 (1)	RCT and PC	Trial relatively small, 80 patients	No effect on walking distance	No serious AEs	Jepson *et al.*, 2013
Ginger *Zingiber officinale*	Nausea and vomiting of pregnancy	1278 (12)	RCT	High risk of bias in blinding	Beneficial effects in reducing nausea symptoms	No risk of major side effects	Viljoen *et al.*, 2014
Ginkgo *Ginkgo biloba*	Macular degeneration	119 (2)	RCT	Small and short studies	Inconclusive results	Adverse effects not reported	Evans, 2013
	Dementia (Alzheimer's, vascular and mixed)	2684 (7)	RCT and PC	Appropriate	More effective than placebo	Generally, no differences between treatment and placebo groups	Gauthier and Schlaefke, 2014
	Intermittent claudication	739 (14)	RCT	Unclear risk of bias	No evidence of efficacy found	Minor side effects	Nicolaï *et al.*, 2013
	Schizophrenia	1033 (8)	RCT and PC	Low or unclear risk of bias	'Ameliorating effect as an adjuvant therapy to antipsychotics'	No difference in treatment and placebo groups	Chen *et al.*, 2015b
	Tinnitus	1543 (4)	RCT	Low risk of bias	No evidence of efficacy	No difference between treated and control groups	Hilton *et al.*, 2013
Ginseng *Panax ginseng*	Alzheimer's disease	259 (4)	RCT	Not promising	No evidence of efficacy	No serious AEs reported	Wang *et al.*, 2016
	Glycaemia	760 (16)	RCT	Modest to good	Some improvement in fasting blood glucose in diabetic/healthy subjects	Not assessed	Shishtar *et al.*, 2014

(Continues)

Table 2. (Continued)

Herbal drug	Condition treated	No patients (trials)	Type of trial	Quality of trials	Main results	Adverse effects	Reference
	Various indications	3843 (65)	RCT	Risk of bias unclear in most studies.	May improve glucose metabolism (6 studies) and immune response (4 studies).	No serious AEs reported.	Shergis *et al.*, 2013
	Menopause symptoms	514 (4)	RCT	Most RCTs with high risk of bias	Limited evidence of efficacy	No differences between treated and control groups	Kim *et al.*, 2013
Ginseng *Panax notoginseng*	Coronary heart disease	1747 (17)	RCT	All evaluated as high risk of bias	Positive effects on angina pectoris related symptoms	No differences between treated and control groups	Shang *et al.*, 2013
Isoflavones (from *Glycine max*, *Trifolium pratense*)	Menopause	1753 (15)	RCT	Low risk of bias (predominantly)	Reduction in the frequency of hot flushes	No serious adverse effects	Chen *et al.*, 2015a
St John's wort *Hypericum perforatum*	Menopause	649 (6)	RCT, DB and PC	Risk of bias noted	More effective than placebo	Hypericum side effects fewer than placebo	Liu *et al.*, 2014a

RCT, randomized clinical trial; DB, double blind; PC, placebo controlled; AE, adverse event.

comparable. This latter limitation can be minimized by performing systematic reviews for specific proprietary standardized extracts. For example, a recent meta-analysis reported some evidence of efficacy and good tolerability of *Ginkgo biloba* extract EGb 761 (a standardized extract of *Ginkgo biloba* leaves containing approximately 24% flavone glycosides and 6% terpene lactones) in patients with dementia (Gauthier and Schlaefke, 2014). Unfortunately, it must be highlighted that in some trials (and consequently in systematic reviews and meta-analyses), information such as the extract type, part of the plant used and the Latin name is omitted. Non-experts on herbal products often do not understand the variability in composition of these and the importance of correct botanical identification and quality control (Chan *et al*., 2012). Many of the herbal products referred to in the reviews are not licenced or registered as medicines; very few have full marketing authorizations, but several have traditional herbal registration (THR) registered under the European Union Traditional Herbal Medicine Directive (EU, 2004). For THR products, quality needs to be assured, but not all THR products are standardized, and efficacy does not need to be proven for registration. So products containing the same herb are not necessarily comparable, unless they contain the same controlled specific extract (such as EGb761) at relevant clinical doses.

ADVERSE EVENTS ASSOCIATED WITH THE USE OF HERBAL REMEDIES

The assumption that 'natural' equals to 'safe' is obviously deceptive. Natural products contain pharmacologically active molecules potentially able to cause danger to human health. Classical examples of toxicity associated with herbal use include the hepatotoxicity due to pyrrolizidine alkaloids-containing plants (Li *et al*., 2011), *Aconitum* poisoning due to *Aconitum* alkaloids, which are highly toxic cardiotoxins and neurotoxins (Chan, 2015) and the severe – in some cases lethal – cardiovascular side effects associated with *Ephedra sinica*, whose sales have been prohibited by the Food and Drug Administration since 2004 (Seamon and Clauson, 2005). On the other hand, recent studies have clearly shown that adverse events due to herbal remedies are relatively infrequent, if assessed for causality (Di Lorenzo *et al*., 2015). In RCTs, very few or no additional side effects compared with placebo are generally observed for herbal remedies (Table 2). However, RCTs cannot reliably detect an increased incidence of rare adverse events or events with significant latency (Berlin *et al.*, 2008). Hence, the majority of adverse effects come into the light subsequently, through spontaneous case reports, case series and post-marketing surveillance studies. Similar to the clinical efficacy, only the totality of the available clinical data (RCTs, case reports, post-marketing surveillance studies and spontaneous reporting schemes) that can be grouped in systematic reviews can provide reliable information on herbal medicines safety.

A recent overview of the literature (Posadzki *et al.*, 2013) identified 50 systematic reviews reporting adverse effects of herbal medicines. From a methodological viewpoint, 7 systematic reviews had no flaws (5 out of 5 points of the modified Oxman scale), 8 had minimal flaws, 20 had minor weakness and 15 had major flaws. Most of the herbal medicines evaluated were associated with only moderately severe or minor adverse effects. Serious adverse effects were noted for four herbal medicines only, namely, belladonna *herbae pulvis standardisatus* (*Atropa belladonna*), creosote bush (*Larrea tridentata*), kava (*Piper methysticum*) and senna (*Cassia senna*) (Posadzki *et al*., 2014). Top methodological systematic reviews described the side effects of saw

palmetto (*Serenoa repens*), agnus castus (*Vitex agnus castus*), hawthorn (*Crategus* spp.), valerian (*Valeriana officinalis*) and mistletoe (*Viscum album*) (Table 3).

Another systematic review, not included in the aforementioned overview, reported that 86.6% of the adverse effects of plant food supplements and botanical preparations were associated with 14 plants only. Two plants were responsible for 32% of the adverse effects reported, that is, soybean (*Glycine max*), for which allergic reactions and hormone-like activity were demonstrated, and liquorice (*Glycyrrhiza glabra*) responsible for hypokalaemia and hypertension (Di Lorenzo *et al*., 2015). A classification of toxicity in traditional Chinese medicine, for the Western reader, which was recently reported (Liu *et al*,. 2014b), showed that estimations of toxicity varied according to clinical context and testing methods used, as well as factors such as processing, which is more common in traditional Chinese medicine than most Western herbal products.

Overall, although many cases of adverse effects have been reported, a careful assessment of causality indicates that their number is significantly low and the number of severe clinical reactions is limited (Posadzki *et al.*, 2014; Di Lorenzo *et al*., 2015). However, because severe, and rarely, fatal adverse effects have been described, vigilance by healthcare professionals is needed.

HERB–DRUG INTERACTIONS

In the last 20 years, multiple case reports, case series and pharmacokinetic trials have clearly highlighted that herbal medicines can interact with prescribed medicines. From a mechanistic viewpoint, interactions can have either a pharmacokinetic and pharmacodynamic basis or both (Izzo *et al*., 2002), and herbal medicines may interact with prescribed drugs at the intestine, liver, kidneys and targets of action. Most of herbal remedies involved in drug interactions have been shown to up-regulate or down-regulate cytochrome P450s and/or P-glycoprotein, but the roles of drug transporters including the organic anion and cation transporters and the nuclear pregnane-X receptor are now becoming increasingly apparent (Chen *et al*., 2012; Cho and Yoon, 2015).

Much of the evidence concerning herb–drug interactions comes from case reports, which, especially in the past, were of poor quality (Izzo, 2012). It should be clear, however, that even well-documented case reports may not be able to establish a cause and effect relationship. Case reports coupled to pharmacokinetic trials constitute the highest level of evidence for herb–drug interactions (Izzo, 2012; Posadzki *et al*., 2013). Examples of well-documented herb–drug interactions are reported in Table 4. While many of the interactions are devoid of serious clinical consequences, some of them require extreme watchfulness. For example, the concomitant use of St John's wort (*Hypericum perforatum*) with immunosuppressive (e.g. cyclosporine), antiretroviral (e.g. indinavir and nevirapine), cardiac (e.g. digoxin) or antineoplastic (e.g. irinotecan and imatinib) drugs may result in reduced plasma concentration of the prescribed drug and, hence, reduced efficacy (Borrelli and Izzo, 2009; Izzo, 2012; Russo *et al*., 2014, Posadzki *et al*., 2013). Cancer (Alsanad *et al*. 2014), and patients with cardiovascular conditions (Tachjian *et al*., 2010; Ge *et al*., 2014; Milić *et al*., 2014) are therefore greatly

Table 3. Safety of herbal medicines: key information extracted from top methodological systematic reviews[a]

Herbal drug	Data sources	Main results	Reference
Agnus castus *Vitex agnus castus*	RCTs, RCTs case reports, case series, surveys and post-marketing surveillance.	Mild and reversible adverse effects, most frequently nausea, headache, gastrointestinal disturbances, menstrual disorders, acne, pruritus and rash.	Daniele *et al.*, 2005
Black cohosh *Cimicifuga racemosa*	Clinical studies, post-marketing surveillance studies and case reports	Black cohosh has been associated with serious safety concerns (issue thought to be associated with quality).	Borrelli and Ernst, 2008
Hawthorn *Crataegus* spp.	WHO spontaneous reporting scheme; clinical trials	Generally mild-to-moderate AEs, dizziness, vertigo and gastrointestinal. Eight severe AEs reported.	Daniele *et al.*, 2006
Milk thistle *Silybum marianum*	RCTs, cohort studies and case reports	Safe and well tolerated	Jacobs *et al.*, 2002
Phyllanthus spp	RCT	No serious AEs reported	Liu *et al.*, 2001
Saw palmetto *Serenoa repens*	RCTs, non-RCTs, uncontrolled trials, case reports and post-marketing surveillance	Well tolerated, with mild, infrequent and reversible AEs (abdominal pain, diarrhoea, nausea, fatigue, headache, decreased libido and rhinitis)	Agbabiaka *et al.*, 2009
Valerian *Valeriana officinalis*	Clinical trials	Valerian is rarely associated with AEs	Taibi *et al.*, 2007
Mistletoe *Viscum album*	Clinical trials	Flu-like symptoms, fever and local reactions at the injection site. Occasionally, allergic reactions. Reversible hepatotoxicity at high doses	Kienle *et al.*, 2011

[a]according to Posadzki *et al.*, 2013.

RCT, randomized clinical trial; AE, adverse event.

Table 4. Examples of well-documented herb–drug interactions[a]

Herbal drug	Prescribed drug	Result of interaction
Betel nut *Areca catechu*	Procyclidine	Rigidity, bradykinesia and jaw tremors
Danshen *Salvia milthiorriza*	Warfarin	Increased anticoagulant effect
Don quai *Angelica sinensis*	Warfarin	Increased anticoagulant effect
Evening primrose *Oenothera biennis*	Fluphenazine	Seizures
Garlic *Allium sativum*	Chlorzoxazone	Increased plasma concentration of chlorzoxazone
	Paracetamol	Changes in paracetamol pharmacokinetics
	Saquinavir	Decreased saquinavir blood concentration
Ginkgo *Ginkgo biloba*	Omeprazole	Decreased omeprazole blood concentration
	Tolbutamide	Decreased tolbutamide blood concentration
	Tanilolol	Increased tanilolol blood concentration
Ginseng (Red or Korean) *Panax ginseng*	Phenelzine	Sleeplessness, tremor and headaches
Ginseng (American) *Panax quinquefolius*	Warfarin	Reduced warfarin blood concentration and anticoagulation
Goji (Chinese wolfberry) *Lycium barbarum*	Warfarin	Increased anticoagulant effect
Goldenseal *Hydrastis canadensis*	Debrisoquine	Decreased debrisoquine urinary recovery ratio
Green tea *Camellia sinensis*	Folic acid	Decreased folate blood concentration
Hibiscus (Roselle) *Hibiscus sabdariffa*	Chloroquine	Reduced blood concentration of chloroquine
	Paracetamol	Changes in paracetamol pharmacokinetics
Kava *Piper methysticum*	Chlorzoxazone	Decreased 6-hydroxychlorzoxazone/chlorzoxazone serum ratio
Milk thistle *Silybum marianum*	Metronidazole	Decreased metronidazole blood concentration
Peppermint *Mentha piperita*	Felodipine	Increased felodipine blood concentration
Schisandra chinensis	Tanilolol	Increased tanilolol blood concentration
St John's wort *Hypericum perforatum*	Alprazolam, amitriptyline, bupropion, ciclosporin, digoxin, fexofenadine, gliclazide, imatinib, indinavir, irinotecan, methadone, midazolam, nevirapine, nifedipine, omeprazole, phenprocoumon, verapamil and warfarin, zolpidem	Decreased blood concentration of the concomitantly used prescribed drugs. In the case of cyclosporine, changes in pharmacokinetics were associated with rejection episodes in transplant patients.
	Oral contraceptive	Reduced efficacy and increased breakthrough bleeding
	Paroxetine and venlafaxine	Serotonin syndrome

[a]Data extracted from Izzo, 2012. Well-documented herb–drug interactions are those highlighted by (i) well-documented case report; multiple case reports and case series (level of evidence three out of five), (ii) pharmacokinetic trials in patients or healthy volunteers (level of evidence four out of five) or (iii) case report(s) and confirmed by clinical pharmacokinetic trials (level of evidence five out of five) (Izzo, 2012).

at risk, as are those taking immunosuppressant drugs (Colombo *et al*., 2014). The anticoagulant warfarin is the most common drug involved in all kinds of drug interactions, including herbal, and St John's wort the most common herb involved in all herb–drug interactions (Izzo, 2012; Milić *et al*., 2014), so caution should be used whenever these are used in combination with other drugs.

USE OF HERBAL REMEDIES DURING PREGNANCY AND BY BREASTFEEDING WOMEN

Complementary and alternative therapies, including herbal medicines, are widely used during the third trimester of pregnancy, and pregnant women tend to believe that such treatments are safer than prescribed drugs (Pallivalapila *et al*., 2015). According to a British survey, 57.8% of pregnant women used one or more herbal remedies, the most common being ginger (*Zingiber officinale*), cranberry (*Vaccinium macrocarpon*), raspberry (*Rubus ideaus*) leaf, chamomile (*Matricaria recutita*), peppermint (*Mentha piperita*) and echinacea (*Echinacea* spp.) (Holst *et al*., 2011).

Although many clinical reports exist on the efficacy of herbal remedies in pregnancy, the authors of a recent systematic review, identified 'only' 14 RCTs related to herb efficacy in pregnancy (Dante *et al*., 2013). The quality of these trials, assessed by the Jadad score, was satisfactory. Ginger was the most investigated herb (ten trials), and it was consistently found to attenuate nausea symptoms in pregnant women (Dante *et al*., 2013). Among the other investigated herbs, St John's wort was beneficial as a wound healing remedy in women who underwent caesarean section (one trial), cranberry did not prevent urinary tract infection (one trial), garlic was not efficacious in pre-eclampsia prevention (one trial) and raspberry (*Rubus ideaus*) leaf did not shorten the first stage of labour (one trial) (Dante *et al*., 2013).

Herbal remedies have been associated with perils to pregnant women and their babies (Ernst 2002). According to Smeriglio and colleagues (2014), among the most

frequently herbal remedies used by pregnant women, raspberry leaf has been postulated to induce labour, cranberry may cause gastrointestinal upsets, blue cohosh (*Caulophyllum thalictroides*) might exert abortifacient properties and it has been associated with perinatal stroke (Smeriglio *et al*., 2014). In addition, case reports have documented ovarian hyperstimulation following agnus castus (*Vitex agnus castus*) ingestion, maternal hypertension following dong quai (*Angelica sinensis*) and occipital meningo-encephalocele and cerebellar agenesis in an infant whose pregnant mother took *Tripterygium wilfordii* (Ernst, 2002; Smeriglio *et al*., 2014). Clearly, causality needs to be established.

Herbal medicines are also used by breastfeeding women. According to recent systematic reviews (Budzynska *et al*., 2012; Amer *et al*., 2015), herbal medicines have been evaluated in survey studies, safety studies and efficacy studies. However, because of the poor methodological quality of the clinical data, there is little evidence supporting their efficacy and safety among the lactating women. The most common herbs that have been evaluated are St John's wort (*Hypericum perforatum*), garlic (*Allium sativum*) and senna (*Cassia senna*) (Budzynska *et al*., 2012; Amer *et al*., 2015). Despite the wide use of herbal remedies by pregnant and breastfeeding women, few studies have evaluated their efficacy and the safety in these specific situations and further studies are needed. Herbal remedies contain pharmacologically active molecules and have been associated with risks to pregnant women and their babies (Ernst, 2002; Smeriglio *et al*., 2014) so as a general and judicious rule, should be considered to be contraindicated during pregnancy unless otherwise proven to be helpful and safe (e.g. ginger for nausea and peppermint water for dyspepsia).

USE OF HERBAL REMEDIES IN THE PAEDIATRIC AND ADOLESCENT POPULATION

Herbal remedies are popular in paediatric and adolescent populations. For example, in 2014, an estimated 5.8% of German children and adolescents between the ages of 0 and 17 years (Du *et al*., 2014) and 3.9% among children 0–17 years old in the USA used herbal remedies (CDC National Health Statistics Report, 2007). It is therefore crucial to define their efficacy and possible risks in children.

In contrast to the adult population, there is a paucity of systematic reviews related to the efficacy of herbal remedies in paediatrics. A recent overview of the literature (Hunt and Ernst, 2011) identified only two systematic reviews, one addressing the effectiveness of ivy leaf (Hofmann *et al*., 2003) for childhood bronchial asthma and another evaluating the effect of an herbal combination in the treatment of infant colic (Garrison and Christakis, 2000). Both treatments were found to yield preliminary evidence of efficacy. Furthermore, a Cochrane review of *Echinacea purpurea* for common cold included studies in children that revealed a trend or no effect in reducing the duration and the symptoms (Karsch-Völk *et al*., 2014).

Concerning the risks related to the use of herbal remedies in children, a recent systematic review identified 128 cases of possible adverse events associated with the use of herbal remedies in children (Gardiner *et al*., 2013). Of the 128 cases, 23% occurred in children between the ages of 9–18 years, 38% between the ages of 2 and 8 years and 37% in children under 2 years old. Main adverse events reported include neurological (35% seizures, central nervous system depression and lethargy), cardiovascular (10% hypertension and blood concerns) and gastrointestinal (14% nausea, vomiting and diarrhoea) systems as well as liver toxicity and jaundice (11%) (Gardiner *et al*. 2013). Many of the case reports were poorly documented. Among the best-documented case reports, fleeceflower (*Polygonum multiflorum*) root and kava (*Piper methysticum*) were associated with acute hepatitis, blue cohosh (*Caulophyllum thalictroides*) with neonatal congestive heart failure and Siberian ginseng (*Eleutherococcus senticosus*) with neonatal hirsutism. The accidental ingestion of tea tree (*Melaleuca alternifolia*) oil was associated with ataxia and unresponsiveness (Gardiner *et al*., 2013).

USE OF HERBAL REMEDIES IN THE GERIATRIC POPULATION

Many elderly subjects use herbal products for the relief of symptoms or medical diseases that are believed to be not easily treated by conventional prescribed remedies. This cohort of patients usually suffers from a number of chronic diseases and takes concomitantly more prescribed drugs than the younger population. A recent survey of the published literature (de Souza Silva *et al*., 2014) identified 16 articles involving the use of herbal remedies in the elderly population. The majority of the studies were performed in the USA. The most commonly used herbs were gingko (*Ginkgo biloba*) and garlic (*Allium sativum*), and both of them have the potential to interact with prescribed drugs, especially in patients under anticoagulants (Tachjian *et al*., 2010; Milić *et al*., 2014). Other herbal remedies frequently used by elderly subjects include ginseng (*Panax ginseng*), *Aloe vera*, chamomile (*Matricaria recutita*), ginger (*Zingiber officinale*) and spearmint (*Mentha spicata*). A number of studies pointed on the use of herbal remedies to treat constipation (Cherniack, 2013; Cirillo and Capasso, 2015), a condition that is very common in the geriatric population. It is therefore incumbent that medical doctors be aware of the use of herbal products among the elderly subjects when prescribing a specific pharmacological treatment.

CONCLUSIONS

Assessing the safety and efficacy of herbal medicines remains problematic, with inadequate or inconsistent methods being used, and the issues have been discussed here using examples of recent systematic reviews and meta-analyses. It is apparent that generalizations about the efficacy and safety of herbal remedies are not advisable, even though many have been effectively used for diseases and as functional foods, especially in Asian

countries. Certain herbal medicines have been shown to be efficacious (e.g. ginger for preventing and treating nausea and vomiting), whereas others have been shown to be effective for a specific indication but not others (e.g. ginseng for improving glucose metabolism, but not for Alzheimer's disease) (Table 2). Several herbs have been associated with serious adverse events, including herb–drug interactions (St John's wort in particular). However, many clinical studies have been performed without sufficient rigour and recorded detail; therefore, the findings must be interpreted cautiously.

Clearly, more high quality research in this field is needed to firmly establish the efficacy and/or safety of many herbal products. Most importantly, herbal research should be conducted with the same meticulous care as any other medical research, and as part of this, all herbal products administered to patients should ideally be chemically characterized, standardized if possible, and of known quality. For many herbs, monographs of pharmacopoeial standards are available and contain validated general methods for testing for microbiological and other forms of contamination. Furthermore, all clinical studies should conform to the standards reported in the Consolidated Standards of Reporting Trials and Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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