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Review

Assessing safety of herbal products for menopausal complaints: An international perspective

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ABSTRACT

Future research of herbal products for menopausal women should include long-term safety assessments because women may use these products for prolonged periods of time. Growing numbers of women take prescription medications and concurrently use herbal products for alleviation of menopausal symptoms. Because of possible herb–drug interactions, both drug and supplement manufacturers should provide basic pharmacokinetic data to reduce the risk of adverse interactions. In addition, herbal products produced to high quality standards are essential for ensuring consumer safety. Regulatory frameworks must be in place to ensure that herbal ingredients' identities have been verified, that they have been properly quantified per unit dose, that the product is within tolerance limits for contaminants, that the product's safety and effectiveness under the recommended conditions of use have been assessed before sale to the public, and that a system is in place to detect and deal with adverse reactions when they arise. This article explores these and related concerns.

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1. Introduction

When the Women's Health Initiative (WHI) study was discontinued in 2002 because of unanticipated increases in risk for breast cancer, stroke, heart attack, and blood clots among women taking hormone replacement therapy (HRT) [1], the search for alternative treatments that were perceived to offer beneficial effects with less risk intensified. The 2002 National Health Interview Survey (NHIS) found that women between 50 and 59 years of age reported the highest rate of complementary and alternative medicine (CAM) use during the previous 12 months [2]. Discontinuation of the WHI study, and its preliminary observations of safety concerns from estrogen use, likely contributed to the growing use of CAM by menopausal women in general and the use of herbal products in particular. A survey in the United Kingdom reported that women's desire for personal control over their health was the strongest motive for using herbal products [3]. Their dissatisfaction with conventional treatment, as well as concerns about the side effects of hormone medications, were secondary motives [3].

Although a wide variety of herbal remedies have been used across the centuries, many plant-based products available in the marketplaces of the United States (US), Europe, Canada, and Australia bear little resemblance to traditional preparations that generally were water based. Medicinal plant extracts are often highly concentrated extracts prepared with a range of organic solvents, often in combination with other botanicals. When marketed as dietary supplements, they are often consumed for extended periods of time. This is certainly the case for prolonged use of herbal dietary supplements during menopause and other conditions associated with aging. Quality issues including adulteration, misidentification, and contamination continue to be concerns. Of particular concern for women who choose or are advised not to use estrogen hormones to treat menopause-related symptoms is the potential effect of herbal products on estrogen-receptive cancers. Are they safe for a woman at risk for, or diagnosed with, breast cancer? In addition, many women have chronic health conditions and concomitantly use over-the-counter and prescription drugs with herbal products. Considering all these factors, it is not reasonable to assume safety for a given herb based only on a long history of use.

This article cannot address every one of these issues in depth, so the authors explored the current mechanisms for assessing the safety of herbal products, the issues relevant to safety assessment, and other considerations that may be particularly relevant for menopause.

2. Assessing safety and toxicity

Although the overall incidence of adverse effects from herbal products appears to be low compared to those associated with estrogen preparations, harm from herbal products can still occur because of the inherent toxicity of the plant, as well as from contamination, adulteration, plant misidentification, and interactions with other herbal products or pharmaceuticals. In most countries, safety assessment is conducted in order to meet regulatory requirements or for product registration. Some countries, such as the European Union and Canada, require a combination of traditional knowledge and clinical/experimental data, the assessment of adverse event reports (AERs), and the review of published toxicity data [4]. In the US, herbal products meeting the requirements of Dietary Supplement Health and Education Act of 1994 (DSHEA) are regulated as dietary supplements and are presumed to be safe as "foods" (unless proven otherwise). Although DSHEA does not permit disease treatment claims for dietary supplements, products intended to mitigate the symptoms of menopause are currently allowed on the market as dietary supplements (with appropriate structure–function claims).

Despite regulatory differences, any thorough safety review must include comprehensive information from human data—including clinical safety studies, post-marketing surveillance, adverse event reports, herb–drug interactions, animal pharmacological data, reproductive toxicity, pharmacokinetics, safety margins (akin to therapeutic index), context of historical use, and regulatory status and regulatory actions in other countries. Because many countries do not require controlled clinical studies and animal experimental toxicological studies in order to establish the safety of herbal products, AERs can act as safety indicators after critical review by experts using appropriate causality algorithms and/or other tools for analysis. Suitable risk mitigation advisories may be needed to alert health care providers and consumers, commensurate with the level of safety concern. All herbal product safety assessments must also include ongoing monitoring to identify signals that might trigger a safety re-evaluation of these products.

2.1. Causality assessment methods

Spontaneous or mandatory human AERs filed with regulatory agencies and case reports published in peer-reviewed journals provide valuable information concerning the safety of an herbal product. In some countries (like the US) post-marketing safety studies or periodic safety update reports are not available for all herbal products. As a result, detection of adverse events for products in wide use provides an indication for safety monitoring in the general population. Such detection also provides valuable information about an ingredient's safety profile in vulnerable populations, e.g., during menopause, pregnancy, or lactation, and in the elderly, children, or prescription medication users. A recent publication [5] describes several weaknesses of AERs, including under-reporting, incomplete case information, and lack of verification of the herb's identity, as well as confounding variables such as alcohol use, use of other concurrent medications, and preexisting risk factors. Despite these limitations, proper analysis of information from AERs helps in generating hypotheses regarding the safety of a product [6].

Several causality algorithms are available to assess AERs and case reports, including the World Health Organization (WHO) causality method [7], the Naranjo scale [8], the Jones scale [9], and the Kramer scale [10]. These instruments allow the analysis of AERs using a variety of parameters such as a patient's previous experience with the substance, spatio-temporal correlation, correlation to dose and duration of intake, evaluation of alternative etiologies, and de-challenge/re-challenge information. These tools score the responses to specific questions to assign the likelihood of causation: doubtful/unlikely, possible, probable, and definitive/certain. For analysis of the information, tools such as the proportional representation ratio (PRR) aid in identifying a signal of safety concern (PRR considers the number of reactions of interest vs. all other reactions for the product of interest vs. reactions for all other products in the class). Although several causality assessment scales are available, unfortunately no method is universally accepted [11]. Because no universal comprehensive guideline or standard is available to identify the safety of an herbal product from the analysis of case reports and AERs, expert opinion is required for analysis of data from multiple sources [12]. International collaboration in the development of harmonized causality assessments more appropriate for the analysis of AERs associated with herbal products is a highly desirable goal.

AERs are collected by national regulatory agencies such as US Food and Drug Administration MedWatch, Canada Vigilance Program, British Medicines and Healthcare Products Regulatory Agency (MHRA), and Australian Adverse Drug Reactions Advisory Committee (ADRAC). These programs identify signals of safety concern and provide appropriate advisories to consumers and health care practitioners. The WHO Uppsala Monitoring Center (WHO-

Table 1

Numbers of individual case reports and ADR terms grouped by system organ class of suspected ADRs associated with single-ingredient preparations of herbal substances of interest held in the Vigisearch database of WHO-UMC for the period up to 29 November 2009^a.

	<i>Angelica sinensis</i>	<i>Cimicifuga racemosa</i>	<i>Glycine max</i>	<i>Humulus lupulus</i>	<i>Lepidium meyenii</i>	<i>Trifolium pratense</i>
Total number of reports	4	272	38	6	1	24
Total number of ADR terms	9	633	71	18	1	41
ADR terms by system organ class						
Blood and lymphatic system disorders	0	5	2	1	0	0
Cardiac disorders	0	14	1	0	0	3
Congenital, familial, and genetic disorders	0	0	0	0	0	2
Ear and labyrinth disorders	0	3	2	0	0	1
Endocrine disorders	0	1	0	0	0	0
Eye disorders	0	15	3	0	0	
Gastrointestinal disorders	3	74	5	0	0	8
General disorders, administration site conditions	0	62	8	3	0	3
Hepatobiliary disorders	0	58	1	0	0	0
Immune system disorders	0	2	2	0	0	0
Infections and infestations	1	13	2	0	0	0
Injury poisoning and procedural complications	0	3	0	3	0	0
Investigations	0	84	7	2	0	1
Metabolism and nutrition disorders	0	14	1	0	0	0
Musculoskeletal and connective tissue disorders	0	16	2	0	0	2
Neoplasms benign, malignant, and unspecified	0	6	1	0	0	1
Nervous system disorders	4	52	5	3	0	10
Pregnancy, puerperium, and perinatal conditions	0	0	0	0	0	0
Psychiatric disorders	0	25	0	3	0	3
Renal and urinary disorders	0	14	3	0	0	0
Reproductive system and breast disorders	0	67	2	1	0	0
Respiratory, thoracic, and mediastinal disorders	0	11	4	0	0	4
Skin and subcutaneous tissue disorders	1	70	17	2	1	3
Social circumstances	0	1	0	0	0	0
Surgical and medical procedures	0	4	0	0	0	0
Vascular disorders	0	19	3	0	0	0

^a Caveat statement: The information shown is not homogeneous at least with respect to origin or likelihood that the herbal substance caused the adverse reaction. The information does not represent the opinion of WHO.

UMC) is an international initiative that collates safety information. Table 1 summarizes individual case reports of AERs for herbal substances commonly used by menopausal women.

Reports from WHO-UMC represent only a fraction of all reports that are submitted to national authorities. UMC reports are assessed according to the WHO causality assessment method [7].

Black cohosh is a commonly used herbal product taken for alleviation of menopausal symptoms. For black cohosh (*Actaea racemosa* L., synonym *Cimicifuga racemosa* (L.) Nutt., Ranunculaceae), the greatest numbers of ADR terms (not individual reports—each report may contain one or more ADR terms) are classed under the system organ classes (SOC): general, gastrointestinal, hepatobiliary, nervous system, reproductive, breast, and skin and subcutaneous tissue disorders. Several of these SOCs include ADR terms that are signs or symptoms of liver disease: for example, gastrointestinal disorders include nausea and vomiting ($n=24$ for black cohosh), abdominal pain ($n=15$), and liver function analyses ($n=62$). For another commonly used herbal product, soy (*Glycine max* (L.) Merr., Fabaceae), the greatest number of ADR terms for single-ingredient products relates to skin and subcutaneous tissue disorders such as rash ($n=5$), pruritus ($n=4$), and erythematous rash ($n=2$) (n.b.: these are sub-categories within the general headings listed in Table 1). Although these AERs help generate hypotheses, the weaknesses in reporting and assessment provide weak data (n.b. the caveat statement: The information shown is not homogeneous at least with respect to origin or likelihood that the herbal product caused the adverse reaction. The information does not represent the opinion of WHO).

3. Regulatory environment

National regulations vary widely regarding how herbal products are classified – prescription drugs, traditional medicines, or food

(or dietary supplements) – and expectations regarding safety vs. benefit. Illustrated below are two different regulatory approaches (US and Canadian) that show how safety is assessed in different regulatory environments.

In the US, manufacturers of herbal dietary supplements are not required to submit to FDA safety information before marketing grandfathered (i.e., pre-DSHEA) dietary ingredients. However, for new dietary ingredients the manufacturer must submit to FDA a pre-marketing package with information about the basis upon which the company has concluded that a dietary supplement containing a new ingredient can reasonably be expected to be safe for human consumption. Current good manufacturing practices (cGMPs) for dietary supplements are in effect in the US. According to DSHEA, FDA is responsible for determining if a dietary supplement product presents a significant or unreasonable risk of illness or injury under labeled conditions of use, and FDA may take action accordingly. To identify problems, FDA's MedWatch portal collects mandatory serious AERs submitted by manufacturers, along with spontaneous AERs from consumers. These AERs are triaged by the agency's Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS). Still, an FDA-commissioned study estimated that the agency receives less than 1% of all AERs associated with dietary supplements [5]. Absent appropriate reporting, regulatory bodies find it difficult if not impossible to quickly and effectively identify the potential risk associated with the use of a particular dietary supplement.

In Canada, the *Natural Health Products Regulations* (NHPR) [13] under the *Food and Drugs Act* came into force on 01 January 2004. These regulations refer to many products considered dietary supplements in US, including herbal products, as natural health products (NHP). The Canadian NHPR are the legal basis for a mandatory review system in which each NHP must receive market authorization from the federal Department of Health (Health

Canada) before it can be legally sold. Health Canada issues a product license after reviewing an application demonstrating that the product is safe under the recommended conditions of use without a prescription, is effective for the proposed health claims, and is of high quality. Each importer, manufacturer, packager, and labeler of NHP must have a site license issued on the basis of evidence of compliance with cGMPs created specifically for natural health products.

Although both Canada and the US require DS manufacturers to report serious AERs to appropriate government agencies, the Canadian system offers more assurances of safety because it requires regulatory review and approval for all natural health products.

4. Variation in herbal preparations

Assessing the safety of herbal products is more complex than the safety assessment of conventional pharmaceuticals. Herbs are complex mixtures of constituents that can vary extensively depending on growth and harvesting conditions, as well as processing and formulation variables that can influence the quality, safety, and effectiveness of the finished herbal product. Specifically, the nature of the extract, fraction, or the isolated group of constituents present in the final formulation can vary widely among different products with the same or similar names. Matrix variability between products could have ramifications for systemic absorption and bioavailability. Because compliance with quality public standards in USP is voluntary in the US, two manufacturers may make a soy or red clover product, for example, but the consumer or clinician has no way of knowing whether the two products are similar or how they differ unless both claim compliance with the same standards. Similarly, researchers using diverse extracts or isolates in clinical trials often produce conflicting results because of such variability. When evaluating the toxicity of herbal products, one must consider the quality of the product under investigation and must not generally ascribe the results to the herb *per se*.

5. Product quality

One of the critical issues for assessing the safety and toxicity of a particular herb is quality control, primarily because of problems with identity, purity, strength, and performance characteristics. Purity issues include the presence of incorrect plant parts, contaminants such as pesticides and pollutants, toxic metals, bacteria, molds and mycotoxins, processing impurities, and solvent residues. Studies have shown that some herbal products contain significant levels of heavy metals, toxic herbs, and undeclared pharmaceuticals [14,15]. Finished products may also be adulterated with pharmaceuticals that can be very hard to detect using traditional laboratory analysis. In some cases, more expensive herbs such as ginseng (*Panax ginseng* C.A. Mey., Araliaceae) are adulterated with cheaper herbs to increase profit margins [16].

Because of the intrinsic toxicity of certain plants, misidentification and substitution can lead to adverse reactions and injuries. For instance, black cohosh (*A. racemosa* L., Ranunculaceae) has been incorrectly identified and may have inadvertently posed a consumer safety risk. Four serious AERs in Canada were assessed as having a probable causal association with a specific product labeled as black cohosh that was shown to contain the wrong species. Using HPLC analysis and mass spectrometry, analysts found that the suspect product did not contain authentic black cohosh but probably the Asian species *Actaea cimicifuga* L. (synonym *Cimicifuga foetida* L.) [17]. Subsequent investigations by Health Canada and manufacturers have led at least seven different companies to recall products after learning the companies had been supplied with the wrong species of black cohosh [18]. Adulteration of black cohosh

with blue cohosh (*Caulophyllum thalictroides* (L.) Michx., Berberidaceae) is also a matter of concern [19]. Alkaloids and saponins in blue cohosh preparations were recently reported to produce birth defects, neonatal heart failure, and uterine-stimulating effects [20]. Black cohosh may also be mixed with yellow cohosh (*Actea podocarpa* DC., synonym *Cimicifuga americana* Michx.) because of similarity in above-ground appearance and common growing habitat (General Chapter “2030” in [21]). Concerned with adulteration of black cohosh, a number of researchers have developed analytical methods to ensure the correct identification of *A. racemosa* [22–26].

6. Quality standards

Public quality standards for herbal products are available from various pharmacopeias such as the *United States Pharmacopeia* [21], the *European Pharmacopoeia* [27], and the *British Pharmacopoeia* [28], which are widely used in many countries around the world. In addition to addressing the quality of raw materials, the pharmacopeias note that the quality of the finished product is influenced by manufacturing, packaging, labeling, importation, distribution and storage, or warehousing activities, which are also part of cGMPs.

Because regulatory paradigms vary among nations, the requirements in pharmacopeial monographs and their compliance requirements are not uniform. For example, Health Canada monographs (<http://webprod.hc-sc.gc.ca/nhp/nd-bdipsn/monosReq.do?lang=eng>) primarily provide labeling information (including uses, dose and duration of use, and risk information). In contrast, European Medicines Agency (EMA) community monographs (<http://www.emea.europa.eu/hums/human/hmpc/hmpcmonographs.htm>) additionally address qualitative and quantitative composition and pharmacological properties for well-established use and traditional-use applications. In the US, compliance with dietary supplements standards in USP is voluntary unless a manufacturer chooses to put “USP” on the product label. In that case, the product must comply with all applicable USP standards or else FDA can deem the product misbranded by FDA. USP monographs for botanical dietary supplements are developed after their safety review [29] and include tests, procedures, and acceptance criteria for quality attributes of identity, purity, strength, and limits for contaminants.

An illustration of pharmacopeial requirements (not a complete reproduction) for black cohosh is presented in Table 2.

In addition to the guidance provided by individual jurisdictions, WHO has published guidelines for the quality of herbal medicines with reference to contaminants and residues [32], for cGMPs for herbal medicines [33], for Good Agricultural and Collection Practices (GACP) for medicinal plants [34], and for quality control methods for medicinal plant materials [35]. The American Herbal Pharmacopoeia (AHP) has also developed monographs for the quality, effectiveness, and safety of botanical medicines commonly used in the US. The American Herbal Products Association (AHPA), a national trade association for the herbal products industry in the US, published *The Botanical Safety Handbook* in 1997. This handbook uses a safety classification for herbs based upon data collated from human and animal toxicity, traditional use, and regulatory status in various countries. *The Botanical Safety Handbook* is currently being revised and updated. The USP *Dietary Supplements Compendium* [36] includes quality standards for dietary supplements, guidance documents from AHPA and other trade associations, and illustrations of the quality parameters (such as macroscopic and microscopic photographs and chromatograms) for identification of plant specimens and determination of contaminants from closely related plant species.

International collaboration on the further development of standards for the quality of herbal medicines is being promoted through the International Regulatory Cooperation for Herbal Medicines

Table 2
Examples of pharmacopeial requirements for black cohosh.

USP [21]	EMA [30]	Health Canada [31]
Composition Black cohosh consists of the dried rhizome and roots of <i>Actaea racemosa</i> L. [<i>Cimicifuga racemosa</i> (L.) Nutt.] (Fam. Ranunculaceae). It is harvested in the summer. It contains not less than 0.4 percent of triterpene glycosides, calculated as 23- <i>epi</i> -26-deoxyactein (C ₃₇ H ₅₆ O ₁₀) on the dried basis.	<i>C. racemosa</i> (L.) Nutt., rhizoma (black cohosh). Herbal preparations: dried extract from <i>Cimicifuga</i> rhizoma (5–10:1) ethanol 58% (v/v); dried extract from <i>Cimicifuga</i> rhizoma (4.8–8.5:1) ethanol 60% (v/v); dried extract from <i>Cimicifuga</i> rhizoma (5–10:1) propan-2-ol 40% (v/v).	<i>A. racemosa</i> L. (Ranunculaceae) Synonym <i>C. racemosa</i> (L.) Nutt. Common names: black cohosh, black snakeroot, black bugbane. Root, rhizome.
Use/indications Not listed.	Well-established use: herbal medicinal product for the relief of minor neuro-vegetative menopausal complaints (such as hot flushes and sweating).	Traditionally used (in Western herbalism) to help relieve menopausal symptoms.
Dose/duration of treatment Not listed.	Extracts equivalent to 40 mg of the herbal substance per day in divided doses, for not more than 3 months without medical advice.	300–3000 mg dried root or rhizome per day for traditional uses. Consult a health care practitioner for use beyond 1 year.
Risk information Discontinue use and consult a health care practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice.	Patients with a history of liver disorder should take <i>Cimicifuga</i> preparations with caution. Patients should stop taking <i>Cimicifuga</i> preparations and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury. <i>Cimicifuga</i> preparations should not be used together with estrogens unless advised by a doctor.	Consult a health care practitioner before use if you have a liver disorder or develop symptoms of liver trouble.
Pregnancy and lactation If you are pregnant or nursing a baby, seek the advice of a health professional before using this product.	In the absence of sufficient data, use during pregnancy and lactation is not recommended.	Do not use if you are pregnant.
Specifications^a Specifies tests, procedures, and acceptance criteria for macroscopic and microscopic botanical characteristics, chromatographic identification tests, content of triterpenoids, microbial enumeration, limits for residual solvents, pesticide residues, and heavy metals. Provides limits and methods for measuring weight variation and disintegration of tablets.	Not listed.	Must comply with the minimum specifications outlined in the current NHPD Compendium of Monographs.

^a A quality monograph for black cohosh is not yet available in the *European Pharmacopoeia* or the *British Pharmacopoeia*.

[37]. International harmonization of quality standards is highly desirable to ensure quality, identity, and label uniformity in international commerce, irrespective of how the herbal products are labeled and regulated—whether as traditional medicines, drugs, or supplements.

7. Herb–drug interactions

Herb–drug interactions are an important consideration for safety, especially regarding pharmaceutical products with narrow therapeutic indexes. Because herbs contain pharmacologically active compounds, potential drug interactions can occur when multiple herbs are consumed or when pharmaceuticals are administered to a patient who uses herbs. A classic example is the popular antidepressant St. John's Wort (*Hypericum perforatum* L., Hypericaceae), which is also used alone or in combination with black cohosh for the relief of menopause-related symptoms. St. John's wort can interact with numerous drugs that are substrates of CYP 3A4 and p-glycoprotein [38]. The results of a phase II trial sponsored by the National Cancer Institute titled *H. perforatum* in Relieving Hot Flashes in Postmenopausal Women with Non-Metastatic Breast Cancer [39] should be published soon. If results of this study are positive, more women may use St. John's Wort for symptomatic relief, and clinicians must be prepared to answer questions regarding its safe use with other medications.

Pharmacokinetic properties of active constituents of herbs must be considered in evaluating herb-induced adverse reactions. Constituents of herbs that are absorbed at different rates or have limited bioavailability may not exhibit toxicities that are identical to those

observed *in vitro*. For example, genotoxic effects of genistein, a soy phytoestrogen, have been reported to include apoptosis, cell growth inhibition, and topoisomerase inhibition that are observed *in vitro* at high concentrations. However, the *in vivo* levels corresponding to such *in vitro* concentrations are not reached when genistein is taken orally and thus should be less of a factor in toxicity [40]. Conversely, herbs that are rapidly absorbed may potentially cause hepatic and other organ damages due to the sudden insult by high concentrations of toxins. Some herbal constituents may be converted to toxic or even mutagenic and carcinogenic metabolites by CYP 450 enzymes and less frequently by Phase II-conjugating enzymes [41].

Unfortunately, few pharmacokinetic data have been published about the large number of herbs available in the marketplace and even fewer about products that contain multiple herbs. Because of the number of women ages 45–60 taking prescription medications and using herbal products, it seems a wise step to require manufacturers to provide some basic pharmacokinetic data for their products in order to avoid potentially dangerous interactions.

For the purposes of this paper, published case reports, *in vivo* and *in vitro* studies, clinical trials, and systematic reviews were reviewed for herbals that are commonly used for the management of menopause related symptoms. The evidence was gathered by searching PubMed/MEDLINE, EMBASE, and *International Pharmaceutical Abstracts* through November 2009. Search terms were seven selected herbs (black cohosh, dong quai, hops, maca, red clover, soy, and St. John's wort) in combination with “interactions,” “drug interactions,” “adverse effects,” “case reports,” “cytochrome P450,” “pharmacokinetics,” “safety,” and “toxicity.” Table 3 is an

Table 3
Herb-drug interactions.

Herb	Drug	Interaction	Possible Mechanism	Advise	Reference
Black cohosh	Atorvastatin	Increased ALT	Inhibition of CYP3A4	Avoid concurrent use of black cohosh with atorvastatin	[41]
Black cohosh	Midazolam	No change in AUC, Cmax	No effect on CYP3A4	Black cohosh does not effect CYP3A4 substrates	[39]
Black cohosh	Docetaxel, 4-hydroperoxycyclophosphamide	Decreased cytotoxicity of docetaxel and 4-hydroperoxycyclophosphamide to EMT6 mouse mammary tumor cells	Unknown	Further studies are needed before recommending concurrent use of black cohosh with docetaxel or 4-hydroperoxycyclophosphamide can be made	[44]
Dong quai	Warfarin	Wide spread bruising, increased INR	Inhibition of platelet aggregation	Avoid concurrent use of warfarin with dong quai	[45,46]
Hops	Sedatives	Theoretical potentiation of sedative effects	Additive CNS depressant effects	There are no case reports; the interaction is based on the mechanism of effect	[47]
Maca	NA	There are no reported drug interactions with maca	None	None	Not-applicable [48,49]
Red clover	Warfarin	Theoretical potentiation of bleeding	Contains coumarin-like compounds	Avoid concurrent use of warfarin with red clover; if dong quai is stored improperly, the more potent dicoumarol can be formed by microbial transformation	[50]
Soy	Iron	Reduced absorption of iron	Unknown; soy proteins may inhibit absorption of iron	Administration of iron and soy should be separated by at least 2 hours	[51]
Soy	Levothyroxine	Hypothyroidism	Soy may decrease absorption of levothyroxine	Administration of levothyroxine and soy should be separated by at least 2 hours	[52]
Soy	Warfarin	Decreased INR	Unknown; modulation of P-gp mediated efflux	Soy may decrease the efficacy of warfarin	[42,53,54]
St. John's Wort	Anesthetic agents (fentanyl, nitrous oxygen, propofol, sevoflurane, tubocurarine, suxamethonium, succinylcholine)	Decreased response to vasopressors and/or delayed emergence from anesthetics	Unknown	The American Society of Anesthesiologists advises discontinuation of St. John's wort 2–3 weeks prior to surgery	[42,53,54]
St. John's Wort	Glucalide	Decreased AUC, t1/2, apparent clearance	Mechanism independent of CYP2C9 genotype	The clinical significance is unknown	[42,53,54]
St. John's Wort	Mefenytroin, omeprazole, voriconazole	Increased urinary metabolites, and/or decreased AUC, Cmax	Induction of CYP2C19	St. John's wort effects CYP2C19 substrates	[42,53,54]
St. John's Wort	Bupropion, buspirone, eletriptan, nefazodone, paroxetine, sertraline	Possible serotonin syndrome; nausea, weakness, fatigue, grogginess, lethargic state	Excess serotonergic agonism	St. John's wort should not be used with 5-HT inhibitors/ligands	[42,53,54]
St. John's Wort	Alprazolam, amitriptyline, atorvastatin, cyclosporine, Digoxin, erythromycin, fexofenadine, imatinib, indinavir, irinotecan, ivabradine, methadone, midazolam, nevirapine, nifedipine, oral contraceptives, phenprocoumon, quazepam, simvastatin, tacrolimus, talinolol	Decreased AUC and Cmax, decreased serum concentrations	Induction of CYP3A4 and/or P-glycoprotein	St. John's wort may decrease the effectiveness of these medications	[42,53,54]
St. John's Wort	Theophylline	Decreased theophylline serum concentration; researches showed no significant changes in pharmacokinetics	Induction of CYP2E1 and CYP3A4	Concurrent use of theophylline with St. John's wort is not recommended	[42,53,54]

abbreviated table for potential drug interactions with common herbals used during menopause.

8. Assessing estrogenicity

Although the question does not directly involve toxicity, for women who use herbal products for the relief of menopause-related symptoms a valid question is to what extent these herbs influence estrogen-responsive tissues. Estrogen exerts its effects on target tissues by interacting with two different members of the nuclear receptor super-family of hormone-regulated transcription factors, namely estrogen receptors (ER) ER α and ER β . Many naturally occurring compounds such as flavonoids, coumestan derivatives, and lignans are ubiquitous in plants and have demonstrated varying levels of estrogenic activity [42,43]. For the most part, determination of the effects of these naturally occurring estrogens (phytoestrogens) on estrogen-responsive cancers has been determined *in vitro* in various breast cancer, endometrial, and cervical cancer cell lines, as well as in rodent models including hollow fiber, xenograph, and the rat *N*-methyl-*N*-nitrosourea (MNU) model [44–50]. In addition, assessment of estrogenic and progestagenic effects of these phytoestrogens and plant extracts on ER binding, ER- and PR-responsive reporter, and endogenous gene assays is often performed [51–54].

The most commonly used cells lines for studying ER activities are MCF-7 (human breast cancer) cell line and derivatives thereof. Reporter gene assays in transfected MCF-7 or Ishikawa cells are a standard method of determining estrogenic and antiestrogenic effects of plant extracts [52–55], which may be problematic because MCF-7 cells are ER α predominant and many phytoestrogens appear to bind more readily to ER β [53]. Given these limitations, however, extracts or pure compounds that up-regulate the expression of estrogen-responsive reporter genes should be tested to determine their effect on endogenous gene expression. Although numerous genes may be investigated, some of the more common include those associated with breast cancer such as pS2, PR, and PTGES, up-regulation of which in MCF-7 cells is indicative of estrogenic effects via ER α [51].

pS2 expression is regulated in MCF-7 cells by estrogens, and pS2 is predominantly, but not exclusively, expressed in ER-dependent cancers [56]. How herbal extracts influence pS2 expression in women with breast cancer has not been well investigated. Because of the large number of women worldwide who use herbal extracts, investigations of the effects of such extracts on mammary tumors would be of significant value. Plant extracts and pure compounds that are active in endogenous gene assays could then be investigated in various microarrays and, more importantly, in animal models.

Ginseng is an herbal remedy used by menopausal women to improve mood and vitality and is often taken by patients undergoing chemotherapy to reduce fatigue and enhance the immune system. A chloroform–methanol extract of American ginseng (*Panax quinquefolius* L. Araliaceae) induced expression of pS2 RNA and protein in MCF-7 cells [57], and low concentrations of a methanol extract produced an estrogenic response using the ER-positive MCF-7 human breast cancer cell model [58]. However, King et al. [58] report that the water extract of *P. quinquefolius* had no estrogenic effect and that both methanol and water extracts showed an inhibitory effect on estrogen receptors at “high concentrations.” Does this mean drinking ginseng tea would be a better option for a woman concerned about breast cancer? Can the “high” concentration *in vitro* be achieved with oral use *in vivo*? How does the methanol extract compare to products found in the marketplace? This research highlights the need to study the herb using solvents relevant to human use. Although *in vitro* data can be predictive of

potential estrogenicity and carcinogenicity, testing in animal models is critical to assessing the overall potential impact in humans, even given the limitations inherent in conducting hormone research in animals. These types of investigations should be performed for botanical products targeted for use by menopausal populations, particularly to determine if these products can or should be used in women with a history of estrogen-responsive cancers.

9. Conclusions

Women are the largest consumers of herbal medicine, and many choose to use herbal products for relief of menopause-related symptoms. A recent report [59] suggested that about 49% of older adults in the US use dietary supplements concurrently with prescription medications. Future research of herbal products for menopausal women should include long-term safety assessments because women may use these products for prolonged periods of time. Growing numbers of women take prescription medications, so both drug and supplement manufacturers should provide basic pharmacokinetic data to reduce the risk of adverse herb–drug interactions. Products produced to high quality standards are essential for ensuring consumer safety. Regulatory frameworks must be in place to ensure that herbal ingredients’ identities have been verified, that they have been properly quantified per unit dose, that the product is within tolerance limits for contaminants, that the product’s safety and effectiveness under the recommended conditions of use have been assessed before sale to the public, and that a system is in place to detect and deal with adverse reactions when they arise. International collaboration in the development of harmonized quality specifications and causality algorithms specifically tailored to herbal products is highly advisable, as is stronger collaboration between regulatory agencies around the globe for the early detection of any significant safety issues associated with a particular product.

Contributors

Tieraona Low Dog is a primary author.

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Competing interest

None declared.

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