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HERBAL CARE FOR WOMEN: A GUIDE TO PHYTOTHERAPEUTIC AGENTS IN GYNAECOLOGY AND REPRODUCTIVE HEALTH

CHAPTER 9: SAFETY, STANDARDIZATION, AND FUTURE PERSPECTIVES OF HERBAL THERAPEUTICS IN WOMEN'S HEALTH

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ABSTRACT

Herbal medicines are used by a large proportion of women for menstrual, reproductive, pregnancy-related and menopausal conditions, often on the assumption that a natural product is inherently safe. That assumption is incorrect, and the benefit of any herbal drug depends on its safety profile and on the consistency of the product. This chapter examines three connected questions. The first is safety. Intrinsic toxicity is illustrated by aristolochic acid nephropathy, first recognised in women taking a slimming preparation, by pyrrolizidine alkaloid liver injury and by pennyroyal poisoning; pregnancy and lactation present special risks, including neonatal cardiac failure after maternal use of blue cohosh; and herb–drug interactions, of which St John's wort induction of cytochrome P450 3A4 and consequent oral contraceptive failure is the clearest example, affect women in all life stages. The use of phytoestrogens by women with oestrogen-sensitive cancers is considered against current observational and regulatory evidence. The second question is quality. Adulteration with heavy metals, undeclared pharmaceuticals and substituted species is documented in products sold in India and internationally. Standardisation is explained through the distinction between standardised, quantified and other extracts, the choice of active and analytical markers, and the analytical





WISELEAF SCIENTIFIC VENTURES

methods now available, from macroscopy and high-performance thin-layer chromatography fingerprinting to liquid chromatography–mass spectrometry and DNA barcoding. Regulatory frameworks in India, the European Union and the United States, and the role of pharmacovigilance, are compared. The third question is the future. Metabolomics, network pharmacology, reverse pharmacology, microbiome-guided personalisation, improved delivery systems, and better-reported clinical trials offer a route by which traditional knowledge can be converted into evidence-based gynaecological therapy, provided that conservation and sustainable sourcing of the plants are addressed.

Keywords: Herbal safety; Standardisation; Herb–drug interactions; Pharmacovigilance; Quality control; Women’s health

9.1 Introduction

The World Health Organization reports that 170 of its 194 member states acknowledge the use of traditional and complementary medicine by their populations [1]. Women are the predominant users, and gynaecological and obstetric indications are among the most frequent reasons for use. A multinational survey in 23 countries found that about 29% of pregnant women had used at least one herbal product during pregnancy [2]. In India, where Ayurveda, Siddha and Unani systems are recognised officially, herbal preparations are sold both as licensed classical formulations and as proprietary products, and are frequently taken alongside allopathic medicines.

The preceding chapters of this book have considered the mechanisms and clinical evidence for herbal agents in individual conditions. This chapter considers what determines whether those benefits can be realised safely and reproducibly: the toxicity and interaction profile of the plants, the identity and quality of the product, the regulatory and pharmacovigilance systems that oversee them, and the research directions most likely to strengthen the field.

9.2 Safety of Herbal Drugs in Womens Health

Adverse effects of herbal drugs are classified by cause into four categories: intrinsic toxicity of the correct plant, adverse effects in physiologically vulnerable states such as pregnancy, interactions with conventional drugs, and extrinsic harm from adulteration or contamination. The categories require different preventive measures, and the distinction is the first step in assessing any adverse event.





WISELEAF SCIENTIFIC VENTURES

9.2.1 Intrinsic toxicity

Some plants are toxic in their correct botanical identity and at the doses used traditionally. Table 9.1 lists examples of particular relevance to women.

Table 9.1. Examples of intrinsic toxicity of herbal drugs relevant to women's health

Plant or constituent	Traditional or marketed use	Toxicity	Mechanism or comment
<i>Aristolochia</i> spp. (aristolochic acids)	Substituted for <i>Stephania</i> in a slimming regimen; traditional Chinese formulas	Progressive interstitial renal fibrosis; urothelial carcinoma	DNA adducts; nephrotoxic and carcinogenic
Pyrrolizidine alkaloid-containing plants (<i>Crotalaria</i> , <i>Heliotropium</i> , <i>Symphytum</i>)	Teas, poultices, contaminants of grain	Hepatic sinusoidal obstruction syndrome	Hepatic bioactivation to reactive pyrroles
Pennyroyal oil (<i>Mentha pulegium</i> ; pulegone)	Emmenagogue, abortifacient	Hepatic necrosis, multi-organ failure, death	Pulegone metabolised to menthofuran
Blue cohosh (<i>Caulophyllum thalictroides</i>)	Induction of labour	Neonatal myocardial infarction and congestive heart failure	Vasoconstrictive glycosides; nicotinic alkaloids
Liquorice (glycyrrhizin)	PCOS, digestive complaints	Hypertension, hypokalaemia, oedema	11 β -HSD2 inhibition (pseudoaldosteronism)
Black cohosh (<i>Actaea racemosa</i>)	Menopausal symptoms	Rare idiosyncratic hepatitis	Causality uncertain; product identity often unverified
Kava (<i>Piper methysticum</i>)	Anxiety	Hepatotoxicity	Led to withdrawal in several countries

HSD, hydroxysteroid dehydrogenase; *PCOS*, polycystic ovary syndrome.

The case of aristolochic acid established the modern concern with herbal toxicity. In 1993, a Belgian clinic reported rapidly progressive renal fibrosis in young women who had followed a slimming regimen containing Chinese herbs; the plant *Stephania tetrandra* had been replaced by *Aristolochia fangchi*, whose Chinese name is similar [3]. Many of these women required





WISELEAF SCIENTIFIC VENTURES

dialysis or transplantation, and a high proportion subsequently developed urothelial carcinoma [4]. The episode demonstrated three recurring features of herbal harm: a vulnerable population seeking a “natural” treatment, substitution of one species for another, and delayed toxicity that ordinary short-term observation would not detect.

Pennyroyal illustrates the danger of emmenagogue and abortifacient traditions. Ingestion of the oil to induce menstruation or abortion has caused fulminant hepatic failure and death, and the toxic metabolite menthofuran has been measured in fatal cases [5]. Plants with a traditional reputation for “bringing on the menses” should be regarded as potential abortifacients and avoided whenever pregnancy is possible.

9.2.2 Pregnancy and lactation

Pregnancy presents the greatest uncertainty, because controlled trials in pregnant women are rare and the teratogenic potential of most herbs has never been tested. Absence of reported harm is not evidence of safety. Specific concerns include uterotonic effects (blue cohosh, pennyroyal, rue and tansy), fetal toxicity from maternal use (neonatal congestive heart failure and myocardial infarction after maternal blue cohosh [6]), anti-androgenic action on the male fetus (liquorice, spearmint, saw palmetto), and anticoagulant or antiplatelet effects at delivery (dong quai, high-dose ginger, garlic, ginkgo).

Ginger is the best-studied herb in pregnancy. It is used for nausea and vomiting and has not been associated with an increase in malformations in observational studies. Even so, doses above those used in trials and use near delivery in women with bleeding risk are avoided.

During lactation, many constituents pass into breast milk, and the infant’s immature hepatic conjugation increases exposure. Galactagogue herbs such as fenugreek and shatavari are widely used in India; fenugreek can cause a maple-syrup odour in the infant, hypoglycaemia with antidiabetic drugs, and cross-reactive allergy in women allergic to peanut or chickpea. The Drugs and Lactation Database (LactMed) of the United States National Library of Medicine provides evaluated monographs for many herbs and is a reliable first reference [7].

9.2.3 Phytoestrogens and oestrogen-sensitive cancers

Whether women with breast or endometrial cancer, or at high risk of it, can safely take phytoestrogens is a frequent question. The laboratory evidence is conflicting: genistein stimulates oestrogen-responsive breast cancer cells at low concentrations and can antagonise tamoxifen in some rodent models. The human evidence is more reassuring for dietary soy. In





WISELEAF SCIENTIFIC VENTURES

the Shanghai Breast Cancer Survival Study of 5042 women, higher soy food intake was associated with lower mortality and recurrence, including among women taking tamoxifen [8]. The European Food Safety Authority reviewed isolated isoflavone supplements in peri- and postmenopausal women and found no adverse effect on the breast, the uterus or the thyroid at the doses and durations studied, while noting that the data did not permit conclusions for women with a history of oestrogen-dependent cancer [9].

The practical position follows from this. Dietary soy in normal amounts is acceptable for breast cancer survivors. Concentrated supplements, hop extracts with ER α -agonist activity, and other phytoestrogen concentrates are not recommended in women with oestrogen-dependent cancer unless the treating oncologist agrees.

9.2.4 Herb–drug interactions

Pharmacokinetic interactions are the most frequent clinically significant adverse effects of herbal drugs, because they alter the efficacy of conventional drugs that women depend on. Pharmacodynamic interactions arise when two agents act on the same system. Table 9.2 summarises the interactions of greatest relevance to women's health.

Table 9.2. Clinically relevant herb–drug interactions in women's health

Herb	Interacting drugs	Mechanism	Consequence
St John's wort	Combined oral contraceptives, progestogen implants, emergency contraception	Induction of CYP3A4 and P-glycoprotein via PXR	Breakthrough bleeding; contraceptive failure
St John's wort	SSRIs, SNRIs, triptans	Additive serotonergic activity	Serotonin syndrome
Goldenseal	Tamoxifen and other CYP2D6 and CYP3A4 substrates	CYP inhibition	Altered active metabolite exposure
Dong quai, ginkgo, garlic, high-dose ginger	Warfarin, antiplatelet agents, heparins	Coumarin content; antiplatelet effect	Increased bleeding risk
<i>Vitex agnus-castus</i>	Bromocriptine, cabergoline, antipsychotics, metoclopramide	Dopaminergic activity	Opposing or additive effects on prolactin
Liquorice	Diuretics, corticosteroids, digoxin	Potassium loss	Hypokalaemia; digoxin toxicity





WISELEAF SCIENTIFIC VENTURES

Herb	Interacting drugs	Mechanism	Consequence
Berberine	Metformin, sulfonylureas, insulin; ciclosporin	Additive hypoglycaemic effect; CYP3A4 inhibition	Hypoglycaemia; raised ciclosporin levels
Valerian	Benzodiazepines, alcohol, antihistamines	Additive CNS depression	Excessive sedation

CYP, cytochrome P450; PXR, pregnane X receptor; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–noradrenaline reuptake inhibitor; CNS, central nervous system.

The St John's wort interaction is the model case. Hyperforin binds and activates the pregnane X receptor, the nuclear receptor that regulates transcription of CYP3A4 [10]. In women taking a combined oral contraceptive, St John's wort increased the clearance of norethindrone and reduced exposure to ethinylestradiol, and breakthrough bleeding increased [11]. Unintended pregnancies have been reported. Goldenseal, in contrast, inhibits CYP2D6 and CYP3A4 in human phenotyping studies [12]; since tamoxifen depends on CYP2D6 for conversion to endoxifen, inhibitors of this enzyme are best avoided during tamoxifen therapy.

The main barrier to prevention is non-disclosure. Many women do not regard herbs as medicines and do not report them unless asked directly. A routine question about herbal, Ayurvedic and dietary supplement use at every medication review is the single most effective preventive measure.

9.2.5 Adulteration, contamination and substitution

Extrinsic harm arises when the product does not contain what the label states. Three problems are documented. The first is heavy metal content. Of 70 Ayurvedic herbal medicine products purchased in the Boston area, 20% contained lead, mercury or arsenic at levels that could exceed regulatory standards if taken as directed [13]; a later study of products sold via the Internet found a similar proportion in both US- and Indian-manufactured products [14]. Some of these metals are intentional components of rasa shastra preparations, which raises a separate question about the safety of traditional metallic formulations. The second is pharmaceutical adulteration, in which undeclared corticosteroids, non-steroidal anti-inflammatory drugs, sildenafil analogues or sibutramine are added to produce a noticeable effect. The third is species substitution, often between plants with similar vernacular names or appearance. Chemical analysis of black cohosh supplements sold in the United States identified several products containing Asian *Actaea* species instead of *A. racemosa* [15]. Microbial contamination, aflatoxins and pesticide residues complete the list.





WISELEAF SCIENTIFIC VENTURES

9.2.6 Practical measures for safe use

Most serious harm from herbal drugs is preventable, and the measures that prevent it are simple. The following apply to every pharmacist and clinician who advises women on herbal products.

1. **Ask directly.** Every medication history should include a specific question about herbal, Ayurvedic, homoeopathic and dietary supplement use, with the product name and, where possible, the container.
2. **Establish reproductive status.** Pregnancy, the possibility of pregnancy, breastfeeding, and reliance on hormonal contraception change the advice for almost every herb discussed in this book.
3. **Check for hormone-sensitive disease.** A history of breast, endometrial or ovarian cancer, endometriosis, or uterine fibroids alters the risk assessment for phytoestrogens and ER α agonists.
4. **Screen for interactions.** Anticoagulants, antiplatelet drugs, antidepressants, antidiabetic drugs, antiepileptics, immunosuppressants, antiretrovirals, and tamoxifen are the interacting drugs of greatest concern.
5. **Recommend identifiable products.** A product should state the botanical name, plant part, extract type and ratio, marker content, batch number and manufacturer; products that make disease-cure claims or are sold without such labelling are best avoided.
6. **Define duration and review.** A trial period (commonly 8 to 12 weeks), with a stated outcome, prevents indefinite use of an ineffective product.
7. **Recognise and report adverse effects.** Jaundice, unexplained bleeding, palpitations, rash, or a change in the effect of a regular medicine should prompt discontinuation and a report to the pharmacovigilance system described in Section 9.4.

9.3 Standardisation and Quality Control

9.3.1 Concepts and definitions

Standardisation is the set of processes that ensures a herbal product contains a consistent, defined composition from batch to batch. It begins with the plant and ends with the finished dosage form. Consistency matters for efficacy as well as safety, because clinical evidence obtained with one extract applies only to products of comparable composition (Chapter 8).





WISELEAF SCIENTIFIC VENTURES

The European Medicines Agency classifies herbal extracts into three types [16]. A **standardised extract** is adjusted to a defined content of constituents with known therapeutic activity, within an acceptable tolerance, as senna extracts are adjusted to their hydroxyanthracene glycoside content. A **quantified extract** is adjusted to a defined range of constituents that contribute to activity but are not solely responsible for it, for example the flavonoids and terpene lactones of ginkgo. **Other extracts** are defined by the production process and the drug-to-extract ratio because no constituent responsible for activity is known. Most extracts used in gynaecology (black cohosh, chaste tree, ashwagandha) belong to the last two groups.

A **marker** is a chemically defined constituent used for quality control. An active marker contributes to the therapeutic effect; an analytical marker is used only for identification or quantification. The distinction is important because a product can meet its marker specification and still differ in the constituents that matter. Withanolide content in ashwagandha, and triterpene glycoside content in black cohosh, are markers of this kind, and marker content alone does not guarantee equivalence between products. The **drug-to-extract ratio** (DER) states the quantity of crude drug used to produce one part of native extract; a DER of 5–10:1 means that 5 to 10 g of dried plant yielded 1 g of extract.

9.3.2 The quality framework from field to product

Quality is established at each stage. Good agricultural and collection practices govern species identification, cultivation or wild collection, harvest time, drying and storage [17]. The concentration of active constituents varies with genotype, geography, season and plant part; the withanolide profile of *Withania somnifera* differs between root and leaf, and only the root is the official drug in the *Ayurvedic Pharmacopoeia of India*. Pharmacopoeial monographs then set identity, purity and assay standards for the raw material and extract. The *Indian Pharmacopoeia* and the *Ayurvedic Pharmacopoeia of India* provide monographs for many Indian medicinal plants, and the World Health Organization publishes methods for quality control of herbal materials, including limits for heavy metals, pesticide residues, aflatoxins and microbial contamination [18]. Good manufacturing practice at the finished-product stage, prescribed for Ayurveda, Siddha and Unani drugs in India under Schedule T of the Drugs and Cosmetics Rules, 1945, completes the chain.

9.3.3 Analytical methods

Table 9.3 summarises the methods used at each level of quality control.





WISELEAF SCIENTIFIC VENTURES

Table 9.3. Analytical methods for the quality control of herbal drugs

Quality attribute	Method	Information obtained
Identity (crude drug)	Macroscopy, microscopy, powder characteristics	Botanical identity; detection of gross substitution
Identity (species)	DNA barcoding (ITS2, <i>rbcL</i> , <i>matK</i>)	Species identification, including powders; not applicable to highly processed extracts
Chemical fingerprint	HPTLC, HPLC-UV/DAD	Pattern of constituents; comparison with reference extract
Quantification of markers	HPLC, LC-MS, GC for volatile oils	Content of active or analytical markers
Comprehensive profile	LC-MS/MS, NMR-based metabolomics	Whole-extract composition; detection of adulterants and undeclared drugs
Heavy metals	ICP-MS, atomic absorption spectroscopy	Lead, mercury, arsenic, cadmium
Contaminants	GC-MS, LC-MS/MS; microbial limit tests	Pesticide residues, aflatoxins, microbial load
Physicochemical	Ash values, extractive values, moisture, swelling index	Purity and consistency of crude drug

HPTLC, high-performance thin-layer chromatography; HPLC, high-performance liquid chromatography; UV/DAD, ultraviolet/diode array detection; LC-MS, liquid chromatography–mass spectrometry; GC, gas chromatography; NMR, nuclear magnetic resonance; ICP-MS, inductively coupled plasma–mass spectrometry; ITS2, internal transcribed spacer 2.

High-performance thin-layer chromatography (HPTLC) fingerprinting is the most widely used identity test in pharmacopoeias, because it is inexpensive, runs many samples in parallel, and displays the whole pattern of constituents rather than a single peak [19]. DNA barcoding complements it by identifying the species in raw and powdered material, but DNA is degraded during extraction, so barcoding cannot confirm the identity of most finished extracts. The two approaches are therefore used together: DNA methods for the raw material and chemical fingerprinting for the extract.





WISELEAF SCIENTIFIC VENTURES

9.4 Regulation and Pharmacovigilance

Regulatory approaches differ widely. In India, Ayurveda, Siddha, Unani and Homoeopathy drugs are regulated under the Drugs and Cosmetics Act, 1940 and its Rules, with the Ministry of AYUSH responsible for policy. Classical formulations described in authoritative texts can be licensed on the basis of traditional use, whereas proprietary formulations require safety data. In the European Union, the Traditional Herbal Medicinal Products Directive (2004/24/EC) created a simplified registration for products with at least 30 years of medicinal use, including 15 years within the Union, which can be marketed for minor self-limiting conditions without efficacy trials but must meet full quality standards [20]. In the United States, the Dietary Supplement Health and Education Act of 1994 classifies most herbal products as dietary supplements, which do not require pre-marketing approval for safety or efficacy.

Pharmacovigilance for herbal medicines is hampered by under-reporting, by uncertainty about the identity of the product actually consumed, and by the frequent use of multi-herb preparations. The World Health Organization guidelines on safety monitoring of herbal medicines recommend that reports record the botanical name, plant part, preparation and batch, and that suspect products be retained for analysis [21]. For herb-induced liver injury, the updated Roussel Uclaf Causality Assessment Method (RUCAM) provides a structured causality score [22]. In India, a Central Sector Scheme for pharmacovigilance of Ayurveda, Siddha, Unani and Homoeopathy drugs was approved by the Ministry of AYUSH in November 2017 and implemented from 2017–18, building on an earlier programme for ASU drugs begun in 2008, with a network of peripheral and intermediary centres; pharmacists and physicians should report suspected adverse reactions to herbal products through it as they would for any other medicine.

9.5 Quality of the Clinical Evidence

Clinical trials of herbal drugs in women's health share recurrent weaknesses: small sample sizes, short duration, inadequate description of the product, high placebo responses, non-validated outcome measures, and a predominance of single-centre trials from one country. Negative trials are less likely to be published. The CONSORT extension for herbal interventions requires reporting of the botanical name, plant part, type and ratio of extract, marker content, and the method of authentication, yet many published trials still omit these details [23]. Without them a trial cannot be reproduced and its result cannot be applied to any product on the market. Adherence to this reporting standard, prospective trial registration, and





WISELEAF SCIENTIFIC VENTURES

the use of validated scales (the Menopause Rating Scale, the Daily Record of Severity of Problems for premenstrual disorders, and standard fertility endpoints such as live birth) are the minimum conditions for evidence that can change practice.

9.6 Future Perspectives

Metabolomics and chemical profiling. Liquid chromatography–mass spectrometry and nuclear magnetic resonance metabolomics can describe the whole composition of an extract and relate it statistically to biological activity. Such profiles will allow specifications based on the full constituent pattern rather than on one marker, and will enable detection of adulteration that single-marker assays miss.

Network pharmacology and systems biology. As outlined in Chapter 2, network approaches can map multiple constituents onto multiple disease targets. Their value will depend on coupling predictions with measured tissue concentrations and experimental confirmation.

Reverse pharmacology. This approach begins with documented traditional clinical experience, proceeds to observational and exploratory clinical studies, and then works backward to identify active constituents and mechanisms [24]. It is well suited to India, where a large body of classical formulations for gynaecological conditions (for example preparations containing *Asparagus racemosus*, *Saraca asoca* and *Symplocos racemosa*) awaits systematic evaluation.

Personalised phytotherapy. Variation in gut microbial metabolism (equal producers and non-producers) and in drug-metabolising enzymes explains part of the variation in response to phytoestrogens. Stratifying trial participants by such markers could reveal effects that are diluted in unselected populations.

Delivery systems. Phospholipid complexes, nanoparticles, self-emulsifying systems and vaginal delivery platforms can overcome the poor bioavailability of constituents such as curcumin and berberine, or deliver them locally for genitourinary conditions. Each new formulation requires fresh safety assessment, since increased exposure may also increase toxicity.

Integration and global policy. The World Health Organization traditional medicine strategies call for integration of evidence-based traditional medicine into health systems, supported by regulation and research [25]. The WHO Global Centre for Traditional Medicine, established at Jamnagar, Gujarat in 2022, provides a focal point for this work in India.





WISELEAF SCIENTIFIC VENTURES

Conservation and sustainable sourcing. Rising demand threatens wild populations of several gynaecologically important plants. *Saraca asoca* and wild *Asparagus racemosus* are over-harvested in India, and North American black cohosh is largely wild-collected. Cultivation under good agricultural practice, with authenticated planting material, is necessary both for conservation and for consistent quality.

9.7 Conclusion

The safe use of herbal drugs in women's health depends on four conditions: knowledge of the intrinsic toxicity of the plant, particular caution in pregnancy and lactation, systematic screening for herb–drug interactions, and assurance that the product contains the correct species at a defined composition without contamination. The history of aristolochic acid nephropathy, the documented heavy metal content of some Ayurvedic products and the interaction between St John's wort and oral contraceptives show that each condition has been breached with serious consequences. Standardisation, using pharmacopoeial monographs, chromatographic fingerprinting and DNA-based authentication, links the product in the patient's hand to the product tested in the trial. Robust pharmacovigilance, better-reported trials and research methods such as metabolomics, reverse pharmacology and microbiome-guided stratification offer the means to turn traditional gynaecological knowledge into dependable evidence. The value of herbal medicine for women will rise or fall on the quality of that evidence and of the products it describes.

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WISELEAF SCIENTIFIC VENTURES

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WISELEAF SCIENTIFIC VENTURES

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