



## WISELEAF SCIENTIFIC VENTURES

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

#### CHAPTER 8: MANAGEMENT OF PERIMENOPAUSE AND MENOPAUSE SYMPTOMS THROUGH HERBAL DRUGS

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#### ABSTRACT

The menopausal transition brings vasomotor symptoms, sleep disturbance, mood change, genitourinary atrophy and accelerated bone loss, and in many women these persist for several years. Menopausal hormone therapy remains the most effective treatment, but concern about breast cancer and thromboembolic risk, contraindications in some women, and personal preference lead many to seek herbal alternatives. This chapter reviews the herbal drugs most widely used for perimenopausal and postmenopausal symptoms and grades the clinical evidence for each. Isoflavone preparations from soy and red clover are the most extensively studied; meta-analyses show a modest reduction in hot flush frequency and severity, of roughly one fifth to one quarter beyond placebo, with more consistent effects for genistein-rich preparations and in women who produce equol. Black cohosh (*Actaea racemosa*) has been evaluated in many trials, but the Cochrane review found insufficient evidence of benefit over placebo, and rare cases of hepatotoxicity require label warnings. Hop extract standardised to 8-prenylnaringenin, St John's wort combined with black cohosh for mood-dominant symptoms, ashwagandha, maca, valerian for sleep and sea buckthorn oil for vaginal dryness





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have smaller evidence bases with some positive trials. Dong quai, flaxseed and evening primrose oil have not shown consistent benefit for hot flushes. Safety considerations centre on hepatotoxicity, cytochrome P450 induction by St John's wort, anticoagulant interactions, and use in women with oestrogen-sensitive cancers. The chapter concludes with a symptom-oriented framework for selecting a herbal agent, setting realistic expectations of benefit given the large placebo response in menopause trials, and deciding when referral for hormonal or non-hormonal prescription therapy is needed.

**Keywords:** Menopause; Vasomotor symptoms; Isoflavones; Black cohosh; Phytoestrogens; Herbal medicine

### 8.1 Introduction

Menopause is defined retrospectively as the final menstrual period, confirmed after twelve consecutive months of amenorrhoea not explained by another cause. Perimenopause is the preceding phase of cycle irregularity and fluctuating ovarian hormone secretion, which extends to one year after the final period. The Stages of Reproductive Aging Workshop (STRAW+10) system divides these phases by bleeding pattern and follicle-stimulating hormone (FSH) level: the early menopausal transition begins with a persistent difference of seven days or more in consecutive cycle lengths, and the late transition with intervals of amenorrhoea of 60 days or longer [1]. In India the mean age at natural menopause is about 46 years, several years earlier than in Western populations [2].

Symptoms are neither brief nor trivial. In the longitudinal Study of Women's Health Across the Nation, frequent vasomotor symptoms lasted a median of 7.4 years overall, and more than a decade in women whose symptoms began early in the transition [3]. Herbal drugs are used widely for this period, frequently without the knowledge of the treating physician. A clear understanding of which agents have evidence, how large the effect is, and where the risks lie is required of every pharmacist and clinician who advises these women.

### 8.2 Pathophysiology of Menopausal Symptoms

The principal symptoms fall into five groups, and a herbal agent is rational only when its mechanism matches the relevant group.

**Vasomotor symptoms.** Hot flushes and night sweats arise from narrowing of the thermoneutral zone in the preoptic hypothalamus. Falling oestradiol removes inhibition of kisspeptin–





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neurokinin B–dynorphin (KNDy) neurons in the infundibular nucleus, whose neurokinin B signalling activates heat-dissipation pathways at small rises in core temperature. Serotonergic and noradrenergic inputs modulate the same centre. The approval of the neurokinin-3 receptor antagonist fezolinetant confirmed this pathway as a therapeutic target [4].

**Sleep disturbance.** Insomnia results partly from night sweats and partly from independent changes in sleep architecture and mood.

**Mood and cognitive symptoms.** Irritability, low mood and anxiety increase during perimenopause, particularly in women with prior depression or premenstrual dysphoria.

**Genitourinary syndrome of menopause.** Oestrogen withdrawal causes thinning of the vaginal epithelium, loss of glycogen and lactobacilli, a rise in vaginal pH, dryness, dyspareunia, and urinary urgency and recurrent infection. The term genitourinary syndrome of menopause (GSM) replaced “vulvovaginal atrophy” in 2014 [5].

**Skeletal and cardiometabolic change.** Bone resorption accelerates in the years around the final menstrual period, and lipid profiles shift towards higher low-density lipoprotein cholesterol.

### 8.3 Conventional Therapy and the Place of Herbal Drugs

Oestrogen, with a progestogen in women who have a uterus, remains the most effective treatment for vasomotor symptoms and GSM, and prevents bone loss. The Women’s Health Initiative trial reported in 2002 that combined conjugated equine oestrogen and medroxyprogesterone acetate increased the risk of invasive breast cancer, coronary events, stroke and venous thromboembolism in women with a mean age of 63 years [6]. Later analyses showed that the balance of benefit and risk is favourable for most healthy women who start therapy before 60 years of age or within ten years of menopause, but the 2002 findings caused a sustained fall in hormone use and a rise in demand for alternatives. Non-hormonal prescription options include selective serotonin and serotonin–noradrenaline reuptake inhibitors (paroxetine, venlafaxine), gabapentin and fezolinetant.

Herbal drugs are considered in three situations: when hormone therapy is contraindicated or declined, when symptoms are mild, and when a woman chooses a botanical approach after informed discussion. The 2023 position statement of The North American Menopause Society reviewed non-hormonal options and did not recommend any herbal or dietary supplement for vasomotor symptoms, on the grounds of inconsistent evidence of benefit [7]. That conclusion





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is the correct starting point. It does not mean that all herbal agents are inactive; it means that the effect sizes are small, the trials are heterogeneous, and product quality varies.

### 8.4 Herbal Agents for Vasomotor Symptoms

#### 8.4.1 Soy isoflavones

Soy isoflavones (genistein, daidzein and glycitein) are ER $\beta$ -preferring partial agonists whose mechanism is described in Chapter 2. They are the most extensively trialled botanical intervention for hot flushes. A meta-analysis of 17 randomised trials found that extracted or synthesised soy isoflavones, at a median dose of 54 mg (as aglycones) daily for periods of 6 weeks to 12 months, reduced hot flush frequency by 20.6% and severity by 26.2% more than placebo [8]. Preparations containing more than 18.8 mg of genistein were about twice as effective as those with less. The Cochrane review of phytoestrogens reached a similar position: no conclusive evidence of benefit across all phytoestrogen products, but a possible benefit for supplements providing more than 30 mg of genistein daily [9].

Onset is slow. The same analysis estimated that half the maximal effect took about 13 weeks to appear, against about 3 weeks for oestradiol, and women should be told this before starting. Equol-producer status (Chapter 2) explains part of the variation in response, and S-equol supplements have shown a reduction in hot flush frequency in a meta-analysis of randomised trials [10]. Dietary soy (tofu, soy milk) supplies 25 to 40 mg of isoflavones per serving and is a reasonable first measure.

#### 8.4.2 Red clover

Red clover (*Trifolium pratense*) contains mainly the methylated isoflavones biochanin A and formononetin, which are demethylated in vivo to genistein and daidzein. In the Isoflavone Clover Extract (ICE) study, two red clover preparations providing 82 mg and 57 mg of isoflavones daily produced no clinically important reduction in hot flushes compared with placebo over 12 weeks [11]. A pooled analysis of plant-based therapies found that phytoestrogens as a group were associated with a reduction of about 1.3 hot flushes per day and with less vaginal dryness, but not with fewer night sweats [12]. Red clover is therefore best regarded as having weaker evidence than soy.





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### 8.4.3 Black cohosh

Black cohosh (*Actaea racemosa*, formerly *Cimicifuga racemosa*) has the longest history of commercial use for menopausal symptoms in Europe and North America. Its effect is mediated chiefly through serotonergic mechanisms rather than oestrogen receptors (Chapter 2). The isopropanolic extract (iCR) is used at 40 mg of herbal drug equivalent per day in divided doses, and a 12-week randomised trial of this extract showed a greater reduction in the Menopause Rating Scale than placebo, with the benefit concentrated in women in early menopause [13]. Other trials have been negative. The Herbal Alternatives for Menopause (HALT) trial found no difference from placebo for black cohosh alone, a multibotanical preparation, or the multibotanical with dietary soy, while conjugated oestrogen was clearly effective [14]. The Cochrane review of 16 trials in 2027 women concluded that there was insufficient evidence to support black cohosh for menopausal symptoms [15].

The discordance probably reflects differences between extracts. Black cohosh products vary in solvent, drug-to-extract ratio and triterpene glycoside content, and some commercial products have been found to contain Asian *Actaea* species or no black cohosh at all. Results obtained with one standardised extract should not be generalised to others.

### 8.4.4 Hops

Hop (*Humulus lupulus*) strobiles contain 8-prenylnaringenin, a potent ER $\alpha$  agonist. In a randomised trial, a hop extract standardised to 100  $\mu$ g of 8-prenylnaringenin daily reduced the Kupperman index more than placebo at six weeks, although the difference was no longer significant at 12 weeks and a higher dose was not more effective [16]. Because 8-prenylnaringenin acts on ER $\alpha$ , it has a more classical oestrogenic profile than the soy isoflavones, and the same precautions as for oestrogen apply in women with a uterus or with oestrogen-sensitive disease.

### 8.4.5 Agents with negative or inconsistent trials

**Dong quai** (*Angelica sinensis*) is a central herb of traditional Chinese gynaecology but is seldom prescribed alone in that tradition. As a single agent at 4.5 g of root daily for 24 weeks, it produced no change in endometrial thickness, vaginal maturation index or hot flush frequency compared with placebo [17]. It contains coumarins and potentiates warfarin.





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**Flaxseed** provides lignans that are converted to enterolactone. A phase III trial of flaxseed providing 410 mg of lignans daily found no reduction in hot flushes compared with placebo [18].

**Evening primrose oil** (*Oenothera biennis*), a source of  $\gamma$ -linolenic acid, reduced the intensity but not the frequency of hot flushes in one six-week trial [19]; the overall evidence remains weak.

**Ginseng** (*Panax ginseng*) improved general well-being and depression scores but not vasomotor symptoms in a trial of a standardised extract in postmenopausal women [20].

**Fennel** (*Foeniculum vulgare*), whose anethole has weak oestrogenic activity, improved the Menopause Rating Scale score in a small triple-blind trial [21]; replication is needed.

### 8.5 Herbal Agents for Mood, Sleep and Quality of Life

Mood symptoms often dominate the perimenopausal picture, and here the evidence for St John's wort (*Hypericum perforatum*) is more persuasive than for hot flushes. A 16-week randomised trial of a combination of black cohosh and St John's wort reduced both the Menopause Rating Scale and the Hamilton Depression Rating Scale more than placebo [22]. St John's wort alone improved menopause-specific quality of life and sleep-related symptoms in a smaller pilot trial [23]. The major limitation is interaction. Hyperforin activates the pregnane X receptor and induces cytochrome P450 3A4 and P-glycoprotein. In a controlled study, St John's wort increased the clearance of norethindrone and ethinylestradiol and caused breakthrough bleeding in women taking a combined oral contraceptive [24]. Perimenopausal women who still rely on hormonal contraception must be warned of this, and the herb is not combined with antidepressants because of the risk of serotonin syndrome.

Ashwagandha (*Withania somnifera*), a rasayana herb of Ayurveda, was tested in perimenopausal women as a root extract of 300 mg twice daily for eight weeks. It reduced the total Menopause Rating Scale and the psychological and somatic subdomains compared with placebo, and was associated with a rise in oestradiol and a fall in FSH and luteinising hormone [25]. This is a single trial, but the effect on psychological symptoms is consistent with the HPA-axis activity of the plant.

Maca (*Lepidium meyenii*), at 3.5 g of powdered root daily, reduced anxiety, depression and sexual dysfunction scores in postmenopausal women without altering oestradiol, FSH or sex hormone-binding globulin, which indicates a non-hormonal mechanism [26].





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Valerian (*Valeriana officinalis*) extract taken twice daily for four weeks improved the Pittsburgh Sleep Quality Index in postmenopausal women with insomnia [27]. It is the most reasonable herbal choice when poor sleep is the principal complaint, and it has additive sedation with alcohol, benzodiazepines and antihistamines.

Shatavari (*Asparagus racemosus*) is prescribed widely in India as a female reproductive tonic across all life stages, including menopause. Its steroidal saponins and adaptogenic properties provide a plausible rationale, but randomised trials in menopausal women with validated outcome measures are lacking, and its use rests on traditional authority rather than clinical evidence.

### 8.6 Genitourinary, Skeletal and Cardiometabolic Outcomes

For GSM, low-dose vaginal oestrogen is highly effective and minimally absorbed, and no herbal preparation matches it. Oral sea buckthorn (*Hippophae rhamnoides*) oil, rich in palmitoleic and other fatty acids, improved the integrity of the vaginal epithelium in a three-month placebo-controlled trial [28]. Vaginal gels containing isoflavones and moisturisers based on hyaluronic acid or aloe provide symptomatic relief, and phytoestrogens as a group have been associated with less vaginal dryness [12].

The skeletal case for isoflavones has weakened with better trials. In the three-year Soy Isoflavones for Reducing Bone Loss (SIRBL) trial, 80 mg or 120 mg of soy isoflavones daily did not prevent loss of spine or hip bone mineral density in postmenopausal women [29]. Herbal agents should not be used as a substitute for calcium, vitamin D, weight-bearing exercise and, where indicated, bisphosphonate or hormonal therapy in women at risk of osteoporosis.

Soy protein produces a small reduction in low-density lipoprotein cholesterol, of the order of a few per cent, which is attributed to the protein fraction and fibre rather than to isolated isoflavones.

Table 8.1 summarises the herbal agents discussed, their studied doses, and the strength and direction of evidence.





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**Table 8.1.** Herbal agents for perimenopausal and menopausal symptoms: studied dose, evidence and principal safety concern

| Herbal agent                     | Studied preparation and daily dose                  | Principal symptom target               | Direction of evidence               | Principal safety concern                                      |
|----------------------------------|-----------------------------------------------------|----------------------------------------|-------------------------------------|---------------------------------------------------------------|
| Soy isoflavones                  | Extract, about 54 mg aglycones (genistein >18.8 mg) | Hot flush frequency and severity       | Modest benefit in meta-analysis     | Theoretical concern in oestrogen-sensitive cancer; slow onset |
| S-equol                          | Supplement; dose varies between trials              | Hot flushes                            | Modest benefit, limited trials      | As for isoflavones                                            |
| Red clover                       | Extract, 40–82 mg isoflavones                       | Hot flushes                            | Inconsistent; ICE study negative    | As for isoflavones                                            |
| Black cohosh                     | Isopropanolic extract, 40 mg herbal drug equivalent | Hot flushes, overall climacteric score | Inconsistent; Cochrane insufficient | Rare hepatotoxicity; product substitution                     |
| Hops                             | Extract, 100 µg 8-prenylnaringenin                  | Climacteric score                      | Short-term benefit, one trial       | ER $\alpha$ agonism; endometrial stimulation possible         |
| Black cohosh with St John's wort | Fixed combination                                   | Mood and climacteric score             | Positive trial                      | CYP3A4 induction; contraceptive failure; serotonin syndrome   |
| Ashwagandha                      | Root extract, 300 mg twice                          | Psychological and somatic symptoms     | One positive trial                  | Rare liver injury; thyroid stimulation                        |
| Maca                             | Powdered root, 3.5 g                                | Anxiety, sexual function               | Small positive trial                | Few data                                                      |
| Valerian                         | Extract, twice daily                                | Sleep quality                          | Small positive trial                | Additive sedation                                             |
| Sea buckthorn oil                | Oral oil, 3 g                                       | Vaginal epithelial integrity           | One positive trial                  | Few data                                                      |
| Dong quai                        | Root, 4.5 g                                         | Hot flushes                            | Negative trial                      | Warfarin potentiation; photosensitivity                       |
| Flaxseed                         | Lignans, 410 mg                                     | Hot flushes                            | Negative phase III trial            | Bowel effects                                                 |





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### 8.7 Safety Considerations Specific to Menopausal Use

**Hepatotoxicity.** Several dozen case reports of liver injury associated with black cohosh have been published, including cases of acute liver failure. A review by the United States Pharmacopeia found the causality possible in a minority of cases, attributed uncertainty to poor product identification, and required a cautionary statement on the label of black cohosh products [30]. Women taking black cohosh should stop it and seek assessment if they develop jaundice, dark urine, abdominal pain or unexplained fatigue. Rare cases of liver injury have also been reported with ashwagandha products.

**Oestrogen-sensitive disease.** Women with a history of breast or endometrial cancer present the hardest question. Observational data from Asian cohorts do not show harm from dietary soy in breast cancer survivors, and some suggest benefit; the evidence and the case of women taking tamoxifen or aromatase inhibitors are discussed in Chapter 9. Concentrated supplements, hop extracts and preparations containing ER $\alpha$  agonists are best avoided in this group unless the oncologist agrees.

**Drug interactions.** The clinically important interactions in this age group are St John's wort with hormonal contraceptives, antidepressants, anticoagulants and many other CYP3A4 substrates; dong quai and other coumarin-containing herbs with warfarin; and additive sedation with valerian.

**Endometrial safety.** Women with a uterus who take an ER $\alpha$ -active preparation for a long period, or who develop postmenopausal bleeding while taking any botanical product, require endometrial assessment. Bleeding must never be attributed to a herb without investigation.

### 8.8 A Practical, Symptom-Oriented Approach

The first step is an accurate diagnosis and a clear account of the dominant symptom. Thyroid disease, anaemia, depression unrelated to menopause, and medication effects produce overlapping complaints and should be excluded. The second step is a discussion of the options, including hormone therapy where it is suitable, since the woman is entitled to know that hormonal treatment is considerably more effective than any botanical agent.

When a herbal agent is chosen, selection follows the dominant symptom. For hot flushes of mild to moderate severity, a genistein-rich soy isoflavone extract has the most consistent evidence; a standardised black cohosh extract is an alternative, with liver precautions. Where





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low mood and irritability dominate and no interacting drugs are taken, the black cohosh and St John's wort combination is supported by trial evidence. For insomnia, valerian is appropriate. For vaginal dryness, local non-hormonal moisturisers are used first and vaginal oestrogen considered if they fail.

Expectations must be realistic. Menopause trials show a large placebo response, and much of the improvement a woman notices on any supplement is not specific to it. A trial of 8 to 12 weeks, with a symptom diary or a validated score such as the Menopause Rating Scale before and after, allows an honest judgement of benefit. If symptoms do not improve, the product should be stopped rather than supplemented with a second. Only products with a stated botanical name, plant part, extract ratio and marker content from manufacturers with good manufacturing practice certification should be recommended, since the positive trials were conducted with such products.

Referral for prescription therapy is indicated when symptoms are severe or disrupt work and sleep, when mood symptoms reach the threshold of depression, when bleeding is abnormal, and when the woman has risk factors for osteoporosis that require assessment.

### 8.8.1 Special clinical situations

**Premature ovarian insufficiency and early menopause.** Loss of ovarian function before 40 years (premature ovarian insufficiency) or before 45 years (early menopause) carries long-term risks of osteoporosis, cardiovascular disease and possibly cognitive decline. The deficiency is of oestrogen itself, and hormone replacement is recommended at least until the average age of natural menopause. Herbal agents do not replace oestrogen in this setting and should not be offered as an alternative, although they can be considered as adjuncts for residual symptoms.

**Surgical menopause.** Bilateral oophorectomy produces an abrupt fall in oestradiol and testosterone, and vasomotor symptoms are usually more severe than after natural menopause. The modest effect sizes of botanical agents make them unlikely to control symptoms adequately on their own, and hormonal or prescription non-hormonal therapy is generally required when hormone therapy is not contraindicated.

**Breast cancer survivors.** Vasomotor symptoms in these women are often intensified by tamoxifen or aromatase inhibitors. Venlafaxine, gabapentin and, where appropriate, fezolinetant are the evidence-based options. Among herbs, black cohosh has not been shown to stimulate breast tissue, but its evidence for efficacy is weak and it should be used only with





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the agreement of the oncologist; concentrated phytoestrogen supplements are avoided, and paroxetine and other strong CYP2D6 inhibitors are avoided with tamoxifen (Chapter 9).

**Women still menstruating.** Perimenopausal women can conceive, and many continue to rely on hormonal contraception. For them, the choice of herbal agent must take account of contraceptive interactions (St John's wort) and of the possibility of pregnancy, in which several of the herbs above have no safety data.

### 8.9 Conclusion

Herbal drugs have a limited but legitimate place in the management of perimenopausal and menopausal symptoms. Soy isoflavones, particularly genistein-rich extracts, reduce hot flushes by about one fifth to one quarter beyond placebo over three months. Black cohosh has inconsistent evidence that depends on the extract used and carries a small risk of liver injury. Combinations of black cohosh with St John's wort, and single trials of ashwagandha, maca, valerian and sea buckthorn oil, support targeted use for mood, sleep and vaginal symptoms, while dong quai, flaxseed and red clover have not shown convincing benefit for vasomotor symptoms. None of these agents matches hormone therapy in efficacy, and none has been shown to prevent bone loss. Sound practice rests on matching the agent to the dominant symptom, using standardised products at the doses studied, screening for interactions and hepatotoxicity, and referring women whose symptoms or risk profile require prescription therapy. Better-designed trials of standardised Indian medicinal plants, with validated outcome scales and adequate duration, are needed before these can be recommended beyond traditional use.

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