

HERBAL THERAPEUTICS

(9) WOMEN'S HEALTH

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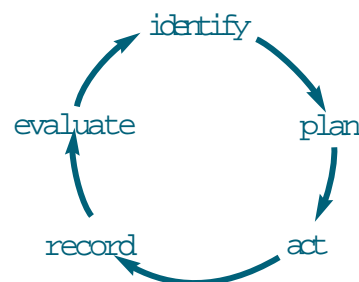
Continuing our series on European herbal products, this article considers evidence for the efficacy and safety of herbal medicines used for various conditions experienced by women and for which over-the-counter treatment is usually appropriate



identify gaps in your knowledge

1. Name three European herbs used in women's health.
2. How is cranberry juice thought to work to treat or prevent urinary tract infections?
3. Why have Epogam and Efamast lost their product licences?

This article relates to the Royal Pharmaceutical Society's core competencies of "medicinal products" and "evidence-based practice" (see "Medicines, ethics and practice — a guide for pharmacists", number 26, June 2002, pp105–6). You should consider how it will be of value to your practice.



Many women who experience conditions such as premenstrual syndrome (PMS) or urinary tract infections (UTIs) are interested in trying herbal products and there are numerous such remedies available. In terms of clinical investigation, there has been particular focus on the effects of agnus castus (*Vitex agnus-castus* L.) for PMS and mastalgia, black cohosh (*Cimicifuga racemosa* Nutt.) for menopausal symptoms, and cranberry (*Vaccinium macrocarpon* Ait) for the treatment and prevention of UTIs. These herbs have all been used traditionally in these conditions.

The use of evening primrose (*Oenothera biennis* L.) oil for the treatment of mastalgia has arisen in a modern context. Several other herbs, such as bilberry (*Vaccinium myrtillus* L.), St John's wort (*Hypericum perforatum* L.) and ginkgo (*Ginkgo biloba* L.), which have not been used traditionally for specific women's ailments, have nevertheless undergone preliminary scientific investigation in dysmenorrhoea (bilberry) and PMS (St John's wort, ginkgo) but require further study.¹ The uses of St John's wort in depression and ginkgo in cognitive disorders were considered in previous articles (*PJ*, 29 June 2002, pp908–10 and 3 August 2002, pp160–2, respectively). Red clover (*Trifolium pratense* L.) flowers contain the isoflavones daidzein, genistein and others, which are also found in soya bean. Soya isoflavones have been investigated for their effects in relieving menopausal symptoms although at present evidence is inconclusive (*PJ*, 6 Jan 2001, pp16–9).

It is beyond the scope of this article to consider the aetiology, classification, diagnosis and treatment of the conditions mentioned above, and pharmacists are advised to consult standard reference texts for this information. Pharmacists are encouraged to probe discreetly, where possible, individual's reasons for purchasing herbal products used for women's health complaints, and to apply usual protocols to establish why herbal treatment is considered necessary (eg, as a preventive measure or in response to symptoms), treatments already tried or being used, other action taken, lifestyle factors and so on.

For women presenting with dysmenorrhoea, secondary dysmenorrhoea (pain secondary to serious conditions, such as endometriosis) should be excluded. For some individuals, including those whose symptoms persist or worsen despite treatment and who

are not already under medical supervision, referral to a general practitioner may be necessary.

BACKGROUND

The parts of plants used pharmaceutically in women's conditions include:

- Fruit (berries) of agnus castus, bilberry and cranberry
- Rhizome and root of black cohosh
- Seed oil of evening primrose
- Leaf of ginkgo
- Herb (aerial parts) of St John's wort

Monographs for dried and fresh bilberry fruit, ginkgo leaf and St John's wort herb are included in the European Pharmacopoeia. Cranberry and bilberry are widely used in foods. St John's wort is a natural source of food flavouring, and evening primrose oil has long been used as a source of essential fatty acids in food supplements. Agnus castus, black cohosh and ginkgo are not used in foods.¹ Black cohosh should not be confused with blue cohosh (*Caulophyllum thalictroides*), an entirely different plant used for different purposes.

The prescription only medicines Epogam and Efamast, which contain gamolenic acid derived from evening primrose oil, were licensed in the United Kingdom for the treatment of mastalgia (and for symptomatic relief of atopic eczema). However, in October 2002, the product licences for these preparations were withdrawn due to a lack of data sufficient to support efficacy in these conditions.² Unlicensed preparations (which cannot make efficacy claims) of evening primrose oil remain available.

MAJOR CONSTITUENTS

Constituents of agnus castus include diterpenes and flavonol derivatives, particularly casticin, although it is unclear which constituents are responsible for pharmacological activities. The triterpene glycosides (eg, actein and cimicifugoside) and flavonoids are considered to be the active components of black cohosh. The anthocyanins are thought to be active constituents of bilberry and, for cranberry, the proanthocyanidin constituents may be important.¹ The reputed activity of evening primrose oil has been attributed to its essential fatty acid content.

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EVIDENCE OF EFFICACY

The issue of variation between manufactured products, and the suggestion that evidence for efficacy and safety should be considered to be extract- or product-specific, were raised in the first article in this series (*P7*, 8 June 2002, pp 804–6).

Casticin is used by some manufacturers as a marker to standardise products containing agnus castus, and some manufacturers standardise preparations of black cohosh on content of triterpene glycosides. Cranberry is available as encapsulated powder prepared from dried fruits, and also as cranberry juice cocktail, which contains around 25 to 30 per cent cranberry juice (it also contains sugar or corn syrup as sweetener).

Analysis of 11 different marketed products containing evening primrose oil available in the United States revealed that at least one showed signs of spoilage (rancidity).³

Premenstrual syndrome and mastalgia Rigorous clinical investigation of the effects of agnus castus in PMS is limited and, overall, data are inconclusive. One of the most robust studies was a randomised, double-blind, placebo-controlled trial in which 170 women with PMS received a casticin-standardised agnus castus extract (20mg daily) or placebo, for three menstrual cycles. At the end of the third cycle, self-assessed improvements in PMS symptoms (eg, irritability, mood alteration, headache, breast fullness, bloating) were significantly greater in the agnus castus group, compared with the placebo group ($P<0.001$).⁴ Clinical global impression (CGI) scores for severity of condition, general improvement and overall benefit-risk were also significantly better for agnus castus, compared with placebo ($P<0.001$).

Another randomised, double-blind, controlled trial involving women with PMS ($n=175$) compared the effects of an agnus castus extract with those of pyridoxine (vitamin B₆) over three menstrual cycles. Similar reductions in self-assessed and physician-assessed PMS symptom scores were reported for both groups.⁵ However, the results of this study should be interpreted with caution because evidence for pyridoxine being able to reduce PMS symptoms is at present inconclusive. Therefore, a placebo response in both groups cannot be excluded.

Results of randomised, double-blind, placebo-controlled trials involving women with mastalgia alone who received a combination preparation (Mastodynon) containing agnus castus extract and five other herbs have provided some evidence of efficacy for this product although definitive studies are still required.¹ One such study involving 104 women who received the preparation (formulated as a solution or as tablets) or placebo for three menstrual cycles found that breast pain was reduced to a significantly greater extent with the preparation than with placebo ($P=0.0067$ and $P=0.0076$ for solution and tablets, respectively, versus placebo). A similar trial involving 97 women with cyclic mastalgia who received Mastodynon solution or placebo (administered orally) found statistically significant differences in reduction of breast pain intensity as measured by visual analogue scale scores (see Panel 1) between treatment and placebo after one and two menstrual cycles ($P=0.018$ and $P=0.006$, respectively), but no statistically significant difference ($P=0.064$) after three menstrual cycles.¹ The daily dose of Mastodynon used in these studies was equivalent to 32.4mg agnus castus extract.

Authoritative reviews of studies assessing the effects of evening primrose oil preparations have concluded that there are no reliable data on their efficacy in relieving symptoms of PMS, including mastalgia.^{2,6}

Menopausal symptoms Definitive clinical trials of the effects of black cohosh extracts on menopausal symptoms are lacking and further well-designed randomised controlled trials are required to establish clearly its benefits.

A randomised, double-blind, placebo-controlled trial involving 80 women with menopausal symptoms who received a standardised black cohosh extract (Remifemin, 40mg twice daily), conjugated oestrogens 0.625mg daily or placebo for 12 weeks found that at the end of the study somatic and psychological symptoms, measured by the Kupperman Menopausal Index and the Hamilton Anxiety Scale (see Panel 1), improved significantly in the black cohosh group, compared with the oestrogen and placebo groups ($P<0.001$).¹ However, for several reasons, the results of the study cannot be consid-

PANEL 1: GLOSSARY

Visual analogue score A visual analogue score consists of a 10cm line drawn between two extremes (eg, no symptoms and severe symptoms). The subject quantifies how he or she feels by making a mark along the line.

Kupperman Menopausal Index The Kupperman Menopausal Index is an assessment tool that involves grading major menopausal symptoms from 0 (symptom not present) to 3 (symptom is severe) and using the total score to quantify symptom severity. The symptoms assessed include depression, headache, palpitations, hot flushes, joint pain, loss of concentration, profuse perspiration, sleep disturbances and irritability or nervousness.

Hamilton Anxiety Scale The Hamilton Anxiety Scale was developed to quantify the severity of anxiety. It consists of 14 items such as fear, cardiovascular symptoms and depressed mood, each rated on a five-point scale (0= not present, 4= severe).

ered conclusive. For example, only small numbers of women were involved, and because oestrogen was found to be no better than placebo, this casts some doubt on the results. In this study, each 20mg black cohosh tablet contained 1mg triterpene glycosides calculated as 27-deoxyactein.

In another randomised, double-blind, placebo-controlled trial, involving 85 women with a history of breast cancer, black cohosh extract taken for 60 days had no greater effect than placebo on the frequency and intensity of hot flushes. A subgroup analysis comparing the effects in users and non-users of tamoxifen also did not show statistically significant differences for black cohosh extract compared with placebo.¹

Several other studies involving women with menopausal symptoms have explored the effects of black cohosh, but most have an open (not blinded) or uncontrolled design or both, and therefore do not provide an unbiased assessment of efficacy.¹ One such study, compared black cohosh tincture (80 drops daily) with oestrogen 0.625mg daily and diazepam 2mg daily over a 12-week period and reported improvements in psychological symptoms, such as self-assessed depression in all three groups.

Urinary tract infections Several controlled clinical trials have investigated the effects of cranberry preparations in the prevention and treatment of UTIs. However, because of methodological limitations, these trials do not provide convincing evidence for either the efficacy, or lack of efficacy, of cranberry products in these indications. Several controlled trials claiming to involve random assignment to treatment either did not employ true randomisation, or the method of randomisation was not stated.¹ Also, trials have differed in the formulations of cranberry, doses and treatment periods tested. Further investigation in the form of properly randomised, double-blind, controlled trials using appropriate outcome measures is warranted. Prevention trials should be of at least six months' duration to take account of the natural course of the condition.⁷

A Cochrane systematic review included four randomised or quasi-randomised, controlled (placebo or water) trials of cranberry juice or cranberry capsules in the prevention of UTIs.⁷ Two trials reported statistically significant effects for cranberry compared with placebo in preventing symptomatic or asymptomatic UTIs. However, because the methodological quality of the included studies was poor, the reliability of the results is questionable. The largest study, a randomised, double-blind, placebo-controlled trial, involved 153 older women (mean age 78.5 years) who received cranberry juice cocktail 300ml daily, or placebo, for six months.⁸ Bacteriuria with pyuria (pus in urine) occurred significantly less frequently in cranberry recipients, compared with placebo recipients ($P=0.004$) but again, the validity of these results has been questioned because of the study's methodological limitations.

Several other trials of cranberry preparations for the treatment of UTIs have been carried out, but because of methodological flaws none met the inclusion criteria for a Cochrane systematic review.⁹

action : practice points

1. Revise your knowledge on PMS and review the products you might recommend.
2. Consider how you might advise a woman with menopausal symptoms who wished to use a herbal product.
3. Visit the Bandolier website and look at reference 6.

evaluate

How could your learning have been more effective?
What will you do now and how will this be achieved?

MECHANISMS OF ACTION

The aetiology of PMS is unknown, although several theories have been proposed. For example, the rationale for the use of evening primrose oil in PMS was partly that hypersensitivity to prolactin (the hormone that stimulates breast development) is due to low concentrations of prostaglandin E₁, and that women with PMS have low concentrations of gamolenic acid, a precursor of prostaglandin E₁. There is evidence from clinical investigations that agnus castus extracts can reduce raised serum prolactin concentrations, possibly mediated through dopaminergic activity.

In vitro studies investigating the oestrogenic activity of black cohosh extracts and their constituents report conflicting results. Certain constituents of black cohosh extracts bind to oestrogen receptors, and oestrogenic activity in an oestrogen-receptor positive breast cancer cell line has been reported for fukinolic acid (a constituent of black cohosh). However, in another *in vitro* study using oestrogen-receptor positive breast cancer cells black cohosh extract did not exhibit oestrogen-like effects¹ and, recently, similar *in vitro* studies have described antioestrogenic effects for black cohosh extracts. In addition, there is conflicting clinical evidence with regard to the effects of black cohosh extract on vaginal epithelial cell proliferation. So, it is not clear whether the reputed effects of black cohosh in menopausal symptoms are attributable to oestrogenic effects.

It was thought initially that the antibacterial effect of cranberry juice was due to its ability to acidify urine and, therefore, to inhibit bacterial growth. However, recent work has focused on the effects of cranberry in inhibiting bacterial adherence and on determining constituents with anti-adhesion properties. Bacterial adherence to uroepithelial cell surfaces is facilitated by protein fibres on bacterial cell walls (fimbriae) which produce adhesins. There is evidence from *in vitro* studies that cranberry cocktail and proanthocyanidins extracted from cranberries inhibit the adherence of *Escherichia coli* (a common cause of UTIs) to uroepithelial cells.¹ Results of other experimental studies have suggested that a high molecular weight substance found in cranberry might also be important in this respect.

SAFETY ASPECTS

Formal investigation of the safety of agnus castus, black cohosh and cranberry preparations is limited, although there are some studies worth noting.

In an observational study involving 1,634 women with PMS who took agnus castus extract for three menstrual cycles, suspected adverse drug reactions (none of which was considered serious) were reported by physicians for 1.2 per cent. Ninety-four per cent of patients reported the tolerability of the preparation as "good" or "very good".¹⁰

In a similar post-marketing surveillance study involving 629 women with menopausal symptoms who received a standardised black cohosh extract for up to eight weeks, the tolerability of the preparation was rated as "good" by 93 per cent of participants. Mild, transient gastrointestinal symptoms were noted in 7 per cent of participants, although causality has not been established.¹ The National Institutes of Health in the United States say that women with breast cancer may wish to avoid black cohosh until its effects on breast tissue are understood.

To date, no adverse effects have been documented for cranberry. However, it is worth noting that some cranberry drinks have a high sugar content. Information on safety aspects of gamolenic acid from evening primrose oil is available in standard pharmaceutical texts. Adverse effects include headaches and minor gastrointestinal symptoms. Hypersensitivity reactions may occur rarely.

Interactions Agnus castus has dopaminergic activity and should not be used with dopamine receptor agonists or antagonists.

There are no reported drug interactions for black cohosh and cranberry, although interference with dipstick tests for glucose and haemoglobin in urine has been reported in patients who drank up to 150ml cranberry juice daily for seven weeks.¹ However, the documented pharmacological activities of these herbs should be considered when assessing whether they can be used concurrently with particular conventional medicines.

Evening primrose oil may have the potential to make manifest symptoms of undiagnosed temporal lobe epilepsy, especially in schizophrenic patients and patients taking known epileptogenic drugs (such as phenothiazines). It should be used with caution by such patients and those with a history of epilepsy.

Pregnancy and breastfeeding Because of the lack of toxicity data, agnus castus and black cohosh (which has other reputed uses besides treating menopausal symptoms) should be avoided during pregnancy and breastfeeding. Agnus castus has been reported to stimulate breast milk secretion without altering the composition of the milk. However, as a general precaution, agnus castus should be avoided during breastfeeding until further information is available on its safety.¹

Doses of cranberry greatly exceeding amounts used in foods should not be taken during pregnancy and breastfeeding.¹ Linoleic acid and gamolenic acid (constituents of evening primrose oil) from dietary sources normally are present in breast milk, so recommended doses of evening primrose oil may be taken during breastfeeding. Due to a lack of safety information, evening primrose oil should not be taken during pregnancy.

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