USE OF ALTERNATIVE MEDICINE BY MENOPAUSAL WOMEN

Complementary and alternative medicine (CAM) includes a broad range of healing philosophies, approaches and therapies that conventional or allopathic medicine does not commonly use or accept.

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Upon retirement as academic head of the Department of Obstetrics and Gynaecology and chief specialist at Johannesburg Hospital, the University of the Witwatersrand conferred the title of Emeritus Professor on Ernst Sonnendecker. As from 2002 Stellenbosch University appointed him as an Extraordinary Professor on which capacity he teaches postgraduates. He also consults privately at the Vincent Pallotti Hospital in Cape Town. He was the founding President of the South African Menopause Society (SAMS) and currently still serves as a council member. In his capacity as a member of the editorial board of Climacteric *(the official journal of the International Menopause Society), much of his time is taken up as a referee.*

Many women who choose CAM therapies do so because these health care approaches mirror their own values, beliefs, and philosophical orientations toward health and life. Some turn to CAM therapies because of their dissatisfaction with conventional medicine, or fear of adverse effects of hormone therapy (HRT). The publicity surrounding recent findings that HT increases certain risks has intensified the promotion of herbal preparations and phyto-oestrogens as natural and safe alternatives to oestrogen.

Consumers often believe that 'natural' therapies are safe. However, it is unrealistic to believe that a treatment can provide benefit without the potential for negative effects.

Many CAM users also use conventional medication. Despite the reticence of allopathic medicine concerning CAM, on 15 January 2004 the North American Menopause Society (NAMS) issued the following position statement on the treatment of hot flushes: 'For women who need relief from mild hot flashes, NAMS recommends first considering lifestyle changes, such as strategies to keep the body cool, participating in regular exercise, and using paced respiration. These changes can be done either alone or combined with a non-prescription remedy, such as dietary isoflavones, black cohosh, or vitamin E. Even though the published evidence does not conclusively support the effectiveness of those remedies, short-term use does not cause serious harm.' From this it is clear that medical practitioners now need to be knowledgeable about CAM.

GROUPING OF CAM THERAPIES

The National Center for Complementary and Alternative Medicine, established by the US Congress in 1998, groups CAM therapies into 5 major domains:

- alternative medical systems that include traditional cultural systems, acupuncture, homeopathy and naturopathic medicine
- mind-body interventions that employ a variety of techniques including hypnosis and biofeedback
- manipulative and body-based methods, for example chiropractic and massage therapy
- energy therapies that focus on energy fields originating within the body (biofields) or those from other sources (electro-magnetic fields)
- biologically based treatment.

The category of biologically based treatment includes special dietary, orthomolecular, and individual biological therapies, as well as herbal therapies. This article only reviews controlled studies of commonly used botanical therapies, mainly herbs, used to treat menopause-related conditions. The term botanical refers to a food or supplement derived from any part of a plant whereas herbal typically refers only to the leaves and/or stems.

Table I lists the natural products and their observed effects.

Table I. **'Natural products' and their observed effects**

Biologically based treatment	Benefits	Risks	Drug interactions
Soy	• Dietary soy reduces cholesterol • Extracts may increase spinal (not hip) bone • Hot flushes improved in 4 out of 9 studies	• Endometrial hyperplasia • May increase breast cell proliferation	None known
Red clover	• Raises HDL cholesterol • Hot flushes improved in 2 out of 5 trials • Improved systemic arterial compliance • Less lumbar spine density loss (no change in hip)	• None observed	Anticoagulants Hormonal therapies
Black cohosh	• Better than placebo for hot flushes	• GIT disturbances • Skin rash • Headache • Autoimmune hepatitis	None known
St John's wort	• Improves depression	• GIT disturbances • Photosensitivity • Cataract formation	Psychotropic meds Warfarin Digoxin Theophylline Indinavir Cyclosporine Oral contraceptives
Wild yam	• Very little		
Kava	• Some	• Hepatotoxic	
Dong quai	• No effect	• Photosensitivity • Anticoagulation	
Evening primrose	• Decreases night flushes	• Inflammation • Thrombosis • Immunosuppression • Nausea • Diarrhoea	Anticoagulants Phenothiazines
Ginseng	• Improves wellbeing	• Increases blood pressure • Lowers glucose levels • Lengthens bleeding time	
Ginkgo	• Improves cerebral insufficiency	• GIT distress • Headache • Bleeding	
Herbal combinations	• Inconclusive		

Consumers often believe that 'natural' therapies are safe. However, it is unrealistic to believe that a treatment can provide benefit without the potential for negative effects.

The most convincing health effects have been attributed to the actions of soy protein supplements on plasma lipid concentration.

There is no credible evidence that either soy protein or soy isoflavone extracts reduce vaginal dryness.

Clinicians and patients should be aware that transdermal progesterone will not protect the endometrium against the risk of endometrial cancer associated with oestrogen therapy.

PHYTO-OESTROGENS

The most studied of the botanicals for menopause-related conditions are phyto-oestrogens.'Phyto-oestrogens' is a descriptive term applied to non-steroidal diphenolic plant compounds that have oestrogen-like biological activity or are metabolised into compounds with oestrogenic activity. They have far greater binding affinity to the beta-oestrogen receptor than the alpha receptor, thus preferentially expressing oestrogenic activity in the CNS, blood vessels, bone and skin with little or no stimulation of the breast or uterus. Despite a low affinity for the alpha receptor, circulating levels many times that of steroidal oestrogens produce the potential for biological activity. The phyto-oestrogens are also characterised by mixed oestrogenic and anti-oestrogenic actions, depending on the target tissue (acting like a natural SERM).

Phyto-oestrogens are classified into 3 main groups — isoflavones, lignans, and coumestans. They are present in about 300 plants, especially legumes. Soybeans, a rich source of phyto-oestrogens, contain isoflavones, the most common form of phyto-oestrogens, consisting mainly of the compounds genistein and daidzein, and a little glycitin. Biochanin and formononetin are methylated precursors that are metabolised to genistein and daidzein. Red clover and lentils contain significant amounts of these precursors. The isoflavones are in the active, deconjugated forms in fermented soy foods such as miso and tempeh. The concentration of isoflavones in tofu is highly variable.[1]

Isoflavones in plants are bound as glycoside conjugates attached at the 3 position, called glycones. The carbohydrate component requires gut bacteria to remove the sugar moiety to produce active compounds, the aglycones. Individual variability in gastrointestinal microflora, as well as absorption, influences the bioavailability of isoflavones, accounting for inter-individual response variability.

SOY (*GLYCINE MAX*) ISOFLAVONES

It needs to be underlined again that functionally, isoflavones can exert both oestrogenic and anti-oestrogenic effects, depending on their concentration, the concentration of endogenous sex hormones, and the specific end organ involved. In addition, it is not clear whether the observed health benefits in human beings are attributable to isoflavones alone or to isoflavones plus other components in whole foods.[2]

The most convincing health effects have been attributed to the actions of soy protein supplements on plasma lipid concentration. A meta-analysis by Anderson *et al.*[3] of 38 published controlled clinical trials of soy protein consumption (47 g/day on average), concluded that soy protein was associated with a mean 9.3% reduction in total cholesterol, 12.9% reduction in LDL, and 10.5% reduction in triglycerides with no change in HDL. However, while intact soy protein diets have positive effects on the serum lipids in peri- and postmenopausal women, isoflavones extracted from soy do not have the same short-term effect, but longer treatment courses with isoflavone supplements may have beneficial lipid effects.[2]

The effect of soy protein or isoflavone supplement intake on bone metabolism during peri- or postmenopause is small, but in those whose intestinal microflora produce equol, it may increase spinal bone, although in most studies there are no effects on hip bone.

A systematic review of soy for the treatment of perimenopausal symptoms was recently published by Huntley and Ernst.[4] Only randomised controlled trials (RCTs) of soy or soy isoflavones as a monotherapy which scored 3 or above on the Jadad scale (to exclude bias) were considered. Ten of the 13 RCTs fitted their strict inclusion criteria. Four were positive, suggesting soy preparations are beneficial for perimenopausal symptoms. Five were

negative, and the remaining 1 showed a positive trend. Based on level I evidence, the authors concluded that, although it is difficult to make a definitive statement, there is some evidence for the efficacy of soy preparations for perimenopausal symptoms. The adverse events data, apart from gastrointestinal side-effects, suggested that there are no serious safety concerns with soy products in short-term use. Nevertheless, an RCT of 376 postmenopausal women using either 150 mg/day of soy isoflavone tablets or placebo after 5 years of treatment, revealed endometrial hyperplasia (but no cancer) in 3.8% of the soy group compared with none in the placebo group ($p < 0.05$).[5]

Interestingly, a meta-analysis of RCTs by Krebs *et al.*[6] showed significant improvement of hot flushes in only 1/11 soy food or beverage trials using 34 - 134 mg/day of isoflavones, whereas soy extract in a dose of 50 - 150 mg/day significantly improved the situation in 4/9 studies.

There is no credible evidence that either soy protein or soy isoflavone extracts reduce vaginal dryness. This is not surprising as during the menopause transition, women lose beta-oestrogen receptors from the vaginal walls with only alpha-oestrogen receptors remaining.[2]

Although epidemiological data suggest that isoflavone consumption is associated with a decreased risk of breast cancer, some short-term data suggest that isoflavone consumption may increase breast cell proliferation. Moreover, genistein exhibits a biphasic effect on the growth of MCF-7 cells *in vitro*. Nevertheless, in a critical review of the literature (288 references), Messina and Loprinzi[7] concluded that overall, the data do not convincingly suggest that the adult consumption of soy affects the risk of developing breast cancer or that soy consumption affects the survival of breast cancer patients. Consequently they concluded that 'if breast cancer patients enjoy soy products, it seems reasonable for them to continue to use them'.

However, NAMS cautions that it is unknown whether breast cancer survivors should be advised to avoid soy/phyto-oestrogens.[2]

RED CLOVER (*TRIFOLIUM PRATENSE*) ISOFLAVONES

The red clover plant is unusual in that it contains high total isoflavone levels and contains the four compounds (genistein, daidzein, and their respective methylated forms, biochanin and formononetin), identified as having potential health benefits.

Supplements that deliver a standardised dose in an aglycone state have been developed in order to avoid the variability in intestinal uptake of legumes that require fermentation to cleave the glycoside before absorption can occur. Such preparations achieve a more reliable delivery and uptake of isoflavones. One such proprietary red clover preparation formulated in tablet form (Promensil; Novogen Ltd, Australia), contains genistein, daidzein, biochanin and formononetin in a standardised ratio, delivering a total isoflavone dose of 40 mg.

In 2003 Huntley and Ernst[8] systematically reviewed the RCTs which had evaluated the effect of red clover on hot flushes. Only 4 trials fulfilled their inclusion criteria and all had utilised the same proprietary brand of red clover (Promensil) albeit in a dosage varying from 40 to 160 mg/day. One study showed a greater, but not statistically significant, reduction in flushing at 4 - 8 weeks; in two studies there were statistically significant decreases but the remaining study found no significant improvement even at 160 mg/day. The reviewers concluded that this red clover preparation may be of benefit for more severe menopausal symptoms. Although no adverse effects were reported they cautioned that theoretically it may interfere with anticoagulants and hormonal therapies.

In a recent meta-analysis of 5 RCTs in which 40 mg/day of Promensil had been utilised, 2 showed significant improvements of hot flushes with red clover.[6]

In preliminary studies in Australia, HDL cholesterol was increased in menopausal women taking 57 mg of a modified red clover isoflavone ratio, optimised for bone and cholesterol effects. While an increase in HDL was apparent after 3 months, this did not reach significance until after 6 months of continuous treatment. Moreover, 40 mg and 80 mg red clover isoflavone aglycones showed significant improvement in systemic arterial compliance (SAC), averaging 23%, within 5 weeks of treatment.[9] SAC is an index of the proximal arterial circulation to expand or dilate in response to an increased volume of blood ejected from the left ventricle of the heart. Howes *et al.*[10] investigated the effects on cognitive function of isoflavones from red clover in postmenopausal women older than 60 years. The 6 months of active therapy in this randomised, placebo-controlled, double-blind trial, consisted of a standardised extract of isoflavones from red clover formulated as tablets containing approximately 25 mg of formononetin,

2.5 mg of biochanin and less than 1 mg of genistein and daidzein. The results of this study suggest that red clover isoflavones do not lead to major short-term positive effects on cognitive function in postmenopausal women.

An RCT in 205 women aged 49 - 65 years assigned to red clover-derived isoflavones or placebo for 1 year showed significantly less loss of lumbar spine mineral content and density in the red clover recipients.[11] However, bone density in the hip showed no changes.

BLACK COHOSH (*ACTEA/CIMICIFUGA RACEMOSA*)

Preparations made from the rhizomes of black cohosh have been used by North American Indians for hundreds of years and have been used in European phytotherapy for the treatment of menopausal symptoms for over 50 years. It is the most widely studied herb in menopause treatment.

A number of the plant's constituents include triterpene glycosides, flavonoids and phenolic acids. There are reports of oestrogenic action, providing rationale for describing it as a phyto-oestrogen. However, recent studies of the isopropanolic extract marketed as Remifemin have reported no oestrogenic effect on FSH, vaginal epithelium or breast cancer cell lines.[2] Its mode of action may be dopaminergic.

In clinical trials with black cohosh, women have reported improvements in hot flushes, depression and well-being superior to placebo. A systematic review of four RCTs by Huntley and Ernst[8] showed that in one Remifemin 4 mg/day produced 'greatest improvement', in 2 significant improvements were similar to oestrogen therapy/oestrogen-progestogen (ET/EPT) therapy). In the remaining trial involving 85 breast cancer survivors, both placebo and Remifemin groups improved but not significantly. They concluded that the evidence for black cohosh was promising, albeit limited by poor methodology. There are no published studies that have followed up women for more than 6 months.

Adverse events include occasional gastrointestinal disturbances, rashes and headache. Recently a case study was reported of autoimmune hepatitis associated with the use of black cohosh.[12]

ST JOHN'S WORT (*HYPERICUM PERFORATUM*)

The leaves and flowering tops of St John's wort are used for their medicinal properties. Hyperforin is the most frequently cited constituent. The usual dose is 300 mg 3 times daily. Onset of action occurs in 2 - 4 weeks.

In a database review by the Cochrane group, 27 trials using St John's wort to treat mild to moderate depressive disorders involving 2 291 patients were identified (17 placebo-controlled). Most trials were 4 - 6 weeks long. The data indicate that St John's wort was superior to placebo and was as effective as standard antidepressants.[2]

Gastrointestinal side-effects and fatigue may occur and in rare cases it can increase sensitivity to sunlight and may contribute to cataract formation. St John's wort should not be used concomitantly with psychotropic medication and may decrease the activity or serum levels of warfarin, digoxin, theophylline, indinavir, cyclosporine, and oral contraceptives.

WILD YAM (*DIOSCOREA VILLOSA / BARBASCO*)

Wild yam creams are marketed as progesterone precursors or balancing formulas. Yam contains plant steroidal glycosides based on the sapogenin diosgenin, which can be converted to progesterone in a chemical laboratory but not in the human body. Many of the branded creams have from 480 to 1 020 mg of progesterone added per 30 g, with varying amounts of other ingredients such as wild yam, red clover, vitamin E and evening primrose oil.

Although studies demonstrate that progesterone in cream form can be absorbed through the skin, they indicate very little systemic absorption with great variability. Thus clinicians and patients should be aware that transdermal progesterone will not protect the endometrium against the risk of endometrial cancer associated with oestrogen therapy.[1] While studies demonstrate mixed results on symptom relief in menopausal women, no controlled studies have shown improvement of bone, lipids, moods, sexuality, or endometrial response.

KAVA (*PIPER METHYSTICUM*)

The kava used for soothing mild anxiety, hot flushes, and sleep disruption, comes from the rhizome of the kava shrub. Three RCTs have investigated its value for menopausal symptoms. Unfortunately, 2 of the trials only performed statistical tests compared with baseline, not placebo. Nevertheless, based on a systematic review, it was concluded that there is some beneficial evidence.[8] Because of dermatological problems and possible interaction with anxiolytics, but especially in view of possible hepatotoxicity, it may be advisable to avoid its use until more is known.[2]

DONG QUAI (*ANGELICA SINENSIS*)

Among Chinese therapies, this aromatic herb is the most extensively used in treating gynaecological conditions. The only RCT found that 4.5 g/day of dong quai used for 12 weeks was no more helpful than placebo in relieving hot flushes.[8] Chinese herbalists counter that dong quai is not meant to be used alone, but within an individually tailored mixture of herbs.[2] Side-effects include photosensitivity and anticoagulation.

EVENING PRIMROSE (*OENOTHERA BIENNIS*)

The seeds are rich in oils containing linoleic acid. The usual dose of evening primrose oil (EPO) in supplement form is 1 500 - 3 000 mg daily. One RCT found that the only significant improvement was a reduction in the maximum number of night-time flushes ($p < 0.05$) over baseline but EPO offered no benefit in any of the measures over placebo.[8] Side-effects include inflammation, thrombosis, immunosuppression, nausea and diarrhoea. EPO should not be used with anticoagulants or phenothiazines.[2]

GINSENG (*PANAX GINSENG*)

The multi-branched root of this perennial, shade-loving plant is used in botanical medicine. In an RCT of 384 menopausal women it was shown that only the psychological general well-being index ($p < 0.01$) and its subscales for depression, well-being and health ($p < 0.05$) showed a statistically significant improvement with ginseng compared with placebo.[8] Although the plant does not contain phyto-oestrogens, based on case reports of uterine bleeding, it is suspected to have oestrogenic effects. It can raise blood pressure or produce low glucose levels and because of antiplatelet effects, may lengthen bleeding time.[2]

GINKGO (*GINKGO BILOBA*)

Preparations made from the leaves of the ginkgo tree go back to about 3 000 BC. It is reputed to increase blood flow through small vessels, including cerebral arteries, and acts as an antioxidant and blood thinner.

All 8 of the well-controlled trials included in a meta-analysis of 40 trials for 'cerebral insufficiency', showed a significant benefit for the ginkgo group.[2] The most common side-effects are gastrointestinal distress and headache, while the most serious is bleeding, as ginkgo inhibits platelet function.

HERBAL COMBINATIONS

A review by Huntley and Ernst of 4 different combination products provided inconclusive evidence of efficacy.[8] With only 1 study on each of the herbal combinations, it is impossible to say anything definitive on their therapeutic value.

CONCLUSIONS

As over half of all participants in the Study of Women's Health Across the Nation (SWAN) used CAM, and as CAM users were using more conventional health care resources than non-users,[13] it is clear that medical practitioners need to question menopausal women about their use of CAM and must be able to provide them with appropriate knowledge.
Although botanicals appear to be helpful, further scientific studies into the efficacy, safety and correct dosage of herbal medicinal products for menopausal symptoms is warranted before they become an integral part of allopathic medical practice.

References available on request.

IN A NUTSHELL

Many users of complementary and alternative medicine (CAM) also use conventional medicine.

Botanical therapies, which are mostly herbs, are used to treat menopausal conditions.

The most studied of the botanicals for menopause related conditions are phyto-oestrogens.

Phyto-oestrogens are non-steroidal diphenolic plant compounds that have oestrogen-like biological activity or are metabolised into compounds with oestrogenic activity.

Phyto-oestrogens have a high affinity to bind with the beta-oestrogen receptor but a low affinity for the alpha receptor. They can act like a selective oestrogen receptor modulator (SERM).

Isoflavones, found especially in soy beans and red clover, are the main class of phyto-oestrogens used to treat menopausal conditions.

Randomised controlled trials considered in this article show that generally results are mixed.

The mode of action of preparations made from black cohosh appears to be dopaminergic rather than oestrogenic.

Wild yam creams, marketed as progesterone precursors or balancing formulas, only have progestogenic effects if their diosgenin has been hemisynthetically converted to progesterone or the latter has been added. Although they are absorbed, these creams do not provide endometrial protection.

Medical practitioners need to be knowledgeable about CAM and must question their patients about the use of herbal preparations because of possible interactions and side-effects outlined in this article.