International Journal of Gynecology and Obstetrics 79 (2002) 195–207

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

Review article

Use of alternative and complementary medicine in menopause

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Received 17 June 2002; received in revised form 12 September 2002; accepted 13 September 2002

Abstract

Objectives: To review the clinical evidence available for the treatment of menopausal symptoms with alternative and complementary medicine. *Methods:* The MEDLINE, PREMEDLINE and COCHRANE electronic databases for the years 1980–2002 were searched for articles concerning soy products, black cohosh, dong quai, acupuncture, ginseng and evening primrose oil. Studies pertaining to menopausal vasomotor symptoms, lipid profiles and bone mineral densities of postmenopausal women were included. The data from clinical trials were reviewed. *Results:* Soy isoflavones slightly decrease total cholesterol and LDL levels. The clinical significance of this small change is yet to be determined. The synthetic isoflavone derivative ipriflavone increases bone mineral density in healthy peri- and postmenopausal women with moderate bone mineral densities. Although earlier reports have claimed that soy is beneficial for the improvement of vasomotor symptoms, recent data do not support this claim. There are insufficient data on the other alternative therapies for treating menopausal symptoms at this time. *Conclusion:* Alternative and complementary medicine may play a role in the management of menopause, however, well-designed large studies are still needed.

Keywords: Alternative and complementary medicine; Menopause

1. Introduction

This is a time of unprecedented growth in the popularity of alternative and complementary medicines for the management of the symptoms of menopause. Forty percent of Americans reported using alternative therapies to treat medical conditions in 1997 [1]. Menopausal women account for one of the largest segments of alternative medicine users, with 80% of women aged 45–60 reporting the use of non-prescription therapies for the management of menopausal symptoms [2]. These therapies include herbal remedies, meditation, traditional Chinese medicine, vitamins and minerals, homeopathy, acupuncture and chiropractic

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0020-7292/02/$ - see front matter
PII: S0020-7292(02)00297-7

practices [3]. Women cite a large number of reasons for their interest in these therapies. They are perceived to be safer than hormone replacement therapy, and some women report feeling that they are taking more personal control over their health care by using alternative therapies [4]. Other reasons women cite against hormone replacement therapy include fear of cancer, dislike of side effects such as vaginal bleeding, and the view that the menopause is a natural transition [5].

The regulation of alternative therapies has not kept pace with the fast growth of the industry. The 1994 Dietary Supplement Health and Education Act (DSHEA) stated that dietary supplements, including herbs and vitamins, would not be considered foods, and therefore would no longer require a pre-market safety evaluation [6]. This regulation was passed in response to both consumer and manufacturer demand. Large discrepancies have been found between label content and the actual active ingredients found in many of these dietary supplements after the passage of the DSHEA. Some herbal supplements have even been found to contain unreported contaminants [7]. A study by the Food and Drug branch of the California Department of Health Services found that 32% of Asian patent medicines contained undeclared pharmaceuticals or heavy metals [8]. In addition, claims of dietary supplements do not have to adhere to rigorous clinical standards.

There is a dichotomy between the vast amount of alternative medicine lay literature that women may be reading and the lack of clinical evidence available for physicians on these same topics. Randomized, placebo-controlled clinical trials are just beginning to be performed on just a few of the major, non-traditional therapies, with very little clinical information available on the vast majority of alternative dietary supplements. This paper will discuss the alternative therapies associated with the treatment and management of menopausal symptoms, and will present and analyze the most recently published clinical information pertaining to these alternative therapies. The clinical data are classified and presented by menopausal symptom category.

2. Alternative therapies

2.1. Soy products

Derived largely from soy products, phytoestrogens are currently the most popular alternative to hormone replacement therapy [9]. They are plant-derived compounds that are structurally and functionally similar to estradiol [10]. Isoflavones are one class of phytoestrogens. Genistein and daidzein are the two major types of isoflavones. They are found in soy, clover, lentils, beans and chickpeas. In humans, gastrointestinal tract enzymes convert isoflavones into heterocyclic phenols that have a structural similarity to estrogen [11]. The beneficial effects of soy supplements in postmenopausal women have been attributed to these isoflavones.

Isoflavones appear to be selective estrogen receptor modulators with modest agonist activity at the beta estrogen receptor, at approximately one-third the potency of estradiol. They also appear to have very weak alpha estrogen receptor activity, with 0.001 the potency of estradiol [12]. The relative expression of alpha and beta estrogen receptors varies between tissues in the body. Isoflavones appear to have both estrogenic and anti-estrogenic behavior [13].

2.2. Black cohosh

Black cohosh (*Cimicifuga racemosa*) is an indigenous Eastern North American plant that has been used by Native Americans for gynecological conditions since before the arrival of European settlers to North America. Called ‘squaw root’ because it was used primarily for female disorders, it was first listed in the *Pharmacopoeia of the United States* in 1830 under the name ‘black snakeroot.’ It was the primary ingredient of Lydia Pinkham’s tonic compound for ‘female complaints,’ which sold widely for more than 50 years in the early twentieth century [14]. In 1989, the German Commission E, an expert panel commissioned by the German government to address herbal products, approved black cohosh as a non-prescription medicine for the treatment of climacteric ailments. The commission recommended,

however, that black cohosh be used for no longer than 6 months due to an uncertainty about its possible long-term side effects [15]. The treatment of menopausal signs and symptoms has been the primary therapeutic application of black cohosh. It is the main ingredient in the often-used over-the-counter menopausal preparation 'Remifemin' (Schaper Brummer, Germany, distributed by PhytoPharmica, Green Bay, WI).

The mechanism by which black cohosh may exert its effects is unclear. It was once believed that it may have estrogen-like activity, but the results of various studies have been varied. One study reports that black cohosh binds competitively to the beta estrogen receptor [16], but studies by Remifemin's manufacturer report that it does not perform as a true estrogen [17]. The biologically active component of black cohosh is attributed to a number of triterpene glycosides. Remifemin is standardized in respect to triterpene glycoside content.

2.3. Dong quai

Dong quai is an herb native to Eastern Asia and China. It has been used for more than 1000 years as a spice, tonic and medicine in traditional Chinese medicine. Dong quai is known as the 'female ginseng' and is currently the second best-selling herb in China [18]. It is indicated for dysmenorrhea, irregular menstruation and as a supportive herb for menopausal complaints [19]. In the West, dong quai has become popular as an herb for treating menopausal symptoms.

Dong quai was one of the first alternative therapies to which potentially adverse effects were attributed, for it potentates the effects of warfarin. Dong quai contains furocoumatins, which are coumarin-like substances that act as anticoagulants [20].

2.4. Acupuncture

Acupuncture is another component of Chinese medicine that dates back at least 2500 years. The term 'acupuncture' describes a number of different practices that involve puncturing the body (as with thin needles) at specific points to cure disease or relieve pain. The mechanism of action is thought to involve the release of opioid peptides at the acupuncture sites. There may also be activation of the hypothalamus and the pituitary gland, causing a broad spectrum of systemic effects [21]. The benefits of acupuncture are being evaluated for a vast array of health conditions from post-chemotherapy nausea and vomiting, to menstrual cramps, stroke rehabilitation and the symptoms of menopause.

2.5. Ginseng

The word 'ginseng' is derived from 'panacea,' meaning cure-all. It is said to boost immunity, energy and vigor, and has been reported to have estrogenic properties. There have been a number of studies reported by *Consumer Reports*, the *Los Angeles Times* and Consumerlab.com that have criticized the production quality of ginseng products. One study reported that only 25% of the commercially available products actually contained ginseng [22]. Large quantities of caffeine have also been found in many ginseng products [23].

2.6. Evening primrose oil

Evening primrose oil comes from the seeds of the yellow primrose, a North American wildflower. It has a long history of use by Native Americans. The seeds contain oils rich in linolenic acid and γ-linolenic acid, precursors of prostaglandin E. Disorders for which evening primrose oil have been tested include atopic dermatitis, rheumatoid arthritis, mastalgia, breast cysts, premenstrual syndrome and menopausal hot flashes [24].

3. Methods

The MEDLINE, PREMEDLINE and COCHRANE databases from January 1, 1980 through April 9, 2002 were searched for articles using the keywords 'alternative medicine,' 'phytoestrogens,' 'isoflavones,' 'soy,' 'black cohosh,' 'dong quai,' 'ginseng,' 'evening primrose oil' and 'acupuncture,' and cross-referenced with the terms 'menopause,' 'hot flashes,' 'night sweats,' 'coronary disease,' 'hyperlipidemia,' 'bone mineral density'

and 'osteoporosis.' The reference lists of published articles and abstracts were searched for relevant articles that were not found in the database searches. Lay literature concerning alternative medicine use was obtained through Internet searches. Criteria for the selection of articles for analysis included human subjects and appeared in the English language. This review only considers evidence from clinical trials and randomized controlled studies performed from 1996 to 2002.

4. Results

Although a large amount of medical literature is available on alternative therapies, very little of this literature contains clinical data from well-conducted studies. The majority of the clinical data that is available is on the soy isoflavones, with a small amount of clinical data available on black cohosh, dong quai, acupuncture, ginseng and evening primrose oil.

4.1. Hot flashes

Hot flashes and night sweats are the most common manifestations of the climacteric in the United States. They often occur in the perimenopausal and early menopausal phase, with up to 75% of women experiencing varying degrees of these symptoms [25]. The majority of women do not consider these vasomotor symptoms to be overly unpleasant, and only approximately one-fifth find them distressing enough to seek medical assistance [26]. Hormone replacement therapy (HRT) is currently recognized as the most effective treatment for the short-term symptoms of menopause. One study found that there was a 77% reduction in the frequency of hot flashes, and that symptom severity was also significantly reduced in HRT users as compared to the placebo [27].

The hypothesis that soy isoflavones may exert pro-estrogenic effects on menopausal symptoms originated in part from epidemiological observations that hot flash occurrence is much lower in Asian countries than in Western countries. Less than 25% of Japanese women report experiencing hot flashes [28]. It is estimated that the Japanese consume 200 mg of phytoestrogens per day, 50 mg of which are isoflavones [29]. Some researchers maintain that the high dietary intake of phytoestrogens may explain why Japanese women experience fewer hot flashes than their Western counterparts. A 2001 cohort study of Japanese women revealed an inverse relationship between soy product intake and hot flashes [30].

Although a large number of clinical trials have reported a decrease in hot flashes in women treated with soy protein, many of these trials did not prove that soy was superior to the placebo. Five clinical studies demonstrated no statistical difference between soy treatment and placebo groups (see Table 1) [31–35]. The placebo effect in these studies was quite high, with hot flash reduction values in the placebo groups ranging from 20 to 25%. The St. Germaine study commented on the strong placebo effect, noting that greater than 50% of the women participating in their trial stated at the conclusion of the trial that they believed they were in the high isoflavone treatment group. Only one-third of the women were actually in the treatment group [35].

However, two clinical trials have reported a significant decrease in hot flashes in the group treated with soy product over the placebo [36,37]. Hot flash frequency was reduced by 45% and 28%, respectively, in these trials. The placebo effect was high in both of these studies, with values of 30% and 18%. The dose and method of administration necessary to produce symptom improvements remains unclear at this time. The trials performed thus far have utilized 50–150 mg of isoflavone with conflicting results, with no apparent relationship between isoflavone dose and symptom relief.

Other herbal supplements have been reported in the lay literature to relieve vasomotor symptoms in menopausal women. One clinical trial examined dong quai vs. placebo in postmenopausal women. Both the treatment group and the placebo group experienced a benefit in terms of reduced number and intensity of hot flashes, with no statistical difference between the two treatment arms. The authors did note that treatment with dong quai alone can be criticized because Chinese practitioners never prescribe the herb alone, but rather typically use it in conjunction with other herbs.

Table 1
Hot flashes

Author	Design	Intervention	Subjects	Results
Knight et al., 2001 [31]	Double-blind, randomized, placebo-controlled trial	Powder containing 134.4 mg of isoflavones	24 women[a] >3 HF/day	No improvement in HF over placebo
Murkies et al., 1995 [32]	Double-blind, randomized, placebo-controlled trial	Soy flour	58 women[a] >14 HF/week	HF decreased 40% in soy flour group
Brzezinski et al. 1997 [33]	Double-blind, randomized, placebo-controlled trial	Phytoestrogen-rich diet	145 women[b]	No improvement in HF over placebo
Quella et al., 2000 [34]	Double-blind, randomized, parallel, placebo-controlled trial	Soy tablets containing 50 mg soy isoflavone	177 breast cancer survivors with HF	No improvement in HF over placebo
St. Germain et al., 2001 [35]	Double-blind, randomized, placebo-controlled trial	80.4 mg isoflavone, vs. 4.4 mg isoflavone	69 women[c] >10 HF/day	No improvement in HF over placebo
Albertazzi et al., 1998 [36]	Double-blind, parallel, randomized, placebo-controlled trial	Soy protein containing 76 mg of isoflavone	104 women[a] >7 HF/day	HF statistically improved in soy group
Upmalis et al., 2000 [37]	Double-blind, parallel, placebo-controlled trial	Soy isoflavone extract containing 50 mg genistein, 50 mg daidzen	177 women[a] >5 HF/day	HF statistically improved in treatment group
Hirata et al., 1997 [38]	Double-blind, randomized, placebo-controlled trial	Dong quai	71 women[a]	No improvement in HF over placebo
Wiklund et al., 1999 [39]	Double-blind, randomized, parallel group trial	Ginseng	384 women[a]	No improvement in HF over placebo
Davis et al., 2001 [40]	Double-blind, randomized, placebo-controlled trial	Chinese medicinal herbs	55 women[a] >14 HF/day	No improvement in HF over placebo
Jacobson et al., 2001 [41]	Double-blind, randomized, placebo-controlled trial	Black cohosh	85 women with breast cancer	No improvement in HF over placebo
Chenoy et al., 1994 [42]	Double-blind, randomized, placebo-controlled trial	Evening primrose oil 1000 mg	56 women[d] >3 HF/day	No improvement in HF over placebo
Wyon et al., 1994 [43]	Randomized, placebo-controlled trial	Electrostimulated acupuncture vs. superf needle position acupuncture	24 women[d]	Number of hot flashes remained consistently decreased in acupuncture group
Kraft et al., 1999 [44]	Randomized, single-blind placebo-controlled trial	Acupuncture	10 women[a]	Significant reductions in menopausal complaints

[a] Postmenopausal.
[b] Peri- and postmenopausal.
[c] Perimenopausal.
[d] Menopausal.

However, one study found that women in the United States typically take dong quai alone as a single entity [38]. A study performed by the Ginsana Corporation, the largest manufacturer of ginseng products worldwide, also reported no improvement in hot flashes over the placebo [39].

An Australian study examined whether a defined formula of Chinese medicinal herbs could relieve menopausal symptoms. The authors state that the Chinese medicinal herbs were comprised of a modified traditional formula of herbs, and listed the 12 herbs contained in the formula, but did not

give further information about their choice of selection of herbs for this formula. Again, there was no significant or clinically relevant difference in the frequency of vasomotor symptoms between placebo and Chinese medicinal herb therapy, with both groups experiencing a statistically significant decline in symptoms [40].

A clinical trial published in 2001 that studied the effects of black cohosh on breast cancer patients who experienced hot flashes also showed no difference between treatment groups and the placebo. The authors' state that they believe that the patients' feeling of security from taking a medication believed to control hot flashes could have reinforced the tendency for the positive placebo response in participants [41]. Another trial performed on evening primrose oil showed that there was no statistical difference in the relief of vasomotor symptoms between the treatment group and the placebo group [42].

Although not many studies have examined the effects of acupuncture on hot flashes, two European studies have reported promising findings. A Swedish study examined the effects of electrostimulated acupuncture and superficial needle position acupuncture on hot flashes. It found that patients benefited from the electrostimulated acupuncture, and not from the placebo superficial needle position acupuncture [43]. A German study published in 1999 reported a decrease in menopausal complaints after acupuncture therapy vs. a placebo [44].

There is still a paucity of clinical data on these various alternative therapies for the treatment of menopausal symptoms. A greater number of randomized controlled clinical trials need to be performed on black cohosh, dong quai, evening primrose oil and acupuncture for the treatment of menopausal symptoms.

4.2. Bone mineral density

Osteoporosis has become a very important health issue, with more than 23% of women over 65 years old having osteoporosis [45]. The primary cause is currently thought to be a decrease in endogenous estrogens at menopause. HRT and bisphosphonates are currently accepted to be the best pharmaceutical method to maintain bone mineral density in postmenopausal women [46].

Ipriflavone is a synthetic isoflavone that has been reported to reduce the rate of bone loss in postmenopausal women. This drug is produced commercially from the isoflavone daidzen. It became evident from the earliest studies that ipriflavone was effective in increasing the calcium content of skeletal tissue in animals [47]. Early studies also reported that ipriflavone may be as effective as estrogen in its ability to prevent bone loss, and a combination of the two treatments was complementary [48]. Ipriflavone is reported to work by inhibiting osteoclast activity and stimulating osteoblast activity [49].

A three-year study performed by the Ipriflavone Multicenter European Fracture Study reported that ipriflavone had no beneficial effect over the placebo. The authors note that their participants could have had too little initial bone mass to benefit from treatment (see Table 2) [50]. This study reported conflicting results as compared to four other clinical trials performed on women with osteoporosis or osteopenia, which have mostly reported the beneficial effects of ipriflavone on bone mineral density. Ipriflavone effectiveness has been measured by bone mineral density measurements, urinary bone resorption marker detection and biochemical markers of bone resorption [51–54]. In the study by Halpner et al., the subjects on the treatment arm received a dietary supplement containing vitamin D and calcium, as well as the ipriflavone. There was no explanation given for the contents of the placebo supplement, and one can infer that the placebo may not have contained the vitamin D and calcium. Therefore, the decreased rates of urinary bone resorption markers may not have been purely due to the ipriflavone, but rather may have been due to the combined effect of the other components in the supplement. Although there are some conflicting data from the clinical trials performed on ipriflavone, it appears that it does have at least some effect on decreasing bone turnover and maintaining bone mineral density. Additional research is needed to further characterize which menopausal women would benefit from this treatment, and the clinical significance of the magnitude of benefit in decreasing fractures.

Table 2
Bone mineral density

Authors	Design	Intervention	Subjects	Outcome measures	Results
Alexandersen et al., 2001 [51]	Randomized, double-blind placebo-controlled trial, 3 years	Ipriflavone 600 mg	292 women[a] with osteoporosis	Spine, hip, forearm BMD, biochemical markers of bone resorption	No difference in BMD
Agnusdei et al., 1997 [52]	Randomized, double-blind, placebo-controlled, parallel group study, 2 years	Ipriflavone 600 mg	198 women[a] with BMD 1 S.D. below normal	L2–L4 vertebral BMD, biochemical markers of bone resorption	Significant increase in vertebral BMD in treatment group
Adami et al., 1997 [53]	Randomized, prospective, double-blind, parallel group trial, 2 years	Ipriflavone, 600 mg	250 women[a] with BMD 1 S.D. below mean	Radial BMD, biochemical markers of bone resorption	Radial BMD decreased in placebo, maintained BMD in treatment group
Gennari et al., 1998 [54]	Randomized, placebo-controlled trial	Ipriflavone 600 mg	56 women[a] with low BMD	BMD, urine hydoxyproline/creatinine	BMD decreased in placebo, no change in BMD in treatment group
Halpner et al., 2000 [55]	Placebo-controlled trial	300 mg ipriflavone, Vit D, Ca dietary supplement	7 healthy women[a]	Urinary N-linked telopeptide levels	N-linked telopeptide declined 29% in patients receiving supplement
Bassey et al., 2000 [56]	Randomized, placebo-controlled trial, 1 year	Efacal (1.0 g Ca, 4.0 g evening primrose oil) vs. 1.0 g Ca	43 women[b] 42 women[a]	BMD, biochemical markers of bone resorption	No significant difference between treatment and placebo
Kruger et al., 1998 [57]	Randomized, placebo-controlled, 18 months	γ linolenic acid and eicosapentaenoic acid	65 women[a] with osteoporosis	BMD, biochemical markers of bone resorption	Significant increase in lumbar and femoral BMD in treatment group

[a] Postmenopausal.
[b] Premenopausal.

A small number of clinical studies have explored the effects of evening primrose oil on bone mineral density. A study of the dietary supplement Efacal (Efamol Nutraceuticals Inc, Boston, MA), which contains 1.0 g of calcium, 4.0 g of evening primrose oil and 440 mg of marine fish oil, found no difference in bone mineral density or bone turnover markers in premenopausal and postmenopausal women in the treatment arm of the study. The authors conclude that Efacal has no effect on bone mineral density in women [55]. When the γ-linolenic acid component of evening primrose oil was separately tested, bone mineral densities increased in the treatment groups, and decreased in placebo groups [56]. More studies need to be performed to clarify whether evening primrose oil is helpful in delaying bone mineral density loss in postmenopausal women.

4.3. Lipid profiles

The relationship between soy products and lipid profiles has been investigated for many years. Animal studies as early as the 1940s demonstrated the beneficial effect of soy proteins on lipid profiles [57]. Recent animal studies also demonstrated the benefits of soy isoflavones on total cholesterol and LDL [58]. In addition, various cross-sectional analyses demonstrated an inverse relationship between soy intake and cholesterol levels [59,60].

A meta analysis of 38 clinical trials that examined the relationship between soy protein intake and serum lipids report that the consumption of soy in men and women is associated with a significant decrease in serum cholesterol, LDL and triglyceride levels. This association was strongest for subjects with higher initial levels of cholesterol. In 34 out of the 38 studies, serum cholesterol levels decreased in treatment subjects following the consumption of soy. The four trials that found no effect from the consumption of soy consisted of women with fairly low initial cholesterol levels. The authors of this meta analysis report that an average intake of 47 g of soy protein per day resulted in statistically significant reductions in total cholesterol, LDL and triglyceride levels [61].

A recently published randomized controlled cross-over trial examined the effects of isoflavone in 18 postmenopausal women with either normal or mildly elevated cholesterol levels. LDL was found to be 6.5% lower in the high-isoflavone treatment group, and was also significantly lower in the low isoflavone treatment group. The LDL/HDL ratio was also lower in the isoflavone treatment groups, although the low dose isoflavone group actually had lower values than the high isoflavone group (see Table 3) [62]. A study that tested soy protein on patients with moderately elevated cholesterol levels reported similar lipid-lowering results [63]. Another study that was performed on perimenopausal women with normal lipid profiles reported similar lipid lowering results [64]. A randomized, double blind placebo-controlled trial examined the effects of dietary soy supplements containing 118 mg isoflavones on the lipid profiles of men and postmenopausal women with relatively normal cholesterol levels. The LDL/HDL ratio was again decreased in the isoflavone treatment groups, but there was no reported change in total cholesterol [65].

The mechanism by which soy isoflavones are thought to alter lipid profiles remains unknown, but a study that examined the effects of 56 mg and 90 mg of isoflavones on hypercholesterolemic postmenopausal women reported increased HDL cholesterol and increased messenger RNA levels in the isoflavone treatment groups. The authors proposed that soy protein may improve lipid profiles by altering LDL receptor quantity or quality [66]. When markers of lipid peroxidation and resistance of LDL to oxidation were examined in men and women treated with isoflavone vs. placebo, researchers found a reduced lipid peroxidation in vivo, and increased resistance of LDL to oxidation. LDL oxidation is considered to be a prerequisite for the uptake of LDL by macrophages in the artery wall, an early step in the formation of atheroma. The authors concluded that the antioxidant action of soy isoflavones could be significant in reducing cardiovascular disease risk and atherosclerosis [67]. Other mechanisms that have been proposed for the hypocholesterolemic effect of soy include enhancement of bile acid excretion, increased hepatic metabolism of cholesterol, and altered variations in hormone secretion [68].

Table 3
Lipid profiles

Author	Design	Intervention	Subjects	Outcome measures	Results
Wangen et al., 2001 [63]	Randomized, cross-over trial, 93 days	65 mg isoflavone vs. 132 mg isoflavones	18 women[a], with normal or mildly elevated cholesterols	TC, LDL, HDL, Apo A-1, apo B, TG	Significantly decreased LDL, LDL/HDL ration in 132 mg isoflavone group
Crouse et al., 1999 [64]	Randomized, double-blind parallel trial, 9 weeks	Soy protein containing 3, 27, 37, 62 mg isoflavones	38 women,[a] 24 women,[b] 94 men, moderately elevated cholesterol	TC, LDL, HDL, TG	TC and LDL decreased in high isoflavone treatment groups
Washburn et al., 1999 [65]	Randomized, double-blind, cross-over trial, 6 weeks	34 mg phytoestrogen	51 healthy women	TC LDL, HDL, TG	6% lower TC, 7% lower LDL in soy treatment groups
Teede et al., 2001 [66]	Randomized, placebo-controlled, double-blind 3 months trial	Dietary soy supplements containing 118 mg isoflavones	96 men, 83 women[a] with normal cholesterol	TC, LDL, HDL, TG, lipoprotein A	Decreased TG, LDL/HDL ratio, increased lipoprotein A in treatment group
Baum et al., 1998 [67]	Parallel group, double-blind trial	Soy protein with 56 mg isoflavone vs. 90 mg isoflavone	66 women[a] with high cholesterols	TC, LDL, HDL, LDL receptor mRNA	mRNA increased in isoflavone groups
Wiseman et al., 2000 [68]	Randomized, cross-over trial	Soy protein high in isoflavone	19 women, 5 men	8-epi-PGF2α, F2 isoprostane, resistance of LDL to oxidation	8-epi-PGF2α levels were lower, LDL oxidation lag time was longer in high isoflavone groups
Howes et al., 2000 [70]	Randomized, double-blind increasing dose placebo-controlled trial, 10 weeks	Isoflavone extract containing 26 mg biochanin A, 16 mg formononetin, 0.5 mg genistein, 1 mg daidzein from red clover	75 women[a] with moderately elevated cholesterol	TC, LDL, HDL, TG.	Treatment group showed no change in total cholesterol, LDL, HDL or TG
Hodgson et al., 1998 [71]	Randomized, double-blind, placebo-controlled parallel group design 8 weeks	Tablet containing 55 mg isoflavone	46 men, 13 women[a] with average serum lipid profiles	Total chol, LDL, HDL, triglycerides, lipoprotein	No change in any of the lipid parameters
Ishikawa et al., 1989 [75]	Placebo-controlled, cross-over design, 116 weeks	Evening primrose oil	19 patients with high cholesterols	LDL, apolipoprotein B	LDL, apolipoprotein B levels decreased in treatment group

TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides.
[a] Postmenopausal.
[b] Premenopausal.

Some studies report no change in lipid profiles from the ingestion of isoflavone. When isoflavone extract from red clover was administered to postmenopausal women with moderately elevated cholesterol levels, the treatment groups showed no change in LDL, HDL, triglyceride or total cholesterol levels. The authors maintain that although they used the red clover isoflavones biochanin A and formonetin, these compounds are metabolized in vivo to genistein and daidzein, respectively [69]. When isoflavone was administered in a tablet form to men and women with average lipid profiles, no change was reported in any of the lipid parameters [70]. This study may have conflicting results due to the lower lipid profile levels of its participants, for soy isoflavones appear to be most beneficial for patients with elevated lipid profile levels. Overall it appears that soy protein isoflavones are able to play a role in reducing cardiovascular risk factors in at least some patients. It also appears that the beneficial effects are greatest in subjects with initially elevated lipid profile levels.

Several animal studies report a beneficial effect of evening primrose oil on hyperlipidemia [71–73]. A clinical trial performed in the early 1980s reports that evening primrose oil was effective in lowering LDL levels and apolipoprotein B levels in hypercholesterolemic men and women [74].

5. Discussion

The explosion of public interest in alternative and complementary therapies for the treatment of menopausal symptoms will continue to grow and expand in the years ahead. The medical literature examining these therapies needs to grow as well for there is too little clinical evidence currently available. As the number of studies increases, better evidence will become available. At this time, soy isoflavones do not offer benefits superior to placebo in the alleviation of hot flashes. However, there does appear to be a lipid-lowering benefit to soy isoflavones, with the greatest benefit occurring in women with elevated initial lipid levels. In terms of osteoporosis prevention, the synthetic isoflavone ipriflavone may prove to be beneficial in preserving bone mineral density in postmenopausal women with higher initial bone mineral densities.

There is a great paucity of literature regarding black cohosh. Most clinical trials have been performed in Germany, with a large proportion of the studies having been performed by the Remifemin manufacturer. At this point, the only English study has been performed on breast cancer survivors experiencing hot flashes. This trial reports no decrease in hot flashes in participants taking black cohosh over placebo, but it must be noted that a number of the patients were taking tamoxifen at the time of the study.

Although dong quai is not as well known or popular in the United States, it is of great importance since it has been found to have anticoagulant properties. Seventy percent of Americans who use alternative medicines report not discussing these therapies with their physicians [75]. Therefore it is critical that caregivers try to open a dialogue with their patients on this subject.

Despite the vast amount of lay literature regarding alternative therapies for relieving menopausal symptoms, there have been very few clinical trials performed on them. Ginseng, acupuncture and evening primrose oil have all been reported to decrease menopausal symptoms. However, there are insufficient data at this time to make any conclusions on their potential efficacy and safety for the treatment of symptoms in menopausal women.

Public interest in complementary and alternative therapies for the relief of menopausal symptoms continues to increase as many baby boomers are at this stage in life. Because of the 1994 Dietary Health and Education Act (DSHEA), there is currently no surveillance of safety or efficacy of nutritional supplements. Women are conducting uncontrolled trial on themselves when they take these compounds. This makes it more necessary for the clinical knowledge to continue to grow so that physicians will be able to better discuss and advise their patients on these topics.

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