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Review

The pros and cons of plant estrogens for menopause

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ABSTRACT

Concerns pertaining to the risk of estrogen exposure through HT have prompted an increase in the use of natural alternatives. Phytoestrogens may provide postmenopausal women with a practical alternative and many women have already begun to utilize phytoestrogen supplements. However, research regarding the efficacy of phytoestrogens as a hormone therapy alternative has been previously pessimistic or questionable at best. This review scrutinizes the most current research regarding the efficacy of three types of phytoestrogens, isoflavones, lignans and coumestans, and their specific effect on the reduction of climacteric symptoms, specifically vasomotor symptoms, vaginal atrophy, insomnia and osteoporosis. A discussion of the research pertaining to the relative safety of each phytoestrogen in terms of breast and endometrial health is also included. Overall, current research demonstrates that phytoestrogens are effective in reducing the intensity of hot flushes, and some phytoestrogen combinations result in a decreased frequency. Certain phytoestrogens have also been shown to decrease vaginal atrophy, improve sleep and cognition, and positively affect bone health. Even though initial research was generally unconvincing, the more recent evidence reviewed here is rather positive. In terms of safety and reports of adverse reactions, trials have not shown an increase in breast cancer risk or increase in endometrial hyperplasia following phytoestrogen use, but trials explicitly designed to find neoplasia have not been reported. Moreover, unlike hormone therapy, lignans may not increase clotting risk in postmenopausal women, thus supplements may serve as a treatment option for patients who have contraindications to hormone therapy. Phytoestrogens may provide a safe and partially effective alternative to HT. However, because research regarding phytoestrogens is relatively new, pharmaco-vigilence is still required, as these products are not yet FDA-approved.

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Contents

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1. Introduction

Menopause is inevitable. Advances in healthcare and public initiatives toward healthy living have increased the number of women in the menopausal age group. This exposure to age-related diseases presents not only a distinctive challenge for patients, but healthcare providers are called on to offer alternatives that are preventive and improve quality of life. The menopausal transition results from declining ovarian function and leads to dramatic decreases in estrogen, which is clinically seen as several physical and mental conditions including vasomotor symptoms, histological changes to estrogen sensitive tissues, dyspareunia, vaginal atrophy, increased risk of developing osteoporosis and insomnia. Because climacteric symptoms result from a decrease in estrogen it naturally follows, and has been clinically proven, that replacing estrogen through hormone therapy (HT) is effective against menopausal symptoms. HT is the most effective treatment for conditions faced by post-menopausal women and has consistently demonstrated to reduce both the frequency and intensity of hot flushes, is effective against vaginal atrophy and insomnia, and positively affects bone loss and risk of fracture. HT may also prevent cardiovascular disease.

Despite the above responses to HT, more than 80% of women who may benefit from it are unwilling or unable to undergo treatment due to various medical or personal reasons, including increased clotting risk, liver disease or fear of cancer [1]. Concerns pertaining to the risk of estrogen exposure through HT have prompted an increase in the use of non-steroidal estrogen mimetic agents. Food sources rich in phytoestrogens, or naturally occurring estrogen-like compounds found in plants, for example, may provide postmenopausal women with a practical alternative. Women have in fact already begun to utilize phytoestrogen supplements. Despite inconsistencies amongst the data, there is growing evidence supporting the efficacy of phytoestrogens in the reduction of menopausal symptoms. As the commercial popularity and availability of phytoestrogen supplements begins to grow, however, so does concern regarding safety of long-term exposure to levels exceeding those obtained from diet alone; phytoestrogen supplement tablets allow for the possibility of ingesting large amounts of phytoestrogens per day [2]. It is thus vital to assess data regarding both the efficacy and safety of phytoestrogen therapies. This review will assess isoflavones, lignans and coumestans; we will not specifically address soy protein, except to account for its use in conjunction with isoflavones. However, it is important to note that soy protein has been shown to have similar effects as soy and that most commercial products contain both soy and soy protein.

2. Biochemistry

The term phytoestrogen is generally used to define a class of compounds that is non-steroidal and is either of plant origin or metabolically derived from plant precursors [3]. Hundreds of foods have been shown to contain phytoestrogens. Most belong to one of three classes: isoflavones, lignans or coumestans. Isoflavones are found in beans from the legume family with soybeans and soy products being the major dietary source. Lignans are found in high fiber foods such as unrefined grains, cereal brans and beans, with flaxseed containing the largest amount. Foods containing the highest amount of coumestans include alfalfa and clover sprouts, with lesser amounts also found in split peas, pinto beans and lima beans [4]. Dietary consumption by national groups naturally follows agricultural patterns of growth and cuisines.

After the consumption of plant isoflavones, lignans and coumestans, enzymatic metabolic conversions occur in the gut, resulting in the formation of heterocyclic phenols; isoflavones are metabolized to aglycones, genistein and daidzein, lignans to secoisolariciresinol-diglucoside (SDG), and coumestans to coumestrol [5]. The breakdown products all contain the presence of a phenolic ring that can compete for binding to the "pocket" of estrogen receptors. These compounds thereby structurally resemble estrogen and have weak estrogenic activity; therefore they are termed phytoestrogens. However, all are selective estrogen receptor modulators and each has a profile of action of its own.

2.1. Phytoestrogens as selective estrogen receptor modulators

SERMs are defined as a group of compounds that behave like estrogen agonists in certain tissues, and like antagonists in others [6]. All estrogens, including steroidal estrogens, such as estradiol, and many xenobiotics are SERMs, and their properties depend on both the tissue in which they are acting, and the relative
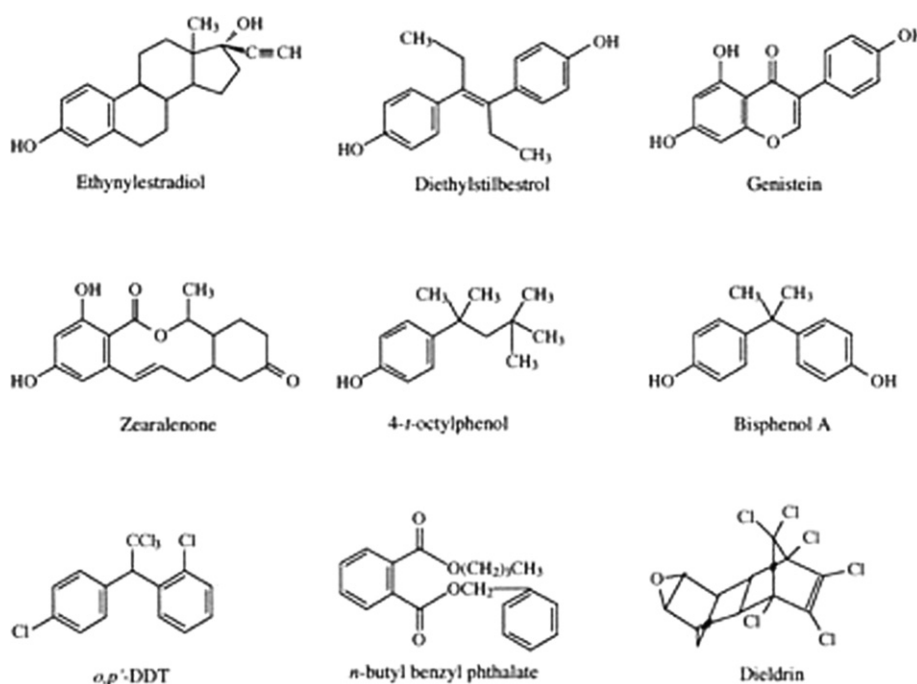
Fig. 1. Examples of reported SERMs; ethynylestradiol and diethyl-stilbestrol, phytoestrogens (genistein), mycoestrogens (zearalenone), industrial compounds (bisphenol A, 4-t-octylphenol and n-butyl benzyl phthalate), and pesticides (o,p′-DDT and dieldrin) [90].

Permission obtained from Cayman Chemical.

amount of other SERMs present. Many naturally occurring and synthetically derived SERMs are recognized today (Fig. 1). Tamoxifen and raloxifene serve as classic examples of SERMs with tissue-specific effects. For example tamoxifen serves as an antagonist in the breast and an agonist in the bones and uterus, while raloxifene serves as an antagonist in the breast and uterus and agonist in the bone. While tamoxifen is an effective treatment for all stages of hormone-responsive breast cancer, its partial estrogenic activity in the uterus is associated with an increased incidence of endometrial hyperplasia and cancer in this tissue [7]. Raloxifene, approved for the prevention and treatment of osteoporosis in postmenopausal women, also appears to prevent breast cancer, but does not increase the incidence of endometrial cancer. Brown et al. demonstrated that recruitment of either a coactivator or corepressor complex allows tamoxifen and raloxifene to retain different functions at a given tissue [8]. Because of these differing properties, when evaluating a SERM it is essential to be able to characterize it in the organ of interest, as well as in relation to the biochemical balance of competing SERMs. Moreover, for the sake of pharmaco-vigilence, it is vital to investigate the potential effects in other tissues than the tissue of interest for menopausal treatment. As SERMs, phytoestrogens possess compound-specific estrogenic/anti-estrogenic effect on various tissues, the details of which will be explored through this paper.

2.2. Resveratrol

Resveratrol is a natural phenol that is found in grape skin and a variety of medicinal plants. Because of its high concentration in grape skin, significant amounts of resveratrol are present in red wine. The effects of resveratrol have been proposed as a partial explanation for the apparent ability of moderate consumption of red wine to reduce the risk of cardiovascular disease [9]. Goldberg et al. found that platelets from human volunteers who consumed 2 mg of resveratrol per day showed diminished thromboxane B2 synthesis and reduced thrombin-induced aggregation compared with controls. This suggests that daily consumption of some red wines might produce pharmacologically significant serum concentrations of resveratrol [10]. In addition to these cardioprotective effects, several in vivo studies have demonstrated that resveratrol also carries anti-viral [11], anti-inflammatory [12], anti-diabetic [13], and neuroprotective [14] effects. Additional animal studies have also demonstrated its effects as a cancer preventative agent [15]. In many ways, resveratrol appears to act much like a modern "shmoo [16]," as it seems to be an ideal substance with multiple utilities and exists purely to improve and enhance human existence. And, much like Al Capp's shmoo, the mechanism through which resveratrol exerts its effects are not entirely clear.

Resveratrol is a phytoestrogen, as it has been shown to bind to the human estrogen receptor [9]. As a phytoestrogen, resveratrol is a SERM and its relative agonistic and antagonistic effects have yet to be fully elucidated. Some studies show that in the absence of 17β-estradiol, resveratrol demonstrates mixed agonistic and antagonistic effects in the breast, but in the presence of 17β-estradiol, it functions as an antagonist. Bhat et al. showed that in animal models, carcinogen-induced preneoplastic lesions and mammary tumors are inhibited with its use. This data suggest that resveratrol may have beneficial effects if used as a chemopreventive agent for breast cancer [17]. More recent research suggests that resveratrol exerts its cancer-protective properties through a combination of its interaction with the estrogen receptor as well as its role in tyrosine kinase signaling [18]. Resveratrol may prove to have promising effects regarding breast cancer, but further short and long term clinical research is required. No reports have appeared regarding effects on menopausal signs and symptoms.

2.3. Isoflavones

The most frequent sources of phytoestrogens used for the treatment of menopause are soybeans, which contain the highest amount of isoflavones. Studies demonstrate that isoflavones contain a phenolic ring in a position analogous to estradiol, the

predominant female hormone [19] (Fig. 1). Their structure allows isoflavones to fit the binding domain of the estrogen receptor, and thereby exhibit properties similar to endogenous estrogens. After soybean isoflavones are ingested they are hydrolyzed by intestinal enzymes to aglycones, daidzein and genistein, which may be absorbed or further metabolized by intestinal bacteria to other compounds, including equol. This metabolic pathway is clinically relevant since the estrogen-agonist potency of equol is an order of magnitude higher than that of its precursor, daidzein. Equol thus serves as the reference compound associated with the health benefits of isoflavone consumption [20]. However, the extent of equol formation is highly variable among individuals and can lead to individual outcomes; women are often classified as "non-producers" of equol if they lack the proper intestinal microflora to produce it [19]. Moreover, the intestinal microbiome can change depending on factors including diet, antibiotic use and illness, and thereby affect the equol-producing status of an individual. This makes the establishment of an optimal dose required to have clinical effect difficult, but it is generally believed that at least 40–70 mg/day of total soy isoflavones [20] or 50 mg per day [21] is sufficient. This dose is consistent with intakes in countries that consume soy as a staple, and is also the level at which clinical endocrine effects can be seen in premenopausal women [21]. Specific dose-response relationships as well as additional factors that govern individual absorption and metabolism remain to be established [22]. Long-term studies also are needed before the true value of equol is established.

2.4. Phytoestrogens vs. soy protein

Soy protein is isolated from the soybean during the usual process of preparing "soy." The distinction between soy protein and isoflavones is important because when consumers purchase soy products for health use they must know what they are purchasing; the consumption of different "soy" products may not yield the same results. Soy protein has beneficial health effects. Studies conducted by Clarkson et al. have shown these effects on the cardiovascular system [23]. In 1999 the U. S. Food and Drug Administration approved the recommendation of 25 g of soy protein a day (as part of a low fat and low cholesterol diet) to help reduce the risk of heart disease [24]. The effects of soy protein include a reduction in LDL cholesterol of roughly 13%, a reduction in plasma triglycerides of roughly 10% and a varying increase in HDL cholesterol with an average of 2% [23].

Research by Clarkson et al. has been conducted in an attempt to differentiate the effects of isoflavones and soy proteins on cardiovascular health. To distinguish the relative contributions of soy protein versus phytoestrogens for cardiovascular protection, they studied young male cynomolgus macaques fed a moderately atherogenic diet and randomly assigned to groups that received either a soy protein with isoflavone diet, or a soy protein diet without isoflavones. They concluded that the beneficial effects of soy protein on atherosclerosis appear to be mediated primarily by the phytoestrogen component, as the monkeys consuming soy protein with isoflavones developed the lowest LDL and highest HDL levels compared to monkeys consuming diets with the isoflavones removed [25]. While the mechanism of action of soy proteins remains a mystery, research has shown that isoflavones used in conjunction with soy protein yield more robust LDL-lowering effects [23].

2.5. Lignans

Among edible plant foods, flaxseed is the richest source of lignans, which are reported to have both weak estrogenic and anti-estrogenic activities [26]. During digestion the main lignan precursor in flaxseed, secoisolariciresinol diglucoside (SDG), is converted by colonic bacteria to enterodiol and enterolactone. Lignans and their metabolites function by interfering with sex hormone metabolism. They achieve this through stimulating hepatic synthesis of sex hormone binding globulin (SHBG), which decreases the clearance of circulating estrogens. Moreover, lignans and their metabolites bind estrogen receptors in a dose-dependent manner, thereby acting as SERMs [27]. A lignan in Femarelle® termed DT56a appears to be an ERα selective SERM [28]. As SHBG is found in breast cancer cells, the binding of lignans to SHBG may interfere with estrogen-mediated tumorigenic processes [27]. Additional studies indicate that flaxseed may also possess antioxidant properties and play a role in limiting osteoclast formation and bone resorption, thereby serving to reduce bone loss in postmenopausal women [6]. There are no long-term studies of lignan ingestion.

2.6. Coumestans

Foods such as alfalfa and clover sprouts contain the highest concentrations of coumestans [4]. Overall, consumption of coumestans is not as great as that of isoflavones and lignans. In fact, a study investigating the phytoestrogen content of twenty-one nonvitamin, nonmineral supplements commonly consumed by women found that coumestrol was either not present or present only in very small amounts [29]. Despite its relatively decreased prevalence in foods and supplements compared to isoflavones and lignans, several biochemical properties of coumestans have been elucidated. Once digested, coumestans are broken down into several compounds including coumestrol, which has strong affinity for the estrogen receptor. Coumestrol (as well as genistein) has been shown to preferentially bind to ERβ than to ERα [30]. Amongst several phytoestrogen metabolites studied (including genistein and daidzein), coumestrol was shown to have the strongest binding affinity for the estrogen receptor [30]; other studies showed that coumestrol binds to the estrogen receptor with an affinity only five- to ten-fold less than that of 17β-estradiol [31]. This relatively strong binding affinity for the estrogen receptor has led some researchers to postulate that coumestans are potentially the most potent phytoestrogen [4], however this has yet to be proven in clinical situations.

3. Clinical outcomes

The structural similarities to SERMs and resulting clinical implications have guided clinicians and women to select phytoestrogens as a practical alternative to hormone replacement therapy (HRT) during their climacteric transition. Isoflavones, lignans and coumestans each have estrogen-like properties, and isoflavones and lignans have been studied regarding their efficacy as a HRT substitute. Since phytoestrogens do not apparently induce endometrial proliferation [32–35], they are commonly taken without addition of a progestin. Results of these studies, though overall promising, are generally mixed, leading to concern about the efficacy and short and long-term safety of phytoestrogens. The following attempts to clarify the current findings for each of these phytoestrogens regarding their safety and ability to improve quality of life for menopausal women.

Currently, the literature regarding the efficacy of phytoestrogen use is difficult to evaluate because the majority consists of effectiveness research, rather than *comparative* effectiveness research between hormone therapy and phytoestrogens. Additionally, conflicting research also exists and may be related to an individual's ability to metabolize phytoestrogens effectively. Therefore, only the efficacy of individual phytoestrogens can be assessed.

3.1. Vasomotor symptoms

Hot flushes are one of the top reasons for women to seek hormone replacement therapy. They have a prevalence ranging from 22 to 74% in post-menopausal women [20]. Flushes are triggered by small temperature elevations acting within a reduced thermoneutral zone. This results in a heat-dissipation response that consists of peripheral vasodilatation and sweating on the face, neck and sternal area [36]. Flushes have a negative impact on quality of life and though more frequent and severe in the perimenopausal and early postmenopausal years, they are still important in 14.6% and 8.6% of women in their sixties and seventies respectively [20]. Therefore there exists a group of postmenopausal women who require long-term treatment. Moreover, women undergoing adjuvant treatment for breast cancer with either tamoxifen or aromatase inhibitors also suffer from vasomotor symptoms, and must elect a symptom relief regimen that does not hinder the effectiveness of their cancer treatment. Phytoestrogens can fill this need especially in light of the lack of known long-term complications.

3.1.1. Isoflavones and vasomotor symptoms

Studies demonstrating the relative efficacy of isoflavones in the management of vasomotor symptoms have been somewhat inconsistent, though overall promising. A recent meta-analysis of nineteen studies concluded that even though the overall combined results showed a significant tendency in favor of soy, it was still difficult to establish conclusive results given the high heterogeneity of the studies [37]. In a Cochrane review of phytoestrogen treatment of vasomotor symptoms for peri- and postmenopausal women, 30 studies were reviewed showing that soy extract preparations globally demonstrate mixed results; however, three placebo-controlled studies conducted from 2002 to 2008 showed a significant reduction in flush frequency: 61%, 74% and 50% compared with placebo (21%, 43% and 38% reduction respectively). Severity scores of hot flushes were inconclusive and differed significantly between trials [20]. This review also reported that significant improvements in vasomotor symptoms have been described in the more recent placebo-controlled trials with soy products. One such study in 2010 showed improvement of hot flushes equal to hormone therapy. In this double-blind, randomized, controlled trial 60 symptomatic, postmenopausal women aged 40–60 years were assigned to use daily dietary soy supplementation (containing 90 mg of isoflavone), low-dose hormone therapy (1 mg estradiol and 0.5 mg norethisterone acetate) or placebo for 16 weeks. Users of soy supplementation and hormone therapy faced a 49.8% and 45.6% respective reduction in hot flushes, indicating soy is an effective, and nearly equivalent, alternative therapy to low dose estrogen HRT [38]. However, since most studies show a greater reduction in hot flushes with hormone therapy, some approaching 90%, the near equal response between the two regimens could be an indictment of the effectiveness of low dose HRT.

Another systematic review and meta-analysis of hormone therapy and soy extracts related to the reduction of flushes in postmenopausal women versus placebo was conducted in 2010 by Bolanos-Diaz et al. They too conclude that HT and soy interventions are efficacious in reducing flushes in postmenopausal women compared to placebo; however using indirect comparison, they found a statistically significant different between HT and soy extracts in their respective effects on hot flushes. To depict this finding, a head-to-head comparative design study by Crisafulli et al. was analyzed. Results of this trial included a reduction of daily hot flushes by 22% after 12 weeks of a genistein concentrate treatment compared to a 53% reduction after 12 weeks of daily estrogen-progestogen therapy compared to a placebo [32]. This trial demonstrates that both interventions prove to be sufficient for vasomotor symptom relief, with hormone therapy being favored [39].

Conversely, other studies fail to show positive effects of isoflavones on vasomotor symptom relief. In an attempt to overcome the inadequacies of prior trials on soy products (including short duration, small sample size and poor design) the National Institute of Health funded the Soy Phytoestrogens as Replacement Estrogens (SPARE) study in 2004. This single-center, randomized, double-blind, placebo-controlled clinical trial assigned 248 healthy women with the onset of menopause within 5 years of enrollment to receive either daily soy isoflavones (200 mg) or placebo for two years. No significant difference was found between the soy group and placebo group regarding hot flushes, with 48% and 32% of women still reporting symptoms after two years [40]. Interestingly, this study did not attempt to differentiate between reduced frequency and reduced intensity of hot flushes after isoflavone use. However, studies that account for this distinction demonstrate a positive effect. For example, 169 postmenopausal women studied by Drews et al. reported a decrease in both frequency and intensity of their hot flushes after taking up to 104 mg of isoflavones per day [41].

3.1.2. Lignans and vasomotor symptoms

Trials exploring the effectiveness of lignans in the reduction of hot flushes have had mixed results. The most recent study from 2012 reveals both flaxseed and placebo were able to reduce hot flushes without a significant difference between these two treatments. A total of 188 postmenopausal women were assigned to consume a flaxseed bar (providing 410 mg of lignan) or a placebo bar daily for 6 weeks while recording daily flushes in a diary. At the conclusion of the trial, both groups showed slightly more than one third of women reporting a 50% reduction in their hot flush score [42]. Another study in 2010 displayed similar findings. Thirty-eight women who had been postmenopausal for 1–10 years were randomly assigned to consume bread containing 46 mg of lignans or bread containing <1 mg lignan (control) daily for 12 weeks. Both groups had significant but similar reductions in hot flushes after three months [43]. The remarkably durable effect of placebos on hot flushes raises question about the length of these studies.

3.1.3. Combined isoflavones and lignans and vasomotor symptoms

Some trials have studied the combined effect of isoflavones and lignans for the treatment of hot flushes. Notably, a trial conducted by Sammartino et al. assigned 80 recently menopausal women (last menses at least 6 months but no more than a year before enrollment) to receive either a tablet containing 60 mg isoflavones and 20 mg lignans or a tablet containing calcium (control). Flushes were then evaluated every month for three months. Patients receiving the phytoestrogen tablet had a significant reduction in flushes compared to placebo [44]. The authors postulated that the effect is likely due to the observation that isoflavones are absorbed early while lignans are removed later, leading to synergistic effect that results in a better reduction of vasomotor symptoms over a 24-h period [44]. Currently the nutritional supplement Femarelle® that contains roughly 322 mg soy extract and 108 mg flaxseed powder is commercially available. A 2004 study demonstrated its efficacy in vasomotor symptom reduction as women who received the standard and low dose experienced a 76% and 78% reduction of vasomotor symptoms, respectively, after 12 months of treatment [45].

3.1.4. Conclusions

Despite the presence of conflicting (mostly older) trials, there is evidence that soy extracts overall are beneficial in vasomotor symptom relief for postmenopausal women. Short-term studies that demonstrate no difference between isoflavones and placebo for the relief of hot flushes, such as the SPARE trial, must be reviewed with

care. As well, this trial included women whose last menses was up to five years before enrollment. Hot flushes predominate during the first two postmenopausal years, and decline to an incidence of roughly 20% after four years [46]. As such, an improvement over time can be expected without medical intervention. Some studies have taken this phenomenon into account and have attempted to control for it, specifically the above-mentioned trial by Sammartino et al. This trial included only women who had recently entered menopause, and the combined effect of an isoflavone and lignan supplement showed a significant reduction in flushes compared to placebo.

Dietary lignan supplements do not demonstrate a strong correlation to symptom relief but this is perhaps related to a lack of existing well-designed trials. Given their apparent efficacy when used in combination with isoflavones, further studies could demonstrate their relative benefits in that regard. Evidence demonstrating the effectiveness of isoflavones and lignans in reducing vasomotor symptoms when taken in combination continues to be promising. The effect of coumestans on vasomotor symptom relief has yet to be studied, and their combined effect with isoflavones and lignans is a topic that warrants exploration.

More importantly, most studies look at hot flush frequency as an endpoint for evaluating the effectiveness of phytoestrogens in reducing vasomotor symptoms. This is perhaps why some studies demonstrate conflicting results. Trials that focused on the reduction of the intensity of hot flushes are more consistent, and suggest that phytoestrogens are effective at attenuating, rather than alleviating vasomotor symptoms in postmenopausal women. While measuring a decrease in frequency may be easier for an investigator and participant to measure, the relative intensity of a hot flush may be more important to evaluate in terms of lifestyle, and future research should take into account this distinction.

3.2. Vaginal atrophy

Vulvovaginal atrophy results in vaginal dryness, irritation, itching, dyspareunia and urinary incontinence. Atrophy is common amongst postmenopausal women, with prevalence ranging from 10 to 50% [47]. A lack of circulating estrogen and a resulting adverse effect on collagen and elasticity underlies vulvovaginal atrophy experienced by women in menopause. The dryness and decreased lubrication can lead to painful intercourse, resulting in women losing interest in sexual activity. Roughly 57% of sexually active menopausal women experience atrophy and 55% experience sexual dysfunction [47]. This can dramatically affect a woman's quality of life and negatively affect their sexual health. As such, women may rely on a form of estrogen replacement for relief. While trials of HRT continue to show a positive effect on vaginal atrophy, studies on phytoestrogens are mixed [48].

3.2.1. Isoflavones and vaginal atrophy

In a 2005 report, sixty-four postmenopausal women with a history of breast cancer were randomized to a treatment arm in which tablets containing 114 mg of soy isoflavonoids were taken daily for 3 months, or to a placebo arm. The treatment regimens were crossed-over after a 2-month washout period, and the participants were studied before and on the last day of each treatment period. At the end of the trial, isoflavones did not relieve vaginal dryness, and the maturation index of the vaginal epithelium remained unchanged. Contrastingly, in the placebo group the maturation index decreased. This suggests that there may exist a differential effect of soy on advancing atrophy of the vagina, which netted no significant treatment difference [33]. Results from a trial in 2006 are similar. In this randomized, cross-over trial thirty-six menopausal women whose periods had ceased at least three months prior to enrollment were assigned to either a soy-free or soy-rich (more

than 50 mg isoflavones per day) diet for two 12-week periods with two 4-week washout periods. The amounts of soy protein are not known. At baseline, the enrolled subjects experienced at least one urinary or genital symptom owing to atrophy. At the conclusion of the trial, urogenital status did not change in either period, as measured by vaginal pH, vaginal health index, karyopyknotic index and maturation index. Despite this, the symptoms of urge incontinence and vaginal dryness had significantly increased after 12 weeks of the normal diet [49]. While neither of these studies demonstrated a positive effect of isoflavones on vaginal atrophy, both imply at least a mild protective effect, demonstrated by a worsening of dryness or vaginal epithelium maturity in the placebo groups.

More recent research and opinions indicate that a longer period of phytoestrogen exposure is necessary to illustrate positive effects on vaginal epithelium and resulting dryness [50]. Chiechi et al. analyzed the effects of a 6-month soy-rich diet on the vaginal epithelium of 187 women whose menses had ceased at least six months prior to enrollment. Subjects were randomized to either 6 months of a soy-rich diet (at least 20–30 mg soy per day, the amounts of soy protein are not known), hormonal replacement group or a control group. The results showed an improvement in both the maturation and karyopyknotic index in both the diet group and hormonal replacement group [51]. Similar results were observed in a trial in which 60 symptomatic postmenopausal women were allocated to use dietary soy supplements (90 mg isoflavones, the soy protein is not stated) or HRT or placebo. After 16 weeks of treatment, urogenital symptoms improved significantly in HRT users (decreased 38.6%) and soy supplement users (decreased 31.2%). The placebo group did not exhibit improvement [38].

3.2.2. Combined isoflavones and lignans and vaginal atrophy

Recently a pilot study of Femarelle®, the combined isoflavone and lignan supplement, investigated the efficacy of this phytoestrogen combination on vaginal epithelium. Twelve postmenopausal women were treated with 322 mg Femarelle® twice a day for 12 weeks. A Bachmann vaginal atrophy assessment, vaginal pH and quality of life questionnaires evaluated patients' vaginal atrophy and its resulting symptoms both objectively and subjectively. All patients reported improvements in overall quality of life, sexual quality of life and their most bothersome symptom related to vulvovaginal atrophy after twelve weeks. Additionally, vaginal pH changes improved to statistically significant values at four weeks and continued to improve through the twelfth week, and a significant improvement in the maturation index in 10 out of 12 women was observed [52].

3.2.3. Conclusions

As discussed above, SERMs have different profiles of action in the body. It appears that the combined profiles of isoflavones plus lignans could be favorable to genital tissues. While limits of the Femarelle® study include a small patient population and relatively short duration, the established promising effects of a combined isoflavone and lignan intervention for atrophy are apparent and warrant further exploration. In terms of isoflavones, short-term use suggests at least a protective effect, and positive effects become apparent with more prolonged usage. No studies investigate the effects of isolated lignans or coumestans on postmenopausal vaginal atrophy; additional studies comparing either the isolated or combined effects of these compounds are necessary to further clarify the overall effect of phytoestrogens on vaginal epithelium.

3.3. Central nervous system

Sleep is another aspect of quality of life that undergoes changes during the menopausal transition. Post-menopausal women have a greater number of sleep disturbances compared to premenopausal

ones, frequently displaying less than six hours of sleep per night [53]. Additionally, menopausal women are more likely to report increased fatigue or difficulty in initiating and maintaining sleep [53]. Polysomnographic findings indicate that menopausal women display longer total wake time and lower sleep efficiency than premenopausal ones [54]. Studies have reported HRT to improve sleep patterns [55,56]. Despite this, caution has been recommended not to attribute menopause as the sole causative role for sleeping disorders, as sleep patterns are often attributable to a collection of other factors including psychological distress, headaches, dizziness, palpitations, depression and weight gain [53,57].

Because sleep is related to a variety of causes, studies attempting to control for these factors may be difficult to design; thus there is little research regarding the efficacy of phytoestrogens and sleep disturbance. Though limited, the existing data implies a positive effect of phystoestrogens on insomnia and cognitive function.

3.3.1. Isoflavones and sleep

In 2011 a controlled, double-blind study placed postmenopausal women with insomnia into groups receiving either 80 mg isoflavones or a placebo daily for four months. Polysomnography confirmed a significant increase in sleep efficiency in the isoflavone group at the conclusion of the study; among women in the placebo group, 94.7% had moderate or intense insomnia at the beginning of the study compared with 63.2% at the end, whereas in the isoflavone group the percentages were 89.5% and 36.9% respectively [58]. A study in 2007 likewise showed a diminishment of sleep disturbances and intensity of tiredness after use of either 52 mg or 104 mg of isoflavones for 12 months [41].

3.3.2. Lignans and cognition

Lignans have demonstrated effects on cognition. A cross-sectional study involving 301 women ages 60–75 years examined the relationship between isoflavone and lignan intake on memory, processing capacity and speed, and executive function. While no association was found between dietary isoflavone intake and cognitive function, high lignan intake was associated with a better performance in processing capacity and speed, and executive function [59].

3.3.3. Conclusions

These studies in combination reveal encouraging data regarding the efficacy of phytoestrogens in the relief of symptoms related to sleep and cognition. No data exists in terms of the effects of isolated coumestans in this regard, and this, as well as trials examining the combined effects of phytoestrogens compared to traditional HRT, merits investigation. As with all of these matters, long-term studies are needed.

3.4. Bone health

Decreased bone mineral mass is another morbidity faced by menopausal women. Rate of bone mass loss in women accelerates to 2–5% per year during early menopause then tailing off, leading to a higher risk of osteoporosis and fractures later in life [40]. Available pharmacological agents for the management of postmenopausal osteoporosis include oral bisphosphonates, hormone therapy, other SERMs and calcitonin. However, these regimens are not appropriate for all women. Oral bisphosphonates are generally considered first line therapy for patients with osteoporosis but may be limited by their gastrointestinal side effects and other side effects [60]. HRT, the most effective treatment, has been side-lined by the WHI trial. Phytoestrogens have received attention as a possible alternative therapy for the management of bone loss in patients unwilling or unable to undergo standard beard treatment regimens. It is postulated that the beneficial effects of phytoestrogens on bone

health result from increased bone formation by osteoblasts. Though exact mechanisms remain unclear, this phenomenon is partially explained by the presence of estrogen receptors on osteoblastic cells, to which genistein has been shown to bind [60].

3.4.1. Isoflavones and bone health

Regarding isoflavones, as of a decade ago, a limited number of small, short-term clinical studies had examined the effects of soy and soy protein on bone mineral density (BMD) or other indices of bone turnover. These studies produced mixed and inconclusive results [6]. Explanations for the inconsistencies included differences in menopausal status, age, inadequate doses of isoflavones and relatively short duration of isoflavone treatment. Several studies suggest that at least one year is required to observe significant changes in BMD and the clinical studies published then did not come close to this time period [6]. And, in fact, studies of the past ten years that followed patients for longer time intervals tend to demonstrate a beneficial effect of isoflavones on BMD. Some trials have not shown a favorable effect. One such study was the previously mentioned short-term SPARE (Soy Phytoestrogens as Replacement Estrogens) trial. After two years, both women receiving either placebo or 200 mg daily isoflavones had an approximate 2% decline in bone density. Additionally, subgroup analysis did not indicate benefit in women who were determined to be equol producers [40,61]. Contrastingly, a two-year study in which postmenopausal osteopenic Italian women were given less daily isoflavones (54 mg per day) showed an increase in spinal BMD by 5.8%, whereas users of a placebo faced a decrease of 6.3%. Similar effects were noted at the hip and differences between groups were even greater during the 3rd year of the study [62].

Despite a small number of contrasting studies, when the recent data is pooled and scrutinized via meta-analyses, the benefits of isoflavones on bone mass are clear. A Cochrane review and literature search performed in 2010 found that most studies imply a positive relationship between isoflavones and bone health of both peri- and postmenopausal women. Data collected in this analysis indicated a daily dose of at least 90 mg for at least six months to be effective [60]. A more recent review through 2011 affirmed the notion that six months of treatment is sufficient for benefits to manifest in isoflavone users, and further suggest that benefits may be specific to skeletal areas. Specifically, isoflavones significantly improved lumbar spine BMD in a moderate manner, but did not affect total hip, femoral neck, and trochanter BMD in menopausal women [63,64]. In contrast, nothing is known of the effect of soy protein on bone health.

3.4.2. Lignans and bone health

Regarding flaxseed and its derivatives, existing research indicates a possible benefit on bone health, but this is not necessarily attributable to the lignan component. It has been theorized that due to structural similarity to the SERMs estradiol and tamoxifen, lignans should demonstrate similar beneficial effects on bone density [65]. Additionally, as described above, lignans present in flaxseed may possess antioxidant properties. Oxygen-derived free radicals have been reported to increase in chronic inflammatory diseases, including osteoporosis. Both in vivo and in vitro findings indicate that these free radicals enhance osteoclast formation and thereby facilitate bone resorption. Thus flaxseed may in part counter the rapid rate of bone loss experienced by postmenopausal women by enhancing antioxidant status [6]. However, in clinical trials these hypotheses have not yet been proven. In 2001 Arjmandi et al. assigned sixty postmenopausal women to receive either 40 g flaxseed or a placebo for three months, at the end of which no effect on BMD was demonstrated [6]. Similarly, in 2005 Dodin et al. gave 199 women either 40 g flaxseed or a placebo daily for 12 months and found no difference in BMD between groups at the

trial's conclusion [66]. More recently, studies have indicated that the potential positive effects on bone demonstrated by flaxseed may be due to components other than lignans; alpha-linolenic acid, a major constituent of flaxseed, may decrease bone resorption rates by inhibiting the synthesis of prostaglandins [67]. In 2011, a literature review concluded that supplementation with flaxseeds may contribute to some improvement in osteoporotic bone properties but the bone-protective effect may be attributed to alpha-linolenic acid, and not to the lignan fraction [68].

3.4.3. Coumestans and bone health

Less research exists regarding the effect of coumestans on bone health, but studies in rats have shown that coumestrol can enhance bone marrow stem cell differentiation toward osteoblast progenitors [69]. Moreover, coumestrol was also shown to decrease bone loss in oophorectomized rats after one week of treatment, though not as strongly as those treated with estrogen [70].

3.4.4. Conclusions

Overall, phytoestrogens positively affect bone health. For the effects of isoflavones to be seen, long-term use of at least six months seems to be required. Research concerning flaxseed has also shown protective effects on bone, but this appears to be due to alpha-linolenic acid rather than lignan components. Regarding coumestans, animal models demonstrate a positive effect on bone health through increased synthesis of osteoblasts and decreased bone resorption. Further studies are warranted regarding the effects of coumestans on humans, as well as longer-term research concerning the effects of various components of flaxseed.

3.5. Breast cancer

The potential risk of breast cancer or its recurrence is of concern in the use of any SERM. While phytoestrogens could increase breast cancer risk, the tissue-specific dependence of SERM's actions on tissues makes this association less certain [71]. However, because of their antagonistic effects on tamoxifen and anastrozole in women with breast cancer, some have recommended that isoflavones be avoided in patients taking these drugs [19]. There is no support for this view in the literature. The historically low breast cancer mortality rates in soy-consuming countries in Asia have led to postulations regarding the potential cancer-protective effects of phytoestrogens [72]; isoflavones act through various mechanisms by which they may be cancer protective including antiproliferative effects [73], tyrosine kinase inhibition [74], induction of apoptosis [75], and inhibition of angiogenesis [76].

3.5.1. Isoflavones and breast cancer

In 2011 the North American Menopause Society held a symposium to cover the latest evidence-based science on the role of isoflavones in menopausal health. They found that soy foods generally appear to be breast cancer protective and recommended moderate lifelong dietary soy consumption as part of a healthy lifestyle. Soy food consumption is associated with lower risk of breast and endometrial cancer in observational studies, and soy food consumption or intervention in women does not promote breast cancer growth or cancer recurrence. However, specific recommendations regarding breast cancer survivors and soy or isoflavone consumption could not be reached, as studies in humans imply a null or protective effect, whereas animal studies indicate potential for risk [77]. A recent literature review focused on four epidemiological studies that reported protective effects in Asian-American women. The reductions in risk ranged from 28 to 60% if soy consumption occurred in early childhood and/or adolescence [72]. Additional reports suggest that this association is stronger in women who have high soy intake over ten years [34].

Regarding breast cancer patients, recent research has suggested that clinicians no longer need to advise against soy consumption for women with treated breast cancer [78]. After reviewing food questionnaires from 3088 breast cancer survivors in the Women's Healthy Eating and Living (WHEL) study, Caan et al. became the third group to report no adverse effects of soy food intake, either alone or in combination with tamoxifen, on the incidence of breast cancer recurrence or total mortality [78–80]. Rather, they found a trend toward lower mortality with increasing soy intake that did not differ by the breast tumor hormone receptor status [78]. The Shanghai Breast Cancer Study demonstrated a lack of tumor-promoting effect in breast cancer patients. In this study dietary soy consumption by breast cancer survivors was associated with significantly lower risk of recurrence and death ($P < 0.01$) [79]. Similar findings were encountered in western US women and women receiving anastrozole therapy in the Life After Cancer Epidemiology trial; in these trials the consumption of isoflavones before diagnosis was not associated with adverse effect on survival [80,81].

3.5.2. Lignans and breast cancer

Less data exists regarding lignans, but a lack of increased breast cancer risk has been observed. Similar to the effects of isoflavones, a prospective study in 2007 found a decrease in breast cancer risk with dietary lignan intake. They followed 58,049 postmenopausal French women (who were not taking isoflavone supplements) for a median of 7.7 years and found that subjects in the highest quartile of lignan intake (>1395 mg/day) had a reduced risk of ER- and PR-positive breast cancer ($P = 0.02$) [82].

3.5.3. Coumestans and breast cancer

Clinical data concerning coumestans and breast cancer risk is very limited. One prospective population-based cohort study of 45,448 pre- and postmenopausal women found that intermediate levels of coumestrol intake were associated with a decreased risk for receptor-negative breast tumors. However, the authors of this trial were not convinced that this finding was true as there was a relatively low intake of coumestrol-containing food in the study population. The authors proposed that the low level of coumestans consumed was not likely to furnish sufficient estrogenic activity to compete with endogenous estrogens and that the seemingly protective effect of coumestrol may have been due to chance [83].

3.5.4. Conclusions

Limited trials depict either a null or protective effect of phytoestrogens and breast cancer risk and recurrence rates. In regards to isoflavones, long-term dietary intake of soy may offer a protective effect, and in breast cancer survivors soy consumption does not affect recurrence rates. Though less data exists regarding the effects of lignans and coumestans, research is consistent with a protective effect. For breast cancer patients, current research regarding the concomitant use of soy and tamoxifen or anastrozole intake suggests that anti-estrogenic effects are not antagonized. Overall, though current research is promising, studies in this area are lacking and are needed to truly assess phytoestrogen effects on breast cancer recurrence.

3.6. Endometrial health and safety

Before definitive recommendations can be made to patients regarding phytoestrogen use, a careful review of their safety profiles must be obtained. As SERMs, the effects of phytoestrogens on the endometrium warrant vigilant scrutiny. Uterine endometrial cell proliferation is fostered by estrogen and inhibited by progesterone; clinical studies have shown that exposure to estrogens increases the risk of endometrial hyperplasia and carcinoma [34]. Tamoxifen serves a an example of a SERM that was initially praised

for its anti-cancer effects at the breast; only years later did clinicians and researchers realize that its use increased the risk of uterine hyperplasia and subsequent cancer. Now the American Cancer Society lists tamoxifen as a known carcinogen [84]. Women considering phytoestrogen therapy as a treatment for their climacteric symptoms may be cautioned, however studies have yet to demonstrate harmful uterine effects. In fact, most of the studies reviewed here suggest a minimal health risk associated with phytoestrogen supplementation.

3.6.1. Isoflavone safety

In general, as analyzed by a meta-analysis of randomized trials published in 2009 [20], short-term studies show no serious side effects with isoflavones. As an example, a study of sixty-four postmenopausal women concluded that 114 mg of daily isoflavones did not cause any objective endometrial findings after three months [32], and studies following the use of 54 mg isoflavones daily for up to one year similarly showed no negative impact on endometrial thickness [32]. Recent longer-term studies did not report any adverse endometrial effects in postmenopausal women who received up to 70 mg isoflavones daily for 3 years [34]. Further, a case-controlled study concluded that some isoflavones, specifically genistein and daidzein, at the levels consumed in the typical American-style diet, are associated with reduced risk of endometrial cancer (OR = 0.67, 0.68 respectively) [35].

Despite the seemingly overwhelming lack of proliferative effects of isoflavones, isolated case reports of abnormal uterine bleeding and proliferative endometrium have been reported [34]. Additionally, a study looking at daily isoflavone use for five years demonstrated six cases out of 298 women with endometrial hyperplasia. All cases occurred in the fifth year of treatment [20]. This suggests that isoflavones could stimulate the endometrium after long-term use. A literature review performed in 2010 analyzing twenty years of soy research found that only the incidence of gastrointestinal disturbances might be higher in soy consumers. These disturbances included changes in stool caliber, constipation, bloating and nausea [72]. Concerning other safety aspects, most studies failed to show serious side effects.

3.6.2. Lignan safety

Lignans also have a good safety profile. Like isoflavones, some studies suggest a protective effect of lignan consumption on endometrial cancer risk. Lignans were associated with a reduced risk of endometrial cancer [35]. However, not all studies exhibit this association. After reviewing food frequency questionnaires from a total of 424 women with endometrial cancer and 398 controls, Bandera et al. found only limited evidence of an association with lignans and decreased cancer risk [85]. Even though a protective relationship was not established, it is important to note that lignan use did not demonstrate an increase in risk. Regarding their side effect profile, like isoflavones, lignan study patients mainly reported gastrointestinal effects. This is likely related to their fiber content [86]. Additionally, a recent study of Femarelle® (a combined isoflavone and lignan supplement) also demonstrated a lack of effect on platelet reactivity in normal or thrombophilic postmenopausal women [87]. This shows that unlike traditional estrogen therapies combined isoflavone and lignan supplementation fail to demonstrate an increased clotting risk.

3.6.3. Coumestan safety

Less data exists regarding the safety profile of isolated coumestan use; effects appear to be similar to those of lignans and isoflavones. Coumestrol intake was not associated with changes in endometrial cancer risk [35]. Similarly, the study conducted by Bandera et al. did not find an association between coumestan-containing foods and increased risk [85]. Moreover, in models of

ovariectomized rats, coumestrol does not cause endometrial hyperplasia [88]. The limited number of studies of isolated coumestan supplementation makes risk assessment difficult. Future studies will elucidate their full side effect profile.

3.6.4. Conclusions

In general, phytoestrogen use appears to be very safe. In all of the literature reviewed, few side effects were reported, the most serious of which related to gastrointestinal discomfort. Moreover, specific compoundings of phytoestrogens lack some of the negative effects seen with hormone therapy, as in the case of Femarelle®'s protection against thromboembolic markers and events [87]. Overall, there is little evidence that phytoestrogens cause endometrial hyperplasia or other adverse health effects when used at usual doses for a short period of time in postmenopausal women [34]. On the contrary, a few existing studies imply a protective effect of isoflavone and lignan use and endometrial cancer risk. While endometrial hyperplasia has been reported after five years of use, this is not clearly related to phytoestrogen consumption. The available studies should not serve as an absolute contraindication to phytoestrogen use; moreover, a lack of increased thromboembolic risk may make phytoestrogen use appealing to both clinicians and patients since the same compound has been shown to ameliorate menopausal symptoms, as described above.

4. Summary

In order to derive conclusions regarding the efficacy and safety of an alternative to HRT for postmenopausal women, the effects of phytoestrogens on specific climacteric symptoms were individually explored.

- Regarding hot flushes, while past studies displayed mixed results, more recent publications demonstrate an improvement in symptoms, especially intensity, with isoflavone use. The effects of isolated lignans on hot flushes are mixed, and no data was found regarding the effects of coumestans. The most promising results are seen with the supplements containing both isoflavones and lignans, as demonstrated by the Femarelle® study in 2004 [45].
- Femarelle® is similarly promising in terms of vulvovaginal atrophy, as demonstrated by a recent pilot study. Isoflavones have also been shown to have a positive effect on vaginal epithelium after prolonged use.
- In regards to benefits for sleep and cognition, studies are limited but isoflavones have demonstrated moderate benefits for insomnia and use of lignans has shown improvements in various aspects of cognition.
- Regarding bone health, after at least six months of use, positive effects on bone are seen, though preferentially in the lumbar spine.
- Prolonged use of isoflavones, especially during adolescence, has been shown to correlate with a decreased risk of breast cancer. Less data exists regarding the effects of lignans and coumestans, but a protective effect has been suggested. Importantly, neither an increased risk amongst current breast cancer patients nor an increase in recurrence rates in survivors was demonstrated in the studies reviewed.
- Endometrial cancer risk also was not increased with use of any phytoestrogen, and some studies suggest a possible protective effect with combined isoflavone and lignan use. Aside from rare incidences of endometrial hyperplasia, which may not be different from the prevalence in the general population, only gastrointestinal side effects were reported with phytoestrogen use. Moreover, recent trials of Femarelle® demonstrated a lack of

hypercoagulability risk, unlike HRT, making phytoestrogen combinations a more appealing option for certain patients.

After extensively reviewing the literature, several interesting and important points were noted that may help guide future studies. Regarding vasomotor symptoms, several studies found that a placebo appears to be as effective as phytoestrogens in reducing symptoms. This improvement may be expected to a certain extent, as hot flushes generally diminish over time in frequency and severity without the aid of therapy. By focusing on studies that only include women who have entered menopause within a year, such as the study conducted by Sammartino et al., a significant benefit is seen with a combined isoflavone and lignan supplement compared to that demonstrated by a placebo [44]. Additionally, studies focusing on the reduction of hot flush intensity and not purely frequency will likely show a stronger effect, as this appears to be the mechanism through which patients experience relief with phytoestrogen use.

Another important point is that studies investigating soy use did not distinguish between the effects of soy proteins from isoflavones. It would be expected that studies in which participants received a dietary soy element, as opposed to pure isoflavone supplements, were receiving both soy protein and isoflavones, and perhaps the benefits that resulted were due to a complementary effect of both materials. Perhaps future studies should examine the relative effects of each compound both separately and simultaneously.

Even if the above-mentioned factors are accounted for, we do not yet fully possess the means to identify which women will actually receive benefits from phytoestrogen use. As partially explored in this review, differences may be due to an individual's ability to metabolize phytoestrogen compounds, as determined by their unique intestinal microflora. Additionally, many factors such as diet, smoking, antibiotics and obesity may affect the relative amount of circulating phytoestrogen levels in the body [89]. Regardless of their potential differences, phytoestrogens in general have shown to be beneficial for several of the symptoms faced by postmenopausal women. While the effects of isolated isoflavones, lignans and coumestans in treating climacteric symptoms previously ranged from speculative to encouraging, current research is sufficiently conclusive that findings are positive, and the most promising effects seem to arise when a combination of phytoestrogens, such as Femarelle®, is used. Because research on isolated or combined phytoestrogens is relatively new, comparative effectiveness research in which phytoestrogens are directly compared to hormone therapy is warranted. Importantly, all of the studies reviewed here have indicated that phytoestrogen intake is without serious adverse events. This is fortunate for clinicians because recommending their use is unlikely to lead to harm. Phytoestrogens appear to serve as a reasonable alternative to hormone therapy for postmenopausal women and deserve further research and consideration for therapy.

Acknowledgement

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