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Review Article

Current Status of Anti-Aging Medicine, Especially Involving Management of the Menopause, as a Component of Complementary and Alternative Medicine in Korea

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Abstract

Recently, many developing countries have had changes in the composition of population and have become aging societies. Therefore, anti-aging medicine which is believed to have beneficial effect on the risk factors of geriatric associated diseases has been paid much attention. Complementary and alternative medicine (CAM) has been widely accepted by the general population, and is consequently known to account for a large share of health care costs in many countries.

Hormone therapy (HT) is the gold standard to alleviate menopausal symptoms, but only 2.3% of Korean menopausal women are on HT. Many other women seek alternative means, including Korean traditional medicine, phytoestrogen-containing products such as black cohosh, soy (isoflavone), Dong quai, Ginseng, and evening primrose oil. Bioidential hormone therapy (BHT) is HT with individually compounded recipes of steroids in various doses. Its efficacy is yet to be confirmed and the risks of developing endometrial hyperplasia and breast cancer have been reported. Other CAM methods involving lifestyle and behavioral interventions include exercise, calorie restriction, weight reduction, and ‘mind-body medicine (homeopathy).’ Dermatologic, plastic, and ophthalmologic interventions have been introduced through the exhibition, as well.

Physicians have ignored this novel trend of patients preference to ‘natural hormonal therapy,’ however, they should be aware of the pros and cons of CAM and be able to guide their patients to make right choices. Clinical trials, and the evaluation of every CAM practice should be undertaken.

KEY WORDS: anti-aging, complementary and alternative medicine, CAM, bioidentical hormone

Introduction

Aging occurs gradually throughout one’s lifespan because of the apoptosis and down-functioning of cells which make up the body. These ‘aged’ cells have low metabolic rates and somehow lose their ability to divide. During the process of aging, the elderly usually suffer from chronic diseases, which can be relieved with proper preventive solutions or treatments focusing on painful symptoms. Postponing clinical illness, as proposed by Fries 1), requires staying in a good state of health by reducing painful periods before death. The main aim of health improvement is to live a relatively healthy life and compress our illnesses into a short period of time just before death 2).

Recently, many developing countries have been transformed into an aging society. In Korea, the percentage of the population which is elderly was 7.1% at 2000, and estimated to be more than 14% in 2022. This increase in the elderly population and the accompanying health problems poses an economic threat to society 3).

The change in the composition of the population toward an aging society has had a great impact on the healthcare system. Anti-aging medicine, which can neutralize risk factors for geriatric-associated diseases (e.g., cardiovascular diseases, diabetes, cancers, senile Alzheimer’s, and arthritis), has emerged and influenced the health behavior. Therefore, ‘anti-aging’ is one of the most important issues in society. The Anti-Aging Expo was held in Seoul on July 2009. This exhibition had such a positive influence. Many categories of products and services were presented. For instance, medical markets presented anti-aging plastic surgery, skin management, and general health screening. Pharmaceutical companies displayed generic diet supplements, such as coenzyme Q10 (COQ10), urso-deoxy- cholic acid, and glucosamine. Moreover, certain biotechnology corporations advertised stem cell techniques, penile implants for men following prostate surgery, milk products containing growth hormone, blood-glucose-level-reducing rice, donepezil, fillers, and various other goods for the elderly. Through the Expo anti-aging medicine proved itself as a medicine of the future. Throughout the Expo, it was the complementary and alternative medicine (CAM) which received most of the attention. A number of goods, the effects and side effects of CAM which have not been demonstrated yet, were vigorously advertised there.
Although these therapies are unproven in every aspect, CAM has become more and more popular around the world. Recent surveys show that CAM is widely used in Korea, with usage rates ranging from 29%-53% among various patient populations. CAM also accounts for a large share of health care costs. Such a trend appears to be a ubiquitous phenomenon. An estimated 5.75 million people per year in the United Kingdom visit to the complementary practitioner for treatment and ten million per year use some form of CAM and about 1.6 billion pounds is spent on CAM. Four studies have examined the use of CAM by older adults. The use of CAM in the United States varies from 30%-64% and in Japan it is more frequent than in the United States.

For unknown reasons, many people have unfounded beliefs about CAM. Countless menopausal women are hoping for the next ‘black cohosh agent’ instead of seeking traditional medications from their gynecologists. Indeed, conventional medicine suggests that such women should take hormone therapy (HT). Because the benefits of HT are overlooked and drawbacks are extremely exaggerated among people, they easily fall into an erroneous assumption that HT is harmful. On the other hand, CAM, including phytoestrogens, is believed to be safe, regardless of the lack of information (the drawbacks, and in some cases, even the benefits are unknown).

Physicians tend to be unaware of their patients’ use of these therapies. Considering this peculiarity of the health care market structure, doctors should understand their patients’ preference for CAM over conventional medicine. They also have an obligation to make people understand that the majority of anti-aging medications, including CAM, does not have any scientific or medical basis, and in addition to everything else, the process of aging itself remains a mystery which we just begun to unravel and understand. This act will eventually prevent potential dangers and the unnecessary expenditure on CAM. Nevertheless, there are a few promising therapies among the numerous bogus anti-aging therapies.

In this paper we will examine strategies of alternative anti-aging medicine from a gynecologic point of view in terms of the management of menopausal women.

Methods

The literature was searched in the following databases to locate English language published trial results and systematic reviews: Medline (Pubmed), KMBASE, Cochrane, the National Centre of Complementary and Alternative Medicine (NCCAM). Most of the literature has previously been cited elsewhere many times. The search strategy was constructed by using a combination of subject headings and text words relating to CAM for menopause, or anti-aging for woman. The search terms used include ‘complementary,’ ‘anti-aging,’ ‘estrogen replacement therapy,’ ‘phytoestrogen,’ ‘bio-identical hormone therapy,’ ‘hot flushes,’ and ‘alternative.’

The preference and understanding of Korean people was searched in websites, including ‘naver.com,’ ‘Miznet.daum.net,’ ‘miiclub.com,’ and many hospital homepages.

Results

As society increases in age, the female and male climacterium will become important issues in health care. In 2015, 45% of women in the US will be 45 years or older, thus they will spend one-third of their life after the loss of reproductive activity. In the menopause, female hormone levels are lower than before menopause.

Not only the reproductive system, but also the cardiovascular (e.g., coronary artery) and musculoskeletal systems (e.g., bone loss prevention) are influenced by female hormones. Female hormones are also known to regenerate skin, modulate pain sensitivity via opioid receptors in the brain, and govern the metabolism of certain drugs. These various functions of female hormones are necessary for women to maintain their health status, in addition to playing a key role in slowing the aging process.

HT is the gold standard and has been routinely prescribed for alleviating various menopausal symptoms, such as vasomotor symptoms (hot flushes), psychogenic manifestations (sleep disorders or depression), genital atrophy, skin changes, and sexual symptoms.

HT presents several benefits in various diseases. HT can prevent the loss of bone mineral density and osteoporotic fracture. Prevention of colon cancer is also supported by the WHI and observational studies. The incidence of cardiovascular disease in woman is negligible before menopause and increases dramatically thereafter. Some epidemiologic data have suggested that HT reduces the occurrence of coronary artery disease. An observational study suggested that HT may reduce the risk of dementia, and cerebrovascular diseases by 25%-50% in treated women compared with a non-treated control group. However, there are some controversies over these results. According to the WHI memory study (WHIMS) the therapeutic group with HT had twice the risk compared to the placebo group. Rapp et al. reported that there is no additional benefit with respect to cognitive function in the HT group. Thus, the use of HT is not recommended for women for prevention of cardiovascular disease, stroke, and dementia.

In Korea, only 23.3% of naturally menopausal women are on postmenopausal HT. Many other women seek alternative solutions, which include Korean traditional medicines and phytoestrogen-containing products. Phytoestrogens have been perceived to be more natural than HT, and very popular among women who have had doubts about the safety of HT. Some medical professions have suggested that it is reasonable for menopausal women to take phytoestrogen agents rather than do nothing. Phytoestrogens are an ingredient in a number of botanical species, and the subject of current research.

1) Functional Mechanism of Phytoestrogens

Phytoestrogens are diphenolic compounds found in grains, legumes, and grasses. Because phytoestrogens have a phenolic ring, they are able to bind to estrogen receptors, mimicking the effect of estrogen. However, most phytoestrogens have a greater affinity for estrogen receptor-β than estrogen receptor-α. The clinical consequences of these relationships remain to be elucidated. An important point is that even though phytoestrogens can bind to the estrogen receptor, they are much weaker than human estrogens. While many classes of phytoestrogens exist, those pertinent to treating menopausal symptoms are isoflavones, lignans, and coumestans. Lignans are found in grains and cereals, such as alfalfa, and isoflavones are found primarily in legumes, such as soy beans and soy products.
2) **Black cohosh**

Black cohosh is an American herb native to eastern North America. Black cohosh has been traditionally used by Native Americans to treat gynecologic conditions, including menopause and menstrual cramps. Currently, black cohosh agents are used to treat hot flushes in breast cancer patients.\(^{24,25}\) Black cohosh was commercially marketed in the 19th century as Lydia Pinkham’s Vegetable Compound, in the 20th century as Huntington’s 11, and most recently in the 21st century as remifemin (a 20 mg tablet containing black cohosh).\(^{26}\) Black cohosh is marketed in Korea by several pharmaceutical companies. The active ingredients of black cohosh are terpene and glycosides. Recent studies suggest that black cohosh may function as a selective estrogen receptor modulator (SERM) with a mild central estrogenic effect. Black cohosh may also have activity as serotonin receptors, which may be a mechanism that can explain how it relieves hot flushes and improves mood. Some trials show an improvement in the severity of hot flushes, sleep disorders, sexual dysfunction, and sweating.\(^{27}\) Recently, two randomized control trials involving black cohosh (a phytoestrogen sometimes classified as a phytoestrogen) failed to demonstrate a significant benefit with regard to menopausal symptom management in women with breast cancer.\(^{26,27}\) No long-term studies with black cohosh exist, and thus it has been recommended that treatment should be administered no longer than 6 months. Side effects are limited, but include gastrointestinal disturbances, bradycardia, headaches, and nausea.

3) **Soy (isoflavone)**

Soy isoflavone extract is effective in reducing the frequency and severity of hot flushes without stimulation of the endometrium. Soybeans contain three different types of isoflavones (genistein, daidzein, and glycitein), and these soy isoflavones are known to have weak estrogenic activity. Soy isoflavones and other phytoestrogens can bind to estrogen receptors, mimicking the effects of estrogen in some tissues and antagonizing (blocking) the effects of estrogen in others.\(^{28}\)

Interests in soy phytoestrogen have been fueled by epidemiologic studies that have suggested a low incidence of breast cancer in countries in which the population has a high soy intake, and this has been followed in *in vitro* and *in vivo* studies suggesting a potential role for phytoestrogens in preventing breast cancer development. Although most case-control studies have indicated some protective effects of soy, the findings have been inconsistent, and some have failed to show any relationship between phytoestrogen intake and breast cancer development.\(^{29}\)

4) **Dong quai**

Dong quai is used in China and Korea to treat the female reproductive system and support for menopausal complaints.\(^{30,31}\) Dong quai is believed to act by enhancing endogenous estrogen production.\(^{32}\) A study performed by Hirata et al. showed no difference in the reduction of menopausal symptoms between placebo and the Dong quai treatment group.\(^{33}\) In Korean traditional medicine, some research has demonstrated an improvement in menopausal complaints by using Dong quai, but more scientific studies about its molecular-based mechanisms are needed.

Dong quai contains coumarins, and may potentiate the activity of warfarin. Women with estrogen-sensitive cancers should be advised to avoid Dong quai as *in vitro* studies have yielded conflicting information regarding its estrogenic profile.\(^{34}\)

5) **Ginseng**

Ginseng is a special product of Korea. It is one of the most popular anti-aging herbal medicines in Korea. Hong Sam, ginseng steamed red, is a popular medicine in menopausal women. Korean red ginseng has been used in the Orient as a elixir for hundreds of years. Recent data has shown that Korean red ginseng is effective in treating various perimenopausal symptoms. Noh et al. performed a study on the efficacy and safety of Korean red ginseng in women with menopausal symptoms.\(^{35}\) Patients with symptoms of mild-to-moderate severity showed a clinically significant improvement in symptoms.\(^{35}\) However, more evidence and research is needed.

The ginseng root contains saponin, which is a subtype of isoflavone. The effects of ginseng have been attributed to its estrogenic effects; alternatively, ginseng may have an effect on mood by directly affecting the hypothalamic-pituitary axis.\(^{36}\) However, there are some controversies about its efficacy. Many studies suggest that ginseng has no significant effect in reducing menopausal symptoms.\(^{37}\) Some opinions exist that ginseng is helpful in alleviating psychosomatic symptoms;\(^{38}\) thus, the findings are conflicting.\(^{39}\)

6) **Evening primrose oil**

Evening primrose oil is gaining popularity by Korean women. Many women claim that it is very efficacious. Evening primrose oil contains alpha and gamma linolenic acid (prostaglandin E1).\(^{30}\) Gamma linolenic acid is believed to reduce vasomotor symptoms,\(^{31}\) but its mechanism of action is still unknown and the use of evening primrose oil has not conclusively demonstrated efficacy for relieving symptoms in menopausal women. One randomized double-blind, placebo-controlled trial suggested that evening primrose oil was no more efficient than placebo.\(^{40}\) More epidemiologic and biochemical studies need to be done to determine whether or not evening primrose oil is effective.

There is no established connection between cancer development and HT. However, people have doubts about the safety of HT, and they believe that ‘natural’ products are safe. One form of ‘natural product’ is bioidentical hormone therapy. Natural or bioidentical hormone therapy (NHT) is used to describe HT with individually compounded recipes of steroids in various doses, including dehydroepiandrosterone, pregnenolone, testosterone, progesterone, estrone, estradiol, and estriol. Based on the study of a person’s salivary hormone levels, the final composition of the compounded dose form is individualized to the specific person.\(^{41}\) NHT was among the first therapeutics used for the relief of menopausal symptoms in the 1930s, and bioidentical HT (BHT) has attracted much interest.\(^{42,43}\)

The terms bioidentical and natural may obscure safety to consumers. A survey involving 82 women at a compounding pharmacy found that 74 had heard about natural hormones and 37 had used natural hormones. Nineteen women who had heard about natural hormones believed that natural meant “not synthetic/not man-made/no chemicals” and 45% thought the term meant plant-derived. Only 11% agreed that natural meant “identical to human hormones.” Greater than two-thirds (71.4%) of respondents believed that natural hormones had fewer risks than pharmaceutical hormones.\(^{44}\) In a second small survey conducted among a similar demographic population of postmenopausal women at compounding pharmacies prior to the WHI published results, the majority of women reported that they believed that BHT was equal to or better than HT in efficacy and thought BHT...
posed fewer or no safety risks. Not surprisingly, based on the majority of their beliefs and the location of the survey, most had switched from HT to compounded BHT. Popular hormones have contributed to misconceptions about hormones. Actress Suzanne Somers has published three books promoting BHT in 3 years. In her latest book, Ageless: the Naked Truth About Bioidentical Hormones, Somers states, “Hormones are our life force; the decline of hormones is the hallmark of aging.” “Without hormone replacement, we will end up mere shells of our former selves;” and “Disease doesn’t develop when hormones are in perfect balance.”

Despite developing breast cancer and undergoing a hysterectomy for endometrial hyperplasia while taking bioidentical hormones, Somers remains a hormone enthusiast. Several physicians promote these hormones. Erica Schwartz, MD, author of The Hormone Solution: Naturally Alleviate Symptoms of Hormone Imbalance from Adolescence Through Menopause and The 30-Day Natural Hormone Plan: Look and Feel Young Again—Without Synthetic HT, evaluates patients through telephone interviews and prescribes hormone treatment. Schwartz states on her web site that “Natural” bioidentical hormones are exactly the same as the hormones your body made when you were younger except they don’t have the same adverse side effects commonly associated with “synthetic” hormone replacement therapy.”

1) Efficacy of BHT

There are no large, prospective, well-controlled clinical trials to date that address the most commonly compounded ratios and mixtures of estrogens, such as triest and biest. A substantial body of clinical evidence, primarily based on branded HT products in both the United States and Europe, support the use of estradiol in the treatment of the most common vasomotor-related complaints, including hot flushes and night sweats; different administrative forms and preparations appear to provide significant dose-dependent relief, as demonstrated in randomized, double-blind, placebo-controlled clinical trials. Similarly, well-controlled, randomized trials support the efficacy of estradiol in preventing menopause-associated bone loss through various routes of administration.

In another study, Yang et al. found that 2 mg/day of estriol succinate improved climacteric symptoms, but failed to prevent bone loss among 20 Chinese women in a 2-year, open-label, non-placebo-controlled study. This finding was consistent with another open-label, non-placebo-controlled study reported by Takahashi et al. of 68 Japanese women administered estradiol cyclically (4 weeks on and 1 week off) during continuous calcium lactate (104 mg/day) administration, which reported safe, effective relief of vasomotor symptoms, no effect on lipid levels, and no effect on markers for bone metabolism during a 50-week period. In a third double-blind study, estril hemisuccinate (12 mg/day) did not appreciably prevent bone loss in 28 postmenopausal women, leading the study authors to conclude that doses of 14 mg/day are required for efficacy. In this same study, estril (4 mg daily), was ineffective in controlling postmenopausal symptoms; 35% of the patients required a 14 mg dose, and 5 patients were dissatisfied even with that dose.

BHT advocates claim that although progestin significantly differs from endogenous progesterone in both its molecular structure and function, bioidentical formulations of this steroid are natural, and therefore more effective and safer than the latter. Historically, however, the oral administration of progesterone has been considered ineffective because of its poor gastrointestinal absorption and short half-life. Transdermal creams with a very popular formula are available not only at compounding pharmacies with a prescription, but also OTC at health stores and from mail-order companies. The quality of these products, however, varies considerably (some lack bioactive hormones altogether). Although some proponents of this therapy claim that progesterone cream is sufficient to eradicate climacteric symptoms, prevent osteoporosis, improve the lipid profile, and reduce mood changes, scientific evidence shows that currently available creams containing progesterone (compounded and OTC) are not able to fulfill the necessary criteria to be used in conjunction with HT. A randomized, placebo-controlled, prospective, double-blind study comprised of 80 patients showed transdermal progesterone (32 mg/day) did not induce detectable changes in vasomotor symptoms, mood characteristics, or sexual feelings.

The authors suggest that commonly used doses of transdermal progesterone cream do not allow sufficient amounts of hormone to enter the body to achieve a biological effect. The safety and efficacy of testosterone administration have been evaluated in a number of studies varying in size. In a randomized, parallel-group study conducted in 10 women, human testosterone was compared with estradiol, estradiol-estrone, and estradiol/estrone therapy showed a direct correlation with significantly increased bone density and bone turnover.

2) Risk of BHT

(1) Risk of endometrial (EM) hyperplasia

Compounding chemists can “hand make” pharmaceuticals in novel delivery systems. Currently, these compounds are not directly regulated by the Therapeutic Goods Administration. Thus, little is known about quality control, pharmacokinetics, safety and efficacy of these treatments. Compounded HT is often termed “bioidentical” HT. Typically, BHT contains three estrogens (estrone, estradiol, and estriol), progesterone, and androgens, such as testosterone and DHEA, and is usually given either as a cream rubbed onto the skin or as troches. Often, BHT is monitored using blood or salivary levels of sex hormones. If the dose of progesterone is insufficient to prevent estrogen-induced EM hyperplasia, consequently these treatments can lead to endometrial carcinoma. When testing new HT regimens, endometrial assessment is one of the most important safety endpoints. Three cases reported here raise the possibility that the estrogen component of the troche was significantly absorbed, but the dose of progesterone was inadequate, thereby causing EM hyperplasia.

(2) Risk of breast cancer

Estriol is believed by BHT proponents to decrease breast cancer risk. However, six of 24 subjects with breast cancer who took estriol developed metastases, and 2 developed EM hyperplasia. High levels of endogenous estradiol and estrone are associated with an increased breast cancer risk, and estriol has also been implicated in increased risk. In breast cancer cell lines, estriol stimulates breast cancer cell growth more than other estrogens. Breast tissue from women with breast cancer,
compared to women without breast cancer, contains higher levels of estriol, estrone, and estradiol.  

3) Ethical problems with BHT

One of the central ethical problems with BHT surrounds the principle of respect for persons and the doctrine of informed consent. The doctrine of informed consent demands that patients have the genuine capacity to understand and appreciate the potential risks and benefits of their therapies, and other available options. However, as with Somer’s book (one of the best-selling books in 2006 and 2007) and the internet, which are the main sources of misguided beliefs, BHT enthusiasts urge that extracted porcine and bovine hormones used in BHT are much safer than HT because it is from nature. They also point out that human hormones, as used in HT, are artificially made from genetic engineering and are somewhat less secure than the ‘natural’ hormone extracts. Somers, who touts BHT for ovarian hormone replacement, advises that porcine thyroid hormone is superior to bioidentical thyroid hormone (levothyroxine) because it is ‘natural.’ It is easily believed that synthetic hormones have more side effects than the extracted hormones merely because it is synthetic. This irrational superstition is the result of biased manipulations and inappropriate information by CAM practitioners and marketing advisors. They use this misconception to sell their products. When statements about BHT are inaccurate or misleading, informed consent cannot take place. Finally, it remains problematic that the majority of BHT patients do not understand and appreciate the differences between standard of care and innovative therapies.

Among the numerous CAM methods, there are but also methods without drugs. Exercise has proved to have the protective effect against hormone-related cancer. However, exercise does not reduce any other menopausal symptoms, like hot flushes or night sweats. Other than exercising, caloric restriction, and weight reduction, the rest of this field is now known as mind-body medicine, which includes respiratory training, relaxation training, reflexology, and biofeedback. Mind-body medicine uses the means of meditation, guided imagery, biofeedback and autogenic training, breathing and movement, and self-expression through words and drawings to achieve self-care and stress management. It is also used in psychiatric fields to treat post-traumatic stress disorder; moreover, it has alleviated menopausal symptoms. Consequently, lifestyle and behavioral interventions have become a popular prescription for relief of menopausal symptoms. One randomized, controlled trial has demonstrated a significant improvement in menopausal symptoms in breast cancer survivors following comprehensive menopausal assessment and counseling by a nurse. There is another popular CAM, mind-body medicine (homeopathy). It has roots in the Oriental medical philosophy. Homeopathic therapy uses drugs that contain natural ingredients or diluted ingredients for promoting self-healing and self-repair. Is it useful for climacteric women? The answer is ‘maybe.’ Bordet et al. conducted a study involving 438 postmenopausal women aged 45 years or older, and suggested that homeopathic therapy reduced hot flushes significantly and the symptoms of 90% of patients were reduced or disappeared within 15 days. However, a randomized controlled trial in needed to verify the efficacy of homeopathic therapy. Thompson and Reilly suggested homeopathy may help breast cancer survivors suffering from menopausal symptoms. A randomized, double-blind controlled trial showed no difference between the homeopathy and control groups. However, the advantage of homeopathy is compliance and the fact that there are no side effects. Homeopathy can serve as an alternative therapy when HT is contraindicated. Although, this field is not based on sufficient results, homeopathic therapy is trusted by many early stage patients, and seems to have an enormous potential.

During research, it seems obvious that the interests of many women have converged upon anti-aging ‘outward’. A number of dermatologic, plastic surgery, and ophthalmologic clinics at the Anti-Aging Expo has verified that point. Dermatologic clinics vigorously advertise laser procedures which can be done for face lifts, skin firming, chloasomes relief, overweight management, and skin peeling. They even have various cosmetic products under their own clinic names. In ophthalmologic clinics, surgical reversal of presbyopia (SRP) and cosmetic eye whitening procedures are the main advertising materials. Also, in plastic surgery clinics, fillers, prosthetics, structural fat graft, and numerous facial lift surgeries are representative of surgical procedures of anti-aging. Through this exhibition, a number of anti-aging procedures available in Korea were investigated.

Conclusions

Aging is an important health care issue in Korea. Women represent a greater proportion than men in the aging population. Therefore, anti-aging for women will definitely be a huge market for anti-aging medicine, and may even play a role in scholastic breakthroughs.

CAM is thought to increase its market share in the future. It is no longer possible for doctors to practice medicine without CAM. Most patients who visit a doctor’s office ask about CAM, visit CAM practitioners, or purchase CAM products. In addition, a portion of CAM is now used as clinical procedures. For example, CAM is proven to decrease or diminish vasomotor symptoms, sleep disorders, and CNS symptoms with help from clonidine and SSRIs, and an increasingly greater number of clinicians incorporate these findings into their clinical procedures. However, the supporting evidence is insufficient; clinical trials must be done quantitatively and also qualitatively. Every CAM practice should be evaluated for risks and benefits. Moreover, menopausal symptoms vary between human races; specifically, Caucasians have hot flushes, and Asians have joint pains, therefore bioactive phytoestrogen agents (soy extract, evening primrose oil, black cohosh, and Dong quai) should be verified regarding ethnic differences.

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