Female Hormone Restoration

Until 2002, mainstream physicians routinely prescribed conventional hormone replacement therapy (HRT) pills to alleviate menopausal symptoms. Conventional HRT comprises oral conjugated estrogens, derived from the urine of pregnant mares (horses), and synthetic *progestins* (compounds that activate progesterone receptors) such as medroxyprogesterone acetate (NAMS 2017). In 2002, however, the landmark Women's Health Initiative study identified substantial risks associated with conventional oral HRT:

- 26% increased risk of breast cancer,
- 29% increased risk of coronary heart disease,
- 41% increased risk of stroke, and
- double the risk of blood clots relative to the untreated group.

With time, much of this risk was attributed to medroxyprogesterone acetate, the synthetic progestin used in the WHI studies (Stanczyk 2015). As awareness about these risks associated with conventional oral HRT spread, many women became concerned about using HRT. In the United States, the use of conventional HRT dropped dramatically (Schonberg 2005). A sharp decline in breast cancer incidence observed in 2003 among women over 50 correlated with this decrease in conventional HRT use (Ravdin 2007).

Life Extension was not surprised by the results of the WHI study. The *equine estrogens* and *synthetic progestins* used in the study differ in chemical structure from the natural hormones produced in a woman's body (Samaras 2014). Many studies have shown that the synthetic progestin medroxyprogesterone acetate poses several health risks, including increased risks of breast cancer, stroke, and cognitive dysfunction (Stanczyk 2015). Life Extension has long recognized the value of *bioidentical hormone replacement therapy*, which uses hormones that are identical to those naturally produced in the body (Moskowitz 2006; Whelan 2011).

Bioidentical HRT may be associated with fewer side effects than conventional HRT. Bioidentical topically applied estrogens appear to pose less blood clot risk—and possibly overall cardiovascular risk—than oral equine estrogens used in conventional HRT (L'Hermite 2017). This was demonstrated in a large case-control study that showed that use of oral equine estrogens alone (not in combination with synthetic progestins) resulted in about 50% greater risk of venous blood clots compared with controls. When equine estrogens were used in combination with synthetic progestins, the risk increased to about 90% greater than that of control participants (Vinogradova 2019). Also, bioidentical progesterone, unlike the most widely used synthetic progestin, does not increase cardiovascular or breast cancer risk (Holtorf 2009). Indeed, the appeal of bioidentical hormone therapy has not been lost on the public or the medical community: nearly one-third of women who now use hormone therapy do so with bioidentical hormones (Gass 2015).

Many FDA-approved commercial preparations now utilize bioidentical hormones, which is helping spread acceptance of bioidentical HRT among conventionally minded physicians. See Table 1 for a list of FDA-approved bioidentical hormone preparations.

Moreover, supplementation with scientifically studied herbs such as Dong quai (*Angelica sinensis*) and licorice (*Glycyrrhiza glabra*) root can further promote healthy metabolism of female hormones and complement the actions of bioidentical HRT.

In this protocol, you will learn how to approach bioidentical HRT judiciously. You will also learn how using readily available blood tests may help guide your therapy in partnership with a qualified healthcare provider.

Age-Related Hormone Decline and Associated Health Concerns

During the postmenopausal period, when female sex hormone levels have decreased significantly, aging women are at increased risk of several diseases including heart disease, osteoporosis, Alzheimer disease, and dementia compared with premenopausal women.

Heart disease is the leading cause of death in American women (CDC 2017), and women's incidence of coronary heart disease increases sharply after menopause (Tandon 2010; Clearfield 2004). Compared with premenopausal women, postmenopausal women have higher blood pressure and higher levels of low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, and homocysteine levels, as well as markers of chronic inflammation and metabolic disturbance (Saha 2013; Fonseca 2017; Lee 2009). In addition, high-density lipoprotein (HDL) cholesterol levels drop significantly after menopause (Saha 2013; Fonseca 2017). Estrogenic activities are vital for maintaining the integrity of the vascular endothelium, where atherosclerotic changes begin (Arnal 2009). HRT may combat some of these changes. In a clinical trial, 75 peri- and postmenopausal women given compounded transdermal (topical) bioidentical estrogen therapy, with or without progesterone, experienced improvements in cardiovascular risk and inflammatory markers over 36 months (Stephenson 2013).

Menopause and perimenopause are associated with bone loss, which can lead to **osteoporosis** and increased fracture risk.

Inadequate estrogen signaling contributes to increased production of pro-inflammatory cytokines, which disturb the balance between bone formation and bone breakdown and cause bone loss (Pietschmann 2016; Weitzmann 2006).

Hormone loss is also associated with **neuronal degeneration** and increased risk of dementia, Alzheimer disease, and Parkinson disease (Depypere 2016; Blair 2015; Rocca 2008). Estrogen stimulates degradation of the toxic protein beta-amyloid, which contributes to Alzheimer disease (Liang 2010). Deficiencies in pregnenolone and dehydroepiandrosterone (DHEA), which are both neuroprotective hormones, are also linked to memory problems and brain cell death associated with Alzheimer disease (Vallee 2016; Yao 2002). These two hormones appear to play an important role in regulating neurotransmitter systems involved in learning and memory, stress, mood, and motivation (Maayan 2008; Zaluska 2009; Vallée 2001; Zheng 2009).

Menopause often causes **disrupted sleep patterns** and associated symptoms such a night sweats (Jehan 2015). Importantly, disordered sleep is linked to increased cardiovascular risk in menopausal women. One study showed that sleep disorders in menopausal women were associated with arterial stiffness—stiff, inflexible arteries are less healthy (Zhou 2017). Evidence from an observational cohort study suggests bioidentical HRT may reduce sleep disturbances in postmenopausal women, but more study is needed (Ruiz 2014).

Hormone Replacement Therapy – Background

The rationale for HRT is that replacing hormones lost with age may help prevent manifestations of declining hormone levels. Although this basic premise that historically spurred the advent of conventional HRT was theoretically correct, we now know that optimal hormone restoration is much more nuanced and complex.

All steroid hormones are derived from cholesterol in a metabolic cascade. The first hormone in the cascade is pregnenolone, which can subsequently be converted into all other steroid hormones including DHEA, progesterone, testosterone, and various forms of estrogen (Hu 2010). These hormones are interrelated, yet each performs unique physiological functions. Biologically sound hormone therapy should aim to harmonize the physiological response to the milieu of hormonal signaling that is constantly taking place throughout the body.

One problem with classical HRT is that conjugated equine estrogens (CEE) stimulate a more pronounced estrogenic signal in some parts of the body compared with the endogenous estrogens produced by a woman's body, potentially leading to adverse consequences (L'Hermite 2017). CEE, which is obtained from the urine of pregnant mares (horses) (Bhavnani 2003), is usually given in combination with a synthetic progestin, a chemical that stimulates progestogen signaling. However, CEE and chemical progestins cannot replicate the complex network of signaling stimulated by the diverse array of hormones and their metabolites under natural conditions in a woman's body.

Another problem with conventional HRT is that CEE preparations contain other hormones, such as androgens and progestins, that differ from those naturally produced by humans (Notelovitz 2006). Also, because CEE has different forms and proportions of estrogens than those that occur in the body, its use may lead to different and disproportionate amounts of hormone metabolites than would be produced through metabolism of endogenous hormones (Bhavnani 1998). One manifestation of this divergent hormonal metabolism arising from oral equine estrogens is increased blood clotting risk, a well-known side effect of CEE (L'Hermite 2017).

Progesterone

In healthy reproductive-aged women, progesterone and estrogen are in a state of dynamic balance during the menstrual cycle. Progesterone has unique and essential functions in ovulation, implantation, pregnancy, and breast development and function (Ismail 2003; Al-Asmakh 2007), as well as in the brain (Mani 2012).

Progesterone can play a major role in relieving menopausal symptoms. Several studies have reported that women experienced similar or greater reductions in menopausal symptoms and improvements in quality of life, as well as fewer estrogen therapy-related side effects, with progesterone compared with medroxyprogesterone acetate, a synthetic progestin (Hargrove 1989; Montplaisir 2001; Ryan 2001; Lindenfeld 2002). In one study, symptom scores were 30% lower for sleep problems, more than 50% lower for anxiety, 60% lower for depression, 40% lower for cognitive difficulties, and 30% better for sexual function in progesterone users compared with users of a synthetic progestin. In addition, 80% of women using bioidentical progesterone reported overall satisfaction with their hormone therapy (Fitzpatrick 2000).

Progesterone has been shown to be safer than synthetic progestins for cardiovascular health. Certain synthetic progestins, but not progesterone, have been found to worsen the negative effect of oral estrogen therapy on risk of blood clots (Binkowska 2014; Scarabin 2014). The combination of conjugated equine estrogen and the synthetic progestin medroxyprogesterone acetate was found in a large case-control study to more than double the risk of venous thrombosis (Vinogradova 2019). Progesterone has demonstrated cardiovascular safety in postmenopausal women when used alone (Prior 2015). In one study, progesterone enhanced estrogen's positive effect on blood flow to the heart muscle: when added to estrogen therapy, progesterone substantially improved coronary blood flow during treadmill exercise in women with a history of heart attack or coronary artery disease, but a synthetic progestin had no effect (Rosano 2000).

Progesterone plays a role in regulating cognitive function, social behavior, and mood, and has demonstrated neuroprotective and anti-inflammatory properties in the nervous system (Giatti 2016; Arbo 2016). Since some progesterone metabolites have anti-anxiety effects, it is thought that progesterone depletion may contribute to the increased incidence of anxiety and mood disorders seen in early menopause (Toriizuka 2000).

Estrogen

There are a number of naturally occurring forms of estrogen. The main estrogens in humans are estrone, estradiol, and estriol (Taioli 2010; Samavat 2015). Estrogens are produced by the ovaries during the reproductive years and in smaller amounts by the adrenal glands and other tissues throughout life. Non-ovarian sources of estrogens become more important after menopause (Rettberg 2014; Simpson 2003).

Estradiol is the most potent form in non-pregnant, reproductive-aged females and primarily aids in the cyclic release of eggs from the ovaries (ovulation) (Barbieri 2014; Chai 2014). Estradiol has beneficial effects on the heart, bone, brain, and colon (Cui 2013). Fluctuations and overall decline in estradiol levels contribute to common peri- and postmenopausal symptoms, such as hot flashes, mood swings, and vaginal atrophy (Freedman 2014; Finch 2014), and estradiol depletion after menopause impacts tissues throughout the body, contributing to a range of disease risks and frailty (Dalal 2015; Nedergaard 2013). Estrone is the dominant estrogen in postmenopausal women; it is produced by fat tissue (Wharton 2012). Estriol is a comparatively weak estrogen; because it is secreted by the placenta, estriol is the main estrogen during pregnancy (Liang 2013; Ali 2017).

The three main types of estrogen can be converted into many metabolites. Estrone, for example, may convert into the following metabolites among others (Ziegler 2015):

- 2-hydroxyestrone
- 4-hydroxyestrone
- 16-alpha-hydroxyestrone

Some evidence suggests metabolism of estrogen into 2-hydroxylated forms may protect against breast cancer in postmenopausal women (Ziegler 2015; Moore 2016). However, more research is needed before firm conclusions can be drawn about the role of ratios among the various estrogen metabolites in breast cancer risk.

Estriol. Estriol has weaker estrogenic effects than other forms of estrogen. Studies have shown that estriol effectively treats menopausal hot flashes, night sweats, and insomnia. In addition, some studies have shown that estriol combats menopausal bone loss (Ali 2017). When taken together with estradiol, estriol opposes some of estradiol's stronger estrogenic effects (Holtorf 2009). Applied vaginally, estriol is an excellent treatment for urinary and vaginal symptoms of menopause (L'Hermite 2017).

Estriol has been studied in the context of a range of chronic diseases. Researchers in Japan have conducted numerous trials showing that estriol may improve blood pressure, vascular function, and blood lipids (Takahashi 2000; Hayashi 2000; Kano 2002; Itoi 2000; Yamanaka 2005).

Emerging research suggests estriol has a potential role in the treatment of the autoimmune disease multiple sclerosis as well as other neurodegenerative conditions, in part through modulating immune function. This theory stems from the observation that remission and relapse of multiple sclerosis during and shortly after pregnancy is correlated with the secretion of estriol by the placenta (Ali 2017).

Estriol is not yet available in FDA-approved commercial formulations, but can be obtained through compounding pharmacies.

Beyond Estrogen and Progesterone: The Complete Hormonal Picture

In addition to estrogen and progesterone, it is important to consider the roles of the hormones pregnenolone, DHEA, and testosterone. Ideal bioidentical HRT involves comprehensive evaluation of all declining hormone levels.

DHEA. DHEA is a steroidal hormone secreted by the adrenal gland, gonads, and brain (Maninger 2009). Both men and women experience an age-related decline in DHEA (Labrie 2010). Peak levels are typically reached when women are in their 30s, after which they begin to lose approximately 2% per year (Fouany 2013). Decreased levels of DHEA and DHEA-sulfate (DHEA-s, a circulating form of DHEA) after menopause can impact cognition, mood, and sexuality (Pluchino 2015), and are thought to contribute to cancer, insulin resistance, decreased immune defenses, and psychiatric illness (Genazzani 2010).

DHEA has been shown to influence mood and neurological function (Dong 2012), immune function (Bauer 2013), energy and feelings of well-being (Rutkowski 2014), vascular health (Weiss 2012), insulin resistance and inflammatory marker levels (Weiss 2011), and the maintenance of muscle and bone mass (Kenny 2010; Weiss 2009). Furthermore, DHEA has been found to enhance sexual function and the use of intravaginal DHEA in particular has demonstrated efficacy as a treatment for postmenopausal vulvovaginal atrophy (Pluchino 2015; Archer 2015).

Testosterone. Like DHEA, testosterone levels in women gradually decrease with age (Schneider 2003). Loss of testosterone affects libido, bone and muscle mass, vasomotor symptoms, cardiovascular health, mood, and well-being (Bain 2007; Simon 2001; Watt 2003; Cameron 2004).

Testosterone therapy in women has been shown to improve quality of life, mood, concentration, bone health, markers of cardiovascular risk, cognitive function, and vulvovaginal atrophy (Braunstein 2002; Davis 2015). In addition, testosterone, both alone and in conjunction with estrogen therapy, has been shown to be effective in treating low libido and increasing sexual satisfaction in women (Bolour 2005; Achilli 2017; Cappelletti 2016; Al-Azzawi 2010). Because DHEA can be converted into testosterone, it may be possible to obtain some of the benefits of testosterone using DHEA (Cameron 2004; Labrie 2017).

Pregnenolone. As is the case with some other hormones, a significant reduction of pregnenolone begins when women reach their early 30s (Havlikova 2002). As the initial hormone in the overall steroid hormone cascade, pregnenolone is derived from cholesterol mainly in the adrenals, gonads, brain, and other tissues. In addition to acting as a precursor for other hormones, pregnenolone appears to have direct effects on regulation of neurological function (Vallee 2016; Zheng 2009). Pregnenolone may be especially important for age-related sleep and cognitive changes (Mayo 2003), and deficiencies have been associated with diminished brain function and dementia (Mellon 2007).

Hormones and Cancer Risk

Although many factors affect breast cancer risk, it is well established that high estrogen levels and increased estrogen exposure over a lifetime, especially due to an early onset of puberty, are associated with an increased risk of breast cancer (Dall 2017). Establishing a proper balance of hormones and incorporating foods and supplements that support healthy hormone metabolism may help mitigate estrogen's breast cancer-promoting properties.

Current evidence suggests that, while CEE appear not to increase breast cancer risk, the synthetic progestin used in conventional HRT (primarily medroxyprogesterone acetate) *is* associated with increased risk (L'Hermite 2017). In the Women's Health Initiative, CEE alone did not increase breast cancer risk, while CEE plus medroxyprogesterone acetate was associated with increased risk (Chlebowski 2010; Zhao 2014; Shah 2006).

The use of bioidentical progesterone in combination with estrogen has not been found to increase breast cancer risk (Fournier 2008). In fact, *in vitro* research suggests progesterone may actually reduce estrogen-triggered cell proliferation (Mohammed 2015). Although more research is needed to clearly establish the risks and safety of progesterone therapy with regard to breast cancer, evidence to date suggests it is safer than synthetic progestins, particularly medroxyprogesterone acetate (Asi 2016; Prior 2015).

In addition, studies suggest testosterone has anti-proliferative effects on breast tissue, countering the cancer-promoting effect of estrogen (Glaser 2015). In one study, women with breast cancer were found to have lower salivary testosterone levels than cancer-free women (Dimitrakakis 2010). In another study, postmenopausal HRT that included estrogen, progestin, and testosterone was associated with a substantially lower occurrence of breast cancer than that predicted using historical data on HRT without testosterone (Dimitrakakis 2004).

Moving Forward with Bioidentical HRT

Given the evidence demonstrating the superiority of bioidentical HRT, one prominent HRT researcher proclaimed, *"Physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their… animal-derived [non-bioidentical] counterparts. Until evidence is found to the contrary, bioidentical hormones remain the preferred method of HRT"* (Holtorf 2009).

Women should always consult a physician before beginning any HRT, especially if they have had or are at high risk of developing hormone-responsive breast or endometrial cancer. In some cases, prescribing practitioners may want to monitor hormone levels periodically to ensure the attainment of safe and adequate levels (Sood 2011).

Dosing and Delivery Methods

Bioidentical hormone formulations can be obtained as FDA-approved preparations (Table 1) or from a compounding pharmacy with a physician's prescription.

Various preparations and modes of delivery are available for bioidentical hormones. For example, estradiol is available in FDA-approved oral tablets; topical gels, patches, and creams; and vaginal rings and suppositories. Bioidentical micronized progesterone is available as FDA-approved oral pills or vaginal gel (Files 2011; Santoro 2016). There are no currently approved preparations combining both bioidentical estradiol and progesterone. No FDA-approved formulation currently provides bioidentical estriol (FDA 2017). Some authors suggest the current evidence indicates that oral micronized progesterone plus topical/transdermal estradiol is the optimal approach to bioidentical HRT (L'Hermite 2017).

Importantly, the non-oral route is preferred for bioidentical estradiol. This is because the liver metabolizes orally ingested estradiol before it is available to the rest of the body. This is called the "first-pass effect." Also, oral estrogens, but not topical or vaginal estrogens, are associated with increased blood clot risk (Simon 2012; Binkowska 2014). Transdermal estradiol, on the

other hand, is not associated with increased risk of deep venous thrombosis (Vinogradova 2019). Oral progesterone does not increase the risk of blood clots and is an acceptable method of bioidentical progesterone delivery (Binkowska 2014).

The most commonly prescribed compounded bioidentical estrogen formulas are called *bi-est* and *tri-est*. Bi-est consists of 20% estradiol and 80% estriol, and tri-est contains 10% estradiol, 10% estrone, and 80% estriol (Taylor 2001). Bi-est and tri-est are available in various oral, transdermal, and vaginal preparations (Files 2011). Although some physicians prefer bi-est or tri-est formulations based on their clinical experience, studies have yet to establish that estriol-containing bi-est or tri-est formulations provide clear advantages over FDA-approved bioidentical products that contain estradiol (FDA 2017). In certain situations, an experienced physician tailors an individualized prescription based upon an assessment of symptoms, and sometimes lab values, to the needs of a specific woman. In addition to estrogens, a comprehensive hormone restoration program may include progesterone, DHEA, pregnenolone, and possibly testosterone (Files 2011).

To obtain contact information for physicians in your area who are knowledgeable about bioidentical HRT, call 1-800-226-2370.

Women taking any kind of estrogen replacement therapy (including bioidentical) should refer to the Breast Cancer protocol in order to understand the importance of making healthy lifestyle choices that could reduce the risk of breast cancer.

Table 1. FDA-Approved Bioidentical Hormone Preparations

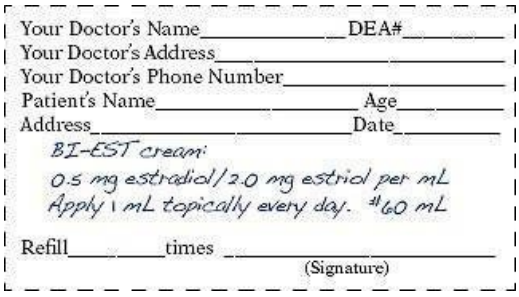
Hormone	Delivery Preparation	Brand Name	Available Dosages/Strengths
Estradiol	Oral – Pill/Tablet/Capsule (NOTE: even though these preparations are bioidentical, the non-oral route of administration is preferred to avoid the hepatic first-pass effect)	Estrace	0.5 mg; 1 mg; 2 mg
		generic	0.5 mg; 1 mg; 2 mg
	Vaginal Cream	Estrace Vaginal	0.1 mg/g
	Transdermal Patch (typically applied once or twice weekly)	Alora	0.025 mg/day; 0.05 mg/day; 0.075 mg/day; 0.1 mg/day
		Climara	0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.06 mg/day; 0.075 mg/day; 0.1 mg/day
		Menostar	0.014 mg/day
		Vivelle-Dot	0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.075 mg/day; 0.1 mg/day
		Minivelle	0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.1 mg/day
		generic	0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.06 mg/day; 0.075 mg/day; 0.01 mg/day
	Topical Gel or Lotion	Estrasorb	4.35 mg per packet
		EstroGel	0.06% concentration: 0.75 mg per pump
		Elestrin	0.06% concentration: 0.52 mg per pump

		Divigel	0.01% concentration: 0.25 mg per packet; 0.5 mg per packet; 1 mg per packet
	Topical Spray	Evamist	1.53 mg per spray
	Vaginal Ring	Estring	Applied once every three months: 0.075 mg/day
	Vaginal Tablet	Vagifem (estradiol hemihydrate)	Typically applied twice weekly: 0.01 mg per tablet
Progesterone (micronized)	Oral – Pill/Tablet/Capsule	Prometrium	100 mg per capsule; 200 mg per capsule
		generic	100 mg per capsule; 200 mg per capsule
	Vaginal Gel	Crinone	4% concentration: 45 mg per applicatorful; 8% concentration: 90 mg per applicatorful

How Compounded Bioidentical Hormones are Prescribed

Compounded bioidentical hormone prescriptions are primarily based on symptoms and, to some degree, blood test results. A physician experienced in writing compounded bioidentical hormone prescriptions will work closely with a woman to determine a starting dosage.

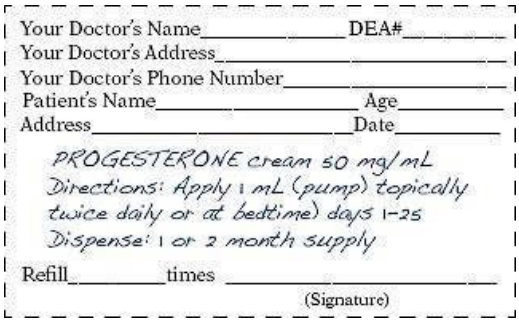
The strength of a compounded hormone preparation is generally indicated in milligrams (mg) per milliliter (mL) or per cubic centimeter (cc). A milliliter and a cubic centimeter have the same volume. A typical starting dose for bioidentical estrogen cream might read as follows:


Your Doctor's Name_____DEA#_____
Your Doctor's Address_____
Your Doctor's Phone Number_____
Patient's Name_____ Age_____
Address_____Date_____
BI-EST cream:
0.5 mg estradiol/2.0 mg estriol per mL
Apply 1 mL topically every day. #60 mL
Refill_____times _____
(Signature)

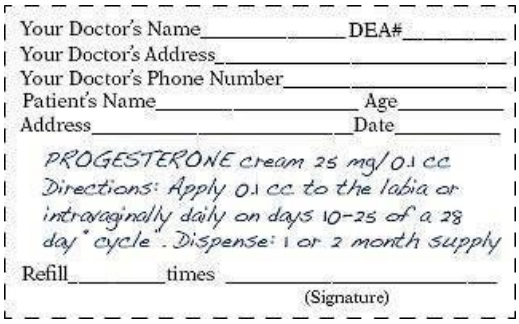
Please note this is one example of an initial prescription. It represents the most commonly used bioidentical HRT script for a postmenopausal woman with typical symptoms. A physician experienced in bioidentical hormone replacement would tailor a prescription to the individual's needs.

Women on an estrogen replacement regimen should also be prescribed *progesterone* (in contrast to synthetic progestin drugs like Provera which do not have the same molecular structure as natural progesterone). Progesterone has a number of benefits when properly balanced with estrogen (Prior 2015; Spark 2012), and is particularly helpful for menopause-related sleep disturbances (Leeangkoonsathian 2017; Caufriez 2011). For oral progesterone, a typical dose is between 100–200 mg per day for 10–12 days per month; for transdermal progesterone, a typical dose is 50–100 mg per day (Randel 2012; Cobin 2017). These dosages can vary depending upon a woman's individual biochemical needs. It is usually recommended that progesterone cream be applied twice daily to different parts of the body.

As with estrogen therapy, the dose of progesterone can be adjusted depending on the individual's symptoms and response to treatment. For a postmenopausal woman, a prescription for topical progesterone cream from a compounding pharmacy might be written as follows:



A prescription for a peri-menopausal woman might read as follows:



Compounded hormone formulas are applied via a syringe (with no needle) onto the skin or intravaginally, allowing for precise dosage adjustment. In some situations, a baseline blood test may be useful for determining doses of bioidentical hormones. A physician experienced in bioidentical hormone therapy may want to measure testosterone levels and prescribe bioidentical testosterone if needed (Davis 2008).

Since DHEA can be converted to testosterone in a woman's body, a woman with low testosterone might be able to increase her level by taking up to 50 mg DHEA daily, which is available as a dietary supplement (Weiss 2009; Caufriez 2013).

Identifying High-Quality Compounding Pharmacies

Given the potential for error inherent in preparing individualized compounded products, it is important that the pharmacy with which you are working adheres to high quality and safety standards.

One way you can ensure your compounding facility adheres to high quality and safety standards is to inquire whether the facility is accredited by the Pharmacy Compounding Accreditation Board (PCAB) (ACHC 2017). More information and relevant directories of accredited facilities can be found at the following link: https://healthfinder.gov/FindServices/Organizations/Organization.aspx?code=HR3886

You can also ask your pharmacy directly whether the facility adheres to guidelines laid out by the United States Pharmacopeial Convention (USP). Specifically, USP General Chapter 795 identifies important standards relevant to bioidentical hormone compounding to which a compounding pharmacy should adhere to ensure safety and quality (USP 2014). Reputable pharmacies should be able to provide clear information regarding their adherence to USP guidance. One aspect of the PCAB accreditation mentioned previously is attestation to the accredited facility's adherence to relevant USP guidelines.

Pros and Cons of Different Hormone Testing Methods

There is continuing debate regarding the best testing methods for hormone status. Hormones can be analyzed in the blood, urine, or saliva. There are benefits and drawbacks to each of these methods.

Saliva Testing

Pros - This easy, at home collection process is a measurement of bioavailable hormone levels.

Cons - Accuracy and testing variability are issues to consider. Hormone levels in saliva can vary with saliva flow rate, time of day, timing of hormone therapy, eating, and tooth brushing, as well as gum disease (even if subclinical), and there are no salivary tests for hormone metabolites (Sood 2011; Larsen 2014).

Urine Testing

Pros - This method provides a 24-hour picture of hormone levels. Because it captures both the peaks and troughs that occur during the day, it is not susceptible to moment-to-moment fluctuations. A 24-hour urine test can be used to assess the three main

estrogens— estrone, estadiol, and estriol—as well as progesterone, pregnenolone, testosterone, and DHEA. Urine testing can also be used to assess metabolites like 2- and 16-hydroxyestrone (Larsen 2014). Urine testing is excellent at providing an overview of an individual's hormone metabolism that cannot be seen in blood or saliva.

Cons – Urine testing is considered less convenient by some patients, and comprehensive 24-hour urine panels may be more expensive than other types of testing (Larsen 2014). It can show high levels of hormones despite low blood levels for hormones like testosterone which are carried by sex hormone binding globulin (SHBG). If SHBG levels are low in the blood, testosterone is not preserved adequately and the free form is excreted from the kidney in excess and thus can show high levels despite low levels in the blood.

Blood Testing

Pros - This method has been used consistently for decades and has well-established reference ranges. Serum testing is relatively inexpensive, routine, and readily available through blood draw centers (Larsen 2014).

Cons - Blood draws involve needle sticks. Blood testing provides only single-point evaluation, and because hormone levels can fluctuate widely during the day, reference ranges are typically broad. Although estradiol, estrone, testosterone, and DHEA can be evaluated, blood testing has limited ability to assess non-pregnancy levels of estriol in women using transdermal preparations so it is not suggested to test blood levels of estriol. Furthermore, with the exception of testosterone, these tests generally measure total amounts (bound and unbound) of hormones being tested, which are not as clinically meaningful as free hormone levels. Finally, there is no blood hormone metabolite testing available (Larsen 2014).

Phytoestrogens and Nutritional Support

Phytoestrogens are dietary bioactives and natural compounds found in some plants that are similar in structure to estrogens. Although several types of plant compounds are classified as phytoestrogens (Landete 2016), the most studied of these are isoflavones and lignans (Chen 2015). Phytoestrogens in plants are largely inactive but are metabolized into active compounds by intestinal bacteria (Vitale 2013; Gencel 2012). Once absorbed, activated phytoestrogens exert estrogen-like effects in the body and may be an alternative to bioidentical HRT for some women (Sirotkin 2014; Landete 2016).

Some of the best evidence to support the use of phytoestrogens comes from Asia, where menopausal symptoms are milder and less common, and breast cancer incidence is lower than in Europe and North America. One explanation may be the phytoestrogens found in soy and other plant products commonly consumed in Asian diets (Aso 2010; Cho 2010; Sarkar 2003).

Phytoestrogens bind to estrogen receptors and help modulate estrogen activity (Zittermann 2003; Hajirahimkhan, Dietz 2013; Vitale 2013). The estrogenic effects of phytoestrogens vary but are generally weak relative to estradiol; in the presence of estradiol, they appear to have anti-estrogenic effects as they compete with estradiol for estrogen receptor binding sites (Hajirahimkhan, Dietz 2013; Ko 2014). Phytoestrogens have been shown to reduce menopausal symptoms and may decrease the risk of some chronic diseases including cardiovascular disease, osteoporosis, and breast cancer (Bawa 2010; Cho 2010; Miyake 2009; Vitale 2013; Messina 2014; Mainini 2013).

Intriguingly, phytoestrogens seem to preferentially bind estrogen receptor (ER)-*beta*, as opposed to ER-*alpha*, which is more strongly activated by estradiol and some other mammalian estrogens (Sirotkin 2014; Messina 2014). ER-beta activation has been proposed as a mechanism for preventing emotional and neurological aspects of aging and menopause (Vargas 2016), and appears to protect against cancerous changes in breast, ovarian, and possibly other tissues (Gallo 2012; Bardin 2004; Bossard 2012; Omoto 2015).

Dietary and supplemental phytoestrogens present a way for women to obtain limited hormonal support without the use of hormone therapy.

Cardiovascular benefits. Unlike conventional HRT, which has been shown to raise the risk of heart attack among postmenopausal women, phytoestrogens appear to have a positive effect on the heart (Gencel 2012; Sirotkin 2014). In 1999, the FDA authorized the use of health claims on food labels that link increased soy consumption with a reduced risk of coronary artery disease (Vincent 2000).

There are many studies examining the cardiovascular effects of phytoestrogens. Overall, research suggests isoflavones may lower high blood pressure (Sureda 2017; Messina 2014), improve lipid disturbances, lower homocysteine levels (Li 2016), improve vascular health, and prevent atherosclerosis (Gencel 2012; Messina 2014). Lignans similarly have been associated with lower blood pressure (Khalesi 2015), improved lipid metabolism (Gencel 2012), and reduced cardiac risk (Chun 2014; Landete 2016).

In addition to their ability to weakly activate estrogen receptors, phytoestrogens have strong anti-inflammatory and oxidative stress-reducing effects, which may contribute to their cardiovascular benefits (Gencel 2012; Landete 2016).

Brain protection. Estrogen and estrogen-like compounds protect brain cells from degenerative changes due to aging, oxidative stress, and stroke-induced damage (Nabavi 2015; Evsen 2013; Bhavnani 2003; Linford 2002). Several studies have shown that the phytoestrogen genistein protects experimental animals from the effects of brain ischemia, the kind of injury seen

in stroke (Schreihofer 2009; Donzelli 2010; Ma 2010). In addition, genistein has demonstrated anti-apoptotic activity, protecting cultured brain cells from self-destructing over time (Yu 2009).

Osteoporosis and bone health. A number of studies have been conducted on phytoestrogens and bone health. Clinical trials have found that phytoestrogens can increase bone mineralization, reduce bone resorption, enhance bone formation, and improve markers of bone metabolism. Taken together, their findings suggest phytoestrogens (mainly soy foods and isoflavones) may help mitigate bone loss after menopause (Messina 2014; Abdi 2016; Chiang 2013).

Cancer protection. A number of studies have noted an association between isoflavone consumption and decreased breast cancer risk (Wada 2013; Dong 2011; Fritz 2013). Soy isoflavones are safe in women with a high risk of breast cancer, including breast cancer survivors (Fritz 2013; Messina 2016), and do not increase the risk of uterine cancer (Parazzini 2015). In addition, flaxseeds, which are high in phytoestrogenic lignans, have been shown to reduce breast cancer risk and reduce breast cancer tumor growth (Mason 2014; Flower 2014).

Phytoestrogens may protect against breast cancer in part by improving estrogen metabolism. A diet containing 113–202 mg daily (depending on body size) of genistein and daidzein was found in one trial to increase the ratio of protective 2-hydroxylated estrogens to harmful 16-hydroxylated estrogens in the urine of premenopausal women, an effect that may contribute to a lower long-term risk of breast cancer (Lu 2000). Furthermore, emerging evidence suggests phytoestrogens inhibit aromatase, the enzyme that catalyzes the conversion of testosterone to estrogen, and this effect may contribute to their association with lower breast cancer risk (Lephart 2015).

Lignans are phytoestrogens found mainly in flaxseeds, with smaller amounts occurring in sesame seeds, some sprouts, and many other plant foods. A comprehensive review of 21 studies found that postmenopausal women with higher lignan intake were significantly less likely to get breast cancer (Buck 2010).

In one clinical trial, 32 women awaiting surgery for breast cancer were randomized to receive a muffin either with or without (control group) 25 grams of flaxseed. Analysis of the cancerous tissue after surgery revealed that markers of tumor growth were reduced by 30–71% in the flaxseed group, but not in the control group (Thompson 2005). A study published in 2010 found that a combination of lignans, indole-3-carbinol (I3C), and calcium-d-glucarate along with other herbs favorably altered the ratio of estrogen metabolites in 47 pre- and 49 postmenopausal women (Laidlaw 2010).

Menopause symptoms. Several studies have demonstrated that natural phytoestrogens can improve menopausal symptoms (Sirotkin 2014), particularly hot flashes (Chen 2015). A comprehensive meta-analysis that included results from 17 clinical trials found that treatment with an average of 54 mg of genistein per day for between six weeks and 12 months safely decreased hot flash frequency by 20.6% and hot flash severity by 26.2% (Taku 2012).

Additional Natural Ingredients to Target the Symptoms of Menopause

Black cohosh. Black cohosh (*Actaea racemosa* or *Cimicifuga racemosa*) root has a long history of traditional use in treating gynecologic disorders and has become a popular herbal medicine for relieving menopausal symptoms (NIH 2017). Randomized controlled trials have demonstrated its efficacy in treating menopausal symptoms such as hot flashes, low libido, sleep disturbance, and other physical and emotional symptoms (Jiang 2015; Shahnazi 2013; Mohammad-Alizadeh-Charandabi 2013; Ross 2012). Black cohosh has a track record of safety and the preponderance of evidence supports its use in treating menopausal symptoms (Shams 2010; Beer 2013; Czuczwar 2017; Sarri 2017). Black cohosh and closely related species have conveyed anti-proliferative effects on breast cancer cells in the laboratory (Fang 2010; Al-Akoum 2007; Hostanska 2004), and the use of black cohosh is not associated with increased breast cancer risk or recurrence rates (Fritz 2014). Data from one clinical trial and several animal studies suggest it is comparable to estradiol and another anti-osteoporosis medication for preventing bone loss (Nisslein 2003; Seidlova-Wuttke 2005; Wuttke 2003; Seidlova-Wuttke 2003).

Dong quai. Dong quai (*Angelica sinensis*) is used in traditional Chinese medicine for gynecological symptoms such as painful menstruation or pelvic pain, recovery from childbirth or illness, and fatigue/low vitality, and is therefore referred to as “female ginseng” (Al-Bareeq 2010; Goh 2001; Hardy 2000). Randomized controlled trials have shown that dong quai, in combination with other plant extracts, can relieve symptoms of menopause (Trimarco 2016; Kupfersztain 2003), and in one animal study dong quai was as effective as estradiol at preventing bone loss (Lim 2014).

Licorice root. Licorice (*Glycyrrhiza glabra*) root exerts estrogen-like effects with selective activation of ER-beta (Hajirahimkhan, Simmler 2013). Laboratory research suggests licorice constituents inhibit serotonin reuptake, an effect that may contribute to its positive impact on menopausal symptoms (Ofir 2003; Hajirahimkhan, Dietz 2013). In a randomized controlled trial, treatment with 330 mg of licorice root three times daily reduced both frequency and severity of menopausal hot flashes more than placebo during eight weeks of treatment and for two weeks following the end of treatment (Nahidi 2012). Licorice root constituents have also been shown in the laboratory to support arterial and bone health, thus reducing the risk of cardiovascular disease and osteoporosis (Somjen, Knoll 2004; Somjen, Katzburg 2004).

Vitex agnus-castus. Herbal formulas containing extracts from *Vitex agnus-castus* (Vitex), also known as chasteberry, have been shown to improve menopausal symptoms such as sleep disturbance, hot flashes, and psychosocial wellness (De

Franciscis 2017; van Die 2009; Rotem 2007). Vitex, obtained from the dried fruit of the chaste tree, has been used in the context of women's health for centuries. It has been shown to modulate hormonal and neurotransmitter signaling and to relieve premenstrual symptoms in several small studies. Laboratory studies have shown that compounds in vitex can bind estrogen receptors and modulate hormone-responsive genes (Dietz 2016).

Nutrients to Support Healthy Estrogen Metabolism

Vitamin D. Vitamin D appears to confer significant protective effects against breast cancer. Women with higher vitamin D levels had a nearly 70% reduction in their risk of breast cancer compared to women with the lowest levels in one study (Abbas 2008), while another study linked low vitamin D levels with reduced survival in breast cancer patients (Vrieling 2011). Laboratory studies have shown that vitamin D suppresses growth and development of breast cancer by:

- blocking signals that stimulate cancer cell growth
- enhancing signals that inhibit cancer cell growth
- modulating mammary gland sensitivity to carcinogenesis (Welsh 2017)
- inducing cancer cell death (apoptosis) (Thyer 2013; Fleet 2012)

Cruciferous vegetables. Cruciferous vegetables such as, cauliflower, cabbage, kale, and Brussels sprouts contain compounds that may help detoxify estrogen breakdown products that promote cancer growth (Marconett 2012; Lampe 2009; Ambrosone 2004). One such compound is I3C, which prevents the conversion of estrogen to the breast cancer-promoting metabolite *16-alpha-hydroxyestrone*, while increasing conversion to the cancer-fighting metabolite *2-hydroxyestrone* form (Acharya 2010; Weng 2008; Muti 2000).

Fish oil. Fish oil, with its high omega-3 fatty acid content, reduces cancer risk by a number of mechanisms. Fish oil reduces oxidative stress and suppresses production of many inflammatory mediators that contribute to cancer development (Saoudi 2017; Kansal 2011). It can sensitize tumor cells to chemotherapy effects even when metastases are present, potentially reducing the doses of chemotherapy required for treatment (Bougnoux 2009). In an animal model of breast cancer, fish oil supplementation was shown to reduce bone metastasis (Mandal 2010).

Green tea. Green tea polyphenols, particularly one called epigallocatechin gallate (EGCG), suppressed the growth and reproduction of human breast cancer cells in the laboratory and reduced the number of breast cancer tumors in animal models of the disease (Thangapazham, Passi 2007; Thangapazham, Singh 2007; Leong 2008). Green tea has also inhibited the production of tumor blood vessels while down-regulating cancer-promoting estrogen receptors and increasing apoptosis (Leong 2008; Masuda 2002; Farabegoli 2007; Hsuuw 2007).

Pomegranate. Pomegranate has been extensively studied for its antioxidant properties and cancer-fighting potential (Taheri Rouhi 2017; Li 2017; Panth 2017). With respect to breast cancer, pomegranate is an especially promising agent due to its ability to inhibit the cancer-promoting enzyme aromatase and suppress the generation of blood vessels by tumors (Toi 2003; Sturgeon 2010).

Female Hormone Restoration

References

Abbas S, Lineisen J, Slanger T, et al. Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer—results of a large case-control study. Carcinogenesis. 2008 Jan;29(1):93-9.

Abdi F, Alimoradi Z, Haqi P, Mahdizad F. Effects of phytoestrogens on bone mineral density during the menopause transition: a systematic review of randomized, controlled trials. Climacteric: the journal of the International Menopause Society. Dec 2016;19(6):535-545.

Acharya A, Das I, Singh S, Saha T. Chemopreventive properties of indole-3-carbinol, diindolylmethane and other constituents of cardamom against carcinogenesis. Recent Pat Food Nutr Agric. 2010 Jun;2(2):166-77.

ACHC. Accreditation Commission for Health Care. PCAB Accreditation. http://www.achc.org/compounding-pharmacy.html. Accessed 10/19/2017.

Achilli C, Pundir J, Ramanathan P, Sabatini L, Hamoda H, Panay N. Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis. Fertility and sterility. Feb 2017;107(2):475-482.e415.

Al-Akoum M, Dodin S, Akoum A. Synergistic cytotoxic effects of tamoxifen and black cohosh on MCF-7 and MDA-MB-231 human breast cancer cells: an in vitro study. Can J Physiol Pharmacol. 2007 Nov;85(11):1153-9.

Al-Asmakh M. Reproductive functions of progesterone. Middle East Fertility Society Journal. 2007;12(3):147-152.

Al-Azzawi F, Bitzer J, Brandenburg U, Castelo-Branco C, Graziottin A, Kenemans P, Lachowsky M, Mimoun S, Nappi RE, Palacios S, Schwenkhagen A, Studd J, Wylie K, Zahradnik HP. Therapeutic options for postmenopausal female sexual dysfunction. Climacteric. 2010 Apr;13(2):103-20.

Al-Bareeq RJ, Ray AA, Nott L, Pautler SE, Razvi H. Dong Quai (angelica sinensis) in the treatment of hot flashes for men on androgen deprivation therapy: results of a randomized double-blind placebo controlled trial. Canadian Urological Association journal = Journal de l'Association des urologues du Canada. Feb 2010;4(1):49-53.

Ali ES, Mangold C, Peiris AN. Estriol: emerging clinical benefits. Menopause (New York, N.Y.). Apr 03 2017.

Ambrosone CB, McCann SE, et al. Breast cancer risk in premenopausal women is inversely associated with consumption of broccoli, a source of isothiocyanates, but is not modified by GST genotype. J Nutr. 2004;134(5): 1134-1138.

Arbo BD, Bennetti F, Ribeiro MF. Astrocytes as a target for neuroprotection: Modulation by progesterone and dehydroepiandrosterone. Progress in neurobiology. Sep 2016;144:27-47.

Archer DF. Dehydroepiandrosterone intra vaginal administration for the management of postmenopausal vulvovaginal atrophy. The Journal of steroid biochemistry and molecular biology. Jan 2015;145:139-143.

Arnal JF, Laurell H, et al. Estrogen receptor actions on vascular biology and inflammation: implications in vascular pathophysiology. Climacteric. 2009;12 Suppl 1: 12-17.

Asi N, Mohammed K, Haydour Q, Gionfriddo MR, Vargas OLM, Prokop LJ, . . . Murad MH. Progesterone vs. synthetic progestins and the risk of breast cancer: a systematic review and meta-analysis. Syst Rev. 2016;5.

Aso T. Equol improves menopausal symptoms in Japanese women. J Nutr. 2010 Jul;140(7):1386S-9S.

Bain J. The many faces of testosterone. Clinical interventions in aging. 2007;2(4):567-576.

Barbieri RL. The endocrinology of the menstrual cycle. Methods in molecular biology (Clifton, N.J.). 2014;1154:145-169.

Bardin A, Boulle N, Lazennec G, Vignon F, Pujol P. Loss of ERbeta expression as a common step in estrogen-dependent tumor progression. Endocr Relat Cancer. 2004 Sep;11(3):537-51.

Bauer ME, Muller GC, Correa BL, Vianna P, Turner JE, Bosch JA. Psychoneuroendocrine interventions aimed at attenuating immunosenescence: a review. Biogerontology. Feb 2013;14(1):9-20.

Bawa S. The significance of soy protein and soy bioactive compounds in the prophylaxis and treatment of osteoporosis. J Osteoporos. 2010 Mar 8;2010:891058.

Beer AM, Osmers R, Schnitker J, Bai W, Mueck AO, Meden H. Efficacy of black cohosh (Cimicifuga racemosa) medicines for treatment of menopausal symptoms - comments on major statements of the Cochrane Collaboration report 2012 "black cohosh (Cimicifuga spp.) for menopausal symptoms (review)". Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology. Dec 2013;29(12):1022-1025.

Bhavnani BR. Estrogens and menopause: pharmacology of conjugated equine estrogens and their potential role in the prevention of neurodegenerative diseases such as Alzheimer's. J Steroid Biochem Mol Biol. 2003; 85(2–5):473–482.

Bhavnani BR. Pharmacokinetics and pharmacodynamics of conjugated equine estrogens: chemistry and metabolism. Proc Soc Exp Biol Med. Jan 1998;217(1):6-16.

Binkowska M. Menopausal hormone therapy and venous thromboembolism. Przeglad menopauzalny = Menopause review. Oct 2014;13(5):267-272.

Blair JA, McGee H, Bhatta S, Palm R, Casadesus G. Hypothalamic-pituitary-gonadal axis involvement in learning and memory and Alzheimer's disease: more than "just" estrogen. Frontiers in endocrinology. 2015;6:45.

Bolour S, Braunstein G. Testosterone therapy in women: a review. International journal of impotence research. Sep-Oct 2005;17(5):399-408.

Bossard C, Busson M, Vindrieux D, Gaudin F, Machelon V, Brigitte M, . . . Lazennec G. Potential role of estrogen receptor beta as a tumor suppressor of epithelial ovarian cancer. PloS one. 2012;7(9):e44787.

Bougnoux P, Hajjaji N, et al. Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial. Br J Cancer. 2009;101(12): 1978-1985.

Braunstein GD. Androgen insufficiency in women: summary of critical issues. Fertil Steril. 2002;77(Suppl 4):S94–S99.

Buck K, Zaineddin AK, Vrieling A, Linseisen J, Chang-Claude J. Meta-analyses of lignans and enterolignans in relation to breast cancer risk. Am J Clin Nutr. 2010 Jul;92(1):141-53.

Cameron DR, Braunstein GD. Androgen replacement therapy in women. Fertil Steril. 2004;82(2):273-289.

Cappelletti M, Wallen K. Increasing women's sexual desire: The comparative effectiveness of estrogens and androgens. Hormones and behavior. Feb 2016;78:178-193.

Caufriez A, Leproult R, L'Hermite-Baleriaux M, Kerkhofs M, Copinschi G. Effects of a 3-week dehydroepiandrosterone administration on sleep, sex steroids and multiple 24-h hormonal profiles in postmenopausal women: a pilot study. Clinical endocrinology. Nov 2013;79(5):716-724.

Caufriez A, Leproult R, L'Hermite-Baleriaux M, Kerkhofs M, Copinschi G. Progesterone prevents sleep disturbances and modulates GH, TSH, and melatonin secretion in postmenopausal women. The Journal of clinical endocrinology and metabolism. Apr 2011;96(4):E614-623.

CDC. Centers for Disease Control and Prevention. Women and Heart Disease Fact Sheet. http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_women_heart.htm. Last updated 8/23/17. Accessed 10/24/2017.

Chai NC, Peterlin BL, Calhoun AH. Migraine and estrogen. Current opinion in neurology. Jun 2014;27(3):315-324.

Chen MN, Lin CC, Liu CF. Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. Climacteric: the journal of the International Menopause Society. Apr 2015;18(2):260-269.

Chiang SS, Pan TM. Beneficial effects of phytoestrogens and their metabolites produced by intestinal microflora on bone health. Appl Microbiol Biotechnol. Feb 2013;97(4):1489-1500.

Chlebowski RT, Anderson GL, Gass M, et al. WHI Investigators. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010 Oct 20;304(15):1684-92.

Cho YA, Kim J, Park KS, Lim SY, Shin A, Sung MK, Ro J. Effect of dietary soy intake on breast cancer risk according to menopause and hormone receptor status. Eur J Clin Nutr. 2010 Sep;64(9):924-32.

Chun JN, Cho M, So I, Jeon JH. The protective effects of Schisandra chinensis fruit extract and its lignans against cardiovascular disease: a review of the molecular mechanisms. Fitoterapia. Sep 2014;97:224-233.

Clearfield M. Coronary heart disease risk reduction in postmenopausal women: the role of statin therapy and hormone replacement therapy. Preventive cardiology. Summer 2004;7(3):131-136.

Cobin RH, Goodman NF. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON MENOPAUSE-2017 UPDATE. Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. Jul 2017;23(7):869-880.

Cui J, Shen Y, Li R. Estrogen synthesis and signaling pathways during aging: from periphery to brain. Trends in molecular medicine. Mar 2013;19(3):197-209.

Czuczwar P, Paszkowski T, Lisiecki M, Woźniak S, Stępniak A. The safety and tolerance of phytotherapies in menopausal medicine – a review of the literature. Przeglad menopauzalny = Menopause review. Mar 2017;16(1):8-11.

Dalal PK, Agarwal M. Postmenopausal syndrome. Indian journal of psychiatry. Jul 2015;57(Suppl 2):S222-232.

Dall GV, Britt KL. Estrogen Effects on the Mammary Gland in Early and Late Life and Breast Cancer Risk. Frontiers in oncology. 2017;7:110.

Davis SR, Moreau M, Kroll R, Bouchard C. Testosterone for low libido in postmenopausal women not taking estrogen. N Engl J Med. 2008 Nov 6;359(19):2005-17.

Davis SR, Wahlin-Jacobsen S. Testosterone in women--the clinical significance. The lancet. Diabetes & endocrinology. Dec

2015;3(12):980-992.

De Franciscis P, Grauso F, Luisi A, Schettino MT, Torella M, Colacurci N. Adding Agnus Castus and Magnolia to Soy Isoflavones Relieves Sleep Disturbances Besides Postmenopausal Vasomotor Symptoms-Long Term Safety and Effectiveness. Nutrients. Feb 13 2017;9(2).

Depypere H, Vierin A, Weyers S, Sieben A. Alzheimer's disease, apolipoprotein E and hormone replacement therapy. Maturitas. Dec 2016;94:98-105.

Dietz BM, Hajirahimkhan A, Dunlap TL, Bolton JL. Botanicals and Their Bioactive Phytochemicals for Women's Health. Pharmacol Rev. Oct 2016;68(4):1026-1073.

Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. Menopause (New York, N.Y.). Sep-Oct 2004;11(5):531-535.

Dimitrakakis C, Zava D, Marinopoulos S, Tsigginou A, Antsaklis A, Glaser R. Low salivary testosterone levels in patients with breast cancer. BMC cancer. 2010;10:547.

Dong JY, Qin LQ. Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. Breast Cancer Res Treat. Jan 2011;125(2):315-323.

Dong Y, Zheng P. Dehydroepiandrosterone sulphate: action and mechanism in the brain. Journal of neuroendocrinology. Jan 2012;24(1):215-224.

Donzelli A, Braida D, et al. Neuroprotective effects of genistein in mongolian gerbils: estrogen receptor-beta involvement. J Pharmacol Sci. 2010;114(2): 158-167.

Evsen MS, Ozler A, Gocmez C, Varol S, Tunc SY, Akil E, . . . Kaplan I. Effects of estrogen, estrogen/progesteron combination and genistein treatments on oxidant/antioxidant status in the brain of ovariectomized rats. European review for medical and pharmacological sciences. Jul 2013;17(14):1869-1873.

Fang ZZ, Nian Y, Li W, Wu JJ, Ge GB, Dong PP, Zhang YY, Qiu MH, Liu L, Yang L. Cycloartane triterpenoids from Cimicifuga yunnanensis induce apoptosis of breast cancer cells (MCF7) via p53-dependent mitochondrial signaling pathway. Phytother Res. 2010 Jun 17. [Epub ahead of print].

Farabegoli F, Barbi C, et al. (-)-Epigallocatechin-3-gallate downregulates estrogen receptor alpha function in MCF-7 breast carcinoma cells. Cancer Detect Prev. 2007;31(6): 499-504.

FDA. US Food and Drug Administration. Bio-Idenitcals: Sorting Myths from Facts. Available at https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm049311.htm. Last updated 03/2017. Accessed 09/08/2017.

Files JA, Ko MG, Pruthi S. Bioidentical hormone therapy. Mayo Clinic proceedings. Jul 2011;86(7):673-680, quiz 680.

Finch CE. The menopause and aging, a comparative perspective. The Journal of steroid biochemistry and molecular biology. Jul 2014;142:132-141.

Fitzpatrick LA, Pace C, et al. Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey. J Womens Health Gend Based Med. 2000;9(4): 381-387.

Fleet JC, DeSmet M, Johnson R, Li Y. Vitamin D and cancer: a review of molecular mechanisms. The Biochemical journal. Jan 01 2012;441(1):61-76.

Flower G, Fritz H, Balneaves LG, Verma S, Skidmore B, Fernandes R, . . . Seely D. Flax and Breast Cancer: A Systematic Review. Integrative cancer therapies. May 2014;13(3):181-192.

Fonseca MIH, da Silva IT, Ferreira SRG. Impact of menopause and diabetes on atherogenic lipid profile: is it worth to analyse lipoprotein subfractions to assess cardiovascular risk in women? Diabetol Metab Syndr. 2017;9:22.

Fouany MR, Sharara FI. Is there a role for DHEA supplementation in women with diminished ovarian reserve? Journal of assisted reproduction and genetics. Sep 2013;30(9):1239-1244.

Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. Jan 2008;107(1):103-111.

Freedman RR. Menopausal hot flashes: mechanisms, endocrinology, treatment. The Journal of steroid biochemistry and molecular biology. Jul 2014;142:115-120.

Fritz H, Seely D, Flower G, Skidmore B, Fernandes R, Vadeboncoeur S, . . . Fergusson D. Soy, red clover, and isoflavones and breast cancer: a systematic review. PloS one. 2013;8(11):e81968.

Fritz H, Seely D, McGowan J, Skidmore B, Fernandes R, Kennedy DA, . . . Fergusson D. Black cohosh and breast cancer: a

systematic review. Integrative cancer therapies. Jan 2014;13(1):12-29.

Gallo D, De Stefano I, Grazia Prisco M, Scambia G, Ferrandina G. Estrogen receptor beta in cancer: an attractive target for therapy. Current pharmaceutical design. 2012;18(19):2734-2757.

Gass ML, Stuenkel CA, Utian WH, LaCroix A, Liu JH, Shifren JL. Use of compounded hormone therapy in the United States: report of The North American Menopause Society Survey. Menopause (New York, N.Y.). Dec 2015;22(12):1276-1284.

Genazzani AR, Pluchino N. DHEA therapy in postmenopausal women: the need to move forward beyond the lack of evidence. Climacteric. 2010 Aug;13(4):314-6.

Gencel VB, Benjamin MM, Bahou SN, Khalil RA. Vascular effects of phytoestrogens and alternative menopausal hormone therapy in cardiovascular disease. Mini reviews in medicinal chemistry. Feb 2012;12(2):149-174.

Giatti S, Melcangi RC, Pesaresi M. The other side of progestins: effects in the brain. Journal of molecular endocrinology. Aug 2016;57(2):R109-126.

Glaser R, Dimitrakakis C. Testosterone and breast cancer prevention. Maturitas. Nov 2015;82(3):291-295.

Goh SY, Loh KC. Gynaecomastia and the herbal tonic "Dong Quai". Singapore Med J. 2001;42(3, pp. 115–116.

Hajirahimkhan A, Dietz BM, Bolton JL. Botanical modulation of menopausal symptoms: Mechanisms of action? Planta Med. May 2013;79(7):538-553.

Hajirahimkhan A, Simmler C, Yuan Y, Anderson JR, Chen SN, Nikolic D, . . . Bolton JL. Evaluation of estrogenic activity of licorice species in comparison with hops used in botanicals for menopausal symptoms. PloS one. 2013;8(7):e67947.

Hardy ML. Herbs of special interest to women. J Am Pharm Assoc (Wash). 2000;40(2):234–242.

Hargrove JT, Maxson WS, et al. Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone. Obstet Gynecol. 1989;73(4): 606-612.

Hasper I, Ventskovskiy BM, Rettenberger R, Heger PW, Riley DS, Kaszkin-Bettag M. Long-term efficacy and safety of the special extract ERr 731 of Rheum rhaponticum in perimenopausal women with menopausal symptoms. Menopause (New York, N.Y.). Jan-Feb 2009;16(1):117-131.

Havlikova H, Hill M, Hampl R, et al. Sex- and age-related changes in epitestosterone in relation to pregnenolone sulfate and testosterone in normal subjects. J Clin Endocrinol Metab. 2002 May;87(5):2225-31.

Hayashi T, Ito I, et al. Estriol (E3) replacement improves endothelial function and bone mineral density in very elderly women. J Gerontol A Biol Sci Med Sci. 2000;55(4): B183-190; discussion B191-183.

Heger M, Ventskovskiy BM, Borzenko I, Kneis KC, Rettenberger R, Kaszkin-Bettag M, Heger PW. Efficacy and safety of a special extract of Rheum rhaponticum (ERr 731) in perimenopausal women with climacteric complaints: a 12-week randomized, double-blind, placebo-controlled trial. Menopause (New York, N.Y.). Sep-Oct 2006;13(5):744-759.

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? Postgrad Med. 2009;121(1): 73-85.

Hostanska K, Nisslein T, Freudenstein J, et al. Evaluation of cell death caused by triterpene glycosides and phenolic substances from Cimicifuga racemosa extract in human MCF-7 breast cancer cells. Biol Pharm Bull. 2004;27(12):1970–1975.

Hsuuw YD, Chan WH. Epigallocatechin gallate dose-dependently induces apoptosis or necrosis in human MCF-7 cells. Ann N Y Acad Sci. 2007;1095: 428-440.

Hu J, Zhang Z, Shen WJ, Azhar S. Cellular cholesterol delivery, intracellular processing and utilization for biosynthesis of steroid hormones. Nutrition & metabolism. Jun 01 2010;7:47.

Ismail PM, Amato P, Soyal SM, DeMayo FJ, Conneely OM, O'Malley BW, Lydon JP. Progesterone involvement in breast development and tumorigenesis--as revealed by progesterone receptor "knockout" and "knockin" mouse models. Steroids. Nov 2003;68(10-13):779-787.

Itoi H, Minakami H, et al. Comparison of the long-term effects of oral estriol with the effects of conjugated estrogen on serum lipid profile in early menopausal women. Maturitas. 2000;36(3): 217-222.

Jehan S, Masters-Isarilov A, Salifu I, Zizi F, Jean-Louis G, Pandi-Perumal SR, . . . McFarlane SI. Sleep Disorders in Postmenopausal Women. Journal of sleep disorders & therapy. Aug 2015;4(5).

Jiang K, Jin Y, Huang L, Feng S, Hou X, Du B, . . . Li L. Black cohosh improves objective sleep in postmenopausal women with sleep disturbance. Climacteric: the journal of the International Menopause Society. Aug 2015;18(4):559-567.

Kano H, Hayashi T, et al. Estriol retards and stabilizes atherosclerosis through an NO-mediated system. Life Sci. 2002;71(1): 31-42.

Kansal S, Negi AK, et al. Evaluation of the role of oxidative stress in chemopreventive action of fish oil and celecoxib in the initiation phase of 7,12-dimethyl benz(alpha)anthracene-induced mammary carcinogenesis. Tumour Biol. 2011;32(1):167-77.

Kaszkin-Bettag M, Beck S, Richardson A, Heger PW, Beer AM. Efficacy of the special extract ERr 731 from rhapontic rhubarb for menopausal complaints: a 6-month open observational study. Altern Ther Health Med. Nov-Dec 2008;14(6):32-38.

Kaszkin-Bettag M, Ventskovskiy BM, Kravchenko A, Rettenberger R, Richardson A, Heger PW, Heger M. The special extract ERr 731 of the roots of Rheum rhaponticum decreases anxiety and improves health state and general well-being in perimenopausal women. Menopause (New York, N.Y.). Mar-Apr 2007;14(2):270-283.

Kaszkin-Bettag M, Ventskovskiy BM, Solskyy S, Beck S, Hasper I, Kravchenko A, . . . Heger PW. Confirmation of the efficacy of ERr 731 in perimenopausal women with menopausal symptoms. Altern Ther Health Med. Jan-Feb 2009;15(1):24-34.

Kenny AM, Boxer RS, et al: Dehydroepiandrosterone combined with exercise improves muscle strength and physical function in frail older women. J Am Geriatr Soc.2010 Sep;58(9):1707-14.

Khalesi S, Irwin C, Schubert M. Flaxseed consumption may reduce blood pressure: a systematic review and meta-analysis of controlled trials. The Journal of nutrition. Apr 2015;145(4):758-765.

Ko KP. Isoflavones: chemistry, analysis, functions and effects on health and cancer. Asian Pacific journal of cancer prevention: APJCP. 2014;15(17):7001-7010.

Konda V, Swick A, Troup JD, Montalto MB, Wilson M, Heidt K, . . . Komarnytsky S. Efficacy of Rheum rhaponticum ERr 731® extract in alleviating vasomotor menopausal symptoms in an ovariectomized rat model. Paper presented at: NAMS Annual Meeting 2014; Washington, D.C.

Kupfersztain C, Rotem C, Fagot R, Kaplan B. The immediate effect of natural plant extract, Angelica sinensis and Matricaria chamomilla (Climex) for the treatment of hot flushes during menopause. A preliminary report. Clinical and experimental obstetrics & gynecology. 2003;30(4):203-206.

Labrie F, Martel C, Belanger A, Pelletier G. Androgens in women are essentially made from DHEA in each peripheral tissue according to intracrinology. The Journal of steroid biochemistry and molecular biology. Apr 2017;168:9-18.

Labrie F. DHEA, important source of sex steroids in men and even more in women. Prog Brain Res. 2010;182:97-148.

Laidlaw M, Cockerline CA, Sepkovic DW. Effects of A Breast-Health Herbal Formula Supplement on Estrogen Metabolism in Pre- and Post-Menopausal Women not Taking Hormonal Contraceptives or Supplements: A Randomized Controlled Trial. Breast Cancer (Auckl). 2010 Dec 16;4:85-95.

Lampe JW. Interindividual differences in response to plant-based diets: implications for cancer risk. Am J Clin Nutr. 2009 May;89(5):1553S-1557S. Epub 2009 Mar 18.

Landete JM, Arques J, Medina M, Gaya P, de Las Rivas B, Munoz R. Bioactivation of Phytoestrogens: Intestinal Bacteria and Health. Critical reviews in food science and nutrition. Aug 17 2016;56(11):1826-1843.

Larsen PK, M.; Alvarado, L.; Lee, M. Hormone testing: When to use serum, saliv, and urine. Townsend Letter. 2014.

Lee CG, Carr MC, Murdoch SJ, Mitchell E, Woods NF, Wener MH, . . . Brunzell JD. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. The Journal of clinical endocrinology and metabolism. Apr 2009;94(4):1104-1110.

Leeangkoonsathian E, Pantasri T, Chaovisitseree S, Morakot N. The effect of different progestogens on sleep in postmenopausal women: a randomized trial. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology. Jun 13 2017:1-4.

Leong H, Mathur PS, et al. Inhibition of mammary tumorigenesis in the C3(1)/SV40 mouse model by green tea. Breast Cancer Res Treat. 2008;107(3): 359-369.

Lephart ED. Modulation of Aromatase by Phytoestrogens. Enzyme Res. 2015;2015:594656.

L'Hermite M. Bioidentical menopausal hormone therapy: registered hormones (non-oral estradiol +/- progesterone) are optimal. Climacteric: the journal of the International Menopause Society. Aug 2017;20(4):331-338.

Li J, Liu Y, Wang T, Zhao L, Feng W. Does genistein lower plasma lipids and homocysteine levels in postmenopausal women? A meta-analysis. Climacteric: the journal of the International Menopause Society. Oct 2016;19(5):440-447.

Li Y, Li S, Meng X, Gan RY, Zhang JJ, Li HB. Dietary Natural Products for Prevention and Treatment of Breast Cancer. Nutrients. Jul 08 2017;9(7).

Liang J, Shang Y. Estrogen and cancer. Annual review of physiology. 2013;75:225-240.

Liang K, Yang L, et al. Estrogen stimulates degradation of beta-amyloid peptide by up-regulating neprilysin. J Biol Chem. 2010;285(2): 935-942.

Lim DW, Kim YT. Anti-osteoporotic effects of Angelica sinensis (Oliv.) Diels extract on ovariectomized rats and its oral toxicity in rats. Nutrients. Oct 16 2014;6(10):4362-4372.

Lindenfeld EA, Langer RD. Bleeding patterns of the hormone replacement therapies in the postmenopausal estrogen and progestin interventions trial. Obstet Gynecol. 2002;100(5 Pt 1): 853-863.

Linford NJ, Dorsa DM, et al. 17beta-estradiol and the phytoestrogen genistein attenuate neuronal apoptosis induced by the endoplasmic reticulum calcium ATPase inhibitor thapsigargin. Steroids. 2002;67(13-14):1029-1040.

Lu LJ, Cree M, Josyula S, et al. Increased urinary excretion of 2-hydroxyestrone but not 16alpha-hydroxyestrone in premenopausal women during a soya diet containing isoflavones. Cancer Res. 2000;60(5):1299–1305.

Ma Y, Sullivan JC, et al. Dietary genistein and equol (4', 7 isoflavandiol) reduce oxidative stress and protect rats against focal cerebral ischemia. Am J Physiol Regul Integr Comp Physiol. 2010;299(3): R871-877.

Maayan R, Touati-Werner D, Shamir D, Yadid G, Friedman A, Eisner D, . . . Herman I. The effect of DHEA complementary treatment on heroin addicts participating in a rehabilitation program: a preliminary study. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology. Jun 2008;18(6):406-413.

Mainini G, Torella M, Di Donna MC, Esposito E, Ercolano S, Correa R, . . . De Franciscis P. Nonhormonal management of postmenopausal women: effects of a red clover based isoflavones supplementation on climacteric syndrome and cardiovascular risk serum profile. Clinical and experimental obstetrics & gynecology. 2013;40(3):337-341.

Mandal CC, Ghosh-Choudhury T, Yoneda T, Choudhury GG, Ghosh-Choudhury N. Fish oil prevents breast cancer cell metastasis to bone. Biochem Biophys Res Commun. 2010 Nov 26;402(4):602-7.

Mani SK, Oyola MG. Progesterone signaling mechanisms in brain and behavior. Frontiers in endocrinology. 2012;3:7.

Maninger N, Wolkowitz OM, Reus VI, Epel ES, Mellon SH. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front Neuroendocrinol. 2009 Jan;30(1):65-91.

Marconett CN, Singhal AK, Sundar SN, Firestone GL. Indole-3-carbinol disrupts estrogen receptor-alpha dependent expression of insulin-like growth factor-1 receptor and insulin receptor substrate-1 and proliferation of human breast cancer cells. Molecular and cellular endocrinology. Nov 05 2012;363(1-2):74-84.

Mason JK, Thompson LU. Flaxseed and its lignan and oil components: can they play a role in reducing the risk of and improving the treatment of breast cancer? Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. Jun 2014;39(6):663-678.

Masuda M, Suzui M, et al. Epigallocatechin-3-gallate decreases VEGF production in head and neck and breast carcinoma cells by inhibiting EGFR-related pathways of signal transduction. J Exp Ther Oncol. 2002;2(6): 350-359.

Mayo W, George O, Darbra S, Bouyer JJ, Vallee M, Darnaudery M, . . . Abrous N. Individual differences in cognitive aging: implication of pregnenolone sulfate. Progress in neurobiology. Sep 2003;71(1):43-48.

Mellon SH. Neurosteroid regulation of central nervous system development. Pharmacol Ther. 2007 Oct;116(1):107-24.

Messina M. Impact of Soy Foods on the Development of Breast Cancer and the Prognosis of Breast Cancer Patients. Forschende Komplementarmedizin (2006). 2016;23(2):75-80.

Messina M. Soy foods, isoflavones, and the health of postmenopausal women. The American journal of clinical nutrition. Jul 2014;100 Suppl 1:423s-430s.

Miyake A, Takeda T, Isobe A, et al. Repressive effect of the phytoestrogen genistein on estradiol-induced uterine leiomyoma cell proliferation. Gynecol Endocrinol. 2009 Jun;25(6):403-9.

Mohammad-Alizadeh-Charandabi S, Shahnazi M, Nahaee J, Bayatipayan S. Efficacy of black cohosh (Cimicifuga racemosa L.) in treating early symptoms of menopause: a randomized clinical trial. Chinese medicine. Nov 01 2013;8(1):20.

Mohammed H, Russell IA, Stark R, Rueda OM, Hickey TE, Tarulli GA, . . . Carroll JS. Progesterone receptor modulates ERalpha action in breast cancer. Nature. Jul 16 2015;523(7560):313-317.

Montplaisir J, Lorrain J, et al. Sleep in menopause: differential effects of two forms of hormone replacement therapy. Menopause. 2001;8(1): 10-16.

Moore SC, Matthews CE, Ou Shu X, Yu K, Gail MH, Xu X, . . . Ziegler RG. Endogenous Estrogens, Estrogen Metabolites, and Breast Cancer Risk in Postmenopausal Chinese Women. Journal of the National Cancer Institute. Oct 2016;108(10).

Moskowitz D. A comprehensive review of the safety and efficacy of bioidentical hormones for the management of menopause

and related health risks. Altern Med Rev. 2006 Sep;11(3):208-23.

Muti P, Bradlow HL, Micheli A, et al. Estrogen metabolism and risk of breast cancer: a prospective study of the 2:16alpha-hydroxyestrone ratio in premenopausal and postmenopausal women. Epidemiology. 2000;11(6):635–640.

Nabavi SF, Daglia M, Tundis R, Loizzo MR, Sobarzo-Sanchez E, Orhan IE, Nabavi SM. Genistein: A Boon for Mitigating Ischemic Stroke. Current topics in medicinal chemistry. 2015;15(17):1714-1721.

Nahidi F, Zare E, Mojab F, Alavi-Majd H. Effects of licorice on relief and recurrence of menopausal hot flashes. Iranian journal of pharmaceutical research: IJPR. Spring 2012;11(2):541-548.

NAMS. The North American Menopause Society. Hormone Therapy: Benefits & Risks. 2017. http://www.menopause.org/for-women/menopauseflashes/menopause-symptoms-and-treatments/hormone-therapy-benefits-risks. Accessed 7/26/2017.

Nedergaard A, Henriksen K, Karsdal MA, Christiansen C. Menopause, estrogens and frailty. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology. May 2013;29(5):418-423.

NIH. National Institutes of Health. Black Cohosh. https://ods.od.nih.gov/factsheets/BlackCohosh-HealthProfessional/. Last updated 3/3/2017. Accessed 10/24/2017.

Nisslein T, Freudenstein J. Effects of an isopropanolic extract of Cimicifuga racemosa on urinary crosslinks and other parameters of bone quality in an ovariectomized rat model of osteoporosis. J Bone Miner Metab. 2003;21(6):370–376.

Notelovitz M. Clinical opinion: the biologic and pharmacologic principles of estrogen therapy for symptomatic menopause. MedGenMed: Medscape general medicine. Mar 28 2006;8(1):85.

Ofir R, Tamir S, et al. Inhibition of serotonin re-uptake by licorice constituents. J Mol Neurosci. 2003;20(2):135-140.

Omoto Y, Iwase H. Clinical significance of estrogen receptor beta in breast and prostate cancer from biological aspects. Cancer science. Apr 2015;106(4):337-343.

Panth N, Manandhar B, Paudel KR. Anticancer Activity of Punica granatum (Pomegranate): A Review. Phytotherapy research: PTR. Apr 2017;31(4):568-578.

Parazzini F, Di Martino M, Candiani M, Vigano P. Dietary components and uterine leiomyomas: a review of published data. Nutr Cancer. 2015;67(4):569-579.

Pietschmann P, Mechtcheriakova D, Meshcheryakova A, Foger-Samwald U, Ellinger I. Immunology of Osteoporosis: A Mini-Review. Gerontology. 2016;62(2):128-137.

Pluchino N, Drakopoulos P, Bianchi-Demicheli F, Wenger JM, Petignat P, Genazzani AR. Neurobiology of DHEA and effects on sexuality, mood and cognition. The Journal of steroid biochemistry and molecular biology. Jan 2015;145:273-280.

Prior JC. Progesterone or progestin as menopausal ovarian hormone therapy: recent physiology-based clinical evidence. Current opinion in endocrinology, diabetes, and obesity. Dec 2015;22(6):495-501.

Randel A. AACE Releases Guidelines for Menopausal Hormone Therapy. American family physician. 2012;86(9):664-868.

Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, . . . Berry DA. The decrease in breast-cancer incidence in 2003 in the United States. The New England journal of medicine. Apr 19 2007;356(16):1670-1674.

Rettberg JR, Yao J, Brinton RD. Estrogen: a master regulator of bioenergetic systems in the brain and body. Frontiers in neuroendocrinology. Jan 2014;35(1):8-30.

Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology. 2008 Jan 15;70(3):200-9.

Rosano GM, Webb CM, et al. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women. J Am Coll Cardiol. 2000;36(7): 2154-2159.

Ross SM. Menopause: a standardized isopropanolic black cohosh extract (remifemin) is found to be safe and effective for menopausal symptoms. Holistic nursing practice. Jan-Feb 2012;26(1):58-61.

Rotem C, Kaplan B. Phyto-Female Complex for the relief of hot flushes, night sweats and quality of sleep: randomized, controlled, double-blind pilot study. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology. Feb 2007;23(2):117-122.

Ruiz AD, Daniels KR. The effectiveness of sublingual and topical compounded bioidentical hormone replacement therapy in postmenopausal women: an observational cohort study. Int J Pharm Compd. Jan-Feb 2014;18(1):70-77.

Rutkowski K, Sowa P, Rutkowska-Talipska J, Kuryliszyn-Moskal A, Rutkowski R. Dehydroepiandrosterone (DHEA): hypes and hopes. Drugs. Jul 2014;74(11):1195-1207.

Ryan N, Rosner A. Quality of life and costs associated with micronized progesterone and medroxyprogesterone acetate in hormone replacement therapy for nonhysterectomized, postmenopausal women. Clin Ther. 2001;23(7): 1099-1115.

Saha KR, Rahman MM, Paul AR, Das S, Haque S, Jafrin W, Mia AR. Changes in lipid profile of postmenopausal women. Mymensingh medical journal: MMJ. Oct 2013;22(4):706-711.

Samaras N, Papadopoulou MA, Samaras D, Ongaro F. Off-label use of hormones as an antiaging strategy: a review. Clinical interventions in aging. 2014;9:1175-1186.

Samavat H, Kurzer MS. Estrogen metabolism and breast cancer. Cancer letters. Jan 28 2015;356(2 Pt A):231-243.

Santoro N, Braunstein GD, Butts CL, Martin KA, McDermott M, Pinkerton JV. Compounded Bioidentical Hormones in Endocrinology Practice: An Endocrine Society Scientific Statement. The Journal of clinical endocrinology and metabolism. Apr 2016;101(4):1318-1343.

Saoudi M, Hmida lB, Kammoun W, Rebah FB, Jamoussi K, Feki AE. Protective effects of oil of Sardinella pilchardis against subacute chlorpyrifos-induced oxidative stress in female rats. Archives of environmental & occupational health. Apr 10 2017:1-8.

Sarkar FH, Li Y. Soy isoflavones and cancer prevention. Cancer Invest. 2003;21(5):744–757.

Sarri G, Pedder H, Dias S, Guo Y, Lumsden MA. Vasomotor symptoms resulting from natural menopause: a systematic review and network meta-analysis of treatment effects from the National Institute for Health and Care Excellence guideline on menopause. BJOG: an international journal of obstetrics and gynaecology. Sep 2017;124(10):1514-1523.

Scarabin PY. Hormone therapy and venous thromboembolism among postmenopausal women. Frontiers of hormone research. 2014;43:21-32.

Schneider HP. Androgens and antiandrogens. Ann NY Acad Sci. 2003;997:292-306.

Schonberg MA, Davis RB, et al. After the Women's Health Initiative: decision making and trust of women taking hormone therapy. Womens Health Issues. 2005;15(4): 187-195.

Schreihofer DA, Redmond L. Soy phytoestrogens are neuroprotective against stroke-like injury in vitro. Neuroscience. 2009;158(2): 602-609.

Seidlova-Wuttke D, Jarry H, Becker T, Christoffel V, Wuttke W. Pharmacology of Cimicifuga racemosa extract BNO 1055 in rats: bone, fat and uterus. Maturitas. Mar 14 2003;44 Suppl 1:S39-50.

Seidlova-Wuttke D, Jarry H, Pitzel L, Wuttke W. Effects of estradiol-17beta, testosterone and a black cohosh preparation on bone and prostate in orchidectomized rats. Maturitas. Jun 16 2005;51(2):177-186.

Shah NR, Wong T. Current breast cancer risks of hormone replacement therapy in postmenopausal women. Expert opinion on pharmacotherapy. Dec 2006;7(18):2455-2463.

Shahnazi M, Nahaee J, Mohammad-Alizadeh-Charandabi S, Bayatipayan S. Effect of black cohosh (cimicifuga racemosa) on vasomotor symptoms in postmenopausal women: a randomized clinical trial. Journal of caring sciences. Jun 2013;2(2):105-113.

Shams T, Setia MS, Hemmings R, et al. Efficacy of black cohosh-containing preparations on menopausal symptoms: a meta-analysis. Altern Ther Health Med. 2010 Jan-Feb;16(1):36-44.

Simon JA. Safety of estrogen/androgen regimens. J Reprod Med. 2001 Mar;46(3 Suppl):281-90.

Simon JA. What's new in hormone replacement therapy: focus on transdermal estradiol and micronized progesterone. Climacteric: the journal of the International Menopause Society. Apr 2012;15 Suppl 1:3-10.

Simpson ER. Sources of estrogen and their importance. The Journal of steroid biochemistry and molecular biology. Sep 2003;86(3-5):225-230.

Sirotkin AV, Harrath AH. Phytoestrogens and their effects. European journal of pharmacology. Oct 15 2014;741:230-236.

Somjen D, Katzburg S, Vaya J, Kaye AM, Hendel D, Posner GH, Tamir S. Estrogenic activity of glabridin and glabrene from licorice roots on human osteoblasts and prepubertal rat skeletal tissues. The Journal of steroid biochemistry and molecular biology. Aug 2004;91(4-5):241-246.

Somjen D. Knoll E, Vaya J, et al. Estrogen-like activity of licorice root constituents: glabridin and glabrene, in vascular tissues in vitro and in vivo. J Steroid Biochem Mol Biol. 2004;91(3):147–155.

Sood R, Shuster L, Smith R, Vincent A, Jatoi A. Counseling postmenopausal women about bioidentical hormones: ten discussion points for practicing physicians. J Am Board Fam Med. Mar-Apr 2011;24(2):202-210.

Spark MJ, Willis J. Systematic review of progesterone use by midlife and menopausal women. Maturitas. Jul 2012;72(3):192-202.

Stanczyk FZ, Bhavnani BR. Reprint of "Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe?". The Journal of steroid biochemistry and molecular biology. Sep 2015;153:151-159.

Stephenson K, Neuenschwander PF, Kurdowska AK. The effects of compounded bioidentical transdermal hormone therapy on hemostatic, inflammatory, immune factors; cardiovascular biomarkers; quality-of-life measures; and health outcomes in perimenopausal and postmenopausal women. Int J Pharm Compd. Jan-Feb 2013;17(1):74-85.

Sturgeon SR, Ronnenberg AG. Pomegranate and breast cancer: possible mechanisms of prevention. Nutr Rev. 2010 Feb;68(2):122-8.

Sureda A, Sanches Silva A, Sanchez-Machado DI, Lopez-Cervantes J, Daglia M, Nabavi SF, Nabavi SM. Hypotensive effects of genistein: From chemistry to medicine. Chem Biol Interact. Apr 25 2017;268:37-46.

Taheri Rouhi SZ, Sarker MMR, Rahmat A, Alkahtani SA, Othman F. The effect of pomegranate fresh juice versus pomegranate seed powder on metabolic indices, lipid profile, inflammatory biomarkers, and the histopathology of pancreatic islets of Langerhans in streptozotocin-nicotinamide induced type 2 diabetic Sprague-Dawley rats. BMC complementary and alternative medicine. Mar 14 2017;17(1):156.

Taioli E, Im A, Xu X, et al. Comparison of estrogens and estrogen metabolites in human breast tissue and urine. Reprod Biol Endocrinol. 2010 Aug 2;8:93.

Takahashi K, Okada M, et al. Safety and efficacy of oestriol for symptoms of natural or surgically induced menopause. Hum Reprod. 2000;15(5): 1028-1036.

Taku K, Melby MK, Kronenberg F, Kurzer MS, Messina M. Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. Menopause (New York, N.Y.). Jul 2012;19(7):776-790.

Tandon VR, Mahajan A, Sharma S, Sharma A. Prevalence of cardiovascular risk factors in postmenopausal women: A rural study. Journal of mid-life health. Jan 2010;1(1):26-29.

Taylor M. Unconventional estrogens: estriol, biest, and triest. Clin Obstet Gynecol. 2001;44(4):864–879.

Thangapazham RL, Passi N, et al. Green tea polyphenol and epigallocatechin gallate induce apoptosis and inhibit invasion in human breast cancer cells. Cancer Biol Ther. 2007;6(12): 1938-1943.

Thangapazham RL, Singh AK, et al. Green tea polyphenols and its constituent epigallocatechin gallate inhibits proliferation of human breast cancer cells in vitro and in vivo. Cancer Lett. 2007;245(1-2): 232-241.

Thompson LU, Chen JM, et al. Dietary flaxseed alters tumor biological markers in postmenopausal breast cancer. Clin Cancer Res. 2005;11(10): 3828-3835.

Thyer L, Ward E, Smith R, Fiore MG, Magherini S, Branca JJ, . . . Pacini S. A novel role for a major component of the vitamin D axis: vitamin D binding protein-derived macrophage activating factor induces human breast cancer cell apoptosis through stimulation of macrophages. Nutrients. Jul 08 2013;5(7):2577-2589.

Toi M, Bando H, Ramachandran C, Melnick SJ, Imai A, Fife RS, Carr RE, Oikawa T, Lansky EP. Preliminary studies on the anti-angiogenic potential of pomegranate fractions in vitro and in vivo. Angiogenesis. 2003;6(2):121-8.

Toriizuka K, Mizowaki M, Hanawa T. [Menopause and anxiety: focus on steroidal hormones and GABAA receptor]. Nihon Yakurigaku Zasshi. Jan 2000;115(1):21-28.

Trimarco V, Rozza F, Izzo R, De Leo V, Cappelli V, Riccardi C, Di Carlo C. Effects of a new combination of nutraceuticals on postmenopausal symptoms and metabolic profile: a crossover, randomized, double-blind trial. International journal of women's health. 2016;8:581-587.

USP. The United States Pharmacopeial Convention. Compounding Standards: USP General Chapter <795> Pharmaceutical Compounding - Nonsterile Preparations. http://www.usp.org/compounding/general-chapter-795. 1/1/2014. Accessed 10/12/2017.

Vallée M, Mayo W, Le Moal M. Role of pregnenolone, dehydroepiandrosterone and their sulfate esters on learning and memory in cognitive aging. Brain Res Brain Res Rev. 2001 Nov;37(1-3):301-12.

Vallee M. Neurosteroids and potential therapeutics: Focus on pregnenolone. The Journal of steroid biochemistry and molecular biology. Jun 2016;160:78-87.

van Die MD, Burger HG, Teede HJ, Bone KM. Vitex agnus-castus (Chaste-Tree/Berry) in the treatment of menopause-related complaints. Journal of alternative and complementary medicine. Aug 2009;15(8):853-862.

Vargas KG, Milic J, Zaciragic A, Wen KX, Jaspers L, Nano J, . . . Franco OH. The functions of estrogen receptor beta in the female brain: A systematic review. Maturitas. Nov 2016;93:41-57.

Vincent A, Fitzpatrick LA. Soy isoflavones: are they useful in menopause? Mayo Clin Proc. 2000;75(11):1174–1184.

Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ (Clinical research ed.). Jan 9 2019;364:k4810.

Vitale DC, Piazza C, Melilli B, Drago F, Salomone S. Isoflavones: estrogenic activity, biological effect and bioavailability. European journal of drug metabolism and pharmacokinetics. Mar 2013;38(1):15-25.

Vrieling A, Hein R, Abbas S, Schneeweiss A, Flesch-Janys D, Chang-Claude J. Serum 25-hydroxyvitamin D and postmenopausal breast cancer survival: a prospective patient cohort study. Breast cancer research: BCR. Jul 26 2011;13(4):R74.

Wada K, Nakamura K, Tamai Y, Tsuji M, Kawachi T, Hori A, . . . Nagata C. Soy isoflavone intake and breast cancer risk in Japan: from the Takayama study. International journal of cancer. Journal international du cancer. Aug 15 2013;133(4):952-960.

Watt PJ, Hughes RB, et al. A holistic programmatic approach to natural hormone replacement. Fam Community Health. 2003;25(1):53-63.

Weiss EP, Shah K, Fontana L, et al. Dehydroepiandrosterone replacement therapy in older adults: 1- and 2-y effects on bone. Am J Clin Nutr. 2009 May;89(5):1459-67.

Weiss EP, Villareal DT, Ehsani AA, Fontana L, Holloszy JO. Dehydroepiandrosterone replacement therapy in older adults improves indices of arterial stiffness. Aging Cell. Oct 2012;11(5):876-884.

Weiss EP, Villareal DT, Fontana L, Han DH, Holloszy JO. Dehydroepiandrosterone (DHEA) replacement decreases insulin resistance and lowers inflammatory cytokines in aging humans. Aging (Albany NY). May 2011;3(5):533-542.

Weitzmann MN, Pacifici R. Estrogen deficiency and bone loss: an inflammatory tale. J Clin Invest. 2006 May;116(5):1186-94.

Welsh J. Vitamin D and breast cancer: Past and present. The Journal of steroid biochemistry and molecular biology. Jul 23 2017.

Weng JR, Tsai CH, Kulp SK, Chen CS. Indole-3-carbinol as a chemopreventive and anti-cancer agent. Cancer Lett. 2008 Apr 18;262(2):153-63.

Wharton W, Gleason CE, Olson SR, Carlsson CM, Asthana S. Neurobiological Underpinnings of the Estrogen - Mood Relationship. Current psychiatry reviews. Aug 01 2012;8(3):247-256.

Whelan AM, Jurgens TM, Trinacty M. Defining bioidentical hormones for menopause-related symptoms. Pharm Pract (Granada). Jan 2011;9(1):16-22.

Wober J, Moller F, Richter T, Unger C, Weigt C, Jandausch A, . . . Vollmer G. Activation of estrogen receptor-beta by a special extract of Rheum rhaponticum (ERr 731), its aglycones and structurally related compounds. The Journal of steroid biochemistry and molecular biology. Nov-Dec 2007;107(3-5):191-201.

Wuttke W, Seidlova-Wuttke D, Gorkow C. The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas. Mar 14 2003;44 Suppl 1:S67-77.

Yamanaka Y, Matsuo H, et al. Effects of combined estriol/pravastatin therapy on intima-media thickness of common carotid artery in hyperlipidemic postmenopausal women. Gynecol Obstet Invest. 2005;59(2): 67-69.

Yao Z-X, Brown RC, Teper G, et al. 22R-Hydroxycholesterol protects neuronal cells from β-amyloid-induced cytotoxicity by binding to β-amyloid peptide. J Neurochemistry. 2002 Dec;83(5):1110-19.

Yu HL, Li L, et al. Neuroprotective effects of genistein and folic acid on apoptosis of rat cultured cortical neurons induced by beta-amyloid 31-35. Br J Nutr. 2009;102(5): 655-662.

Zaluska M, Janota B. [Dehydroepiandrosteron (DHEA) in the mechanisms of stress and depression]. Psychiatria polska. May-Jun 2009;43(3):263-274.

Zhao S, Chlebowski RT, Anderson GL, Kuller LH, Manson JE, Gass M, . . . Prentice RL. Sex hormone associations with breast cancer risk and the mediation of randomized trial postmenopausal hormone therapy effects. Breast cancer research: BCR. Mar 26 2014;16(2):R30.

Zheng P. Neuroactive steroid regulation of neurotransmitter release in the CNS: action, mechanism and possible significance. Progress in neurobiology. Oct 2009;89(2):134-152.

Zhou Y, Yang R, Li C, Tao M. Sleep disorder, an independent risk associated with arterial stiffness in menopause. Sci Rep. May 15 2017;7(1):1904.

Ziegler RG, Fuhrman BJ, Moore SC, Matthews CE. Epidemiologic studies of estrogen metabolism and breast cancer. Steroids. 2015;99(Pt A):67-75.

Zittermann A. [Phytoestrogens]. Zentralbl Gynakol. 2003;125(6):195–201.