

The Safety of Phytoestrogens in Menopause, Prostate and Breast Cancer

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ABSTRACT

Plant based natural products have been proposed as alternatives to the use of hormones for the treatment of menopausal symptoms, which has been associated with an increased risk of breast cancer and coronary artery disease. Specific herbal compounds such as Thai Kudzu root (*Pueraria mirifica*) have shown beneficial effects in the treatment of peri-menopausal symptoms and menopausal-related osteoporosis when used as an adjunct or as a single medicine. *Pueraria mirifica* has been used in conjunction with Vitex Berry (*Vitex agnus-castus*), Red Clover (*Trifolium pratense*) Sage (*Salvia officinalis* and *S. miltiorrhiza*), and Black Cohosh (*Actaea racemosa*), with the optional addition of natural progesterone and soy milk. Clinically, these compounds require careful dosing and are associated with variable times to efficacy. No known drug interactions exist, although research on the effects of phytoestrogens is limited. Phytoestrogens have not been associated with increased risk of cancer and therefore provide a safe alternative to standard treatment modalities.

Keywords: Phytoestrogens; Prostate cancer; Breast cancer

CLINICAL IMPLICATIONS

The therapeutic use of hormones to relieve menopausal symptoms has been linked to an increased risk of breast cancer as well as coronary artery disease. Therefore, specific herbs (e.g. Thai Kudzu Root (*Pueraria mirifica*)) may be beneficial in the management of peri-menopausal hot flashes, vaginal atrophy, and loss of bone density post-menopause. Further, these herbs are indicated as they are not implicated with an increased risk of cancer and offer a safe alternative to standard treatment modalities.

PRIMARY INDICATION

Peri-menopausal symptoms and menopausal-related osteoporosis

ADJUNCTIVE OR STAND-ALONE TREATMENT

Adjunctive or Stand-Alone

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CLINICAL IMPLICATIONS (CONTINUED)

DOSE OF BIOACTIVE CONSTITUENTS

Pueraria mirifica (whole plant extracts 400-900 mg per day; containing 2.5 mg of Puerarin. *Synergistic Herbal Formula*: Thai Kudzu root (*Pueraria mirifica*, Vitex Berry (*Vitex agnus-castus*), Red Clover (*Trifolium pratense*) Sage (*Salvia officinalis* and *S. miltiorrhiza*), Black Cohosh (*Actaea racemosa*). Natural progesterone and the dietary addition of soy milk are additional options to relieve specific symptoms.

DURATION OF TIME FOR EFFICACY

Physicians have noted that therapeutic results occur more reliably at higher doses; at lower doses, results have been disappointing. At correct dosage, results can be seen within a month.

LAB TEST TO ASSESS EFFICACY

None known

TIME TO CLINICAL EFFICACY

Variable

DRUG INTERACTIONS AND CAUTIONS

These herbs can be safely consumed when used appropriately

UNSUBSTANTIATED THEORETICAL CONCERNS

Pueraria may increase the anticoagulant effects and bleeding risk of anticoagulant and anti-platelet medications. *Pueraria* may inhibit Tamoxifen from binding to some estrogen receptors, and may competitively inhibit the effects of oral contraceptives and estrogen therapy. *Pueraria* may also lower blood glucose levels and may have additive effects when used with glucose lowering medications and supplements, increasing the risk of hypoglycemia in some patients. No clinical or scientific evidence has validated any of these concerns.

DISCUSSION

Embryologic development of the breasts, prostate and reproductive organs involves both estrogens and androgens. Exposure to exogenous estrogens in the neonatal period such as hormonally active synthetic chemicals, may increase the risk of hormonally-related cancers later in life.^{1,2} Similarly, steroidal metabolism and signaling may be disrupted early in life through exposure to hormonally-active synthetic chemicals. This phenomenon is referred to as “endocrine disruption.” Conversely, natural plant-based compounds such as phytoestrogens may reduce the chances of hormone-related reproductive cancers later in life.³ Phytoestrogens may mitigate the severity of endocrine disruptors, and offer positive hormonal influences on the breast and prostate. Furthermore, genes that control cellular and hormonal receptor quantities and response are also shown to be unfavorably influenced by exogenous chemicals^{4,5} and favorably influenced by phytoestrogens.^{6,7}

This review suggests that phytoestrogens offer a positive influence (as early as *in utero*) on hormonal balance, when included in the diet on a regular basis. Phytoestrogens also appear to be valuable in the treatment protocols for breast and prostate cancers.^{8–11} Although phytoestrogens can exert weak estrogenic effects themselves, there is emerging evidence that such hormonal actions do not stimulate cancer cell growth, but rather mitigate (or even block) endogenous hormone effects by: 1) inhibiting hormone receptors, 2) modulating enzyme systems that process hormones, and 3) interact with hormone-regulating genes.^{12–14}

Standard doses of specific phytoestrogens include Pueraria Extract (400 mg *twice per day*), or Genistein (50 mg *twice per day*). Side-effects of high-dose soy extract containing phytoestrogens have been implicated in causing a mild increase in TSH for post-menopausal women.^{15,16} However, this effect was only present in patients with low iodine levels; to date, no adverse interactions between phytoestrogens and prescription drugs have been published.

In animal models (at andropause and middle-age, when thyroid function may decline) in many species—both daidzein and genistein were reported

by Sobic-Jurjevic *et al* to induce microfollicular changes in the thyroid and depress thyroid function enough to produce a measureable increase in TSH.¹⁷ However, other researchers have suggested substances other than soy isoflavones are responsible for the thyroid function suppression.¹⁸ In animals, Doerge *et al* suggest that pre-existing iodine deficiency is necessary for soy to exert a thyrosuppressive effect.¹⁶

PHYTOESTROGENS AS SELECTIVE ESTROGEN-RESPONSE MODIFIERS

Alpha and beta estrogen receptors oppose and balance one another. While alpha subtype receptors direct cellular proliferation, beta estrogen receptors direct cellular differentiation and apoptosis.¹⁸ Research to develop specific estrogen receptor subtypes found in specific tissue types as a means to improve the treatment of estrogen-dependent



Actaea racemosa of the Ranunculaceae family

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cancers and disease is currently underway. These therapeutic agents are referred to as Selective Estrogen Response Modifiers or SERMs.

Genistein (an isoflavone type of phytoestrogen common in legumes) is a beta subtype estrogen receptor agonist, and thus can be considered a natural SERM. Genistein is one of the most well-researched and active isoflavone phytoestrogens. Genistein may affect gene expression due to direct activity at estrogen receptors. Studies have shown that Genistein may improve the response of estrogen positive cancers to radiation,¹⁹ and inhibit prostate cancer cell growth.²⁰ Genistein also positively influences steroid-producing genes, and activates several genes associated with tumor suppression.²¹ Therapeutic supplementation with isoflavones in dosages that exceed typical dietary amounts may slow the progression of prostate cancer without any noticeable side effects or toxicity.²² In one study, male patients diagnosed with prostate cancer were administered isoflavones in the form of soy milk to deliver a standardized amount of Genistein three times per day (for a total of 141 mg *per day*) for one year.²¹ For nearly all of the research subjects, serum equol was increased; for many men the upward trend of PSA levels was either stabilized or even reversed.^{23,24} Note: Equol is a metabolite of daidzein produced in the gut, and a high level has been associated with health benefits.²⁵

THE AMPHOTERIC ACTION OF PHYTOESTROGENS

When phytoestrogens bind to estrogen receptors, they can act as either agonists or antagonists. This activity and ligand affinity may render phytoestrogens the ideal SERMs. For example, isoflavones might act as weak agonists in situations of low estrogen in the body, yet might also reduce estrogenic stimulation. This dual action of phytoestrogens—to both offer estrogenic support and reduce excessive estrogen stimulation—is referred to as “amphoterism” by many clinical herbalists. Inclusion of isoflavones and other phytoestrogens either in the form of herbal supplements or in the diet is believed to offer many health benefits such as protection against hormone-related cancers.^{23–27} In a cellular assay, synthetic phytoestrogen-like compounds were tested, and interestingly displayed

no such amphoteric action.²⁸ In terms of phytoestrogens and hormonal enzyme systems, the enzymes affected by phytoestrogens include aromatase, dehydrogenase, reductase and sulphotransferase enzyme; in turn, all of these enzymes may affect hormonally-related cancers.

Sulfotransferases

Sulfotransferases are Phase II detoxifying (conjugation) enzymes. Sulfotransferases add sulfur to estrogens, rendering them less active²⁹; this occurs because sulfated estrogens do not bind to estrogen receptors.³⁰ Genistein, Quercetin, and Resveratrol have been shown to promote the activity of sulfotransferases.^{31,32}

Dehydrogenases

17-beta dehydrogenase enzymes are responsible for oxidizing steroids, making them less active and reducing the overall amount of active hormone circulating in the bloodstream. Breast cancer, prostate cancer and endometriosis are thought by some to be steroid-dependent diseases that display imbalances of dehydrogenase enzymes and the hormones they regulate.³³ Many phytoestrogens (including flavonoids, coumarins, and coumestans) have been noted to inhibit 17-beta dehydrogenase.^{34–36}

5 Alpha Reductase Inhibitors

5-alpha-reductase is the enzyme that is responsible for the conversion of testosterone into its active form, dihydrotestosterone (DHT). Since DHT has greater stimulatory and proliferative effects on the prostate gland compared to testosterone, prostate enlargement and cancer treatment may include inhibition of this enzyme. Finasteride (*Proscar*) is a synthetic pharmaceutical agent used for this purpose. High fat diets (which affect the genes that control 5-alpha-reductase in the prostate) stimulate prostate enlargement; this may be mitigated by dietary enhancement with Genistein.^{37–41} Some botanicals that inhibit 5-alpha-reductase activity are Saw Palmetto (*Serenoa repens*), Pygeum Bark (*Pygeum africanum*), Nettle Root (*Urtica dioica*) and Green Tea (*Camellia sinensis*) catechins.³⁹ In animal models, *Serenoa repens* had been shown to inhibit tumorigenesis and induce apoptosis of prostate cancer cells.⁴¹ Habib *et al* demonstrated

that *Serenoa* inhibits 5-alpha-reductase and reduces circulating levels of active testosterone in humans.⁴² Other sources claim that *Serenoa* is weak in its ability to block 5-alpha reductase, for example Rhodes *et al.*⁴³ Interestingly, Habib and colleagues also found that *Serenoa repens* (10 µg/ml) could reduce enzyme activity by 72% without interfering with secretion of prostate specific antigen (PSA).⁴²

Aromatase Inhibitors

Aromatase enzymes are abundant in peripheral lipid cells, convert circulating androgens into active estrogens, and have been found in high amounts in prostate cells.⁴⁴ Research studies are investigating the effects of aromatase inhibitors as breast and prostate cancer therapy since aromatase inhibitors suppress circulating estrogen levels and, thus, may inhibit the proliferation of estrogen dependent cancer cells.^{45, 46}

Phytoestrogens, especially those containing a *coumarin* backbone (rather than the isoflavone or steroid ring structures) have been shown to inhibit

aromatase, thereby reducing circulating estrogen levels by approximately 96-98%.⁴⁷ Additionally, phytoestrogens abrogate autocrine and paracrine estrogen production by peritumoral stromal cells located in both primary and metastatic tumor sites.⁴⁷ These phytoestrogens are common in legumes such as *Glycyrrhiza glabra*, *G. uralensis* (Licorice).⁴⁸ It has also been reported that a compound isolated from *Glycyrrhiza* (isoliquirtigenin), displayed significant activity against aromatase in non-cellular, and *in vivo* assays (3.8 and 3 µM IC₅₀, respectively).⁴⁶

PHYTOESTROGENS AS A TREATMENT FOR REPRODUCTIVE CANCERS

Phytoestrogens have only recently become a focus of attention in the treatment of reproductive cancers. The most effective treatment strategies and dosages of phytoestrogens are still undetermined. As recently as 10 years ago, the administration of phytoestrogens to cancer patients was highly controversial, owing to concerns over the possible

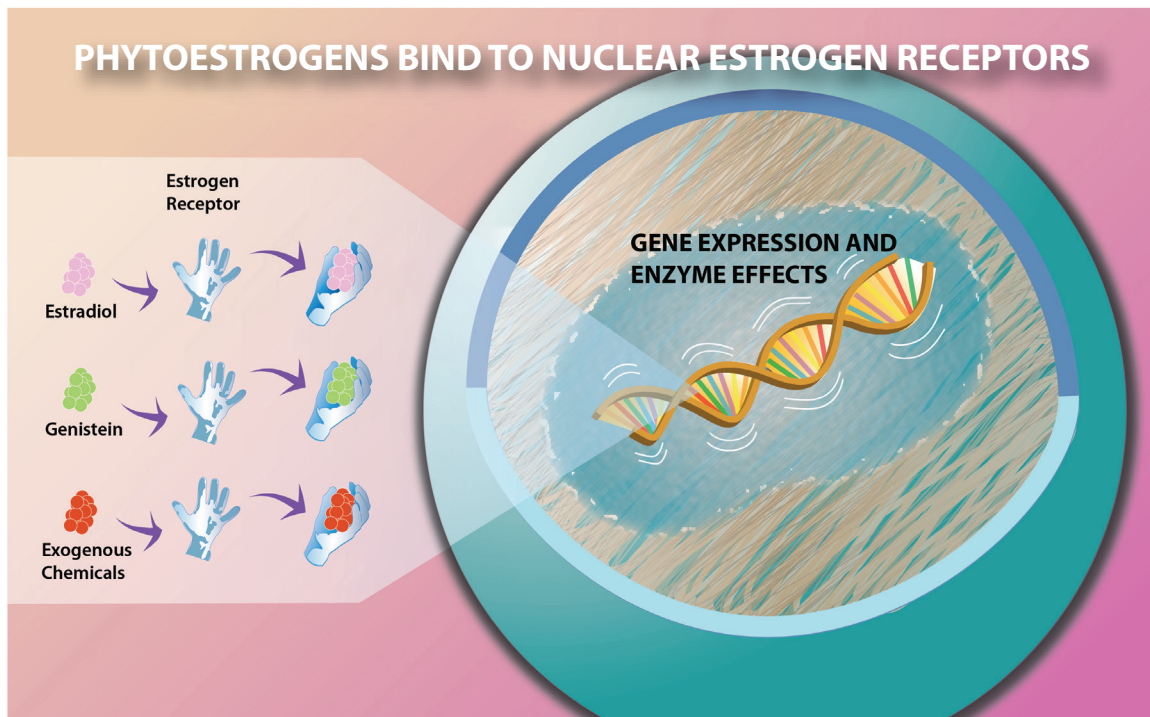


Figure: Estrogen enters cells, travels to the nuclear membrane, and binds to the membrane, eliciting effects on the nuclear DNA. Phytoestrogens can also bind nuclear estrogen receptors and have physiologic/medicinal effects. copyright 2013 © AARM

proliferative effects that these natural estrogen derivatives might display. However, recent studies have shown that phytoestrogen supplementation is not associated with an increased risk of breast or endometrial cancer.⁴⁹ In fact, selected phytoestrogens were associated with a favorable prognosis in progesterone receptor-positive breast cancer cells.⁵⁰

In 2012, the results of a human clinical trial on men (50-75 years of age) with elevated PSAs and negative prostate biopsies investigated the use of isoflavone (at a dose of 60 mg daily) on PSA and equol levels, as well as the progression to prostate cancer within a 12 month period. While there were no significant differences observed in PSA and equol levels between the clinical trial and placebo groups, a diagnosis of prostate cancer was significantly lower in the group receiving the isoflavone.⁵¹

The above-described effects of phytoestrogen activity combined with the results of recent research suggest that phytoestrogen consumption may be beneficial for the prevention and treatment of breast and prostate cancers.

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DISCLOSURE OF INTERESTS

Dr. Saunders reports personal fees related to employment or seeing patients from CCNM, the Dundas Naturopathic Centre, and from Beaumont Health Systems, Troy Hospital, MI, outside the submitted work. Dr. Winston reports personal fees from Herbalist & Alchemist, Inc, outside the submitted work. Dr. Stansbury has nothing to disclose.

REVIEW ESSAY

Many nutrients and herbs that have not been the subject of randomized controlled studies are used regularly by clinicians. They have also been used traditionally for hundreds, sometimes thousands of years. Review Essays contain the opinions of professionals and experts in the fields of nutritional and botanical medicine on how to most effectively use herbs and nutrients in clinical practice. The dosages recommended are based on clinical experience. Side effects that are described in “Unsubstantiated Theoretical Concerns” have not been seen in clinical practice or clinical studies but are speculative based on, for example, possible mechanisms of action.

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