

PHYTOESTROGEN REVIEW

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Estrogen and Estrogen Receptor Basics

Estrogens and all steroids play many important physiologic roles in both men and women. Not only do the estrogens (estradiol, estriol, and estrone) help direct basic sexual characteristics, but they also affect the central nervous system in terms of masculinization, feminization, and sexual behavior. In addition, estrogens help regulate follicle-stimulating hormone (FSH) in a feedback loop, which in turn plays a role in testicular and ovarian development.

Estrogen receptors are also abundant in the bone tissues of both men and women, and estrogen plays a role in the closure of the epiphyseal plates of long bones during adolescence. Estrogens also play an important role in the vasculature, where they are involved with vasodilation. Less understood, but presently under investigation, are the roles that estrogens play in the prostate gland and in male sexual organ function in general. Estrogen appears important both in the development as well as the life-long function of fluid formation within the prostate gland and testes.¹ Both deficiencies and excesses of estrogen can affect embryologic development and can be associated with infertility and other issues of sexual function in men and women.

Alpha and Beta Estrogen Receptors

In addition to there being several forms of estrogen, there are also several types of estrogen receptors. The alpha subtype of estrogen receptor (ER- α) is most active early in the fetal and neonatal periods, directing growth and proliferation; while the beta subtype (ER- β) dominates in puberty and adulthood where it acts to regulate differentiation of steroid-sensitive cells and tissues. When the balance between alpha and beta receptors (as well as the balance between androgens and estrogens) is disrupted, reproductive health is impaired.² This phenomenon is referred to as ‘endocrine disruption.’ Steroidal metabolism and signaling may be ‘disrupted’ early in life through exposure to hormonally active compounds. DES (diethylstilbestrol), for example, is a profound endocrine disruptor and one of the first such chemicals studied.

In addition to steroids themselves, heavy metals, PCBs, pesticides, and numerous other chemicals are reported to act as endocrine disruptors.³ Exposure to endocrine disruptors during the fetal and pubertal periods appears especially harmful to steroidal signaling and homeostatic balances; thus pregnant women and preteens should especially avoid exposure to pollutants and exogenous estrogens of all types.

In tissues possessing both alpha and beta estrogen receptors, the two types seem to counteract and balance one another. In general, ER- α directs cellular proliferation while ER- β directs differentiation and apoptosis.⁴ Intensive research is underway to develop therapies that target specific subtypes of receptor and are specific to individual tissue types. These therapeutic agents are referred to as SERMs – selective estrogen response modifiers.

Many phytoestrogens have a higher binding affinity for ER- β than for ER- α . Because more beta receptors are found on reproductive organs and bone, and more alpha receptors are found on the

vasculature, phytoestrogens are natural SERMs having vast therapeutic potential. Most phytoestrogens are found to offer benefits for menopausal symptoms and bone density without carrying the risks of heart disease, coronary artery damage, or peripheral vascular issues.⁵ Therapies for breast, endometrial, and other hormonally-sensitive cancers have been improved with the advent of pharmaceutical SERMs (e.g., tamoxifen and raloxifene); and phytoestrogens are increasingly being researched for cancer as well as for the management of hormonal and reproductive pathologies.

Phytoestrogens and Gene Expression

In addition to direct estrogen-related risk factors, estrogen-driven gene expression phenomena may also increase the risk of hormonal cancers. Specific genes associated with prostate, breast, and endometrial cancers may be over- or under-expressed due to altered hormonal balances or deranged nutritional and physiologic status of the entire biochemical ecosystem.⁶ For example, system-wide dominance of certain estrogens or androgens may cause genes associated with those steroids to be over expressed.⁷ Androgen-dependant tumors, such as prostate cancer, typically involve the over-expression of genes coding for the synthesis of androgens in the first place.⁸ And even more complex, altered pancreatic genes that regulate insulin transcription and over-expression of choline kinase and certain neuropeptides⁹ are being revealed as playing roles in the development of prostate and hormonal cancers. A normal anti-tumor gene has been demonstrated to be 'turned off' in some situations and is found to be lacking in patients with prostate cancer and many other types of cancer as well.¹⁰ Cadherin genes affect cell-to-cell communication and adhesion and are found to be involved with prostate cancer and bone metastasis.¹¹

As viruses are known to turn certain genes on and off, they are being investigated as potentially therapeutic anticancer agents as well as for their causative roles in certain types of cancer. The human papilloma virus (HPV) is associated with cervical cancer. And the intraprostatic injection of a certain adenovirus has been explored for men with localized prostate cancer as a means of stimulating anti-tumor gene expression.¹²

Phytoestrogen Basics

Isoflavones, coumestans, lignans and their metabolites, flavonoids, and stilbenoids may all be considered phytoestrogens as they can interact with estrogen receptors, alter gene expression, and otherwise affect hormones. Isoflavones and coumestans are particularly high in the legume family, which includes many different edible beans such as soy, lima, lentils, peas, kidney, pinto, and green beans, and the common medical plants *Trifolium*, *Medicago*, and *Glycyrrhiza*.

Isoflavones / Isoflavonoids

The isoflavones include genistein, biochanin A, formononetin, and daidzein, with genistein being the most active and daidzein the least. Genistein is high in *Trifolium*, *Phaseolus*, *Glycine*, and *Pueraria*. Formononetin occurs in *Trifolium*, *Astragalus*,¹³ *Pueraria*,¹⁴ and *Glycyrrhiza*. Genistin is the glycoside of genistein and is sometimes mentioned in the literature. *Humulus lupulus* contains the prenylated flavanone, 8-prenylnaringenin, confirmed to have ligand activity at

estrogen receptors.¹⁵ *Pueraria mirifica* is rich in phytoestrogens including daidzin. Animal studies have reported an estrogenic effect from *Pueraria*.¹⁶

Coumestans

Coumestans are reported to have the most pronounced estrogenic effect of all the phytoestrogens. The most common and most studied coumestan is coumestrol, found in *Trifolium*, *Pisum*, *Medicago*,¹⁷ *Glycyrrhiza*,¹⁸ *Glycine* and especially Brussels sprouts (*Brassica oleracea*, Gemmifera group). Coumestans are the least commonly ingested phytoestrogen in the typical diet. *Lespedeza*¹⁹ and *Eclipta prostrata*²⁰ are both reported to contain coumestans.

Stilbenoids

Stilbenoids are being studied for their chemopreventive effects, lipid-lowering and vascular activities, as enhancers of insulin sensitivity, and as agents to increase lifespan in general. Resveratrol, the most common and most studied stilbenoid, is found in red wine and other brightly pigmented fruit juices. Grape (*Vitis vinifera*) is the most notable source and other berries also contain stilbenoids. Peanuts (*Arachis* spp.) contain resveratrol, particularly found in the papery skin around the nut.²¹ Pistachios also contain resveratrol. While resveratrol is most often discussed in terms of its vascular effects (similar to flavonoids), it has some phytoestrogenic activity as well. Piceid is a metabolite of resveratrol found in the same plant sources as resveratrol,²² and pterostilbene is another less commonly mentioned stilbene also found in grapes and berries.²³ *Morus australis* contains the dimeric stilbenes australfurans B and C.²⁴

Lignans and metabolites

Lignans include matairesinol, secoisolariciresinol, lariciresinol, pinoresinol, and their metabolites desmethylangolensin, enterodiol, enterolactone, and equol. Of all the phytoestrogens, lignans are the most common in the general diet. Lignans are fiber-like indigestible substances consumed when eating whole grains, flax seeds, and seedy fruits and vegetables. They are metabolized by intestinal bacteria into derivatives (e.g., enterolactone, enterodiol, and equol) with increased phytoestrogenic activity. As has been demonstrated for breast cancer risk, intestinal metabolites of lignans appear to have a hormone-modulating effect. Because plant lignans are converted into weakly estrogenic compounds by the intestinal microflora, intestinal dysbiosis can affect hormonal status in the body.

The estrogenic lignan metabolites appear to have beneficial effects on hormone status in the body by exerting very weak hormonal effects themselves. By competing for binding sites with the much stronger endogenous and exogenous estrogens, these lignan metabolites may help to reduce excessive hormonal stimulation on estrogen-sensitive tissues, offering a protective effect against breast and prostatic cancers.²⁵ Enterolactone is so-named because it is a lactone produced within the intestines (*entero-* refers to the gut). Enterolactone has been shown to inhibit the proliferation of prostate cancer cell lines, induce apoptosis, and favorably alter gene expression.²⁶ The production of mammalian enterolactone is enhanced by a diet rich in lignans.

The use of antibiotics may abolish the ability of intestinal flora to produce active phytoestrogen metabolites, and women who use antibiotics repeatedly may incur increased risk of breast cancer as a result. Smoking and obesity are also associated with a reduction in enterolactone production while coffee, tea, and of course fiber intake are noted to enhance the production of enterolactone.

Flavonoids

Flavonoids with estrogenic activity abound; among the most commonly studied and discussed are rutin, catechin, apigenin, kaempferol, luteolin, chrysin and puerarin.²⁷ The isoflavones, categorized separately in this paper, are closely related to the flavonoids, as are the chalcones (e.g., isoliquiritigenin). Subtypes of the flavonoids include the flavanones, flavones, and flavonols, many of which are reported to have estrogenic activity. The various flavonoids and all of their physiologic activities are too vast and diverse to list. A few examples of plants with hormonally active flavonoids include *Vitex agnus-castus*, with its vitexin and penduletin reported to selectively bind estrogen receptors.²⁸ Pomegranate (*Punica granatum*) fruits and juice contain luteolin, kaempferol, and quercetin.²⁹

Rutin is found in violets, spinach, rhubarb, buckwheat, parsley, *Hydrangea*, *Sambucus*, *Tussilago*, *Amaranthus*,³⁰ *Indigofera*,³¹ tomatoes,³² *Ilex paraguariensis*,³³ numerous *Ruta* species (for which the compound was named), and many other plants as well. Chrysin occurs in *Passiflora*, *Scutellaria*,³⁴ propolis, and numerous herbs. Apigenin is found in *Matricaria*, *Achillea*, *Chrysanthemum*, *Scutellaria*, and others. Kaempferol occurs in *Ginkgo*,³⁵ *Carthamus tinctorius*,³⁶ *Azadirachta*, *Pisum*, *Thespesia*, *Brassica oleracea*, *Allium schoenoprasum*, *Delphinium consolida*, *Cuscuta reflexa*, and *Siparuna apiosyce*. Luteolin is found in *Thymus*, *Aspalathus linearis*, *Cyperus rotundus*, *Passiflora incarnata*, *Swertia pseudochinensis*, *Vitex polygama*, and many other plants.

A Closer Look at Genistein

Genistein is one of the most active and well-studied of the isoflavonoid phytoestrogens. It gets its name from the Mediterranean leguminous plants *Genista morisii* and *G. ephedroides*. Genistein may affect gene expression due to direct activity at estrogen receptors. Animal studies show that genistein consumed in the maternal diet can pass in breast milk to nursing infants. Although it binds both alpha and beta estrogen receptors, genistein is reported to have greater affinity for ER- β than for ER- α . Favoring the beta receptors over the alpha receptors is believed to reduce hormonal stimulation and proliferation of hormonally sensitive tissues.

There have been over 4,500 studies on genistein alone describing various hormonal effects. Around a fifth of these address a variety of anticancer effects. Numerous studies have noted an amphoteric biphasic effect, where genistein reduces the stimulation of estrogen receptors at some dosage ranges, but may stimulate them at high dosages; this suggests caution in regards to active hormonal cancers. For example, one group of researchers reported genistein to promote the growth of breast cancer cell lines and to interfere with the inhibitory effects of tamoxiphene on estrogen-dependant cancer cell lines.³⁷

However, genistein has mostly been noted to inhibit hormone-related carcinogenesis in animal models. It has been shown to inhibit human cancer cell proliferation due to modulation of genes involved with cell turnover, and to enhance apoptosis of cancer cells. Genistein may also antagonize estrogen- and androgen-mediated cancer growth, as well as exert anti-angiogenic effects in cancer lines.³⁸ Genistein and isoflavones also act as aromatase inhibitors.³⁹ Aromatase is a cytochrome p-450 enzyme family member that converts androgens (androstenedione and

testosterone) into estrogens (estrone and estradiol, respectively); high levels of aromatase enzymes are associated with breast, adrenal, and prostate cancers (see below).

Genistein and breast cancer

One human clinical study on women with a family history of breast cancer reported *Trifolium* isoflavones to be safe and observed them to exert no proliferative effects on breast or endometrial tissue.⁴⁰ Another study investigated blood concentrations of genistein and daidzein in women with benign proliferative breast conditions, active breast cancer, and age-matched controls. The study demonstrated an inverse relationship between serum isoflavone levels and cancer risk.⁴¹

Genistein and prostate cancer

One *in vitro* study on prostate cancer cells showed genistein to improve the response to radiation therapy in estrogen-positive cancers. Investigations have reported genistein to have inhibitory effects on prostate cancer cell lines via antiproliferative activity as well. Genistein inhibits the proliferation of prostate cells in part due to influencing the expression of steroidal-producing genes. Genistein is reported to activate several genes associated with tumor suppression and is one proposed mechanism of protection against prostate cancer. Supplementation with isoflavones in dosages that exceed typical dietary amounts is noted to slow the progression of prostate cancer, without noticeable side effects or toxicity.

Current Investigative Methods for Phytoestrogens

- *In vitro* estrogen receptor binding assays
- Estrogen receptor-related gene activation
- Estrogen's metabolic enzyme assays
- Estrogen-prompted protein synthesis assays
- Estrogen's agonistic versus antagonistic receptor effects
- Estrogen's proliferative or antiproliferative effects on sensitive tissues
- Estrogen's effect on prepubertal animals

Dietary Phytoestrogens

Although both plant phytoestrogens and pharmaceutical HRT exert effects on the endocrine system, research overall suggests that unlike synthetic estrogens, phytoestrogens are protective and beneficial when consumed in whole foods. Rather than disrupting endocrine balance as do so many synthetic chemicals, normal dietary levels of phytoestrogens appear to have a balancing effect.⁴²

One of the theories to explain the significantly lower rates of breast and prostate cancers in Asia (as compared to the U.S. and Europe) is the frequent consumption of soy products and the phytoestrogens they contain. For example, when ingested throughout a lifetime, genistein may offer a protective effect against estrogen-dependant cancers, based on its ability to block the hyperproliferative activity of more powerful endogenous and exogenous estrogens.⁴³

Animal studies on dietary phytoestrogens

Animal studies show that genistein consumed in the maternal diet is passed to nursing infants in the breast milk. Prolonged exposure to genistein in early life is reported to reduce the risk of hormonally related cancers later in life. Research suggests that although they are weakly estrogenic, phytoestrogens are protective and beneficial when consumed in normal dietary levels, rather than disruptive to endocrine balance as is the case with many synthetic chemicals.

One mouse study compared the results of a high-phytoestrogen soy feed to a low-phytoestrogen, soy-free feed on hormonal parameters in offspring. The offspring whose mothers received low-phytoestrogen feed had higher estradiol levels in general, with early puberty in the females and larger prostates and smaller testes in the males; while the high-phytoestrogen offspring displayed healthier reproductive status.⁴⁴ Furthermore, the low-phytoestrogen group displayed a tendency to obesity and altered glucose regulation later in life. Researchers have suggested that these effects become even more pronounced over several generations of similar dietary influences.

High levels of urinary isoflavones are associated with a decreased risk of breast cancer. Although it is thought that lifelong consumption is most associated with decreased cancer risk, it appears that inclusion of isoflavones in the diet for as little as one month may alter urinary estrogen metabolites in a significant and beneficial way.⁴⁵

Human studies on dietary phytoestrogens

One large, seven-year study followed men with BPH, obtaining diet and lifestyle information over the years and monitoring for the progression of symptoms over time. Researchers reported that lycopene, zinc, and supplemental vitamin D appeared to weakly reduce the progression of BPH, while a diet low in fat and red meat and high in protein and vegetables slowed the hypertrophy and the emergence of symptoms overall.⁴⁶

Another study evaluated the effects of year-long supplementation with *Trifolium* isoflavones on men with elevated PSA levels. PSA levels were shown to decline by around 30% by the end of the year without significant alteration of other hormone levels in the body.⁴⁷

Yet another study treated men with recurrent prostate cancer with isoflavones in the form of a standardized soy milk, dosed 3 times per day for one year. For nearly all men, serum equol was increased, and for many men the upward trend of PSA levels was either stabilized or in some cases reversed.⁴⁸

Phytoestrogens and Amphotericism

Amphotericism, an old concept in herbal medicine, embraces the observation that phytoestrogens appear to balance estrogen in both directions, whether excessive or deficient. Phytoestrogens (being SERMs) have such varying activity and affinity for different estrogen receptor subtypes in various tissues that they most certainly could be said to have amphoteric effects in the body. For example, isoflavones might act as weak estrogen receptor agonists in situations of low endogenous estrogen, exerting an overall estrogenic effect; yet that weak agonism can compete with a high endogenous estrogen load to reduce overall estrogenic stimulation in a situation of hyperestrogenism. While *SERM* is a term arising out of modern molecular and pharmaceutical research, *amphotericism* comes from traditional herbalism. There is research to support the

herbal concept; for example, the inclusion of isoflavones and other phytoestrogens in the diet or as medicine is noted to treat menopausal symptoms as well as to protect against breast cancer.⁴⁹

The herbal concept of amphotericism is also echoed by the pharmacologic concept of dose-dependent curves, also referred to as U (or J or S) curves. In one study involving normal tissue and hormonal status, low doses of phytoestrogens were reported to be aromatase inhibitors and to reduce estrogenic activity, while higher doses became estrogenic in net effect displaying a classic U-shaped curve. Synthetic phytoestrogen-like compounds were also tested and interestingly displayed no such amphoteric action.⁵⁰ Phytoestrogens may agonize or antagonize estrogen receptors to different degrees depending on the estrogen load in the general system. Phytoestrogens may also affect alpha and beta estrogen receptor subtypes differently, as well as affecting enzyme subtypes differently under different circumstances.

Phytoestrogens and Estrogen-Sensitive Cancers

As a general rule, the consumption of phytoestrogen-containing plants in the diet or in dietary supplements appears beneficial. However, in the case of hormonal cancers, it would not be wise to inundate the body with isoflavones and risk estrogenic stimulation. Small frequent doses, such as from sipping herbal teas throughout the day or including legumes in the diet, may be safer than consuming concentrated nutraceutical isoflavones in situations involving active estrogen receptor-positive cancers.

While many studies have suggested a chemopreventive effect for genistein, a few have reported that long-term use may induce chromosomal imbalances that may predispose to breast cancer.⁵¹ There is also some evidence that supplementation with genistein could abolish the anti-tumor effects of tamoxifen in cases of breast cancer.⁵² Other researchers looked at individual phytoestrogens – genistein, daidzein, and equol, alone and in combination – and reported that the combination appears to be safest and to modify the effects of any one phytoestrogen used alone. Researchers reported that when using whole-food combinations, a binding preference for ER-β is observed more so than when using genistein alone.⁵³

Outside of cancer, however, aggressive supplementation with isoflavones might be appropriate (e.g., with osteoporosis) because isoflavones have also been shown to build bone mass and density.

The Anticancer Effects of Phytoestrogens

Much of the research on phytoestrogens involves their ability to inhibit the development of hormonal cancers, an activity known as chemoprevention. Hundreds of studies have shown phytoestrogens to reduce the proliferative effects of actual human steroids and synthetic substances on hormonally sensitive tissues. Dietary flavonoids have been classified as phytoestrogens due to numerous chemoprevention abilities that include hormonal mechanisms. Research has revealed that not only do isoflavones act as natural SERMs, but they also induce apoptosis, affect gene expression, and influence various enzyme systems in positive ways – all mechanisms helping to reduce excessive estrogen stimulation of hormonally sensitive tissues.⁵⁴

The specific steroidal enzyme systems affected by phytoestrogens include the aromatase, dehydrogenase, sulphotransferase, and reductase enzymes. Sulphotransferases are involved with estradiol production and may be over-expressed in many estrogen-dependant cancers. Phytoestrogens are noted to reduce sulphotransferases when excessive,⁵⁵ thus reducing hormonal excess, yet many phytoestrogens offer weak estrogenic effects themselves.

Using genistein as the single most studied example, phytoestrogens exhibit anticancer effects by a variety of different mechanisms. Genistein is noted to inhibit tyrosine kinase, topoisomerase, aromatase, dehydrogenase, and other enzymes involved with signal transduction and DNA replication, transcription, and repair – all potential anticancer mechanisms. Genistein and daidzein are also reported to induce apoptosis in breast cancer cell lines⁵⁶ and ovarian cancer cell lines.⁵⁷

Phytoestrogen consumption is associated with a decreased risk of prostate cancer. Genistein is noted to down-regulate androgen receptors and to limit androgen-stimulated proliferation of the prostate gland.⁵⁸ Daidzein also has demonstrated an ability to block the proliferative effects of testosterone on the prostate in animals.⁵⁹ Isoflavones have been shown to arrest growth and induce apoptosis in prostate cancer cells, both *in vitro* and *in vivo*.⁶⁰ Mechanisms of this effect include inhibition of the dehydrogenase, aromatase, and 5-alpha reductase enzymes.⁶¹

The binding of phytoestrogens to ER- β has been reported to be involved with the prevention of colorectal cancer.⁶² ER- β has been implicated in the development of adenomatous polyps in the colon and in their cancerous transformation.

Diosmetin is metabolized to luteolin via aromatic demethylation and has been found to be cytotoxic to breast cancer cell lines.⁶³ *Withania somnifera* contains unique steroidal lactones known as withanolides which are credited with reducing inflammatory cytokines and being chemopreventives for prostate cancer.⁶⁴

Phytoestrogens and Hormone-Metabolizing Enzymes

Aromatase inhibitors

Aromatase enzymes convert testosterone and progesterone into estrogen, and aromatase inhibitors therefore will also reduce estrogenic stimulation. Arimidex[®] is a pharmaceutical aromatase inhibitor used by patients with breast and uterine cancers. Aromatase is a cytochrome p-450 enzyme family member that, more specifically, converts androgens (androstenedione and testosterone) into estrogens (estrone and estradiol, respectively); high levels of aromatase enzymes are associated with breast, adrenal, and prostate cancers.⁶⁵ Many such cancers over-express aromatase enzymes, leading to excessive levels of estrogen. Aromatase enzymes are abundant in peripheral lipid cells, but have also been found in high amounts in prostate cells themselves.⁶⁶

Several groups of phytochemicals have been shown to be natural aromatase inhibitors, with the flavonoids thought to be the most active. Some companies are attempting to synthesize aromatase-inhibiting isoflavones, though most herbalists question the logic of this.

In addition to flavonoids, many phytoestrogens such as lignans, coumestrol, and isoflavonoids are noted to be aromatase inhibitors.⁶⁷ *Coix lacryma-jobi*, a barley-like seed, is commonly used in traditional Chinese medicine for endocrine dysfunction, but has not been well studied. One recent investigation reported *Coix* to reduce estradiol due to a variety of mechanisms including aromatase inhibition.⁶⁸ White button mushrooms (*Agaricus bisporus*) have also demonstrated aromatase inhibition⁶⁹ and can thereby reduce estrogen levels, and have also been shown to reduce testosterone-induced cell proliferation in cancer cell lines.⁷⁰ The activity is thought to be due to lignans and fatty acids including linoleic acid, an EFA.

Flavonoid aromatase inhibitors

Numerous flavonoid molecules have been shown to be aromatase inhibitors. Grape seeds and juice, red wine, blueberries, pomegranates, and other brightly pigmented plants high in flavonoids are potent antioxidants and anti-inflammatories; they are also noted to improve hormonal balance via a variety of mechanisms. The colorless isoflavones, prominent in the legume family, are also among the widely studied aromatase inhibitors. These are probably best for prevention of hormonal cancers, but may also be attempted aggressively with dietary and herbal supplemental measures in cases of hormonally sensitive cancers. Specific to hormonal cancers, isoflavones have been shown to arrest growth and induce apoptosis in prostate cancer cells, both *in vitro* and *in vivo*.⁷¹ The anticancer mechanisms of isoflavones include inhibition of the dehydrogenase, aromatase, and 5-alpha reductase enzymes. The hydroxyflavanones are one group of flavonoids that may treat or prevent hormone-dependent cancers.

Dehydrogenase inhibitors

The 17-beta dehydrogenase (17 β -HSD) family of enzymes contains various isozymes (subtypes) responsible for either oxidizing and reducing various steroids (both estrogens and androgens), making them either more or less potent and controlling the amount of active hormones circulating in the bloodstream. There are at least 15 subtypes of these enzymes; breast cancer, prostate cancer, and endometriosis have all been shown to involve imbalances of 17- β dehydrogenases and the hormones that they regulate. Thus drugs and natural agents that accelerate the enzymatic inactivation of steroids, or prevent the synthesis of excessive steroids in the first place, are an important research arena for breast, endometrial, prostate, and other hormone-dependant cancers.⁷²

Many phytoestrogens including flavonoids, isoflavones, coumarins, and coumestans are noted to inhibit certain 17 β -HSD isozymes in addition to being aromatase inhibitors.^{73,74,75} *Serenoa repens* contains phytosterols that may inhibit the conversion of testosterone into the more active dihydrotestosterone via inhibition of some 17 β -HSD isozymes. Licorice (*Glycyrrhiza glabra*) is reported to inhibit some of the steroid dehydrogenases, due in part to its glycyrrhetic acid content.⁷⁵

Certain 17 β -HSD isozymes are particularly prominent in the breasts and prostate gland where they play a role in regulating ligand access to androgen and estrogen receptors. Inhibitors of these isozymes are believed to reduce hormonally stimulated proliferation of tissues and thereby have anticancer effects.⁷⁶

5-alpha reductase inhibitors

5 α -reductase is the enzyme that converts testosterone into the more active dihydrotestosterone. Because dihydrotestosterone is noted to have increased stimulatory and proliferative effects on the prostate gland compared to testosterone, inhibition of this enzyme is a present therapy in the management of prostate enlargement and cancer. Finasteride (Proscar[®]) is a synthetic pharmaceutical used for this purpose. Genes that control 5 α -reductase in the prostate are induced by high-fat diets and inhibited by genistein.⁷⁷ *Serenoa repens*, *Pygeum africanum*, *Urtica* spp. and green tea (*Camellia sinensis*) catechins are botanical agents found to inhibit 5 α -reductase activity.⁷⁸ *Serenoa* is noted to inhibit tumorigenesis and to induce apoptosis in animal models of prostate cancer.⁷⁹ One study showed the combination of astaxanthin with *Serenoa* to inhibit prostate cancer more than *Serenoa* alone.⁸⁰ Human investigations have supported the ability of *Serenoa* to inhibit 5 α -reductase and reduce circulating levels of active testosterone.⁸¹ A review of 18 randomized controlled trials on the effects of *Pygeum africanum* versus placebo on subjective and objective BPH symptoms summarized that *Pygeum* appeared useful and warranted further investigation.⁸²

Common black pepper (*Piper nigrum*) has been found to be a 5 α -reductase inhibitor.^{83,84} Cubebin, a lignan found in many types of pepper, is credited with some of the physiologic activity; and piperine, a major alkaloid of black peppercorns, has been shown to be anti-androgenic via 5 α -reductase inhibition when tested in isolation. The pepper leaf as well as the corns displays inhibition of the reductase enzymes.⁸⁵ *Piper cubeba* has also been found to down-regulate androgen receptors in general.⁸⁶ As male-pattern baldness is also associated with the activity of this enzyme, *Piper* extracts are being explored as potential oral and topical therapy for baldness.

Numerous common and medicinal mushrooms are noted to have anticancer effects as well as 5 α -reductase inhibiting activity. One study reported *Ganoderma lucidum* to be the strongest reductase inhibitor of ten mushrooms tested.⁸⁷

Neuroprotection and Phytoestrogens

Many phytoestrogens are also reported to be neuroprotective. Soy, for example, is observed to protect the brain from damage in experimental models of stroke. Individual soy phytoestrogens including genistein, daidzein, and the metabolite equol were all found to protect the brain from glutamate toxicity via activity at estrogen receptors.⁸⁸

Estrogen is believed to have positive effects on cognition, improving memory and particularly verbal skills. The isoflavone group of phytoestrogens weakly bind estrogen receptors and one clinical trial reported soy supplementation to improve women's performance of a memory exercise.⁸⁹ Isoflavones are believed to have a protective activity for women at risk of Parkinson's disease by having neuroprotective effects on dopaminergic neurons.⁹⁰

Menopausal Therapy and Phytoestrogens

Isoflavones from soy are probably the most studied phytochemicals for improving bone density and treating menopausal symptoms.⁹¹ Isoflavones from *Trifolium* have been shown to improve bone density, tissue integrity, and vaginal blood flow.⁹² Although black cohosh (*Actaea*

racemosa) was reported in earlier studies to contain the isoflavone formononetin, contemporary analyses have not been able to detect this compound in the plant; therefore, other constituents must be responsible for its ability to alleviate hot flashes and improve bone density.⁹³

Vascular Effects

There are estrogen receptors on blood vessels that play roles in vasodilation, amongst other things. Metabolic syndrome may have a relationship to estrogen in that insulin, C-reactive protein, and leptin all respond to changes in estrogen levels in the body. Phytoestrogens are known to improve cholesterol and lipids and may be therapeutic to metabolic syndrome.⁹⁴

Medicago sativa phytoestrogens are believed to have beneficial activities on the vasculature such as hyperlipidemic effects.⁹⁵ The animal studies on dietary phytoestrogens (previously cited) also noted a protection from hyperlipidemia and metabolic syndrome. Phytoestrogens may also affect blood cells themselves and thereby have immune effects. Many are noted to improve white blood cell immune response.⁹⁶

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