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Isoflavones and the prevention and treatment of prostate disease: Is there a role?

■ ABSTRACT

Epidemiologic and experimental data suggest that isoflavones have benefits for preventing and treating some prostate disease. Isoflavone supplements may therefore be an important tool for men concerned about prostate disease, such as those with benign prostatic hypertrophy undergoing watchful waiting or those concerned about the potential for prostate cancer. Conclusive proof of a relationship between isoflavones and the prevention and treatment of prostate disease can only come from prospective, randomized, controlled clinical trials.

■ KEY POINTS

Isoflavones are found predominantly in legumes and in red clover.

Isoflavones have plausible mechanisms of action to explain any effect on benign prostatic hypertrophy (BPH) or prostate cancer.

Men in Japan and China have higher plasma levels of isoflavones and lower risk for prostate disease than do men in Finland, Portugal, and Britain.

Soybeans contain vitamin K, which can interfere with some drugs, notably warfarin. People who take this drug should consult their physician before adding soy foods to their diet.

No trials have investigated whether any toxicities are associated with daily intake of isoflavones.

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CAN MEN avoid or treat benign prostatic hypertrophy (BPH) or prostate cancer by consuming a diet rich in isoflavones or by taking isoflavone supplements? And if so, what foods should they eat or what supplements should they take?

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This article provides an overview of the epidemiological and experimental data regarding the role of isoflavones, obtained through diet or via supplements, in the prevention and treatment of BPH, and their possible role in preventing prostate cancer. However, conclusive proof of an ability of isoflavones to prevent or treat prostate disease can only come from prospective, randomized, controlled clinical trials.

■ BPH IS A COMMON PROBLEM AND AFFECTS QUALITY OF LIFE

BPH is common. About 50% of men over age 50 experience some symptoms of this condition,¹ and close to 90% of those over age 80 have histologically proven BPH.²

The major clinical effect of BPH is constriction of the urethra, which prevents complete voiding of the bladder. However, the irritative symptoms of BPH (urinary urgency, urinary frequency, and nocturia) have a greater impact on quality of life than do the obstructive symptoms (hesitancy, straining, decreased urinary flow rate, urinary retention, and postvoid dribbling).³ Symptom severity correlates with overall health status.⁴

■ TREATMENT OPTIONS FOR BPH

Early treatment of BPH can relieve symptoms and prevent progression to more severe disease. Advanced disease generally requires more radical, invasive types of therapy that are associated with significant morbidity.

While surgery is mandatory for men with advanced prostate disease, the best therapy is less clear for men with less advanced disease and moderate symptoms of BPH. These men can opt for watchful waiting, behavior modification, surgery, or medication.

No available treatment is ideal, but treatment is generally preferable to no therapy, particularly if symptoms are bothersome.

Surgery

In a prospective, randomized trial, surgery was more effective than watchful waiting in reducing the rate of treatment failure and improving symptoms and quality of life.⁵

Transurethral resection is the most common surgery performed for BPH,⁵ but it may not always be necessary or even beneficial.⁶ Less invasive, heat-based methods such as microwave thermotherapy,^{7,8} radiofrequency thermotherapy,⁹ and interstitial laser therapy¹⁰ appear to compare favorably with transurethral resection, but head-to-head comparisons have not been carried out extensively, and no concrete guidelines for choosing among the noninvasive methods have been established.¹¹

Medical therapy

In some cases, drug therapy may be preferable.

The 5- α reductase inhibitor finasteride shrinks the prostate and improves symptoms of BPH, increases urinary flow, and decreases prostate volume.¹² A second 5- α reductase inhibitor for BPH, dutasteride, was recently approved.

The alpha-adrenoreceptor blockers terazosin and tamsulosin relieve symptoms of BPH by relaxing smooth muscles in the bladder neck and prostate.^{13,14}

Drug therapies also have their limitations. Finasteride can cause impotence and reduced libido,¹⁵ while alpha-blockers can cause

fatigue, hypotension, dizziness, drowsiness, and nasal congestion.¹³ The adverse effects may preclude the use of these agents for many patients.

Nutritional therapies and supplements

An alternative is nutrition therapy: changing one's diet by including potentially beneficial foods, excluding potentially harmful ones, or adding a nutritional supplement.

Although the advantages of nutrition therapy for BPH have not yet been fully determined, patients may comply with it better than with pharmacotherapy. In 1990, about 34% of the public reported using some type of unconventional therapy for a medical problem.¹⁶ For the 10 most common principal medical conditions, 1 in 4 respondents reported using unconventional therapy and 1 in 10 reported consulting with a provider of unconventional therapy.¹⁶

Many physicians are ill prepared to address dietary issues with their patients. Only about 25% of medical schools in the United States currently require their students to take courses in nutrition. As many as 50% of schools offer nutrition as an elective, but only about 6% of medical students enroll in elective nutrition classes.^{17,18} Patients, however, increasingly want to explore nutritional and complementary therapies, propelling physicians to face these issues.

■ WHAT ARE ISOFLAVONES?

Isoflavones are polyphenolic compounds found predominantly in legumes (soy, chickpeas, lentils, and beans) and in red clover. The four main isoflavones are formononetin, its demethylated product daidzein, biochanin, and its demethylated product genistein.¹⁹

Isoflavones occur unconjugated (aglycone forms) or conjugated to sugars (glucoside forms).²⁰ The aglycone isoflavones are biologically active at the receptor level. In humans, aglycone forms of isoflavones, as found in red clover, readily enter the bloodstream, while the glucoside forms, as found predominantly in soy, are metabolized in the gastrointestinal tract to yield a variety of aglycone isoflavone compounds.²¹

Half of men
over age 50
have some BPH
symptoms

After isoflavones are absorbed, a variety of the aglycone forms can be found in the plasma and the urine (reviewed by Setchell).²² As discussed below, these agents have activities that may be important in treating or preventing BPH and prostate cancer.

■ POSSIBLE ISOFLAVONE MECHANISMS OF ACTION

Effects on sex hormone synthesis and metabolism

Isoflavones may play an important role in steroid metabolism and synthesis, thus affecting the proliferation of hormone-dependent prostate cells.

5-alpha reductase inhibition. Testosterone is converted to 5-alpha dihydrotestosterone, the main prostatic androgen, by the enzyme 5-alpha reductase in the prostate. The isoflavones genistein and biochanin A are effective inhibitors of 5-alpha reductase activity in genital skin fibroblasts and in BPH homogenates.²³

17-beta hydroxysteroid dehydrogenase inhibition. Another enzyme, 17-beta hydroxysteroid dehydrogenase (17-beta-HSD), also plays an essential role in the metabolism of androgens and estrogens. Genistein and biochanin A are effective inhibitors of 17-beta-HSD activity in genital skin fibroblasts and in enzymatic assays conducted with steroid substrates.^{23,24}

UDPGT activation. UDP-glucuronosyltransferase (UDPGT) catalyzes the conjugation of steroid hormones with UDP-glucuronic acid, inactivates them, and facilitates their elimination from tissues. This, in turn, can affect androgen levels. Thus, activation of UDPGT would be expected to down-regulate androgen activity. UDPGT is stimulated by isoflavones *in vitro*.²⁵

Aromatase inhibition. The androgen/estrogen balance is thought to be important in stromal cell hyperplasia. This balance can change as men age and their androgen levels decrease and estrogen levels increase.²⁶

Estrogen levels are directly regulated by the enzyme aromatase (estrogen synthetase). Aromatase inhibitory activity is believed to reduce estrogen levels and, as a result, inhibit stromal cell proliferation.^{27,28} Biochanin A is a potent inhibitor of aromatase activity *in vitro*.²⁹

Estrogen receptor agonism and antagonism. On the other hand, isoflavones may exert their effect by directly binding to estrogen receptors (ERs), thus having antiestrogenic or weak estrogenic effects analogous to those of tamoxifen.^{30–32} In a breast cancer cell system, genistein was shown to have both ER-dependent and ER-independent growth-inhibitory activity.

Since prostate cancers and BPH specimens can express estrogen receptors, their growth may also be subject to estrogenic or antiestrogenic effects of isoflavones.^{33,34} Indeed, tamoxifen has been shown to increase the sensitivity of prostate cancer cells to the growth-inhibitory effects of other antineoplastic agents.³⁵ Genistein and daidzein are agonists of both estrogen receptor alpha and estrogen receptor beta, the two major forms of estrogen receptors, and the two isoflavones have different effects at these receptors.^{36,37}

Molecular and cellular effects

Growth factor inhibition. Isoflavones have demonstrated activity as inhibitors of protein tyrosine kinases, which are involved with growth factor-stimulated proliferation of tumor cells.^{38,39} Indeed, genistein and biochanin A have been found to inhibit growth factor-induced cancer cell proliferation.³⁸ Genistein affects the signal transduction pathway associated with epidermal growth factor, but the exact point in the pathway at which it acts is unknown.⁴⁰

Antioxidant properties. Antioxidants have received considerable attention as cancer-preventive agents. Genistein and daidzein appear to inhibit hydrogen peroxide production and superoxide anion generation in cells, possibly via an indirect regulation of antioxidant enzyme levels.⁴¹ In addition, isoflavones and their reduced derivatives can inhibit microsomal lipid peroxidation *in vitro*.⁴² These findings suggest that isoflavones may inhibit prostate disease by protecting cellular components against oxidative damage.

Promoting cell adhesion. Isoflavone consumption is associated with a low incidence of metastatic prostate cancer, even in populations exhibiting a high basal rate of localized prostate cancer. This has led to the notion that these compounds may promote cell adhe-

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sion, thereby inhibiting metastasis. Genistein has been shown to stimulate cell flattening and cell adhesion in prostate cancer cell lines and to promote complex formation between focal adhesion kinase and beta-1 integrin,⁴³ a key component of a cell's interaction with its extracellular environment. Although this finding is highly suggestive, its biological significance is not known.

Angiogenesis inhibition. Isoflavones might also affect angiogenesis. Genistein has been demonstrated to inhibit angiogenesis and proliferation of vascular endothelial cells in vitro. Other isoflavones, such as equol and daidzein, were less effective inhibitors of endothelial cell proliferation.⁴⁴

■ POSSIBLE PROTECTIVE EFFECTS OF ISOFLAVONES

Epidemiologic evidence

Epidemiologic data indicate that there is a link between diet and the incidence of BPH.

Men in Japan and China have a significantly lower risk for prostate disease than do men in Finland, Portugal, and Britain, all of whom are at high risk.^{45,46} These differences in risk appear to be associated with differences in consumption of isoflavones. Japanese and Chinese men have higher plasma levels of isoflavones than men in the other countries.

Moreover, when men from countries with a low incidence of BPH migrate to countries with a higher incidence and adopt the local dietary customs, their risk of BPH and prostate cancer rises dramatically.^{47,48}

In a recent prospective study of Seventh-Day Adventist men who reported on their intake of soy milk, an association was observed between frequent consumption of soy milk (more than once a day) and reduced risk of prostate cancer (relative risk 0.3).⁴⁹ A separate cohort study of diet, lifestyle, and prostate cancer in 15,000 Seventh-Day Adventist men found that increased consumption of beans, lentils, or peas (at least 3 times/week) was associated with significantly decreased risk of prostate cancer (relative risk 0.53).⁵⁰

A retrospective cross-national analysis indicated a significant ($P = .0001$) protective effect of soy consumption against prostate cancer mortality.⁵¹

Studies in animals

Isoflavones have been shown to promote activity against prostate disease in animals.

Rats fed soy-containing diets had a significantly lower incidence of prostatitis compared with rats on a soy-free diet.⁵²

Furthermore, in a rat model of carcinogen-induced prostate cancer, rats fed a high-isoflavone diet before or after receiving a carcinogen had a lower incidence of prostate cancer compared with rats fed a low-isoflavone diet.⁵³

Case study

Isoflavones may also possess activity against established tumors. A 66-year-old man took 160 mg/day of a standardized isoflavone preparation made from red clover extract for 1 week before undergoing radical prostatectomy for moderately high-grade adenocarcinoma; the prostatectomy specimen showed evidence of apoptosis consistent with androgen deprivation and typical of a response to estrogen therapy. There were no adverse events in the case.⁵⁴

■ DIET OR SUPPLEMENT?

Given the epidemiologic and mechanistic link between isoflavone consumption and decreased prostate disease, a strategy of using isoflavones to protect against prostate disease seems reasonable.

The question becomes, then, whether to increase intake of isoflavones through diet or to use a dietary supplement. Although ultimately a question of personal preference, several factors are worth considering when making this decision.

Advantages and disadvantages of diet

Some people prefer to modulate their diet instead of taking a pill. Adding isoflavones through diet also obviates concerns about the safety or lot-to-lot variability of a supplement, and it may provide a more natural mix of beneficial food components.

However, the recommended intake of dietary soy, the legume most often used for its isoflavone content, is about 8 oz/day (approximately 230 g/day).⁵⁵ This may not be practical for many of us accustomed to a Western diet. It may also be difficult for some people to

Soy and rice contain phytates, which can chelate zinc, copper, and calcium

**TABLE 1****Isoflavone composition of various phytoestrogen supplements**

PRODUCT	TOTAL ISOFLAVONES (MG/G)*	AGLYCONES (%)	ISOFLAVONES PER CAPSULE OR TABLET (MG)	
			MEASURED	CLAIMED†
Carlson Easy Soy	18	7	10	13
Carlson Easy Soy Gold	47	15	36	50
Erdic (Busting Out)‡	?	?	?	Not stated
Estroven§	8	11	8	50
Solgar	7	1	9	15
Kudzu Root Extract§	36	13	12	3
Healthy Woman	68	10	49	55
One a Day	10	1	13	42
PhytoEstrin	17	6	10	14
Phyto Soya	32	2	13	18
Soy Extract	32	12	11	13
Phyto Estrogen-Power	10	3	7	5
Promensil	78	100	42	40
PhytoEstrogen Solaray	18	2	11	10
H & B Soya Isoflavones	21	2	16	17
Soyamax	2	9	58 [#]	60 [#]
Soy Care	66	4	23	25
N Resources Soy Isoflavones	96	6	43	50
Soy Plus	37	5	18	20
Naturally Preferred Soy Germ	24	6	12	10
Trinovin	74	96	37	40
Basic Soy Isoflavones	28	9	17	25
Nature's Bounty Flash Fighters	12	10	17	22
Herbal Blends Menopause Balance	3	86	2	8
NovaSoy	67	5	41	50
New Phase-Sunsource	7	26	9	80
Spring Valley	24	10	13	7
Sundown	83	6	39	40
Phytosoy	10	47	3	4
Soy Choice Vitanica	70	9	26	56
Revival	2	10	9 [#]	14 [#]
Nutri Soy**	3	8	3	Not stated
Soy Life 25 ^{††}	20	2	20	25

*Values are mean of four analyses

†A number of manufacturers indicate a range for isoflavone content, in which case the minimum amount was selected

‡Questionable peaks detected by mass spectrometry, but too low for reliable quantification

§Measurement does not include puerarin glycosides, due to lack of pure standards for quantification

^{||}Soy standard extract

^{||}Contains mainly methoxylated isoflavones from clover as its aglycones

[#]Powdered supplement; isoflavone content expressed per serving

**Toasted soy flour used as an ingredient

^{††}Soy germ extract used as an ingredient

ADAPTED FROM SETCHELL KD, BROWN NM, DESAI P, ET AL. BIOAVAILABILITY OF PURE ISOFLAVONES IN HEALTHY HUMANS AND ANALYSIS OF COMMERCIAL SOY ISOFLAVONE SUPPLEMENTS. J NUTR 2001; 131(SUPPL 4):1362S-1375S.



become accustomed to the taste and texture of soy products.

In addition, soy foods and rice contain phytates, which can chelate zinc, copper, and calcium and prevent their absorption. People on high-soy diets should consider mineral replacement because of the phytates.

Soybeans also contain vitamin K, which can interfere with some drugs, notably warfarin. People who take this drug should consult their physician before adding soy foods to their diet.⁵⁵

Advantages of supplements

An alternative is to take an isoflavone supplement that contains 25 to 40 mg of the four main isoflavones, consistent with the amount in the traditional Asian diet.⁵⁶ This obviates the potential problems of phytates and vitamin K and may make it easier for those who cannot obtain enough isoflavones through their normal diet. Other advantages: it is easy to regulate the dose, and there is no increased caloric intake. If possible, it should be dosed once daily to encourage compliance.

To ensure its safety and quality, a good supplement should be standardized and pure, be produced via good manufacturing procedures, and provide pharmaceutical-grade preparations. It should be assayed for heavy metals and pesticides. It should cause few associated adverse events. Finally, it should provide the active ingredients in a quantity sufficient to meet therapeutic goals.

Disadvantages of supplements

The available isoflavone supplements vary in the types and quantities of isoflavones they contain. The labeling of two preparations shown in **TABLE 1** does not indicate what quantity of isoflavones they contain.⁵⁷ Even among the supplements that are labeled as to isoflavone content, many do not provide enough isoflavones to be likely to have a therapeutic effect.

On the other hand, patients should be urged not to try to achieve high isoflavone levels by taking megadoses of these agents, since the efficacy and safety of such an approach has not been tested.

Drug interactions are possible but have not been adequately addressed. Medications

commonly used by older men include antihypertensive agents, anticholesterol agents, and antidiabetic agents and conventional treatments for prostate disease. The possibility of adverse interactions is particularly important given the widespread use of supplements, often without the knowledge of a patient's general practitioner or oncologist. The field could benefit from well-designed *in vitro* studies, animal studies, and clinical trials that specifically investigate isoflavone interactions with a variety of common pharmacologic agents.

■ A FINAL CAVEAT

Even though there appears to be ample epidemiologic and mechanistic evidence to support using isoflavones as protection against prostate disease, a word of caution is warranted. A theoretical mechanism of action and epidemiologic data do not always translate into clinical efficacy when they are pursued as preventive or therapeutic strategies. A few examples with antioxidants illustrate this point.

Beta-carotene, an antioxidant tested for its possible protective effects against the development of lung cancer, was actually shown to increase the risk of the disease among heavy smokers.^{58,59} Likewise, vitamin E showed considerable promise as a supplement that might protect against coronary heart disease and atherosclerosis, but clinical trials failed to confirm such benefits.^{60,61} In fact, antioxidants (vitamin E, vitamin C, beta-carotene, and selenium) were found to attenuate the lipid-modifying and cardiovascular-protective effects of the cholesterol-lowering drugs simvastatin and niacin in patients with coronary disease.⁶¹

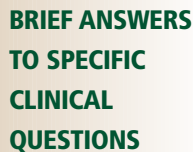
Taken together, these findings underscore the importance of performing rigorous clinical trials to determine the true benefits of any suspected component of a particular diet or food source. In addition, we have no data regarding the long-term daily use of isoflavones. Isoflavones are unlikely to cause adverse effects at daily dietary levels; however, some care is warranted until controlled clinical trials have been performed to determine possible toxicities associated with prolonged intake.

Supplements vary in the types and quantities of isoflavones they contain



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