



PHYTOESTROGENS: RISKS AND BENEFITS

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Accepted on: 23-05-2011; Finalized on: 25-08-2011.

ABSTRACT

Phytoestrogens are plant derived substances that are structurally and functionally similar to estrogens and are found in many foods. Mainly there are three classes of phytoestrogens - isoflavones, coumestans and lignans. Phytoestrogens may be protective against various types of cancers, menstrual irregularities, osteoporosis and cardiovascular diseases but it has some adverse effects on health. Present review examines the potential role of phytoestrogens in health and illness as evidenced by current medical literature.

Keywords: Phytoestrogen, cancer, cardiovascular disease, osteoporosis.

INTRODUCTION

Phytoestrogens are defined functionally as substances that promote estrogenic actions in mammals and are structurally similar to mammalian estrogen 17 β -estradiol (E2)^{1,2}. Phytoestrogens mainly belong to a large group of substituted polyphenolic compounds, the coumestans, prenylated flavonoids and isoflavones. These three compounds are most active in estrogenic effects in this class. The diverse biological activity of phytoestrogens is their ability to act estrogenically as estrogen agonists and antiestrogenically as antagonists. As estrogen agonists, phytoestrogens mimic endogenous estrogens and cause estrogenic effects. As estrogen antagonists, they may block or alter estrogen receptors (ER) and prevent estrogenic activity causing antiestrogenic effects³. Consumption of a phytoestrogen-rich diet is protective against diseases such as breast, prostate bowel cancer and cardiovascular disease⁴. These compounds appear to be biomarkers of a 'healthy' diet. Apart from plant source, compounds with estrogen like activity are also found in animals (ovarian steroids), microorganisms (e.g., mycoestrogens from molds)⁵, as well as industrially manufactured estrogenic compounds such as bisphenol A and nonylphenol⁶.

MECHANISM OF ACTION

Both genomic and nongenomic mechanisms have been proposed to explain phytoestrogenic effects on human health⁷. Phytoestrogens are able to interact with enzymes and receptors because of their stable structure and low molecular weight they can pass through cell membranes⁸. These interactions allow them to bind to ERs, induce specific estrogen-responsive gene products, stimulate ER-positive breast cancer cell growth, interfere with steroid hormone metabolism or action⁸ and alter ER structure and affect transcription⁹. Some genomic mechanisms of action include estrogenic and antiestrogenic effects on ERs¹⁰. Nongenomic effects that do not involve ERs include: induction of cancer cell differentiation, inhibition

of tyrosine kinase and DNA topoisomerase activities, suppression of angiogenesis and antioxidant effects of phytoestrogens¹¹.

CLASSIFICATION OF PHYTOESTROGENS

Phytoestrogens have been categorized based on their chemical structures which resemble estrogen. Phytoestrogens are classified as flavonoids which include isoflavones, coumestans and non-flavonoids such as lignans (Fig 1).

Isoflavones are the most well known of the phytoestrogens. Naturally occurring isoflavones that have shown estrogenic activity are: the aglycones, daidzein (4',7-dihydroxyisoflavone) and genistein (4',5,7-trihydroxyisoflavone); the glycosides, daidzein and genistin; and biochanin A and formononetin, 4'-methyl ethers of daidzein and genistein (Price and Fenwick, 1985; Kurzer and Xu, 1997). In plants, they can often be found as glycosides¹². Mammals consume isoflavones, daidzein and genistein are metabolized in the gastrointestinal tract. Biochanin A and formononetin can metabolize to genistein and daidzein respectively. Daidzein may be further metabolized to dihydrodaidzein and then to O-desmethylangolensin (O-DMA) and equol¹¹. Equol is not metabolized equally in all humans¹³.

Coumestans are another group of plant phenols that show estrogenic activity. Coumestrol was first reported in 1957 by Bickoff and coworkers as a new phytoestrogen that was isolated from ladino clover (*Trifolium repens* L., Fabaceae), strawberry clover (*Trifolium fragiferum* L., Fabaceae) and alfalfa or lucerne (*Medicago sativa* L., Fabaceae)¹⁴. Their presence in fodder crops has been associated with disrupting reproductive performances of livestock^{1,15}. The main coumestans with phytoestrogenic effects are coumestrol and 4'-methoxycoumestrol. *In vitro* coumestrol has been reported to inhibit bone resorption and to stimulate bone mineralization¹⁶.



Lignans were first identified in plants and later in biological fluids of mammals. As a class of compounds they contain a dibenzylbutane skeleton and in plants they aid in the formation of lignin used to construct the plant cell wall¹⁷. The most well known phytoestrogenic lignans are secoisolariciresinol and matairesinol which are converted by bacterial action in the gut into enterodiol and enterolactone mammalian lignans not found in plants¹⁷.

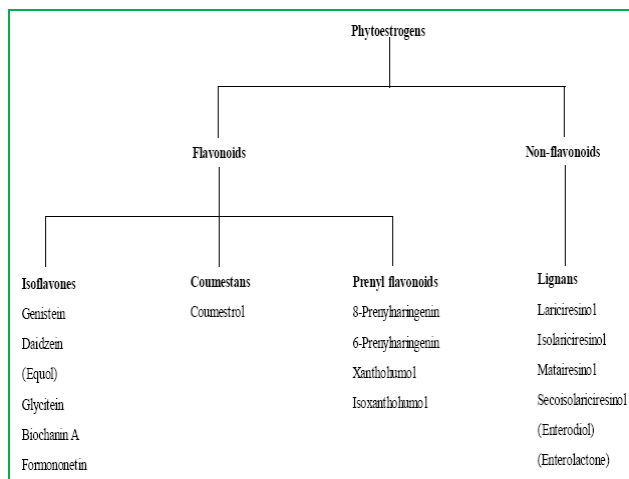


Figure 1: The relationship between the various groups of phytoestrogens (given in bold) and members of each group.

The compounds in brackets are not inherently present in plants but are estrogenic products resulting from metabolism of members of that class of phytoestrogen.

HEALTH AND PHYTOESTROGENS

Phytoestrogens are utilized in treating breast cancer, endometrial cancer, liver disease and prostate cancer^{1,18}. Additional research has shown that intestinal bacteria are seen as important in the metabolism of phytoestrogens and have the ability to refine phytoestrogens into compounds similar in structure to E2 that protect against cancer¹⁹. Some of the proposed mechanisms by which phytoestrogens may inhibit cancer cells are: inhibition of DNA topoisomerase, suppression of angiogenesis, induction of differentiation in cancer cell lines and induction of apoptosis²⁰. Better designed clinical trials are needed to assess the beneficial effects of phytoestrogens on health²¹.

Breast cancer

Phytoestrogens act as weak estrogens and exhibit estrogenic activity in a low-estrogen environment; therefore it has been postulated that they show anti-estrogenic activity in a high-estrogen environment¹⁰. This explanation suggests that prior to menopause when there is a high-estrogen environment phytoestrogens may protect against breast cancer and after menopause when there is a low-estrogen environment they may stimulate breast cancer⁷. The risk of development of breast cancer may be decreased by isoflavones²². Both tumorigenic²³

and antitumorigenic^{24,25} effects of phytoestrogens have been reported. At lower concentration, they tend to stimulate the proliferation of two ER-alpha-dependent breast cancer cell lines; whereas, at high concentration, they exert strong cytotoxic effect²⁶. Overall, though experimental and epidemiological studies are promising, more research is required to validate the role of phytoestrogens in the prevention of breast cancer. A recent study reported that short-term administration of phytoestrogen supplement in healthy male volunteers had no observable effect on the endocrine measurements, testicular volume or semen quality²⁷. In animal models, the studies investigating the effects of soybean have shown reduced tumorigenesis²⁸. Thus, *in vitro* animal studies, it may be suggested that dietary phytoestrogens may play a protective role in the prevention of breast cancer.

Prostate cancer

In vitro studies using human prostate cancer cells have shown the inhibition of cell growth with high concentrations of phytoestrogens²⁹. Rats consuming soy and rye bran had delayed growth of implanted prostate tumors³⁰. Further testing with the same phytoestrogens increased apoptosis of the tumors and reduced tumor growth in nude mice implanted with human prostate tumors. However, estrogen has shown controversial effects, such as growth of prostate cancer and benign prostatic hyperplasia and therefore phytoestrogens may have similar effects²⁹. Adlercreutz³¹ reviewed some of the more recent studies on prostate cancer and stated that findings support the hypothesis that soy consumption prevents prostate cancer, yet more studies are needed. Several epidemiological studies suggest the beneficial use of phytoestrogens in reducing prostate cancer³². There is a paucity of research on the effects of phytoestrogens and prostate cancer. Although the present studies show a positive association between phytoestrogens and prostate cancer risk, more clinical studies are needed to confirm this hypothesis.

Cardiovascular disorders

Current evidence suggests that phytoestrogens have a significant potential in reducing CAD via favorable effects on the lipid profile³³. The serum total, LDL, and VLDL cholesterol levels have been shown to be significantly lower in both male and female rhesus monkeys fed on phytoestrogen-rich diet³⁴. Phytoestrogens also appear to play a protective role in atherosclerosis. The phytoestrogens may modulate the lipoprotein metabolism due to their estrogenic activity³⁴. The antioxidant property of phytoestrogens may also contribute to reducing the oxidation of lipids as evidenced by a recent study in healthy volunteers³⁵. Other mechanisms by which phytoestrogens exert cardioprotective effects include inhibition of tyrosine kinase³⁶ and inhibition of platelet aggregation¹.

Several mechanisms of action reported to explain the hypocholesterolemic effects of phytoestrogens which



include: increased bile acid secretion, which aids removal of low density lipoprotein (LDL); affected hepatic metabolism coupled with increased removal of LDL by hepatocytes; and enhanced thyroid function³⁷. LDL shows increased oxidative resistance when isoflavones are incorporated into LDL cholesterol³⁸. Kurzer and Xu¹¹ reviewed antioxidant effects of isoflavones from *in vitro* and *in vivo* studies and reported that soy isoflavones act as antioxidants by directly or indirectly enhancing the activities of catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase enzymes. Most of the research has been conducted with soy isoflavones and limited research has been conducted to evaluate the effects of lignans and coumestans on cardiovascular disease.

Menopausal symptoms

The symptoms associated with menopause cause many women to seek medical solutions. The mechanisms of action are still poorly understood because of the complex biological actions observed in phytoestrogens. The target tissue, the kinds of ERs and the concentration of endogenous estrogens are all factors that affect phytoestrogen activity at the cellular level. Other non-receptor mechanisms may also explain the biological effects of phytoestrogens on menopausal symptoms, such as antioxidation, blocking of enzymes involved in the biosynthesis of estrogen, inhibition of protein kinase which is part of intracellular signaling, and inhibition of 5-reductase and aromatase²⁹. The reduction of bioavailability levels of free sex steroids such as estrogen may also be the result of phytoestrogens stimulating sex hormone-binding globulin (SHBG) synthesis²⁹. Several reviews have discussed the studies conducted on phytoestrogens and menopausal symptoms and still much contradictory evidence exists as to the benefits of phytoestrogens^{39,40}. More research is needed in this area, especially studies examining the long-term effects of phytoestrogens on endometrial tissue and bone loss.

Osteoporosis

Osteoporosis is often associated with women in menopause. In postmenopausal women, estrogen deficiency is a major risk factor for osteoporosis⁴¹. A diet rich in phytoestrogens has been shown to be accompanied by an increase in bone mineral density (BMD)²². Studies carried out in ovariectomised rat model of osteoporosis to evaluate the role of phytoestrogens in preventing bone loss due to estrogen deficiency are also convincing⁴². Recent discovery of ER-beta in osteoblast cells⁴³ may explain the protective role of phytoestrogens in bone loss. The phytoestrogens have a conservatory effect on calcium excretion⁷. Isoflavones have been proposed to inhibit activities of osteoclast-like cells by interfering with tyrosine kinase activity of epidermal growth factor receptor protein⁴⁴. *In vivo* and *in vitro* studies indicate that osteoclast formation and bone resorption are enhanced due to the generation of free radicals. Since phytoestrogens have been reported to

exert antioxidant properties⁴⁵ they may reduce the rate of bone loss in postmenopausal women partly by antioxidant effects.

OTHER EFFECTS

The role of phytoestrogens on memory, attention and frontal lobe function in healthy volunteers and found improved cognitive performance was reported by File et al.⁴⁶ (2001). The improvement in brain function has also been reported in animal studies, which is recently reviewed by Lephart et al.⁴⁷. The consumption of phytoestrogens has been shown to be protective in the prevention of thyroid, lung, stomach, colon, and skin cancers⁴⁷⁻⁴⁹. There is increasing evidence that phytoestrogens may be beneficial in chronic renal disease⁵⁰.

CONCLUSION

Evaluation of benefits and risks of phytoestrogens is a complex task due to inter-individual variation and complexity in absorption and metabolism. Overall, it is naive to assume that consumption of phytoestrogens may be good. On the other hand, inappropriate or excessive use may be detrimental. Before making widespread recommendations for phytoestrogens intake, extensive data on specific intracellular effects, duration of exposure and disease, and results from prospective randomized studies in humans is essential. It is also necessary to determine the potential side effects of phytoestrogens. Among various phytoestrogens, isoflavones (genistein and diadzein) have been most studied. Studies on lignans are few and for coumestans very few. Genetic modification of soybean and other plants and improvement in food technology to enhance phytoestrogen production is inevitable.

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