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Review Article

PHYTOESTROGENS IN CANCERS AND SOME OTHER DISORDERS

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ABSTRACT
Phytoestrogens are natural plant compounds which have a similarity to human estrogens. They hold great potential for health benefits. Recent epidemiological studies have suggested that typical Asian diets, which have always been much higher in these substances than Western diets, appear to be associated with a significantly lower risk of breast, prostate and colon cancer as well as a reduced incidence of heart disease and osteoporosis. The benefits of phytoestrogens to good health and against several disorders are mainly due to the effects they have on the body's hormonal balance, acting as both agonists and antagonists. Phytoestrogens are thought to act as estrogen agonists by occupying estrogen receptor sites when natural estrogens are unavailable. Phytoestrogens are also thought to act as estrogen antagonists by occupying estrogen receptor sites ahead of the body's natural estrogens and equally importantly ahead of synthetic estrogens and also environmental estrogens derived from chemical products, otherwise known as bad estrogens or xenoestrogens. The biologically useful forms of phytoestrogens, the metabolites, are dependent for their existence upon a digestive system in good order and complete with adequate microflora capable of converting the basic plant compounds (phytochemicals) into active forms.
KEYWORDS: Phytoestrogens, Phytochemicals, Estrogen, Cancers and other diseases.

INTRODUCTION

Phytoestrogens (also known as phytosterols) are a group of phytochemicals or natural plant compounds that can act like estrogen hormone. Estrogen is a hormone necessary for childbearing, and is involved with bone and heart health in women. 'Phyto' is from Greek origin, which is generally used as a prefix to describe substances derived from plants. Phytoestrogens, therefore, are substances from plants which have estrogen-like qualities[1-2]. However, excessive and prolonged use and exposure of estrogens may increase the risk of various cancers, especially the cancers of breast, uterus, ovary, vagina, pituitary, colon, etc.[2-4].

The prevailing scientific opinion on the phytoestrogens is favourable as there is substantial research indicating that they hold great potential for health benefits. Recent epidemiological studies have suggested that typical Asian diets, which have always been much higher in these substances than Western diets, appear to be associated with a significantly lower risk of breast, prostate and colon cancer as well as a reduced incidence of heart disease and osteoporosis. These degenerative diseases have in fact long been associated with modern Western diets and, therefore, the studies have truly caused no surprise by reinforcing this idea and favouring Asian diets for good health. The benefits of phytoestrogens to good health are mainly due to the effects they have on the body's hormonal balance, acting as both agonists and antagonists. To understand how these substances help the body's hormonal balance, it is useful to recall what hormones are and how they work. Hormones are chemical substances produced by the body's endocrine glands and released into the bloodstream to act as chemical messengers, travelling through the body with instructions to trigger activity in their target tissues. These target tissues each contain receptor sites specific to a particular hormone and the required effect is initiated when the hormone in question arrives and docks at those receptor sites. For example, estrogens are released from the ovaries and travel through the blood to the breast area where they dock and deliver the instruction to initiate mammogenesis[1].

About 50 years ago, researchers became aware that phytoestrogens in alfalfa and clovers could affect the fertility of livestock. Recently, multiple epidemiological studies showed a relationship between high dietary intake of isoflavones and lignans, and lower rates of certain cancers, cardiovascular problems and menopausal symptoms. As far back as 1985, it was known that phytoestrogens could compete with estradiol for binding to intercellular estrogen receptors (ERs). Although, scientific evidence is accumulating to suggest that

phytoestrogens may have a role in preventing chronic diseases. A strong body of evidence suggests that they may be effective in preventing and treating prostate cancer, due to their antiandrogenic properties[5]. In these context, the present article elucidates the benecificial effects of phytoestrogens in various cancers and other diseases.

Plants / foods with phytoestrogens

Phytoestrogens have been found in more than 300 types of food. Most of the food phytoestrogens are from one of two chemical classes: (a) Flavonoids (e.g., isoflavonoids or isoflavones, flavones and coumestans or coumestrols); (b) lignans (e.g., secoisolariciresinol, matairesinol, pinoresinol and lariciresinol). Isoflavonoids or isoflavones (genistein, daidzein, glycitein and formononetin) are present in highest amounts in soybeans, soybean products (e.g., tofu), alfalfa, linseed, fenugreek, fennel and red clover; soy being a major potential source of human exposure. Lignans are found in higher fibre foods such as cereal brans and beans; flax seeds contain large amounts of lignans. Coumestans (coumestrols) are found in various beans such as split peas, pinto beans and lima beans; alfalfa and clover sprout foods contain highest amount of coumestans. Estrogen is available in medically formulated pills. However, dietary estrogen (phytoestrogen) can be also present in variety of food products (including herbs). The Canadian researchers analyzed 121 food samples, of which the food samples with the highest total phytoestrogen content were nuts and oil seeds followed by soy products. The two most important soy isoflavones at present are genistein and daidzein. But lignans are also a very important source of these subsances in the British diet as they are present in most fibre providing foods[1-2].

Phytoestrogens useful in cancers and other diseases

Some research studies have indicated that phytoestrogens may provide good health, including potential reduction in the cancers of breast, prostate and colon, and cardiovascular disease risks; and possible protection against osteoporosis (bone loss) and menopausal symptoms. Besides, both flavonoid and lignan phytoestrogens have antioxidant activity. Asian diets, which have always been much higher in these substances than Western diets, appear to be more beneficial in the above diseases which have long been associated with Western diets[1-2].

The effect of phytoestrogens against cancer has been seen in animal studies, especially when exposed during breast development. Isoflavonoids and lignans stimulate proliferation of ER and breast cancer cells. Hence, the phytoestrogens at high concentrations inhibit cell growth. The antiangiogenic (anticardiac) effects of genistein, daidzein and biochanin A may contribute to antitumor activity. Consumption of soy isoflavones @ 30 mg/day may reduce the hot flashes by 30-50%. Isoflavone intake increases the bone mineral density and can be useful in preventing post-menopausal osteoporosis. Average intake of 47 g/day soy protein results in 9% decrease in total cholesterol, 13% decrease in LDL cholesterol and a trend towards HDL cholesterol. Flavanoids decrease the platelet aggregation; the genistein-induced inhibition of growth factor activity can interfere with platelet and thrombin action. Phytoestrogens also regulate the delayed menstrual cycle in women as they reduced the LH, FSH and progesterone. The action of phytoestrogen genistein on the uterus and vagina of ovariectomized DA/Han rats after 3 day oral administration (25, 50 or 100 mg/kg/day) was compared to ethinyl oestradiol (0.1 mg/kg/d). A dose dependent increase of the uterine wet weight and the uterine and vaginal epithelial height, a dose dependent up-regulation of complement C3, down-regulation of clusterin mRNA expression and a stimulation of the vaginal cornification was observed. Uterine gene expression and vaginal epithelium respond to genistein at doses where no significant effects on uterine wet weight were detectable. In general, the vagina was more sensitive to genistein than the uterus. To analyse the action of genistein in malignant uterine tissue, the impact of a 28 day treatment with 50 mg/kg/day of genistein on the in vivo tumour growth of endometrial adenocarcinoma cells, following subcutaneous inoculation into syngeneic DA/Han rats, was assessed. In contrast to ethinyl oestradiol (0.1 mg/kg/day), a dose of 50 mg/kg/day of genistein did not affect tumour growth. In conclusion, four independent uterine and vaginal parameters indicated that genistein is a weak ER agonist in the uterus and vagina of female DA/Han rats, and evidence provided for a selective estrogen receptor modulator-like action of genistein in normal and malignant uterine tissue[6]. Some bone-sparing effects have been demonstrated with natural and commercial phytoestrogens and the synthetic Ipriflavone through limited studies. Research has yielded positive, yet inconsistent, trends with respect to bone turnover markers, bone mineral density and bone mineral content, but little fracture data exists. Adequate phytoestrogen dosages for osteoporosis have yet to be determined; except 200 mg of ipriflavone three times a day is an established dosage in most trials. Inconsistency in positive results also exists for menopausal symptoms and breast cancer, although evidence is established for reduction of cardiovascular disease[7].

Based on results from some in vitro and animal studies, concern has arisen that the estrogen agonist effects of

isoflavones might increase the growth of breast cancer cells. Though there is still some controversy, the majority of scientific opinions indicate that phytoestrogen-containing foods prevent and treat the breast cancer. Several studies have indicated that countries with the highest phytoestrogen consumption have the lowest rates of breast cancer. No studies have found an increased risk of breast cancer with increased soy consumption. Many in vitro experiments detected anticancer effects from phytoestrogens at high concentrations (but mild stimulatory effects at lower concentrations). Several reports have indicated that exposure of young rats (but not adult rats) to genistein results in a large reduction in mammary cancer later in life. One human study found a similar protective pattern for women who ate tofu as teenagers. Several studies quoted that phytoestrogens have antiangiogenesis effects, discouraging the growth of new blood vessels that tumours need for survival. Equol is a metabolite of daidzin, the glucoside form of daidzein. It is produced by some 30-40% of people who ingest the isoflavone. In ER assays, equol exhibits roughly the same binding affinity as genistein; however, it tends to stay in circulation longer, presumably increasing exposure of tissues to its effects. The ability to produce equol seems to be genetic and not influenced by diet. Reports suggest that people who produce equol have hormonal profiles associated with a lower risk of breast cancer: lower concentrations of androstenedione, dehydroepiandrosterone, estrone, cortisol, and testosterone; and higher concentrations of sex hormone binding globulin. Lignans have demonstrated beneficial effects with breast, prostate, and colon cancer as well as with hypercholesterolemic atherosclerosis and chronic kidney disease. In the colon, bacteria convert the botanical lignans into the mammalian lignans enterodiol and enterolactone. Evidence suggests that a healthy colon flora population may be necessary for humans to derive significant benefit from lignans. In vitro, lignans have been demonstrated to bind to sex hormone binding globulin, displacing estradiol and testosterone. Several animal studies showed that lignans have significant anticarcinogenic effects. The latest research indicates that high levels of lignans are associated with lower breast cancer risk[5]. Numerous epidemiological studies have shown an inverse correlation between cancer incidence and fruit and vegetable consumption[5,8]; lignans are among the many compounds likely to be responsible for this effect. It has also been demonstrated that women with breast cancer have lower plasma levels of lignans than women without breast cancer. Further, a recent study compared the neurotrophic effects of six different isoflavones to the effect of estradiol in order to determine if the isoflavones had estrogen agonist properties in cultured human hippocampal cells. Estradiol protected neuronal mitochondria from damage and promoted neuron process outgrowth (a cellular correlate of memory). The phytoestrogens, however, demonstrated a modest protective effect on the cell membranes, which the researchers suspected was due to their antioxidant properties. Numerous studies have demonstrated that isoflavones can affect the brain metabolism and neurological performance of mice and rats. Furthermore, soy has long been known to have effects on the thyroid. Isoflavones in soy (and flavonoids from other sources as well) inhibit the enzyme thyroid peroxidase, which is involved in thyroid hormone synthesis. This study explored the inhibitory effects of genistein and daidzein, which were completely reversed with the addition of sufficient iodine. Clinical problems from ingesting high levels of phytoestrogens, such as aggravated hypothyroidism or goiter, can occur in iodine-deficient or hypothyroid individuals. There is some speculation that soy formula could be contributing to the increase in premature puberty among American girls, but scientific data is lacking. Phytoestrogens exhibit the antioxidant activity in vitro and in vivo, hence they act against the cancer[5].

MECHANISM OF ACTION OF PHYTOESTROGENS

Phytoestrogens may act by many ways in the body. The chemical structure of phytoestrogens is similar to estrogen, and they may act as mimics (copies) of estrogen. On the other hand, phytoestrogens also have effects that are different from those of estrogen. Working as estrogen mimics, phytoestrogens may either have the same effects as estrogen or block estrogen's effects. Which effect the phytoestrogen produces can depend on its dose. The phytoestrogen can act like estrogen at low doses but block estrogen at high doses. Estrogen activates a family of proteins called 'estrogen receptors' (ERs). Recent studies have shown that phytoestrogens interact more with some members of the ER family, but more information is needed about how these receptors work, especially in breast cancer. Phytoestrogens acting differently from estrogen, may affect communication pathways between cells, prevent the formation of blood vessels to tumours or alter processes involved in the processing of DNA for cell multiplication. Which of these effects occur is unknown. In the breast, phytoestrogens travel to deliver instruction to initiate the mammogenesis and for that reason they are used in herbal preparations for natural breast enhancement or natural breast enlargement[2].

Phytoestrogens are thought to act as estrogen agonists by occupying ER sites when natural estrogens are unavailable. For example, the body's natural estrogen levels inevitably decline with the onset of menopause and phytoestrogens may help to offset this decline if they can fill receptor sites instead. Once docked on the sites they exert estrogen-like activity and may initiate the required effect just as natural estrogen would have done. Phytoestrogens are also thought to act as estrogen antagonists by occupying ER sites ahead of the body's natural estrogens and equally importantly ahead of synthetic estrogens, and also environmental estrogens derived from chemical products, otherwise known as 'bad estrogens' or 'xenoestrogens'. In order words, where estrogen levels are high, phytoestrogens are able to compete with the bod's natural estrogens or the artificial estrogens present and may fill the receptor sites before they do. If this happens, they will in effect decrease the estrogenic activity in the body, because the effect of docked phytochemicals on the target tissues will be less than if the available estrogens had been allowed to dock. A limitation on the hormone balancing actions of phytoestrogens is that they do not have estrogenic properties when still in the plant or even at the time they are consumed, but acquire them only during the digestive process through the actions of bacteria residing in the gastrointestinal tract. The bacteria cause the phytochemicals to undergo complex metabolic conversions, leading to the formation of an estrogen-like metabolite which can then be absorbed by the body. This means that the biologically useful forms of phytoestrogens, the metabolites, are dependent for their existence upon a digestive system in good order and complete with adequate microflora capable of converting the basic phytochemical into active forms. This is a limitation on the effectiveness of phytoestrogens for the simple reason that there are a number of factors that can adversely affect the stability of normal gastrointestinal flora. Poor or inappropriate diets, stress and antibiotics can all significantly disrupt the ideal healthy balance of gastrointestinal organisms. Antibiotics in particular can quickly destroy friendly bacteria, as well as the invading organisms they are actually meant to destroy. High fat intake is another culprit. However, a high-fibre diet is known to help the metabolism of phytochemicals[1].

Recent research suggests that phytoestrogens may be natural 'Selective Estrogen Receptor Modulators' (SERMs), which means that they can bind to certain ERs in some tissues, either activating or down-regulating cellular responses. Depending on concentrations of endogenous estrogens, as well as on which receptor complexes are activated or down-regulated, SERMs can have either estrogenic or antiestrogenic effects. Through preferential binding to beta-ER, phytoestrogens activate cardioprotective and bone-stabilizing metabolic processes. Simultaneously, they appear to down-regulate the activity of alpha-ER prominent in breast and uterine tissue. This is one possible mechanism behind their proposed anticancer effects. In addition, phytoestrogens can favourably affect the balance of estrogen metabolites in the body. 'Bad' metabolites (16 alpha-hydroxyestrone, 4-hydroxyestrone and 4-hydroxyestradiol) are genotoxic and mutagenic. The ratio of 'good' (2-hydroxyestrone) to 'bad' metabolites is increasingly being used as a marker to assess cancer risk. Non-ER mediated effects on growth regulation in human breast cancer cells have also been documented for genistein. Many in vitro studies have indicated that phytoestrogens have some 1/100 to 1/1000 the binding affinity of estradiol for cellular ERs. This has led to the interpretation that phytoestrogens are 100 to 1000 times weaker than estradiol. In addition to binding affinity, another factor to consider is the influence of high plasma levels of phytoestrogens which can be present at some 100 to 1,000 times the concentration of endogenous estrogens (and even higher in soy-formula-fed infants). In addition, phytoestrogens may have different bioavailabilities than endogenous estrogens, due to the fact that they bind less tightly to steroid hormone serum transport proteins. This is because that many phytoestrogens are converted by human colon bacteria into other compounds (including enterodiol, enterolactone, and equol). Some of these metabolites are more potent than their precursors, while others are less so. Different individuals, depending on factors such as their particular gut flora and/or genetic makeup, produce different concentrations and proportions of these metabolites. There is also evidence that phytoestrogen activity is modulated by the levels of a person's endogenous estrogens. Further, the estrogenic effect of any particular compound is not the same in different types of cells and tissues; nor is it identical in different species, so it is not possible to directly apply the results of in vitro and animal research to humans. Finally, the different sexes (in both animals and humans) can have different responses to phytoestrogens. Receptor-binding affinity, then, is only one factor amongst many that determines the actual hormonal effects of any particular phytochemical. Overall, the situation is far more complex; many biochemical factors are involved; all phytoestrogens are not the same; all tissues do not respond identically; some people respond differently than others. There is also evidence that isoflavones and lignans may exert anticancer effects through other mechanisms, independent of their

interactions with ER. For example, isoflavones at physiological concentrations have been found to inhibit an enzyme which catalyzes the transformation of the weaker estrogen, estrone, into the more cancer-promoting estradiol. Another study found that phytoestrogens inhibit a second enzyme important in steroid biosynthesis. Isoflavones also exhibit some antioxidant activity, which may contribute to anticancer effect[5].

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