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〈Review Paper〉

Endocrine-Mimicking Phytoestrogens : Health Effects and Signaling

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Abstract - Phytoestrogens display estrogen-like activity because of their structural similarity to human estrogens and exhibit high affinity binding for the estrogen receptors (ERs). The prevalence of phytoestrogens in our diets and the biological effects that they may cause need to be fully examined. ER is the ancestral receptor from which all other steroid receptors have evolved. Although phytoestrogens serve specific signaling functions between the plants and insects, fungi, and bacteria, many chemical signals are often misinterpreted as estrogenic signals in non-target organisms such as vertebrates. There are no ERs in plants or in their most common partners, insects. However, *Rhizobium* soil bacteria have NodD proteins which is an intended target of phytoestrogen signaling and share genetic homology with the ER. These two evolutionarily distant receptors both recognize and respond to a shared group of chemical signals and ligands, including both agonists and antagonists. This review briefly summarizes estrogen and estrogen receptors, kinds of important phytoestrogens, their health effects as well as some of the evolutionary aspects of mechanism by which phytoestrogen mimics the endogenous ER signaling in our body.

Key words : estrogen, phytoestrogen, estrogen receptor, heath effect, signaling

INTRODUCTION

Phytoestrogen are non-sterodal compounds found in a wide variety of plant foods. Phytoestrogens, plant chemicals classified as isoflavones, coumestans and lignans, display estrogen-like activity because of their structural similarity to human estrogens and exhibit high affinity binding for the estrogen receptor. The interest in phytoestrogens has recently been increased by the realization that hormone replacement therapy (HRP) for the endocrine controlled diseases in bone, cardiovascular system, cancers, central nervous system and reproductive organs is not as safe or effective as previously thought (Hays *et al.* 2003). The prevalence of phytoestrogens in our diets, the biological effects and mechanism by which phytoestrogen mimics the endocrine signaling in our body should be addressed.

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ESTROGEN AND ESTROGEN RECEPTORS

Estrogens, largely produced in the ovaries, have many biological effects in the body beyond the reproductive system. The dominant estrogen in the body is 17β estradiol (Fig. 1). When bound to an estrogen, the estrogen receptors (ER) in the nucleus interact with the estrogen response element (ERE) which regulates transcription of estrogen responsive genes (Razandi *et al.* 1999; Xu *et al.* 2003). There are two known estrogen receptors, ERα and ERβ which are vary in tissue distributions and can

have different effects on mixed agonists and antagonists (Nilsson and Gustafsson 2002). Although any compound that induces receptor dimerization and subsequent binding to the ERE, can be considered an estrogen, antagonistic effects can occur when a compound is able to bind to ER but dimer formation either does not occur or the correct configuration to activate the ERE is not attained. Some compounds such as tamoxifen act as estrogen agonists and antagonists and are referred to as Selective Estrogen Receptor Modulators (SERMs) (Macgregor and Jordan 1998). These agonist/antagonistic effects are believed to be responsible for the differential effects of phytoestrogens compared to estradiol. Both ERα and ERβ function in normal ovarian follicles, vascular endothelia cells, myocardial cells, smooth muscle, and breast tissue (Nilsson and Gustafsson 2002). ERα is involved in bone maturation in both males and females, however, only ERβ plays a role in bone maintenance in females (Nilsson and Gustafsson 2002). ERα is more important in maintaining follicle stimulating and luteinizing hormone concentrations in blood, and ERβ is involved in frontal lobe mediated learning and memory (Nilsson and Gustafsson 2002).

PHYTOESTROGENS

Some plant-derived compounds could cause an estrogenic effect (Bennetts *et al.* 1946). Currently, four different families of plant phenolic compounds are considered phytoestrogens : the isoflavonoids, stilbenes, lignans and coumestans. Diverse compounds within each class of phytoestrogen affect the estrogen-mediated response in different ways.

1. Isoflavonoids

The flavonoids are a large chemical class formed through the phenylpropanoid-acetate biodemial pathway. Sheep grazing the red clover had multiple fertility problems including early onset of puberty, failure to get pregnant and miscarrige. The clover had high amounts of the isoflavones, formononetin and biochanin A (Rossiter and Beck 1966). Genistein and daidzein are the most studied isoflavonoids (Dixon and Ferreira 2002). Genistein (Fig. 1) has one-third the potency of estradiol in interaction with ERβ, and one thousandth of the potency of estradiol in interaction with ER (Kuiper *et al.* 1998) and can induce similar responses as estradiol (Wang *et al.* 2003). In some tissues such as mammary tissue (Murrill *et al.* 1996), breast tumors (Fritz *et al.* 1998), and prostate (Mentor-Marcel *et al.* 2001; Fritz *et al.* 2002) genistein can act as an estrogen antagonist. Genistein also shows non-genomic effects through the ER receptors in the cell membrane. However, daidzein, did not show any non-genomic effects. Some gene is upregulated by genistein and unresponsive to estradiol (Ramanathan and Gray 2003). The ability of genistein to block cell proliferation of normal mammary cells may contribute to the preventive effect of a high soy diet on risk of breast cancer. The major source of isoflavonoids in the diet is from soy-based foods. Even though genistein has relatively low potency compared to estradiol, high concentrations in plasma may be sufficient to cause a variety of physiological effects. A closely related compound to the isoflavonoids is 8-prenyl naringenin, a

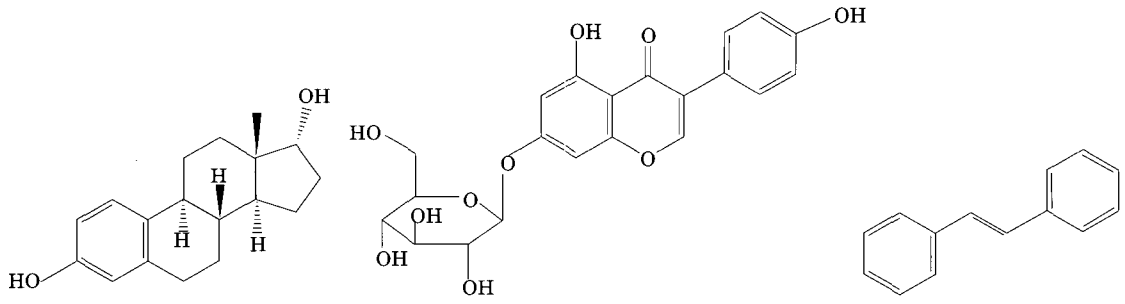

Fig. 1. Structure of 17β estradiol, genistein (isoflavonoid), coumestrol (coumestan), trans-resveratrol (stilbene), matairesinol (lignan) and 8-prenyl naringenin.

flavanone, found in beer ingredient hops (*Hummulus lupulus*). The in vivo potency of this compound is weak.

2. Stilbenes

Stilbenes (Fig. 1), like the flavonoids, are produced through the phenylpropanoid-acetate pathway. The main dietary source of phytoestrogenic stilbenes is resveratrol from red wine and peanuts. Although there are two isomers of resveratrol, *cis* and *trans*, only the *trans* form has been reported to be estrogenic (Gehm *et al.* 1997). Recent research demonstrates that trans-resveratrol binds to human estrogen receptors and increases estrogenic activity in the body (Bagchi *et al.* 2001). Resveratrol has been isolated from the roots of *Polygonum cuspidatum* (Japanese Knotweed or Mexican Bamboo) (Vastano *et al.* 2000), several grass species (Powell *et al.* 1994) pine bark (Mannila and Talvitie 1992) ivy and lilies (Creasy and Creasy 1998). Resveratrol has high bioavailability and physiological levels can be obtained through drinking red wine (Schmitt *et al.* 2002). Resveratrol has shown agonistic and antagonistic activity (Bowers *et al.* 2000; Brownson *et al.* 2002) and has a greater capacity to activate the ERβ than ERα (Klinge *et al.* 2003).

3. Lignans

The term lignan is used for a diverse class of phenylpropanoid dimers and oligomers. Secoisolariciresinol and matairesinol are two lignan dimers that are not estrogenic by themselves, but are readily converted to the mammalian lignans, enterodiol and enterolactone, respectively, which are estrogenic (Glitso *et al.* 2000). The phytolignans appear in high amounts in flaxseed, whole grain breads, vegetables, and tea.

4. Coumestans

Although there are a large number of coumestans, only a small number have shown estrogenic activity, predominantly coumestrol and 4′ methoxycoumestrol. The main dietary source of coumestrol, is legumes; however low levels have been reported in brussel sprouts and spinach. Clover and soybean sprouts have the highest concentration, 28 and 7 mg/100 g dry wt., respectively; mature soybeans only have 0.12 mg/100 g dry wt (Franke *et al.* 1994).

HEALTH EFFECTS OF PHYTOESTROGEN

There have been many clinical and epidemiological studies examining the health effects of phytoestrogen.

1. Bone density

Estrogen plays an important role in maintaining bone density by regulating the formation and resorption of bone (Nilsson and Gustafsson 2002). Hormone replacement therapy (HRT) aims to prevent or lower the incidence of osteoporosis in postmenopausal women. Phytoestrogens are somewhat effective in maintaining bone mineral density (BMD) in postmenopausal women (Ho *et al.* 2001; Mei *et al.* 2001). The effects of soy isoflavones in premenopausal women showed no effect on bone mineral density levels (Mei *et al.* 2001), while significant effects were observed in postmenopausal women.

2. Cardiovascular health

Estrogen can affect the vascular system both directly, through the ERs located in vascular tissue, and indirectly through altering the lipoprotein profile (Rubanyi *et al.* 2002). Epidemiological studies showed that women taking HRT were 50% less likely to experience severe cardiovascular disease (CVD) (Stampfer *et al.* 1985; Rubanyi *et al.* 2002). However, postmenopausal women who have already developed CVD also did not receive any benefit from 3 years of treatment (Hodis *et al.* 2003). In normotensive men and postmenopausal women, soy improved blood pressure and lipids but, overall, did not improve vascular function including systemic arterial compliance and pulse wave velocity (Teede *et al.* 2001). Isoflavonoids or soy protein and flaxseed have the ability to lower total cholesterol (Washburn *et al.* 1999; Lucas *et al.* 2002), LDL cholesterol (Lemay *et al.* 2002; Lucas *et al.* 2002) and to raise HDL (Potter *et al.* 1998). Soy may affect the synthesis of cholesterol even in newborns, as male infants fed soy-based formula had lower cholesterol fractional synthesis rates than infants fed breast milk or cow milk-based formula (Cruz *et al.* 1994). In animal experiment, treatment of rats under a hyperlipidemic

diet with genistein can induce weight loss in peri-menopausal or post-menopausal states (Park and Shin 2002). Also, genistein supplementation improves endothelial dysfunction induced by oophorectomy in rats and reduces infarct size in an experimental model of myocardial ischaemia-reperfusion injury (Altavilla *et al.* 2004)

3. Brain function

Some neurons in the CNS have ERs and respond to ovarian estrogens to regulate ovarian function. In post-menopausal women, cognitive function is frequently down regulated and HRT is been known to improve cognitive function by means of attenuating the neural cell death (Wise 2002). But some studies also suggest no significant effect of HRT. A few studies have examined the effect of phytoestrogens on cognitive function. Diets high in soy increased long term and short-term memory and mental flexibility (File *et al.* 2001; Duffy *et al.* 2003). Genistein is been known to protect human neuronal cells from oxidative stress and attenuate the neural cell death (Sonee *et al.* 2004).

4. Cancer

Eepidemiological studies have shown that people who consume high amounts of isoflavonoids in their diets have lower rates of several cancers including breast (McCann *et al.* 2002), prostate, thyroid (Horn-Ross *et al.* 2002), ovarian (McCann *et al.* 2003), and colon cancer (American Institute for Cancer Research 1997). Resveratrol in fact inhibits the metabolic activation of carcinogens, has antioxidant and anti-inflammatory properties, decreases cell proliferation and induces apoptosis. Data on the availability of resveratrol in vivo are however still lacking (Bianchini and Vainio. 2003). The protective effect of phytoestrogens on cancer may be due to their role in lowering circulating levels of unconjugated sex hormones free from binding to sex hormone binding globulin (SHBG) or albumin (Martin *et al.* 1996).

5. Reproductive function including menopause symptoms

Some women experience a decrease in the quality of life during menopause due to sleep deprivation, hot flashes, mood swings, forgetfulness and difficulty concentrating. These symptoms are linked to the declining and erratic production of estrogen by the ovaries. With the lower than expected effectiveness of HRT, phytoestrogen supplementation has a benefit in the reduction of menopause symptoms but there is currently not enough clinical evidence for the effectiveness of phytoestrogens for the reduction of menopausal symptoms. On the contrary, other study suggest that phytoestrogens available as soy foods, soy extracts, and red clover extracts do not improve hot flushes or other menopausal symptoms (Krebs *et al.* 2004). In male, estradiol treatment and chronic exposure of phytoestrogen may cause receptor-mediated pathophysiologic changes in erectile function, leading to erectile dysfunction (Srilatha and Adaikan 2004). Recent studies in men consuming soyfoods or supplements containing 40-70 mg d^{-1} of soy isoflavones showed few effects on plasma hormones or semen quality (Mitchell *et al.* 2001; Kurzer 2002). In animal experiment, gestational plus lactational exposure to genistein and subsequent dietary exposure to genistein have no adverse effects on gametogenic function in male rats (Roberts *et al.* 2000).

EVOLUTION OF ER SIGNALING

1. Chemical signaling in animals and plants

Chemical communication is a common means of endogenous and exogenous signaling for reproduction, development and differentiation in organisms. For example, some insects and crustaceans rely on ecdysteroids to signal molting and growth (Oberdorster *et al.* 2001), and the slime mold *Dictyostelium* relies on a chlorinated alkyl phenone for the cellular differentiation (Kay 1998). In vertebrates agonistic as well as antagonistic hormone signals control sexual development and reproduction (McLachlan 2001). For example, circulating 17β-estradiol (E_2) control growth in organs such as breast, ovary, uterus in female. Recent evidence showed that E_2 is also essential for male reproductive functions by germ cell survival and sperm maturation in epididymis (Carreau 2000). In plants, versatile chemical signals, called phytochemicals or phytoestrogens, which serve both as endogenous signals within the plant and exogenous

signals for communication with other organisms, such as predatory herbivores (Wynne-Edwards 2001). Although phytoestrogens serve specific signaling functions between the plants and insects, fungi, and bacteria, many chemical signals are often misinterpreted as estrogenic signals in nontarget organisms such as vertebrates. For chemical communication to occur within or between organisms, a receptor must have affinity for specific chemical ligands or signals, and this recognition must initiate a response. In fact, a wide variety of natural and synthetic chemicals exist in the environment that mimic hormones and disrupt endocrine signaling in vertebrates through interaction with various nuclear receptors and signal transducer proteins, including the estrogen receptor, orphan receptors, and the thyroid receptor (Takeshita *et al.* 2001; Moriyama *et al.* 2002; Ishihara *et al.* 2003).

2. How can plants and humans share steroid signals?

Phytochemical signals produced by plants are intercepted by humans and affect estrogenic signaling by binding to ERs and influencing estrogen-responsive gene expression. Some flavonoid phytoestrogens are able to bind ERα and ERβ and act as weak agonists (Collins-Burow *et al.* 2000) that compete with endogenous E_2 for ER binding and activation of estrogen-responsive genes (Kuiper *et al.* 1998). Despite their ability to bind these receptors, phytoestrogens exhibit only a fraction (10^{-2}-10^{-3}) of the estrogenic activity of E_2 (Collins-Burow *et al.* 2000). The specific affinity for and recognition of similar natural and synthetic ligands by receptors such as ER provide an example of shared or analogous functionality (Fox *et al.* 2001, 2004). How can plants and humans share the ability to produce and recognize steroid signals? There are no ERs in plants or in their most common partners, insects. However, one intended target of phytoestrogen signaling, *Rhizobium* soil bacteria, have ligand-dependent transcriptional activator proteins/receptors, called NodD proteins, which have been reported to share genetic homology with the human ER (Gyorgypal and Kondorosi 1991). These two evolutionarily distant receptors both recognize and respond to a shared group of chemical signals and ligands, including both agonists and antagonists. Convergent evolution may explain the shared ligand recognition properties common to both ER and NodD proteins (Thompson 1999). ER is the earliest ancestral receptor of the entire steroid receptor family (Thornton *et al.* 2003). Conversely, the endogenous natural ligand for ER, E_2, is the terminal product of the steroid biochemical pathway. Therefore, the ER may have arisen long before its endogenous ligand, E_2, was produced. In this absence of E_2, ancestral ERs may yet have functioned as receptors for exogenous/environmental signals. At the time of the birth of ER, organisms such as insects, fungi, bacteria, and plants existed and may have been actively producing chemical signals that served as potent ER ligands. These environmental signals may have included a wide variety of phytoestrogens, including those that signal through rhizobial NodD receptors to initiate symbiosis. Therefore vertebrate ER proteins and rhizobial NodD proteins can also be affected by many of the same environmental ligands and phytoestrogens. ER can also be activated in a ligand-independent manner via cross-talk with growth factor signaling pathways (Frigo *et al.* 2002; Klotz *et al.* 2002). This suggests that the original signaling function of ER may have been as a receiver and translator of many varied environmental signals.

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