Review Article

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RELATIONSHIP BETWEEN DIETARY PHYTOESTROGENS AND ENDOGENOUS ESTROGEN: A REVIEW

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ABSTRACT

Phytoestrogens are a group of plant-derived compounds that have selective estrogen receptor-mediated agonist or antagonist effects and show potential benefits for human health. This review discusses the interactions between phytoestrogens intake and endogenous estrogen. Phytoestrogens act the same way as estrogen and may also exert biological activity by other mechanisms to modulate endocrine system function. These phytochemicals may interact with estrogen receptors and induce various estrogenic or antiestrogenic effects. Phytoestrogens stimulate also the synthesis and the release of sex hormone-binding globulin, thus decrease free estradiol levels in circulation associated with reduced risk form any disease, such as breast cancer. Furthermore, there is growing evidence that phytoestrogens may directly modulate concentrations of circulating estradiol *via* interactions with enzymes involved in the estrogen biosynthesis and metabolism such as 17β-hydroxysteroid dehydrogenase, aromatase and steroid sulfatase and through regulation of hypothalamic-pituitary-ovarian axis.

Keywords: Phytoestrogens; estrogen receptors; sex hormone-binding globulin; estrogen biosynthesis; hypothalamic-pituitary-ovarian axis

INTRODUCTION

Phytoestrogens are bioactive substances found in a large variety of fruits and vegetables. They belong to a wide group of chemical compounds such as isoflavones, coumestans and lignans[1–4]. The assessment of the benefits and the risks of phytoestrogens is a complex task due to inter-individual variation and the complexity in the absorption and metabolism[5]. Dietary phytoestrogens are metabolized by intestinal bacteria, absorbed, conjugated in the liver, circulated in plasma and excreted in urine[6,7]. With the exception for flavanols, most of phytoestrogens are usually in the form of conjugated glycosides. They are hydrolyzed by gastrointestinal β-glucosidases into biologically active aglycones[8]. The aglycones can then be metabolized by the gut microflora and transformed into hormone-like compounds. Lignans can be converted into mammalian lignans, enterodiol and enterolactone, whereas the isoflavones daidzein can be converted into O-desmethylangolensin and equol[9–12].

Phytoestrogens may have a considerable impact on human health and disease, including cardiovascular diseases, cancer and osteoporosis, as well as the reduction of menopausal symptoms[13,14]. These potential health benefits suggest that phytoestrogens act on a physiological and pathological processes by modulating the impact of estrogen on the targeted cells. This review will address the recent advances in the understanding of the molecular mechanisms by which phytoestrogens interact with endogenous estrogen.

Phytoestrogen interactions on estrogen receptors

Because of their structural similarity with endogenous estrogen, 17β-estradiol (E2), phytoestrogens may exert estrogenic or antiestrogenic actions by interacting with estrogen binding sites[4,15,16].

In general, phytoestrogens act through nuclear estrogen receptors; ERα and ERβ, influencing transcription of their target genes. They exert effects on cellular processes that include proliferation, apoptosis and migration. The estrogen receptors can also be associated with the plasma membrane and cause rapid cytosolic signaling. Phytoestrogens serves also as ligands for the non-classical membrane G-protein coupled estrogen receptor (GPR30) and induces estrogenic responses in cardiovascular and metabolic regulation through mitogen-activated protein kinases, phosphoinositide 3-kinase, adenylyl cyclase and phospholipase C signaling pathway[17,18].

Influence of phytoestrogens on sex hormone binding globulin (Figure 1)

Sex hormone-binding globulin (SHBG) is the main transport binding protein for E2 and other sex steroid hormones in plasma. This glycoprotein regulates their accessibility to target cells[19]. SHBG is composed of 373 amino acid residues (40.509 kDa)[20], it is encoded by a gene located on chromosome 17p[21].

A variety of hormones and drugs, as well as metabolic and nutritional factors, can influence the expression of human SHBG and plasma SHBG levels[19,22]. It has been shown that phytoestrogens can modulate the levels of human sex hormone-binding globulin (hSHBG) *in vitro*[23]. Several studies demonstrated that lignans and isoflavones can increase both the synthesis and the secretion of hSHBG in human liver cancer cells[23–26]. It was also reported that enterolactone (1-10 M) stimulated the synthesis of hSHBG up to 50%, in a dose dependent manner but that higher concentrations of enterolactone (50 M) inhibited synthesis[24]. Other studies showed that genistein (5-30 M) dose dependently induced SHBG production up to 7-fold by human hepatocarcinoma (Hep-G2) cells in culture[23]. These findings suggested that phytoestrogens may stimulate the

synthesis and release of SHBG, thus reducing the proportion of free estradiol circulating in plasma and indirectly lowering breast cancer risk[22].

In this context, phytoestrogen, as estrogen,can increase the human SHBG expression by boosting the hepatic levels of the transcription factor, hepatocyte nuclear factor 4 alpha (HNF4α)[27]. HNF4α expression would be regulated *via* the MAPK kinase (MEK)-1/2 and c-Jun N-terminal kinase (JNK) MAPK signaling pathways[28].

More evidence shows that SHBG can participate in signal transduction *via* its own membrane receptor (SHBG-R). First, SHBG must bind to a membrane (through SHBG-R), and a ligand must then interact with the SHBG bound to the membrane. It is only at this point that the biological effect is elicited. If the ligand is bound to SHBG before the protein binds to the membrane, it is blocked from interacting with membranes[22]. In breast cancer, SHBG binds to SHBG-R and activates adenylyl cyclase, leading to the generation of the second messenger, cAMP and its target PKA[29,30]. The increased PKA levels may inhibit the MAP kinase pathway and then estradiol-induced cell proliferation[22,31]. It has also been reported that inhibition of ERK causes inhibition of the anti-apoptotic effects caused by estradiol[30,32].

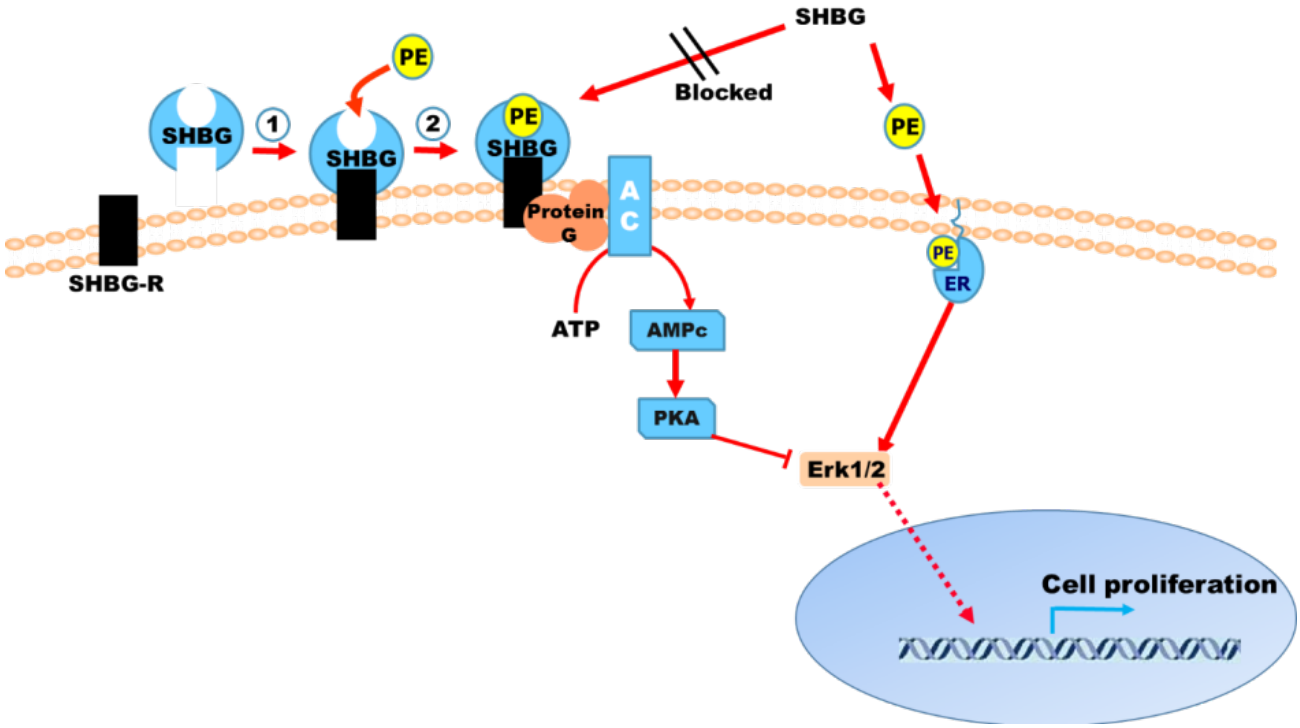

Figure 1: Model of SHBG mediating signaling pathways

In its steroid-free configuration, SHBG binds to its receptor (SHBG-R). After binding to estradiol (E_2) or phytoestrogen (PE), the complex activates adenylyl cyclase (AC), leading to cAMP generation, which in turn inhibits ERK. Phytoestrogen can also bind either to its membrane receptor (ERm), leading to ERK activation, or to the intracellular ER (ERα), activating the genomic pathway. Therefore, SHBG and phytoestrogen or estradiol membrane-initiated pathways have opposite effect on cell growth and apoptosis.

Interaction with the metabolism of steroid hormones and estrogen production (Figure 2)

In premenopausal non-pregnant women, estrogens are predominantly synthetized in ovaries and, to less extent, in peripheral tissues. In post menopausal women, the source of estrogen production shifts toward the peripheral tissues. Estrogens can be produced by de novo synthesis from cholesterol or *via* local desulfatation of estrogen precursors[33]. Several steroidogenic enzymes catalyse reactions that have an estrogen as a substrate and/or a product. The reactions catalysed include aromatisation, oxidation, reduction, sulfonation, desulfonation, hydroxylation and methoxylation[34]. Two pathways are important for estrogen biosynthesis. In the first pathway named "sulfatase pathway", biological inactive steroid sulfates are the source for E2, whilst in the "aromatase pathway", E2 is derived from androgenic precursors[35–37]. The sulfatase pathway is the dominant pathway for *in situ* estradiol synthesis in postmenopausal breast cancers[38].

Phytoestrogens may modulate the endogenous steroid concentrations by binding to and inactivating the enzymes involved in their biosynthesis and metabolism[39].

Inhibition of 17ß-hydroxysteroid dehydrogenase

The 17ß-hydroxysteroid dehydrogenase (17ß-HSD) enzymes, occur as two isoforms 17ß-HSD1 and 17ß-HSD2, involved in the interconversion of estrone to the more active estrogen, estradiol[34,40]. 17ß-HSD1 and 17ß-HSD2 are key enzymes in estrogen biosynthesis and metabolism and are expressed selectively in steroidogenic and some estrogen sensitive tissues. The type 1 enzyme converts estrone to estradiol and type 2 catalyses the reverse reaction[34]. Therefore, inhibition of 17ß-HSD1 produces an anti-estrogenic effect by reducing concentrations of estradiol and converting it to the less active estrogen, estrone. At the opposite, inhibition of the reverse reaction catalysed by 17ß-HSD2 would produce an estrogenic effect by increasing estradiol and reducing estrone concentrations[41].

Phytoestrogens have been found to alter the activities of 17ß-HSD1 and 2 to shift the equilibrium concentrations of estrone and estradiol[40,42–44]. However, the direction of this equilibrium shift is dependent on phytoestrogen structure[45]. The kinetics analysis shows that the degree of hydroxylation significantly influences the overall inhibitory efficacy of the flavonols[42,43,46].

Aromatase inhibition

Aromatase (CYP19A1) is an enzyme involved in estrogen synthesis, converting androgen to estrogen[34,47].

Many studies have shown that phytoestrogens can interact with aromatase activity and/or expression[33]. Lignans, flavones and isoflavones, can inhibit aromatase in a competitive manner and therefore, may increase the ratio of endogenous androgen to estrogen[47–51]. In general, phytoestrogens act as aromatase inhibitors by decreasing aromatase gene expression, inhibiting the aromatase enzyme itself, or in some cases acting at both levels of regulation[47].

Inhibition of steroid sulfatase and sulfotransferase

In some tissues, estrogens can be made on demand, estrogen can be stored in the form of estrone sulfate and dehydroepiandrosterone (DHEA) sulfate[34]. These steroids sulfate are synthesized from respectively, estrone and dehydroepiandrosterone, by the action of estrogen sulfotransferase (SULT). Unlike, the biologically active estrogens is produced from the less active estrone sulfate and DHEA sulfate through the steroid sulfatase (STS) activity[34,52].

As sulfated estrogens are unable to bind to the estrogen receptors, sulfonation of estrogens results in their inactivation. Therefore, conjugation with sulfate protects cells and tissues from an excess of active estrogens, and this may contribute to the prevention of hormone-dependent cancer cells[35].

It has been shown that genistein and daidzein are potent inhibitors of estradiol sulfation *in vitro*. In contrast, these compounds were poor inhibitors of STS[33,53,54]. This suggests that they may act to either reduce the concentrations of circulating sulfated steroids or, conversely, to increase the concentration of active steroids in peripheral tissues, depending on the location of the affected enzymes[53,55].

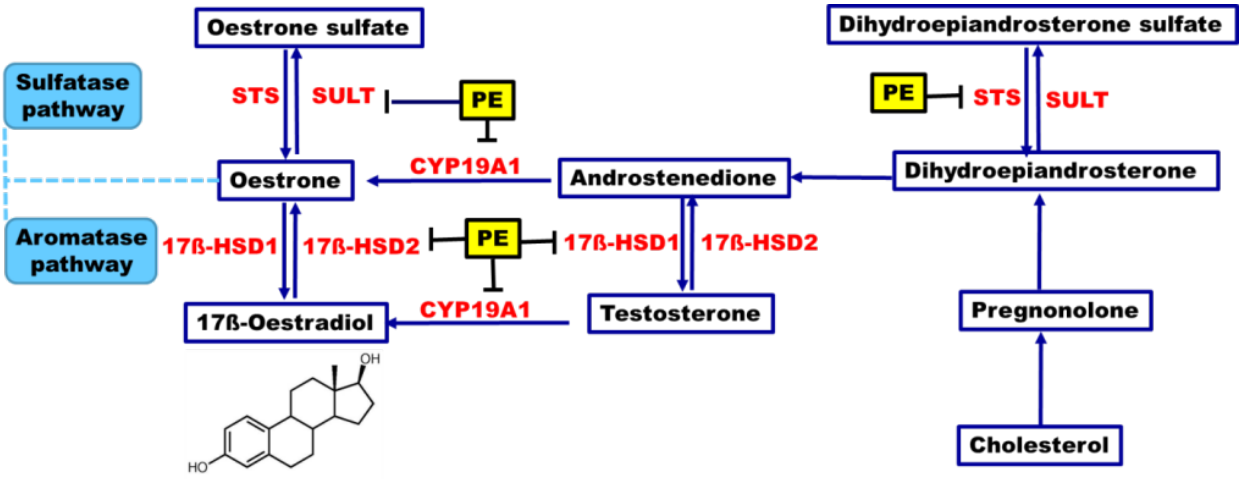

Figure 2: Enzymes involved in estrogen biosynthesis and metabolism

The cholesterol is converted to pregnenolone, which is metabolized to androstenedione. Androstenedione, in turn, is further converted by the enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD) into testosterone, and then P450 aromatase (CYPA9A1) is the main enzyme involved in the synthesis of 17β-estradiol (E2) from testosterone.

Additionally, the conversion of inactive sulfated estrogens to E2 is accomplished by the steroid sulfatase (STS), whilst, estrogen sulfotransferase (SULT) converts active estrone and dehydroepiandrosterone to their inactive sulfates.

Phytoestrogens (PE) may modulate the steroid concentrations by inactivating the enzymes involved in their biosynthesis and metabolism.

Effects on hypothalamo-pituitary-ovary axis (Figure 3)

Estrogen production requires the interaction of components of the hypothalamo-pituitary-ovary axis. Kisspeptin is a potent stimulator of this axis and in fact, it is the most potent gonadotrophin-releasing hormone (GnRH) secretagogue currently known[56]. The location of kisspeptin neurons within the hypothalamus is different among species, residing within the anteroventral periventricular nucleus (AVPV) and the arcuate nucleus (ARC) in rodents, and within the preoptic area (POA) and the infundibular nucleus in humans[57].

Recently, it has been shown that two other neuropeptides (neurokinin B and dynorphin) are thought to be co-secreted with kisspeptin to regulate GnRH secretion ; neurokinin B is generally stimulatory to GnRH release, whilst dynorphin inhibits it[56]. The kisspeptin neurons are so called KNDy neurons by reference to the three secreted peptides[56,58].

Kisspeptin signals directly to the hypothalamic GnRH neurons *via* kisspeptin receptor to release GnRH into the portal circulation, which in turn stimulates the anterior pituitary gonadotropes to produce gonadotrophins, FSH and LH. Following their release, LH and FSH stimulate the maturation of the ova resulting in an increased conversion of testosterone into estradiol by the enzyme, aromatase. When sufficient levels of estradiol have been reached, estradiol exerts a negative feedback effect on the anterior pituitary gland and on the hypothalamic arcuate nucleus inhibiting further secretion of GnRH. Conversely, it exerts positive feedback on GnRH *via* kisspeptin neurons in

AVPV[59,60]. Thus, Kisspeptin neurons in the arcuate region of the hypothalamus regulate the tonic pulsatile release of GnRH, whereas those in the AVPV generate the preovulatory LH surge in females[59,61].

Many of the reproductive disruption caused by phytoestrogens are related to the hypothalamic-pituitary-ovary axis. Phytoestrogens (flavones, isoflavones and coumestanes) mimic E2 negative feedback to inhibit the activity of the hypothalamic GnRH pulse generator and thereby serum LH levels in rats[62,63]. Additional work demonstrated that genistein alters hypothalamic kisspeptin signaling pathways associated with decreased GnRH activation and kisspeptin fiber density in the hypothalamus[64]. At the same time, genistein is capable of decreasing E2 concentrations in plasma[63,65].

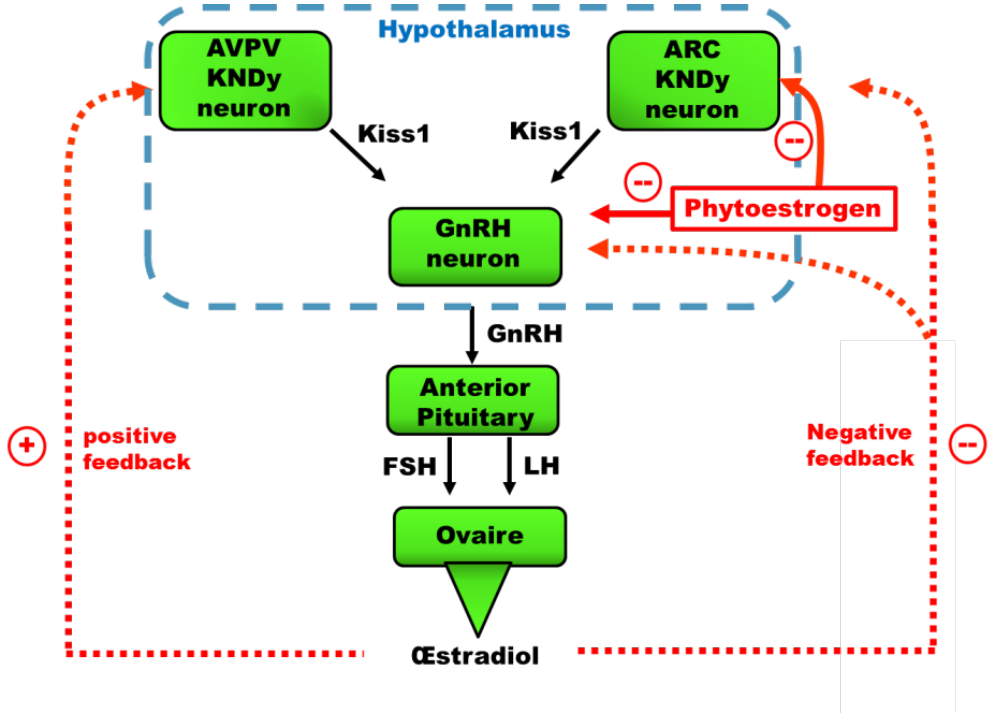

Figure 3: Diagram showing positive and negative feedback inputs into thehypothalamic-pituitary gonadal axis through Kiss-1 neurons in the anteroventral periventricular nucleus and arcuate nucleus within the hypothalamus

The diagram shows that kisspeptin (Kiss1) stimulates gonadotrophin-releasing hormone (GnRH) secretion and subsequently gonadotrophin release. Testosterone is aromatised to estrogen, which exerts negative feedback on the anterior pituitary gland and hypothalamus. Estradiol exerts negative feedback on GnRH *via* Kp neurons in the arcuate nucleus (ARC) and positive feedback on GnRH *via* Kp neurons in the anteroventral periventricular nucleus (AVPV).

Phytoestrogens mimic estradiol negative feedback to inhibit the activity of the hypothalamic GnRH pulse generator and thereby serum LH levels.

CONCLUSION

Phytoestrogens found in the human diet can have many beneficial effects on health, such as vasorelaxant and anti-proliferative effects. They exert their biological effects *via* similar mechanisms of endogenous estrogens action through genomic or non-genomic pathway. Phytoestrogens can also regulate plasma levels of SHBG and displace 17β-estradiol from SHBG binding sites, thereby reducing the circulating concentration of free bioactive hormones. Moreover, phytoestrogens can affect steroid biosynthesis by inhibiting steroidogenic enzymes as aromatase and also have beneficial effects on female reproduction by acting direct and indirect effects on the hypothalamic-pituitary-ovarian axis.

Thus, phytoestrogen can produce the same or opposite effects to endogenous estradiol and the interactions between these compound activities may have a definite impact on human health. However, many questions remain unclear and further studies are required to clarify the ability of chemical classes of phytoestrogens to modulate cellular activities under physiological and physiopathological conditions, in order to use these compounds as an alternative or complementary herbal treatment.

ABBREVIATIONS

cAMP, cyclic adenosine monophosphate; E2, 17β-estradiol; ER, estrogen receptor; HNF4α: hepatocyte nuclear factor 4 alpha; MAPK, mitogen-activated protein kinases; PE, phytoestrogen ; PKA, protein kinase A; SHBG, sex hormone-binding globulin; STS: Steroid sulfatase; SULT: estrogen sulfotransferase; 17ß-HSD: 17ß-hydroxysteroid dehydrogenase, FSH: follicle-stimulating hormone; LH: luteinizing hormone.

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