Review Article

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INTERACTIONS OF PHYTOESTROGENS WITH ESTROGEN-SIGNALLING PATHWAYS AND THEIR IMPLICATIONS IN PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES: A REVIEW

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ABSTRACT

Phytoestrogens are a group of biologically active compounds derived from plants that structurally or functionally mimic some of the effects of estrogens and show potential benefits for human health. Further research continues to demonstrate the biological complexity of phytoestrogens, which act through diverse mechanisms. This review discusses the mechanisms of phytoestrogens intake and their interactions with estrogen receptors. Phytoestrogen actions are mediated through the classical nuclear receptors, ER α and ER β , directly or through a tethered transcription factors binding. In addition to full length ER α (ER66), two truncated isoforms of ER α , ER46 and ER36, can associate with the plasma membrane and influence rapid cytosolic signaling. Phytoestrogens serve also as ligands for the non-classical estrogen receptor GPR30 and can activate the mitogen-activated protein kinases, phosphoinositide 3-kinase, adenylyl cyclase and phospholipase C signaling pathways.

Keywords: Phytoestrogens; estrogen; estrogen receptors; mitogen-activated protein kinases; signaling pathways

INTRODUCTION

Phytoestrogens are polyphenolic non-steroidal compounds present naturally in several fruits, vegetables and leguminous plants such as soybean and flax¹⁻³. Phytoestrogens include a wide variety of structurally different compounds such as flavones (Kaempferol and quercetin), isoflavones (genistein, daidzein and equol), coumestans (coumestrol), lignans (secoisolariciresinol, matairesinol, pinoresinol, and lariciresinol) and stilbenes (resveratrol)³⁻⁶.

Phytoestrogens have a structural similarity with 17 β -estradiol and can bind to the estrogen receptor sites^{3,7,8}. Furthermore, there is evidence that phytoestrogens are directly responsible for the estradiol concentrations in circulation. Phytoestrogens stimulate the synthesis and the release of sex hormone-binding globulin, thus reducing the proportion of free estradiol circulating in plasma. Phytoestrogens can also inhibit enzymes involved in the estrogen biosynthesis and metabolism, such as 17 β -hydroxysteroid dehydrogenase, aromatase and steroid sulfatase and through regulation of hypothalamic-pituitary-ovarian axis⁹.

Phytoestrogens may have a considerable impact on human health and diseases^{10,11}. They play an important role in the prevention of cardiovascular disease, and osteoporosis^{1,4,12}. Phytoestrogens influence the reproductive performance^{6,13} and improve cognitive performance^{14,15}. They are also used as a natural alternative to hormone replacement therapy and to reduce postmenopausal symptoms¹⁶. Furthermore, phytoestrogens have antineoplastic effects with inhibition of cellular proliferation as well as angiogenesis¹⁷; properties that could be protective against cancer development¹⁸, particularly on hormone-dependent cancers (breast and prostate)¹⁹.

These health benefits may be attributable to the multiple targets and a variety of cellular and molecular mechanisms of

phytoestrogens action in physiological and pathological processes. This review will focus on the action of phytoestrogens and their potential roles in the interaction with estrogen receptors.

Nuclear estrogen receptors: ER α and ER β

Due to their similarity with the endogenous hormones, phytoestrogens can bind two types of intracellular estrogen receptors, estrogen receptor α (ER α) and estrogen receptor β (ER β)^{20,21}.

Estrogen receptors structure

The two major nuclear ER are encoded by genes located on different chromosomes. ER α is encoded on chromosome 6q25.1, while the gene encoding human ER β is localized on chromosome 14q (23-24)^{22,23}. The full-length human ER α protein has 595 amino acids and a molecular size of 66 kDa while the full-length human ER β protein has 530 amino acids and a molecular size of 54 kDa²⁴.

Like other steroid receptors, ER α and ER β have six functional domains, A/B, C, D, E and F domains. The N-terminal A/B domains are completely different between the two receptors and is involved in protein-protein interactions and transcriptional activation of target-gene expression. The central highly conserved C-domain represents the DNA-binding domain (DBD) and is involved in specific DNA binding and receptor dimerization. The D-domain is not well-conserved between ER α and ER β (30%) and promotes the association of ER with heat shock protein 90 (Hsp90) and nuclear localization of ER. The C-terminal E/F domains shares about 50% amino acid homology and contains the ligand-binding domain (LBD). The differences within the ligand binding cavities are only based on two amino acid positions: Leu384 and Met421 in ER α are replaced by Met336 and Ile373, respectively, in ER β ²⁴⁻²⁶. There are two

activation domains in the estrogen receptors, an N-terminal activation function (AF-1) and a C-terminal activation function (AF-2) and these regions act synergistically to recruit co-regulatory proteins (co-activators or co-repressors) and thus regulate transcription machinery^{23,27,28}.

In addition to the wild type estrogen receptors, there are multiple variant isoforms that originate by the protein truncation²⁹. Compared to the classical nuclear estrogen receptor- α (ER α), also named estrogen receptor- α 66 (ER α 66) in view of its molecular weight, two truncated splice variants, 46 kDa estrogen receptor (ER α 46) and 36 kDa estrogen receptor (ER α 36), have been identified³⁰. ER α 46, does not have the AF-1 transactivation domain, whilst ER α 36 devoid of the AF-1 and AF-2 transactivation domains and part of the ligand binding domain in the C-terminal is replaced by an unique 27 amino acid sequence^{31–33}. Otherwise, in addition to the expression of wild-type ER β (ER β 1), different isoforms (ER β 2 to ER β 5) have been described with a variable ligand-binding domain^{34,35}, but as of today their functional significance is poorly understood^{36,37}. However, it has been reported that ER β 2 and ER β 5, but not ER β 1, promote survival in breast cancer patient^{35,38} and all splice ER β variants can inhibit transcriptional activity of ER α ²⁷.

There is a distinct tissue expression of ER α and ER β . ER α is a major subtype in the tissues of breast, liver, uterus, ovary (thecal cells), cervix, vagina and other reproductive organs. ER β is distributed in the ovary (granulosa cells), prostate (epithelium), testis, spleen, lung, colon, hypothalamus and thymus^{26,39–41}.

Moreover, phytoestrogens may not only bind to ERs but may also modulate the recruitment of specific coregulators through which specific gene transcription could be achieved^{27,42,43}. Thus, estrogenic ligands will have different effect in different tissues;

the same ligand may be an agonist in certain tissues, where coactivators predominate, while acting as an antagonist in other tissues, in which corepressors prevail⁴⁴.

The binding affinity of phytoestrogens to ERs is related to their stereochemical structure especially according to the arrangement of the two ring structures divided by two carbon atoms, and spacing between hydrophobic and hydrogen bond interaction^{40,45,46}. Although, most of phytoestrogens have much lower affinity (up to 100 folds) compared to endogenous ligands⁶. Thus, even low concentrations of environmental estrogens can trigger an altered response of the biological systems [8, 58]. Phytoestrogens may bind differentially to estrogen receptor proteins (ER α and ER β). Competition binding experiments revealed higher affinity of the phytoestrogens for ER β than for ER α ^{6,47}. Genistein has high affinity for ER β , almost identical to that of E2, while its affinity for ER α is only 6% of E2⁴⁸. In addition, the relative estrogenic potency of genistein for ER β is 30-fold higher than for ER α ⁴⁹. Thus, the net effect of exposure to a particular phytoestrogen may depend on the distinctive patterns of ER α and ER β expression in different cell types. Moreover, phytoestrogens induce the transcription of estrogen-responsive target genes to much greater levels when bound to ER β than when bound to ER α ⁵⁰.

The actions of ER α and ER β on gene transcription can be opposite, depending on cell context^{24,51}. In breast tissue, ER α activation can stimulate proliferation whilst ER β activation can counteract this proliferative effect and may function as tumor suppressor^{24,26}. The ratio of ER α to ER β has been suggested to be a prognostic marker in breast cancer, ER β expression is a sign of a benign tumors, where ER α is an indicator of malignant and aggressive tumors^{50,52,53}.

Figure 1: Activation and interaction of nuclear estrogen receptors with cell-signaling pathways and inhibition by phytoestrogens.

The classical (direct) pathway includes ligand activation and a direct DNA binding to estrogen response elements (ERE) before modulation of gene regulation. The tethered pathway includes protein-protein interaction with other transcription factors (TF), AP1(C-fos/C-Jun) or SP1 or NF- κ B, after ligand activation, and thereby gene regulation is affected by indirect DNA binding. The ligand-independent pathway includes activation through other signaling pathways, like growth factor signaling. In this case, activated kinases phosphorylate ERs and thereby activate them to dimerize, bind DNA, and regulate genes.

Phytoestrogens such Genistein is a potent tyrosine kinase inhibitor and inhibits signal transduction of growth factors. Genistein can also down-regulate the expression of Akt, which can inhibit NF- κ B activity.

Figure 2: Schematic representation of the estrogen receptor dimers effects on gene transcription. Phytoestrogens (PE) bind preferentially to ERβ, dimers of which may bind to the estrogen response element (ERE) on the DNA or to other response elements such as AP-1 and SP-1 and activate/inhibit genes that regulate tumor growth. Binding to ERβ may also induce heterodimerization with ERα and hence silence its activation of genes stimulating cell proliferation.

Figure 3: Proposed Mechanism by which E2/PE Promotes Cancer Cell Survival through membrane-associated ERα36. Phytoestrogen (PE) interacts with ERα36 at the cell membrane initiating a signaling cascade consisting of phosphatidylinositol-specific phospholipase C (PLC)-dependent cleavage of PIP₂ to IP₃ and DAG. IP₃ signals Ca²⁺ release from the smooth endoplasmic reticulum, although DAG anchors PKC to the membrane. The membrane localization along with Ca²⁺ association with PKC leads to its activation, with downstream activation of ERK1/2 mitogen-activated protein kinase (MAPK). Activation of ERK1/2 can affect cell proliferation as well as phosphorylation of transcription factors that can activate or repress gene transcription, possibly leading to expression of factors associated with metastasis and tumor aggressiveness. ER36 can also activates PI3K/AKT signaling pathways and stimulates cells proliferation.

Figure 4: ER α activation by phytoestrogen or estrogens induces eNOS increased activity and NO production. Signaling pathway by which phytoestrogen (PE) interacting with ER α , activates rapidly eNOS and increases NO production in endothelial cells by PI3-K/Akt or via Src/ERK1/2 pathways.
eNOS : nitric oxide synthase, NO : nitric oxide, GLC : guanylyl cyclase, GMPc : cyclic-GMP, PKG : protein-kinase G.

Figure 5: Signaling Pathways activated by GPR30. Stimulation of GPR30 activates heterotrimeric G proteins, which trigger multiple effectors resulting in cAMP production. Matrix metalloproteinase (MMP) activation leads to HB-EGF release that can transactivate epidermal growth factor receptors (EGFRs). EGFR activation leads to multiple downstream events including activation of MAP kinases (MAPKs) and PI3 kinases (PI3Ks), which result in expression of transcription factors such as c-fos. As a result, estrogen stimulation can lead to the expression of target genes whose promoters do not contain steroid response elements (EREs). The combined effects of these signaling and transcriptional events often lead to cell cycle progression and cell proliferation. GPR30 can also activate the phospholipase C (PLC) and then produces inositol triphosphate (IP3), which further leads to intracellular calcium mobilization. Increased in [Ca²⁺] and PKC exerts many intracellular physiological effects, such as vascular smooth muscle contraction.

Mechanisms of nuclear estrogen receptor signaling pathway

Because of their stable structure and their low molecular weight, phytoestrogens can go through cell membranes and bind to ERs⁵⁴. The genomic action of ERs occurs in the nucleus of the cell, when the receptor binds specific DNA sequences directly (classical pathway) or indirectly (non-classical pathway)³⁶. (Figure 1)

In the classic pathway of ER activation, after ligand binding, a ligand-specific conformational change of the receptor occurs, allowing its dissociation from chaperone molecules, such as HSP90⁵⁵ and homo/heterodimerization of the estrogen-ER complexes. The activated ERs dimerizes, either as homodimers (ER α /ER α or ER β /ER β) or heterodimers (ER α /ER β), forms a complex for binding directly to a specific DNA sequence, the consensus estrogen response element (ERE). The coregulator complexes, such as p160 and the CBP/P300 family proteins, are believed to be essential for ER action and influence the level of expression the estrogen-response genes^{38,55}. The ER dimers exert different functions on intracellular estrogen signaling pathways. The ER α /ER α homodimer was reported to stimulate estrogen-induced cell proliferation, whereas the ER β /ER β homodimer exerts inhibitory effects on estrogen-dependent cell proliferation in breast carcinoma cells. In addition, ER α /ER β heterodimers was also known to inhibit cell proliferation because ER β inhibits ER α -mediated cell proliferation through the co-expression of ER α and ER β in estrogen responsive cells^{27,38,55}.

As regards the endogenous ER α variants, ER α 46 forms also homodimers or heterodimers form with ER α 66 and binds to an ERE⁵⁶. Furthermore, in the ER α 46/66 heterodimers form, ER α 46 acts competitively to inhibit transactivation mediated by the AF-1 domain of ER α 66 and then regulates genomic estrogen signaling pathway and represses cellular proliferation in response to E2^{56,57}.

The other ER α variant ER α 36 retains protein dimerization domains and is able to form heterodimers with ER α 66 or ER β which may block transcription activities and genomic estrogen signaling of ER α 66 and ER β ^{32,57}. Likewise, given that ER α 36 lacks AF1 and AF2 domains, which are important for cofactor recruitment to the DNA, the activated ER α 36 homodimer may recognize EREs in the nucleus, but be unable to initiate signaling once bound, thereby acting as an inhibitor of genomic estrogen signaling⁵⁸.

In non-classic pathway, ligand-ER complex interacts with several transcription factors complexes like activator protein-1 AP-1 (cFos/cJun dimers), stimulating protein-1 (SP-1) or nuclear factor-kappa B (NF-kB) and influencing transcription of genes whose promoters do not harbor ERE³². However, there is an interesting difference between ER α and ER β at AP-1 sites; the activation of ER α induces AP-1 driven reporter activity, whereas ER β has no effect^{36,59,60}. Moreover, ER α and ER β also exhibit different transcriptional effects in regulation of the cyclin D1 promoter; ER α mediates the stimulatory effect of estrogen on cyclin D1 expression, whereas ER β has a repressive effect^{60,61}.

Another genomic pathway is mediated by a ligand-independent manner, showing that the estrogen receptor can also be activated in the absence of a ligand by phosphorylation the AF-1 region of ER α and ER β . For full activity of ER α AF-1, the phosphorylation of a Ser-118 is very important, whilst for ER β this effect is mediated *via* Ser-124. Phosphorylation may also take place at tyrosine residues of ER α , especially at Tyr-537 which regulates the ligand binding step^{34,62}.

Growth factors as epidermal growth factor (EGF), insulin like Growth Factor-1 (IGF-1) and transforming growth factor β (TGF β) leads to the activation of kinases that may phosphorylate and activate ERs through mechanisms involving the Ras signal transduction pathway. Several studies have shown that phosphorylation by extracellular signal-regulated kinases 1 and 2 (Erk1/2), mitogen-activated protein kinase (MAPK), stimulates ER activity in the absence of ligand^{23,63-65}.

In this context, it has been reported that phytoestrogens can interact with growth factor signaling pathways (Figure1). Thus, phytoestrogens can modulate the responses to growth factors or kinases, which may alter ligand-independent transcriptional activity of estrogen receptors or other transcription factors such as AP-1 and NF-kB⁶⁴. For example, genistein is a tyrosine kinase inhibitor and has been shown to alter the activity/expression of both extracellular regulated kinase (ERK) and the PI3/Akt pathway by EGF⁶⁶. Long-term treatment of breast cancer cells with dietary levels of genistein down-regulate the expression of AKT and AKT signaling pathways by decreasing its phosphorylation at serine 473, which can inhibit NF-kB activity^{53,66,67}.

Many phytoestrogens appear to have a biphasic effect on cell proliferation, stimulating growth at low concentrations and suppressing growth at high concentrations^{50,68}. Genistein was shown to increase growth in estrogen-sensitive cells at low concentrations but decreased cell growth, suppressed DNA synthesis, and induced cell death at high concentrations^{50,53,69}. Phytoestrogens at high doses (> 10 μ mol/L) have been shown to inhibit cyclin D1 expression but increase the expression of cyclin-dependent kinase inhibitors (p21 and p27) and the tumour suppressor gene p53^{19,53,70}. Phytoestrogens can also stimulate apoptosis and increase the Bax/Bcl-2 ratio but evidence as to whether this effect is due to increased or decreased activity of ERK1/2 is controversial^{53,71}.

The differential affinities of phytoestrogens for ER α and ER β suggest that physiologic concentrations of phytoestrogens may be enough to activate ER β but not ER α . Thus, phytoestrogens, rather than acting *via* the classical ER α pathway, may activate ER β and induce its antiproliferative effects²⁷. In breast cancer cell lines, activation of ER β inhibits cells growth and it is now generally thought that dimerization of ER β with ER α silences the growth-promoting effects of ER α ^{27,72} (Figure 2). ER β may be considered as a dominant-negative regulator of ER α modulating transcriptional responses to estrogens. The ratio of ER α vs β within a cell may determine the cell sensitivity to estrogens and its biological responses to the hormone⁷³.

Membrane-associated estrogen receptors

Both ER α and ER β , the two ER isoforms, have been localized in many cells to the plasma membrane⁷⁴. It is estimated that about 5 to 10% of total cellular ERs are localized at the plasma membrane and contribute to non-genomic (rapid) effects of estrogen^{4,75,76}. Previous reports have described membrane-associated estrogen receptors identical with the classical nuclear estrogen receptors⁷⁷⁻⁷⁹.

Nature of membrane ER (mER)

The cellular localization of different ERs usually depends on cell types. Classical ERs like ER α 66 and ER- β are mainly expressed in nucleus and cytoplasm, little is found in plasma membrane. ER α 36 is mainly localized in plasma membrane and cytoplasm, but incidentally found in nucleus. The majority ER α 46 are

distributed in a similar manner to ER α 66 and still found in the nuclear and cytoplasmic fraction^{58,80}.

Moreover, the relative amount of ER α and ER β at the plasma membrane can differ among cell types. Both the ER α and ER β are found to be present at the plasma membrane of vascular endothelial cells. In breast cancer cells, ER α is found to be in lower than ER β , meanwhile in reproductive tissue, ER α is more abundant than ER β ⁷⁶.

All endogenous ER α , ER α 66 and its trunca isoforms ER α 46 and ER α 36, are tethered to the plasma membrane by a mechanism involving post-translational modifications such as palmitoylation, which has been shown to increase association of the receptor with the plasma membrane³⁰. Some reports reveal that palmitoylation in the Golgi apparatus by palmitoyl acyl transferases may target classical ERs to the cytoplasmic face of the plasma membrane^{25,79,81}. Attachment of fatty acid residues such as palmitic acid is a post-translational modification, which increases hydrophobicity, thereby facilitating insertion of protein in to the cell membrane invaginations (caveolae) involved in signal transduction and endocytosis^{79,82}. Interactions with caveolae proteins such as caveolin-1 is an essential step of ER α and ER β joining to cell membrane, and this process is facilitated by prior ER palmitoylation at Cys 447^{74,76,83}. Both proteins, ER and caveolin, are closely coupled, and serine 522 present in the domain E of ER is directly responsible for this interaction, and subsequent translocation to the plasma membrane^{76,79}.

Additional reports have suggested the involvement of adaptor proteins, such as Src^{81,84} in the recruitment of ER α to caveolae rafts within the cell membrane. Src binds to a protein named modulator of the non-genomic action of ER (MNAR) *via* its Src-homology 3 (SH3) domain and to the phosphorylated Tyr537 of ER *via* its SH2 domain. This complex is capable of activating ERK/MAPK signaling cascades. Other authors have suggested the involvement of adaptor proteins Shc as a bridge between c-Src and ERK1/2^{81,84}. Others studies demonstrated that amino acids 251 to 260 and 271 to 595 of ER α bind directly to G α i and G β γ ^{76,85}.

Membrane-associated estrogen signaling pathways

After binding to the ligand, mER form a complex with many signal proteins (called signalosome), whose nature and consequently activated downstream signaling pathway, depends on the cell type^{79,86}.

Role in Breast cancer

The palmitoylated ERs are translocated to the membrane as monomers and the dimerization of the membrane ERs occurs within seconds of ligand exposure⁵⁷. The activated mER induces the discreation of the G-protein α subunit to trigger the activation of Src kinases and PI3-K, respectively followed by downstream kinase cascade to Erk, which are involved in proliferation and survival of tumor cells as in breast cancer⁴⁰. The PI3-K activation also triggers the recruitment of AKT, a serine-threonine kinase to control cell survival *via* activating downstream anti-apoptotic signals (e.g. Bcl-2) and transcription factors (e.g. NF-kB and CREB)^{40,87}.

ER36 has been shown to mediate both estrogen and anti-estrogen activation *via* MAPK/ERK and PI3K/AKT signaling pathways and stimulation of cells proliferation^{30-32,37}. The activation of signaling through ER α 36 can also promote PKC activation through PLC, diacylglycerol (DAG), and inositol trisphosphate

(IP3). This rapid activation of PKC can lead to proliferative pathways including MAP kinase signaling⁸⁸. (Figure 3)

Physiological role

One of the best characterized non-genomic actions is represented by vasodilatation that occurs in a matter of seconds to minutes⁷⁵. This acute effect is the result of the regulation of ion flows as well as of vasoactive molecules release on endothelial cells and vascular smooth muscle cells (VSMCs). E2-mediated vasodilation has been attributed to increased endothelial nitric oxide synthase (eNOS) transcription *via* genomic pathways as well as increased eNOS activity and nitric oxide (NO) production *via* non-genomic endothelial cells activation^{23,89}. NO secretion contributes to the protective effect of phytoestrogens, like estradiol, on the cardiovascular system⁴⁸. The physiological function of NO is dependent on its concentration. At low concentrations, NO acts as a signaling molecule regulating blood vessel relaxation, angiogenesis, migration and invasion, cell survival and proliferation whereas at high concentrations it is toxic and can prevent tumor growth by increasing the apoptosis rate of cells⁹⁰⁻⁹². (Figure 4)

Signaling pathway by which phytoestrogens interact with ER α , activates rapidly eNOS and increases NO production in endothelial cells by PI3-K/Akt or *via* Src/ERK1/2 pathways^{76,93}. Upon polyphenolic compounds binding, membrane-localized ER α forms a complex with p85 α , the regulatory subunit of PI3K and with SH2 domain of c-Src. The formation of the ER α /PI3K complex leads to the activation of AKT and ERK1/2. Theses Kinases then directly activate eNOS by serine 1177 phosphorylation, thus transforming L-arginine to L-citrulline and improving NO release⁹⁴. NO is able to activate guanylyl-cyclase in smooth muscle cells inducing increased levels of GMPc with subsequent protein-kinase G activation, reducing intracellular calcium and inducing vascular relaxation^{79,95,96}. The increase in Ca²⁺ together with calmodulin promotes the dissociation of eNOS from caveolin leading to increased eNOS activity⁴⁸.

G protein-coupled seven transmembrane estrogen receptors

Structure and tissues distribution of GPR30

G protein-coupled receptor 30 (GPR30) also named GPER1 (G protein coupled estrogen receptor 1), is identified as an orphan member of the seven-transmembrane receptor family^{79,97,98} and showed highest homology to the interleukin 8 receptors⁹⁸.

GPR30 has an extracellular N terminal, seven transmembrane α helices, 3 exo-loops involved in ligand binding, 3 or 4 cyto-loops involved in G protein subunit binding, and a C terminal linked to the membrane through lipid addition, and also involved in binding G protein subunits²³. GPR30 gene is located on chromosome 7p22⁹⁹.

GPR30 is expressed broadly in numerous human tissues, such as breast, prostate, ovary, placenta, subcutaneous adipose, visceral adipose, arteries, vessels, heart, liver, lung and intestine tissues¹⁰⁰.

Recent studies demonstrate that GPR30 showed high affinity but low-capacity binding to estrogens/phytoestrogens¹⁰¹. It is implicated in mediating both rapid and transcriptional events in response to estrogen⁹⁸.

GPR30 plays a crucial role in some of the physiological systems as in reproduction, metabolism, bone, nervous and immune systems and exerts a protective actions in vascular smooth muscle

contraction (VSM) ^{102,103}. GPR30 has also been speculated to have a potentially important role in cancer ^{104,105}. The overexpression of GPR30 was associated with increased tumor size, the presence of distant metastases and recurrence in human breast tumors, indicating that GPR30 might be a predictor of biologically aggressive disease in breast cancer ^{104,106}.

Signal transduction pathways

GPR30 is able to bind with a high affinity to E2, mediating non-genomic estrogenic signals in cardiovascular and metabolic regulations ¹⁰⁷. Phytoestrogens as Genistein also exhibits high binding affinity for GPR30, and activates the downstream signaling pathways ⁸¹.

Estrogen/Phytoestrogen-mediated GPR30-related cell proliferation was associated with stimulation of the MAP kinase, Erk1/2 and PI3-kinase signaling pathway *via* EGFR transactivation ^{105,108,109}. Estrogen binding to GPR30 results in the dissociation of G α -GTPase from the heterotrimeric G $\alpha\beta\gamma$ complex. Dissociated G $\beta\gamma$ -subunit activates, *via* Src kinases, matrix metalloprotease (MMP) production ¹⁰³, which cleaves pro-heparan-bound epidermal growth factor (pro-HB-EGF) releasing free HB-EGF. Several publications indicate that integrin $\alpha 5\beta 1$ acts as a conduit between Src and metalloproteases. Activation of Src promotes the formation of Shc-integrin complexes and through these a fibronectin matrix assembly and metalloprotease activation ^{110,111}. The release of HB-EGF allows it to activate the EGF receptor (EGFR) resulting in the induction of the MAPK pathway and activation of multiple molecules such as Ras, Erk1/2, PI3K and AKT ^{100,108}. (Figure 5)

E₂ and phytoestrogens activates phosphoinositide 3-kinases (PI3K) through GPR30 and results in the accumulation of phosphatidylinositol 3, 4, 5-trisphosphate (PIP₃) and the downstream activation of anti-apoptotic and proliferative kinase AKT ¹¹¹. On another side, GPR30 mediates a rapid Erk1/2 activation ¹¹².

These GPR30 signaling events triggers more long-term transcriptional responses, such as c-fos in macrophages ¹¹², activation of the transcription factor CREB, Cyclin D2 ¹¹³ and Bcl2 in keratinocytes ^{111,114}. The combined effects of these signaling and transcriptional events often lead to cell cycle progression and cell proliferation. Subsequently, G α -GTPase acts on membrane-associated adenylyl cyclase (AC), generating the second messenger cAMP ^{98,103}. Somewhat paradoxically, the generation of cAMP attenuates MAPK activity *via* the inhibitory activity of protein kinase A on Raf1 ^{101,115,116}. It is likely that the exact balance between inhibition and stimulation of the MAPK pathway will depend on timing and cell type ¹¹¹.

GPR30 also binds to the G-couple protein α subunit and activates the phospholipase C (PLC). Activated PLC results in inositol triphosphate (IP₃) production, which further binds to its receptor and leads to intracellular calcium mobilization ¹⁰⁰. Increased in calcium exerts many intracellular physiological effects, such VSM. PKC also activates a cascade of protein kinases that ultimately interact with the VSM contractile myofilaments and enhance contraction ¹¹⁷.

CONCLUSION

Phytoestrogens are common in the human diet and are able to exert many beneficial health effects such as vasorelaxant and anti-proliferative effects. These estrogenic compounds and their activities are complex and often specific to each species.

Phytoestrogens exert their biological effects through genomic or non-genomic pathways *via* similar mechanisms to the endogenous estrogens action. They induce various estrogenic or anti-estrogenic effects, depending on the tissue, estrogen receptor (ER) expression and concentration of circulating endogenous estrogens. This may explain tissue-specific variability of phytoestrogenic action and explicit different pathways for their actions.

In general, phytoestrogens act through nuclear estrogen receptors, influencing transcription of their target genes. They exert effects on cellular processes that include proliferation, apoptosis and migration. The estrogen receptors can also associate with the plasma membrane and influence cytosolic signaling. In addition, a third membrane-bound ER has described, G protein-coupled receptor 30 (GPR30), which mediates estrogenic responses in cardiovascular and metabolic regulation. GPR30 was also identified in specific intracellular sites (endoplasmic reticulum membrane and mitochondria) but his activities are still debated.

ABBREVIATIONS

AP1, Activator protein 1; DBD: DNA-binding domain; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; DAG: diacylglycerol; E₂, 17 β -estradiol; EGF, epidermal growth factor; EGFR, EGF receptor; ERK1/2, extracellular signal-regulated kinase 1/2; ER, estrogen receptor; eNOS: endothelial nitric oxide synthase; ERE, estrogen response element; GPR30, G protein-coupled receptor30; Hsp90, heat shock protein 90; IGF-1, insulin like Growth Factor-1; LBD: ligand-binding domain; MAPK, mitogen-activated protein kinases; MMP: matrix metalloprotease; NF- κ B, nuclear factor kappa B; MNAR, modulator of nongenomic actions of steroid receptors; NO, nitric oxide; PE, phytoestrogen; PI3K, phosphatidylinositol 3-kinase; PIP₂, phosphatidylinositol 4, 5-bisphosphate; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; SH2: Src-homology 2; SH3: Src-homology 3; SP-1: stimulating protein-1; TGF β , transforming growth factor β ; VSMC: vascular smooth muscle cell.

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