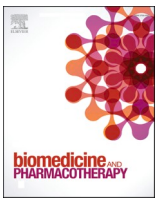
Biomedicine & Pharmacotherapy 160 (2023) 114341

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Review

Phytoestrogens, novel dietary supplements for breast cancer

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ARTICLE INFO

Keywords:
G protein-coupled estrogen receptor
Phytoestrogens
Breast cancer
Signing pathway

ABSTRACT

While endocrine therapy is considered as an effective way to treat breast cancer, it still faces many challenges, such as drug resistance and individual discrepancy. Therefore, novel preventive and therapeutic modalities are still in great demand to decrease the incidence and mortality rate of breast cancer. Numerous studies suggested that G protein-coupled estrogen receptor (GPER), a membrane estrogen receptor, is a potential target for breast cancer prevention and treatment. It was also shown that not only endogenous estrogens can activate GPERs, but many phytoestrogens can also function as selective estrogen receptor modulators (SERMs) to interact GPERs. In this review, we discussed the possible mechanisms of GPERs pathways and shed a light of developing novel phytoestrogens based dietary supplements against breast cancers.

1. Introduction

According to the latest report of International Agency for Research on Cancer (IARC) in 2022, breast cancer leads to the fifth mortality rate among all female cancer diseases [1]. It was demonstrated that estrogens play critical roles in the occurrence and development of breast cancer [2], via the interaction with estrogen receptors (ERs) [3]. 17β-estradiol (E2) is the most potent endogenous estrogen which is secreted predominantly by ovaries [4], and consequently, E2 can also induce proliferation and metastasis of breast cancer cells [5]. Thus, to suppress the occurrence of breast cancer, adjuvant endocrine therapy is an effective approach to decrease the endogenous estrogen secretions [6]. Correspondingly, endocrine therapies block the estrogen-ER signaling pathway by interfering with ER-ligand interactions using selective ER modulators (SERMs) e.q. tamoxifen [7] However, the effect of endocrine therapies is limited in ER-negative patients [8], in addition, ER-positive patients can also eventually develop resistances to drug response [9]. Therefore, understanding the mechanism of endocrine treatment induced internal resistance is of great significance to develop new treatment strategies and improve the survival rate of breast cancer patients [10]. Traditional Chinese medicine (TCM) has unique philosophies [11,12] for the prevention and treatment of breast cancer at various stages [13–16]. In the previous studies, Chinese herbal medicine is rich in phytoestrogens resources, which can effectively inhibit breast tumor progress and enhance the patients' quality of life via relieving their discomfort [17,18]. The phytoestrogens are a group of E2 analogs, showing strong affinities with estrogen receptors and produce E2-like function responses. The estrogen-like effects of phytoestrogens

Abbreviations: IARC, International Agency for Research on Cancer; ERs, estrogen receptors; E2, 17β-estradiol; SERMs, selective ER modulators; TCM, Traditional Chinese medicine; GPER/GPR30, G protein-coupled estrogen receptor 1 / G protein-coupled receptor30; TNBCs, triple-negative breast cancers; PRs, progesterone receptors; HER2, human epidermal growth factor receptor-2; EGFR, epidermal growth factor receptor; cAMP, cyclic AMP; MAPK, mitogen-activated protein kinase; Akt, Protein Kinase B; ERK, extracellular regulated protein kinases; CTGF, connective tissue growth factor; PI3K, phosphoinositide 3-kinase; CAF, Carcinoma-associated fibroblasts; HB-EGF, heparin tyrosine kinase; VEGFR-2, Vascular Endothelial Growth Factor Receptor 2; VEGFs, Vascular endothelial growth factors; PLC, phospholipase C; PMCA2, plasma membrane calcium ATPase 2; PMCA4, plasma membrane calcium ATPase 4; HIF2, hypoxia-inducible factor 1; AC, adenosyl cyclase.

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https://doi.org/10.1016/j.biopha.2023.114341
Received 11 December 2022; Received in revised form 26 January 2023; Accepted 27 January 2023
Available online 6 February 2023

suggested their potential roles in the endocrine replacement therapy, opening up new avenues for the prevention and treatment of breast cancer [19].

Recent evidences indicates that phytoestrogens not only activate the classic ERα and ERβ estrogen receptors [20,21], but also bind specifically to G protein-coupled estrogen receptor 1 / G protein-coupled receptor30 (GPER/GPR30) [22–26]. As representative of a transmembrane receptor protein, GPER are participated in non-genomic response of estrogens [27–30]. Based on the recent progress, this review discusses the potential roles of phytoestrogens and GPERs in the novel breast cancer treatments [21,31,32]. In the end, we also proposed that subsequent research on phytoestrogens should: 1) focus on more precise cellular crosstalk pathway [33]; 2) understand the dynamic structures of GPERs [34,35]; 3) improve bioavailability and enhance stability of phytoestrogens; 4) and develop novel dietary supplements of phytoestrogens in the breast cancer treatment [36–38].

2. Overview research of GPER

Biological role of estrogen, attributed to its role as a ligand that recognizes the corresponding receptor protein.

The main target for estrogen therapy in breast cancer is the nuclear receptor Erα [39], however, about 40% of breast cancer are considered as Erα negative [40], such as triple-negative breast cancers (TNBCs) [41], which is a subtype characterized by the absence of ERs, progesterone receptors (PRs) and human epidermal growth factor receptor-2 (HER2) [42]. Although TNBCs lack classic nuclear ERs, non-nuclear steroid hormone receptors represented by GPER, are frequently expressed in TNBC [43]. In contrast, the Gβγ subunit activates the membrane-associated matrix metalloproteinase cascade and transactivates epidermal growth factor receptor (EGFR)[44–48]. It has been demonstrated that Gα·GTP and Gβγ subunits are released when GPER is recognized by its specific ligands [49,50]. Among them, Gα·GTP regulates Ca^{2+} channels and stimulates membrane-associated enzymes (AC and phospholipase C), which in turn produce second messengers such as cyclic AMP (cAMP) and Ca^{2+}[48,49]. When binding to membrane estrogen receptors, E2 triggers rapid non-genome signals pathway. For instance, E2 stimulating EGFR-related protein kinase cascade in cells [51–53]. Filardo et al. provides several lines of evidence that estrogen can activates the mitogen-activated protein kinase (MAPK) pathway via rapid GPER-dependent activation independent of interactions with ERα or Erβ [28]. Thomas et al. demonstrated that E2 specifically binds to GPER in SKBR3 breast cancer cells, which lack nuclear receptors for estrogen [24]. Ye et al. also demonstrated that GPER can influence breast cancer cell proliferation and migration elicited by estrogen binding, subsequently involved in the proliferation of breast cancer cells known as regulators of tumor transformations [54].

The non-genetic pathway of E2 is consistent with the signal after GPER is activated, and estrogen exerts cellular functions by acting on GPER, which provides a reasonable explanation for its simultaneous activation of second messenger and protein kinase cascade [28,29,55]. Therefore, scientists have proposed that GPER is the receptor that promotes the rapid signaling of estrogen. Since then, increasing evidence has shown that GPER functions as an estrogen receptor [28,56]. Filardo et al. provides several lines of evidence that estrogen can activates the MAPK pathway via rapid GPER-dependent activation independent of interactions with ERα or ERβ [28]. Thomas et al. demonstrated that E2 specifically binds to GPER in SKBR3 breast cancer cells, which lack nuclear receptors for estrogen [24]. Ye et al. also demonstrated that GPER can influence breast cancer cell proliferation and migration elicited by estrogen binding, subsequently involved in the proliferation of breast cancer cells known as regulators of tumor transformation [54]. Since then, increasing evidence has shown that GPER functions as an estrogen receptor, such as activating Protein Kinase B (AKT) [57,58], extracellular regulated protein kinases (ERK) and other protein kinases [59–62]. Last but not the least, E2 has been found to stimulate the production of classical second messengers, including cAMP [59,63,64] and promotes the process of Ca^{2+} mobilizations [65,66].

2.1. Localization and structure of GPER

GPER is a seven-transmembrane G protein-coupled receptor composed of seven hydrophobic residue peptides through seven helices [67], localized predominantly in the plasma membrane [24,68] and in the endoplasmic reticulum [69]. In addition, Shi et al. found that GPER exists in various types of tumor cells [70], which subcellular localization of GPER varies in the cell membrane, endoplasmic reticulum membrane, mitochondrial membrane, Golgi apparatus, and the nucleus of tumor-associated fibrocytes [69,71,72]. For instance, GPER expressions in T47D cells, mainly concentrated in the cytoplasm [73], while GPER expression in the nucleus were not found. But the current lack of three-dimensional structure of GPER crystals limits the in-depth understanding of GPER protein structure. The total number of GPER-related research articles in PubMed exceeds 1000 [74], but to date, there are fewer relevant studies on GPER protein structure, and we did not find the three-dimensional (3D) protein structure of GPER in the Protein Structure Data Bank (PDB). To date, scientists commonly use homology modeling to predict the 3D protein structure of GPER [74,75]. It reminds us that the dynamic changes of GPER protein structures in the interaction with the specific ligand may open up an avenue for research against breast cancers.

2.2. The role of estrogens and GPER in breast cancer

Mediating gene transcription and non-genomic signaling pathway, GPER is a novel estrogen receptor, mainly found in estrogen-sensitive breast [4,76,77]. It was also demonstrated that after binding to E2, GPER in turn rapidly activates multiple estrogen-dependent cellular non-genomic signaling pathways [40,78] and affects the expression of multiple signaling molecules, which can ultimately affect the development and progression of breast cancer [79–82].

After binding to E2, GPER can transactivate EGFR signaling pathway [28]. Subsequently, connective tissue growth factor (CTGF) is activated in an EGFR-dependent manner, in contributing to the promotion of TNBC cell metastasis [83]. Transactivation of EGFR also initiates the phosphoinositide 3-kinase (PI3K) pathway, MAPK pathway [4], as well as the Akt pathway [84], which will induce tumor cells cycle progression and proliferation. Moreover, GPER was also found acting at the breast tumor microenvironment [85]. Juan et al. suggested that activation of GPER increases the level of Carcinoma-associated fibroblasts (CAFs), the active components within the tumor microenvironment, cell proliferation under hypoxic conditions [85,86], Marco Pupo et al. showed that GPER is involved in Notch-dependent transcription and can activate Notch signaling pathways in both breast cancer cells and CAFs, promoting tumor cell invasion and metastasis [87,88]. Numerous findings have demonstrated that, GPER expression is positively correlated with breast cancer progression [89–91].

Therefore, the role of GPER in the treatment of breast cancer is crucial. Inhibition of GPER expression can downregulate EGFR and reduced the production of second messengers. Down-regulation of EGFR, thereby blocking multiple EGFR-induced downstream signaling pathways, these EGFR downstream signals promote proliferation and progression of breast cancer cells. Changes in second messengers affect cell development, for example, decrease of Calcium ion inhibits calcium-dependent cellular signals, most of which promote proliferation and migration of breast cancer cells. Down-regulation of GPER can also inhibit Notch gene transcription, reduce CAFs proliferation, improve tumor microenvironment, reduce tumor cell migration and invasion in the treatment of breast cancer. The effects of GPER on breast cancer suggest the effective strategies of tolerance and desensitization in anti-breast cancer drug development.

2.3. The downstream signaling pathway of GPER

The regulatory role of GPER plays in breast cancer as described in detail below (Fig. 1).

2.3.1. EGFR/MAPK/ERK signaling pathway

In the breast cancer cells, GPER is activated by the corresponding ligand such as estrogen, leading to formation of heterotrimeric G protein. Thereafter, free βγ-G dimer induces heparin tyrosine kinase (HB-EGF) by activating non-receptor tyrosine kinases and matrix metalloproteinases. (HB-EGF) is released to activate the MAP kinase pathway, thereby activating the EGFR, activated EGFR promotes ERK phosphorylation[55], GPER/EGFR/ERK signaling pathway up-regulates the expression of cyclin A, cyclin D1 and c-Fos, which is involved in increased cell growth, survival and migration/invasion [28,31,92].

2.3.2. PI3K/AKT signaling pathway

Estrogen transactivates EGFR through binding to GPER and induces the activation of PI3K, which activates its downstream kinase AKT. Conversely, it degrades the activity of the tumor suppressor FOXO3a in the nucleus [93], and inhibits apoptosis by phosphorylating the activity of apoptosis agonists, such as BAD[94] and Caspase 9. Activation of PI3K/AKT signaling pathway affects the function of Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2) and regulates the transcription of Vascular endothelial growth factors (VEGFs) mediating angiogenesis, thereby promoting cell migration and survival [95–98]. They also induce breast cancer cell cycle progressions and promote the development of breast cancers [69, 99–101].

2.3.3. Ca^{2+} signaling pathway

The process of GPER binding to the corresponding ligand is accompanied with rapidly increase of the intracellular calcium concentrations through two pathways. On one hand, the released α-subunit of heterotrimeric G-proteins can activate phospholipase C (PLC), promote the transformation of IP3, and thereby releases Ca^{2+} from cytosolic calcium-stores. On another hand, activated GPER opens the Ca^{2+} channel in the cytoplasmic membrane, allowing Ca^{2+} to flow to the external environment [69,102,103].

Changes in intracellular Ca^{2+} homeostasis activate a variety of highly flexible signals in breast cancer cells, Ca^{2+} activates calcium-dependent transcription factors, including as c-Myc, c-Jun and c-Fos [104], which induce the expression of cell cycle-related proteins. Ca^{2+} also mediates the expression of telomerase to increase cell replication [105], and ultimately participate in cell proliferation and differentiation. Increased Ca^{2+} in breast cancer cells exhibits anti-apoptotic effects, increased transcription factor c-Myc activity downregulates the expression of the pro-apoptotic protein Bax [106,107]. The elevated calcium ion concentration in breast cancer cells stimulates plasma membrane calcium ATPase 2 (PMCA2) and plasma membrane calcium ATPase 4 (PMCA4) [104], where PMCA2 interacts with calcium-regulated phosphatases to reduces the ligand of the pro-apoptotic protein Fas [108], while PMCA4 activates the NFκB signaling pathway to exert anti-apoptotic effects [109]. Ca^{2+} is a key factor in the activation of hypoxia-inducible factor 1 (HIF1) [110], which is involved in the transcription of VEGF. It promotes the proliferation of vascular endothelial cells to maintain angiogenesis and tumor blood supply [26], leading to tumor growth, migration and invasion [105].

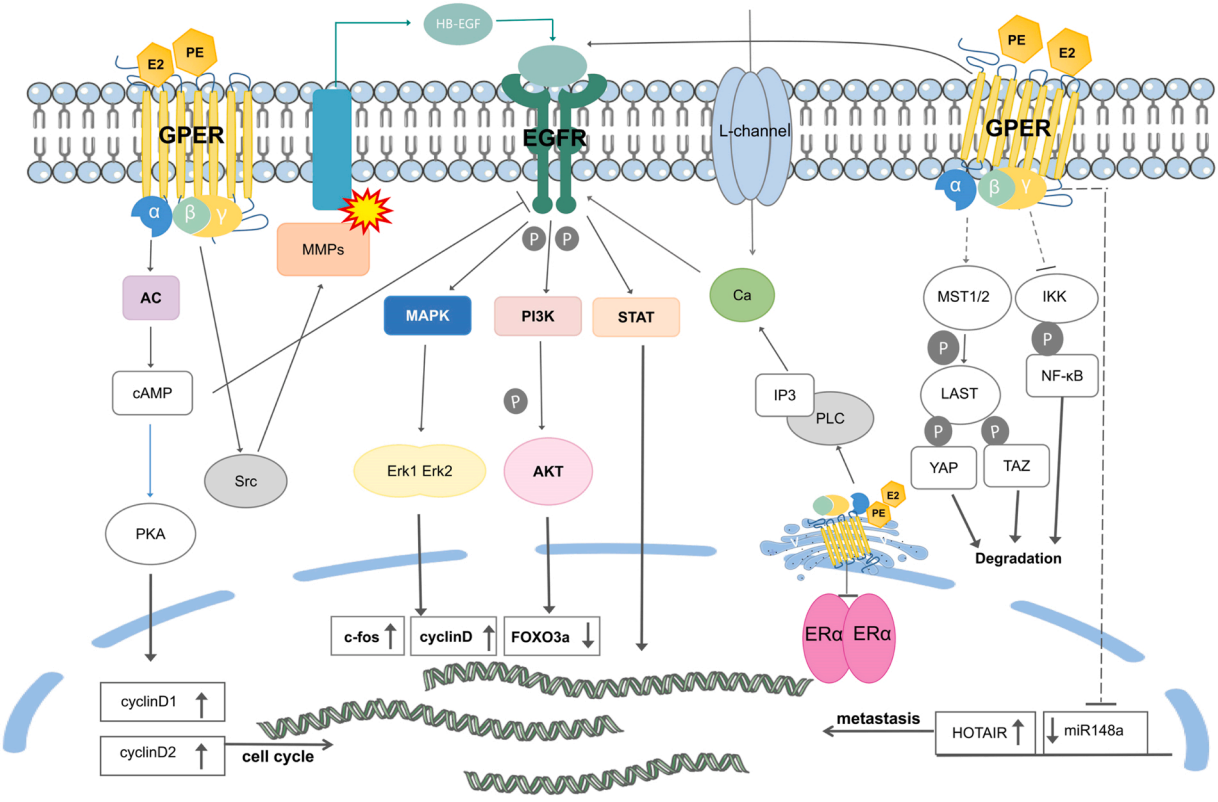


Fig. 1. The downstream signaling pathway of GPER in breast cancer. PE, Phytoestrogen; GPER, G protein coupled estrogen receptor; AC, adenosyl cyclase; cAMP, cyclic adenosine-monophosphate; PKA, protein kinase A; MMPs, matrix metalloproteinases; HB-EGF, heparin tyrosine kinase; EGFR, epidermal growth factor receptor; ERK1/2, extracellular regulated kinase 1 and 2; PI3K, phosphoinositol-3-kinase; AKT, protein kinase B; FOXO3a, forkhead box 3a; STAT, signal transducer and activator of transcription PLC, phospholipase C; IP3, inositol-triphosphate; MST1/2, mammalian sterile 20-like 1 and 2; LATS, large tumor suppressor; YAP, yes-associated protein; TAZ, transcriptional coactivator with PDZ binding motif; IKK, inhibitor of kappa B kinase; HOTAIR, HOX-transcript antisense intergenic RNA.

2.3.4. cAMP/PKA signaling pathway

The α-G protein released after GPER activation can also bind to adenylyl cyclase (AC) in the cytoplasmic matrix, thereby activating AC to produce cAMP [111]. The related experiments of breast cancer cell line SK-Br3 and MAD-MB-231 cells transfected with GPER gene showed that the release of cAMP attenuated the activation of ERK1/2 and inhibited the expression of EGFR/ERK cell signaling signal pathways. In addition, cAMP can activate protein kinase A (PKA), PAK phosphorylation transcription factor (CREB), induce the transcription of target genes such as cyclinD1 and cyclinD2, and participate in supporting the cell growth cycle [91,112,113].

Therefore, some reports speculate that estrogen may balance the activity of GPER in breast cancer through stimulates two opposing cellular signals of cAMP [114]. On the one hand, activation of GPER/-cAMP signaling inhibits the EGFR/ERK signaling pathway, thereby slowing the progression of breast cancer, while on the other hand, the release of cAMP activates the expression of many cell-associated cyclins, promoting the proliferation of breast cancer cells.

2.3.5. Hippo signaling pathway

Zhou et al. reported that estrogen and other ligands can activate transcriptional co-mediators (YAP/TAZ) downstream of the Hippo pathway through GPER [115]. The Hippo signaling pathway consists mainly of mammalian sterile line 20-like kinase (MST1/2), large tumor suppressor (LATS1/2), and YAP/TAZ. GPER has little effect on MST1/2, but can inhibits LATS1/2, which in turn induces dephosphorylation of YAP/TAZ and enhances YAP/TAZ stability [115–118]. YAP/TAZ mediates tumor development and pairs with the TEAD transcription factor family to trigger breast cancer cell development and metastasis. [119, 120].

Therefore, the Hippo/YAP/TAZ pathway play a role in GPER-mediated gene expression and cellular physiological function, which is related to the occurrence and development of breast tumors [115,121, 122]. In addition, there are some cellular signals that have not yet been elucidated, such as the HOTAIR signaling pathway [123], and etc. However, their precise function in breast cancer is still remain to be determined.

3. Phytoestrogens as novel compounds targeting Breast GPER

Results from ligand binding assays evidenced that human endogenous estrogens interact with GPER, including Estrone Esrtiol and E2 [124]. Estrogen is a steroid hormone whose parent nucleus is an estrostan composed of 18 carbon atoms, and the A ring is an aromatic ring with phenolic hydroxyl group at C_3 position, C_{17} with hydroxyl or carbon group [125] (Fig. 2). V C Jordan et al. suggested that the phenolic hydroxyl group at the C_3 position of the estrogen A ring is a key factor in its ability to bind to the estrogen receptor (Fig. 3 A), and found that phenolic compounds occupy the estrogen receptor binding site and thus act in vivo [126]. Subsequently, Schultz et al. and Hamblen et al. successively demonstrated the importance of the hydroxyl group at 3 position carbon atoms in the structure of compounds with estrogenic properties (i.e., xenoestrogens) for their estrogen-like effects [127,128]. Anstead & Kym studied the chemical structure of benzo[*a*] anthracene by molecular modeling and concluded that its AB ring, which is similar to that of steroid hormones, is the determinant of its binding to estrogen receptors factor [129] (Fig. 3 B). Combined with previous studies by scientists on the structural properties of many different estrogen receptor ligands, it was concluded that the AB ring structure similar to that of steroid hormones and the phenolic hydroxyl group at the C_3 position are central in determining their conformational relationships.

A large variety of naturally occurring chemicals from Chinese herbs plant can bind to the estrogen receptors named as “phytoestrogens” [130,131]. According to their chemical structure, phytoestrogens are classified into phenolic and non-phenolic phytoestrogens. In addition, phenolic phytoestrogens contain both flavonoid phytoestrogens and non-flavonoid phytoestrogens. Flavonoid phytoestrogens, with 2-phenyl-chromen-4-one as the parent nucleus [132], mainly include flavone phytoestrogens (e.g., 8-prenylnaringenin) [133,134], isoflavone phytoestrogens (e.g., genistenin) [135], flavonol phytoestrogens (e.g., kaempferol) [136], dihydroflavone phytoestrogens (e.g., quercetin and naringin) [137–139], chalcone phytoestrogens (e.g., licochalcone) [140–142], etc. The main non-flavonoid phytoestrogens are coumestans (e.g., psoralen) [143], having benzopyrone as the parent nucleus, and lignans (e.g., deoxychizandrin) [144,145], having the three-dimensional structure of phenyl propane as the structural basis, respectively. Non-phenolic phytoestrogens are mainly terpenoids [125], which are derived from mevalonate. They have a molecular backbone with two or more isoprene units connected at the first place, which can be classified as monoterpenoids, diterpenes, triterpenes according to the number of isoprene units. For example, bakuchiol is a monoterpenoids [146], tanshinone IIA and cryptotanshinone are two classical diterpenes phytoestrogens [147–149]. Ginsenoside and oleanolic acid family together with many other saponins in Chinese medicine are triterpenes phytoestrogens [150–157] (Fig. 4).

Researchers use in silico molecular docking studies examine the binding mode of some phytoestrogens to the GPER, demonstrated they are in a similar manner as E2 [158,159], Herein, we summarized a number of phytoestrogens that have good affinity for GPER, respectively, including oleuropein [160], resveratrol [161], quercetin [162], genistein [163–165], daidzein [166], tan-shinone IIA [167], cryptotanshinone [168,169]. The herb sources and chemical structures are presented in (Table 1).

3.1. Oleuropein

Oleuropein is a secoiridoid mainly obtained from ***Olive, S. vulgaris and Fructus Ligustri Luci-di.*** consisting of three structural subunits: hydroxytyrosol, an elenolic acid, and a glucose molecule [170]. Oleuropein has the potential to regulate various metabolic diseases and prevent cardivascular diseases due to its anti-inflammatory and antioxidant effects [180–184]. In addition, its estrogenic effect in combination with GPER has generated a lot of attention in recent years. Chimento et al. confirmed oleuropein display a good affinity for GPER by docking simulations and ligand-binding studies. Using western blot assay, it proved that oleuropein could activate ERK1/2 pathway through GPER [160].

3.2. Resveratrol

Resveratrol is a natural stilbenoid, which is found in human diet. Gehm et al. conclude that resveratrol is a phytoestrogen [185], having

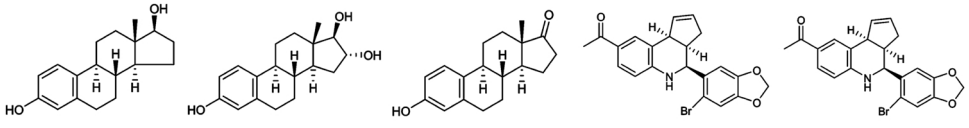


Fig. 2. Structures of Endogenous GPER ligands and selective GPER receptor, Compound shown include the three endogenous estrogen ligands (17β-estradiol, estrone and estriol), the G-1(a selective GPER agonist) and G15 (a selective GPER antagonist).

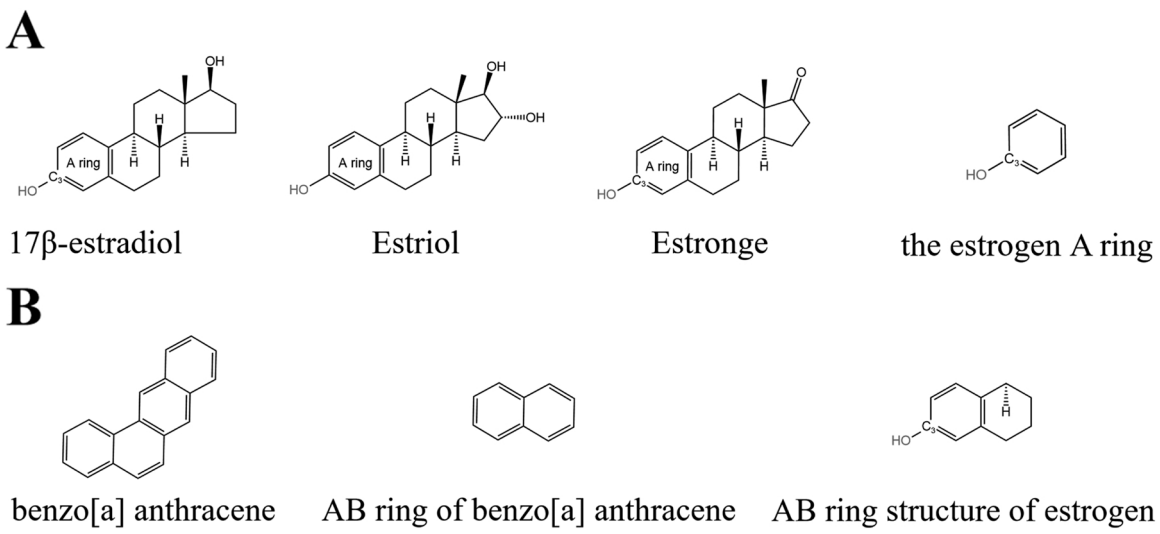


Fig. 3. The structure common characteristic, A: Estrogens have the common A ring structure, the A rings are the key factor of their conformational relationships. B: The AB ring of benzo[*a*] anthracene is similar to the AB ring structure of estrogen.

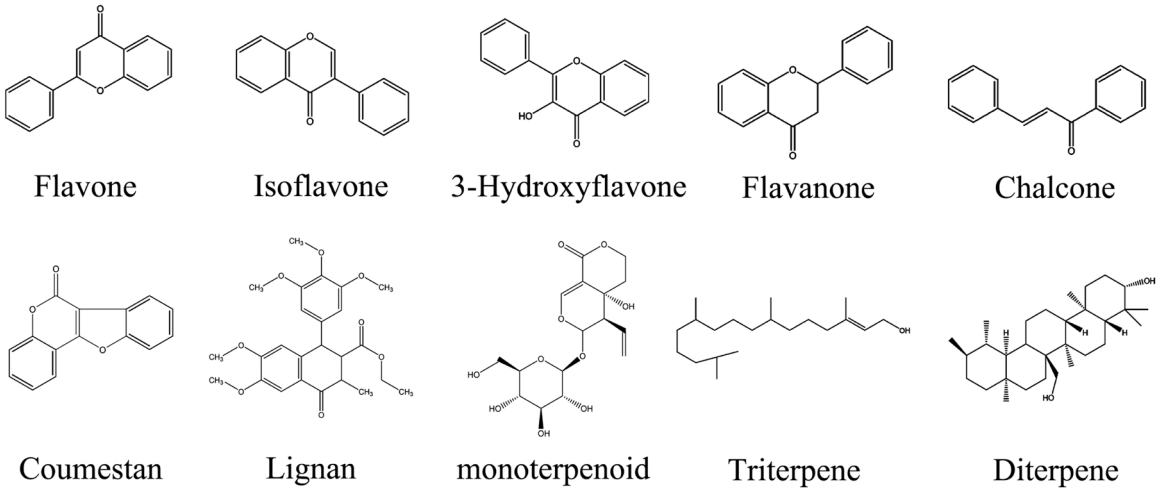


Fig. 4. Structures of phytoestrogens, Compound shown include flavone, isoflavone, 3-Hydroxyflavone, dihydroflavone, chalcone, coumestan, lignans, monoterpenoids, diterpenes, triterpenes.

antimicrobial, antioxidant, anti-inflammatory and anti-cancer activities [186]. They can be well absorbed in vivo and therefore has great medicinal research value [187]. D'Arrigo et al. predict resveratrol have a great capability of binding for GPER by comparative computational docking simulations, the binding energy is value − 8.791 [188]. Meyer and Barton also proved that resveratrol could therapy and prevent coronary artery disease through the interactions with GPER [189].

3.3. Quercetin

Quercetin is categorized as flavonoid subclass, ubiquitously present in human diets and some herbs, such as ***Caryophylliflos, Radix Bupleruri, Sophora Japonical L., Fructusspphorae, Ginkgo Semen*** [172]. They have valuable bioactive and health-promoting properties, and also can promote the apoptosis of cancer cells and inhibit cancer cells cycle thus resisting breast cancer breast cancer[190–193]. In the molecular docking simulations experiments, the energy value between quercetin and GPER was − 7.726 [188]. Masuhara and co-workers demonstrated that quercetin reduce bone resorption and osteoclastogenesis through direct binding to GPER [194].

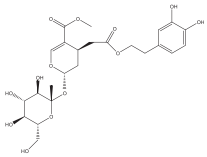
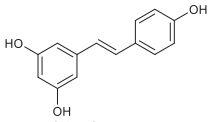
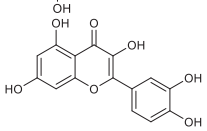
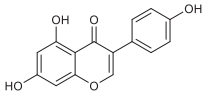
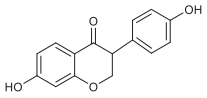
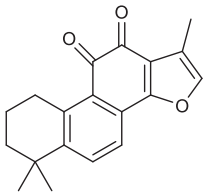
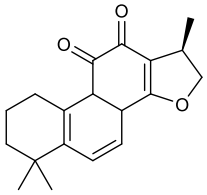
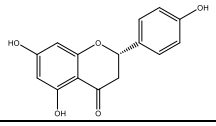
3.4. Genistein

Genistein is a natural isoflavone and a phytoestrogen, having a broad range of Biological effects [195]. Many herbal medicines such as ***Fructussophorae, Belamcandae Rhizome, Cistanches Herba, Radix Puerariae*** contain large amounts of genistein. Thomas and Dong found that add genistein in transfected Human HEK293 cells significantly increase cellular cAMP levels through activate GPER [22]. Ariyani et al. knock downed RNA expression of GPER and used G15 (a selective GPER antagonist) in mouse primary cerebellar astrocytes, proved that genistein and daidzein exert their action via the activate the GPER/PI3K/-FAK/Akt signaling pathway [159]. In the molecular simulation docking experiment, D'Arrigo calculated that the energy value of GPER binding to quercetin was − 7.010 [188].

3.5. Daidzein

Daidzein is a natural isoflavone, in addition to fermented soybeans, ***Cyathulae Radix, Olibanun, Sojae Semen Praepar-atum, Puerariae Flos, Radix Puerariae*** and other herbs are also important sources of soybean glycosides [196]. Many studies have reported varying degrees

Table 1
chemical structural and herb sources of some Phytoestrogens that target GPER.

number	phytoestrogens	chemical structures	classical	Herb source	reference
1	Oleuropein		secoiridoid	***Fructus Ligustri Lucidi*** , ***Olive***	[170]
2	Resveratrol		stilbenoid	***Polygonum Cuspidatum***, ***Mori Cortex***	[171]
3	Quercetin		flavonols	***Caryophylliflos,*** ***Radix Bupleruri,*** ***Sophora Japonica L., Fructussophorae,*** ***Ginkgo Semen***	[137,172]
4	Genistein		isoflavone	***Fructussophorae,*** ***Belamcandae Rhizome, Cistanches Herba,*** ***Radix Puerariae***	[135,173]
5	Daidzein		isoflavone	***Cyathulae Radix,*** ***Olibanun,*** ***Sojae Semen Praepar-atum,*** ***Puerariae Flos,*** ***Radix Puerariae***	[174,175]
6	Tanshinone IIA		diterpene	***Radix Salviae,*** ***Peucedani Radix***	[147,167]
7	Cryptotanshinone		diterpene	***Nardostachyos Radix Et Rhizoma,*** ***Radix Salviae***	[169,176]
8	Naringenin		isoflavone	***Citri Exocarpium Rubrum, Citri Grandis Exocarpium, Canarii Fructus, Aurantii Fructus Immaturus, Citrus reticulata***	[177–179]

of therapeutic effects of soy glycosides on metabolic diseases, neurological disorders, cancer, inflammatory conditions, and etc. [197–199]. Daidzein also has a strong estrogenic effect, which activates the physiological effects of GPER. Kajta et al. co-treatment mouse hippocampal cells with daidzein and G15 (a selective GPER antagonist), demonstrated the triggered GPER intracellular signaling pathways inhibited the pro-apoptotic and neurotoxic effects of glutamate in the neuronal cell [166].

3.6. Tanshinone IIA

Tanshinone IIA is abundantly found in the Chinese medicine ***Salvia*** miltiorrhiza as an important diterpene plant compound [148]. ***Salvia*** has been used in Chinese medicine for thousands of years to treat various cardiovascular and neurological diseases. In recent years, tanshinone IIA has been shown to have antioxidant, anti-inflammatory, anti-tumor and estrogenic effects, among other biological activities [147]. Tanshinone IIA has also been found to interact with the membrane receptor GPER. For example, Mao et al. observed that tanshinone IIA significantly reduced collagen deposition and promoted elastin production in cardiac fibroblasts, thus exerting a cardio-protective effect. Interestingly, tanshinone IIA can bind to GPER and selectively activating the PKA/-CREB phosphorylation pathway [167].

3.7. Cryptotanshinone

Cryptotanshinone is another important natural diterpene compound extracted form ***Salvia miltiorrhiza***, exhibiting a multiple of pharmacologic properties, including anti-inflammatory, anti-cancer, anti-infection and etc. [200,201], cryptotanshinone has also been found to bind to estrogen receptors and GPER. Shi et al. found that cryptotanshinone have antiproliferative effect for SKBR-3 cells, while combination with G-1(the specific GPER agonist) enhanced this anti-effect [168], evidenced that the anti-proliferative ability of cryptotanshinone against SKBR-3 cells is achieved by GPER.

3.8. Naringenin

Naringenin is a flavanone, which is found mainly in citrus fruits like grapefruits and others such as ***Citri Exocarpium Rubrum, Citri Grandis Exocarpium, Canarii Fructus, Aurantii Fructus Immaturus, Citrus reticulata*** medicinal plants[177–179]. Naringenin has anticancer and

estrogen-like effects, making it as a potential therapeutic agent for a variety of metabolic diseases [179]. In the molecular docking simulations experiments, the energy value between Naringenin and GPER was − 8.132. When the energy value was below − 1.2, it indicated that the two docked well, thus demonstrating the good binding ability of Naringenin and GPER [188].

4. Phytoestrogens and breast cancer

Phytoestrogens are natural compound that derived from fruits, vegetables, grains, and leguminous plants, largely exist in human diet and in traditional Chinese herbal medicine [202,203]. Phytoestrogens offer a wide range of pharmacologic characteristics and benefits, for instance, anti-oxidation, cardiovascular protection, anti-inflammatory, anti-tumor, regulate of endocrine effect and so on [204]. Phytoestrogen are a class of valuable natural health-promoting dietary supplement. In addition, based on the similar chemical structural to E2, phytoestrogens could bind to estrogen receptors as endocrine disruptors, that could compete with E2 for the receptor's ligand-binding domain, thereby affecting molecular functions in breast cancer cells [205,206]. According to our summary above, many phytoestrogens have good binding ability to GPER, which is an important target in the treatment of breast cancer, suggesting phytoestrogens have potential ability to treat breast cancer as SERMs of GPER.

Most phytoestrogens impede breast cancer cells proliferation and tumor formation. For instance, daidzein had been proved that arrest the cycle of MCF-7 and MDA-MB-453 cells in a dose- and time-dependent manner [207]. Asgharzade et al. demonstrated that oleuropein upregulate expression ratio of anti-apoptotic factors and pro-apoptotic factors in MCF-7 and MDA-MB-453 cells, activates tumor suppressor genes, as well as inhibits the development of breast tumors [208]. In a certain dosage range, quercetin also caused MCF-7 cells to die [209]. Li et al. verified the effect of naringenin on breast carcinoma, showing that naringenin decreases tumor cell viability, activates the release of pro-apoptotic factors, and inhibits the growth potential of breast cancer cells [210]. In another research, naringenin had been found to inhibit the migration and invasion of MDA-MB-231 cells by reduce the protein expression of β3 integrin [211]. Zhou et al. revealed that cryptotanshinone plays anti-tumor action for breast cancer by downregulate the PKM2/β-catenin pathway and JAK2/STAT4/perforin pathway [212, 213]. Cryptotanshinone can induce the apoptosis of breast cancer SKBP-3 cells, related to its regulatory effect of GPER and PI3K/AKT pathway [168].

However, evidence suggests that phytoestrogens have different effect on ER-positive or ER-negative breast cancer [214], presenting a biphasic effect according to disparate concentrations [215]. Low concentrations of resveratrol, quercetin and genistein can reduce ER-negative breast cancer cell proliferation [185, 216–221]. However, in the ER-positive breast cancer cell line, resveratrol, biochanin A, quercetin and genistein were shown to stimulate breast cancer cell growth at low concentrations, but inhibited proliferation and induced cell death at high concentrations [216, 218, 219, 221–224]. Another study found that phytoestrogens, such as genistein and biochanin, had a time-dependent inhibitory impact on breast cancer cells, whereas long-term therapy promoted the proliferation of breast cancer cells [224,225].

Similarly, research on the effect of certain phytoestrogens on breast tumor in vivo was found to be contradictory. Through the athymic mouse tumor implant model, Allred et al. explored genistein's involvement in estrogen-dependent breast tumors. They demonstrated genistein substitution of endogenous estrogens can accelerate mammary gland tumor growth [226,227]. It was found that, genistein's impact on estrogen-dependent breast tumors may be related to endogenous estrogen levels, and that genistein is more likely to promote tumor growth when endogenous estrogen levels are low [228]. However, in the in vivo xenograft experiments and in vitro cellular studies by Shao et al., genistein was found to reduce cellular angiogenesis and promote apoptosis, suppressing not just nuclear estrogen receptor-positive breast cancer but also nuclear estrogen receptor-negative breast cancer [229].

5. Discussion

Numerous studies have shown that most phytoestrogens exhibit anti-breast cancer effects, inhibiting tumor migration, invasion and proliferation via multiple targets and pathways. However, there is still substantial debate over the effects of various phytoestrogens on breast cancer, and these phytoestrogens exhibited variability depending on the measure and timing of their effects. In the preceding sections, we summarized and discussed several phytoestrogens based binding studies. After meta-analysis, we speculate that GPER, an estrogen membrane receptor protein, may be a key factor in the differential effects for phytoestrogens binding. It is undeniable that phytoestrogens, when coupled with GPER, could have biological effects in breast cancers, acting through GPER downstream signaling pathways [230]. But the role of phytoestrogens in GPER, whether they act as antagonists or agonists, is not fully understood. GPER can activate the majority of pathways in breast cancer cells, such as EGFR/MAPK, EGFR/STAT, PI3K/AKT, and cAMP/PKA [40,158,231]. These pathways signaling induce tumor cell proliferation and development by influencing the expression of target genes including FOS, JUN, EGR1, CTGF, ATF3, ATF2, STAT, etc. When phytoestrogen works as an agonist of GPER, it promotes breast cancer progression, while phytoestrogen has an anti-breast tumor impact as an antagonist of GPER.

Earlier research on phytoestrogens in the prevention and treatment of breast cancer have focused on acting on (affecting) the estrogen nuclear receptor, ignoring the important role of phytoestrogens interacting with the membrane receptor GPER in breast cancers. The perspective "phytoestrogens act as SMERs for GPER to effect breast cancer" that we proposed, provides a new direction for development of phytoestrogen-based dietary supplements. Through the review of this paper, we summaries several viewpoints as follow. First, GPER is considered as a significant target to give a fresh viewpoint on breast cancer development and therapy. Most present breast cancer therapies focus on the role of estrogen nuclear receptors in the development of breast cancer, which has resulted in side effects such as drug resistance and poor results. GPER regulation is anticipated to be crucial for both breast cancers treatment and prevention.

Second, after meta-analysis of available reports, many natural phytoestrogen compounds have potential anti-breast cancer/tumor-preventive characteristics. In many scenarios, these chemicals have strong anticancer properties, such as inhibition of breast cancer cell growth, promotion of apoptosis, and downregulation of migration. However, a few phytoestrogens produce somewhat conflicting consequences under certain settings and conditions, rather than promoting breast tumor progression. Therefore, we suggest that these contradictory results may be related to the receptor GPER, as a complexity role in breast cancer. This concept has far-reaching ramifications for the future development of phytoestrogens as therapeutic candidates and dietary supplements against breast cancer. For example, biased agonists/antagonists of GPER were designed based on the molecular structure of phytoestrogens. Targets specific downstream signaling pathways, and selective activation or antagonism of GPER [232]. Thereby inhibiting the proliferation development of breast cancer, and amplifying the protective effect of GPER on breast cancer.

Third, to develop phytoestrogens candidates for the treatment of breast cancer based on a GPER perspective, we need also consider the complexity of how phytoestrogens function in vivo, where phytoestrogens exert their effects by binding to estrogen receptors. Because of the several estrogen receptor-dependent methods of action, phytoestrogens cannot precisely target to GPER. And its interaction with other ligands will crosstalk the downstream signaling pathway of GPER. Therefore, in-depth understanding of the interactions between phytoestrogens and their target molecules is critical [33, 36–38, 233].

Various ways are still in the path of discovery to achieve the better GPER-targeted therapy, for example modifying the side chains in the chemical structure of phytoestrogens [234,235].

Fourth, determination the medication dose and the proper method of administration is also critical for the safe use of phytoestrogens. As mentioned in the previous article, various doses of phytoestrogens might produce therapeutic changes, or even entirely opposing therapeutic benefits. In addition, many phytoestrogens have poor solubility and low bioavailability in vivo, slowing down the process of phytoestrogens development and utilization. For instance, resveratrol and quercetin have valuable bioactive and health-promoting properties [171, 186, 236–238], which has the effect of inhibiting breast cancer [186, 239–241]. However, resveratrol and quercetin have been challenging in drug development, with problems of solubility, poor stability, and low bioavailability [242]. We can amendment these deficiencies to improve the efficacy using nanomaterial drug delivery technology or advanced dosage formulations. Nanomaterials technology facilitates the manipulation of material properties and structures at the nanoscale encapsulating drugs within nanoparticles, improving bioavailability, biocompatibility, solubility and tailored biological properties of drugs [242–246]. Sharifi-Rad et al. prepared novel berberine nanoparticles (Nano-Ber) have better aqueous solubility [247]. In preclinical studies for the treatment of breast cancer, nanomaterial drug delivery technology has proven to be a valuable technique, showing unique characteristics including high biocompatibility, high bioavailability and targeted drug delivery [248–252]. Jullian et al. through compatibility measurements and kinetic studies found that, cyclodextrin quercetin improves the solubility and biological activity of quercetin [253]. Anandam et al. prepared carbonate nanosponges significantly improved the solubility and stability of quercetin, providing a new drug delivery for the quercetin preparations[254]. It was also demonstrated that carbonate nanosponges enhanced the stability and solubility of resveratrol [254]. Briskey et al. utilize the LipiSperse delivery technology to increase the dispersion of lipophilic resveratrol in an aqueous environment, hence improving resveratrol's oral bioavailability [255]. Azzi et al. reported that the liposome-coated quercetin had better chemical stability and bioactivity[256]. Many phytoestrogens are currently being employed to boost their pharmacological effects using nanomedicine approaches, and exploration of their interaction mechanisms with GPER and breast cancer cells, will be a future focus.

CRediT authorship contribution statement

Shuo Huang: Conceptualization, Methodology, Data collection and analysis, Writing – original draft. **Baowen Qi**: Analysis, Revision and Supervision **Ling Yang**: Data collection and analysis. **Xue Wang**: Data collection and analysis. **Jing Huang**: Data collection and analysis. **Ya Zhao**: Data collection and analysis. **Wenjing Xiao**: Revision, Supervision. **Yonghe Hu**: Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data that support the finding of this study are available from the corresponding suthor upon reasonable request.

Acknowledgements

Supported by Key project of Sichuan Provincial Health Commission (No 19ZD020); National Natural Science Foundation of China (Grant Nos. 81402507 and 81703457); Science and Technology Department of Sichuan Province (No 2019YFS0542, No 2018SZ0033, 2020YFS0122).

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