Effects of ginseng on two main sex steroid hormone receptors: estrogen and androgen receptors

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Abstract

Ginseng has been used in China for at least two millennia and is now popular in over 35 countries. It is one of the world’s popular herbs for complementary and alternative medicine and has been shown to have helpful effects on cognition and blood circulation, as well as anti-aging, anti-cancer, and anti-diabetic effects, among many others. The pharmacological activities of ginseng are dependent mainly on ginsenosides. Ginsenosides have a cholesterol-like four trans-ring steroid skeleton with a variety of sugar moieties. Nuclear receptors are one of the most important molecular targets of ginseng, and reports have shown that members of the nuclear receptor superfamily are regulated by a variety of ginsenosides. Here, we review the published literature on the effects of ginseng and its constituents on two main sex steroid hormone receptors: estrogen and androgen receptors. Furthermore, we discuss applications for sex steroid hormone receptor modulation and their therapeutic efficacy.

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1. Introduction

Ginseng has been used for over 2,000 y as a medicine in East Asia. It is a popular herb in the world, and is used in more than 35 countries as a food, health supplement, and natural remedy [1]. Ginseng has been demonstrated to have an extensive range of pharmacological effects on the reproductive, cardiovascular, endocrine, and immune systems. Its ability to diminish fatigue, enhance blood circulation, aid menopausal symptoms, boost immune function, and enhance concentration has been verified in certain countries [2]. Many components of ginseng, such as ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids, have been isolated and characterized [3,4]. However, further research is necessary to understand how these components contribute to ginseng’s pharmacological properties. Among these constituents, dammarane-type ginsenosides, comprising a rigid steroid skeleton consisting of four trans rings with a modified side chain at C−20, have received considerable attention because of their biological activity [5,6]. To date, more than 100 different ginsenosides with various pharmacological effects have been isolated and identified from the root of Panax ginseng, with ginsenosides Rb1, Rb2, Rg1, and Re being most abundant. In addition, steaming and drying during processing of ginseng can affect its pharmacological activity by altering the characteristics of the constituent ginsenosides [7–12]. Red ginseng, produced by steaming fresh ginseng, possesses unique ginsenosides (Rg3, Rg5, Rh2, Rh3, Rh4, Rs3, and F4) [13–15]. The molecular target of ginsenosides may be located either in the cellular membrane or inside the cell, depending on the hydrophobicity of the ginsenoside [16]. Most ginsenosides are lipophilic in nature; with their steroidal backbone they can traverse cell membranes by simple diffusion, and regulate cellular functions by binding to specific intracellular target proteins in the cytoplasm and nucleus [16]. The nongenomic pathway of ginsenoside activity involves binding to membrane-associated receptors that initiate the activation of the phosphorylation cascade and generation of second messengers. Ginsenosides activate the genomic pathway by initially binding to intracellular nuclear hormone receptors, such as the glucocorticoid receptor, progesterone receptor, androgen receptor (AR), mineralocorticoid receptor, estrogen receptor (ER),...
**2. Effects on ERα and ERβ**

**2.1. Genomic and nongenomic action**

Estrogens are female steroid hormones that are produced mainly by the ovaries through the conversion of cholesterol. Estrogens can also be produced locally in the placenta, adrenal glands, adipose tissue, and brain, where they act in a paracrine fashion [34]. Estrogens are essential in the development and maintenance of the female reproductive system, immune system, cardiovascular system, and central and peripheral nervous systems; they also regulate bone metabolism [35]. As a consequence of their wide range of physiological roles, estrogens are also involved in many pathological states, including cancer, metabolic and cardiovascular diseases, neurodegeneration, and osteoporosis [36].

Phytoestrogens are compounds of plant origin that can exert estrogenic properties, through either direct binding to ER or indirectly activating ERs [36–38]. Phytoestrogens, such as genistein and daidzein, have shown protective effects on conditions related to decreased estrogen, including menopause, osteoporosis, and cognitive disorders [39,40]. The interest in the use of phytoestrogens stems from epidemiologic studies suggesting a decreased incidence of breast cancer, and lower occurrence and complaints of menopausal symptoms and osteoporosis in women from countries with high consumption of phytoestrogens, mainly found in soy products [41–44].

Cellular effects of estrogens are mediated by ERs, which are transcription factors activated by ligands. Two distinct isoforms exist: ERα and ERβ. The expression patterns of these two receptors differ and display distinct characteristics. ERα is expressed mainly in reproductive tissues such as the uterus and ovary, breast, bone, white adipose tissue, and liver. ERβ is expressed mainly in the ovary, central nervous system, cardiovascular system, lung, prostate, colon, and the immune system [36,45,46].

The classical estrogen action model suggests that nuclear ER changes its conformation upon ligand binding, binds to the cognate estrogen-responsive element, and modulates the transcription of target genes [47,48]. Hundreds of coactivator/corepressor regulatory proteins affect the ER-mediated transcriptional response. ERs are mainly found in the nucleus and also in the cytoplasmic membrane. Estrogen binds to the membrane receptors and stimulates signaling proteins. The nongenomic pathway triggers G protein-coupled receptors, generates calcium flux, stimulates cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) production, and activates the PI3K and extra-cellular-signal-regulated kinase (ERK) pathways [49–51]. Recent researches indicate that ERs were also identified in mitochondria and endosomes, and that the act of signaling from all these sites must be integrated with nuclear ER action to produce the final

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**Fig. 1.** Ginsenosides modulating estrogen receptor pathway. A summarized diagram of ginsenosides affecting the estrogen receptor pathway via genomic and nongenomic pathways. COX-2, cyclooxygenase-2; eNOS, endothelial nitric oxide synthase; ER, estrogen receptor; iNOS, inducible nitric oxide synthase; PI3K, phosphatidylinositol-3 kinase; NO, nitric oxide; MAPK, p38 mitogen-activated protein kinase; AMPK, AMP-activated protein kinase.
| Ginsenosides/total ginseng | Experimental model systems | Observations | Signaling molecules monitored | Reference no. |
|---------------------------|----------------------------|--------------|-------------------------------|---------------|
| **Total ginseng**         |                            |              |                               |               |
| Korean Red Ginseng        | SK-N-SH human neuroblastoma cells, mate ICR mice model | Inhibits oxidative stress and apoptosis | PADI4, p53, Bcl-2, COX-2, ERβ | [24]          |
|                          | SK-N-SH human neuroblastoma cells | Antioxidant and represses apoptosis | PI3K/Akt, Bcl-2, p53, Caspase-3 | [61]         |
| P. ginseng               | Immature Kunming mice | Estrogen effect on reproductive tissues | ERα, ERβ | [25] |
|                          | Ovariectomized mice | Can treat postmenopausal symptoms through action as an estrogen agonist | ERα, ERβ | [26] |
| **Ginsenosides**          |                            |              |                               |               |
| Rb1                      | MCF-7 human breast cancer cells, COS monkey kidney cells | Estrogen-like activity |              | [63]          |
|                          | Human umbilical vein endothelial cells | Inhibits capillary morphogenesis |              | [71]          |
|                          | Ovariectomized mice | Estrogen-like effect on brain 5-HT levels |              | [72]          |
|                          | PC12 rat pheochromocytoma cells | Prevents MPP+–induced apoptosis | ERK1/2, SAPK/JNK, p38 MAPK | [73]          |
|                          | Human articular chondrocytes | Anti-inflammatory and apoptotic properties | IL-1β, PGE2, COX-2, iNOS, Caspase-3, NO2–, MMP-3 | [74]          |
| Rg1                      | MCF-7 human breast cancer cells | Proliferation | IGF-IR | [75]          |
|                          | MCF-7 human breast cancer cells | Estrogen-like activity | MAPK | [76]          |
|                          | Ovariectomized rat model of Alzheimer's disease | Neuroprotective effect | Caspase-3 | [77]          |
|                          | Primary rat cerebrocortical neurons | Neuroprotective effect | ERK1/2 | [19]          |
|                          | HT-22 hippocampal neuronal cells, SH-SYSY human neuroblastoma cells, Ovariectomized rats | Promotes nonamyloidgenic cleavage of beta-amyloid precursor protein | PI3K/Akt, MAPK | [78]          |
|                          | N2a-APP694 mouse neuronal cells | Prevents memory loss | PPARγ | [28]          |
|                          | SK-N-SH human neuroblastoma cells | Apoptosis | IGF-IR | [79]          |
|                          | Bone marrow stromal cells | Proliferation, activates ER-mediated signaling |              | [80]          |
|                          | MCF-7, MDAMB human breast cancer cells | Estrogen-like activity |              | [81]          |
|                          | PC-3M prostate cancer cells | Inhibits migration | AQP1, p38 MAPK | [29]          |
|                          | ECV304 human endothelial cells | Endothelial NO production | PI3K/Akt, AMPK, JNK, p38 MAPK | [82]          |
| Re                       | Embryonic rat thoracic aortic smooth muscle cells from DBIX rat (A10 cells) | 1. Releases NO via membrane sex steroid receptors | PI3K/Akt | [83]          |
|                          | 2. Promotes vasodilation | 3. Activates potassium channels |              |               |
|                          | Single ventricular myocytes, MCF-7 human breast cancer cells, LNCap human prostate cancer cells | Activates cardiac potassium channels via nonnongenic pathway of sex hormone |              | [84]          |
| Notoginsenoside F1        | Rat mesenteric arteries model | NO-mediated relaxation | PI3K/Akt, ERK1/2 | [20]          |
| Notoginsenoside R1        | Endotoxemic mice | Anti-inflammation, protects the heart from septic shock | NF-κB, IκB, P38 MAPK | [22]          |
|                          | Rat primary osteoblastic cells | Stimulates osteoblast differentiation via ER signaling | PI3K/Akt | [85]          |
| RG3                      | MCF-7 human breast cancer cells | Weak phytoestrogen |              | [86]          |
| Gnisenoside metabolites   | Primary human umbilical vein endothelial cells | Functional ligands for both GR and ERβ |              | [87]          |
| Protopanaxadiol           | Primary human umbilical vein endothelial cells | Functional ligands for both GR and ERβ |              | [88]          |
| Protopanaxatriol          | LNCap human prostate cancer cells | Inhibit AR signaling by stimulating the degradation of AR protein | AR | [21] |
| AR                       | LNCap human prostate cancer cells | Antiproliferation, apoptosis |              | [22]          |
| C57BL/6 mice model, human hair follicle papilla cells | Inhibits the expression of androgen receptors, antiproliferation, apoptosis | PARP, Bax, Bcl-2, cyclin D |              | [23]          |

*AR, androgen receptor; COX-2, cyclooxygenase-2; ER, estrogen receptor; GR, glucocorticoid receptor; IL, interleukin; iNOS, inducible nitric oxide synthase; MMP-3, matrix metalloproteinase-3; NF-κB, nuclear factor-κB; NO, nitric oxide; P38, phosphatidylinositol-3 kinase; PPAR, peroxisome proliferator-activated receptor; 5-HT, 5-hydroxytryptamine*
functions of the steroid [52,53]. Studies using a xenograft model of MCF-7 human breast cancer cells injected into nude mice have shown that engagement of only the membrane receptor by an estrogenic compound failed to stimulate tumor proliferation [54]. This indicates that nongenomic and genomic pathways of ER communicate, which is likely to play a role in promoting human breast tumor growth. Cellular effects of ginsenosides can be influenced by many factors, including concentration, receptor status, amount of endogenous estrogens, and target tissue [55]. Some phytoestrogens display different affinities to ER isoforms [56]. No study has shown antiestrogenic effects of ginsenosides, but both estrogenic and antiestrogenic activities have been reported for genistein [57,58].

Treatment with P. ginseng upregulated both ERα and ERβ in the reproductive organs (e.g., uterus and vagina) of both normal and ovariectomized mice, demonstrating that P. ginseng had a potent estrogenic activity [25,26]. However, P. ginseng upregulated the expression of ERα to a greater extent than that of ERβ in the uterus and vagina, suggesting that P. ginseng selectively binds to ERα in these reproductive tissues [25,26]. However, ERβ antagonizes ERα-mediated effects in reproductive tissues, such as the breast, ovary, prostate, and uterus [59,60]. In contrast to the effects seen in reproductive organs, treatment of immobilized mice brains and in vitro treatment of neuroblastoma SK-N-SH cells with hydrogen peroxide depressed ERβ, but not ERα [24]. Korean Red Ginseng (KRG) upregulates ERβ and subsequently mitigates stress-induced gene expression [24]. Consistently, in vitro studies also demonstrated that KRG represses apoptosis by potentiating PI3K/Akt signaling via ERβ upregulation [61,62]. For instance, KRG appears to repress stress-induced tumor necrosis factor-α converting enzyme and nuclear factor-κB in immobilized mice brains and H2O2-induced neuroblastoma SK-N-SH cells, thus preventing the production of reactive oxygen species and protecting brain cells from apoptosis [24,61,62]. Thus, in the brain, ERβ seems to inhibit apoptosis and antagonize oxidative stress.

Regarding the mechanisms of action of KRG components, the major ginsenoside Rb1 dose dependently activated both ERα and ERβ in COS monkey kidney cells, but it did not bind to the ER receptors in MCF-7 breast cancer cells [63]. In contrast, the antiangiogenic effects of the ginsenoside Rb1 have been ascribed to its interaction with ERβ in vitro. Rb1 specifically increased the expression of a potent antiangiogenic protein pigment epithelium-derived factor by binding to ERβ, but not to ERα, resulting in the inhibition of endothelial tube formation [64]. These results suggest that KRG might affect ERβ expression in a tissue- and organ-specific manner.

Reproduction is controlled mainly by estradiol in an ERα-dependent manner. Furthermore, brain functions are profoundly mediated by ERα, but not by ERβ [65,66], and most research on ERβ has focused on brain function and behavior [67]. However, in the brain, ERα and ERβ are usually tightly controlled in an interrelated and estradiol-dependent manner for a particular brain function [67]. ERβ modulation is also common; for example, hypernatremia stress and immobilization stress downregulate ERβ expression [24,68]. In contrast, P. ginseng may upregulate ERβ in the brain, and ERβ may counteract stress via antiapoptotic and antioxidative activities [24]. Although the underlying mechanism for this effect requires further study, one possible explanation is that KRG upregulates the steroidogenic enzyme P450 (Cyp11a1) [69]. Cyp11a1 catalyzes the initial and rate-limiting step in steroid hormone synthesis, and cleaves the cholesterol side chain into pregnenolone with a steroidogenic potential [70]. However, an interaction between ERα and ERβ cannot be ruled out; further research on the interaction between these two proteins in the brain is therefore required to clarify the underlying mechanism.

Fig. 1 and Table 1 summarizes the modulating effects of ginsenosides upon the ER pathway.

2.2. Clinical studies on menopausal symptoms, erectile dysfunction, and women’s sexual function

Ginseng has often been used for management of menopausal symptoms in postmenopausal women, and sexual function in both men and women. One systematic review suggested that the evidence on efficacy of ginseng for managing menopausal symptoms was limited [89]. Three randomized controlled trials (RCTs), which were included in the review, tested the efficacy of KRG compared with placebo, and their results showed superior effects of KRG on sexual arousal and global health [90–92]. Another trial reported favorable effects of ginseng supplements on well-being and depression as compared with placebo [93].

Regarding the efficacy of KRG for sexual function in men, one systematic review investigated the efficacy of KRG for erectile dysfunction (ED) compared with placebo [94]. This review included seven RCTs, and their results suggested superior effects of KRG on improvement of ED compared with placebo. Recently, two additional RCTs also reported positive effects of KRG on ED [95,96]. Collectively, the evidence on the efficacy of KRG for treating ED is highly significant.

For the effects of KRG on women’s sexual function, three crossover RCTs tested the efficacy of KRG for the sexual function of women compared with placebo control [90,97,98]. One RCT showed positive effects of KRG on sexual arousal [90], and the other two RCTs reported improvement of sexual function without statistical significance compared with placebo control [97,98].

3. Effects on AR

Androgens mediate a wide range of male developmental processes, and are especially important in male sexual differentiation as well as pubertal maturation, maintenance of spermatogenesis, and male gonadotropin regulation [99]. Testosterone and its metabolite 5α-dihydrotestosterone, two principal androgens, exert their function predominately through AR-mediated pathways [100]. Disorganization of the androgen–AR complex results in androgen insensitivity syndrome, eventually leading to dysfunctions of the male reproductive system, such as subfecundity or infertility. Defects in the AR lead to distinct signs of undervirilization and undermasculinization in males [101]. Disturbance of the androgen–AR complex is triggered mainly by mutations in the AR gene. Mutations in the AR gene are inherited in an X-linked recessive pattern and, therefore, affect males much more frequently than females [102].

Melo et al [103] studied the relationship between male infertility and androgen AR mutations in Brazilian patients, and postulated that patients who do not produce sperm have a higher number of AR mutations than those with merely impaired sperm production.

While the expression level of AR itself, as well as luteinizing hormone receptor (LHR) and follicle-stimulating hormone receptor (FSHR), may also contribute to androgen insensitivity and male sub- and/or infertility, this idea has not received much scientific attention to date. This topic has largely been overlooked in the biochemical and pharmacological communities, as well as in urology. The expression levels of proteins and mRNAs for AR, LHR, and FSHR in testicular tissue from aged and doxorubicin-sensitized Sprague-Dawley rats, were significantly downregulated in these animals as well as in animals stress loaded by intermittent immobilization (2 h/d for 8 wk/6 mo) and heat (32°C, 2 h/d for 8 wk/6 mo). Pretreatment with KRG markedly prevented the
downregulation of these receptors [104,105]. Wang et al [106], at the Center for Disease Prevention and Control in Shenyang Command, Shenyang, China, carried out a similar experiment in cold-stressed rats. They reported that ginseng polysaccharides upregulated AR mRNA expression levels and promoted testosterone. These results indicate that P. ginseng plays an important role in maintaining healthy levels of steroid hormone receptors, including AR, which in turn ensures the proper functioning of androgens.

4. Conclusion

Ginseng has been used for various pathological problems, as well as for preventing and enhancing overall physiological functions. The effects of ginsengs in cancer chemoprevention and therapeutics are one of the most intensively studied areas. Identification of active red ginseng compounds still requires further therapeutics are one of the most intensively studied areas. Identifications. The effects of ginsengs in cancer chemoprevention and as well as for preventing and enhancing overall physiological functions. The effects of ginsengs in cancer chemoprevention and therapeutics are one of the most intensively studied areas. Identifications. The effects of ginsengs in cancer chemoprevention and as well as for preventing and enhancing overall physiological functions. The effects of ginsengs in cancer chemoprevention and therapeutics are one of the most intensively studied areas. Identifications. The effects of ginsengs in cancer chemoprevention and as well as for preventing and enhancing overall physiological functions. The effects of ginsengs in cancer chemoprevention and therapeutics are one of the most intensively studied areas. Identifications. The effects of ginsengs in cancer chemoprevention and as well as for preventing and enhancing overall physiological functions. The effects of ginsengs in cancer chemoprevention and th...
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