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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.

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 transrings 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),

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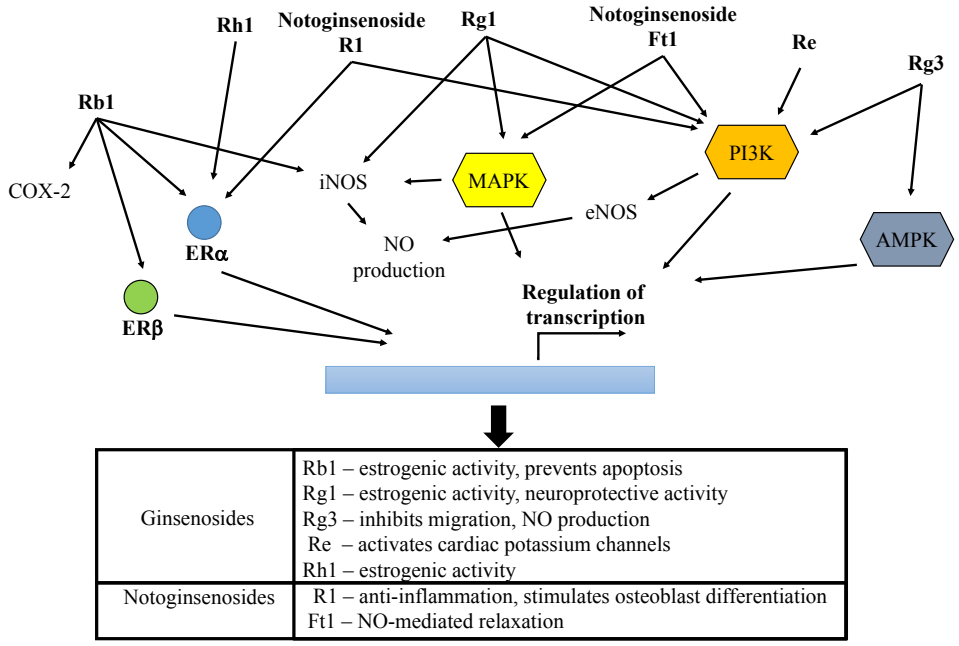

Ginsenosides	Rb1 – estrogenic activity, prevents apoptosis Rg1 – estrogenic activity, neuroprotective activity Rg3 – inhibits migration, NO production Re – activates cardiac potassium channels Rh1 – estrogenic activity
Notoginsenosides	R1 – anti-inflammation, stimulates osteoblast differentiation Ft1 – NO-mediated relaxation

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.

peroxisome proliferator-activated receptor, and liver X receptor [17–29]. Many studies have shown that ginsenosides act through nuclear hormone receptors. For example, one study found that administration of ginseng extract for about 1.5 wk inhibited the activity of peroxisome proliferator-activated receptor-α and the expression of several genes associated with lipid and lipoprotein metabolism [30]; presumably, ginsenosides were the active constituents. Ginsenosides enhanced the expression levels of glucocorticoid receptor in the brain cytosol of heat-injured rats [31]. In another study, the interaction of ginsenoside-activated glucocorticoid receptors triggered the activation of the phosphatidylinositol-3 kinase (PI3K)/Akt pathway and increased nitric oxide production in human umbilical vein endothelial cells [32]. Ginsenosides act through not only steroid hormone receptors, but also ion channels. One study showed that ginsenosides inhibit voltage-dependent calcium, potassium, and sodium channel activities in a stereospecific manner, and block subtypes of nicotinic acetylcholine and 5-hydroxytryptamine type 3 receptors [33].

Here, we review the ginsenosides that affect estrogen and androgen activities, including those that directly or indirectly modulate ERs and ARs. We also discuss clinical studies of ginseng on female and male reproductive functions.

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 directly 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 extracellular-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

Table 1
Ginsenosides modulating estrogen receptor pathway

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]
Radix Ginseng	Immature Kunming mice	Estrogen effect on reproductive tissues	ERα, ERβ	[25]
P. ginseng	Ovariectomized mice	Can treat postmenopausal symptoms through action as an estrogen agonist	ERα, ERβ	[26]
	MCF-7 human breast cancer cells	Estrogenic activity *in vitro* but not *in vivo*	ERα	[27]
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, NO^{2-}, 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-SY5Y 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]
Rg3	PC-3M prostate cancer cells	Inhibits migration	AQP1, p38 MAPK	[29]
	ECV304 human endothelial cells	Endothelial NO production	PI3K/Akt, AMPK, JNK, p38	[82]
Re	Embryonic rat thoracic aortic smooth muscle cells from DBIX rat (A10 cells)	1. Releases NO via membrane sex steroid receptors 2. Promotes vasodilation 3. Activates potassium channels	PI3K/Akt	[83]
	Single ventricular myocytes, MCF-7 human breast cancer cells, LNCaP human prostate cancer cells	Activates cardiac potassium channels via nongenomic pathway of sex hormone		[84]
Notoginsenoside Ft1	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, I-κB, PI3K/Akt	[85]
	Rat primary osteoblastic cells	Stimulates osteoblast differentiation via ER signaling		[86]
P. ginseng ginsenoside Rh1	MCF-7 human breast cancer cells	Weak phytoestrogen		[87]
Ginsenoside metabolites				
Protopanaxadiol	Primary human umbilical vein endothelial cells	Functional ligands for both GR and ERβ		[88]
Protopanaxatriol	Primary human umbilical vein endothelial cells	Functional ligands for both GR and ERβ		[88]
AR				
P. ginseng	LNCaP human prostate cancer cells	Inhibit AR signaling by stimulating the degradation of AR protein Antiproliferation, apoptosis	AR	[21]
	C57BL/6 mice model, human hair follicle papilla cells	Antiandrogen, promotes hair growth in humans	ERK, Akt	[23]
20(*s*)-25-Methoxyl-dammarane-3beta, 12beta, 20-triol (20-OCH3-PPD)	– *In vitro*: Human LNCaP (P53 wild type, androgen dependent), PC3 (P53 null, androgen independent), IMR90-EEA and IMR90-E1A human primary fibroblast cell lines – *In vivo*: Prostate cancer (PC3) xenograft model	Inhibits the expression of androgen receptors, antiproliferation, apoptosis	PARP, Bax, Bcl-2, cyclin D	[22]

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; PI3K, 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 H_2O_2-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 5-α-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 cellular targets responsible for such activity and characterization of active red ginseng compounds still requires continuous research. Nuclear hormone receptors are one of the cellular targets of ginsenosides that are lipophilic in nature. ER is one of the well-studied targets for ginsenosides among the members of nuclear steroid hormone receptors. Modulation of ERs by ginseng components can be beneficial to estrogen-dependent cancer and many physiological states deriving from low levels of estrogen hormones due to aging as well as inevitable ovary-related surgery in younger women. As shown, studies targeting ARs and androgen-associated physiological states are less studied. Even with accumulating data on estrogen-mimicking or supplemental activity of ginseng in humans, additional accumulative data are still required to establish and provide a scientific basis of ginseng use on sex steroid hormone-dependent function.

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