•Review•

Advances on hormone-like activity of Panax ginseng and ginsenosides

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[ABSTRACT] Traditional Chinese medicine (TCM) has been paid much attentions due to the prevention and treatment of steroid hormone disorders. Ginseng, the root of Panax ginseng C. A. Meyer (Araliaceae), is one of the most valuable herbs in complementary and alternative medicines around the world. A series of dammarane triterpenoid saponins, also known as phytosteroids, were reported as the primary ingredients of Ginseng, and indicated broad spectral pharmacological actions, including anti-cancer, anti-inflammation and anti-fatigue. The skeletons of the dammarane triterpenoid aglycone are structurally similar to the steroid hormones. Both in vitro and in vivo studies showed that Ginseng and its active ingredients have beneficial hormone-like role in hormonal disorders. This review thus summarizes the structural similarities between hormones and dammarane ginsenosides and integrates the analogous effect of Ginseng and ginsenosides on prevention and treatment of hormonal disorders published in recent twenty years (1998–2018). The review may provide convenience for anticipate structure-function relationship between saponins structure and hormone-like effect.

[KEY WORDS] Panax ginseng; steroid hormones; triterpenoid saponins; hormone-like activity; molecular signaling

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Introduction

Steroid hormones play an indispensable role in regulating physical and emotional growth, sex differentiation, reproduction, immune functions, protein synthesis and metabolism[1]. Generally, the steroid hormones can be grouped into four main classes by their structural characteristics: progestogens, corticosteroids, androgens and estrogens (Fig. 1A)[2]. The clinical practice showed that the imbalance of hormone level would directly or indirectly lead to the occurrence of many physiological and psychological diseases [3, 4]. With the increasing environmental pollution and social pressure, the disorder of endocrine system is becoming more complicated and serious [5, 6]. Many diseases caused by hormone imbalance were treated with synthetic hormones, nevertheless, prolonged intake of these artificial drugs might lead to severe adverse effects [7, 8]. Therefore, due to lower cost and minor adverse effects, a large number of researchers are concentrating on using available and alternative traditional Chinese medicine (TCM). Especially, plant-derived natural products which are similar to synthetic hormones are applied to prevent endocrine disorder and treat disease [9-13].

Panax ginseng C. A. Meyer, is a perennial plant belongs to the genus Panax of Araliaceae family. It is widely used for curing miscellaneous diseases all over the world. As early as 4000 years ago, P. ginseng was acquainted as “The king of the grass bouquet” by means of nourishing weakness, replenishing energy, supporting body balance and consolidating robustness [14, 15]. Nowadays, there are plenty of herbal preparations including tablets, capsules, granules that containing ginsenosides [16, 17]. Triterpenoid saponins are the principal components in Panax species, which refer to a range of dammarane- or oleanane-type triterpenoid ginsenosides [18-21].

Ginsenoside Ro belongs to oleanane-type (OA) saponins which has a five-link trans ring [22]. Dammarane-type ginsenosides share a four-ring hydrophobic steroid-like structure skeleton, and can be divided into two functional groups based on their preferred glycosylation sites at C6 position: protopanaxadiol (PPD), such as ginsenoside Rb1, Rg3; protopanaxatriol (PPT) such as ginsenoside Rg1, Rh1 (Fig. 2) [18, 23]. Triterpenoid saponins are considered to be the main pharma-
Fig. 1  (A) The main steroidal structure of the four categories of hormones from cholesterol. The steroid hormones are divided into the progestogens, corticosteroids, androgens and estrogens are shown in purple, green, blue and red respectively. (B) Carbon numbering of a typical steroid scaffold and common functionalized positions (C3, 11, 17, 20, and 21); Carbon numbering of dammarane ginsenoside skeleton, the common functionalized positions at C17, 23, 24 and 25, the typical glycosylation group sites at C3, 6, 20 for these aglycone are labeled in green.

Fig. 2 Classification and chemical structure of dammarane ginsenosides and oleanane ginsenosides. PPD, Protopanaxadiol; PPT, Protopanaxatriol; Glc, β-D-glucopyranosyl; GlcA, β-D-glucuropyronosyl; OA, Oleanane acid

cological bioactive ingredients. They can boost immunity from diseases and enhance physical functions, such as antioxidant, cardiovascular system protection, anti-inflammatory, and anti-tumor. More to the point, the study also showed
that ginsenosides act as an estrogen analogue by activating estrogen receptor (ER) \[29, 30\].

In the last decades, in vitro and in vivo results have revealed that *P. ginseng* and its active compounds are equipped with hormone analogous effects. Many studies have demonstrated that dammarane ginsenosides possess greater potential in hormone-like effects \[31, 32\]. Therefore, to gather all of the literature relevant to hormone-like activities of *P. ginseng* and ginsenosides is of great importance. The objective of this review is to provide valuable research results on the roles and mechanisms of the hormone-like activities of *P. ginseng* and ginsenosides between 1998 and 2018 from the Web of Science, ScienceDirect and GeenMedical databases. And it may provide insight into opportunity for anticipating structure-function relationship of saponins in the activity of hormone-like.

**Structure of Endogenous Steroid Hormones and Dammarane Ginsenosides**

The structure characterization of endocrine steroid hormones and triterpenoid saponins lead to a better understanding of their semblable biological activities \[33\]. Eighteen steroid hormones are derived from cleavage of the cholesterol side chain by cytochrome P450 cholesterol side-chain cleavage enzyme (SCC) \[34, 35\]. Cholesterol is converted into progestogens in mammals by SCC, corticosteroids and androgens are bioconverted from progestogens by enzyme CYP21 and CYP17, respectively. And then enzyme CYP19 turns the androgen into estrogen (Fig. 1A) \[36, 37\]. These enzymes play a crucial role in transformation of one hormone into another in line with indicating arrow \[38, 39\].

Visually from the structure of ginsenosides and hormones: 1) all steroids share the same basic 17 carbon backbone which are known as the cyclopanenanphenanthrene ring. Three six-carbon cyclohexane rings are designated A, B, and C rings and the five-carbon cyclopentane ring is denoted as the D ring. All of the A ring are lipid rings, except for oestrogens—the C18 steroids estranges, which A ring is aromatic \[40\]. The other three main groups of steroids of interest in clinical endocrinology consist of 21, 19 or 21 carbon atoms, representing the progestogen, androgen and corticosteroid skeleton \[41, 42\]. Similarly, the parent ring of PPD and PPT type ginsenosides have a steroid-like four-link trans ring, and the C17 side chains of ginsenosides are similar in structure to cholesterol \[43, 44\]. 2) In addition, most of steroids have angular methyl group in C10 or C13. Similarly, the structure of a saponin comprises a sapogenin moiety and one or two glycosyl units and/or chains, and the sapogenin has the same angular methyl group in C10 or C13 as the parent nucleus of the hormone. 3) Generally, steroid has shown to possess at least one hydroxy (−OH) or ketone (=O) or methyl (−CH3) group at various carbon positions (typically C3, 11, 17, 20, and 21) of their scaffold \[45\]. Besides, there also have structures of ginseng saponins whose genin has a hydroxyl (−OH) or methyl (−CH3) group or double bond at some carbon sites (generally C17, 23, 24 and 25), and glycosyl (Glc, Ara, etc.) group at C3, 6, 20 (Fig. 1B) \[46\]. In terms of the molecular structure, ginsenosides is analogous to steroid hormones, and it would provide a solid structural basis for the hormone-like effect of dammarane ginsenosides.

**Hormone-like Activity of *P. ginseng* and Ginsenosides**

*In vitro study on the hormone-like activity of Ginseng and ginsenosides*

A few studies have demonstrated that the hormone-like effects of *P. ginseng* and ginsenosides in hormone-associated cells. In oestrogen receptor-positive cells, such as human breast cancer MCF-7 cells, often used as the preferred cell line for estrogen assay, exhibited cells proliferation distinctly after treatment with *P. ginseng* water extract and ginsenoside Rg1 \[47\]. In glucocorticoid receptor-related cells, like murine macrophagic RAW264.7 cells, ginsenoside Rg1 could enhance the effect of anti-inflammatory by up-regulating glucocorticoid receptor (GR) expression \[48\]. These may indicate that *P. ginseng* and ginsenosides regulate the production, conversion and metabolism of hormones in different organs and cells.

*In vivo study on the hormone-like activity of ginseng and ginsenosides*

Except extracorporeal exploration, internal experiments also verified the analogous steroid hormone effects of *P. ginseng* and ginsenosides in many explorations. *In vivo* studies, surgical removal of sexual organs, drinks or drug-induced hormonal disorders and ageing rats were commonly used as experiment model systems. In a general way, castrated rats or ovariectomized (OVX) rats have been adopted for simulating model of testosterone deficiency or estrogen decline in considerable literatures \[49, 50\]. Chronic alcohol consumption may bring about the problem of nervous system and male infertility \[51\]. Cyclosporine A (CsA), which has been reported that the concentration in serum were negatively correlated with vitality and motility of sperm \[52\]. Hence, Pan et al. \[53\] have adopted mice model of cyclosporine-induced damage of spermatogenic apoptosis and testosterone synthesis to investigate the potential protective effects of decoction, which containing *P. ginseng*. In addition, using ageing-induced testosterone deficiency or estrogen decline rat model in a natural state is also a good alternative method to perform an exploration, which could limit the risk of damage to experimental animals and in line with the provisions of the experimental animal protection laws \[54, 55\].

This is the fact that accumulating evidence have demonstrated *P. ginseng* or its saponins have a potent steroid hormonal activity by evaluating physiological change compared with placebo control. The regain of estrus cycle, improvement of target tissue function, reversal of the atrophy of the vagina and uterus could be regarded as the effective reflections of *P. ginseng* and ginsenosides estrogen-like activity in OVX rats. Moreover, the balance of steroid hormone levels in...
serum or plasma is also the expression of effectiveness of ginsenosides, which were detected by radioimmunoassay (RIA) kit or ultra-performance liquid chromatography hyphenated with mass spectrometry (UPLC-MS/MS) after treatments [56-58]. In the testosterone decline male rat model, the number and vitality of fully mature sperm cells at the center of the tubules was limited; the number of cells lining the tubular membrane was decreased; and the tissue around the tubule was degraded, these symptoms all indicated that cells was late maturation arrest or premature death in reproductive organ [59, 60]. Hence, the improvement of symptoms can be analyzed to evaluate the androgen-like effect of P. ginseng and ginsenosides [61-63]. The level and activity of oxidative stress kinase are also common index in functional organs [64-66]. According to the enzyme-immunoassay (EIA), ginsenoside Rg1 could protect tissue and cell from oxidative stress damage by increasing the activities of superoxide dismutase (SOD) and catalase (CAT) and decreasing the level of malondialdehyde (MDA) [67, 68]. Additionally, observing change of rat sex organs weight, like epididymis, testis and seminal vesicles, were often considered as a simple and widespread assessment [56, 69]. Table 1 displays the hormone-like activity of Ginseng and ginsenosides in detail.

**Mechanism research on the hormone-like activity of Ginseng and ginsenosides**

Many studies have shown that the molecular target path-

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### Table 1 Preclinical studies of Ginseng and ginsenosides for hormone-like activities compared with placebo control

<table>
<thead>
<tr>
<th>Active substance material</th>
<th>Experimental model</th>
<th>Dose (mg·kg⁻¹)</th>
<th>Treatment duration (weeks)</th>
<th>Steroidal activity</th>
<th>Treatment activities</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. ginseng water extract</td>
<td>Nile tilapia</td>
<td>Oral, 400</td>
<td>12</td>
<td>Androgen</td>
<td>Improved: testes and spleen somatic indexes; plasma T level</td>
<td>[69]</td>
</tr>
<tr>
<td>Korean red ginseng water extract</td>
<td>Ageing -induced testicular dysfuction rat</td>
<td>Oral, 200</td>
<td>24</td>
<td>Androgen</td>
<td>Improved: body and testis weights; serum T level; cell numbers; the process of spermatogenesis</td>
<td>[54]</td>
</tr>
<tr>
<td>Korean red ginseng water extract</td>
<td>T-induced prostate hyperplasia rat</td>
<td>IP, 100 or 200</td>
<td>4</td>
<td>Androgen</td>
<td>Improved: apoptosis of prostate epithelial cells. Decreased: epithelial layer thickness; prostate cells proliferation</td>
<td>[117]</td>
</tr>
<tr>
<td>P. ginseng water extract</td>
<td>OVX rat</td>
<td>Oral, 6000</td>
<td>8</td>
<td>Estrogen</td>
<td>Improved: estrous stage; uterine weight index; serum E2 level. Decreased: body weight; serum LH level</td>
<td>[50]</td>
</tr>
<tr>
<td>P. ginseng water extract</td>
<td>Immature and OVX mice</td>
<td>Oral, 24000</td>
<td>4</td>
<td>Estrogen</td>
<td>Improved: serum E2 level; uterus and vagina weights. Decreased: LH and FSH level</td>
<td>[118]</td>
</tr>
<tr>
<td>P. ginseng water extract</td>
<td>MCF-7 cells</td>
<td>0.1–100 μg·mL⁻¹</td>
<td>-</td>
<td>Estrogen</td>
<td>Improved: cells Proliferation</td>
<td>[118]</td>
</tr>
<tr>
<td>Ginsenoside Re</td>
<td>Human sperm</td>
<td>1 and 10 μg·mL⁻¹</td>
<td>-</td>
<td>Androgen</td>
<td>Improved: sperm motility; sperm progression</td>
<td>[119]</td>
</tr>
<tr>
<td>Ginsenoside Rb1</td>
<td>OVX mice</td>
<td>IP, 10</td>
<td>1</td>
<td>Estrogen</td>
<td>Improved: 5-HT concentration; HTP accumulations. Decreased: MAO activity</td>
<td>[120]</td>
</tr>
<tr>
<td>Ginsenoside Rg3</td>
<td>Allotransplantatio n-induced EM rat</td>
<td>Oral, 10</td>
<td>4</td>
<td>Estrogen</td>
<td>Improved: apoptosis of ectopic endometrial cells. Decreased: serum E2 level; volume and height of ectopic endometrial lesions</td>
<td>[120]</td>
</tr>
<tr>
<td>Ginsenoside Rg1</td>
<td>Ethanol-induced infertility rat</td>
<td>Oral, 20 and 40</td>
<td>4</td>
<td>Androgen</td>
<td>Improved: epididymis, testis and seminal vesicles weights; the count, viability, and motility of testicular sperm; serum T level; SOD and CAT activities. Decreased: MDA levels</td>
<td>[51]</td>
</tr>
<tr>
<td>Ginsenoside Rg1</td>
<td>Gonadectomized rat</td>
<td>Chronic unpredictable stress rat</td>
<td>Oral, 20</td>
<td>4</td>
<td>Androgen; corticosteroid</td>
<td>Improved: sleep disruption; AR protein level. Decreased: serum CORT level</td>
</tr>
<tr>
<td>Ginsenoside Rg1</td>
<td>ALD-induced MPC5 mouse podocyte cells</td>
<td>0.08 μg·mL⁻¹</td>
<td>-</td>
<td>Corticosteroid</td>
<td>Improved: T-SOD activity. Decreased: oxidative stress; autophagy; MDA level; ROS production</td>
<td>[123]</td>
</tr>
<tr>
<td>Protopanaxatriol saponins and metabolites</td>
<td>ACTH-stimulated bovine adrenal fasciculata cells</td>
<td>9.53 μg·mL⁻¹</td>
<td>-</td>
<td>Corticosteroid</td>
<td>Decreased: corticosteroid generation; the conversion from cholesterol to pregnenolone</td>
<td>[113]</td>
</tr>
</tbody>
</table>

T, testosterone; IP, Intraperitoneal; E2, estradiol; LH, luteinizing hormone; LHR, luteinizing hormone receptor; FSH, follicle-stimulating hormone; CORT, corticosterone; HPA axis, The hypothalamic-pituitary-adrenal axis; HPG axis, The hypothalamus- pituitary-gonadal axis; VEGF, Vascular endothelial growth factor; 5-HT, 5-hydroxytryptamine; HTP, tryptophan hydroxylase; MAO, monoamine oxidase; EM, endometriosis; ALD, Aldosterone; ROS, reactive oxygen species
way of *P. ginseng* and ginsenosides effect on steroid hormones by binding or activating intracellular nuclear, cytosol or cell membrane hormone receptors, such as ER, androgen receptor (AR), GR, either directly or indirectly, and subsequently regulating the associated hormone levels [76-78]. Saponins regulate intracellular hormone balance by non-genetic pathways of intracellular signaling molecules [75, 76]. On the other hand, ginsenosides also could activate the expression of related invertases like endogenous antioxidant enzymes by regulating intracellular target proteins or genes [77, 79]. In many cases, ginsenosides can cross-talk with multiple signaling pathway at the same time, from enzyme level, protein level to gene level, which directly or indirectly play an important role in preventing and treating diseases caused by hormone disorders [81].

Androgens play their biological roles predominately in binding to the AR whether directly or indirectly [82, 83]. By binding to receptors, *P. ginseng* and ginsenosides have ability to deeply regulate genes level of hormone metabolism in the nucleus [80, 81]. And on the membranes of mitochondria, *P. ginseng* and ginsenosides have ability to active ER and ERα [81, 91-93]. Ginsenosides not only have sex hormone-like activity, but also bind GR to produce corticosteroid-like effects. Ginsenosides has been observed to promote the upregulation of cytoplasmic and nuclear GR protein level in the rat liver and lipopolysaccharide (LPS)-stimulated RAW264.7 macrophage cells [84]. Table 2 displays the possible pathway of the regulation mechanisms of action of *Ginseng* and ginsenosides.

**Table 2** Pathway of the regulation mechanisms of hormone-like effect of *Ginseng* and ginsenosides

<table>
<thead>
<tr>
<th>Active substance material</th>
<th>Observations</th>
<th>Steroidal activity</th>
<th>Experimental model</th>
<th>Signaling molecules monitored</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korean red ginseng water extract</td>
<td>Steroids metabolism improvement</td>
<td>Androgen; Estrogen and Corticosteroid</td>
<td>Aged male rat testes</td>
<td>CYP11a1</td>
<td>[80]</td>
</tr>
<tr>
<td>Korean red ginseng water extract</td>
<td>AR transcription suppression</td>
<td>Androgen</td>
<td>LNCaP cells</td>
<td>Kallikrein-3 Mma, AR</td>
<td>[117]</td>
</tr>
<tr>
<td>Korean red ginseng water extract</td>
<td>Spermatogenesis</td>
<td>Androgen</td>
<td>Aged male rat</td>
<td>Inhibin-α, nectin-2, CREB-1</td>
<td>[124]</td>
</tr>
<tr>
<td>Ginsenoside Ro</td>
<td>5α-reductase inhibitory</td>
<td>Androgen</td>
<td>Androgenetic alopecia rat</td>
<td>5α reductase</td>
<td>[125]</td>
</tr>
<tr>
<td>Ginsenosides Rh4 and Rg5</td>
<td>Endothelial NO production</td>
<td>Androgen</td>
<td>Hydrocortisone-induced male mice</td>
<td>NO/cGMP/PKGI</td>
<td>[87]</td>
</tr>
<tr>
<td>20(S)-protopanaxadiol</td>
<td>AR protein level diminution</td>
<td>Androgen</td>
<td>C4-2 xenograft tumors</td>
<td>AR</td>
<td>[126]</td>
</tr>
<tr>
<td><em>P. ginseng</em> water extract</td>
<td>Estrogen-like activity</td>
<td>Estrogen</td>
<td>OVX mice</td>
<td>ERα, ERβ</td>
<td>[118]</td>
</tr>
<tr>
<td><em>P. ginseng</em> water extract</td>
<td>Estrogen-like activity</td>
<td>Estrogen</td>
<td>Female immature mice</td>
<td>ERα, ERβ</td>
<td>[127]</td>
</tr>
<tr>
<td>Ginsenoside Rb1</td>
<td>Estrogen-like activity</td>
<td>Estrogen</td>
<td>MCF-7 cells</td>
<td>ER</td>
<td>[128]</td>
</tr>
<tr>
<td>Ginsenoside Rg3</td>
<td>Endometriosis-associated angiogenesis</td>
<td>Estrogen</td>
<td>Allotransplantation-induced rat</td>
<td>PI3K-Akt-mTOR</td>
<td>[121]</td>
</tr>
<tr>
<td>Ginsenoside Rh1</td>
<td>Estrogen-like activity</td>
<td>Estrogen</td>
<td>MCF-7 cells</td>
<td>ER</td>
<td>[129]</td>
</tr>
<tr>
<td>Ginsenoside Rg1</td>
<td>Estrogen-like activity</td>
<td>Estrogen</td>
<td>MCF-7 cells</td>
<td>ERE-luciferase</td>
<td>[47]</td>
</tr>
<tr>
<td>Ginsenoside Rg1</td>
<td>Estrogen-like activity</td>
<td>Estrogen</td>
<td>MCF-7 cells</td>
<td>pS2 gene expression, ERα</td>
<td>[81]</td>
</tr>
<tr>
<td>Ginsenosides</td>
<td>Glucocorticoid-like activity</td>
<td>Corticosteroid</td>
<td>Hydrocortisone-induced rat</td>
<td>GR, TAT, mRNA</td>
<td>[94]</td>
</tr>
<tr>
<td>Ginsenoside Rg6</td>
<td>GR translocation suppression</td>
<td>Corticosteroid</td>
<td>Human cancer cells</td>
<td>GR</td>
<td>[130]</td>
</tr>
<tr>
<td>Ginsenoside Rh1</td>
<td>GR transcription improvement</td>
<td>Corticosteroid</td>
<td>CIA mice</td>
<td>NF-Kb, DUSP1</td>
<td>[131]</td>
</tr>
<tr>
<td>Ginsenoside Rg1</td>
<td>Glucocorticoid-like activity</td>
<td>Corticosteroid</td>
<td>RAW 264.7 cells</td>
<td>eNOS, TNF-α, GR</td>
<td>[48]</td>
</tr>
<tr>
<td>Ginsenoside Rg1</td>
<td>GR activation</td>
<td>Corticosteroid</td>
<td>Human umbilical vein endothelial cells</td>
<td>GR</td>
<td>[132]</td>
</tr>
</tbody>
</table>

PI3K/Akt/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; ERE, estrogen response element; CIA, collagen-induced arthritis; NF-κB, nuclear factor kappa B; DUSP1, dual specificity protein phosphatase 1; eNOS, endothelial nitric oxide synthase; NO, Nitric oxide.
**P. ginseng** and ginsenosides. The summarized pathway of the regulation mechanisms of representative ginsenosides effect on the steroid hormones are shown in Fig. 3.

**Conclusion and Future Perspectives**

TCM have attracted considerable concern from the public, medical community, and governmental agencies, the search for lower side effects with a similar endogenous hormones effect of steroidal constituents like phytohormones instead of synthetic hormones has been in full swing [86-87]. In this review, from the perspective of structure-activity relationship, dammarane ginsenosides possess cholesterol-like four connected trans-ring steroid skeleton with various free or sugar-bound hydroxyl groups. Meanwhile, there are similarities between ligand of saponins and hormones, all the more so the degraded minor ginsenosides, such as ginsenoside Rg5, 25-OH-PPD [88]. Internal studies have manifested that the ginseng water extract, or individual ginsenosides have activity of analogous endogenous hormone in mammals. Different from fresh *P. ginseng*, the main ingredients of Korean Red ginseng are the minor ginsenosides. And according to the results, the minor ginsenosides may have stronger activities than the native ginsenosides [87]. Further, ginsenosides could bind and activate nuclear hormone receptors to maintain a healthy level of physiology in target tissues or cells. In addition, the moderating effect of dammarane saponins on the expression of some invertase proteins also promotes the balanced transformation and metabolism of hormones.

To expand structure–activity relationship between ginsenosides and hormones, thus attention also should be paid to the structure of ginsenosides after metabolism. Studies on metabolism of ginsenosides revealed that ginsenosides were transformed via multiple pathways including deglycosylation, dehydration, oxygenation and hydration both *in vitro* and *in vivo*, these transformed ginsenosides further contribute to the chemical diversity of minor ginsenosides [89]. For example, under the conditions of artificial gastric juice, the deglycosylated and dehydrated ginsenosides possessed slightly increased than primary ginsenosides [90]. And *in vivo* studies, there have reported that the gut microbiota moieties could degrade ginsenosides *via* cleavage of the sugar [91-94]. The degraded minor ginsenosides have been proven to traverse membrane more efficient than the intact ginsenosides, and further yield higher bioavailability in cells [94, 95]. Therefore, lower polar ginsenosides might have great potential to be absorbed into circulation system [96-97]. For instance, ginsenoside Rg3, Rg5, Rh1 has been demonstrated to exhibit remarkable anticancer and antioxidant pharmacological activities than polar ginsenosides [98-100]. Thus, we would be correct to assume that the rare minor ginsenosides may play a more effective role in keeping regular of hormonal level after treatment with *P. ginseng* saponins.

Current studies speculate that sugar linkage at C-6 was more active than linkage at C-3, total number of sugar molecules within a ginsenoside indicated the negative correlation with steroid hormones effect, elimination of glycosyl bonds may be consistent with their steroid hormone-like effects, the steamed red ginseng better than untreated ginseng [113, 114]. However, whether stereoselectivity, C17 side-chain variation or location of hydroxyl group have a significant impact on the biological activity of ginsenosides still need to be further investigated, whether oleanane type saponins

![Fig. 3](image-url)  
**Fig. 3** A summarized pathway of the regulation mechanisms of representative ginsenosides effect on the steroid hormones via genes and transcriptions pathways. PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; eNOS, endothelial nitric oxide synthase; NO, Nitric oxide; MEK, mitogen-activated protein kinase kinase
like ginsenoside Ro are more active than dammarane type still need to be further explored. In addition, many diseases are linked to endogenous steroid hormones, such as depression and menopause (18, 19). The possible related mechanisms by which ginsenosides act may differ, the mechanism of different types of ginseng corresponding to its activity also deserves further research.

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