

Ginseng and male reproductive function

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Keywords: ginseng, ginsenosides, sexual behavior, sperm, spermatogenesis, steroid receptor

Abbreviations: ACh, acetylcholine; AR, androgen receptor; cGMP, cyclic guanosine monophosphate; CREM, cAMP-responsive element modulator; CP, cyclophosphamide; DA, dopamine; ER, estrogen receptor; GABA, gamma-aminobutyric acid; GDNF, glial cell-derived neurotrophic factor; GR, glucocorticoid receptor; LH, luteinizing hormone; NO, nitric oxide; NOS, nitric oxide synthase; PR, progesterone receptor; ZEA, zearalenone

Ginseng is often referred to as the King of all herbs, and is found to be a promising agent to improve general well-being. Ginseng has also been reputed as an aphrodisiac, and is used to treat sexual dysfunction as well as to enhance sexual behavior in traditional Chinese medical practices. Data from animal studies have shown a positive correlation among ginseng, libido, and copulatory performances, and these effects have been confirmed in case-control studies in human. In addition, ginseng is found to improve the sperm quality and count of healthy individuals as well as patients with treatment-related infertility. These actions are mostly attributed to ginsenosides, the major pharmacological active components of ginseng. This review compiles the current knowledge about the multifaceted effects of ginseng on male reproductive function, and also focuses on its mechanisms of action that may represent novel therapeutic strategies for the treatment of male reproductive diseases or disorders.

Introduction

Infertility is a growing problem in the world. In 2010, an estimated 48.5 million couples worldwide were infertile.¹ In approximately 40% of these couples, the male partner has been either the sole or a contributing cause of infertility.^{2,3} Herbal therapy is increasingly popular worldwide as a way to treat infertility. In the United States, 17% constantly visited herbal therapist in the past 18 mo out of the 29% of infertile couples who use complementary and alternative medicine.³ In a clinic-based survey conducted in Jordan, 44% of infertile patients use herbal medicine as part of their infertility treatment.⁴ Among them, 8% went for Chinese medication.⁴ In South Australia, 29% of interviewed infertile subjects use herbal remedies, in which 4.2% uses ginseng.⁵

Ginseng is one of the most precious herbs in traditional Chinese medicine. There are at least nine species of ginseng and are mostly named by their geographical origins, such as Asian ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolium*), and Japanese ginseng (*Panax japonicus*). The genus name

“Panax” is given to ginseng by the Russian botanist Carl A Meyer in 1843. “Panax” means “all-healing” in Greek, and *Panax ginseng* is conventionally referred to the Asian ginseng. Ginseng has been reported to have diverse physiological effects in multiple systems, including cardiovascular, immune, and neuronal. It has also been used to enhance sex performance and satisfaction. In this review, we will summarize the effects of ginseng on male sex performance and spermatogenesis. Recent evidences on its mechanisms of action that may represent novel therapeutic strategies for the treatment of male reproductive diseases or disorders will be discussed.

Sex Performance

Erection

Ginseng is commonly taken by itself or with an herbal formula to enhance sexual performance in traditional Chinese medical practices. The beneficial effects have been scientifically evaluated and confirmed in meta-analyses of randomized clinical trials.⁶ For example, in a double-blind, placebo-controlled study, 45 men with moderate to severe erectile dysfunction had found improvement in their scores on erectile performance and sexual satisfaction after treated with three times daily doses of 900 mg Korean red ginseng for 8 wk.⁷ A similar study on 60 men with erectile dysfunction also reported marked improvement in erectile function including rigidity, penetration, and maintenance of erection after taking Korean red ginseng (1000 mg) three times daily for 12 wk.⁸

In animal studies, treatment with Korean red ginseng and ginseng berry extract has been shown to significantly relax the pre-contracted penile corpus cavernosum smooth muscles of rabbits in vitro, and increase the intracavernosal pressure of rats in vivo.^{9,10} Data from studies on ginseng berry extract suggest that this action is nitric oxide (NO) dependent. The pharmacologically active components of ginseng, ginsenosides, are known to be able to induce NO synthesis in endothelial cells and perivascular nerves, and to augment vascular smooth muscle cell's sensitivity to NO.^{11,12} This release of NO causes smooth muscle to relax, thus allowing more blood to enter the erectile bodies known as corpus cavernosum and causing erection.¹³ Among the ginsenosides, Rg1 has been found for NO production in endothelial cells by glucocorticoid receptor (GR)-dependent, non-genomic

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Submitted: 09/04/2013; Accepted: 09/05/2013
<http://dx.doi.org/10.4161/spmg.26391>

mechanisms,¹⁴ and administration of Rg1 (10 mg/kg) significantly enhances NO release and cyclic GMP (cGMP) accumulation in corpus cavernosum of mice.¹⁵

Libido

Studies on rodents reveal that both Asian ginseng (*Panax ginseng*)¹⁶ and American ginseng (*Panax quinquefolium*)¹⁷ can facilitate copulatory behavior. Daily treatment of Asian ginseng (25–100 mg/kg) or ginsenoside Rg1 (2.5–10 mg/kg) demonstrates a dose-dependent increase in mounting, intromission, and penis licking in mice which are exposed to estrous females.¹⁸ Such effects are not observed in mice treated with ginsenoside Rb1, Rb2, and Ro.

Sex drive in higher mammals involves a complex coordination between the hormonal and neuronal components. The male sex steroid, testosterone, is synthesized in the Leydig cell under the control of luteinizing hormone (LH), which is produced by the anterior pituitary.¹⁹ Testosterone levels are strongly correlated with libido and testosterone is therefore one of the main forms of prescription given to men with reduced sex drive.²⁰ Interestingly, rats fed with 5% *Panax ginseng* in their diet for 60 d have shown significantly increased blood testosterone levels, whereas treatment with 1% *Panax ginseng* had no effect.²¹ Ginsenoside Rg1 (10 mg/kg), the major active constituent in *Panax ginseng*, is responsible for the increase of serum testosterone levels and improvement of copulatory behavior observed.¹⁵ Ginsenoside Rb1 (10 µg/kg), a key ginsenoside found in American ginseng, is found to increase the secretion of LH by acting directly on the anterior pituitary gland.²² In a clinical study that involves 66 participants, the use of Asian ginseng extract has been shown to significantly increase the levels of plasma total and free testosterone, follicle stimulating hormone, and LH.²³ However, oral administration of American ginseng (10–100 mg/kg) for 28 d does not seem to alter testosterone and LH levels in rats,¹⁸ suggesting that type of ginseng and treatment duration could make a difference in the libido-enhancing ability.

Several neurotransmitters have been implicated in libido, such as dopamine (DA) for desire, acetylcholine (ACh) for arousal, and (GABA) for orgasm. Ginsenoside Re has been shown to increase extracellular DA and ACh levels in rat brain.²⁴ The action of ginsenoside Rb1 on ACh release is associated with an increase of choline uptake into nerve endings.²⁵ American ginseng extracts were shown to modulate GABAergic neurotransmission in rat brainstem neurons.²⁶ Receptor-ligand binding assays have demonstrated that ginsenosides Rb1, Rb2, Rc, Re, Rf, and Rg1 are agonists of GABA(A) receptor, and Rc is also an agonist for GABA(B) receptor.²⁷ These findings suggest that ginseng may regulate the pituitary-testis axis at both hormonal and neuronal levels.

Sperm Production and Quality

Researches over the past 20 y have shown sperm counts declining in many countries across the world. For instance, a study on 26000 French males has shown a continuous decrease in sperm concentration over a 17-y period.²⁸ A 32% reduction is found when comparing the average sperm level of a 35-y-old man

between 1989 and 2005.²⁸ The reasons are not fully known, but the reduction in fertility worldwide could indicate a general deterioration of male's well-being, which is becoming a major health concern. Thus, there is a need to further understand the causes and to establish measures to prevent it.

Sperm count and motility

The initial evidence that ginseng may have positive effects on spermatogenesis was first published in 1977. Here it was demonstrated that the stimulatory effect of ginseng extracts on DNA and protein syntheses in rat testes.²⁹ Later studies in both rodents and humans have shown that ginseng can increase sperm count. Ginseng-treated rats have demonstrated an increased rate of spermatogenesis via glial cell-derived neurotrophic factor (GDNF) expression elevation in Sertoli cells,³⁰ and activation of testicular cAMP-responsive element modulator (CREM).³¹ GDNF is a possible regulator of the survival and cell fate decision of undifferentiated spermatogonial cells,^{32,33} and CREM is essential for spermatid maturation.³⁴ Men with little or no CREM protein/mRNA show specific arrest of round spermatids, which could be a possible cause of infertility.³⁵ Both oligoasthenospermic patients and age-matched healthy counterpart showed an increase in spermatozoa density and motility after the use of *Panax ginseng*.²³ Asthenospermia patients treated with ginseng also showed a significant increase in progressive sperm motility.³⁶ The aqueous, organic, and polysaccharide fractions of *Panax notoginseng* have been shown to enhance the directional motility of human sperms in 60–120 min.³⁷ Similarly, ginsenosides Rc and Rb2 (0.01 mg/ml) have been shown to enhance sperm progression in vitro.³⁸ To pinpoint on specific active components for this action, these effects are found to be mediated through induction of nitric oxide synthase (NOS) activities and NO production.³⁹ NO is also closely related to sperm function. Ginsenoside Re (1–100 µM) has been shown to facilitate human sperm capacitation and acrosome reaction through enhancing intracellular NO production.⁴⁰

Sperm preservation

Ginseng is also found to help preserve the ejaculated sperms. It has been shown that the sperm count of ejaculated sperms that were incubated with ginseng extract was significantly higher than those treated with vehicle.⁴¹ Treatment with ginsenoside Rg1 (50 µg/ml) significantly increases sperm motility and membrane integrity of post-thawed sperms as compared with fresh and untreated thawed sperms.⁴² These findings suggest that the addition of ginseng extract to the cryogen for sperm storage could enhance fertility.

Effects of Ginseng on Spermatogenesis During Disease States

It is known that conventional cancer treatments often lead to various degrees of reproduction impairment, and that these effects could be either temporary or permanent. Cyclophosphamide (CP) is an alkylating agent that shows cytostatic effects by forming covalent DNA adducts. Since CP targets rapidly dividing cells, it is extensively used to suppress tumor malignancy, and as an immunosuppressant for organ transplantation patients. However, this drug often leads to gonadal toxicity, and infertility

as a consequence discourages many patients from choosing CP treatment. It has been shown that intake of American ginseng (500 mg/kg/day) can protect sperms, in particular by increasing the sperm count, reducing sperm death and abnormalities, and resuming sperm motility from CP insult in adult male Wistar rats as compared with CP treatment alone.⁴³ Furthermore, treatment of protopanaxatriol saponin is shown to markedly reduce the chemotherapeutic agent (busulfan)-induced structural defect of the testis in mice, suggesting that ginseng may have applications in the recovery of male infertility after cancer treatments.⁴⁴

Radiation therapy is sometimes given to patients as part of the cancer therapy. However, the unselective action of radiation therapy can also damage normal cells, leading to side effects. Amifostine (WR-2721) is one of the radioprotectants that is registered for human use, but its usage leads to many negative side effects, such as hypertension, nausea, and vomiting.⁴⁵ This compound is also cytotoxic to stem spermatogonia, thus limiting its clinical use.⁴⁶ It is interesting to note that intraperitoneally injection of *Panax ginseng* extract (10 mg/kg) given to adult male Swiss albino mice for 4 d can protect germ cell population and function against γ -radiation, and dramatically reduce γ -radiation-associated sickness, including anorexia, diarrhea, weight loss, lethargy, and epilation.⁴⁷

Zearalenone (ZEA) is an estrogenic mycotoxin that commonly contaminates the environment as its presence in the crops, which causes reproductive disorders in farm animals. The consumption of Korean red ginseng (300 mg/kg) for 4 wk every other day has been shown to be able to prevent ZEA-induced spermatogenesis impairment in rats via modulating Fas/Fas-L expression.⁴⁸

Males with non-insulin-dependent diabetes mellitus (type 2 diabetes) often suffer from sexual dysfunction.⁴⁹ Studies have found the benefits of ginseng intake. For example, the administration of standardized ginseng extract (100 mg/kg) daily for 90 d in streptozotocin-induced diabetic rats has been shown to result in a significant improvement of fertility parameters and decrease in testicular pathological signs, such as degenerative changes of the seminiferous tubules.⁵⁰ Furthermore, the consumption of Korean red ginseng (30 mg/kg, three times a week for 1 mo) can help streptozotocin-induced type 2 diabetic male rats to improve on libido and sexual performance.⁵¹ In addition, ginseng has been shown to be able to stabilize diabetes disease progression. In a double-blinded, placebo-controlled study, it has been shown that daily ginseng intake (100 or 200 mg) among type-2 diabetic patients demonstrated significant reduction in fasting blood glucose and body weight, and improvement in glycated hemoglobin, serum N-terminal propeptide concentration, psychological performance, and physical activities.⁵² Similarly, Korean red ginseng has been shown to be able to enhance cGMP levels of the corpus cavernosum in rats with metabolic syndrome and may therefore improve erectile function.⁵³

A continuous exposure to environmental toxins is considered to be a cause of fertility decline. Ginseng has been demonstrated to have a cytoprotective effects against these toxins, in which administration of *Panax ginseng* extract is reported to significantly reduce the 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced pathological and genotoxic damages in rat testes.⁵⁴ In addition,

treatment of *Panax ginseng* is found to protect Sertoli cells from the cytotoxic effects of bisphenol A.⁵⁵

Mechanisms of Action on Spermatids

Ginsenosides are triterpenoid saponins that structurally resemble the steroid hormones. Thus, it is tempting to speculate that the effects of ginsenosides on sexual function and spermatogenesis are a result of activation of steroid receptors. Androgens are sex steroids that are essential for the development and maintenance of male sexual characteristics, and regulate normal spermatogenesis. Androgen receptor (AR) is abundantly expressed in male genital tissues and in spermatozoa,⁵⁶ and its expression is significantly decreased in infertile men.⁵⁷ Ginsenoside Rb1 and Re have been reported to be AR agonists, through which these ginsenosides stimulate NO production via the activation of NOS.^{58,59} Ginseng berry extract GB0710, of which ginsenoside Re is the key ingredient, could improve erectile dysfunction in rats by inducing NO production.¹⁰ Re-induced NO production in sperm has also been shown to be involved in capacitation and acrosome reaction, and that these effects could be a result of the non-genomic activities of the Re-AR interaction.⁴⁰

Estrogen is another hormone with profound effects on sexual function of both male and female. Estrogen supplements have been shown to improve sexual function of testosterone deficiency men.⁶⁰ In this regard, although estrogen receptor (ER) α -knockout mice have undisrupted reproductive tract development, these mice display less masculine sexual behavior⁶¹ and have a much lower fertility rate.⁶² Several ginsenosides, including Rb1, Re, Rg1, Rg3, and Rh1, are agonists of ER α that have been shown to elicit both receptor-dependent transcriptional and non-transcriptional estrogenic actions in multiple cell types.^{58,63-66} In this regard, ER has been reported on human spermatozoa and that it is located mainly on the plasma membrane,⁶⁷⁻⁷⁰ suggesting that ginsenosides may modulate male sexual function through non-genomic interactions of ER.

Expression of progesterone receptor (PR) was observed on human sperms, and a strong correlation between PR expression and sperm function has been demonstrated.⁷¹ Intriguingly, unlike estrogens, progesterone promotes the capacitated sperm to undergo acrosomal reaction.^{72,73} In concordance, a handful of in vitro studies have demonstrated an inhibitory action of progesterone on estrogens and vice versa. For example, the estrogen-induced forward movement of human spermatozoa into the oviduct could be effectively suppressed by progesterone.⁷⁴⁻⁷⁷ In addition, it was shown that progesterone, which was secreted by the culmus cells surrounding the oocyte to induce sperm hyperactivation, was inhibited in the presence of estrogen.⁷⁸ On the other hand, estrogen and progesterone may cooperate to optimize their effects on fertilization.^{79,80} Ginseng extracts contain a mixture of ginsenosides that can activate either or both ER and/or PR, and, hence, may modulate different aspects of sperm function. The ginsenoside Re-induced motility enhancement effect in spermatozoa could be related to the findings that Re is found to be both ER and PR agonists.⁵⁸

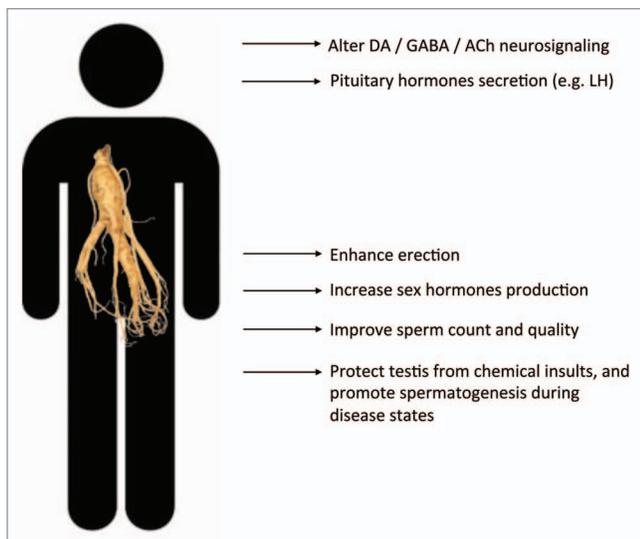


Figure 1. Summary of the ginseng's effects on male sexual function. Ginseng enhances sexual performance, improves male fertility through modulating the neuronal and hormonal systems, promotes spermatogenesis, and acts directly on sperms via steroid receptors. Ginseng also preserves male fertility during disease states.

Concluding Remarks and Future Perspectives

Ginseng is a vital constituent of traditional Chinese medicine and has been used to treat various physical conditions for

thousands of years, importantly as an aphrodisiac and is used to treat sexual dysfunction as well as to enhance sexual behavior and gonadal functions (Fig. 1). Therefore, use of ginseng appears to be important for the development of novel therapeutics or to increase the effectiveness of the current treatment strategies for male reproductive diseases or disorders. However, its molecular mechanisms of action remain elusive. Research in this area should be carried further. A versatile assay for high-throughput expression profiling will prove useful to reveal the molecular functions of different ginsenosides and how the different signal networks are orchestrated. Further evaluations are also needed to validate some of the medicinal benefits using modern analytical tools and technology-based analyses. Different approaches to synthesize and/or modify natural ginsenosides can also be considered to increase the efficacy/potency, metabolic stability, and oral bioavailability for clinical applications.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by the Health and Medical Research Fund 1121191, Hong Kong Jockey Club Charities Trust (HKJCCT), HKU Strategic Research Theme on Drug, and Croucher Senior Research Fellowship to Alice ST Wong.

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