

Effects of Ginseng on Fertility



Bo Hyon Yun^{1,2}, Young Sik Choi^{1,2}, SiHyun Cho^{1,2}, Byung Seok Lee^{1,2}, Si Kwan Kim³ and Seok Kyo Seo^{*1,2}

¹Department of Obstetrics and Gynecology, Severance Hospital, Yonsei University College of Medicine, Republic of Korea

²Institute of Women's Life Medical Science, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

³Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

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***Corresponding author:** Seok Kyo Seo, M.D., Department of Obstetrics and Gynecology, Severance Hospital, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu 120-752, Seoul, Republic of Korea

Abstract

Ginseng is a representative, traditional Eastern Asian herb used as a tonic for slowing down the aging process. It has become one of the most popular dietary supplements throughout the world. The major active ingredient of ginseng is the ginseng saponin, which is composed of various ginsenosides. Currently, approximately 30 ginsenosides have been identified. Few research studies have attempted to identify the exact effects exerted by each type and constituent of ginseng. Interestingly, the induction of apoptosis of cancer cell lines has been reported in several malignancies, and effects on dopamine release pathways in the brain have been shown. In addition to the traditional medicinal property of ginseng, which has been thought to be a tonic, a few studies have been conducted to identify whether it can improve fertility. However, whether ginseng affects fertility or not remains experimental since most of the studies have been performed *in vitro*. The aim of this present study was to review relevant studies on the effect of ginseng on male and female reproduction, especially infertility.

Keywords: Female and Male Infertility; Fertility; Ginseng

Abbreviations: LH: Luteinizing Hormone; GABA: Gamma Aminobutyric Acid; GDNF: Glial Cell Derived Neurotrophic Factor; CAMP: Cyclic Adenosine Monophosphate; KRG: Korean Red Ginseng; PCOS: Polycystic Ovary Syndrome

Introduction

Ginseng is a representative, traditional Eastern Asian herb used as a tonic for slowing down the aging process [1]. The major active ingredient of ginseng is the ginseng saponin, which is composed of various ginsenosides. Currently, approximately 30 ginsenosides have been identified [2-4]. There are at least 9 known species of ginseng, including the Asian (*Panax ginseng*), American (*Panax quinquefolium*), and Japanese (*Panax japonicus*) ginseng. These varieties have shown effects such as antioxidant effects, enhancement of diverse physiologic effects including immunostimulatory effects [5,6] effects on the neuronal system [7,8] and control of the metabolic state [9-11]. In addition to the traditional properties of ginseng, which has been thought to be tonic, a few studies have been conducted to identify whether it can improve fertility. However, whether ginseng affects fertility or not and its underlying mechanisms of action remain to be investigated in humans since most related studies have been performed *in vitro*. The aim of this mini-review is to assess and highlight previous relevant studies of the effect of ginseng on male and female reproduction, especially fertility.

Ginseng and Male Fertility

The relationship between ginsenosides and male reproduction has been evaluated for over 20 years. However, few studies have been performed in humans, and most have used animal models. Ginseng has been considered a tonic, and therefore, a considerable number of experiments have been conducted to investigate its effects on sexual performance. In terms of libido, enhancement of copulatory behavior after treatment with *Panax ginseng* and *Panax quinquefolium* has been demonstrated in rodent models [12]. Not all varieties of ginseng have shown the advantage of increasing the sex drive in studies, which may have been caused by different components that may or may not increase serum testosterone and luteinizing hormone (LH) levels. *In vitro* studies on neurotransmitters such as dopamine, acetylcholine, and gamma aminobutyric acid (GABA) have also shown an association with ginsenoside [13-16]. Ginsenoside Rb1 treatment increased LH secretion in the anterior pituitary gland of male rats [17].

In terms of ginseng's effects on semen, numerous studies have shown that it improved semen quality in animal models. In

rats, various ginsenosides have shown enhancing effects on sperm count and motility after treatment. Saponins from the cultured root of wild *P. ginseng* showed effects on spermatogenesis in male rats [18]. In the study, the researchers administered *P. ginseng* powder orally after inducing oligospermia in rats using dioxin and examined the sperm count and testes histologically. The *P. ginseng* saponin revived spermatogenesis in their study, suggesting its possible role in reversing the damage. In previous studies, ginseng-treated rats have shown increased spermatogenesis by increasing the glial cell-derived neurotrophic factor (GDNF) expression in Sertoli cells [19] and testicular cyclic adenosine monophosphate (cAMP)-responsive element modulator (CREM) [20]. GDNF is known to be a possible regulating factor of the lifespan of spermatogonial cells, and CREM is an essential factor for spermatid maturation. An animal study using *P. ginseng* showed sperm hyperactivation at the genetic level, suggesting possible improvement of sperm quality [21]. In rat models of induced genito-urinary inflammation such as epididymo-orchitis and prostatitis, Korean Red ginseng (KRG) enhanced the anti-infective effects when it was administered with antibiotics. In addition, it increased sperm motility while decreasing apoptosis in testicular tissue and stimulating the yield of normal spermatozoa [22,23]. In their study performed in rats treated with cyclophosphamide and ginseng, Akram et al. [24] showed possible gonadoprotective effects of ginseng. They suggested that the possible protective role may be related to a ginseng-induced decrease in reactive oxygen species.

In human studies, ginseng has shown positive effects on sexual performance in men. In a double-blind, placebo-controlled study involving 45 men with erectile dysfunction, subjects showed an improvement in erectile performance and sexual satisfaction after treatment with KRG for 8 weeks [24]. Moreover, the beneficial effect of KRG on erection in men with erectile dysfunction has been identified in meta-analyses of randomized controlled trials [25]. *In vitro* studies showed increased nitric oxide synthesis in endothelial cells after treatment with ginsenosides [26,27], which has been suggested as a possible underlying mechanism for improving erectile dysfunction. However, although meta-analyses and *in vitro* studies showed the effectiveness of KRG, the exact mechanism remains largely unclear. However, diverse results have been shown in investigations of whether ginseng improves semen quality or not. When human semen was directly treated with ginseng extract *in vitro*, significant changes were observed in the motility and viability of the sperm [28]. In a case-control study, treatment with *P. ginseng* was reported to improve the sperm quality and sex hormone profiles [12]. However, the characteristics of the participants were diverse, and the number of participants was small. Recently, a randomized, double-blinded clinical study performed in 80 men with varicocele has shown significant improvement in semen parameters [29] after treatment with KRG for 12 weeks. However, this study also failed to show any differences in pre- and post-treatment serum hormonal levels.

Under disease conditions such as cancer and diabetes, and in the post-radiation period, ginseng showed improvement of sperm

profiles after treatment of animals exposed to varying degrees of radiation [30] suggesting a future positive role for ginseng in this area. However, most of the data have been obtained from animal studies and not studies in humans. Moreover, there is a lack of knowledge about the effective dose recommended for humans, and studies evaluating the effects of ginseng on infertile couples or patients with male infertility, or pregnancy outcomes are lacking.

Ginseng and Female Fertility

Although a few studies have evaluated the effect of ginseng on the male reproductive system, much fewer studies have been conducted in female subjects. In the few studies conducted thus far, there has been emphasis on polycystic ovary syndrome. Polycystic ovary syndrome (PCOS) or polycystic ovary has been frequently associated with oligo-/anovulation, which causes difficulty in achieving pregnancy. A previous study delineating the changes in the structure of the ovarian theca internal cells following KRG administration in a rat model suggested that KRG possibly stimulated steroid-producing cells [31]. Subsequently, intraperitoneal infusion and oral administration of KRG improved the polycystic ovary morphology, with decreased neuronal growth factor expression in the ovaries, suggesting a possible role of KRG in PCOS [1,32, 33].

A study conducted by Zhu et al. [35] showed the protective effect of American ginseng in premature ovarian failure in rats. They selected molecular markers (PLA2G4A, miR-29a, and miR-144) of ovarian function based on their previous study, and measured mRNA and protein expression as well as prostaglandin E2, LH, follicle-stimulating hormone, and estradiol levels before and after treatment with American ginseng [34,35]. The analysis of transcriptional and protein variations, as well as variations in hormone levels, suggested that American ginseng might have protected the ovaries against failure by regulating prostaglandin biosynthesis, ovulation, and preventing ovarian aging. In contrast, in a previous study, KRG saponins have shown significantly positive effects on oocyte quality in rats, decreasing the proportion of abnormal oocytes [36]. In that study, KRG saponins improved the hormonal profiles of female rats during the ovulatory cycle. Ginsenoside Rb1 significantly decreased preovulatory serum levels of androgens and 17-beta estradiol, and ginseng protopanaxadiol saponins significantly increased postovulatory serum progesterone levels. In addition to improving the oocyte quality, ginsenosides have been shown to stimulate antioxidant enzymes in rat embryos, which may lead to improvements in the quality of embryos [37]. Lee et al. showed a significant increase in mRNA expression levels of glutathione peroxidase after treatment with ginsenoside Rb1, Rc, and Re.

One of the most well-known effects of ginseng may be its role as a complementary medicine in perimenopausal women. A randomized study conducted in 384 Swedish postmenopausal women showed improvement in the quality of life but no improvement in vasomotor symptoms and hormonal profiles [38]. However, a randomized, double-blinded clinical trial conducted using KRG in 72 Korean peri- and post-menopausal women has

shown significant improvements in vasomotor symptoms [39]. Moreover, in that study, KRG showed favorable changes in the markers of cardiovascular diseases, such as total cholesterol, low-density lipoprotein cholesterol, and carotid intima-media thickness. Until now, as a complementary medicine, ginseng was thought to mainly have a tonic effect, possibly improving vasomotor symptoms in postmenopausal women.

Ginseng and Pregnancy Outcome

The first report of the effects of ginseng on pregnancy outcome was published in 1990: it was a case report of neonatal androgenization with a mother who had used Siberian ginseng constantly during pregnancy to early breastfeeding [40]. In China, a study group reported the possible beneficial effect of ginseng use during pregnancy in mothers showing fetal intrauterine growth restriction. However, the case-control study was composed of a small number of participants [41]. Few studies have evaluated the effect or toxicities of ginseng since the early 1990s.

The investigation of the effect of ginseng on embryos has been focused on ginseng's antioxidative activity and potential teratogenicity. Because of ethical limitations, studies cannot be performed on human embryos and have only been performed in animals. The antioxidant effect of ginseng has been evaluated in alcohol-induced toxicity during pregnancy. For example, in embryo cultures of Japanese ricefish, co-culturing with *P. ginseng* has been shown to improve the effects of ethanol toxicity [42]. Black ginseng has been shown to recover antioxidant enzyme levels and inhibit teratogenesis induced by ethanol in mouse embryo cultures [43]. However, despite the positive effects of ginseng, concerns have been raised over potential teratogenicity. Although no unfavorable effects on neonates of mothers who had consumed ginseng during pregnancy were noticed in a large birth cohort data [44] ginsenoside Rg1 has been proven to be embryotoxic in rat and mouse embryo developmental models [45]. Although ginseng has possible benefits for assisted reproductive technology or pregnancy, the available data on whether ginseng has positive or negative effects on embryonic development are limited.

Conclusion

Although ginseng is one of the most popular herbs consumed globally and specifically believed to have antifatigue, immunological, hormonal, and tonic effects, not many studies have been performed to investigate its reproductive effects. Considering the possible effects of ginseng on the hormone profiles of male and female subjects and its antioxidant property, further investigations of its application in reproductive medicine is expected.

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