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Original Article

Effects of tissue-cultured mountain ginseng (*Panax ginseng* CA Meyer) extract on male patients with erectile dysfunction

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Abstract

Korean ginseng and mountain ginseng (*Panax ginseng* CA Meyer) are important traditional herbal plants whose ginsenosides are generally accepted as serving to improve sexual functions, such as penile erection. We investigated the effects of tissue-cultured mountain ginseng extract (TMGE) on male patients with erectile dysfunction (ED). A double-blind, placebo-controlled study was conducted with 143 patients experiencing ED. Over the course of 8 weeks, one group took 1 000 mg of TMGE twice a day, and the other group took 1 000 mg of placebo twice a day. The effects of the TMGE and the placebo were analyzed using the Korean version of the International Index of Erectile Function (IIEF) questionnaire. A total of 86 patients completed 8 weeks of treatment. The scores on the five domains of the IIEF after medication were significantly higher than the baseline scores in the group treated with TMGE ($P < 0.05$), whereas no significant improvement was observed in the placebo group ($P > 0.05$). Erectile function and overall satisfaction scores after medication were significantly higher in the TMGE group than in the placebo group ($P < 0.05$). Erectile function of patients in the TMGE-treated group significantly improved, suggesting that TMGE could be utilized for improving erectile function in male patients.

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1 Introduction

Recent epidemiological studies have shown higher frequencies of erectile dysfunction (ED) compared with earlier reports [1]. The first line of treatment is oral medication therapy; specifically, 5-phosphodiesterase (PDE) inhibitors such as sildenafil, tadalafil and vardenafil are generally prescribed by urologists to treat ED [2, 3]. Although earlier studies showed strong efficacy of 5-PDE inhibitors in ED irrespective of etiology, phytotherapies have recently been given more attention as natural alternatives to synthetic pharmaceuticals and have become more widely available. Many patients with ED prefer phytotherapies. Korean ginseng (*Panax ginseng* CA

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Meyer) is effective in the treatment of male ED and has been used as an alternative medication [4–6]. In a review of red ginseng-based treatment of ED, Jang *et al*. [7] reported that randomized clinical studies have suggested therapeutic efficacy for red ginseng, but these studies typically do not have high methodological quality. Well-controlled clinical studies of Korean mountain ginseng have thus far not been performed, except for a preliminary report that claimed an effect of mountain ginseng extract on male ED [8]. Kim *et al*. [8] suggested that mountain ginseng extract could be another candidate for treatment of ED. In this preliminary study, all patients took 1 g of mountain ginseng extract twice a day for 12 weeks. Kim *et al*. [8] only analyzed the five-item version of the International Index of Erectile Function (IIEF-5) when comparing mountain ginseng extract with a placebo. In our study, we planned to use the same mountain ginseng extract and placebo that were administered in the preliminary study by Kim *et al*. [8]. It is difficult to clinically apply wild Korean mountain ginseng because of its scarcity and high cost. Recent advances in plant biotechnology have made it possible to produce mountain ginseng extracts on a large scale using adventitious root cultures in bioreactors [9]. In this study, we investigated the effects of mountain ginseng on male patients with ED using tissue-cultured mountain ginseng extract (TMGE).

2 Materials and methods

A total of 143 patients participated in this study. The patients were selected from the Outpatient Departments of Kyung Hee University, East-West Neo Medical Center (Seoul, Korea). ED was defined as difficulty in acquiring and maintaining an erection for normal intercourse. We estimated the patients' status of ED using the Korean version of the IIEF questionnaire. Selection criteria included having a total IIEF score under 51, no allergy to ginseng and no acute illness. All patients consented to the purpose of the study and to the study itself after explanation. Informed consent was obtained from each subject, and the study was approved by the Institutional Review Board of Kyung Hee University, East-West Neo Medical Center. Patients with severe neurological disorders such as spinal cord injury and multiple sclerosis, or with a history of radical prostatectomy, genital anomaly or drug abuse were excluded from the study. The 143 patients selected were randomly divided into two groups, one receiving TMGE and the other receiving a placebo. The TMGE group comprised 75 men; whereas the placebo group contained 68 men. The TMGE and placebo were supplied by the Research Center for the Development of Advanced Horticultural Technology, Chungbuk National University (Cheongju, Korea), where large-scale cultures of mountain ginseng adventitious roots have been developed. TMGE was approved by the Korean Food & Drug Administration (KFDA) in 2003. The major ingredients of the placebo were Avicel 101 (45.31%), lactose 95 (45.31%) and ginseng aroma powder (1.81%). The minor ingredients of the placebo were glucose anhydrocrystalline (4.53%), green color from Gardenia jasminoides (1.36%), monascus color (0.72%), magnesium stearate (0.91%) and enzymatically modified stevia glucosyl stevia (0.05%). All patients gave a complete history and underwent physical examinations. In addition, the levels of various serum molecules, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were measured. Testosterone (analytical sensitivity, 0.04 ng mL^{-1}; normal range, 3–10 ng mL^{-1}), estradiol (analytical sensitivity, 8 pg mL^{-1}; normal range, 0–44 pg mL^{-1}), prolactin (analytical sensitivity, 0.5 g mL^{-1}; normal range, 1–18 ng mL^{-1}), follicle-stimulating hormone (FSH) (analytical sensitivity, 0.2 mIU mL^{-1}; normal range, 1.3–11.5 mIU mL^{-1}) and luteinizing hormone (LH) (analytical sensitivity, < 0.2 mIU mL^{-1}; normal range, 0.5–10 mIU mL^{-1}) were also measured using radioimmunoassays. The daily dose of TMGE was established in the preliminary study conducted by Kim *et al*. [8]; more recently, Mahady *et al*. [10] suggested that a safe and effective dose of Korean red ginseng is 0.5–2 g per day. We used this range when determining the daily dose of TMGE for our study. Many earlier studies applied ginseng or red ginseng treatment for 4–12 weeks [7]. The duration of treatment within the preliminary study conducted by Kim *et al*. [8] was 12 weeks. As there was no definitive reference for treatment duration, we analyzed the preliminary study conducted by Kim *et al*. [8] and concluded that 8 weeks of medication with mountain ginseng extract should be sufficient to identify an effect in patients with ED. Thus, medications were distributed for 8 weeks using a double-blind method. Patients in the TMGE group took 1 000 mg TMGE twice a day in the morning and evening, and patients in the placebo group took 1 000 mg placebo in the morning and evening. Patients visited the hospital on

weeks 4 and 8 in order to be checked for effects of the medication, including changes in erectile function and sexual satisfaction. All data were analyzed using SPSS software (version 12.0). Paired *t*-test, Mann-Whitney test and Pearson correlation test were used to analyze the differences. Unpaired *t*-test was also used to analyze some variables. Statistical significance was accepted for $P < 0.05$.

3 Results

Sixty-five patients in the TMGE group completed 8 weeks of medication. Three patients stopped taking the medication because of minor headaches; these patients were included among the 10 treated patients who dropped out. Of the 68 patients in the placebo group, only 21 completed the study. Most patients who dropped out of the study saw no improvement in their erectile function or sexual satisfaction. One reason for the high drop-out rate in the placebo group might be that many patients in this group wanted to experience a faster response to the drug; however, we could not confirm that this was a major factor. Our final results were influenced by the much smaller size of the placebo group compared with the TMGE group at the end of the study. We did not use any artificial methods to select the patients. The mean age of the patients was 58.1 ± 1.1 (33–79) years, and the ages of the most of the patients were close to the mean age. The mean age of the TMGE group was 57.51 ± 1.24 years and that of the placebo group was 60.19 ± 2.02 years. There were no statistically significant differences in age across the groups ($P = 0.279$). The number of patients with accompanying cardiovascular disorders (including hypertension), diabetes mellitus, hyperlipidemia and benign prostate hyperplasia (BPH) are shown in Table 1. No patient in either group showed abnormal testosterone, prolactin or estradiol levels before medication ($P > 0.05$). The total IIEF and the five IIEF domain scores showed no significant differences between the two groups before administration of medication ($P > 0.05$). After 8 weeks, the total IIEF score of the TMGE group had significantly increased from 29.78 ± 13.14 to 39.86 ± 15.29 ($P < 0.001$). Domain scores for erectile function, orgasmic function and sexual desire also significantly increased from 11.89 ± 5.89, 4.09 ± 2.49 and 4.32 ± 1.59 to 16.37 ± 7.08, 5.32 ± 2.74 and 5.58 ± 2.03, respectively ($P < 0.001$, $P = 0.008$, $P < 0.001$) (Table 2). The total IIEF score in the placebo group increased from 29.71 ± 10.58 to 33.33 ± 10.17 after 8 weeks of medication, but this difference was not statistically significant. No significant changes were observed in the domain scores for erectile function, orgasmic function or sexual desire in the placebo group ($P > 0.05$ for all three scores). In the TMGE group, the scores for sexual intercourse satisfaction and overall satisfaction after 8 weeks were 6.83 ± 2.95 and 5.74 ± 1.93, respectively, which were higher than the scores before medication ($P = 0.001$ for both). In the placebo group, the sexual intercourse satisfaction and overall satisfaction scores also increased, but without statistical significance ($P = 0.859$ and $P = 0.106$, respectively) (Table 2). After TMGE and placebo medication, erectile function, intercourse satisfaction and overall satisfaction scores in the five domains of the IIEF were significantly higher in the TMGE group than in the placebo group ($P < 0.05$) (Table 3). The levels of testosterone in the TMGE group were higher than those before medication, but the increase was not statistically significant ($P = 0.076$). Levels of FSH, LH, prolactin and estradiol did not change significantly in either group ($P > 0.05$) (Table 4), nor did the levels of several serum markers after medication ($P > 0.05$).

Table 1. Medical characteristics of patients with erectile dysfunction.

	Number of patients (%)
Total	86
Hypertension	15 (17)
Diabetes mellitus	19 (22)
Hyperlipidemia	16 (19)
Benign prostate hyperplasia	21 (24)

4 Discussion

Medical treatment is the most common solution to ED; 5-PDE inhibitors are commonly used as an initial treatment [2, 3]. ED is an important aspect of sexual dysfunction, and occasionally male patients with sexual dysfunction are treated with multi-drug treatment and psychotherapy. Ginseng has been widely used as a medicine throughout Asia and as an ingredient in health food in Korea. Ginsenosides, the primary active compounds in ginseng, have cardioprotective, immunostimulatory, anti-fatigue and hepatoprotective physiological and pharmacological effects [11–13]. In this study, significantly increased total IIEF scores and scores in five IIEF domains were detected in the TMGE-treated patient group compared with the placebo-treated

Table 2. IIEF scores of the TMGE-treated group and the placebo-treated group.

Group (*n*)	Pre-medication (Mean ± sd)	Post-medication (Mean ± sd)	*P*-value
Total IIEF			
TMGE (65)	29.78 ± 13.14	39.86 ± 15.29	< 0.00
Placebo (21)	29.71 ± 10.58	33.33 ± 10.17	0.242
EF domain			
TMGE (65)	11.89 ± 5.89	16.37 ± 7.08	< 0.00
Placebo (21)	11.38 ± 4.78	13.05 ± 4.27	0.390
OF domain			
TMGE (65)	4.09 ± 2.49	5.32 ± 2.74	0.008*
Placebo (21)	4.38 ± 1.47	5.00 ± 1.76	0.199
SD domain			
TMGE (65)	4.32 ± 1.59	5.58 ± 2.03	< 0.00
Placebo (21)	4.33 ± 1.68	4.67 ± 1.62	0.411
IS domain			
TMGE (65)	5.12 ± 2.93	6.83 ± 2.95	0.001*
Placebo (21)	5.57 ± 2.7	15.81 ± 2.54	0.859
OS domain			
TMGE (65)	4.29 ± 1.89	5.74 ± 1.93	< 0.00*
Placebo (21)	4.05 ± 1.32	4.81 ± 1.44	0.106
IIEF-5			
TMGE (65)	11.02 ± 5.08	15.34 ± 6.13	< 0.00*
Placebo (21)	11.95 ± 4.44	13.52 ± 4.46	0.471

Abbreviations: EF, erectile function; IIEF-5, the five-item version of the International Index of Erectile Function; IS, intercourse satisfaction; OF, orgasmic function; OS, overall satisfaction; sd, standard deviation; SD, sexual desire; TMGE, tissue-cultured mountain ginseng extract. *Statistical significance was tested using the paired *t*-test and the Mann-Whitney test.

Table 3. Log-scaled IIEF scores of the TMGE-treated group and the placebo-treated group after 8 weeks of medication.

	TMGE group (Mean ± sd)	Placebo group (Mean ± sd)	*P*-value
Total IIEF	3.57 ± 0.55	3.46 ± 0.34	0.029*
EF domain	2.65 ± 0.64	2.50 ± 0.41	0.018*
OF domain	1.64 ± 0.52	1.52 ± 0.48	0.181
SD domain	1.64 ± 0.45	1.46 ± 0.47	0.068
IS domain	1.94 ± 0.41	1.66 ± 0.46	0.012*
OS domain	1.67 ± 0.44	1.53 ± 0.30	0.018*
IIEF-5	2.60 ± 0.60	2.54 ± 0.38	0.062

Abbreviations: EF, erectile function; IIEF-5, the five-item version of the International Index of Erectile Function; IS, intercourse satisfaction; OF, orgasmic function; OS, overall satisfaction; sd, standard deviation; SD, sexual desire; TMGE, tissue-cultured mountain ginseng extract.
*Statistical significance was determined using the Mann-Whitney test. Mean ± sd indicate log-scaled scores of IIEF.

Table 4. Estimates of serum hormonal levels in the TMGE group and placebo group.

Group (*n*)	Pre-medication (Mean ± sd)	Post-medication (Mean ± sd)	*P*-value
Testosterone (ng mL^{-1})			
TMGE (49)	4.22 ± 1.17	4.74 ± 1.64	0.076
Placebo (21)	4.02 ± 0.87	4.21 ± 1.78	0.649
LH (mIU mL^{-1})			
TMGE (39)	4.25 ± 0.38	4.19 ± 0.40	0.690
Placebo (16)	3.72 ± 0.61	3.60 ± 0.73	0.963
FSH (mIU mL^{-1})			
TMGE (32)	5.37 ± 0.67	6.65 ± 1.30	0.783
Placebo (10)	3.37 ± 0.76	2.20 ± 0.70	0.329
Prolactin (ng mL^{-1})			
TMGE (43)	10.09 ± 0.88	13.94 ± 2.47	0.095
Placebo (16)	10.43 ± 1.88	11.11 ± 2.60	0.763
Estradiol (pg mL^{-1})			
TMGE (38)	30.35 ± 1.59	29.67 ± 1.47	0.893
Placebo(11)	33.54 ± 3.31	33.68 ± 4.42	0.821

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone; sd, standard deviation; TMGE, tissue-cultured mountain ginseng extract.

patient group. These results suggest that TMGE can improve erectile function in patients with ED. The degree of improvement in the Korean version of the IIEF questionnaire was not correlated with patient age, total IIEF score or the score in each IIEF domain before TMGE treatment ($P > 0.05$). Thus, TMGE might improve ED regardless of age and severity of disease. It is generally known that nitric oxide (NO) plays an important role in penile erection by relaxing cavernosal smooth muscle cells. Ginsenosides increase NO synthesis and play an important role as antioxidants [14, 15]. We speculate that the ginsenosides in TMGE caused the increase in total IIEF scores and its five domains. Guan *et al*. [16] reported that the ginsenoside-Rb of Panax notoginseng blocks calcium influx through store-operated calcium channels and receptors in vascular smooth muscle cells. On chemical testing, TMGE showed a higher concentration of ginsenoside-Rb than ginseng and red ginseng [17]. If ginsenoside-Rb has the activity to block calcium influx in vascular smooth muscle cells, then TMGE might be still more effective in improving erectile function than ginseng and red ginseng. The IIEF score of patients with ED was increased after medication with Korean red ginseng, but penile blood flow did not increase on penile Doppler

ultrasonography after intracavernous injection of a vasoactive mixture [5]. We did not compare penile tumescence with penile rigidity, but various factors, including ginsenosides, increase NO synthesis, function as antioxidants and block calcium influx, all of which might increase the IIEF score of patients with ED. If we had performed nocturnal tumescence or ultrasound studies, we could have evaluated the mechanism of the observed effects of TMGE. The 5-PDE inhibitors have a minimal effect on orgasm, sexual desire and intercourse satisfaction, given their mechanism of action. It is likely that sexual dysfunction involves aberrations of normal mechanisms that regulate erection, orgasm and ejaculation; these factors are often associated with lower levels of satisfaction with sexual behaviour. The role of 5-PDE inhibitors is to induce erections by enhancing the relaxation of cavernosal smooth muscle cells. This action is localized to cavernous smooth muscle cells, rather than being systemic. In intracavernous and transurethral injection therapy using PGE1, alprostadil also shows local action. Ali *et al*. [18] reported that ginseng induces lipid peroxidation and activation of antioxidative systems, suggesting that ginseng contributes to erectile function through systemic rather than peripheral, localized effects. We have hypothesized that such a general elevation of body function is important for the beneficial effects on erectile function observed with TMGE. Apomorphine is a representative drug that acts on the central nervous system, specifically on dopamine receptors, and induces neurotransmission, which results in erection. No drugs used thus far for treatment of ED have shown simultaneous effects on the peripheral and central nervous systems. Ginsenosides have various effects on the central nervous system that are related to various neurotransmitters, including Gamma-Aminobutyric Acid (GABA), glutamate, dopamine, noradrenaline and serotonin [19–21]. In this study, TMGE significantly increased the scores of erectile function, intercourse satisfaction and overall satisfaction on the IIEF questionnaire ($P < 0.05$). TMGE might thus have positive effects on the central nervous system, overall well-being and general state of health in male patients with ED. After taking the medication, patients in the TMGE group showed increased testosterone levels, although the changes were not statistically significant. TMGE also appeared to enhance the patients' overall sense of well-being.

This study suggests that TMGE could be an effective complementary agent for improving erectile function in male patients. The reasons for the efficacy of TMGE in patients with ED are still unclear. Further *in vitro* studies are necessary for mechanistic analysis.

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