Effect of HTE001, an Herbal Formulation, on Electric Stimulation-induced Penile Erection in Rats

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ABSTRACT

Objectives: This study was conducted to investigate the effect of HTE001, a multi-herbal mixture consisting of 10 herbs, Cornus Frutus, Schizandrae Fructus, Rhu Fructus, Cnidi Fructus, Acanthopanacis senticosi Radix, Cinnamomi Cortex, Eucommiae Cortex, Allii Bulbus, Rehmanniae Radix and Ginseng Radix, on electrostimulation-induced penile erection in rats.

Methods: Intracavernous pressure (ICP) and mean arterial blood pressure (MAP) were simultaneously monitored through electric stimulation of the cavernous nerve after the oral administration of HTE001 (30, 100, 300 mg/kg) in normal rats. Statistical analysis was performed on maximal intracavernous pressure (ICP), maximal intracavernous pressure/mean arterial blood pressure (ICP/MAP) ratio, and the area under the curve (AUC) of ICP/MAP ratio.

Results: Oral administration of HTE001 300 mg/kg caused the ICP to increase in a frequency-dependent manner. And HTE001 300 mg/kg treatment group showed the highest value in the ICP/MAP ratio and the AUC value of the ICP/MAP ratio compared to the control group at 2 Hz, 6 Hz and 10 Hz, respectively without an effect on the mean arterial blood pressure under the same stimulation of the cavernous nerve.

Conclusions: These results show that HTE001 improve penile erection and prolong the decay period in normal rats without affecting mean arterial blood pressure, and suggest that HTE001 could be a good therapeutic candidate to treat erectile dysfunction.

Key words: HTE001, erectile function, intracavernous pressure, cavernous nerve stimulation, rat

Introduction

Sexual relationships are some of the most important social and biological relationships in human life. Next to hunger, thirst and sleep, the sexual urge is the most powerful biological drive⁴. Sexual dysfunction is a
common disease with an increasing incidence as a result of longer lifespan, the increasing prevalence of degenerative diseases as well as the increase in injuries and stress associated with industrialized lifestyles\(^2\). Sexual dysfunction is reported to occur in 10–52% of men and in 25–63% of women. Men age 40–70 years are found to have 34.8% of moderate to erectile dysfunction (ED)\(^9\). ED occurrence is highly correlated with aging, and aging of the global population will result in a substantial increase in the number of men with ED in the future\(^4\). Analysis of an aging study showed that the incidence rate of ED rises from 1.2% per year for men aged between 40 years and 49 years to 4.6% for men aged between 60 years and 69 years\(^6\). Since the elderly population is growing markedly, the number of men worldwide with ED is estimated to be 322 million by 2025\(^4\). In Korea, the prevalence of ED was reported to be 11.8%, and that of moderate of ED was 84.3%, which demonstrates that most Korean men over 40 years of age have some form of ED\(^5\).

In recent years, there has been renewed activity in the search for traditional herbs to treat ED\(^9\), because traditional herbs are a potential source of natural drugs for therapy against ED\(^10\). In traditional Korean medicine (TKM), male ED usually implies a yang deficiency and thus is called yang-wi (withered yang). Donguibogam, written by Huh, Jun during the 17th century, in particular has much exemplary evidence of treating yang-wi.

HTE001, a multi-herbal mixture consisting of 10 herbs, Cornus officinalis, Schizandra chinensis, Rubus coreanus, Cnidium monnieri, Acanthopanax senticosus, Cinnamomum cassia, Eucommia ulmoides, Allium sativum, Rehmannia glutinosa and Panax ginseng, is used to treat yang-deficiency syndrome in TKM. HTE001 was created after more than 50 herbs were screened based on in vivo data of erectile enhancing effects and on TKM composition theory for treatment of sexual health and problems. Schizandra chinensis has long been used as a traditional medicine for tonic and sedative effects and has contributed to vasorelaxation in the isolated rat thoracic aorta\(^11\). Rubus coreanus has been reported to be increase the level of testosterone in the blood\(^12\). Cornus officinalis has been reported to be increase the levels of RNA in the interstitial cells of the testicle\(^13\). Cnidium monnieri has been used mainly for treatment of male impotence and has contributed to relaxed rabbit corpus cavernosum tissue in vitro\(^14\). Eleutherococcus senticosus has been used as a tonic and adaptogen to strength in TKM\(^15\). Cinnamomum cassia-derived material in nitric oxide (NO) production in RAW 264.7 cells was determined through the evaluation of NO production\(^16\). Eucommia ulmoides increased the expression of nNOS in penile tissue and enhanced the erectile function of diabetic rats\(^17\). Allium scorodoprasum has been used mainly as an anti-fatigue agent in many countries\(^18\). Rehmannia glutinosa has been widely used in Asian countries for the treatment of renal diseases\(^19\). Panax ginseng has been used as a tonic and restorative to maintain physical vitality and showed a dose-related relaxing effect on the isolated rabbit corporal smooth muscle strip\(^20\).

In the present study, we investigated the effect of HTE001 on electrical stimulation-induced penile erection in the normal rat model. ICP and MAP were simultaneously monitored through electric stimulation of the cavernous nerve, before and after oral administration of HTE001.

### Material and methods

#### 1. Preparation of HTE001

All herbs were purchased from Omni Herb, Daegu, Korea. HTE001 was identified by Professor Dr. Hocheol Kim, and a voucher specimen has been deposited at the Department of Herbal Pharmacology. HTE001 consists of 10 herbs. The composition is Cornus officinalis (18.18%), Schizandra chinensis (9.09%), Rubus coreanus (9.09%), Cnidium monnieri (4.55%), Eleutherococcus senticosus (9.09%), Cinnamomum cassia (9.09%), Eucommia ulmoides (4.55%), Allium sativum (18.18%), Panax ginseng (9.09%) and Rehmannia glutinosa (9.09%). HTE001 was extracted by boiling for 6 hr using a 70% ethanol aqueous mixture. The 70% ethanol filtrate was evaporated and dried in vacuum, and then stored at -20°C.

#### 2. Sample administration

HTE001 were suspended in distilled water and administered orally at three different doses of 30, 100 and 300 mg/kg. Sildenafil was suspended in distilled water and administered orally at a dose of 20 mg/kg using a syringe.

#### 3. Surgical preparation

All surgical procedures were conducted according to