

In Vivo and in Vitro Animal Investigation of the Effect of a Mixture of Herbal Extracts from *Tribulus terrestris* and *Cornus officinalis* on Penile Erection

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ABSTRACT

Introduction. Herbal preparations have long been used as folk remedies for erectile dysfunction (ED).

Aim. This study examined the effects of *Tribulus terrestris* and *Cornus officinalis* extracts on relaxation of the smooth muscle of the corpus cavernosum (CC), their mechanisms of action, and the effects of oral administration of a mixture of the herbal extracts on penile erection.

Methods. The relaxation effects and the mechanisms of action of *T. terrestris* extract, *C. officinalis* extract, and the mixture of both extracts on the rabbit CC were investigated in an organ bath. To evaluate whether the relaxation response of the CC shown in an organ bath occurs in vivo, intracavernous pressure (ICP) was calculated in rats after oral administration for a month. Additionally, adenosine 3',5'-cyclic monophosphate (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP) in the CC were measured using immunoassay.

Main Outcome Measures. Smooth muscle relaxation was expressed as the percent decrease in precontraction induced by phenylephrine. ICP was assessed in rats after the oral administration of a mixture of both extracts for 1 month and changes in cGMP and cAMP concentrations were measured based on the concentration of the mixture of both extracts.

Results. *T. terrestris* extract, *C. officinalis* extract, and the mixture of both extracts showed concentration-dependent relaxation effects of the CC. In both the endothelium-removed group and N(G)-nitro-L-arginine methyl ester pretreatment group, *T. terrestris* extract inhibited relaxation. ICP measured after oral administration of the extract mixture for a month was higher than that measured in the control group, and a significant increase in cAMP was observed in the mixture group.

Conclusions. *T. terrestris* extract and *C. officinalis* extract exhibited concentration-dependent relaxation in an organ bath. In the in vivo study of the extract mixture, ICP and cAMP was significantly potentiated. Accordingly, the mixture of *T. terrestris* extract and *C. officinalis* extract may improve erectile function. **Kam SC, Do JM, Choi JH, Jeon BT, Roh GS, and Hyun JS. In vivo and in vitro animal investigation of the effect of a mixture of herbal extracts from *Tribulus terrestris* and *Cornus officinalis* on penile erection. J Sex Med 2012;9:2544–2551.**

Key Words. *Tribulus terrestris*; *Cornus officinalis*; Erection; Penis; Herbal Preparations

Introduction

Erectile dysfunction (ED) is one of the most common male sexual disorders. The prevalence rate of ED reportedly increases with age. One study reported that about 40% of men experience ED at 40 years of age, and the rate increases up to approximately 67% at ages beyond 70 years

[1]. The prevalence rate of ED is very high, and ED influences not only sexual behaviors but also human relationships and social activities [2]. Additionally, according to a recent study, ED is associated with the development of cardiovascular diseases and dysfunction of the endothelium in blood vessels, highlighting the importance of diagnosing sexual disorders including ED [3]. In the

past, ED was considered to be a complication of chronic diseases such as hypertension, cardiovascular diseases, or diabetes. However, many recent epidemiologic surveys have shown that ED can be a marker of cardiovascular diseases [4–6].

Phosphodiesterase type (PDE)-5 inhibitors, a new therapy for ED, have adverse effects such as visual disorders, headaches, facial flushing, rhinitis, and dyspepsia [7]. Thus, medications with fewer adverse effects and better efficacy are being developed. Moreover, studies on herbal extracts are being conducted in many research centers.

For a long time, herbal preparations such as extracts of ginseng, *Tribulus terrestris*, *Ferula hermonis*, *Epimedium brevicornum*, *Cinnamomum cassia*, *C. officinalis*, and *Lepidium meyenii*, have been utilized as folk remedies to treat ED [8–13]. The increasing interest in herbal medicine prompted studies on the clinical effects of ginseng or red ginseng [14,15]. However, laboratory data on the effects and mechanisms of action of these herbs are not sufficient.

We have carried out many preliminary experiments using various herbs [16–18]. Among various herbal preparations, we selected the two most effective herbal preparations, *T. terrestris* and *C. officinalis*. *T. terrestris* and *C. officinalis* are widely known and have been used as sexual function tonifiers. The action mechanisms of herbs are very diverse and, sometimes, combinations of herbal preparations can be expected complementary or synergistic effects.

Aims

In this study, the relaxation effects and mechanisms of action of *T. terrestris* and *C. officinalis* extracts were investigated. The erectogenic effects of oral administration of these extracts were also examined.

Materials and Methods

Organ Bath Study of the Corpus Cavernosum (CC)

New Zealand white male rabbits weighing 2.5–3.0 kg, eight animals per group, were used (Hanasangsa, Busan, South Korea). All of the animals were cared for in accordance with the National Research Council publication *Guide for Care and Use of Laboratory Animals*. The animal experiments were approved by the Institutional Animal Care and Use Committee of the Research Institute at Gyeongsang National University. The rabbits

were sacrificed by an overdose of ketamine hydrochloride (50 mg/kg) injected into the marginal vein of the ear, the penis was dissected immediately, and $2 \times 2 \times 10$ -mm sections of the CC were prepared. CC sections were transferred to an organ bath; one end was connected to a muscle fixation ring and the other end was connected to an isometric tension transducer (SG-10, Physilab Co., Busan, Korea). CC sections were connected to a force displacement transducer (TSD 125C, Biopac Inc., Goleta, CA, USA), which is an isometric tension transformer, and the signals were recorded on a personal computer using a four-channel data acquisition and analysis system for Windows (MP36R 4-Channel Systems, Biopac Inc.). The signals were relayed to a physiography instrument (PowerLab, ADI Instruments, Sydney, NSW, Australia) and measured. Chart 5 software (ADI Instruments) was used for real-time monitoring of tension. Krebs–Henseleit (KH) solution was used for the organ bath at 37°C and pH 7.4 and gassed continuously with 95% O₂/5% CO₂. When the initial tension of each section was maintained at approximately 2 g, the KH solution was changed approximately every 30 minutes (total equilibration period: 2 hours) and allowed to reach a stable condition. Once a stable condition was reached, phenylephrine (PE) was added, and the contraction level was observed. Each section was progressively stretched to the optimal point on its length–tension curve as determined by the active tension developed to PE. Afterward, a stable condition was restored by washing the preparation with KH solution three more times. These steps were repeated, and contracture within $100 \pm 10\%$ of the previous contraction was defined as the ideal resting optimal isometric tension. While maintaining resting optimal isometric tension, tissues were contracted by pretreatment with PE (5×10^{-6} M) within the bath; *T. terrestris* extract, *C. officinalis* extract, and a mixture of both extracts in fivefold dilutions from 0.25 mg/mL to 4 mg/mL was added, and the relaxation level were assessed by observing the change in the tension curve. *T. terrestris* extracts and *C. officinalis* extracts were dissolved in dimethyl sulfoxide (DMSO) diluted with saline. The final concentration of DMSO was less than 0.04%. Neither DMSO nor saline in the final organ bath concentrations had a significant effect on the relaxations of CC. Mixtures of both extracts were set at six different ratios: *T. terrestris* extract vs. *C. officinalis* extract—100%:0%, 90%:10%, 80%:20%, 70%:30%, 60%:40%, and 0%:100%. *T. terrestris* and *C. offi-*

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