



# Current Status and Clinical Studies of Oriental Herbs in Sexual Medicine in Korea

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Erectile dysfunction (ED) is one of the most common diseases among aging men. Although previous studies have shown that type 5 phosphodiesterase inhibitors (PDE5-Is) are very effective for the treatment of ED, many researchers are currently attempting to identify therapeutic agents from natural sources with comparable or better effects than PDE5-Is. Herbal medicine is thought to be advantageous because it is natural; moreover, it not only treats isolated symptoms, but also maintains general well-being. Furthermore, since newly created chemical compound libraries have limited structural diversity with regard to pharmaceutical agents, more attention has recently been paid to the ability of oriental herbs to enhance physical health, including sexual function. Herein, we review the current status of Korean preclinical or clinical studies of the application of oriental herbs to sexual medicine.

**Key Words:** Erectile dysfunction; Herbal medicine; Medicine, East Asian traditional; Reproductive health

## INTRODUCTION

Between 30% and 50% of the adult population in industrialized nations use some form of complementary and alternative medicine to prevent or treat a variety of health-related problems [1,2]. Asian countries, and Korea in particular, have a long history of herbal and complementary medicine. The prescription of herbal medicine is regulated by the Korean Food and Drug Administration. Herbal medicine and complementary medicine utilize a range of fruits and vegetables, acupuncture, and mox-

ibustion to treat a variety of conditions, and the use of those materials remains an important field of medical activity in Korea. The public consumption of functional foods has been tracked by the Korean Food and Drug Administration. The Korean government also regulates functional foods. Sales of over-the-counter functional foods are thought to currently be approaching 770 million dollars [2]. Men who suffer sexual dysfunction or women who have a husband with erectile dysfunction (ED) are particularly interested in the use of herbal or complementary medicine. They believe that treatments drawn

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from herbal and complementary medicine are more natural and not only treat isolated symptoms, but also maintain general well-being. Herbal medicine provides general health benefits beyond those related to ED. Doctors of herbal medicine have treated ED patients with herbal medicines such as Korean fresh ginseng, Korean white ginseng, Korean red ginseng (KRG), *Gingko biloba*, *Rubus coreanus*, *Schisandra chinensis*, *Epimedium koreaum*, *Lepidium meyenii*, male silkworm extract, *Artemisia capillaris*, *Cuscuta chinensis*, and plant mixtures. The documentation of herbal medicine in Korea dates from the seventeenth-century Donguibogam ('Mirror of Eastern Medicine') written by Huer [3]. Western-style medication results in a quick response, whereas herbal medicine leads to a slower response. Western-style medication is administered as a single agent, but herbal medicine involves a mixture of many kinds of medicines, which have a similar effect and work together additively.

Cocktails of medications have been developed to treat ED and used with patients. These mixtures target different aspects of the mechanism of erection and libido. Natural products provide a valuable and rich pool for the discovery of drug candidates. Trying to discover valuable therapeutic agents from natural sources is also very important at the present time, since libraries of developed chemical compounds for pharmaceutical use are characterized by limited structural diversity [4].

## PHARMACODYNAMICS OF PHYTOCHEMICALS

Herbal plants contain chemical compounds, vitamins, plant hormones, and minerals that are needed for a growing plant. These products protect the plant from noxious environmental stimuli and unavoidable harmful insects. Humans and animals need phytochemical compounds, hormones, vitamins, and active elements to achieve a balanced metabolism for healthy living. The philosophy of using herbal medicine is to adopt and imitate the natural pharmacodynamic action that is already within the plant. Purifying phytochemicals to a single agent would be similar to the production of a synthetic chemical [5]. Western-style medication may not address the totality of the disease in ED, and instead focus on providing an in-

stant erection. Herbal medicine acts by affecting dynamic, interactive, and complicated processes. Therefore, the purification of herbal medicine sometimes weakens or eliminates its effectiveness, compared to the original phytochemicals or mixtures of herbs.

## TYPES OF HERBAL MEDICINE USED TO TREAT ELECTILE DYSFUNCTION

### 1. Korean ginseng

Ginseng has been an essential herb in traditional Chinese medicine for many years. Ginseng cultivated in Korea is divided into three types, depending on how it is processed. Fresh ginseng is less than four years old, white ginseng is four to six years old and dried after peeling, and red ginseng is harvested when it is six years old, steamed, and dried [6]. Traditionally, ginseng has been used to restore and enhance the normal well-being of the body. The effects of ginseng are due to its reactions with the central nervous system, metabolism, immune function, and cardiovascular system. The principal active compounds in ginseng are ginsenosides, which are triterpene saponins. Over 20 different ginsenosides have been identified from extracts of the roots, leaves, and seeds of the ginseng plant.

#### 1) Animal studies

Ginseng has been reported to lead to a significant enhancement in copulatory behavior parameters in male rats and mice [7-9]. Oral doses of powdered ginseng root sufficient to alter sexual behavior in male rats were as low as 10 mg/kg, and significant changes in libido were measured within one week of daily oral ginseng treatment [8]. The daily treatment of male mice with an extract of Korean ginseng (25~100 mg/kg, intraperitoneal) or ginsenoside Rg1 (2.5~10 mg/kg, intraperitoneal) produced a dose-dependent increase in the number of mice displaying copulatory behaviors (mounting, intromission, and penis licking). However, ginsenosides Rb1, Rb2, and Ro had no effect in sexual behavior. These data suggest that specific ginsenosides may be responsible for ginseng-mediated effects on copulatory behavior [10]. Sung et al [11] reported the ginsenoside-induced activation of large-conductance KCa channels in human corporal smooth muscle cells. Ginsenoside induces smooth muscle relaxation by hyperpolarizing the smooth muscle membrane via the activa-

tion of large-conductance KCa channels. The researchers suggested that the activation of large-conductance KCa channels by ginsenoside could be one mechanism of ginsenoside-induced relaxation in corporal smooth muscle.

## 2. Korean red ginseng (*Panax ginseng*)

KRG belongs to the Araliaceae family and is grown in Korea and China. KRG is one of the most commonly used ginseng products in Korea, and is sold under many brand names. KRG contains numerous active compounds, the major active ingredients being triterpene saponins known as ginsenosides [12]. The ginsenosides relax the penile smooth muscle through the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway. In this mechanism, KRG increases the production of NO, which leads to improved erectile function and vascular endothelial function. The yield of water extracts of KRG was found to be 4.76% of the yield of 100% ethanol extracts of KRG. The water extract of KRG contains ginsenosides Re, Rf, Rg1, Rg2, Rg3, and other minor ginsenosides and components (Table 1, Fig. 1, 2) [13].

### 1) Animal studies

Laboratory findings have shown that KRG causes a dose-dependent relaxation by increasing the levels of NO in the corpus cavernosum and vaginal smooth muscle of rabbits [14]. Kim et al [15] have recently reported that KRG improved erectile function in a rat model of metabolic syndrome. KRG was found to inhibit fibrosis of the corpus cavernosum of the penis. This result demonstrates that KRG can be used as an alternative medicine to improve metabolic syndrome and to recover erectile function in patients with metabolic syndrome and ED.

### 2) Human studies

In a clinical trial, a therapeutic effect was observed in approximately 60% of the patients taking ginseng, as compared to 30% of the patients in the placebo and drug groups. In randomized clinical studies, KRG has been shown to have beneficial effects for psychogenic ED. KRG has the ability to increase NO levels and to reduce fatigue, insomnia, and depression [16,17]. In another study, treatment for eight weeks with a thrice daily dose of 1,000 mg of oral ginseng significantly improved International Index of Erectile Function (IIEF) scores compared to placebo (ginseng,  $16.4 \pm 2.9$  to  $21.0 \pm 6.3$ ; control,  $17.0 \pm 3.1$  to

$17.7 \pm 5.6$ ). Of the patients, 66.6% reported improved erectile function, meaning that significant improvement was noted for the global efficacy question [18,19].

## 3. Extract of tissue-cultured Korean mountain ginseng

### 1) Human studies

In a human study, treatment with 1 g of an extract of tissue-cultured Korean mountain ginseng twice per day for eight weeks significantly improved IIEF scores from  $29.78 \pm 13.14$  to  $39.86 \pm 15.29$ . The erectile function domain, orgasmic function domain, and sexual desire domain in the tissue-cultured Korean mountain ginseng extract group were significantly improved compared to the placebo group ( $11.89 \pm 5.89$  to  $16.37 \pm 7.08$ ,  $4.09 \pm 2.49$  to  $5.32 \pm 2.74$ ,  $4.32 \pm 1.59$  to  $5.85 \pm 2.03$ , respectively). Minor headaches developed in 4.6% of the patients in the cultured Korean mountain ginseng group (Table 1, Fig. 1, 2) [20].

## 4. *Ginkgo biloba*

*G. biloba*, like ginseng, is mentioned in the traditional Chinese pharmacopoeia. The main indications for *G. biloba* are symptoms of peripheral vascular disease, such as intermittent claudication and, more importantly, cerebral insufficiency. *G. biloba* can improve vascular perfusion, and in a German study, was found to improve chronic cerebrovascular insufficiency [21]. *G. biloba* contains flavonoid glycosides, mainly composed of kaempferol, quercetin isorhamnetin with glucose or rhamnose, and bilobalides, which are the characteristic terpenes of ginkgolides [21]. These have a complicated mechanism of pharmacological action, and improve damage to the vessel walls as well as dysfunction in the tension of blood vessels (Table 1, Fig. 1, 2).

### 1) Animal studies

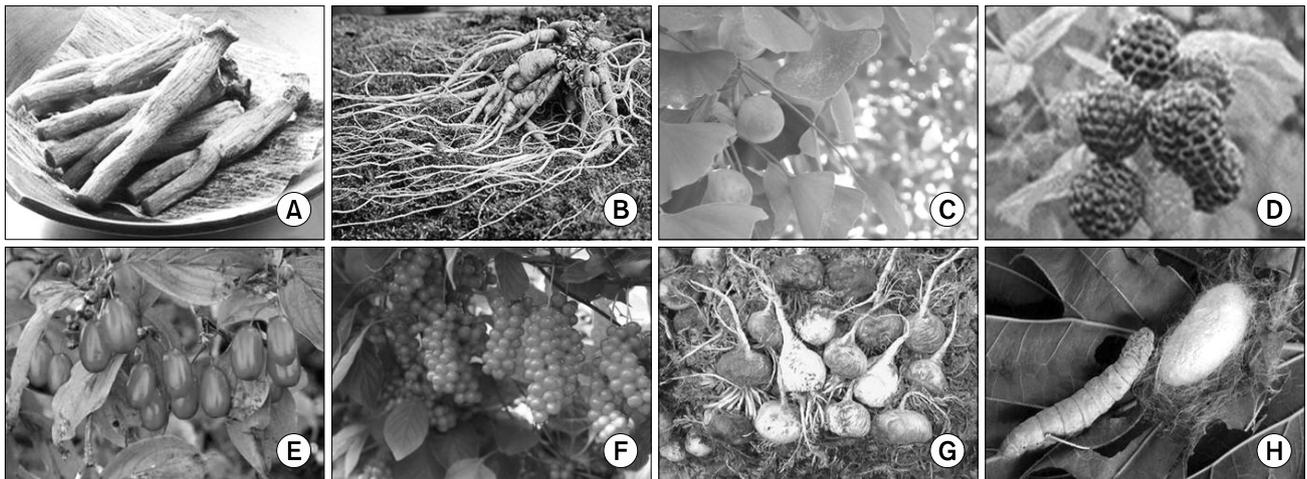
*G. biloba* induced the relaxation of the corpus cavernosum in a dose-dependent manner and also effectively increased the relaxant potency of mirodenafil in rabbit corpus cavernosum tissue, even at the minimal effective dose [22].

### 2) Human studies

In a clinical study evaluating the effects of an extract of *G. biloba* (60 mg for 12 ~ 18 months), blood perfusion was found to improve after six to eight weeks. Of the patients with ED, 50% regained erectile function after six months

**Table 1.** Characteristics of various herbal medicines and mixtures of multiple plants

Scientific name	Substance	Direction	Efficacy	Side effects, contraindications, and areas for caution
Korean red ginseng ( <i>Panax ginseng</i> )	Korean red ginseng root concentrate mixed with <i>Lycium barbarum</i> , <i>Cuscuta chinensis</i> Lam, <i>Rubus coreanus</i> Miq., <i>Torilis japonica</i> fruit, schisandra fruit concentrate	Take 3 tablets after meal with water (adults).	Enhancement of general physical health for men.	Reduce the dosage when symptoms such as fever, skin irritation, indigestion, or chest problems occur.
Korean mountain ginseng	Korean mountain ginseng culture root extract (saponin, 140 mg/g, 0.024%), Korean red ginseng (red ginseng saponin, 70 mg/g, 0.15%), <i>Angelica gigas</i> Nakai, <i>Astragalus membranaceus</i> , fructose	One pack per day (180 mL×6 packs/set).	Enhancement of general physical health for men.	Not stated.
<i>Gingko biloba</i>	<i>Gingko biloba</i> (100%)	Gingko supplements are usually taken in the range of 40~200 mg/d.	Sexual dysfunction, enhancement of general physical health for men.	Gingko may have undesirable effects, especially for individuals with blood circulation disorders and who take antidepressants.
<i>Rubus coreanus</i>	<i>Rubus coreanus</i> (95%), citric acid (3%), and honey (2%)	Take twice a day (morning and evening).	Sexual dysfunction, enhancement of general physical health for men.	Not stated.
<i>Schisandra chinensis</i>	Schisandrol A, schisandrin B, schisandrin C	Take 2~3 times a day at any time (a total of 30~40 pills for adults).	Sexual dysfunction, enhancement of general physical health for men.	Not stated.
<i>Cornus officinalis</i>	<i>Cornus officinalis</i> (49%), <i>Schisandra sinensis</i> , <i>Rubus coreanus</i> , and arginine (1,000 mg)	Take 1~2 times a day at any time (a total of 40 pills for adults).	Sexual dysfunction, enhancement of general physical health for men.	Persons who have high body temperature, sweating, and priapism should not consume this product.
<i>Lepidium meyenii</i>	<i>Lepidium meyenii</i> powder (49.9%), bean powder (6.0%), Adlay powder (6.0%), <i>Polygonum multiflorum</i> powder (5.0%)	Take 3 times a day at any time (1 pill at a time).	Has been used for energy, stamina, athletic performance, impotence, fertility enhancement, aphrodisiac qualities, erectile dysfunction, hormone balancing, and increasing testosterone levels.	Not stated.
Male silkworm extract	Royal jelly (20%), silkworm and cocoon (18.2%), <i>Acanthopanax senticosus</i> (5.6%), <i>Rubus coreanus</i> , and <i>Schisandra chinensis</i> Baillon.	Take 3 times a day at any time (2 pills at a time).	Effective not only in boosting men's vigor, but also in helping to recover from physical exhaustion.	Mild adverse effects such as digestive difficulties, sputum production, temporary chest palpitations, drowsiness, and increased stool frequency.



**Fig. 1.** The raw materials of various herbal medicines and mixtures of multiple plants. (A) Korean red ginseng, (B) Korean mountain ginseng, (C) *Ginkgo biloba*, (D) *Rubus coreanus*, (E) *Cornus officinalis*, (F) *Schisandra chinensis*, (G) *Lepidium meyenii*, (H) male silkworm extract.



**Fig. 2.** Commercial products of various herbal medicines and mixtures of multiple plants. (A) Korean red ginseng, (B) Korean mountain ginseng, (C) *Ginkgo biloba*, (D) *Rubus coreanus*, (E) *Cornus officinalis*, (F) *Lepidium meyenii*, (G) male silkworm extract, (H) SS cream.

of administration [23]. In a clinical study, sexual dysfunction caused by the use of selective serotonin reuptake inhibitor antidepressants improved in 76% of men when 209 mg/day of *G. biloba* was taken for approximately one month. *G. biloba* also improves other aspects of sexual function, including enhanced desire, excitement, orgasm, and resolution [24]. *G. biloba* can produce adverse events, such as bleeding, nausea, headache, gastroenteric upset, diarrhea, and anxiety.

### 5. *Rubus coreanus*

*R. coreanus* is commonly used in the treatment of several diseases in Korea, and grows in the southern part of Korea. The season in which it is harvested is also very important for its efficacy. The dried unripe fruit of *R. coreanus* has been used for centuries as an herbal medicine, meaning that its safety has been proven to some degree. Crude *R. coreanus* is used for the management of impotence, spermatorrhea, enuresis, asthma, and allergic diseases, and it also has been used as a stomachic and ton-

ic in Korea (Table 1, Fig. 1, 2).

### 1) Animal studies

In an animal study, penile corpus cavernosum relaxation was found to be induced by extract of *R. coreanus* in a concentration-dependent manner, and enhanced sildenafil-induced corpus cavernosum relaxation was observed [25]. The perfusion of penile cavernous tissue with unripe *R. coreanus* extract increased cGMP and cyclic adenosine monophosphate (cAMP) levels in the tissue and in the perfusate, as well as the expression of NO synthase in the tissue. The unripe *R. coreanus* extract exerted a relaxing effect on penile cavernous tissue in part by activating the NO-cGMP system, and it may improve cases of ED that do not completely respond to sildenafil citrate [26]. *R. coreanus* acts through endothelium-independent and endothelium-dependent pathways to relax the corpus cavernosum. *R. coreanus* may inhibit voltage-dependent  $\text{Ca}^{2+}$  channels and  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum [26].

## 6. *Schisandra chinensis*

*S. chinensis* is a deciduous woody vine native to the forests of Korea, China, and Russia. Its berries have been used in oriental herbal medicine for ED, enuresis, frequency, spontaneous sweating, night sweats, cough, asthma, sputum, wheezing, jaundice, and diabetes. Additionally, recent pharmacological studies have shown that *S. chinensis* exerts a dose-dependent relaxation effect on vascular smooth muscle, that vascular relaxation was mediated by an endothelium-dependent NO pathway, and that a direct effect was exerted on vascular smooth muscle cells via dephosphorylation of the myosin light chain (Table 1, Fig. 1) [27].

### 1) Animal studies

*S. chinensis* was found to induce concentration-dependent relaxation of contracted corporal smooth muscle tissue, and the removal of the endothelium did not significantly affect its relaxation potency. In corporal smooth muscle cells, the extracellular application of *S. chinensis* significantly increased whole-cell calcium-sensitive  $\text{K}^+$  channel currents (117.4%) and inward rectifier  $\text{K}^+$  channel currents (110.0%). The relaxatory effects of *S. chinensis* on corporal smooth muscle were, in part, due to the activation of  $\text{K}^+$  channels and the inhibition of canonical tran-

sient receptor potential  $\text{Ca}^{2+}$  channel 6, resulting in decreased  $\text{Ca}^{2+}$  [28]. In another study, the effect of the ethanol extract and the active components of the fruit of *S. chinensis* was evaluated on rabbit penile corpus cavernosum. The lignans (schisandrol A and schisandrol B) isolated from the fruits of *S. chinensis* enhanced sildenafil citrate-induced relaxation and may exert a synergistic action in patients who do not completely respond to sildenafil [29].

## 7. *Epimedium koreanum*

*E. koreanum* is used in traditional Korean herbal medicine as a potent enhancer of erectile function. Icariin is the main active component and has many biological effects, such as improving cardiovascular function, hormone regulation, modulation of immunological function, and anti-tumor activity [30].

### 1) Animal studies

In a study of sexual behavior in rats, 300 mg/kg and 750 mg/kg of *E. koreanum* were administered daily for 10 days. The number of acts of intromission increased to  $23.3 \pm 2.6$  in the 300 mg/kg group and to  $20.1 \pm 2.3$  in the 750 mg/kg group. The number of ejaculations per day increased to  $2.6 \pm 0.4$  in the 300 mg/kg group compared with  $1.1 \pm 0.3$  in the placebo group. The latency period of ejaculation was reduced to  $9.8 \pm 1.5$  minutes in the 300 mg/kg group compared with  $14.2 \pm 1.8$  minutes in the placebo group [30].

## 8. *Lepidium meyenii*

*L. meyenii* is a root vegetable cultivated in the central Peruvian Andes that belongs to the brassica family. Dried *L. meyenii* root is rich in amino acids, iodine, iron, and magnesium. Traditionally, it has been administered as an aphrodisiac and/or for its fertility-enhancing properties (Table 1, Fig. 1, 2). In Korea, *L. meyenii* has been used for some time and was recently approved as a supplement to infertility treatment. However, no Korean studies have been performed on *L. meyenii*, so we referred to the results from clinical trials that were performed in other countries [31-33].

### 1) Animal studies

In male mice, the number of intromissions during a three-hour period was  $16.33 \pm 1.78$ ,  $46.67 \pm 2.39$ , and  $67.01 \pm 2.55$  for the control group, M-01 group, and M-02

group, respectively. M-01 and M-02 are the name of purified products of macaene and macamide using in study of Zheng et al [33], and its ingredients and content were not so difference. The latency period of ejaculation of male rats with ED was  $112 \pm 13$  seconds with a regular diet (control group). The oral administration of M-01 at a dose of 180 or 1,800 mg/kg and M-02 at a dose of 45, 180, or 1,800 mg/kg per day for 22 days reduced the latency period of ejaculation to  $54 \pm 12$  seconds,  $54 \pm 13$  seconds,  $71 \pm 12$  seconds,  $73 \pm 12$  seconds, and  $41 \pm 13$  seconds, respectively [33].

## 2) Human studies

In a double-blind clinical trial, a dose of 1,500 or 3,000 mg per day for 12 weeks was found to improve sexual desire compared to placebo [31]. Zenico et al [32] carried out a double-blind clinical trial on 50 Caucasian men affected by mild ED, randomized to treatment with 2400 mg of dry-extracted *L. meyenii* or with a placebo. The effect of this treatment on ED and subjective well-being was tested by administering the IIEF-5 before and after the 12-week course of treatment. After 12 weeks of treatment, both *L. meyenii* and placebo-treated patients experienced a significant increase in their IIEF-5 score ( $p < 0.05$  for both groups). However, patients taking *L. meyenii* experienced a more significant increase than those taking placebo ( $1.6 \pm 1.1$  vs.  $0.5 \pm 0.6$ ,  $p < 0.001$ ).

## 9. Male silkworm extract

Male silkworm extract is composed of male silkworm moth (*Bombyx mori*), *Acanthopanax centicosus*, *S. chinensis*, *R. coreanus*, L-glutamine, freeze-dried royal jelly, *Lycium chinense* Mill., and tocopherol. Male silkworm extract is a combined natural herbal product and is believed to enhance masculinity without side effects. It is produced in prescription-grade quality in Donguibogam, and has been used in young and old men with reduced physical function or strength, weak urinary function, or complaints of fatigue (Table 1, Fig. 1, 2).

### 1) Animal studies

In male rats, male silkworm extract has been found to increase relevant hormone levels by 32.8%, compared to 9.9% in a group that was administered sildenafil. NO content increased by 16.6% in the male silkworm extract group, compared to 5.4% in the sildenafil group. The

sperm count increased by 41% in the male silkworm extract group, compared to 11.9% in the sildenafil group [34,35]. Oh et al [35] reported the effects of male silkworm pupa powder (SPP) on the levels of NO synthase expression, nitrite, glutathione, lipid peroxidation, the libido, and the erectile response of the corpus cavernosum of the rat penis. They induced ED in the study animals by oral administration of 20% ethanol over eight weeks. The SPP-treated male rats were divided into three groups that were orally administered 200 mg/kg, 400 mg/kg, and 800 mg/kg of SPP, respectively. The libido of the SPP-treated male rats was higher than that of the rats in the ethanol control group. In addition, after the administration of SPP, the erectile response of the corpus cavernosum was restored to a level similar to that of the normal group without ED. Lipid peroxidation in the corpus cavernosum of the male rats that received SPP decreased significantly. The levels of nitrite and NO synthase expression in the corpus cavernosum of SPP-treated male rats increased significantly. These results indicated that SPP effectively treated ethanol-induced ED in male rats.

### 2) Human studies

In a clinical study with 168 volunteers, two capsules were administered three times per day for four weeks, after which three capsules were administered three times per day for an additional two weeks to the volunteers who did not respond to the initial treatment. In 80 volunteers followed by per protocol analysis, male silkworm extract increased testosterone levels from 4.4 nmol/L to 4.9 nmol/L. A statistically significant improvement was noted in the symptoms of fatigue, ED, impotence, weak urinary stream, muscular atrophy, and sleep disturbances beginning two weeks after the initiation of therapy. Male silkworm extract was found to produce mild adverse effects such as digestive difficulty, sputum production, temporary chest palpitations, drowsiness, and increased stool frequency [36].

## 10. *Artemisia capillaris*

*A. capillaris* has been used as a food material and as a treatment for liver cirrhosis, liver cancer, jaundice, and cholecystitis in Asian countries. Scoparone (6,7-dimethoxycoumarin), a major component of *A. capillaris*, has been used as an antipyretic, anti-inflammatory, diuretic, and

choleric agent for the treatment of hepatitis and bilious disorders [37]. Study group of *Artemisia capillaris* [38,39] first reported that *A. capillaris* had a significant relaxing effect on pre-contracted rabbit penile corpus cavernosum smooth muscle and increased sildenafil citrate-induced relaxation. *A. capillaris* had a significant relaxant effect on penile corpus cavernosum tissue and increased the relaxation induced by phosphodiesterase type 5 inhibitors. Increased cAMP and cGMP levels in the perfusate and the inhibition of capillarisin relaxation with NG-nitro-L-arginine-methyl ester and 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one suggested that capillarisin may be involved in penile erection through the NO-cGMP and cAMP signaling pathways. Their study suggested that *A. capillaris* may be a new medicine or supplement to treat patients with ED.

### 11. *Cuscuta chinensis*

The dried seeds of *C. chinensis* Lam (family Convolvulaceae), are an important Chinese traditional medicine that is widely used to improve sexual function, to prevent and treat cardiovascular disease, to treat osteoporosis, and to prevent senescence. The active constituents of *C. chinensis* include flavonoids, lignans, quinic acids, and polysaccharides. These compounds may be responsible for the pharmacological activities of *C. chinensis*. *C. chinensis* significantly relaxed corporal tension and increased cAMP and cGMP levels in penile corpus cavernosum tissue, suggesting that its mechanism of action partly involves the NO-cGMP pathway. The ability of *C. chinensis* to improve sildenafil citrate-induced relaxation may be helpful for patients who do not respond to sildenafil citrate [40].

### 12. Garlic

Garlic has long been used as a spice and has been reported to possess medical and pharmacologic properties. Garlic has hypoglycemic, anticoagulative, antihypertensive, and hypolipidemic properties. Garlic may enhance hormone-regulated protein anabolism. No clinical data have been reported on the effect of garlic on improving erectile function, although garlic has been used for ED due to word of mouth.

## 13. Mixtures of multiple plants

### 1) Chonbo-204<sup>®</sup>

Chonbo-204<sup>®</sup> (Korea Bio Medical Science Institute, Seoul, Korea) is based on the ojayounjonghwon described in the Donguibogam and the Asian concepts of yin and yang [41,42]. The major ingredients of this herbal formula are seeds obtained from five plants: *Cornus officinalis* Sieb. Et Zucc. (Cornaceae, 32%), *R. coreanus* Miq. (Rosaceae, 16%), *C. chinensis* Lam. (Convolvulaceae, 16%), *L. barbarum* (Solanaceae, 32%), and *S. chinensis* Baill. (Schisandraceae, 4%) in different ratios (KH<sub>2</sub>O<sub>4</sub>: Korea Patent No. 0364684). In the preparation of this product, a mixture of the dried seeds of five plants undergoes extraction by being boiled with tap water (0.25 g/mL) for three hours. The extract is filtered and concentrated in a vacuum, and then lyophilized. This product was developed as a health supplement by the Korea Bio Medical Science Institute, which is developing oriental herbal medicines (Table 1, Fig. 1).

**(1) Animal studies:** In aged rats with diabetes mellitus, a daily dose of 100 mg/kg of this herbal formula for 10 days restored the severely reduced peak intracavernous pressures. The penile expression levels of NO synthase activities and cGMP concentrations were significantly increased in the rats treated with Chonbo-204<sup>®</sup>. Hypertensive rats were treated with 100 mg/kg or 300 mg/kg of this extraction per day for four weeks. The ratio of the intracavernous pressure to the mean arterial pressure was markedly increased in the group treated with the herbal formula compared to the placebo group. The expression of endothelial and neuronal NO synthases was significantly increased in the group treated with Chonbo-204<sup>®</sup> compared to the placebo group [43].

**(2) Human studies:** The commercial product Chonbo-204<sup>®</sup> has been registered as the patent name of an herbal formula for improving penile erection with lasting effects, and is available as small tablets prepared with a water-extracted mixture. Treatment with 30 g per day for four weeks significantly improved the total IIEF score from  $42.45 \pm 7.25$  to  $53.58 \pm 11.87$ , compared to  $41.90 \pm 17.37$  to  $48.48 \pm 17.22$  in the placebo group. The erectile function domain and overall satisfaction domain were significantly improved in the Chonbo-204<sup>®</sup> group, compared

to the placebo group. The rate of side effects was 7.5% in both groups. The side effects were headache (2.5%) and nausea (5%) [42].

## 2) Mixture of *Tribulus terrestris* extract and *Cornus officinalis* extract

*Tribulus terrestris* extract and *Cornus officinalis* extract demonstrated concentration-dependent relaxation in an organ bath. In an *in vivo* study of the extract mixture, intracavernous pressure was improved and the cAMP pathway was significantly potentiated [44].

## 3) SA1

SA1 (Chungbuk Technopark Oriental Medicine Center, Jecheon, Korea) is a mixture of 9 Oriental herbs (KRG, fermented soybean, *T. terrestris*, *Rubus Chingii* Hu, *L. barbarum* L., *Semen Cuscutae Cuscuta chinensis* Lam, *Dioscorea rhizome*, *C. officinalis*, and *Crataegus pinnatifida*). These herbs are widely used as energizing and vitalizing agents in indigenous Asian systems of medicine and have been alleged to improve sexual function in men. *In vitro*, SA1 significantly enhanced the relaxation response to acetylcholine. SA1 significantly increased the ratio of intracavernous pressure to mean arterial pressure. The male rats used to examine copulatory behavior were administered either a placebo or SA1 (30 mg/kg, 100 mg/kg, 300 mg/kg, or 600 mg/kg) orally for two weeks. An overall increase was observed in copulatory behavior parameters in the SA1-treated rats [45].

## 4) SS cream

SS cream (Cheil Jedang Pharmaceutical, Seoul, Korea) is a topical agent derived from the extracts of nine natural products (*Ginseng radix alba*, *Angelicae gigantis radix*, *Cistanchis herba*, *Zanthoxylli fructs*, *Torlidis semen*, *Asiasari radix*, *Caryophylli flos*, *Cinnamoni cortex*, and *Bufonis veneum*) for the treatment of premature ejaculation (Fig. 1).

**(1) Animal studies:** SS cream prolonged the mean latency of somatosensory evoked potential from  $21.57 \pm 1.86$  milliseconds to  $23.09 \pm 0.85$  milliseconds and  $27.49 \pm 2.4$  milliseconds at 30 and 60 minutes after application of SS cream, respectively. SS cream also decreased the mean amplitude somatosensory evoked potential to  $1.83 \pm 0.07$   $\mu$ V and  $1.72 \pm 0.05$   $\mu$ V at 30 and 60 minutes after the application of SS cream, respectively [46].

**(2) Human studies:** In a Phase III clinical study, the effi-

cacy and safety of SS cream were evaluated in 106 volunteers who suffered from premature ejaculation. The mean ejaculatory latency time was prolonged to  $10.92 \pm 0.92$  minutes in the SS cream group compared to  $2.45 \pm 0.29$  minutes in the placebo group. The percentage of patients who prolonged their ejaculatory latency time by over two minutes in the placebo and SS cream groups was 15.09% and 79.81%, respectively. SS cream elicited a sense of mild local burning and pain [47].

## CONCLUSIONS

In this review, we presented a range of oriental herbal treatments, including both individual herbs and mixtures of multiple plants, which may be effective complementary agents for improving sexual function in male patients. Moreover, since it is natural, herbal medicine usually does not have significant side effects and is considerably safer than Western-style medications. In the future, quality control in the production of oriental herbs and randomized controlled clinical trials will further validate evidence-based herbal therapy in sexual medicine.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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