



(86) Date de dépôt PCT/PCT Filing Date: 2002/12/20  
 (87) Date publication PCT/PCT Publication Date: 2003/07/10  
 (45) Date de délivrance/Issue Date: 2009/12/15  
 (85) Entrée phase nationale/National Entry: 2004/06/08  
 (86) N° demande PCT/PCT Application No.: KR 2002/002407  
 (87) N° publication PCT/PCT Publication No.: 2003/055504  
 (30) Priorité/Priority: 2001/12/21 (KR10-2001-82978)

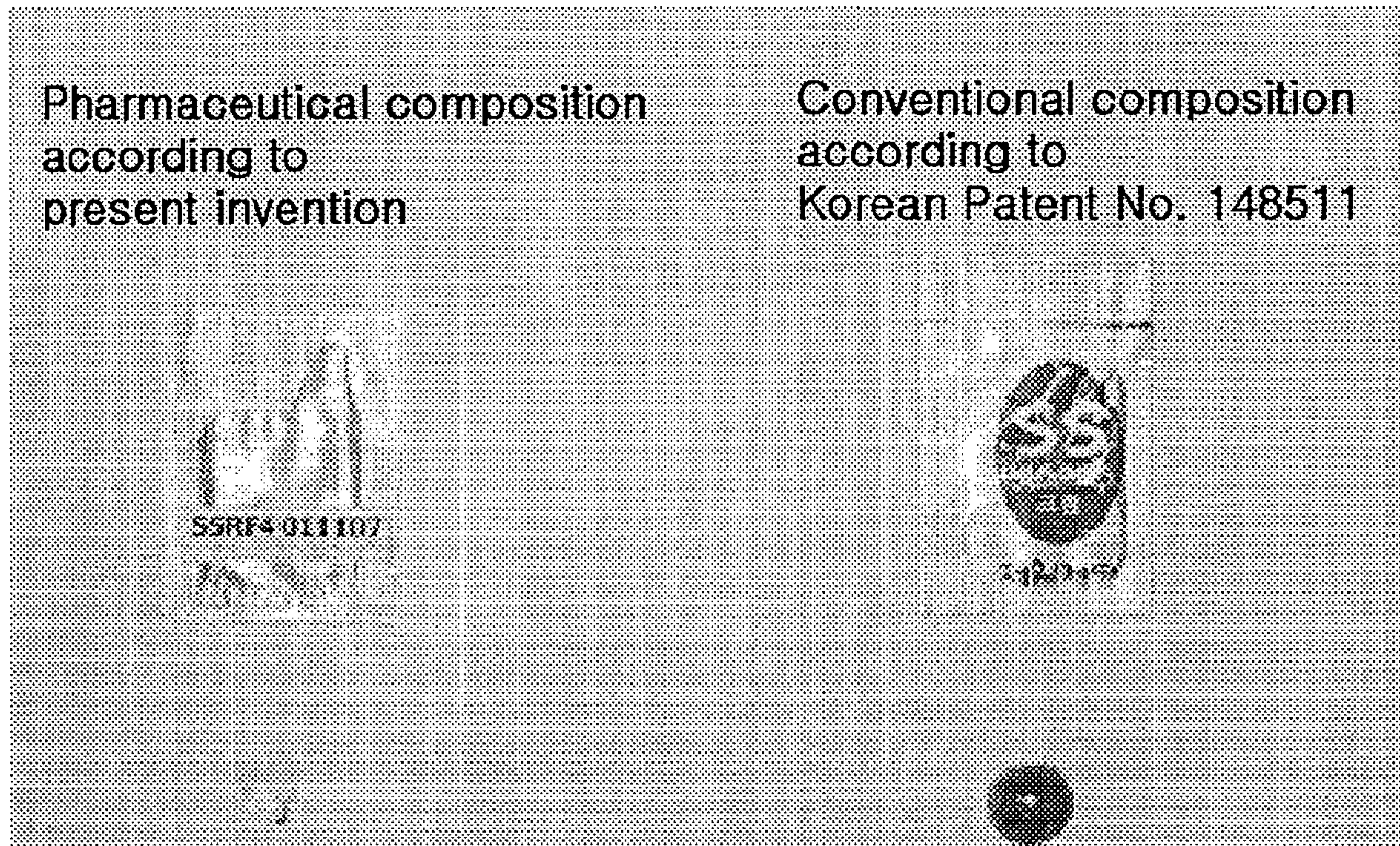
(51) Cl.Int./Int.Cl. *A61K 35/56* (2006.01),  
*A61K 31/19* (2006.01), *A61K 31/704* (2006.01),  
*A61K 47/10* (2006.01), *A61K 9/06* (2006.01),  
*A61P 15/00* (2006.01), *A61P 15/08* (2006.01)

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(54) Titre : COMPOSITION PHARMACEUTIQUE POUR LA PREVENTION ET LE TRAITEMENT DE L'EJACULATION PRECOCE ET/OU DE L'HYPERSENSIBILITE A LA STIMULATION SEXUELLE  
 (54) Title: PHARMACEUTICAL COMPOSITION FOR PREVENTION AND TREATMENT OF PREMATURE EJACULATION AND/OR HYPERSENSITIVITY OF SEXUAL STIMULATION



(57) **Abrégé/Abstract:**

A pharmaceutical composition for the prevention and treatment of premature ejaculation and/or hypersensitivity of sexual stimulation is provided. The composition contains purified sumsoo extract and purified ginseng extract containing saponin as the main component, without other herbal essential oil components.

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
10 July 2003 (10.07.2003)

PCT

(10) International Publication Number  
**WO 03/055504 A1**(51) International Patent Classification<sup>7</sup>: **A61K 35/78,**  
35/56

(21) International Application Number: PCT/KR02/02407

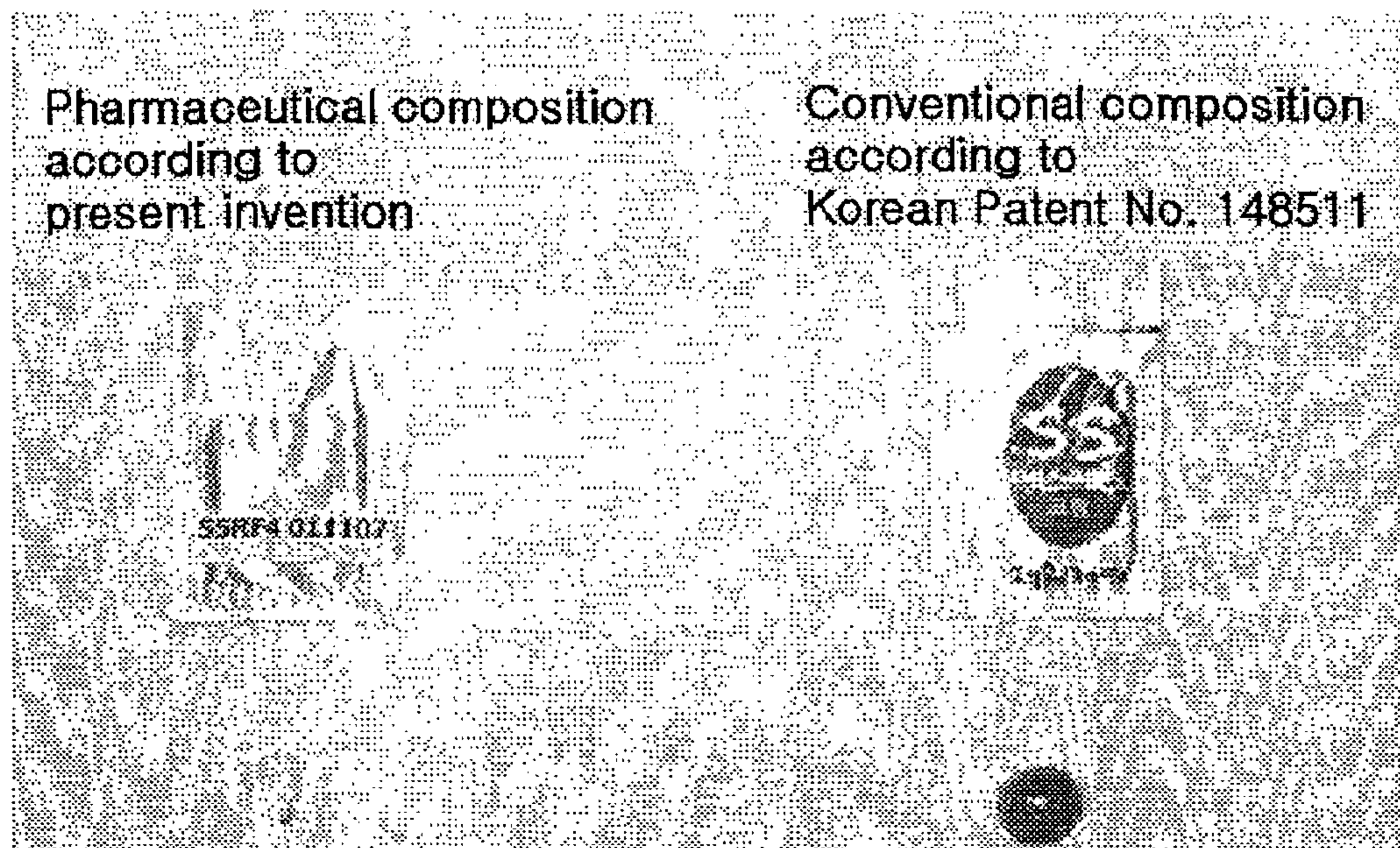
(22) International Filing Date:  
20 December 2002 (20.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
10-2001-82978 21 December 2001 (21.12.2001) KR(71) Applicant: **CJ CORPORATION** [KR/KR]; 500, Nam-  
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1571-18, Seocho-dong Seocho-gu, 137-874 Seoul (KR).(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CO, CR, CU, CZ,  
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,  
HR, HU, ID, IL, IN, IS, KE, KG, KP, KZ, LC, LK, LR, LS,  
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,  
NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL,  
TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA,  
ZM, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,  
ML, MR, NE, SN, TD, TG).

[Continued on next page]

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WO 03/055504 A1

**WO 03/055504 A1**



**Published:**

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

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**PHARMACEUTICAL COMPOSITION FOR PREVENTION AND  
TREATMENT OF PREMATURE EJACULATION AND/OR  
HYPERSENSITIVITY OF SEXUAL STIMULATION**

5 Technical Field

The present invention relates to a pharmaceutical composition for the prevention and treatment of premature ejaculation and/or hypersensitivity of sexual stimulation.

Background Art

10 Hypersensitivity of sexual stimulation is known to be caused generally due to a disorder in the complex cooperation between the peripheral nervous system and the central nervous system. Hypersensitivity of sexual stimulation is known to lead in frequent cases to the onset of ejaculation before or shortly after vaginal penetration, or  
15 an inability to keep erection or control ejaculation for a sufficient amount of time for a partner's sexual pleasure.

According to recent statistics in Korea, approximately 30-50% of adult males suffer from these sexual dysfunctions resulting from hypersensitivity of sexual stimulation, which leads to domestic discord in  
20 relationships and loss of self-confidence.

Generally, hypersensitivity of sexual stimulation is caused by a malfunction of the central nervous system due to chronic fatigue of the neurotransmitter system, hypersensitivity of the urinary duct or the glans receptor, endocrinal disorders, psychological causes, and the like.  
25 However, it was recently deduced that since the above-mentioned causes may react on the nerve system in simultaneous and complex manner, or a cooperation system between the central sexual nerve system in a man may be disrupted, a reflective ejaculation can easily be caused.

30 Hypersensitivity of sexual stimulation has been treated by

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psychotherapy and drug therapy. The psychotherapy involves long-term sexual behavioral counseling therapy provided by a specialized therapist to both the patient and his partner. However, such long-term treatment programs are complicated, expensive, can be  
5 uncomfortable for the patient and/or his partner, and have a poor success rate of less than 50%.

Drug therapy has been used more widely than psychotherapy because of the prompt therapeutic effect. Available drugs include psychotropic agents which suppress excitation of the sexual nerve  
10 system, such as antidepressants, and topical anesthetic agents which desensitizes the sexual peripheral nerve to delay ejaculation. However, the central nerve depressants likely make it impossible to have sexual relationships due to a loss of sexual desire, and the topical anesthetic agents, such as lidocaine ointment or spray, are not preferred because  
15 they should be applied just before intercourse due to their short duration. Therefore, sexual dysfunctions resulting from hypersensitivity of sexual stimulation cannot be effectively treated with drugs.

Korean Patent No. 148511 discloses a preventive and therapeutic pharmaceutical formulation for hypersensitivity of sexual stimulation,  
20 which essentially contain ginseng, dang-gui(Angelicae Gigantis Radix), yuk-jong-yong(Cistanchis Herba), cinnamon(Cinnamomi Cortex), sesin(Asiasari Radix), and sumsoo (Bufonis Venenum ). The effect of this formulation on hypersensitivity of sexual stimulation has been proven through animal and clinical tests, and it is commercially available for  
25 external application.

However, since the formulation contains essential oils of herbal components, such as dang-gui, cinnamon, sesin, etc., the scent of the herbal components is so strong that it smells even after washing with soap, thereby limiting the use of the formulation. Also, the formulation  
30 is prepared from the crude extracts of essential herbal components, including dang-gui, ginseng, sumsoo, yuk-jong-yong, cinammon, sesin,

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etc., without purification. Accordingly, the product appears an unpleasant unique dark brown color from the extracts of herbal components and may contaminate underwear. Thus, it is difficult for a patient to conceal the application of the therapeutic formulation from his partner. Further, application of the formulation is inconvenient because it takes 30 minutes to 1 hour for the local anesthetic to take effect. Moreover, since the crude sumsoo extract is used without purification, non-pharmacological substances for hypersensitivity of sexual stimulation in the unpurified sumsoo extract, such as epinephrine and serotonin, may result in various side effects, such as penile smooth muscle contraction and impotence.

WO 0147539A1, pharmaceutical composition for preventing and treating erectile impotence using purified sumsoo extract, discloses sumsoo extraction and purification methods for preparing a pharmaceutical composition containing only Bufadienolides, excluding catecholamines, such as epinephrine, and indolalkylamines, such as serotonin. The purified sumsoo extract effectively eliminates the side effects of sumsoo extract obtained using water or alcohol as an extraction solvent in Korean Patent No. 0148511, such as impotence, penile smooth muscle contraction, and pain.

However, Bufadienolides used as the pharmaceutical component for treating hypersensitivity of sexual stimulation have both topical anesthetic and penial smooth muscle contraction effects. Therefore, side effects such as impotence cannot be suppressed only with the purified sumsoo extract alone.

#### Disclosure of the Invention

The invention provides a scent free, colorless composition for the prevention and treatment of premature ejaculation and/or hypersensitivity of sexual stimulation, which includes purified sumsoo(Bufonis Venenum) extract and purified Ginseng Radix extract containing saponin as the

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main component, excluding any herbal essential oil component, and minimize side effects such as impotence and burning.

The composition for the prevention and/or treatment of premature ejaculation and/or hypersensitivity of sexual stimulation according to the present invention includes the purified Bufonis Venenum extract and the purified Ginseng Radix extract containing saponin as the main component, excluding any herbal essential oil component, wherein the penial smooth muscle contraction effect of Bufadienolides, which are known as pharmacological components of Bufonis Venenum, is suppressed.

Bufadienolides, the pharmacological components in the Bufonis Venenum extract, adversely cause contraction of the penial smooth muscle and in turn cause impotence. However, according to the present invention, the penial smooth muscle contraction effect is markedly reduced by mixing the Bufonis Venenum extract with the purified Ginseng Radix extract containing saponin as the main component.

According to the present invention, herbal essential oil components, such as dang-gui, yuk-jong-yong, cinnamon, etc., which appear unpleasant dark brown and smell strong, are excluded. The combination of the purified Bufonis Venenum extract and the purified Ginseng Radix extract containing saponin as the main component is proven to be an effective treatment for hypersensitivity of sexual stimulation. It is believed that the inhibition of smooth muscle contraction is by the saponin component of the purified Ginseng Radix extract.

The Bufonis Venenum extract used in the composition for the treatment of hypersensitivity of sexual stimulation according to the present invention is obtained by using, preferably, ethylacetate, dichloromethane, or chloroform, as an extraction solvent.

Extracting the Bufonis Venenum using at least one solvent

selected from the group consisting of ethylacetate, dichloromethane and chloroform may be followed by an additional purification, for example, solvent fractionation or chromatography.

The pharmaceutical composition according to the present invention contains 0.01-3% by weight of the Bufonis Venenum extract and 0.01-5% by weight of the Ginseng Radix extract, based on the total weight of the composition. Preferably, the pharmaceutical composition according to the present invention contains 0.05-0.2% by weight the Bufonis Venenum extract and 0.1-0.2% by weight the Ginseng Radix extract, based on the total weight of the composition.

The Ginseng Radix extract used in the therapeutic composition for hypersensitivity of sexual stimulation according to the present invention is prepared by extracting a crude Ginseng Radix extract from raw Ginseng Radix using ethanol and purifying the crude Ginseng Radix extract by solvent fractionation with diethylether and butanol.

The pharmaceutical composition according to the present invention may be produced in any form suitable for application, for example, ointment, solution, suspension, gel, dispersion or the like, with gel form being preferred.

In the pharmaceutical composition according to the present invention, the amount of the extract in the final composition is reduced to 1/50<sup>th</sup> or less of the amount of the crude extract used in the same volume of the conventional composition of Korean Patent No. 148511. Accordingly, percutaneous absorption enhancers, for example, lauroglycol, pharماسolve<sup>TM</sup>, transcutol, carbomer, etc, which cannot be used in the conventional composition due to insolubility problems, can be further incorporated into the pharmaceutical composition according to the present invention. Compared with the conventional composition which takes effect 30 minutes to 1 hour after application, the pharmaceutical composition according to the present invention takes effect within about 5 minutes after application, and thus is convenient to use.

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Brief Description of the Drawing

FIG. 1 shows the appearances of a conventional composition and a pharmaceutical composition for the prevention and treatment of premature ejaculation and hypersensitivity of sexual stimulation according to the present invention.

Best mode for carrying out the Invention

The present invention will be described in greater detail with reference to the following examples. The following examples are for illustrative purposes and are not intended to limit the scope of the invention.

**Example 1**

(a) 2000 mL of ethylacetate was added to 400 g of Bufonis Venenum powder, and the mixture was subject to hot extraction in a water bath equipped with a reflux condenser at 70°C for 4 hours and filtered. An equal amount of ethyleacetate was added to the filter cake and was again subject to extraction. The filtrate was combined with the previously obtained filtrate, concentrated under a reduced pressure, and dried to yield 62 g of dry extract.

(b) 1.5 g of the brown Bufonis Venenum-ethyleacetate extract obtained in step (a) was loaded onto a silicagel column, which was packed with 12g of silicagel particles of 230-400 mesh, followed by elution with a solvent mixture of normal hexane and ethyleacetate. Through a rabbit corneal reflex test using each fraction of the eluent, each eluate fraction was subjected to a rabbit corneal reflex test and 1.1 g of colorless efficacious fractions having a topical anesthetic effect were collected.

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(c) 500 mL of ethanol was added to 50 g of Ginseng Radix powder. The mixture was subject to hot extraction at 80°C for 4 hours, twice, in a water bath equipped with a reflux condenser and filtered to obtain 8 g of crude Ginseng Radix extract. The crude Ginseng Radix  
5 extract was dissolved in 100 mL of distilled water, followed by shaking extraction, twice, with an addition of the equal amount of diethylether, to separate an aqueous fraction. The aqueous fraction was subject to shaking extraction, twice, with the addition of 100 mL of butanol hydrate, and the resulting butanol fraction was concentrated under a reduced  
10 pressure to yield 4.5 g of Ginseng Radix extract powder, which was partially purified and containing saponin as the main component.

(d) 130 mg of the Bufonis Venenum extract powder prepared in step (b) and 150 mg of the Ginseng Radix extract powder prepared in  
15 step (c) were mixed thoroughly with a base composition consisting of lauroglycol, pharماسolve, transcutool, and carbomer to obtain 100 g of colorless, odorless gel composition.

**Experimental Example 1: Topical anesthetic effect verification**  
20 **through rabbit corneal reflex test**

The topical anesthetic effect of the pharmaceutical composition prepared in Example 1 was confirmed through a rabbit corneal reflex test.

Three adult male rabbits were bound up, and a lower eyelid of  
25 each rabbit was stretched away from the eyeball and fixed without anesthetization. 0.1 mL of the composition prepared in Example 1 was applied into the eye, and the eyelid was shut for about 1 minute to prevent loss of the composition. The corneal was irritated with a brush ten times after 5 minutes, 10 minutes, 20 minutes, and 30 minutes from  
30 application, and the number of resulting corneal reflexes was recorded.

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An incomplete shutting of the eyelid or a slow corneal reflex was counted as a half of a reflex. The same corneal reflex test was carried out using 0.1 mL of the base composition for comparison.

The results of the rabbit corneal reflex test are shown in Table 1.

5

Table 1. Rabbit corneal reflex test results

Sample	The number of subject animals	Average number of corneal reflexes			
		5 min	10 min	20 min	30 min
Control group	3	9.0	9.3	8.7	9.0
Present invention	3	0.7	0.3	1.3	1.7

As is apparent from the results of the rabbit corneal reflex test for topical anesthetic effect evaluation in Table 1, the pharmaceutical composition according to the present invention significantly suppressed the corneal reflex providing a good topical anesthetic effect, compared to the control group to which only the base composition was applied.

**Experimental example 2: Anti-impotence effect verification through rabbit penile cavernous smooth muscle tissue contraction test**

Rabbits were anesthetized by intravenously injecting pentobarbital via ear vein and killed by bleeding. The penis was isolated from the rabbits and immersed in Tyrode's solution, and the penile cavernous tissue was isolated just before the test. The connective tissue and surrounding muscles of the penis were removed and the tissue membrane was incised using a surgical knife to isolate the pure penile cavernous tissue.

The isolated penile cavernous tissue was trimmed into 2×2×6

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mm segments. One end of each tissue segment was fixed to the bottom of an organ bath containing a Tyrode's solution while the other end was bound to a force displacement transducer to record the contraction of the penile tissue segment on a polygraph. During the test, warm water was circulated through the double-jacketed walls of the organ bath so as to keep the Tyrode's solution at a temperature of 37°C, and a gas mixture of 95% oxygen and 5% carbon dioxide was continuously supplied so as to keep the Tyrode's solution at pH 7.4. The initial tension applied was increased by a force corresponding to 0.5 g every 30 minutes over 1-2 hours up to a force of 2 g, and the tension of the penile cavernous tissue at pause was maintained under the force of 2 g for stabilization. The stabilized penile cavernous tissue was treated using 0.1 mL of Bufonis Venenum extract solution in ethanol at a concentration of 0.02 mg/mL, wherein the Bufonis Venenum extract was obtained in step (b) of Example 1. When the penile cavernous tissue was contracted to a maximum level in the polygraph, 1 mL of Ginseng Radix extract solution, wherein the Ginseng Radix extract was obtained in step (c) of Example 1, in ethanol at concentrations of 0.25 mg/mL, 0.5 mg/mL, 1.0 mg/mL, and 2.0 mg/mL was applied to the contracted tissue. Then, the contraction force of the cavernous smooth muscle tissue to which Ginseng Radix extract solution was applied was measured and compared with the control to which Ginseng Radix extract solution was not applied. The smooth muscle contraction inhibitory ratio was calculated for the tissues to which the Ginseng Radix extract solutions were applied. The results are shown in Table 2.

Table 2. Results of the rabbit penile cavernous smooth muscle contraction test

Concentration of Ginseng Radix extract solution (mg/ml)	Smooth muscle contraction inhibitory ratio (%)
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0	-
0.25	22.4 ± 2.5 **
0.5	48.1 ± 8.5 **
1.0	62.3 ± 8.1 **
2.0	100 **

\*\*; significant at  $p < 0.01$

As can be seen in Table 2, compared with the control using the Bufonis Venenum extract alone, when the Bufonis Venenum extract and the Ginseng Radix extract were used together, the smooth muscle contraction was relieved in proportion to the concentration of the Ginseng Radix extract. Therefore, it was evident that the addition of the Ginseng Radix extract to the Bufonis Venenum extract had an effect of relieving reduced erectile response caused by the penile smooth muscle contraction.

### **Experimental example 3: Color and odor evaluation**

The color, viscosity, and odor of the pharmaceutical composition according to the present invention was evaluated comparatively with the conventional composition disclosed in Korean Patent No. 0148511, which is commercially available under the brand name "SS cream<sup>TM</sup>."

The appearances of the pharmaceutical composition according to the present invention and the conventional SS cream<sup>TM</sup> are shown in FIG. 1.

As shown in FIG. 1, the SS cream<sup>TM</sup> is dark brown, whereas the composition according to the present invention is colorless. The SS cream<sup>TM</sup> has strong herbal odor, whereas the composition according to the present invention is odorless. The SS cream<sup>TM</sup> is a solution with low fluidity, whereas the composition according to the present invention is a thick gel. Therefore, the pharmaceutical composition according to the

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present invention is determined to be very convenient to use in terms of color, odor, and viscosity.

**Experimental example 4: Primary clinical test**

5        The therapeutic effect of the gel composition prepared in Example 1 for hypersensitivity of sexual stimulation was tested using 35 male volunteers suffering from hypersensitivity of sexual stimulation. The subjects were instructed to uniformly apply 0.2 g of the gel composition prepared in Example 1 to the penis glans, wash it off about 5 minutes  
 10 later, and have sexual intercourse after 1 hour from the washing. Later, the subjects were asked how much longer the sexual intercourse lasted compared to their normal duration. The results are shown in Table 3.

Table 3. Prolonged sexual intercourse duration effect

Prolonged sexual intercourse duration	The number of subjects	Ratio (%)
15 min or longer	9	25.7
10-15 min	15	42.8
2-10 min	9	25.7
2 min or less	2	5.7

15

As can be seen in Table 3, 94% of the test subjects (33 of the 35 subjects) were greatly satisfied with the extension of sexual intercourse, and about 26% (9 of the 35 subjects) reported an extension of 15 min or longer. Only two subjects complained of reduced erectile response due  
 20 to penile muscle contraction. Evidently, the composition according to the present invention exhibits reduced side effects.

Industrial Applicability

As described above, the pharmaceutical composition for the

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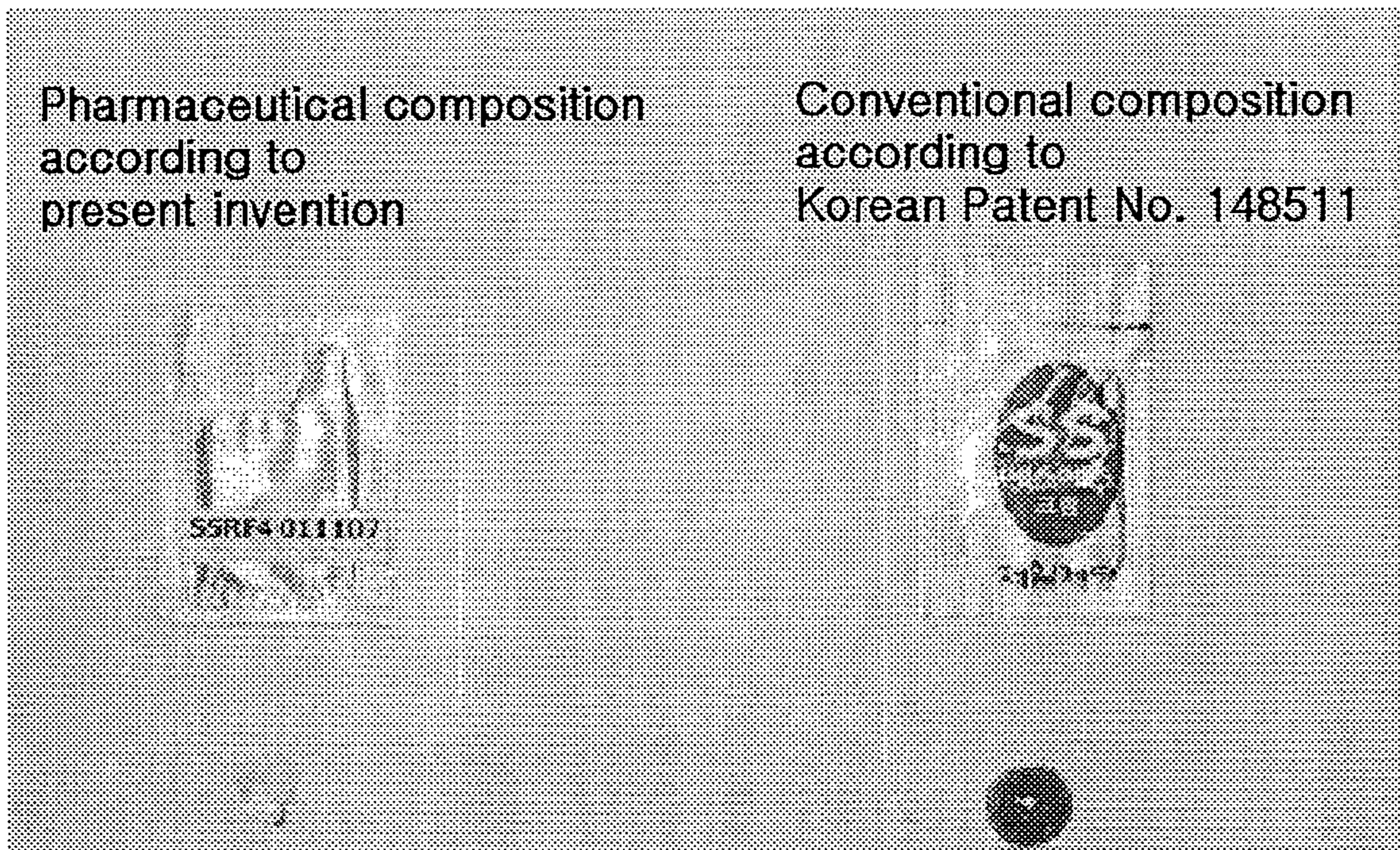
prevention and treatment of premature ejaculation and hypersensitivity of sexual stimulation according to the present invention is convenient to use, has reduced side effects, such as reduction of erectile response, extends sexual intercourse and leads to a satisfactory sexual life by enhancing  
5 sexual performance.

What is claimed is:

1. A topical pharmaceutical composition for the prevention and treatment of premature ejaculation and/or hypersensitivity of sexual stimulation, the topical pharmaceutical composition comprising a herbal component, wherein the herbal component consists of purified sumsoo extract and purified ginseng extract containing saponin, wherein the purified sumsoo extract is obtained by using at least one solvent selected from ethylacetate, dichloromethane, and chloroform as an extraction solvent and wherein the purified ginseng extract is obtained through solvent fractionation or column chromatography after being extracted using ethanol.
2. The topical pharmaceutical composition of claim 1, wherein the purified sumsoo extract is contained in an amount of 0.01-3% by weight and the purified ginseng extract is contained in an amount of 0.01-5% by weight based on the total weight of the pharmaceutical composition.
3. The pharmaceutical composition of claim 1, further comprising a percutaneous absorption enhancer.
4. The pharmaceutical composition of claim 3, wherein the percutaneous absorption enhancer is selected from Lauroglycol, Pharmasolve™, Transcutol, and a mixture of the forgoing substances.
5. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in gel form.

1/1

Fig. 1



Pharmaceutical composition  
according to  
present invention



Conventional composition  
according to  
Korean Patent No. 148511

