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(54) Title: COMPOSITION FOR PREVENTION AND TREATMENT OF URINARY INCONTINENCE

(57) Abstract: The present invention is related to a composition comprising pumpkin seed oil or pumpkin seed extract, Rubus coreous extract and soybean isoflavone. As a composition of the present invention can reduce incidence of urinary incontinence and diurina and increase closing pressure of urethra (ability to regulate urethra sphincter), it can be used in treatment or prevention of urinary incontinence. Also, as the components of the composition have been widely used as safe materials and the composition of the present invention showed no acute toxicity, the present invention is useful for pharmaceutics and functional foods for prevention and treatment of urinary incontinence.

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TITLE OF THE INVENTION

COMPOSITION FOR PREVENTION AND TREATMENT OF URINARY INCONTINENCE

FIELD OF THE INVENTION

The present invention relates to a composition having minimized side effects and the useful for pharmaceutics and functional health foods for prevention and treatment of urinary incontinence. Particularly, the present invention relates to a composition comprising pumpkin seed oil or pumpkin seed extract, *Rubus coreous* extract and soybean isoflavone optimally mixed.

BACKGROUND ART

Urinary incontinence is defined, as a symptom that urine is running down from urethra regardless of one's own will. It occurs when the interior pressure of bladder is larger than the resistance of urethra.

It is reported that urinary incontinence generally results from the decrease in ability to regulate urethra due to drooping of bladder, extension of pelvic muscle and weakness of urethra sphincter.

It happens more frequently in older women and 32% or more of them are patients. Also, 1 of 2 women having birth experience shows the symptom since

etiology of urinary incontinence in women increases owing to birth.

The disease often accompanies offensive odor and cutaneous disorder and can affect patient's emotional and psychological well-being. As a result, their social activities are limited, which cause social problems and economic losses.

Many people with bladder control problems do not recognize their symptoms as urinary incontinence or are reluctant to be treated due to their shame. So, the percentage of being treated substantially is smaller than 10% of total patients.

There are several types of urinary incontinence:

Stress incontinence happens when body movements put pressure on the bladder suddenly;

Urge incontinence happens when people can not hold their urine long enough to get to the toilet in time due to sensitivity of bladder muscle and when bladder leaks urine to serious stimulus;

Reflex incontinence happens to ankylosing paraplegia patients;

Overflow incontinence happens to flaccid paraplegia patients;

Psychogenic incontinence happens to dementia patients.

There is a tendency that stress incontinence increases from 51% to 77%, urge incontinence increases from 10% to 12% stably while other combined incontinences decrease from 39% to 11%(*J. Clin. Epidemiol.*, 48, 339 (1995)).

There are medicament therapy, pelvic muscle reinforcement and surgery for treating urinary incontinence. Surgery requires high cost, while pelvic muscle reinforcement needs steady exercise for a long time.

For medicament therapy to stress incontinence phenylpropanolamines, alpha adrenalin drugs, have been used, but they were prohibited for side effects to heart.

Anticholinerinergic drugs have been used in treatment for urge incontinence to relax tension of bladder muscle: terodilins were prohibited for serious side effects to heart (*Eur. J. Clin. Pharmacol.*, 42, 577 (1992)); emepronium bromides showed no good results in clinical data by random double-blinded test; tolterodins, propiperines, flavoxates and the like remain.

However, since most of the drugs used in medicament therapy have serious side effect and low efficiency, development of novel drugs having no side effect and able to improve the symptoms has been highly demanded.

Thus the present inventors have studied to develop a novel pharmaceutical compound having no side effects and sufficient medical properties for urinary incontinence and accomplished the present invention by confirming that a novel composition comprising pumpkin seed oil or pumpkin seed extract, *Rubus coreous* extract and soybean isoflavone which have been widely used and proved to be safe is showing the excellent therapeutic effects on urinary incontinence.

DESCRIPTION OF THE INVENTION

TECHNICAL PROBLEMS

It is an object of the present invention to provide a novel composition having good effects on treatment of urinary incontinence and minimized toxicity for pharmaceutics and functional health foods.

TECHNICAL SOLUTION

The present invention provides a composition comprising pumpkin seed oil or pumpkin seed extract, *Rubus coreous* extract and soybean isoflavone. More particularly, the present invention provide a composition comprising 100 parts by weight of pumpkin seed oil or pumpkin seed extract, 20-80 parts by weight of *Rubus coreous* extract and 5-30 parts by weight of soybean isoflavone.

The dried pumpkin seed extract has been known to be useful for the treatment of prostatic hypertrophy (*Forsch Komplementarmed Klass Naturheikd* 7, 200 (2000)), and woman micturition disorder (*Kmmission E. monograph* No. 11/1991.01.17).

The pumpkin seed contains cucurbitacin, lignan, phytosterol (plant sterol), tocopherol, unsaturated fatty acid, zinc and selenium. It has been reported that phytosterol (plant sterol) inhibits the conversion testosteron into dihydrotestosteron to

reduce the size of prostate.

Soybean isoflavone has been called plant female hormone. It is widely used since it has the same effect as female hormone in the organism without any side effect. Also, it has been known that it alleviates climacteric symptom, diminishes cancer incidence and demonstrates anti-oxidation effect and curative effect to osteoporosis

It has been reported that *Rubus coreous* has antipyretic action, cardio-tonic effect and diuresis action and has been used in the treatment of urinary frequency, enuresis and erectile dysfunction (e.g. impotence) in Oriental medicine.

The pumpkin seed oil used in the preparation of the composition of the present invention is obtained by pressing only or pressing while heating pumpkin seed.

Pumpkin seed extract in the preparation of the composition of the present invention is obtained by extracting pumpkin seeds by water-containing alcohol and concentrating it to concentrated liquid or powder form.

Rubus coreous extract is prepared by extracting with water or water-containing ethanol while heating or by concentrating to the concentrated liquid or powder form wherein the ratio of concentration is usually larger than 3:1.

Soybean isoflavone containing 10 to 50% of isoflavone is purchased in the market.

The composition of the present invention can be useful for pharmaceutics or

functional health foods and can be applied diversely through usual formulation method for those purposes. For example, the composition of the present invention can include additive, emulsifier, lubricants, conglutinant, sweetener, odorant, vitamin etc. and can be manufactured in the forms of soft capsules, pills, suspensions, granules, tablets or liquid medicine.

The dosage of the composition of the present invention is generally 2,500-7,500 mg for an adult and it is preferable to be administrated 2-3 times a day.

Practical and presently preferred embodiments of the present invention are illustrative as shown in the following examples.

However, it will be appreciated that those skilled in the art, on consideration of this disclosure, may make modifications and improvements within the spirit and scope of the present invention.

EXAMPLES

Examples 1: Preparation of soft capsules 1

6,820 g of pumpkin seed oil, 2,920 g of powder form of *Rubus coreous* extract (3:1), 682 g of soybean isoflavone (isoflavone 30%), 288 g of recitin and 290 g of beeswax were well mixed together and soft capsules were prepared according to the conventional producing method by the dosage unit of 550 mg using the gelatin as a soft

capsule base.

Examples 2: Preparation of soft capsules 2

3,410 g of pumpkin seed extract, 1,460 g of powder form of *Rubus coreous* extract (3:1), 341 g of soybean isoflavone (isoflavone 30%), 12 g of vitamin B_6 hydrochloride, 0.2 g of vitamin B_{12}, 0.4 g of folate, 104.4 g of recitin and 114 g of beeswax were well mixed together and soft capsules were prepared according to the conventional producing method by the dosage unit of 550 mg using the gelatin as a soft capsule base.

Examples 3: Preparation of soft capsules 3

5,500 g of soybean oil, 3,410 g of pumpkin seed oil, 1,460 g of powder form of *Rubus coreous* extract (3:1), 341 g of soybean isoflavone (isoflavone 30%), 288 g of recitin and 290 g of beeswax were well mixed together and soft capsules were prepared according to the conventional producing method by the dosage unit of 1,100 mg using the gelatin as a soft capsule base.

Examples 4: Preparation of soft capsules 4

1,000 g of pumpkin seed oil, 200 g of powder form of *Rubus coreous* extract (3:1), 50 g of soybean isoflavone (isoflavone 10%), 25 g of recitin and 25 g of beeswax

were well mixed together and soft capsules were prepared according to the conventional producing method by the dosage unit of 350 mg using the gelatin as a soft capsule base.

Examples 5: Preparation of soft capsules 5

1,000 g of pumpkin seed oil, 800 g of powder form of *Rubus coreous* extract (3:1), 50 g of soybean isoflavone (isoflavone 10%), 25 g of recitin and 25 g of beeswax were well mixed together and soft capsules were prepared according to the conventional producing method by the dosage unit of 350 mg using the gelatin as a soft capsule base.

Examples 6: Preparation of soft capsules 6

1,000 g of pumpkin seed oil, 200 g of powder form of *Rubus coreous* extract (3:1), 300 g of soybean isoflavone (isoflavone 10%), 25 g of recitin and 25 g of beeswax were well mixed together and soft capsules were prepared according to the conventional producing method by the dosage unit of 350 mg using the gelatin as a soft capsule base.

Examples 7: Preparation of soft capsules 7

1,000 g of pumpkin seed oil, 780 g of powder form of *Rubus coreous* extract (3:1), 280 g of soybean isoflavone (isoflavone 10%), 25 g of recitin and 25 g of beeswax were well mixed together and soft capsules were prepared according to the

conventional producing method by the dosage unit of 350 mg using the gelatin as a soft capsule base.

Examples 8: Preparation of pills

200 g of pumpkin seed oil, 100 g of powder form of *Rubus coreous* extract (3:1), 45 g of soybean isoflavone (isoflavone 30%), 600 g of crystallized cellulose and 200 g of corn starch were well mixed together and pills were prepared according to the conventional producing method by the dosage unit of 350 mg.

Examples 9: Preparation of suspensions

100 g of pumpkin seed oil, 60 g of powder form of *Rubus coreous* extract (3:1), 6 g of soybean isoflavone (isoflavone 30%), 10 g of carboxymethylcellulosesodium and 5 g of tween-60 were added to water and the mixture was dispersed using a sonicater. After that, water was added to obtain 1,000 ml of suspension.

Examples 10: Preparation of tablets

100 g of pumpkin seed oil, 75 g of powder form of *Rubus coreous* extract (3:1), 15 g of soybean isoflavone (isoflavone 45%), 1,000 g of crystallized cellulose and 10 g of magnesium stearate were well mixed together and tablets were prepared according to the conventional producing method by the dosage unit of 500 mg.

Comparative example 1

3,410 g of pumpkin seed oil, 341 g of soybean isoflavone (isoflavone 30%), 1,460 g of dextrin, 145 g of beeswax and 144 g of recitin were well mixed together and soft capsules were prepared according to the conventional producing method by the dosage unit of 550 mg.

Comparative example 2

3,410 g of soybean oil, 1,460 g of powder form of *Rubus coreous* extract (3:1), 341 g of dextrin, 145 g of beeswax and 144 g of recitin were well mixed together and soft capsules were prepared according to the conventional producing method by the dosage unit of 550 mg.

Comparative example 3

3,410 g of soybean oil, 1,460 g of dextrin, 341 g of soybean isoflavone (isoflavone 30%), 145 g of beeswax and 144 g of recitin were well mixed together and soft capsules were prepared according to the conventional producing method by the dosage unit of 550 mg.

Reference example 1: Preparation of pumpkin seed extract

3 kg of pumpkin seeds was grinded and extracted with 30 L of 70% ethanol twice while heating for about 3 hours and the extract was cooled and filtered. After concentrating the filtrate on the decompressed condition, 280 g of extract was obtained.

Experimental example 1: Effects of the composition of the present invention on incidence of urinary incontinence and urinary frequency.

After 50(52-70 years old) women having 7-9 incidences of urinary incontinence a week (Grade III) and 10-12 diurina were divided into 5 groups randomly, soft capsules prepared in example 1 and example 3 and comparative examples 1, 2 and 3 were administrated to each group twice a day (morning and evening) by 3 capsules each time for 6 weeks and incidence of urinary incontinence and diurina were measured and compared with those before administration.

As demonstrated in table 1, in case 'improved', 'good' and 'excellent' are considered to be effective, the effects of *Rubus coreous* extract (comparative example 2) and soybean isoflavone(comparative example 3) on incidence of urinary incontinence were ignorable but pumpkin seed oil and isoflavone(comparative example 1) showed effectiveness of 40%. Also, the composition of the present invention of example 1 and example 3 prepared by mixing said 3 components showed effectiveness of 90% and that degree of increase is remarkable.

Table 1

Effect of a composition of present invention on incidence of urinary incontinence

	Example 1	Example 3	Comparative example 1	Comparative example 2	Comparative example 3
Excellent(decreased more than 5 times)	3	4	1	0	0
Good(decreased 3-4 times)	5	4	2	0	1
Improved(decreased twice)	1	1	1	2	1
No difference (decreased once, increased once or no difference)	1	1	6	7	7
Aggravated(increased 2 times or more)	0	0	0	1	1
Total	10	10	10	10	10
Unit : number of person					

Table 2

Effect of a composition of present invention on diurina

	Example 1	Example 3	Comparative example 1	Comparative example 2	Comparative example 3
Excellent(decreased more than 5 times)	3	3		0	0
Good(decreased 3-4 times)	3	2	1	0	1
improved(decreased twice)	2	3	2	1	1
No difference (decreased once, increased once or no difference)	2	2	6	8	8
Aggravated(increased 2 times or more)	0	0	0	1	0
Total	10	10	10	10	10
Unit : number of person					

As demonstrated in table 2, in case 'improved', 'good' and 'excellent' are considered to be effective, effects of *Rubus coreous* extract (comparative example 2) and soybean isoflavone(comparative example 3) on daytime incidence of urination were ignorable but pumpkin seed oil and soybean isoflavone(comparative example 1) showed effectiveness of 40%. Also, the composition of the present invention of example 1 and example 3 prepared by mixing said 3 components showed effectiveness of 80% and that degree of increase is remarkable.

Experimental example 2

Effect of a composition of the present invention on closing pressure of urethra

30 female rabbits having a body weight of about 3.5 kg were divided into 6 groups (5 rabbits/a group). Thereafter, a mixture of 1,020 g of pumpkin seed oil, 438g of powder form of *Rubus coreous* extract (3:1) and 102 g of soybean isoflavone (isoflavone 30%)[a composition of the present invention 1], a mixture of 1,020 g of pumpkin seed extract and 102 g of soybean isoflavone (isoflavone 30%), a mixture of 438 g of powder form of *Rubus coreous* extract (3:1) and soybean isoflavone(isoflavone 30%)[a composition of the present invention 2], a mixture of 1,020 g of pumpkin seed oil and 102 g of soybean isoflavone(isoflavone 30%), and powder form of *Rubus coreous* extract (3:1) and soybean isoflavone (isoflavone 30%) were dispersed with 2% tween-80(polyoxyethylene sorbitan monoolate) aquous solution and the solution was orally administrated into each animal group twice a day(morning and evening) for 30 days using sonde. Then, maximum closing pressure of urethra was measured using micro catheters. Table 3 shows average percentage of the value changed before and after administration.

As demonstrated in table 3, the groups which were administrated with *Rubus coreous* and soybean isoflavone showed ignorable effect on closing pressure of urethra, while the groups which were administrated with the mixture of pumpkin seed oil and

soybean isoflavone showed average 16.6% of increase.

The groups administrated with the composition 1 of the present invention showed a dose-dependent manner, so the group administrated with high dosage or low dosage of composition showed 32.6% and 24.8% of increase each.

Also, the groups administrated with the composition 2 of the present invention showed 32.2% and that degree of increase is remarkable.

Table 3

Effect of a composition of the present invention on closing pressure of urethra

A composition of present invention 1 1000 mg/kg	A composition of present invention 1 500mg/kg	A composition of present invention 2 1000 mg/kg	Pumpkin seed oil + soybean isoflavone 700 mg/kg	*Rubus coreous* extract 264 mg/kg	Soybean isoflavone 62mg/kg
32.6	24.8	32.2	18.6	10.2	4.5
Unit: % of increase					

Experimental example 3 : Acute toxicity test

ICR 40 mice having a body weight of 23 g were divided into 2 groups and orally administrated with 5,000mg/kg of a composition 1 or composition 2 of the present invention prepared by experimental example 2 once a day for 7 days. Observation had been performed for 2 weeks after administration, no mouse died.

Industrial Applicability

The composition of pumpkin seed oil or pumpkin seed extract, *Rubus coreous* extract, and soybean isoflavone have showed the ability to decrease remarkably incidence of urinary incontinence and diurina and can be used as a therapeutic agent for urinary incontinence. In an animal model, as the phenomenon that closing pressure of urethra increases that is, ability to regulate urethra sphincter increases was observed, so the composition of the present invention can be useful for prevention of urinary incontinence as well as treatment.

Also, as the components of the composition have been widely used as safe materials and proved to show minimized side effects, the composition of the present invention can be extremely useful for the production of pharmaceutics and functional health foods for prevention and treatment of urinary incontinence.

What is claimed is:

1. A composition for prevention or treatment of urinary incontinence comprising pumpkin seed oil or pumpkin seed extract, *Rubus coreous* extract and soybean isoflavone as effective ingredients.

2. A composition for prevention or treatment of urinary incontinence in claim 1, wherein said composition comprises 100 parts by weight of pumpkin seed oil or pumpkin seed extract, 20-80 parts by weight of *Rubus coreous* extract and 5-30 parts by weight of soybean isoflavone.

3. A composition for prevention or treatment of urinary incontinence in claim 1 or claim 2, wherein said composition is produced in the forms of soft capsules, pills, suspensions, granules, tablets or liquid medicine.

4. A composition for prevention or treatment of urinary incontinence in claim 1 or claim 2, wherein said composition comprises at least one selected from the group consisting of additive, emulsifier, lubricant, conglutinant, sweetener, odorant, and vitamin etc.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 35/78, A23L 1/29

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KOREAN PATENTS AND APPLICATIONS FOR INVENTIONS SINCE 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
PubMed on-line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2001-342142 A (NISSUI PHARM. CO., LTD.), 11 December 2001 See entire document	1-4
A	US 6326366 B1 (PROTEIN TECHNOLOGIES INTERNATIONAL), 04 December 2001 See abstract	1-4
A	KR 2004-0036278 A (CHUNG-ANG UNIVERSITY et al.), 30 April 2004 See abstract	1-4
A	WO 02/17929 A1 (INTREAT PYT LIMITED), 07 March 2002 See entire document	1-4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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