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[Article in Japanese]

Translation from the original

Open Clinical Study of Effects of Pumpkin Seed Extract/ Soybean Germ Extract Mixture-containing Processed Food on Nocturia

Abstract

An open clinical study was conducted to investigate the efficacy and safety of a processed food containing a mixture of pumpkin seed *(Cucurbita pepo* L) extract and soybean germ extract (abbreviated as PEP, hereinafter) when given to elderly female patients with nocturia. The following results were obtained:

(1) PEP decreased the frequency of urination during both the night and daytime and frequency of incontinence with statistical significance, and also improved patients' sleep - related satisfaction.

(2) The frequency of urination incontinence was significantly decreased compared with before dosing PEP.

(3) There were 17 adverse events (43.6%) observed with 14 subjects (35.9%) in the total 39 subjects. Two subjects showed the increase of testosterone level in which the' causality of PEP was excluded with one subject and unknown with another. One of the two subjects recovered to the initial testosterone level on the 68m day after the end of administration, while another recovered on the 143m day. There were neither abnormal changes nor ether adverse events in which the causality of PEP was suspected. All the findings indicated PEP hag a feature of high safety.

In conclusion, PEP has demonstrated a highly favourable effect on various symptoms including nocturia in postmenopausal women as well as a high safety and tolerance.

I. Introduction

Urinary frequency becomes more common as the age advances, and nearly a half of elderly persons older than 60 years are known to suffer from nocturia, that is two or more episodes of micturition during the night. Nocturia is caused by a variety of factors such as prostate hypertrophy, uterine/ovarian disease, prostatitis, cystitis, diabetes insipidus, diabetes mellitus and neurogenic factors (particularly, cerebrovascular disorders, insomnia and stress). Urinary frequency and incontinence during the night have been indicated not only to induce insomnia and marked deterioration of patients' QOL, hut also to adversely affect the vital prognosis[1)]. As therapy for nocturia, various modalities such as pelvic floor muscle exercise, drug therapy, surgical procedures and ethers are available. Nevertheless, only a small proportion of the affected population visit hospitals, because most patients are likely to consider their symptoms as an inevitable complication of aging.

PEP is a health food product of SANA Co., Ltd., composed of triangle-shaped tablets containing pumpkin seed (Cucurbita pepo L. of Cucurbitales, Cucurbitaceae) extract and soybean germ extract. Pumpkin seed extract hag been granted approval by the German Federal Ministry für Health (published on B. Anz. No. 223 dated Nov. 3O, 1985 and revised B Anz. No.11 dated Jan. 17, 1991) as a therapeutic agent with the indications of irritable bladder (urinary frequency, pressure, incontinence, and sensation of residual urine) and early-stage prostate hypertrophy as described in Commission E Monograph, and is known to be effective in improving symptoms such as oliguria, sensation of residual urine, necessity to go to the toilet frequently during the night, and insomnia due to frequent micturition episodes at night[1),2)]. Soybean germ extract contains phytoestrogen of isoflavones[3)] and is potentially effective in ameliorating symptoms of geriatric disorders associated with estrogen deficiency such as osteoporosis, climacteric disorders (psychoneurological symptoms like headache, insomnia, depressive mood, etc.), atrophy of urogenital organs (including senile vaginitis, urinary incontinence, etc.) and cardiovascular disorders (including atherosclerosis, hypertension, etc.)[4)].

The design of the present study on the efficacy and safety of PEP in the treatment of nocturia was as follows.

II. Methods

1. Study subjects

The study subjects enrolled in the present study included “postmenopausal female patients (aged 55 to 79 years) who reported two or more micturition episodes during the night excluding an episode at leaving bed in the morning", who were outpatients of Medical Corporation Shinsenkai-Daiichi Hospital, Medical Corporation Juntenkai-Houshasen-Daiichi-Hospital and Medical Corporation Ohnishi Clinic. Before the study, written informed consent was obtained from the patients after providing with information on PEP.

Exclusion criteria included patients with (1) a fasting blood sugar level of 131 mg/dL or higher; (2) symptoms such as difficulty of urination, urinary retention, etc. indicative of definite obstruction of the lower urinary tract and urinary frequency due to cystitis; (3) severe complications disease such as heart, liver, kidney or hematologic disease; (4) regular consumption of a large amount of alcohol; (5) treatment with agents für urinary frequency within three months prior to the study; (6) known allergy to soybean or pumpkin; and (7) those who were judged as inappropriate at the investigator's discretion due to other reasons.

2. Study food

The study food used was a processed food product containing a mixture of pumpkin seed extract and soybean germ extract (PEP: SANA Co., Ltd.) Pumpkin seed extract (EFLA®940: Production No. 3012501) was procured from Emil Flachsmann AG, Switzerland, and soybean germ extract was procured from Tokiwa Phytochemical Co., Ltd. Six PEP tablets (1.5 g) contained 525 mg pumpkin seed extract and 100 mg soybean germ extract.

3. Study duration and dosage schedule

The duration of the study was 7 weeks in total, consisting of one week für observation and six. weeks für study food dosing. In weeks 1 and 2 of dosing, 10 tablets of PEP were given a day (corresponding to 875 mg pumpkin seed extract and 167 mg soybean germ extract), and in weeks 3, 4, 5 and6 of dosing, 6 tablets were given a day (corresponding to 525 mg of pumpkin seed extract and 100 mg soybean germ extract), each divided into two doses, in the morning and evening, together with a sufficient amount of co1d water or moderately warmed water.

4. Disallowed medication / allowable concomitant meditation

In principle, medication with agents that .might affect the assessment results of the study food including parasympatholytics and antispasmodics was prohibited. However, concomitant use of anticholinergics, tranquilizers, α-blockers, Ca-antagonists and antidepressants was allowed in unavoidable cases without changing the type and posology of concomitant medication(s) throughout the study period.

5. Assessment items and methods

(1) Subjective symptoms and objective findings

In the dosing period, the study subjects were asked to evaluate daily each of the items listed in Table 1 by themselves, and to make a record in a study diary, and the investigator conducted an interview to determine any objective findings each on the day and after 2 and 6 weeks of dosing.

Table 1 Diary items

- Subjective symptoms

[Frequency of urination during the night]

(number of episodes of going to the toilet during the period from the previous bedtime to the time of getting up in the morning)

[Frequency of urination during the daytime]

(number of episodes of going to the toilet during the period from getting up in the morning to bedtime)

[Frequency of urinary incontinence during the daytime]

(number of episodes of involuntary leakage of urine during the period trom getting up in the morning to bedtime)

[Degree of satisfaction]

(fulfilment following sleeping)

1. Fulfilled 2. Incompletely fulfilled 3. Not fulfilled

[Any findings to be reported]

(anything without restraint)

(2) Efficacy

Efficacy was rated as one of four grades "Markedly improved", "Improved", "No change" and "Worsened", by the investigator based on his (her) global judgment of subjective symptoms (by each item in the study diary) and objective findings each after 2 and 6 weeks of dosing.

(3) Other examinations

Vital sign recording (body weight, blood pressure, pulse rate), laboratory tests and hormone determinations (estrone, estradiol, progesterone, testosterone) were performed before and after 2 and 6 weeks of dosing. The laboratory tests performed included hematologic tests (WBC, RBC, hemoglobin, hematocrit and platelet count), blood biochemical tests (total bilirubin, BUN, creatinine, GOT, GPT, ALP and y-GTP) and urinalysis (qualitative tests of protein, glucose and urobilinogen).

(4) Adverse events

Adverse events in relation to subjective symptoms, objective findings and various laboratory test results were closely scrutinized of various factors including newly appearing symptom(s) (test item(s) with abnormal value), date of anger, degree, action, outcome, relation to the study food, etc. Abnormal laboratory test results were assessed by the investigator according to the "Severity Classification Criteria for Adverse Drug Reactions (former MHW Guidelines)" as cited in Table 2, and any change with a shift in grade toward higher severity was defined as an adverse event.

< Table 2 >

Table2: Severity Classification Criteria tor Adverse Drug Reactions
(N= the upper limited value of at each clinicals)

	Grade 1	Grade 2	Grade 3
Leucocyte (count/μl)	< 4000	3000	2000
Erythrocyte (count/μl)	$< 35 \times 10^6$	30×10^6	25×10^5
Hgb (g/dl)	11	9.5	8
Platelet (count/μl)	1×10^6	7.5×0^3	50×10^3
GOT, GPT	N x 1.25	N x 2.5	N x 5
ALP	N x 1.25	N x 2.5	N x 5
γ-GTP	N x 1.25	-	-
Total bilirubin (mg/dl)	1.6	3.0	10
BUN (mg/dl)	N	25	40
Creatinine (mg/dl)	N	2	4

III. Results

1. Study subjects

Age-related inclusion criteria were stipulated in the study protocol to include ages from 55 to 79 years, while informed consent was actually obtained from 42 women aged 52 to 86 years based on discretion that this difference in age ranges would not be a matter of concern from the viewpoint of patient characteristics, since the subjects were all in a postmenopausal state. Among these 42 subjects, one was excluded from the study because the blood sugar level exceeded the inclusion criterion in the pre-study screening examination, and two withdrew their consent to participate in the study voluntarily after registering for entry. The subject No.N-04 showed an abnormal high testosterone level of 227.4 ng/dL before dosing (female standard range: 6~86 ng/dL), but other aspects remained eligible with clinical data. As a result, 39 study subjects were eligible for efficacy and safety assessment, their characteristics being shown in Table 3. Mean age was 68.4 years old.

< Table 3 >

Table 3: Characteristics being of the subjects

Characteristics being (n=39)		Number of the subjects (%)
Age	52 - 59	7 (17.9)
	60 - 64	6 (15.4)
	65 - 69	9 (23.1)
	70 - 74	9 (23.1)
	75 - 79	4 (10.3)
	80 - 86	4 (10.3)
	Means ±SD	684+ 7.9
Frequency of urination during the night	2 times a day	14 (35.9)
	3 times a day	11 (28.2)
	4 times a day	8 (20.5)
	5 times a day	4 (10.3)
	6 times a day	2 (5.1)
	Means ±SD	3.4 ± 1.7 times a day
Past history	No	36 (92.3)
	Yes	3 (7.7)
Complication	No	23 (59.0)
	Yes	16 (41.0)
Concomitant medication	No	24 (61.5)
	Yes	15 (38.5)

2. Study results

1) Efficacy

(1) Records in study diary

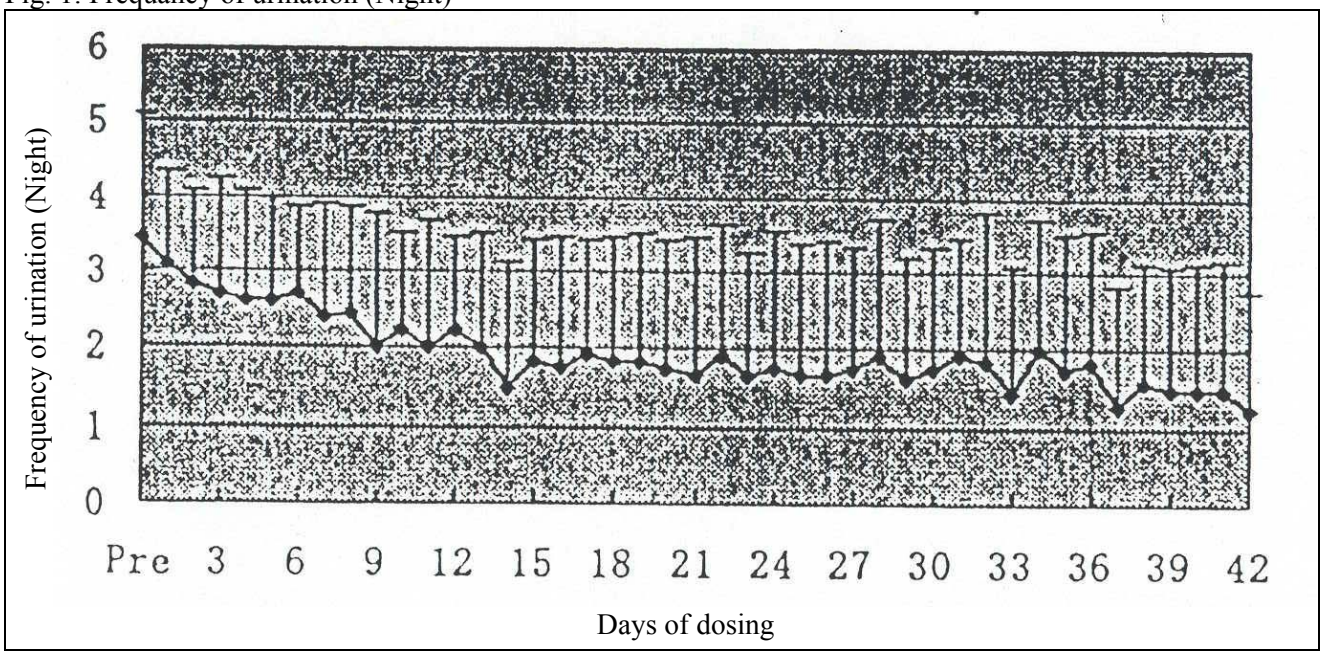
Figures 1 to 3 depict the time-course of changes in frequency of urination during the night, frequency of urination during the daytime, and subject satisfaction in the 39 efficacy assessment-eligible subjects. Subjective satisfaction was rated according to a scoring system of "l (fulfilled)", "2 (incompletely fulfilled)" and "3 (not fulfilled)", and items left blank due to the subject's unintentional omission were handled as missing values. Data analysis was performed by comparison of the median before (pre) and after dosing using paired *t-test* to determine statistical significance (Table 4). Effects on the frequency of urinary incontinence were examined using the data obtained from 16 particular subjects who experienced episodes of incontinence during the observation period, by comparing total episodes a week, during weeks 1, 2, 4 and 6 of dosing with total episodes in the observation period, using paired *t-test* to determine statistical significance (Table 5).

The following results were obtained: The frequency of urination during the night and daytime was already

markedly improved ($p<0.01$) at the week-l assessment, followed by continuing improvement at the week-2 assessment and no further additional improvement at the week-4 assessment and thereafter. The degree of satisfaction was improved ($p<0.05$) at the week-l assessment, followed by marked improvement ($p<0.01$) at the week-2 assessment. The frequency of urinary incontinence was improved ($p<0.05$) at the week-2 assessment, followed by marked improvement ($p<0.01$) at the week-4 assessment.

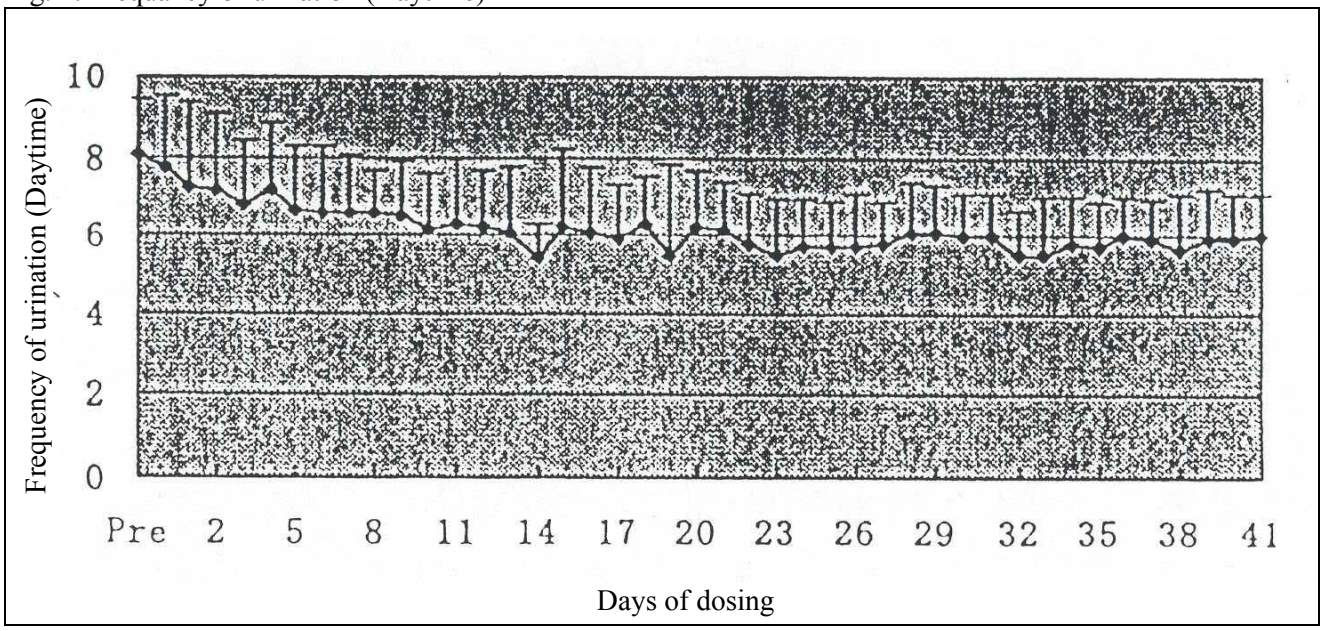
<Fig.l >

Fig. 1: Frequancy of urination (Night)

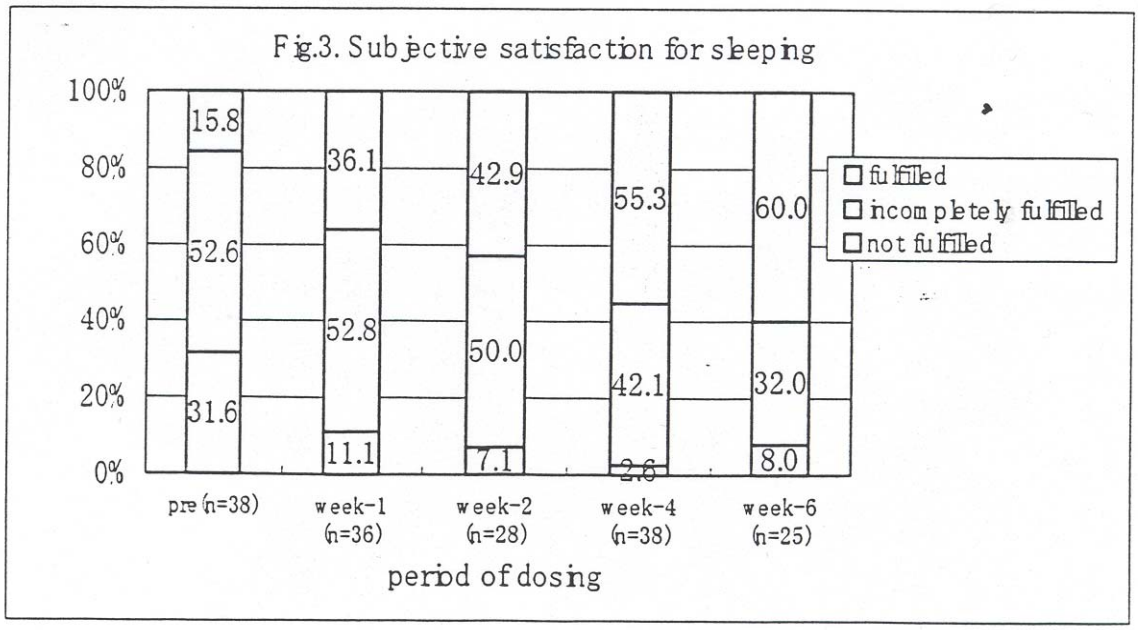


<Fig.2 >

Fig. 2: Frequancy of urination (Daytime)



< Fig. 3 >



< Table 4 >

Table 4: Subjective symptoms score: Frequency of urination during the night and the daytime, and subjective satisfaction.

	Means ± SD				
	Before dosing	Week 1	Week 2	Week 4	Week 6
Frequency of urination during the night (n)	3.3 ± 1.6 (39)	2.6 ± 1.5** (39)	2.5 ± 22** (31)	2.3 ± 1.9** (39)	2.0 ± 2.3** (28)
Frequency of urination during the day (n)	8.0 ± 2.6 (39)	7.0 ± 2.5** (39)	6.8 ± 2.9** (39)	6.5 ± 2.0** (39)	6.7 ± 2.3** (36)
Subjective satisfaction (n)	2.1 ± 0.6 (38)	1.8 ± 0.6* (36)	1.6 ±0.6** (28)	1.5 ± 0.6** (25)	1.5 ± 0.7** (25)

Mean ± S.D: ** $p < 0.01$, * $p < 0.05$

< Table 5 >

Table 5: Subjective symptoms score: Frequency of urination during the night and the daytime, and subjective satisfaction.

	Means ± SD				
	observation period (-7 – -1 days)	1st Week (0 – 6 days)	2nd Week (7 – 13 days)	4th Week (28 – 34 days)	6th Week (35 – 41 days)
Frequency of the urinary incontinence (n=16)	7.3 ± 8.3	5.5 ± 3.4	4.1 ± 3.5*	2.2 ± 2.2**	1.5 ± 2.7**

Mean ± S.D: ** $p < 0.01$, * $p < 0.05$

(2) Hormone determinations

Table 6 shows the results of hormone determinations. Statistical analysis was performed using paired *t*-test for comparison of the measurements before and after each of the dosing periods. There were no statistically significant changes in the levels of estrone, estradiol and progesterone.

The mean value of testosterone at the week-6 measurement (42.61±111.62 ng/mL) was higher than those obtained before dosing and at week-2 measurement, and this higher value was found to be ascribable to higher values in 2 of the 39 subjects. Testosterone levels in these two subjects were found to be higher than the mean value for normal men even at the pre-study measurement, the background of these higher values not being clear except for some possible involvement of high physiological sensitivity to testosterone of these subjects or effects of the study food.

After excluding these two subjects, testosterone level at week-2 and week-6 was 20.71±11.90 and 17.82±7.96 ng/mL, respectively, and the changes were found to be statistically insignificant by paired *t*-test.

Table 6: Results of hormone determination before and after each of the dosing periods.

Analysis items			Period of evaluation		
			Before dosing (n=39)	Week 2 (n=38)	Week 6 (n=39)
Hormones concentration in blood	Estrone (pg/mL)	Means ± SD (Max-Min)	17.0 ± 3.51 (28.2-15.0)	17.23 ± 3.39 (26.1-15.0)	16.78 ± 5.39 (46.0-15.0)
		paired *t*-test	-	p=0.79	p=0.75
	Estradiol (pg/mL)	Means ± SD (Max-Min)	9.86 ± 4.88 (28.6-8.0)	11.62 ± 10.17 (57.8-8.0)	11.78 ± 13.97 (90.3-8.0)
		paired *t*-test	-	p=0.30	p=0.24
	Progesterone (ng/mL)	Means ± SD (Max-Min)	0.26 ± 0.14 (0.6-0.1)	0.23 ±0.14 (0.6-0.1)	0.25 ± 0.15 (0.8-0.1)
		paired *t*-test	-	p=0.35	p=0.92
	Testosterone (ng/mL)	Means ± SD (Max-Min)	27.54 ± 34.48 (227.4-5.0)	38.58 ± 87.89 (536.9-5.0)	42.61 ±111.62 (619.1-5.9)
		paired *t*-test	-	p=0.29	p=0.13

Measurements below the determination limit (Estrone: 15 pg/mL, Estradiol: 8 pg/mL, Progesterone: 0.1 ng/mL)

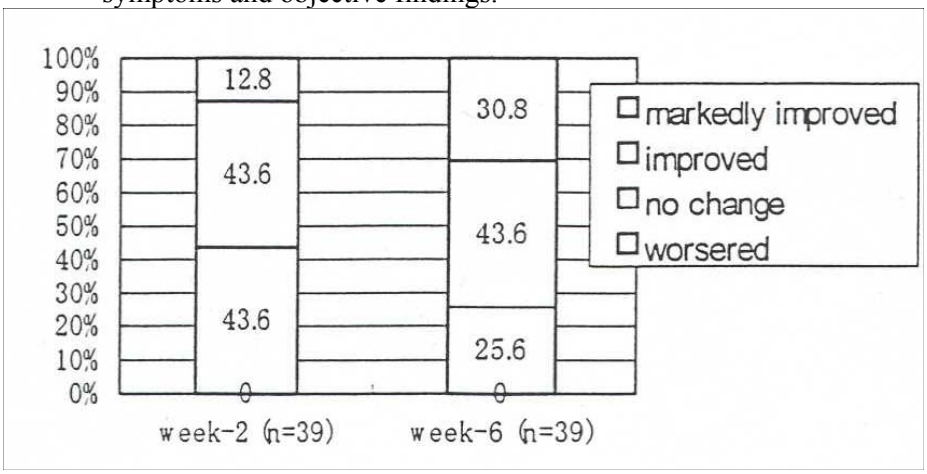
(3) Global improvement rate

Figure 4 depicts the global improvement rate based on global judgment of subjective symptoms and objective findings in the 39 subjects eligible for efficacy assessment. At the week-2 assessment, 12.8% and 59.0% of subjects were rated as "Markedly improved" and "Improved" or better, respectively, and at the week-6 assessment, 30.8% and 74.4% of me subjects were rated as "Markedly improved" and "Improved" or better,

respectively. The subject No.N-04 with high testosterone level before dosing was rated " Improved " at the week-2 and " Markedly improved" at the week-6. The subject No.D-20 with a remarkable increase of testosterone level during the test period was rated " No change" at the week-2 and "Improved" at the week-6. Figure 5 depicts the same global improvement rate in a particular subgroup of 33 subjects in whom me frequency of urination during the night was 2 to 4 episodes/day during the observation period. 5 subjects (15.2%) and 21 subjects (63.6%) were rated as "Markedly improved" and "Improved" or better, respectively, at the week-2 assessment, and 12 subjects (36.4%) and 27 subjects (81.8%) were rated as "Markedly improved" and "Improved" or better, respectively, at the week-6 assessment.

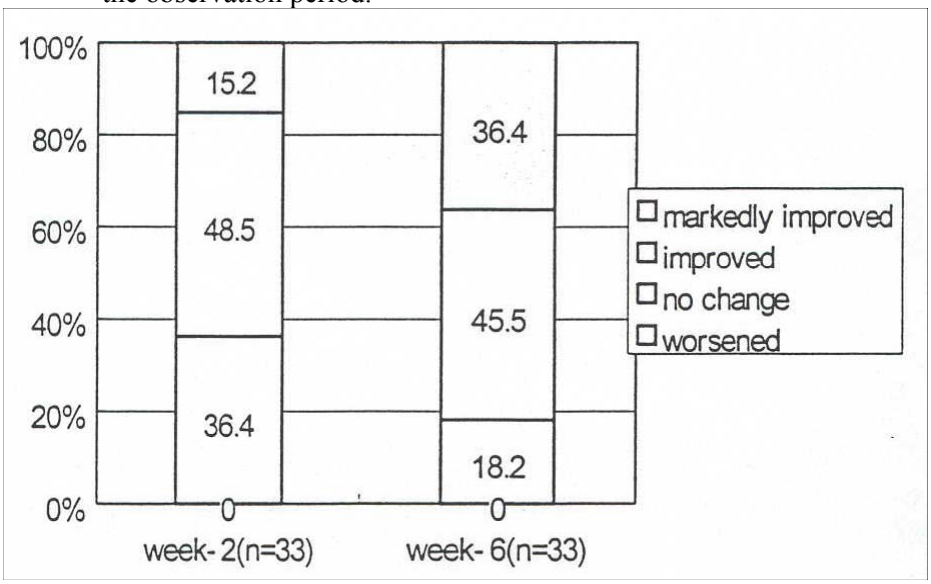
<Fig.4 >

Fig. 4: The global improvement rate based on global judgment of subjective symptoms and objective findings.



<Fig.5 >

Fig. 5: Global improvement rate in a particular subgroup of 33 subjects the frequency of urination during the night was 2 to 4 episodes/day during the observation period.



2) Safety

(1) Vital signs and laboratory test results

As shown in Table 7, there were no changes of clinical concern in mean values of vital signs and laboratory test results in the 39 subjects.

(2) Adverse events

Abnormal changes in laboratory test results and ether determinations are shown in Table 8, and adverse events in relation to subjective symptoms and objective findings are shown in Table 9.

Among the assessed 39subjects, the causality of PEP was not denied of the increase of testosterone level with the subject No. D-20 who showed an increase of estron and estradiol levels as well. In this case the causality was first considered to be ascribable to instability of sex hormone levels and/or disorder of adrenal function. However it was not identified and concluded unknown in the outcome of the present study.

In relation to other adverse events, causality of the study food was ruled out.

Table 7: Vital signs and laboratory test results before and after each of the dosing periods (n=39).

		Standard value		Period of evaluation		
				Before dosing	Week 2	Week 6
Vital sign	Weight	- (kg)	Means ± SD (Max-Min)	51.8 ± 11.0 (85-34)	51.9 ± 11.0 (85-35)	51.8 ± 10.8 (89-34)
	Systolic blood pressure	90-140 (mmHg)	Means ± SD (Max-Min)	136.7 ± 21.3 (196-95)	137.7 ± 23.1 (190-98)	130.4 ± 19.8 (164-82)
	Diastolic blood pressure	~ 90 (mmHg)	Means ± SD (Max-Min)	74.9 ± 12.7 (100-50)	75.5 ± 13.16 (102-42)	72.1 ± 13.7 (100-50)
	Pulse	50-110 (/min)	Means ± SD (Max-Min)	74.4 ± 10.7 (100-60)	73.3 ± 10.4 (100-54)	73.4 ± 9.7 (96-60)
Blood	Leucocyte	40-80 (count/μl)	Means ± SD (Max-Min)	67.4 ± 18.6 (123-34)	64.9 ± 17.3 (106-38)	68.5 ± 21.7 (141-43)
	Erythrocyte	370-490 (count/μl)	Means ± SD (Max-Min)	427.6 ± 36.2 (521-357)	421.8 ± 38.43 (532-335)	423.5 ± 42.6 (510-309)
	Hgb	10.7-15.0 (g/dl)	Means ± SD (Max-Min)	13.41 ± 1.20 (15.8-9.6)	13.17 ± 1.27 (15.5-9.6)	13.21 ± 1.33 (15.9-9.1)
	Hematocrit	34.4-44.0 (%)	Means ± SD (Max-Min)	39.82 ± 3.47 (47.6-30.2)	39.43 ± 3.69 (46.2-29.1)	39.51 ± 3.94 (45.8-28.7)
	Platelet	15-40 (count/μl)	Means ± SD (Max-Min)	22.51 ± 5.75 (40.3-12.7)	22.09 ± 6.23 (43.2-14.7)	22.48 ± 6.73 (39.0-12.3)
Biochemical	GOT	10-35 (IU/L)	Means ± SD (Max-Min)	23.4 ± 5.8 (42-16)	22.8 ± 5.4 (45-16)	21.9 ± 4.6 (34-14)
	GPT	5-38 (IU/L)	Means ± SD (Max-Min)	20.0 ± 10.4 (67-9)	19.1 ± 10.7 (68-9)	18.2 ± 8.4 (47-9)
	ALP	70-250 (IU/L)	Means ± SD (Max-Min)	180.2 ± 60.2 (366-82)	177.1 ± 57.8 (308-94)	173.5 ± 55.0 (296-174)
	γ-GTP	4-63 (IU/L)	Means ± SD (Max-Min)	22.3 ± 14.6 (62-7)	22.1 ± 14.9 (64-5)	23.0 ± 18.1 (96-5)
	Total bilirubin	0.2-1.2 (mg/dl)	Means ± SD (Max-Min)	0.65 ± 0.24 (1.2-0.2)	0.64 ± 0.25 (1.4-0.3)	0.67 ± 0.22 (1.1-0.2)
	BUN	8.0-20.0 (mg/dl)	Means ± SD (Max-Min)	16.03 ± 3.73 (25.2-11.2)	15.33 ± 3.82 (26.5-8.7)	15.25 ± 3.49 (22.3-8.2)
	Creatinine	0.5-1.1 (mg/dl)	Means ± SD (Max-Min)	0.64 ± 0.14 (1.0-0.4)	0.62 ± 0.11 (1.0-0.5)	0.61 ± 0.12 (0.9-0.4)
Urin	Protein	- ~ ±	+	1	0	2
			±	6	6	3
			-	32	33	34
	Urine sugar	- ~ ±	+	0	0	0
			±	0	0	0
			-	39	39	39
	Urobilinogen	- ~ ±	+	2	0	0
			±	37	39	39
			-	0	0	0

< Table 8 >

D-06	62	Erythrocyte count	37-49 ($x10^6$/μL)	35.7*	34.4* mild	36.1	recovery during dosing	No
D-08	59	systolic blood pressure	90 –140 mmHg	144*	160	82* mild	need no follow- up study	No
D-20	52	testosterone	6 - 86 ng/dL	46.2	183.6*	383.3* middle	recovery to 27.1 ng/dL after 143 days of study	unclear
D-21	74	Erythrocyte count	37 – 49 ($x10^6$/μL)	36.6*	35.1*	33.0* mild	need no follow- up study	No
		Hgb	10.7 - 15.0 g/dL	9.6*	9.6*	9.1* mild	need no follow- up study	No
		Protein	- ~ ±	±	±	+* mild	need no follow- up study	No
D-22	71	Erythrocyte count	4-8 ($x10^6$/μL)	4.6	3.8* mild	4.4	recovery during dosing	No
D-26	69	BUN	8.0 -20.0 (mg/dL)	15.2	21.3* mild	14.4*	recovery during dosing	No
		Protein	- ~ ±	±	±	+* mild	recovery ± after 29 days of indication	No
D-28	71	γ-GTP	4-63 (IU/L)	62	64	96* mild	need no follow- up study	No
D-29	79	BUN	8.0 -20.0 (mg/dL)	22.3*	26.5* mild	18.4	recovery during dosing	No
N-03	84	Erythrocyte count	37-49 ($x10^6$/μL)	37.1	33.5*	30.9* mild	need no follow- up study	No
N-04	59	Testosterone	6-86 (ng/dL)	227.4*	536.9*	619.1* middle	recovery to 101ng/dL after 68 days of indication	No

< Table 9 >

Table 9: Adverse events based on subjective symptoms and objective findings.

Subject No.	age	symptoms	time of occurrence	grade of symptom	Medical treatment	exitus	relevancy
D-12	74	cold syndrome	after 3 days	mild	No	Disappear after 2 days	No
D-16	80	cold syndrome	after 11 days	mild	treatment with general medicine	recover after 2 days	No
D-24	57	Abdominal distension	the day starting to	mild	No	Disappear bifore starting to dose	No
D-34	61	diarrhea	after 38 days	mild	No	Disappear at the day having diarrhea	No

IV. Discussion

The results of the present study revealed that the frequency of urination during the night and daytime, degree of satisfaction following sleeping, and number of episodes of urinary incontinence were decreased with statistical significance after six weeks of intake of the processed food product containing a mixture of pumpkin seed extract and soybean germ extract (PEP) compared with be fore its intake. These favourable effects were reflected in high improvement rates as shown by global improvement rating of "Improved" or better in 59.0% (23/39) and 74.4% of subjects (29/39) at the week-2 and week-6 assessment, respectively. In addition, in the 33 subjects with 2 to 4 episodes of nocturia per night, the improvement rate was ever higher, as shown by a rating of "Improved" or better in 81.8% of subjects (27/33) at the week-6 assessment. This high efficacy is considered to be ascribable to anti-inflammatory, antimicrobial and bladder tissue-reinforcement effects;) of pumpkin seed extract, and affinity to SHBG (sex hormone binding globulin), and 5a-reductase- and aromatase-inhibitory effects of lignan, one component of pumpkin seed extract, as well as estrogen-like effects3) of soybean germ extract, resulting not only in reducing the frequency of urination bur also in ameliorating climacteric disorder-associated symptoms such as psychoneurological symptoms including insomnia and urinary incontinence[4)]. Other pathologic conditions causing urinary frequency and urinary incontinence, however, include central nervous system disorders associated with cerebral infarction or cerebral thrombosis, spinal cord injury and aging-associated spondylosis deformans. The finding obtained in the present study that the study food could achieve higher improvement rates in the subjects with urinary frequency suffering from relatively fewer episodes of urination is considered to be due to the general circumstances that patients with intractable neurogenic bladder are not incorporated in the population of patients with a few episodes of urination. Neurogenic bladder is known to present same problems in that 10 to 20% of patients do not respond positively to medication with anticholinergic agents, and attention should be paid to their possible adverse drug reactions such as urinary disturbance, mouth dryness, constipation, etc. as well as to concomitant diseases and medications, and thus, introduction of the study food into practical use would be highly valuable.

The adverse events were observed of 17 cases with 14 subjects (Table 8). There was no considerable fluctuation in the change in vital signs and laboratory test results. In hormone determinations, levels were not significantly different before and after dosing, allowing us to exclude the involvement of hormone, esp. female sex hormone, in the outcomes of the present study. The abnormal increase of testosterone level was observed with the subject No. D-20 whose global improvement was however rated "Improved" at the week 6 assessment. In this case the causality of PEP was not identified and concluded unknown in the outcomes of the present study.

In relation to other abnormal changes and adverse events, causality of PEP was ruled out, indicating PEP has a feature of high safety and tolerance.

In conclusion, the study food, containing a mixture of pumpkin seed extract and soybean germ extract, has demonstrated that it is a promising health food endowed with favourable effects on various symptoms including mild nocturia in postmenopausal women.

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