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Clinical Study of mixed processed foods containing pumpkin seed extract and soybean germ extract on pollikiuria in night in elderly men

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English Translation

Clinical study of mixed processed foods containing Pumpkin seed extract and soybean germ extract on pollakiuria in night in elder men

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Abstract

To confirm the efficacy and safety of the mixed processed foods (PEP®) containing of Pumpkin seed extract EFLA®940 and soybean germ extract on pollakiuria in night, a clinical study was performed by 6-week intake using 54 males (age 65 – 88) with pollakiuria in night symptoms. The results showed the following:

1) The frequency of urination in the night was significantly reduced in all 45 cases included in the efficacy evaluation, as compared to before intake.
2) Out of 51 cases included in the safety evaluation, adverse events were observed in 33 incidences in 22 cases (43.1%). Those for four incidences in 3 cases (5.9%) were judged 'could be related to PEP® intake'. Since all of them were mild, followed by disappearance of or recovery from symptoms later, the results suggest that PEP® is highly safe.

Thus, PEP® effectively improves symptoms of pollakiuria in night and PEP® is used safely.

Introduction

PEP®, a granular product in triangular shape, is sold by Tervis Co., Ltd. It is a nutrition-supplemental food containing a water-soluble extract of Pumpkin seed EFLA®940 in the squash group of the melon family and soybean germ extract. The edible Pumpkin seed are approved as an effective therapeutic against hyperactive bladder (pollakiuria, urgency, incontinence, and residual) and early stages of prostatic hypertrophy in the guideline for plant therapeutics from the Ministry of Health in Germany (published on November 30, 1985). They are reported to be effective against symptoms of smaller volume of urination, residual feeling, pollakiuria, and insufficient sleep due to pollakiuria in the night[2)3)]. Soybean germ extract contains isoflavone-derived phytoestrogen[4)] and is known to relieve aging symptoms such as osteoporosis due to estrogen insufficiency, psychological/sympathetic nerve symptoms (menopausal syndromes such as headache, insomnia, and depression), urinary symptoms (prostatic symptoms and erectile dysfunction), and cardiovascular symptoms (arteriosclerosis and hypertrophy).

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Clinical study of mixed processed foods containing of Pumpkin seed extract EFLA®940 and soybean germ extract on pollakiuria in night in elder men

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Key words: pumpkin seed, soybean germ, pollakiuria in night, elderly men, clinical study

Pollakiuria in night is defined as 'the condition in which one is awakened by an urge to urinate during sleep in the night' {The Word Standards by International Continence Society (ICS), 2002}. According to the 'epidemiological study on urination' performed by the Japanese Urination Function Society in 2002, pollakiuria in night occurs with about an 80% frequency in one's 60s and more than 90% in people over the age 80.

Pathology of pollakiuria in night are classified in the two main groups: (1) lower-urinary tract-associated (urinary disease) and (2) lower-urinary tract-non-associated (non-urinary disease).

Urinary diseases include prostatic hypertrophy, prostatitis, neuropathic bladder, and hyperactive bladder which cause a decrease of organic and functional bladder volume resulting from bladder involution and residual urine.

On the other hand, non-urinary diseases include cardiac and renal dysfunction, excessive water intake, age-associated decrease of diuretic hormone secretion, and sleep disorder. Sleep disorder reduces the threshold for urination sensation, leading to reduction in functional bladder volume and pollakiuria in night. In elderly men, these complex symptoms make diagnosis and treatment difficult.

It has been reported in efficacy studies that PEP® is significant effect on pollakiuria in night and abdominal pressure-associated incontinence in women[5) 6)]. The present study examines the efficacy and safety of PEP® on pollakiuria in night in men.

I. Methods

1. Subjects

Between January and June 2004, the subjects were men older than 65 years of age who woke up more than two times for urination in the night and who were selected from among the out-patients at Shinseikai-Daiichi Hospital in Imabari City in Ehime Prefecture, Ohnishi Clinic in Ochi-Gun in Ehime Prefecture, and Saito Internal Medicine & Urology Clinic in Maebashi City in Gunma Prefecture. Prior to the study, written consent was obtained from each subject after explaining about the test method and PEP®. The following patients were excluded from the study: (1) Ones with serious complications involving the heart, liver, kidney or blood, (2) ones with allergies to soybeans and Pumpkin, (3) ones who received surgical therapy for prostatic hypertrophy in the past year, (4) ones who had had hormone drugs for prostatic hypertrophy in the past month, (5) ones with urinary tract stent or urinary tract catheter, (6) ones with urinary tract disorder from urinary calculus or pollakiuria from acute inflammation in the urinary tract such as, for example, cystitis, (7) ones who may have taken health food known to have effects on pollakiuria in night during the study period, (8) ones who have drunk excessive alcohol, (9) ones with a fasting blood level higher than 140 mg/dL glucose, and (10) ones who are judged 'improper' by the physician-in-charge for other reasons.

2. Food tested

The test sample was the mixed processed food (PEP®, Tervis Co., Ltd.) containing of water-soluble extract EFLA®940 of edible Pumpkin seed and soybean germ. Ten tablets of PEP® (2.5 g) contained 875 mg of water-soluble extract EFLA®940 of edible Pumpkin seed and 167 mg of soybean germ extract, and six tablets of PEP® (1.5 g) contained 525 mg of water-soluble extract EFLA®940 of edible Pumpkin seed and 100 mg of soybean germ extract.

3. Study period and intake method

The study period was one week of observation (Step 1) followed by six weeks of intake, in a total of 7 weeks. In the first and second weeks of intake (Step 2), five tablets were taken with cool water or warm water twice a day in the morning and evening. In the following third week through the sixth week (Step 3), three tablets were taken twice a day.

4. Drugs prohibited or restricted from concurrent use

Hormone drugs (anti-androgens and estrogen drugs) which are used as therapeutics for prostatic hypertrophy and may influence the efficacy evaluation of the test food were prohibited from concurrent use. The following drugs were allowed without changes in drug type, method of use, and

Table 1. Entries in subject's diary

[Intake compliance for test food]	
Morning/evening	
[Subjective symptoms]	
• Urination frequency during the day:	The number of times you went to bathroom between the times you woke up and went to bed.
• Urination frequency during the night:	The number of times you woke up to go to bathroom through the night.
• Satisfaction with sleep:	Satisfaction level about sleep after consideration of urination in the night. 1. Satisfied 2. Slightly satisfied 3. Slightly unsatisfied 4. Unsatisfied
• Comments:	Describe any changes noticed in yourself.

Table 2. Evaluation standards for abnormality in laboratory analyses
(Partially quoted from the standards by the Japanese Chemotherapy Society)

[Blood biochemistry]
AST (GOT), ALT (GPT), ALP, LDH, γ-GTP, BUN, creatinine
[1] Standard range to outside of standard range
Abnormal changes are those which are more than 1.2 times the upper limit of standard range.
[2] Outside of standard range to outside of standard range
Abnormal changes are those which are more than 2 times the previous level.
[Urinalysis]
1. Urinary protein: Changes of more than 2 grades from (-) to (+)
2. Urinary glucose: Changes by more than 2 grades
3. Urobilinogen: Changes by more than 1 grade

dosage: α-receptor blockers, plant extracts/Chinese medicines, amino acid drugs and α, β receptor stimulators, anticholinergics, anti-anxiety drugs, and antidepressants.

5. Evaluation items and methods

1) Subjective and objective symptoms

During the study period, subjects recorded each day intake compliance and subjective symptoms (**Table 1**). Based on the records, the physician-in-charge questioned subjects on the day of intake start (after Step 1 completion), after intake for two weeks (after Step 2 completion) and after intake for six weeks (after Step 3 completion) and made evaluations on subjective symptoms.

2) Improvement of subjective symptoms

Comprehensively judging based on responses to questioning and records made by subjects (Table1), the physician-in-charge evaluated improvements of subjective symptoms by the four grades of 'significantly improved', 'improved', 'unchanged', and 'aggravated'.

3) Laboratory analysis

Laboratory analyses were performed at the time of Step 1 start and after completion of Steps 2 and 3, including blood biochemistry (AST, ALT, ALP, LDH, γ-GTP, BUN, and creatinine) and urinalysis (qualitative protein, qualitative glucose, and qualitative urobilinogen).

4) Adverse events

Symptoms (including abnormal changes in laboratory analyses), time of occurrence, grade (severity and seriousness), treatment, outcome, and relatedness to the test food were examined for all adverse events.

Adverse events included all subjective and objective symptoms identified in subject's records which were not beneficial to subjects who took the test food.

For the evaluation of abnormal changes in laboratory analyses, the physician-in-charge determined them to be 'adverse events' in reference to 'Evaluation standards for abnormality of laboratory analyses' (a part of the Japanese Chemotherapy Society Notification: **Table 2**).

Table 3. Background factors of subjects (n=51)

Background factor			Number of cases (%)
Age (years)		65 - 69	27 (52.9)
		70 - 74	14 (27.5)
		75 - 79	8 (15.7)
		80 - 84	1 (2.0)
		85 - 88	1 (2.0)
		Mean±SD	70.4±4.8
Age of onset of pollakiuria in night (years)		53 - 59	3 (5.9)
		60 - 69	31 (60.8)
		70 - 79	8 (15.7)
		80 - 81	1 (2.0)
		Unknown	8 (15.7)
		Mean±SD	65.4±5.3
Period with pollakiuria in night (years)		<1	2 (3.9)
		1 - 4	23 (45.1)
		5 - 9	11 (21.6)
		10 - 14	6 (11.8)
		15 - 19	1 (2.0)
		Unknown	8 (15.7)
		Mean±SD	5.3±3.8
The number of urination in the night at Step 1, (times/night)		1.7 - 1.9	2 (3.9)
		2.0 - 2.9	28 (54.9)
		3.0 - 3.9	10 (19.6)
		4.0 - 4.9	8 (15.7)
		5.0 - 9.3	3 (5.9)
		Mean±SD	3.09±1.30
Presence or absence of soybean or Pepo Pumpkin allergy		No	51 (100.0)
		Yes	0 (0.0)
Complications	Presence/ absence	No	22 (43.1)
		Yes	29 (56.9)
	Disease name[*2]	Hypertension	15
		Prostatic hypertrophy[*1]	7
		Insomnia	4
		Hyperuricemia	3
		Arrhythmia	3
		Angina pectoris	3
		Constipation	3
		Gastritis	3
		Gonarthrosis	2
		Obliterating arteriosclerosis	2
		Hyperlipidemia	2
		Pollakiuria	1
		Old myocardial infarction	1
		Chronic bronchitis	1

Background factor			Number of cases (%)
Complications	Disease name[*2]	Hypotension	1
		Thoraco-abdominal aneurysm	1
		Cerebral infarction	1
		Parkinson's disease	1
		Direct hernia	1
		Right upper arm nerve pain	1
		Lumbar slipping	1
		Rib fracture	1
		Gout	1
		Osteolumbago	1
		Cerebral infarction after-effect	1
		Atrial fibrillation	1
		Supraventricular premature beat	1
		Osteomyelopathy	1
		Neurogenic bladder	1
		Alcoholic hepatopathy	1
		Gastric ulcer	1
		Anxiety neurosis	1
Disease history	Presence/ absence	No	25 (49.0)
		Yes	26 (51.0)
	Disease name[*2]	Appendicitis	3
		Cholecystitis	3
		Prostatic hypertrophy	2
		Direct hernia	2
		Lung cancer	2
		Duodenal ulcer	2
		Angina pectoris	1
		Cerebral thrombosis	1
		Colon cancer	1
		Rectal polyp	1
		Bladder tumor	1
		Left wrist fracture	1
		Acute myocardial infarction	1
		Maxillary empyema	1
		Pulmonary Aspergillosis	1
		Dysentery	1
		Herniated disc	1
		Pulmonary tuberculosis	1
		Drug-associated hepatopathy	1
		Cataract	1
		Pleurisy	1
		Abdominal arterial aneurysm	1
		Acute pancreatitis	1
		Unknown	1
Presence or absence of concurrent use of drugs for pollakiuria		No	43 (84.3)
		Yes	8 (15.7)

*1: Name of diagnosed diseases recorded in clinical records. *2: Include multiple answers.

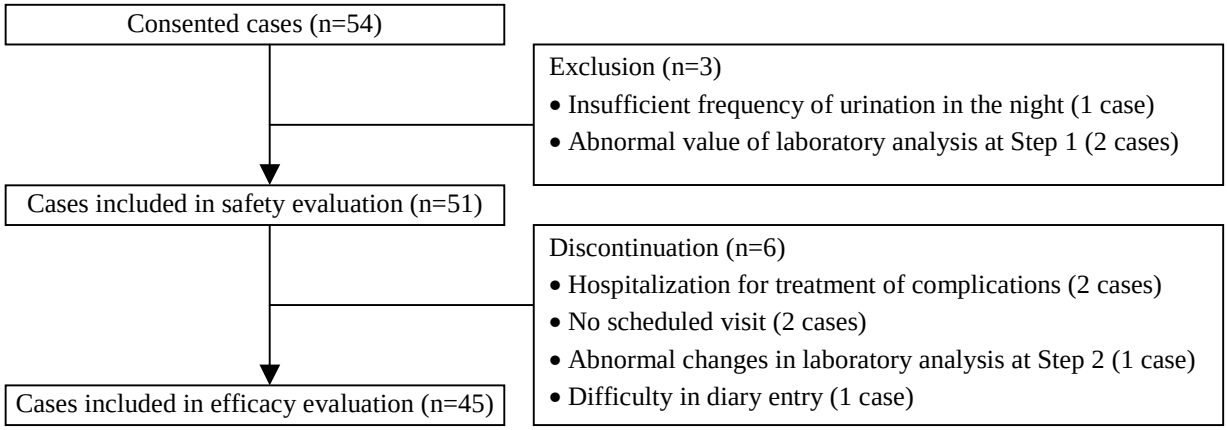

Fig. 1. The number of cases

II. Results

1. Subjects

Consents were obtained from a total of 54 subjects between ages 65 and 88. However, three cases were excluded from the study before the start of PEP® intake, including one subject who did not meet the selection standard for pollakiuria in night and two subjects with highly abnormal values (grade 3) by the laboratory analysis performed at the start of Step 1. Therefore, the safety was evaluated in a total of 51 cases who took PEP®. **Table 3** shows the background factors of these subjects.

In addition, the study was discontinued in the following six cases; two cases who were hospitalized for the treatment of complications during the study period, two cases who could not make scheduled visits to hospital for personal reasons, one case with a Grade 3 abnormality in laboratory analyses performed at Step 2 completion, and one case who had somebody else make record entries due to a difficulty of recording in diary by himself. Thus, the efficacy was evaluated in a total of 45 cases (**Fig. 1**).

Among the 45 cases included in the efficacy evaluation, seven subjects had complications of prostatic hypertrophy, and four subjects had a prostate condition apparently associated with hypertrophy. In addition, there were one subject each with complications of pollakiuria and neurogenic bladder and four subjects with complications of insomnia. No particular condition was identified in the backgrounds of the other cases.

Compliance for intake of the test food was examined from the records in the diaries made by the subjects themselves. **Table 4** shows an excellent compliance in intake for all subjects, showing no interference for evaluations.

Table 4. Compliance with schedule for test food intake (n=45)

Intake compliance	Step 2	Step 3
Total mean (%)	99.01±3.00	99.04±3.02

2. Study results

1) Efficacy

[1] Night and daytime urination frequency

Fig. 2 shows the changes in total frequency (%) after Step 2 and Step 3, in comparison to total urination frequencies in the day and night at Step 1, which was taken as 100%. The urination frequency in the night appeared to decrease, showing about a 40% decrease after intake for 6 weeks.

On the other hand, no significant change in urination frequency in the daytime was observed after intake for 6 weeks.

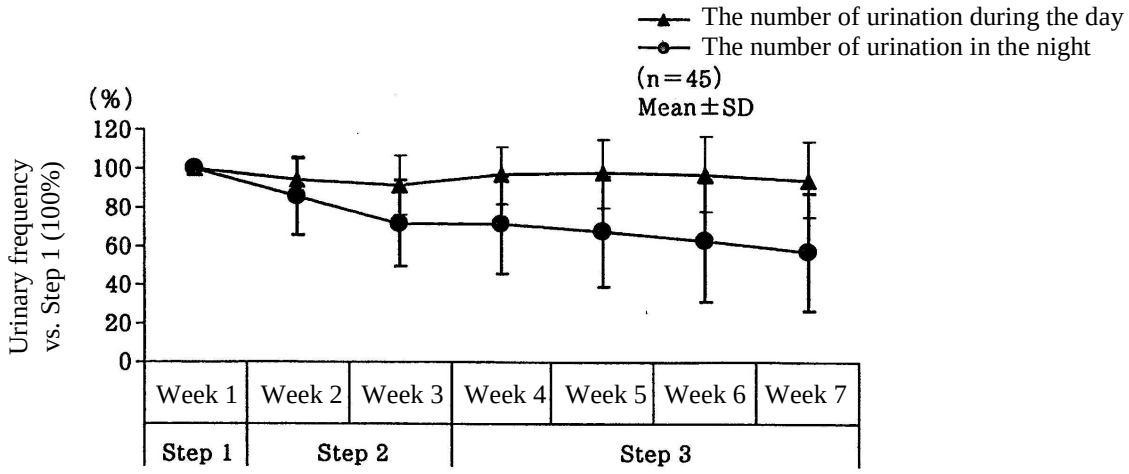

Fig. 2. Change in urination frequency (1) – Average weekly urination frequency

Table 5. Number of urinations in the night (times/night)

	Mean±SD		
	Step 1	Step 2	Step 3
Total (n=45) (highest-lowest)	3.04±1.30* (9.3 - 1.7)**	2.46±1.35* (9.4 - 1.0)	2.08±1.65** (10.2 - 0.2)
Group A (n=8) (concurrent use of urination drugs)	3.45±2.50 (9.3 - 2.0)	3.50±2.52 (9.4 - 1.7)	3.45±3.01 (10.2 - 1.0)
Group B (n=37) (no concurrent use of urination drugs)	2.95±0.89†‡ (5.9 - 1.7)	2.23±0.84† (4.4 - 1.0)	1.79±1.02‡ (5.5 - 0.2)

*, **, †, ‡ : p<0.01

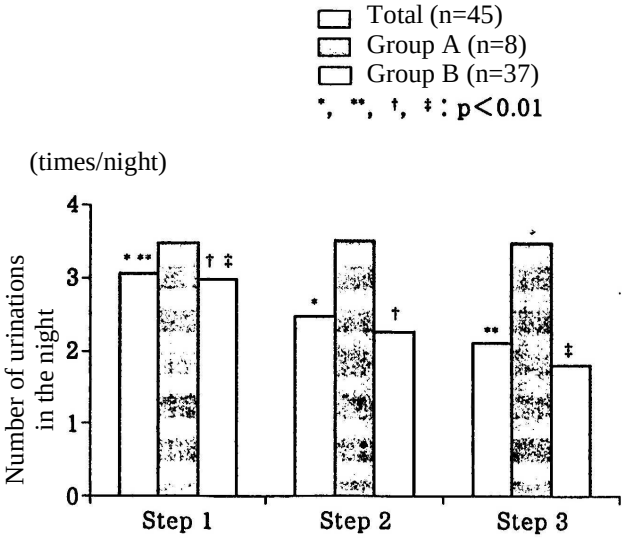

Fig. 3. Change in urination frequency (2)
Average nocturnal urination frequency in the night

The 45 cases included in the efficacy evaluation were divided into the two groups; one with concurrent use of therapeutic drugs for pollakiuria (Group A) and another without (Group B). **Table 5** and **Fig. 3** show mean values of urination frequency in the night at each step.

Corresponding t test was performed between the mean values at Step 1 and after intake (Step 2 and 3). A significant decrease was observed in the frequencies for the total and Group B ($p<0.01$). On the other hand, there was no significant change in Group A.

[2] Sleep satisfaction level

The sleep satisfaction level was scored by 2 points for 'satisfied', 1 point for 'slightly satisfied', -1 point for 'slightly unsatisfied', and -2 points for 'unsatisfied'. The mean value was calculated for each Step (**Table 6**). The sleep satisfaction level was analyzed in the two groups similarly as described above, one with concurrent use of therapeutic drugs for pollakiuria (group A) and another without (Group B), among 45 cases included in the efficacy evaluation. Corresponding t test was performed between Step 1 and after intake (Step 2 and 3).

Table 6. Sleep satisfaction (points)

	Mean±SD		
	Step 1	Step 2	Step 3
Total (n=45) (highest-lowest)	0.08±1.17* (2.0 - -2.0)**	0.73±0.97* (2.0 - -1.2)	0.90±0.93** (2.0 - -1.3)
Group A (n=8) (concurrent use of urination drugs)	0.00±1.34 (2.0 - -2.0)	0.04±1.13 (1.9 - -1.2)	0.24±1.13 (1.6 - -1.3)
Group B (n=37) (no concurrent use of urination drugs)	0.10±1.15†‡ (2.0 - -2.0)	0.88±0.88† (2.0 - -1.0)	1.04±0.83‡ (2.0 - -1.0)

*, **, †, ‡ : $p<0.01$

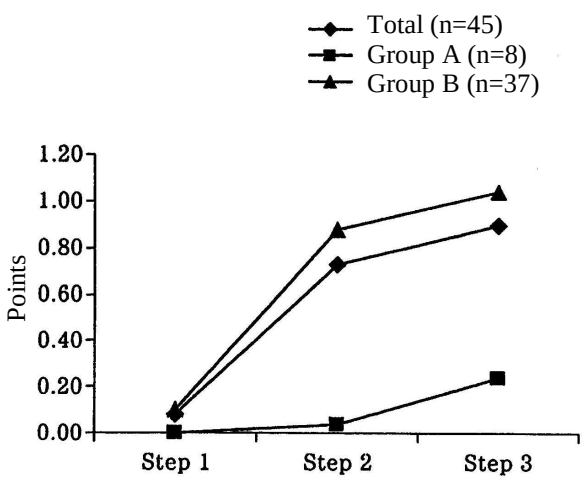

Fig. 4. Change in sleep satisfaction level

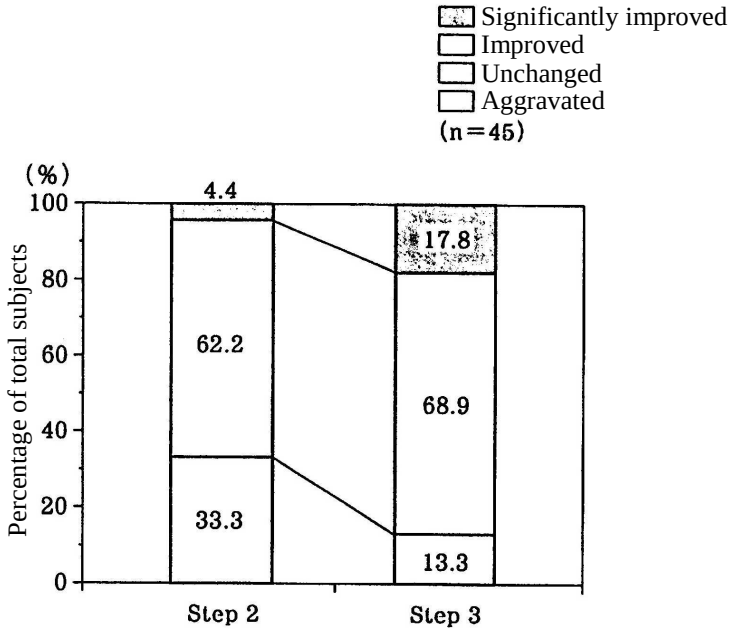

Fig. 5. Changes in subjective symptoms improvement

As shown in **Fig. 4**, a significant improvement was observed ($p<0.01$) in the total and Group B. In particular, when Step 1 and Steps 2 are compared, almost no change is observed in Group A, whereas there was a significant improvement in Group B.

[3] Improvement level of subjective symptoms

Fig. 5 shows the improvement levels of subjective symptoms which were comprehensively evaluated by the physician-in-charge by questioning and diary entries of 45 cases included in the efficacy evaluation. At Step 2, 2 cases (4.4%) were 'significantly improved' and 28 cases (62.2%) were 'improved'. At Step 3, 8 cases (17.8%) were 'significantly improved' and 31 cases (68.9%) were 'improved'. There was no 'aggravated' case in both periods.

2) Safety

Table 7 shows adverse events observed in subjective symptoms and objective observation. Abnormal changes in laboratory analyses are shown in **Table 8**. Adverse events were observed on 33 incidences in 22 out of 51 cases (43.1%). Among them, the relationship to PEP® could not be excluded on 4 incidences in 3 cases (5.9%). Other 29 incidences in 19 cases (37.3%) were judged to be not related to the test food.

Table 7. Adverse events identified by subjective symptoms and objective observation

Subject identification code	Age (years)	Symptom	Time of occurrence	Severity[*1]	Treatment/ procedure	Outcome	Relationship to test food[*2]
A-01	67	Diarrhea	Intake day 2	Mild	Yes	Disappeared on the day of appearance	No
A-04	66	Thoracic aortic aneurysm	Intake day 3	Severe	Yes	Improved	No
A-06	75	Common cold	Intake day 14	Mild	Yes	Disappeared on the next day	No
A-08	68	Abdominal distension	Intake day 4	Mild	No	Disappeared on the next day	Probably related
		Abdominal distension	Intake day 35	Mild	Yes	Disappeared after 5 days	Probably related
A-11	68	Cerebral infarction	Intake day 25	Severe	Yes	Improved	No
A-16	72	Itchiness	Intake day 10	Mild	No	Disappeared after 5 days	Probably related
C-01	74	Common cold	Intake day 23	Mild	No	Disappeared on the day of appearance	No
C-02	67	Common cold	Intake day 11	Mild	Yes	Disappeared on the day of appearance	No
C-05	66	Diarrhea	Intake day 16	Mild	No	Disappeared on the day of appearance	No
C-06	66	Constipation	Intake day 7	Mild	No	Disappeared after 2 days	No
C-10	70	Flu	Before intake	Mild	Yes	Disappeared after 9 days	No
C-11	70	Diarrhea	Intake day 7	Mild	No	Disappeared on the next day	No
C-12	65	Common cold	Intake day 8	Mild	No	Disappeared after 2 days	No
C-18	66	Common cold	Intake day 28	Mild	Yes	Disappeared after 2 days	No
		Gastric pain	Intake day 30	Mild	Yes	Disappeared on the day of appearance	No
		Diarrhea	Intake day 30	Mild	Yes	Disappeared on the day of appearance	No
		Abdominal distension	Intake day 1	Mild	Yes	Disappeared after 18 days	Probably related
C-19	66	Common cold	Intake day 1	Mild	No	Disappeared on the day of appearance	No
		Palpitation	Intake day 10	Mild	No	Disappeared on the next day	No
		Irregular pulse	Intake day 10	Mild	No	Disappeared on the next day	No
C-28	71	Common cold	Intake day 4	Mild	Yes	Disappeared on the day of appearance	No
		Toothache	Intake day 5	Mild	Yes	Disappeared after 3 days	No
		Flare in both forearms	Intake day 27	Mild	No	Disappeared after 11 days	No
C-30	81	Constipation	Intake day 3	Mild	No	Disappeared on the next day	No

*1: Severity: Physician-in-charge determines in reference to 'Severity Classification Standards of Drug Side Effects' (The Ministry of Welfare and Health Guideline).
Mild (Grade 1) / Moderate (Grade 2) / Severe (Grade 3)

*2: Causal relationship:
None: (There are clear evidences that other factors besides the test food are responsible or that it cannot be caused by test food from its pharmacological effects)
Probably related: (The causal relationship to test food cannot be excluded.)
Related: (Other factors, besides test food, cannot at all be responsible.)

[1] Subjective symptoms and objective observations

As shown in Table 7, abdominal distension developed sporadically 4 days after intake in case A-08. Similarly in case C-18, abdominal distension occurred 1 day after intake. In both cases, the relationship to PEP® could not be excluded, and the causal relationship was judged 'probably related'.

Itchiness developed 10 days after intake in case A-16. Although it had been observed previously in this subject, a relationship to PEP® could not be excluded, and it was judged 'probably related'.

[2] Laboratory analyses

Among the abnormal changes in laboratory analysis results shown in Table 8, a follow-up survey was performed on cases with abnormal changes at the time of study completion (or discontinuation). From the results, a relationship to PEP® was excluded in all these cases.

Table 9 shows the changes of laboratory values over time. The number of cases is shown for each category of urinalysis results. There was no case with clinically significant changes from the mean value of the cases included in the evaluation.

Table 8. Abnormal changes of laboratory values

Subject identification code	Age (years)	Analysis item	Standard range	Test values			Notes	Causal relationship
				Step 1	Step 2	Step 3		
A-02	75	AST (IU/L) ALT (IU/L) γ-GTP (IU/L)	8 - 38 4 - 44 4 - 63	31 34 406*	66* 61* 404*	52* 47* 591*	77* By follow-up (after 49 days) 58* By follow-up (after 49 days) 626* By follow-up (after 49 days)	None None None
A-05	67	Urinary glucose	–	–	–	⫴*	– By follow-up (after 40 days)	None
A-18	76	AST (IU/L)	8 - 38	18	24	58*	17 By follow-up (after 34 days)	None
B-02	78	Urinary glucose	–	–	⧺*	–	Transient change	None
C-02	67	BUN (mg/dL)	8.0 - 22.0	18.5	16.7	27.1*	19.9 By follow-up (after 8 days)	None
C-13	71	Urinary protein	–	–	⫴*		⧺* By follow-up (after 7 days)	None

*: Outsides the standard range

Table 9. Changes in laboratory values

Analysis item		Unit		Time of performance		
				Step 1 (n=51)	Step 2 (n=49)	Step 3 (n=45)
Blood biochemistry	AST	IU/L	Mean±SD (Max - Min)	23.1±7.0 (36 - 8)	23.2±8.5 (66 - 11)	24.1±8.5 (58 - 11)
	ALT	IU/L	Mean±SD (Max - Min)	22.5±9.3 (58 - 12)	22.3±10.1 (62 - 11)	21.0±9.2 (47 - 9)
	ALP	IU/L	Mean±SD (Max - Min)	214.9±78.5 (452 - 73)	215.7±79.7 (490 - 96)	222.7±80.9 (445 - 74)
	LDH	IU/L	Mean±SD (Max - Min)	248.0±93.5 (471 - 139)	243.3±99.1 (499 - 135)	235.5±97.3 (447 - 135)
	γ-GTP	IU/L	Mean±SD (Max - Min)	48.3±61.6 (406 - 10)	47.8±60.8 (404 - 10)	54.2±89.7 (591 - 10)
	BUN	mg/dL	Mean±SD (Max - Min)	16.0±4.6 (27.3 - 8.4)	16.3±4.2 (29.1 - 9.1)	16.3±4.0 (27.1 - 10.3)
	Creatinine	mg/dL	Mean±SD (Max - Min)	0.877±0.205 (1.40 - 0.40)	0.860±0.194 (1.34 - 0.40)	0.840±0.154 (1.31 - 0.50)
Urinalysis	Protein (qualitative)		⫴ ⧺ + ± –	0 2 2 8 39	1 1 1 9 37	0 0 1 4 40
	Glucose (qualitative)		⫴ ⧺ ± –	1 0 0 50	0 1 2 46	1 0 0 44
	Urobilinogen (qualitative)		+ ±	1 50	3 46	1 44

III. Discussions

The present study shows that the processed food (PEP®) containing of a mixture of edible Pumpkin seed EFLA®940 and soybean germ extracts significantly decreased urination frequency in the night and elevated sleep satisfaction by its intake twice a day for 6 weeks. In addition, an excellent efficacy was shown by the improvement level of subjective symptoms after completion of intake in which 86.7% of subjects (39/45 cases) evaluated 'significantly improved' or 'improved'.

No significant changes were observed in either urination frequency in the night or sleep satisfaction in Group A (the group which continued to use drugs for pollakiuria during intake: n=8). On the other hand, sleep satisfaction improved as urination frequency in the night decreased in Group B (the group without concurrent use of drugs: n=35), showing a correlation between urination frequency in the night and sleep satisfaction.

Since four out of the six cases whose improvement level of subjective symptoms was 'unchanged' at the end of Step 3 were in Group A, PEP® is not effective in the cases with complications of prostatic hypertrophy and neurogenic bladder. However, it is very interesting that there were four out of seven subjects with complications of prostatic hypertrophy whose improvement level of subjective symptoms was 'improved' at Step 3, suggesting improvement of the symptoms in the early stage of prostatic hypertrophy including urination dysfunction such as urinary tract blockage and urination urgency. Many types of drugs were used for pollakiuria in 8 cases, but there were no differences in improvement level between drugs.

A high percentage of people have symptoms of pollakiuria in the night. However, most of them do not seek medical attention. In fact, the subjects in the present study had symptoms of pollakiuria in night for relatively long periods, an average of 5.3±3.8 years, but only 15.7% of the total subjects used drugs for pollakiuria. Thus, it is clear that few people attempt to receive treatment even in the presence of symptoms.

Among elderly persons over the age 65, the risk of falling is 2.15 fold higher for those whose urination frequency in the night is not less than three, as compared to those with urination frequency in the night of less than one[1)]. Thus, pollakiuria in night influences the QOL significantly. In the present study, there were comments that subjective sleep condition was improved not only for the subjects themselves, but also for family members and care-takers who attend to the subject's need for urination. Thus, improvement of QOL can be expected from the use of PEP® in patients as well as people involved in their lives.

Adverse events were observed on 33 incidences in 22 out of 51 cases (Tables 7 and 8). There were no clinically significant changes in laboratory analyses. In subjective symptoms and objective observations, itchiness was observed in one case. Since its cause was not clear, the relationship to PEP® was judged 'unknown'. Two cases complained of abdominal distension whose relationship to PEP® could not be excluded. Similar adverse events were reported in the study of PEP® in abdominal pressure-associated urination incontinence[6)]. In consideration of the report on side effects in the digestive systems by plant extract drugs such as Eviprostat, the causal relationship was judged 'probably related'. The tablet of PEP® is relatively large, and three to five tablets are taken at once, needing a significant volume of water upon swallowing. The large volume of water intake could have caused the abdominal distension. The relationship to PEP® was excluded for other adverse events. Since prohibition of concurrent use, side effects, and the interaction with other drugs are not reported on Pumpkin seed in the guideline for plant therapeutics by the Ministry of Health of Germany, PEP® is highly safe.

A large number of therapeutic drugs for pollakiuria including α, β receptor stimulants and estrogen drugs are available for treatment for pollakiuria in night, but cautions are required upon their use due to side effects, complications and restricted drugs for concurrent use. On the other hand, there was no development of adverse events which were judged 'related', even when subjects with various backgrounds took PEP®. In addition, there was no case in which subjective symptoms were 'aggravated'.

Thus, the nutrition supplemental food PEP® can be safely used regardless of complications and concurrent use of drugs due to the components in edible Pumpkin seed EFLA®940 and soybean germ extracts. PEP® is a useful supplement as a first step for improvement of QOL for those who suffer from urination condition without seeking therapeutics.

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References

1) Stewart RB et al.: J Am Gerlatr Soc **40** : 1217-1220, 1992.

2) Tanioka T et al.: Clinical efficacy of TS-57 (oxybutinin hydrochloride fine granule) in neurogenic and unstable bladder. New Drugs and Clinic **43** (11): 2325-2332, 1994.

3) Schiebel-Schlosser G et al. : Kürbissamen in der phytotherapie der BPH. Zeitschrift für Phytotherapie **19** : 71-76, 1998.

4) Murkies AL, Wilcox G. Davis SR : Clinical review 92 "Phytoestrogens". J Clin Endocrinol Metab **83** : 297-303, 1998.

5) Sogabe H, Terado T: General clinical study of mixed processed foods containing of drug-use Pepo Pumpkin seed and soybean germ extracts in pollakiuria in night. Medicine and Pharmaceutical Sciences **46** (5): 727-738, 2001.

6) Yanagisawa M, Satoh I: Efficacy study in abdominal pressure-associated urinary incontinence with mixed processed foods containing of Pepo Pumpkin seed and soybean germ extracts. Medicine and Pharmaceutical Sciences **50** (3): 313-322, 2003.