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Study of Effectiveness of Mixed Processed Food Containing Cucurbita Pepo Seed Extract and Soybean Seed Extract on Stress Urinary Incontinence in Women

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Translated from Japanese

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Abstract

An effectiveness test was conducted for fifty female patients (aged between 35 and 84) with overactive bladder and stress urinary incontinence for six weeks to investigate the improvements in conditions and safety of PEP, a mixed processed food containing Cucurbita pepo seed extract and soybean seed extract, (hereinafter referred to as “PEP”). The results revealed by the test are as follows:

1) In forty-eight cases, the number of stress urinary incontinence was significantly reduced compared to the state before the administration.

2) In twenty-eight cases (56.0%) of fifty cases, there were 30 adverse events (56.0%), where the doubtful relevance with the intake of PEP were shown in four cases (8.0%) with 6 adverse events. Considering that the adverse events were mild and also quickly disappeared, PEP was regarded as highly safe.

From the above, it is suggested that PEP is highly effective and safe to improve the conditions of the stress urinary incontinence.

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Clinical study of mixed processed foods containing of pumpkin seed extract and soybean germ extract on stress urinary incontinence (SUI) in women

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Key words: pumpkin seed, soybean germ, SUI, women, clinical study

Introduction

Irritable bladder syndrome has been reported to affect 20% to 40% of moderately aged women, where 70% to 80% of those women suffer from stress urinary incontinence[1)].

The stress incontinence is a urinary disease that includes involuntary loss of urine during physical exertion with increased intra-abdominal pressure due to coughing and sneezing. It is caused by obesity, aging, delivery of births, etc.

The preservation treatments for stress urinary incontinence include pelvic floor stimulation aiming at strengthening and toning weak pelvic floor muscles, via medications such as α- and β-receptor stimulant or estrogen, and electromagnetic stimulation which pulses electromagnetic waves through an electrode to vagina, anus, perineum and so on [2)]. However, most patients give up receiving therapeutic treatments for the syndrome because they take it for granted as a natural process of aging mechanism and thus there are not many patients who actually receive outpatient treatments.

PEP is a triangular tablet sold by Tervis Co., Ltd. and a supplementary food for nutrition which contains Cucurbita pepo seed extract and soybean seed extract. On one hand, Cucurbita pepo seed was approved as an efficacious treatment for irritable bladder syndrome (such as frequent urination, urgent urination, urinary incontinence, and constant urination feeling) and benign prostatic hypertrophy at the early stage in the Guideline of Plant-Derived Medicines made by the German Ministry of Health (released on November 30, 1985), and it was reported to be effective in the treatment for syndromes such as reduced volume of urine, constant feeling of urination, frequent urination at night, which may disturb sound sleep.[3)] On the other hand, soybean seed extract contains phytoestrogen[4)] which is derived from less active ingredient isoflavone, and it is proven to relieve geriatric diseases[5)] such as cardiovascular diseases (arteriosclerosis, hypertension, etc.), involution of urogenital organs (geriatric vaginitis, urinary incontinence, etc.) psychiatric syndromes (headache, insomnia, depression and other menopause disorders), and osteoporosis which is caused due to lack of estrogen.

In Japan so far, it has been reported that the intake of PEP significantly reduces the number of urinations per day as well as per night [6)]. In this study, PEP will be examined and reviewed to identify any improvement and safety against stress urinary incontinence as one of the methods of evaluating the Effectiveness test of PEP.

I. Evaluation Method

1. Subject

We selected female outpatients suffering from stress incontinence, except pregnant women, who had visited Hakwaikai Ichinoseki Hospital in Ichinoseki Iwateken and Satoh Ladies' Clinic in Maebashi Gunmaken from January to May 2003 and explained to them about the test method and PEP prior to their participation in the test and obtained their written consent.

Since it is common to conduct pelvic floor stimulation or other treatments at least for consecutive twelve months until the effect is revealed, we decided to exclude patients who had continuously received non-medication therapies such as pelvic floor exercise or electromagnetic stimulation, and failed to complete 12 weeks from the onset of the test on the date from the acquisition of the consent because it was considered that they would affect the evaluation of effectiveness of PEP. In addition, we excluded those patients who had complication such as serious diseases from heart, liver, stomach and blood, and who had an allergy to soybeans or pumpkins in the aspect of safety as well as patients who had previously received surgical therapies because of stress urinary incontinence, and those a doctor in charge considers inappropriate for other reasons.

2. Ingredients

We used a mixed process food called 'PEP' (manufactured by Tervis Co., Ltd.) that contains Cucurbita Pepo seed extract and soybean seed extract. The extract of Cucurbita Pepo seed (EFLA 940) was prepared by Swiss firm Emil Flaschsmann and the extract of soybean seed (ISOMAX-30) was manufactured by Tokiwa Phytochemical Co., Ltd.

PEP contains 875mg of Cucurbita Pepo seed extract and 167mg of soybean seed extract per 10 tablets (2.5g). It also contains 525mg of Cucurbita Pepo seed extract and 100mg of soybean seed extract per 6 tablets (1.5g).

3. Period of Test and Administration

The duration of the test included one week of observation period (hereinafter referred to as the "Step 1") and six weeks of administration period. The total period to be expected is 7 weeks. The patient took 5 tablets every time and twice (morning and night) per day from the first week to the second week of the administration period (referred to as the "Step 2") and 3 tablets every time and twice per day from the third to the sixth week (referred to as the "Step 3") with plenty of water

or warm water.

4. Combination Prohibited Drugs / Combination Limited Drugs

In principle, estrogen and α- and β-receptor stimulant, which are considered to be effective in the effectiveness evaluation of the test food and are used in the treatment for stress incontinence, are prohibited to be combined with the food. If there is no choice, in principle, but to combine α- and β-receptor inhibitor, anti-cholinergics, anti-anxiety medication, sleeping pill, herb medicine (*Bojungikgitang, Galgeuntang,*and *Dangguijakyaksan*) during the test period without changing medicines, usage and dosage, the combination was allowed for only a very limited period of time.

Table 1: Items to be filled in a daily report by a patient

【Food Administration Time】 day and night
【Number of Urinations per Day】 Number of urinations from rising to sleeping
【Satisfaction】 Satisfaction grade based on urinary incontinence, etc. 1. Satisfied 2. Quite satisfied 3. Quite disappointed 4. Disappointed
【Subjective Symptoms】 Comments by subjects

5. Test Items and Test Method

1) Subjective Symptoms and Objective Symptoms

During the test period, patients were requested to keep daily record with respect to the items in Table 1 and doctors asked patients detailed questions about their conditions on the date of outset of intake (after the completion of Step 1), two weeks from the date (after the completion of Step 2), and six weeks from the date (after the completion of Step 3) on the basis of the daily report.

2) Improvement

Comprehensively judging from the daily report recorded by patients and the detailed information asked by doctors, we classified the improvement levels into four phases: “remarkably improved”, “improved”, “unchanged” and “aggravated” after the completion of Step 2 and Step 3.

3) Clinical Trial

We conducted biochemical profile (AST, ALT, ALP, DLH, γ-GTP, BUN, creatinine, TG, T-Cho, HDL and LDL) and urine test (protein, sugar, urobilinogen) at the time of outset of Step 1 and after the completion of Step 2 and Step 3 in the clinical trial.

4) Adverse Event

We investigated the adverse events shown in subjective symptoms, objective symptoms and the clinical trial with respect to detailed symptoms (including abnormal changes of clinical test value), time of occurrence, rating (seriousness, critical condition), treatment, disease progress and the relevance with the test food. The adverse events of clinical test values were judged by the doctor in charge with reference to “Standard on Judgment of Abnormality of Clinical Test Value” in Table 2. If the doctor finds any abnormal changes, they were determined as adverse events.

Table 2: Standard on Judgment of Abnormality of Clinical Test Value
(The proposal of the Japanese Society for Chemotherapy partially applied to the Standard.)

【Biochemical Profile】

〔AST(GOT), ALT(GPT), ALP, LDH, γ-GTP, BUN, Creatinine, TG, T-Cho, LDL〕

□ Within the limit → Off the limit
If the value exceeds the upper limit by 1.2 times, it is considered as an adverse event.

□ Off the limit → Off the limit
If the value exceeds the upper limit by 2 times, it is considered as an adverse event.

〔HDL〕

□ Within the limit → Off the limit
If the above value is 0.8 times less than the lowest limit, it is considered as an adverse event.

□ Off the limit → Off the limit
If the above value is 0.5 times less than the lowest limit, it is considered as an adverse event.

【Urine Test】

1. Urine protein: Adverse event in case of having changes of two or more steps in (-)→(+)
2. Urine sugar: Adverse event in case of having changes of two or more steps
3. Urobilinogen: Adverse event in case of changes of one or more step

II. Result

1. Subject

Fifty two patients aged between 35 and 84 agreed to give case reports on the test. There was a case record that a combination of estradiol and testosterone (prohibited from combination)

was used once a month, but the combination had been administered without a change in usage or dosage for one year and it did not give any effect in the stress incontinence. Therefore, the subject was admitted to participate in the test as being judged that it would give no impact on the evaluation of effectiveness of PEP. In addition, two patients failed to administer PEP because one patient withdrew the consent for the reason that it was impossible to keep daily report and the other patients could not keep daily report due to the worse complication during the observation period. As for one patient, who failed to visit hospital as scheduled due to a flu (one case), we suspended the test because the patient was not able to cooperate in the test. After the completion of the test, it was found that one case breached the criteria for exceptional exclusion.

From the above information, the test cases of effectiveness were set to total of 48 cases and the test cases of safety were set to 50 cases in the medication of PEP. Of total 48 cases, patients with hay fever reached six cases. There were no significant factors in medical history of the other patients. Table 3 showed the background factors of 52 cases. The mean value of their age was 53.5.

Table 3: Background Factors of Patients

Background Factor (n=52)		Cases (%)
Age	35□39	3(5.8)
	40□49	18(34.6)
	50□59	17(32.7)
	60□69	9(17.3)
	Mean SD	53.5 10.3
Age when stress incontinence is developed*	23□29	3(6.5)
	30□39	8(17.4)
	40□49	19(41.3)
	50□59	11(23.9)
	60□69	4(8.7)
	Mean SD	48.0 11.0
Allergy to pumpkin	None	52(100.0)
	Yes	0(0)
Surgical treatment	None	52(100.0)
	Yes	0(0)
Complication	None	18(34.6)
	Yes	34(65.4)
Combined therapy	None	51(98.1)
	Yes	1(1.9)

Menopause	None Yes	22(42.3) 30(57.7)

* 6 Cases were unidentified.

2. Test Result

1) Effectiveness

□ Intake rate of test food

The PEP intake rate of patients is shown in Table 4.

Table 4: Intake Rate of Test Food (n=48)

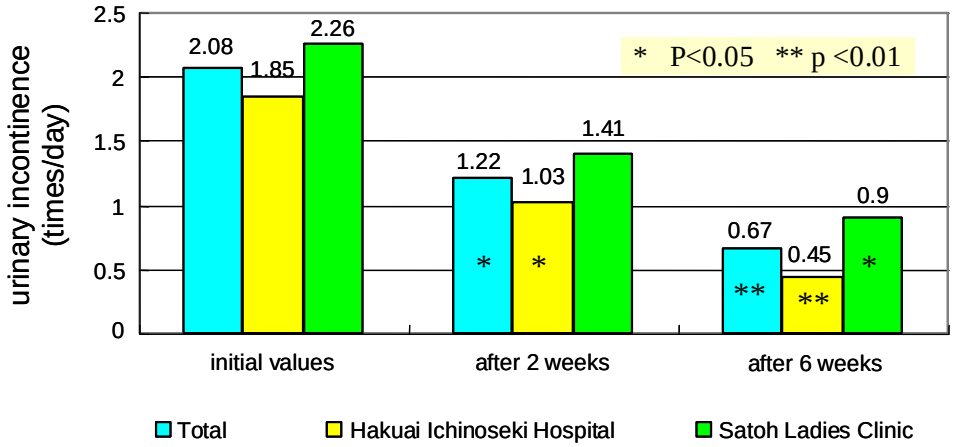
	Step 2	Step 3
Total	94.3%	95.6%
Hakwaikai ichinoseki Hospital	94.4%	94.7%
Satoh Ladies' Clinic	94.1%	96.5%

□ Number of incontinence episodes per day

The transition of the number of incontinence per day in Step 1, Step 2 and Step 3 of 48 cases in the test of effectiveness in Figure 1. After comparing the mean values of the number of incontinence of Step 1 with the average values after intake (Step 2 and Step 3), we conducted a paired sample t-test. As a result, the number of incontinence per day was significantly reduced in Step 3 ($p<0.01$) (Table 5).

Three cases of six patients with hay fever showed an improvement in the number of urinary incontinence. Two other cases showed the reduction in the number of urinary incontinence in Step 2 but there was no significant change in Step 3. In case of the other case, the number of incontinence reached 2.71 times per day in Step 1, but increased to 6.21 times per day due to the aggravated hay fever during the period when pollen flied in Step 2. The number of incontinence reached 7.57 times per day in Step 3. Even three cases, which did not show any decrease in frequent incontinence, showed the reduction in the amount of urine.

【Figure 1】

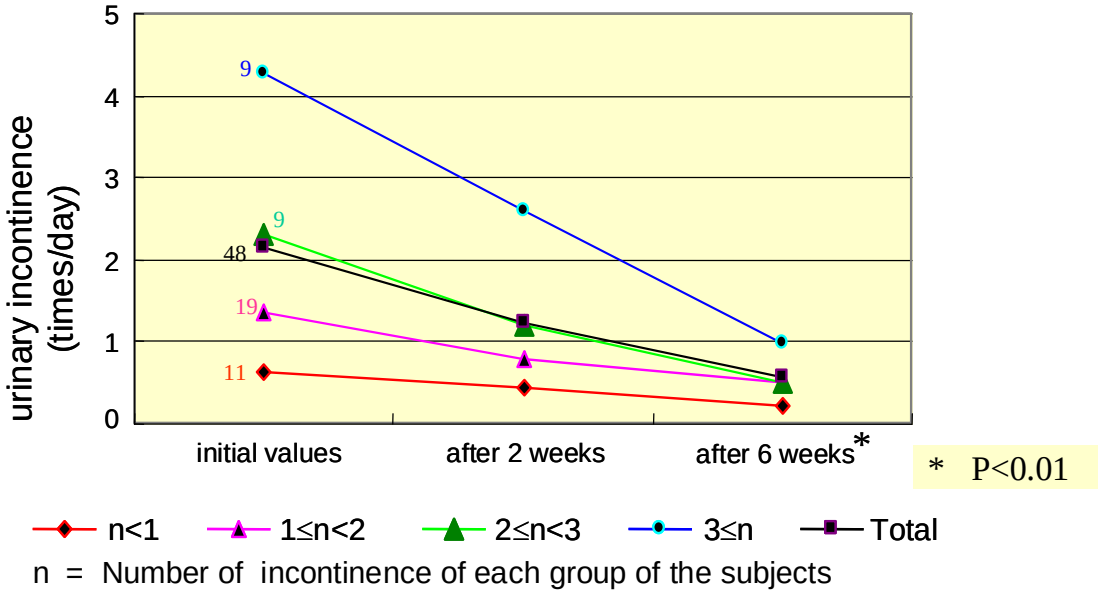


In comparison of the cases in the number of urinary incontinence in Step 1, irrespective of the frequency of incontinence during the observation period, it showed significant reduction after six weeks from the food intake (Figure 2: $p<0.01$). In particular, the patients who had the large number of incontinence showed the significant reduction.

Table 5: Number of Urinary Incontinence per Day (n=48)

Number of urinary incontinence per day (Times/Day)	Mean SD		
	Step 1	Step 2	Step 3
Total (Max□Min)	2.08 2.0 (12□0)	1.22 1.3* (6.21□0)	0.67 1.2** (7.57□0)
Hakwaikai ichinoseki Hospital	1.85 1.6	1.03 1.2*	0.45 0.5**
Satoh Ladies' Clinic	2.26 2.4	1.41 1.4	0.90 1.6*

【Figure 2】



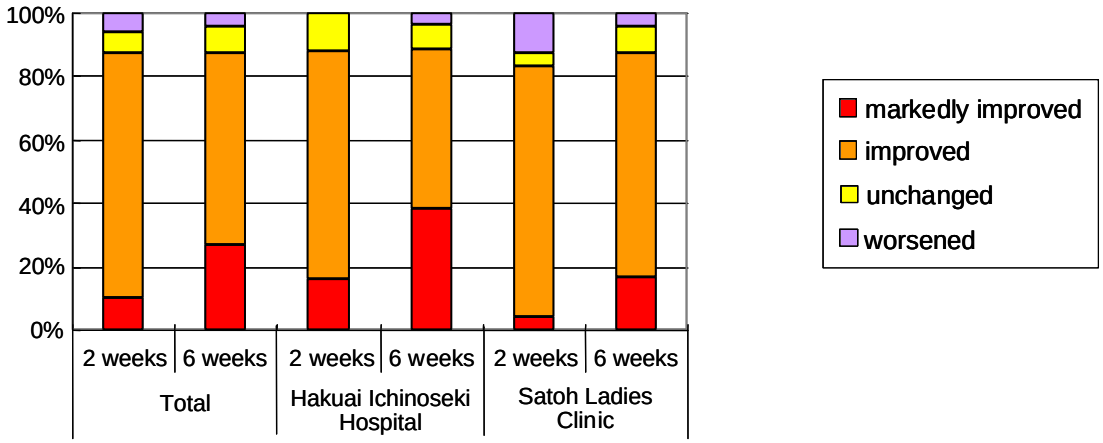
n = Number of incontinence of each group of the subjects

□ Improvement

Figure 3 showed overall improvement as judged comprehensively by doctors in the subjective symptoms from 48 patients in the Effectiveness test. Both of the medical institutions showed similarly significant results as follows: “remarkably improved” cases reached five (10.4%) and “improved” cases were 42 patients (87.5%) in Step 2 and “remarkably improved” cases reached 13 patients (27.1%) and “improved” cases were 42 patients (87.5%) in Step 3.

Of the cases which were shown “unchanged” or “aggravated” in the improvement, most patients showed an increase in frequent urinary incontinence by coughing or sneezing due to diseases such as aggravated hay fever as complication or flu. Yet we confirmed the reduction of the amount of urine from the daily reports of most patients and the number of incontinence was reduced when the patients recovered from hay fever or a flu.

【Figure 3】



2) Safety

□ Clinical test value

Table 6 showed the transition of clinical test values. There was no transition of 50 cases in the safety test which might trigger problems in a clinical trial.

Table 6: Transition of Clinical Test Value (n=50)

Test Item		Unit		Test Period		
				Outset of Observation	2 weeks after food intake	6 weeks after food intake
Biochemical Profile	AST	IU/L	Mean SD (Max□Min)	22.0 6.6 (49□12)	23.0 7.6 (48□13)	21.6 6.2 (43□12)
	ALT	IU/L	Mean SD (Max□Min)	21.9 14.7 (96□6)	22.1 14.6 (87□6)	20.0 11.8 (67□6)
	ALP	IU/L	Mean SD (Max□Min)	220.8 69.1 (402□118)	221.7 72.4 (457□123)	215.8 68.7 (406□107)
	LDH	IU/L	Mean SD (Max□Min)	185.9 27.6 (243□128)	189.4 29.2 (252□125)	190.0 31.3 (267□129)
	γ-GTP	IU/L	Mean SD (Max□Min)	21.0 9.6 (49□8)	20.6 10.8 (62□8)	20.4 12.5 (71□8)
	BUN	mg/dL	Mean SD (Max□Min)	14.0 3.6 (22.1□7.3)	13.2 2.7 (19.0□7.0)	13.6 3.0 (21.7□7.0)
	Creatinine	mg/dL	Mean SD (Max□Min)	0.62 0.12 (0.9□0.4)	0.61 0.11 (0.8□0.4)	0.57 0.10 (0.8□0.4)
	TG	mg/dL	Mean SD (Max□Min)	149.4 110.5 (613□42)	134.3 94.3 (550□38)	122.6 73.4 (358□42)
	T-Cho	mg/dL	Mean SD (Max□Min)	209.8 34.1 (315□134)	205.1 31.1 (321□135)	207.7 34.1 (355□146)
	HDL	mg/dL	Mean SD (Max□Min)	60.7 15.6 (110□34)	60.8 15.5 (112□34)	62.9 15.5 (107□39)
	LDL	mg/dL	Mean SD (Max□Min)	121.3 29.8 (203□66)	116.6 27.4 (215□63)	119.8 28.7 (246□59)
Urine Test	Urine Protein		+ + + + -	1 1 6 42	0 2 8 40	0 3 4 42
	Urine Sugar		+ + + + + + + + + +	0 0 1 1 1 47	0 2 0 1 0 47	1 0 1 1 0 46
	Urobilinogen		+ + -	0 50 0	0 50 0	1 48 0

□ Adverse Event

Table 7 describes the adverse events of clinical test and Table 8 shows the adverse

events shown in subjective and objective symptoms. There were 39 adverse events from 28 cases (8.0%) from total of 50 cases, of which 6 events (8.0%) from four cases were related to the relevance of PEP. Conducting urine sugar (++□+++) tracking survey of Patient No. A-27, we found that the sugar was recovered to the limit value. It was considered that the patient would possibly have the disease of sugar metabolism but we could not find the cause from this test alone. In addition, the urine protein (+) of patient No. B-21 had no problem in the test for stomach function and in a clinical trial. Accordingly, it was judged that the tracking survey is not required. Since we could not specify the relevance with PEP in all causes of the two cases through this test, the relevance was judged as “possible”.

When the tracking survey of TG level of patient No. A-18 (358 mg/dl) was conducted, the level was detected at 231 mg/dl. The changed level of TG was thought to be influenced by meals because the TG level is sharply influenced by food and also the range of fluctuation was wide. Provided that the blood-gathering was conducted with the same condition as usual, we could not find the cause of the high level of TG and this made us judge “possible factor”.

Since we could specify the causes with respect to the adverse events of clinical test irrelevant to PEP, the tracking survey was judged to be unnecessary.

The uneasiness of the stomach which occurred three times two days after the intake of Patient No. B-6 had been frequently shown when the patient had overeaten. The symptom did not occur in Step 3. Since the patient had no good stomach, it was appropriate to make the patient administer PEP three pills each time. We could not deny the possibility that the uneasiness was caused by the administration of five pills each time but it was judged as “possible” because we could not find the relevance with PEP through the test. Besides, the relevance with the test food was denied in 30 adverse events of 22 cases (44.0%).

Table 7: Adverse Events in Clinical Trial

No. of Patients	Age	Test Item	Limit Value	Test Value			Remark	Relevance
				Before intake	2 weeks	6 weeks		
A-3	59	Urine Sugar	-	+ - *	+++* Moderate	+++* Moderate	Unnecessary to track	None
A-6	69	LDH (IU/L)	106□211	208	222* Mild	267* Mild	Unnecessary to track	None
A-18	40	TG (mg/dL)	50□150	186*	150	358* Mild	231 Tracking (14 days after intake)	Possible
A-27	53	Urine Sugar	-	+ *	++□+++* Mild	++* Mild	- Tracking (10 days after intake)	Possible
B-7	61	TG (mg/dL)	30□149	114	188* Mild	79	Unnecessary to track	None
B-21	81	Urine Protein	-	-	+ *	+ *	Unnecessary to track	Possible

*: Deviation of limit value

Table 8: Adverse Event in Subjective/Objective Symptoms

No. of Patient	Age	Symptom	Occurrence	Seriousness	Treatment	Disease Progress	Relevance
A-1	52	Flu	8th day from intake	Mild	Antibiotics	Disappeared after 3 days	None
A-2	36	Flu	9th day	Mild	Cold medicine	Disappeared after 6 days	None
A-4	54	Thigh rash Constipation	9th day / 10th day	Mild Mild	Non treatment Non treatment	Pleasant after intake Disappeared after 2 days	None None
A-9	84	Flu	18th day	Mild	Cold medicine	Disappeared after 3 days	None
A-16	59	Abdominal disease	15th day	Mild	Non treatment	Disappeared after one day	None
A-20	52	Face/leg trauma	22nd day	Mild	Antibiotics	Pleasant after intake	None
A-21	42	Flu	10th day	Mild	Antibiotics	Disappeared after 30 days	None
A-22	46	Toothache	15th day	Mild	Sedative/ Antipyretics	Disappeared after 2 days	None
A-24	46	Sore throat	11th day	Mild	Antibiotics	Disappeared after 2 days	None
A-25	45	Flu Insomnia	13th day 20th day	Mild Mild	Cold medicine Hypnotics	Disappeared after 3 days Disappeared on the day	None None
A-27	53	Sour stomach	6th day	Mild	Digestive	Disappeared after 2 days	None
A-28	49	Flu	31st day	Mild	Cold medicine	Disappeared the next day	None
B-3	57	Diarrhea Diarrhea	2nd day 12th day	Mild Mild	Non treatment Non treatment	Disappeared on the day Disappeared on the day	None None
B-6	55	Stomach Uneasiness Stomach Uneasiness Stomach Uneasiness	2nd day 6th day 14th day	Mild Mild s Mild	Digestive Digestive Digestive	Disappeared on the day Disappeared on the day Disappeared on the day	Possible Possible Possible
B-7	61	Flu	18th day	Mild	Cold medicine	Disappeared after 3 days	None
					Medicine for		

III. Conclusion

This test revealed that the mixed processed food (PEP) containing Cucurbita pepo seed and soybean seed extract significantly reduces the number of incontinence nearly 6 weeks after its intake and improves the conditions of the disease overall. In addition, the patients showed the high improvement up to 87.5 percent (42 cases/48 cases) after the completion of the intake in consideration with the level 'improved" or better conditions. In comparison of effectiveness by the frequency of incontinence before the intake of PEP, PEP significantly improved all the incontinence and showed excellent efficacy even in cases with comparatively serious incontinence.

Despite the sharp decrease in quality of life of patients with urinary incontinence, few patients are still treated by doctors because the disease is rarely considered as a condition which may give them a life-threatening danger and even patients may not perceive that urinary incontinence is a disease indeed. Some drugs such as α- and β-receptor stimulant or estrogen are used to treat stress incontinence but it is necessary to make precautions on side effects and possible complications, combinatory medications. It is true that pelvic floor stimulation exercise is usually used to treat mild stress incontinence. To obtain satisfactory results and effects, patients, however, the therapy should be conducted several times per day on a regular basis for a period of from two to three months.

Notwithstanding the short period of test which lasted for six weeks, we found that PEP intake with two pills per day significantly reduced the number of incontinence. Furthermore, considering that there were cases that showed the significant reduction in the amount of incontinence a day without the improvement in the number of incontinence, we believe that PEP will largely contribute on the improved quality of life of patients.

Twenty-eight out of fifty cases showed 39 adverse events (Tables 7 and 8) but they did not bring significant change in the transition of clinical test values. Patient No. B-6 expressed uneasiness of the stomach as subjective symptom which occurred two days after the intake of PEP and had been frequently experienced when the patient had overeaten. However, we could not find any relevance with PEP from this test alone and we thus judged it would be possible that they may be relevant. Through the test, we failed to ascertain the cause of urine sugar (++□+++) and urine protein (+), the relevance of which is unclear with PEP. With respect of other adverse events, the relevance with PEP was denied. The Guideline of Plant-Derived Medicines made by the German Ministry of Health did not disclose any incompatibilities, adverse effects or any interactions with any other drugs thus showing the superior safety of PEP.

In conclusion, the supplementary food (PEP) containing Cucurbita pepo seed and

soybean seed extract is shown highly effective in improving the conditions of stress urinary incontinence.

Please allow me to show my deepest thanks to Tervis president Dachizaki Masaru for their contributions to the test food ‘PEP’ and the opportunity for conducting the test.