ORYZA OIL & FAT CHEMICAL CO., LTD.

Inhibitory effect of EVENING PRIMROSE EXTRACT on increased blood sugar in response to diet loading in patients with borderline or mild diabetes

—A crossover study using a placebo as a control drug—

Oryza Oil & Fat Chemical Co., Ltd

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Inhibitory effects of EVENING PRIMROSE EXTRACT on increased blood sugar in response to diet loading in patients with borderline or mild diabetes

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1. Purpose of this study

Previous basic studies have shown that EVENING PRIMROSE EXTRACT inhibits disaccharidase. We conducted a diet loading study using a placebo as a control drug in patients with borderline or mild diabetes, and investigated the inhibitory effects of EVENING PRIMROSE EXTRACT on increased blood sugar.

2. Study methods

(1) Test agents

EVENING PRIMROSE EXTRACT is extracted by defatting evening primrose seeds, and contains a high concentration of polyphenol. We conducted a diet loading study using 200 mg of EVENING PRIMROSE EXTRACT as the intake per meal. As a placebo, 200 mg of cleaned rice powder was used. The dosage form of the two test samples was a brown capsule. It was confirmed that the two test samples were not distinguishable in appearance, taste, and odor.

(2) Study methods

A crossover diet loading study using a placebo as a control drug was conducted. Subjects were fasted after 9:00 p.m. the day before this study. Consumption of drinks other than water was prohibited. On the day of the first study (July 21, 2001), the subjects assembled at 8:00 a.m. After resting, consultation and blood collection were started at 8:20 a.m. Thereafter, the test samples were given at 8:45 a.m. Of our subjects, capsules containing EVENING PRIMROSE EXTRACT were provided to 10 subjects, while placebo capsules were provided to 10 subjects. At 8:50 a.m., diet loading was started. For diet loading, commercially available packaged cleaned rice (Sato no gohan: Koshihikari (200 g) reaped in Niigata Prefecture) was used in all subjects. The rice consisted of 302 kcal of energy, 4.6 g of protein, 1.2 g of lipids, 68.0 g of glucose, and 6 mg of Na. The subjects were instructed to completely eat the loaded diet with 200 cc of water within 10 minutes. Thereafter, venous blood was collected at 9:30 (30 minutes after loading), 10:00 (60 minutes after loading), 10:30 (90 minutes after loading), and 11:00 (120 minutes after loading), and blood sugar, serum insulin and neutral fat levels were measured.

The second study was performed 7 days after the first study (July 28, 2001)(washout period: 6 days). The test samples were switched among subjects, and a similar schedule was conducted.

In the 1st and 2nd studies, blood examination (blood biochemistry, blood cell components) and urinalysis were performed prior to loading.

(3) Subjects

This study included 18 adults who showed fasting blood sugar levels ranging from 110 mg/dl to 180 mg/dl on preliminary examination prior to this study. Patient backgrounds are shown in Table 1.

(4) Ethics

This study was conducted after written informed consent was obtained from all subjects according to the Helsinki declaration under approval by the Ethics Committee, Comprehensive Medical Science Institute (chairman: M. Inoue, lawyer).

3. Results

This crossover study was conducted, with an interval of 1 week. Blood biochemical findings and blood cell components before ingestion of the active ingredient or placebo are shown in Table 2. There were no significant differences between the two test samples, suggesting that there were no differences in patient backgrounds before ingestion.

Table 3 shows the changes in blood sugar after diet loading. In the group receiving placebos before diet loading, the mean pre-loading blood sugar level was 128.8±39.2 mg/dl. The level rapidly increased to 186.4±40.2 mg/dl, 225.3±52.2 mg/dl, 226.9±62.3 mg/dl, and 213.0±62.1 mg/dl thirty, 60, 90, and 120 minutes after diet loading, respectively. In the group receiving the active ingredient, the mean pre-loading blood sugar level was 124.7±26.1 mg/dl. Values were 165.5±30.4 mg/dl, 209.7±40.1 mg/dl, 209.1±45.9 mg/dl, and 192.2±47.1 mg/dl thirty, 60, 90, and 120 minutes after diet loading, respectively. At all time points, the elevation of blood sugar was inhibited compared to that in the placebo group. In the placebo group, the area under the increased blood sugar curve after loading was significantly lower than that in the active ingredient group ($p<0.05$).

Fig. 1 shows the rate of change in blood glucose level after diet loading. In the active ingredient group, the elevation of blood glucose level was always inhibited compared to that in the placebo group. Values were significantly lower 30 and 90 minutes after loading.

Furthermore, Table 4 shows the changes in insulin levels on loading. Although there was no significant difference between the two groups prior to diet loading, insulin secretion in the active ingredient group was inhibited 30 and 60 minutes after loading. The area under the insulin elevation curve until 120 minutes after loading in the active ingredient group (39.4±34.5 μU.hr/dl)

was lower than that in the placebo group (46.8±31.2 μU.hr/dl), although there was no significant difference.

Table 5 shows the changes in neutral fat levels. There were no significant differences in neutral fat between the two groups.

4. Discussion and Conclusion

The results of this study showed that EVENING PRIMROSE EXTRACT inhibited rapid increases in blood sugar after diet loading. Furthermore, the inhibition of rapid increases in blood sugar resulted in the inhibition of rapid increases in insulin secretion. It is suggested that EVENING PRIMROSE EXTRACT not only prevents postprandial hyperglycemia but also relieves insulin secretion stress in diabetics with poor insulin secretion.

Previous basic studies using animals demonstrated that EVENING PRIMROSE EXTRACT inhibited disaccharidase. The results of this study in humans support previous studies, and suggest that EVENING PRIMROSE EXTRACT is also effective in humans. In addition, there were no adverse reactions in this study. This finding suggests that EVENING PRIMROSE EXTRACT is highly safe at the intake employed in this study.

In conclusion, EVENING PRIMROSE EXTRACT may stabilize blood sugar by inhibiting diet-related rapid increases in blood sugar in diabetics with reduced insulin secretion and insulin-resistant diabetics, and may prevent complications.

[Table 1] Patient backgrounds (before ingestion of the active ingredient)

Gender	male: 15
	Female: 3
Age (year)	53.5±7.1
Height (cm)	167.6±6.3
Body weight (kg)	70.9±10.3
Body Mass Index	25.2±2.5
Fasting blood sugar (mg/dl)	124.7±26.1
HbA1c (%)	6.0±1.1
Total cholesterol (mg/dl)	201.4±36.1
Triglyceride (mg/dl)	198.7±101.6
Total protein (g/dl)	7.5±0.8
Patients with abnormal	++ 1
urine sugar levels	+ 3
	± 2
	- 12
Systolic blood pressure (mmHg)	143.7±12.2
Diastolic blood pressure (mmHg)	88.2±14.2

[Table 2] Main hematological data before loading

Item (unit)		Group	Before ingestion	Examination procedure
Leukocyte	3500-9700	active	6139±1180	Electric resistance detection method
	(/μl)	placebo	6439±1575	
Erythrocyte	377-577	active	474±52	SLS-Hb method
	(×10000/μl)	placebo	451±73	
Platelet	14-38	active	22.9±5.8	Erythrocyte pulse wave high value detection method
	(×10000/μl)	placebo	22.8±6.2	
Total protein	6.5-8.2	active	7.5±0.8	Biuret method
	(g/dl)	placebo	7.4±0.6	
GOT	5-40	active	33.3±23.7	UV method
	(U/l)	placebo	33.3±20.7	
GPT	5-45	active	38.5±31.0	
	(U/l)	placebo	38.0±28.0	
γ-GTP	0-60	active	109.9±127.5	L-γ-glutamyl-3-carboxy-4-nitroanide substrate method
	(U/l)	placebo	110.6±126.2	
Total cholesterol	150-220	active	201.4±36.1	Enzyme method
	(mg/dl)	placebo	205.1±35.6	
Triglyceride	50-150	active	198.7±101.6	
	(mg/dl)	placebo	173.2±107.9	
HbA1c	4.3-5.8	active	6.0±1.1	Latex aggregation method
	(%)	placebo	6.0±1.0	
Urea nitrogen	8-20	active	17.8±5.6	Urease UV method
	(mg/dl)	placebo	17.4±5.3	
Creatinine	0.6-1.3	active	1.5±1.8	Alkaline picric acid method
	(mg/dl)	placebo	1.5±1.6	
Na	135-145	active	140.3±1.8	Electrode method
	(mEq/l)	placebo	140.9±1.7	
K	3.5-5.0	active	4.9±0.5	
	(mEq/l)	placebo	4.8±0.5	
Cl	98-108	active	102.8±2.1	not significant
	(mEq/l)	placebo	102.4±1.9	

[Table 3] Blood sugar (mg/dl) and the area under the curve on diet loading

groups	Diet loading study Blood sugar (mg/dl)					Area under the Increased blood sugar curve (mg・hr/dl)
	Before loading	30min	60min	90min	120min	
active	124.7±165.5	165.5±30.4	209.7±40.1	209.1±45.9	192.2±47.1	123.9±41.3
placebo	128.8±39.2	186.4±40.2	225.3±52.2	226.9±62.3	213.0±62.1	147.1±60.2
Significant Deference Between the Two groups	n.s	p<0.05	p<0.1	p<0.05	p<0.01	p<0.05

paired t test

[Table 4] Serum Insulin levels and the area under the curve on diet loading

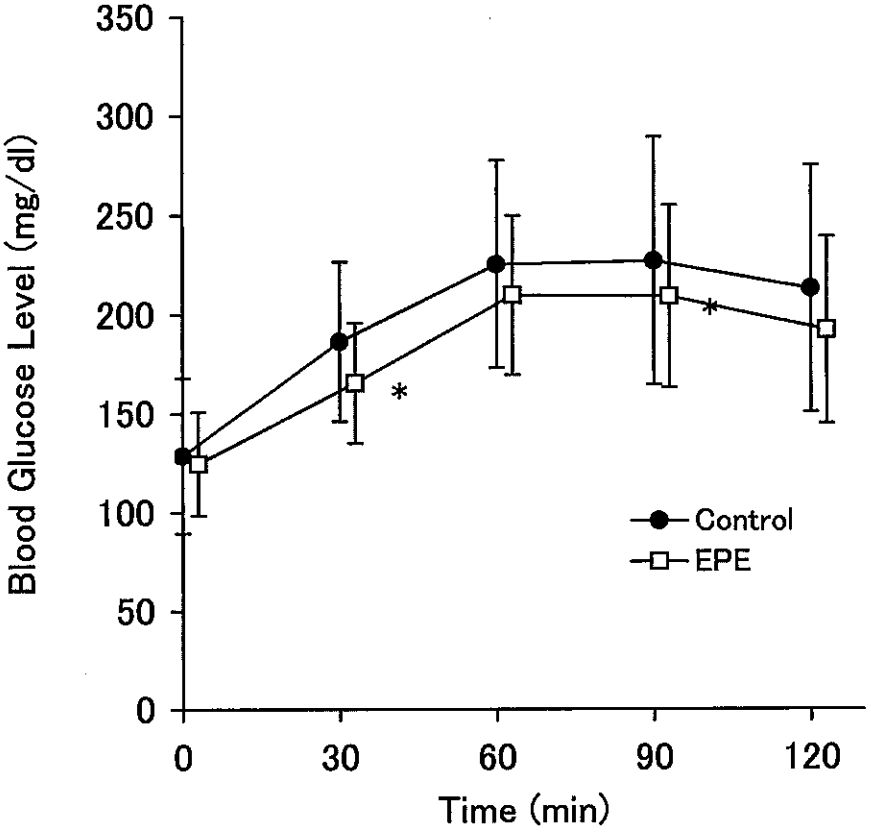
groups	Diet loading study Insulin level (μU/dl)					Area under the Insulin elevation curve (mg・hr/dl)
	Before loading	30min	60min	90min	120min	
active	12.7±9.8	22.4±14.5	35.8±33.1	43.7±35.9	42.7±31.4	39.4±34.5
placebo	13.3±15.0	28.4±23.9	40.0±31.1	43.6±28.1	50.1±30.0	46.8±31.2
Significant Deference Between the Two groups	n.s	p<0.1	n.s	n.s	n.s	n.s

paired t test

[Table 5] Neutral fat levels on diet loading

	Diet loading study Neutral fat level (mg/dl)				
	Before loading	30min	60min	90min	120min
active	199±102	275±125	333±129	356±141	340±107
placebo	173±108	251±114	298±142	314±129	303±135
Significant Deference Between the Two groups	n.s	n.s	n.s	n.s	n.s

paired t test



[Fig. 1] Effects of EPE on the Postprandial Glucose Level in Diabetic Patients. Each points represents the mean±SD (n=9). Statistically significant from control (*$p<0.05$).

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