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Evaluation of the Effects of Food Containing *Epilobium angustifolium* Extract on Quality of Life Related to Nocturia Urination Using the N-QOL Questionnaire: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

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Abstract

Background: Nocturia, characterized by waking during the night to urinate, is a common condition that significantly impacts quality of life (QOL) by disrupting sleep and reducing daytime vitality. *Epilobium angustifolium*, a medicinal plant, has shown potential in improving nocturia-related symptoms due to its active constituent, oenothein B, which possesses anti-inflammatory and antioxidant properties. This study aimed to evaluate the effects of *Epilobium angustifolium* extract on nocturia-related QOL using the Nocturia Quality of Life Questionnaire (N-QOL). **Methods:** We conducted a 9-week, randomized, double-blind, placebo-controlled, parallel-group trial involving healthy adults with frequent urination and self-perceived sleep disturbances. The participants were randomly assigned to receive either tablet containing *Epilobium angustifolium* extract providing 15 mg/day of oenothein B or a placebo for 8 weeks. The primary outcome was the N-QOL score, assessed at baseline, and at 4 and 8 weeks. **Results:** A total of 47 participants completed the study and were included in the analysis. The active group showed significantly greater improvements in the N-QOL total score and Sleep/Energy score compared to the placebo group at both 4 and 8 weeks. No significant differences were observed to the Bother/Concern score or Overall Health Percep-

tion. No adverse events related to the study food were reported. **Conclusions**: The intake of *Epilobium angustifolium* extract providing 15 mg/day of oenothein B significantly improved the nocturia-related QOL, particularly in the domains of sleep and energy, in adults with frequent urination tendencies and sleep complaints. These findings suggest that *Epilobium angustifolium* extract may serve as a practical and safe approach to managing nocturia-related QOL.

Keywords

Epilobium angustifolium Extract, Nocturia, N-QOL Questionnaire

1. Introduction

Nocturia is defined as waking one or more times during the main sleep period to void and is a highly prevalent lower urinary tract symptom, affecting over 50% of individuals in their 50s and more than 70% of those aged 80 years or older [1]. Repeated nocturnal awakenings to urinate fragment sleep and induce daytime sleepiness and reduced vitality, leading to multidimensional declines in quality of life (QOL) [2].

The disease-specific quality of Life questionnaire for nocturia (Nocturia Quality of Life Questionnaire (N-QOL)) consists of an N-QOL total score and three subscales: Sleep/Energy, Bother/Concern, and Overall Health Perception [3]. It is one of the recommended questionnaires for evaluating QOL improvement following nocturia treatment [4].

As QOL deterioration—including reduced sleep quality—due to nocturia has gained social attention, there has been growing interest in complementary and alternative therapies that can be used safely over the long term. The European Association of Urology (EAU) Guidelines on Lower Urinary Tract Symptoms (LUTS) introduce phytotherapy as a therapeutic option in addition to pharmacotherapy and suggest that plant-based preparations may improve nocturnal voiding frequency and QOL measures [5].

Among phytotherapies, *Epilobium angustifolium*, a medicinal plant in the family Onagraceae, has long been used in North America and Europe for benign prostatic enlargement and voiding disorders. Its active constituent, oenothein B, has been reported to inhibit 5α-reductase and exert anti-inflammatory and antioxidant effects, drawing attention as a potential approach to improving nocturia-related QOL [6].

Regarding efficacy in humans, a 9-week, placebo-controlled trial of *Epilobium angustifolium* extract providing 30 mg/day of oenothein B demonstrated significant reduction in both the visual analog scale (VAS) score for "discomfort that wakes you up at night to go to the toilet" and the nocturnal awakening time. The intake of *Epilobium angustifolium* extract providing 15 mg/day of oenothein B significantly shortened nocturnal awakening time, although without a significant

change in the VAS score [7]. Thus, while certain aspects of nocturia-related QOL have been examined, no study has evaluated the multidimensional QOL associated with nocturia using the N-QOL.

This study aimed to investigate the effect of *Epilobium angustifolium* extract providing 15 mg/day of oenothein B on the N-QOL total score and subscales in individuals with a tendency toward frequent urination and self-perceived sleep disturbance. We conducted a randomized, double-blind, placebo-controlled, parallel-group trial in healthy men and women with a tendency toward frequent urination and self-perceived sleep disturbance.

2. Materials and Methods

2.1. Study Participants and Setting

Eligible participants were generally healthy adults who met all the inclusion criteria and none of the exclusion criteria. Before enrollment, all the candidates received a sufficient explanation of the study and provided written informed consent.

Inclusion criteria:

1) Healthy Japanese men or women aged 20 to 79 years old at consent; 2) individuals with a tendency toward frequent urination and self-perceived sleep disturbance; 3) individuals with the capacity to consent who received an adequate explanation of the study's objectives and content, voluntarily agreed to participate, and provided written informed consent.

Exclusion criteria:

1) Individuals receiving outpatient care at the time or with a current medical history of diseases that could have affected this study; 2) Individuals suspected of overactive bladder according to the Overactive Bladder Symptom Score (OABSS): urgency score (Question 3) > 2 and total OABSS ≥ 3; 3) Individuals suspected of benign prostatic hyperplasia; 4) Individuals with gastrointestinal diseases or a surgical history that could affect digestion and absorption; 5) Individuals regularly using medications that could have influenced the study; 6) Individuals unable to discontinue the use of drugs, supplements, or health foods related to urination or sleep; 7) Individuals engaged in night shifts, rotating shifts, or heavy labor; 8) Individuals with a current or past history of drug or alcohol dependence; 9) Individuals who were pregnant, breastfeeding, or intended to become pregnant during the study; 10) Individuals living with a care-dependent person or caring for an infant; 11) Individuals with allergies to components of the study foods; 12) Individuals who were at the time participating in or intending to participate in other clinical studies that could have affected this study at baseline; 13) Individuals deemed unsuitable by the principal investigator for other reasons.

The study protocol was registered in the clinical trial registry operated by the University Hospital Medical Information Network Research Center (UMIN-CTR) under ID UMIN000053746 (trial title: A Study to Evaluate the Effects of a

Plant Ex-tract-containing Food on Sleep Complaints: A Randomized, Double-blind, Placebo-controlled, Parallel-group Trial).

2.2. Research Methods

This was a 9-week, randomized, double-blind, placebo-controlled, parallel-group trial (allocation ratio, 1:1), consisting of a 1-week pre-observation period followed by an 8-week intake period. No methodological changes were made after the study's initiation.

Paid volunteers were recruited. The principal investigator enrolled participants according to the inclusion and exclusion criteria. A statistician performed block randomization with adjustment for age and sex, allocating the participants to two groups. An allocation officer not directly involved in the trial allocated them to an active group and placebo group. This officer prepared and sealed a key-code table and kept it sealed until the analysis population had been finalized, to maintain blinding for all except the allocation officer. The study foods were dispensed in plain aluminum pouches containing 8-week tablets at the daily dose to ensure blinding of the participants and implementers.

The participants were instructed throughout the study to maintain their usual lifestyle (in terms of diet, alcohol consumption, exercise, bedtime, and smoking); refrain from using drugs, supplements, and health foods (including Foods for Specified Health Uses and Foods with Function Claims) that might have affected the study; and avoid binge eating/drinking or staying up late. If medication was unavoidably required due to illness, the participants were to consult the study site in advance.

A prior placebo-controlled study in healthy Japanese adults reported a significant reduction in nocturnal awakening time with *Epilobium angustifolium* extract intake compared with placebo [7]. Based on these data, a sample size calculation for the present study (two-sided $\alpha = 0.05$; power = 0.80) yielded 20 participants per group. Allowing for attrition, the target enrollment was set at 25 per group (total $n = 50$).

2.3. Consumption of Study Foods

During the intake period, the participants consumed the assigned study food. The active food was a compressed tablet containing *Epilobium angustifolium* extract, along with reduced maltose syrup, cellulose, calcium stearate, and silicon dioxide. The placebo matched the active food in appearance; the *Epilobium angustifolium* extract was replaced with caramel coloring, and the quantities of reduced maltose syrup, calcium stearate, and silicon dioxide were adjusted. The daily intake for both the active and placebo foods was one tablet (250 mg) once daily with cold or lukewarm water.

The nutritional compositions of the tablets are presented in **Table 1.** The active food provided 15 mg/day of oenothein B derived from *Epilobium angustifolium* extract.

Table 1. Nutrient compositions of study food.

	Placebo food	Active food
	(1 tablet)	(1 tablet)
Energy (kcal)[a]	1	1
Protein (g)[b]	0.0	0.0
Fat (g)	0.0	0.0
Carbohydrate (g)	0.2	0.2
Salt equivalent (g)	0.000	0.000

[a]Calorie conversion factors: protein, 4; fat, 9; and carbohydrate, 4; [b]Nitrogen protein conversion factor: 6.25.

2.4. Evaluation Items

The primary outcome was the N-QOL score, assessed at baseline, and 4 and 8 weeks of intake. The N-QOL comprises 13 items: 6 items for Sleep/Energy, 6 for Bother/Concern, and 1 for Overall Health Perception. For the first 12 items, lower raw scores indicate better QOL and range from 0 (highest QOL) to 4 (lowest QOL). For analysis, these 12 items were reverse-scored so that higher scores indicate better QOL, ranging from 0 (lowest QOL) to 4 (highest QOL). Overall Health Perception is rated from 0 (not at all) to 10 (very much), with higher scores indicating better QOL. The scores are presented as the Total Score (the sum of the 12 items excluding the last item); the two subscales of Sleep/Energy (the sum of 6 items) and Bother/Concern (the sum of 6 items); and the single-item Overall Health Perception [4].

The two subscales were scaled to a 0 - 100 metric as follows (with one Bother/Concern item treated as missing if the response "no family/household members" was given to the item concerning annoyance to family/housemates):

$$\text{Subscale total score} = \left(\text{sum of item scores for the subscale}/24\right)\times 100$$

The total score was scaled to 0 - 100 as follows [4]:

If all 12 items were answered:

$$\text{N-QOL total score} = \left(\text{sum of the 12 item scores}/48\right)\times 100$$

If 1 item was missing (11 items answered):

$$\text{N-QOL total score} = \left(\text{sum of the 11 item scores}/44\right)\times 100$$

No changes were made after the study's initiation.

The participants were provided with a food diary and a participant log and instructed to record the following daily from one week before the start of intake through the intake period: 1) Study food intake status; 2) Sleep duration; 3) The use of medications (excluding nutritional drinks but including newly designated quasi-drugs and quasi-drugs within the new scope); 4) The presence of physical changes; 5) Changes in lifestyle and their details; 6) Dietary content (including supplements, health foods, drink products, and alcohol).

At screening, the OABSS was administered to characterize the background related to overactive bladder. A questionnaire survey was conducted to confirm whether participants met the inclusion criteria of "individuals with a tendency toward frequent urination and self-perceived sleep disturbance".

2.5. Statistical Analysis

The analysis population was the per-protocol set (PPS). Repeated-measures ANOVA was used to assess the group-by-time interaction. Between-group comparisons (active vs. placebo) at each time point were conducted using unpaired t-tests on observed values and changes from baseline. All tests were two-sided with a significance level of 5%. Statistical analyses were performed using IBM SPSS Statistics, version 28. The participant characteristics are presented as means ± standard deviations; other data as means ± standard errors. No additional analyses were conducted. If a score was missing during the study, that participant was excluded from analyses of the corresponding score.

3. Results

3.1. Study Participants

A total of 50 participants (29 male, 21 female) were enrolled and randomized; none dropped out before starting the intervention. In total, 25 were allocated to the active group and 25 to the placebo group. During the study, 1 participant in the active group (female) discontinued for reasons unrelated to the study, leaving 49 completers. After study completion, 2 participants met exclusion criteria due to violations of study precautions (1 per group), resulting in 47 participants (28 male, 19 female) in the PPS. The analyses were performed according to the original allocation.

Recruitment through follow-up occurred from February to June 2024. The study concluded after all the participants had completed follow-up. The baseline characteristics are shown in Table 2, and the CONSORT flow diagram is presented in Figure 1.

Table 2. Participants characteristics.

Parameter	Placebo group	Active group
	(n = 24)	(n = 23)
Male/Female	13/11	15/8
Age (years)	44.7 ± 13.1	43.3 ± 12.9
Height (cm)	165.3 ± 8.6	168.4 ± 8.2
Body weight (kg)	65.9 ± 15.4	66.6 ± 10.9
BMI	23.9 ± 4.4	23.5 ± 3.7
OABSS total score	2.0 ± 1.2	2.2 ± 1.1

Values are expressed as means ± SDs; No significant difference was observed.

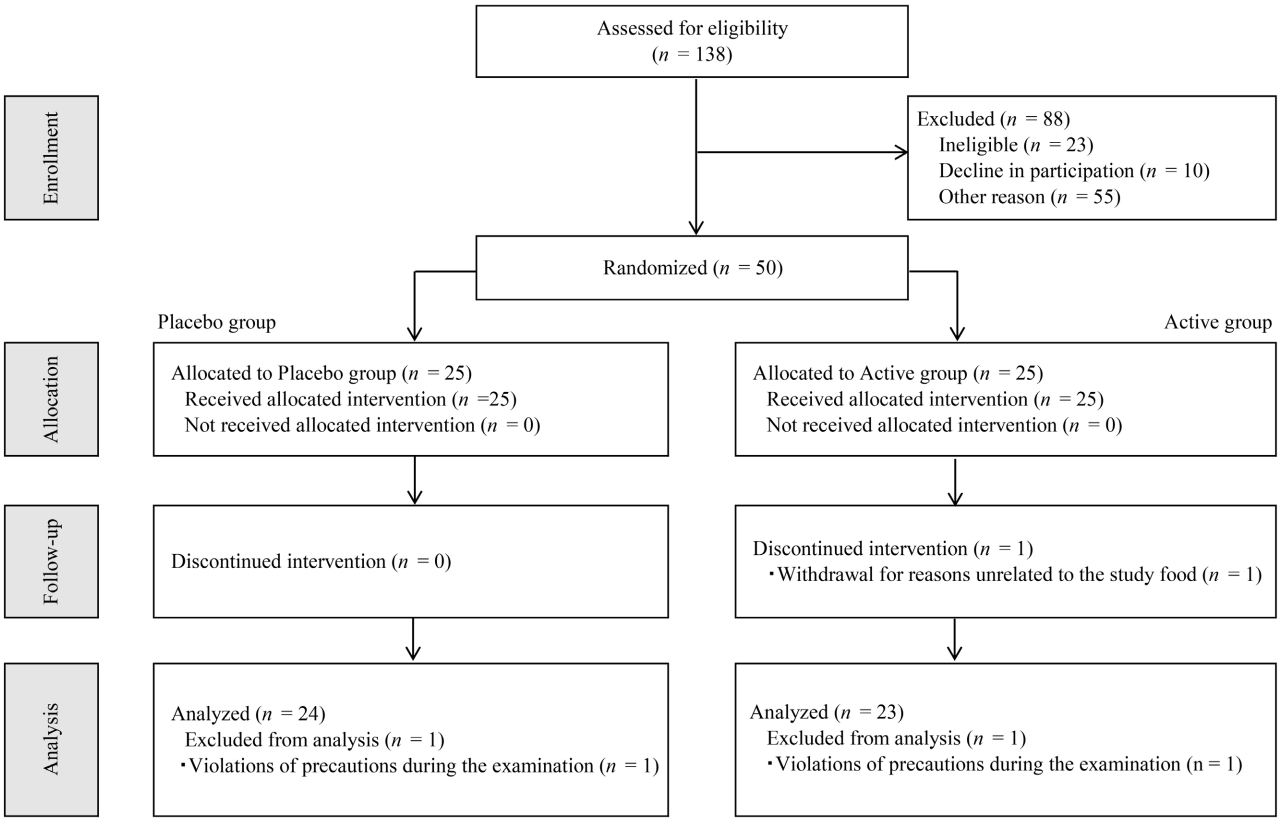

Figure 1. Flow diagram of progression through phases of this randomized, double-blind, placebo-controlled, parallel-group study.

3.2. Analysis Results

The N-QOL scores are summarized in Table 3. Significant group-by-time interactions were observed for the N-QOL total score and Sleep/Energy score. In between-group comparisons of changes from baseline at each assessment, the active group showed significantly greater improvements than the placebo group at 4 and 8 weeks. No significant interactions or between-group differences were observed for Bother/Concern or Overall Health Perception.

Table 3. N-QOL score.

	Group		Baseline	4 Weeks	8 Weeks	*P*-value (Interactions between Groups and Time Points)
N-QOL total score	Placebo (*n* = 24)	Measured	79.2 ± 2.5	80.4 ± 3.1	80.9 ± 4.1	*P* = 0.029
		Changes from baseline	—	1.2 ± 1.8	1.7 ± 2.9	
	Active (*n* = 23)	Measured	78.8 ± 3.0	86.5 ± 2.4	87.9 ± 2.5	
		Changes from baseline	—	7.7 ± 1.7*	9.1 ± 1.9*	

Continued

Sleep/Energy	Placebo (n = 24)	Measured	75.7 ± 3.2	78.5 ± 3.4	77.8 ± 4.2	P = 0.032
		Changes from baseline	—	2.8 ± 1.9	2.1 ± 3.0	
	Active (n = 23)	Measured	75.4 ± 3.7	85.7 ± 2.7	86.8 ± 3.0	
		Changes from baseline	—	10.3 ± 2.3*	11.4 ± 3.1*	
Bother/Concern	Placebo (n = 19)	Measured	81.1 ± 2.9	80.3 ± 4.0	81.4 ± 5.2	P = 0.224
		Changes from baseline	—	−0.9 ± 2.4	0.2 ± 4.0	
	Active (n = 17)	Measured	82.8 ± 4.1	87.5 ± 3.5	88.2 ± 3.8	
		Changes from baseline	—	4.7 ± 1.8	5.4 ± 1.4	
Overall Health Perception	Placebo (n = 24)	Measured	2.5 ± 0.3	2.8 ± 0.4	2.5 ± 0.4	P = 0.256
		Changes from baseline	—	0.3 ± 0.3	0.0 ± 0.3	
	Active (n = 23)	Measured	3.0 ± 0.5	2.7 ± 0.5	2.2 ± 0.5	
		Changes from baseline	—	−0.3 ± 0.5	−0.8 ± 0.3	

Values are expressed as means ± Ses; Significantly different from the placebo group (*P < 0.05).

3.3. Adverse Events

No adverse events attributable to the study food were observed during the trial.

4. Discussion

This randomized, double-blind, placebo-controlled, parallel-group trial evaluated the effects of *Epilobium angustifolium* extract providing 15 mg/day of oenothein B on nocturia-related QOL in healthy adults with a tendency toward frequent urination and self-perceived sleep disturbance. The active group showed significantly greater improvements than placebo in changes from baseline for the N-QOL total score and Sleep/Energy, whereas no significant differences were observed for Bother/Concern or Overall Health Perception.

An improvement in the N-QOL total score reflects overall gains across the Sleep/Energy and Bother/Concern domains, indicating an improvement in the comprehensive nocturia-related QOL [3]. Although a previous study using oenothein B at 15 mg/day did not detect a significant improvement in a single VAS item reflecting "dis-comfort from waking to use the toilet at night" [7], the present study observed improvements in the multidimensional N-QOL total score at the same oenothein B dose, suggesting that 15 mg/day may improve nocturia-related

QOL more globally. The N-QOL total score correlates with sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) [8]. Given the improvement in Sleep/Energy observed here and the previously reported shortening of nocturnal awakening time, these results are consistent. Therefore, the intake of *Epilobium angustifolium* extract providing 15 mg/day of oenothein B likely improves the nocturia-related QOL and may reduce nocturnal awakening time.

A plausible mechanism for the observed QOL improvement is attenuation of oxidative stress. Oxidative stress has been implicated in urinary frequency symptoms [9]. When urinary levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative stress, were measured in patients with overactive bladder, they were found to be significantly higher than those in healthy controls [10]. Reactive oxygen species (ROS) produced in the body have been shown to damage detrusor mitochondria, impairing detrusor contractility [11]. Research has also shown that increased oxidative stress impairs urethral function [12]. Therefore, oxidative stress is thought to cause frequent urination.

Epilobium angustifolium extracts possess antioxidant activity, and oenothein B itself has been reported to have antioxidant effects. Thus, reducing systemic oxidative stress via *Epilobium angustifolium* extract intake may alleviate nocturia-related symptoms, thereby improving QOL.

The absence of significant changes in Bother/Concern and Overall Health Perception may be explained as follows. Bother/Concern reflects psychological distress and social constraints directly related to nocturia [3]. Such psychological and social dimensions may improve more slowly than symptoms, and an 8-week duration may have been insufficient. Overall Health Perception is a single 10-point item; as a single-item measure, it likely has lower sensitivity than composite scores like the N-QOL total score. Indeed, even with the nocturia medication desmopressin, significant improvements in this scale have not been consistently observed [13].

Overall, the intake of *Epilobium angustifolium* extract providing 15 mg/day of oeno-thein B improved nocturia-related QOL in adults with frequent urination tendencies and sleep complaints. It was also demonstrated to be safe; there were no adverse events attributable to the study food.

However, this study has limitations. We only evaluated the nocturia-related QOL and did not measure nocturnal voiding frequency or nocturnal awakening time in this cohort; thus, direct effects on these endpoints remain unclear. Future studies should concurrently assess nocturia-related QOL together with objective nocturnal voiding frequency and nocturnal awakening time within the same participant cohort. Regarding the N-QOL "Bother/Concern" score, for which no significant improvement was observed in this study, the 8-week test period may not have been sufficient, and longer-term verification is therefore necessary. Furthermore, this study did not target patients with clinically diagnosed nocturia or overactive bladder, but rather "healthy adults with frequent urination tendencies and sleep complaints". For this reason, the results of this study cannot be immediately

extrapolated to the population of patients receiving diagnosis and treatment at medical institutions, and future research will involve verifying the results in a population that includes patients with nocturia and overactive bladder.

5. Conclusion

In healthy adults (men and women) with a tendency toward frequent urination and self-perceived sleep disturbance, an 8-week intake of *Epilobium angustifolium* extract-containing food providing 15 mg/day of oenothein B significantly improved the N-QOL total score and the Sleep/Energy score. These findings indicate that *Epilobium angustifolium* extract intake improves QOL impaired by nocturia and may serve as a practical, easily administrable approach, for example, via supplements for adults experiencing frequent urination and sleep difficulties.

Authors' Contributions

Conceptualization, T.K. and K.T.; methodology, Y.H.; validation, N.O.; formal analysis, N.O. and S.M.; investigation, S.I., and N.K.; writing—original draft preparation, N.O. and Y.H.; writing—review and editing, K.F.; visualization, N.O. and S.M.; supervision, K.T. and Y.I.; project administration, T.O. and T.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study was reviewed and approved (approval date: 29 February 2024) by the Ethics Committee of Miura Clinic, Medical Corporation Kanon-kai (Chair: Shinmei Nishi), and conducted in accordance with the Declaration of Helsinki (October 2013, WMA, Fortaleza, Brazil) and the Ethical Guidelines for Life Science and Medical Research Involving Human Subjects (partial revision, 27 March 2023). The trial was conducted under physician supervision at the Clinical Evaluation and Analysis Center of Toyo Shinyaku Co., Ltd.

Informed Consent Statement

Informed consent was obtained from all participants involved in the study.

Data Availability Statement

The data used in this manuscript are not publicly available because of commercial restriction, but are available upon reasonable request.

Conflicts of Interest

Toyo Shinyaku Co., Ltd. supplied the study foods. The coauthor Yukinao Ishibashi is a physician affiliated with the Medical Corporation Chidori-kai Ishibashi

Orthopedic Clinic and served as the principal investigator. Toyo Shinyaku Co., Ltd. has a consultancy agreement with the Medical Corporation Chidori-kai Ishibashi Orthopedic Clinic.

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