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Urtica dioica for treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a common problem of the elderly population. This study was conducted to investigate the effect of *Urtica dioica* on the clinical symptoms of BPH. This double-blind clinical trial included 248 patients with symptomatic BPH in Shohada Ashayer Hospital of Khorramabad. The patients were randomly divided into four groups of treatment with *U. dioica* 3 g, *U. dioica* 5 g, *U. dioica* 7 g and treatment with prazosin 1 mg alone as the control group. The clinical symptoms, patients' quality of life and level of serum prostate-specific antigen (PSA) were measured before and 2 months after the intervention. The results of the study showed significant differences between the four groups after the intervention for the scores of clinical symptoms and patients' quality of life, while no significant differences were found for serum PSA levels. Sheffe *post hoc* comparisons showed significant improvements in the scores of the patients' clinical symptom in the *U. dioica* 5 g/d and *U. dioica* 7 g/d groups. The results of the study showed that simultaneous consumption of higher doses of *U. dioica*, up to 7 g/d, plus prazosin, compared with the consumption of prazosin alone, resulted in significant improvements in the clinical symptoms of BPH.

Key words: Benign prostatic hyperplasia • Prazosin • *Urtica dioica*

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most important urological problems that affects the elderly population (Vitalone et al., 2001), and its symptoms are manifested as the lower urinary tract syndrome. This syndrome is manifested as a series of storage and voiding symptoms, and its severity is to such an extent that it affects the patients' daily life and quality of life (Girman *et al.*, 1998; Lopatkin *et al.*, 2007). The storage symptoms are associated with prostatic urethra narrowing, and include delay in starting urination, weak or intermittent urine stream and urine dribbling. In addition, many patients suffer from the voiding symptoms including the feeling of incomplete emptying of the bladder and nocturia urgency (Ekman, 1989).

The use of plant extracts (phytotherapy) for the treatment of the lower urinary tract symptoms was first introduced in the 15th century in Egypt (Melo *et al.*, 2002). Plant extracts are now being used in many European countries and the USA as over-the-counter (OTC) drugs (Bales *et al.*, 1999; Melo *et al.*, 2002). In the Iranian traditional medicine, the extracts of some herbs such as *U. dioica* (stinging nettle) are used to treat BPH (Safarinejad, 2005; Goodarzi *et al.*, 2006). According to Astin, the reasons for people's tendency toward phytotherapy include changes in values and beliefs, increases in public awareness of health and well-being, and nature as well as mild and non-recurring side effects of medicinal herbs (Astin, 1998; Melo *et al.*, 2002).

Urtica dioica has beneficial effects on the treatment of BPH clinical symptoms, and no significant adverse effects have been reported by patients after taking the herb (Lopatkin *et al.*, 2005; Safarinejad, 2005). This

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study was conducted because most of the conducted studies have examined combinations of stinging nettle with other herbs (Krzeski *et al.*, 1993; Metzker *et al.*, 1996; Wilt *et al.*, 2005). Some other studies have used only the prepared liquid extract of stinging nettle roots or capsules containing the plant. In these studies, the combinations of the liquid extract have not been accepted by the patients due to its unpleasant smell (Vontobel *et al.*, 1985; Englemann *et al.*, 1996). One study reported only an improvement in the urinary flow parameters in the patients with mild to moderate symptoms of BPH compared with the use of placebo (Dathe and Schmid, 1987). Another study showed that taking *U. dioica* along with other phytotherapeutic agents influenced the symptoms of LUTS, but *U. dioica* alone did not have any effects on the clinical symptoms of prostate (Wilt *et al.*, 2005). Moreover, most of the mentioned studies have used the extract of *U. dioica* root, while in Iran mostly the stems and leaves of the plant are used for therapeutic purposes, and the processed combinations of the plant are less available. Moreover, the plant is prepared at home traditionally (boiled or steamed) and the sellers of the plant do not prescribe a particular dose for patients so that the dose varies from one apothecary to another one. One the other hand, *U. dioica* has some effects including decrease in blood sugar (Kavalali *et al.*, 2003), and its high consumption leads to problems such as decrease in consciousness level and risk of falling, particularly in elderly patients.

Considering the conflicting results presented in the above-mentioned studies, we tried to investigate whether the use of the boiled root and leaves of the plant would result in improvements in the clinical symptoms of BPH, and whether differences would be found in improvements in the clinical symptoms with an increase in doses. Therefore, this study was conducted to determine the effect of different doses of *U. dioica* on the lower urinary tract symptoms associated with BPH.

MATERIALS AND METHODS

This double-blind clinical trial included 248 patients with BPH referring to the urology clinic of Shohada Ashayer Hospital in Khorramabad (west of Iran) according to the inclusion criteria of the study. The subjects were selected using the convenience sampling, and were divided into four groups of *U. dioica* 3 g/d, *U. dioica* 5 g/d, *U. dioica* 7 g/d and the control group using the randomized block sampling. The first group consumed prazosin 1 mg/d plus *U. dioica* 3 g/d for 60 d, the second group prazosin 1 mg/d plus *U. dioica* 5 g/d for 60 d, the third group prazosin 1 mg/d plus *U. dioica* 7 g/d for 60 d, and the fourth group, as the control group, took only prazosin 1 mg/d for 60 d (Figure 1). A sample size of 62 persons in each group was calculated based on previous studies and considering the loss rate.

The inclusion criteria of the study included: males over 50 years old; newly diagnosed BPH cases; International Prostate Symptom Score (IPSS) scores of 8 and over; lack of bacteriuria, serum creatinine levels lower than 1·5 mg/dL; and prostate-specific antigen (PSA) levels lower than 4 ng/mL. The exclusion criteria included: a history of prostatic cancer, neurogenic bladder, diabetes mellitus, nephropathy and congestive heart failure (CHF); consumption of two or more than two antihypertensive drugs, or any other prescribed or OTC chemical or herbal drugs to treat the urinary symptoms of BPH during the 4 weeks prior to the study; incidence of complications due to medicinal herbs; and unwillingness to continue participating in the study.

The tool applied in this study was the IPSS questionnaire, which was prepared by the American Urology Association and is a valid tool in determining the need for treatment in patients and controlling their responses to the treatment regularly. The questionnaire is composed of seven questions on the voiding symptoms (urinary hesitancy, incomplete emptying, straining to void and weak stream) and the storage symptoms (frequency, urgency and nocturia) (Liao *et al.*, 2011) (Appendix 1).

All the patients suspected of BPH with the IPSS scores of over 8 were included when they fulfilled the inclusion criteria of the study. These subjects were then introduced to a laboratory for blood and serum PSA tests. After that, those who had the inclusion criteria were randomly assigned to one of the four groups. Considering the age and local dialect of each subject, the questioner read the IPSS questionnaire and tried to help the subjects in understanding it through the local dialect. The questioner and the subjects were unaware of type of treatment in each group.

All the samples were given appropriate doses of dried *U. dioica* in separate proportions needed for 2 months considering the group in which they were. *U. dioica* was prepared for all the subjects from the same apothecary. The subjects were instructed orally and in written form how to prepare boiled *U. dioica*. They were asked not to use any other medicinal herbs to relieve urinary symptoms, and to immediately see a doctor in case of any complications. The telephone numbers of all the subjects in each group were written down by the co-researcher, and the way of drug consumption and their possible side effects were followed up on the phone. The majority of the samples were visited by a urologist after 1 month of intervention, and the intervention was continued for 2 months.

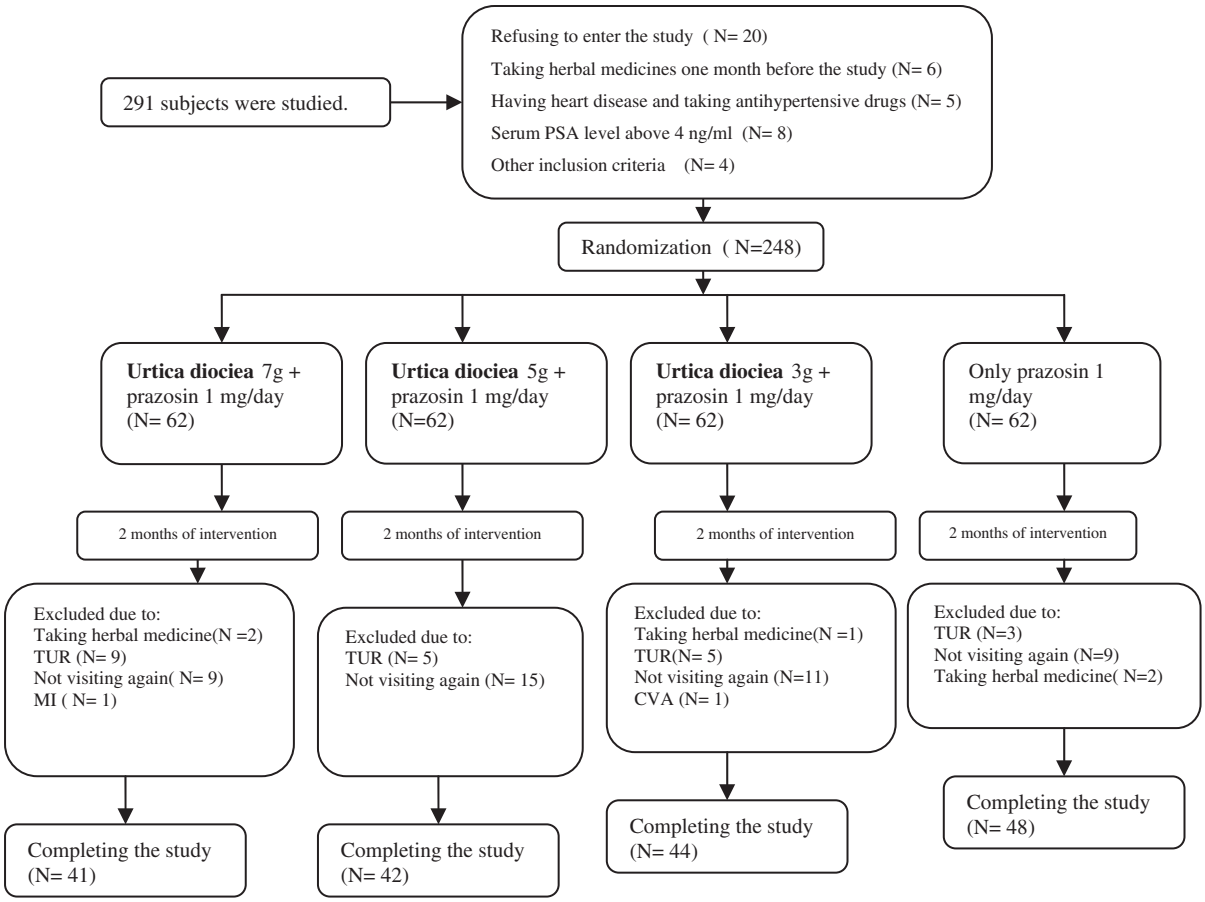

Figure 1 Disposition of study participants and the study trend.

The sampling was performed from May 2012 to November 2012. The IPSS questionnaire was recompleted for each sample at the end of the second month of intervention, and the serum PSA level was re-examined. As *U*. *dioica* may cause side effects including decline in blood pressure and blood sugar (Legssyer *et al.*, 2002; Kavalali *et al.*, 2003), and prazosin can result in decline in blood pressure and its associated side effects, the subjects were advised to consume prazosin and boiled *U*. *dioica* at night. Finally, considering the normal distribution of the questionnaire scores, the collected data were analysed using one-way analysis of variance (ANOVA), *post hoc* tests, and paired t-tests.

RESULTS

The mean age of the subjects was $56{\cdot}25 \pm 9{\cdot}22$ years, and no significant differences were found between the four groups in terms of age. In addition, before the intervention, no significant differences were found between the four groups in terms of storage symptoms scores, voiding symptoms scores, total IPSS scores, patients' life quality scores and serum PSA levels ($p > 0{\cdot}005$).

The results of the paired t-tests before and after the intervention in the *U*. *dioica* 3 g/d group showed significant differences in terms of storage symptom scores, voiding symptom scores and total IPSS scores, but no significant differences were found in terms of patients' quality of life scores, and serum PSA levels (Table 1). In the groups of *U*. *dioica* 5 g/d and *U*. *dioica* 7 g/d, in addition to a difference in the total IPSS scores and its sub-scores, a significant difference was found for the scores of quality of life before and after the intervention. Also, a significant difference was found for the scores of serum PSA level before and after the intervention in the *U*. *dioica* 7 g/d group, so that there was an increase of 0·05 score after the intervention. In the control group, in which the patients used only prazosin, a significant difference was found for storage symptoms scores and total IPSS scores before and after the intervention, but no significant differences for the scores of voiding symptoms and quality of life.

Table 1 A comparison between the mean scores of clinical symptoms, serum PSA level, and quality of life in the four groups before and after the intervention

Group / Variable	Urtica diocieа 3 g before intervention	Urtica diocieа 3 g after intervention	Mean change (95% CI)	Urtica diocieа 5 g before intervention	Urtica diocieа 5 g after intervention	Mean change (95% CI)	Urtica diocieа 7 g before intervention	Urtica diocieа 7 g after intervention	Mean change (95% CI)	Control group before intervention	Control group after intervention	Mean change (95% CI)
Variable												
IPSS voiding Score†	9·52 (3·58)	7·4 (3·55)	**2·11 (1·49–2·73)	8·85 (3·39)	6·38 (2·65)	**2·47 (1·69–3·26)	10·09 (2·97)	5·36 (3·05)	**4·73 (4·05–5·41)	10·68 (3·1)	9·61 (3·44)	*1·07 (−0·1–2·26)
IPSS storage score†	12·11 (6·09)	9 (5·47)	**3·11 (2·09–4·1)	10·71 (3·92)	6·21 (3·42)	**4·5 (3·28–5·71)	11·8 (3·9)	5·8 (4·25)	**5·92 (5·24–6·61)	8·08 (2·55)	7·16 (1·96)	*0·92 (0·7–1·77)
Total IPSS Score†	21·63 (9·17)	16·4 (8·64)	**5·22 (3·71–6·74)	19·57 (9·17)	12·78 (8·64)	**6·78 (5·03–8·53)	21·7 (6·35)	11·24 (6·92)	**10·46 (9·21–11·71)	18·79 (4·64)	16·79 (5·29)	*2 (0·25–3·74)
Serum PSA level†	1·85 (0·86)	1·72 (1·62)	0·13 (−0·3–0·56)	2·03 (1·06)	2·01 (1·04)	0·02 (−0·02–0·02)	1·5 (0·6)	1·55 (0·55)	**−0·04 (−0·08–−0·01)	1·96 (1·47)	1·89 (1·51)	0·07 (−0·4–0·18)
Quality of life	3·02 (0·59)	2·9 (1·41)	0·11 (−0·18–0·40)	3·28 (1·17)	2·57 (1·3)	**0·71 (0·41–1·01)	3·24 (0·66)	2·21 (0·98)	**1·02 (0·79–1·25	3·04 (0·5)	3·16 (0·63)	−0·12 (−0·33–0·08)

CI, confidence interval; PSA, prostate-specific antigen.
** $P < 0.0001$, * $P < 0.05$.
†t-Student test.

On the basis of the obtained results, the rates of decreases in the clinical symptoms were 10·6% (2 scores) in the control group, 24·1% (5·22 scores) in the *U*. *dioica* 3 g/d group, 34·6% (6·78 scores) in the *U*. *dioica* 5 g/d group and 48·2% (10·46 scores) in the *U*. *dioica* 7 g/d group. As seen in the table, increases in *U*. *dioica* doses resulted in improvements in the clinical symptoms. Furthermore, the improvement rates in the voiding symptoms were 7·59% (1·07 scores) in the control group, 21·5% (2·11 scores) in the *U*. *dioica* 3 g/d group, 29·2% (2·47 scores) in the *U*. *dioica* 5 g/d group and 47·3% (4·73 scores) in the *U*. *dioica* 7 g/d group, while the improvement rates in the storage symptoms were relatively higher than those for the voiding symptoms and included 13·2% (0·92 scores) in the control group, 25·6% (3·11 scores) in the *U*. *dioica* 3 g/d group, 38% (4·50 scores) in the *U*. *dioica* 5 g/d group and 35·5% (5·92 scores) in the *U*. *dioica* 7 g/d group. However, after the intervention, the analyses by one-way ANOVA showed significant differences between the four groups in terms of the mean change scores of storage symptoms, voiding symptoms, total IPSS ($p = 0·0001$) and patients' quality of life scores ($p = 0·001$), whereas the differences in the mean change scores of serum PSA levels were not significant ($p = 0·258$).

The results of *post hoc* tests showed that the differences in voiding, storage and total IPSS mean change scores were between the *U*. *dioica* 7 g/d group and the two groups of *U*. *dioica* 3 g/d and the control, and that the improvement in the voiding symptoms scores in the *U*. *dioica* 7 g/day group was much more than the improvements in the *U*. *dioica* 3 g/d and the control groups (Table 2). Moreover, the scores of quality of life in the *U*. *dioica* 7 g/d group improved significantly compared with the scores in the *U*. *dioica* 3 g/d and the control groups, while the differences between the *U*. *dioica* 5 g/d and the *U*. *dioica* 7 g/d groups were not significant (Table 2).

DISCUSSION

This study clearly showed that the consumption of boiled *U*. *dioica* resulted in improvements in the clinical symptoms of the lower urinary tract symptoms associated with BPH based on the standardized IPSS questionnaire. The highest rate of improvement (48·2%) was found in the *U*. *dioica* 7 g/d, and the lowest rate (10·16%) in the control group.

Breza *et al.* reported an improvement of 40% in the patients who consumed Pygeum africanum 100 mg/d (Breza *et al.*, 1998). Although they used Pygeum africanum in their study, their results for this plant as a phytotherapeutic agent are consistent with our

Table 2 *Post hoc* comparison between the four groups in terms of the mean change scores of clinical symptoms, and quality of life

Variable	Group I Mean change	Group J Mean change	Mean change Difference (I — J)	*P*
IPSS voiding score	Urtica 7 g (4·73)	Urtica 3 g (2·11)	2·61(0·85–4·37)	0·001
		Urtica 5 g (2·47)	2·25(0·47–4·03)	0·006
		Control (5·22)	3·65(1·93–5·37)	0·001
	Urtica 5 g (2·47)	Urtica 3 g (2)	0·36 (—1·38–2·11)	0·952
		Control (1·07)	1·39(—0·33–3·11)	0·154
	Urtica 5 g (4·5)	Urtica 3 g (3·11)	1·38(—0·52–3·3)	0·246
		Control (0·92)	3·59(1·72–5·47)	0·0001
IPSS storage score	Urtica 7 g (5·92)	Urtica 3 g (3·11)	2·86(0·93–4·78)	0·001
		Urtica 5 g (4·5)	1·47(—0·47–3·42)	0210
		Control (0·92)	5·07(3·18–6·96)	0·0001
	Urtica 5 g (6·78)	Urtica 3 g (5·22)	1·55(—1·63–4·74)	0·594
		Control (2)	4·78(1·66–7·90)	0·0001
Total IPSS score	Urtica 7 g (10·46)	Urtica 3 g (5·22)	5·23(2·02–8·44)	0·0001
		Urtica 5 g (6·78)	3·67(0·43–6·92)	0·01
		Control (2)	8·46(5·31–11·60)	0·0001
	Urtica 7 g (1·02)	Urtica 3 g (0·11)	0·91	0
		Urtica 5 g (0·71)	0·31	0·438
Quality of life score	Urtica 5 g (0·71)	Control (—0·012)	1·14	0
		Urtica 3 g (0·11)	0·6	0·01
		Control (—0·012)	0·83	0·0001

results. In a study by Safarinejad, an improvement rate of 40·4% (8 scores) was reported in the IPSS scores, and 7·8% (1·5 scores) in the placebo group, being relatively consistent with our results (Safarinejad, 2005). However, a significant difference was found between the clinical symptom scores in the experimental and placebo groups after 6 months of treatment with 25 mg of Pygeum africanum and *U. dioica* combination (Melo *et al.*, 2002). In a study by Keland, in which a combination of Saba and *U. dioica* was used compared with finasteride, 3·1 and 4·8 scores of reduction were found in the IPSS scores after 24 and 48 weeks, respectively, showing no significant difference between the experimental and the placebo groups, and inconsistency with our results (Keland, 2000). In Lopatkin *et al.*'s study, the consumption of *U. dioica* and Sabal resulted in an improvement of 50% in the IPSS scores (Lopatkin *et al.*, 2007).

In our study, the rate of the improvement in the storage symptoms, proportionate to the increase in *U. dioica* doses, was higher than the rate in the voiding symptoms. In Keland's study, the voiding symptom scores in the patients with the prostatic volumes more than 40 mL improved more than the storage symptom scores (Keland, 2000). In Melo *et al.*'s study, most of the voiding symptoms improved after the consumption of Pygeum africanum for 6 months, being inconsistent with our results (Melo *et al.*, 2002).

The significant improvements in the clinical symptoms, particularly in the sub-scores of the storage symptoms, may be due to the decreases in the prostatic volumes. In Safarinejad's study, the prostatic volume in the *U. dioica* group decreased from 40·1 to 36·3 cc. The consumption of *U. dioica* 300 × 3 mg/10 kg for 100 d resulted in a reduction in prostate volume and serum testosterone levels in dogs (Daube, 1988; Safarinejad, 2005).

In our study, the score of life quality improved significantly only in the *U. dioica* 5 g/d (21%) and *U. dioica* 7 g/d (31%) groups. In Lopatkin *et al.*'s study, an improvement rate of 50% was reported in life quality scores, and this difference between their study and our study can be attributed to the longer intervention period (96 weeks) in their study (Lopatkin *et al.*, 2005). Significant improvement rates were reported in two studies by Stahl and Tosch, and Schneider and Rubben after the consumption of *U. dioica* for 9 weeks (Stahl and Tosch, 1996; Schneider and Rubben, 2004).

In our study, the serum PSA levels in the four groups did not show significant differences, being consistent with the results of the studies by Rong *et al.*, Stephen *et al.* and Safarinejad (Safarinejad, 2005; Stephen *et al.*, 2006; Shi *et al.*, 2007).

Our results showed that the consumption of boiled *U. dioica* alone, not combined with other phytotherapeutic agents, resulted in significant improvements in the clinical symptoms associated with BPH. Wilt *et al.* in their review of the literature reported that the consumption of *U. dioica* extract alone does not affect the treatment of the clinical symptoms of prostate, being inconsistent with our results.

On the basis of the studies conducted on animals, the compounds available in this plant resulted in the

cessation of growth factors, the suppression of the prostate metabolism, and thus, the decrease in the growth of prostatic cells (Hirano *et al.*, 1994; Wagner *et al.*, 1994; Hryb *et al.*, 1995). Some other studies have introduced the inhibition of the conversion of testosterone to dehydro-testosterone as the effective mechanism of *U. dioica* (Lowe and Ku, 1996). One reason that justifies the rates of improvement with increases in dose is the consumption of the aqueous extract of *U. dioica*, and this is confirmed by two studies. In the study of Hartmann *et al.* (1996), only the high dose of the methanolic extract of *U. dioica* resulted in the inhibition of 5-α-reductase. However, in a study Hryb by *et al.*, which was conducted to investigate the effects of various extracts of *U. dioica* roots on the interaction of sex hormone-binding globulin (SHBG) with its receptors in the human prostatic membrane, only the aqueous extract of *U. dioica* actively inhibited the bondage of SHBG with its receptors, and the inhibition of the receptors was dependent on dose, which started from a low dose (0·6 mg/mL) and caused the complete inhibition of the SHBG receptors in a 10 mg/mL dose. The results of this study are consistent with our results (Hryb *et al.*, 1995).

Our study had some limitations including lack of rectal ultrasound and uroflowmetry due to their unavailability, and lack of the placebo group. Therefore, it is recommended that these limitations be removed in future studies in order to investigate more precise results on the effects of various doses of *U. dioica* on the treatment of lower urinary tract symptoms. Moreover, no serious side effects were reported in our study as *U. dioica* was consumed at night. In future studies, higher doses of *U. dioica* can be tested cautiously in order to obtain more therapeutic effects.

CONCLUSIONS

The results of the study showed that the simultaneous consumption of prazosin and *U. dioica*, at least in the *U. dioica* 5 g/d dose, compared with the consumption of prazosin alone, is more effective in improving the clinical symptoms of BPH, and that an increase in the dose to 7 g/d increases the rate of improvement in the symptoms. Therefore, it is recommended that *U. dioica* be prescribed with effective drugs to treat the symptoms of BPH.

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WHAT IS KNOWN ABOUT THIS TOPIC

- Benign prostatic hyperplasia is a common health problem in elderly men, which affects their quality of life.

WHAT THIS PAPER ADDS

- In this study, we found which simultaneous consumption of boiled U. dioica plus prazosin resulted in higher improvement in lower urinary tract symptoms associated with benign prostatic hyperplasia.

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APPENDIX 1

International Prostate Symptom Score (IPSS) Questionnaire Patient name: —— ; Age: —— ; Date completed: ——

	Not at all	Less than one in five times	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
2. Over the past month, how often have you had to urinate again less than 2 h after you finish urinating?	0	1	2	3	4	5	
3. Over the past month, how often have you stopped and started again several times when you urinate?	0	1	2	3	4	5	
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	One time	Two times	Three times	Four times	Five or more	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Total symptom score							

BPH, benign prostatic hyperplasia.
Score: 1–7: mild; 8–19: moderate; 20–35: severe.
The possible total runs from 0 to 35 points with higher scores indicating more severe symptoms.
Scores less than seven are considered mild and generally do not warrant treatment.