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Research Article
Urtica Dioica Root Extract on Clinical and Biochemical Parameters in Patients with Benign Prostatic Hyperplasia, Randomized Controlled Trial

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Abstract

Background and Objectives: Benign Prostatic Hyperplasia (BPH) is a common urological disorder as men get older. BPH can cause uncomfortable urinary tract symptoms. Given the high incidence of the disease, further research is an undeniable necessity for its better management. In this research, the efficacy of Urtica Dioica root extract (UDE) on clinical and biochemical parameters were evaluated in this type of patients. **Materials and Methods:** Participants were 60 men with BPH that randomly allocated to two equal groups (Intervention = 30 and Comparison = 30). Block balanced Randomization method was performed using a computer by a trained nurse. Intervention and comparison groups received 450 mg day^{-1} UDE and placebo as tablets for 12 weeks, respectively. The main outcome was changes in International Prostate Symptoms Score (IPSS) from baseline to end of treatment. Data were collected by completing a standard questionnaire and performing relevant tests based on common laboratory methods. **Results:** UDE had an intermediate effect on IPSS, a small effect on serum high-sensitivity C-reactive protein (hs-CRP), intermediate to large effect on malondialdehyde (MDA) levels and intermediate effect on superoxide dismutase (SOD) activity. The magnitude of the effects of UDE on other parameters was overall negligible compared to the comparison and not significant. No side effects were seen in these patients following tablet usage. **Conclusion:** UDE consumption for 12 weeks among BPH patients had clinically significant effects on IPSS, serum hs-CRP, MDA and SOD activity.

Key words: Stinging nettle, inflammatory markers, oxidative stress, international prostate symptom score

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

BPH is a common urological disorder after non-malignant prostate enlargement. As age increases, its incidence increases so that in men over 50 years, about 25% may be involved and this increases by 75% in the seventh decade of life[1]. BPH increases the size of the prostate that can lead to symptoms including frequent urination with burning, urinary incontinence and incomplete emptying of the bladder[2]. Though the main reason leading to BPH has not been clear up to now, several studies have concluded that BPH is a multifactorial disorder and factors such as disruption of estrogen and androgen hormone balance, genetics[3], obesity, age[4], oxidative stress processes[5] and inflammatory factors[6] are related to the extension of the disease. It is unclear which factor is the first cause of the disease[7]. During the last decade, advances in medical treatments for BPH have led to a decrease in the use of surgical interventions for this disorder[8]. Today, the available therapies for BPH are 5-alpha-reductase inhibitors and alpha-adrenergic antagonists or alpha-blockers. They also have some side effects such as nasal congestion, hypertension, fatigue, dizziness and retrograde ejaculation, decreased libido, gynecomastia, impotence, reduced ejaculate volume, depression, fibrosis of the prostate tissue[9–12]. These side effects gradually increase interest in herbal products that have fewer side effects. *Urtica dioica* L. (stinging nettle) belongs to the family of Urticaceae and genus *Urtica*. is one of the most valuable herbs for the remedy of lower urinary tract disorders[13]. This herb is a rich source of fiber, vitamins, fatty acids, trepans, phenylpropanes, lignans, coumarins, ceramides, sterols and lectins[14]. Several studies have exhibited the beneficial effects of UDE alone or in combination with other herbal extracts in the treatment of BPH in human and/or animal models. Ghorbanibirgani *et al*., documented taking 600 mg UDE for 8 weeks, significantly reduced IPSS and improved clinical symptoms in patients with BPH[15]. 600 or 900 mg/kg/day of combined extracts of *Sabal serrulata* and *Urtica dioica* for 28 days significantly reduced prostate weight and prostate inflammation in a transgenic mouse model of BPH[16]. Significant reduction in prostate volume, tissue injury, apoptosis and oxidative stress has been documented in the rat model following UDE consumption[17,18]. In rat model of the mammary tumor, it has been shown that UD components reduced lipid peroxidation and tumor formation in the breast, but increased activity of certain antioxidant enzymes[19]. In addition, Vajic *et al*., [20] demonstrated the positive effect of UDE on plasma antioxidant capacity in an animal model of hypertension. Protective properties of UDE contrary to airway inflammation has been documented by Zemmouri *et al*.[21]. Based on present knowledge, there is no trial to measure the effect of UDE on the clinical index, markers of inflammatory and oxidative stress in BPH patients, simultaneously. UDE effectiveness on clinical and biochemical parameters in BPH patients was evaluated in this trial.

MATERIALS AND METHODS

Patients: Eighty five volunteer men, aged 50 to 80 years who had BPH were enrolled for initial screening at urology clinic affiliated to QUMS, Qazvin, Iran, from July 2018 to March 2019. All participants were examined by a urologist and their illness was confirmed according to the American Urological Association guideline[22]. Information concerning medical history and using any drug, nutritional complements and or herbal extract were collected by interviewing patients and completing the questionnaire. The Subjects who had IPSS score less than 8 and more than 19, diabetes mellitus, hypertension, hypo/hyperthyroidism, metabolic syndrome, renal failure and gastrointestinal complications were excluded. Finally, a total of 60 persons who had $8 \leq$IPSS score≤ 19 and other inclusion criteria come into the study.

Study design: This study was a randomized, double-blind, placebo-controlled with 12-weeks follow up period. Block balanced randomization method (http://www.randomization.com) was performed to create the random allocation of 60 patients to enter the two studied groups. Each group received either 150 mg UDE tablets or a placebo three times per day for 12-weeks. Participants were examined three times as follows: before, sixth weeks and end of the trial. For the duration of each visit, in addition to clinical assessment, unanticipated adverse effects of tablets were asked from the subjects. Bodyweight was evaluated with a standard scale while they were lightly dressed and barefoot. A wall-mounted height meter was used for height measurement. The Body Mass Index (BMI) was measured by dividing the weight (kg) to height (m^2). All study personnel was blinded to treatment assignment. Adherence to study intervention was measured by pill count at each visit. The protocol of the study has been approved by the institutional ethics board of QUMS (IR.QUMS.REC.1396.396) and all participants completed the informed consent form.

Urtica dioica root extract preparation: UDE extract (Urtidin® Film-Coated tablet that approved by the Iranian Food and Drug Administration (IRC: 1228104589), as well as a placebo, were designed and produced by Barij Essence Pharmaceutical Company, Kashan, Iran. Briefly, UDE containing dried extract

of root of stinging nettle (*Urtica dioica*) with active ingredient including polysaccharides, phytosterols, flavonoids and triterpenic acids that were standardized based on presence of 22 mg alanine amino acid in each F.C. tablet.

Outcomes: Diminution in the IPSS score was selected as the primary end-point. Serum PSA, hs-CRP, omentin, MDA, GSH and SOD were considered as the secondary outcomes.

Primary outcome assessment: A standard checklist containing seven questions was used for calculation of IPSS score[15]. This score was classified as follows: 1-7: Mild, 8-19: Moderate and 20-35: Severe symptoms, respectively[23].

Secondary outcomes measurement: Eight milliliter whole blood samples were taken after 12 h of fasting at Research Core Laboratory affiliated to QUMS, at the beginning and end of the intervention in both groups. Patients' serum was separated after centrifugation of clotted blood samples at 3000 rpm for 10 min and kept in a freezer at -80°C until performing the tests[24]. hs-CRP levels were assayed by ELISA kits (LDN, Nordhorn, Germany) with inter-assay CVs lower than 9%. PSA levels were quantified using ELISA kit (Pishtaz Teb, Tehran, Iran) with inter-assay CVs of 7%. Glutathione (GSH)[25], malondialdehyde (MDA)[26] and superoxide dismutase (SOD) activity were assayed based on the colorimetric method using spectrophotometer[27] with inter-assay CVs lower than 10%.

Sample size: Considering IPSS score as the primary end-point, SD = 0.50 and d = 0.3 based on the previous trial[28] also $\alpha = 0.05$ and $\beta = 0.20$, the calculated sample size was 26 subjects that taking into account the 15% dropout, 30 participants were considered for each group.

Statistical analysis: Histogram and Shapiro-Wilk tests were used for determining the normal assumption of variables. Assessing relationship, multivariable linear regression models were used for evaluation of UDE effects on primary and secondary end-points that adjusted for covariate factors including age and BMI. Furthermore, clinical changes have considered as B(SEM) and standardized coefficient of regression (β) was considered as the effect size of the intervention on outcomes with 95% confidence interval as well as values of 0.1, 0.3, 0.5 and higher are overall interpreted as, trivial, small, intermediate and strong effect, respectively[29]. The statistical significance level was at $p \leq 0.05$. Obtained data from the study were analyzed by SPSS statistical software (SPSS;23 Inc., Chicago, Illinois, USA).

RESULTS

Eighty five men were enrolled in this study. Twenty five patients were excluded because they were not eligible for the study. Sixty eligible participants were allocated to two equal groups named intervention and comparison. In the intervention group, 2 persons did not want to continue for personal reasons and were dropped out. The exclusions in the comparison group were also 2 patients due to supplements use. Finally, 56 patients completed the trial and were analyzed (Fig. 1).

The baseline characteristics of patients have been listed in Table 1. There were no significant differences between the anthropometric, clinical and biochemical parameters as well as the kind of medications of the participants (p-value>0.05) (Table 1).

Primary result: Just as mentioned IPSS score was considered as a clinical index and primary outcome. The primary analysis revealed significant reduction (p-value <0.001) in IPSS score in the intervention group compared to the comparison group following 12 weeks usage of UDE (Fig. 2)

Secondary results: Complementary analysis for secondary outcomes showed significant changes in hs-CRP magnitude (p-value 0.013), MDA level (p-value <0.001) and SOD activity (p-value <0.001). No significant changes (p-value >0.05) in other secondary outcomes have occurred following intervention (Table 2).

Table 1: Baseline demographic and clinical characteristics for each group

Variables	Comparison group (n = 28)	Intervention group (n = 28)
Age (Year)	63.3 (5.8)	62.6 (5.9)
BMI (kg m^{-2})	25.5 (2.6)	26.0 (2.8)
PSA (ng mL^{-1})	5.6 (1.0)	5.7 (1.3)
Medications		
Finasteride, n (%)	11 (36.7%)	12 (40%)
Tamsulosin, n (%)	26 (86.7%)	27 (90%)
Terazosin, n (%)	19 (66.7%)	19 (63.3%)

All values are Means(SD), There were no significant differences between the variables among two groups, BMI: Body mass index, IPSS: International prostate symptoms score

Table 2: Biochemical parameters at study baseline and after 3 months between comparison and intervention groups

	Groups (n = 28) Mean(SD)							
	Comparison		Intervention				95% CI	
Variables	Before	After	Before	After	Mean changes (B) (SEM)	Effect size (β)	(Confidence Interval)	p-value
PSA (ng mL^{-1})	5.6 (1.0)	4.9 (0.92)	5.7 (1.3)	4.7 (1.1)	-0.26 (0.1)	-0.130	-0.56, 0.04	0.091
hs-CRP (ng mL^{-1})	915.9 (73.5)	911.6 (66.1)	945.7 (74.9)	887.2 (91.7)	-44.30 (17.3)	-0.280^{+}	-78.90, -9.73	0.013*
Omentin (ng L^{-1})	44.8 (11.7)	44.2 (10.6)	48.7 (14.9)	47.9 (14.2)	0.30 (1.1)	0.011	-1.90, 2.45	0.801
MDA (μmol L^{-1})	11.7 (2.6)	11.2 (2.0)	12.2 (2.4)	9.5 (2.6)	-2.00 (0.5)	-0.410‡	-3.02, -0.92	<0.001*
GSH (μmol L^{-1})	442.5 (48.4)	439.6 (49.2)	441.2 (63.7)	448.6 (67.8)	10.10 (6.8)	0.090	-3.44, 23.77	0.1
SOD (IU mL^{-1})	11.6 (2.7)	10.9 (1.9)	12.0 (2.6)	13.5 (3.1)	2.40 (0.6)	0.420‡	1.14, 3.64	<0.001*

All values are Means (SD), UDE significantly decreased MDA level and SOD activity (p-value <0.001) with intermediate effect as well as decreased hs-CRP (p-value <0.013) but with small effect, ‡: UDE had intermediate effect of on MDA level and SOD activity, +: Indicating small effect of UDE on the variable, *: Indicating statistically significant difference, PSA: Prostate specific antigen, hs-CRP: high Sensitive-C- reactive protein, MDA: Malondialdehyde, GSH: Glutathione, SOD: Superoxide dismutase

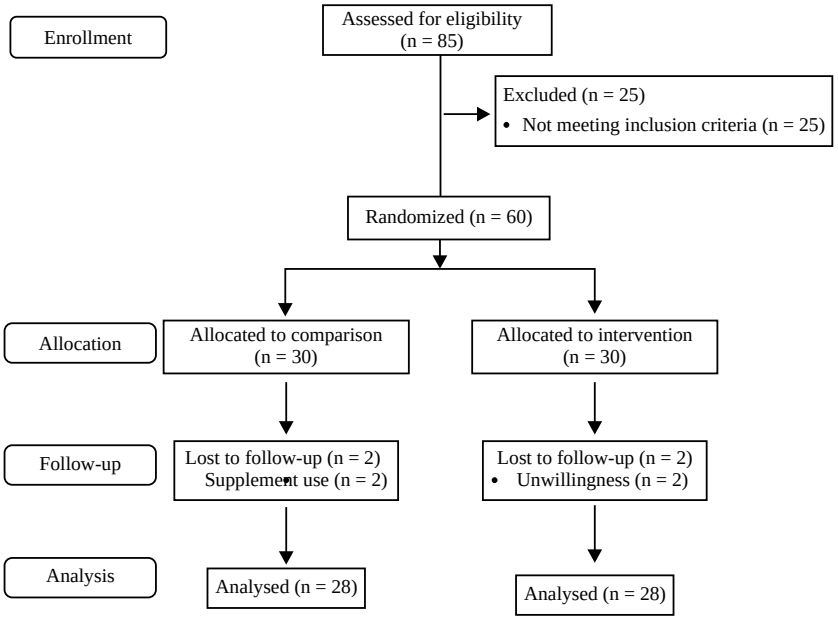

Fig. 1: Summary of patients' flow diagram

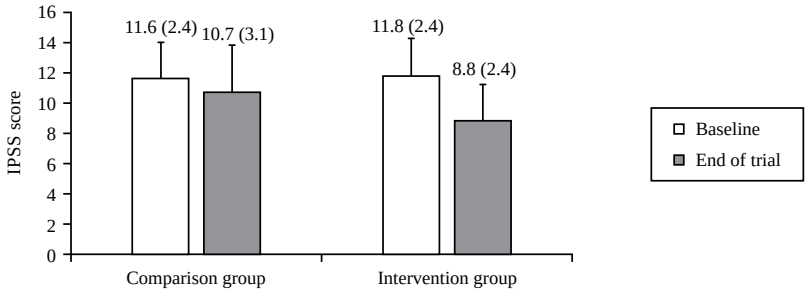

Fig. 2: IPSS score in comparison and intervention group

DISCUSSION

In order to assess the effectiveness of UDE on the clinical index and other BPH related parameters, this double-blind randomized controlled trial was performed. It has been documented that the IPSS score is the most important clinical index[30] and also biomarkers of oxidative stress and inflammation are two important parameters[31] in the etiology of BPH. The present study which to our knowledge is the first of its kind demonstrated that UDE usage for 12 weeks resulted

in considerable clinical and small to intermediate effectiveness in IPSS score. Similarly, a small effect on hs-CRP as an inflammatory parameter, small to intermediate effect on MDA level and intermediate effect on SOD activity as two oxidative stress evaluation index were revealed. Based on the above results, it may be stated the considerable effect of the extract on the IPSS score may be resulted from its capability to affect oxidative and inflammatory markers or potentiate the efficacy of the BPH related drugs. Administration of 100 mg/kg/day ethanolic UDE for 9 weeks prevented atherosclerotic lesions in the aorta in atherosclerotic rats but had no significant effect on total antioxidant capacity and MDA level[32]. In 2015, Oguz *et al*.[33] reported that *Urtica dioica* oil 2 mg/kg/day for 7 days decreased MDA level and improved SOD activity and GSH level in the liver tissue of rats. Reduced markers of oxidative stress in renal tissue following 4 weeks consumption of UDE has been reported by Shokrzadeh *et al*.[34]. Those studies overall were examined on animals. Therefore, further studies especially randomized control trials are needed to assess the effectiveness of UDE. Administration of 100 mg kg^{-1} hydro-alcoholic UDE among subjects with type 2 diabetes for 8 weeks significantly led to a decrease in interleukin-6 and hs-CRP and an increase in total antioxidant capacity and SOD activity. It is necessary to mention that the effect of this extract on MDA was ignorable[35,36]. Likewise, increased SOD activity has been documented after 8 weeks of taking UDE by 50 women with type 2 diabetes[37]. The difference between the results of the current study and those mentioned may be attributed to the type of disease, duration of use of the extract, the dosage of the extract, the extract preparation method, alteration in the analysis method and enrollment criteria.

The present study had certain limitations. The inability to achieve the strong effect of the extract on IPSS score, as the primary outcome, maybe due to the shortening of the intervention duration. Also, we did not evaluate the efficacy of the extract on other clinical signs such as prostate volume and postvoid residual urine volume. In order to attain the possible efficacy of the extract on other clinical and biochemical parameters, it is recommended to increase the intervention period or usage dose of the extract.

CONCLUSION

Overall, this study demonstrated that UDE consumption for 12 weeks among BPH patients had considerable effectiveness on IPSS, hs-CRP, MDA and SOD activity, although its effect on other measured markers was ignorable.

SIGNIFICANCE STATEMENT

For the first time in literature efficacy of the extract was examined on the IPSS score as the most important clinical index as well as markers of oxidative stress and inflammations as important factors in the pathogenesis of BPH, simultaneously. We showed UDE significantly improved BPH condition by decreasing biomarkers of inflammation and oxidative stress. We believe our article creates a paradigm for future studies of the efficacy of the extract on other clinical and biological parameters

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