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THE EFFICACY AND SAFETY OF *URTICA DIOICA* IN TREATING BENIGN PROSTATIC HYPERPLASIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Changping Men[1], Meng Wang[1#], Maimaiti Aiyireti[2], Yuanshan Cui[1]*

[1] Department of Urology, Yantai Yuhuangding Hospital Affiliated to Medical College of Qingdao University, NO.20 East Yuhuangding Road, 264000 Yantai, China
[2] Department of Surgery, Mingyuan Hospital of the Personnel, Affiliated to Xinjiang Petrolic Company, Urumqi 830000, China
Co-first author: Meng Wang
*** Corresponding author E-mail:** doctorcuiys@163.com

Abstract

Background: Urtica dioica is extract from the root of a stinging nettle.

Materials and Methods: We carried out a systematic review and meta-analysis to assess the efficacy and safety of *Urtica dioica* for treating Benign prostatic hyperplasia (BPH). A literature review was performed to identify all published randomized double-blind, controlled trials of *Urtica dioica* for the treatment of BPH. The search included the following databases: MEDLINE, EMBASE, and the Cochrane Controlled Trials Register. The reference lists of the retrieved studies were also investigated.

Results: Five publications involving a total of 1128 patients were used in the analysis. Primary efficacy end points: the international prostate symptom score (IPSS) (the standardized mean difference (SMD) =-10.47, 95% confidence interval (CI) =-18.12 to -2.82, p=0.007); the peak urinary flow rate (Qmax) (SMD=4.37, 95%CI=1.55 to 7.19, p=0.002) and prostate volume (SMD=-3.63, 95%CI=-4.67 to -2.57, p＜0.00001) indicated that *Urtica dioica* was more effective than the placebo or controls. Safety assessments included prostatic specific antigen (PSA) (SMD=-0.08, 95%CI=-0.23 to 0.07, p=0.31) showed that PSA levels were unaffected in both groups.

Conclusion: This meta-analysis indicates that *Urtica dioica* to be an effective and safe treatment for LUTS associated with BPH.

Key words: *Urtica dioica*, lower urinary tract symptoms, benign prostatic hyperplasia, meta-analysis, Randomized controlled trial

The list of abbreviations: BPH=Benign prostatic hyperplasia; LUTS=lower urinary tract symptoms; RCTs=randomized controlled trials; IPSS=international prostate symptom score; Qmax=the peak urinary flow rate; PSA=prostatic specific antigen; SMD=standardized mean difference; CI=confidence interval.

Introduction

Benign prostatic hyperplasia (BPH) is the most common disease in aging men (Porst et al., 2013). BPH leads to lower urinary tract symptoms (LUTS) with storage, voiding, and post-micturition symptoms that adversely affect the individual's health-related quality of life by interfering with normal daily activities and sleep patterns (Hollingsworth et al., 2014). During recent years, the number of surgical interventions in BPH has decreased in favor of medical treatments (Russo et al., 2014). The drugs mainly administered for LUTS include α1-blockers, 5α-reductase inhibitors, and phyto-pharmaceuticals. As some α1-blockers may be associated with postural hypotension, and 5α–reductase inhibitors may cause sexual dysfunction (Russo et al., 2014), there is a great interest in well-tolerated and efficacious herbal remedies. Indeed, drugs from the latter group are still very common all over the world (Chughtai et al., 2013).

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Urtica dioica is an extract from the root of a stinging nettle and it is widely used in Europe (Azimi et al., 2012). The extracts of the roots of the stinging nettle contain a complex mixture of water-and alcohol-soluble compounds such as fatty acids, sterols (β-sitosterol, campesterol, and stigmasterol), and flavonoids. *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; Pagano et al., 2014). Currently, there are no efficacy data on the effects of *Urtica dioica* for the treatment of LUTS secondary to BPH.

There is a general perception that herbal products are, at worst, harmless placebos, but this is not always true. As early as the 15th century BC, the use of plant extracts for the symptomatic treatment of BPH was described on Egyptian papyrus. Unfortunately, many questions remain unanswered; therefore the scientific case for their use remains unproven. The goal of the present study was to perform a meta-analysis to evaluate the safety and efficacy of *Urtica dioica* in treating BPH, which may resolve some of the current controversies over the use of the drug.

Materials and Methods

Search Strategy

Medline (1966 to Feb 2015), Embase (1974 to Feb 2015), and Cochrane Controlled Trials Register databases were searched to identify randomized controlled trials (RCTs) that referred to the impact of *Urtica dioica* in treating BPH; we also searched the reference lists of the retrieved studies. The following search terms were used: *Urtica dioica,* lower urinary tract symptoms OR lower urinary tract symptom, benign prostatic hyperplasia, randomized controlled trial OR randomized controlled trials

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Inclusion Criteria and Trial Selection

Randomized controlled trials that met the following criteria were included: (1) The study design included treatment with *Urtica dioica*; (2) the study provided accurate data that could be analyzed, including the total number of subjects and the values of each index; and (3) the full text of the study could be accessed. When the same study was published in various journals or in different years, the most recent publication was used for the meta-analysis. If the same group of researchers studied a group of subjects with multiple experiments, then each study was included. A flow diagram of the study selection process is presented in Figure 1.

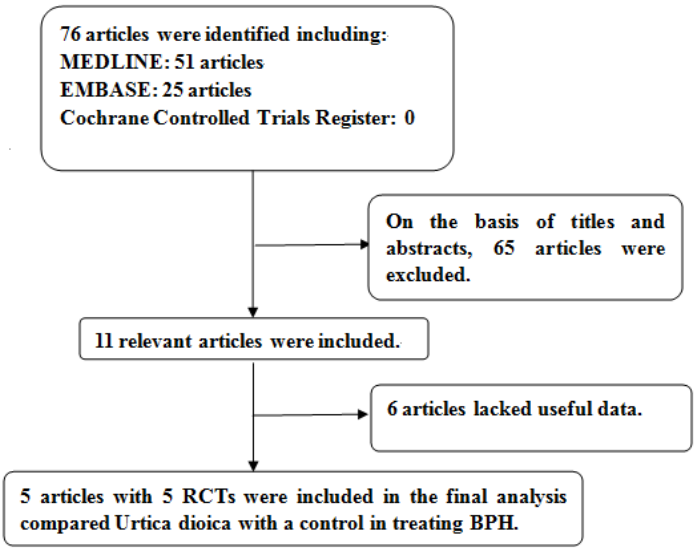

Figure 1 A flow diagram of the study selection process.
RCT: randomized controlled trial BPH: benign prostatic hyperplasia

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Quality Assessment

The quality of the retrieved RCTs was assessed using the Jadad scale (Jadad, 1998). All the identified RCTs were included in the meta-analysis regardless of the quality score. The methodological quality of each study was assessed according to how patients were allocated to the arms of the study, the concealment of allocation procedures, blinding, and data loss due to attrition. The studies were then classified qualitatively according to the guidelines published in the *Cochrane Handbook for Systematic Reviews of Interventions* v.5.1.0 (Higgins et al., 2011). Based on the quality assessment criteria, each study was rated and assigned to one of the three following quality categories: A, if all quality criteria were adequately met, the study was deemed to have a low risk of bias; B, if one or more of the quality criteria was only partially met or was unclear, the study was deemed to have a moderate risk of bias; or C, if one or more of the criteria was not met or not included, the study was deemed to have a high risk of bias. Differences were resolved by discussion among the authors.

Data Extraction

The following information was collected for each study: (1) the name of the RCT; (2) the study design and sample size; (3) the therapy that the patients received; (4) the country in which the study was conducted; and (5) data including the international prostate symptom score (IPSS), the peak urinary flow rate (Qmax), prostate volume and prostatic specific antigen (PSA).

Statistical Analysis and Meta-Analysis

The meta-analysis of comparable data was carried out using RevMan v.5.1.0 (Cochrane Collaboration, Oxford, UK) (Higgins et al., 2011). Changes in the IPSS, Qmax, prostate volume and PSA were determined as differences between baseline (study entry) and study completion. We estimated the relative risk for dichotomous outcomes and the standardized mean difference (SMD) for continuous outcomes pooled across studies by using the DerSimonian and Laird random-effects model (DerSimonian et al., 1986). We used a 95% confidence interval (CI). If the result of analysis showed $p > 0.05$, we considered the studies homogeneous and so chose a fixed-effect model for meta-analysis. Otherwise, a random-effect model was used. We quantified inconsistency using the I^2 statistic, which describes the proportion of heterogeneity across studies that is not due to chance, thus describing the extent of true inconsistency in results across trials (Higgins et al., 2003). I^2 <25% reflects a small level of inconsistency and I^2 >50% reflects significant inconsistency.

Results

Characteristics of the Individual Studies

The database search found 76 articles that could have been included in our meta-analysis. Based on the inclusion and exclusion criteria, 65 articles were excluded after reading the titles and abstracts of the articles. Six articles lacked useful data. In all, 5 articles (Schneider et al., 2004; Safarinejad, 2005; Eduard et al., 2010; Ghorbanibirgani et al., 2013; Hosseinabadi et al., 2014) reporting data from a total of 5 RCTs that compared *Urtica dioica* with placebo or controls, were included in the analysis (Fig. 1). The baseline characteristics of the studies included in our meta-analysis are listed in Table 1.

Quality of the Individual Studies

All 5 RCTs were double blinded, and three of them described the randomization processes that they had used. Four of them included a power calculation to determine the optimal sample size (Table 2). The level of quality of each identified study was

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showed in Table 2. The funnel plot provided a qualitative estimation of publication bias of the studies, and no evidence of bias was found (Fig. 2).

Table 1 Study and patient characteristics

Study	Therapy in Experimental group	Therapy in control group	Age, yr, median	Country	Sample size (experimental)	Sample size (Control)	Administration method	Duration of treatment	Dosage	Inclusion population
Schneider T 2004	U	placebo	63.5	Germany	114	112	Oral	12 mo.	459mg/d	No prostate cancer, had no lower urinary tract problem other than BPH.
Safarinejad MR 2005	U	placebo	63	Iran	287	271	Oral	6 mo.	360mg/d	No cancer, the laboratory findings were normal; had no lower urinary tract problem other than BPH.
Bercovich E 2010	Pluvio contains high dose of U	control	66.1	Italy	60	60	Oral	6 mo.	400-600mg/d	With severe LUTS caused by BPH, who were candidates for surgery.
Ghorbanibirgani A 2013	U	placebo	62.4	Iran	50	50	Oral	2 mo.	600mg/d	No acute urinary retention, renal infection or renal failure.
Hosseinabadi R 2014	U +prazosin	prazosin	56.3	Iran	62	62	Oral	2 mo.	500mg/d	IPSS≥8, lack of bacteriuria, serum creatinine levels lower than 1.5 mg/dL, PSA ＜4 ng/mL

U: Urtica dioica BPH: Benign prostatic hyperplasia LUTS: lower urinary tract symptoms
PSA: prostate-specific antigen

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Table 2 Quality assessment of individual study

Study	Allocation Sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	Level of quality
Schneider T 2004	A	A	A	0	YES	Analysis of variance	A
Safarinejad MR 2005	A	A	A	61	YES	Unpaired t-test	A
Bercovich E 2010	B	A	A	0	YES	NCSS® program	A
Ghorbanibirgani A 2013	B	A	A	0	NO	SPSS Statistical Package	B
Hosseinabadi R 2014	A	A	A	0	YES	Analysis of variance	A

A - all quality criteria met (adequate): low risk of bias.
B - one or more of the quality criteria only partly met (unclear): moderate risk of bias.
C - one or more criteria not met (inadequate or not used): high risk of bias.

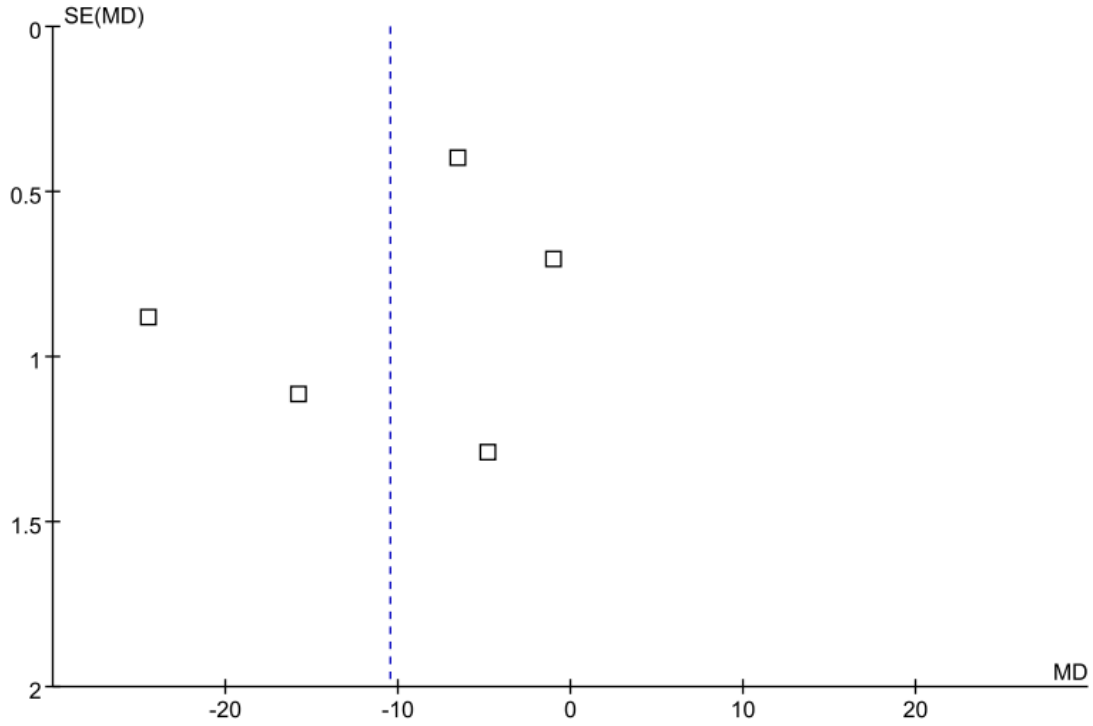

Figure 2 Funnel plot of the studies represented in our meta-analysis. MD: mean difference, SE: standard error.

Efficacy

The IPSS

Five RCTs, representing 1,128 participants (573 in the *Urtica dioica* group and 555 in the control group) (Fig. 3) were

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identified. Based on the heterogeneity existed among the trials (P ＜0.00001), the random-effects model was chosen for the meta-analysis. The pooled estimate of SMD was -10.47, and the 95% CI was -18.12 to -2.82 (p=0.007). This result suggests that *Urtica dioica* showed statistically significant reductions in the IPSS compared to controls.

The Qmax

The three RCTs included the Qmax data representing a cohort of 904 participants (461 in the *Urtica dioica* group and 443 in the control group, Fig. 3). The heterogeneity test showed P ＜0.00001, thus the random-effects model was adopted. The pooled estimate of SMD was 4.37, and the 95% CI was 1.55 to 7.19 (p=0.002). This result suggests that *Urtica dioica* showed statistically significant increases in the Qmax compared to controls.

The Prostate Volume

Two of the RCTs encompassed the prostate volume data representing a cohort of 678 participants (347 in the Urtica dioica group and 331 in the control group) (Fig. 3). The fixed-effects estimate of the SMD was -3.63, and the 95% CI was -4.67 to -2.57 (p ＜0.00001). This result suggests that *Urtica dioica* had significantly greater decreases in the prostate volume.

Safety

The PSA

Three RCTs, representing 802 participants (409 in the *Urtica dioica* group and 393 in the control group), included the PSA data (Fig. 3). The fixed-effects estimate of the SMD was -0.08, and the 95% CI was -0.23 to 0.07 (p=0.31). These results indicate no apparent differences between *Urtica dioica* and controls in changes in PSA levels.

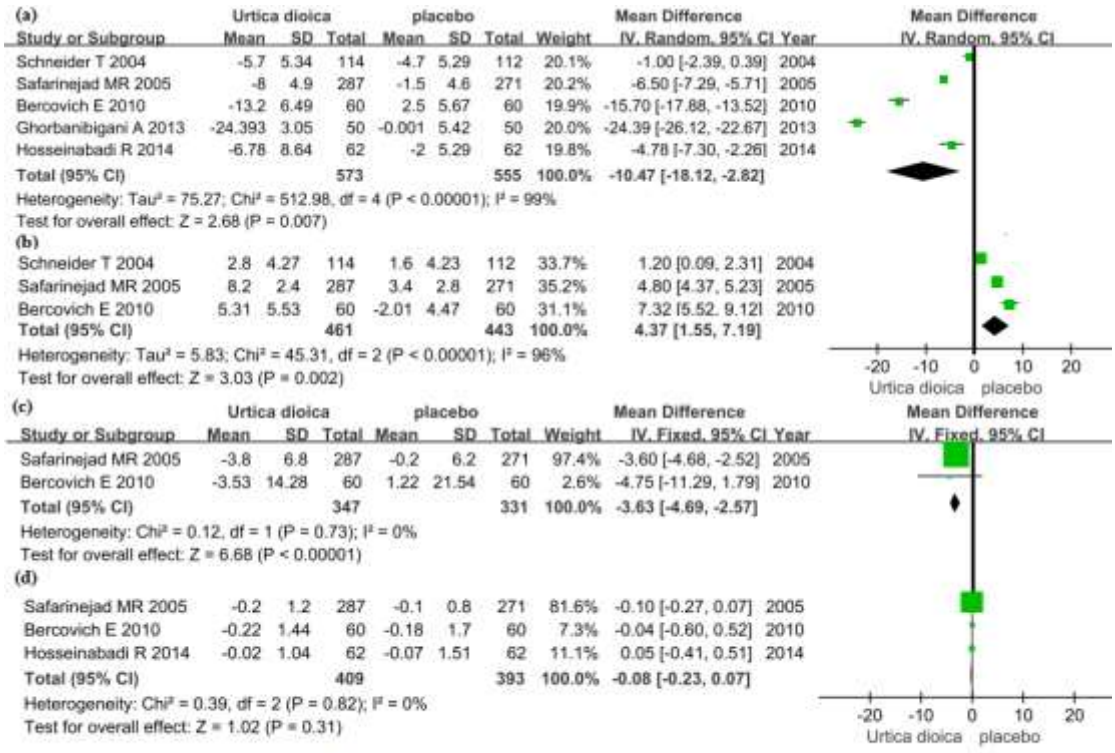

Figure 3 **Forest plots showing changes in (a) IPSS, (b) Qmax, (c) prostate volume and (d) PSA levels in the treatment studies. IPSS: international prostate symptom score, Qmax: peak urinary flow rate, PSA: prostatic specific antigen, SD:standard deviation, IV:inverse variance, CI:confidence interval**

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Discussion

The advantages of pharmacological therapy for BPH are its effectiveness, its safety, and the reduced number of associated side effects. The goal of pharmacological therapy for BPH is to alleviate symptoms, to relieve smooth muscle spasms of the prostatic capsule and bladder neck and urination resistance, and to prevent urine retention, urinary tract infection, and renal dysfunction. Current pharmacological therapies for this condition can be classified into three major categories: (1) α1-adrenoceptor blockers, (2) 5α-reductase, and (3) phytotherapic preparations, whose mechanisms of action variously combine weak hormonal activity and anti-inflammatory effects (Silva et al., 2014). In the past decade, the use of phytotherapic agents has become particularly popular in men with LUTS secondary to BPH. One of the most commonly used herbal remedies is *Urtica dioica*, which causes anti-inflammatory, anti-tumor, anti-viral effects, modulating of immune system, and relieves the symptoms of benign prostatic hyperplasia due to the compounds it contains such as phytosterols, lignans and polysaccharides (Chrubasik et al., 2007).

Our study reveals that *Urtica dioica* 360-600 mg per day is superior to controls in improving the IPSS, Qmax and decreasing prostate volume. One of the included studies comparing outcome of treatment with a new combination of plants extracts which contains a high dose of *Urtica Dioica*. By removing it, the analysis showed that the results of IPSS in the *Urtica dioica* and placebo groups matched our finding (SMD was -9.17, and the 95% CI was -18.03 to -0.30, p=0.04). Two of the RCTs evaluating the median volume of residual urine also showed that *Urtica dioica* was superior to placebo in improving the post-voided residual urine volume. Besides, two non-English double-blind, randomized trials demonstrated superiority over placebo in improving the uroflow parameters of patients suffering from mild-to-moderate BPH (Dathe et al., 1987; Vontobel et al., 1985). The recommended dosage of plant extract is 400-600 mg per day. At recommended dosages, *Urtica dioica* exhibits efficacy in improving the IPSS.

The *Urtica dioica* also proved to be safe in terms of its impact on PSA levels, there were no significant variations in the PSA measurement between *Urtica dioica* and controls after 2 to 12 months. Two of the included RCTs reported there were no apparent differences between *Urtica dioica* and controls in urinary tract infection or urinary retention. All of the RCTs demonstrated that no serious side effect was reported by the patients in the end of the studies.

There have been three studies that suggest different mechanisms of action for stinging nettle. These include inhibition of prostatic growth factor interaction (Wagner et al., 1994), inhibition of membrane sodium and potassium-adenosine triphosphate in the prostate, which results in the suppression of prostate cell metabolism and growth (Hirano et al., 1994), and modulation of binding of sex hormone-binding globulin to its receptor on prostate cell membranes (Hryb et al., 1995). In a word, *Urtica dioica* 360-600 mg per day is an effective and safe treatment for BPH.

This meta-analysis includes studies which are all findings from randomized double-blind, controlled trials. According to the quality-assessment scale that we developed, the quality of the individual studies in the meta-analysis was conforming. The results of this analysis acquire great importance from scientific standpoint but also in the everyday clinical practice. However, there are only 5 studies engaged in this meta-analysis. So, the results based on the data above are not statistically reliable enough and the power of statistics is limited. The longer term safety, efficacy, and persistence of *Urtica dioica* cannot be extrapolated from this article. In addition, unpublished studies' data were not included in the analysis. These factors may have resulted in a bias. More high-quality trials with larger samples are proposed to learn more about the efficacy and safety of the therapy on BPH.

In summary, this meta-analysis indicates that *Urtica dioica* to be an effective and safe treatment for LUTS associated with BPH. More high-quality trails with larger samples are warranted to learn more about the efficacy and safety of the agent.

Conflict of Interest Statement: The authors had no conflicts of interest to declare in relation to this article.

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