Effect of Nettle Extract and Pumpkin Seed on Prostate Specific Antigen and Urinary Symptoms in Patients Taking Alfa-blocker for Benign Prostatic Hyperplasia

Farzad Allameh1, Seyed Mohammad Hosseininia2, Fatemeh Lahooti3, Alvand Naserghandi4,∗, Yasin Zakeri5

1. Men’s Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Department of Urology, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3. Department of Clinical Pharmacy, Faculty of Pharmacy, Medical Branch, Islamic Azad University, Tehran, Iran.
4. Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
5. Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran.

Received: August 2021; Accepted: August 2021; Published online: September 2021

Abstract: Introduction: We aimed to compare the effect of nettle extract and pumpkin seed on Prostate Specific Antigen (PSA) and international prostate symptoms score (IPSS) in patients taking alfa-blocker for benign prostatic hyperplasia (BPH).

Materials and Methods: For this purpose, 90 outpatients were studied in three groups, including men over 40 years of age with benign prostatic enlargement. The first group (Urtidin) contained consumers of nettle extract from Barijessence Company called Urtidin tablets with tamsulosin; the second group took tablets containing pumpkin seed extract called Prosta Barij and tamsulosin; the third group (Control) received only tamsulosin for three months. Patients were not randomly assigned to the groups. PSA, IPSS, and related factors were evaluated and analyzed using SPSS software.

Results: 89 patients completed the study (30/89 in Urtidin group with a mean age of 62.4±7.39 years, 29/89 in Prosta Barij group with a mean age of 65.9±7.32 years, and 30/89 in the control group with a mean age of 64.7±8.64 years). The results showed that nettle and pumpkin seed extracts affect PSA in patients taking tamsulosin for BPH. Also, after the intervention, IPSS had a significant decrease compared with baseline in both drug treatment groups. There was no significant difference in these three types of treatment.

Conclusion: It seems that the desired herbal products did not have a synergistic effect with alpha blockers in the control and treatment of BPH but they can affect the serum PSA level.

Keywords: Benign prostatic hyperplasia, Herbal medicine, Nettle, Plant extracts, Pumpkin seeds


1. Introduction

Benign prostatic hyperplasia (BPH) is a common complaint and the fourth most common diagnosis in men over 50 years of age (1). Conventional treatment for benign prostatic hyperplasia includes drug therapy with alpha-adrenergic blockers or 5 alpha reductase inhibitors such as finasteride and combination drug therapy, or prostate surgery (2). Prostate surgery is known as the standard treatment for BPH. However, this method has long-term complications including retrograde ejaculation, bladder neck stenosis, and impotence (3).

On the other hand, the use of drug therapy for BPH reduces its side effects (4). Medications commonly prescribed for urinary tract problems include: α1-blockers, and 5α-reductase inhibitors. Phyto-pharmaceuticals. Some α1-blockers may be associated with orthostatic hypotension, and 5α-reductase inhibitors may cause sexual dysfunction (4). Considering the side effects of chemical drugs, many researchers have focused on the use of medicinal plants. Nettle plant with the scientific name of Urtica dioica is a perennial herbaceous plant with a height of about one meter and has...
trichomes capable of biting (5, 6). Urtica dioica is a genus of Urtica and the reason for its name is that it grows on the surface of the stem and leaves of the plant. This plant has two bases. Non-female flowers are placed on both bases of the plant at the same time. The parts of the plant used are fresh leaves, roots, and seeds (7,8).

Research has shown that nettle can improve symptoms of BPH and inhibit the conversion of testosterone to dihydrotestosterone by the enzyme 5-alpha reductase (9-11). This plant can also bind directly to sex hormone-binding globulin (SHBG) and prevent hormones from binding to protein (12). Other studies have shown that nettle can prevent the protein complex from binding to hormones and finally to receptors in prostate cells or reduce estrogen production by inhibiting the enzyme required for this function (7, 10).

Pumpkin is an herbal medicine that has been used around the world for centuries and its therapeutic effect has been recommended in many reference books and manuscripts. The genus Cucurbita includes very wide species in Europe, Asia, and America. Cucurbita pepo in the form of soft ethanolic extract of pumpkin seeds has been used mainly as a treatment for various problems related to enlarged prostate gland or overactive bladder during the last thirty years in European societies (13, 14). The active ingredients in pumpkin seeds include sterols θ5, θ6, and θ8. Sterols θ5 are predominant in this plant and are considered as key active compounds in pumpkin seeds in the treatment of benign prostatic hyperplasia. Very small amounts of sterols θ6 and θ8 are also present in pumpkin seeds (13, 15). Large amounts of unsaturated carotenoids and fatty acids and fat-soluble vitamins such as vitamin E are involved in the function of these sterols (15).

Previous experimental studies confirm support for the role of pumpkin seeds in the treatment of BPH (16-18). Pumpkin extract inhibits the enzyme 5-alpha reductase and prevents the conversion of testosterone to dihydrotestosterone (19). Moreover, many of its vitamins and minerals, including vitamin E, vitamin B6, and zinc, have anti-cancer activity and act as antioxidants (20).

With respect to the long-term complications of prostate surgery and the mentioned benefits of herbal plants, herbal treatment of this disease is of interest, so we aimed to compare the effect of nettle extract and pumpkin seed on PSA and IPSS in patients who consume tamsulosin for BPH.

2. Materials and Methods

2.1. Materials

Tamsulosin

Tamsulosin for patients with BPH usually starts with 0.4 mg once daily. It is better to be used half an hour before bedtime. If a person does not receive a proper response after two to four weeks, the dose may be increased to 0.8 mg once daily. If tamsulosin slow-release capsules are prescribed, the maximum dose is 0.4 mg once daily (21). In this trial we prescribed tamsover 0.4 (Actoverco Pharmaceuticals Company, Iran) every night at bedtime.

Urtidin Barij (Barijessence Company, Iran) Coated Tablets

This pill has nettle root extract and is used to relieve urination problems (such as frequent urination, dribbling and delayed urination) as well as improves overactive bladder (22). In this trial we prescribed this drug twice daily.

Prosta Barij (Barijessence Company, Iran) soft capsule

Prosta Barij soft capsule contains pumpkin seed oil with the scientific name of Cucurbita pepo and vitamin E, which is prescribed for prevention and elimination of urinary problems and it may prevent hair loss (23). In this trial we prescribed this drug once daily.

3. Methods

In this study, 90 outpatients in the clinic of Shohada-Tajrish Hospital in Tehran, Iran affiliated to the urology department were examined in three groups, including men over 40 years with benign prostatic enlargement:

1. The first group (Urtidin) contains consumers of nettle extract from Barijessence Company called Urtidin tablets with tamsulosin; 2. The second group (Prosta Barij) contains pumpkin seed extract called Prosta Barij and tamsulosin; 3. The third group (Control) received only tamsulosin for three months.

The study was conducted in accordance with the principles of the Declaration of Helsinki (1996) and Good Clinical Practice standards. The study protocol, informed-consent form, and the other study-related documents were reviewed and approved by the Human Research Ethics Committee of Islamic Azad University of Medical Sciences, School of Pharmacy (IR.IAU.PS.REC.1398.283). All patients were able to read, and voluntarily signed the informed consent, which was in the patients’ language.

Patients more than 40 years old with symptomatic BPH were included. Those with urinary system infection, urolithiasis, urinary retention, urinary incontinence, urethral stricture, urinary system malignancies, physical and mental disabilities, participation in another research, hernia, hematuria, prostate cancer and neurogenic bladder were excluded. One patient was lost to follow-up. Finally, 89 patients completed the study, 30 patients in the Urtidin group, 29 in the Prosta Barij group, and 30 patients in the control group. International Prostate Symptom Score (IPSS) and total Prostate Specific Antigen (PSA) were primary outcomes and Free PSA and serum creatinine level were secondary outcomes.

PSA: PSA is a type of protein made by normal cells as well as malignant prostate glands. The PSA test is used to check...
the amount of PSA in the blood, which is done by analyzing a blood sample in a laboratory.

**International Prostate Symptom Score (IPSS) questionnaire:** The IPSS questionnaire is an 8-item questionnaire, which consists of seven questions about symptoms and one question about quality of life. The IPSS score was standardized into three categories: mild, moderate and severe. Limitations of this questionnaire include lack of assessment of incontinence, post-urinary symptoms, and discomfort caused by each of the individual symptoms. A score of 0 to 7 is classified as mildly symptomatic, 8-19 as moderately symptomatic, and 20-35 as severely symptomatic. The mentioned parameters were measured in each group and the results were compared before and after taking the supplements. Since we did not find a similar study comparing the three groups, 30 participants were allocated to each group without using a sample size formula.

### 3.1. Analysis of statistical data

Statistical analysis in this study was performed in two parts. In the first part, a frequency table was used to report the descriptive statistics of the participants. For qualitative variables, frequency and percentage indices and for quantitative variables, mean and standard deviation were reported. Because of normal data distribution in the study groups, parametric tests can be used to analyze the data and test the hypotheses. Paired sample t test was used to determine the significant difference before and after the intervention. One-Way ANOVA along with Tukey Post Hoc tests were used to determine the significant differences between Urtidin, Prosta Barij and control groups. Finally, Fisher’s exact and Chi-square tests were used to determine the relationship between multivariate qualitative variables. The significance level of statistical tests is considered to be 0.05. Statistical analysis was performed using the SPSS (Statistical Package for Social Science, Chicago, Illinois) version 24.0.

### 4. Results

#### 4.1. Descriptive statistics

30 patients were in the Urtidin intervention group, 29 patients were in the Prosta Barij intervention group and 30 patients were in the control group. The mean±SD ages of the participants in the Urtidin, Prosta Barij, and control groups were 62.40±7.39, 65.90±7.32, and 64.07±8.64 years, respectively (table 1). The highest history of urinary tract infection was related to 10.3% of participants in the Prosta Barij group and the highest history of Hypertension, diabetes and allergies were related to 36.7%, 16.7% and 13.3% of the participants in an Urtidin group.

#### 4.2. Inferential analysis of data

Due to the normality of the data distribution, which was examined by Kolmogorov-Smirnov (KS) test, Paired sample t test and one-way ANOVA was used in conjunction with Tukey’s post hoc tests. Fisher’s exact test and Pearson’s Chi-square were also used to determine the relationship between multivariate qualitative variables.

#### 4.3. Investigation of the effect of nettle extract and pumpkin seeds on Lab Data

In this section, total, free PSA, and creatinine (Cr) were evaluated separately.

**Evaluation of total PSA in three groups**

ANOVA was used to evaluate the total PSA index in the three groups and the difference before and after the intervention was analyzed. The results of total PSA showed that there was no significant difference between the three groups before and after the intervention (P>0.05). There was a significant difference between the two intervention groups from before to three months after the intervention (P<0.05). In other words, in the intervention Urtidin and Prosta Barij groups, the value of this index decreased significantly three months after the intervention, but in the control group, this index did not change although the decrease in herbal medicine groups was not clinically significant.

**Evaluation of free PSA in three groups**

Analysis of variance was used to evaluate the free PSA in three groups and the difference before and after the intervention was analyzed. The results of free PSA showed that there was no significant difference between the three groups before the intervention (P>0.05) but after the intervention there was a significant difference between the three groups (P<0.05). Post hoc test showed that the Urtidin group had a higher and significant mean than the control group. But the Prostat Barij group and the control group as well as the two intervention groups did not differ significantly. There was no significant difference between the amount of free PSA before and after 3 months of intervention in any of the three groups (P>0.05).

**Evaluation of Creatinine (Cr) in three groups**

Table 4 shows the serum Cr levels. As shown, there was no significant difference between the three groups before and after the intervention (P>0.05). There is no significant difference between the serum levels of Cr in each group before and after the intervention (P>0.05).
4.4. Evaluation of the effect of nettle extract and pumpkin seed on the international prostate symptom score (IPSS)

The results of IPSS score in each of these three categories were evaluated (Table 5). 96.6% of all participants in this study had a moderate score (scores 8 to 19) before the intervention. The results of 3 months after the intervention also show that all participants reported a mild IPSS index (scores 0 to 7).

Then, to evaluate the IPSS index in three groups, ANOVA was used and the difference before and after the intervention was analyzed. The results showed that there was no significant difference between the three groups before and after the intervention (P>0.05). Post hoc test showed that the Prosta Barij group had a higher and more decreased mean than the control group but the difference was not significant. In the control group as well as two intervention groups a significant decrease in IPSS was demonstrated after three months (P<0.05).

5. Discussion and conclusion

In vitro, plant extracts can have anti-inflammatory, anti-androgenic and oestrogenic effects; decrease sexual hormone binding globulin; inhibit growth factor-stimulated proliferation of prostatic cells, $\alpha$-adrenoceptors, $5\alpha$-reductase, muscarinic cholinoceptors; and neutralize free radicals (24-26).

The in vivo effects of these compounds are uncertain, and the precise mechanisms of plant extracts remain unclear. According to the latest European association of urology (EAU) guideline, herbal drug “hexane extracted Serenoa repens (HESr)” improves Qmax and results in fewer voids/night compared to placebo. Some other available EU herbal medicinal products such as saw palmetto, pumpkin seed, and Urtica were listed in this guideline(27).

In the present study, the effect of nettle extract and pumpkin seed on PSA and IPSS levels of patients taking tamsulosin with benign hyperplasia was discussed in three groups. The overall results of testing the hypotheses of this study indicate that nettle and pumpkin seed extracts affect the PSA of patients taking tamsulosin with BPH. In other words, in the intervention groups of Urtidin and Prosta Barij, the value of total PSA decreased significantly three months after the intervention, but in the control group, this index did not change significantly. There was no significant difference before and after three months of intervention in the amount of free PSA in the three groups. Also, three months after the intervention, Cr had a significant decrease compared to before the intervention. But there were no significant changes in the control group. The results of this hypothesis are consistent with the results of other studies (11, 16, 20, 28-35).

Also, after the intervention, IPSS significantly decreased compared to before the intervention in both treatment groups as well as the control group. But when the three groups were compared, no significant change was reported. The results of this hypothesis are not consistent with the results of several other studies (4, 16, 30, 35, 36).

Consistent with our results AUA guideline 2010 also did not recommended use of saw palmetto and Urtica dioica extracts in the management of patients with BPH because of controversial results (37), while encouraging results have been published for the hexane extract of Serenoa repens and for the combination of Serenoa repens (Saw Palmetto Berry) with lycopene and selenium.

According to the above, we cannot conclude that the desired herbal products have a synergistic effect with alpha blockers in the treatment of BPH. Therefore, we need clinical trials testing the use of medicinal plants with BPH treatment properties.

6. Appendix

6.1. Acknowledgment

None.

6.2. Conflict of interest

No conflict of interest.

6.3. Funding support

None.

6.4. Author’s contributions

All the authors have the same contribution.

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### Table 1  Summary of the participants’ information and history of underlying diseases

<table>
<thead>
<tr>
<th></th>
<th>Urtidin (n=30)</th>
<th>Prosta Barij (n=29)</th>
<th>Control (n=30)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td>Number</td>
</tr>
<tr>
<td>History of urinary tract infection</td>
<td>No</td>
<td>30 (100)</td>
<td>26 (89.7)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0 (0)</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>No</td>
<td>19 (63.3)</td>
<td>23 (79.3)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>11 (36.7)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>No</td>
<td>25 (83.3)</td>
<td>25 (86.2)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5 (16.7)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>History of allergies</td>
<td>No</td>
<td>26 (86.7)</td>
<td>29 (100)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4 (13.3)</td>
<td>0 (0)</td>
</tr>
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### Table 2  Summary of Total PSA statistical analysis in the treatment groups (before and after the intervention)

<table>
<thead>
<tr>
<th></th>
<th>Urtidin (n=30)</th>
<th>Prosta Barij (n=29)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Total</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Before</td>
<td>1.44</td>
<td>1.68</td>
<td>1.47</td>
<td>0.92</td>
</tr>
<tr>
<td>3 months later</td>
<td>1.35</td>
<td>1.51</td>
<td>1.38</td>
<td>0.85</td>
</tr>
<tr>
<td>The amount of difference</td>
<td>0.098 decrease</td>
<td>0.095 decrease</td>
<td>0.25 increase</td>
<td></td>
</tr>
<tr>
<td>P-value**</td>
<td>P=0.005</td>
<td>P=0.002</td>
<td>P=0.224</td>
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</table>

* One-Way ANOVA / ** Paired Sample T Test

### Table 3  Summary of free PSA statistical analysis in the treatment groups (before and after the intervention)

<table>
<thead>
<tr>
<th></th>
<th>Urtidin (n=30)</th>
<th>Prosta Barij (n=29)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Free</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Before</td>
<td>0.38</td>
<td>0.42</td>
<td>0.31</td>
<td>0.20</td>
</tr>
<tr>
<td>3 months later</td>
<td>0.46</td>
<td>0.45</td>
<td>0.30</td>
<td>0.20</td>
</tr>
<tr>
<td>The amount of difference</td>
<td>0.078 increase</td>
<td>0.013 decrease</td>
<td>0.002 increase</td>
<td></td>
</tr>
<tr>
<td>P-value**</td>
<td>P=0.166</td>
<td>P=0.292</td>
<td>P=0.907</td>
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</table>

* One-Way ANOVA / ** Paired Sample T Test

### Table 4  Summary of statistical analysis of Cr in the treatment groups (before and after the intervention)

<table>
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<tr>
<th></th>
<th>Urtidin (n=30)</th>
<th>Prosta Barij (n=29)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
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<tr>
<td>Cr</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Before</td>
<td>1.19</td>
<td>0.20</td>
<td>1.00</td>
<td>0.10</td>
</tr>
<tr>
<td>3 months later</td>
<td>1.14</td>
<td>0.18</td>
<td>0.96</td>
<td>0.11</td>
</tr>
<tr>
<td>The amount of difference</td>
<td>0.05 decrease</td>
<td>0.043 decrease</td>
<td>0.027 decrease</td>
<td></td>
</tr>
<tr>
<td>P-value**</td>
<td>P=0.05</td>
<td>P=0.05</td>
<td>P=0.05</td>
<td></td>
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</tbody>
</table>

* One-Way ANOVA / ** Paired Sample T Test

### Table 5  Summary of statistical analysis of IPSS in the treatment groups (before and after the intervention)

<table>
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<tr>
<th></th>
<th>Urtidin (n=30)</th>
<th>Prosta Barij (n=29)</th>
<th>Control (n=30)</th>
<th>P-value*</th>
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<tr>
<td>IPSS</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Before</td>
<td>13.40</td>
<td>1.45</td>
<td>14.14</td>
<td>3.03</td>
</tr>
<tr>
<td>3 months later</td>
<td>6.04</td>
<td>1.11</td>
<td>5.97</td>
<td>1.12</td>
</tr>
<tr>
<td>The amount of difference</td>
<td>7.36 decrease</td>
<td>8.17 decrease</td>
<td>7.50 decrease</td>
<td></td>
</tr>
<tr>
<td>P-value**</td>
<td>P=0.001</td>
<td>P=0.001</td>
<td>P=0.001</td>
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* One-Way ANOVA / ** Paired Sample T Test

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