

Effects of Saw Palmetto Therapy on some Inflammatory Biomarkers in a Sample of Iraqi Male with Symptomatic Benign Prostatic Hyperplasia

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Abstract:

Background Saw palmetto contains powerful anti-inflammatory components commonly used in Benign prostatic hyperplasia (BPH) patients with symptoms. The current study was designed to assess the effectiveness of saw palmetto alone or supplementation

therapy with tamsulosin via measurement of some inflammatory biomarker in male with lower urinary tract symptoms (LUTS) consistent with (BPH).

Methods The present study is an interventional prospective randomized enrolled newly diagnosed patients with moderate to severe symptomatic BPH. The eligible 60 patients were allocated into (3) groups, each group with (20) patients; Group (1) treated with Saw palmetto cap (320 mg); Group (2) treated with Saw palmetto cap (320 mg) and tamsulosin (0.4mg); Group (3) treated with tamsulosin (0.4mg), protocols to be given once daily for 12 weeks. Measurement of prostate specific antigen (PSA), C-reactive protein (CRP), and interleukin 6 (IL-6) was done.

Results There was significant decrease in the serum PSA, CRP and IL-6 level ($P < 0.01$) in group 1 and 2 patients only after treatment when compared to pretreatment. Patients on combination therapy presented with high percent of change compared to other groups. No change in CRP and IL-6 level in patients on tamsulosin alone.

Conclusion From the findings of the present study, phytotherapy with Saw Palmetto alone or as supplement produced significant 3 months drop in both inflammatory markers, the total CRP level and IL-6 level. Also produced significant decrease in PSA level, and may substitute the conventional therapy in mild disease status.

Key words: Benign prostatic hyperplasia, LUTS, Saw palmetto, Inflammatory biomarker

تأثير البلميط المشاري على بعض المؤشرات الحيوية للالتهاب في عينة من الذكور العراقيين مع
اعراض تضخم البروستاتا الحميدة
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الخلاصة:

الخلفية البلميط المنشاري يحتوي على مكونات مضادة للالتهابات شائعة الاستخدام في اعراض تضخم البروستاتا الحميدة. الدراسة الحالية صممت لتقييم تأثير البلميط المنشاري لوحده او علاج مضاف للتامسولوسين من خلال قياس بعض المؤشرات الحيوية عند الرجال الذين يعانون من اعراض المسالك البولية السفلى المتعلقة بتضخم البروستاتا الحميدة. الطرق الدراسة الحالية هي تدخلية احتمالية عشوائية لمرضى مسجلين ومُشخصين حديثا بتضخم البروستاتا الحميدة ذي الاعراض المتوسطة الى الشديدة. توزع ال 60 مريضا المؤهلون الى (3) مجاميع، كل مجموعة تحوي (20) مريضا؛ المجموعة (1) تعاطوا كبسول البلميط المنشاري (320 ملغ)؛ المجموعة (2) تعاطوا كبسول البلميط المنشاري (320 ملغ) والتامسولوسين (0,4 ملغ)؛ المجموعة (3) تعاطوا التامسولوسين (4 و0 ملغ). البروتوكول العلاجي هو اخذ العلاج مرة واحدة يوميا لمدة 12 اسبوع.

تم قياس مستضد البروستاتا النوعي، وبروتين سي التفاعلي وانترليوكين-6. النتائج هناك نقصان واضح في مستضد البروستاتا النوعي، وبروتين سي التفاعلي وانترليوكين-6 في المجموعة (1) و(2) فقط بعد العلاج عند المقارنة مع ما قبل العلاج، أظهر المرضى الخاضعون للعلاج المركب نسبة عالية من التغيير مقارنة بالمجموعات الأخرى. لا يوجد تغيير في بروتين سي التفاعلي والانترليوكين-6 عند المرضى الذين تناولوا التامسولوسين لوحده.

الاستنتاج من نتائج الدراسة الحالية، المعالجة العشبية بالبلميط المنشاري او كمكمل غذائي ينتج نقصان واضح خلال 3 اشهر في كل من العلامات الالتهابية، وهي بروتين سي التفاعلي والانترليوكين-6، ايضا ينتج نقصان واضح في مستضد البروستاتا النوعي

وقد يعوض العلاجات التقليدية في حالات المرض الخفيفة.
الكلمات المفتاحية: تضخم البروستاتا الحميدة، اعراض المسالك البولية السفلى، البلميط المنشاري، المؤشرات الحيوية للالتهابات

Introduction

Benign prostatic hyperplasia (BPH), is a common condition which affects the quality of life as men get older and can cause uncomfortable urinary tract symptoms [1]. The etiology is still unclear, and the hormone theory is still controversial. Hence many objective manifestations are involved with occurrence of LUTs [2]. Nevertheless, it should be noted that not all persons with histological BPH produce substantial LUTs, only those subjected to further prostate-linked conditions such as prostate inflammation or prostatic cancer and certain sub vesical passage obstructions including bladder neck sclerosis and bladder stones [3,4]. The threat for LUTs development is ongoing gland over-development [5,6].

The herbal medicine Saw Palmetto is an extract derived from the deep purple berries of the Saw Palmetto fan palm (*Serenoa repens*), a plant that grows indigenous to the coastal regions of the southern United States and southern California [7,8]. The extract of Saw Palmetto is one of several phytotherapeutic agents available for the treatment of BPH [9]. The

exact mechanisms of action of Saw Palmetto are unknown. Currently 3 mechanisms of action have been investigated in the laboratory setting, including anti-inflammatory, antiandrogenic and pro-apoptotic properties [10]. In BPH tissue Epidermal Growth Factor (EGF) is highly expressed [11], Saw Palmetto decreases proliferation of prostate cells induced by EGF [12].

Saw Palmetto can reduce the symptoms of enlarged prostate, it can also decrease the need to urinate during the night, increase urine flow, and make it easier to empty the bladder completely [13]. the study found the Saw Palmetto and finasteride had similar positive effects on urinary symptom scores and peak urine flow, but with better tolerated and less expensive [14] Saw Palmetto acts as a diuretic, it can improve urine output and urine flow, and also strengthen urinary organs in older men and women following an dropause and menopause. In men with BPH, Saw Palmetto can treat urinary dysfunction and overactive bladder [8]. Saw Palmetto contains powerful anti-inflammatory components like healthy fatty acids and flavonoids, which can reduce inflammation of few of

the diseases that Saw Palmetto supplementation could help improve such as arthritis, Crohn's disease, fibromyalgia, and Parkinson's disease [15].

The current study was designed to assess the effectiveness of saw palmetto alone or supplementation therapy with tamsulosin via measurement of some inflammatory biomarker in male with (LUTS) consistent with (BPH).

Patients and Method:

The present study is an interventional prospective randomized, enrolled male patient who attended the private clinic of urologist diagnosed with BPH. Out of 155 patients, only 60 patients completed the study intervention. This study was conducted between September 2018 to April 2019. The protocol was reviewed and approved by the Scientific and Ethics Committee in the College of Pharmacy/University of Al-Mustansiriayah. Patient written consent was taken after full explanation of the aim of the study and ensures the reliability of the collected information. Participants meet the following eligibility criteria:

- Patient ≥ 45 years of age.
- Newly diagnosed patients with moderate to severe symptomatic BPH
- Patients having Peak urinary flow rate at least 4 ml/sec with a voided volume of at least 125 ml.
- Patients presenting with American Urological Association Symptom Score (AUASS) ≥ 8 and ≤ 24 at screening visit.

Certain exclusion criteria were followed to avoid interference with the study design and include:

- Newly diagnosed patients with severe symptomatic BPH.
- Prostate-specific antigen (PSA) level greater than 10 ng/ml at the first screening visit.

- Documented bacterial prostatitis or history of bladder cancer or prostate cancer.
- Known primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other psychiatric and neurological diseases known to affect bladder function.
- Known clinically significant renal and hepatic impairment
- Patients received anticoagulation with warfarin or heparin, any drug producing androgen suppression or anabolic steroids, and anticholinergic or cholinergic medication (exception: topical anticholinergic eye drops used for glaucoma).

The eligible 60 patients were allocated into 3 groups; Group (1) included 20 patients treated with Saw palmetto cap (320 mg *Serona repenes*) to be given once daily for 12 weeks; Group (2) included 20 patients treated with Saw palmetto cap (320 mg *Serona repenes*) and tamsulosin 0.4mg to be given once daily for 12 weeks; Group (3) included 20 patients treated with tamsulosin 0.4mg to be given once daily for 12 weeks.

All measurements were carried out at baseline and after 12 weeks. Measurement of (PSA) was done using the principle of enzyme immunoassay test follows atypical one-step capture or sandwich' type assay (Eagle Bioscience Company/USA). C-Reactive Protein (CRP) specific antibody was measured via Streptavidin-Peroxidase enzymatic reaction (Abcam company/UK). Normal reference range is < 10 ng/ml [16,17]. Finally, the measurement of interleukin 6 (IL-6) was measured via Human IL-6 solid-phase sandwich ELISA (Thermofisher / USA) [18]. The reference range was 0– 16.4 pg/mL [19].

Results

A total of 60 patients were included in the present study, 20 patients in each study group 1, 2, and 3, as shown in

Table (1). There was no statistically significant difference between study groups with respect to age, Body Mass Index (BMI), smoking status, residency,

duration of symptoms, and concomitant chronic diseases between the study groups ($P \geq 0.05$).

Table (1): Patients demographic and disease characteristics

Study Variable	Study groups			P-value
	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	
Age (year)	63.15±8.48	62.90± 9.48	64.90± 7.95	0.48 ^{NS}
BMI (kg/m ²)	27±2.7	27.4±2.6	25.8±2.5	0.14 ^{NS}
Smoking status	Yes	10 (34.5)	10 (34.5)	0.93 ^{NS}
	No	10 (32.3)	10 (32.3)	
Residence	Urban	14 (35.9)	13 (33.3)	0.80 ^{NS}
	Rural	6 (28.6)	7 (33.3)	
Duration of symptoms (year)	9.4±2.4	7.1±1.4	7.7±2.2	0.107 ^{NS}

Data presented as mean ± SD, Number of patients (n), Percentage (%).

Chi-square test is used for statistical analysis. NS:

No significant differences ($P \geq 0.05$)

BMI: Body Mass Index

Effect of study intervention on Serum PSA level

The changes in serum PSA level shown in Table (2) revealed significant difference between group 1 and 2 at the end of treatment ($P < 0.05$). There was highly significant decrease in the serum PSA

level ($P < 0.01$) within each study group after treatment when compared to pretreatment. Patients in group 2 presented with highest percent of change (-10.59 %) compared to other study groups.

Table (2) Effect of study intervention on Serum PSA after three months

Study variable	Study groups			P ^b value
	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	
PSA(ng/ml)				
Pre-treatment	2.92±2.52	1.51±1.45	1.76±1.51	0.050
Post-treatment	2.83±2.40	1.35±1.31	1.61±1.25	0.019*
Par value	0.001**	0.001**	0.031*	
Percentage of change (%)	-3.08 %	-10.59 %	-8.52 %	

Data presented as mean±SD, Number of patients (n), percentage of change (%).

NS: No significant differences ($P \geq 0.05$), **($P < 0.01$) is considered highly significant. (a): p-value by Paired *t*-test is statistically used to compare between pre- and post- treatment

results in same group.

(b): p-value by one-way ANOVA test is used to compare study intervals among group 1 group 2, and group 3 patients.

Effect of study intervention on Serum C Reactive protein (CRP) level

The changes in total CRP level shown in Table (3) revealed revealed no significant difference between all groups at baseline and after treatment ($P \geq 0.05$). However, the level of CRP was highly significant

different after treatment in group1 and 2 patients only when compared to pretreatment ($P < 0.01$). Group 2 patients showed the highest percentage of change (-5.85 %) while there was no change in group 3 patients.

Table (3) Effect of study intervention on serum (CRP)after three months

Study variable CRP (ng/ml)	Study groups			<i>P^b</i> <i>value</i>
	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	
Pre- treatment	2.32±0.38	2.22±0.30	2.17±0.31	0.35 ^{NS}
Post- treatment	2.21±0.33	2.09±0.29	2.17±0.30	0.40 ^{NS}
<i>P^a</i> value	0.001**	0.001**	0.810 ^{NS}	
Percentage of change (%)	-4.74 %	-5.85 %	0.00 %	

Data presented as mean±SD, Number of patients (n), percentage of change (%).

NS: No significant differences ($P \geq 0.05$), **($P < 0.01$) is considered highly significant. (a): p-value by Paired *t*-test is statistically used to compare between pre- and post- treatment results in same group.

(b): p-value by one-way ANOVA test is used to compare study intervals among group 1, group 2, and group 3 patients.

CRP: C-Reactive protein

Effect of study intervention on Serum (IL6) level:

Table (4) showed the changes in IL-6 level which revealed no significant difference between all groups at baseline and after treatment ($P \geq 0.05$). Meanwhile, IL-6 level

was significantly decreased post treatment in group1 and 2 patients when compared to pretreatment($P < 0.01$). Again, group 2 patients showed the highest percentage of (-12.64 %) compared to others.

Table (4): Effect of study intervention on Serum IL-6 after three months

Study variable IL-6 (pg/ml)	Study groups			<i>P^b</i> <i>value</i>
	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	
Pre-treatment	2.44±0.59	2.61±0.59	2.39±0.60	0.442 ^{NS}
Post-treatment	2.17±0.59	2.28±0.61	2.37±0.60	0.595 ^{NS}
<i>P^a</i> value	0001**	0.001**	0.296 ^{NS}	

Percentage of change (%)	-11.06 %	-12.64 %	-0.83 %	
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Data presented as mean±SD, Number of patients (n), percentage of change (%).

NS: No significant differences ($P \geq 0.05$), $** (P < 0.01)$ is considered highly significant. (a): p-value by Paired *t*-test is statistically used to compare between pre- and post- treatment results in same group.

(b): p-value by one-way ANOVA test is used to compare study intervals among group 1 group 2, and group 3 patients.

IL-6: interleukin 6.

Discussion

Saw Palmetto exert its anti-inflammatory effect in the prostate through inhibiting the enzymes 5-lipoxygenase and cyclooxygenase responsible for synthesis of prostaglandins and leukotrienes [20,21]. Saw Palmetto also reduce tumor necrosis factor- α (TNF- α) and Interleukin-1b (IL-1b) responsible for its anti-inflammatory action [22]. The anti-edematous action has a clinical importance, since the BPH is often accompanied by a congestion and a sterile prostatitis [23].

According to one test-tube study, Saw Palmetto berry extract was able to decrease the growth of prostate cancer cells [24]. Effect of combining Saw Palmetto to tamsulosin on PSA level in the present study produced significant decrease (-10.59 %), similar effect can be obtained when using each treatment alone ($P < 0.01$).

The vast majority of the previous cited reviews and studies reported that Saw Palmetto extract compounds had a same effect as the α -blocker tamsulosin in treating BPH in terms of PSA [25,26]. And the equipotent effect was revealed in many studies, in the 6 months 3 arms studies the mean changes in efficacy ($P = 0.07$) [27], PSA change ($p = 0.521$) [28], and PSA change ($p = 0.41$) [29]. Saw palmetto is rich in antioxidants and shown to decrease inflammation in animal studies. It contains the antioxidant sepicatechin and methyl gallate compounds that prevent

damage to cells, decrease inflammation, and protect against chronic disease which could be beneficial in treating certain clinical conditions [30].

In experimental study it was observed that giving Saw Palmetto extract to mice with enlarged prostate glands decreased swelling and markers of inflammation, including (IL-6)[31,32]. In the present clinical study, results clarify the mentioned pharmacological effect and stratify the experimental findings, in patients received Saw Palmetto mono or combined protocol revealed significant 3 months drop in both inflammatory markers, the total CRP level and IL-6 level ($P < 0.01$) compared to tamsulosin monotherapy. In his review, Paulis G. stated that several previous studies proved that all chemical composition of commercial available Saw Palmetto (phytostrols, fatty acids, etc) possess potent anti-inflammatory and antioxidant effect, besides, other antioxidant substances are present (ferulic acid, vanillic acid, triterpenes, gallic acid, caffeic acid esters, flavonoids isoquercetin, avicularin, astragalin, rutin, manghaslin, and kaempferol)[33]. Finally, in another study, the National Health and Nutrition Examination Survey data were used to assess the associations between supplement use and inflammation , Saw Palmetto was found to minimize the (CRP) concentration at a slight degree but

not significant[34], and has a great role in minimizing IL-6 levels in serum men with benign prostate enlargement[35].

Conclusion

From the findings of the present study, phytotherapy with Saw Palmetto alone or as supplement produced significant 3 months drop in both inflammatory markers, the total CRP level and IL-6 level. Also produced significant decrease in PSA level, hence, it is worth noting that treatment with Saw Palmetto alone may substitute the conventional therapy in mild disease status.

Conflict of interest

The authors declared no financial or non-financial conflict of interest.

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