

Pterostilbene Effect on Inflammatory and Oxidation Markers in Benign Prostatic Hyperplasia Rats Model

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Abstract

Pterostilbene is a potent anti-inflammatory and antioxidant used to treat benign prostatic hyperplasia, which is generated by the induction of testosterone propionate. The objective of the current study is to assess the efficacy of pterostilbene treatment in comparison to finasteride and resveratrol by tracking various inflammatory and oxidative markers in a male rat with lower urinary tract symptoms consistent with benign prostatic hyperplasia.

Forty-eight male rats were divided into six groups: each study group consists of 8 rats, the control group, which given oil vehicle subcutaneously for 42 days; the induction group, which given testosterone propionate (4mg/kg/day) subcutaneously daily dose for fourteen days; and the finasteride group, which given finasteride 0.44 mg/kg orally for twenty-eight days after induction of benign prostatic hyperplasia, and the pterostilbene group, which got pterostilbene 200 mg/kg administered orally for 28 days after 14 day Benign prostatic hyperplasia induction, and the other group, which received pterostilbene at a dose of 100 mg/kg Using oral gavage to provide 100 mg/kg for the same time period. While the Resveratrol group, which received 100 mg/kg of resveratrol orally. During the identical time frame after Benign prostatic hyperplasia Induction.

There were significant differences in the tissue levels of inflammatory markers and oxidative markers tumor necrosis factor alpha (35.54±5.01 ng/ml) and glutathione-peroxidase (263.611±64.45 ng/ml) and malondialdehyde (0.489±0.066 ng/ml) when comparing the pterostilbene 200 group to the induction group ($P < 0.05$). Pterostilbene has potent antioxidant and anti-inflammatory properties that possibly help to lessen the growth of the benign prostatic hyperplasia that testosterone propionate causes.

Keywords: Pterostilbene, Benign prostatic hyperplasia, Tumor necrosis factor alpha, Glutathione-peroxidase, Malondialdehyde.

تأثير التيروسستيلبين على علامات الالتهابات (عامل النخر الورمي ألفا) وعلامات الأكسدة (الجلوتاثيون بيروكسيداز والمالونديالدهيد) في نموذج جردان لتضخم البروستاتا الحميد.

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الخلاصة

التيروسستيلبين هو مضاد قوي للالتهابات ومضاد للأكسدة يستخدم لعلاج تضخم البروستاتا الحميد، والذي يحدث عن طريق تحريض بروبيونات التستوستيرون. كان الهدف من التجربة الحالية هو تقييم فعالية علاج التيروسستيلبين بالمقارنة مع الفيناسترايد والريسفيراترول من خلال تتبع علامات الالتهاب والأكسدة المختلفة في ذكور الجرذ مع أعراض المسالك البولية السفلية المتوافقة مع تضخم البروستاتا الحميد. تم تقسيم الجرذان الثمانية والأربعين الذكور إلى ستة مجموعات: المجموعة الضابطة، والتي تضمنت ثمانية جرذان تم إعطاؤها زيتاً تحت الجلد لمدة ٤٢ يوماً. مجموعة الحث، والتي تضمنت ثمانية جرذان أعطيت جرعة يومية من بروبيونات التستوستيرون (٤ ملغم/كغم/يوم) تحت الجلد لمدة أربعة عشر يوماً وبعدها إعطاء زيت الزيتون تحت الجلد لمدة ٢٨ يوم؛ ومجموعة الفيناسترايد، والتي تضمنت ثمانية جرذان تم إعطاؤهم الفيناسترايد ٠,٤٤ ملغم / كغم عن طريق الفم لمدة ثمانية وعشرين يوماً بعد تحريض تضخم البروستاتا الحميد، ومجموعة التيروسستيلبين، التي تتكون من ٨ جرذان، حصلت على 200 ملغم / كغم من التيروسستيلبين عن طريق الفم لمدة ٢٨ يوماً بعد ١٤ يوماً من تحريض تضخم البروستاتا الحميد، والمجموعة الأخرى، التي تتكون من ٨ جرذان، تلقت كذلك التيروسستيلبين بجرعة ١٠٠ ملغم / كغم استخدم بالتطعيم عن طريق الفم لتوفير ١٠٠ ملغم / كغم لنفس الفترة الزمنية. بينما تناولت مجموعة الريسفيراترول ١٠٠ ملغم / كغم من الريسفيراترول عن طريق الفم. خلال نفس الإطار الزمني بعد تحريض تضخم البروستاتا الحميد. كانت النتائج دالة على فروق ذات دلالة إحصائية قوية في مستويات الأنسجة من علامات الالتهاب وعلامات الأكسدة عامل نخر الورمي ألفا والجلوتاثيون بيروكسيداز ومالونديالدهيد عند مقارنة مجموعة التيروسستيلبين ٢٠٠ مع مجموعة الحث (قيمة $p \geq 0.05$). فالاستنتاج بأن التيروسستيلبين يحتوي على خصائص قوية مضادة للأكسدة ومضادة للالتهابات تساعد على تقليل نمو تضخم البروستاتا الحميد الذي يسببه بروبيونات التستوستيرون.

الكلمات المفتاحية: التيروسستيلبين، تضخم البروستاتا الحميد، عامل نخر الورمي ألفا، الجلوتاثيون بيروكسيداز، المالونديالدهيد.

Introduction

The most prevalent urologic illness in older men is benign prostatic hyperplasia (BPH). It might cause discomfort during lower urinary tracts. Clinical BPH is not present in all men with lower urinary tracts, and not all men with lower urinary tracts have clinical BPH^(1,2). Symptoms of the lower urinary tract are one of the most prevalent and difficult disorders encountered in everyday practice of urology, BPH is characterized by the prostate gland enlargement, which is caused by the increasing proliferation of stromal and glandular prostatic cells as people become older⁽³⁾. The total prevalence of BPH in the male population is reported to be >70% at 60 years old, with >90% by the age of 70⁽⁴⁾.

Reduced urine flow and frequency, difficulty beginning flow, Nocturia, and dribbling are all signs of BPH⁽⁵⁾. Dihydrotestosterone (DHT), a male hormone, was shown to be more potent in BPH patients than in healthy men. Despite the fact that this notion was eventually disproved, since DHT concentrations in prostate tissue actually decline with age, 5 α -reductase inhibitors were given to treat BPH and are still being given with some efficacy⁽⁶⁾. Compared to testosterone, dihydrotestosterone has a stronger affinity for androgen receptors, making it a more potent androgen⁽⁷⁾.

Pterostilbene (4-((E)-2-(3,5-Dimethoxyphenyl)ethenyl)phenol) is a natural plant product that can be found mostly in blueberries and grapes. Pterostilbene has a variety of biological activities, including anticancer actions⁽⁸⁾. Pterostilbene is a lipid-soluble molecule that exists in both cis and trans forms, with the trans form being the most common⁽⁹⁾. Pterostilbene was shown to be extremely safe product due to limited organ or systemic toxicity so can be used in as pharmaceutical product^(10,11). it is pharmaceutically safe. PTE is a resveratrol natural analog (3,5,40-trihydroxystilbene). Furthermore, PTE has a higher lipophilicity and more potential cellular absorption than resveratrol, which has three hydroxyl groups⁽¹⁰⁾. Anti-inflammatory, anti-oxidant, cholesterol lowering, anti-obesity, analgesia, antiaging, antidiabetic and neuroprotective properties are all exhibited by PTE, Pterostilbene's pharmacological actions are frequently reported to be stronger in vitro and/or in vivo than resveratrol's, despite the structural and general bioactivity similarities between the two⁽¹¹⁾.

Materials and Methods

Chemicals and drugs

Testosterone propionate injection by Hammer Lab, Holland and Finasteride Pure from SDI, IRAQ and Resveratrol pure by Fluorochem, United Kingdom, Pterostilbene pure obtained by Sigma Aldrich, Germany. Dimethyl sulphoxide

(DMSO) from Sigma, Germany. Ketamine 10% vial from Alfasan, Holland, and Xylazine 20mg/ml vial by Kepro, Holland. Formaldehyde (37%-40%) from Solvochem, UK and Pure olive oil obtained Natural, Spain.

Experimental animals

Each group consist of 8 animals. Group I (Control Group) received a 42-day subcutaneous of 0.5 ml of olive oil vehicle. Group II (Induction group) given a subcutaneous injection: testosterone propionate (4 mg/kg) daily for (14days) then 0.5 ml of oil vehicle S.C. daily for 28 days.

Group III (finasteride group) the conventional treatment group 0.44 mg/kg given by oral gavage daily for 28 days after testosterone propionate (4 mg/kg) daily dose for 14days⁽¹²⁾⁽¹³⁾.

Group IV (PTE 200 group) the pterostilbene 200mg/kg given by oral gavage daily for 28 days after testosterone propionate (4 mg/kg) daily dose for 14days⁽¹⁴⁾.

Group V (PTE 100 group) the pterostilbene 100mg/kg given by oral gavage daily for 28 days after testosterone propionate (4 mg/kg) daily dose for 14days⁽¹⁵⁾.

Group VI (Resveratrol 100 group) the resveratrol 100mg/kg given by oral gavage daily for 28 days after testosterone propionate (4 mg/kg) daily dose for 14days⁽¹⁶⁾.

Sample collection and Prostate Tissue Homogenate ELISA Test Biomarker:

for anesthetize all rats at the study completion were administered intra-peritoneal to the rats Ketamine at 50 mg/kg with xylazine at 5 mg/kg⁽¹⁷⁾. Rat abdominal cavities were opened with forceps and scissors on day 42, when they were administered ketamine at 50 mg/kg with xylazine at 5 mg/kg to anesthetize rat in order to remove and preserve the prostate for tissue homogenate analysis by Elisa Kits. A small amount of prostate tissues was preserved in 10% buffered neutral formalin to create paraffin-embedded blocks for histopathological diagnosis. ELISA Tissue Test is purchased from (MY BIO SOURCE) Co LTD. depend on instruction of this Co. prostate tissue were cut and harvesting and collecting thin homogenized after add phosphor buffer saline 9 time to the tissue, after that centrifuge for 20 minutes at 3,000 rpm. ELISA Kit test makes for evaluation and determination for Tumor Necrosis Factor -Alfa(TNF α), Malondialdehyde-MDA and Glutathione peroxidase-GPX^(10,11,18).

Statistical Analysis

The Statistical analysis (Post hoc test) was utilized, and a significant result was defined as a p value <0.05. Statistical analysis was performed utilizing SPSS to analyze the collected data, each result's value was represented as a mean plus standard deviation (M \pm S.D). P value < 0.05 was regarded as significant variance.

In the current investigation, Pearson correlation analysis was also conducted to see whether there were any relationships between the biomarker levels in BPH. The strength and direction of the linear association between the biomarkers are classified as per the value of the Pearson correlation coefficient (r).

Ethical statement: under Ethical law of Almustansiriah university in pharmacy college.

Results and Discussion

Concentration of tissue homogenate for inflammatory(TNF-α) marker in studied groups:

Current study results showed significant elevation in tissue homogenate TNFα Level of induction group (373.66±90.89) ng/ml (M±S.D.) compared to other groups (p<0.05) (Table1). Using finasteride as conventional BPH treatment showed significant reduction of TNFα Level (35.98±10.57) ng/ml compared to induction group (p<0.05) while there were no significant differences both PTE treatment groups (p>0.05).

A significant decrease was shown in mean TNFα level of PTE 200 Group was 35.54±5.01 ng/ml. compare with induction group (p ≤0.05).

The results also indicated that the tissue concentration of TNF was not significantly different for PTE 200 group when compared with (control, Finasteride, PTE100, resveratrol) groups P value (0.964,1.00,0.925,0.903 respectively).

The TNFα tissue concentration of PTE 100 group had no significant difference in comparison with (control, Finasteride, PTE200 and resveratrol) groups p value= (1.00,0.932,0.925 and 1.00 respectively). Using resveratrol showed significant reduction of TNFα Level (55.44±11.22) ng/ml, compared to induction group (p<0.05) while there were no significant differences both PTE treatment groups) (p>0.05). The control group, finasteride group, pterostilbene 200 group, PTE100 group and resveratrol group all shown significant depletion comparing with induction group (p<0.05).

Table 1. Mean tissue concentration of TNF-α level of all Groups.

Study Groups	TNF Alpha ng/ml
I-Control Group	51.07±15.33 ^a
II-Induction Group	373.66±90.89 ^b
III-Finasteride Group	35.98±10.57 ^a
IV-Pterostilbene 200 mg/kg Group	35.54±5.01 ^a
V-Pterostilbene 100 mg/kg Group	54.13±8.72 ^a
VI-Resveratrol 100mg/kg Group	55.44±11.22 ^a

-Data represents Mean ± Standard deviation (M±SD).
 -Different lowercase letters indicate significant differences between groups (p<0.05).

Estimation of tissue homogenate oxidative stress markers in studied groups:

The mean GPX tissue concentration of induction group is (16.069±1.12) ng/ml, possessed significant decrease when compared with all groups (control, finasteride, PTE 200, PTE 100 and resveratrol) (p<0.05).

The Mean GPX tissue concentration of the control group is (93.311±29.7) ng/ml, showed significant decrease in comparison with the group of induction (p<0.05). while the GPX tissue concentration of the control group showed significant depletion compared to (PTE 200, PTE 100 and resveratrol) groups (p<0.05). Conversely, the GPX tissue concentration of the control group had no significant differences when compared to Finasteride group (p value =1.00).

Using finasteride as conventional BPH treatment of GPX of prostate tissue concentration (88.363±28.23) ng/ml, showed no significant rise compared to induction group p value= (0.065), while there were significant differences with both PTE and resveratrol treatment groups) (p<0.05).

The mean GPX prostate tissue concentration of PTE 200 group is (263.611±64.45) ng/ml, showed significant increase of GPX level in comparison with induction group (p <0.05). Moreover, the GPX prostate tissue concentration of PTE 200 group possessed significant rise compared to (control, finasteride and PTE 100) groups (p ≤0.05). Conversely for that, The GPX prostate tissue concentration of PTE 200 group revealed no significant increase in comparison with resveratrol group (p value =0.523).

The mean GPX prostate tissue concentration of PTE 100 group is (169.039±89.55) ng/ml, possessed a significant increase in comparison with induction group (p <0.05) moreover the GPX prostate tissue concentration of PTE 100 group had significant rise compared to control group (p <0.05).

The GPX prostate tissue concentration of PTE 100 group had no significant decrease in comparison with resveratrol group (p value =0.199). The GPX prostate tissue concentration of PTE 100 group recorded significant reduction compared to PTE 200 group (p <0.05).at same time the GPX prostate tissue concentration of PTE group had significant increase when compared with Finasteride group (p<0.05).

The mean GPX prostate tissue concentration of resveratrol group is (220.246±36.08) ng /ml, showed no significant elevation in comparison with PTE 200 (p value=0.523).at same time the GPX tissue concentration had no significant rise in comparison with PTE 100 group (p value=0.339).on the contrary for that GPX prostate tissue concentration of resveratrol group possessed significant increase in

compare with (control, induction and finasteride) groups ($p < 0.05$).

The mean MDA prostate tissue concentration of induction group is (3.024 ± 0.45) ng/ml, were recorded significant increase when compared with (control, finasteride, PTE 200, PTE 100 and resveratrol) groups ($p < 0.05$). The mean MDA prostate tissue concentration of the control group is (0.619 ± 0.19) ng/ml, had significant decrease when compared with induction group ($p < 0.05$). Conversely, the MDA prostate tissue concentration for the control group showed no significant depletion in comparison with finasteride, PTE 200, PTE100 and resveratrol) groups (p value = 0.988, 0.860, 0.656 and 0.948 respectively).

The mean MDA prostate tissue concentration of finasteride group is (0.690 ± 0.16) ng/ml, were obtained significant decrease in comparison with induction group ($p < 0.05$). Conversely, the MDA prostate tissue concentration of Finasteride showed no significant reduction comparing with (control, PTE 200, PTE 100 and resveratrol) groups (p value = 0.988, 0.494, 0.948 and 0.657 respectively).

Table 2. Mean Tissue Concentration of oxidative stress biomarker in all studied group.

Study groups	tissue concentration of GPX ng/ml	MDA prostate tissue concentration
I-Control group	93.311 ± 29.7^{ac}	0.619 ± 0.19^a
II-Induction group	16.069 ± 1.12^b	3.024 ± 0.45^b
III-Finasteride group	88.363 ± 28.23^{ab}	0.690 ± 0.16^a
IV-Pterostilbene200 group	263.611 ± 64.45^e	0.489 ± 0.066^a
V-Pterostilbene100 group	169.039 ± 89.55^f	0.791 ± 0.05^a
VI-Resveratrol group	220.246 ± 36.08^{ef}	0.519 ± 0.16^a

Data are representing as Mean \pm Standard deviation (SD).

Different lowercase letters indicate significant differences between groups ($p < 0.05$).

Effect of Pterostilbene on inflammatory (Tumor necrosis factor-alpha) marker:

Cytokine production and growth factor levels may both be increased by inflammation, which will cause prostatic cells to proliferate abnormally⁽¹⁹⁾.

In the current study, the mean prostate tissue TNF α concentration dramatically increased ($p < 0.05$) in induction group by injection of testosterone propionate when compared with control group, These results agreed with previous studies indicate after administrating testosterone propionate subcutaneous injection, there was a significant rise in tumor necrosis factor alpha tissue concentration, this was predicted because BPH is greatly influenced by the 5 α -reductase enzyme ,which transforms testosterone into DHT, DHT stimulates prostate cell proliferation via binding with an androgen receptor and a coactivator of the steroid receptor 1^(13,18).

Administration of pterostilbene after testosterone propionate in Induction group showed a significant decrease in prostate tissue concentration

The mean MDA prostate tissue concentration for PTE 200 group is (0.489 ± 0.066) ng/ml, had significant decrease when compared with induction group ($p < 0.05$). Moreover, the MDA tissue concentration of PTE 200 group was obtained no significant difference compared with (control, Finasteride, PTE100 and resveratrol) groups (p value = 0.860, 0.494, 0.105 and 1.00 respectively).

The mean MDA prostate tissue concentration of PTE 100 group is (0.791 ± 0.05) ng/ml, recorded significant decrease compared to induction group ($p < 0.05$). While the MDA prostate tissue concentration of PTE 100 group had no significant reduction in compare with (control, finasteride, PTE200 and resveratrol) groups (p value = 0.656, 0.948, 0.105 and 0.179).

Using resveratrol showed mean MDA level is (0.519 ± 0.16) ng/ml, possessed significant decrease in comparison with Induction group ($p < 0.05$). while shown no significant reduction when compared with (control, finasteride and PTE 200, PTE100) groups (p value = 0.948, 0.657, 1.00 and 0.197 respectively).

of TNF α compared to induction group, as uses pterostilbene in previous studies agreed with this results had significantly reduction of TNF α level in

human umbilical endothelial cell in comparison with induction group⁽²⁰⁾. And this result agrees with previous studies shown significant reduction in TNF α in the inflammation of prostate by using Resveratrol⁽¹⁶⁾.

On the other hand, in current study the Finasteride group showed a significant decrease in prostate tissue concentration of TNF α when compared with induction group, this results resemble to previous studies that perfect for give finasteride causing a significant reduction in TNF α prostate tissue concentration when compared to induction group in complication of thulium laser resection of prostate⁽²¹⁾.

The Effect of pterostilbene on Prostate tissue concentration of oxidative stress biomarker

One mechanism that activates the elements involved in the onset and progression of prostatic hyperplasia has been identified as oxidative stress⁽¹⁸⁾. One of a diagnostic approach for BPH is to

measure the antioxidant concentrations and the change in lipid, protein, and DNA oxidation levels⁽²²⁾. Benign prostatic hyperplasia is to be influenced by a number of variables includes inflammatory genes, inflammatory mediators, hormones, nutritional variables, and oxidative stress (OS), both direct and indirect growth-promoting effects can be caused by oxidative stress⁽²³⁾.

In current present study, the MDA prostate tissue concentration showed significant increase in the induction group (administrated with testosterone propionate subcutaneous) in comparison with the tissue concentration of the control. In contrast, GPX tissue concentration were significantly decreased, these results were consistent with a number of earlier investigations that discovered testosterone propionate caused benign prostatic⁽²⁴⁾. Hyperplasia by elevating MDA tissue concentration and reducing GPX antioxidant prostate tissue concentration^(25,26).

The prostate tissue concentration of GPX for PTE 200 group in present study was dramatically increase in comparison with induction group, at same time the MDA tissue concentration of PTE group was dramatically reduce comparing with induction group, these findings identical with some previous studies, that stated the MDA and glutathione peroxidase tissue concentration in PTE group its dissimilar significantly by comparing with induction group in experimental animal diabetes^(27,28).

Present data had similar results and didn't differ significantly for MDA and GPX tissue concentration of Finasteride in comparing with control group, the MDA tissue concentration for finasteride shown significant decrease when compared with induction group and tissue concentration of GPX obtained significant rise by compare to induction group, these findings where consistent with previous investigations, stated that MDA tissue concentration of finasteride group had significant depletion in comparison with induction group, while the GPX tissue concentration of Finasteride observed significant rise comparing with induction group^(29,30).

In current study the findings of MDA tissue concentration for resveratrol group observed significant depletion in compare with induction group after administrated testosterone propionate subcutaneous, furthermore, the prostate tissue concentration of GPX for resveratrol group had a significant rise comparing with induction group, these data was agreed with a previous study that stated MDA tissue concentration exhibited a significant reduce in administration of Resveratrol for myocardial ischemia reperfusion and in annual fish *Nothobranchius Guentheri*⁽³¹⁻³⁴⁾.

Simultaneously the GPX tissue concentration after giving Resveratrol possessed a significant arise in annual fish *nothobranchius*

^(32,35,36). In rats given both aluminum and resveratrol, treatment of resveratrol reduced MDA rise. Additionally, resveratrol significantly reduced the inhibition of GPX caused by aluminum administration⁽³⁶⁾.

The development of prostatic tissue inflammation and an Inflammatory cytokine may be produced more often when there is severe oxidative stress. and other growth factors, and include some prostatic epithelial cells may experience cellular senescence as a result of DNA oxidative damage, and the senescence-associated secretory response may cause secondary secretion of a several cytokines⁽³⁷⁾. Oxidative stress is known to directly promote growth activity by activating signaling pathways including MAP kinase and PI3K/AKT and to encourage cellular growth in this way^(38,39).

Conclusion

Pterostilbene reduced level of inflammatory indicators, the anti-inflammatory role in the decline of TNF α , which is a key player in the inflammation pathway, and has anti-oxidative properties against BPH induced by the hormone testosterone propionate. Pterostilbene have significant strong redox status and enhance scavenging for oxidative stress enzyme and non-enzyme after twenty-eight days of treatment.

Conflict of Interest

All authors declare that they have no conflicts of interest.

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Author Contribution

Both authors contributed to the conception, design, analysis and interpretation of data.

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