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Effect of Watermelon & Pumpkin Seeds Extract on Physiological Parameters in BPH Rats

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ABSTRACT

Background: Benign Prostatic Hyperplasia (BPH) is the most widespread condition among older men, causing urinary dysfunction and the risk of renal failure. Our study focuses on using medicinal plants, particularly watermelon and pumpkin seeds, in preventing BPH.

Objective: The present study was to assess the effects of watermelon and Cucurbita pepo seed extracts versus dutasteride on physiological parameters in BPH rats.

Materials and Methods: During the 29-day research period, 42 healthy adult male albino rats were divided into six groups of seven animals each. All groups, except for group 1, received daily subcutaneous testosterone (3 mg/kg) and specific medications as per their designated groups for the first 14 days to induce Benign Prostatic Hyperplasia (BPH), followed by a maintenance phase from days 15 to 29. Group 1 served as the normal healthy control, while group 2 served as the disease control. The treatment groups included: group 3 (3 mg/kg testosterone s.c.+ 0.5 mg/kg dutasteride p.o.), group 4 (3 mg/kg testosterone + 2 g/kg methanolic extract of watermelon seeds p.o.), group 5 (3 mg/kg testosterone s.c.+5 g/kg petroleum ether extract of pumpkin seeds p.o.), and group 6 (3 mg/kg testosterone s.c. +1 g/kg methanolic extract of watermelon seeds p.o.+2.5 g/kg petroleum ether extract of pumpkin seeds p.o.). Body weight & urine output were collected on days 0, 14, and 29. At the end of study, the animals were sacrificed and the prostates were weighed.

Results: The preventive combination of 1 g/kg methanolic extract of watermelon seeds and 2.5 g/kg petroleum extract of pumpkin seeds resulted in a significant increase in urine output by day 14 after BPH induction, which was maintained throughout the duration of the study. This improvement was confirmed by normalized prostatic weight, which was similar to the effects observed with dutasteride.

Conclusions: These findings suggest that the combination of watermelon seed and pumpkin seed extracts may offer a potential natural alternative for managing BPH symptoms. Further research is recommended to explore the underlying mechanisms and confirm the long-term efficacy and safety of this treatment.

Keywords: Body weight, Preventive, Prostate weight, Pumpkin, Urine output, Watermelon.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a condition characterized by increased proliferation of smooth muscle and epithelial cells in the prostate's transition zone, leading to gland enlargement and associated urinary symptoms.[1] In this condition, the prostate gland, which typically weighs between 20 to 30 grams, can enlarge to as much as 50 to 100 grams[2] resulting in lower urinary tract symptoms (LUTS),[3] recurrent urinary infections, bladder stones and eventually renal failure.[4] The incidence of BPH increases as men age, with 80 percent of men over eighty affected by the condition.[5]

As the prostate enlarges, it compresses the urethra, which leads to thickening of the bladder wall. Ultimately, this can cause the bladder to weaken and struggle to empty fully, resulting in the retention of residual urine. The constriction of the urethra and urinary retention are significant factors that contribute to the complications associated with benign prostatic hyperplasia.[6] The etiology and mechanisms underlying BPH are not properly understood. Nevertheless, the growth of the prostate depends on dihydrotestosterone (DHT), which is generated from testosterone in body tissues.[7] In adulthood, elevated levels of DHT can be harmful, resulting in excessive gland growth.[8] The therapeutic goals are to reduce lower urinary tract symptoms and prevent complications while minimizing the adverse effects of treatment.[9] The two medical treatment options for BPH are Alpha blockers and 5 alpha reductase inhibitors.[10] 5 alpha reductase inhibitor (such as Dutasteride or Finasteride) lead to a prolonged reduction in DHT levels.[11] Patients may encounter drug-related problems (DRPs), including dizziness and orthostatic hypotension with alpha blockers, as well as sexual dysfunction and gynecomastia associated with 5 alpha reductase inhibitors.[12] The adverse consequences of allopathic medication have caused researchers to refocus their attention on natural products. rye pollen (Secale cereale), Saw palmetto and African plum tree (Pygeum africanum), and are among the plants that have been studied for their potential as BPH treatments.[13] A dried shell less seeds of watermelon rich in water, protein, fat, carbohydrate, minerals including vitamins thiamine, iron, riboflavin, phosphorus, niacin, calcium and folate.[14] The seed oil consists of glycosides of linoleic, oleic, palmitic, and stearic acids, which is indicative of its high fat content.[15]

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Pumpkin seeds are an excellent source of minerals, vital fatty acids, carbs, and proteins,[16] Tocopherols, Carotenoids[17] & Phytosterols.[18]

In our study testosterone has been used to induce BPH in rats because the changes produced in their prostate resemble the changes produced in humans. We have chosen Citrullus lanatus and curcurbita pepo seed extract for this research as they are easily available, affordable and easy to administer. They have been used for treating BPH in alternative medicine therapeutically only, not prophylactically, in combination and against dutasteride which shall be our study. Dutasteride has been taken as a standard drug in our study, because nowadays it is commonly prescribed for the treatment of BPH. However, it is associated with multiple adverse effects in aged people. It would be interesting to see the prophylactic effects of our plants Citrullus lanatus and Curcurbita pepo seed extracts in comparison to this drug which has not been done before.

MATERIALS AND METHODS

It was an Experimental study. The research was completed in 12 months after approval of synopsis by Institutional Review Board (IRB), Federal Postgraduate Medical Institute, Lahore with IRB letter no. F.39/NHRC/IRB/180. The study was conducted in an experimental research laboratory at the Post Graduate Medical Institute (PGMI), Lahore. Simple random sampling was done by using the lottery method. A sample size of 7 rats was estimated for each of the 6 groups by using 95% confidence level and 93% power. The sample size was calculated using power and precision 3.0 software with a 0.82 effect size with an Error SD of 1.5. Forty-two healthy male albino rats, each weighing between 180 and 200 grams, were obtained from the University of Veterinary and Animal Sciences in Lahore. The rats were kept in typical polypropylene cages where the temperature was regulated at 25±10 degrees Celsius, humidity levels were maintained at 60-70%, and appropriate lighting conditions were ensured.

Group 1	*Healthy Control*
Group 2	*Disease Control*
Group 3	*Provided with (3mg/kg s.c Testoterone+0.5mg/kg p.o dutasteride),*
Group 4	*Provided with (3mg/kg s.c Testoterone+2mg/kg Methanolic Extract of Watermelon seeds p.o)*
Group 5	*Provided with (3mg/kg s.c Testoterone+5mg/kg Petroleum Ether extract of Pumpkin seeds p.o)*
Group 6	*Provided with (3mg/kg s.c Testoterone+1mg/kg Mathanolic Extract of Watermelon seeds p.o+2.5g/kg Petroleum Ether extract of Pumpkin Seeds p.o)*

Operational Definitions

Benign Prostatic Hyperplasia: Benign Prostatic Hyperplasia (BPH) is a medical condition characterized by the non-cancerous enlargement of the prostate gland. It typically occurs in older men and can cause urinary symptoms due to the enlargement of the prostate, which compresses the urethra and obstructs the flow of urine.

Dutasteride: Dutasteride is a medication used in the treatment of Benign Prostatic Hyperplasia (BPH), which is an enlargement of the prostate gland. Dutasteride is classified as a 5-alpha-reductase inhibitor. It works by blocking the enzyme 5-alpha reductase, which is responsible for converting testosterone into dihydrotestosterone (DHT), a hormone that contributes to the enlargement of the prostate. By reducing DHT levels, Dutasteride helps to shrink the prostate, relieve urinary symptoms, and decrease the risk of acute urinary retention or the need for prostate surgery.

Chemicals: Testosterone propionate injection (Tesvot) at a concentration of 250 mg/ml and Dutasteride tablets (Galax smith) at 0.5 mg were obtained from Clinix Pharmacy. Hamdard Dawakhana in Lahore was the supplier of the Citrullus Lanatus and Cucurbita pepo seeds. The petroleum ether extract of pumpkin seeds (PECPS) and the methanolic extract of watermelon seeds (MECLS) were made at PCSIR in Lahore.

Extract Preparation: Watermelon seeds were washed and oven dried at 50 degree Celsius for 24 hours until a constant weight was attained. Thereafter, the dried watermelon seed samples were ground into a fine powder weighing 324g using a mill and pestle. This powdered sample was subjected to percolation in 800 ml of methanol for 48 hours, after which the resulting filtrate was concentrated using a rotary evaporator. The concentrated solution was subsequently diluted with corn oil to produce a 100 mg/ml stock solution for enhanced solubility, stability, and accurate dosing of the extract's bioactive compounds. The desired concentrations were administered using an insulin syringe.[19] Two hundred grams of ground Pumpkin seeds were defatted using petroleum ether in a Soxhlet extractor. After that, Pumpkin seeds were digested with 1.25% (v/v) H_2SO_4 and 1.25% (v/v) NaOH to decompose complex organic matrices, which helps in release and analysis of inorganic nutrients, minerals, and other biochemical components by transforming them into soluble forms. The resulting residues were subjected to heating at 1300°C for 2 hours to promote complete carbonization and ash formation, thereby enhancing the extraction of inorganic minerals or phytochemicals and improving the overall analytical properties of the material. After that, the residues cooled in a desiccator and subsequently weighed.[20]

Variables and Data source:

I. Weight of the rats were taken a day before starting treatment (baseline), on day 14 and on completion of study i.e. on day 29 of treatment through electronic balance.
ii. Prostate weights were taken on electronic balance at day 29.
iii. Mean body weights and prostate/body weight ratios were calculated for each group.
iv. The urine output of individual animals was measured by placing them into designated cages for 24 hrs. at the points of measurements which were at the beginning of the study, on day I4th and after completion of study on day 29.

Statistical Methods

The data was entered and analyzed using SPSS 23.0. Mean ± SEM were given for quantitative variables like prostate weight & prostate/body weight ratio. One-way ANOVA & Post Hoc Tukey was applied to compare the biochemical parameters among groups. As the data was not normal for body weight, non-parametric tests, including Wilcoxin Rank & Mann Witheny tests, were applied & determined the differences among all groups & within pairs of individual groups. A p-value of < 0.05 was considered statistically significant.

RESULTS

Table 01. Weights of animals at baseline, day 14 and day 28 with various drugs and their dosages

	N	Base Line	Day 14	Day 29	Wilcoxin Ranked Test
Weight (g)		Mean ± S.D	Mean ± S.D	Mean ± S. D	
Group 1	7	145.14±0.69	146.00±0.82	149.00±1.15	0.45
Group 2	7	145.86±0.69	160.43±1.13	177.14±1.46	0.018
Group 3	7	141.00±1.29	136.00±1.29	132.71±1.80	0.018
Group 4	7	167.29±1.38	166.29±1.25	165.57±1.51	0.02
Group 5	7	173.00±1.15	172.86±1.57	170.00±1.53	0.018
Group 6	7	192.00±1.63	189.14±2.67	181.29±2.93	0.018

Group 1 Control
Group 2 Testosterone induced
Group 3 Testosterone +Dutasteride
Group 4 Testosterone+MECLS
Group 5 Testosterone+PECPS
Group 6 Testosterone+MECLS+PECPS

Table 02. Prostate weights (gms) of animals at day 28 for various drugs and their dosages

	N	Day 29
Prostate Weight(g)		Mean± S.D
Group 1	7	5.56±1.43
Group 2	7	6.64±0.85
Group 3	7	3.66±1.50
Group 4	7	4.96±1.23
Group 5	7	5.16±1.38
Group 6	7	5.07±0.79
P-value (ANOVA)	7	0.014

Group 1 Control
Group 2 Testosterone induced
Group 3 Testosterone +Dutasteride
Group 4 Testosterone+MECLS
Group 5 Testosterone+PECPS
Group 6 Testosterone+MECLS+PECPS

Table 03. Prostate /body weight ratio of animals on day 29

	N	Day 29	P-Value ANOVA
Prostate/Body Weight Ratio Day 29		Mean± Std. Deviation	
Group 1	7	0.01±0.01	
Group 2	7	0.02±0.10	
Group 3	7	0.02±0.01	0.001
Group 4	7	0.01±0.01	
Group 5	7	0.02±0.01	
Group 6	7	0.02±0.00	

Group 1 Control
Group 2 Testosterone induced
Group 3 Testosterone +Dutasteride
Group 4 Testosterone+MECLS
Group 5 Testosterone+PECPS
Group 6 Testosterone+MECLS+PECPS

Table 04. Urine output of animals on day 0,14,29

	N	Base Line	Day 14	Day 29	Wilcoxin Ranked Test
Urine Output (ml)		Mean ± S.D	Mean ± S.D	Mean ± S.D	
Group 1	7	1.53±0.13	1.53±0.13	1.53±0.13	0.6
Group 2	7	1.71±0.15	0.53±0.13	0.44±1.46	0.018
Group 3	7	1.74±0.15	1.24±0.18	2.74±0.15	1.000
Group 4	7	1.71±0.18	2.29±0.23	2.07±0.37	0.08
Group 5	7	1.71±0.27	2.07±0.42	2.09±0.50	0.249
Group 6	7	1.44±0.14	2.84±0.26	2.84±0.26	0.018

Group 1 Control
Group 2 Testosterone induced
Group 3 Testosterone +Dutasteride
Group 4 Testosterone+MECLS
Group 5 Testosterone+PECPS
Group 6 Testosterone+MECLS+PECPS

DISCUSSION

Studies have shown the anti-prostatic hyperplastic characteristics of Citrullus Lanatus (watermelon) and pumpkin seeds, underlining their individual therapeutic potential which is due to the presence of antioxidants and fatty components. In this research, BPH induction was confirmed on day 14 by assessing the physiological parameters i.e. body weight, urine output, prostate weight and prostate to body weight ratio which are described below. At the start of study, each animal weighed 145-194 grams and remained within this range in normal group. Testosterone BPH induction & prophylactic drug administration for 29 days produced significant results within some groups. Unopposed testosterone administration in the DC group led to a significant and gradual 22% weight gain within animals of this group. This was due to testosterone conversion to DHT which caused cellular multiplication and proliferation of adipose tissue, muscle & bone mass.[21]

In comparison, the other groups whether dutasteride, MECLS, PECPS or MECLS+PECPS treated groups no significant body weight change was noted throughout 29-day study period as exogenous testosterone was opposed by 5 alpha reductase inhibiting activity of dutasteride,[22] MECLS[23] & PECPS[24] which prevented DHT formation which causes weight gain. At the end of the study prostate was excised & weighed. In comparison with normal control group, there was increase in prostate size of about 19% in group 2 (DC) because of exogenous testosterone causing increase prostatic epithelial and stromal cell proliferation through increased DHT production. Exogeneous testosterone administration also resulted in increased prostatic tissue by its conversion into estradiol through estrogen receptor (ER) pathway.[25] However, Dutasteride treatment in group 3 led to a most significant 35% (p value <0.002) decrease in prostate size because of its well documented therapeutic 5 alpha reductase inhibiting activity. In comparison the MECLS, PECPS & MECLS+PECPS (groups 4-6) treatment resulted in a reduction of 10.8% & 8.8% each respectively (p value <0.001) versus normal healthy control group. Similar prostate weight reduction was found in treatment groups (3-6) as compared to DC group. The primary reason behind the decrease in prostate size by MECLS & PECPS was 5 alpha reductase inhibiting activity of both MECLS & PECPS which resulted in DHT reduction & shrinkage of prostate [22]. In addition to this, MECLS richness in vit C, a highly effective antioxidant, decreases prostate size by reducing oxidative stress [23] and PECPS being rich in fatty acids interrupt cell multiplication triggered by testosterone and DHT.[24] Our results are not comparable with other studies where either different dose of MECLS resulted in prostate, seminal vesicle and testes size reduction[25] against finasteride or different PECPS doses were used for testicular size and sperm count reduction.[26] The prostate and body weight ratio (P/BW) is considered a reliable marker of BPH having inverse proportionality to 5 alpha reductase inhibiting activity. In our study, P/BW ratio increased 4.2% (p value <0.016) in the testosterone induced hyper-plastic group[22] and 2.3-6.6% decreased for treatment groups (3-6) in comparison with control group. Similar results were seen when compared with DC group showing individual 5 alpha reductase inhibiting activity of Dutasteride, MECLS & PECPS. No comparable study was available to ratify or refute our results. Urine output was significant but gradually decreased by 70% to 74% in disease control (group 2) throughout the study period. As compared to the healthy control group it was 65% decreased with a p value < 0.005 due to the unopposed action of testosterone resulting in increased production of DHT, an important mediator of prostatic growth. DHT causes increased proliferation of epithelial & stromal cells causing obstruction to urinary outflow, thus reducing urinary output.[27] While in other designated groups (3-6) 29 days of oral prophylactic treatment with either Dutasteride, MECLS & PECPS resulted in marked significant increase in urine output ranging from 18,49 & 35% (p value <0.001) respectively versus DC & normal control group both, and even more with 85% maximum improvement in group 6, the combination group (MECLS+PECPS).

The prominent increase in urinary outflow by either MECLS or PECPS could be due to their 5 alpha reductase enzyme inhibiting activity, resulting in prostatic shrinkage caused by DHT depletion.[22] In addition to this, richness of MECLS in flavonoids & phenols was responsible for removing free radicals and

inhibiting hydrolytic & oxidative enzymes resulting in anti-inflammatory activity, prostate size reduction & thus improving urinary outflow.[24] PECPS contains β-Sitosterol, a plant sterol, which binds to the prostate resulting in the reduction in prostate swelling, inflammation and improved urinary output.[27] Thus, our study showed that both the plants (MECLS & PECPS) in combination have marked and even better potential in improving urinary outflow versus dutasteride.

Limitations

Although the study indicates positive effects of watermelon and pumpkin seed extracts, it did not provide a comprehensive assessment of their long-term safety. Toxicity studies and evaluations of potential side effects with extended use are essential to confirm the safe use of these extracts for managing BPH in the long term.

Future Study Prospects

Future research should investigate the molecular and biochemical pathways through which watermelon and pumpkin seed extracts exert their effects. Gaining insight into how these extracts impact prostate growth, hormone regulation, and urinary function will help confirm their therapeutic potential and enhance their clinical applicability.

CONCLUSION

A new, efficacious & safe alternative to dutasteride was determined in the BPH rat model. Preventive combination treatment with 1g/kg Methanolic Extract of Watermelon Seeds (MECLS) & 2.5g/kg Petroleum Ether extract of Pumpkin Seeds (PECPS) increased rat urinary output more rapidly than individual herbs 2g/ kg MECLS or 5g/kg PECPS underscored by prostatic weight reduction.

Ethical Consideration

This study was approved by Institutional Review Board of Federal Postgraduate Medical Institute, Lahore, Pakistan.

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Conflict of Interest

Authors declared no conflict of interest.

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DATA SHARING STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

AUTHORS' CONTRIBUTION
The following authors fulfill authorship criteria as per ICMJE guidelines;

Aslam BF, Zulfiqar T: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Maqsood S, Alam SS: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Naz N: Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Zia AE: Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.

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