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The Potential Protective Effect for Some Nutritional Sources of Lycopene on Prostatic Hypertrophy in Rats

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is hyperplasia of the stromal and epithelial layers of the prostate. The prostate has an important role in the success of fertilization in most mammalian species.

Objective: This studyaimed at evaluating the protective effect of lycopene, red pepper, and papaya extracts on prostatic hypertrophy in rats.

Materials and methods: Forty-two mature male albino rats were divided into 7 groups, each group had six rats. Group 1, control rats received only corn oil. In Group 2 (BPH), rats were given intraperitoneal (i.p.) injection of 5 mg/kg for 14 days of testosterone propionate (TP), dissolved in corn oil. Group 3 (BPH) rats were given 4 mg/kg/day of lycopene**.** Group 4 and 5 (BPH) rats were given 250 and 500 mg/kg/day of sweet red pepper fruit extract dissolved in distilled water. Group 6 and 7 (BPH) rats were given 250 and 500 mg/kg/day of papaya fruit extract dissolved in distilled water**.** The doses were given via gastric tube daily for 28 consecutive days. At the end of the experimental period, rats were sacrificed, and the weights of rats, feed intake, feed efficiency ratio, and prostate weights were recorded. Liver enzymes and sperm characteristics count were determined.

Results: Oral administration of lycopene, ethanolic extract of red pepper, and papaya fruits improved feed intake (FI), body weight gain % (BWG%), feed efficiency ratio (FER), prostate weight, liver enzymes, sperm count, and sperm motility.

Conclusion: Papaya fruits are a powerful remedy to normalize testosterone-induced BPH in rats.

Keywords: Benign Prostatic Hyperplasia, Feed intake, Prostate, Testosterone.

INTRODUCTION

The prostate is an auxiliary gland of the male reproductive system, and it also performs the role of a muscle-driven mechanical switch between ejaculation and urine. It is found in very few mammals. There are differences in its morphology, chemistry, and physiology amongst species [(1)].

Anatomically, the prostate—which is situated beneath the bladder—is where the urethra passes. It is called having zones in microanatomy and lobes in gross anatomy, respectively. It is composed of glandular and connective tissue and is enclosed in an elastic, fibromuscular capsule

Benign prostatic hyperplasia is the term used to describe the enlargement of the prostate (BPH). When the prostate gland starts to proliferate, it happens. These additional cells cause the prostate gland to enlarge, narrowing the urethra and lowering urine flow. Prostate cancer and BPH are not the same thing, nor does BPH raise the chance of cancer. On the other hand, it may result in symptoms that degrade quality of life. BPH affects a lot of males over 50. It is unclear what causes BPH .The pathogenic process in older dogs and men appears to be endocrine-controlled and involves alterations in the metabolism of androgen and estrogen. Despite the fact that oxidative stress, lifestyle, and food are mentioned as risk factors [(3)].

BPH is regarded as a typical aging disorder, while the precise etiology is uncertain; changes associated with age may play a role. Within the male reproductive system, the prostate is a tiny, muscular gland that surrounds the urethra and produces the majority of the fluid known as semen [(4)].

At the height of a sexual encounter, the prostate's muscular movement helps push fluid and semen through the penis. Prostate enlargement is common in males and can occasionally result in symptoms as well as longer-term consequences. But there are remedies [(5)].

Testosterone is the male sex hormone that is generated in the testicles. The levels of the hormone testosterone are necessary for the healthy growth and operation of the male reproductive system. During puberty, testosterone helps boys develop stronger muscles, a deeper voice, and facial and body hair**.** It is known that the enzyme 5-alpha reductase catalyzes the enzymatic conversion of testosterone into its more active metabolite dihydrotestosterone in the prostatic cells of both men and dogs, which is the known cause of BPH [(6)].

Strong antioxidant lycopene may aid in preventing cell damage. Tomatoes, watermelons, guava, red oranges, and apricots all contain it. Some fruits and vegetables have a red color due to a carotenoid, a kind of organic pigment related to beta-carotene. Prostate cancer, inflammation of the prostate, excessive blood pressure, and high cholesterol are all treated with lycopene [(7)].

Papaya skin, pulp, and seeds are rich in phytochemicals, which rise in the skin and pulp as the fruit ripens. These phytochemicals include carotenoids, polyphenols, benzyl isothiocyanates, and benzyl glucosinates. The red flesh is primarily composed of

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lycopene, but the yellow skin is primarily composed of the carotenoids lutein and beta-carotene. Prunasin is another cyanogenic compound found in papaya seeds. Papayas offer a fantastic source of vitamin C, with just one medium fruit providing 224 percent of the daily needed dose**.** The lycopene content per every 100 grams is 1.8 mg **[8].**

The dried and ripened fruit pod of hot and spicy Capsicum types is known as red pepper. Because of the hot chiles that are grown along the Cayenne River in French Guiana, it is frequently referred to as Cayenne pepper. Red pepper is also known as chili pepper, hot pepper, red chilies, and chili pepper in addition to cayenne**.** Z-β-ocimene (13–3%), 2-hydroxy-2,5-dimethyl-3(2H), benzaldehyde (20.9–3%), and 2-methoxy-3-isobutyl-pyrazine (20.4–9%) furanone (12.7–2.5%), and β-ionone (12.1–0.9%) were the primary components of red pepper volatile oils, both fresh and dried. Because most other plants are unable to synthesis the carotenoids capsanthin and capsorubin, which are produced solely in red peppers, the red hue is caused by these compounds. More than 200 percent of your daily vitamin C needs can be met by eating red peppers. In addition to being a potent antioxidant, vitamin C facilitates iron absorption. For optimal absorption, consider mixing red peppers with your iron supply if you are iron deficient. A 100-gram serving of red peppers might contain anywhere between 1.5 and 8.6 milligrams of lycopene**[8]**. Thus, The current investigation's goal was to ascertain whether lycopene, red pepper, and papaya extracts could prevent rats' prostatic hypertrophy**.**

MATERIALS AND METHODS

1. Plant material and animals

Sweet red pepper and papaya fruits were graciously provided by the Giza, Egypt-based Agricultural Research Center. From the animal colony, 42 male albino rats weighing (150±10) grams were acquired from Vaccine and Immunity Organization, Helwan Farm, Cairo, Egypt. Clinically, the animals were healthy. For a week, they were adjusted to the experimental setup before the start of the trial. Throughout this time, the rats were kept in calm rooms with natural ventilation, a 12:12 light-dark cycle, and plastic cages with iron filter tops. As stated by **Reeves *et al.*, [9]** the rats were fed a standard meal and had unlimited access to water during the trial.

2. Chemicals, kits, and other required materials

El-Gomhoreya Company for dealing in drugs, chemicals, and medical equipment, located in Cairo, Egypt, supplied DL-methionine, cellulose, vitamins, minerals, casein, and other essential substances. The kits required for the biochemical assays were supplied by the Gama Trade Company for Chemicals in Cairo, Egypt. We bought maize starch and oil from Tanta City, Al-Gharbia Governorate Egypt's local market. We bought 50 mg of dietary supplement lycopene and testosterone propionate from NOVARTIS Pharmaceuticals (Cairo, Egypt).

3. Extract preparation

Fruits were dried in the oven at 55ºC and ground into a fine powder. Fruits powdered (1 kg) of the plant were extracted by soaking at room temperature six times with methanol (10 L), then the successive extraction was carried out by using ethanol(70%). Tow extracts were obtained and then concentrated to dryness under vacuum and reduced pressure using the rotary evaporator at 45ºC to achieve the dried ethanol extracts which were kept at 4ºC till further use. The yields of samples were 20.5% and 23.3% respectively according to **(Gaber *et al.*,2020).**

HPLC analysis was conducted using Agilent Technologies 1100 series liquid chromatography equipped with an autosampler and a diode-array detector. The analytical column was an Eclipse XDB-C18 (150 X 4.6 µm; 5 µm) with a C18 guard column (Phenomenex, Torrance, CA). The mobile phase consisted of acetonitrile (solvent A) and 2% acetic acid in water (v/v) (solvent B). The flow rate was kept at 0.8 ml/min for a total run time of 70 min, and the gradient program was as follows: 100% B to 85% B in 30 min, 85% B to 50% B in 20 min, 50% B to 0% B in 5 min and 0% B to 100% B in 5 min. The injection volume was 50 µl, and peaks were monitored simultaneously at 280 and 320 nm for the benzoic and cinnamic acid derivatives. Before injection, all samples were filtered through a 0.45 µm Acrodisc syringe filter (Gelman Laboratory, MI). Peaks were identified by congruent retention times and UV spectra compared with those of the standards **(Kim *et al.*, 2006).**

4. Study design

Seven groups, each with six rats, were created by random assignment of the rats. Group 1 (Negative control group): Only corn oil was given to the control rats. Rats in Group 2, positive control group, (BPH) were given injections intraperitoneally (i.p.) of 5 mg/kg for 14 days of testosterone propionate (TP), dissolved in corn oil, according to **Marghani *et al.* [11].** Group 3 (BPH) rats were given 4 mg/kg/day of lycopene **[12].** Group 4 and 5 (BPH) rats were given 250 and 500 mg/kg/day of sweet red pepper fruit extract dissolved in distilled water **[13].** Group 6 and 7 (BPH) rats were given 250 and 500 mg/kg/day of papaya fruit extract dissolved in distilled water **[14].** The doses were given via gastric tube daily for 28 consecutive days.

5. Sacrifice of rats and sampling

The following were calculated: feed intake, body weight gain, feed efficiency ratio, and relative organ weight at the conclusion of the study period according to **Chapman *et al.* [15].** The animals were permitted to fast for the whole

night following the final injection before being slaughtered while sedated with chloroform. To separate the serum, blood samples from each rat were taken and centrifuged at 3000 revolutions per minute for 10 minutes (r.p.m.). After being thoroughly separated, the serum was placed in clean, dry Eppendorf tubes and stored at -20°C for analysis. Every rat was carefully dissected to remove its prostate, which was then cleansed of any adhesive material using a 0.9% saline solution, dried with filter paper, and weighed.

6. Semen analysis and morphology

Semen was determined according to **Van der Horst and Maree, [16].** For every rat, two slides were used. Distribution was made of the sperm samples taken from the cauda epididymis. The samples were air dried and stained using the Diff-Quik staining method in order to examine their morphology. After that, the slides were inspected at a magnification of 100 using a light microscope. Each slide had 200 sperm cells analyzed, and the percentages of normal, head, and tail abnormalities were calculated using Equation (1) in accordance with **Ulfanov *et al.* [17]:**

Sperm morphology (%) Abnormal (head; tail) sperm count × 100/200

7. Biochemical analysis

The serum's levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured using the protocol outlined by **Bergmeyer *et al.* [18].** Alkaline phosphatase (ALP)was determined in the serum according to the method described by **Roy, [19].**

8. Ethical consideratios:

The International Ethical Guidelines for Biomedical Research and the National Institutes of Health's Guide for the Care and Use of Laboratory Animals were followed throughout all operations. (This experiment was carried out under Egyptian ethical codes for studies on experimental animals and approved by the Ethics Committee of Al-Azhar University. The experimental protocol was approved by the Nutrition and Food Science Department, Faculty of Home Economics, AL-Aahar University,Egypt.

9. Statistical Analysis

SPSS software For statistical analysis, (Version 20) was utilized. The results were shown as mean ± standard deviation (SD). The data were analyzed using the one-way analysis of variance (ANOVA) test. The significance of the mean differences was assessed using the Duncan test as a post-hoc test at $p<0.05$ **[20].**

RESULTS

1. Body weight gain %, feed intake, and feed efficiency ratio

Table 1 displays the studied rats, including their feed intake (FI), body weight gain percentage (BWG%), and feed efficiency ratio (FER). The data demonstrated that the FI, BWG%, and FER of positive control rats significantly dropped in contrast to negative control rats. In contrast to the group under positive control, however, the acquired data showed a significant rise in all treatment groups. The optimal feed efficiency ratio, body weight growth percentage (BWG%), and feed intake (FI) values (FER) of treated rats were found in groups treated with lycopene pure followed by groups treated with red pepper (500 mg/kg) and papaya (500 mg/kg) respectively.

Table 1. The protective effect of lycopene, red pepper, and papaya extracts on feed intake, body weight gain, and feed efficiency ratio in rats with prostatic hypertrophy (M±SD)

Parameters Groups	FI (g)	BWG (%)	FER
Group 1	19.15 ± 0.17^{d}	34.99 ± 2.22^{d}	0.10 ± 0.02^{c}
Group 2	17.75 ± 0.36^{a}	15.85 ± 3.16^{a}	0.05 ± 0.01^{a}
Group 3	19.12 ± 0.23^{d}	18.37 ± 2.79^{c}	0.06 ± 0.02^{b}
Group 4	18.37 ± 0.34^{b}	18.64 ± 1.99^{c}	0.06 ± 0.03^{b}
Group 5	19.00 ± 0.60^{d}	18.22 ± 2.95^{c}	0.06 ± 0.01^{b}
Group 6	18.84 ± 0.04^{bc}	17.36 ± 1.31^{b}	0.06 ± 0.02^{b}
Group 7	18.90 ± 0.28^{bc}	18.93 ± 1.14^{c}	0.05 ± 0.04^{b}

Means with different letters in the same column differ significantly at $p \leq 0.05$ using one one-way ANOVA test, while those with similar letters are non-significant.

FI(food intake) BWE(body weight gain) FER(feed efficiency ratio)

2. Prostates weight

Table 2 declares prostate weight that was significantly higher in control (+) than in control(-); however, it was significantly decreased in all treatments other than control (+). The best lower Prostate weights were found in groups treated with lycopene pure followed by groups treated with red pepper (500 mg/kg) and papaya (500 mg/kg) respectively.

Table 2. The protective effect of lycopene, red pepper, and papaya extracts on prostate weight in rats with prostatic hypertrophy (M±SD)

Parameters Groups	Prostate weights (gm)
Group 1	**0.21 ± 0.03^{a}**
Group 2	**0.55 ± 0.06^{e}**
Group 3	**0.31 ± 0.01^{b}**
Group 4	**0.45 ± 0.02^{d}**
Group 5	**0.37 ± 0.03^{c}**
Group 6	**0.44 ± 0.02^{d}**
Group 7	**0.36 ± 0.03^{bc}**

Means with different letters in the same column differ significantly at p≤0.05 using one one-way ANOVA test, while those with similar letters are non-significant.

3. Liver functions

Table 3 displays the plasma ALT, AST, and ALP concentrations for the different groups under investigation. Rats exposed to a substantial change in liver biomarkers showed ***different changes for plasma*** to the BPH group (positive control (+)) in contrast to typical rats (negative control (-)). Liver indicators significantly increased in BPH rats. Conversely, when compared to the BPH group, the mean values of these liver biomarker indicators significantly decreased for all treatment groups. The best results for plasma ALT, AST, and ALP levels were found in groups treated with lycopene pure followed by groups treated with red pepper (500 mg/kg) and papaya (500 mg/kg) respectively**.**

Table 3. The protective effect of lycopene, red pepper, and papaya extracts on serum liver enzymes (ALT, AST, and ALP) in rats with prostatic hypertrophy (M±SD)

Parameters Group	**ALT (U/L)**	**AST (U/L)**	**ALP (U/L)**
Group 1	28.33 ± 4.11 ^{a}	96.15 ±14.02^{a}	236 ± 11.50 ^{a}
Group 2	73.66 ± 5.50 ^{f}	239.97 ±17.00^{e}	391 ± 16.25 ^{f}
Group 3	39.66 ± 5.76 ^{b}	123.52 ± 13.61 ^{b}	257 ± 21.50 ^{b}
Group 4	56.66 ± 4.30 ^{e}	175.84 ± 16.66 ^{c}	352 ± 15.63 ^{e}
Group 5	44.66 ± 2 .50^{c}	163.44 ± 11.77 ^{c}	292 ± 10.61 ^{c}
Group 6	59.33 ± 4.16^{e}	183. 66 ± 28.05^{cd}	358 ± 8.08 ^{e}
Group 7	48.66 ± 4.60^{cd}	168.35 ±17.06 ^{c}	315 ±12.25 ^{d}

Means with different letters in the same column differ significantly at p≤0.05 using one one-way ANOVA test, while those with similar letters are non-significant.

ALT(serum alanine aminotransferase) AST(aspartate aminotransferase) ALP(alkaline phosphatase).

4. Semen analysis and morphology

Data found in table (4) declared levels of plasma sperm motility (%), abnormal sperm morphology (%), and sperm count (10^6/ml). Rats exposed to BPH group positive control (c+) showed a notable change in sperm count (10^6/ml) and sperm motility (%) as compared to negative control. The mean values of sperm count increased significantly in all treatment groups (10^6/ml), sperm motility (%) as compared to the BPH group positive control. The best results for sperm count (10^6/ml), sperm motility (%) were found in groups treated with lycopene pure followed by groups treated with red pepper (500 mg/kg) and papaya (500 mg/kg) respectively. In the same table, abnormal sperm morphology (%) recorded a significant increase in rats exposed to BPH in comparison to the normal group. Also, there was a significant decrease in rats administrated with lycopene pure followed by groups treated with red pepper (500 mg/kg) and papaya (500 mg/kg) respectively.

Table 3. The protective effect of lycopene, red pepper, and papaya extracts on sperm count, sperm motility (%), and abnormal sperm morphology in rats with prostatic hypertrophy (M±SD)

Parameters Groups	Sperm count (10^6/ml)	Sperm motility (%)	Abnormal sperm morphology (%)
Group 1	114 ± 9.36^{e}	93.33 ± 2.88	5.3 ± 0.1 ^{a}
Group2	58.1 ± 4.80 ^{a}	66.66 ± 2.88	21.66 ± 1.88^{e}
Group3	97.96 ± 11.61	90.3 ± 4.4 ^{d}	7.66 ± 0.51 ^{b}
Group4	73.06 ± 5.49 ^{b}	75.4 ± 2.2 ^{b}	15.32 ± 1.0^{d}
Group 5	91.66 ± 11.10	86.66 ± 2.88	8.31 ± 2.51^{b}
Group6	70.66 ± 5.30 ^{b}	76.6 ± 2.56 ^{b}	16.3 ± 1.73^{d}
Group7	85.13± 8.54^{c}	85.4 ± 3.3 ^{c}	10.15 ± 1.00^{c}

Means with different letters in the same column differ significantly at p≤0.05 using one one-way ANOVA test, while those with similar letters are non-significant.

DISCUSSION

In this work, we looked into potential for protection of lycopene, red pepper, and papaya extracts from prostatic hypertrophy in rats. BPH is defined as an increase in prostatic stromal and epithelial cells that causes a noncancerous enlargement of the prostate. BPH, one of the most common diseases worldwide, starts to show symptoms around age 40 and increases in risk as people age **(21).** Rats with TP-induced BPH in this study had higher prostate weight and significantly lower FI, BWG%, and FER. These outcomes concur with

Sasidharan *et al.*, [22]. They discovered that, in comparison to normal control rats, animals prostatic epithelial hyperplasia, increased DHT and PSA levels, and greater absolute and relative prostate weights were seen in patients with TP-induced BPH. A hormone-related illness called BPH is brought on by an imbalance between the effects of androgen and estrogen **[23].** Prostate development and growth are primarily influenced by androgens**.**-mediated signaling. Furthermore, testosterone contributes to prostatic enlargement in BPH and is essential for the development of male reproductive organs **[24].** The more active metabolite DHT is produced by the prostate's type 1 and type 2 5 a-reductase isoenzymes from testosterone. The transcription of several peptide growth factors, including insulin-like growth factor 1, epidermal growth factor, fibroblast growth factor-related proteins, and many more, is subsequently responsible for activating the androgen receptor (AR) **[25].** Weight gains in the liver and body were considerably inhibited by high-dose TP therapy. The prooxidative-antioxidative balance, the liver antioxidant barrier, and the liver enzyme levels were all considerably disrupted by high-dose TP therapy **[26].**

Oral administration of lycopene, red pepper ethanolic extract, and papaya fruits increased feed intake (FI), feed efficiency ratio (FER), and body weight gain percentage (BWG%) and prostate weight in the current study as well. These outcomes concur with **Ugwor *et al.* [27].** They discovered that the increased anthropometrical and nutritional parameters of obese rats were reduced in a dose-dependent manner after receiving lycopene treatment **[28].**

GSH levels rose while AST, ALT, and MDA levels dropped following lycopene treatment. Lycopene also lessens the histological alterations in the rats' livers caused by acrylamide.

Jiang *et al.* [29] discovered that lycopene therapy can prevent liver damage and the rise of liver function indicators. Additionally, it markedly increased GSH and decreased MDA, indicating that lycopene's antioxidant activity contributes to both its hepatoprotective and ameliorative effects against hepatotoxicity induced by acrylamide. **Cao *et al.* [30]** observed that, the lycopene group's levels of AST, ALT, TG, and TC were considerably lower than those of the model group. The presence of lycopene in the mother's blood may be the cause of the lycopene's ability to alter blood lipid and cholesterol levels. According to reports, lycopene has the ability to prevent low-density lipoprotein from oxidizing, suppress HMG-CoA reductase expression, increase the activity of the low-density lipoprotein receptor on macrophages, and potently neutralize free radicals. Since adipose tissues are where lycopene is primarily stored, reducing the generation of cytokines, which are frequently produced by adipose tissues, can reduce the risk of obesity-related disorders **[31].** Capsiate treatment in red pepper fruit improves liver enzymes**.** Other carotenoids such as lutein, lycopene, capsanthin, and capsorubin are also abundant in pepper fruits. Mature pepper fruits contain capsanthin, the primary carotenoid that gives them their red hue. This pigment is well-known for its ability to reduce obesity and atherosclerosis as well as its anticarcinogenic qualities **[32].**

This is in agreement with the findings by **Rao *et al.* [33]** who reported that, in comparison to the control group, the broiler male chickens' feed efficiency and body weight increase percentage were dramatically enhanced. Papain, which it contains, may be the cause of the improvement. **Awodele *et al.* [34]** discovered that, in comparison to control rats given CCl4 alone, rats pre-treated with extracts of C. Liver indicators were found at lower serum levels in papaya (fruits and leaves). By stopping the hepatic inflammatory tissue caused by high fat from producing an excessive amount of proinflammatory cytokines and activating them, papaya can lessen liver inflammation. The mechanism could stem from papaya's indirect ability to lower ROS and regulate the excessive cytokine production.

Additionally, injection of TP-induced BPH caused the motility and count of sperm to significantly decline (%) in the current investigation. These outcomes concur with **Koşal and Gülyüz [35]** and El-**Sherbiny *et al* . [36]** who discovered that testosterone considerably raised the fraction of aberrant sperm and reduced sperm motility in groups treated with the hormone as compared to control groups. In a dose-dependent way, testosterone administration raises aberrant sperm rate and damages sperm DNA. It is believed that ROS-mediated lipid peroxidation results in sperm DNA damage, lipid matrix degradation, and sperm morphological degeneration**.**

In our investigation, administration of lycopene, sweet red pepper, and papaya fruits improved sperm count and sperm motility. This is in agreement with the findings by **Bintara et al. [37]** who discovered that adding tomato extract to an egg yolk citrate diluent might enhance the spermatozoa's motility and viability, among other qualities of liquid semen. By increasing the antioxidant capacity of sperm, lycopene and lycopene-rich foods like papaya and red pepper fruits are thought to improve male infertility. This theory has led to a few animal and clinical investigations**.** One of the vegetables with the highest lycopene content is red pepper, which has been found to help prevent lung and prostate cancer, among other malignancies**.** Based on epidemiological studies, eating foods high in lycopene may reduce the incidence of breast cancer **[38].**

Beta-carotene, an antioxidant found in papayas, may reduce the risk of cancer. Beta-carotene-rich diets may shield younger men from prostate cancer **[39].**

CONCLUSION

The current study provides evidence that oral delivery of papaya fruits, ethanolic red pepper extract, and lycopene enhanced feed efficiency ratio (FER), prostate weight, feed intake (FI), and body weight gain percentage (BWG%), as well as enhances sperm motility, sperm count, and liver enzymes. They are an effective treatment to return rats' testosterone-induced BPH to normal.

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