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The Therapeutic Effects of Pumpkin (*Cucurbita pepo L.*) Seed Oil for Management of Benign Prostate Hyperplasia Condition in Dogs

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Abstract

Background: The oil from the pumpkin (Cucurbita pepo) seed is claimed to be useful in the management of benign prostatic hyperplasia. This investigation seeks to examine the effect of pumpkin seed oil on testosterone-induced hyperplasia of the prostate in a dog model.

Materials and methods: A total of 6 sexually mature male stray dogs (age: 2-4 years old; weight: 20-25 kg) were housed at the Animal Reproduction Research Institute. Animals were subdivided into 2 equal groups; Control group: continued to receive the same diet without treatment until the end of the study, BPH group: received Testosterone (75mg/dog) (Testonon®250: 0.3 ml/dog) and Estradiol Benzoate (0.75mg/dog) (Folon®: 0.2 ml /dog) via intramuscular injection on days 0, 21, 42, and 63 of the induction periods. The testosterone doses were doubled on days 21, 42, and 63. The same animals (n=3) were taken as Pumpkin treated group: this was a PBH group treated with the Pumpkin seed extract at the dose of 600 mg pumpkin seed oil for 30 days. Blood sampling was performed from the cephalic vein into plain glass tubes on days 0, and 63 before the injection of hormones during induction and after treatment.

Results: Length, depth, height, and volume were significantly higher in the BPH disease group compared to the control group. Moreover, all these physical characteristics were decreased significantly in the Pumpkin treated group. PSA showed a statistically significant increase in the BPH-diseased group (.055±.005 mg/ml) compared to the control group and decreased significantly in the pumpkin-treated group (.024±.001 mg/ml) with no significant change in the testosterone level.

Conclusion: The present study demonstrates that pumpkin seed oil extract effectively mitigates the growth and hyperplasia associated with benign prostatic hyperplasia as evidenced by substantial reductions in prostate length, depth, height, and volume, along with decreased PSA levels.

Keywords: Benign Prostatic Hyperplasia; Pumpkin, PSA, Ultrasound; Dogs

Abbrevations

BPH: Benign Prostatic Hyperplasia; PH: Prostatic Hyperplasia; PSO: Pumpkin Seed Oil; PSA: Prostate-Specific Antigen; PV: Prostatic Volume; SD: Standard Deviation; DHT: Dihydrotestosterone; INOS: Inducible Nitric Oxide Synthase.

Introduction

Benign prostatic hyperplasia (BPH) is the predominant prostatic condition in canines. Pathologists exhibit a lack of consensus over the term "BPH." The phrase "benign" in "benign prostatic hyperplasia" seems superfluous, since hyperplasia inherently refers to benign growth. Nonetheless, the designation BPH is well recognized in global literature. Prostatic hyperplasia (PH), or (BPH), starts as a glandular hyperplasia process that may commence around the age of 2 to 3 years. In intact canines older than 9 years, it impacts nearly 95% of the population [1]. This syndrome is a component of the typical aging process and may include both hyperplastic and hypertrophic phenomena.

Histologically, PH may be categorized into two entities: glandular hyperplasia and complicated hyperplasia. The pH is intricately linked to hormonal stimulation in the prostate, indirectly via estrogen and directly via DHT. Estrogen enhances the expression of DHT receptors, while DHT directly facilitates prostatic development by attaching to the epithelial cell receptors of prostatic cells. Furthermore, older dogs may have elevated testosterone synthesis from the testes, which is then transformed into DHT in the prostate.

Numerous dogs afflicted with PH have no clinical symptoms until the prostate enlarges enough to impede fecal passage due to rectal compression. The predominant clinical manifestations of PH include hematuria, constipation, blood-tinged urethral discharge, and hemospermia. Ultrasonography is useful to assess the degree of lesions in the prostate, which may have a honeycomb look owing to many cysts or present as symmetrical hyperplasia, perhaps including cysts.

Neutering is the most successful and recommended therapy for PH in most dogs, resulting in a 50–70% reduction in prostate volume three weeks post-surgery; however, total reduction may need up to one month. Pumpkin seed oil (PSO) is a regional delicacy produced in southeastern Austria and other areas of Europe that were historically part of the Habsburg monarchy. PSO is physically extracted from the seeds of a certain type of Cucurbita pepo, either *C. pepo var*. styriaca or *var. oleifera*, characterized by an underdeveloped seed coat.

Pumpkin seeds include significant phytoestrogens, including secoisolariciresinol and lariciresinol, which may enhance estrogenic effects and are implicated in the enhancement of fat metabolism, bone remodeling, and the development of mammary gland and uterine epithelial cells. Due to liver tissue damage caused by alternative synthetic estrogen replacement hormone treatment, pumpkin seeds may serve as a viable substitute for hormone therapy in women [2]. Research using animal models utilizing hydroalcoholic extracts of pumpkin seeds demonstrated their advantageous impact on ovulation while preserving liver and kidney integrity [3].

Pumpkin seeds have several actions, such as anti-diabetic, antihypertensive, anticancer, immunomodulatory, antibacterial, antiviral, anti-hypercholesterolemic, intestinal antiparasitic, anti-inflammatory, wound healing, and analgesic properties. The seeds serve as a stimulant, alleviate chest discomfort, bronchitis, and fever, satisfy thirst, benefit cognitive function, and are used for renal issues [4].

This research aims to assess the therapeutic efficacy of pumpkin seeds in treating (BPH) in dogs.

Materials and Methods

Experimental Location

The present study was conducted at Animal Reproduction Research Institute, Egypt from September 2022 to December 2022.

Experimental Animals and Management

This research used six sexually mature male stray dogs (n=6), aged 2-4 years and weighing 20-25 kg. Throughout the trial, all animals were accommodated in enclosures with concrete flooring and a covered outside shelter that prevented exposure to direct sunlight. The dogs were provided commercial dry meal once daily and had unrestricted access to water throughout the day. One tablet of praziquantel and pyrantel pamoate (10 kg/body weight) was administered as an anti-parasitic agent during the first two weeks of preparation (Prazitab®).

Experimental Design

The subjects were categorized into two equivalent cohorts: the Control group (n = 3), which maintained the dog on a consistent diet throughout the research, and the (BPH) group (n = 3).

Induction of BPH

This experiment consisted of two sequential phases: a 63-day (BPH) induction phase and a one-month therapy

phase. On days 0, 21, 42, and 63 of the induction periods, dogs received intramuscular injections of testosterone (75 mg/dog) (Testonon®250: 0.3 ml/dog, Nile Pharmaceutical Company) and estradiol benzoate (0.75 mg/dog) (Folon®: 0.2 ml/dog, Misr Pharmaceutical Company) to induce BPH (day 0 being the initial hormone injection). The testosterone dosages were increased twofold on days 21, 42, and 63 [5]. The induced (BPH) has been validated using prostate volume assessment via B-mode ultrasonography and elevated prostate-specific antigen (PSA) levels. The same animals (n=3) were designated as the pumpkin-treated groups. This BPH dog was given 600 mg of Pumpkin seed oil per day (Pepon®: 2 capsules daily for one month, MEPACO) to treat BPH [6].

Ultrasonography Examination

B-Mode Ultrasonography

The trans-abdominal prostatic ultrasonographic evaluation was conducted using a 7.5 MHz transducer (Esaote MyLab Gamma, Italy). All machine settings, including focal depth and gain, were determined at the first examination for optimal picture quality and kept unchanged for all subsequent tests conducted during the test. Each dog had examination without sedation and was placed in dorsal recumbency [7,8]. Following cleansing and washing, hair was trimmed and shaved on both sides of the prepuce, and coupling gel was applied to the skin to enhance contact. The transducer was positioned on the abdomen wall near the prepuce to get longitudinal and transverse pictures of the prostate.

Ultrasonographic Measurements

The subsequent parameters were assessed in sagittal and transverse images before to and during the administration of pumpkin seed oil treatment. Prostatic volume (PV) was assessed using the bladder as a reference point, measuring height and length in the sagittal plane and breadth in the axial plane [9].

- Prostatic length was measured on sagittal imaging and is defined as the gland's maximal diameter along the urethral axis.
- Prostatic height was measured on both sagittal and transverse imaging and is defined as the diameter of the prostate on a line separating the gland's two lobes.
- The prostatic width was assessed using transverse imaging and is defined as the maximum diameter perpendicular to the height axis.

The size of the prostate is often assessed by measuring the greatest total prostatic width from transverse plane pictures or by calculating the PV using the elliptical volume formula: Volume = length x width x height x 0.523 [10].

Blood Sampling and Biochemical Assays

Blood samples were collected from the cephalic vein into simple glass tubes on days 0 and 63 before to hormone administration during induction and post-treatment. Blood serum was obtained by centrifuging blood samples at 3000 rpm for 10 minutes. At the conclusion of the investigation, serum samples were preserved at -20°C. Serum testosterone (T) was quantified using commercial ELISA kits (DiaSino Laboratories Co., Ltd., Zhengzhou, China) according to the makers' instructions. The coefficients of variation for intra-assay and inter-assay were 3.3% and 4.8%, respectively. The test sensitivity was 0.05 ng/mL. Prostatic-specific antigen (PSA) levels were quantified via an enzyme immunoassay competition technique, culminating in fluorescence detection by ELFA (VIDAS® Total Prostate Specific Antigen (TPSA) kits, bioMérieux, France). The sensitivity of the PSA kit was less than 4.0 ng/ml.

Statistical Analysis

Statistical analysis was conducted with SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were expressed as mean and standard deviation (SD) and compared across the three groups using ANOVA (F) test with a post hoc Tukey test. Qualitative variables were expressed as frequency and percentage (%) and examined using the Chi-square test. A two-tailed P value of less than 0.05 was deemed statistically significant.

Results

Effect of Oral administration of Pumpkin seed oil on the volume of dog prostate

The data in Table 1 illustrates the alterations in the volume of a canine prostate gland as assessed by B-mode ultrasonography. A significantly significant difference ($P<0.05$) in PV was detected between the groups. A temporal escalation in PVwas seen, with peak volume occurring after 63 days in the BPH-affected group relative to the Pumpkin seed oil-treated and control groups. The PV in the Pumpkin seed oil treatment group was substantially ($P<0.05$) larger than that in the control group (Table 1).

Effect on Testosterone and PSA level

PSA exhibited a statistically significant elevation in the BPH-affected group relative to the control group. Furthermore, PSA levels dramatically dropped in the pumpkin-treated group relative to the sick group, while exhibiting a notable

rise compared to the control group (Table 2). Testosterone levels exhibited a statistically significant reduction in the BPH-affected group relative to the control group; however, no significant difference in testosterone levels was observed between the pumpkin-treated group and the diseased group, both of which demonstrated a significant decrease compared to the control group (Table 2).

Item	Control group	BPH group	PSO treated group
Prostatic volume (cm^3)	8.81 ± 0.53^c	27.16 ± 1.97^a	12.74 ± 0.80^b

Mean with different superscripts (a, b, c) within the same row was significantly different at P<0.05

Table 1: Effect of pumpkin seed oil on PVin dogs treated for (BPH) (Mean ± SEM).

PSO treated group	BPH group	Control	Item
1.30±0.05	1.66±0.08	4.13±0.52	Testosterone
0.024 ± 0.0005^b	0.055 ± 0.002^a	0.005 ± 0.0002^c	PSA

Means with different superscripts (a, b, c) within the same row were significantly different at P<0.05. PSA (prostatic specific antigen).

Table 2: Effect of Pumpkin seed oil on serum levels of PSA (ng/dl) and testosterone (ng/ml) in dogs treated for (BPH) (Mean ± SEM).

Discussion

The current investigation revealed that post-BPH induction, the BPH group exhibited a markedly greater mean length, depth, height, and volume relative to the control group, with a substantial reduction in PSA and testosterone levels.

BPH is a prevalent male condition characterized by the abnormal growth of prostate gland and muscle tissue due to aging, influenced mostly by androgens, particularly testosterone [11].

Upon dissociation from its plasma carrier protein, testosterone penetrates the prostate cell and is converted into dihydrotestosterone (DHT) by 5α-reductase. DHT binds to androgen receptors, promoting the proliferation and differentiation of prostate cells, which subsequently leads to hyperplasia of stromal and epithelial cells and (BPH) [12].

Conversely, in older men, a surplus of adipocytes elevates aromatase levels, hence enhancing the conversion rate of androgens to estrogens. Subsequently, they would engage estrogen receptors in the prostate, stimulating the proliferation of stromal and epithelial cell autocrine and paracrine pathways [13].

Consistent with our results, Bakam, et al. [14] reported that testosterone injection resulted in a considerable increase in prostate relative weight, prostate volume, and prostate epithelium height compared to normal rats, hence validating the establishment of BPH [15]. Prostate weight and volume are essential metrics for diagnosing (BPH) and for evaluating possibly advantageous substances. The BPH rat model is extensively used by the scientific community [16]. Consistent with expectations, finasteride, a selective inhibitor of type II 5-α reductase, used as the standard in this investigation, considerably mitigated the effects of testosterone after 28 days of cotreatment.

PSA is a glycoprotein synthesized by the phosphorylation of DHT in prostatic stromal cells. Eleazu, et al. [17] shown that a 28-day continuous dose of testosterone at 3 mg/kg body weight to produce BPH subcutaneously in rats is associated with an elevation in blood PSA levels. Simultaneously with this discovery, testosterone generated a notable elevation in PSA levels.

The current investigation shown that therapy with pumpkin seed oil extract considerably reduced the length, depth, height, and volume in comparison to the BPH group.

Vahlensieck, et al. [18] demonstrated a substantial reduction in prostate volume and size in the pumpkin-treated group relative to the BPH group, corroborating our findings.

Furthermore, Gossell-Williams, et al. [19] demonstrated that pumpkin seed oil derived from the seeds of C. pepo suppressed testosterone-induced hyperplasia of the rat prostate. The efficacy of pumpkin seed oil in the treatment of BPH may therefore include a direct suppression of prostate development.

The present research indicates that therapy with pumpkin seed oil extract significantly reduced PSA levels in comparison to the BPH and control groups. There was no notable difference in testosterone levels between the BPH and pumpkin groups.

Vahlensieck, et al. [18] observed same findings, indicating a substantial reduction in PSA levels in the pumpkin-treated group vs to the BPH group.

The two investigations Gossell-Williams, et al. [19-21] provide contradictory findings regarding the impact of pumpkin seed oil on PSA levels.

Despite the dosages of pumpkin seed oil being 320 and 390 mg in two trials, the results on PSA varied. The variations may be attributed to the chemical compositions of

pumpkin seed oils or the specific species of Cucurbita used for oil extraction. A significant disparity in the nutritional components of several pumpkin species or different cultivation regions has been found. The concentrations of vitamin E, vitamin C, β-carotene, minerals, fatty acids [22], and other primary constituents are influenced by species and cultivation region.

Various mechanisms have been suggested for the efficacy of pumpkin seed oil in (BPH). Prostatitis is associated with (BPH). The overexpression of NF-□B, inducible nitric oxide synthase (iNOS), activation of 5-lipoxygenase, cyclooxygenase-2 (COX-2), and the generation of cytokines and leukotrienes are linked to prostatitis [23].

The anti-inflammatory properties of pumpkin seed oil, along with its ability to defend against free radicals, enable pumpkin seeds to mitigate inflammation in prostatic glands [24]. The other hypothesized mechanism is the diuretic effects of pumpkin seed oil attributed to its fatty acid content. The mechanism of action involves the blocking actions of Δ-7 sterols against DHT and their inhibitory effects on the hyper-proliferation of prostate cells. Esterified Δ7-sterols exhibiting enhanced absorption in the human gastrointestinal system are efficacious medicines for the management of BPH. Pumpkin seed oil, either alone or in conjunction with phytosterol-F, may inhibit testosterone/prazosin-induced prostate enlargement in rats [25].

Daily dose of pumpkin seed oil (14 mg/kg) for 30 days decreased prostate development in testosterone-induced conditions, as reported in Food Reviews International. 5 BPH in a rat animal model. The administration of pumpkin seed oil to testosterone-treated animals mitigates degenerative tissue alterations, alleviates obstructive symptoms, and enhances their quality of life [26].

Conclusion

The present study demonstrates that that pumpkin seed oil extract significantly reduces the development and hyperplasia linked to benign prostatic hyperplasia, as shown by dramatic decreases in prostate length, depth, height, volume, and PSA levels.

Ethical Committee Approval

The Animal Reproduction and Artificial Insemination Research Institute, Egypt, committee granted ethical approval for the study. The animals during the experiment were handled in accordance with the Institutional Animal Care and Use Committee (IACUC), of Animal Reproduction Research Institute (ARRI), Egypt.

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