

2021

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Recommended Citation

Sadeghimanesh, Arezo; Gholipour, Sajedeh; torki, akram; Amini-khoei, hossein; lorigooini, zahra; and Habtemariam, Solomon (2021) "Inhibitory effects of *Nigella sativa* seed oil on the testosterone-induced benign prostatic hyperplasia in rats," *BioMedicine*: Vol. 11 : Iss. 1 , Article 2.

DOI: [10.37796/2211-8039.1083](https://doi.org/10.37796/2211-8039.1083)

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Cover Page Footnote

Abbreviations BPH: benign prostatic hyperplasia PI: prostatic index PV: prostatic volume PSA: prostate-specific antigen DHT: dihydrotestosterone MDA: malondialdehyde Ethics approval and consent to participate All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All stages of experimentation were carried out in accordance with the regulations of the ethic committee of shahrekord university of medical sciences (Ethics code: IR.SKUMS.REC.1394.28). Consent for publication Not applicable. Availability of data and material The data during the current study are available from the corresponding author on reasonable request. Competing interests The authors have declared that they have no conflict of interest. Funding This study was funded by Research and Technology Deputy of Shahrekord University of Medical Sciences (Grant no: 1826). The funders have no role in the design of the study, data collection, analysis, interpretation of data and in writing the manuscript Authors' contributions ZL contributed to the design of the study, supervised the research and manuscript editing, AS and HA helped the supervision and preparation of the manuscript. AS, SG and AT performed the experiments and data collection, and prepared manuscript drafting. All authors have read and confirmed the final version of the manuscript for publication. Acknowledgements The authors gratefully thank the Research and Technology Deputy of Shahrekord University of Medical Sciences and Medical Plants Research Center of Shahrekord University of Medical Sciences for all supports provided.

Inhibitory effects of *Nigella sativa* seed oil on the testosterone-induced benign prostatic hyperplasia in rats

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Abstract

Background: Benign prostatic hyperplasia (BPH) is the most prevalent disease of the prostate in elderly men. Since *Nigella sativa* has been reported to show various pharmacological effects, this study was conducted to examine the effect of *N. sativa* seed oil on experimental BPH.

Methods: The oil was extracted using the cold-pressing method. Fifty rats were divided into five groups of 10 each as follows: Group 1 orally (p.o.) received normal saline; groups 2–5 were castrated and subcutaneously received 5 mg/kg testosterone propionate for four weeks. Group 2, namely, BPH model, underwent no further treatment, Groups 3 and 4 were treated with 400 mg/kg and 800 mg/kg *N. sativa* seed oil, Group 5 received finasteride (0.5 mg/kg, p.o.) for 28 days. All groups received repeated testosterone injections for the following four weeks after BPH induction. After the treatments, rats were sacrificed and the prostate tissues removed. Wet weight, prostatic volume (PV) and prostatic index (PI) were determined. Serum prostate-specific antigen (PSA), dihydrotestosterone (DHT), malondialdehyde (MDA) and antioxidant levels were determined.

Results: Our results showed that oral treatment with 400 and 800 mg/kg *N. sativa* oil led to a significant decrease in PI, PV, DHT concentration, PSA, and serum MDA level, and also significantly increased serum antioxidant capacity.

Conclusions: The study demonstrated that the oil seed exerted anti-BPH effects which may be associated with its antioxidant properties *in vivo*.

Keywords: antioxidant level, benign prostatic hyperplasia, dihydrotestosterone, malondialdehyde, *Nigella sativa* seed oil, prostate-specific antigen

1. Background

Benign prostatic hyperplasia (BPH) is the most prevalent age-related disease of the prostate gland for men [1,2]. Its symptoms include urinary tract obstruction, frequent urination, urinary retention, decreased diameter of the urinary tube and pressure of urine flow, and dribbling at the end of urination [3,4]. The disease is characterized by prostate gland enlargement due to hyperproliferation of cellular

components such as mesenchymal cells. The most common drug treatments for BPH include the use of α -adrenergic antagonists, 5- α -reductase inhibitors and alternative therapies such as natural products [5].

Recent studies have shown the relationship between oxidative stress (OS) and BPH. As a measure of OS, the level of the lipid peroxidation indicator, malondialdehyde (MDA) increases in BPH patients while plasma antioxidants' are suppressed [6,7]. This implies that antioxidant therapies might have potential application in the management of BPH.

Received 26 May 2020; accepted 8 September 2020.
Available online 01 March 2021

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<https://doi.org/10.37796/2211-8039.1083>

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Alpha-adrenergic receptor blockers and 5-alpha reductase inhibitors cause side effects, and the high prices of some of these drugs have led to an increasing tendency to use natural compounds as a source of lead compounds for drug design for the treatment of BPH or as a supplementary drug. Studies showed that alternative and complementary treatment is remarkable options for the management of mild BPH patients including *Serona repen*, *Pygeum africanum*, and *Secale cereal*. There are several reasons for significant attitude for this global approach including their availability, low cost as well as showing better safety profile than the current pharmaceutical medications. Furthermore, due to the universal approach to returning to nature and the use of natural compounds in the treatment of incurable diseases, attention to plants along with other natural resources has increased, among these, it could mention to *Nigella sativa* that it is highly recommended by the researches [5].

Belonging to the plant family of Ranunculaceae, *Nigella sativa* is native to southwestern Asia, southern Europe, northern Africa and Iran [8,9]. Mainly cultivated for its black seeds, *N. sativa* has extensive applications as a spice and medicinal plant. The seeds are also rich sources of fixed oil, which is renowned for a high level of unsaturated fatty acids such as oleic, linoleic and linolenic acid. Previous studies have further reported that these fatty acids can prevent the proliferation of prostate cells induced by testosterone and DHT. Additionally, they are capable of inhibiting the 5- α -reductase, an enzyme drug target of DHT which is known to metabolise testosterone to dihydrotestosterone [10–12]. *N. sativa* has further been demonstrated to exert antioxidant and anti-inflammatory properties [13,14]. No evidence has yet been reported, however, on the use of this plant to treat BPH. This study was thus conducted to evaluate the effect of *N. sativa* seed oil on rat model of BPH.

2. Materials and methods

2.1. Preparation of *N. sativa* seeds and oil extraction

Cultivated *N. sativa* seeds were purchased from Shahrekord Agricultural Faculty, Shahrekord, Iran. Samples were cultivated in the region of (32° 21' 00" North, 50° 49' 00" East) where the average rainfall from cultivation to harvest is reportedly 5–7 mm. A voucher specimen (SKUMS-801) was approved by a botanical expert (Shirmardi, Hamzeh Ali, PhD. at the Iranian Research Center of Agriculture and Natural Resources, P.O. Box 415, Shahrekord) and

deposited in the Herbarium of Medical Plants Research Center affiliated to Shahrekord University of Medical Sciences. The seeds were kept in poly-ethene bags at 4 °C and then the dried seeds were extracted using screw less cold presses machine. The seeds were pressed at 50 °C with nozzle size 7 mm and speed of screw at 20 rpm. The crude oil gained was kept in an amber bottle to store in the freezer (–18 °C) until the next analysis [15].

2.2. Husbandry

Fifty male Wistar rats weighing between 200 and 250 g were obtained from the Pasteur Institute of Iran (Tehran, Iran). The animals were housed under 21–23 °C temperature and 12-h light and 12-h darkness cycles for seven days to acclimatize to the animal house. All stages of experimentation were carried out under the regulations of the ethic committee of shahrekord university of medical sciences (ethics code: IR.SKUMS.REC.1394.28).

2.3. Experimental design

2.3.1. Castration and testosterone-induced rat model of BPH

First, the rats were anaesthetized using 50 mg/kg phenobarbital and their testes were removed under sterile conditions. After castration, penicillin (7.14 × 10⁴ IU/kg body weight) was administrated intramuscularly according to a previously described method [2]. Seven days later, the animals subcutaneously received 5 mg/kg testosterone propionate daily for four weeks. Simultaneously, group 1, as negative controls, were administered with normal saline alone, group 2 were considered BPH model, groups 3 and 4 were orally treated with 400 and 800 mg/kg of the oil of *N. sativa* seed, respectively, group 5 were administered with 0.5 mg/kg oral finasteride and considered positive control [16]. The doses of *N. sativa* seed oil were selected according to previous studies [17,18]. All groups received repeated testosterone injections for the following four weeks after BPH induction (Fig. 1). After 28 days, the rats fasted for 24 h and blood samples were drawn from the abdominal aorta under deep anaesthesia. The prostate glands were then removed for further examinations. At the end of the experiments, rats were euthanized using a high dose of co-administered ketamine and xylazine.

2.3.2. Determination of prostate index (PI) and volume (PV)

After anaesthesia, the whole prostates were collected and immediately weighed. The prostate

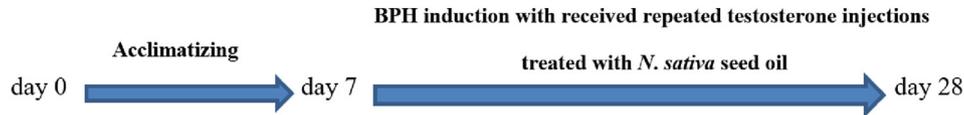


Fig. 1. Schematic of study design.

weight/total body weight ratio was considered to indicate PI [19] and the immersion of prostate in graded acetone was measured to indicate PV [20].

2.3.3. Measurement of prostate-specific antigen (PSA)

The PSA was measured by Biotin double antibody sandwich method utilizing an ELISA kit (Shanghai-cristal Day Biotech Co., China) according to the manufacturer's instructions.

2.3.4. Determination of dihydrotestosterone (DHT)

DHT was measured by mean of standard ELISA kits (Shanghai-cristal Day Biotech Co., China) according to the manufacturer's instructions (Shanghai-cristal Day Biotech Co., China). 10 µl of standard control and serum sample was poured into the plate and 50 µl biotin and 50 µl conjugate were added to them and incubated for 1 h at room temperature and then the plate was washed with a washing machine (Chrom, Asrs Atlantis Washer) and 100 µl of the substrate with the dye solution added to it and for the sample concentration determination was placed inside the Elisa reader. According to the OD standards, the diagram was drawn and the concentration of the samples in ng/ml was determined according to the diagram. From control serum was used for quality control of the kit and to ensure the accuracy of the test result, the concentration of control serum was considered in the range defined by the kit.

2.3.5. Determination antioxidant capacity of the serum

Blood samples were collected from all animals using cardiac puncture, and the serum was separated by centrifugation. The Ferric Reducing Ability of Plasma (FRAP) assay was applied for measuring the total serum antioxidant capacity. This method is based on the ability of the serum to reduce ferric-tripiridyltriazine (Fe^{3+} -TPTZ) to a ferrous form (Fe^{2+}), yielding a blue coloured complex (Fe^{2+} -TPTZ) with maximum optical absorbance at 593 nm [21].

2.3.6. Determination of serum MDA levels

For measuring serum MDA level, 0.5 g of thiobarbituric acid was dissolved in 80 ml 20% acetic acid and then the pH of the solution was set at 3.5 by using NaOH. The final volume of the assay was then

adjusted to 100 ml by addition of 20% acetic acid. Then, 100 µl of the serum sample was dissolved in 2.5 ml of the working solution and 100 µl of 8.1% sodium dodecyl sulfate (SDS). The samples were left in a water bath containing boiling water for 1 h and then cooled and centrifuged at 4000 rpm. The supernatant's optical absorbance was read at a wavelength of 523 nm [22].

2.4. Statistical analysis

The data were presented as mean ± standard error of measurement. Data analysis was performed by one-way ANOVA and Tukey's test using version 7 of the GraphPad Prism software. Data were considered statistically significant at the level of $P < 0.05$.

3. Results

3.1. The effect of *N. sativa* seed oil on PI and PV

As Figs. 2 and 3 illustrate, the highest PI and PV are observed in the BPH model group and the

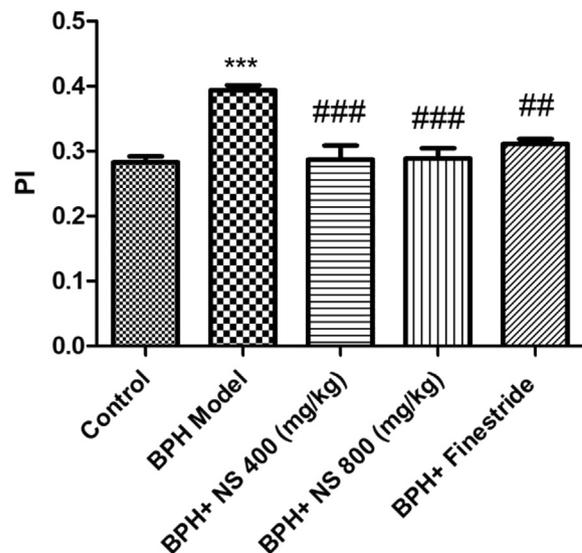


Fig. 2. Effect of *Nigella sativa* seed oil on prostate index; control: Healthy rats, BPH model: Rats with BPH, BPH+ NS 400 (mg/kg): Rats with BPH treated with 400 mg/kg *N. sativa* seed oil, BPH+ NS 800 (mg/kg): Rats with BPH treated with 800 mg/kg *N. sativa* seed oil, BPH+Finestride: Rats with BPH administered with 0.5 mg/kg finasteride; *** significant difference with control group ($p < 0.001$), ###,###,## significant difference with BPH group ($p < 0.001$, $p < 0.001$, $p < 0.01$).

lowest PI and PV levels in the control group ($p < 0.001$). Oral treatment with 400 and 800 mg/kg of the oil of *N. sativa* seed and finasteride significantly decreased the PI and PV when compared to the BPH model group ($p < 0.05$).

3.2. The effect of *N. sativa* seed oil on DHT and PSA concentrations

As shown in Figs. 4 and 5, the highest concentrations of DHT and PSA were observed in the BPH model group while the lowest DHT and PSA concentrations were evident in the control group ($p < 0.001$). Oral treatment with 400 and 800 mg/kg of the oil of *N. sativa* seed and finasteride significantly decreased the DHT and PSA concentrations compared to the BPH model group ($p < 0.05$). The level of DHT also decreased significantly and more markedly in both *N. sativa* seed oil-treated groups when compared to the finasteride-treated group ($p < 0.05$).

3.3. The effect of *N. sativa* seed oil on serum antioxidant capacity and MDA levels

As Fig. 6 illustrates the lowest serum antioxidant capacity level is observed in the BPH model group and the highest serum antioxidant capacity level in the control group ($p < 0.001$). Treatment with 400

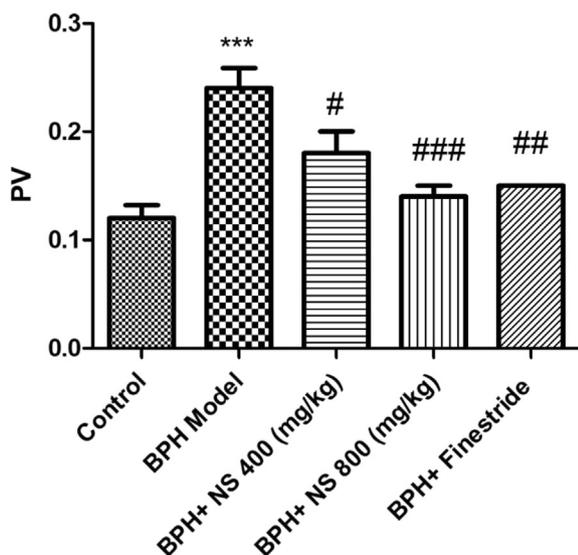


Fig. 3. Effect of *Nigella sativa* seed oil on prostate volume; control: Healthy rats, BPH model: Rats with BPH, BPH+ NS 400 (mg/kg): Rats with BPH treated with 400 mg/kg *N. sativa* seed oil, BPH+ NS 800 (mg/kg): Rats with BPH treated with 800 mg/kg *N. sativa* seed oil, BPH+Finestrade: Rats with BPH administered with 0.5 mg/kg finasteride; *** significant difference with control group ($p < 0.001$), #, ###, ## significant difference with BPH model group ($p < 0.05$, $p < 0.001$, $p < 0.01$).

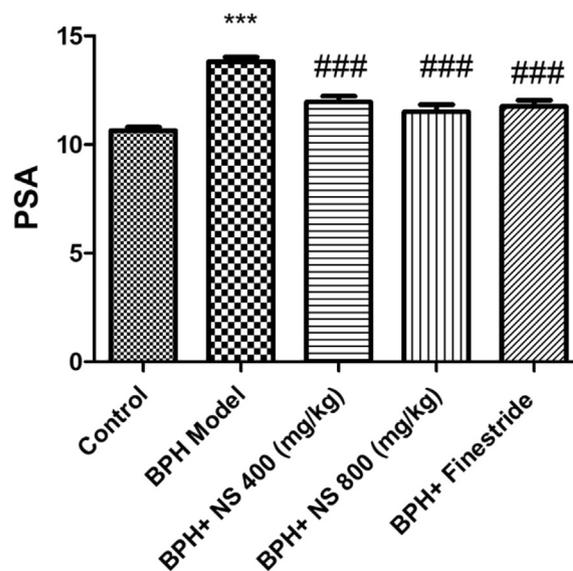


Fig. 4. Effect of *Nigella sativa* seed oil on dihydrotestosterone concentration; control: Healthy rats, BPH model: Rats with BPH, BPH+ NS 400 (mg/kg): Rats with BPH treated with 400 mg/kg *N. sativa* seed oil, BPH+ NS 800 (mg/kg): Rats with BPH treated with 800 mg/kg *N. sativa* seed oil, BPH+Finestrade: Rats with BPH administered with 0.5 mg/kg finasteride; *** significant difference with control group ($p < 0.001$), ### significant difference with BPH model group ($p < 0.001$).

and 800 mg/kg *N. sativa* seed oil and finasteride significantly increased the serum antioxidant capacity level concentration in comparison to the BPH model group ($p < 0.05$). The results showed that treatment with 800 mg/kg of the oil of *N. sativa* seed

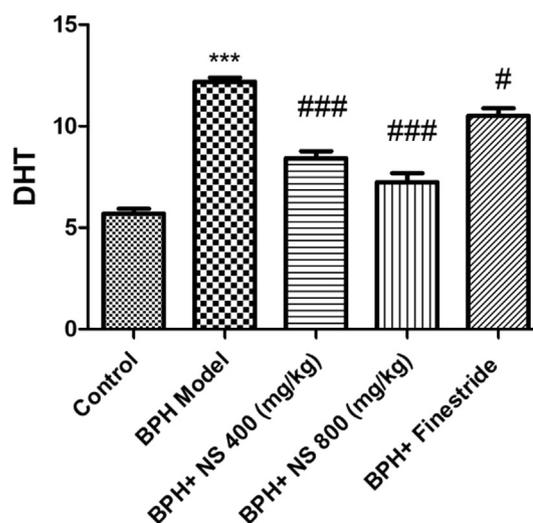


Fig. 5. Effect of *Nigella sativa* seed oil on prostate-specific antigen concentration; control: Healthy rats, BPH model: Rats with BPH, BPH+ NS 400 (mg/kg): Rats with BPH treated with 400 mg/kg *N. sativa* seed oil, BPH+ NS 800 (mg/kg): Rats with BPH treated with 800 mg/kg *N. sativa* seed oil, BPH+Finestrade: Rats with BPH administered with 0.5 mg/kg finasteride; *** significant difference with control group ($p < 0.001$), ###, ##, # significant difference with BPH model group ($p < 0.001$, $p < 0.001$, $p < 0.05$).

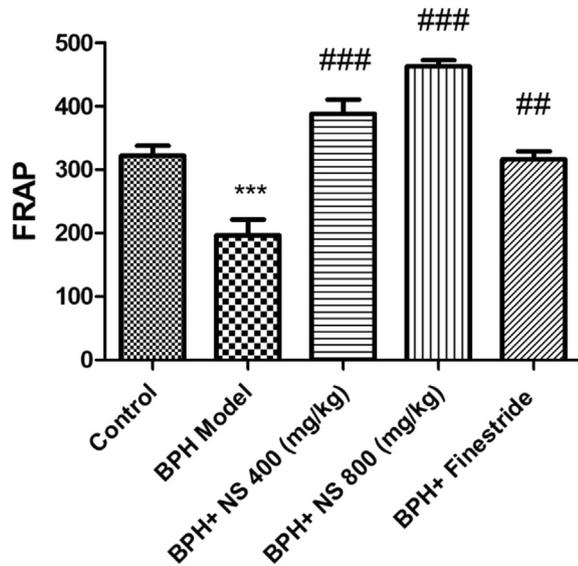


Fig. 6. Effect of *Nigella sativa* seed oil on serum antioxidant capacity; control: Healthy rats, BPH model: Rats with BPH, BPH+ NS 400 (mg/kg): Rats with BPH treated with 400 mg/kg *N. sativa* seed oil, BPH+ NS 800 (mg/kg): Rats with BPH treated with 800 mg/kg *N. sativa* seed oil, BPH+Finestrade: Rats with BPH administered with 0.5 mg/kg finasteride; *** significant difference with control group ($p < 0.001$), ###, ###, ## significant difference with BPH model group ($p < 0.001$, $p < 0.001$, $p < 0.01$).

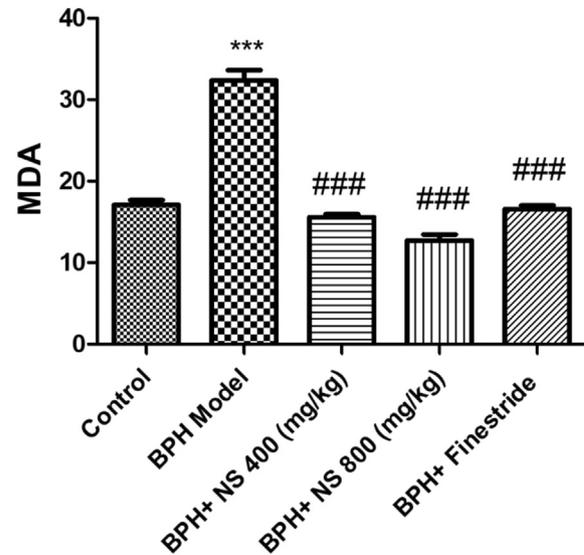


Fig. 7. Effect of *Nigella sativa* seed oil on malondialdehyde concentration; control: Healthy rats, BPH model: Rats with BPH, BPH+ NS 400 (mg/kg): Rats with BPH treated with 400 mg/kg *N. sativa* seed oil, BPH+ NS 800 (mg/kg): Rats with BPH treated with 800 mg/kg *N. sativa* seed oil, BPH+Finestrade: Rats with BPH administered with 0.5 mg/kg finasteride; *** significant difference between control group and other groups ($p < 0.001$), ### significant difference with BPH model group ($p < 0.001$).

significantly increased the serum antioxidant capacity when compared to the finasteride receiving group ($p < 0.001$).

Figure 7 illustrates the effect of oral treatment with *N. sativa* seed and finasteride oil on MDA concentration. the highest MDA level is observed in the BPH model group and the lowest MDA level in the control group ($p < 0.001$). Treatment with 400 and 800 mg/kg *N. sativa* seed oil significantly decreased the MDA concentration in comparison to the BPH model group ($p < 0.001$). Besides, 800 mg/kg *N. sativa* seed oil treatment led to a significant decrease in MDA concentration when compared to the finasteride-treated group ($p < 0.05$).

4. Discussion

The BPH is a non-malignant growth of the epithelial and stromal cells of the prostate gland. 5 α -Reductase inhibitors and alpha-1-adrenergic antagonists are two main agents commonly used to treat BPH. 5 α -Reductase is an essential enzyme that converts testosterone to dihydrotestosterone [23–25].

Finasteride is a classical 5 α -reductase inhibitor that decreases the DTH level, resulting in a decrease in the PV and symptoms of patients with BPH

[26,27]. It has been well established that α_1 -adrenoreceptor blockers relax prostatic smooth muscles thereby increasing urine flow while decreasing the prostate size and PSA [28]. The beneficial effects of medicinal plants in treating BPH have already been confirmed [8]. It has been well established that medicinal plants used to treat BPH decrease the plasma and prostate levels of the DHT and consequently suppress prostate weight and size [29]. In the current study and consistent with previous studies [3,26,28,30], we observed that induction of BPH led to increasing in PSA, DHT, PV, and PI in a rat model. Besides that, our findings showed that *N. sativa* seed oil treatment significantly mitigated these pathological markers that both doses of the 400 and 800 mg/kg showed this effective effect.

In the current study, treatment with 400 and 800 mg/kg of the oil of *N. sativa* seed decreased the DHT level. “Interestingly, we found that the *N. sativa* oil partially at least decreased the DHT level in the BPH model” more than that of finasteride. Hii-pakka et al. reported that treatment with polyphenols isolated from green tea decreased the DHT production, and inhibited prostate cells proliferation. Because *N. sativa* contains polyphenolic compounds [31], it can be argued that, at least, inhibition of 5 α -reductase contributes to the beneficial effect of this plant. The high amount of fatty acids of *N. sativa*

oil has essential unsaturated fatty acids (about 1% omega-3, 25% omega-9 and 58% omega-6) in abundance [10,12]. Abdel-Rahman et al. have argued that compounds rich in fatty acids could prevent prostate cells proliferation by lowering testosterone and DHT concentrations [9]. Liang et al. further demonstrated that fatty acids could inhibit 5 α -reductase [10]. It has been shown that increased prostate weight could be considered a marker to diagnose BPH, while PI is often used to determine the progression of BPH [20]. In the present study, both 400 and 800 mg/kg doses of the oil of *N. sativa* seed significantly decreased the PI and PV in BPH.

Recently, it has been demonstrated that PV and PSA concentrations can be used to predict prostate cells growth. In this regard, PSA can be considered as an alternative index for PV and as a marker to detect the risk of prostate carcinoma [20,32]. Hence, an increased PSA level represents an increased proliferation of prostate cells. In the current study, treatment with 400 and 800 mg/kg *N. sativa* seed oil significantly decreased the PSA concentration compared to the BPH model group. Ren et al. reported that polyphenols can suppress the level of expression of PSA genes [33]. *N. sativa*'s effect in decreasing the PSA may thus be related to the presence of polyphenols.

It has been determined that inflammation contributes to the pathophysiology of BPH because inflammatory factors such as monocyte chemoattractant protein-1 are overexpressed. Hence the levels of interleukin 10 receptor subunit alpha (IL-10RA) and Interleukin 8 receptor, beta (IL-8RB) rise in the BPH [34]. According to the study by Ragheb et al., thymoquinone isolated from *N. sativa* has an anti-inflammatory property and can decrease the expression of the above-mentioned inflammatory factors. It seems that *N. sativa* oil's effect can be to some extent attributed to the presence of thymoquinone in *N. sativa* and the anti-inflammatory property of this plant [35]. According to the study of Jonas et al., the antioxidant activities of plants help regulate cell proliferation and control in BPH [36]. It has been demonstrated that an increase in the level of MDA, which occurs in BPH, is a marker of lipid peroxidation and/or tissues damage. Increased MDA level in BPH has also been reported to be due to OS [6]. Hence, treatment with antioxidants may decrease the level of MDA and other pathological markers of BPH. In our study, treatment with 400 and 800 mg/kg of the oil of *N. sativa* seed decreased

the serum MDA level, which is consistent with the study by Hosseinzadeh et al. [37].

Also, in our study, treatment with 400 and 800 mg/kg of the oil of *N. sativa* seed increased the serum antioxidant capacity level. Houcher reported that the oral treatment with *N. sativa* extract can cause an increase in the FRAP capacity [38], which is consistent with our results.

Therefore, it seems that *N. sativa* oil's effects to inhibit lipid peroxidation and probably its anti-BPH effects are due to the presence of antioxidant and free radical-inhibiting compounds. The results on the serum MDA levels in the current study further demonstrated that these variables increased in the BPH group in comparison to the control group. In addition, the serum MDA levels decreased significantly in *N. sativa* oil-treated groups in comparison to the BPH group, which indicates the protective effects of the compounds present in the *N. sativa* oil could increase the antioxidant capacity of serum and decrease the level of MDA. It seems that this decrease in MDA levels is associated with the antioxidant capacity of the plant.

5. Conclusion

According to the current study, *N. sativa* seed oil in both doses of 400 and 800 mg/kg may have application in treating BPH by decreasing the concentrations of DHT and PSA, and PI and PV and exerting an antioxidant effect. Further studies are required to isolate and identify the active component(s) of the oil.

Funding

This study was funded by the Research and Technology Deputy of Shahrekord University of Medical Sciences (grant number 1826).

Conflict of interest

Dr. Iorigooini has nothing to disclose.

Acknowledgments

The financial support of the Deputy of Research and Technology of Shahrekord University of Medical Sciences is appreciated (Grant No: 1826). The authors of this study appreciate the Medical Plants Research Center Shahrekord, Iran and all laboratory experts in this study.

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