



The effect of Iranian licorice root extract on prostate volume and clinical signs of disease in patients with benign prostatic hyperplasia

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Abstract

Background and aims: Benign prostatic hyperplasia (BPH) is the most common benign tumor in men, and its prevalence increases with age. This study aimed to determine the effect of Iranian licorice root extract on prostate volume and clinical signs of BPH disease.

Methods: Sixty BPH patients over 40 years old with prostate volume above 30 mL, with symptoms of this disease without drug intervention, were included in the study. First, the Symptom Score AUA (AUASS) questionnaire was completed for all individuals, and then an ultrasound was performed on them. They were then randomly divided into two equal groups. For three months, the intervention group received two capsules of 250 mg of licorice extract daily, and the other group received two placebo capsules. After the study, sonography was performed, and the AUASS questionnaire was completed.

Results: 25 and 21 men with BPH in the intervention and placebo groups fully cooperated. At the beginning of the study, prostate volume ($P=0.14$) and AUASS were not significantly different between the two groups ($P=0.88$). Eventually, prostate volume decreased in the two groups, but the difference between the two groups was not significant ($P=0.33$). The AUASS score in the intervention group was significantly lower than the placebo group ($P<0.001$).

Conclusion: In the present study, the dose of licorice root extract reduced the symptoms of BPH. But further studies with a larger statistical population are needed for this extract to enter the clinic as a drug.

Keywords: Prostate volume, Clinical symptoms, Licorice root extract, Benign prostatic hyperplasia, Clinical trial

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Introduction

Benign prostatic hyperplasia (BPH) is the most common benign tumor in men, and its prevalence increases with age (1). The disease begins at age 30 and progresses gradually (2). Clinical studies have shown a direct relationship between prostate volume, blood-free testosterone, and estrogen levels (3,4). The link between aging and BPH is due to increased estrogen levels in aging and the stimulation of androgen receptors, making the prostate sensitive to free testosterone in the blood. However, so far, no studies have been able to prove an increase in estrogen receptor levels in human BPH (5). Also, some studies have pointed to the effect of family history and race on this disease (6,7). Since surgery is not possible in many cases, drug treatment can be the choice of many patients to treat or relieve the disease. The standard chemical treatment for this disease in non-surgical people is alpha-blockers. However, the high therapeutic potential of herbal medicines can be seen Because of the

high natural antioxidants (8). Most patients with BPH, in which Prostatic Cellular Composition in smooth muscle, responded better to treatment with α -blockers. In contrast, for BPH patients with Prostatic Cellular Composition in epithelial predominance, 5- α -reductase inhibitors were more effective. However, patients with significant collagen formations in the stroma may not respond to any treatment (9). Since the above chemical treatments have different effects and other side effects on these patients, finding more effective treatments with fewer side effects is considered. Licorice is one of the most widely used herbal medicines that effectively treat many diseases. Licorice, with the scientific name *glycyrrhiza glabra*, is one of the plants whose underground roots and stems have medicinal uses. Studies have shown the positive effect of two essential licorice compounds, glycyrrhizi, and glyceric acid, on the proliferation and metastasis of melanoma cells (10), prostate cancer (11), stomach (12), and breast (13). Research has also shown that licorice is

an anti-androgen herb and can reduce blood testosterone levels (14). On the other hand, the anti-androgenic properties of licorice have been displayed in the treatment of polycystic ovary disease (15). As mentioned, prostate volume increases with increasing levels of free testosterone and estrogen in the blood. Therefore, according to the anti-androgenic properties of *Glycyrrhiza*, it seems that the consumption of the root of this plant can lead to a decrease in testosterone levels, a reduction in prostate volume, and an improvement in BPH (16). Studies show that glycyrrhizic acid salt (a commercial metabolite of *Glycyrrhiza*) can effectively affect the steroidogenesis of sex hormones (including testosterone) by inhibiting 3β - and 17β -hydroxysteroid dehydrogenases and 17- and 20-dehydrolyases. Furthermore, it has been observed that glycyrrhizin can inhibit testosterone production in cultured testicular Leydig cells stimulated by luteinizing hormone. Although the data from investigating the effects of Na₂ GA and licorice extract on testosterone levels in men show conflicting results, the evidence indicates that these factors have estrogenic and anti-androgenic properties (17). Considering that Iranian licorice has the highest amount of glycyrrhizic acid (18,19), few clinical trial studies have been conducted on the effect of consuming this plant in patients with BPH. Different results have been obtained from these studies; therefore, this study investigated the impact of Iranian licorice root extract on prostate volume and Clinical symptoms in patients with BPH.

Materials and Methods

Statistical Society

This double-blind, randomized clinical trials study was performed on 60 men over 40 years old with BPH with a prostate volume of more than 30 mL and with symptoms

of this disease referred to the clinic of Khorshid Hospital in Isfahan in 2018 (Figure 1). Patient volunteers were randomly selected from among volunteers with a computerized random number list. All patients were given sufficient information about the study, and those who wished to participate filled out and signed an informed consent form to participate. The study protocol was approved by the ethics committee of Payame Noor University under the number IR.PNU.REC.2018.088.

Sample Size

The sample size was estimated using the following formula for randomized clinical trials (According to results of a previous study (20):

$$n = \frac{2(z_1 + z_2)\sigma^2}{d^2}$$

Inclusion and Exclusion Criteria

Inclusion criteria included the diagnosis of BPH with prostate volume above 40 cc on ultrasound. Exclusion criteria included abnormal premature chromosome condensation, suspected prostate cancer on rectal examination or prostate specific antigen test, neurogenic bladder, bladder stones, undergoing rectal examination, and patient failure to continue the study process.

Blindness

Patients, all those involved in care or treatment, and data collectors were blinded to the distribution of treatment. Only the observer of the trial data, who is not involved in patient treatment, care, or admission, was aware of the clinical trial and group treatment process.

Preparation of Aqueous Extract of Licorice

Licorice root number IAUNT17333 was obtained from

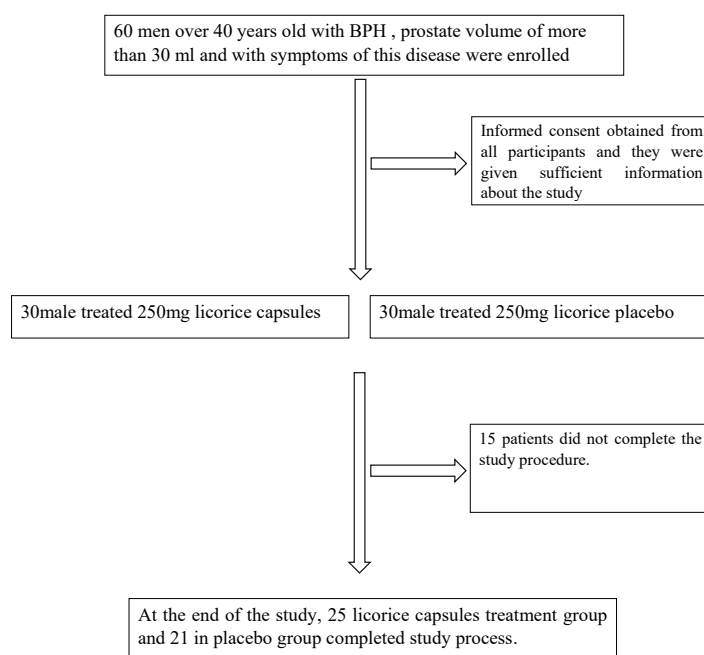


Figure 1. CONSORT flow diagram of the study

the Herbarium of Islamic Azad University, North Tehran branch. After cleaning and taking its flower and stem, it was cut into smaller pieces and dried at 25 °C for one week. Then the roots were ground with a hammer, powdered, and kept in a polyethylene bag in the freezer at -4 °C. Then one weight of root powder and four weights of water were poured into the Soxhlet apparatus and extracted. A rotary evaporator concentrated the extract and thoroughly dried it in an oven at 120 °C. Then, in a wholly disinfected mortar, the dry extract was ground, pulverized, and evaluated for the microbial load before use with 48 hours of culture in a nutrient agar medium. Landa Max was then calculated from an extract prepared by a UV device. After that, the powder solution obtained from licorice extract in deionized water was designed and standardized by the HPLC method using HPLC SY8100 with SY8100 software. Finally, we filled the shells of 250 mg capsules with the prepared extract and packed it; then, we used the same shell of 250 mg capsules to prepare a placebo.

Intervention Procedure

The patients were then randomly divided into two equal groups (30 patients in each group), i.e., intervention and placebo groups. Patients in the intervention group were given a capsule containing 250 mg of dry licorice extract, and patients in the placebo group were given a capsule containing 250 mg of chickpea flour, which were similar in appearance, size, and color. All patients were asked to take two capsules daily for 12 hours for three months. This study used a daily dose of 500 mg (two 250 mg capsules) of licorice extract because this dose had no side effects for patients. Because studies have shown that consuming 50 g of licorice per day for a long time will lead to potassium excretion and sodium retention and thus increase blood flow (21,22). However, 20% of the dried amount is extracted from licorice powder as an extract, and for 500 mg of extract, a minimal amount of licorice is used. This dose will not cause any side effects. Participants were contacted weekly. During each visit, they were asked to indicate whether they were taking the medication they were receiving.

Data Collection

At the beginning of the study, in addition to completing a demographic questionnaire for each patient, an AUASS questionnaire was conducted to determine the scores related to the seven clinical signs of the disease. This questionnaire was prepared by the American Urological Association and is assigned a score of 0 to 5 per patient based on the severity of clinical symptoms (23). Prostate ultrasound was then performed on all participants, and they were asked to use only the medication given to them in this study to treat their disease. After three months of study, the AUASS questionnaire was completed again, and the same doctor performed a prostate ultrasound for all in the exact center where the initial ultrasound was

performed. Patients' prostate volume was determined based on ultrasound results, and the severity of the disease was determined based on the AUASS score before and after the intervention.

Statistical Analysis

At the end of the study, the data of the two groups were entered into a file under SPSS software (Version 20) and statistically analyzed with the same software. After examining the normality of the data, to make comparisons between the two groups before and after the study, the Mann-Whitney non-parametric statistical test and also with the help of the Wilcoxon test, changes were made as a result of intervention in each group.

Results

Investigation of Properties of Licorice Extract

After 48 hours of culture, licorice extract prepared on an agar plate formed no colonies. This condition indicated that the licorice extract powder obtained was free of any microbes. Also, according to Figure 2, the best wavelength for the licorice extract used was 295 nm. According to its standard, the highest peak was related to glycyrrhizic acid, which showed that the active ingredient of glycyrrhizic acid was present in large quantities in our extract (Figures 2 and 3).

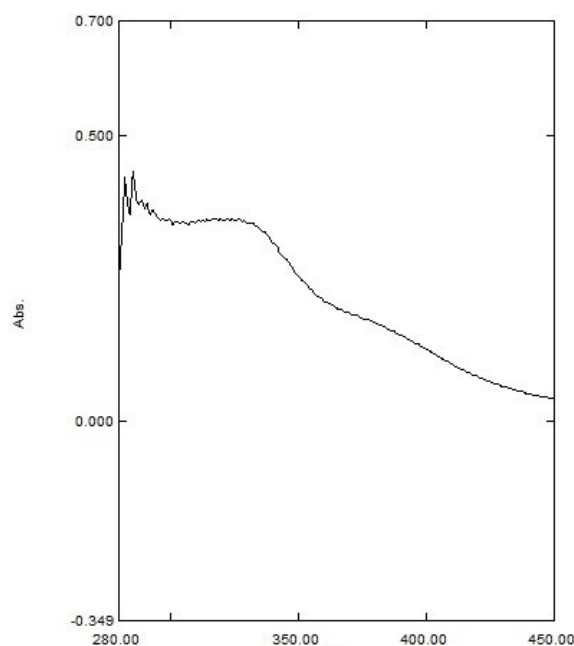


Figure 2. The wavelength of the desired extract by UV device

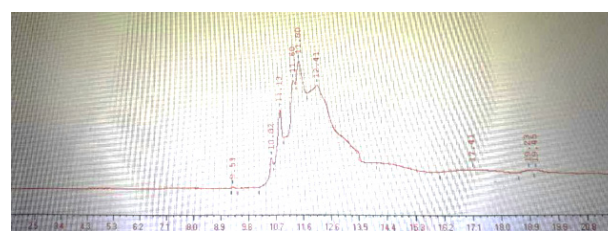


Figure 3. HPLC diagram of licorice root extract prepared and used in this research

Demographic information of the study population

Of the 60 samples studied, 25 in the drug group and 21 in the control group had full cooperation, and the rest were excluded at different times before the end of the study. Details are shown in Figure 1. The reasons for leaving the study included not taking a placebo due to not seeing a positive effect, the effect of the opinions of others on the process of taking the drug in the participating patients, bladder inflammation, prostatitis, and kidney stones in the study process. The mean age of the intervention group was 66.17±7.67 years, and the placebo group was 68.83±6.69 years (P=0.21). Demographic information is shown in detail in Table 1.

Mean prostate volume, AUASS score, and clinical symptom scores in the two groups before and after the intervention

Table 2 compares mean prostate volume and AUASS score in the two groups before and after the intervention. According to the data in this table, at the beginning of the study, prostate volume (P=0.88) and AUASS (P=0.95) were not significantly different between the two groups. At the end of the intervention, prostate volume decreased in the two groups, and the difference between the two groups was significant (P<0.001). The AUASS score decreased in both groups, but the difference between the two groups was not significant (P=0.87). Also, for intra-group comparisons, changes in prostate volume, and AUASS score, between the beginning and end of the study were examined separately for each group. In the intervention group, prostate volume (P=0.001) and AUASS score (P=0.02) were significantly reduced after the study. In the placebo group, prostate volume was insignificant from the beginning to the end of the study (P=0.62); however, although the AUASS score decreased, this difference was statistically significant (P=0.04).

Discussion

Based on the present study’s findings, licorice root extract reduced the clinical symptoms of BPH, including reducing the volume of the prostate and improving its symptoms, and finally, improving the disease. So far, several studies have been conducted in different countries on the effect of herbal medicine on diseases, and some of these plants have been introduced in clinics. In benign prostate cancer, the effects of herbs have also been studied. For example, many clinical trials have confirmed the effectiveness of cherry extract in relieving BPH symptoms (24,25). *Secale cereale* pollen has been reported to improve prostatitis symptoms

and reduce malignant prostate cancer symptoms, most likely through its anti-inflammatory effect by inhibiting the biosynthesis of prostaglandins and leukotriene (26,27).

Fu et al. examined the anti-cancer effect of licorice root on prostate cancer cells. They showed that licorice extract inhibits the growth of prostate cancer cells by inhibiting cyclin B1 and cdc2 (28). Another study showed the effect of licorice root on reducing menopausal symptoms in postmenopausal women (29). Since the anti-androgenic effect of licorice in males plays an essential role in reducing prostate volume by lowering testosterone, it seems to reduce the symptoms of BPH. In addition, Thirugnanam et al. showed that glycyrrhizin, the active ingredient in licorice, could induce apoptosis in prostate cancer cells. The results of our study, in line with these studies, showed the inhibitory effect of licorice extract on prostate cancer (11).

One of the limitations of using chemical drugs is their side effects. For example, in a double-blind clinical study, the effects of two doses of 1 and 5 mg of finasteride compared with a placebo were given to BPH patients for 12 months, and their urinary symptoms were evaluated (30). In this study, treatment of BPH with a daily dose of 5 mg finasteride significantly reduced obstruction symptoms, increased urine flow, and decreased prostate volume but impaired patients’ sexual function. While in our study, licorice root extract, in addition to improving urinary symptoms in a much shorter time, did not have any side effects on patients’ sexual function. One of the plants whose effect on BPH has been studied is the saw palmetto. In one study, two daily doses of 160 mg of Saw palmetto extract in BPH patients for one to three months reduced enuresis by 33% to 74% . Also, an 11 to 43% decrease in the frequency of urination during the day and an increase in the speed of urine flow due to the consumption of this plant extract were observed in these people. Comparing this dose of Saw Palmetto with the daily dose of 5 mg finasteride for six months, a similar effect was observed. Saw palmetto caused several gastrointestinal side effects, such as nausea and abdominal pain (31). However, licorice root extract used in the present study, in addition to treating BPH, also has a beneficial effect on gastrointestinal diseases and gastric ulcers (32,33). The active ingredients in Saw palmetto naturally inhibit 5α-reductase and prevent dihydrotestosterone from

Table 1. Demographic information of the study population

| Variable | Treated with licorice extract (Mean±SD) | Placebo Group (Mean±SD) | P value |
|----------------------------|---|-------------------------|---------|
| Age | 7.67±66.17 | 6.69±68.83 | 0.21 |
| Pre-treatment weight (kg) | 70.26±7.75 | 71±1.75 | 0.43 |
| Post-treatment weight (kg) | 67.26±7.75 | 69.80±1.75 | 0.24 |
| Height (cm) | 178±3.22 | 174.39±5.22 | 0.091 |

Table 2. Comparison of mean prostate volume and AUASS score between consumers of licorice root extract and placebo

| Variable | Treatment | Control | P (between) |
|------------------------------|-----------|----------|-------------|
| | Mean±SD | Mean±SD | |
| AUASS (Before study) | 4.2±1.0 | 4.0±1.91 | 0.95 |
| AUASS (After study) | 2.4±1.1 | 2.3±1.6 | 0.87 |
| P (within) | 0.02 | 0.04 | |
| Prostate size (Before study) | 19.6±6.3 | 18.9±7.9 | 0.88 |
| Prostate size (After study) | 10.3±6.3 | 18.6±8.1 | <0.001 |
| P (within) | 0.001 | 0.62 | |

binding to androgen receptors in the prostate gland, i.e., inhibit androgen and estrogen receptors (31,34). It should be noted that in our study, licorice extract reduced prostate volume, but this reduction was not significant. This may be due to the duration of the medication. Because to cause a substantial reduction in prostate volume, treatment should be continued for 6 to 12 months, while the time of intervention in our study was three months, and it seems that if continued for up to 6 months, the reduction would be significant. Also, the sample size may be effective in this conclusion, and this difference may be substantial with more sample size. The active ingredients of licorice root extract appear to inhibit the conversion of 17-hydroxyprogesterone to androstenedione by inhibiting the enzyme 17-hydroxysteroid dehydrogenase, reducing the production of the hormone dihydrotestosterone, and ultimately reducing prostate volume, facilitating urine flow. It also improves the symptoms of BPH and the disease itself.

Conclusion

Therefore, due to the further reduction of prostate volume and a significant reduction in AUASS score in people consuming licorice root extract compared to placebo, the positive effect of this plant on BPH disease is determined. On the other hand, this plant not only does not have adverse effects on the digestion of consumers but also is used to treat gastrointestinal disorders, which is one of the benefits of this plant. Hence, it can be used as an effective drug in treating this disease. Of course, more research is needed to get it to the clinic.

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Authors' Contribution

Conceptualization: Azam Taheri.

Data curation: Azam Taheri.

Formal Analysis: Hajar Taheri.

Funding acquisition: Azam Taheri.

Investigation: Azam Taheri, Mohammad Fazilati.

Methodology: Azam Taheri.

Project administration: Azam Taheri.

Resources: Azam Taheri.

Software: Azam Taheri.

Supervision: Azam Taheri.

Validation: Azam Taheri.

Visualization: Azam Taheri.

Writing—original draft: Azam Taheri, Farhad Tadayon.

Writing—review & editing: Azam Taheri, Farhad Tadayon.

Competing Interests

There is no conflict of interest.

Ethical Approval

Ethical considerations in this study included obtaining permission from the University's Ethics Committee (IR.PNU.REC.2018.088) and obtaining written consent to participate.

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