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Original Article

Effects of Hydroalcoholic Extract of Black Seed (Nigella Sativa) and Honey on Changes in Serum, Urinary, and Kidney Tissue Factors in Kidney Stones of Male Mice

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HIGHLIGHTS

- The combination of black seed and honey is a viable option for kidney stone prevention and therapy.
- Nigella sativa inhibits the formation of urinary stones.
- Black seed and honey decreased urine calcium concentration significantly.

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ABSTRACT

Introduction

This study aimed to investigate the effect of black seed and hydroalcoholic honey extract on changes in serum, urine, and kidney tissue variables in male mice with kidney stones.

Methods

To do this, 7 groups were first considered, which are: harmful and healthy control groups, treatment with concentrations of 125 and 250mg/kg black seed, treatment with concentrations of 125 and 250mg/kg Honey, and treatment with 125mg/kg black seed with 125mg/kg honey. The required substances were introduced to the groups from the first to the last day of the experiment, and 1 % ethylene glycol was added to the drinking water. The researchers looked at serum variables, including potassium, sodium, calcium, phosphorus, and magnesium, urine factors like citrate, oxalate, and calcium, and tissue factors like kidney weight and crystal count.

Results

The results of this study showed that the accumulation of calcium oxalate crystals in the negative control group increased significantly (P-value<0.001) compared to the combined group of honey and black seed at 125mg/kg (without crystal accumulation). In addition, in other groups, the number of rock accumulations significantly decreased compared to the negative control group (P-value<0.001). Biochemical examination of urine at the end of the experiment showed a significant decrease (P-value<0.001) in urinary oxalate in the combined group of honey and black seed 125mg/kg (0.3±0.07). Urine calcium concentration also decreased significantly (P-value<0.05). In the combined group, honey and black seed had 125mg/kg (5.70±0.75). In addition, serum and tissue parameters in the honey and black seed groups alone (125 and 250mg/kg) and the honey and black seed group (125mg/kg) showed significant changes in the prevention and treatment of kidney stones.

Conclusions

The combination of black seed and honey is a viable option for kidney stone prevention and therapy, which shows the synergistic effects of honey and black seed with each other.

Keywords: Kidney Stones; Black Seed; Honey; Serum; Urinary Factors

Introduction

The deposition of chemicals secreted by the kidneys and the accumulation and formation of crystals are known as kidney stones. After urinary tract infection and prostate illness, it is the third most frequent urinary tract ailment. The sickness is seen in many places of the world (1). This illness is caused by a combination of internal and environmental causes. Internal reasons for the condition include genetic background, age, sex, and disorders such as chronic gastroenteritis and hyperparathyroidism. The climatic conditions of the area of residency, the amount of water drunk and the salts, nutrition, stress, and numerous drugs are the most critical external causes of kidney stones (2, 3). Treatment of kidney stones is based on several interventional strategies with several adverse effects and complications (4-8). The prevalence of this condition is increasing as people's diets change (9). Antispasmodics, ureteroscopy, and metabolic testing are increasingly employed in the acute treatment of kidney stones, in addition to fluid therapy and pain management medicines (10). Invasive treatment and surgery are utilized in the case of more giant stones that do not heal independently (9). Due to the high therapy expenses and the adverse effects of current treatment procedures, herbal treatments such as black seed are receiving much attention these days (11, 12). Black seed was employed as a tonic, diuretic, and lactogen in ancient Indian medicine. It was also used to treat skin ailments as a poultice. Black seed is recommended for treating stomach and liver disorders in Tibetan medicine. For shattering kidney and bladder stones and, with success, for treating urinary difficulties, a combination of the black seed, water, and honey is advised (13-15). The injection of black seed extract into the kidneys has been found to protect them and minimize renal toxicity caused by medications like cisplatin (16). Honey is a helpful food product and a precious elixir that was recognized centuries ago as the highest and most nutritious food, as well as for its therapeutic abilities as a medication in the treatment of most ailments in all nations. Before the bacteria was identified, it was used to heal infected wounds for nearly 2,000 years. It has been proposed that humans can shatter kidney and bladder stones by eating black seeds with water and honey (17-19). Honey's antibacterial properties are frequently employed in treating infected wounds, skin wounds, burn complications, respiratory tract, eye, and genitourinary system inflammatory illnesses (18, 20). The goal of this study was to compare the effects of hydroalcoholic extract of the black seed, honey, and citrate, oxalate, and urinary calcium on changes in blood potassium, sodium, calcium, phosphorus, and magnesium, as well as changes in renal tissue, such as kidney weight and several crystals.

Methods

Preparation of hydroalcoholic extract of black seed

After purchasing the seeds of a black seed plant grown in Semirom, Isfahan province, a herbarium specialist from the Islamic Azad University of Shahrekord recognized them. The Islamic Azad University Ethical committee approved the study (IR.IAU.SHK.REC.1397.051). The soaking procedure, detailed below, was employed to make the extract. 500 grams of black seed powder were ground and steeped in a solution of 80% ethanol and 20% distilled water for 72 hours before being baked at 45° C. Before putting the solution in the oven, give it a good shake for 20 minutes. After this time, a strainer was used to separate the solvent-containing extract from the black seed, and the extract was then placed in rotating equipment to separate the solvent from the extract.

Preparation of honey

Honey was acquired from hives in the Chaharmahal and Bakhtiari provinces', Koohrang area.

Use mice as animal models

A total of 45 male mice weighing 25-30 g were acquired from Shahrekord Azad University's animal house. In Shahrekord Azad University's animal nest, the animals were housed in optimum temperature and humidity conditions. During this time, animals had unrestricted access to water and food. During this time, they were given 8 groups of drinking water containing 1% ethylene glycol. To prevent mice from falling ill and maintain appropriate hygiene, sawdust was spread on the cage floors, and the cages were cleaned twice a week (21).

Animal grouping

The animals were randomly divided into 7 experimental groups with 5 mice in each group. These groups are:

Healthy control group (1): 1% of distilled water was added to the drinking water of this group during the experiment.

Negative control group (2): 1% ethylene glycol was added to the drinking water of this group during 30 days of treatment.

Intervention group (3): In this group, mice were given 125 mg/kg of black seed hydroalcoholic extract by gavage from the first day to the end of the experiment along with the administration of 1% ethylene glycol to drinking water.

Intervention group (4): In this group, mice were given 250 mg/kg of black seed hydroalcoholic extract by gavage from the first day to the end of the experiment with the administration of 1% ethylene glycol in drinking water.

Intervention group (5): In this group, mice were given 125 mg/kg of honey by gavage from the first day to the end of the experiment with the administration of 1% ethylene glycol in drinking water.

Intervention group (6): In this group, mice were given 250 mg/kg of honey by gavage from the first day to the

Table 1. Tukey test results to compare the mean Results of determination of Serum parameters in mice of the negative control group with other groups.

Serum parameters	Negative Control	Control	N. Sativa (125 mg/ml)	N. Sativa (250 mg/ml)	Honey (125 mg/ml)	Honey (250 mg/ml)	N.Sativa & Honey (125 mg/ml)
Serum potassium	5.4±0.65	4.7±0.49	5.1±0.4	3.9±0.59	4.7±0.58	5.1±0.66	3.9±0.28
Serum sodium	181.2±3.4	139.8±6.7	143.4±7.8	131.8±4.8	148.2±7.91	160±12.3	140.1±6.84
Serum calcium	10.34±0.75	8.3±0.84	8.04±0.93	7.38±1.11	8.9± 1.01	9.38±0.77	7.78±0.87
Serum phosphorus	5.48±1.34	5.48±1.13	4.98±1.03	5.26±1.17	6.62±1.24	6.44±1.13	5.86±1.69

Table 2. Tukey test results to compare the mean urinary parameters in the negative control group with other groups

Urinary parameters	Negative Control	Control	N.Sativa (125 mg/ml)	N.Sativa (250 mg/ml)	Honey (125 mg/ml)	Honey (250 mg/ml)	N.Sativa & Honey (125 mg/ml)
Urinary citrate	1.98±0.34*	2.58±0.17	2.68±0.38	3.36±1.02	2.16±0.59	2.48±0.87	4.12±0.27
Urinary oxalate	0.86±0.02***	0.4±0.07	0.5±0.09	0.37±0.07	0.5±0.11	0.6±0.08	0.3±0.07
Urinary calcium	11.26±0.7*3	9.80±1.45	9±0.94	7.44±1.06	8.54±1.11	10.68±0.61	5.70±0.75

Table 3. Tukey test results to compare the mean Kidney weight of the negative control group with other groups

	Negative Control	Control	N.Sativa (125 mg/ml)	N.Sativa (250 mg/ml)	Honey (125 mg/ ml)	Honey (250 mgml)	N.Sativa & Honey (125 mg/ml)
Kidney weight	0.67±0.02	0.25±0.02	0.34±0.10	0.31±0.07	0.40±0.10	0.41±0.11	0.30±0.08

end of the experiment with the administration of 1% ethylene glycol in drinking water.

Intervention group (7): In this group, mice were given 125 mg/kg of black seed hydroalcoholic extract with 125 mg/kg of honey by gavage from the first day to the end of the experiment with the administration of 1% ethylene glycol.

Healing period

Thirty days were handled throughout this period. During therapy, clinical symptoms and mortality were documented. During the treatment, all groups had free access to water and food (the meal was manufactured by Pars Animal Feed Company, which contained all of the required ingredients for a mouse's body) and the water needed by mice to prevent contamination. Every two days, hygiene was altered and measured until the description was completed.

Urine samples were taken after 24 hours. Until further inspection, each sample was kept in the refrigerator. After that, urine samples from each mouse were sent to a medical diagnostic laboratory for biochemical analysis and oxalate, calcium, and citrate measurements. The rats were sedated with short chloroform, and blood samples were obtained straight from their hearts using a syringe after 30 days of therapy. After that, the sera were sent to a medical diagnostic laboratory. The calorimetric technique was used to determine the blood's calcium, phosphorus, magnesium, sodium, and potassium amounts.

Dissection

The mice were dissected at this point, and all of them were taken for pathological evaluation, following which they were weighed and preserved in 10% formalin. The samples were transported to a pathology facility for hematoxylin and eosin staining.

Statistical Analysis

The results of this investigation were statistically evaluated using SPSS software (20) using one-way analysis of variance (ANOVA) and Tukey post hoc tests in the biochemical analysis section. All of the data is presented as Mean Standard Error Mean. The significance of the results (P-value<0.001), (P-value<0.01), and (P-value<0.05) were taken into account. Excel was used to create the graphs. All slides were randomly picked by light microscopy in each section of 10 microscopic fields with magnifications of 40 and 10, and the number of oxalate crystals (tubes containing these crystals) in these microscopic fields were tallied in the histological

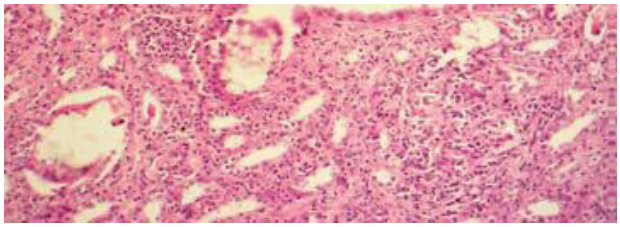

Figure 1. Residues of stones in renal calyces in negative control group (10×)

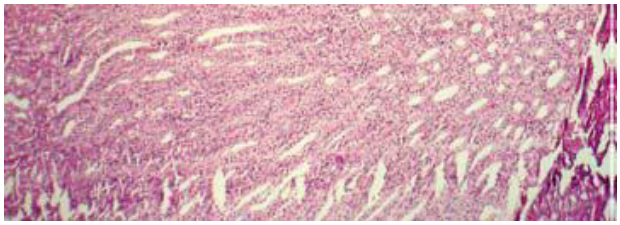

Figure 2. Kidney-free medulla in control group (10×)

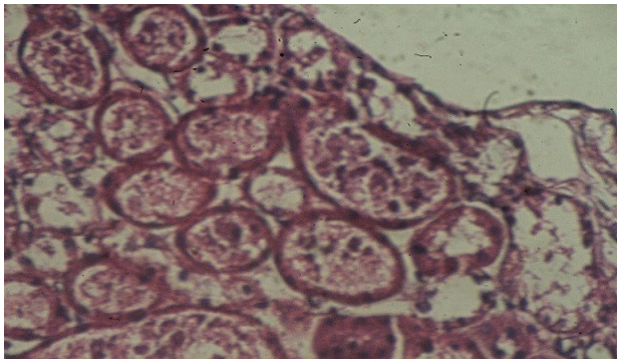

Figure 3. Normal renal cortex in control group (40×)

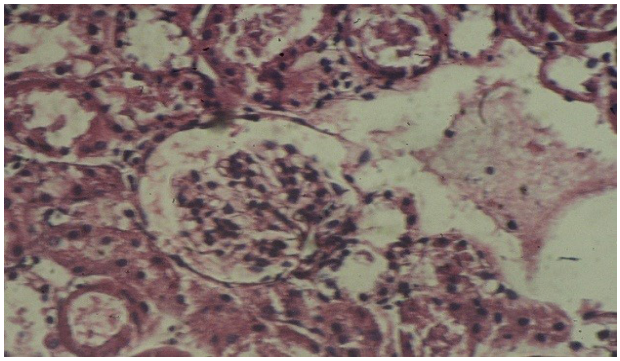

Figure 4. Glomerular damage in the cortex region in the group of 125 mg/kg black seed (40×)

examination section. According to the analysis technique, the data should be provided as (Mean Standard Error Mean).

Results

Results of determination of Serum parameters in mice

The results of the Tukey test showed that the serum potassium content of 250mg/kg groups of black seed hydroalcoholic extract and 125mg/kg of black seed hydroalcoholic extract with honey was considerably lower than the negative control group (P-value<0.01). Comparison of mean serum potassium of negative control group with healthy control group did not show a significant increase (P-value>0.05), Table 1.

Examination of the mean of the data using the Tukey test showed a significant decrease in the amount of serum sodium between the results of different groups with a negative control group (P-value<0.01). The mean serum sodium level of the healthy control group also decreased meaningfully compared to the negative control group (P-value<0.01), Table 1.

The healthy control groups showed 125mg/kg and 250 mg/kg of black seed hydroalcoholic extract, and the combination of honey and black seed showed a significant decrease compared to the negative control group (P-value<0.05), Table 1.

Statistical analysis of the mean amount of phosphorus observed in the negative control group (5.48±0.60mg dl) was not meaningfully different from other groups and increased compared to some groups and decreased compared to some groups (P-value>0. 05), Table 1.

Comparison of the mean serum magnesium levels of all groups with the negative control group showed that only the groups treated with 250mg/kg of hydroalcoholic extract of black seed and also 125mg/kg of hydroalcoholic extract of black seed and honey in combination increased meaningfully compared to the negative control group. (P-value<0.01). Serum magnesium level of the healthy control group did not increase compared to the negative control (P-value>0.05), Table 1.

Results of determination of urinary parameters in mice

Statistical analysis of the results using the Tukey test showed that the amount of urinary citrate in the negative control group increased significantly with the groups of 250mg/kg of hydroalcoholic extract of black seed and 125mg/kg of hydroalcoholic extract of black seed and honey in combination (P-value<0.05). Urine citrate in the healthy control group did not increase significantly compared to the negative control group (P-value>0.05), Table 2.

A comparison of the mean results of urinary oxalate in the treated groups showed that the negative control group had a significant increase compared to all treated groups and the healthy control group (P-value<0.01), Table 2.

Comparison of mean urinary calcium in the negative control group with other groups showed that the intervention groups with 125mg/kg and 250mg/kg black seed hydroalcoholic extract, 125mg/kg honey, and the

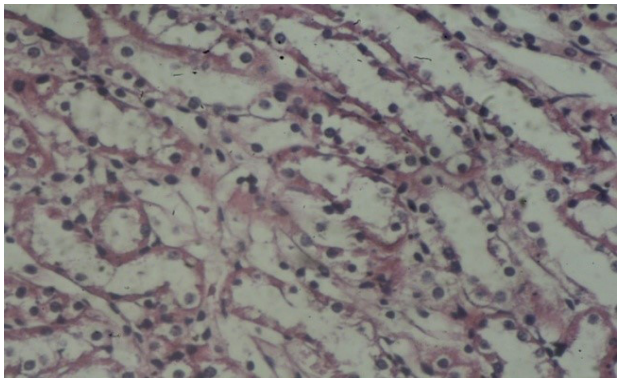

Figure 5. Brief renal tissue damage in the 250 mg/kg black seed group (40×)

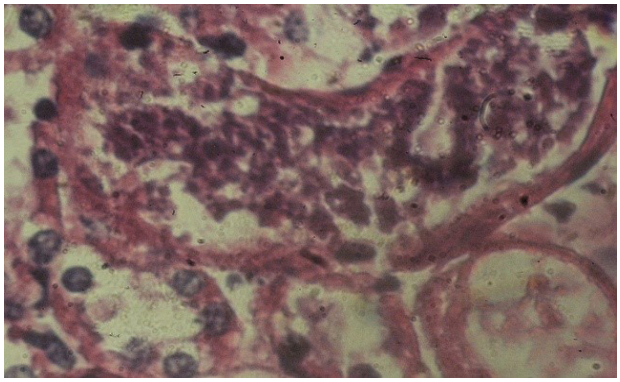

Figure 6. Cortex injury in 125 mg/kg honey group (40×)

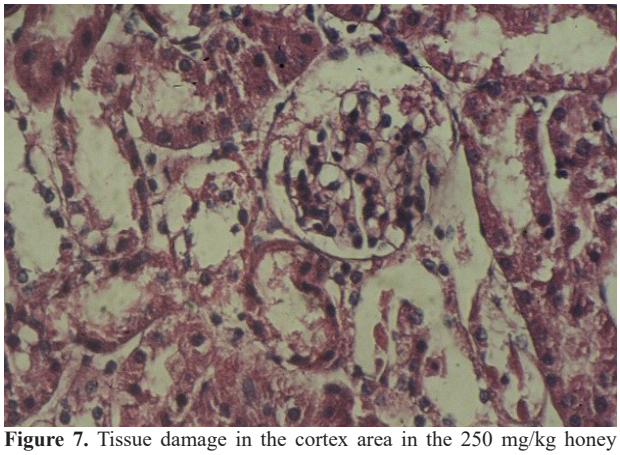

Figure 7. Tissue damage in the cortex area in the 250 mg/kg honey group (40×)

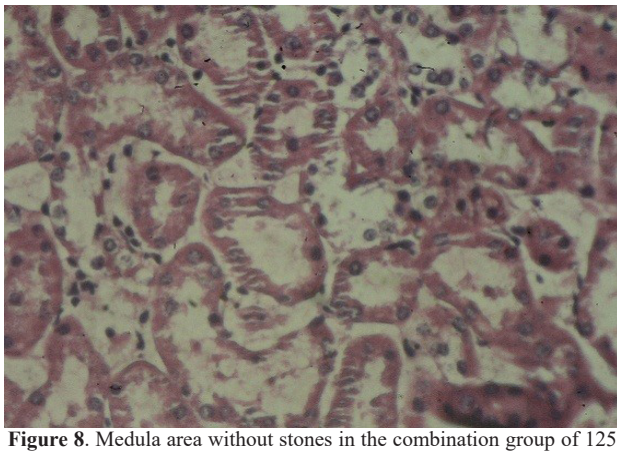

Figure 8. Medula area without stones in the combination group of 125 mg/kg honey and black seed (40×).

combination of black seed hydroalcoholic extract and honey compared to the negative control group showed a significant decrease. Had (P-value<0.05). Decreased urinary calcium levels in healthy and negative controls were not meaningful (P-value>0.05), Table 2.

Results of determining the weight of all mice

Examination of the mean of different groups to determine the existence of significant differences between different groups showed that the intervention groups and the healthy control group had a significant difference with negative control (P-value<0.001), Table 3.

Results of determining the number of crystals in mice

The results for each group are presented separately as follows:

Negative control group), in this group, the cortical region is irregular, the capsular space in the renal bodies is much broader than in the control group, and clear pathological changes are seen in the medullary region so that the central spaces of the tubules are completely filled. This observation results from the formation of oxalate crystals that fill most of the central space of all tubules. The equivalent of 40.7±1.29 crystal units in 10 fields was randomly counted in this group. The pathological changes of this group are pretty evident in filling the central spaces of the tubules, Figure 1.

Control group: In this group, the cortex area, which contains renal bodies (glomerular network and Bowman's capsule) along with Pct and Dct tubules, is normal. In this group, the medulla area is also normal, and no destructive effect is seen in the tissue. No traces of calcium oxalate crystals were seen in each slice, Figures 2 and 3.

125mg/kg group of black seed): In this group, the destruction of the proximal convoluted tubule (PCT) and distal convoluted tubule (DCT) in the cortex area is quite evident; the renal bodies also lose their order, the capsular space expands, and the glomerular network is condensed into the body, which shows changes. Pathological in the area of the cortex. Fewer changes were seen in the medulla region, and more calcium oxalate crystals were observed in the PCT and DCT in the cortex region. The counting unit of this group consisted of crystals more significant than 250mg/kg black seed group and was grouped in groups of 2-3. In this group, the equivalent of 13.1±1.21 crystal units in 10 fields was randomly counted, Figure 4.

250mg/kg black seed group: In this group, minor tissue changes, slight tissue and cell destruction in cortical

Table 4. Tukey test results to compare the mean number of negative control group crystals with other groups

	Negative Control	Control	N.Sativa (125 mg/ml)	N.Sativa (250 mg/ml)	Honey (125 mg/ml)	Honey (250 mg/ml)	N.Sativa & Honey (125 mg/ml)
Number of crystals	40.7±1.08	0 ± 0	13.1±3.84	10.5±2.91	18.1±5.68	23±3.33	0 ± 0

tubules, and a minimal number of calcium oxalate crystals were observed in these areas. The counting unit consisted of small crystals grouped into two groups. In this group, the equivalent of 10.5±0.52 crystal units was counted randomly in 10 fields. This small number of crystals indicates the background of rock formation, Figure 5.

Group (125mg/kg honey) Pathological changes in this group were observed in the form of the destruction of bodies and tubules. In the medulla area, changes were also observed in the Henle tube and the filling of the central spaces of the tubules. The counting unit consisted of crystals more significant than the 125mg/kg black seed group and was grouped into three groups. In this group, 18.1±1.79 crystal units were counted randomly in 10 fields. These crystals were mainly present in the medulla oblongata. A noteworthy point in this group is the tissue damage, many of which is caused by the presence of crystals, Figure 6.

250mg/kg honey group: More tissue damage was observed in this group than in the 125mg/kg honey intervention group because more crystals were formed. These crystals primarily accumulated in the collecting tubules of the medulla oblongata, and no hyperemia was observed in this area, but there were many pathological changes. The counting unit consisted of large crystals and was grouped in groups of 2-3. In this group, 23 crystal units equal to 1.05 were randomly counted in 10 fields, Figure 7.

The combined group of black seed and honey: In this group, no pathological changes were observed, the tubules of the medulla and cortex were normal, and there was no trace of oxalate crystals, Figure 8.

Number of crystals observed

The mean number of crystals in the negative control group was compared with other groups to investigate the significant difference. The negative control group differed significantly from other intervention groups and the healthy control group (P-value<0.001), Table 4.

Discussion

One of the most frequent urinary tract illnesses around the globe is kidney stones. Many herbal medications were utilized to heal ailments in ancient times. Black seed was one of these remedies, which is still used to cure ailments. Black seed is a useful plant with analgesic, anti-inflammatory, fat-burning, and tissue-repair characteristics. It also changes the activity of specific enzymes. Scientists in recent years have considered honey because of its long history of medicinal uses and unique physical and chemical features (21). The serum potassium factor rises in kidney stone disease. Both amounts of black seed and honey reduced serum potassium levels in the intervention groups, indicating the efficacy of these two components in decreasing kidney stones, with the lowest quantity of potassium seen in the honey and black seed 125mg/kg combination. In the combination of honey and black seed, potassium levels in the negative control group declined from 5.40±0.22mg/dl to 3.90±0.12mg/dl (P-value<0.01). This finding was in line with reducing kidney stone disease by combination usage. Kidney stones cause an increase in serum sodium. According to the studies, the blood sodium level dropped following treatment with the substances in this investigation. Honey and black seed individually and in combination reduced serum sodium and can be considered in treating kidney stones. In this study, serum calcium in the negative control group (10.34±0.66mg/dl) was higher than in other intervention groups. Honey and black seed alone (at 125mg/kg and 250mg/kg) and in combination significantly reduced serum calcium. Chapple et al., Investigated the effect of black seed at a concentration of 300 mg/kg on kidney stone formation and measured serum calcium levels, which observed that serum calcium levels increased significantly. In the present study, the amount of calcium decreased after treatment with black seed (22). In kidney stone disease, the number of phosphorus increases. In this study, there was no significant decrease in serum phosphorus in the intervention groups. For example, the amount of phosphorus in the groups treated with both concentrations of honey had high values, which were higher than the negative control group, which was not statistically significant (P-value>0.05). If the serum magnesium level is high, the rate of kidney stone formation will be less. In groups treated with 125 mg/kg of honey and black seed in combination (2.65±0.23mg/dl) and 250mg/kg alone (2.66±0.33 mg/dl), high levels of magnesium was observed to indicate the effect of these compounds in reducing kidney stone formation. The magnesium level in normal human blood is between 1.7- 2.2mg/dL. In this study, serum magnesium levels in healthy control mice were 1.99± 0.11, which is lower than normal human magnesium levels. Magnesium levels increased significantly in Chapple et al., research on the effect of black seed at a dosage of 300mg/kg on kidney stone formation, which was comparable to the results

of our study at a concentration of 250mg/kg (22). The quantity of citrate in the urine reduces due to kidney stone disease. The quantity of citrate rose after treatment with all variables, indicating that these chemicals affected raising citrate and preventing kidney stone development (23-25). The group treated with 125mg/kg of honey and black seed had the greatest quantity of citrate (4.12±0.12 mg/dl), indicating that these substances had a beneficial effect on kidney stone development. Studies have shown that oxalate levels increase in kidney stones, which may be because kidney stones are made of calcium oxalate. In this study, the amount of oxalate decreased compared to the negative control, indicating the effect of honey and black seed in eliminating kidney stones. The amount of oxalate in the negative control group decreased from 0.86±0.03mg/dl to 0.30mg 0.03mg/dl in the intervention group with honey and black seed. In the study of Hajzadeh et al., the effect of black seed extract with a concentration of 250mg/kg on urinary calcium oxalate was investigated, and it was found that treatment with black seed has a role in reducing this urinary factor. The amount of calcium oxalate in the black seed intervention group in the negative control group decreased from 15.57±1.26mg/dl to 10.64±1.2mg/dl in the intervention group. This finding was similar to the result obtained in the present study (26). Kidney stones cause an increase in urinary calcium. The quantity of urine calcium in the intervention groups reduced compared to the negative control group in this research (27, 28). The combination of honey and black seed therapy resulted in the lowest quantity of urine calcium (5.70±0.33mg/dl), demonstrating the influence of these two substances (29). The quantity of kidney weight increases as the number of kidney stones increases. Intervention groups lost weight in their kidneys and avoided the production of kidney crystals. Honey and black seed in combination had the most significant effect on kidney weight reduction, demonstrating the beneficial effect of these two substances in combination in kidney weight loss. There were no crystals in the group treated with honey and black seed in combination, indicating the combined action of these two components in lowering the number of kidney tissue crystals. The cause of these devastations may be traced back to two factors. In another study, researchers showed that black seed extract at a concentration of 200mg/kg prevents the formation and elimination of kidney stones. Sally et al., Showed that ethylene glycol causes stones on day 15 after treatment (30). In one study, the effect of quinolone reaction extract on kidney stones was investigated. In this study, ethylene glycol was used as a stone-forming material. Urine analysis was performed for oxalate, calcium, sodium, and crystals, and histological studies were performed to evaluate the deposition of crystals in kidney tissue. The results showed that the extract's positive effect on reducing the amount of oxalate, calcium, and sodium and reducing the amount of crystal deposition in the kidney could be effective in preventing kidney stones, which is consistent with our results design (31). The number of calcium oxalate crystals and urine oxalate was progressively greater in mice with kidney stones in this investigation. Numerous research has addressed the relevance of the influence of various medicinal herbs in preventing kidney stones. The effectiveness of some of these pharmaceuticals has yet to be determined. Recent research has found that aqueous extract of Ben-Sorkh at dosages of 750 and 1500mg/kg did not prevent ethylene glycol-induced kidney stones in male mice and exacerbated the deposition of calcium oxalate crystals in the kidney (31). In studies on calcium oxalate stone in rats, administration of cycleapllata root powder inhibited stone formation. In the same study, similar to the present study, a decrease in urinary oxalate was observed in the combined group of 125mg/kg of honey and black seed extract (32). Selvam et al., Showed in a study that the effect of A. Lanata extracts on reducing stone formation by increasing volume, reducing calcium, oxalate, phosphorus, and uric acid in the urine (33). In the present study, in the intervention group of 125mg/kg of black seed extract and honey in combination with reduced oxalate and urinary calcium (0.3±0.03mg/dl) and (5.7±0.33mg/dl). Honey has been used to cure various ailments and problems, and many of its health benefits have been verified. Honey is also beneficial in the treatment of renal and urinary tract illnesses. It is an excellent treatment for renal discomfort since it contains no salt and just a small quantity of protein. Honey has more carbohydrates than minerals in the diet, which helps to reduce urinary tract fistula irritation. Honey acts as a disinfectant for the urinary system and aids in the elimination of pollutants (34, 35).

Conclusions

The findings of studying serum and urine factors, as well as tissue changes, revealed that 125mg/kg of honey and black seed extract had a favorable impact on modifying blood and serum factors, as well as tissue changes, in the treatment of kidney stones. Based on the findings of this study, it is recommended that black seed medicinal plants be combined with honey at a dosage of 125mg/kg for 30 days to prevent and cure kidney stones. Using these two chemicals with beneficial qualities to create a combination of therapeutic agents to attack kidney stones might be a novel medication design breakthrough.

Authors' contributions

All authors contributed equally.

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Conflict of interest
All authors declare that there is no potential competing or conflict of interest.

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There was no funding.

Ethics statement
The ethical committee of Islamic Azad University approved this study (IR. TUMS.SINAHOSPITAL-REC.1399.071).

Data availability
Data will be provided on request.

Abbreviations
DCT Distal convoluted tubule
PCT Proximal convoluted tubule

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