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Evaluation of Nigella sativa and honey combination for treatment of kidney stone: a randomized, placebo controlled clinical trial

Laleh Zaheri Abdehvand,[a] Eskandar Moghimipour,[b] Ali Ghorbani,[c] Alireza Malayeri,[d] Amir Siahpoosh,[e] Mahmood Khodadoost,[f] Mehdi Rajaeipour,[g*] and Kambiz Ahmadi Angali[h]

[a]Department of Persian Pharmacy, Faculty of Pharmacy, Ahvaz Jundishapur University of medical Sciences, Ahvaz, Iran.
[b]Department of Pharmaceutics, Faculty of Pharmacy, Ahvaz Jundishapur University of medical Sciences, Ahvaz, Iran
[c]Department of Nephrology, Faculty of Medicine, Ahvaz Jundishapur University of medical Sciences, Ahvaz, Iran
[d]Department of Pharmacology, Faculty of Pharmacy, Ahvaz Jundishapur University of medical Sciences, Ahvaz, Iran.
[e]Department of Pharmacognosy, Faculty of Pharmacy, Ahvaz Jundishapur University of medical Sciences, Ahvaz, Iran.
[f]School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[g]Department of Urology, School of Medicine, Dezful University of medical Sciences, Dezful, Iran.
[h]Department of Biostatistics, School of Health, Ahvaz Jundishapur University of medical Sciences, Ahvaz, Iran.
*Correspondence to Mehdi Rajaeipour (email: Mehdirajaeipour@yahoo.com).
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Objectives The aim of this study was to evaluate the efficacy of *Nigella sativa* (NS) with honey on treatment of kidney stone.
Methods A clinical trial was conducted on 42 patients who were referred to the urology clinic of Ganjavian Hospital, Dezful, Iran and were identified by a sonographist that they had kidney stones smaller than 6 mm, they were without hydronephrosis, and did not require medication. They were randomly assigned to control ($n = 20$) and treatment ($n = 22$) groups. About 8 g of NS and honey combination with one glass of warm water were given daily to the treatment group for 1 month. The control group did not receive medication. Both groups drank 6–8 glasses of water daily.
Results The rate of stone expulsion in the treatment group was significantly higher than the control group ($P = 0.0001$).
Conclusion According to our results, it seems that NS with honey may have some beneficial effects in the treatment of kidney stone.
Keywords *nigella sativa*, ranunculaceae, honey, kidney stones

Introduction

Kidney stone is one of the most common diseases of the urinary tract, with an increasing incidence (6% in white women and 12% in white men).

In recent years, the occurrence of urinary stones has increased, while the age of the onset of the disease has decreased. The incidence of spontaneous recurrence after 5 years is reported between 35 and 50%. In 2005, its occurrence in Iran was 147.2 per 100,000 men and 129.6 per 100,000 women and a mean recurrence rate of 16% after 1 year, 32% after 5 years, and 53% after 10 years. In America, the cost per year for kidney stones is about $ 4.5 billion.[1–5]

The kidney stone may cause obstruction, hydronephrosis, infection, and hemorrhage in the urinary tract. ESW, PNL, and TUL, and laparoscopy are widely used to remove stones; but the use of these invasive methods is not cost effective and causes severe complications, so replacing traditional therapies with medicinal plants or phytotherapy will be valued.[4] In the traditional view, kidney stone is due to thick and sticky khilt (humor) which has lost its moisture through excessive heat over the time.[6] In traditional, medicine kidney stone is treated in various ways, including body cleansing from akhlat (plural of khilt), diet, regulation of activity, sleep and wakefulness, and the use of different herbal, animal or mineral drugs, including *Nigella sativa* (NS) and honey. Shoniz is used in traditional medicine as a diuretic, also with warm water and honey as Mofattit (lithotriptic) of stones.[7–9]

In traditional medicine shoniz due to be hirrif (pungent) is used as majun (mixture) to destroy rih (wind) and heat body rapidly.[10,11] Honey is also introduced as a Mofattit, diuretic and anti osr ol-bawl (difficulty in urinating).[7] It is also a basis for many traditional products. It is used as a thickener, flavoring agent and vehicle in recent years. It has an antimicrobial effect due to its high viscosity too.

Several studies have been carried out on herbal products that affect urinary stones, including shoniz.

In 2007, a study evaluated effect of NS extract on prevention and treatment of calcium oxalate produced by ethylene glycol in 32 Wistar rats. Results indicated a reduced number of calcium oxalate deposits in treatment group.[12] In 2008, another study examined the effect of intraperitoneal thimoquinone, the main components of NS, on 60 male Wistar rats (except for the negative control group). The stones were produced by ethylene glycol. The results showed that 5 mg/kg of thymoquinone significantly reduced the number and size of calcium oxalate deposits in the kidney tubules.[13] In 1997, administration of 1 g of NS (as capsules), two times per day, made significant changes in blood creatinine level in healthy individual in Saudi Arabia.[14]

In 2016, a study on NS and its main component, thymoquinone showed positive effects in prevention or curing kidney stones and renal failure through various mechanism such as antioxidative, anti-inflammatory, anti-eicosanoid and immunomodulatory effects.[15] In a study, in 2016, paracetamol administration significantly increased serum creatinine (0.80 U/L) when compared with the sham group (0.31 U/L). However, serum creatinine level was reduced to 0.64, 0.57, and 0.52 U/L with 250, 500, and 1000 mg/kg doses of the extract, respectively. Kidney histopathological examinations showed that NS antagonized paracetamol-induced kidney pathological damage.[16]

In 2016, a research showed that serum creatinine and blood urea nitrogen (BUN) in PTU group was higher than the control group. A total of 400 mg/kg of NS decreased creatinine, but both 200 and 400 mg/kg dose improved BUN concentration compared with PTU group. The results of this study demonstrate that the hydroalcoholic extract of NS has a protective effect on the renal tissue oxidative damage associated with PTU-induced hypothyroidism during neonatal and juvenile growth in rats.[17] In the formation of kidney stones, biochemical factors may be changed.[14,18] Yet, no comprehensive study has been accomplished on the effect of NS with honey on the stone formation and biochemical parameters of blood and urine in human.

On the other hand, this combination is used as a Mofattit in the folklore. The process is available, inexpensive and not invasive unlike existing stone breaking techniques. In the presence of honey, other excipients are not required. Therefore, the effect of a combination of NS and honey on the kidney stone was investigated in a clinical trial.

Patients and Methods

Methods

Investigation was conducted in accordance with approval protocol from Research Ethics Committee of Ahvaz Jundishapur University of Medical sciences. Code of Ethics: IR.AJUMS.REC.1396.645.

Plant Material

Nigella sativa was purchased from a local herb store in Ahvaz, Iran. The seeds were identified by the Pharmacognosy Department of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. The seeds were powdered using an electric grinder and immediately mixed with honey in a proportion of 1:3. They were packed in disposable containers.

Honey

Honey from Padena Company contains 0.1% polyphenol, 520 mg/kg prolin, 35.8% fructose, 32% glucose, and 15.2% water, while its pH is 5.72.[19]

Kidney Function Study

Calcium, phosphorus, pH, protein, specific gravity, urine volume 24 h, creatinine, BUN, and uric acid levels were measured by commercial assay kits (Parsazmun kit, Iran) using BT 1500 automatic analyzer. Oxalate and citrate levels were measured by commercial assay kits (Drmankav Kit, Iran) using photometer. Cistine was measured by colorimetric test.

Statistical Analysis

SPSS was used for statistical analysis. All data are presented as mean ± SD. The data obtained were tested by independent *t*-test, Mann–Whitney, or Crosstab.

Study Plan

Total amount of polyphenol of NS was measured by Folin–Ciocalteu method. Antioxidant activity was evaluated by the DPPH method. Then a clinical trial was conducted on 42 patients (age >18 years) from 100 patients who refered to the urology clinic of Ganjavian Hospital, Dezful, Ahvaz. They did not need medication. A sonographist recognized that they had kidney stones smaller than 6 mm, without hydronephrosis. They randomly assigned to control (n = 20) and treatment (n = 22) groups. The treatment group took 8 g of the combination with one glass of warm water daily for 1 month. The control group did not receive medication. Both groups drank 6–8 glasses of water per day. At the end, sonography was repeated. Blood and urine biochemical test, 24 h urine volume and urine pH and specific gravity were determined before and after intervention. The rate of stone expulsion was compared in two groups with SPSS. Exclusion criteria were pregnancy, history of the complication or sensitivity to NS, receiving drugs that affect kidney stones, use of stone breaking techniques, and diabetes.

Fig. 1 **Nigella sativa seeds and flower https://sg.carousell.com**

Results

Polyphenolic content and antioxidant activity (IC_{50}) of NS were studied. The results were 18.53 mg (based on tannic acid) and 0.2 mg/ml respectively. About 42 patients from 100 patients with kidney stones who referred to Ganjavian Hospital, 22 were in the treatment group and 20 in the control group; a total of 17 women and 25 men participated in the study. All participants had not cystinuria and proteinuria. There was a significant difference between age in two groups (P = 0.041), mean age in control group was 47.95 ± 9.92 and in treatment group was 56.64 ± 12.84. The rate of stone expulsion in the treatment group (90.9%) was significantly higher than the control group (40%) (P = 0.0001). The mean of stone size and stone number variables were significantly different before and after intervention in the control and treatment groups (respectively P = 0.001, 0.001). The mean difference of stone size in the control group was 1.25 ± 1.55 and in the treatment group was 3.33 ± 0.66 .The mean difference of stone numbers in the control group was 0.4 ± 0.5 and in the treatment group 0.91 ± 0.29. The odds ratio (OR) for stone disposal in the treatment group was 15 (95% confidence interval: 2.7–82.7). On the other hand, the NNT was almost equal to 2.

Comparison of uric acid in both groups before and after intervention showed significant difference (P = 0.025). The mean of this variable was 0.78 ± 0.96 in control group and 0.19 ± 0.66 in treatment group.

The results of the comparison of serum creatinine in the control and treatment groups before and after treatment indicated that the serum creatinine difference was significant in both groups (P = 0.043). The mean of serum creatinine difference in the control group was −0.015 ± 0.13 and in the treatment group was 0.07 ± 0.13.

Other variables did not differ significantly before and after intervention in the two groups (P >0.05).

Comparison of variables and their differences in both groups before and after intervention showed in (Table 1 and 2).

Discussion

This study showed that polyphenolic content and IC_{50} of NS were 18.53 mg and 0.2 mg/ml respectively, indicating higher antioxidant activity of NS than Thomson and Tarocco peel and equal to Sanguinello peel.

In this study, the IC_{50} for NS was 0.2 mg/ml. In a study, IC_{50} mentioned for Tarocco peel was 2.34 mg/ml, for Sanguinello 0.2 mg/ml, and for Thomson peel 3.46 mg/ml.

The amount of polyphenolic compounds in 1 g of dry NS extract was 0.13 mg for Tarocco peel, 0.19 mg for Sanguinello peel, and 0.3 mg for Thomson peel.[20]

The results of this study showed that the mean difference in the size of the stone before and after intervention in the treatment group (3.33 ± 0.66) was more than the control group (1.25 ± 1.55). Also, the mean difference of stone number before and after intervention in the treatment group (0.91 ± 0.29) was more than the control group (0.4 ± 0.5). In both of them, P-value was equal to 0.0001. A study found that the ethanolic extract of *N. sativa* seeds with a dose of 250 mg/kg significantly decreased the number and size of calcium oxalate deposits in different parts of Wistar rat renal tubules and also prevented damages to the tubules and calyxes.[12]

This study confirms the views of Aghili Khorasani, Hakim Arzani, Avicenna, and Razi. Aghili Khorasani, in Makhzan-ul-Advieh, considered honey as Jali (a medicine that serves to wipe the surface of organ cleen), monaqqi (cleansing agent), moqatti (a medicine that cuts abnormal humor off the organ without altering its consistency) of sticky balgham (phlegm) and Moisture, mofatit, diuretic and anti osr ol-bawl. He also introduced honey as a moqatti of hasah (stone), diuretic and anti osr ol-bawl.[7]

Hakim Arzani used NS as a diuretic; also used with warm water and honey as a stone breaker in kidney and bladder.

Table 1. **Comparison of variables in both groups before and after intervention**

Variables		Mean ± SD Control	Mean ± SD Treatment
Age		47.95 ± 9.92	56.64 ± 12.84
Stone size	Before	3.45 ± 0.89	3.39 ± 0.65
	After	2.20 ± 1.96	0.06 ± 0.20
Stone number	Before	1	1
	After	0.60 ± 0.50	0.09 ± 0.29
Vol. 24 h	Before	1470 ± 712.37	1213.64 ± 639.97
	After	1425.50 ± 805.71	1381.36 ± 688.78
Urine Cr 24 h	Before	1.13 ± 0.42	1.27 ± 0.39
	After	0.97 ± 0.46	1.09 ± 0.34
Urine Ox 24 h	Before	16.66 ± 13.50	17.89 ± 15.81
	After	11.24 ± 8.53	13.34 ± 11.07
Urine Cit 24 h	Before	2.21 ± 1.36	1.98 ± 1.48
	After	2.75 ± 1.97	2.11 ± 1.85
Urine UA 24 h	Before	521.68 ± 345.85	369.83 ± 166.54
	After	573.15 ± 405.26	484.47 ± 518.99
Urine Ca 24 h	Before	98.91 ± 54.33	162.32 ± 99.68
	After	79.28 ± 63.68	111.15 ± 55.29
Urine pH	Before	5.45 ± 0.10	5.18 ± 0.39
	After	5.20 ± 0.62	5.09 ± 0.29
Urine S. g.	Before	1023 ± 8.01	1024.64 ± 7.42
	After	1026.80 ± 4.88	1025.68 ± 6.74
BUN	Before	16.88 ± 4.79	21.15 ± 3.38
	After	14.25 ± 5.31	17.82 ± 5.10
Serum Cr	Before	1.04 ± 0.18	1.10 ± 0.20
	After	1.05 ± 0.15	1.03 ± 0.16
Serum Ca	Before	11.08 ± 4.31	9.38 ± 0.48
	After	9.21 ± 0.65	9.23 ± 0.36
Serum P	Before	3.49 ± 0.33	3.46 ± 0.34
	After	3.59 ± 0.49	3.50 ± 0.51
Serum UA	Before	5.02 ± 1.20	5.05 ± 1.30
	After	4.28 ± 1.21	4.73 ± 1.26
GFR	Before	117.94 ± 90.95	104.84 ± 77.60
	After	89.17 ± 53.53	115.20 ± 90.70

BUN: blood urea nitrogen.

Table 2. **Comparison of differences between variables before and after intervention in both groups**

	Variables	Differences mean ± SD	P-value between groups
Stone size	Control	1.25 ± 1.55	0.0001
	Treatment	3.33 ± 0.66	
Stone number	Control	0.40 ± 0.50	0.001
	Treatment	0.91 ± 0.29	
Vol. 24 h	Control	44.5 ± 823.26	0.304
	Treatment	−167.73 ± 397.89	
Urine Cr 24 h	Control	0.16 ± 0.23	0.848
	Treatment	0.18 ± 0.24	
Urine Ox 24 h	Control	5.42 ± 13.15	0.473
	Treatment	4.55 ± 13.46	
Urine Cit 24 h	Control	−0.54 ± 1.26	0.322
	Treatment	−0.13 ± 1.37	
Urine UA 24 h	Control	−51.47 ± 496.05	0.339
	Treatment	−114.65 ± 406.04	
Urine Ca 24 h	Control	19.63 ± 66.45	0.291
	Treatment	51.17 ± 115.37	
Urine pH	Control	0.25 ± 1.16	0.922
	Treatment	0.09 ± 0.53	
Urine S. g.	Control	−3.8 ± 8.04	0.435
	Treatment	−1.05 ± 7.00	
BUN	Control	2.63 ± 6.79	0.689
	Treatment	3.33 ± 3.86	
Serum Cr	Control	−0.015 ± 0.13	0.043
	Treatment	0.07 ± 0.13	
Serum Ca	Control	1.87 ± 4.43	0.677
	Treatment	0.15 ± 0.55	
Serum P	Control	−0.1 ± 0.43	0.689
	Treatment	−0.04 ± 0.59	
Serum UA	Control	0.78 ± 0.96	0.025
	Treatment	0.19 ± 0.66	
GFR	Control	−28.77 ± 83.08	0.087
	Treatment	10.36 ± 47.54	

BUN: blood urea nitrogen.

Avicenna, Razi, considered triturated NS with honey and warm water as an expellent of kidney stones, diuretic, qati (cutter) of digestive thick akhlat.[7–9,11,21] The rate of expulsion in the treatment group (90.9%) was significantly higher than the control group (40%), which indicated a potent stone removal effect of the combination ($P = 0.0001$).

In the formation of kidney stone, 24 h urine volume and blood or urine biochemical factors such as phosphorus, calcium, citrate, uric acid, oxalate, etc. may be changed.[14,18]

Serum uric acid decreased in both groups after the intervention, but its decrease in the treatment group (0.19 ± 0.66) was significantly lower than the control group (0.78 ± 0.96) ($P = 0.025$).

A study in 1997 found that taking 1 g of NS, two times a day, in healthy subjects, resulted in no significant changes in serum uric acid levels.[14]

Serum creatinine increased in the control group and decreased in the treatment group. The mean of serum creatinine differences in the control group was −0.015 ± 0.127 and in the treatment group was 0.07 ± 0.13. Mean serum creatinine before and after treatment in two groups had a significant difference ($P = 0.043$). A study on rats in 2017, found that the serum creatinine was reduced by dose of 400 mg/kg of NS extract.[17] In another study (2016), serum creatinine levels were associated with a significant decrease following the use of 5 mg/kg of NS oil for 28 days in Wistar rats ($P < 0.01$).[22] A research (2016) showed that the administration of paracetamol significantly increased the serum creatinine level (0.80 U/L) compared with the sham group (0.31 U/L); the serum creatinine level was reduced to 0.64, 0.57, and 0.52 U/L with 250, 500, and 1000 mg/kg doses of NS extract, respectively.[16] A study in Saudi Arabia, indicated that administration of 2 g/day of NS, made significant changes in blood creatinine level in healthy individuals.[14]

There were no complications following the use of combination during the study. It can be concluded that there is no renal damage due to treatment with the combination. It confirms the nephroprotectrivy of the combination. A clinical study (2010) found that NS at doses of 1–3 g/day for 3 months did not adversely affect renal and hepatic functions of diabetic patients.[23]

Conclusion

According to the odds ratio (OR > 10), stone expulsion in the treatment group is 15 times more than the control group. Therefore, there is a meaningful relationship between the stone expulsion and intervention type. On the other hand, the NNT is almost equal to 2; that is, clinically in the community, one person is treated from two people who receive the combination. Also, a significant reduction in the stone number and size in the treatment group may be indicated to crush or dissolve the stones by the combination, which approves traditional use of NS majun in kidney sone. The mechanism of action is probably antioxidant and stone breaker.

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Conflict of Interest

None.

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