Therapeutic and Preventive Effects of Aqueous Extract of Date Palm (Phoenix dactylifera L.) Pits on Ethylene Glycol-Induced Kidney Calculi in Rats

Pouria Mohammadparast Tabas[1], Hamed Aramjoo[1], Ali Yousefinia[1], Mahmoud Zardast[2], Mohammad Reza Abedini[3] & 4, Mohammad Malekaneh[5]*

Purpose: Urinary tract stones are one of the most common diseases in the urinary tract. Lack of kidney stone treatment causes irreparable damages to the kidneys, which has many harmful effects. Date palm pits are recommended in traditional medicine as an effective drug in the treatment of kidney stones. The aim of this study was to investigate the effect of aqueous extract of date palm pits on kidney stones induced by ethylene glycol in male rats.

Methods: In this study, 40 rats were classified into five groups (n = 8), including the healthy group receiving normal water, the negative control group, the therapeutic groups with doses of 150 mg/kg and 300 mg/kg, and the prevention group with a dose of 300 mg/kg. In order to induce kidney stones, ethylene glycolated water (1%) was used as drinking water in the studied groups. Blood and urine of rats were collected on days 14 and 28 of the study to assess urinary parameters of calcium, creatinine, uric acid and phosphorus, and serum parameters of blood urea nitrogen, creatinine, uric acid, calcium, and phosphorus. Also, the kidneys of rats were removed from the body on day 28 of the study and were given to a pathologist for examination.

Results: Results of serum parameters show that the use of date palm pits extract in the treatment and prevention groups with a dose of 300 mg/kg significantly ($P < .05$) has reduced the levels of blood urea nitrogen, uric acid, calcium, creatinine, and phosphorus. Also, the results of urinary parameters show that the use of the extract caused a significant decrease ($P < .05$) in creatinine, uric acid, and calcium in the prevention group and a significant decrease ($P < .05$) in creatinine and uric acid in the therapeutic group with a dose of 300 mg/kg. Pathological results show a decrease in the number and size of calcium oxalate crystals in renal tubules in the treatment and prevention groups in a dose-dependent manner.

Conclusion: The results of this study showed that the use of aqueous extract of date palm pits has been effective in the treatment and prevention of kidney stones induced by ethylene glycol in rats.

Keywords: calcium oxalate; date palm pits; ethylene glycol; kidney calculi; rat

INTRODUCTION

Kidney stone (KS) is the most common urinary tract disease due to urinary tract infections and prostate disorders. KSs are formed from organic and inorganic crystals in combination with protein[(1)]. About 80 percent of kidney stones are calcium stones, which are composed of a combination of calcium oxalate (CaOx) and calcium phosphate[(2)]. The prevalence of KS has been increasing globally over the last three decades. As this prevalence has increased, we have also seen an increase in the expenses associated with this disease. By 2030, the United States is expected to spend more than $ 5 billion a year to treat patients with KSs[(3)].

KS formation is associated with a variety of factors including lifestyle, race, genetic background (heritability of ~45-60%), gender, and diet. Underlying diseases such as diabetes, obesity and inactivity, gout, hyperparathyroidism, hyperoxaluria, increased calcium, and changes in urine pH play an important role in the formation of KS[(4-6)]. People suffering from KSs have severe colic pain, and on the other hand, obstruction caused by these stones reduces the urine output and, in some cases, hematuria, and if left untreated, can lead to kidney damage, kidney failure, and urinary tract infections[(7)]. There are currently several methods to remove KSs; supportive methods such as fluid intake and the use of analgesics to remove stones spontaneously and in the case of larger stones, methods such as chemically dissolving stones, removing stones from the urethra, breaking stones with ultrasonic waves and, if necessary, open surgery could be used. In addition to many side effects such as urinary tract infections, tissue damage and the possibility of stone re-formation can impose many

[1]Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran.
[2]Cardiovascular Diseases Research Center, Birjand University of Medical Sciences, Birjand, Iran.
[3]Chronic Disease Program and Regenerative Medicine Program, Ottawa Hospital Research Institute, Ottawa, Canada.
[4]Cellular and Molecular Medicine Research Center, Department of Pharmacology, Birjand University of Medical Sciences, Birjand, Iran.
[5]Department of clinical Biochemistry, Birjand University of Medical sciences, Birjand, Iran.
*Correspondence: Associate Professor of Biochemistry, Department of Clinical Biochemistry, School of Medicine, Birjand University of Medical sciences, Birjand, Iran. Email: Drmalekaneh21@gmail.com.
Received October 2020 & Accepted June 2021

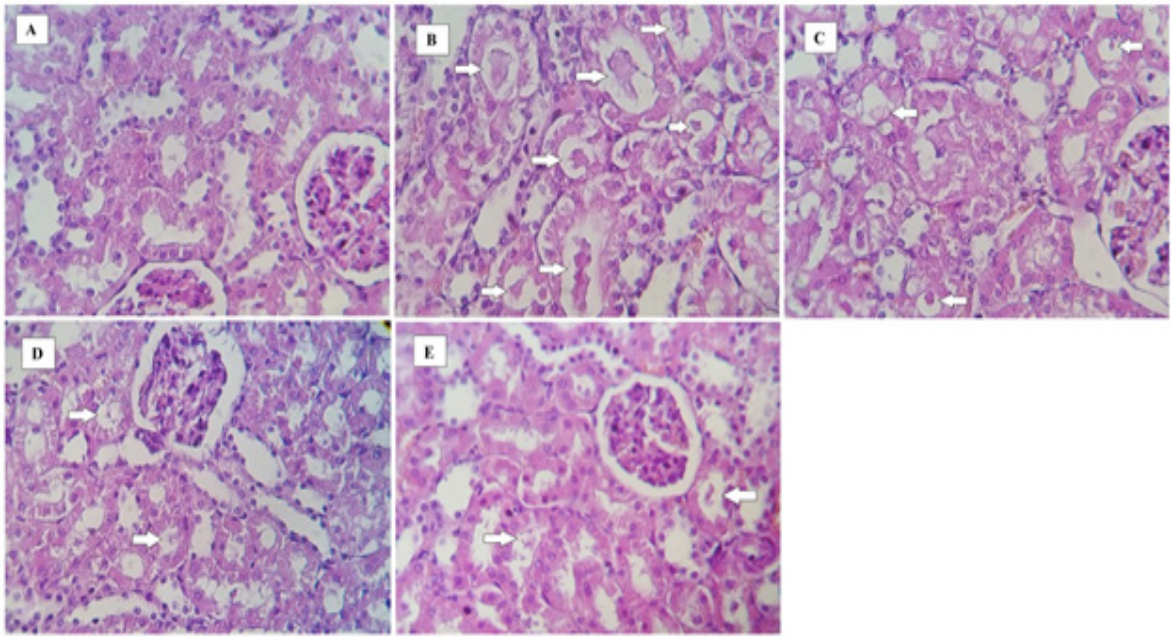

Figure 1. Effect of date palm pits on histopathology of kidney. Histopathological sections of the kidney sample showed that there were no intratubular crystal deposition in the NC group and the tissue showed normal architecture of the renal epithelia and tubular structure **(Fig. 1A)**. The ethylene glycol treated group showed the presence of intratubular deposition of the crystals and necrotic degeneration of the renal epithelia leading to damage to nephron and collecting system **(Fig. 1B)**. Sections from 150mg/kg date palm pits **(Fig. 1C)** and 300mg/kg date palm pits **(Fig. 1D)** treated rats also demonstrated less retention of crystals in tubules and prevented necrotic damage. The sections from the kidney of rats treated with 150mg/kg date palm pits **(Fig. 1C)** exhibited the prevention of retention and tubular deposition of crystals and lesser degree of necrotic damage to renal epithelia (Type of staining: Hematoxylin and Eosin; Magnification ×400).

costs on the patient[8,9]. Nowadays, considering the side effects and severe detrimental effects of chemical drugs, the use of herbal and natural medicines has been considered by contemporary researchers, and in several studies, the effects of various herbs in the treatment of kidney stone disease have been studied[10,11].

Monocotyledonous date palm tree belongs to the Arecaceae or Palmae family is from the Phoenix genus with the scientific name Phoenix dactylifera. Date palms are grown in desert areas, especially in the Middle East, and are native to Iraq and western and southern regions of Iran[12]. Date palm pits extract enriches from polyphenols[13], which exerts many biological properties, including antioxidant, anti-inflammatory, antiviral, and antibacterial activities[14] as well as anti-cancer effects, and could be used for the treatment of diabetes. Moreover, it is useful to prevent neurological disorders and Alzheimer's disease, enhance sexual potency and improve anemia[15-17].

Pits consist of 10 to 15 percent of the date palms weight and contain compounds that are chemically composed of saturated fatty acids such as palmitic acid and stearic acid, and unsaturated fatty acids such as oleic acid and linoleic acid, as well as elements such as zinc, cadmium, calcium, and potassium[18]. It also contains antioxidants such as carotenoids, anthocyanins, glycosidic flavonoids from flavones, flavonols, and flavoxanthines classes, and due to the high percentage of antioxidant activity, they protect the body against oxidative damage [19,20]. Owing to the fact that the medicinal plants have fewer side effects, and patients show higher emotional compliance, date palm pits is recommended as a treatment for kidney and bladder stones in traditional medicine; however, and to our knowledge, no relevant scientific research has been reported so far in this regard. Therefore, the present study was conducted to investigate the therapeutic and preventive effects of date palm (Phoenix dactylifera) pits on kidney stones induced by ethylene glycol in rats.

MATERIALS and METHODS

Preparation of date palm pits extract

To prepare date palm pits extract, some dates known in the market as Zahedi dates were purchased from the local market and after approval in the herbarium section of Birjand University of Medical Sciences were used. the date palm pits were first removed from the fruit and then thoroughly washed to remove any fruit residue and surface contaminants. After the pits dried in the shade, they were grinded using a grinder. To prepare the aqueous extract, 5 g of dried and grinded date palm pits powder was poured into 100 mL of distilled water, twice distilled at 95 °C, and after stirring, brewed for 15 minutes. Then, using filter paper (Blue Ribbon, Grade 589, Germany), the obtained solution was filtered in the specific containers of freeze-dryer (Dena Vacuum Industry, model FD-5005-BT, Iran) and placed in a -20° C freezer. After freezing, the solution was placed in a freeze-dryer and freeze-dried at a -50 °C and vacuum conditions. The dry powder obtained was stored in specific polyethylene containers at 4 °C until use. The extract solution was provided daily.

Animals and study design

In this study, 40 male Wistar rats (200 ± 25 g, 2 months) were kept in stable physical conditions at a temperature of 25 ± 2 °C and a 12-hour light and dark cycle on research center of experimental medicine Birjand

Table1. The pre-operative, baseline characteristics of the two groups

Groups	BUN (mg/dL)	Creatinine (mg/dL)	Uric acid (mg/dL)	Calcium (mg/dL)	Phosphorus (mg/dL)
NC	27 ± 10.23	0.55 ± 0.12	2.12 ± 0.55	8.77 ± 0.3	8.07 ± 0.34
EG	32.5 ± 3.41	0.8 ± 0.08*	3.57 ± 0.26*	10.4 ± 0.75**	8.37 ± 1.34
T150	38.5 ± 2.51	0.72 ± 0.05	2.72 ± 0.48	9.55 ± 0.49	8.12 ± 1.72
T300	40.75 ± 17.32	0.85 ± 0.1	2.72 ± 0.74	9.5 ± 0.34	6.92 ± 1.35
P300	37 ± 5.47	0.82 ± 0.22	3.8 ± 0.75	8.77 ± 0.29##	7.8 ± 0.73
	Chi-Square = 7.29	F = 3.45	F = 5.45	F = 8.18	F = 0.86
	P = 0.12	*P* = 0.03	*P* = 0.006	*P* = 0.001	***P* = 0.5**

Abbreviations: BUN, blood urea nitrogen.
All data were expressed as mean ± SD (n = 8). # *P* < .05, ## *P* < 0.01, and ### *P* < .001 compared with NC group; * *P* < .05, ** *P* < .01, and *** *P* < .001 compared with EG group.

University of medical sciences, Birjand, Iran. The study was approved by the Deputy of research and technology and ethics committee of Birjand University of Medical Sciences (Ethics code: IR.BUMS.REC.1398.156).
The rats had free access to standard food (Javanneh-Khorasan co, Iran) and drinking water, and were grouped 72 hours before the study began and placed in relevant cages to adapt to the new conditions. The duration of the study was considered 28 days, according to previous studies[21-24]. The rats were divided into 5 groups (n = 8):
Group 1: Received regular drinking water and receive 1 mL of normal saline orally per day (gavage) during the study (NC).
Group 2: Received 1 mL of normal saline per day orally and 1% ethylene glycol (Merk, Germany) is added to their drinking water (EG).
Group 3: Received the date palm pits extract 150 mg/kg per day from the 14th day until the end of the study and 1% ethylene glycol was added to their drinking water (T150).
Group 4: Received the date palm pits extract 300 mg/kg per day from the 14th day until the end of the study and 1% ethylene glycol was added to their drinking water (T300).
Group 5: Received 300 mg/kg of date palm pits extract per day orally and 1% ethylene glycol was added to their drinking water (P300).

Collecting urine samples
Each rat was kept in a separate metabolic cage for 24 hours and their urine was collected on days 14 and 28 of the study. Calcium, creatinine, uric acid, and phosphorus in the rats' urine were measured and analyzed with an auto-analyzer (Tokyo Bokei Prestige 24i, Japan).

Collecting blood samples
Blood samples from rats were taken on day 14 of the study through the retro-orbital sinus, and on day 28 of the study through their heart following anesthesia, and the serum was separated by blood centrifugation at 2500 rpm for 10 minutes at 4 °C, and was kept at -80 °C until biochemical analyzes were performed. Serum levels of blood urea nitrogen (BUN), creatinine, uric acid, calcium, and phosphorus were measured by commercially available kits and analyzed.

Histopathological evaluation
To study the kidney's pathology, following anesthesia of the rats with ketamine and xylazine (65:10 mg/kg) on day 28, rats' kidneys were removed, washed with normal saline (0.9%), and placed in 10% formalin solution. After dehydration and embedding in paraffin, 5 microns-thick sections were prepared. From the prepared sections, 4 sections from each kidney (2 sections from each kidney lobe) were selected and stained by hematoxylin and eosin method and were given to the blinded pathologist to examine the possible damage of kidney tissue and formation of calcium oxalate crystals.

Statistical analysis
Finally, all data were entered into SPSS software (Version 19). After testing the normality of the data distribution using a Kolmogorov-Smirnov test, one-way analysis of variance (ANOVA) was performed. Tukey HSD multiple comparisons were performed as a post-hoc test to see any significant differences between each group. Non-parametric variables were compared using the Kruskal-Wallis test followed by Mann-whitney test. The data were presented as Mean ± SD and a P-value of .05 or less was considered statistically significant.

RESULTS
Effects of date palm pits on plasma biochemical parameters

Table2. The effect of date palm pits extract on plasma parameters on day 28.

Groups	BUN (mg/dL)	Creatinine (mg/dL)	Uric acid (mg/dL)	Calcium (mg/dL)	Phosphorus (mg/dL)
NC	26.85 ± 12.64	0.57 ± 0.32	2.28 ± 0.77	8.3 ± 1.48	8.14 ± 2.48
EG	66.5 ± 14.08***	1.08 ± 0.41**	3.22 ± 0.79*	11.45 ± 2.36**	11.37 ± 1.97**
T150	50.75 ± 8.87	0.87 ± 0.21	2.65 ± 0.36	10.63 ± 1.21	9.52 ± 2.1
T300	44.87 ± 18.61#	0.76 ± 0.35#	2.45 ± 0.57#	9.46 ± 1.69	9.48 ± 1.28#
P300	43.87 ± 13.06##	0.7 ± 0.27#	2.05 ± 0.65##	8.9 ± 2.1#	8.1 ± 1.52##
	F = 7.42	Chi-Square = 10.84	Chi-Square = 12.85	F = 3.76	Chi-Square = 13.03
	P < 0.0001	*P* = 0.01	*P* = 0.01	*P* = 0.01	*P* = 0.01

Abbreviations: BUN, blood urea nitrogen.
All data were expressed as mean ± SD (n = 8). # *P* < .05, ## *P* < 0.01, and ### *P* < .001 compared with NC group; * *P* < .05, ** *P* < .01, and *** *P* < .001 compared with EG group.

Table 3. The pre-operative, baseline characteristics of the two groups for proximal

Groups	Creatinine (mg/dL)	Uric acid (mg/dL)	Calcium (mg/dL)	Phosphorus (mg/dL)
NC	34.75 ± 19.8	3.85 ± 2.38	2.52 ± 1.02	23.7 ± 2.04
EG	34.25 ± 10.71	5.82 ± 5.73	5.12 ± 2.03	20.65 ± 0.63
T150	34.75 ± 19.68	5.7 ± 2.48	8 ± 1.59	23.42 ± 0.68
T300	36.75 ± 18.44	4.97 ± 3.1	7.6 ± 2.05	22.52 ± 1.77
P300	28.75 ± 6.29	3.95 ± 0.42	5.9 ± 7.21	19.25 ± 2.67
	Chi-Square = 0.47	F = 0.32	F = 1.5	F = 4.73
	P = 0.97	*P* = 0.86	*P* = 0.25	*P* = 0.01

All data were expressed as mean ± SD (n = 8). # $P < .05$, ## $P < .01$, and ### $P < .001$ compared with NC group; * $P < .05$, ** $P < 0.01$, and *** $P < .001$ compared with EG group.

Examination of BUN and plasma phosphorus levels of rats on day 14 showed an increase in the groups that received ethylene glycol compared to the control group. BUN and plasma phosphorus levels on day 28 in the EG group showed a significant increase compared to the control group ($P < .05$). Consumption of date palm pits extract decreased the amount of BUN and plasma phosphorus in the therapeutic and prevention groups, which was significant in the therapeutic group with a dose of 300 mg/kg (T300) and prevention (P300) ($P < .05$). Examination of creatinine and uric acid levels in the plasma showed a significant increase in the EG group compared to the control group on days 14 and 28, and consumption of date palm pits extract caused a significant decrease in creatinine and uric acid levels of the therapeutic group with a dose of 300 mg/kg (T300) and prevention group with a dose of 300 mg/kg (P300) ($P < .05$). Plasma calcium levels on days 14 and 28 had a significant increase in the EG group compared to the control group, which consumption of the extract caused a significant decrease in plasma calcium levels in the prevention group with a dose of 300 mg/kg (P300) compared to the EG group ($P < .05$).

Effects of date palm pits on urinary biochemical parameters

The urinary levels of creatinine showed a significant decrease and levels of uric acid and calcium showed a significant increase in the EG group compared with the control group on day 28 of the study ($P < .05$). The urinary level of creatinine show significantly increased and uric acid and calcium showed a significant decrease in the prevention group with a dose of 300 mg/kg (P300) in comparison to the EG group ($P < .05$). Also, creatinine showed a significant increase and uric acid showed a significant decrease at the dose of 300 mg/kg (T300 group) compared with the EG group ($P < .05$) (**Table 2**).

Pathological results

While Pathological results did not show any stones or tissue damage in the healthy group, a large number of calcium oxalate crystals were visible in the tubules from the rats in the negative control group. Date palm pits extract decreased calcium oxalate crystals formation and also prevented stone formation in rats' nephrons in a dose-dependent manner (**Figure 1**).

DISCUSSION

In this study, the therapeutic and preventive effects of aqueous extract of date palm (Phoenix dactylifera L.) pits on kidney stones induced by ethylene glycol in male rats were investigated. The results of the study demonstrated that oral treatment of date palm pits extract effectively reduced kidney damage and stone formation in a dose-dependent manner compared with the control group. The results also showed that date palm pits extract had a preventive effect on kidney stone formation.

Ethylene glycol is naturally converted to glycine in the body after being converted to glyoxylic acid by the enzyme alanine-glyoxylate aminotransferase; when the amount of glyoxylic acid reaches too high, it is converted by lactate dehydrogenase to oxalic acid, which in the presence of calcium is converted to insoluble calcium oxalate and deposited in body tissues, especially the kidneys[25].

The study of chemical factors in urine could consider as a good indicator of stone formation rate and type of stone. Urinary saturation with stone constituents is the most important factor in the formation of kidney stones. Previous studies have shown that taking ethylene glycol for fourteen days causes the formation of kidney stones, mainly from calcium oxalate stones in rats, and this is due to the increased concentration of calcium and uric acid in the urine[26-28]. Uric acid plays an important role in calcium solubility. Increasing uric acid prevents the formation of calcium-phosphate and calcium-citrate soluble stones and the production of calcium oxalate stones, thus increasing the production of urinary stones

Table4. The effect of date palm pits extract on urinary parameters on day 28.

Groups	Creatinine (mg/dL)	Uric acid (mg/dL)	Calcium (mg/dL)	Phosphorus (mg/dL)
NC	33.75 ± 12.94	4.47 ± 4.02	2.94 ± 1.53	22.3 ± 3.04
EG	18.5 ± 9.05**	12.28 ± 3.23**	8.2 ± 3.12**	25.25 ± 7.78
T150	22.85 ± 8.6	7.55 ± 3.6#	7.1 ± 1.56	25.7 ± 7.2
T300	27.96 ± 7.78#	5.96 ± 3.13###	6.7 ± 3.7	24.63 ± 6.7
P300	32.2 ± 12.1##	5.51 ± 3.39##	3.02 ± 1.44##	24.15 ± 7.25
	Chi-Square = 11.37	Chi-Square = 16.05	F = 7.43	Chi-Square = 1.78
	P = 0.02	*P* = 0.003	*P* < 0.0001	*P* = 0.77

Data was presented as n (%) and mean ± SD; *Ureteral injury as in European association guideline including I: Mucosal abrasion; II: Ureteral perforation; III: Intussusception / avulsion

[29,30]. Consumption of date palm pits extract in the treatment of kidney stones significantly reduced uric acid and also prevented the increase in urinary uric acid and calcium in a dose-dependent manner thus reduced the risk of formation of kidney stones.

Glomerular filtration rate (GFR) in urolithic rats decreases due to the blockage of urinary tubules by stones formation inside them, and this reduction causes the accumulation of excretory substances such as uric acid, calcium, phosphate, creatinine, and urea in the blood and increases the serum level of these substances and also reduces the excretion substances such as creatinine into the urine and reduces its urinary amounts[27,31,32]. Previous studies have shown that the use of ethylene glycol increases lipid peroxidation and reduces the antioxidant potential of renal tissue, which is an important factor in damaging the tubules and decrease of renal filtration[33]. Treatment with date palm pits extract significantly reduces serum levels of urea, calcium, phosphate, creatinine, and uric acid and also dramatically prevents the increase in serum levels of urea, calcium, phosphate, creatinine, and uric acid and also treatment with date palm pits extract significantly increases urinary creatinine level and also dramatically prevents the reduces urinary creatinine. Increased GFR in therapeutic groups, as well as prevention group, is attributed to antioxidant activity and anti-lipid properties (peroxidation reactions) of date palm pits extract[14,34].

Study of Baghbani et al.[34] on the antioxidant and antimicrobial properties of date palm pits extract and its effects on physicochemical, microbial and sensory properties of cupcake have shown that date palm pits can be considered as an important source of natural antioxidants for medicinal and commercial purposes. Catechins and rutin are found in abundance among the 7 active compounds in date palm pits, including gallic acid, catechin, chlorogenic acid, rutin, vanillin, p-coumaric acid, and sinapic acid. Catechin is the most important polyphenolic compound extracted from date palm pits and flavonoids with significant antioxidant activity. The antioxidant activity of catechins is mostly related to the ortho dihydroxyl groups in the beta ring of the catechin structure, which has anti-free radical activity[35]. It seems that the antioxidant properties of catechins and consequently dates have been one of the main factors in showing the protective properties of date seeds against damage to kidney tissue due to exposure to ethylene glycol.

Previous studies on date palm pits have proven its anti-inflammatory properties, so it could be stated that the aqueous extract of date palm pits may have reduced kidney inflammation.

The microscopic study of kidneys of urolithic rats shows the presence of irregular shapeless crystals inside the tubules, which causes tubule inflammation. Date palm pits extract reduced the number and size of calcium oxalate crystals in the tubules. The results show that the use of date palm pits extract reduces and prevents the formation of urinary stones. It seems that date palm pits extract is effective in preventing recurrent kidney stones.

The precise mechanism of action of date palm pits extract may be due to its antioxidant properties or decrease of the main stone-former constituents in the urine. However, according to our studies knowledge, no study has been reported the effect of date palm pits on kidney stones and the resulting damages; therefore, it is not possible to comment on the exact effects of date palm pits on kidney stones and their possible mechanisms.

CONCLUSIONS

The results of this study show that aqueous extract of date palm pits has been effective in the treatment and prevention of kidney stones induced by ethylene glycol in rats. Its precise mechanism on kidney stones is not clear and requires further investigation. However, its effect may be attributed to the antioxidant and anti-inflammatory properties and the decrease of the main stone-former constituents in the urine.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

ACKNOWLEDGMENTS

This article is the outcome of a research project approved by the Research Council of Birjand University of Medical Sciences (IR.BUMS.REC.1398.153). We hereby would like to thank the Deputy of Research and Technology of Birjand University of Medical Sciences for financing the project (Grant No. 5044), and the Clinical Research Development Unit (CRDU) of Valiasr Hospital, Birjand University of Medical Sciences, Birjand, Iran, for their support, cooperation and assistance throughout the period of study.

REFERENCES

1. Winoker JS, Bamberger JN, Chandhoke RA, Atallah W, Gupta M. What Factors Drive Staghorn vs Nonstaghorn Pattern Growth in Patients with Metabolic Stones? J Endourol. 2019;33:954-9.
2. Evan AP. Physiopathology and etiology of stone formation in the kidney and the urinary tract. Pediatr Nephrol. 2010;25:831-41.
3. Howles SA, Wiberg A, Goldsworthy M, Bayliss AL, Gluck AK, Ng M, et al. Genetic variants of calcium and vitamin D metabolism in kidney stone disease. Nat. Commun. 2019;10:1-0.
4. Coe FL, Worcester EM, Evan AP. Idiopathic hypercalciuria and formation of calcium renal stones. Nat. Rev. Nephrol. 2016;12:519.
5. Khan SR. Is oxidative stress, a link between nephrolithiasis and obesity, hypertension, diabetes, chronic kidney disease, metabolic syndrome? Urol. Res. 2012;40:95-112.
6. Yoshioka I, Tsujihata M, Momohara C, Akanae W, Nonomura N, Okuyama A. Effect of sex hormones on crystal formation in a stone-forming rat model. Urol. J. 2010;75:907-13.
7. Hiller N, Berkovitz N, Lubashevsky N, Salaima S, Simanovsky N. The relationship between ureteral stone characteristics and secondary signs in renal colic. Clin. Imaging. 2012;36:768-72.
8. Cheungpasitporn W, Rossetti S, Friend K, Erickson SB, Lieske JC. Treatment effect, adherence, and safety of high fluid intake for

the prevention of incident and recurrent kidney stones: a systematic review and meta-analysis. J. Nephrol. 2016;29:211-9.
9. Labadie K, Okhunov Z, Akhavein A, Moreira DM, Moreno-Palacios J, del Junco M, et al. Evaluation and comparison of urolithiasis scoring systems used in percutaneous kidney stone surgery. J Urol. 2015;193:154-9.
10. Abdel-Aal E, Daosukho S, El-Shall H. Effect of supersaturation ratio and Khella extract on nucleation and morphology of kidney stones. J. Cryst. Growth. 2009;311:2673-81.
11. Atmani F, Slimani Y, Mimouni M, Aziz M, Hacht B, Ziyyat A. Effect of aqueous extract from Herniaria hirsuta L. on experimentally nephrolithiasic rats. J. Ethnopharmacol. 2004;95:87-93.
12. Hajian S, Hamidi-Esfahani Z. Date palm status and perspective in Iran. Date palm genetic resources and utilization: Springer; 2015. p. 19-47.
13. Hamada J, Hashim I, Sharif F. Preliminary analysis and potential uses of date pits in foods. Food Chem. 2002;76:135-7.
14. Ardekani MRS, Khanavi M, Hajimahmoodi M, Jahangiri M, Hadjiakhoondi A. Comparison of antioxidant activity and total phenol contents of some date seed varieties from Iran. IJPR. 2010;9:141.
15. Dehghanian F, Kalantaripour TP, Esmaeilpour K, Elyasi L, Oloumi H, Pour FM, et al. Date seed extract ameliorates β-amyloid-induced impairments in hippocampus of male rats. Biomed Pharmacother. 2017;89:221-6.
16. Hasan M, Mohieldein A. In vivo evaluation of anti diabetic, hypolipidemic, antioxidative activities of Saudi date seed extract on streptozotocin induced diabetic rats. JCDR. 2016;10:FF06.
17. Orabi SH, Shawky SM. Effect of date palm (Phoenix dactylifera) seeds extracts on hematological, biochemical parameters and some fertility indices in male rats. IJBAS. 2014;17:137-47.
18. Al-Shahib W, Marshall RJ. Fatty acid content of the seeds from 14 varieties of date palm Phoenix dactylifera L. Int. J. Food Sci. Technol. 2003;38(6):709-12.
19. Adeosun AM, Oni SO, Ighodaro OM, Durosinlorun OH, Oyedele OM. Phytochemical, minerals and free radical scavenging profiles of Phoenix dactylifera L. seed extract. JTUSCI. 2016;11:1-6.
20. Habib HM, Ibrahim WH. Effect of date seeds on oxidative damage and antioxidant status in vivo. J Sci Food Agric. 2011;91:1674-9.
21. Christina A, Packia Lakshmi M, Nagarajan M, Kurian S. Modulatory effect of Cyclea peltata Lam. on stone formation induced by ethylene glycol treatment in rats. Methods Find Exp Clin Pharmacol. 2002;24:77-80.
22. Safari H, Esmaeili S, Naghizadeh MS, Falahpour M, Malekaneh M, Sarab GA. The effects of aqueous extract of Eryngium campestre on Ethylene Glycol-Induced calcium oxalate kidney stone in Rats. Urol. J. 2019 Dec 24;16:519-24.
23. Mohammadian N, Rahmani Z, Rassouli FB. Effect of thymoquinone on ethylene glycol-induced kidney calculi in rats. J. Urol. 2008;5:149-55.
24. Sakly R, Chaouch A, El Hani A, Najjar MF. Effects of intraperitoneally administered vitamin E and selenium on calcium oxalate renal stone formation: experimental study in rat. ANN UROL. 2003;37:47-50.
25. Guo C, Cenac TA, Li Y, McMartin KE. Calcium oxalate, and not other metabolites, is responsible for the renal toxicity of ethylene glycol. Toxicol. Lett. 2007;16:173-8.
26. Azaryan E, Malekaneh M, Nejad MS, Haghighi F. Therapeutic effects of aqueous extracts of cerasus avium stem on ethylene glycol-induced kidney calculi in rats. J. Urol. 2017;14:4024-9.
27. Karadi RV, Gadge NB, Alagawadi K, Savadi RV. Effect of Moringa oleifera Lam. root-wood on ethylene glycol induced urolithiasis in rats. J. Ethnopharmacol. 2006;105:306-11.
28. Sikarwar I, Dey YN, Wanjari MM, Sharma A, Gaidhani SN, Jadhav AD. Chenopodium album Linn. leaves prevent ethylene glycol-induced urolithiasis in rats. J. Ethnopharmacol. 2017 Jan 4;195:275-82.
29. Shekarriz B, Stoller ML. Uric acid nephrolithiasis: current concepts and controversies. J Urol. 2002 Oct 1;168:1307-14.
30. Makasana A, Ranpariya V, Desai D, Mendpara J, Parekh V. Evaluation for the anti-urolithiatic activity of Launaea procumbens against ethylene glycol-induced renal calculi in rats. Toxicol. Rep. 2014 Jan 1;1:46-52.
31. Manjula K, Rajendran K, Eevera T, Kumaran S. Effect of Costus igneus stem extract on calcium oxalate urolithiasis in albino rats. Urol. Res. 2012;40:499-510.
32. El Menyiy N, Al Waili N, Bakour M, Al-Waili H, Lyoussi B. Protective effect of propolis in proteinuria, crystaluria, nephrotoxicity and hepatotoxicity induced by ethylene glycol ingestion. Arch Med Res. 2016;47:526-34.
33. Shah JG, Patel BG, Patel SB, Patel RK. Antiurolithiatic and antioxidant activity of Hordeum vulgare seeds on ethylene glycol-induced urolithiasis in rats. Indian J Pharmacol. 2012 Nov;44:672.
34. Baghbani F, Shirazinejad A. Study of Antioxidant and Antimicrobial Activity of Date Seed Extract and its Effects on Physicochemical, Microbial and Sensory Properties of Cupcake. Food Sci. Technol. 2019;16:327-42.
35. Higdon JV, Frei B. Tea Catechins and Polyphenols: Health Effects, Metabolism, and Antioxidant Functions. Crit Rev Food Sci Nutr. 2003;43:89-143.