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CURATIVE EFFECTS OF ETHANOL EXTRACT OF PROSOPIS FARCTA (SYRIAN MESQUITE) AGAINST ETHYLENE GLYCOL INDUCED UROLITHIASIS IN MALE ALBINO RATS

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ABSTRACT:
The present study was designed to evaluate the antiurolithiatic activity of *Prosopis farcta* (*P. farcta*) ethanol fruit extract in ethylene glycol (EG) induced urolithiasis in male albino rats. Lithiasis was induced by oral administration of EG 1% in male albino rats for 28 days. Seventy eight male albino rats weighing 250-300g were used and divided into six experimental groups. Group A is a control group received standard rat chow and tap water *ad libitum*, while, rest of groups namely group B, C, D, E, F animals received 1% EG in water for 28 days, then from day 15 to day 28 in addition to EG administration, group C received cystone, group D, E and F received 100, 200 and 300 mg/kg body weight (B.W.) of ethanol fruit extract of *P. farcta* respectively. On day 28, blood was collected for serum biochemical (serum uric acid, creatinine, urea, electrolytes measurements, malondialdehyde (MDA) and superoxide dismutase (SOD)) determinations. While urine was collected to microscopic analysis of formed crystals besides the kidney weight/ B.W. ratio and B.W. gain/ loss values were determined. Intermediate dose (200mg/kg B.W.) of *P. farcta* extract significantly decreased serum creatinine, urea, MDA and non-significantly recovered SOD toward control value in group E as compared to group B, also significant elevation in kidney weight/ B.W. ratio and reduction in B.W. gains in group B occurred as compared with group A. In conclusion: *P. farcta* fruit extract has potentially therapeutic effects on EG induced kidney stone which can be used as effective antiurolithiatic agent rather than cystone.

KEYWORDS: Antioxidant activity; cystone; ethylene glycol; kidney stone; Prosopis farcta.

1. INTRODUCTION

Medicinal plants are referred to the herbs that use to treat various diseases and medicinal problems due to presence of numerous bioactive compounds (Arshad *et al*., 2020). According to recorded fossil, the use of herbal medicine by human goes back at least 60,000 years (Yuan *et al.,* 2016). In the traditional medicine different plant parts, like leaf, root, fruit, seeds, flowers, skin or even the whole plant possible to use (Phillipson, 2001). It has been reported that chemical constituents in plant may vary according to habitat, harvest season, drying processes and many other factors (Gad *et al.,* 2013). Alkaloids, polyphenols, essential oils, tannins, quinones, sterols, saponins …etc, are some bioactive compounds with various biological activities (Manzoor *et al*., 2016).
It has been recorded that plants products are used to treat different types of disease such as chronic kidney disease (CKD) (Sundaram *et al.,* 2019), joint, skin, gastric disorders (Alvi *et al*., 2018). Also they can act as anti-fever, anti-cancer, anti-proliferation (Lim *et al*., 2019), hypnotic, sedative, cough suppressant, purgative, demulcent, antiseptic, expectorant, vasorelaxant, and antispasmodic, and hence used to manage bronchitis, pertussis, gastrointestinal, asthma and various other ailments (Mahmud, 2015).
Prosopis farcta (Syrian mesquite) in the Fabaceae family belongs to flowering herbs, which is native to Asia and distributed from India to Iran (Keshavarzi *et al.,* 2018). More than 44 species of the genus *Prosopis* have been described. The *Prosopis* species are often spiny trees and shrubs, the average height between 2 to 3 m long may be taller or smaller, well adapted to warm and drought weather (Prabha *et al.,* 2017). *Prosopis farcta*, represents an important plant which used in folk medicine due to the presence of different bioactive compounds (Al-jeboory and Dizaye, 2006).
It has been found that flavonoids, tannins, alkaloids, quinones, phenolics, glycosides, steroids, tannins and triterpenoids are the main bioactive compounds which detected in *Prosopis* species (Sharifi-Rad *et al.,* 2019). In traditional medicine, the fruits of *Prosopis* species can be used as a diuretic (Ewais *et al.,* 2017) and to treat kidney stones (Othman *et al.,* 2018), asthma, callouses, conjunctivitis, diabetes, diarrhea, expectorant, fever, flu, lactation, liver infection, malaria, otitis, pains, pediculosis, rheumatism, scabies, skin inflammations, stomach ache, removal of bladder, pancreas stones (Younis *et al.,* 2018) and cardiovascular disorders (Asadollahi *et al.,* 2010).
Urolithiasis or kidney calculi are the most common kidney problem in the urinary tract diseases. They cause sever hemorrhage, strong ache, close the flow of urine through urinary tract and other risks, due to they necessary to take or break by operation (Bahmani *et al.,* 2016). Recently, it has been investigated that renal calculi affecting nearly 12% of the population, with a rate of recurrence 47-60% in female, and 70-81% in males (Arya *et al*., 2017). It has been investigated that calcium oxalate (CaOx) urolithiasis model which induced by administration of EG (precursor of oxalate formation) use to study the effect of kidney stone on experimental model in rats (Mahmud *et al*., 2021).

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Concerning to the application of *P. farcta* in ethnopharmacology for treatment of kidney stone between the local people, the present study was aimed to find the curative effects of *P. farcta* ethanol extract in EG induced kidney stone in male albino rats.

2. MATERIALS AND METHODS

2.1 Plant Materials and Extraction

The *P. farcta* fruits (Fig. 1) were collected from Soran-Erbil and used during the present study. The plant extraction was performed by soaking 3kg of powdered air-dried *P. farcta* fruits in sufficient amount of ethanol 99% with occasional shaking. This process repeated several times, using a fresh solvent each time. The protocol of Bukhari et al., (2016) with minor modification was followed to filtered extract through filter paper, and the filtrate was concentrated in a rotary evaporator at 25-30 C° under reduced pressure (-760 mmHg).

Figure 1. *Prosopis farcta (Fabacea)* (Othman and Shaswary, 2018).

2.2 Animals Housing and Breeding

Seventy eight male albino rats of about 250-300g B.W. were used in the present study. Animals were bred in animal house, and maintained in plastic cages bedded with wooden chips. Kept housed under standard laboratory conditions, with a photoperiod of 12hrs light followed by 12hrs darkness and at 22 ± 2ºC (Al-Habib *et al.,* 2015). Animals were fed on standard rat chow and tap water *ad libitum.*

2.3 Experimental Design

This experiment was designed to study the curative effects of *P. farcta* on EG induced urolithiasis in male albino rats. Cystone inhibits inducing urolithiasis through the declination of calculi formers (Azarfar *et al*., 2020). Hyperoxalurea and CaOx deposition in the kidney was induced by adding EG to the drinking water to a final concentration of 1% for 28 days (Mahmud *et al*., 2021), for all groups except for the control group. Animals were assigned randomly to six different treatment groups as follow:

Group: A (N= 10)

Control rats supplied with standard rat chow and tap water *ad libitum*.

Group: B *(*N=10)

Rats were given drinking water supplemented with EG (1%) and standard rat chow.

Group: C (N=9)

Rats were given 2.5 tablets of cystone in 100 ml of drinking water supplemented with EG (1%) and 2.5 tablets in 100 g of standard rat chow from day 15 after inducing kidney stone.

Group: D (N=8)

Rats were given ethanol extract of *P. farcta* fruits (100mg/ kg B.W. rat (low dose)) from day 15 and drinking water supplement with EG (1%) and standard rat chow.

Group: E (N=8)

Rats were given ethanol extract of *P. farcta* fruits (200mg/ kg B.W. rat (intermediate dose)) from day 15, drinking water supplement with EG (1%) and standard rat chow.

Group: F (N=7)

Rats were given ethanol extract of *P. farcta* fruits (300mg/ kg B.W. rat (high dose)) from day 15, drinking water supplement with EG (1%) and standard rat chow.

2.4 Collection of Urine Sample

At the end of experiment, the urine samples were collected for urinanalysis to find out CaOX crystals using light microscope in experimental groups

2.5 Collection of Blood Samples

At the end of experiment, the rats were anesthetized with ketamine hydrochloride (80 mg/Kg) and Xylazin (12 mg/Kg) intraperitoneally. Blood samples were taken by cardiac puncture into chilled tubes without ethylene diamine tetra acetic acid (EDTA) (4.5mM) as anticoagulant and centrifuged at 3000 rpm for 15 minute (Mahmud *et al*., 2021), then used for determination of some serum bichemical measurements.

2.6 Biochemical Determination

2.6.1 Determination of Kidney Function Parameters (serum uric acid, creatinine and urea) and Surum Electrolytes (serum sodium, calcium, potassium, chloride and phosphorus) Levels

Serum uric acid, creatinine, urea, sodium, calcium, potassium, chloride and phosphorus were determined by Cobas 6000 C501.

2.6.2 Determination of Serum Malondialdehyde Serum MDA was determined using a microplate enzyme immunoassay (ELISA) MDA kit (Teb Pazhouhan Razi).

2.6.3 Determination of Serum Superoxide Dismutase Activity Serum SOD was determined using a microplate enzyme immunoassay (ELISA) SOD kit (Teb Pazhouhan Razi).

2.7 Statistical Analysis

All data were expressed as means $\pm$ standard error (S.E), normality of data distribution was confirmed by using D'Agostino and pearson test and statistical analysis was carried out using GraphPad Prism 8 program (Version 8) (GraphPad Software, USA).

The comparisons among groups (all experimental groups were compared to model group (EG group)) were done using one-way ANOVA. P-values less than 0.05 ($P<0.05$) were considered as statistically significant. In all figures the symbols, (*, **, ***and ****) represent that mean of differences are significant at the 0.05, 0.01, 0.001and 0.0001 levels, respectively.

3. RESULTS

3.1 Body weight gain/ loss

Rats body weight gain significantly (P<0.0001) reduced by EG administration (-20 ± 3.496 g) as compared to control (40 ± 5.164 g), also cystone and low dose of the *P. farcta* extract significantly (P<0.0001) induced further reduction in B.W. (-50 ± 4.009 g) and (-50 ± 2.998 g) respectively. But high dose of *P. farcta* non-significantly reduced the effects of EG on B.W. as compared to EG treated rats (Fig. 2).

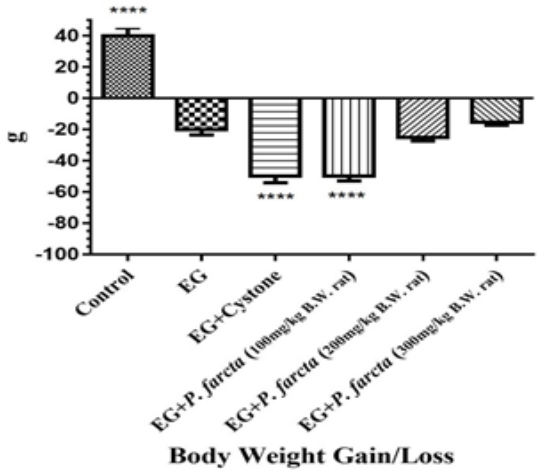


Figure 2. The effect of *P. farcta* extract on body weight.

3.2 Kidney weight/ body weight ratio

In the present study the kidney weight/ B.W. ratio significantly (P<0.0001) increased in EG group (0.0093 ± 0.00064 g) as compared with control group (0.0036 ± 0.00012 g). In EG treated rats cystone and different doses of *P. farcta* extract (100 and 300 mg/kg B.W.) non-significantly increased the kidney weight/ B.W. ratio as compared with EG treated rats (Fig. 3).

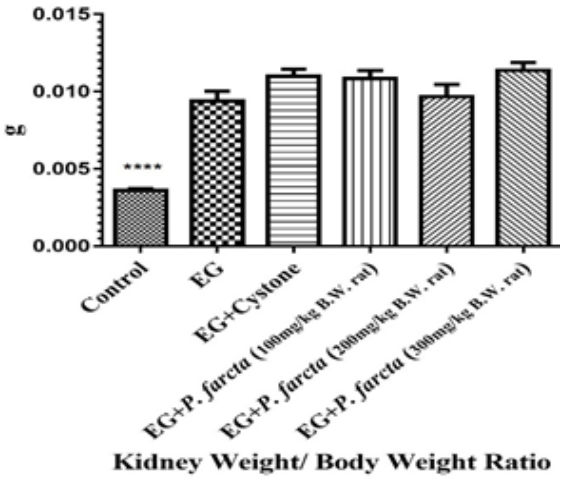


Figure 3. Effect of *P. farcta* extract on kidney weight/ body weight ratio.

3.3 Serum uric acid, creatinine and urea levels

There were no significant differences in serum uric acid concentration in EG treated rats and control rats. But administration of cystone and low (100mg/ kg B.W.) and high (300mg/ kg B.W.) *P. farcta* doses to rats treated with EG non-significantly elevated uric acid concentration as compared to EG treated rats (Fig. 4A).

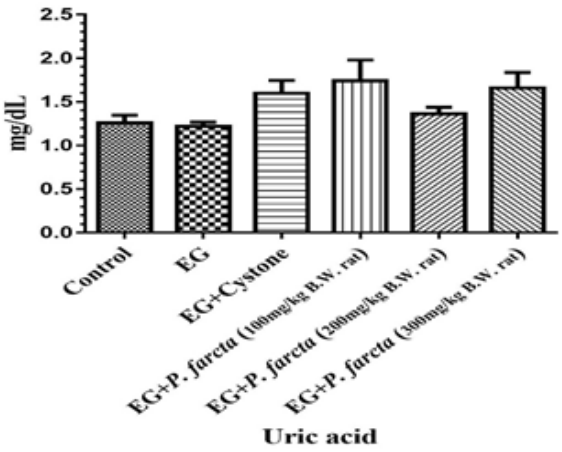


Figure 4A. The effect of *P. farcta* extract on serum uric acid.

As in (Figure 4B) showed that serum creatinine significantly (P<0.0001) increased (1.33 ± 0.1179 mg/dL) in rats treated with EG as compared with control rats (0.4067 ± 0.022 mg/dL). But interestingly the intermediate dose of *P. farcta* extract significantly (P<0.05) and cystone non-significantly decreased the serum creatinine level (0.77 ± 0.059 mg/dL) and (0.813±0.103 mg/dL) respectively as compared with EG treated rats, while low and high doses of *P. farcta* extract didn't make significant changes in the serum creatinine level.

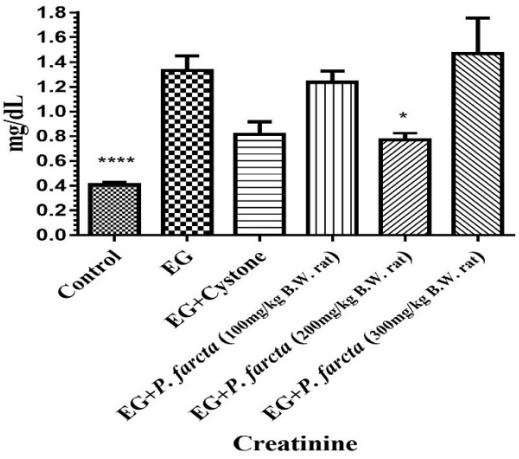


Figure 4B. The effect of *P. farcta* extract on serum creatinine.

Like serum creatinine, serum urea was also markedly (P<0.0001) increased via EG treatment (160.1 ± 10.27 mg/dL) versus control rats (58.37 ± 2.831 mg/dL). Also intermediate dose (200 mg/kg B.W.) of *P. farcta* extract significantly (P<0.05) decreased the serum urea concentration (103.5 ± 8.976 mg/dL), in contrast to intermediate dose, low (100 mg/kg B.W.) and high (300 mg/kg B.W.) doses of *P. farcta* extract significantly (P<0.05) increased serum urea level (220.9 ± 18.34 mg/dL) and (221.9 ± 16.55 mg/dL) respectively. But cystone non-significantly increased the urea concentration in EG treated rats as compared with EG treated rats (Fig. 4C).

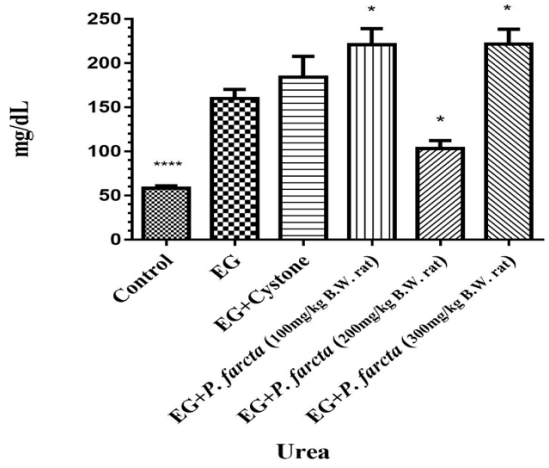


Figure 4C. The effect of *P. farcta* extract on serum urea.

3.4 Serum electrolytes (Na+, Ca+, K+ and Cl- and phosphorus) level

Statistical analysis revealed that during this study there were no any significant differences among the experimental groups in serum Na^+, Ca^+, K^+, Cl^- and phosphorus concentration (Figs. 5 A, B, C, D and E respectively).

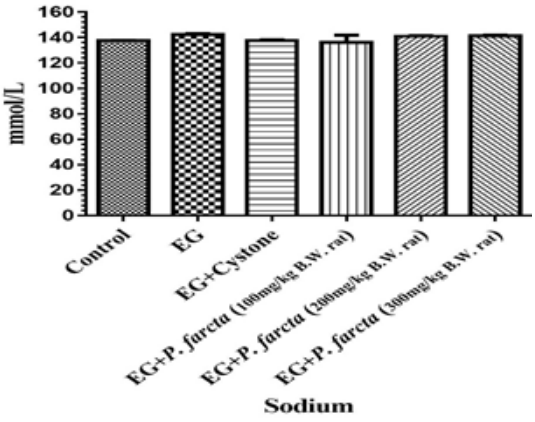


Figure 5A. The effect of *P. farcta* extract on serum sodium.

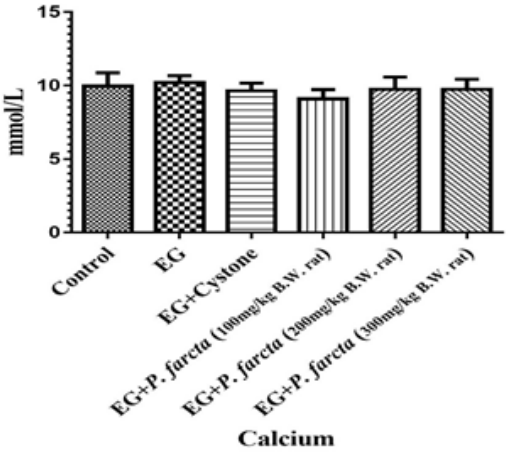


Figure 5B. The effect of *P. farcta* extract on serum calcium.

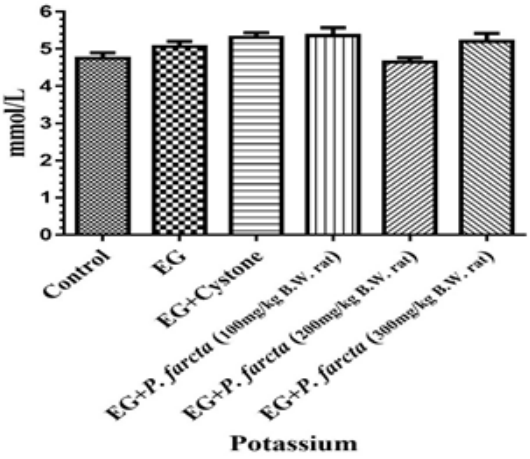


Figure 5C. The effect of *P. farcta* extract on serum potassium.

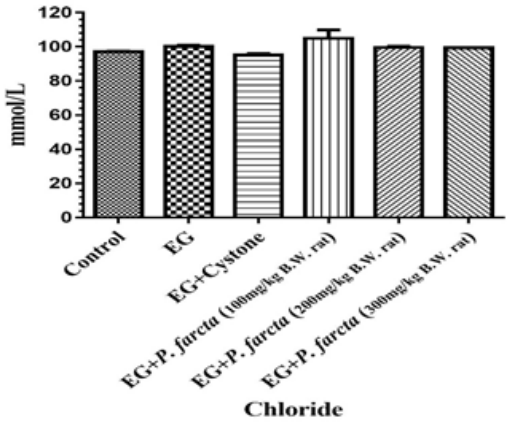


Figure 5D. The effect of *P. farcta* extract on serum chloride.

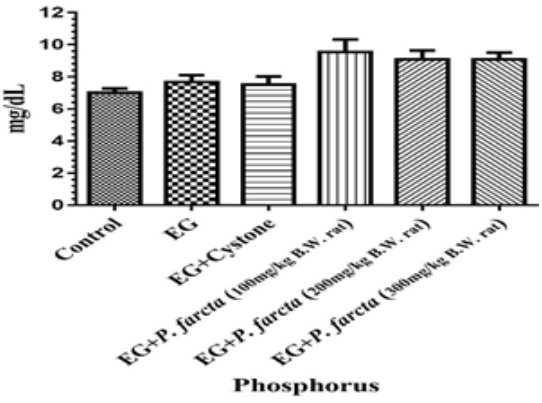


Figure 5E. The effect of *P. farcta* extract on serum phosphorus.

3.5 Serum Malondialdehyde Activity

From the data of the current study, statistical analyse showed that MDA activity strongly ($P<0.0001$) increased in EG treated rats (339.1 ± 32.84 U/mL) as compared with control rats (118.5 ± 9.581 U/mL). In rats treated with EG, the administration of cystone and intermediate dose of *P. farcta* extract significantly ($P<0.001$) reduced the MDA activity close to the control level (162.2 ± 15.07 U/mL) and (172.4 ± 18.98 U/mL) respectively, also low *P. farcta* extract dose could lower the MDA activity but non-significantly (Fig. 6).

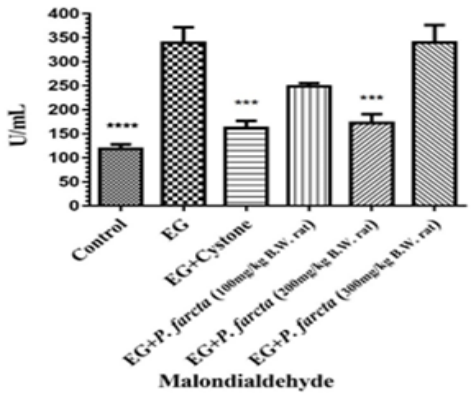


Figure 6. The effect of *P. farcta* extract on malondialdehyde activity.

3.7 Serum Superoxide Dismutase Activity

Total SOD activity was markedly (P<0.001) increased (1.142 ± 1.496 U/mL) in EG treated rats as compared to control rats (-26.59 ± 3.815 U/mL). The supplementation of cystone, low and intermediate doses of *P. farcta* extract, were non-significantly reversed the effects of EG treatment and they reduced the SOD activity as increased by the EG action (Fig. 7).

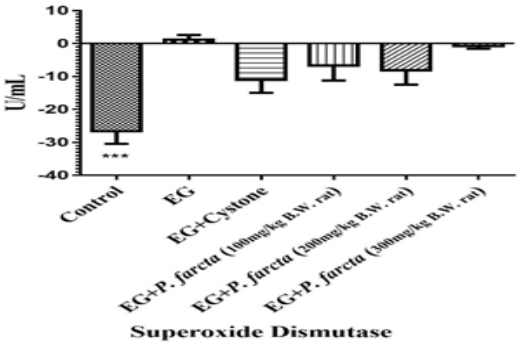
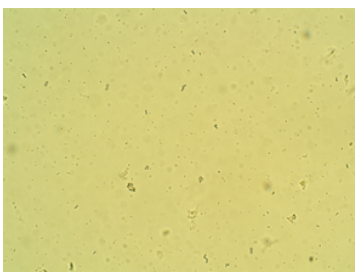


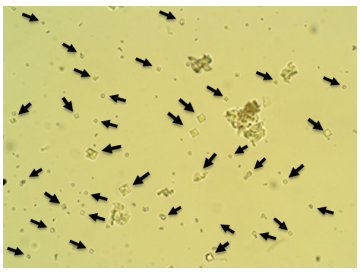
Figure 7. The effect of *P. farcta* extract on superoxide dismutase.

3.6 Micoscopic Urineanalysis

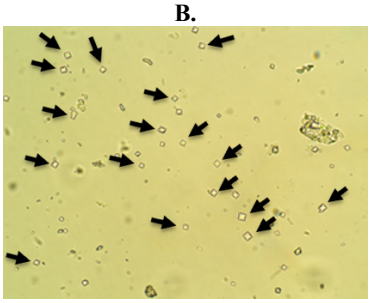
In the rats treated with EG, microscopically urineanalysis revealed that numerouse CaOX crystals deposited as compared to contro rats (Fig. 8 A & B). Administration of cystone to EG treated rats didn't show any significant changes in the quantity of deposite crystals as copared to EG treated rats (Fig. 8 B & C). But, low (100 mg/ kg B.W.) and high (300 mg/ kg B.W.) doses of P. farcta extract in EG treaed rats reduced the deposition of CaOX crystals as compared to EG treated rats (Fig. 8 B, D & F), wherease, supplementation of intermediate dose (200 mg/ kg B.W.) of P. farcta extract in EG treated rats inhibited the deposition of CaOX crystals as compared to EG treated rats (Fig. 8 B & E).



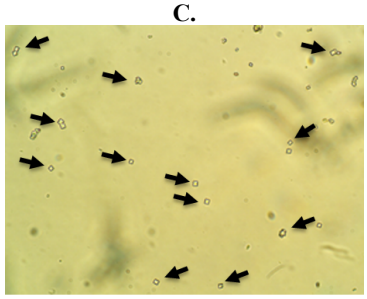
A.



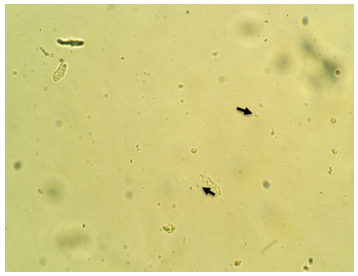
B.



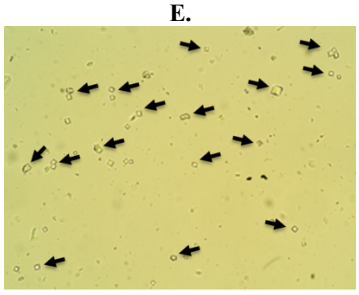
C.



D.



E.



F.

Figure 8: The CaOX crystals viewed in light microscope in urine, **(A)** control group showing normal appearance, **(B)** EG treated group showing crystals deposition, **(C)** EG+cystone treated group showing crystal deposition, **(D)** EG+low *P. farcta* extract dose treated group showing decreased crystal deposition, **(E)** EG+intermediate *P. farcta* extract dose treated group showing prevention crystal deposition, **(F)** EG+high *P. farcta* extract dose treated group showing moderate amount crystal deposition.

4. DISCUSSION

The current results showed that serum creatinine, urea, MDA and SOD levels significantly increased in EG treated rats as compared to control rats, but administration of *P. farcta* extract (200 mg/kg B.W) to EG treated rats significantly reduced serum creatinine, urea and MDA and also non-significantly reduced serum SOD toward control values.

The *P. farcta* fruit extract showed important role in improving kidney disorder. Concerning to obtained data, several studies are in agreement to our investigations. Recently, it has been shown that herbal medicine are effective to improve kidney function parameters and kidney disorders (Ahmed and Sarma, 2017). On the other hand, Mutalib, (2015) reported that herbal medcine could act as therapeutic agent to control urolithiasis disorder. Furthermore, Nirumand *et al*., (2018) showed that herbal medicine cures urolithiasis via different mechanisms such as increasing excretion of urinary calcium, oxalate and citrate, dissolving of stones and inhibition growth of the CaOx crystals, and via its antioxidant, nephroprotective and cytoprotective actions.

As revealed that *P. farcta* extract decreased the concentration of creatinine and urea in EG treated rats. Recent investigation supported the data of the current study that EG elevated kidney function measurements through kidney stone formation; in contrast the herbs could decline these measurements (Sharma *et al.,* 2017). Furthermore, (Byahatti *et al.,* 2010), showed that phenolic compounds could dissolve the CaOx and phosphate renal stones type. Also, the plant extract prevent binding of CaOx crystals to the renal cells' surface because in the plant extract different bioactive compounds particularly polyphenols could react with the renal cells (Cheraft-Bahloul *et al.,* 2017). On the other hand, numerous studies reported that caffeic acid plays crucial roles in kidney disorders treatment (Yagmurca *et al.,* 2004), due to its antioxidant action which blocking the formation of ROS (Sud'Ina *et al.*, 1993). Also in *P. farcta*, polyphenols and caffeic acid (Karimi *et al.,* 2017), might be prevent deposition or dissolve kidney stones.

The data of the present study showed that MDA value markedly elevated in EG treated rats. This result is supported by El Menyiy *et al.,* (2016), finding that EG strongly increased the rate of free radical production and decreased the antioxidant enzymes' activity. It has been shown that in rats EG significantly elevated the concentration of MDA in comparison to normal rats (Aksoy and Aslan, 2017). On the other hand, De Vecchi *et al.,* (2009), recorded that in patient with renal disease and underwent dialysis process the MDA level was higher as compared with healthy person. Some studies discovered that MDA activity elevation in CKD is contributed to raising of oxidative stress and free radical production, as start at the beginning of renal disorder and being to a great level as the GFR fall down (Florens *et al.,* 2016).

In the data of the current investigation appeared that SOD significantly increased in EG treated rats, this observation is agree with Celik and Suzek, (2007) findings in rats EG administration potentially increased the activity of serum MDA and SOD and these deviation may related to damaging of the tissues and failuring in their function. Also, it has been discovered that in CKD, SOD activity markedly elevated (Florens *et al.,* 2016). Furthermore, in kidney disorder case the SOD activity elevated to protect against the induced lipid peroxidation process (Kuo et *al.,* 2005). On the other hand, Koç *et al.,* (2015) indicated that SOD can react with produced free radicals as the first antioxidant enzyme, resulting SOD activity become high to destroying existed free radicals. Moreover, cells can grow to advancement of their antioxidant enzymes including SOD, catalase (CAT) and glutathione-S-transferase (GST) to keep away from adverse effects of free radicals (Karajibani *et al.,* 2017).

The intermediate dose of *P. farcta* extract significantly reduced the elevation of MDA in EG treated rats, also low and intermediate doses non-significantly reduced the effects of EG on SOD activity. This was supported by the observation of Mohammad and his colleague (2018), they showed that in rats treated with thioacetamide induced oxidative stress, the MDA activity was increased, but administration of *P. farcta* inibited thioacetamide effect and declined oxidative stress and serum MDA (Mohammad *et al.,* 2018). The phytochemical screening in *P. farcta* revealed the presence of some bioactive constitutes such as caffeic acid (Karimi *et al.,* 2017), flavonoids (quercetin), glycosides, tannins, alkaloids, saponins, phenols, resins and sterols, and most of these chemicals have powerful antioxidant activity, free radicals scavengers and also prevent oxidation process (Keshavarzi *et al.,* 2018). On the other hand, Luqman *et al.,* (2009), recorded that quercetin is most effective in declination of MDA via prevention of peroxidation of cell lipids. Furthermore, Koltuksuz *et al.,* (1999) concluded that caffeic acid play essential role in prevention of lipoxygenase activities, as well as inhibition lipid peroxidation process. Recently recorded that in induced oxidative rats *P. farcta* strongly decreased elevated MDA concentration which mainly contributed to the present of antioxidant chemicals apigenin, quercetin and flavonoid (Mohammad *et al.,* 2018).

There is no apparent dose response in the effects of *P. farcta* extract on EG-induced kidney toxicity, beacuse statistically revealed that only intermediate dose (200mg/ kg B.W. rat) of *P. farcta* extract partially reversed some EGs' adverse effects, while low (100mg/ kg B.W. rat) and high (300mg/ kg B.W. rat) doses didn't show valuable effects against EGs' action with unknown mechanism, concerning to that additional studies will be need to discover and extend the mechanism of its actions.

5. CONCLUSIONS

From the obtained data of the present study it has been concluded that *P. farcta* had potentially therapeutic effects in urolithiasis problems. Intermediate dose of *P. farcta* extract showed potential effects in lowering serum creatinine and urea as increased by the EG, also it inverted the action of EG on MDA and SOD which recovered their actvity toward the normal values.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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