

## Diuretic Effect of *Prosopis farcta* in Comparison with Spironolactone and Hydrochlorothiazide in Hypertensive Rats

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### Abstract

*Prosopis farcta* has been used traditionally for several diseases as cardiovascular, kidney, diabetes, bacterial infection and it has diuretic activity. This study was designed to evaluate the diuretic effects of *P. farcta* extract in comparison with spironolactone and hydrochlorothiazide in normal and hypertensive rats. Forty eight rats, were divided into Two groups. The First group was consist of Twelve normotensive rats, to represent the control group and normal treated group receiving 50 mg/Kg of *P. farcta* extract; Six rats in each group.

The Second group involved 36 hypertensive rats, were divided into six subgroups, each of six rats. The First subgroups served as a positive control, the Second, Third and Fourth sub-groups were received 25, 50, 100 mg/Kg of *P. farcta* fruit extract respectively. The Fifth and Sixth subgroups were received 5 mg/kg spironolactone, and 25 mg/Kg thiazide orally for a week. *P. farcta* extract produced a significant increase in urine flow, Sodium excretion rate, eGFR and urinary creatinine level. In addition there were significant reduction in heart rate, and serum creatinine and blood urea.

**Conclusion:** *P. farcta* fruit extract has mild diuretic activity in normal and hypertensive rats that resemble the potassium sparing diuretics.

**Keywords:** *Prosopis farcta*, Diuretics, Thiazide, Spironolactone, Antihypertensive.

## فعالية الينبوت كمدد للبول بالمقارنة مع سبيرونولاكتون وهيدروكلوروثيازيد عند الجرذان المصابين بضغط الدم

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### الخلاصة

استخدم الينبوت تقليدياً في العديد من الأمراض مثل أمراض القلب والأوعية الدموية والكلية والسكري والعدوى البكتيرية. و له نشاط مدر للبول. تم تصميم هذه الدراسة لتقييم ومقارنة فعالية الجرعات المختلفة لمستخرج الينبوت بالعقار (الثيازيد وسبيرونولاكتون) وتأثيرها على إدرار البول في الجرذان ذات ضغط طبيعي والم رتفعي الضغط الدم. أجريت الدراسة على ٤٨ جرذاً، تم تقسيمها على النحو التالي؛ المجموعة الأولى تتألف من ١٢ جرذاً مصاباً بارتفاع في ضغط الدم، لتمثيل المجموعة الضابطة والمجموعة الغير مصاب بارتفاع ضغط الدم التي زودت بجرعة ٥٠ ملغ/كغ من مستخرج فواكه الينبوت، ٦ جرذان في كل مجموعة. والمجموعة الثانية تشمل ٣٦ جرذاً مصاباً بارتفاع ضغط الدم، تم تقسيمها إلى ٦ مجموعات فرعية، وتتكون كل منها من ٦ جرذان. زودت المجموعات الفرعية الثانية والثالثة والرابعة بجرعات ٢٥، ٥٠، ١٠٠ ملغ/كغ من المستخرج الينبوت عن طريق الفم على التوالي. وزودت المجموعتين الفرعيتين الخامسة والسادسة ٥ م ملغ/كغ بدواء سبيرونولاكتون، و ٢٥ ملغ/كغ بدواء الثيازيد. أن مستخرج فواكه الينبوت لها تأثير ملحوظ في تدفق البول، ومعدل إفراز الصوديوم، معدل الترشيح الكلوي ومستوى الكرياتينين البولي. بالإضافة إلى ذلك، كان هناك انخفاض في ضغط الدم ومعدل ضربات القلب والكرياتينين في الدم وبوريا الدم في الجرذان غير المصابة بارتفاع ضغط الدم. **الخلاصة:** لقد أوضحنا في هذه الدراسة التي أجريت على الجرذان أن المستخرج فاكهة الينبوت له نشاط خفيف مدر للبول في الجرذان غير مصابة بارتفاع ضغط الدم، ولا يخفض ضغط الدم كثيراً وبشبه مدرات البول المستقبلية للبوواسيوم. الكلمات المفتاحية: فاكهة الينبوت، مدرات البول، الثيازيد، سبيرونولاكتون، الخافضة للضغط.

### Introduction

Nowadays, several medications are either used as a single agent or in combination to manage cardiovascular among

these medications are diuretics. Diuretic frequently prescribed in a clinical setting to control blood pressure and fluid overload <sup>(1)</sup>.

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Generally, this type of medication is affordable, easily accessed, with minimum side effects, and can be used alone or with other antihypertensive drugs to have a blood pressure lowering, as a result avoiding resistant and complications<sup>(2)</sup>.

There are several plants have been reported to show significant diuretic activity<sup>(3)</sup>. Remarkably, there is an increase in the popularity of herbal medicine among the general population; this made it possible to increase in the number of herbal drug manufacturers<sup>(4)</sup>.

In traditional folk medicine, many plants have been used for diuretic purposes, such as *Prosopis farcta* fruit (*P.f.f.*), *Matricaria Chamomilla*, *Mangifera indica*, *Mimosa pudica*, *Lipidium sativum*, and *Achyranthes aspera* and *Doradilla*. In addition *P. farcta* particularly had been studied comprehensively in cardiovascular diseases and have been successful in lowering blood pressure<sup>(5,6)</sup>.

The genre of *P. farcta* classified to as many as 50 species, the tree of *P. farcta* is spiny and grow in the hot and arid climate, which is naturally grown and has been reported to benefit for many Cardiovascular diseases, cancer diabetes, skin disorder<sup>(7)</sup>.

This study is designed to explore the potential diuretic effect of *P. farcta* fruit decoction in normotensive and hypertensive rat model. To this point, as far as the scientific research engine concern in English language there is not known study on diuretic properties of *P. farcta* fruit extract.

## Material and Methods

### Plant material

*Prosopis farcta* fruit was obtained from the Sulaimani province in the Kani Panka area. The taxonomic classification of the collected plant samples was confirmed by expertise in botany and plant sciences at the Faculty of Agriculture in Bakrajo. The fruit was washed and dried then crushed to a fine powder by the grinder, 10 g powder boiled in 200 ml of water for 15 minutes<sup>(8)</sup>. After cooling the solution was passed through a filter paper, and the resulted solution was freshly used.

### Animals

All the experiments used a total of 48 adult rats (200 to 250 g), from the animal facilities of the University of Sulaimani. They were acclimated under a temperature of  $23 \pm 2$  °C, and 12 hours light/12 hours dark cycle. Food and water were given. All experiments followed the experimental protocols previously approved by the Ethics Commission, and the animals were handled according to internationally accepted standard guidelines for animal use. The experiment was terminated when the scientific aims and objectives have

been reached. During the experimental study, we ensured that pain and distress were minimized or relieved.

### Experimental designs

After two weeks of adaptation, 48 rats were allocated into two groups. The first group (A) was twelve normotensive rats; six of them in group (A1) accounted for a healthy or control group, and the other group (A2) of six was normotensive rats receiving 50mg /Kg of *P. farcta* fruit extract (decoction) by oral gavage for One weeks; this was a normal treated group. On the other hand, the second group (B) was 36 hypertensive rats induction carried out by administration of fructose in the feeding bottle for 2 weeks<sup>(9)</sup>; as mentioned in the hypertension induction section.

The hypertensive group was divided into six subgroups; each group consisted of six rats.

The first subgroup was dedicated for a positive control (B1), the second (B2), third (B3) and fourth (B4) subgroup were administered 25mg/kg, 50mg/kg, and 100 mg/kg of the decoction extract of *P. farcta* fruit respectively by oral gavage for One weeks. The fifth (B5) and sixth (B6) subgroup was given 5mg/Kg spironolactone (SPL), and 25/Kg mg of hydrochlorothiazide (HCT) respectively by oral gavage for 1 week; this was according to the pilot study carried out before the study ,it was found that 1 week is sufficient to show the diuretic effect of *P. farcta*, and other drugs. After 1 week when the administration by oral gavage of the fruit extract of *P. farcta*, and drug has ended, the blood collection by direct cardiac puncture (this was an accessible procedure to obtain the required amount of blood after sacrifice ) had carried out to investigate the aforementioned parameters.

### Blood pressure measurements

The rats were placed in a special tube restrainer before starting the blood pressure measurement cuff technique for 15-20 minutes for 2 weeks for adaptation purposes, in order to avoid distress as a result of wrong reading of the BP.

Throughout the procedure the rats were warmed for half an hour at 28°C in a thermostatically controlled heating pad for better detection of tail artery pulse, and they were warmed for 30 min at 28°C where the tail was passed through a cuff and a tail-cuff sensor, the cuff were automatically inflated and deflated at each measurement by this BP measured<sup>(10)</sup>.

In addition to the BP (both systolic and diastolic pressure), heart rate of the conscious rats were measured by the same machine at the same time as the BP recording during the experiment. Later the mean arterial blood pressure (MAP) was calculated using the following formula:

$$\text{MAP} = \text{DBP} + 1/3(\text{SBP} - \text{DBP}) \quad (11)$$

**MAP:** Mean Arterial Pressure

**DBP:** Diastolic Blood Pressure

**SBP:** Systolic Blood Pressure

Mean arterial pressure is the average pressure in arteries during one cardiac cycle, and it is considered as a better indicator to perfusion of coronary arteries, brain, and kidneys.

#### **Hypertension inductions**

Fructose was obtained from Merck KGaA-Germany Chemical to be used in the experiment for the purpose of inducing hypertension. The rats were housed 2 per cage on 12 hours light/12 hours dark cycle and allowed to free access to standard food and drinking water. Fructose was prepared in the form of a solution in a feeding bottle freshly after dissolving 10 % of the fructose in tap water then given ad libitum every day, and the bottles were changed every other day for 2 weeks. During that time of feeding the animal was checked to record a blood pressure increase and be used in the experiments. This type of hypertension induction is reversible once the rats has provided with a normal and healthy regimen<sup>(12)</sup>.

#### **Urine collection**

At the start of the experiment, each rat was placed in a specific metabolic cage for 2 weeks from time to time for adaptation purposes. After such period each rat was allocated in an individual metabolic cage attached with a clean urine collection tube. After 24 hours period, the tube was collected, and fresh urine volume, potassium concentration, urea, creatinine, eGFR, were measured.

#### **Glomerular filtration rate**

The urine collected from different groups was used to calculate eGFR by the renal creatinine clearance<sup>(13, 14)</sup> using the following calculation

$$\text{eGFR} \approx \text{Creatinine clearance} = \left( \frac{\text{Urine creatinine}}{\text{serum creatinine}} \right) \times \text{urine volume}$$

#### **Sodium excretion rate Calculation**

Sodium excretion rate is the product of urine flow and sodium concentration; meaning

$$\text{Sodium excretion rate} = \text{urine flow} \times \text{urine sodium concentration} \quad (15)$$

#### **Blood collection and sampling**

At the end of experimental procedures after 3 weeks ;the blood samples were collected from each allocated group of rats within the standard obtained by the ethical committee. The blood samples were collected by direct cardiac puncture and sent to the scientific laboratory to carry out urine volume, urine and serum electrolytes concentration, urea and creatinine concentration. The blood parameters were measured by the ISE module of the Roche, Hitachi Cobas system.

#### **Statistical analysis**

All data are expressed as Mean  $\pm$  Standard error mean (M  $\pm$  SEM) and the statistical analysis was carried out by using (SPSS version 22). Data analysis was made using one-way analysis of variance (ANOVA). The comparison among the groups done by using Duncan test and student t-test.  $P \leq 0.05$  considered as statistical significance.

#### **Ethical considerations Statistical analysis**

An approval was taken officially from the Ethical Committee of the Faculty of Medical Science/ School of Medicine at Sulaimani University.

## **Results**

#### **Effects *P. farcta* fruit decoction (50mg/Kg) on blood pressure of normotensive rats (n=12)**

There were no significant differences of heart rate and blood pressure between normal (control) rats (A1) and the rats which received 50mg/Kg of the *P. farcta* extract. (Table 1).

**Table 1. Effects *P. farcta* fruit decoction (50mg/Kg) on blood pressure of normal rats (n=12)**

Parameters	Normal/control (A1) (n=6)	Received 50 mg of <i>P. farcta</i> (A2) (n=6)	P-value
Systolic BP (mmHg)	107 $\pm$ 1.72	105 $\pm$ 0.88	0.23
Diastolic BP (mmHg)	80 $\pm$ 0.93	79.67 $\pm$ 0.67	0.828
Mean BP (mmHg)	87.8 $\pm$ 1.62	88.17 $\pm$ 0.48	0.84
Heart rate (bpm)	400 $\pm$ 11	428 $\pm$ 11	0.167

values are expressed as mean  $\pm$  SEM  
P-value of 0.05 or less was considered to be statistically significant

**Effects of *P. farcta* fruit decoction (50mg/Kg) on urine flow, sodium excretion rate, and eGFR in normotensive rats**

Remarkably, the urine flow of the normal rats treated with 50mg decoction of *P. farcta* fruit was significantly higher (100% increase) than the normal rats that did not receive the plant decoction (Table 2).

Sodium excretion rate was significantly increased (>100% increase) in normal rats received fruit decoction of *P. farcta* (Table 2). There was (57%) increase of estimated Glomerular filtration rate in the rats treated with *P. farcta* fruit in comparison to non-treated normal rats.

**Table 2. Effects of *P. farcta* fruit decoction 50mg/Kg on urine flow, sodium excretion rate, and eGFR in normal rats**

Parameters	Normal (A1) (n=6)	Received 50 mg of <i>P. farcta</i> (A2) (n=6)	p-value
Urine flow (ml/kg/hr)	1.26±0.08	2.55 ±0.15	0.001
Sodium excretion rate (mml/hr/kg)	0.22±0.03	0.55±0.05	0.001
eGFR (ml/hr/kg)	486±85	760±35	0.014

values are expressed as mean ± SEM

P-value of 0.05 or less was considered to be statistically significant

**Effects of *P. farcta* fruit decoction on serum**

**Table 4. Comparison between blood pressure parameters in normal and hypertension group after fructose 10 % provision for 3 weeks.**

Parameters	Normal/control (A1)	Hypertensive rats (B1)	P value
Systolic BP (mm.Hg)	107±1.72	149±1	0.01
Diastolic BP (mmHg)	80±0.93	126±3.05	0.01
Mean BP (mmHg)	87.8±1.62	134±2.23	0.01
Heart rate (bpm)	400±11	475±23	NS

- Values are expressed as mean ± SEM ,

- P < 0.05 indicate significant difference

- NS not significant

**electrolytes, serum urea and creatinine concentration in normal rats.**

Serum sodium (Na<sup>+</sup>) concentration of healthy rats treated with *P. farcta* fruit extract was decreased by 4.8%, whereas serum potassium (K<sup>+</sup>) level was significantly increased by 68% (Table 3). Daily administration of *P. farcta* fruit had no significant effect on serum creatinine, however, serum urea concentrations were decreased by 36% in rats treated with 50mg of *P. farcta* fruit extract (Table 3).

**Table 3. Effects of *P. farcta* fruit decoction (50mg/Kg )on serum electrolytes, serum urea and creatinine concentration in normal rats.**

Parameters	Normal (A1)	Treated (A2)	p-value
Serum sodium (mEq/L)	144±0.37	139±0.49	0.01
Serum potassium (mEq/L)	4.46±0.21	7.52±0.19	0.01
Serum urea (mg/dl)	44.93±0.95	28.17±1.01	0.01
Serum Creatinine (mg/dl)	0.49±0.01	0.51±0.01	0.71

values are expressed as mean ± SEM

P-value of 0.05 or less was considered to be statistically significant

**Effect of different doses of *P. farcta* fruit decoction, Spironolactone (5mg/kg), and Hydrochlorothiazide (20mg/kg) on hypertensive rats**

Different doses of *P. farcta* have significantly decrease both systolic and diastolic blood pressure. However, there was no significant change in the heart rate exception seen in the 100 mg of the used plant (Table 5). In addition, the reduction in the blood pressure was significant for both hydrochlorothiazide and spironolactone. However, heart rate was

slightly reduced when hydrochlorothiazide was administered, whereas the reduction in heart rate were significant when spironolactone were used (Table 5)

**Blood pressure parameters in Normal/control rats (A1), and fructose induced blood pressure (B1)**

Feeding normal rats with 10 % of the fructose for 2 weeks has lead to a rise in the blood pressure , this is shown in the table 4.

**Table 5. Effect of different doses of *P. farcta* fruit decoction ,Spironolactone (5mg/kg), and Hydrochlorothiazide (20mg/kg) on hypertensive rats:**

Parameters	Hypertensive rats (B1)	25 mg/Kg P.f.f.e. (B2)	50 mg/Kg P.f.f.e (B3)	100 mg/Kg P.f.f.e (B4)	SPL 5mg/Kg (B5)	HCT 20mg/Kg (B6)
Systolic BP (mm.Hg)	149±1 a	143±1.80 b	144±1.43 b	142±1.35 b	111±0.67 d	137±2.26 c
Diastolic BP (mmHg)	126±3.05 a	115±2.5 b	115± 2.29 b	103±1.77 c	86±1.82 d	111±0.76 b
Mean BP (mmHg)	134±2.23 a	124±2.09 b	125±1.83 b	116±0.82 c	94±1.31 d	120±0.99 bc
Heart rate (bpm)	475±23 a	486±10 ab	452±25 ab	418±19 b	343±4 c	453±5 ab

P.f.f.e. :*Prosopis farcta* fruit extract

SPL:spironolacton

HCT: hydrochlorothiazide

Values are expressed as mean ± SEM , Different letters indicate significant differences at P < 0.05.

**Effects of different doses of *P. farcta* Fruit decoction, Spironolactone (5mg/kg) and Hydrochlorothiazide (20 mg/kg) on urine flow, sodium excretion rate, GFR and in hypertensive rats.**

Urine flow of hypertensive rats receiving 50mg/kg decoction of *P. farcta* fruit was slightly and non- significantly increased. Whereas in hypertensive rats that have received spironolactone or hydrochlorothiazide, urine flow was significantly increased (Table 6). Urinary sodium excretion rate of the hypertensive rats receiving *P. farcta* fruit decoction was non-significantly changed, while

Spironolactone or Hydrochlorothiazide significantly reduced sodium excretion rate (Table 6). Glomerular filtration rate in hypertensive rats receiving *Prosopis farcta* fruit decoction or spironolactone were significantly changed, as shown in ( Table 6). However, eGFR in hypertensive rats receiving hydrochlorothiazide was not significantly changed.

**Table 6. Effets of different doses of *P. farcta* fruit decoction, spironolactone(5mg/kg) and hydrochlorothiazide (20 mg/kg) on urine flow, sodium excretion rate, eGFR and in hypertensive rats.**

Parameters	Hypertensive rats (B1)	25 mg <i>P.f.f.e.</i> (B2)	50 mg <i>P.f.f.e.</i> (B3)	100 mg <i>P.f.f.e.</i> (B4)	SPL 5mg/kg (B5)	HCT 20mg/kg (B6)
Urine flow (ml/min/kg)	1.85±0.19 a	2±0.33 a	2.59±0.27 a	2.16±0.13 a	3.74±0.46 b	3.48±0.33 b
Sodium excretion rate (µEq/min/kg)	0.78±0.03 a	0.22±0.09 ab	0.25±0.05 ab	0.2±0.06 ab	0.33±0.77 b	0.39±0.06 b
GFR (ml/hr/kg)	804±252 a	233±31 b	271±54 b	250±66 b	391±71 b	548±81 ab

*P.f.f.e.*:*Prosopis farcta* fruit extract ,

SPL:spironolactone , HCT: hydrochlorothiazide,

Different letters indicate significant differences at  $P < 0.05$ . Values are expressed as mean  $\pm$  SEM,

**Effects of different doses of *P. farcta* fruit extract,spironolactone (5mg/kg) and hydrochlorothiazide(20mg/kg) on serum electrolytes, serum urea and creatinine concentration in hypertensive rats**

Serum  $\text{Na}^+$  concentrations of hypertensive rats treated with *P. farcta* fruit decoction or Spironolactone or Hydrochlorothiazide were significantly lower than non-treated hypertensive rats (Table 7).

Serum  $\text{K}^+$  concentration of the hypertensive rats received 50mg *P. farcta* fruit decoction was significantly increased , other doses of the fruit decoction were slightly increased Serum  $\text{K}^+$  concentration, However in spironolactone and hydrochlorothiazide treated rats , serum potassium concentration was significantly

changed (Table 7). Serum urea concentration in hypertensive rats treated with *P. farcta* decoction was significantly decreased. This significant decrease was also apparent for spironolactone, and hydrochlorothiazide treated groups. (Table 7).

Serum Creatinine concentration in hypertensive rats that received *Prosopis farcta* decoction, spironolactone, and hydrochlorothiazide was significantly higher than the non-treated group. Noticeably, the doubling dose of *P. farcta* fruit decoction to 100 mg did not lead to further reduction of Serum  $\text{Na}^+$  concentrations neither to further increase in Serum  $\text{K}^+$  concentration in comparison to rats treated with 50 mg of *P. farcta* fruit decoction.

**Table 7. Effects of different doses of *P. farcta* fruit extract, spironolactone (5mg/kg) and hydrochlorothiazide(20mg/kg) on serum electrolytes, serum urea and creatinine concentration in hypertensive rats( n=36)**

Parameters	Hypertensive rats (B1)	25 mg/Kg <i>P.f.f.e.</i> (B2)	50 mg/Kg <i>P.f.f.e.</i> (B3)	100 mg/Kg <i>P.f.f.e.</i> (B4)	SPL 5mg/Kg (B5)	HCT 20mg/kg (B6)
Serum Sodium (mEq/L)	143±1.12 a	140±0.37 b	136±0.56 c	139±1.41 b	135±0.73 c	139±0.67 b
Serum Potassium K <sup>+</sup> (mEq/L)	6.76±0.25 b	7.17±0.17 b	9.98±0.34 c	8.19±0.89 b	8.93±0.94 c	3.98±0.08 a
Serum Urea (mg/dl)	59±1.23 a	25±0.6 c	38±2.62 b	35±4.2 b	20.16±0.70 c	26±1.56 c
Serum Creatinine (mg/dl)	0.39±0.008 a	0.43±0.01 2 b	0.47±0.02 4 b	0.56±0.06 b	0.43±0.008 b	0.42±0.01 b

*P.f.f.e.*:*Prosopis farcta* fruit extract

SPL :spironolactone

HCT: hydrochlorothiazide

Values are expressed as mean ± SEM

Different letters indicate significant differences at P < 0.05.

## Discussion

This is the first systematic study to investigate the effect of *Prosopis farcta* fruit extract (*P.f.f.e.*) in comparison to Spironolactone and Hydrochlorothiazide in animal model in both control (healthy) rats and hypertension rats induced by oral administration of freshly prepared fructose.

Interestingly, none of the rats in the experiment died as a result of oral gavage of the *Prosopis farcta* fruit extract, Spironolactone and Hydrochlorothiazide in our study which support the concept of safety and non-toxic effect of the extract.

In this study, urine flow of normal rats was significantly increased after receiving the extraction of *P. farcta* fruit. The possible mechanisms could explain this increase in urine flow; is an inhibition of sodium reabsorption<sup>(16)</sup>, as the consequence urinary sodium concentration and urinary excretion rate of sodium is increased significantly.

The study investigated the serum concentration of sodium and potassium.

There was a reduction of serum sodium concentration by 4.8%, in healthy-control rat however there was a marked rise of serum potassium level by 68% that accounts for almost a double in value was seen for serum potassium concentration, which could cause hyperkalemia.

The diuretic activity of the *P.f.f.e.* is not resemble to the mode of action of the thiazide group because the fruit extract increased sodium concentrations significantly that is responsible for producing both diuresis and natriuresis. Eventually causing hyperkalemia, opposite to the hypokalemia result from usage of Thiazide<sup>(17)</sup>.

Furthermore; in term of onset of action ; *P.f.f.e.* diuretic properties can not be attributed to the blockage of aldosterone secretion because the fruit decoction diuretic activity was observed after two hours, in contrast to the aldosterone antagonists in which their diuretic effect usually appears after more extended period, because aldosterone antagonists compete aldosterone for mineralocorticoid receptor, which is an intracellular receptor of the nuclear receptor family located in the kidneys, it modulates DNA transcription, causing the synthesis of protein mediators as the mechanism of gene transcription, thereby inhibiting distal sodium retention and potassium secretion<sup>(18)</sup>.

It can be suggested that the diuretic activity of *Prosopis farcta* fruit extract could be resemble the directly acting potassium sparing diuretic; inhibiting sodium ions reabsorption by blocking luminal sodium channels and decreasing potassium ions excretion.

This brings about a significant increase in the distal tubular concentration of sodium, reducing the high intensity of the surrounding interstitium, and less water reabsorption in the collecting duct. This result is in agreement with other studies when an aqueous extract of *Urtica dioica* studied in rats and rabbits<sup>(19)</sup>.

As further study will be required to find out the exact mechanism of the ingredients present in the fruit extract of *P. farcta*, there are suggestion that the fruit extract and their metabolites could work by one of these possible mechanisms; stimulating regional blood flow or initial vasodilatation, or by producing inhibition of tubular reabsorption of water and electrolytes, or by increasing renal circulation and thus the rate of glomerular filtration which finally result in diuresis<sup>(20,21)</sup>.

In this study hypertension was induced by administration of freshly prepared fructose. In addition there are many mechanisms explain the effect of fructose on hypertension in animal studies<sup>(22)</sup>, for instance, high-fructose diets up-regulation of sodium and chloride transporters, which result in a state of salt overload, hence increases blood pressure. Besides, excess fructose has also been found to activate vasoconstrictors, inactivate vasodilators, and over-stimulate the sympathetic nervous system. In recent years there was research to understand the cause of such high blood pressure, for example, increased salt absorption, endothelial dysfunction, and chronic stimulation of the sympathetic nervous system<sup>(23)</sup>.

In our study, the urine flow of hypertensive rats receiving the extract of *P. farcta* fruit was slightly but not significantly increased, this indicates that *P. farcta* fruit decoction has mild diuretic properties in the hypertensive rats. Also there was change in sodium ion concentration but not significant As far as Spironolactone and Hydrochlorothiazide concerns, there was a substantial increase in their blood flow.

Hydrochlorothiazide function by inhibition of the sodium chloride ion co-transporter in the renal distal convoluted tubule helps the absorption of sodium from the distal tubules. By decreasing sodium reabsorption, acutely result in an increase in fluid loss to urine; this eventually leads to a reduction in Blood pressure<sup>(24)</sup>.

However, spironolactone is a competitive aldosterone antagonist around the junction of the distal convoluted tubule and collecting duct where it inhibits sodium-potassium exchange. This is responsible for the increases in sodium excretion while reducing potassium loss at the distal renal tubule. It has a gradual and prolonged action.

Also, spironolactone can work on receptors in the arterioles, where it antagonizes aldosterone-induced vasoconstriction<sup>(25)</sup>.

Glomerular filtration rate of the hypertensive rats receiving *P. farcta* fruit extract was significantly lowered. This was witnessed in the renal impairment, which is known as fructose-induced Metabolic Syndrome<sup>(26)</sup>.

In the current study, there was a significant lowering in eGFR when Spironolactone administered; this was similar to the lowering effect produced by the fruit of the *Prosopis farcta*. On the other hand, the eGFR of the thiazide was not significantly decreased.

We have noted that, hypertensive rats received *P. farcta* fruit decoction significantly decreased serum sodium concentration, and it was visible from the beginning of the experiment. This effect is related to inhibition of sodium reabsorption in the renal tubules. On the other hand, serum potassium concentration was significantly increased when a dose of 50 mg of *P. farcta* administered, which was similar to the significant increase of the spironolactone. However, other treatments were slightly but not significantly increased serum K ions concentration.

Serum creatinine concentrations of hypertensive rats receiving *P. farcta* fruit decoction were significantly increased; this is considered a routine change; this indicates that fruit extract is safe during renal disorders<sup>(27)</sup>. However, serum urea concentration of hypertensive rats receiving *P. farcta* fruit extract were significantly decreased, this is due to an increase in urine volume.

The Serum creatinine of hypertensive rats treated with Spironolactone and Hydrochlorothiazide was almost similar to the fruit extract of *P. farcta*.

The study had shown that different doses of *P. farcta* fruit decoction has significantly decreased both systolic and diastolic blood pressure; this is not due to diuretic activity, this could be explained by unknown mechanisms, and binding to different receptors. However, there was not a significant change in the heart rate, and this is not a significant factor for a reduction in blood pressure<sup>(28)</sup>.

In the context of hypertension, the reduction in blood pressure were seen for both systolic and diastolic after administration of hydrochlorothiazide and spironolactone; however, heart rate was slightly reduced when hydrochlorothiazide was administered, whereas the reduction in heart rate was significant when spironolactone was provided.

## Conclusion

In this animal study we demonstrated that *P. farcta* fruit extract has mild diuretic activity in normal rats and without significant blood pressure reduction that resemble the potassium sparing diuretics.

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