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Comparison of hypotensive, diuretic and renal effects between cladodes of *Opuntia ficus-indica* and furosemide

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ABSTRACT

Objective: To investigate the diuretic, hypotensive and renal effect of *Opuntia ficus-indica* in two different species in oral and intravenous administration.

Methods: Diuretic activity was evaluated in rats with the plant cladode gel and aqueous extract administrated orally, and was evaluated in rabbits with plant extract administered intravenously. Single and repeated doses of cladode gel or aqueous extract of cladode were tested. Urine volume and blood and urine creatinine, sodium and potassium were measured, and creatinine clearance was calculated. The hypotensive effect of lyophilized extract of cladode was evaluated in rabbits. Two polyethylene PE50 catheters were used: one in the jugular vein for the infusion of the plant extract and the other in the carotid for the evaluation of the arterial pressure.

Results: The cladode gel or aqueous extract increased urine volume, creatinine clearance and urinary excretion of sodium and potassium without significant effect on serum creatinine or blood urea. Furosemide, gel and aqueous extract of cladode insignificantly lowered plasma potassium in rats. Intravenous administration of the lyophilized extract caused a significant decrease in mean arterial pressure in rabbits with a significant increase in urine volume and urine sodium and potassium; the effect was dose dependent. Intravenous administration of lyophilized extract did not affect plasma sodium or potassium.

Conclusions: Gel and aqueous extract of *Opuntia ficus-indica* cladode have a significant diuretic effect on rats, and the lyophilized extract has a diuretic and hypotensive effect on normotensive rabbits without deterioration in renal function test. Additional studies on active ingredients are essential to pave the way for clinical studies on diuretic and hypotensive effect of the plant.

1. Introduction

Opuntia species have been used for a long time as a folk medicine in the management of diseases. *Opuntia ficus-indica* (*O. ficus-indica*) (Cactus) is a tropical or subtropical plant, which belongs to the Cactaceae family. Its fruits (prickly pears) are imported crop in most of the world. The cactus grows in America, Africa, Australia and the Mediterranean. In Mexico, the plant is called *nopal*, while the fruit is called tuna. Furthermore, *O. ficus-indica* has been used in Mexico for the treatment of skin diseases, inflammation and ulcerations [1,2].

Cladodes (cladophylls or phylloclades) are stems of *O. ficus-indica* which become flattened, and covered with spines and multicellular hairs or trichomes. They have no leaves and contain high amounts of water. Moreover, they are rich in protein, dietary fiber, carbohydrates, antioxidants, flavonoids, minerals, and vitamins [3–5].

O. ficus-indica is a natural source of flavonoids [6–8]. The fruit contains minerals, ascorbic acid, fibers, vitamin E, carotenoids, amino acids, polysaccharides, polyphenols, flavonoids, betaxanthin, alkaloids, indicaxanthin, neobetanin, and

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betacyanin [9,10]. These compounds have antioxidant and anti-inflammatory properties and have been proposed to be responsible for hypoglycemic and hypolipidemic action [11–13]. Flours of Nopal (*O. ficus-indica*) cladodes at a dose of 50 mg/body weight (b. wt) decreased the postprandial blood glucose in streptozotocin-induced diabetic rats [14]. It was found that the aqueous extract prepared from the cladodes of *O. ficus-indica* (L.) caused hypoglycemia and increased basal plasma insulin levels [15]. The polysaccharides extracted from *O. ficus-indica* cladodes have antioxidant and antiglycated activities [16]. Another study showed that *O. ficus-indica* extract inhibits nitric oxide, COX-2, TNF-α, and IL-6 production [7].

Studies have shown that cladodes have hepatoprotective, antiulcer, antioxidant, and diuretic activities [17–21]. Furthermore, it has been shown that *O. ficus-indica* flower increases diuresis and natriuresis [22]. Another study showed that *O. ficus-indica* cladode, fruit and flower, increase diuresis, natriuresis and kaliuresis [19].

In the traditional medicine of Morocco, *O. ficus-indica* is used for treatment of diabetes mellitus, digestive system diseases, kidney and urinary infections, and allergy [16,22,23]. In Morocco, the people distinguish three varieties of *O. ficus-indica*; Christians' nopal, Muslims' nopal and Moses nopal [24].

The plant with a long history in traditional medicine has a high nutritional value and biologically active substances; therefore the present study has been conducted to investigate the effect of the plant on kidney function, blood pressure and urine and blood electrolytes. Two different species were used to explore the diuretic effect and two different modes of administration, oral and intravenous, were applied.

2. Materials and methods

2.1. Diuretic effects on rats

2.1.1. Experimental animals

Forty-eight adult male Wistar rats [(200 ± 40) g] were used in the experiment. The animals were kept in a standard animal cage under standard temperature and light exposure, and were exposed freely to water and food *ad-libitum*. The study was conducted in accordance with the internationally accepted principles for laboratory animal use and care as found in the European Community guidelines (EEC Directive of 1986; 86/609/EEC). The approval from the Ethical Committee at Faculty of Sciences, Féz, Morocco was obtained.

2.1.2. Plant collection

Cladodes of *O. ficus-indica* plant were collected from the area surrounding Fez, Morocco. The plant was identified as *O. ficus-indica*. (cactaceae) by Professor Amina Bari, Faculty of Science (Fez, Morocco) where the voucher specimen was deposited.

2.1.3. Extracts preparation

Fresh cladodes of *O. ficus-indica* were cut into small pieces, dried in the shade and grinded well to powder. Ten grams of the dried powder of cladodes were mixed with 100 mL of water, and boiled at 100 °C under reflux for 10 min. The decoction obtained was centrifuged, filtered and kept in the refrigerator.

Fresh cladodes of *O. ficus-indica* were obtained, and after removing the spines and glochids, they were cut into pieces and then crushed. The gel obtained was centrifuged at 4 000 rpm/min for 10 min. Finally, a green gel was obtained and used for the experiment.

2.1.4. Reference drug

Furosemide (Lasix, Pharma 5, Morocco) was used as the reference drug.

2.1.5. Biochemical methods

Blood was collected in capillary tubes containing EDTA by retro-orbital puncture under light diethyl ether anesthesia. Plasma was separated by centrifugation at 10 000×*g* for 10 min, and was analyzed for plasma electrolytes that included sodium and potassium. Plasma creatinine and urea were estimated and creatinine clearance was calculated from plasma and urinary creatinine levels.

Experiment 1 was conducted to investigate the diuretic activity of a single dose of the plant in rats. After 12 h fasting, the rats were divided into four groups of six rats each. The animals in each group were treated orally as follows: group 1 received distilled water 10 mL/kg b. wt; group 2 received the aqueous extract of cladode powder 100 mg/kg b. wt; group 3 received cladode gel 100 mg/kg b. wt; group 4 received furosemide (reference drug) at a dose of 15 mg/kg b. wt.

Urine was collected in a graduated cylinder and measured at 1, 2, 4, 6 and 24 h after the administration of each intervention.

Experiment 2 was carried out to study the diuretic activity of the plant in rats. The animals were placed individually in metabolic cages. They were divided into four groups of six rats each and subjected to treatment in the morning as in experiment 1. The experiment lasted for eight days. For each rat, 24 h urine collection was performed daily in a graduated cylinder and the urine volume was measured. The concentrations of urinary sodium and potassium were measured in each urine specimen. Sodium, potassium and creatinine levels were measured in plasma on day eight. Urinary creatinine excretion was also determined and its clearance was calculated on day eight. Osmolar clearance was determined from plasma osmolarity, urinary osmolarity and urine flow. Free water clearance was determined from plasma osmolality, urinary osmolarity and urine flow. T_{CH_2O} (free water reabsorption) was assessed by C_{H_2O} according to the following formula:

$$T_{CH_2O} = -(C_{H_2O})$$

2.2. Diuretic and hypotensive effect on rabbits

2.2.1. Experimental animals

Eight normotensive rabbits (780–1 200 g) were used for the experiment. The animals were raised in a laboratory animal facility under standard condition. They received a diet consisting of cicalime, and had free access to water. Four control rabbits were treated with sodium chloride and four other rabbits were treated with a lyophilized extract of the plant.

2.2.2. Preparation of lyophilized extract

Thirty grams of the cladode powder was boiled in 300 mL of distilled water in a flask heated to reflux for 15 min. The decoction obtained after cooling was centrifuged (4 000 rpm/min for 15 min), filtered and frozen in vials of 25 mL for 48 h, and lyophilized.

2.2.3. Experimental protocol

The rabbits were anesthetized with an intraperitoneal injection of ethyl urethane 10% (15 mL/kg b. wt). The animals were fixed in a supine position on a table. Neck dissection was done, and cannulation of the jugular and the carotid artery was performed. Two polyethylene PE50 catheters filled with a solution of normal saline and heparin were introduced, one in the jugular vein for the infusion of the plant extract and the other in the carotid artery for the measurement of arterial blood pressure and to carry out the blood sampling. The latter was also connected to a system for converting the physiographic mechanical signals to the blood pressure reading. In addition, a catheter was inserted into the bladder to collect the urine.

The experiment was divided into two phases: the first phase was an equilibration phase which continued for 60 min, and was conducted by perfusion of normal saline at a flow rate of 250 µL/min/kg b. wt using a peristaltic pump through the jugular vein. All the eight rabbits undergone the equilibration phase. In second phase effects of the plant on urine volume and urine and plasma electrolytes were compared with normal saline infusion. Four rabbits received continuous infusion of normal saline at a flow rate of 250 µL/min/kg b. wt while four other rabbits received continuous infusion of lyophilized extract at the same flow rate. The infusion was carried out through rabbits' jugular vein. The infusion of both interventions continued for 80 min, which was divided into four periods, 20 min each, during which collection of blood and urine was conducted. Furthermore, four doses of the lyophilized extract were used for intravenous infusions (40 mg/kg b. wt was infused during the first 20 min, 60 mg/kg b. wt was infused during period 20–40 min, 80 mg/kg b. wt was infused during period 40–60 min, and 100 mg/kg b. wt. was infused during period 60–80 min). Urine samples were collected during each time interval in tubes (Eppendorf), in order to study the effects of on urine volume, sodium and potassium. Blood samples were collected at the beginning and at the end of experiments to assess plasma concentrations of sodium and potassium.

2.3. Statistical analysis

ANOVA test with Tukey's *Post Hoc* test was used for statistical analysis. All the data were expressed as mean ± sem. Different at $P < 0.05$ was considered as significant.

3. Results

The cladode gel and furosemide had a comparable diuretic action while the aqueous extract was more potent than the gel and furosemide (Table 1). These effects were evident during seven days of the experiment. In acute administration of the interventions, the aqueous extract was more potent than both furosemide and the gel during 24 h following the administration (Table 2). However, furosemide was more potent than cladode gel and the aqueous extract during the first 6 h after the administration. The aqueous extract was more potent than the gel at all time intervals. This meant that cladode powder extract was more potent as a diuretic with use of a single dose or repeated doses than the cladode gel and furosemide. The diuretic effect of all the interventions was more significant on day 7 than on other days of the experiment.

The effects of the interventions on urinary excretion of sodium, potassium and creatinine are summarized in Table 3. The treatment with furosemide, the aqueous extract and the gel of *O. ficus-indica* cladodes caused a significant increase in the urinary excretion of sodium, potassium and creatinine, as compared to the control group. The aqueous extract and the gel of *O. ficus-indica* caused significantly higher sodium and potassium excretion as compared to furosemide. However, the gel was more potent than the aqueous extract as natriuretic while the aqueous extract of *O. ficus-indica* cladode caused higher potassium excretion than that caused by cladode gel.

The oral administration of the aqueous extract and gel of *O. ficus-indica* for eight days did not cause significant changes in the plasma concentrations of sodium, potassium, urea and creatinine, as compared to the control (Table 4).

A significant increase in the creatinine clearance was observed in the group treated with the aqueous extract and the gel of *O. ficus-indica* or furosemide; the aqueous extract was more potent than the gel and furosemide (Table 5).

The aqueous extract of cladodes and the gel of *O. ficus-indica* caused a significant increase in the urine osmolarity, free water clearance and osmolar clearance compared to the control group. Furosemide increased free water clearance and osmolar clearance, and decreased urine osmolarity (Table 6). No effect on plasma osmolarity was noticed in all groups.

Table 7 showed that normal saline infusion did not cause any significant changes in mean arterial blood pressure, urine sodium

Table 1
Effect of aqueous extract and gel of *O. ficus-indica* and furosemide on urine volume (mL/24 h) in normal rats.

Groups	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Group 1	5.70 ± 0.11	6.14 ± 0.30	6.26 ± 0.22	6.07 ± 0.24	6.16 ± 0.29	6.37 ± 0.31	6.69 ± 0.19
Group 2	22.70 ± 0.22$^{*+\#}$	23.45 ± 0.16$^{*+\#}$	25.61 ± 0.17$^{*+\#}$	25.70 ± 0.24$^{*+\#}$	26.48 ± 0.12$^{*+\#}$	27.18 ± 0.10$^{*+\#}$	28.40 ± 0.14$^{*+\#}$
Group 3	13.73 ± 0.32*	17.38 ± 0.23*	18.69 ± 0.23*	21.50 ± 0.18*	22.38 ± 0.17*	22.91 ± 0.14*	23.73 ± 0.13*
Group 4	15.45 ± 0.12*	16.59 ± 0.18*	20.24 ± 0.15*	20.90 ± 0.20*	22.55 ± 0.17*	22.80 ± 0.19*	22.97 ± 0.16*

$^{*}P < 0.05$, compared with the Group 1, $^{+}P < 0.05$, compared with Group 4, $^{\#}P < 0.05$, compared to Group 3. Data is expressed as mean ± sem.

Table 2
Acute effect (single dose) of aqueous extract and gel of *O. ficus-indica* and furosemide on urine volume (mL) in normal rats.

Groups	1 h	2 h	4 h	6 h	24 h
Group 1	1.60 ± 0.22	3.93 ± 0.36	4.58 ± 0.37	5.35 ± 0.33	6.18 ± 0.36
Group 2	3.03 ± 0.27$^{+*\#}$	3.50 ± 0.11$^{+\#}$	6.15 ± 0.14$^{+*\#}$	10.43 ± 0.31^{+*}	27.86 ± 0.29$^{+*\#}$
Group 3	1.33 ± 0.19^{+}	2.25 ± 0.10^{+*}	5.00 ± 0.26^{+}	9.16 ± 0.19^{+*}	21.66 ± 0.45*
Group 4	7.00 ± 0.36*	11.00 ± 0.22*	13.00 ± 0.30*	16.66 ± 0.33*	19.58 ± 0.41*

$^{*}P < 0.05$, compared with the Group 1, $^{+}P < 0.05$, compared with Group 4, $^{\#}P < 0.05$, compared to Group 3. Data is expressed as mean ± sem.

Table 3

Effect of aqueous extracts and gel of *O. ficus-indica*, and furosemide on urinary excretion of creatinine, sodium and potassium in rats on day eight.

Groups	Creatinine (mg/dL)	Concentration of ions		Saluretic index		Ratio
		Sodium (mEq/L)	Potassium (mEq/L)	Sodium	Potassium	Sodium/Potassium
Group 1	47.0 ± 1.2	108.00 ± 0.28	43.75 ± 1.28	1.00	1.00	2.46
Group 2	49.0 ± 0.9	151.16 ± 0.43$^{*+\#}$	110.16 ± 0.28$^{*+\#}$	1.39	2.51	1.37
Group 3	50.0 ± 1.5	182.16 ± 0.49^{*+}	79.50 ± 0.02^{*+}	1.68	1.81	2.29
Group 4	53.4 ± 0.4*	147.80 ± 0.43*	65.83 ± 0.28*	1.36	1.50	2.17

$^{*}P < 0.05$, compared with the Group 1, $^{+}P < 0.05$, compared with Group 4, $^{\#}P < 0.05$, compared to Group 3. Saluretic index = test mEql·L/control mEql·L. Data is expressed as mean ± sem.

Table 4

Effect of aqueous extracts and gel of *O. ficus-indica*, and furosemide on plasma levels of sodium, potassium, urea and creatinine on day eight (mean ± sem).

Groups	Plasma electrolytes		Urea (mg/dL)	Creatinine (mg/dL)
	Sodium (mEq/L)	Potassium (mEq/L)		
Group 1	145.0 ± 1.9	5.30 ± 0.40	36.00 ± 0.73	0.30 ± 0.02
Group 2	142.0 ± 1.3	3.90 ± 0.30	35.17 ± 1.30	0.33 ± 0.10
Group 3	146.5 ± 0.8	4.60 ± 0.70	35.90 ± 0.50	0.38 ± 0.10
Group 4	147.1 ± 1.5	4.10 ± 0.23	36.15 ± 0.60	0.41 ± 0.10

Table 5

Effect of aqueous extract and gel of *O. ficus-indica* and furosemide on creatinine clearance (mL/min) measured on day one and day seventh.

Groups	Day 1	Day 7
Group 1	0.70 ± 0.10	0.72 ± 0.12
Group 2	0.79 ± 0.06	2.92 ± 0.19$^{*+\#\wedge}$
Group 3	0.71 ± 0.10	2.16 ± 0.12^{*+}
Group 4	0.80 ± 0.04	2.07 ± 0.11^{*+}

$^{*}P < 0.05$, compared with Group 1, $^{+}P < 0.05$, as compared to day 1, $^{\#}P < 0.05$, compared with Group 4, $^{\wedge}P < 0.05$, compared to Group 3. Data is expressed as mean ± sem.

and urine potassium while it significantly increased urine volume and potassium excretion after 60 and 80 min. Interestingly, the intravenous administration of the lyophilized extract of the plant induces a significant decrease in mean arterial blood pressure, and this effect was dose dependent (Table 7). Furthermore, it caused a significant increase in the urine volume, and urinary sodium and potassium excretion by all doses tested (40–100 mg/kg b. wt). The administration of the lyophilized extract had no effect on plasma sodium or potassium level (Table 8).

Table 6

Effect of aqueous extracts and gel of *O. ficus-indica*, and furosemide on plasma osmolarity; urine osmolarity; osmolar clearance and clearance of free water on day eight.

Variables	Group 1	Group 2	Group 3	Group 4
Urinary volume (μL/min)	4.64 ± 2.50	19.72 ± 2.00*	16.47 ± 3.10*	15.69 ± 2.80*
U_{osm} (mosm/kgH_2O)	447.5 ± 12.1	522.64 ± 13.00^{*+}	523.32 ± 21.20^{*+}	427.26 ± 3.90*
P_{osm} (mosm/kgH_2O)	290.0 ± 5.0	284.0 ± 18.0	293.0 ± 20.0	294.2 ± 19.0
C_{Osm} (μL/min)	7.16 ± 1.10	36.29 ± 1.90$^{*+\#}$	29.41 ± 20.00^{*+}	22.78 ± 3.50*
C_{H_2O} (μL/min)	−2.52 ± 1.00	−16.57 ± 5.00$^{*+\#}$	−12.94 ± 2.20^{*+}	−7.09 ± 1.00*
$T_{C\ H_2O}$ (μL/min)	2.52 ± 1.00	16.57 ± 5.00$^{*+\#}$	12.94 ± 2.20^{*+}	7.09 ± 1.00*

$^{*}P < 0.05$, compared with Group 1, $^{+}P < 0.05$, compared with Group 4, $^{\#}P < 0.05$, compared to Group 3. Data is expressed as mean ± sem.

Table 7

Effect of different doses of lyophilized extract of *Opuntia ficus-indica* and normal saline on mean arterial pressure, urine flow, and urine potassium and sodium excretion in rabbits.

Variables	Interventions	Time (min)				
		Baseline (pretreatment)	20	40	60	80
Mean arterial blood pressure (mmHg)	Normal saline	104.75 ± 2.16	103.25 ± 1.24	98.75 ± 1.24^{+}	101.50 ± 2.19	101.25 ± 1.13
	Lyophilized extract	98.50 ± 4.01	80.84 ± 4.16^{*+}	58.10 ± 1.85^{*+}	50.60 ± 1.57^{*+}	45.17 ± 1.52^{*+}
Urine flow (μL/min)	Normal saline	14.00 ± 0.70	14.82 ± 0.79	16.25 ± 0.80	17.30 ± 0.73+	17.12 ± 0.83^{+}
	Lyophilized extract	15.00 ± 1.06	16.47 ± 0.98*	17.87 ± 1.27^{+}	34.75 ± 2.16^{*+}	49.87 ± 2.12^{*+}
Urine sodium excretion (mEq/L)	Normal saline	167.87 ± 5.10	159.75 ± 3.54	160.00 ± 3.53	163.50 ± 7.36	166.50 ± 4.60
	Lyophilized extract	161.25 ± 7.78	167.25 ± 5.71*	166.50 ± 4.08^{*+}	243.25 ± 8.89^{*+}	296.37 ± 7.36^{*+}
Urine potassium excretion (mEq/L)	Normal saline	131.25 ± 2.85	131.50 ± 1.03	135.75 ± 1.24	137.00 ± 2.66^{+}	136.50 ± 2.04^{+}
	Lyophilized extract	133.25 ± 5.40	143.25 ± 5.42^{*+}	150.25 ± 5.48^{*+}	220.00 ± 12.74^{*+}	253.25 ± 13.38^{*+}

$^{*}P < 0.05$ compared with normal saline, $^{+}P < 0.05$ compared with baseline values.
Data is expressed as mean ± sem.

Table 8
Effect of lyophilized extract of *Opuntia ficus-indica* on plasma sodium and potassium in rabbits.

Variables	Intervention	Plasma level	
		Baseline	After 80 min
Sodium (mEq/L)	Normal saline	145.20 ± 1.30	146.20 ± 1.34
	Lyophilized extract	144.33 ± 1.60	143.83 ± 1.25
Potassium (mEq/L)	Normal saline	5.00 ± 0.69	5.30 ± 1.20
	Lyophilized extract	5.58 ± 0.69	5.85 ± 1.20

Data is expressed as mean ± sem.

4. Discussion

The use of diuretics in clinical settings is an important intervention in cases of hypertension and fluid retention due to renal, hepatic, or cardiac reasons, or in cases of electrolyte disturbances. The diuretic and hypotensive effect of the cladode gel and the extract was evaluated in normal rats and rabbits, and compared with the effect produced by a standard reference drug, furosemide and distilled water.

The results showed that a single oral dose of the gel of cladode or its aqueous extract increased the urine volume and creatinine clearance in rats, which was more pronounced with the use of cladode's aqueous extract. The effect of gel was almost similar to that obtained by furosemide. Furthermore, similar results were obtained by the use of repeated doses of the gel or the extract. The gel and the extract increased urine potassium and sodium, and the effect was more potent than the result caused by furosemide. Interestingly, all the interventions caused mild and insignificant hypokalemia which was more pronounced with the use of furosemide. All interventions, including furosemide, gel and the extract, increased urine osmolarity, and they have no significant effect on the plasma osmolarity.

The effect of fruit *O. ficus-indica* on diuresis and blood pressure was not widely investigated. In this regard, it was demonstrated that sun-dried and coarsely ground *Opuntia* cladodes added to Dorper sheep's diet increased daily total urinary excretion [25]. Furthermore, 15% infusion of *O. ficus-indica* cladodes, flowers and fruits significantly increased diuresis and caused a modest but not significant increase in natriuresis and kaliuresis. This effect was more marked during the chronic treatment with flowers [26]. Another study showed that daily oral administration of *O. ficus-indica* extract in rats for 7 d at the dose of 240 mg/kg/d significantly increased the urine output with no significant effect on the urine sodium, potassium and uric acid [27]. Feeding cactus cladodes caused diuresis and reduced urinary potassium excretion in goats, however, it showed no effect on urinary sodium or creatinine clearance [28]. These studies are in agreement with the present study's findings that *O. ficus-indica* causes diuresis. Although the present result showed that *O. ficus-indica* increased urine potassium and sodium, other two studies did not show the same effect [27,28]. However, another study demonstrated almost similar findings to that obtained from the present study [26]. Another type of *Opuntia* (*Opuntia megacantha*) and its leaves' extracts significantly increased urinary sodium excretion in diabetic and nondiabetic rats resulting in significantly low plasma sodium concentration. The extract also significantly increased fractional excretion of sodium and glomerular filtration rate, and caused insignificant lowering of urinary potassium [29]. In the present study, *O. ficus-indica* did not cause any significant changes in plasma sodium or potassium.

The results presented are important since the extract and the gel might have a potential to be used as a diuretic without causing hypokalemia, a common finding encountered with the use of diuretics such loop or thiazide diuretics. Furthermore, the extract and the gel increased creatinine clearance and investigating their effect in cases of kidney failure might explore the potential effect that helps to increase creatinine clearance or to alleviate acute/chronic kidney failure.

The mechanism of action is not clear. However, the plant's extracts might have a similar action to loop diuretics since they increased urinary potassium and sodium excretion similar to furosemide. It is known that loop diuretics such as furosemide increases urinary flow rate and electrolyte excretion such as sodium, potassium and chloride. Data showed that flavonoids have a diuretic activity [30–32]. It is well-known that the plant is a natural source of flavonoids, mainly isorhamnetin glycosides [23,33]. Therefore, the diuretic activity of the extracts might be attributed to the presence of flavonoids. Further studies are needed to explore the mechanism of action.

Intravenous administration of the lyophilized extract of *O. ficus-indica* caused a significant decrease in the blood pressure in rabbits. The hypotensive activity of the extract was dose dependent. In addition, the extract increased urine volume and urinary excretion of sodium that might explain its hypotensive effect. The diuretic effect of the plant was demonstrated in the two species, rats and rabbits. Furthermore, oral and intravenous mode of administration caused diuresis and increased urine sodium. Data published recently in a systematic review and meta-analysis of randomized clinical trials showed that consumption of *O. ficus-indica* can cause significant reduction in blood pressure [34]. It was found that intravenous administration of methanolic extract of *Opuntia dillenii* cladodes decreases blood pressure of normotensive rats in a dose dependent manner. It caused 28% and 54% fall in arterial blood pressure at the doses of 1 mg/kg and 10 mg/kg, respectively. In addition, intraperitoneal and oral modes are also effective in reducing the blood pressure [35]. In athletes, it was found that a diet supplement of *O. ficus-indica* increases the high-frequency and low-frequency activities and also decreases heart rate [36].

Using whole extract might contain substances that induce local irritation at the site of the infusion. If such an event has occurred, vasoconstriction will mostly take place and then the elevation of blood pressure will be encountered. Nevertheless, the results showed that intravenous infusion causes a significant drop in blood pressure. Our future study will include oral administration to study the effect of plant on blood pressure and heart rate. Isolation of the main plant's ingredients to be tested as an intravenous infusion decreases or eliminates any local effect that might arise from the administration of crud intervention or its extract.

The hypotensive effect might be a result of diuresis and increased urine sodium and potassium excretion which are evident with the use of intravenous administration of the plant's extract in rabbits and with oral administration of the plant cladode gel and extract in rats. The plant's extract might have a vasodilatory effect which needs further investigation.

Similar to the diuretic activity, the effect on blood pressure might be due to the antioxidant content of the plant since it has

been shown that antioxidants can lower blood pressure in hypertensive rats [37–39].

In conclusion, the aqueous extract and the gel of *O. ficus-indica* showed significant diuretic, natriuretic and kaliuretic effect in rats and rabbits and the lyophilized extract of the plant has a hypotensive effect in rabbits. The diuretic effect was evident in two different species and with use of oral and intravenous modes of administration. Isolation and characterization of the main ingredients of the plant that have a favorable effect on blood pressure, kidney function and urine volume will pave the way to introduce new natural medicine into the clinical practice. Such a project is currently in progress in our laboratories. Furthermore, repeated plant extract administrations were used to explore the diuretic effects and multiple doses were used intravenously to evaluate plant effect on blood pressure, urine volume and the main urine electrolytes. In future work, we will use multiple doses of the gel or the extract or their main ingredients to explore the most effective dose.

Conflict of interest statement

The authors declare that they have no competing interests.

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