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Antioxidant and diuretic activity of co-administration of *Capparis spinosa* honey and propolis in comparison to furosemide

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ABSTRACT

Objective: To study the antioxidant properties of *Capparis spinosa* (*C. spinosa*) honey and propolis and the effect of combined honey and propolis administration on urine volume and electrolytes in rats.

Methods: *C. spinosa* honey [1 000 mg/kg body weight (b.wt)], propolis (100 mg/kg b.wt), honey/propolis mixture (*C. spinosa* honey 1 000 mg/kg b.wt/ propolis extract 100 mg/kg b.wt), distilled water (1 mL/kg b.wt) and furosemide (10 mg/kg b.wt) were orally administered to five groups of rats for 21 d. Urine volume, blood and urine sodium, potassium and chloride were measured. The antioxidant activity of propolis and honey was assessed and their total phenols and flavonoids were determined.

Results: Propolis and *C. spinosa* honey contain polyphenols including flavonoids and propolis demonstrated higher antioxidant activities than honey. Honey significantly increased urine volume and urine electrolyte excretion. Propolis had no significant effect on urine volume, but co-administration of propolis and honey caused significant diuresis. No major changes were observed in plasma electrolytes with the use of honey, propolis or their combination.

Conclusions: Honey and propolis have antioxidant activity and contain polyphenols including flavonoids that are more pronounced in propolis. Honey has a significant diuretic activity alone or in combination with propolis. This is the first study comparing the diuretic effect of co-administration of propolis and *C. spinosa* honey with furosemide.

1. Introduction

It was found that honey has potential therapeutic effects. In modern medicine, honey has been introduced, in particular, as part of wound and ulcer management. Many studies including ours have found that honey has various biological activities including anti-inflammatory effect by modulating levels of cytokines and prostaglandins, antimicrobial activity against a wide range of pathogenic microbes, and antioxidant properties by upgrading antioxidant system [1–6].

Regarding the kidney function, we have found that honey has beneficial effects on renal function in normal volunteers such as increasing urine output and creatinine clearance. It also increases urinary nitric oxide and decreases urinary prostaglandins level in human [6]. In addition, our studies demonstrated that honey could protect liver and kidney during acute blood loss and after carbon tetrachloride intoxication by normalization of liver enzymes and kidney function [7,8]. In the earlier observation, we found that honey increases urine output and creatinine clearance and has protection against lead-induced toxicity [9]. Other studies showed that honey has a favorable effect in hypertension, diabetic nephropathy and in cisplatin and cyclophosphamide induced nephro-toxicity [10–12]. Recently, it was found that carob honey collected from Morocco has diuretic, natriuretic and kaliuretic activity without side effects of hypokalemia that was observed with the use of widely prescribed diuretic, furosemide [13].

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Honey has been mentioned in Holy books, the Talmud, the Bible, and the Quran as a healer of human diseases. In the Surat Al-Nahel (the Bee chapter) it says (translating the meaning): and thy LORD taught the bee to build its cells in mountains, on tree and in men's habitations, then to eat of all the fruits of the earth and find with skill the spacious paths of its LORD, there issues from within their bodies a drink of varying colors, wherein is healing for men, verily in this is a sign for those who give thought.

Propolis is another bee product that bees collect from different plant sources and use it as part of the defense mechanism in their hives. Large amount of data demonstrated that propolis has vast majority of biological activities such as antioxidant and free radical scavenger activity with high content of antioxidant ingredients, antimicrobial activity against wide range of pathogens, immune stimulating and anti-malignant effect, and anti-inflammatory activities by modulating various pro-inflammatory cytokines [14–18].

Propolis has ameliorating effect on kidney function in diabetic nephropathy as well as a reno-protective effect in paracetamol, carbon tetrachloride and doxorubicin induced nephrotoxicity [19–23]. Recently, it was found that Moroccan propolis extract decreases urinary protein excretion and ameliorates the deterioration of liver and kidney function caused by ethylene glycol ingestion as well as it has a potential to be used in the treatment and prevention of urinary tract calculus, crystaluria, and proteinuria [24].

In Morocco, honey and propolis are widely used in traditional medicine as part of the management of various diseases. However, scientific investigations regarding their biological activities are limited, and the diuretic effect of *Capparis spinosa* (*C. spinosa*) honey has not been studied.

The present study aimed to evaluate the effect of combined administration of *C. spinosa* honey and propolis collected in Morocco on urine volume and urinary and plasma electrolyte including sodium, potassium, and chloride. The different phenolic contents of propolis and honey were assessed, and the antioxidant capacities of propolis and honey were studied. This is the first study investigating the diuretic effect of co-administration of propolis and honey and their effect on plasma and urine electrolytes in comparison to furosemide, a widely prescribed diuretic in clinical practice.

2. Materials and methods

2.1. Preparation of samples

Moroccan propolis samples were obtained from beekeeper's association, Fez, Boulemane, Morocco. The collected propolis was crushed to fine powder, and was extracted with the use of ethanol 70%. The alcoholic extract solution was then filtered through a filter paper and the alcohol content was evaporated with the use of a rotary evaporator under reduced pressure. The residue was dissolved in a minimal volume of ethanol and stored at a low temperature (−20 °C) until it was used in the experimentation. *C. spinosa* honey was also obtained from beekeeper's association, Fez, Boulemane, Morocco, and was used in the experiment. A loop diuretic, furosemide (Lasilix, Pharma 5, Morocco), was used as a reference drug (control) for the comparison.

2.2. Determination of total phenolic, total flavonic and flavonolic content

Each experiment was repeated three times on *C. spinosa* honey or propolis and the results were expressed as mean ± SEM. The total polyphenol content in both propolis and *C. spinosa* honey samples was determined using the method of Slinkard and Sinleton [25]. Using a calibration curve, the total polyphenol content was expressed as mg/g of gallic acid equivalents (GAE). The concentration range of gallic acid was 1 mg/mL. The amount of flavones and flavonols in the propolis extract and *C. spinosa* honey samples was determined according to the method of Miguel *et al* [26]. The total flavones and the flavonols contents were calculated as rutin equivalents (mg/g) using a calibration curve. The concentration range of rutin was 1 mg/mL. Furthermore, the total amount of flavanones and dihydroflavonols compounds was determined with the use of 2, 4-dinitrophenylhydrazine, and the absorbance was measured at 700 nm [27]. UV/visible spectrophotometer, Ultrospec 1100 pro, Amersham Biosciences, Texas, USA was used.

2.3. Antioxidant activity assays

The antioxidant capacity of the propolis and *C. spinosa* honey was determined by evaluating their ability for scavenging free radicals, azino-bis3-ethylbenzothiazoline-6-sulphonic acid (ABTS) and nitric oxide (NO), and by their reducing power. The latter was determined according to the method described by Laskar *et al* [28]. *C. spinosa* honey (50 µL) or propolis (50 µL) were mixed with 500 µL of 0.2 M sodium phosphate buffer (pH = 6) and 500 µL of 1% potassium ferricyanide. The mixture was incubated at 50 °C for 20 min and then was centrifuged for 10 min at 3 000 rpm. The supernatant liquid (500 µL) was mixed with 500 µL of distilled water and 100 µL of 0.1% ferric chloride. The absorbance of the mixture was measured at 700 nm. Ascorbic acid was used as a positive control.

$ABTS^{+\bullet}$ radical scavenging activity was determined as described by Aazza *et al* [29]. Briefly, the ABTS radical was generated by reaction of a 7 mM $ABTS^{+\bullet}$aqueous solution with $K_2S_2O_8$ (2.45 mM) in the dark for 16 h and adjusting the absorbance at 734 nm to 0.7 at room temperature. Twenty-five microliter of *C. spinosa* honey or propolis extract were added to 275 µL of $ABTS^{+\bullet}$ and absorbance at 734 nm was read after 6 min. The capability to scavenge the $ABTS^{+\bullet}$ was calculated using the formula: ABTS scavenging activity (%) = $[(A_0–A_1)/A_0] \times 100$ (%), where A_0 is the absorbance of the control (without sample) and A_1 is the absorbance in the presence of honey or propolis sample. The sample concentration providing 50% inhibition (IC_{50}) was obtained by plotting the inhibition percentage against honey or propolis concentrations. Butylated hydroxytoluene (BHT) was used as a positive control. NO scavenging activity was measured with the use of Griess reagent and ascorbic acid was used as a positive control [30].

2.4. Diuretic effects of propolis and C. spinosa honey

Thirty male Wistar rats [(190 ± 40) g] were obtained from the animal house-breeding center, Faculty of Science, Dhar Mehrez, Fez, and were housed under standard environmental conditions. The animals had a free access to tap water and standard

laboratory rat food. The protocol was approved by the institutional committee on animal care following the French Technical Specifications for the Production, Care and Use of the Laboratory Animals, University Sidi Mohamed Benabdelah, Faculty of Science, Dhar Mehrez, Fez.

The animals were divided into five groups six rats each. Group 1 were treated with oral honey 1 000 mg/kg body.weight (b.wt); group 2 were treated with oral propolis extract 100 mg/kg b.wt; group 3 were treated with a mixture of propolis extract 100 mg/kg b.wt and honey 1 000 mg/kg b.wt; group 4 were treated with oral furosemide 10 mg/kg b.wt; group 5 were treated with oral distilled water (1 mL/kg b.wt). The experiment continued for a total of 21 d. Each rat was individually kept in a metabolic cage and the urine output was collected, measured, and filtered for testing.

Blood samples were collected in capillary tubes containing ethylene diamine tetraacetic acid by retro-orbital puncture under light diethyl ether anesthesia. Blood and urine sodium, chloride and potassium were measured with the use of flame spectrophotometer.

2.5. Statistical analysis

All the data were analyzed using graph pad prism (version 5) and the results were expressed as mean ± SEM. ANOVA test and student's *t*-test were used for analysis. Data with $P < 0.05$ was considered significant.

3. Results

3.1. Total phenolic, flavones and flavonols contents

Propolis showed a high amount of phenolic compounds [(327.039 ± 0.020) mg/g of GAE], which is significantly higher than that found in the honey [(2.538 ± 0.020) mg/g of GAE]. The amount of flavones and flavonols content in *C. spinosa* honey was (0.190 ± 0.100) mg eq rutin/g, which is significantly less than the level of flavones and flavonols in propolis [(159.500 ± 0.090) mg eq rutin/g, $P < 0.05$]. The propolis extract showed a higher amount of total flavanones and dihydroflavonols content [(132.235 ± 0.060) mg eq naringin/g] than that found in *C. spinosa* honey [(0.140 ± 0.060) mg eq naringin/g, $P < 0.05$].

3.2. Antioxidant activity assays

As the absorbance increases, the antioxidant activity increases. The propolis extract and honey have high total antioxidant activity measured by the ferric reducing antioxidant power assay. The effect was dose-dependent in all samples (Table 1). However, ascorbic acid and propolis had higher antioxidants activity than honey, which was evident by higher absorbance with lower concentration of ascorbic acid or propolis.

Propolis showed a high antioxidant capacity towards the ABTS radical [IC_{50} = (0.016 ± 0.01) mg/mL] which was not significantly different from BHT [(0.014 ± 0.016) mg/mL]; whereas *C. spinosa* honey showed a lower scavenging activity towards the $ABTS^{+\bullet}$ radical [IC_{50} = (11.460 ± 0.02) mg/mL] as compared to the propolis extract ($P < 0.05$) or BHT. Propolis had a greater NO scavenging activity [IC_{50} = (0.45 ± 0.01) mg/mL] than *C. spinosa* honey [IC_{50} = (20.69 ± 0.04) mg/mL] but its activity was lower than ascorbic acid [IC_{50} = (0.05 ± 0.01) mg/mL, $P < 0.05$].

3.3. Effect on urine volume

C. spinosa honey increased urine volume and caused significant diuresis, which was obviously starting on day 1, and became significant at day 5 of the experiment. The urine volume remained significantly higher for the honey-treated rats than the control rats at all-time intervals (Table 2). The propolis extracts decreased urine volume, which was insignificant when it was compared to the urine volume before propolis administration. However, the mixture of propolis and *C. spinosa* honey caused a significant increase in the urine volume on days 19 and 21 (Table 2).

3.4. Effect on urinary electrolyte excretion

C. spinosa honey significantly increased excretion of sodium, potassium and chloride as compared to baseline, while furosemide significantly increased the excretion of sodium and potassium without significant changes in the chloride urinary excretion. In contrast, propolis extracts significantly decreased sodium and potassium excretion ($P < 0.05$). However, the mixture of propolis and honey increased urine sodium and chloride excretion and decreased potassium excretion (Table 3).

3.5. Effect on plasma electrolyte levels

There was no significant effect of *C. spinosa* honey, propolis, or propolis/honey mixture on plasma levels of sodium and potassium while honey and furosemide significantly decreased plasma chloride level ($P < 0.05$) (Table 4).

Table 1
Reducing power of honey, propolis and ascorbic acid solutions at different concentrations (mean ± SEM).

Honey		Propolis		Ascorbic acid	
Concentration (mg/mL)	Absorbance (700 nm)	Concentration (mg/mL)	Absorbance (700 nm)	Concentration (mg/mL)	Absorbance (700 nm)
3.91	0.09 ± 0.01*	0.08	0.12 ± 0.01*	0.03	0.22 ± 0.01
7.81	0.09 ± 0.01*	0.16	0.15 ± 0.01*	0.06	0.31 ± 0.01
15.63	0.11 ± 0.01*	0.31	0.20 ± 0.01*	0.13	0.44 ± 0.01
31.25	0.14 ± 0.01*+	0.63	0.29 ± 0.01*	0.25	0.67 ± 0.01
62.50	0.18 ± 0.01*+	1.25	0.61 ± 0.01*	0.51	0.93 ± 0.04
125.00	0.26 ± 0.01*+	2.50	0.65 ± 0.08*	1.01	1.60 ± 0.02
250.00	0.43 ± 0.01*+	5.00	0.91 ± 0.08*	2.02	2.87 ± 0.07
500.00	0.66 ± 0.02*+	10.00	1.61 ± 0.08*	4.04	2.99 ± 0.01

As compared to ascorbic acid $^{*}P < 0.05$; as compared to propolis $^{+}P < 0.05$.

Table 2
Urine volume (mL) with daily oral administration of propolis, *C. spinosa* honey, honey and propolis mixture, furosemide, and distilled water (mean ± SEM).

Groups	Day 0 (baseline)	Day 5	Day 7	Day 15	Day 19	Day 21
Control	5.30 ± 0.75	5.25 ± 0.60	5.37 ± 0.20	5.85 ± 0.20	4.75 ± 0.40	5.62 ± 0.40
Honey	4.25 ± 0.20	7.00 ± 0.60$^{*+\#}$	8.70 ± 0.70$^{*+\#\wedge}$	10.50 ± 0.50$^{*+x\#\wedge}$	11.25 ± 0.40$^{*+x\#\wedge}$	11.50 ± 0.40$^{*+x\#\wedge}$
Propolis	6.10 ± 0.50	5.20 ± 0.50$^{x\wedge}$	4.30 ± 0.22$^{x\wedge}$	4.30 ± 0.60$^{x\wedge}$	4.50 ± 0.20$^{x\wedge}$	4.95 ± 0.20$^{x\wedge}$
Honey/Propolis	6.00 ± 0.40	6.60 ± 0.70$^{+\#}$	6.30 ± 0.20$^{x\#}$	6.60 ± 0.60$^{+x\#}$	7.60 ± 0.20$^{*+x\#}$	8.00 ± 0.40$^{*+x\#}$
Furosemide	4.25 ± 0.40	7.50 ± 0.58^{+}	9.00 ± 0.30^{*+}	12.75 ± 0.20^{*+}	13.10 ± 0.40^{*+}	13.25 ± 0.40^{*+}

As compared to day 0 (baseline), $^{*}P < 0.05$; as compared to the control, $^{+}P < 0.05$; as compared to furosemide, $^{x}P < 0.05$; as compared to propolis, $^{\#}P < 0.05$; as compared to honey/propolis mixture, $^{\wedge}P < 0.05$.

Table 3
Effect of oral administration of propolis, *C. spinosa* honey, honey and propolis mixture, furosemide and distilled water on urine electrolytes level in normal rats (mean ± SEM).

Groups	Dose (mg/kg b.wt)	Urine sodium (meq/L)		Urine potassium (meq/L)		Urine chloride (meq/L)	
		Baseline	Day 21	Baseline	Day 21	Baseline	Day 21
Honey	1 000	74.0 ± 1.0	83.0 ± 1.0*	22.40 ± 0.50	44.60 ± 0.50*	105.05 ± 2.00	123.02 ± 1.00*
Propolis	100	79.0 ± 1.0	71.0 ± 1.0*	16.10 ± 1.00	11.25 ± 1.00*	101.45 ± 3.00	99.50 ± 3.00
Honey/Propolis	1 000/100	74.0 ± 1.0	80.0 ± 1.0*	17.70 ± 1.00	14.20 ± 1.00*	90.02 ± 1.00	97.00 ± 1.00*
Furosemide	10	49.0 ± 0.9	88.0 ± 0.1*	16.10 ± 2.00	24.25 ± 1.00*	99.00 ± 1.00	101.00 ± 2.00

$^{*}P < 0.05$ compared to baseline.

Table 4
Effect of oral administration of propolis, *C. spinosa* honey, honey and propolis mixture, furosemide, and distilled water on plasma electrolyte levels in normal rats (mean ± SEM) (meq/L).

Treatment	Baseline			Day 21		
	Sodium	Potassium	Chloride	Sodium	Potassium	Chloride
Water (control)	142.50 ± 5.50	2.79 ± 0.40	109.50 ± 4.00	141.00 ± 3.50	3.00 ± 0.70	112.00 ± 2.00
Furosemide	142.50 ± 5.50	2.88 ± 0.40	110.75 ± 5.00	140.00 ± 6.50	2.80 ± 0.90	99.75 ± 4.00
Honey	143.25 ± 5.40	2.83 ± 0.40	118.00 ± 2.00	143.00 ± 2.70	3.04 ± 0.50	108.00 ± 3.00*
Propolis	141.25 ± 3.50	2.95 ± 0.50	106.00 ± 5.00	140.00 ± 5.00	3.05 ± 0.50	104.00 ± 2.00*
Honey/Propolis	140.50 ± 5.00	2.70 ± 0.50	113.50 ± 9.00	141.00 ± 3.50	3.00 ± 0.60	104.00 ± 5.00

$^{*}P < 0.05$ compared to the control and to baseline.

Table 5
Effects of oral administration of propolis, *C. spinosa* honey, honey and propolis mixture, furosemide, and distilled water on various parameters measured (mean ± SEM).

Groups	Uosm (mOsm/kgH_2O)	Posm (mOsm/kgH_2O)	Cosm (μL/min)	CH_2O (μL/min)
Control	1 580 ± 9	286.0 ± 6.0	27.62 ± 2.00	−22.62 ± 2.50
Honey	1 660 ± 9*	286.0 ± 6.9	46.40 ± 3.50*	−38.50 ± 4.30*
Propolis	1 421 ± 8*	280.0 ± 8.8	12.68 ± 0.90^{*+}	−10.68 ± 1.30^{*+}
Honey/Propolis	1 600 ± 9*	282.0 ± 7.5	34.04 ± 1.20^{*+}	−28.04 ± 1.90^{+}

As compared to the control $^{*}P < 0.05$; as compared to *C. spinosa* honey, $^{+}P < 0.05$.

3.6. Effect on osmolarity and clearance of free water

C. spinosa honey, propolis, or the mixture of honey/propolis showed no significant effect on the plasma osmolarity (Table 5). However, *C. spinosa* honey or the mixture of honey/propolis significantly increased urine osmolality and osmolar clearance while the propolis extracts significantly decreased urine osmolality and osmolar clearance ($P < 0.05$).

4. Discussion

The results presented showed that propolis collected from Morocco contains high amount of total phenols. Recently, it was shown that propolis collected from different regions of Morocco contains phenols, flavonoids, and has antioxidant and anti-inflammatory activities [31]. High total phenols contents were found in Portuguese propolis samples (329.00 mg/g of GAE), and in Chinese propolis samples [(302.0 ± 4.3) mg/g of GAE]. However, lesser amount of total phenols was found in Portugal (151 mg/g of GAE) and in Brazilian propolis [(120.0 ± 3.5) mg/g of GAE] [27,32,33]. In the present study, Moroccan propolis showed a higher amount of phenolic compounds [(327.039 ± 0.020) mg/g of GAE] than that reported in Chinese, Portugal and Brazilian propolis.

The results showed that *C. spinosa* honey contains phenolic compounds, but less than propolis. The amount of phenolic compounds in *C. spinosa* honey was lesser than that previously reported for Tualang honey [(251.7 ± 7.9) mg gallic acid/kg] and

for Manuka honey [(52.63 ± 1.21) mg gallic acid/100 g] [34,35]. However, the mean flavones and flavonols content in *C. spinosa* honey was higher than that reported for Croatian acacia honey (43.66 mg/kg), and for Burkina Faso acacia honey (61.4 mg/kg) [36,37]. This could be due to the different floral and geographical origins of honey sources since the compositions of bee honey depend on its geographical floral origin, season, environmental factors and treatment of beekeepers [38].

The antioxidant activities of chestnut (*Castania sativa* Mill.) honeys and propolis in Turkey were evaluated and found to be high and related to the sample concentrations. Furthermore, the ethanolic propolis extracts showed the highest antioxidant activity, which is similar to our findings that propolis extracts explored higher antioxidant activity than honey [39]. Recent study conducted on 32 different chestnut honeys collected from different areas in the Black Sea region of Turkey showed that the levels of phenolic materials ranged from 70 mg GAE/100 g to 105 mg GAE/100 g which was lower than *C. spinosa* honey [(2.538 ± 0.020) mg GA/g], and the levels of total flavonoid between 4.04 mg QUE/100 g and 7.01 mg QUE/100 g. However, the concentrations of compounds from all three polyphenol classes varied depending on the unifloral character of the chestnut honey. Ferric reducing/antioxidant power was used to measure antioxidant capacities of chestnut honey and its values ranged from 330 μmol $FeSO_4$/100 g to 470 μmol $FeSO_4$/100 g, the antioxidant capacity of honey depends on its unifloral character [40].

$ABTS^{+\bullet}$ method was used for evaluating the ability of propolis and *C. spinosa* honey samples for scavenging free radicals that gives an indication of the total antioxidant capacity of the samples. HBT and $ABTS^{+\bullet}$ assay demonstrated a better activity than *C. spinosa* honey samples. Nevertheless, the activity of propolis was not significantly different from the activity of HBT. The propolis extract has a higher ferric reducing power than *C. spinosa* honey.

NO is an important bio-regulatory molecule generated from the amino acid L-arginine. It has important effects on various biological systems. However, during infections and inflammations, its concentrations become higher. It was demonstrated that chronic exposure to inducible NO radical is associated with various carcinomas and inflammatory conditions [41,42]. In the present study, propolis and honey showed NO scavenging activity in which propolis was more pronounced. It is well known that phenolic compounds and flavonoids have NO scavenging activity. Therefore, flavonoids and phenolic compounds present in propolis or honey might be responsible for the observed NO scavenging activity. We have found that honey increases NO end products in various human biological fluids such as blood and urine [43,44]. However, it was found that gelam honey inhibited inducible NO and PGE_2 in rat inflammatory model [45]. This makes honey having a dual function: it can increase NO when there is a demand for it to facilitate normal physiological functions or to recover abnormalities related to low availability of NO, and honey can scavenge extra amount of NO generated in inflammatory and pathological conditions.

The administration of honey causes a significant increase in the urine volume and urinary excretion of sodium and chloride. Furthermore, there was no effect of honey on plasma electrolytes. This is similar to our previous study in which carob honey collected from Morocco showed a diuretic activity without causing hypokalaemia [13]. Propolis did not reveal significant effects on urine volume, though it caused a mild reduction in urine volume. However, the mixture of *C. spinosa* honey and propolis caused a moderate diuretic effect.

Several studies have shown that flavonoids exhibit diuretic effects [46,47]. This effect could explain, partially, the diuretic activity of *C. spinosa* honey. The glucose and fructose in honey sample might cause diuresis. However, we found that the use of artificial honey did not result in a significant increase in urine volume in normal individuals [6]. In spite of higher amount of flavonoids and phenols found in propolis as compared to *C. spinosa* honey, propolis did not show a diuretic activity in the present study. More studies should be conducted to verify the effect of propolis on urine volume and urine electrolytes. Different doses or different ways of collection and preparation might result in different propolis activity. In this regard, we have found that propolis extract caused a significant increase in urine output in rat exposed to ethylene glycol toxicity and in restored renal function test, it increased creatinine clearance [24].

Studies have shown that NO causes natriuresis and diuresis and inhibits fluid reabsorption in renal tubules [48,49]. In renal physiology, PGE_2 was found to inhibit sodium chloride transport in the collecting ducts [50]. We have found that oral honey increases urinary NO and decreases urinary prostaglandins level in normal individuals [51]. These findings might explain, partially, the diuretic effect of honey observed in this study.

Aberrantly, the results are interesting and have potential clinical application. The present study is the first to investigate the effect of combined administration of propolis and honey on urine output and plasma and urine electrolytes compared with furosemide. More studies including the effect of such combination on histopathology of the kidney will be useful. Although *C. spinosa* honey has a similar diuretic activity to the Moroccan carob honey and honey collected from United Arab Emirates was better than artificial honey [6,13], comparison of this type of honey with other types of honey such as Manuka honey or artificial honey will help to explore whether different honey samples have a different diuretic activity. The result will pave the way for further studies, including clinical trial, to investigate the diuretic effect of honey and the use of honey and propolis in acute or chronic kidney pathological entities where oxidative process plays a major role in the pathogenesis.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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