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Basic Study

Effect of propolis and honey in hyperglycemia-induced kidney and liver injuries, proteinuria, and oxidant and antioxidant parameters

Soumaya Touzani, Noori Al-Waili, Hassan Laaroussi, Abderrazak Aboulghazi, Nawal Hamas, Hamada Imtara, Asmae El Ghouizi, Ilham ElArabi, Ahmed Al-Waili, Badiaa Lyoussi

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Soumaya Touzani, Laboratory of Mini-Invasive Surgery, Robotics, Artificial Intelligence and Educational Innovations, Faculty of Medicine Pharmacy and Dentistry, University Sidi Mohamed Ben Abdellah, Fez 30000, Morocco

Noori Al-Waili, Ahmed Al-Waili, Clinical Nephrology, New York Medical Care for Nephrology, Queens, NY 11418, United States

Hassan Laaroussi, Abderrazak Aboulghazi, Asmae El Ghouizi, Ilham ElArabi, Badiaa Lyoussi, Laboratory of Natural Substances Pharmacology Environment Modeling Health and Quality of Life, Faculty of Sciences Dhar El Mahraz, University Sidi Mohamed Ben Abdellah, Fez 30000, Morocco

Nawal Hamas, Department of Pathology, University Hospital Hassan II, Fez 30000, Morocco

Hamada Imtara, Department of Biology and Biochemistry, Faculty of Medicine, Arab American University, Ramallah, Palestine

Co-corresponding authors: Soumaya Touzani and Noori Al-Waili.

Corresponding author: Noori Al-Waili, Chairman, MD, PhD, Clinical Nephrology, New York Medical Care for Nephrology, 87-40 134 Street, Queens, NY 11418, United States.
noori786@yahoo.com

Abstract

BACKGROUND

Propolis and honey are known for their antioxidant, hypoglycemic, and antiproteinuric effects.

AIM

To explore the effect of propolis, and honey, against D-glucose-induced hyperglycemia, acute kidney injury (AKI), liver injury, dyslipidemia, and changes in the oxidants and antioxidants in renal, hepatic, and pancreatic tissues.

METHODS

The chemical analysis and antioxidant content of propolis and honey and their effect on alpha-amylase and alpha-glucosidase activity were studied. The study included five groups of male rats; four groups (2, 3, 4 and 5) were treated with D-

glucose, and one group was untreated, group 1. In addition to D-glucose, groups 3, 4, and 5 were treated with propolis, honey, and their combination, respectively. Blood glucose levels, liver and renal function tests, urine protein and electrolytes, oxidant and antioxidant parameters, and histopathological changes in hepatic, renal, and pancreatic tissues were examined.

RESULTS

Propolis contains a higher level of total protein and exhibits a higher antioxidant activity. Honey has a higher alpha-amylase and glucosidase inhibitory activity than propolis. D-glucose caused a significant elevation of blood glucose, insulin, homeostasis model assessment, blood urea, creatinine, lipid parameters, liver enzymes, and urine protein levels. It significantly increases malondialdehyde and decreases antioxidant parameters in pancreatic, hepatic, and renal tissues. D-glucose caused histopathological changes in hepatic, renal, and pancreatic tissues; these changes were significantly ameliorated by honey and propolis.

CONCLUSION

Propolis, honey, or their combination treated hyperglycemia, AKI, proteinuria, liver injury, and dyslipidemia induced by D-glucose, most likely, through their antioxidant activity and alpha-amylase and alpha-glucosidase inhibitory activity. This will pave the way for testing this natural combination in the prevention of diabetic complications, as a complement to basic therapies.

Key Words: Honey; Propolis; D-glucose; Antioxidant; Diabetes; Kidney; Liver; Pancreas

Core Tip: Diabetes is a prevalent condition , and hyperglycemia significantly impacts the antioxidant system and the metabolism of carbohydrates, fats, and proteins. In this experimental study, the combination of Moroccan propolis and honey prevented D-glucose induced hyperglycemia, acute kidney injury, proteinuria, liver injury, and dyslipidemia in murine model, suggesting a synergistic effect most likely through their hypoglycemic and antioxidant activities.

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INTRODUCTION

Diabetes mellitus is still a challenging health problem. It is estimated that more than 400 million individuals have diabetes worldwide. Diabetes causes millions of deaths each year. The prevalence and number of cases are rapidly increasing[1,2], and will be reach 783 million cases in 2045, according to the International Diabetes Federation estimations[3]. Diabetes causes significant complications, including cardiovascular and renal diseases[4]. Despite effective management that involves various medications, insulin therapy, and self-management training, it is not always possible to avoid or delay complications.

Honey and propolis are natural bee products that showed various biological and therapeutic activities in pre-clinical and clinical studies conducted in animals and humans. Honey improves diabetic nephropathy caused by streptozotocin [5]. It prevents hyperglycemia and ameliorates renal and hepatic injury in diabetic mice[6]. Besides its hypoglycemic effect, honey prevents dyslipidemia and histopathological damage to pancreatic islets in diabetes-induced rats[7]. It was proposed that honey containing of antioxidants, zinc, copper, and selenium might play a role in honey's hypoglycemic effect[8,9].

Regarding kidney function, honey protects renal and hepatic injuries and increases urine volume in lead and carbon tetrachloride (CCl_4) intoxication[10], alongside its diuretic, natriuretic, and kaliuretic activity[11]. Moreover, honey appears to mitigate the oxidative stress damages related to diabetes induction in rats[12]. A recent study showed that honey, administered in doses of 1, 2, and 3 g/kg b.wt for 16 weeks, ameliorates renal dysfunction, metabolic acidosis, and renal histological changes in high-fructose diet-fed Wistar rats[13]. In a clinical study, honey has been shown to benefit kidney function and inflammatory mediators, prostaglandins, and nitric oxide[14].

Honey has been praised as a remedy for illness in numerous religious texts (Talmud, Old and New Testaments of the Bible, the holy Quran). The following is an English translation from a section (68-69) from Surat Al-Nahel (The Bee Chapter) from the Quran: "And your Lord inspired the bees: "Make your homes in the mountains, the trees, and in what people construct, and feed from the flower of any fruit and follow the ways your Lord has made easy for you". From their bellies comes forth liquid of varying colors, in which there is healing for people, verily in this is a sign for those who give thought.

Data showed that propolis has antioxidant and, renal and hepatic protective activities, with a higher antioxidant activity than honey[11]. In diabetic rats, propolis significantly improves blood glucose levels, increases insulin sensitivity, and decreases oxidative stress[15-17]. Propolis exhibits anti-advanced glycation end-product activity[17,18]. Furthermore, it has been found that propolis may prevent hepatorenal injury by inhibiting lipid peroxidation and enhancing the activity of antioxidant enzymes[19].

Hyperglycemia triggers the release of pro-inflammatory factors through activating oxidative stress[20]. Evidence suggests that inflammatory processes are involved in insulin resistance[21]. Another study has shown that hyperglycemia induces oxidative stress and liberates reactive oxygen species that damage DNA and lipids[22]. Conclusively, antioxidants and anti-inflammatory activity might help control hyperglycemia and complications of diabetes. In this regard, it is well known that propolis and honey exhibited anti-inflammatory and antioxidant properties. Hence, propolis and honey are possible candidates for diabetes management, and their combination might have a synergistic or additive effect. The present study investigated effects of Moroccan honey, propolis, and their combination, collected from Morocco, on blood glucose and insulin levels, renal and hepatic function, proteinuria, and lipid parameters in D-glucose-induced diabetic rats. The investigations included the physicochemical characterization of both propolis and honey samples. This study is the first to investigate the therapeutic effects of honey, propolis, and their combination in D-glucose-induced diabetes and its complications.

MATERIALS AND METHODS

Propolis and honey samples and extract preparations

Propolis and organic multifloral honey samples were collected from hives installed in the Sefrou region of Morocco, which are typically pesticide-, mite-, and pathogen-free. The propolis sample was frozen at -20 ℃, and the organic honey was stored at three ℃ throughout the experiment. A raw propolis sample (1 g) was macerated in 30 mL of ethanol (70%, v/v) under mechanical stirring for one week. The final extracts were filtered (Whatman, grade 1), and the filtrate was concentrated in a rotary evaporator. Distilled water was added to achieve the target concentration (200 mg/kg b.wt and 100 mg/kg b.wt)[23]. Honey was dissolved in distilled water (1 g/kg b.wt and 2 g/kg b.wt) to use for animal feeding.

Chemical analysis of honey and propolis extracts

Total carbohydrates: Total carbohydrate content was determined using the phenol-sulfuric acid method described by Ferreira-Santos *et al*[24]. Honey or propolis extract (50 µL) was first mixed with 150 µL of sulfuric acid (96%-98% v/v) before adding 30 µL of phenolic reagent (5%). The resulting mixture was then heated at 90 ℃ for 5 minutes. The absorbency was determined at 490 nm on a microplate reader following a 5-minute cool-down at room temperature. Glucose (10-600 mg/L) served as a calibration standard (R2 = 0.992)[25]. Overall carbohydrate content was reported in milligrams of glucose equivalents (GlcE) per gram of extract (mg GLcE/g).

Soluble protein content: Soluble protein content was assessed by a slightly modified Bradford test[26]. After mixing a 20 µL sample of honey or propolis extract with 230 µL Bradford dye reagent, the microplate was kept in darkness for 5 minutes. Absorbance was determined at a 595 nm wavelength by a UV/V spectrophotometer (Synergy HT, BioTek Instruments, Inc., United States). Bovine serum albumin was used for the standard curve (33-1000 mg/L, R2 = 0.989). The results were reported as milligrams of BSA equivalents per gram of extract (mg BSA/g).

Total protein content: Total nitrogen quanfication was performed following acid digestion of the sample on a Kjeldahl digester (Tecator, FOSS, Denmark). Nitrogen conversion factor (N × 6.25) was applied to assess the total protein content of honey and propolis[26].

Total phenolic content: Total phenolic content was assessed *via* the Folin-Ciocalteu method[27]. In short, 60 µL of Folin-Ciocalteu reagent and 15 µL of sodium carbonate solution (75 g/L) were combined with 5 µL of hydro-ethanol extract of propolis or honey, before incubating the mixture at 60 ℃ for 5 minutes and the, recording the subsequent color concentration at 700 nm by a UV/V spectrophotometer (Synergy HT, BioTek Instruments, Inc., United States). Gallic acid (0-500 mg/L) was used to produce the calibration curve (R2 = 0.996), and results were reported as mg gallic acid equivalent (GAE) per gram of extract (mg GAE/g).

Total flavonoid content: After combining a total of 100 microliters of honey or ethanolic extract of propolis with sodium nitrite (5%) and 150 µL of $AlCl_3$ solution (10%), an additional 200 µL of NaOH solution (1%) was added after 6 minutes. The mixture was thoroughly mixed and kept in darkness for 60 minutes. The absorbance was recorded at 510 nm. Quercetin (2.6–142 mg/L) was used for the standard curve (R2 = 0.997), and the results were reported as milligrams of quercetin equivalent (QE) per gram of extracts (mg QE/g)[28].

Identification and quantification of polyphenols compounds by ultra performance liquid chromatography: Honey and propolis samples were analyzed on a Shi-matzo Nexpera X2 ultra performance liquid chromatographic (UPLC) chromatograph featuring a diode array detector (DAD) (Shimadzu, SPD-M20A) according to Ferreira-Santos *et al* method[29]. Separation was carried out 40 ℃ and at a flow rate of 0.4 mL/min on an Acquity UPLC BEH C18 reversed-phase column (2.1 mm × 100 mm, particle size 1.7 µm; Waters) and a pre-column. High performance liquid chromatography grade solvents water/formic acid 0.1% (A) and acetonitrile (B) were used with specific elution gradients for both solvents A and B[29]. Phenolic compounds were identified through by matching UV spectra and retention times with corresponding

standards. Quantification was performed *via* calibration curves for each analyzed compound, at concentrations ranging from 250 to 2.5 mg/L. Individual compounds were identified at different wavelengths (209-370 nm) and the values were reported as milligrams per kilogram of samples (mg/kg). All assays were conducted in triplicate.

Antioxidant activity of honey and propolis extracts

Total antioxidant activity: The phosphomolybdenum method, as described by Prieto *et al*[30] was used. A mixture of 1 mL of reagent and 25 µL of ethanolic extract of propolis or honey was incubated in a water bath at 95 °C for 90 minutes. The absorbance was recorded at 695 nm and ascorbic acid was used for calibration. The results were reported as milligrams of ascorbic acid equivalent (AAE) per gram of the sample (mg AAE/g).

Free radical scavenging activity (diphenyl-1-picryl-hydrazyl-hydrate assay): A mixture of 270 µL of 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) solution and 30 µL of different dilutions of honey or propolis extracts[28] was incubated in darkness at ambient temperature for 1 hour. Ethanol 70% was used as control solution while a standard solution of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid was the positive control. Absorbance was recorded at 515 nm and free radical scavenging activity (% inhibition) was calculated *via* equation (1). The DPPH inhibition concentration at 50% (IC_{50}) was determined and the results were presented as micrograms of extracts per mL.

Alpha-amylase and alpha-glucosidase inhibitory assay

The method used was previously detailed by Laaroussi *et al*[25]. Saccharomyces cerevisiae α-glucosidase (EC 3.2.1.20, type I) and porcine pancreatic (EC 3.2.1.1, type VI) were acquired from Sigma-Aldrich (St. Louis, MO, United States). Ethanol 70% and acarbose were used as negative and positive controls, respectively. α-amylase solution (0.5 mg/mL) was incubated with 500 µL of different concentrations of honey or propolis extracts at 37 °C for 15 minutes, and once again after adding a 500 µL of starch solution (1%). Then after adding of 1 mL of dinitrosalicylic acid color reagent, the mixture was immediately put in a boiling water bath for 10 minutes. The final product was diluted 10 times, and the absorbance of each dilution was determined at 540 nm.

As for the α-glucosidase inhibitory assay, a mixture of various honeys or propolis concentrations and p-nitrophenyl-R-d-glucopyranoside (pNPG, 3 mmol/L) was combined with the α-glucosidase solution (10 U/mL), with an incubation at 37 °C for 15 minute, before finally adding Na_2CO_3 solution (1M). The intensity of the subsequent p-nitrophenol coloration was recorded at 400 nm.

Experimental design

Twenty-five male Wistar rats weighing 150.12 ± 5.1 g were used for the experiments. They were acquired from the Animal Housing and Breeding Center, Department of Biology, Faculty of Sciences, Dhar El Mahraz, University Sidi Mohamed Ben Abdallah, Fez, Morocco. All rats were managed in a well-ventilated, well-maintained environment (Temperature 22 ± 3 °C, humidity 55% ± 5%, 12-hour light/dark cycles). The present research was conducted in compliance with EU directive 2010/63/EU for animal experiments to avoid and minimize animal suffering and the number of animals experimented on, and approved by the local animal ethical committee of Sidi Mohamed Ben Abdellah University of Fez, Morocco, under ethical approval number (USMBA-SNAMOPEQ 2017-03).

For the first seven weeks, groups 2, 3, 4, and 5 received only D-glucose and had free access to tap water and a normal rats' chow diet. On the last day of the seven weeks, rats in groups 3, 4, and 5 with fasting blood glucose greater than 9.4 mmol/L were treated with propolis, honey, and a mixture of honey and propolis for the following three weeks.

Rats were randomly divided into five groups, five rats per group. The following treatments and procedures were performed:

Group 1 (control): Was given distilled water (10 mL/kg b.wt) for 10 weeks.

Group 2 (diabetic): Was given daily by gavage D-glucose (10 g/kg b.wt) for the first 7 weeks.

Group 3 (diabetic + Propolis): Was given daily by gavage D-glucose (10 g/kg b.wt) for the first 7 weeks and then was treated with propolis extract (200 mg/kg b.wt) for the following 3 weeks.

Group 4 (diabetic+ honey): Was given daily by gavage D-glucose (10 g/kg b.wt) for the first 7 weeks and then was treated with honey (2 g/kg b.wt) for the following 3 weeks.

Group 5 (diabetic, propolis, and honey): Was given daily by gavage D-glucose (10 g/kg b.wt) for the first 7 weeks and then was treated daily with 100 mg/kg b.wt propolis extract + 1 g/kg b.wt honey for the following 3 weeks.

At the end of the 10 weeks, blood samples, urine samples, including 24-hour collection, and histopathological specimens were obtained. Both treatment duration and honey and propolis extract doses were selected according to other studies[31,32].

Biochemical analysis

Lactate dehydrogenase (LDH), alkaline phosphatase, triglycerides (TG), total cholesterol (TC), low-density lipoprotein, high-density lipoprotein, serum uric acid, alanine aminotransferases, aspartate aminotransferases, serum creatinine, blood urea, total bilirubin, serum albumin, and serum protein were measured by enzymatic methods, using specific commercial reagent kits. All the kits were purchased from Bio-Maghreb Casablanca, Morocco.

Urine and serum sodium, potassium, chloride, phosphorus and calcium were also analyzed (Architect c8000i biochemistry analyzer).

The radioimmunoassay method was used to determine blood glucose and insulin levels (Rat Insulin RIA kit, Millipore, St. Charles, MO, United States). Model homeostasis evaluation-insulin resistance (HOMA-IR) [Eq. (1)] and homeostatic model-Beta-cell (HOMA-B) function were calculated through the Hill *et al*[33] method. At the same time, quantitative

insulin sensitivity check index (QUICKI) was determined using the method described by Katz *et al*[34].

Liver, pancreas and kidneyantioxidant enzymes activities

At the end of the experiment (10 weeks), the kidney, liver, and pancreas were promptly extracted, immersed in ice-cold saline, and cleared of fat tissue, then homogenized in cold phosphate-buffered saline (0.1 M; pH 7.4) and centrifuged (+4 °C). The collected resulting supernatant was then preserved at -20 °C for further oxidative analysis.

Catalase (CAT) activity was determined using Aebi's method and presented as µmolH2O2/minute/mg protein[35]. The glutathione (GSH) peroxidase (GPx) activity, as described by Flohé and Günzler[36] method, was reported as moles of GSH oxidized/minute/mg protein.

Reduced GSH levels were measured as described in the protocol by Schmidt *et al*[37]. The mixture of 3 mL of sulfosalicylic acid (4%) and 500 mL of homogenate tissues was centrifuged at 2500 *g* for 15 minutes before adding prepared Ellman's reagent to 500 mL of supernatant. The absorbance was measured at 412 nm after 10 minutes. The total GSH content was reported as µg/g of tissue[37].

The formation of products of lipid peroxidation was quantified in liver and kidney according to the method previously detailed by Kassan *et al*[38] and the results were reported as malondialdehyde (MDA) concentration (nmol/g tissue).

Statistical analysis

All data are reported as mean ± SD. Between-group statistical analyses were carried out by one-way analysis of variance followed by Tukey's test using GraphPad Prism® software (version 5.0; GraphPad Software, Inc., SanDiego, United States). A *t*-test was applied to compare the two means. Significance was considered at $P < 0.05$.

RESULTS

Table 1 highlights that propolis has significantly higher total protein and antioxidant activity than honey, whereas carbohydrates are higher in honey than in propolis ($P < 0.05$). The honey sample contains fructose at 34.22 ± 1.92 g/100 g, glucose at 23.34 ± 2.52 g/100 g, maltose and sucrose at 2.11 ± 0.07 g/100 g, and 5-hydroxymethylfurfural at 9.72 ± 0.11 mg/kg. Furfural was not detected.

Table 2 demonstrates various phenolic compounds in both honey and propolis. Propolis has higher concentrations of vanillic acid, naringin, and kaempferol than honey. Table 3 shows that honey has higher alpha-amylase inhibitory activity than propolis and acarbose and higher alpha-glucosidase inhibitory activity than propolis ($P < 0.05$).

Effect of interventions on blood glucose, insulin, HOMA-IR, HOMA-B, and QUICKI

D-glucose caused a significant elevation of blood glucose, insulin, HOMA-B, and HOMA-IR (Table 4). Using propolis, honey, and a combination of propolis and honey with D-glucose decreased these parameters toward the control levels ($P < 0.05$). The combined use of propolis and honey with D-glucose showed a significantly more potent effect than the individual use of propolis or honey.

Effect of interventions on liver function tests and lipid profile

Table 5 shows that D-glucose increases TC, TG, and low density lipoprotein and decreases high density lipoprotein. These changes markedly improved with the use of propolis, honey, and their combination with D-glucose. The use of honey and propolis with D-glucose showed a more substantial effect compared to propolis or honey ($P < 0.05$). D-glucose increased liver enzymes, tuberculosis, and decreased albumin levels ($P < 0.05$). The combined use of honey, propolis or their combination with D-glucose significantly improved these changes toward the control values. The use of honey and propolis combination in rats treated with D-glucose showed a more substantial effect than the effects seen with propolis or honey individually ($P < 0.05$).

Effect of interventions on acute kidney injury induced by D-glucose and blood and urine electrolytes

D-glucose increased blood urea, serum creatinine, serum uric acid, urine protein, and uric acid (Table 6). The use of propolis or honey in rats receiving D-glucose significantly ameliorates the effect of D-glucose on renal function tests by decreasing urine protein, blood urea, and serum creatinine. A combination of propolis and honey demonstrated a stronger effect than propolis or honey individually ($P < 0.05$). Table 7 revealed that D-glucose causes a significant lowering of serum sodium and potassium that was ameliorated with the use of propolis, honey or their combination.

Effects of the interventions on antioxidant parameters, protein, and MDA levels in pancreatic, liver, and kidney tissues

D-glucose caused a significant decrease in GHS, GPx, CAT, and protein and increased MDA levels in pancreatic, liver, and kidney tissues, $P < 0.05$ (Tables 8-10). Using propolis, honey, or their combination significantly ameliorated D-glucose effects by increasing antioxidant parameters and protein and decreasing MDA levels. Table 11 shows the quantity of oxidants and antioxidants in the kidney, liver, and pancreatic tissues. Pancreas tissue contains a higher amount of GHS than the liver and kidney, and the liver tissue contains more MDA than other tissues.

Histological changes caused by the interventions.

Figures 1-3 demonstrate some of the changes caused by D-glucose with and without using honey, propolis, or a combination of honey and propolis. It appears that honey and propolis mitigate the effects of D-glucose on the histopath-

Table 1 Nutritional parameters and antioxidant activity of propolis and honey, mean ± SD

Samples	Carbohydrates (mg Glceq/g)	Soluble proteins (mg BSA/g)	Total proteins (%)	TPC (mg GAE/g)	TFC (mg QE/g)	TAA (mg AAE/g)	DPPH IC_{50} (mg/mL)
Propolis	1.57 ± 0.02	22.18 ± 2.11	2.32 ± 0.02	65.22 ± 3.73	25.98 ± 5.81	79.12 ± 7.04	0.34 ± 0.03
Honey	698.19 ± 5.22[1]	3.42 ± 0.01[1]	0.36 ± 0.01[1]	28.54 ± 1.04[1]	16.35 ± 1.19[1]	68.72 ± 6.51	1.11 ± 0.01
P value	0.001	0.001	0.001	0.001	0.048	0.112	0.001

[1]Significant compared to propolis.
TPC: Total phenolic content; TFC: Total flavonoid content; TAA: Total antioxidant activity; DPPH: 2,2-diphenyl-1-picryl-hydrazyl-hydrate; GAE: Gallic acid equivalent; QE: Quercetin equivalent; AAE: Ascorbic acid equivalent.

Table 2 Phenolic compounds identification and quantification of propolis and honey using ultra performance liquid chromatographic-diode array detector, mean ± SD

Compounds (mg/kg)	Propolis	Honey (*P* value)
Catechin	8.15 ± 0.1	9.3 ± 2.0 (0.376)
Vanilic acid	15.04 ± 0.7	5.8 ± 0.2[1] (0.001)
o-Coumaric acid	Not detected	13.4 ± 0.7
Ferrulic acid	56.78 ± 0.6	17.1 ± 1.0[1] (0.001)
Ellagic acid	78.92 ± 3.8	27.6 ± 0.3[1] (0.001)
Naringin	213.76 ± 0.5	11.8 ± 0.2[1] (0.001)
Hesperidin	121.98 ± 0.3	Not detected
Apigenin	50.37 ± 0.8	24.8 ± 0.2[1] (0.001)
Cinnamic acid	42.87 ± 0.4	4.7 ± 0.3[1] (0.001)
Resveratrol	81.22 ± 0.2	17.6 ± 3.7[1] (0.001)
Rosmarinic acid	105.09 ± 5.2	38.4 ± 4.1[1] (0.001)
Rutin	60.11 ± 2.1	Not detected
Chlorogenic acid	11.19 ± 0.1	Not detected
Quercetin	22.51 ± 1.3	Not detected
Kaempferol	89.64 ± 1.2	14.9 ± 2.8[1] (0.001)
Gallic acid	Not detected	18.8 ± 0.5

[1]Significant compared to propolis.

Table 3 Alpha-amylase and alpha-glucosidase inhibitory activities of propolis and honey samples, mean ± SD

Variables	Alpha-amylase	Alpha-glucosidase	*P* value
Honey	1394 ± 23.47	1083 ± 31.14[1]	< 0.001
Propolis	233 ± 8.97[2]	561 ± 27.13[1,2]	< 0.001
Acarbose	35.69 ± 1.29[2,3]	11003 ± 6.17[1,2,3]	< 0.001
P value	< 0.001	< 0.001	

[1]Significant compared to alpha-amylase activity.
[2]Significant compared to honey.
[3]Significant compared to propolis.

Table 4 Effect of interventions on blood glucose, insulin, homeostatic model assessment-insulin resistance, homeostasis model assessment-beta-cell function, and quantitative insulin-sensitivity check index, mean ± SD

Parameters	Interventions					*F/P* value
	C	D	D + P	D + H	D + P + H	
Glucose (mmol/L)	5.33 ± 0.40	9.92 ± 0.52[1]	7.19 ± 0.16[1,2]	7.58 ± 0.28[1,2]	6.89 ± 0.55[1,2]	82/0.001
Insulin (U/L)	11.71 ± 0.60	25.22 ± 0.86[1]	16.19 ± 0.27[1,2]	21.42 ± 1.4[1,2,3]	14.01 ± 0.62[1,2,3,4]	216.6/0.001
HOMA-IR	2.78 ± 0.33	11.13 ± 0.86[1]	5.17 ± 0.20[1,2]	7.23 ± 0.75[1,2,3]	4.29 ± 0.36[1,2,4]	165/0.001
HOMA-B	40.55 ± 2.31	47.41 ± 2.33[1]	41.51 ± 0.53[2]	52.96 ± 2.27[1,3]	37.35 ± 3.86[2,4]	33.1/0.001
QUICKI	0.16 ± 0.001	0.15 ± 0.007[1]	0.15 ± 0.004[1]	0.15 ± 0.001[1]	0.15± 0.004[1]	6/0.002

[1]Compared to Control.
[2]Compared to D-glucose.
[3]Compared to D-glucose + Propolis.
[4]Compared to D-glucose + Honey.
H: Honey; P: Propolis; C: Control; D; D-glucose; HOMA-IR: Homeostatic model assessment-insulin resistance; HOMA-B: Homeostasis model assessment-beta-cell function; QUICKI: Quantitative insulin-sensitivity check index.

Table 5 Effect of interventions on liver function tests and lipid profile, mean ± SD

Parameters	Interventions					*F/P* value
	C	D	D + P	D + H	D + P + H	
TC	46.71 ± 2.72	64.75 ± 2.30[1]	55.93 ± 2.33[1,2]	57.36 ± 3.13	54.5 ± 8.68	11/0.001
LDL	40.19 ± 3.50	48.69 ± 2.6[1]	44.62± 2.20	45.51 ± 4.27	40.32 ± 4.45	5.4/0.003
HDL	19.73 ± 0.61	13.42 ± 1.36[1]	16.3 ± 1.93	17 ± 2.19	16.68 ± 1.83	9/0.001
TG	27.68 ± 1.72	43.31 ± 2.82[1]	36.71 ± 3.65[1]	36.77 ± 4.28	36.52 ± 3.53	13.7/0.001
ALT	68.13 ± 2.21	94 ± 3.54[1]	80.2 ± 2.95[1,2]	82.88 ± 2.58[1]	76.5 ± 2.23[2]	60.38/0.001
AST	144.4 ± 6.35	198 ± 5.2[1]	170 ± 7.9b	175 ± 11.4[1]	160.9 ± 10.3[2]	28.31/0.001
ALP	52.8 ± 4.66	94.33 ± 13.3[1]	76.9 ± 4.47[1]	79.2 ± 8.33[1]	75.6 ± 6.3[1]	17.85/0.001
LDH	59.9 ± 4.2	99.2 ± 10.35[1]	72.27 ± 8.2[1,2]	73 ± 4.32	72 ± 4.9	22.18/0.001
TB	0.75 ± 0.04	1.32 ± 0.07[1]	1.03 ± 0.04[1,2]	0.92 ± 0.03[1,2]	0.81 ± 0.07[2]	91.06/0.001
Albumin	4.39 ± 0.27	2.69 ± 0.10[1]	3.64 ± 0.17	3.61 ± 0.27	3.76 ± 0.35	30/0.001

[1]Compared to Control.
[2]Compared to D-glucose.
H: Honey; P: Propolis; C: Control; D; D-glucose; TC: Total cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; TG: Triglycerides; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; TB: Tuberculosis.

Table 6 Effect of interventions on kidney function tests, mean ± SD

Parameters	Interventions					*F/P* value
	N	D	D + P	D + H	D + P + H	
Urea (mg/dL)	32.9 ± 4.87	74.5 ± 5.99[1]	52.9 ± 10.9[1]	52.8 ± 5.1[1,2]	47.4 ± 2.9[2]	25.3/0.001
Creatinine (mg/dL)	0.64 ± 0.03	1.23 ± 0.03[1]	0.92 ± 0.02[1,2]	0.97 ± 0.11[1,2]	0.81 ± 0.04[1,2,3]	74.2/0.001
Uric acid (mg/dL)	1.8 ± 0.07	2.55 ± 0.28[1]	2.0 ± 0.14[2]	2.11 ± 0.08	2.07 ± 0.06[2]	16.7/0.001
Urine creatinine(mg/mL)	53.4 ± 4.7	34.5 ± 4.4[1]	47.5 ± 4.5[2]	42.73 ± 8.2	47.8 ± 2.85[2]	8.84/0.001
Urine uric acid (mg/mL)	8.53 ± 0.34	12.34 ± 0.53[1]	9.83 ± 0.43[2]	10.23 ± 0.60	9.99 ± 0.57[2]	63.99/0.001
Urine protein (mg/mL)	27.3 ± 2.16	36.53 ± 1.9[1]	29.9 ± 2.4[2]	32.27 ± 0.8[2]	30.3 ± 2.0[2]	15.94/0.001

[1]Compared to Control.
[2]Compared to D-glucose.
[3]Compared to D-glucose + Propolis.
H: Honey; P: Propolis; C: Control; D; D-glucose.

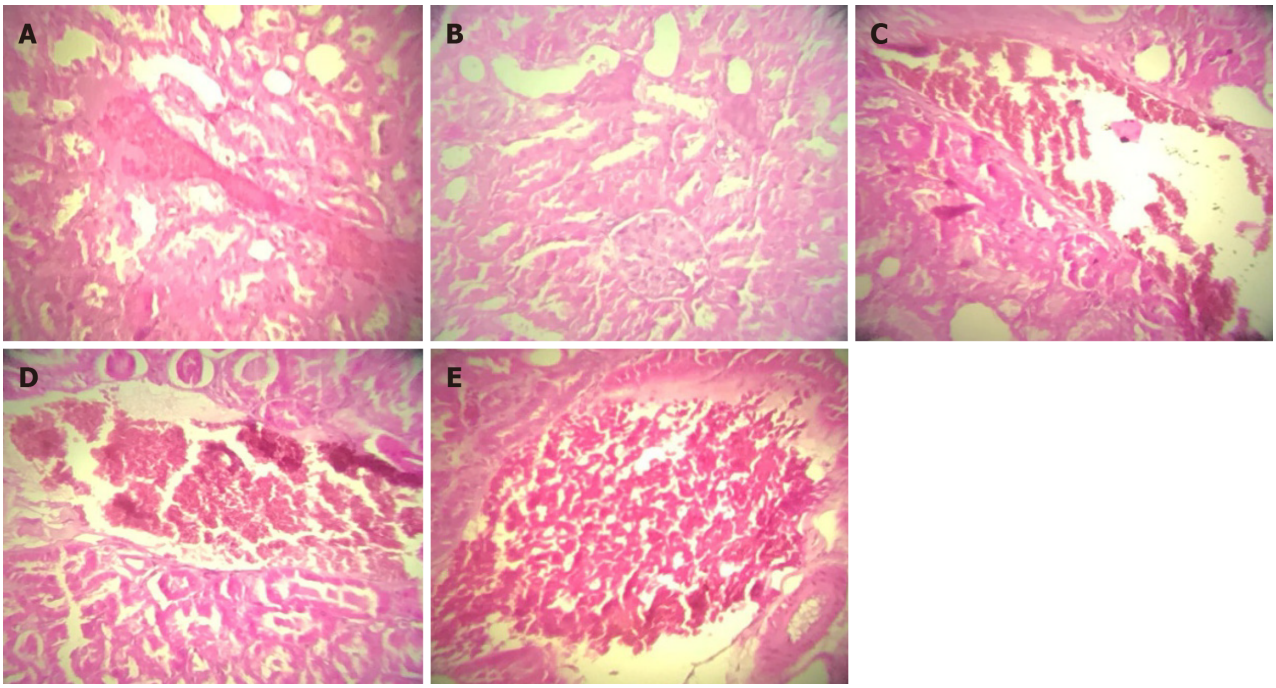

Figure 1 Histopathological changes in kidney tissues after D-glucose administration with and without honey, propolis, and their combination. A: Control, normal; B: D-glucose + honey, mild vascular congestion; C: D-glucose + propolis, mild vascular congestion; D: D-glucose + honey + propolis, mild vascular congestion; E: D-glucose, vascular congestion + hemorrhagic foci of the kidneys.

ological changes in the liver, kidney, and pancreatic tissues.

DISCUSSION

The data showed that treatment with honey, propolis, and their combination significantly alleviated the adverse effects of D-glucose-induced hyperglycemia on blood glucose and insulin levels and acute kidney and liver injuries. Honey and propolis decreased hyperglycemia, reduced insulin blood level, and ameliorated acute kidney injury (AKI), proteinuria, and the elevation of hepatic enzymes. The interventions prevented cross-sectional histological changes in the renal, hepatic, and pancreatic tissues after the induction of hyperglycemia in rats. Interestingly, the combination of honey and propolis was more effective than either honey or propolis alone.

The chemical analysis data demonstrated the presence of phenols and flavonoids in honey and propolis samples, which possess a strong antioxidant capacity. Propolis contains a high amount of protein, while honey contains a high amount of carbohydrates. Honey has a higher alpha-amylase and alpha-glucosidase inhibitory activity than propolis. IC_{50} in the DPPH test was higher in propolis than in honey, and total antioxidant activity was higher in propolis than in honey, indicating higher antioxidant capacity than honey.

The total phenol content of 17 various Moroccan honey samples, including Arbutus unedo honey, ranges between 16.38 mg GAE/100 g (citrus honey) and 92.37 mg GAE/100 (thyme honey)[39]. This implies that the phenolic content in the multiflora honey sample collected from hives installed in the Sefrou region, Morocco (28.54 ± 1.04 mg GAE/g) is higher than that of the other Moroccan honey samples. The content of multiflora honey tested in the present study seems to overcome Manuka (71 mg GAE/100 g) and Iranian (193.8 mg GAE/100 g honey) honey's phenolic content[40]. The data showed that multiflora honey from this study (Sefrou region) lacked epicatechin, a rare flavonol found in Thymus vulgaris and Arbutus unedo honey samples collected from other parts of Morocco[41]. The physicochemical characterization and the antioxidant content of honey samples vary according to their geobotanical origin and season of collection. The presented results showed that multiflora honey's analyzed parameters are in line with the Codex standard for honey and the International Honey Commission requirements[42].

Propolis is characterized by a wide range of phenolic acids and their ester derivatives including 13 compounds identified using UPLC/DAD. All the compounds detected were phenolic acids and their ester derivatives. The results showed that naringin, hesperidin, rosmarinic acid, and kaempferol were the most abundant in the propolis samples test

Table 7 Effects of the interventions on blood and urine electrolytes, mean ± SD

	Electrolytes (mmol/L)				
	Sodium	Potassium	Chloride	Phosphorous	Calcium
Serum level					
C	145.85 ± 7.35	4.45 ± 0.05	105.00 ± 8.42	2.17 ± 0.01	2.82 ± 0.04
D	130.50 ± 5.12[1]	4.17 ± 0.09[1]	107.12 ± 5.64	2.01 ± 0.03[1]	2.75 ± 0.08
D + P	137.64 ± 5.23	4.48 ± 0.03[2]	104.50 ± 5.24	2.09 ± 0.01	2.81 ± 0.01
D + H	147.28 ± 6.38[3]	4.43 ± 0.03[2]	113.00 ± 7.212	2.15 ± 0.05[2]	2.85 ± 0.01
D + P + H	141.12 ± 4.61	4.56 ± 0.07[2,4]	108.76 ± 6.34	2.13 ± 0.02[2]	2.82 ± 0.06
F/P value	6.99/0.001	30/0.001	1.46/0.25	25/0.001	2.81/0.052
Urinary level					
C	90.41 ± 4.37	60.84 ± 3.66	82.16 ± 3.85	1.28 ± 0.03	2.63 ± 0.05
D	110.58 ± 1.23[1]	60.91 ± 5.18	82.10 ± 7.25	1.26 ± 0.07	2.70 ± 0.11
D + P	88.34 ± 6.41[2]	60.85 ± 4.54	80.14 ± 5.68	1.28 ± 0.02	2.67 ± 0.08
D + H	101.62 ± 7.73	60.82 ± 2.97	86.92 ± 5.11	1.27 ± 0.02	2.69 ± 0.06
D + P + H	97.13 ± 6.58	60.88 ± 3.82	83.17 ± 4.94	1.30 ± 0.05	2.61 ± 0.03
F/P value	12.1/0.001	0.06/0.992	1.122/0.374	0.60/0.664	1.47/0.248

[1]Compared to Control.
[2]Compared to D-glucose.
[3]Compared to D-glucose + Propolis.
[4]Compared to D-glucose + Honey.
H: Honey; P: Propolis; C: Control; D; D-glucose.

Table 8 Effect of interventions on D-glucose-induced changes in antioxidant enzymes, proteins, and malondialdehyde concentrations in pancreatic tissues, mean ± SD

Parameters/pancreatic tissue	Interventions					*F/P* value
	C	D	D + P	D + H	D + P + H	
GSH (µg/g tissue)	33.1 ± 4.07	11.85 ± 0.28[1]	29.48 ± 6.5[2]	23.0 ± 6.5[2]	28 ± 2.94[2]	15.2/0.001
GPx (nmol GSH/min/mg prt)	12.66 ± 3	4.45 ± 0.35[1]	7.47 ± 1.17[2]	7.97 ± 2.1	8.37 ± 1.06[2]	13.76/0.001
MDA (nmol/g tissue)	28.84 ± 8.15	58.26 ± 8.97[1]	37.7 ± 4.87	31.73 ± 4.47[2]	33.17 ± 6.6[2]	12.11/0.001
CAT (µmol H_2O_2/min/mg prt)	20.54 ± 3	11.25 ± 1.47[1]	17.6 ± 1.66[2]	16.5 ± 0.43[2]	18.49 ± 1.5[2]	20.6/0.001
Protein (mg/g tissue)	7 ± 0.35	5.48 ± 0.03[1]	5.75 ± 0.31[1]	5.27 ± 0.1[1]	6.5 ± 0.16[2,3,4]	53.6/0.001

[1]Compared to Control.
[2]Compared to D-glucose.
[3]Compared to D-glucose + Propolis.
[4]Compared to D-glucose + Honey.
H: Honey; P: Propolis; C: Control; D; D-glucose; GSH: Glutathione; GPx: Glutathione peroxidase; MDA: Malondialdehyde; CAT: Catalase.

in the present study. The analysis conducted in another propolis sample from Morocco identified caffeic acid phenylethyl ester, pinocembrin and pinobanksin-3-O-acetate as the predominant phenolic compounds[39]. DPPH test results demonstrated that propolis has a higher scavenging capacity against DPPH than honey.

The administration of D-glucose causes diabetes with an elevation of blood glucose and insulin levels. We have previously illustrated a low number of islets of Langerhans on pancreatic tissue examination 15 days after induction of hyperglycemia and streptozotocin injection[39]. Honey and propolis intake after diabetes induction clearly brings hyperglycemia and hyperinsulinemia back within normal limits. D-glucose significantly increased HOMA-IR and decreased QUIKI. Therefore, D-glucose increases blood glucose levels by increasing insulin resistance and reducing insulin sensitivity. In an earlier study, the administration of D-glucose induced hyperglycemia, increased insulin levels, and HOMA-IR index in addition to dyslipidemia, increased liver enzyme levels and changes in blood and urinary renal

Table 9 Effect of interventions on D-glucose-induced changes in antioxidant enzymes, proteins, and malondialdehyde concentrations in liver tissues, mean ± SD

Parameters/liver tissue	Interventions					*F/P* value
	C	D	D + P	D + H	D + P + H	
GSH (μg/g tissue)	16.0 ± 1.15	12.36 ± 2.98	15.2 ± 2.29	15.48 ± 1.56	15.66 ± 2.07	2.56/0.65
GPx (nmol GSH/min/mg prt)	10.38 ± 0.75	5.56 ± 0.27[1]	8.18 ± 0.2[2]	9.81 ± 1.2[2]	11.96 ± 2.33[2]	7.18/0.001
MDA (nmol/g tissue)	40.58 ± 11.2	70.2 ± 12[1]	49.87 ± 12.6	46.87 ± 5[2]	47.6 ± 6.11	6.56/0.001
CAT (μmol H_2O_2/min/mg prt)	27.28 ± 5.2	14.6 ± 2.1[1]	20.85 ± 3.3	30.3 ± 6.32	23.9 ± 2.22[2]	11.49/0.001
Protein (mg/g tissue)	6.4 ± 0.15	4.44 ± 0.21[1]	5.1 ± 0.17[1,2]	5.33 ± 0.17[1,2]	5.2 ± 0.5[1,2]	34/0.001

[1]Compared to Control.
[2]Compared to D-glucose.
H: Honey; P: Propolis; C: Control; D; D-glucose; GSH: Glutathione; GPx: Glutathione peroxidase; MDA: Malondialdehyde; CAT: Catalase.

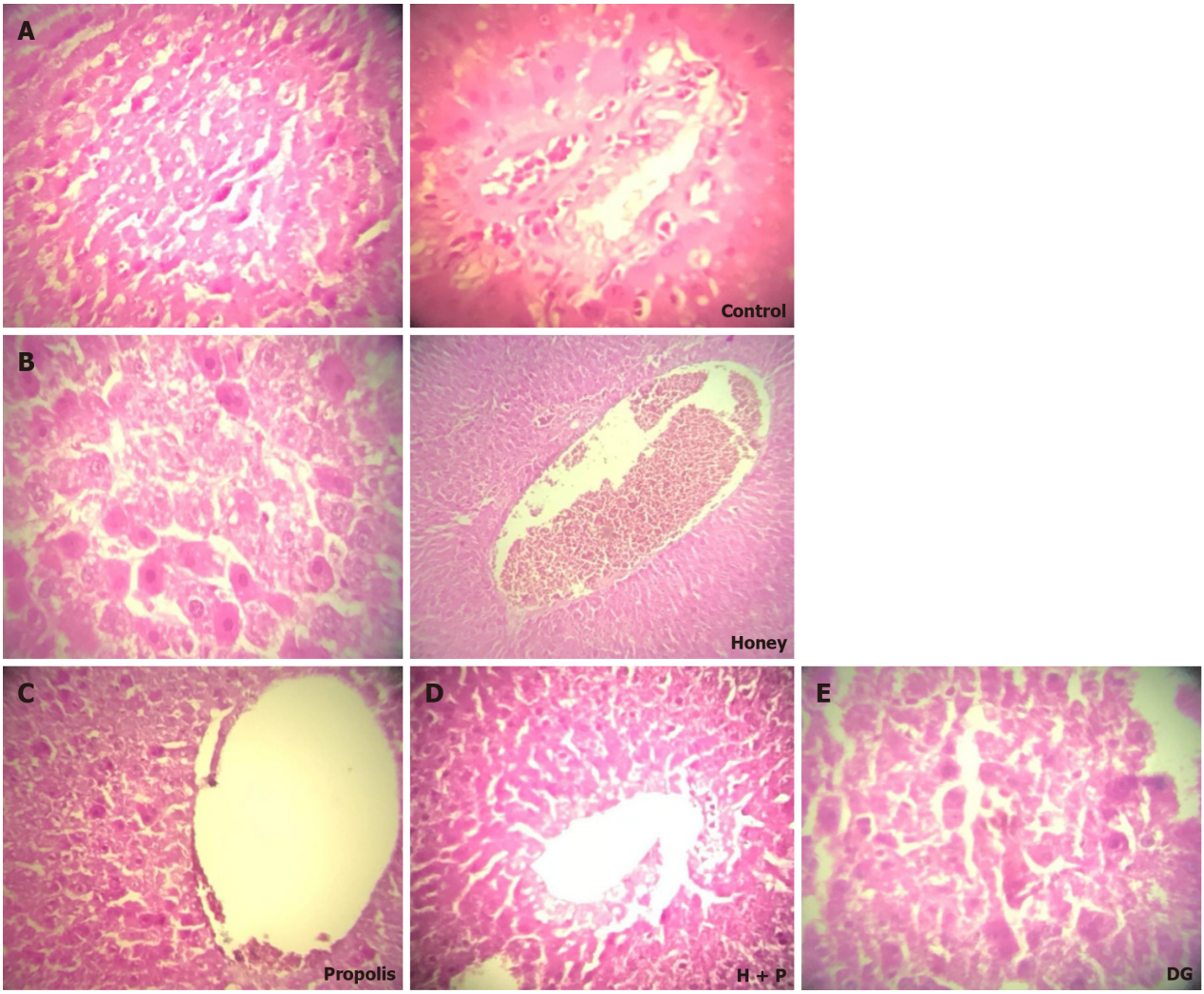

Figure 2 Histopathological changes in liver tissues after D-glucose administration with and without honey, propolis, and their combination. A: Control, hepatocytes in the process of necrosis and inflammatory infiltrate in the portal tracts; B: Honey, hepatocyte necrosis and dilation of the centrilobular vein; C: Propolis, vascular congestion and hepatocyte necrosis; D: Honey + Propolis, normal; E: D-glucose, hepatocyte necrosis. DG: D-glucose; H: Honey; P: Propolis.

Table 10 Effect of interventions on D-glucose induced changes in antioxidant enzymes, proteins, and malondialdehyde concentrations in kidney tissues

Parameters/kidney tissue	Interventions					*F/P* value
	C	D	D + P	D + H	D + P + H	
GSH (μg/g tissue)	21 ± 1.55	9.6 ± 2.4[1]	16.6 ± 0.14[1,2]	16.1 ± 2.56	16.9 ± 1.42[2]	25.5/0.001
GPx (nmol GSH/min/mg prt)	14.4 ± 1.9	8 ± 1.4[2]	12.8 ± 2.22	11.12 ± 1.02	12.8 ± 1.4[2]	11.03/0.001
MDA (nmol/g tissue)	31.7 ± 3.7	47.3 ± 3.3[1]	43.3 ± 4.0[1]	35.3 ± 7.1	37.5 ± 4.2	9.5/0.001
CAT (μmol H_2O_2/min/mg prt)	19.4 ± 1.3	12.9 ± 0.78[1]	16.6 ± 1.86[2]	15.4 ± 0.7[1]	16.28 ± 2.4[1,2]	10.6/0.001
Protein (mg/g tissue)	5.1 ± 0.54	3.4 ± 0.19[1]	4.1 ± 0.7	4.56 ± 0.29[2]	4.33 ± 0.41	8.34/0.001

[1]Compared to Control.
[2]Compared to D-glucose.

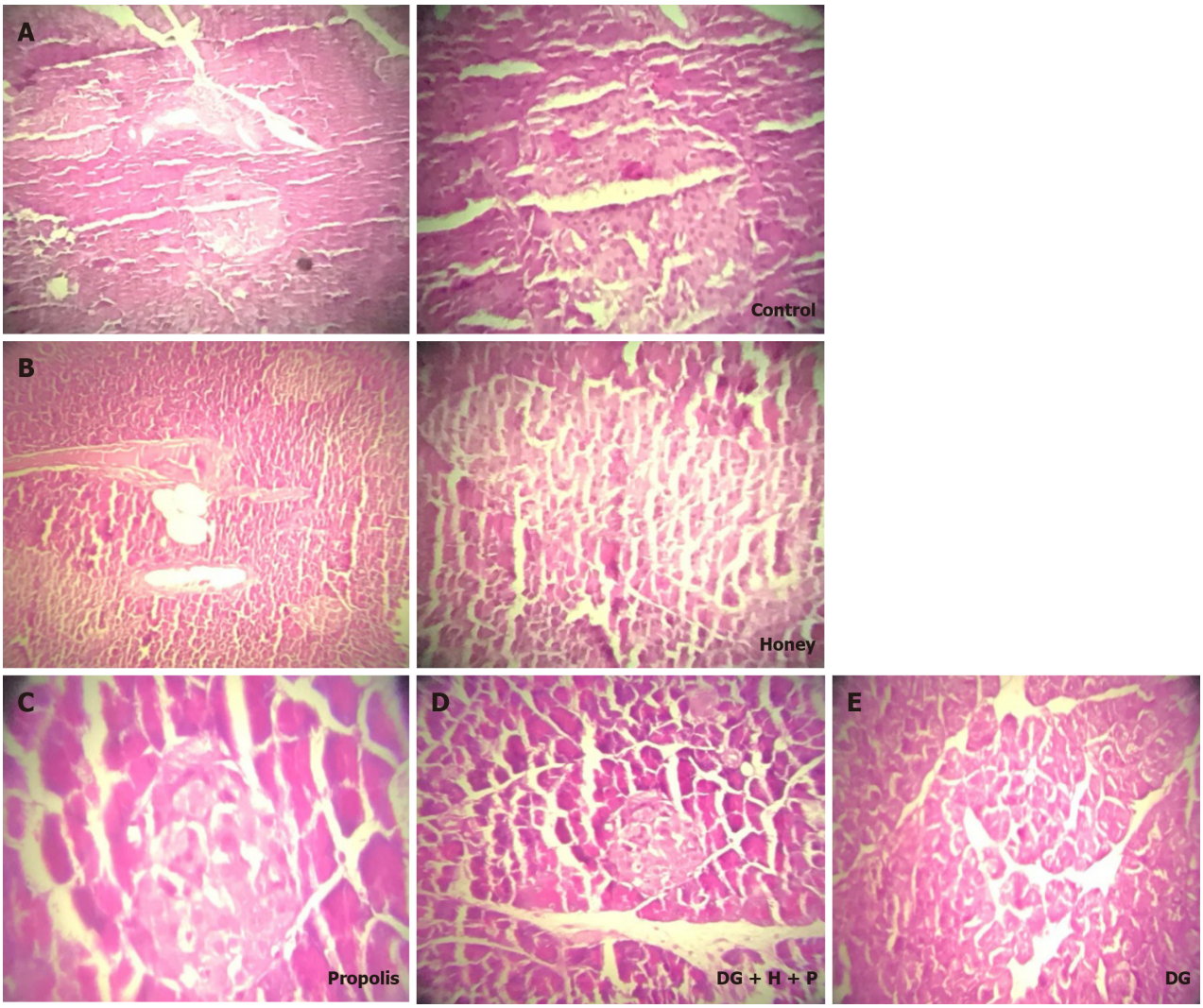

Figure 3 Histopathological changes in pancreatic tissues after D-glucose administration with and without honey, propolis, and their combination. A: Control, many islets of Langerhans and of Langerhans rich in cells (250c/islet); B: Honey, many islets of Langerhans and of Langerhans rich in cells (150c/islet); C: Propolis, few islets of Langerhans and of Langerhans rich in cells (50c/islet).; D: D-glucose + honey + propolis, few islets of Langerhans and of Langerhans rich in cells (50c/ islet); E: D-glucose, absence islets of Langerhans. DG: D-glucose; H: Honey; P: Propolis.

Table 11 Level of oxidant and anti0xidants in the liver, pancreas, and kidney tissues in the control group

Parameters	Organs			*F/P* value
	Liver	Pancreas	Kidney	
GSH (μg/g tissue)	16.86 ± 1.15	33.1 ± 4.07[1]	21 ± 1.55 (2)	58.8/0.001
GPx (nmol GSH/min/mg prt)	10.38 ± 0.75	12.66 ± 3.2	14.4 ± 1.9	4.58/0.333
MDA (nmol/g tissue)	40.58 ± 11	28.84 ± 8.15	31.7 ± 4	2.45/0.127
CAT (μmol H_2O_2/min/mg prt)	27.28 ± 5.2	20.54 ± 3	19.4 ± 1.3[1]	7.5/0.007
Protein (mg/g tissue)	6.4 ± 0.15	7 ± 0.35	5 ± 0.54[1,2]	40/0.001

[1]Compared to Control.
[2]Compared to D-glucose.
H: Honey, P: Propolis, C: Control, D; D-glucose; GSH: Glutathione; GPx: Glutathione peroxidase; MDA: Malondialdehyde; CAT: Catalase.

biomarkers[32].

D-glucose affects insulin receptor tyrosine kinase activity, which inactivates the insulin signalling cascade[43]. These changes were less evident when using honey and propolis because of decreasing insulin levels and HOMA-IR. It was found that D-glucose attenuates L-arginine transport and NO synthesis[44]. It has been clinically demonstrated that honey may reduce hyperglycemia and insulin resistance in diabetic patients[45]. In another study, propolis supplements for 18 weeks in type II diabetic patients could improve antioxidant defense and reduce hyperglycemia-induced product production[46]. It was shown that antioxidants, which are abundant in propolis and honey, ameliorate oxidative stress in the pancreatic tissues and stimulate insulin secretion[47]. Honey contains antioxidants and fructose, which might be responsible for its hypoglycemic effect[48]. These might help explain in part the mechanism of action of propolis and honey in D- D-glucose-induced diabetes.

The data showed that honey, propolis, and their combination alleviate hyperglycemia-induced AKI. Other studies showed similar results when honey and propolis individually were used in streptozotocin-induced diabetic rats[39,49]. Sider honey collected in Egypt showed a favorable effect on regulating oxidative stress and apoptosis in streptozotocin-induced diabetic rats[50]. Furthermore, Nigerian honey improves hyperglycemia and dyslipidemia in alloxan-induced diabetic rats[51].

Complex carbohydrates are hydrolyzed by pancreatic alpha-amylase and alpha-glucosidase enzymes, producing glucose which is absorbed by the intestine. In our study, honey and propolis have alpha-glucosidase and alpha-amylase inhibitory activity; honey has higher inhibitory activity than propolis. Honey and propolis contain flavonoids that have alpha-amylase and glucosidase inhibitory activity[52]. Other studies confirm that honey and flavonoids possess significant alpha-amylase and alpha-glucosidase inhibitory activity[53-55]. These findings might help explain the beneficial effect of honey and propolis on diabetes and might help prevent diabetes mellitus by decreasing postprandial blood sugar.

Proteinuria and kidney disease are common complications of diabetes. Acute hyperglycemia could cause AKI and oxidative stress[56]. D-glucose administration and hyperglycemia led to AKI, proteinuria, an increase in urine uric acid, and a significant decrease in the urinary creatinine excretion. AKI was evident by a significant elevation of serum creatinine and blood urea. Interestingly, the use of honey or propolis significantly ameliorated AKI and proteinuria, and the combination of both showed a better effect. Serum creatinine usually increases 12 weeks after streptozotocin induction of hyperglycemia[57]. However, it may also increase after one week in cases of AKI with tubular injury and/or without chronic glomerular endothelial cell injury[58], leading to oxidative stress[56].

Propolis has exhibited higher antioxidant activity than honey[39]. Other studies have shown that phenols and flavonoids improve AKI, renal fibrosis, and inflammation[59-64]. Therefore, such findings may partly explore the protective effect of honey and propolis mechanisms of action against hyperglycemia-induced AKI and proteinuria.

CONCLUSION

Both honey and propolis provide a high level of antioxidants and antioxidant activity, with propolis featuring a significantly higher antioxidant content and activity. Honey and propolis exhibited alpha-glucosidase and alpha-amylase inhibitory activity, with honey showing a higher inhibitory activity than propolis. This might help explain part of the mechanism of action of the hypoglycemic effect. Administration of D-glucose causes hyperglycemia and a significant increase in serum creatinine and urea, lipidic parameters, hepatic enzymes, LDH, HOMA-IR, and urinary protein excretion. Additionally, the administration of D-glucose causes a significant lowering in insulin levels, QUIKI, HDL, and urine excretion of creatinine. It causes pathological changes in the liver, pancreas, and kidney tissue after 10 weeks. These changes were alleviated by daily treatment with honey, propolis, or their combination, which started 7 weeks after the administration of D-glucose. The exact mechanism behind these effects is not yet known. Still, it may be linked to the synergistic antioxidant activity of propolis and honey, as well as their alpha-amylase and alpha-glucosidase inhibitory activity. The honey and propolis combo could potentially provide a valuable natural therapeutic approach to the

management of proteinuria, acute renal failure, acute liver injury, and diabetic complications. Also, the combination can be used to decrease the incidence of diabetes. Further studies to explore the mechanism of action are fundamental to identify and guide the extraction of the most active ingredients.

FOOTNOTES

Author contributions: Touzani S, HL, Aboulghazi A, Hamas N, Imtara H, El Ghouizi A, ElArabi I, Lyoussi B designed the experimental protocols and participated in the experimental work; Touzani S wrote part of the paper; Al-Waili N analyzed the data and results, wrote the main manuscript text, and submitted the manuscript for publication; Al-Waili A did the statistical analysis and collected data; All authors read and approved the final manuscript.

Institutional animal care and use committee statement: The present work was designed under ethical approval number (USMBA-SNAMOPEQ 2017-03), certified by Sidi Mohamed Ben Abdellah University, Fez, under the responsibility of the Animal Facility and the Laboratory of Natural Substances, Pharmacology, Environment, Modeling, Health, and Quality of Life. The manipulation of animals respected the EU Directive 2010/63/EU for animal experiments to avoid and minimize animal suffering and the number of animals experimented.

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Country of origin: United States

ORCID number: Noori Al-Waili 0000-0002-4763-4444.

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