The biological effects of fermented camel milk fortified with sage (Salvia officinalis L.) and mint (Mentha piperita) leaves powder on alloxan-induced diabetic rats

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Research Article

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Abstract

Background: Diabetes mellitus (DM) is a chronic metabolic condition described by persistent hyperglycemia due to low secretion of insulin, insulin resistance, or a combination of both. Many studies suggested the potential anti-diabetic effect of camel milk and the important role of the bioactive components of mint and sage in decreasing the side effects of diabetes disease. This study was designed to assess the anti-diabetic potential of fermented camel milk fortified with sage or mint leaves powder (1 and 1.5%) in alloxan-induced diabetic rats.

Methods: Forty-two adult normal male albino rats were taken for the study where one group was kept as the non-diabetic control group (6 rats) while the other 36 rats were made diabetic by alloxan injection (150 mg/kg of body weight). Among diabetic rats, a control (+) group (6 rats) was kept and referred to as diabetic control whereas the other 5 groups (7rats each) of diabetic rats were fed on fermented camel milk (FCM) or fermented camel milk fortified with sage or mint leaves powder(1 and 1.5%).

Results: The oral administration of fermented camel milk fortified with sage or mint leaves powder caused a significant decreased in blood glucose level and lipid profile, and increased in insulin level compared to the control (+) and FCM groups, and the best results were observed with fermented camel milk fortified with 1.5% sage powder. The results also found that the fermented camel milk fortified with sage or mint leaves powder improved the liver and kidney functions of diabetic rats. Importantly, treatment of diabetic animals fermented camel milk fortified with sage or mint leaves powder resulted in significant amelioration of the histopathological changes of pancreatic, liver, and kidney observed in diabetic animals.

Conclusion: Our study recommends the use of sage and mint leaves powder (at a ratio of 1.5%) with fermented camel milk to produce functional food products with anti-diabetic activity.

Keywords: *Camel milk, Fermented milk, Anti-diabetic, Sage, Mint, Antioxidants*

Background

According to the most recent food and agriculture organization (FAO) statistics, Camels world population is estimated to be around 32.6 million [1]. Camel's milk is a vital part of the staple diet in several parts of the world, especially in the arid and semi-arid zones. Camel's milk is rich in health-

beneficial substances, such as lactoferrin, lysozyme, lacto-peroxidase, bioactive peptides, mono and polyunsaturated fatty acids, minerals (calcium, magnesium, copper, iron, zinc, phosphorous, potassium and sodium), immunoglobulins and vitamins including, B1, B2 and C [2,3,4,5]. Camel milk has been known as a source for the production of dairy products with excellent therapeutic properties such as fermented milk [6]. Raw and fermented camel milk is found to have many health benefits such as anticancer, antimicrobial, antioxidant, anti-inflammatory, antidiabetic, anti-diarrhea, hypocholesterolemic, angiotensin I-converting enzyme (ACE) inhibitory activities [7, 8, 9, 10].

According to the available data from IDF confirmed that, in 2021, the number of people (20 to 79-year-old) suffering from diabetes was predestined near 537 million [11] . This number is foreseeable to reach 643 million in 2030 and 783 million by 2045. Diabetes mellitus (DM) is a chronic metabolic condition described by persistent hyperglycemia due to being incapable to produce enough insulin, cannot using the produced insulin (insulin resistance), or a combination of both [12, 13]. Camel milk is a unique source of nutrients and is considered as a super food with high medicinal values [14]. Camel milk has been shown to improve other pathophysiological aspects related to diabetes as a chronic disease such as obesity, insulin resistance, wound healing, and inflammation [12,15, 16]. Camel milk improves diabetes complications such as wounds, kidney and liver failures and oxidative stress. Also, Camel milk improves diabetes complications such as liver and kidney failures, wounds, and oxidative stress [17]. Fallah *et al.* [18] found that the raw camel milk caused an increase in insulin secretion, and reduce bout 30–35% of required insulin in type 1 diabetes patients.

One therapeutic ways suggested to reduce postprandial hyperglycemia is by the inhibition of two key enzymes linked to type II diabetes mellitus, namely α- glucosidase and α- amylase, in the digestive organs. Despite its traditional applications in food flavoring, *Mentha* spp are widely used for treating not only fever and cold but also cardiovascular and gastrointestinal disorders as folk medicines [19]. Rajeshwari *et al.* [20], reported that the administration of mint leaves powder (5g/day) to type 2 diabetes patients for 60 days reduced the oxidative stress by decreased lipid peroxidation, protein oxidation, increased serum beta carotene, vitamin A, E, and C levels. In addition, improved the activity of some antioxidant enzymes i.e. glutathione-S-transferase (GST), in addition to the content of reduced glutathione (GSH). Also, Chandirasegaran et al. [21] detected a significant decrease in blood glucose and creatinine levels as well as an increase in insulin levels of diabetic rats after being treated with mint (300 mg/kg B.W) for 45 days. These findings cleared that mint possesses antidiabetic activity against streptozotocin-induced diabetic rats.

Sage is well reputed to cure diabetes or restrain its complications [22]. Khashan and Al-Khefajim [23] found that the treatment of alloxan-induced diabetic rats with aqueous and ethanol extracts of *Salvia officinalis* leaves at a concentration (100 mg/kg B.W) for 14 days decreased the levels of blood glucose, triglycerides, and total cholesterol. The suggested mechanisms for anti-diabetic actions of salvia species extracts are the increase of insulin sensitivity, activation of pancreatic b-cells, and peripheral use of glucose, inactivation of insulinase enzyme, glycogenolysis reduction, decreases the absorption of glucose from the intestine, and increase the synthesis of glucose in the liver [24]. The present study aimed to evaluate the effects of camel milk fortified with sage and mint leave powder on the biochemical markers and histopathological of the alloxan-induced diabetic rats.

Material and Methods

Materials

Camel milk (total solids 11.84 %, protein 3.22%, fat 3.43%, pH 6.60, and acidity 0.175%) was obtained from a private farm in El-Arish, North Sinai Governorate, Egypt. Commercially- vailable lyophilized culture (Yo-fast 88, contains *Streptococcus thermophillus* and *Lactobacillus delbrueckii* ssp. *bulgaricus*) was purchased from Chr. Hansen Laboratories, Hoersholm, Denmark. Mint (*Mentha piperita*) and Sage (*Salvia officinalis*) leaves were obtained from El-Arish local market, North Sinai Governorate, Egypt. Alloxan monohydrate, analytical reagent grade purchased from Sigma Chemical Co. (Sigma-Aldrich Company Ltd., UK). 1, 1-diphenyl-2-picryl-hydrazyl (DPPH) was purchased from Sigma-Aldrich (Munich, Germany). Potassium ferricyanide, Ferric chloride and gallic acid were purchased from Loba Chemie, Mumbai, India.

Methods

Preparation of mint and Sage leaves powder

The leaves of mint and sage were dried at 30-40 ºC by the hybrid solar convective drying system (C.C.P. Parma – Italy) then grind the leaves until it becomes a powder.

Preparation of sage and mint extracts

Five grams of mint and sage leaves powders were mixed with 100 mL ethanol solution 75%, stirring for 2 hours at room temperature. Finally, the mixtures were filtered by Whatman No.1 and the extracts were stored at 4 °C until analysis [25].

Antioxidant activity of sage and mint extracts

Determination of total phenolic contents of sage and mint extracts

TP contents of sage and mint extracts were determined according to the method of Abirami et al. [26]. Folin–Ciocalteu's reagent (1.5 mL, diluted 10 times) and Na2CO3 (1.2 mL, 7.5% w/v) were added to sage and mint extracts extract (300 µl). Mixtures were shaken and kept at room temperature for 30 min (in dark) before measuring absorbance at 765 nm using a spectrophotometer (Pg T80+, England), tests were carried out in triplicate. Total phenol content (TPC) was expressed as Gallic acid equivalent (mg GAE/g plant material or extract).

Determination of total flavonoids (TF)

The TF content of sage and mint extracts were determined based on the method of Barros et al. [27]. Half milliliter of sage and mint extracts was mixed with distilled water (2 ml) followed by addition of $NaNO_2$ (150 µL, 5%) solution. After 6 min, 150 µL of $AlCl_3$ (10% w/v) was added and allowed to stand for another 6 min before 2 ml of NaOH (4% w/v) was added. The last mixture was brought to 5 mL with distilled water, and then allowed to stand for 15 min at room temperature. The absorbance was measured at 510 nm using a spectrophotometer (Pg T80+, England). A calibration curve of Rutin was prepared and TF content was determined.

DPPH scavenging activity %

Scavenging activity of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical was determined according to the method of Lim and Quah [28]. Two milliliters of 0.15 mM DPPH was added to 1 ml of extracts in different dilutions. A control was prepared by adding 2 ml of DPPH to 1 ml of methanol. The contents of the tubes were mixed and allowed to stand for 30 min, and absorbance was measured at 517 nm using a spectrophotometer (Pg T80+, England). Triplicate tubes were prepared for each extract. The results were expressed as % radical scavenging activity.

$$\text{Radical scavenging activity\%} = \frac{(\text{A control} - \text{A sample})}{\text{Acontrol}} x100$$

IC_{50} which denotes the amount (mg) of the plant powder in 1 ml solution required to reduce initial concentration of DPPH radicals by 50% was also calculated. Ascorbic acid was used as a standard.

Ferric reducing antioxidant power (FRAP)

The FRAP was determined according to the method of Oyaizu [29]. One milliliter of sage and mint extracts in different dilutions was added to 2.5 ml phosphate buffer (pH 6.6, 0.1 M) and 2.5 ml potassium ferricyanide (1% w/v). Then the mixture was incubated in a water bath at 50ºC/ 20 min, followed by cooling to room temperature and adding 2.5 mL of trichloroacetic acid (10% w/v). The contents of the tubes were centrifuged at 10,000 ×g for 10 min at 4˚C. Two and half milliliters of supernatant was removed from each tube, and then mixed with of distilled water (2.5 mL) and ferric chloride solution (0.5 mL, 0.1% w/v). The mixtures were allowed to stand for 30 min in dark at room temperature. The absorbance measurements were taken at 700 nm using a spectrophotometer (Pg T80+, England). Triplicate tubes were prepared for each extract. The FRAP values, expressed in mg GAE/g, were derived from a standard curve.

Physicochemical analysis of camel milk

Total solids (%), protein (%) and fat (%) of camel milk were determined using the AOAC procedures [30]. The pH of camel milk was measured using a digital pH meter (Martini, Italy). Titratable acidity (lactic acid %) of raw camel milks was evaluated by titration with NaOH (0.1 N) in the presence of phenolphthalein as an indicator. All analyses were performed in triplicate.

Preparation of fermented camel milk's (FCMs)

Camel milk was divided into five portions. The first portion served as a control (FCM). Four portions of camel milk were supplemented with sage and mint leave powder at levels of 1 and 1.5% (FCMS1(1% sage), FCMS2 (1.5% sage), FCMM1 (1% mint), and FCMM2 (1.5% mint)). Fermented milk was prepared according to Tamime and Robinson [31]. Camel's milk was heated at 72°C/15 sec, cooled to 40°C, and then inoculated with 0.3 % yoghurt starter culture. Camel milk was incubated at 42±1 °C until the pH value was decreased to approximately 4.6. The resultant fermented camel milk of all treatments was kept in a refrigerator (4±1°C) until use.

Animals and Treatments

The induction of experimental diabetes:

Alloxan was dissolved in saline solution (0.9% sodium chloride, pH 7). Diabetes was induces in normal healthy male albino rats by received intra-peritoneal injection dose of alloxan 150 mg/kg body weight, according to the method described by Desai and Bhide [32]. After three days of the injection with

alloxan, fasting blood samples were obtained to estimate fasting serum glucose higher than 200 mg/dL rats which were considered diabetes by The National Diabetes Data Group [33].

Experimental design

The experimental protocol was approved by Research Ehtical Committee (REC), The Institutional Animal Care and Use Committee (ICUC), Tanta University, Egypt, (Approval number: IACUC-SCI-TU-0246). Forty-two adult normal male albino rats of Sprague Dawley strain (140±10 g) were obtained from Vaccine and Immunity Organization, Ministry of Health, Helwan, Egypt. Animals were housed 6 per cage and fed on basal diet prepared base on American Institute of Nutrition [34] and consisting of 12% casein, 10% sugars, 10% sun flower oil, 1% vitamin mixtures, 4% mineral mixtures, 4% fiber, 58.50% starch, 0.3% DL-methionin and 0.2%, choline chloride, and given free access to fresh water *ad libitum*. Rats were acclimated for 2 weeks at 25 ± 1°C with a 12-h dark and light cycle [35]. The experimental period was 8 weeks after stabilization of diabetes for 1 week and the animals were divided into 7 major groups (6 rats per group) as follows:

Group 1: healthy rats (negative control); Group 2: positive diabetes control (positive control);

Group 3: Diabetic rats received fermented camel milk without additives (FCM); Group 4: Diabetic rats received fermented camel milk supplemented with 1.0 % (W/V) leaves powder sage (FCMS1);

Group 5: Diabetic rats received fermented camel milk supplemented with 1.5 % (W/V) leaves powder sage (FCMS2); Group 6: Diabetic rats received fermented camel milk supplemented with 1.0 % (W/V) mint leaves powder (FCMM1); Group 7: Diabetic rats received fermented camel milk supplemented with 1.5 % (W/V) mint leaves powder (FCMM2).

Fermented camel milks were given orally by gavages daily for eight weeks.The oral dose of fermented camel milk was 85 ml/kg B.W /day, based on the study of Althnaian et al. [36]. At the end of the experimental period, rats were fasted for 12 h, anesthetized with ether, and killed. Fasting blood samples were collected in heparinized tubes from the killed animals, and then centrifuged at 7,200 × gat 4°C for 20 min (Sigma centrifuge 113, VWR International) to obtained plasma. The obtained plasma was stored at −80°C until used for analyses [37].

Blood biochemical and enzymes activities

Stored plasma samples were analyzed for plasma glucose concentration according to the method of Trinder [38], National Diabetes Data Group [39]. Urea was determined according to the method of

Chaney and Marbach [40], Searcy *et al.* [41], Tabacco *et al.* [42]. Creatinine was determined according to the method of Bartels and Böhmer [43], Fabiny and Ertingshausen [44]. Triglycerides was determined according to the method of Bucolo and David [45], Fossati and Prencipe [46]. Cholesterol was determined according to the method of Meiattini *et al.* [47]. High-density lipoprotein (HDL) cholesterol was determined according to the method of Grove [48], Burstein *et al.* [49]. Low-density lipoprotein (LDL) was determined by the calculation (cholesterol-(TG/5+HDL). Very low-density lipoprotein (VLDL) was calculated by dividing the values of TG by factor of 5. The activities of plasma aspartate transaminase (AST) and alanine transaminase (ALT) were assayed by the method of Reitman and Frankel [50]. Alkaline phosphatase (AlP) activity was determined in plasma according to the method of Belfield and Goldberg [51]. Commercial kitts of the previous assays were obtained from Biosystems S.A. (Spain) (for Glucose, Cholesterol, HDL, TG, Urea, Creatinine); QUIMICA CLINICA APLICADA S.A (Spain) (for AST, ALT); Biodiagnostic (ARE) (for ALP).

Determination of blood insulin level

Insulin levels were estimated according to Abraham et al. [52] and Wilson and Miles [53] by using ELISA kit by Linco Research Inc. USA.

Histopathological investigation:

Small specimens of the organs (liver, kidney and spleen) were taken from each experimental group. Fixed in neutral buffered formalin, dehydrated in ascending concentration of ethanol (70, 80 and 90%), cleared in xylene and embedded in paraffin. Histopathology examinations were described according to Bancroft *et al.* [54].

Statistical analysis:

The data were analyzed using a completely randomized factorial design when a significant main effect was detected; the means were separated with the Student-Newman-Keuls Test. Differences between treatments of ($P \leq 0.05$) were considered significant using Cost at Program. Biological results were analyzed by One Way ANOVA.

Results

Antioxidant activity of saga and mint leaves powder

Many studies noted that the components with combined antioxidant potential anti-diabetic and anti-glycation properties such as *Mentha arvensis* extracts are effectively used to treat diabetes mellitus [55]. Data in Table (1) showed the antioxidant activity of mint and sage extracts. The results found that sage extract was higher in total phenolic contentment (7.35 mg GAE/g) than mint extract (7.35 mg GAE/g), while, the mint extract was the highest in total flavonoids (184 µg/ml). Moreover, the higher DPPH scavenging activity (%) was found with sage extract, while, the higher FRAP value was observed with mint extract.

Table (1) Antioxidant activity of saga and mint leaves extracts

Property	sage	mint
DPPH (%)	71.64±3.45[a]	45.32±3.45[b]
FRAP (mg GAE/g)	0.236±0.008[b]	0.466±0.041[a]
Total phenolic (mg GA/g)	7.35±0.026[a]	6.60±0.137[b]
Total flavonoids (µg/ml)	170.87±4.04[b]	184.92±4.96[a]

Mean values (± standard deviation), with different small letters are significantly different at $P < 0.05$.

Effect of fermented camel milk on alloxan-induced diabetic rats

Serum glucose and Insulin determination

The anti-diabetic properties of camel milk are very complex involving many cellular and molecular mechanisms and aspects of metabolism and transport of glucose as well as the synthesis and secretion of insulin [56, 57].

Data presented in Figure (5) showed the effect of fermented camel milk fortified with sage and mint leaves powders by ratio 1 and 1.5% on plasma glucose and insulin levels of diabetic rats. Results indicated that higher plasma glucose level (253 mg/dl) was observed with the positive control group. On the other hand, the oral intake of fermented camel milk with or without fortification by sage and mint leaves powders significantly ($P<0.05$) decreased the plasma glucose level in diabetic rats, while the normal rats was not affected. The oral intake of fermented camel milk fortified with saga and mint powder (FCMM1 ,FCMM2, FCMS1 and FCMS2) caused a significantly decreased in plasma glucose

level compared with the group of fermented camel milk (FCM), and the higher decreased was found with FCMM2 and FCMS2 groups (186.3 and 175.2 mg/dl, respectively). The induction with alloxane caused a significant ($P<0.05$) decreased in the insulin level in rats plasma (Figure 1). The higher significant ($P<0.05$) decreased was observed with positive control group (8.2 µU/ml), while the oral intake of fermented camel milk with or without sage and mint powder significantly ($P<0.05$) increase the insulin level in the blood again. The results showed that the higher insulin levels were observed with negative control group (35.9 µU/ml) followed by the animal groups intake fermented camel milk fortified with 1 and 1.5 % sage powder (29.11 and 30.2 µU/ml, respectively), while, no significant ($P>0.05$) differences were found between FCM, FCMM1 and FCMM2 groups (27.3, 27.4 and 28.6 µU/ml, respectively).

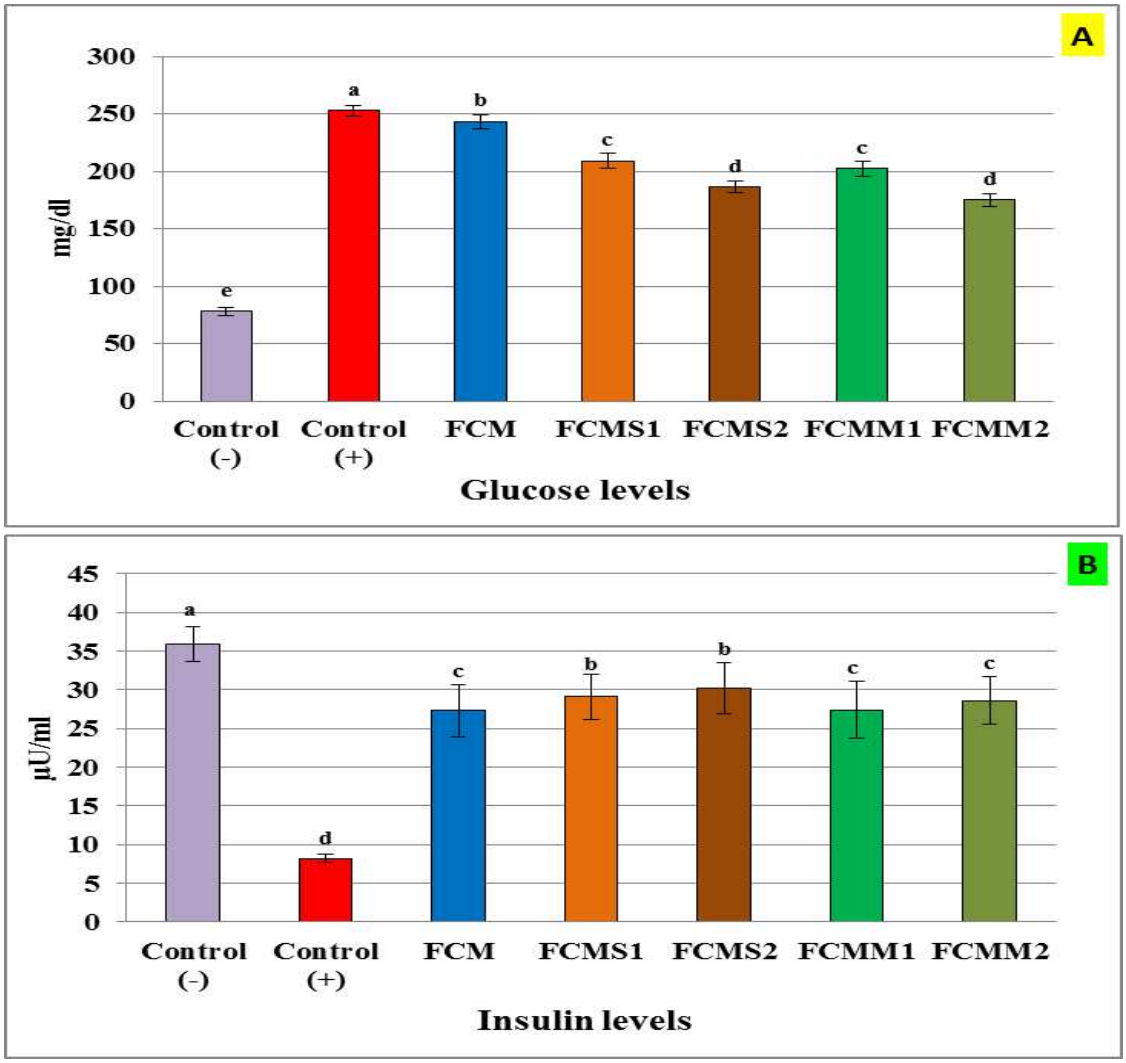

Figure (1): Effect of fermented camel milk fortified with sage and mint leave powders on glucose and insulin levels of normal and diabetic rats. *Control (-): normal healthy rats; Control (+): control diabetic rats; FCM: fermented camel milk, FCMS1: fermented camel milk with 1.0% sage leave powder, FCMS2: fermented camel milk with 1.5% sage leave powder, RCMM1: fermented camel milk with 1.0% mint leave powder, FCMM2: fermented camel milk with 1.5% mint leave powder. Values are expressed as mean ± SD, n=6, Mean values in each column having different superscript a, b, c, d are significant at ($p<0.05$) by different and vice versa.*

Lipid profile

Data in Figure (2) showed that after eight weeks of animals induction using alloxan, the animal untreated with fermented camel milk (control +) displayed an increase in plasma total triglyceride (TG) and total cholesterol (TC) compared with control (-) and animal groups treated with fermented camel milk (FCM with or without mint and sage powders (FCMS and FCMM). The results showed that the oral administration of FCM or FCMS and FCMM significantly decreased TG and TC in diabetic rats groups. A higher decrease in TG and TC levels was found with FCMS2 and FCMM2 groups compared to FCMS1, FCMM1, and FCM groups.

The results cleared that the oral administration of fermented camel milk (FCM) or fermented camel milk fortified with 1 and 1.5 % of sage or mint powder (FCMS and FCMM) caused a significant decrease in low-density lipoprotein cholesterol (LDL-c) and very-low-density lipoprotein cholesterol (VLDL-c) levels compared with control(+) group, while the high-density lipoprotein cholesterol (HDL-c) was significantly increased. The higher decrease in LDL values was found with FCMS2 and FCMM2 groups and there were no significant differences between the two groups, while, the lowest value of VLDL was observed with FCMM2. Also, higher values of HDL were found with FCMM2 and FCMS2 groups compared with all other groups. From these results, it could be concluded that the oral administration of fermented camel milk fortified with sage and mint powder by a ratio of 1 and 1.5% improved the lipid profile of diabetic rats, and the best results were found with an addition ratio of 1.5% of each herpes powder.

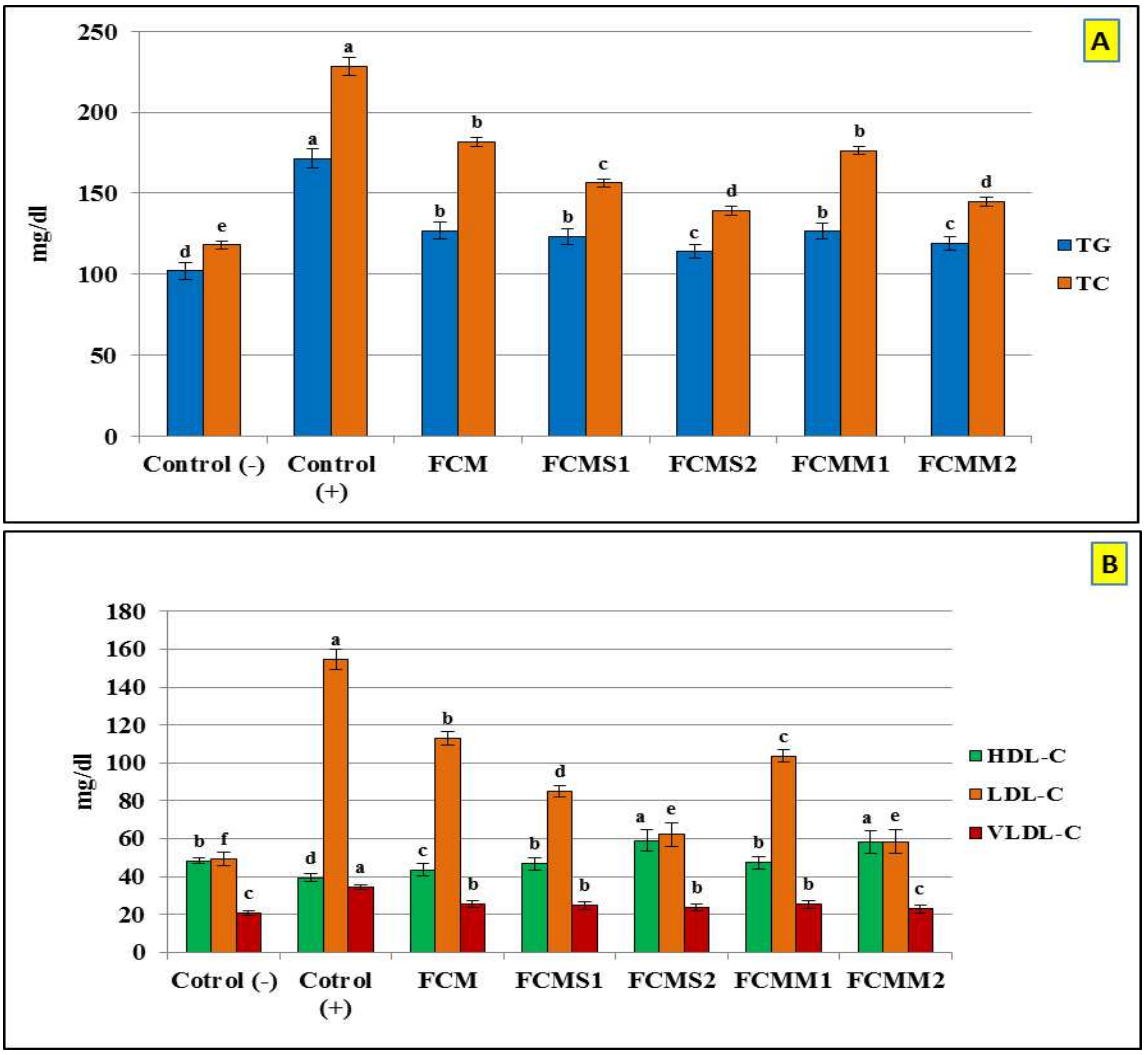

Figure (2): Effect of fermented camel milk fortified with sage and mint leave powders on lipid profile in plasma of normal and diabetic rats. *Control (-): normal healthy rats; Control (+): control diabetic rats; FCM: fermented camel milk, FCMS1: fermented camel milk with 1.0% sage leave powder, FCMS2: fermented camel milk with 1.5% sage leave powder, RCMM1: fermented camel milk with 1.0% mint leave powder, FCMM2: fermented camel milk with 1.5% mint leave powder. Values are expressed as mean ± SD, n=6, Mean values in each column having different superscript a, b, c, d are significant at ($p<0.05$) by different and vice versa.*

Liver functions

In the current study, 8 weeks of treatment of diabetic rats with fermented camel milk's significantly improved liver functions as evidenced by the following observations. Induction of rats with alloxan alone (control (+) group) caused a significant ($P<0.05$) increase in ALP, AST, and ALT compared with the healthy control group (Figure 3). These increases in ALP and AST were significantly ($P<0.05$) decreased after being treated with FCM (FCM group) and FCM fortified with 1 or 1.5 % of sage and mint powder. Meanwhile, the values of ALT were significantly ($P<0.05$) decreased in FCMS1, FCMS2, and FCMM2 groups, while, FCM and FCMM1 were not affected, compared with the control (+) group. The treatment with fermented camel fortified with 2% sage powder (FCMS2 group) reduced the increase in liver functions to be close to the normal range. No significant ($P>0.05$) differences were observed between FCMS1 and FCMM2.

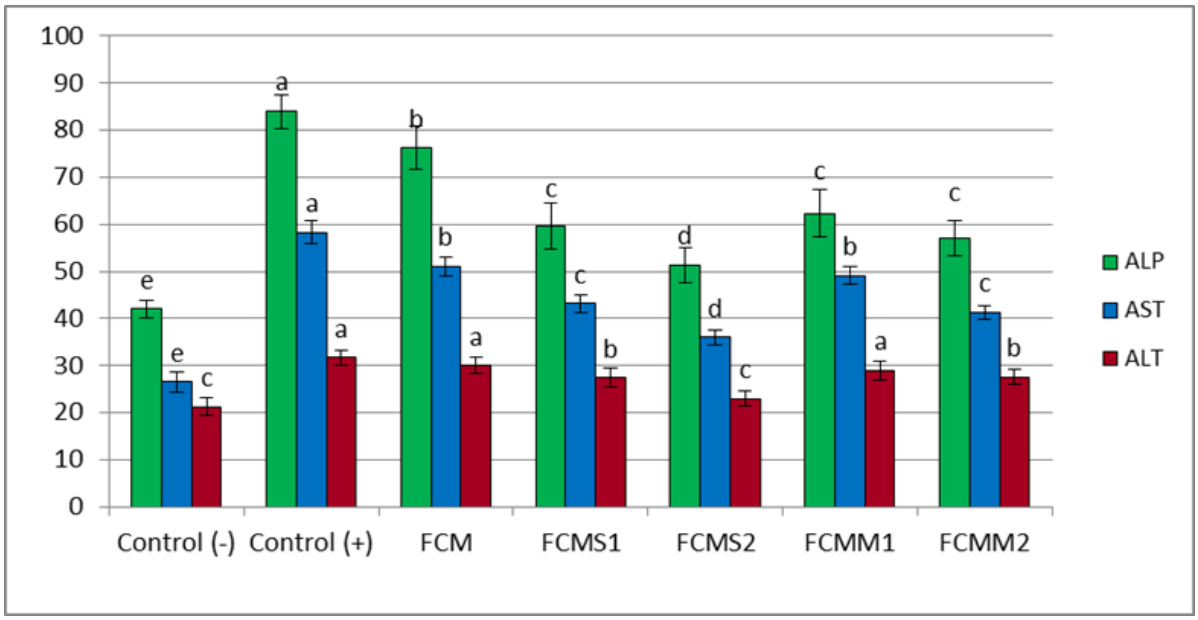

Figure (3): Effect of fermented camel milk fortified with sage and mint leave powders on liver enzymes in plasma of normal and diabetic rats. *Control (-): normal healthy rats; Control (+): control diabetic rats; FCM: fermented camel milk, FCMS1: fermented camel milk with 1.0% sage leave powder, FCMS2: fermented camel milk with 1.5% sage leave powder, RCMM1: fermented camel milk with 1.0% mint leave powder, FCMM2: fermented camel milk with 1.5% mint leave powder. Values are expressed*

as mean ± SD, n=6, Mean values in each column having different superscript a, b, c, d are significant at ($p<0.05$) by different and vice versa.

Kidney functions

A serious complication of diabetes disease is diabetic nephropathy (DN), which is the most popular cause of chronic kidney disease, especially in western countries, affecting 30-40% of patients with type 1 and type 2 diabetes [58]. The induction of rats with alloxan significantly ($p< 0.05$) increased serum urea and creatinine levels and the high values was found with positive control group as compared to negative control group. Treatment with FCM or FCM fortified with sage and mint powder significantly decreased of serum urea and creatinine levels. The higher decease in urea level was observed with fermented camel milk samples containing of 1.5 % of sage or mint powder (FCS2 and FCMM2) followed by the samples containing 1% of sage and mint powder (FCS1 and FCMM1), then sample of FCM alone. Concerning of creatinine level in diabetic rats groups, the results showed that the creatinine levels was significantly decreased administration of FCM, FCMS and FCMM, and the higher decreased was found with FCMS1, FCMS2 and FCMM2, followed by FCMM1 and FCM groups.

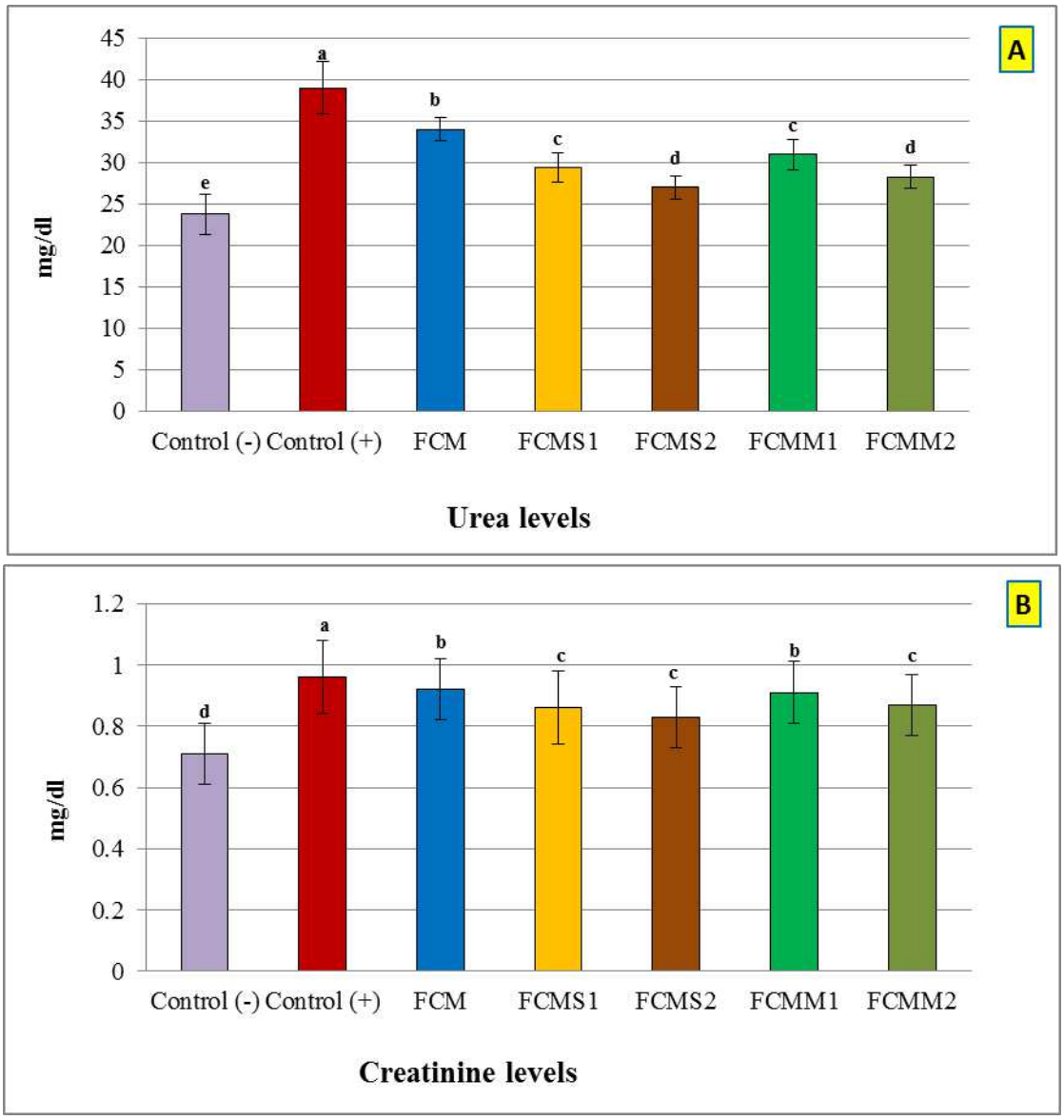

Figure (4): Effect of fermented camel milk fortified with sage and mint leave powders on urea and creatinone levels of normal and diabetic rats. *Control (-): normal healthy rats; Control (+): control diabetic rats; FCM: fermented camel milk, FCMS1: fermented camel milk with 1.0% sage leave powder, FCMS2: fermented camel milk with 1.5% sage leave powder, RCMM1: fermented camel milk with 1.0% mint leave powder, FCMM2: fermented camel milk with 1.5% mint leave powder. Values are expressed as mean ± SD, n=6, Mean values in each column having different superscript a, b, c, d are significant at ($p<0.05$) by different and vice versa.*

Histopathological examination

Histopathological of pancreatic tissues

Microscopic examination of pancreatic tissue of the normal control (-) group showed normal pancreatic parenchyma with alveolar shaped and closely packed acini, normal pancreatic ducts and ductules, and normal pancreatic islets (Fig. 5A). While pancreatic tissue of the control positive group revealed necrotic pancreatitis with hyperplasia in pancreatic islets and vasculitis with thick muscle walled blood vessel and leucocytic cells infiltration (Fig. 5B). Moreover, the pancreatic tissue of FCM group showed slight hyperplasia in the pancreatic islets (*) and slightly improved pancreatic parenchyma (Fig. 5C). The pancreatic tissue of FCMS1showing hyperplasia in the pancreatic duct (arrow) with slightly improved pancreatic parenchyma (Fig. 5D). While the pancreatic tissue of the FCMS2 group showed markedly improved pancreatic parenchyma which appeared healthy with normal pancreatic acini (Fig. 5E). Moreover, the pancreatic tissue of the group treated with fermented camel milk fortified with 1.0% mint (FCMM1) showed congested blood vessels with vasculitis (arrows), the pancreatic parenchyma showed slight improvement (Fig. 5F). While the pancreatic tissue of FCMM2 showed markedly improved pancreatic parenchyma which appeared healthy with normal pancreatic acini (Fig. 5G).

Histopathological of liver tissues

Liver of normal control (healthy) rats group revealed the normal histological structure of hepatic lobule (Fig. 6 a). Some liver sections of untreated diabetic rat group (positive control) showed vacuolar degeneration of hepatocytes, congestion of hepatic sinusoids and hepatic necrosis with inflammatory cell infiltration (Fig. 6 B). Meanwhile, another liver section of FCM treated group showed cytoplasmic vacuolization of hepatocytes and presence of few leucocytes in the hepatic sinusoids (Fig. 6 C)**.** The liver sections from FCMS1group showed congestion of hepatic sinusoids with mononuclear cells infiltration (Fig. 6 D). Also, the examined liver sections of FCMS2 group showed no histopathological changes (Fig. 6 E). Whereas, the examined liver sections of FCMM1group showed slight hydropic degeneration of hepatocytes and hypergranular cytoplasm (Fig. 6 F). However, the examined liver sections of FCMM2 group showed slight hydropic degeneration of hepatocytes and hypergranular cytoplasm (Fig. 6G).

Histopathological of kidney tissues

Microscopically, kidney of normal control rat group revealed normal histological structure of renal parenchyma (Fig.7A). Some examined kidney sections of positive control rat group revealed hypertrophy of glomerular tuft and thickening of parietal layer of Bowman's capsule (Fig. 7B). Moreover, the kidney sections of the FCM group showed revealed cystic dilatation of renal tubules with cellular cast in their lumen (Fig. 7C). Meanwhile, the kidney sections of FCMS1 treated group showing no histopathological changes (Fig. 7D). The examined kidney sections of the FCMS2 group showed cystic dilatation of renal tubules (Fig. 7E). The examined kidney sections of the treated FCMM1 group showed peritubular leucocytic cells infiltration (Fig. 7F). However, the examined kidney sections of the treated rats of FCMM2 group revealed no histopathological changes (Fig. 7G).

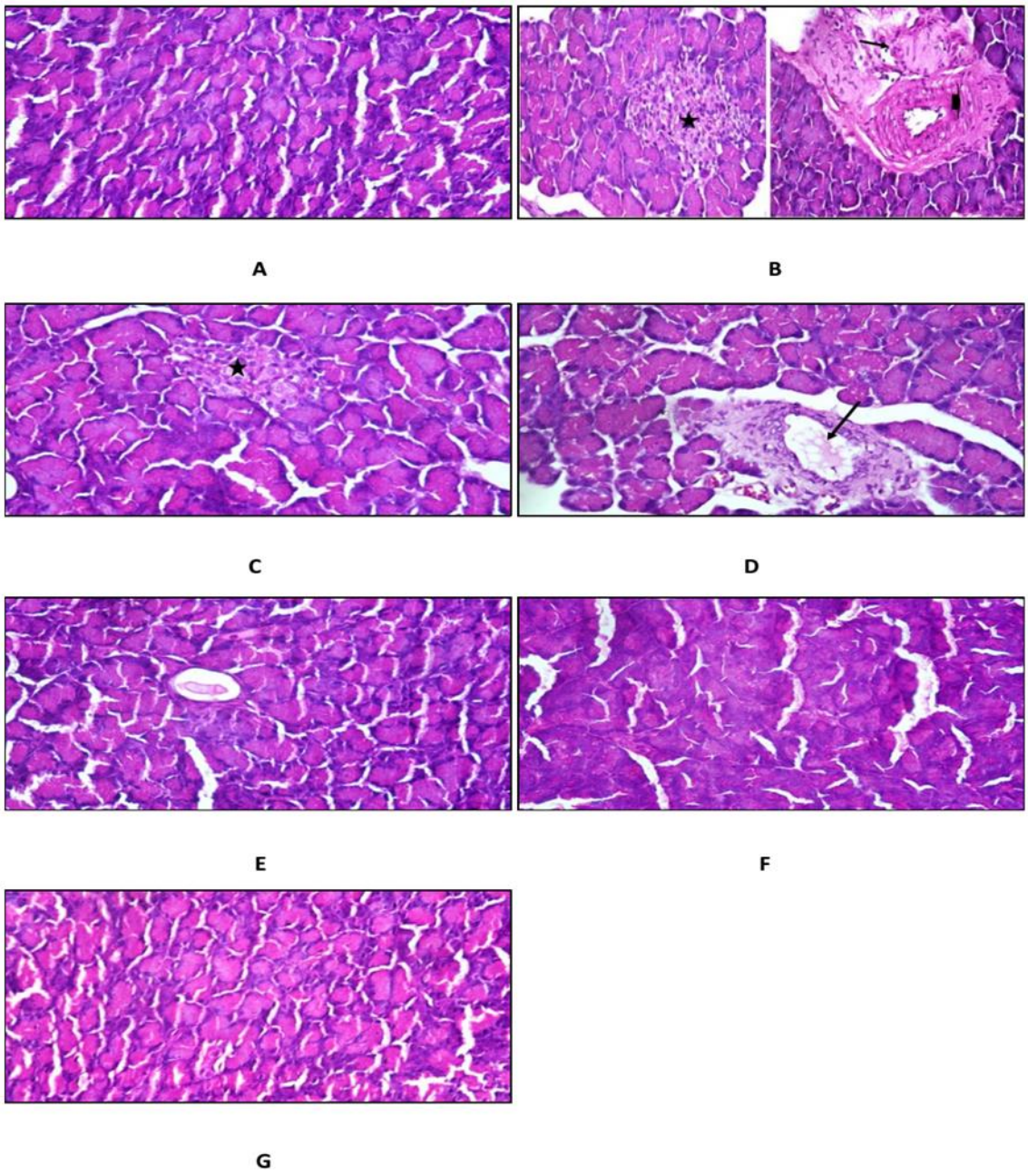

Figure (5) Effect of fermented camel milk fortified with sage and mint leaves powder treatment on pancreatic histopathology of the control and diabetic rats. ***A)*** *normal healthy rats (Control-);* ***B)*** *control diabetic rats (Control +) ;* ***C)*** *fermented camel milk (FCM group);* ***D)*** *fermented camel milk with 1.0% sage leave powder (FCMS1 grouop),* ***E)*** *fermented camel milk with 1.5% sage leave powder (FCMS2 group),* ***F)*** *fermented camel milk with 1.0% mint leave powder(RCMM1 group),* ***G)*** *fermented camel milk with 1.5% mint leave powder (FCMM2 group).*

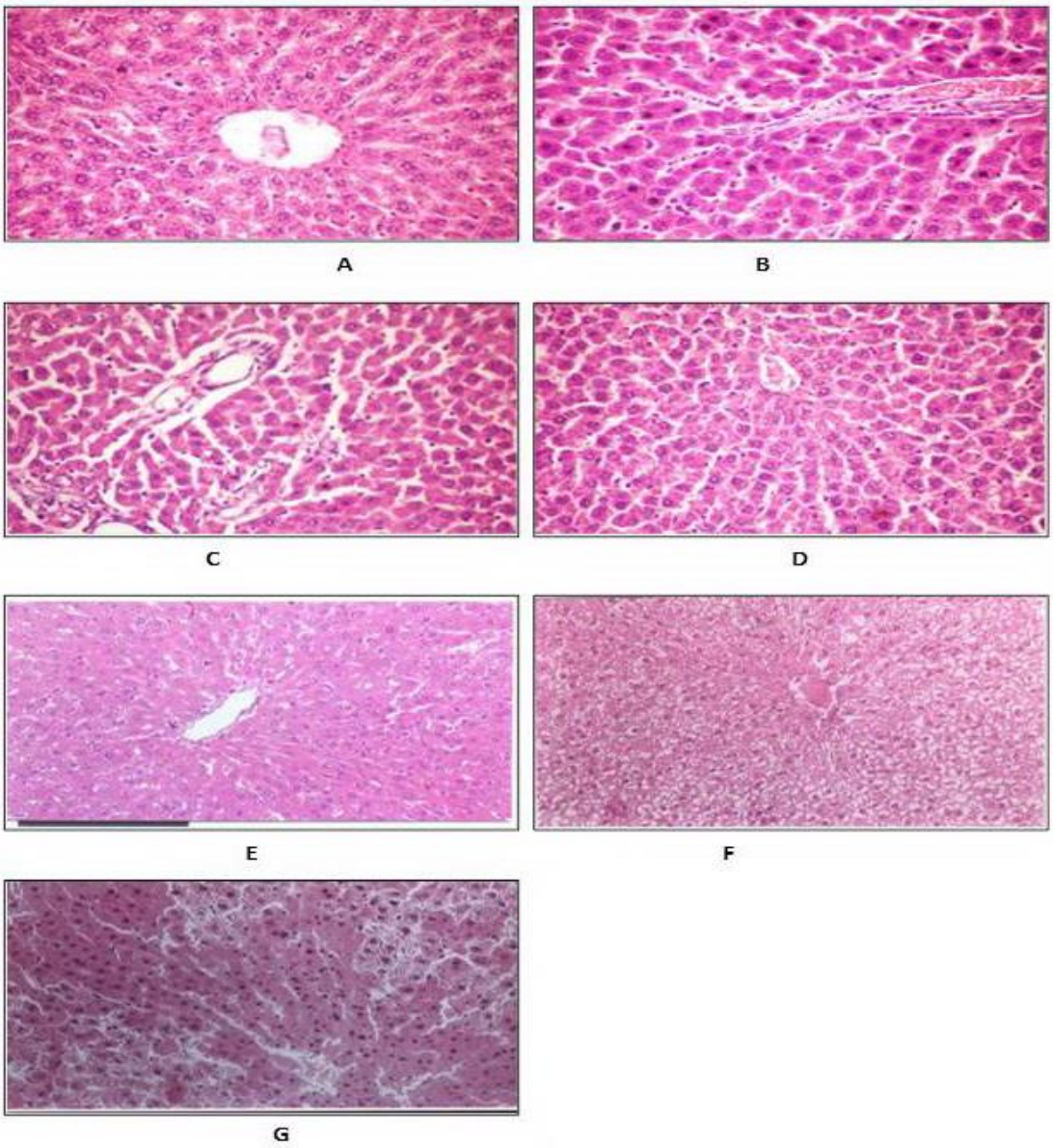

Figure (6) Effect of fermented camel milk fortified with sage and mint leaves powder treatment on liver histopathology of the control and diabetic rats. ***A)*** *normal healthy rats (Control-);* ***B)*** *control diabetic rats (Control +) ;* ***C)*** *fermented camel milk (FCM group);* ***D)*** *fermented camel milk with 1.0% sage leave powder (FCMS1 grouop),* ***E)*** *fermented camel milk with 1.5% sage leave powder (FCMS2 group),* ***F)*** *fermented camel milk with 1.0% mint leave powder(RCMM1 group),* ***G)*** *fermented camel milk with 1.5% mint leave powder (FCMM2 group).*

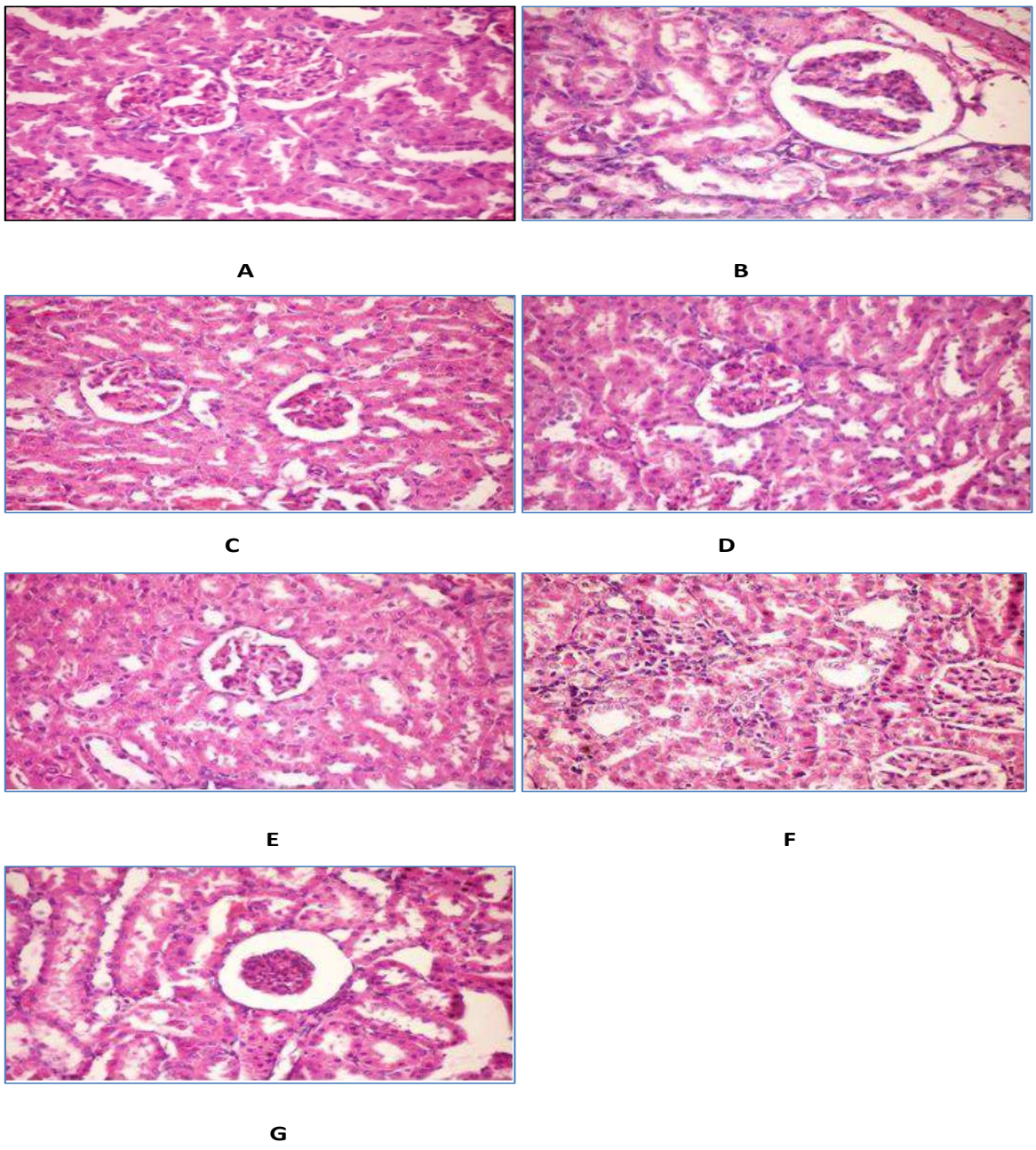

Figure (7) Effect of fermented camel milk fortified with sage and mint leaves powder treatment on kidney histopathology of the control and diabetic rats. ***A)*** *normal healthy rats (Control-);* ***B)*** *control diabetic rats (Control +) ;* ***C)*** *fermented camel milk (FCM group);* ***D)*** *fermented camel milk with 1.0% sage leave powder (FCMS1 grouop),* ***E)*** *fermented camel milk with 1.5% sage leave powder (FCMS2 group),* ***F)*** *fermented camel milk with 1.0% mint leave powder(RCMM1 group),* ***G)*** *fermented camel milk with 1.5% mint leave powder (FCMM2 group).*

Discussion

In the present study, we confirmed that the supplementation of fermented camel milk with sage and mint powder increased its antidiabetic effects on alloxan-induced diabetic rats. Whereas, the oral administration of fermented camel milk fortified with sage and mint powder caused a significant decrease in blood glucose level and lipid profile and increased in insulin level compared to the control (+) and FCM groups. Many studies reported the relationship between the antioxidant components in medicinal herbs such as sage and mint and potential anti-diabetic properties. Menthol and other volatile compounds in the leaves of M. piperita may be responsible for antioxidant and antioxidant activities [59]. Also, mint (*M. piperita)* leaf extract possesses high amount of phenolic content, flavonoids content, and flavonols. Rosmarinic acid, caffeic acid and its derivatives, and chlorogenic are the main phenolic compounds of the genus *Mentha* as well as present of some salvianolic acids [19, 60]. *In vitro* assays have shown free radical (hydroxyls radicals, nitric oxide, hydrogen peroxide radicals, superoxide radicals, and DPPH radical) scavenging activities of extracts from different *Mentha* spp [61, 62, 63]. Agawane et al. [55] found that the methanolic leaves extract of *Mentha arvensis* L. showed ability to scavenge DPPH free radical which was found to be 78% at concentration 1000mg/mL. The effect of antioxidative components on inhibition of DPPH radical is considered to be due to their ability of hydrogen-donating [64].

The significant decrease of blood glucose level in these study are in agreement with that found by Hussain et al. [65], who observed that the mean blood glucose in diabetic mice decreased from 346 (mg/dl) to 140 (mg/dl) after treated with camel milk (83ml/ kg body weight for 7 weeks) which is not significantly different from the diabetic mice receiving glibenclamide (antidiabetic druge) in a dose of 600 µg/kg body weight (blood glucose of 125 mg/dl). Also, Shori and Baba [66], reported that the fermented plain camel milk had higher anti-diabetic activity than fermented plain cow milk. The orally intake of camel milk (at a dose of 250 ml /24 hours/15 rats) reduced the blood glucose level from 462.3±37.8 to 96.7±11.1 mg/dL [67]. While, oral administration of camel milk for three weeks decreased the level of blood glucose of alloxan-induced diabetic rats from 10.88 ± 0.55 to 6.22 ± 0.5 mmol/l [68]. In the same side, Hamad et al. [69] noted that the camel milk had the higher anti-diabetic activity (49%) compared with buffalo and cow milk (11%) in diabetic Sprague-Dawley rats. In Agrawal et al. [70, 71] work, the results observed that camel milk had a significant hypoglycemic effect when administered to type 1 diabetic patients as an adjunct therapy for 3 months. Also, Agrawal et al. [72]

reported that camel milk as an adjunct to insulin therapy appears to be safe and efficacious in improving long-term glycemic control and helps in reduction in the doses of insulin in patients with type 1 diabetes. One of the suggested mechanisms of the anti-diabetic effect of camel milk might be attributable to the inhibition of various metabolic enzymes such as dipeptidyl peptidase IV [DPP-IV, an enzyme that degrades the insulin-secreting incretin hormones gastric inhibitory polypeptide (GIP) and glucagon-like peptide (GLP) , α-glucosidase and α-amylase [73]. The potential inhibition of DPP-IV is due to bioactive peptides resulting after hydrolysis of camel milk proteins throughout proteolysis or fermentation process [8], especially bioactive peptides released from whey proteins [74,75]. Additionally, presence of hydrophobic amino acids in the bioactive peptides is considered an additional factor for DPP-IV inhibition because these amino acids may further enhance interaction with the active site of DPP-IV [76, 77]. Another study suggested that the anti-diabetic activity of camel milk due to its effect on the insulin receptors [78]. While Mehaia et al. [79] reported that the content of insulin-like proteins in camel milk was 3 times more than in cow milk.

In the present study, it was observed that the corporation between sage or mint powder and fermented camel milk increased the anti-diabetic activity (decreased glucose level and increased insulin level in blood plasma). This is due to anti-diabetic activity of sage and mint powder. According to the previous studies, the antidiabetic activity of sage leaves powder due to its activity in reduced the blood glucose level and also inhibits the activity of the intestinal maltase and sucrase enzymes [23, 80]. Jose et al. [81] found that the oral administration of Peppermint juice for 21 days significantly ($p < 0.0010$) decreased the blood glucose level in alloxan induced diabetic rats. Diabetes is associated with an increase in oxidative stress as shown by an increase in free radicals, and decreased the activities of catalase (CAT), superoxide dismutase (SOD), glutathione S-transferase (GST), glutathione peroxidase (GPX) and GSH [82]. Free radicals play an important role in the development of both type I and type II diabetes [83]. Eidi et al. [84] reported that the elevation in plasma insulin levels in the sage extract-treated STZ diabetic rats could be due to substances present in the plant extract which stimulate insulin secretion or which protect the intact functional b-cells from further deterioration so that they keep active and continue to insulin production. Eidi *et al*. [84] showed that the methanol extract of *S. officinalis* causes a significant reduction in glucose concentrations on STZ -induced hyperglycemic rats. Also, Khashan and Al-Khefajim [23], found that the alloxan-induced diabetic rats treated with aqueous and ethanol extracts (100 mg/kg) of sage (*Salvia officinalis*) leaves showed a significant reduction ($P<0.05$) in fasting blood glucose. The effects of plants on diabetes disease were summarized in increasing

insulin secretion, increasing glucose uptake by fat tissues and skeletal muscle, inhibiting the production of liver glucose, and inhibiting the absorption of glucose in the intestinal [24].

These results in agree with Mansour et al. [67] who noted that the oral administration of camel milk reduced the increased in TG, TC, LDL-C and VLDL-C in diabetic rats compared with the diabetic control group. Hanieh et al. [85] evaluated the effects of camel milk on the TC, HDL and TG levels in type 1D and type 2D respectively, their findings agreed with our results that, camel milk normalized the alteration in TG and HDL-c , while reduced the increase in total cholesterol (TC) levels. Therefore, camel milk can give promising results when used as dietary supplement for patients of type 1D. In the same side, Khattab *et al.* [86] found that treated diabetic rats with sage leaves induced significant improvement in lipid profile parameters as compared with the non-treated diabetic group and concluded that sage had a potent hypoglycemic activity and related this effect to its antioxidant activities.

Regulating the levels of cholesterol and triglyceride in the blood is an important way to protect humans from coronary heart disease. It was found that administration of sage infusion for 12 weeks reduced total cholesterol, triglycerides, low-density lipoprotein(LDL-c) in rats, while, HDL-c was increased [87]. Also, Khashan and Al-Khefajim [23] indicated that ethanolic and water extracts of Sage leaves significantly lowered cholesterol and TG levels. Moreover, many studies cleared the significant role of mint leaves on diabetic rats. This hypolipidemic effect of sage may be related to the inhibition of hepatic de novo synthesis or the activation of b-oxidation [87]. Barbalho *et al.*[88] reported that treatment of diabetic rats with *M. piperita* caused a reduction on the levels of cholesterol, LDL-c, and triglycerides and increase the levels of HDL-c. Also, Nickavar et al.[89] also found that treatment of hyperlipidemic rats with aqueous extract of Mentha piperita leaves extract for 21 days significantly reduced serum total cholesterol, triglycerides, and LDL-c, and associated with a significant increase in HDL-c levels and decrease in the atherogenic index in indicating its potent anti-hyperlipidemic and antiatherogenic activity.

AST, ALT, and LDH are enzymes mainly found in hepatocyte cytosol and cell membrane. They are good markers considerably used to evaluate hepatotoxicity and integrity of the membrane [90]. The increase in activities of plasma ALT, AST, ACP, ALP, and LDH mean that diabetes caused hepatic dysfunction . Therefore, the increment of the activities of ALT, AST, ACP, ALP, and LDH in plasma

687 may be mainly due to the leakage of these enzymes from the liver cytosol into the bloodstream which
688 gives an indication of the hepatotoxic effect of alloxan [91, 92]. Belhadj *et al*.[90] noted that increase in
689 liver enzymes activities in diabetic rats were reduction after treated with sage essential oil. Similarly, in
690 alloxan diabetic rats, ALT, AST, and ALP activities were superior to those in normal rats, but recovered
691 after oral administration of fermented camel milk fortified with sage and mint powder. these results
692 similar that found by Eidi et al. [84] who reported that the recovery of liver cell integrity was obtained
693 after treatment by Sage. Orally administration of ethanolic extract of sage leaves to diabetic rats,
694 lowered serum glucose, triglycerides, total cholesterol, urea, creatinine, AST, ALT, and enhanced
695 plasma insulin depending on the increasing dose [93, 23].
696
697 Induction of hyperglycemia caused an increase in serum creatinine and urea levels, excessive
698 proteinuria, and marked deterioration of kidney function, and microscopic examination of sections of
699 the kidneys of diabetic animals showed pathological features of glomerulosclerosis, with abnormal
700 extracellular matrix (ECM) accumulation, glomerular matrix expansion, tubular alveolar degeneration,
701 and fibrosis, fourth, increased urinary excretion [12]. The observed increase in serum creatinine, urea,
702 and uric acid of diabetic animals compared with the nondiabetic control group agree with Eidi and Eidi
703 [93]. While, the consumption of camel milk caused a significant decreased in creatinine, urea of diabetic
704 rats and this could be attributed to the hypoglycemic and antioxidant effects of camel milk [12]. The
705 reported powerful hypoglycemic action of camel milk in diabetic patients is hypothesized to abolish the
706 glucose-driven metabolic pathways. The intensive glycemic control in type 1 and type 2 diabetes
707 mellitus patients results in a decrease in microalbuminuria. So, the observed renal protective effects of
708 camel milk treatment, in diabetic rats, could be assigned to the glucose homeostatic action of camel
709 milk. This was in accord with the earlier findings by Agrawal et al., [70] of a significant reduction of the
710 microalbuminuria in type 1 diabetes mellitus patients receiving camel milk along with their standard
711 antidiabetic therapy suggesting a direct protective effect of camel milk against diabetic nephropathy
712 [65,94,95].
713
714 Kilari *et al.* [96] found that the histology of liver and pancreatic tissue displayed the absence of lipid
715 accumulation in hepatocytes and preservation of β-cells in camel milk protein hydrolysate treated groups
716 compared with the diabetic control group. Our results cleared that orall administration of fermented
717 camel milk fortified with sage and mint leaves powder showed restoration of insulin secretion in diabetic

718 rats and this means that the Langerhans islets β-cells restored their activity. these results may be due
719 to the regeneration has occurred of distorted β-cells, or the undamaged β-cells secretes insulin with
720 overdose to compensate the shortage caused by damaged cells, or the camel milk reduced the
721 damage in β-cells which related to alloxan, as well as the antioxidant activities of fermented camel milk,
722 sage and mint powder [97,98, 99, 100, 101]. Mansour et al., [67] reported that Immunohistochemical
723 findings revealed that Camel Milk administration restored the immunostaining reactivity of insulin and
724 GLUT-4 in the pancreas of diabetic rats. We boosted our investigation by the immunohistochemical test.
725 STZ induced diabetes by destroying the pancreatic β-cells [102, 103]. Checking the amount of produced
726 insulin is a good indicator of the normal case of Langerhans islets β-cells because the active insulin is
727 secreted from secretory granules in the β-cells [104]. The results indicated that; the reduction of GLUT-
728 4 appeared in the diabetic rats (under immunohistochemical examination) reflects the decrease in insulin
729 secretion. Because the expression of GLUT-4 is stimulated by cascade gene regulation enhanced by
730 secretion of insulin hormone [105]. Administration of camel milk restored the expression of GLUT-4 in
731 the pancreas tissue which is detected by the immunohistochemical staining, camel milk already contains
732 insulin as mentioned in different articles [106, 107, 108] as well as it restored the activity of the β-cells
733 as we mentioned previously. Belhadj et al.[90], stated that the hepatic tissue in the Cont+ Sage EO group
734 showed a good quality, similar to that examined in Cont group. Serum enzyme measurements are
735 beneficial tool in clinical diagnosis, providing information on the effect and nature of pathological
736 damage to any tissue in the body [109].
737 The increase in serum Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)
738 activities may indicate liver tissue damage probably by altered cell membrane permeability leading to
739 the leak of the enzymes from the tissues to the serum. Alanine and aspartate aminotransaminases are
740 considered to be sensitive indicators of hepatocellular damage and within limit can provide a quantitative
741 evaluation of the degree of damage to the liver [110]. Diabetes has a strong relationship with renal and liver
742 diseases [111]. Camel milk protected the liver and kidney function from failure; we suppose that camel
743 milk contains insulin nanoparticles that safeguard the role of kidney and liver by restoring the normal
744 glucose levels in the blood. Korish et al. [12] found that the administration of camel milk to the control
745 animals caused insignificant changes in the glomerulotubular morphology in comparison to the non-
746 camel milk treated control animals . Furthermore, the kidney slices obtained from the diabetic animals
747 and stained with the Hematoxylin and Eosin showed glomerular expansion and tubular alveolar
748 degeneration. Eze et al. [112] mentioned that the induction with streptozotocin caused damage to the

kidney tissue of diabetic rats, the untreated group showed severe glomerular necrosis with lymphocyte hyperplasia when compared with the normal. This result is similar to the work carried out by Trujillo et al. [113] who reported that the abnormal levels of serum urea usually signifies decreased renal function, so plasma urea is a recognized marker of glomerular filtration rate (GFR) and in nephropathy.

Conclusion

In this study camel milk supplemented with sage and mint leaves powder ameliorated and normalized the changes in glucose, total cholesterol, and triglycerides levels in the blood of diabetic rats. The best results were found with the fortification of fermented camel milk with sage leaves powder at a ratio of 1.5%. The histopathological confirmed the biochemical assays results of insulin, glucose levels, and liver and kidney functions. From these results, it could be concluded that sage and mint leaves powder (at a ratio of 1.5%) can be used to produce healthy and functional fermented camel milk with high antioxidant activity and anti-diabetic activity.

Acknowledgements

Not applicable.

List of abbreviations

CM: Camel milk, FCM: Fermented camel milk, DM: Diabetes mellitus, IDF: International Diabetes Federation, DPPH: 1, 1-diphenyl-2-picryl-hydrazyl, TPC: Total phenol content, FRAP: Ferric reducing antioxidant power, HDL-c: High density lipoprotein cholesterol, LDL-c: Low- density lipoprotein cholesterol, VLDL-c: Very low- density lipoprotein cholesterol, TG: Triglycerides, TC: total cholesterol, AST: aspartate transaminase, ALT: alanine transaminase, AlP: Alkaline phosphatase.

Declarations

Ethics approval and consent to participate

Ethics approval of studies using rats was obtained from Research Ethical Committee (REC), The Institutional Animal Care and Use Committee (ICUC), Tanta University, Egypt, (Approval number: IACUC-SCI-TU-0246), under Protocol entitled "The biological effects of Rayeb camel milk fortified with sage and mint leaves powder on alloxan-induced diabetic rats". Mice were maintained in the faculty

of science, Tanta University, Egypt, according to recommendations in the Guide for the Care and Use of Laboratory Animals of The Institutional Animal Care and Use Committee (ICUC).

Consent for publication

Not applicable.

Availability of data and materials

The data used during the study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests

Authors'contributions

All the authors contributed to the work approved the final version of the manuscript. Particularly, contributions were: study design: MRS, MIE. Data collection: MRS, MIE, AAE; Data analyses and interpretation: MRS, MIE, AAE; Manuscript drafting: MRS, MIE; Critical revision of the manuscript: MRS, MIE, AAE. All authors read and approved the final manuscript.

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Figure legend

Figure (1): Effect of fermented camel milk fortified with sage and mint leave powders on glucose and insulin levels of normal and diabetic rats. *Control (-): normal healthy rats; Control (+): control diabetic rats; FCM: fermented camel milk, FCMS1: fermented camel milk with 1.0% sage leave powder, FCMS2: fermented camel milk with 1.5% sage leave powder, RCMM1: fermented camel milk with 1.0% mint leave powder, FCMM2: fermented camel milk with 1.5% mint leave powder. Values are expressed as mean ± SD, n=6, Mean values in each column having different superscript a, b, c, d are significant at ($p<0.05$) by different and vice versa.*

Figure (2): Effect of fermented camel milk fortified with sage and mint leave powders on lipid profile in plasma of normal and diabetic rats. *Control (-): normal healthy rats; Control (+): control diabetic rats; FCM: fermented camel milk, FCMS1: fermented camel milk with 1.0% sage leave powder, FCMS2: fermented camel milk with 1.5% sage leave powder, RCMM1: fermented camel milk with 1.0% mint leave powder, FCMM2: fermented camel milk with 1.5% mint leave powder. Values are expressed as mean ± SD, n=6, Mean values in each column having different superscript a, b, c, d are significant at ($p<0.05$) by different and vice versa.*

Figure (3): Effect of fermented camel milk fortified with sage and mint leave powders on liver enzymes in plasma of normal and diabetic rats. *Control (-): normal healthy rats; Control (+): control diabetic rats; FCM: fermented camel milk, FCMS1: fermented camel milk with 1.0% sage leave powder, FCMS2: fermented camel milk with 1.5% sage leave powder, RCMM1: fermented camel milk with 1.0% mint leave powder, FCMM2: fermented camel milk with 1.5% mint leave powder. Values are expressed as mean ± SD, n=6, Mean values in each column having different superscript a, b, c, d are significant at ($p<0.05$) by different and vice versa.*

Figure (4): Effect of fermented camel milk fortified with sage and mint leave powders on urea and creatinone levels of normal and diabetic rats. *Control (-): normal healthy rats; Control (+): control diabetic rats; FCM: fermented camel milk, FCMS1: fermented camel milk with 1.0% sage leave powder, FCMS2: fermented camel milk with 1.5% sage leave powder, RCMM1: fermented camel milk with 1.0% mint leave powder, FCMM2: fermented camel milk with 1.5%*

mint leave powder. Values are expressed as mean ± SD, n=6, Mean values in each column having different superscript a, b, c, d are significant at (p<0.05) by different and vice versa.

Figure (5) Effect of fermented camel milk fortified with sage and mint leaves powder treatment on pancreatic histopathology of the control and diabetic rats. ***A)*** *normal healthy rats (Control-);* ***B)*** *control diabetic rats (Control +) ;* ***C)*** *fermented camel milk (FCM group);* ***D)*** *fermented camel milk with 1.0% sage leave powder (FCMS1 grouop),* ***E)*** *fermented camel milk with 1.5% sage leave powder (FCMS2 group),* ***F)*** *fermented camel milk with 1.0% mint leave powder(RCMM1 group),* ***G)*** *fermented camel milk with 1.5% mint leave powder (FCMM2 group).*

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Figure (7) Effect of fermented camel milk fortified with sage and mint leaves powder treatment on kidney histopathology of the control and diabetic rats. ***A)*** *normal healthy rats (Control-);* ***B)*** *control diabetic rats (Control +) ;* ***C)*** *fermented camel milk (FCM group);* ***D)*** *fermented camel milk with 1.0% sage leave powder (FCMS1 grouop),* ***E)*** *fermented camel milk with 1.5% sage leave powder (FCMS2 group),* ***F)*** *fermented camel milk with 1.0% mint leave powder(RCMM1 group),* ***G)*** *fermented camel milk with 1.5% mint leave powder (FCMM2 group).*

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