

Effect of aqueous extract of tops of date palm leaves on blood glucose of diabetic rats

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Abstract: Present study was carried out to examine the effect of tops of date palm leaves extract on blood glucose of streptozotocin induced diabetic rats. Forty male Sprague Dawley rats (120-130g) were housed individually and randomly allocated to two main groups; diabetic group (n=30), and normal group (n=10) in the animal lab, Faculty of Agriculture and Veterinary Medicine, Qassim University, Saudi Arabia. An aqueous extracts were prepared from tops of date palm leaves (EDPL) and were orally administered to rats. Later, the determination of glucose, BUN, creatinine, uric acid, ALT, and AST was examined. Pancreas sample were taken for histopathological examination. It was clear that the higher the concentration of EDPL the lower the weight gain ($P<0.001$). Glucose concentration of normal group changed by -0.79% and decreased by -20.4% among diabetic control group, while feeding 1% and 2% EDPL had no significant effects, and the higher the amount of EDPL the higher the concentration of blood glucose. The thought that tea made from date palm leaves decrease blood glucose level has been denied by the results of this study and this tea may worsen diabetes patient's status.

Keywords: Blood glucose, rats, streptozotocin.

INTRODUCTION

Increased blood glucose level is a physiological change leading to certain impairments, which usually results in some abnormalities of physiologic process that may be life threatening for humans (Duran-Salgado and Rubio-Guerra, 2014). An extensive research work has been conducted concerning the herbs that might have a protective effect against the higher sugar levels because of the side effects linked with the oral hypoglycemic agents for the cure of the diabetes (Abuelgassim, 2010). The medicinal plants can be a good source of the types of drugs, according to the World Health Organization (WHO, 2010). There are many societies which have shown their interest in using plants in order to cure the disease. It has been observed that microbes are associated closely with the welfare and health of human beings in which some are detrimental and some are beneficial. Plants and their products can be used as a treatment and as a curative and preventive measure for the infections. The traditional medicines system over the conventional treatment increases due to the safer actions as a global interest in terms of side effects and tolerance for chronic illness. An extensive research work has been conducted.

A study conducted by Hasan and Mohieldein (2016) has evaluated the antioxidative, hypolipidaemic, antidiabetic activities and the profile of liver and kidney of the seed extracts of Ajwa/ Sukkari date on Streptozotocin induced diabetic rats. The study has verified the anti-diabetic properties of seed extracts of aqueous solution of the

different varieties of dates namely of Kingdom of Saudi on Streptozotocin induced diabetic rats. The treatment applied on this study showed that the extract reinstates the balances of the oxidative stress state in diabetic treated rats and function of kidney and liver. The study intended to observe the effects of aqueous extract of tops of date palm leaves on blood glucose among streptozotocin induced diabetic rats.

Some agricultural regions in Gulf region usually use date-palm leaves as essential ingredient in livestock feed, generally consumed by sheep and goats (Hassan and Mohieldein, 2016). A preliminary study, carried out by Pillaya *et al* (2003) detected that chromium and arsenic occurred at unexpectedly high levels in the date-palm leaves. In their recent and published study, Pillaya *et al.* (2003) found appreciable levels of chromium and arsenic in date-palm leaves by emission spectroscopy. However, the toxicity of chromium and arsenic are widely evident (Pillay *et al.*, 2003), and higher levels, both of arsenic and chromium, which may cause several disorders including cancer (Hasan and Mohieldein, 2016). On the contrary, a study carried out by Abuelgassim (2010) investigated the effect of date-palm leaves on glucose level among diabetic rats (Alloxan induced diabetes), which found that extract of date-palm leaves had a hypoglycemic and hypopidemic properties.

Because of the high prevalence of diabetes in Kingdom of Saudi Arabia (14.4%), WHO (2010), some diabetic patients look for alternative medicine for treatments and most of them using folk medicine. Recently, some

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diabetic Saudi farmers have been used tea made from the tops of date palm leaves as hypoglycemic drink. The researchers in the current study tried to find out any published information about this beverage or the plant and only one article has been found, which carried out on the leaves and fed it to alloxan induced diabetes rats; therefore, it is decided to investigate the effect of that tea on Streptozotocin induced-diabetic rats, along with study its effect on renal and liver biomarkers. Moreover, it was tried to determine the chemical compounds occurred in the plant as well.

Rationale of the study

The research was intended to remove the gaps in the literature related to the effects of tops of date palm leaves extract on blood glucose. This study has contributed to understand that the effect of tea made from date palm leaves on blood glucose level is not as good as expected. It has also contributed to understand that the tea made from the tops of date palm leaves might be harmful for human health and negatively affects the condition of diabetic patient.

Hypothesis

H₀: The tea made from date palm leaves does not decrease blood glucose level

H_A: The tea made from date palm leaves decreases blood glucose level

MATERIALS AND METHODS

Animals

Forty male Sprague Dawley rats (n=40) weighing 120-130 grams were purchased from Animal Unit, Faculty of Pharmacy, King Saud University, Saudi Arabia. The rats were kept in a positive/negative control housing unit, having ventilated caging system, obtained from Allentown, Pennsylvania, USA. Rats were housed at 22°C, 56% humidity (40 to 70%) in Allentown cages, and in a 12-h light /12-h dark cycle. Rats were provided with free access to tap water and food. Lab at Faculty of Agriculture and Veterinary Medicine, Qassim University, Saudi Arabia was selected to conduct the experiment between the time period of March and April 2015. National Institutes of Health Guiding Principles in the Care and Use of Animals were used to perform all the associated procedures. Rats were allocated in two groups according to their weight. Diabetic group comprised of 30 rats and normal group comprised of 10 rats.

Diet and induction of diabetes

The standard diet used was bought from the Animal Unit of Faculty of Pharmacy in King Saud University, Saudi Arabia. The diet possessed energy of 2850.0kcal/kg; 64.0% carbs; 4.0% crude fat; 20.0% crude protein; 3.5% crude fiber; 0.50% salt; 6.0% ash; vitamin A 20.0 IU/g; and trace elements, including Cobalt, Copper, Iodine,

Iron, Manganese, Selenium, and Zinc. The experiment was conducted according to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. Streptozotocin (STZ) (Sigma-Aldrich, St. Louis, MO, USA) with 0.1M citrate buffer (pH 4.5) was injected to 30 male Sprague-Dawley rats at a dose of 75mg/kg. The fasting blood samples were collected for determination of glucose from rats. It was collected from the retro-orbital veins (Baird, 2000). Rats, who have >250mg/dl blood glucose level were taken as diabetic rats and recruited in the procedure.

Preparation of aqueous extracts

Initially the aqueous extracts were prepared according to the method given by the Saudi farmers who uses it as hypoglycemic drink. The aqueous extracts were made from the tops of date palm leaves (*Phoenix dactylifera*, Family: palmaceae) cultivated in Qassim, Saudi Arabia (fig. 1). Only hale dry parts of the tops of date palm leaves were collected and cleaned then washed with distilled water and left to dry. The tops were crushed and converted into powder, then have been used for preparing aqueous extracts in two concentrations; 1%- by adding 1 gram/ 100ml (10mg/ml) distilled water and 2%- by adding 2gram/100ml (20mg/ml) distilled water. The converted powder obtained from tops of date palm was then boiled using distilled water and then filtered twofold. Firstly, it was filtered using cheese cloth, which was 50% polyester and 50% cotton. Secondly, it was filtered using filter paper (Whatman No.2). Distilled water was added for the correction of obtained solution and achieved the targeted concentration. After correcting the concentration the solution was preserved in sterile dark bottles at 4°C.

Determination of active chemical compounds

The plant was cleaned under running tap water, air dried, pulverized then extracted. Two liters of methanol (99.9%) was added to 200g of the powdered plant, agitated and left for 72 hours, then filtered and the filtrate kept in clean dry flask. This process was repeated for 4 times until a complete exhaustion and clear filtrate was obtained. The methanol extracts were concentrated under reduced pressure using Rotary Evaporator (BUTCHI, Switzerland) at temperature not higher than 50°C and the yield percentages were recorded. Until the evaluation by Gas Chromatography- Mass Spectrum analysis, the concentrated extraction was stored at -4°C. GC/MS analysis of methanol extracts, obtained from the plant, was evaluated (Soumya *et al.*, 2014) by the use of Agilent Gas Chromatography (6890N Model) along with the 5973 Mass Selective Detector (MSD) USA, in the solvent of methanol. The recorded outcomes were studied in comparison to the in-built main Library (C:/Database/NIST08.L). The library assisted us in confirming the presence of phyto-chemicals in the plant and Gas chromatograph interfaced to a Mass Spectrophotometer. These were well equipped with Elite -5MS (5% diphenyl /

95% Dimethyl poly siloxne), 30 x 0.25mm x 0.25 μ mdf. For GC/MS detection, an electron ionization system in combination of ionization energy of 70Ev was employed. Helium gas (99.999%) was involved into the investigation, in the form of a carrier gas that had constant flow rate of 1ml/min. and an injection volume of 2 μ l (Split ratio 10:1). Injector temperature was maintained to be kept at 250°C while the temperature of ion source was programmed at 200°C. The oven temperature was set at 110°C (isothermal for 2min), with an increment rate of 10°C/min, to 200°C, then 5°C/min to 280°C, terminating with a 9min isothermal at 280°C. Mass spectra were obtained at 70 eV; a scan interval of 0.5 sec and fragment from 45-450 Da. Total GC running time was 36min. The relative percentage amount of every part was evaluated by comparing its average peak area to the total areas (fig. 1a). Software incorporated to maintain mass spectra and chromatograms was Turbo Mass Ver 5.2 (El-Ashmawy and Salama, 2006).

Experimental design

After 72 hours of STZ injection, blood glucose was determined for all normal (9 rats) and diabetic rats (23 rats, 7 died), also rats were weighed and distributed in the experimental groups. The group included the Normal control group, which was composed of 9 rats and fed standard diet only. Diabetic control group was composed of 8 diabetic rats and fed standard diet only. 1% date palm leaves group, which was composed of 8 diabetic rats fed standard diet and 2ml/day of 1% aqueous extracts of date palm leaves (20mg/ day). 2% date palm leaves group that included 7 diabetic rats fed standard diet and 2 ml/day of 2% aqueous extracts of date palm leaves (40mg/ day). In order to ensure and fed the exact amount, all aqueous extracts (1% and 2%) made from date palm leaves were given orally.

Blood sampling and laboratory analysis

Blood samples were collected after twenty eight days from control and diabetic groups after eight hours fasting at the completion of experiment. The experiment comprised of the rats that were given ether anesthetized, when scarified. Blood samples were taken in the tubes from hepatic portal vein then centrifuged directly for the duration of ten minutes at 3000 rpm in order to separate the serum. Later, it was carefully transferred after aspiration into clean tubes and stored at -20°C frozen for analysis. Determination of glucose, BUN, creatinine, uric acid, ALT, and AST was done by analyzing all serum samples. Samples of pancreas were fixed and obtained in 10% neutral buffered formalin for almost twenty-four hours. Paraffin sections were prepared, which were 6 μ m thick. It was then stained with hematoxylin and eosin (H & E) 24 for the light microscopy examination. The histopathology process was conducted in the histology lab at Faculty of Veterinary Medicine in Cairo University, Egypt.

All obtained data was statistically analyzed and presented as mean \pm SD, also the significant differences between different groups were calculated by ANOVA and LSD at confidence interval 95%. Differences between treatments for the same group were calculated by paired-sample t-test at confidence interval 95%.

Ethical approval

This study has been approved as a part from a big project by: Kingdom of Saudi Arabia, Qassim University and Ministry of Health, Qassim Regional Research Ethics Committee No: 45/44/391 dated 10 Feb 2015

RESULTS

As shown in table 1, there was a slight difference in initial body weight between groups, but after intervention the differences were very high especially between normal control group (228.3 \pm 16.93 g) and both of 1% and 2% palm leaves extracts (180.4 \pm 44.7 and 185.3 \pm 33.2g respectively, at P<0.05). Moreover, we noticed that the higher the concentration of date palm leaves extract the lower the weight gain (P<0.001).

As shown from table 2, there was no significant differences between values of BUN among all animal groups (ranged from 38.6 \pm 0.9mg/dl to 40.3 \pm 1.6mg/dl). Although, there was no significant differences between studied groups in relation to uric acid level, but the mean value of group fed 1% date palm leaves extract was the highest (2.0 \pm 0.5mg/dl) and mean value of diabetic control and 2% date palm leaves extract were the lowest (1.4 \pm 0.6 and 1.4 \pm 0.3mg/dl respectively). It was clear that feeding 1% or 2% of date palm leaves extract resulted in significant increment of creatinine concentration (0.63 \pm 0.18 and 0.64 \pm 0.21mg/dl respectively, at P<0.05) in comparison with normal and diabetic control groups (0.39 \pm 0.13 and 0.36 \pm 0.12mg/dl respectively). As for, liver enzymes, ALT values was inconsistent and no conclusion could be made from it. As for AST the result was consistent, where the mean value of AST for normal group was significantly (P<0.001) the lowest (60.1 \pm 2.2 IU/ml), while mean value of 1% date palm leaves extract was significantly the highest (105.4 \pm 6.6 IU/ml), in addition, mean value for 2% date palm leaves extract (74.7 \pm 14.2 IU/ml) was significantly lower than diabetic control and 1% date palm leaves extract groups.

As shown in table 3, the mean value of glucose concentration before intervention for normal group was significantly the lowest (127.4 \pm 8.4 mg/dl), and the values for the three diabetic groups were ranged from 314.8 \pm 65.2 mg/dl for diabetic control to 411.1 \pm 84.2 mg/dl for 1% date palm leaves extract, the statistical analysis showed significant differences between that two groups (P<0.001). After 28 days of the experiments the values of glucose of normal group changed by -0.79%,

Table 1: Body Weight and Relative Organs Weight of Experimental Rats

	Normal Control (n=9)	Diabetic Control (n=8)	1% Palm leave extract (n=8)	2% Palm leave extract (n=7)	ANOVA	
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	F	Sig.
Baseline Weight (g)	136.9±1.8 ^a	125.3±3.6 ^b	127.7±1.0 ^b	136.6±0.6 ^a	47.5	0.000
Final Weight (g)	228.3±16.9 ^a	205.0±19.4 ^{ab}	180.4±44.7 ^b	185.3±33.2 ^b	3.4	0.039
Weight Gain (g)	92.9±12.6 ^a	79.7±16.8 ^a	56.0±22.4 ^b	48.7±12.8 ^b	9.2	0.000

Table 2: Serum Concentration of BUN, Uric Acid, Creatinine, AST and ALT of Experimental Rats

	Normal Control (n=9)	Diabetic Control (n=8)	1% Palm leave extract (n=8)	2% Palm leave extract (n=7)	ANOVA		Measuring time
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	F	Sig.	
BUN (mg/dl)	39.8±1.1 ^a	39.9±3.1 ^a	38.6±0.9 ^a	40.3±1.6 ^a	0.93	0.443	2 hours
Uric Acid (mg/dl)	1.9±0.8 ^a	1.4±0.6 ^a	2.0±0.5 ^a	1.4±0.3 ^a	1.58	0.225	2 hours
Creatinine (mg/dl)	0.39±0.13 ^a	0.36±0.12 ^a	0.63±0.18 ^b	0.64±0.21 ^b	4.77	0.014	3 hours
AST (IU/ml)	60.1±2.2 ^a	98.3±9.1 ^b	105.4±6.6 ^b	74.7±14.2 ^c	17.10	0.000	2 hours
ALT(IU/ml)	50.4±19.6 ^a	44.9±43.0 ^a	101.6±83.5 ^a	49.2±36.1 ^a	1.37	0.288	1 hour

ANOVA= Analysis of variance. SD= Standard deviation. Mean values subscribed with different letters show significant differences between these values as calculated by one-way ANOVA and LSD at P<0.05.

Table 3: Serum Concentration of Glucose before and after Interventions of Experimental Rats

	Normal Control (n=9)	Diabetic Control (n=8)	1% Palm leave extract (n=8)	2% Palm leave extract (n=7)	ANOVA	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	F	Sig.
Glucose before (mg/dl)	127.4±8.4 ^a	314.8±65.2 ^b	411.1±84.2 ^c	359.8±66.2 ^{bc}	27.03	0.000
Glucose after (mg/dl)	126.2±22.7 ^a	258.9±136.5 ^{ab}	399.7±172.2 ^b	378.6±194.4 ^b	5.10	0.009
% Change	-0.79%	-20.4%	-4.9%	5.6%		
Sig.	0.89	0.37	0.90	0.84		

while it decreased by -20.4% among diabetic control group. Furthermore, the intervention with either 1% or 2% date palm leaves extracts had no significant effect on blood glucose level, and we noticed that the higher the amount of date palm leaves extract the higher the concentration of blood glucose (table 3). The results of this table denied the advocate that date palm leaves decrease blood glucose level, and the researchers believe that this drink may be harmful and could be risky on human health and worsen diabetes patient's status.

The analysis of GC-MS has identified the existence of 12 bioactive compounds in the methanol extract as shown in table 4. Concentration %, retention time, molecular weight, and molecular formula were used to identify the bioactive compounds. The predominant compounds present are Hexadecanoic acid, methyl ester (16.96%), Hexadecanoic acid, 2,3-dihydroxypropyl ester (15.86%), 4a-Hydroxy-4-nitroperhydronaphthalen-1-one (11.02%), Vitamin E (10.74%), Octadecanoic acid, 2-hydroxy-1-(hydroxymethyl) ethyl ester (8.07%), 6-(3-Hydroxy-but-1-enyl)-1,5,5-trimethyl-7-oxabicyclo[4.1.0]heptan-2-ol (7.27%), 10-Octadecenoic acid, methyl ester (6.95%), Octadecanoic acid, methyl ester (5.68%), n-Hexadecanoic

acid (5.28%), Epiglobulol (4.86 %), 2-Hexadecanol(4.36 %) and Behenic alcohol (2.89 %).

Examination of pancreas from histopathology process presented that there were no histopathological changes (H & E X 400) in the normal control group of rats. Necrosis of islet's of Langerhans's, associated with inflammatory cells infiltration (H & E X 400), were observed in the pancreas among control group. Moreover, the treatment with 1% streptozotocin has presented vacuolation of islets of Langerhans's (H & E X 400). Additionally, pancreas of rat who was treated with 2% streptozotocin has presented necrosis and vacuolation of Langerhans's (H & E X 400) as shown in fig. 2.

DISCUSSION

Present study has indicated the effect of aqueous extract of tops of date palm leaves on blood glucose of diabetic rats for assessing the use of aqueous extract of date palm leaves for treatment of diabetes. The amplified oxidative stress is an important and most common issue for the delayed healing of wound in diabetics (Guo & DiPietro, 2010). Therefore, the important strategy might be

Table 4: Phytocomponents identified in the methanol extract of date palm leaves.

Retention time (min)	Name of the compound	Molecular formula	MW	Peak area %
13.157	Hexadecanoic acid, methyl ester	C17H34O2	270	16.96
21.227	Hexadecanoic acid, 2,3-dihydroxypropyl ester	C19H38O4	330	15.86
14.213	4a-Hydroxy-4-nitroperhydronaphthalen-1-one	C10H15NO4	213	11.02
30.196	Vitamin E	C29H50O2	430	10.74
24.132	Octadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	C21H42O4	358	8.07
13.051	6-(3-Hydroxy-but-1-enyl)-1,5,5-trimethyl-7-oxabicyclo[4.1.0]heptan-2-ol	C13H22O3	226	7.27
15.445	10-Octadecenoic acid, methyl ester	C19H36O2	269	6.95
15.784	Octadecanoic acid, methyl ester	C19H38O2	268	5.68
13.582	n-Hexadecanoic acid	C16H32O2	256	5.28
12.207	Epiglobulol	C15H26O	222	4.86
9.312	2-Hexadecanol	C16H34O	242	4.36
11.578	Behenic alcohol	C22H46O	326	2.89

reduction or termination of the consistent elimination and inflammation of free radicals by presenting antioxidants and anti-inflammatory agent into the treatment process of wounds to improve the healing process of diabetic wound. The increased oxidative stress and prolonged inflammation impair healing in diabetics.

Kant *et al.*, (2014) conducted a study to evaluate the wound healing potential of the curcumin applied topically in diabetic rats. Open removal of skin wound was produced in streptozotocin induced wounded rats and diabetic rats were separated into different groups. The application of curcumin decreased the expression of the inflammatory enzymes. The application of curcumin increased the anti-inflammatory levels of Cytokine. The overall findings of the study revealed that the anti-oxidants and anti-inflammatory potential of curcumin caused better and faster wound healing in diabetic rats.

There are many traditional agents used to control the diabetes along with the management of lifestyle. Despite of various medicinal plants and their extracts, there has been no entirely effective recovery from diabetes reported in the diabetes treatment (Hasan and Mohieldein, 2016). For the treatment of diabetes, herbal medicines have been used since long time and continues to be accepted as a substitute therapy. Pancreatic beta cells regenerating, fighting the insulin resistance issue and insulin releasing are possessed by the active principles present in the medicinal plants (Singh *et al.*, 2009). Similarly, several studies found that date palm leaves contains higher amounts of chromium and arsenic, a toxic compounds that may damage vital organs such as liver and pancreas (Radojevic and Bashkin, 1999; Hasan and Mohieldein, 2016; Pillay *et al.*, 2003).

There are many studies conducted on the date palm pulp but still there is very little information present about the benefits of date palms on health. The date pits and by-products obtained from the processing of date fruit can

provide many potential benefits for health and nutrients to the human body (Shi *et al.*, 2014). In past years, there is a building interest to extract the dietary fiber, polyphenols and essential oils from the date seeds (Kant *et al.*, 2014) and it has also been concluded that date seeds were challenging to the thermal treatment during thirty to forty hours, which is a long period concerning the high stability of some of the parameters.

Date fruit has been reported as a good source of fibre, sugars and minerals (Ali *et al.*, 2009), which exhibit many effective benefits to health such as antimutagenic (Vayalil, 2002), antioxidant (Mrabet *et al.*, 2016), antitumoral (Ishurd & Kennedy, 2005), and antifungal (Shraideh *et al.*, 1998). A study by Zangiabadi *et al.*, also reported that date fruit extracts are deliberated as an effective treatment in preventing diabetic diseases and in enhancing the pathological parameters concerned with diabetic neuropathy. Additionally, gastroprotective properties were reported by decreasing ethanol-induced gastric ulcer in rats.

It has been evident that plants are rich and important sources of constituents with antioxidants and anti-diabetic properties such as amino acids, gallotannis and other related polyphenols. There is a presence of antihyperglycaemic activities in the medicinal plants, owing to the low cost and lesser side-effects (Mousa *et al.*, 2014).

Regarding the effect of date palm leaves on glycemia, the results of the current study proved that it has no effect and the higher concentration of date palm leaves will also increase the concentration of blood glucose. The present study showed that the aqueous extract of date palm is beneficial for balancing the oxidative stress situations among diabetic rats but it is risky for human health, as it decreases the blood glucose level. In contrast, Abuelgassim (2010) found that date palm leaves had hypoglycemic properties, and such difference could be

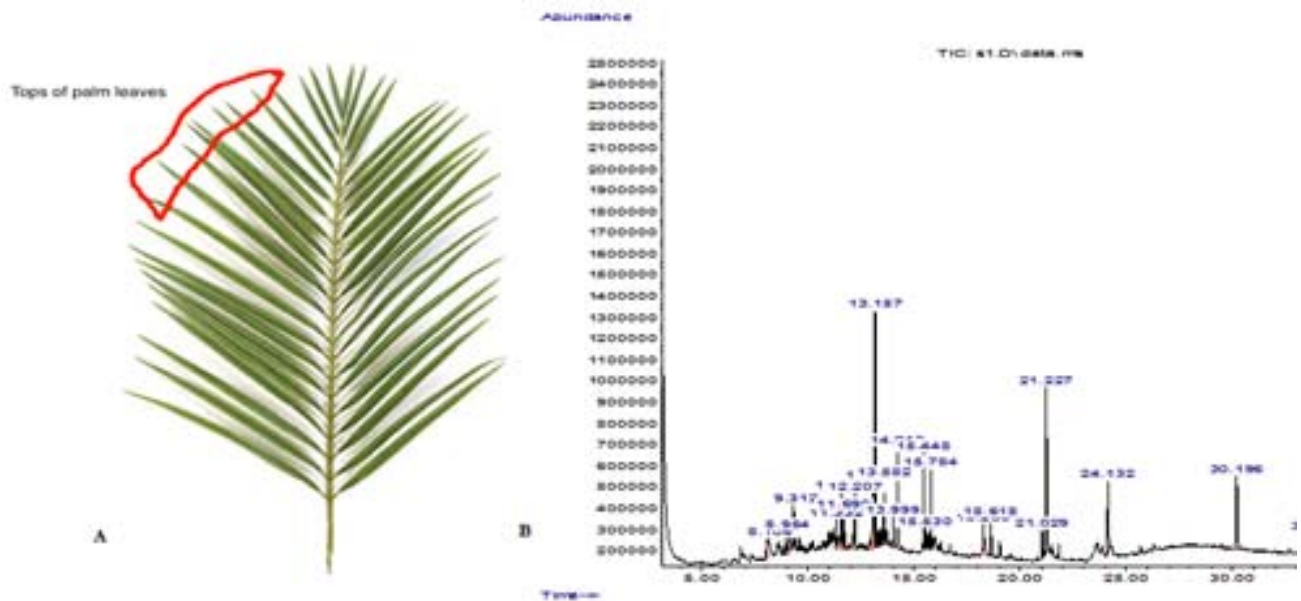


Fig. 1: (A) Tops of palm leaves that used for preparation of palm tea: (B) GC-MS chromatogram of methanol extract of date palm leaves

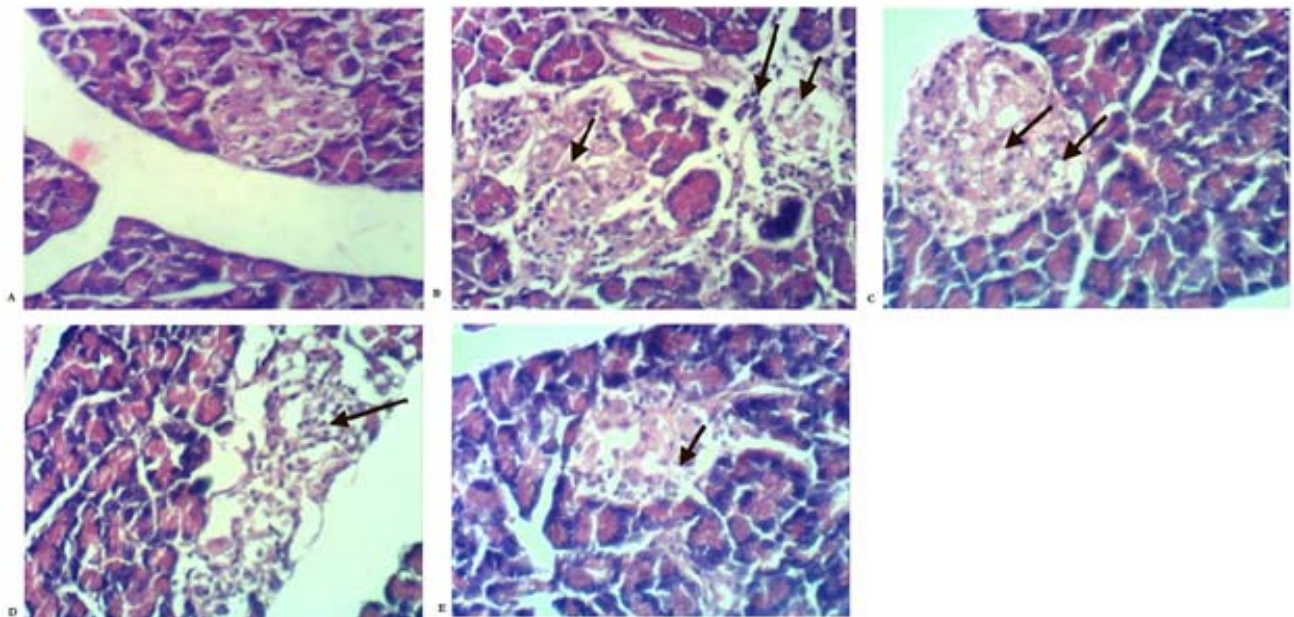


Fig. 2: (A) No histopathological changes (H & E X 400): (B) Necrosis of islet's of langerhans's associated with inflammatory cells infiltration (H & E X 400): (C) vacuolation of islet's langerhans's (H & E X 400): (D) vacuolation and necrosis of islet's of langerhans's (H & E X 400): (E) vacuolation and necrosis of islet's of langerhans's (H & E X 400)

attributed to several factors, where the current study used STZ for induction of diabetes. Moreover, the results of current study were ascertained by histopathological examination, which revealed certain changes in pancreas especially at higher concentration.

CONCLUSION

It is evident from the results and in comparison with normal or diabetic control that the date palm leaves could not significantly decrease the level of blood glucose;

moreover, it could be harmful for human health and the status of diabetic patient could get worse. The previous studies included in the study shown that the aqueous extract of date palm is beneficial for balancing the oxidative stress situations in diabetic rats but it is harmful for human health. The limitation of the study was that it mainly conducted on the rats with diabetes.

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