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Effect of Hayani Date (*Phoenix dactylifera* L) Peels on Blood Sugar, Blood Lipids, Liver and Kidney Functions, and Inflammation in Diabetic Rats

Elsayed Elbadrawy [a*], Ashraf Elzainy [a], Hala Elkewawy [a] and Nagia Elsaid [a]

[a] Home Economics Department (Nutrition and Food Science), Faculty of Specific Education, Mansoura University, Mansoura, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

This study aimed to investigate the effect of Hayani date peel powder and its methanolic extract on glycemia and lipidemia in streptozotocin-induced diabetic rats as well as their effects on kidney and liver functions in addition to their anti-inflammatory activity. Twenty-four rats were used in this study, six of them served as normal control (group 1) which continued feeding on the basal diet, while the remaining 18 rats were injected with streptozotocin (50mg/kg) to induce diabetes. The diabetic rats were divided into three groups (6 rats each), one of them feeding on the basal diet only which acted as diabetic control (group 2), another group fed on the basal diet and treated

**Corresponding author: Email: s_elbadrawy@mans.edu.eg & m_s_elbadrawy@yahoo.com;*

orally with the peel extract in a concentration of 250 mg/kg body weight (group 3), while the third group was treated with peel powder merged in the basal diet with a concentration of 5% w/w (group 4). The results showed that the extract and the powder of the peels significantly decreased the blood glucose, glycated hemoglobin (HbAlc), total cholesterol (TC), total triglycerides (TG), low density lipoprotein cholesterol (LDL-c), very low density lipoprotein cholesterol (VLDL-c), alanine transaminase (ALT), aspartate transaminase (AST), creatinine, and uric acid as well as cyclooxygenase-2 (COX-2), prostaglandin 2 (PGE2), tumor necrosis factor alpha (TNF-α), interleukin 1B (IL-1β), and inducible nitric oxide synthase (iNOS) levels. In contrast, significant increases in serum insulin, high density lipoprotein cholesterol (HDL-c), and albumin were noticed in comparison to diabetic control. Generally, the peel extract was more effective than the peel powder. It is recommended by eating the whole fruit of date without peeling.

Keywords: Diabetes; insulin; date peel; lipid profile; liver enzymes; creatinine; anti-inflammatory.

1. INTRODUCTION

"Diabetes mellitus (DM) is one of the most common diseases in the world resulting from a variety of factors including environmental and genetic alterations" [1]. "Diabetes mellitus is a metabolic disorder that has a huge economic and physiological load all over the world and causes different chronic and acute complications such as diabetic ketoacidosis, cardiovascular disease, foot ulcers, kidney disorders, eye damage, and finally death" [2].

"The International Diabetes Federation (IDF) listed Egypt among the world's top 10 countries in the number of patients with diabetes. It is expected this number will jump up to 13.1 million by 2035" [3]. "The global diabetes prevalence in 2019 is appreciated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The prevalence is higher in urban (10.8%) than in rural (7.2%) areas, and in high-income (10.4%) than in low-income countries (4.0%). One in two (50.1%) people living with diabetes do not know that they have diabetes. The global prevalence of impaired glucose tolerance is projected to be 7.5% (374 million) in 2019 and is projected to reach 8.0% (454 million) by 2030 and 8.6% (548 million) by 2045" [4].

"The date palm tree (*Phoenix dactylifera* L.), one of the oldest crops, is a member of the Arecaceae family and is mostly planted in Asia (countries of the Middle East), followed by North Africa [5], consisting of about 200 genera and more than 2,500 species". "Phoenix (*Coryphoideae phoeniceae*) is one of the genera with approximately 14 species that are native to the tropical or subtropical regions of southern Asia or Africa, including *Phoenix dactylifera* L" [6,7].

Egypt currently produces 1.7 million tons of palm date fruit yearly, accounting for 17.7% of the world's total production and 24.4% of the production in Arab nations [8]. Date fruit is high in specific nutrients and offers a respectable source of instant energy due to its high content of glucose, maltose, fructose, and sucrose [9]. Knowing the health benefits of dates may encourage their use as a nutraceutical as a result [10,11]. Due to their high quantity of essential nutrients, date fruits have become significantly more important in the human diet [9].

"Much attention has been paid to health promotion related to phytochemical activity, and the isolation of novel bioactive phytochemicals derived from special medicinal plants in the past few years. Palm date (*Phoenix dactylifera* L.) is one of the most important fruit crops in the Middle East and North Africa that produce edible and delicious dates. Date palms are spread across Iraq, Iran, Saudi Arabia, Egypt, Tunisia, Algeria, Libya, United Arab Emirates (UAE), Bahrain, and Oman" [12].

Plants produce flavonoids and phenolic compounds to defend themselves or to promote growth under difficult conditions. These chemicals scavenge reactive species to terminate the chain reaction before the survival of the cell is significantly impacted. Moreover, polyphenols may reduce inflammation by controlling the activity of inflammatory cells and regulating the actions of enzymes involved in the metabolism of arachidonic acids such as phospholipase A2, cyclooxygenase (COX), lipoxygenase (LOX), and arginine (NOS), and lowering the secretion of other pro-inflammatory molecules [13].

"Dates are a low-cost source of nutrients including dietary minerals, proteins, carbs, and

amino acids (selenium, potassium, calcium, magnesium, manganese, iron, dietary fiber, vitamins, carotenoids, and fatty acids). Additionally, it has a great antioxidant capacity and includes polyphenols, anthocyanins, carotenoids, tannins, procyanidins, sterols, flavonols, flavones, anthocyanidins, isoflavones, phytoestrogens, phenolic acids, and derivatives of cinnamic acid. Date fruit-glucan has substantial anti-tumor, immune-modulating, anti-diabetic, anti-inflammatory, and cholesterol-lowering properties. It also promotes the development of healthy gut flora. Date fruit flesh, peel, and pits have been proven in pre-clinical investigations to exhibit anti-mutagenic, hepatoprotective, anti-inflammatory, anti-diabetic, anti-bacterial, antiviral, anti-fungal, anti-tumor, and nephroprotective characteristics" [10].

This study was conducted to evaluate and benefit from the hayani date peel, which is considered a waste, and encourage people to eat it with the fruit (without peeling). The effects of the peel powder and its methanolic extract were studied on diabetic rats by evaluating the serum levels of glucose, lipid profile, and kidney and liver functions. In addition, their effect on inflammation was also studied.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Hayani date palm

Phoenix dactylifera L. was obtained from the Faculty of Agriculture, Mansoura University, Egypt.

2.1.2 Chemicals

All chemicals and kits of biochemical analysis were purchased from Sigma-Aldrich Company. Cairo, Egypt.

2.1.3 Animals

24 healthy adult male albino rats (*Sprague Dawley*) weighing (170 ± 10g) were purchased from the Faculty of Pharmacy, Mansoura University, Egypt.

2.1.4 Basal diet

The basal diet is prepared as follows: 20% casein, 49.7% corn starch, 3% cellulose, 10% sugar, 5% corn oil, 2% vitamin mixture, 10% minerals, and 0.3% DL-methionine according to the modified method of Reeves et al. [14].

2.2 Methods

2.2.1 Preparation of date peel powder

The fresh Hayani date (*Phoenix dactylifera* L.) fruits were washed with tap water, then the peels were carefully removed and washed with tap water. The obtained peels were dried in an electric oven at 60°C to a constant weight, then crushed carefully to make powder.

2.2.2 Preparation of date peel extract

300 g of dried peel powder was soaked in methanol overnight, then filtered and the residue was resoaked in methanol for 24 hours and filtered. The residue was immersed in methanol for another day and then filtered. The three obtained filtrates were collected and subjected to evaporation using a rotary evaporator to separate the solvent (methanol) and obtain the peel extract. The resulting extract (18.52 g) was stored in a dark glass bottle under freezing until analysis.

2.2.3 Estimation of the chemical composition of peel powder

Moisture, ash, crude fiber, crude protein, and crude lipid contents were determined in the dried date peel according to the methods described in AOAC [15]. Carbohydrate content was calculated by difference.

- **Minerals:** The peels minerals concentrations were determined using Inductivity Coupled Plasma apparatus (iCAP™ 7000 Plus Series ICP-OES, Thermo Scientific™) after acid digestion using HNO3 (69%) and HF (40%) in a microwave digestion apparatus (model Milestone MLS 1200 Mega) as mentioned by Khan et al. [16].

- **Total amino acid:** Sykam Amino Acid Analyzer (Sykam GmbH, Germany) was used in the determination of peels' amino acids as mentioned by Zakaria et al. [17].

2.2.4 Phytochemicals screening of the date peel extract

Phytochemical screening was performed in the peel methanolic extract to identify the presence of bioactive compounds [18].

2.2.5 Biological experiments

Animal experiment design: Twenty-four adult male albino rats weighing 170 ± 10 g were kept in stainless steel cages for a week for adaptation. All rats have full access to feed and water *ad libitum*. After the acclimatization period, six rats remain feeding on the basal diet until the end of the experiment which served as normal control (group 1). The remaining rats were injected intraperitoneally with Streptozotocin (50 mg/kg b.w.) to induce diabetes. Four days later, the rats with fasting blood glucose levels of more than 200 mg/dl were considered diabetic and divided into three groups (6 rats each). One of the diabetic groups fed on the basal diet only which served as diabetic control (group 2), another group that fed on the basal diet was treated with the peel extract orally in a concentration of 250 mg/kg b.w. (group 3), while the third group was treated with peel powder merged in the basal diet with a concentration of 5% w/w (group 4). Over the course of the 28 days, weekly changes in body weight and feed intake were recorded. Feed intake (gm.) was determined every 7 days according to Chapman et al. [19]. Body weight gain percentage (BWG %) and feed efficiency ratio (FER) was calculated by using the following equations:

$$BWG(\%) = \frac{\text{final weight(g)} - \text{intial weight(g)}}{\text{intial weight(g)}} \times 100$$

Feed efficiency ratio (FER) = weight gain (g) / Feed intake (g)

Blood sample collection: After 28 days, rats were sacrificed after overnight fasting, and the blood of each rat was drawn from the eye vein using the capillary tube. Blood samples were received into clean, dry centrifuge tubes, allowed to clot at room temperature, and then spun at 5000 rpm for 10 min to separate serum. The serum samples were kept in a deep freezer at -18°C until used for biochemical analyses.

Biochemical analysis of serum:

- Glucose was determined according to Trinder [20].
- Insulin was determined according to Burgi et al. [21].
- HbAlc was determined according to Sudhakar and Pattabiraman [22].
- Total cholesterol, Triglycerides, and HDL_{-C} were determined according to Allain et al. [23], Fassati and Prencipe [24], and Lopes et al. [25], respectively.
- LDL_{-C} and $VLDL_{-C}$ were calculated by using the following equations according to Friedewald et al. [26].
  LDL-c = Total cholesterol - (HDL_{-C} + $VLDL_{-C}$)
  VLDL-c = TG / 5
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured according to the method described by Burtis et al. [27].
- Serum albumin was colorimetrically determined by the method of Doumas et al. [28]
- Serum uric acid was determined according to Fassati et al. [29]
- Creatinine was determined according to the method described by Young [30].

Measurement of pro-inflammatory markers:

- Serum tumor necrosis factor-alpha (TNF-α) was measured according to the method described by Brouckaert et al. [31].
- Determination of prostaglandin E2 (PGE2) level was carried out based on the Competitive-ELISA detection method as mentioned by Lee et al. [32].
- Concentrations of Inducible nitric oxide synthase (iNOS) were measured using a rat iNOS ELISA kit as mentioned by Afolabi et al. [33].
- Determination of serum interleukin-1 beta (IL-1β) level was measured using the ELISA Kit (Elabscience® rat IL-1β and Elabscience® rat IL-6) as mentioned by Fristiohady et al. [34].
- Cyclooxygenase 2 (COX-2) level was determined according to the method of Kulmacz and Lands [35].

2.3 Statistical Analysis

The collected data were presented as means ± S.D. Statistical analysis was performed using one-way analysis of variance (ANOVA). The means between groups were compared using (LSD) statistic test at 5%, using the computer program [36].

3. RESULTS AND DISCUSSION

3.1 Nutritional Value of Date Peel

The data in Table 1 represented the chemical composition of dried date peel. The moisture content, ash, protein, fat, fiber, and carbohydrates were 7.81±0.14%, 1.72±0.05%, 9.85±0.11%, 2.06±0.06%, 36.5±0.04%, and

57.94±0.19%, respectively. From these results, it is clear that date peel contains a moderate amount of protein and a high amount of fiber and edible carbohydrates.

According to Whitney and Rolfes [37], protein mediates cell responses, acts as an enzymatic catalyst, and regulates growth and cell differentiation. Although dates are not a significant source of proteins [38], the protein content increases by eating the whole fruit with the peel.

The result in Table 1 showed also that the major element in date palm peel was calcium (666.70±3.70 mg/100g), this indicated that date peel is a good source of calcium, which is required for healthy bone formation, muscle contraction, and blood pressure. Whereas potassium recorded a value of 54.99±2.67 mg/100g, magnesium (96.06±1.50 mg/100 g), and phosphorus (160±2 mg/100g). The examined trace elements were Fe, Cu, Zn, Se, Mn, Cr, and Co with a value of 25.78±0.08, 1.76±0.07, 4.36±0.05, 0.17±0.03, 2.19±0.06, 3.63±0.08 and 0.04 mg/100g, respectively. The peels contain a high amount of iron which is important for many functions in the body such as hemoglobin formation and oxidative phosphorylation. The high content of elements in sokary date peel was indicated by Kuras et al. [39] who mentioned that iron content in the peel was at least 15 times higher than in the flesh, while manganese content was 4.8 times higher in the peel than the flesh.

Concerning the amino acid content of date palm peels, the data in Table 1 illustrated nineteen types of amino acids including nine essential amino acids and ten non-essential amino acids. Methionine (960 mg/100g) was the predominant essential amino acid followed by arginine (620 mg/100g) valine, histidine, isoleucine, threonine, lysine, leucine, and phenylalanine. As for the non-essential amino acid, it was found that proline was the major amino acid (974 mg/100g), while the lowest one was tyrosine (22 mg/100g). These important amino acids are found in date fruits and are crucial for human red and white blood cell production as well as muscular growth [40].

3.2 Phytochemical Screening of Date Peel Extract

Data in Table 2 presented the phytochemical screening of date peel extract. The results indicated that date peels contain a moderate amount of flavonoids, tannins, phenolics, glycosides, and a little amount of saponins and alkaloids.

Table 1. Proximate chemical composition, amino acids, and minerals of date peel powder

Nutritional value of date peel powder						
Proximate chemical composition (%) (n = 3)	**Moisture**	**Ash**	**Protein**	**Fat**	**Fiber**	**Carbohydrates**
	7.81±0.14	1.72±0.05	9.85±0.11	2.06±0.06	36.5±0.04	57.94±0.19
Amino acids (mg/100 g)	**Essential amino acids**			**Non-essential amino acids**		
	Histidine	268		Cystine	599	
	Isoleucine	136		Alanine	272	
	Leucine	27		Serine	227	
	Lysine	77		Tyrosine	22	
	Methionine	960		Glycine	314	
	Phenylalanine	3		Aspartic Acid	302	
	Threonine	115		Proline	974	
	Valine	515		Glutamic	229	
	Arginine	620				
Minerals (mg/100 g)	**Major minerals**			**Trace minerals**		
	Ca	666.70±3.70		Fe	25.78±0.08	
	K	54.99±2.67		Cu	1.76±0.07	
	Mg	96.06±1.50		Zn	4.36±0.05	
				Se	0.17±0.03	
	P	160±0.02		Mn	2.19±0.06	
				Cr	3.63±0.08	

Alkaloids are widely used in medicine for the creation of medications because they have noticeable physiological effects when administered to animals [41].

The protective role of flavonoids, especially flavones, has been identified as having a preventive impact against cardiovascular and cancer diseases [42]. According to previous studies, tannins have antiviral, antibacterial, and anticancer properties. Moreover, some tannins were reportedly used as a diuretic [43]. Saponin is a substance with a variety of pharmacological effects [44]. Phenolics can manifest in type II diabetes by inhibiting the activities of α glycosidase and α amylase to decrease blood glucose levels [45] As it is known, phenolic compounds are potent antioxidants that are important in protecting the cells from damage [39,43].

3.3 Biological Assays

3.3.1 Effect of date peel powder and extract on weight gain, feed intake, and feed efficiency ratio (FER) in diabetic rats

The data in Table 3 illustrated the initial, and final weight, weight gain %, feed intake, and feed efficiency ratio (FER) in normal control, diabetic control, and diabetic groups treated with date palm peel extract and powder. The initial body weight of all rats did not show significant differences between all groups. The normal control group recorded the highest final weight (250.00±3.61 g), weight gain (72.67±3.06g), feed intake (20.83±0.30g), and FER (0.125±0.003), while the diabetic control group showed significant decreases in the final body weight gain (14.67±5.51g), feed intake (16.17±0.46g), and FER (0.032±0.011) compared to the normal rats. The results revealed that the peel extract significantly increased the body weight gain (33.41±3.03), feed intake (19.75±0.33), and FER (0.107±0.007) compared to the diabetic control. On the other hand, the group of date peel powder showed no significant difference in the final weight, weight gain%, feed intake, and FER as compared to diabetic control. This may be due to its high content of dietary fiber.

3.3.2 Effect of date peel powder and extract on serum glucose, insulin, and HbA1c levels in diabetic rats

Table 4 data revealed that the serum glucose increased significantly in the diabetic control group which reached 559.00±21mg/dl compared to the normal control group (87.00±6.00 mg/dl). Also, a significant increase in HbA1c was noticed in the diabetic control group (9.32%±0.98%) while it was 5.30±0.45% in the normal control. The two treated groups with the peel extract and peel powder showed a significant decrease in serum glucose level where the decrease percentage reached 70.48% in the peel extract group and 53.37% in the peel powder group. Also, a significant decrease in blood HbAlc was observed in the peel extract group (5.69±0.43%) and the peel powder group (5.77±0.48%) compared to the diabetic group (9.32±0.98%). On the other hand, a significantly low level of insulin (78.67±11.93 pg/ml) was noticed in the diabetic control compared to the normal control group (237.33±5.51 pg/ml). The peel extract and the peel powder groups showed significant increases in the level of serum insulin compared to the diabetic control. The increases percentages were 135.58% and 64.40% respectively. It was evident that the peel extract was more effective than the peel powder in improving the serum levels of glucose and insulin in diabetic rats. These results are attributed to the high content of flavonoids, phenolic acids, and fiber in the Hayani date peel.

Fiber is an effective food element and strategy for reducing oxidative processes in food items [46]. Foods with high fiber content aid in digestion and reduce the risk of cancer [47]. Fiber is important in slowing the digestion and conversion of starch to simple sugars, a crucial step in the control of diabetes, and in reducing the absorption of cholesterol from the stomach [48]. According to Singh et al. [49], the active components found in medicinal plants can regenerate pancreatic beta cells, release insulin, and combat the issue of insulin resistance.

Table 2. Phytochemical screening of date peel extract

Component / Samples	Saponins	Flavonoids	Alkaloids	Tannins	Glycosides/ carbohydrates	Phenolic compounds
Date peel extract	+	++	+	++	++	++

Table 3. Effect of date peel powder and extract on weight gain, feed intake, and feed efficiency ratio (FER) in diabetic rats

Variables / Groups	Initial weight (g)	Final weight (g)	Weight gain (g)	Weight gain %	Feed intake (g)	FER
Normal Control	177.33±0.58a	250.00±3.61a	72.67±3.06a	40.97±1.60a	20.83±0.30a	0.125±0.003a
Diabetic Control	179.33±1.53a	194.00±5.57cd	14.67±5.51c	8.18±3.08c	16.17±0.46cd	0.032±0.011b
D-Peel extract	177.67±1.15a	237.00±4.00b	59.33±5.03b	33.41±3.03b	19.75±0.33b	0.107±0.007a
D-Peel powder	177.00±1.00a	193.33±7.09d	16.33±7.77c	9.24±4.44c	16.11±0.59d	0.036±0.016b

** Each value is the mean ± SD*

**The values in each column with the same letters are not significantly different at P ≤ 0.05*

Table 4. Effect of date peel powder and extract on serum glucose, insulin, and HbAlc levels in diabetic rats

Parameter / Groups	Glucose (mg/dl)	Insulin (pg/ml)	HbA1C (µg/ml)
Normal Control	87.00±6.00d	237.33±5.51a	5.30±0.45b
Diabetic Control	559.00±21.66a	78.67±11.93d	9.32±0.98a
D-Peel extract	165.00±14.18c	185.33±10.60b	5.69±0.43b
D-Peel powder	260.67±29.70b	129.33±18.15c	5.77±0.48b

** Each value is the mean ± SD*

**The values in each column with the same letters are not significantly different at P ≤ 0.05*

3.3.3 Effect of date peel powder and extract on the lipid profile of diabetic rats

Table 5 results showed that there are significant increases in total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-c) in the diabetic control group compared to the normal control, while HDL-c level decreased significantly in the diabetic control.

The results showed that the two treated groups with peel extract and powder revealed significant decreases in their blood TC, TG, and LDL-c levels in comparison with the diabetic group (positive control). The peel extract was better than the peel powder in this respect. The reduction percentages were 42.1%, 35.6%, and 66.6% for TC, TG, and LDL-c, respectively in the peel extract group while their reduction percentages were 21.3%, 28.4%and 21%, respectively in the peel powder group compared to the diabetic group. On the other hand, the serum HDL-c level increased significantly in the peel extract group with an increasing percentage of 31.9% whereas the peel powder group showed no significant difference compared to diabetic control. This means that the date palm peel extract is good for improving the lipid profile in diabetic patients.

Food fibers may directly fixate LDL cholesterol, and bile acid, and prevent bile acid from moving through the enterohepatic system, this will aid in the LDL cholesterol's elimination through feces [50].

According to previous research, several phytocomponents, particularly saponins, and steroids, can prevent intestinal fat absorption by acting like resin and inhibiting lipase activity [51,52].

The level of flavanols, yphenolspol, unsaturated fatty acids, vitamin C, and vitamin E, and fibers of date seeds are proven to be beneficial for anti-atherogenic [53] because they act as antioxidants. Antioxidants prevent the free radicals oxidation thus decreasing LDL-c oxidation.

3.3.4 Effect of date palm peel powder and extract on liver and kidney functions:

Data in Table 6 revealed the effect of the extract and powder of date peel on liver and kidney function tests in diabetic rats. The serum levels of ALT and AST enzymes increased significantly in the diabetic control group, while the serum level of albumin decreased significantly. Also, the levels of serum creatinine and uric acid increased significantly compared to the normal control group. This means that the diabetic control group induced by STZ showed the impaired function of the liver as well as the kidney functions. The results showed that the diabetic group treated with peel extract showed a significant decrease in ALT and AST enzymes level and an increase in serum albumin levels compared to diabetic control. The decreases in ALT and AST were 48.98% and 57.9 %, while the increase in serum albumin was 39.2%. On the other hand, serum creatinine and uric acid levels which represent tests of kidney function decreased significantly in the group treated with peel extract. The percentage reduction was 34.7% and 28.7 %, respectively. As for the diabetic group that was treated with the peel powder, significant decreases in serum ALT and AST enzymes and a significant increase in serum albumin were observed. The percentages of decrease in ALT and AST enzymes were 21.3% and 26.9%, while the increased percentage of serum albumin was 16.5 %. Also, a significant decrease in serum creatinine and uric acid was observed in the peel powder group compared to the diabetic control group, their reduction percentages were 34.7 and 19 %, respectively. The peel extract was more effective than the peel powder in improving liver and kidney functions in diabetic rats. A decrease in serum albumin and an increase in serum liver enzymes; alanine transaminase (ALT) and aspartate transaminase (AST) have been found in diabetics, indicating impaired liver function that may be caused by hepatic damage as a result of hyperglycemia [54,55].

Diabetic nephropathy, one of the severe consequences of diabetes, is the leading cause of end-stage kidney failure as well as other serious health issues. Reactive oxygen species are produced by severe hyperglycemia, and this oxidative stress alters numerous intracellular metabolic pathways in the body. This gradual deterioration eventually leads to poor kidney function. However, significant randomized data showed that metabolic control can be regained to achieve normoglycemia and significantly slow the formation and progression of diabetic nephropathy in the early stages of the disease [56]. In our study, both date peel extract and powder improved liver and kidney functions as they raised serum albumin and decreased serum ALT, AST, creatinine, and uric acid levels in diabetic rats.

Table 5. Effect of date peel powder and extract on the lipid profile of diabetic rats

Parameter / Groups	TC (mg/dl)	TG (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
Normal Control	58.67±5.86d	79.00±6.24d	39.33±3.51b	3.53±1.97d	15.80±1.25d
Diabetic Control	114.00±10.54a	194.00±9.00a	32.33±7.0bc	42.87±2.64a	38.80±1.80a
D-Peel extract	82.00±5.00c	125.00±7.00c	42.67±3.06a	14.33±6.33c	25.00±1.40bc
D-Peel powder	89.67±7.02b	139.00±17.06b	28.00±2.65c	33.87±6.60b	27.80±3.41b

TC=Total cholesterol, TG=Triglycerides, LDL-c=Low density lipoprotein cholesterol, HDL-c= High density lipoprotein cholesterol, VLDL-c= Very low-density lipoprotein cholesterol

** Each value is the mean ± SD*

**The values in each column with the same letters are not significantly different at P ≤ 0.05*

Table 6. Effect of date peel powder and extract on liver and kidney functions

Parameter / Group	Liver function tests			Kidney function tests	
	ALT (U/L)	**AST (U/L)**	**Albumin (g/dl)**	**Creatinine (mg/dl)**	**Uric acid (mg/dl)**
Normal Control	22.33±3.06d	77.33±4.73a	4.75±0.07a	0.58±0.05d	2.05±0.09d
Diabetic Control	62.67±4.73a	254.00±16.00a	3.09±0.23d	1.50±0.17a	3.42±0.15a
D-Peel extract	32.00±3.00c	107.33±12.01c	4.30±0.04b	0.98±0.05c	2.44±0.14c
D-Peel powder	49.33±7.09b	185.67±12.50b	3.60±0.12c	1.15±0.09b	2.77±0.14b

** Each value is the mean ± SD*

**The values in each column with the same letters are not significantly different at P ≤ 0.05*

Table 7. Effect of date peel powder and extract on inflammatory parameters

Parameter / Group	COX-2 (pg/mL)	PGE2 (pg/mL)	IL-1β (pg/mL)	TNF-α (pg/mL)	iNOS (ng/mL)
Normal Control	134.67±10.02d	137.37±4.96c	85.27±8.45d	83.93±8.97c	1.30±0.20c
Diabetic Control	613.00±63.51a	447.00±32.91a	441.43±24.10a	254.97±9.42a	5.17±0.42a
Peel extract	251.67±20.03b	225.63±6.70b	219.03±25.35b	127.27±5.40b	2.33±0.15b
Peel powder	226.00±13.89bc	226.73±5.25b	139.63±8.38c	116.83±9.09b	2.73±0.25b

** Each value is the mean ± SD*

**The values in each column with the same letters are not significantly different at P ≤ 0.05*

3.3.5 Effect of date peel powder and extract on inflammatory markers

The results in Table 7 showed that all the inflammatory parameters; cyclooxygenase 2 (COX-2), prostaglandins 2 (PGE2), interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α) and inducible nitric oxide synthase (iNOS) increased significantly in the diabetic groups compared to the normal control group. The treated groups revealed a significant decrease in all the mentioned parameters compared to the diabetic control group. It was observed that the effect of peel powder was more effective in reducing the levels of COX-2, IL-1β, and TNF-α than the peel extract while their effects were similar in reducing the levels of PGE2, and iNOS. The improvement in the inflammatory parameters in the two treated groups with the peel powder and extract is attributed to the high content of fiber and phenolic compounds in the date peel.

Free radical exposure causes alterations in pro-inflammatory cytokines. Streptozotocin (STZ) is a substance that produces free radicals which cause tissue damage and create diabetes and inflammation.

The enzyme cyclooxygenase mediates the conversion of phospholipids to arachidonic acid. Because it is constitutively produced, COX-1 contributes to the defense of the stomach mucosa. An inflammatory trigger can increase COX-2 expression [57]. The synthesis of COX-2, PGE2, TNF-α, interleukin-1 (IL-1), and iNOS are dramatically increased during the initial immunological response to inflammation brought on by diabetes disease, which promotes the progression of the inflammatory process. Numerous studies have shown that dates dramatically enhance the immunological Th1 response. The palm date polyphenol and polysaccharide content have been linked to these benefits [58]. Studies on animals have revealed that date palm extract administration can raise antibody titers and plaque-forming cell counts. It may have protective effects by regulating cytokine expression [59]. Other findings suggest that date may also help to reduce plasma fibrinogen and leg edema [60].

Flavonoids can inhibit lipoxygenase activity, PGE2 synthesis, COX2, NO, and TNF-α-mediated monocyte adhesion, which suppresses pro-inflammatory gene expression [61].

4. CONCLUSION

This research aims to shed light on the importance of the Hayani date peel, which is removed during eating the date fruit. The study showed that the date peel has nutritional value and contains biologically active substances such as phenolic acids, flavonoids, and fibers to which the vital activity of the date peel is attributed. The results showed that the peel contains high percentages of carbohydrates, dietary fiber, essential amino acids, and high levels of K, Ca, Mg, and Fe minerals, besides its content of important phytochemicals. The effect of the date peel powder and its methanolic extract was studied on diabetic rats. Peel powder and its extract significantly decreased blood glucose level and HbA1c while they increased the serum insulin level compared to diabetic control. They also caused significant improvements in blood lipid, liver enzymes (ALT & AST), albumin, creatinine, and uric acid but the effect of the peel methanolic extract was higher than the peel powder. In terms of anti-inflammatory activity, peel powder showed better results than peel extract in reducing inflammatory factors. Therefore, it is recommended to eat whole Hayani date fruits without peeling.

ETHICAL APPROVAL

The animals' treatments were subjected to the ethical standards approved by the scientific research ethics committee of Mansoura University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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