Pretreatment with Ajwa dates (*Phoenix dactylifera* Linn) prevents development of alloxan-induced diabetes in rats

Amer Hassan Siddiqui[1]*, Mahwash Malik[2], Sadia Chiragh[3]

ABSTRACT

Background and Objective: A global increase in the prevalence of diabetes mellitus (DM) is associated with increased morbidity and mortality. Oxidative stress is a fundamental component in the pathogenesis of DM Ajwa dates are known to have a high antioxidant content, especially in their seeds. Hence this study was designed to determine the preventive effects of Ajwa date fruit on alloxan-induced diabetes in an experimental rat model.

Methods: This experimental study was conducted at the Post Graduate Medical Institute, Lahore, Pakistan. A total of forty Sprague-Dawley rats were divided into five groups with eight animals in each. Rats in group A were normal control, whereas rats in group B were induced with intraperitoneal alloxan (160 mg/kg body weight) to develop diabetes. Groups C, D, and E rats were fed on a diet supplemented with Ajwa flesh, seed, and whole Ajwa respectively for 1 week. Blood and urine glucose levels were measured on days 0, 7 (pre-alloxan) and 11, 14, 19 (post-alloxan). Serum insulin, homeostatic model assessment (HOMA) for β-cell function (HOMA-β), and insulin resistance (HOMA-IR) were estimated terminally.

Results: Diabetes was induced successfully in animals of all experimental groups except the normal control group. Rats of the Ajwa-seed group (D) showed relative resistance to diabetes induction with three non-diabetic rats on day 19. In group E, rats had lower blood sugar levels than rats in group C (p = 0.010). Serum insulin, HOMA-β and HOMA-IR, revealed partial beta cells restoration in the experimental animals of groups D and C. Insulin resistance was significantly higher, despite the highest insulin level (3.77 µIU/ml; p value <0.001) in group C.

Conclusion: Ajwa date seed powder appears to provide relative protection against the development of diabetes in rats induced by alloxan.

Keywords: Ajwa, date fruit, prediabetes, diabetes mellitus, antioxidants.

Introduction

Diabetes mellitus (DM) is a clinical condition characterized by hyperglycemia, glycosuria, polyuria, and other metabolic disturbances.[1] Insulin is required for the metabolism of carbohydrates and its deficiency causes a decrease in peripheral glucose uptake or increased glucose synthesis by rapid glycogenolysis in the liver. This pathological hyperglycemia causes blood vessel damage that results in end organ failure mainly in the lower limbs, eyes, and other highly perfused tissues/organs of the body.[2]

Globally, diabetes is becoming a major health concern. The number of people with DM is expected to increase to 693 million by the year 2045, according to the International Diabetes Federation Atlas.[3] Second National Diabetes Survey of Pakistan showed the prevalence of diabetes as 28.3% and 25.3% in urban and rural areas respectively. This indicates the urgent need for national policies for early diagnosis and effective management as well as cost-effective diabetes primary prevention programs in Pakistan.[4]

Poor strata of society are most vulnerable to the serious effects of the disease because of inadequate health facilities and non-compliance.[5] Prediabetes leads to established DM when the underlying process has already started but not yet reached the diagnostic threshold of the disease. Persistence of this condition causes frank DM.[6] Oxidative stress plays an important role in the pathogenesis of DM.[7] Genetics, increased oxidative stress and free radicals are considered risk factors triggering DM development.[8] Current treatment

options available for diabetes act by different mechanisms to lower blood glucose levels but none of them affect oxidative stress. Therefore, the use of targeted therapies may be beneficial in managing the disease by scavenging the free radicals.[9]

Date palm, *Phoenix dactylifera*, is a monocotyledonous plant belonging to the Arecaceae family with almost 200 varieties grown over the world. Some known major types are Ajwa, Mabroom, Zahidi, Aseel, Dhakki, Halawi, Lash, Deggla, and Bamy. Ajwa is the most expensive variety cultivated in Madina Munawwara Sharif and its surroundings.[9,10]

Ajwa dates flesh contains the highest reducing sugars with very low sucrose as compared to other varieties.[11] While the highest ratio of antioxidant chemicals like gallic, chlorogenic, and ferulic acid are present in Ajwa date seeds than other dates.[12] Literature shows the antioxidant and anti-inflammatory potential of Ajwa dates and their use in different diseases as antibacterial, antifungal, antiviral, anti-asthmatic, anti-diabetic, anticancer, antimutagenic, nephroprotective, hepatoprotective, gastrointestinal protective, neuroprotective, cerebro-protective, immunostimulator, and aphrodisiac.[10,13] Ajwa date seeds lower serum glucose levels in experimental models of diabetes, decrease insulin resistance and improve beta cell function.[14]

This study is aimed to evaluate the preventive effect of Ajwa date on Alloxan-induced diabetes in an experimental rat model in relation to glycemic parameters and serum insulin levels.

Methods

This experimental study was conducted at the Post Graduate Medical Institute Lahore, Pakistan, after getting approval from the Institutional Ethical A total of forty Sprague-Dawley rats weighing between 120 and 150 g were procured from the University of Animal Sciences, Lahore, Pakistan. They were randomly divided by using the lottery method into five groups with eight animals in each group. Group A comprised of normal control rats and group B was induced with diabetes by intraperitoneal alloxan. Rats of groups C, D, and E were fed on a diet supplemented with Ajwa flesh, Ajwa seed, and Ajwa whole, respectively. (Table 1). Rats were acclimatized with a 12-hour light/dark cycle for 1 week at ±25°C and fed *ad libitum* before starting an experiment.

Preparation of Ajwa date feed

After purchasing from the local date market, Ajwa's date was verified by the Department of Botany, Government College University, Lahore, Pakistan (Voucher number: GC. Herb. Bot. 3447). The diet of the experimental animals was prepared with Ajwa date flesh (finely mashed in water) and Ajwa seed powder (finely ground). They were mixed with regular rat chow (1/100 g) to prepare 1% Ajwa flesh, seed, or whole diet and was provided *ad libitum* to rats.[15]

Induction of diabetes

Alloxan monohydrate (Sigma Aldrich, USA; 99% pure) was mixed in normal saline to prepare a fresh 5% *w/v* solution. After giving 1 week of group-specific diet, a dose of 160 mg/kg body weight of alloxan was administered intraperitoneally to the rats (day 07).[16] Equivalent amount of normal saline was injected in the normal control group. Thirty minutes post-injection, rats were given a 10% glucose solution for the first 24 hours to prevent acute hypoglycemia development. This method of alloxan administration was expected to establish hyperglycemia in the diabetes control group after 03 days and stabilize blood sugar levels (BSL) in 12 days.[17] BSL of 126 mg/dl or higher on day 11 (4 days post alloxan) was set as a cut-off to label the rats as diabetic. Rats with diabetes were further categorized as type 1 with a BSL of 300 mg/dl and those with a BSL of 127-300 mg/dl as type 2.

Blood sampling and parameters

Blood glucose levels were measured as a baseline on days 0, 07 (prior to alloxan administration), day 11 (4th-day post-alloxan), day 14 (7th-day post-alloxan), and day 19 (12th-day post-alloxan). The samples were taken by tail vein tapping after 12 hours fast and measured by a portable glucometer (Accucheck Performa by Roche).[18] Urine glucose was measured by the dipstick method.[19]

Serum glucose and insulin levels were measured from blood obtained terminally through cardiac puncture under chloroform anesthesia. Serum glucose levels were estimated by using a commercially available kit (Kashef Diagnostics, Saudi Arabia) based on the production of chromogen by enzymatic oxidation, which was then quantified by a spectrophotometer (Pictus B by Diatron, Hungary). Enzyme-linked immunosorbent assay technique was used for measuring serum insulin levels (µIU/ml) by using a rat-specific kit [Glory Bioscience Company (USA)].[20]

Homeostatic model assessment (HOMA) was used to measure beta cell function and insulin resistance. Mathematical calculation of homeostatic model assessment insulin resistance (HOMA-IR) and homeostatic model assessment β-cell (HOMA-b) was done by the following formulae. A value greater than 2 shows resistance to insulin.[21]

$$\text{HOMA} - \text{IR} = \frac{(\text{Fasting insulin} \times \text{Fasting blood glucose})}{405}$$

$$\text{HOMA-}\beta \text{ cell function (\%)} = \frac{360 \times \text{Fasting insulin}}{\text{Fasting blood glucose-63}}$$

Statistical analysis

Data were analyzed through Statistical Package for the Social Sciences version (SPSS 22.0). The normality of data was verified using Shapiro-Wilk and Kolmogorov test. Mean ± SD was calculated; one-way ANOVA and post hoc Tukey tests were applied to compare and check differences among the groups. Differences within a group at various measurement occasions were determined by applying paired *t*-tests. The *p*-value < 0.05 was considered significant.

Results

All the rats in the normal control group were non-diabetic throughout the study while the rats in the diabetes control group and other experimental groups, except the Ajwa seed group (D) developed diabetes as shown in Table 1. In the Ajwa seed group, three rats were non-diabetic at the end of the study and five rats were diabetic. The number of rats with BSL of more than 300 mg/dl was more in group C and lesser in group D (Table 1). However, this difference was statistically insignificant when both groups were compared.

Fasting blood glucose

The normal control group remained euglycemic throughout the study, while the rats of all experimental groups except Ajwa seed group D, had significantly raised BSL. It was significantly more in the rats of group C than in groups A, B, and D rats (*p* value <0.001, 0.020, and <0.001, respectively) (Table 2).

Urinary glucose estimation

Urinary glucose was nil in group A rats whereas it was detected in alloxan-administered groups (Table 2). It was significantly higher in Ajwa flesh group C than in other alloxanized groups (*p*-value 0.018 for diabetic control group B, <0.001 for Ajwa seed group D and 0.010 for Ajwa whole group E) (Table 2).

Terminal serum glucose

Terminal serum glucose level was significantly lesser in the rats of Ajwa seed group D than in other alloxan-administered groups (Figure 1). Terminal serum glucose revealed no significant difference between diabetic control group B and groups C and E (Figure 1).

Table 1. *Effect of dietary modifications in rats of all experimental groups (n = 8).*

Group.	Normal control (A)	Alloxan-induced diabetes control(B)	Ajwa flesh group (C)	Ajwa seed group (D)	Ajwa whole group (E)
Feed	Regular rat chow	Regular rat chow	One Ajwa flesh (7 g) mixed with 100 g of regular rat chow	One Ajwa seed powder (1 g) mixed with 100 g of regular rat chow	One Ajwa flesh (7 g) and seed powder (1 g) mixed with 100 g of regular rat chow
Diabetes induction	No	Yes	Yes	Yes	Yes
Non-diabetic rats	8 (100%)	Zero	Zero	3 (37.5%)	Zero
Diabetic rats	Zero	8 (100%)	8 (100%)	5 (62.5%)	8 (100%)
>300 mg/dl Type1	Zero	5 (62.5%)	7 (87.5%)	2 (25%)	5 (62.5%)
127-300 mg/dl Type 2	Zero	3 (37.5%)	1 (12.5%)	3 (37.5%)	3 (37.5%)

Table 2. *Fasting blood glucose and urine glucose levels in alloxan-induced diabetic rats (n = 8).*

Groups →		Normal control(A) (mean ± SD)	Alloxan-induced diabetic control (B) (mean ± SD)	Ajwa flesh (C) (mean ± SD)	Ajwa seed(D) (mean ± SD)	Ajwa whole (E) (mean ± SD)
Day 0	Bl Glucose	91.57 ± 6.9	90.45 ± 9.16	90.36 ± 4.48	91.12 ± 8.33	88.8 ± 8.18
	Ur Glucose	0	0	0	0	0
Day 7	Bl Glucose	88.87 ± 12.8	93.15 ± 11.41	88.56 ± 4.66	87.07 ± 10.62	90.9 ± 7.44
	Ur Glucose	0	0	0	0	0
Day 11	Bl Glucose	86.17 ± 8.84**	340.35 ± 207.71	554.52 ± 101.67*	218.92 ± 79.95	298.8 ± 187.69
	Ur Glucose	0*	2 ± 1.77	3.8* ± 0.45	0.25* ± 0.46	1.17 ± 1.33
Day 14	Bl Glucose	89.32 ± 6.73*	271.12 ± 126.43	427.32 ± 111.39*	205.87 ± 95.62	361 ± 192.43
	Ur Glucose	0	1.25 ± 1.38	3.4** ± 0.55	0.375 ± 0.74	1.83 ± 1.72
Day 19	Bl Glucose	87.97 ± 9.2***	396.45 ± 134.64	485.64 ± 121.69	211.27 ± 120.67*	303 ± 77.12
	Ur Glucose	0***	3 ± 0.75	3.2 ± 0.84	0.625*** ± 0.92	2 ± 0.63

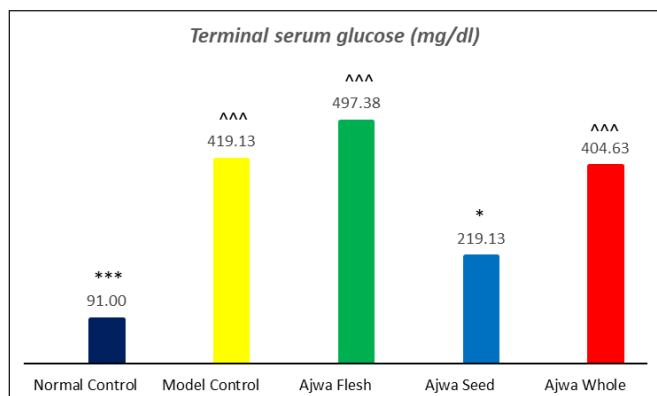*p value ≤ 0.05, **p value ≤ 0.01, ***p value ≤ 0.001 versus alloxan induced group.

Figure 1. *Effect of Ajwa date pretreatment on terminal serum glucose level (mg/dl) of alloxan-administered rats (n = 8). *p value ≤ 0.05, ***p value ≤ 0.001, versus alloxan induced group. ^^^p value < 0.001 versus normal control group.*

Figure 2. *Effect of Ajwa date pretreatment on serum insulin levels (μIU/ml), HOMA-b and HOMA-IR of alloxan-administered rats (n = 8). ***p value < 0.001 versus alloxan-induced groups. ^^^p value < 0.001 versus normal control group.*

Serum insulin

Serum insulin level was found significantly highest in group C (3.77 μIU/ml; *p* value <0.001) than the rest of the groups (Figure 2). Also, the serum insulin level (1.075 μIU/ml) in group D was significantly higher than group B (0.85 μIU/ml). However, there were no significant differences among the rest of the groups.

Homoeostatic model of assessment

Rats of Ajwa flesh group C had significantly elevated HOMA-IR as compared to the rest of the groups with no significant differences. Alloxan treatment significantly reduced HOMA-b in group B and other experimental groups than in the normal control group. Significant differences in HOMA-b were not seen among alloxan-administered groups themselves (Figure 2).

Discussion

Diabetic Mellitus and its dreadful complications are becoming more common globally. Even though a number of different agents have been evaluated for their anti-diabetic properties, little research has been conducted so far to assess their ability to prevent the onset of diabetes. It is believed that diabetes is triggered by unhealthy factors that elevate oxidative stress within the body systems.[22] This observation formed the basis of the study, and the reduction of oxidative storms by the use of antioxidants has been hypothesized and tested as a potential method of preventing the onset or development of DM.

Traditional medicine uses date fruits, rich in antioxidants, in a wide variety of diseases.[23] Ajwa has the highest antioxidant activity with hypoglycemic potential among all other varieties.[12,24] Alloxan was chosen as a diabetogenic chemical because it produces hyperglycemia by causing o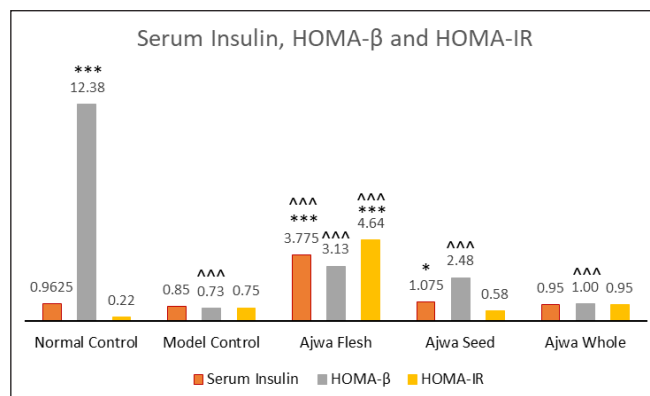xidative damage to beta cells in the pancreas.[17] Ajwa dates are used as antioxidants to prevent this injury and hence induction of diabetes.

The rats in the Ajwa seed group D demonstrated partial protection or resistance to the induction of diabetes despite the fact that diabetes was induced in all model control groups. The induced animals were of more type II than type I as compared to other groups. A current review investigated the effects of date fruits on glycemia among the patients with DM and confirmed their hypoglycemic activity.[25]

The current study showed similar patterns of diabetes development in the Ajwa whole group and model control. Diabetes was induced most severely in Ajwa flesh group C with the highest BSL and seven out of eight animals progressed to severe DM (BSL >300 mg/dl) in this group. A striking observation was the highest serum insulin level in group C despite the highest blood glucose level. The statistically significant difference in insulin level despite the insignificant difference in BSL could be due to the antioxidative activity of Ajwa dates, which may contribute to the recovery and protection of beta cells. The least insulin level in the diabetic control group shows alloxan-induced oxidative injury to beta cells and hence their failure to synthesize insulin despite elevated BSL. This oxidative damage is dose-dependent and the extent of injury to beta cells produces various types of diabetes.[26]

The current study showed an increased level of HOMA-IR in Ajwa flesh-fed group C (4.64 *vs.* 0.75 in diabetic control; *p* < 0.001). The molecular pathogenesis of DM is explained by the development of insulin resistance resulting from excessive intake of carbohydrates resulting in a glucolipotoxic cell environment.[27] High carbohydrates proportion in Ajwa flesh group C may be, therefore, a possible reason for increased insulin resistance and HOMA-IR in this group. Antioxidants in Ajwa flesh were able to prevent the complete exhaustion of

islets of Langerhans as a result of this high insulin demand, thereby allowing more insulin to be secreted to overcome this resistance.[24]

An animal study observed the antidiabetic and antinephropathic potential of Ajwa pit and pulp (*P. dactylifera*) in alloxanized diabetic rats and reported better results with seed powder diet after 8 weeks of treatment.[15] The combination of Ajwa seeds and black pepper improved the glycemic index of alloxan-induced diabetic rats in other studies using different nutraceuticals and their combinations.[28] Furthermore, a study demonstrated that seed extracts from Ajwa and Sukkari dates restored insulin levels to the normal level in streptozotocin-induced diabetic rats.[24] The present study also showed better results of seed powder as compared to flesh and whole fruit. In several reviews and meta-analyses of clinical studies using date flesh (Ajwa and others) in diabetic patients, various results have been summarized showing an optimal control of diabeties as well as prevention of diabetic complications. It is therefore recommended that physicians refrain from limiting the consumption of dates in diabetic patients.[25,29]

The current study focused on the prevention of the development of diabetes, considering a positive result would add a dietary supplement for such population. This study will open the door to do more research on the use of Ajwa date seeds in patients suffering from prediabetes in the future. As of today, the only federal drug authority USA approved drug for the prevention of diabetes, other than lifestyle changes, is metformin.[30] The present study may add Ajwa date seed powder to this list.

Conclusion

It is concluded that Ajwa date seed powder can provide relative protection against the development of alloxan-induced diabetes in rats. The precise mechanism of this protection against diabetes and the hypoglycemic effect of Ajwa date seed should be explored through further studies. Similarly, Ajwa flesh should be further explored for the isolation of phytochemicals with possible insulinogenic and/ or beta-cell protective actions.

Limitations of Study

This study has few limitations. First, blood ketones were not measured which could be used for absolute labeling of the type of induced diabetes in experimental animals. Second, only one type of dates was used. No histology was performed that could provide insight into the extent of beta cell damage.

Acknowledgement

List of Abbreviations

BSL	Blood sugar level
DM	Diabetes mellitus
HOMA-β	Homeostatic model assessment for β-cell function
HOMA-IR	Homeostatic model assessment for insulin resistance

Conflict of interest

None to declare.

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Ethical approval

The study was approved from the Institutional Ethics Committee of Post Graduate Medical Institute (PGMI) Lahore, Pakistan vides Letter No:00-01-S-2018, dated:18-01-2018.

Authors' contributions

AMS: Conception and design of the study, acquisition of data collection and drafting of the manuscript.
MM: Analysis of data, important intellectual input and drafting of the manuscript
SC: Conception and design of the study, Important intellectual input.
ALL AUTHORS: Approval of the final version of the manuscript to be published.

Authors' Details

Amer Hassan Siddiqui[1], Mahwash Malik[2], Sadia Chiragh[3]
1. Assistant Professor, Pharmacology Department, Post Graduate Medical Institute, Lahore, Pakistan
2. Associate Professor, Pharmacology Department, Central Park Medical College, Lahore, Pakistan
3. Professor, Pharmacology Department, Al-Aleem Medical College, Lahore, Pakistan

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