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Research Article

**AMELIORATIVE EFFECT OF PHOENIX DACTYLIFERA (AJWA) ON
RENAL BIOCHEMICAL MARKERS IN ALLOXAN INDUCED DIABETIC
NEPHROPATHIC RATS**

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Abstract:

Background: Dates specially date seeds have shown their preventive effects in controlling hyperglycemia in diabetes mellitus in few recent studies, however there is need to explore the effects of dates on its complications.

Objective: This study was planned to evaluate the preventive effect of whole Ajwa date on nephropathy in alloxan induced diabetic rats

Methods: Whole ajwa date powder mixed in rat chow was administered to male sprague dawley rats after induction of diabetes with alloxan monohydrate for 6 weeks. Serum and urine biochemical parameters were assessed by enzymatic methods.

Results: Oral administration of ajwa date diet significantly ameliorated the elevated levels of fasting blood glucose (167.0 ± 37.5 versus 353.8 ± 67.5 mg/dl), urea (41.3 ± 13.5 versus 75.1 ± 11.2 mg/dl), creatinine (0.49 ± 0.2 versus 0.99 ± 0.2 mg/dl), microalbuminuria (7.4 ± 1.9 versus 14.6 ± 1.7 mg/l), improved the lowered levels of body weight (202.0 ± 40.7 versus 143.8 ± 21.7 g), urinary creatinine (13.8 ± 2.3 versus 7.0 ± 1.6 mg/dl), and creatinine clearance (0.195 ± 0.1 versus 0.55 ± 0.01 ml/min) compared with the untreated diabetic rats.

Discussion and conclusion: The ajwa date powder showed potential protective effects against early diabetic complications of kidney. This effect may be explained by the antioxidant and free radical scavenging capabilities of *P. dactylifera*.

Keywords: Antihyperglycemic, antioxidant, ajwa date, diabetic nephropathy, alloxan.

Abbreviations: Diabetes Mellitus (DM); Fasting blood sugar (FBS); 2,2-diphenyl-1-picrylhydrazyl (DPPH); 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid (ABTS)

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INTRODUCTION:

Hyperglycemia is considered as one of the most promising causes of chronic kidney disease. International diabetes federation states that there are 382 million diabetics worldwide and this figure will augment up to 592 million in next 25 years. Eighty percent of this problem comes from developing countries specially from younger population [1]. In South Asia region, diabetic prevalence has gone up to 10.3 % in 2006 and Pakistan is the main contributor of this load [2].

It has been concluded from several published studies that primary reason of complications from diabetes is the oxidative stress. Oxidative stress during diabetes directs the appearance of free radicals in the body along with less synthesis of defensive enzymes which ultimately results in malfunctioning of the human tissues and organs if not treated well [3].

Alloxan monohydrate is one of the most adopted method for inducing diabetes and its related complications. Oxidative stress produced by alloxan results in severe hyperglycemia leading to renal complications of the disease in animals[4].

Versatile antioxidants have played an important role in increasing the defending enzymes of the body against oxidative stress and in this way protecting kidneys from nephropathic condition. Hence the herbs, plants and fruits with multi-use antioxidant properties are receiving more interest [5].

Protection against multiple diseases by Phoenix Dactylifera (palm date) especially its seeds and fruits have confirmed its antioxidant properties [6]. Fruits of Ajwa are loaded with carotenoids, phenolics, flavonoids and dietary fibers. Highest amount of crude protein (2.94%) is found in ajwa flesh while pits contain highest insoluble dietary fiber (34.6%). Main minerals in flesh are potassium, zinc, calcium, selenium and magnesium [7]. Ajwa seeds are the greatest source of zinc (1.91mg/g) and flesh supplies the highest concentration of magnesium(1.5mg/g) and potassium (6.45mg/g) [8].

Phenolic content of Ajwa fruit ranges between 245mg and 455 mg/100g [9]. Major phenols include derivatives of gallic, caffeic, coumaric and ferulic acid. The flavonoids content of Ajwa date fruit is 2.7mg/100g [10] and is packed with major flavonoids like rutin (6.50mg/kg), catechin (7.30mg/kg) [9] and luteolin. Phenols in date seeds are absorbed very easily, and are in large quantity than in fruit. Quercetin (1.3mg/100g) and iso-quercetin are the

major flavonoids present in seeds [11]. The polyphenolics & flavonoids present in fruit and pits have immense antioxidant and free radical scavenging properties [12].

Anti hyperglycemic effect of Aqueous extract of Phoenix Dactylifera seed and its possible mechanism through increased production of insulin has been established in few studies [13,14].

A very recent study [15] reported decrease in fasting blood sugar level, serum urea and creatinine along with amelioration of histological changes in kidneys of diabetic rats after oral administration of Hayani date seed extract.

Flesh of Ajwa date has also been tested for its ameliorative effects on renal function and tubular damage by Ocratoxin[16]. However the nephroprotective effect of Ajwa date in diabetes is still unexplored.

Keeping in view the role of oxidative stress in diabetic nephropathy and the above studies showing high levels of antioxidants in Ajwa date, antihyperglycemic effect of date seed and nephroprotective potential of date flesh and seed of other date varieties, this study was designed to assess the effects of whole Ajwa date on disturbed renal functions of diabetic rats.

MATERIALS AND METHODS:

Chemicals: All chemicals for all assays were obtained by Sigma, USA.

Preparation of Ajwa Diet:

Ajwa date was obtained from Aseel market Madina Munawara. The date was identified by Botany department of Government College University Lahore. A voucher specimen number GC. Herb. Bot. 2954 was kept in the herbarium of the said department. One medium size Ajwa date weighed about 8-9grams. The seeds were separated from flesh with knife, separated seeds washed with tap water and remaining fruit pulp was removed with hand by gentle rubbing. Seeds were spread widely spaced on malmal clean and dry cloth for air drying. After drying, they were gathered and saved in a plastic transparent jar. They were labeled and ground to make powder. Flesh was mashed finely. Both were mixed. One date mix was added to 100 gram rat chow for animals of Ajwa diet group and given ad libitum. The Ajwa diet pellets were made on weekly basis and stored in dry, cool place. The daily rat feed requirement was calculated on the basis of seven dates daily for adult human being as mentioned in Ahadith [17] and provided *ad libitum*.

Animals:

Adult male Sprague dawley rats weighing 120-150g were bought by University of Veterinary and Animal Sciences Lahore. The animals had free access to food and water ad libitum and maintained in the controlled environment under standard conditions of temperature and humidity with an alternating 12 h light and day cycle. The protocol of the study was approved by the Animal Ethics Committee of Post Graduate Medical Institute, Lahore. The study was conducted in accordance with advance board approval from University of Health Sciences, Lahore for animal experiments.

Induction of experimental diabetes

Alloxan was freshly dissolved in normal saline just before use and given as single intraperitoneal injection (150mg/kg) to fasting rats. After about 72 hours, animals showing blood glucose fasting level more than 250 and less than 500 were chosen as diabetics and divided into groups for study.

Dosage and treatment:

Twenty four rats were divided into three groups by lottery method. Each group contained eight rats. Group 1 is normal control group and received a normal saline single injection. Group 2 is diabetic group. It received single intra peritoneal injection of alloxan (150mg/kg) and no treatment was given to this group. Group 3 is the Ajwa diet group. Animal of this group were given ajwa date diet daily for six weeks after getting single injection of alloxan.

Serum Biochemical Parameters:

Fasting blood glucose level was determined by the glucometer. Serum Urea and creatinine levels were

assayed by enzymatic methods. All serum parameters were assessed using commercial diagnostic kits (Crescent diagnostics).

Urine Biochemical Parameters:

Urine creatinine was measured by enzymatic method using commercially available kit (Crescent diagnostic), Microalbuminuria was assessed using log logit method (Randox diagnostic kit). Creatinine clearance was measured by using formula.

STATISTICAL ANALYSIS:

All obtained data were expressed as mean±SEM. Statistical analysis was performed by one way analysis of variance (ANOVA) followed by Tuckey's test for multiple comparisons using SPSS 16 version. Paired t test was applied for comparison between the groups. $p < 0.05$ was considered statistically significant. Appropriate graphs were plotted using Microsoft Excel 2008.

RESULTS:**Effect of ajwa date on growth and fasting blood sugar of diabetic rats.**

As displayed in Table 1, the alloxan induced diabetes caused significant growth retardation compared with the control rats ($p < 0.001$). Oral administration of ajwa diet improved the growth significantly compared with the diabetic group (p value 0.001). The diabetic group also showed sharp increase in fasting blood glucose level compared with the control group ($p < 0.001$). Treatment with ajwa date diet decreased the blood glucose level compared with the diabetic group ($p < 0.001$). However, the ajwa diet did not restore the normal blood glucose values ($p < 0.01$ compared with control group).

Table 1: Body weight and fasting blood sugar levels

Parameter	Control	Diabetic	Diabetic + ajwa diet
Body weight gain	231.1±9.1	143.8±21.7	202.0±40.7
FBS 0 weeks	81.0±7.9	335.8±66.3	335.6±66.9
FBS 4 weeks	85.7±6.3	347.6±67.1	216.6±37.9
FBS 6 weeks	89.5±5.2	353.8±67.5	167.0±37.5

Effect of Ajwa date diet on serum renal function parameters:

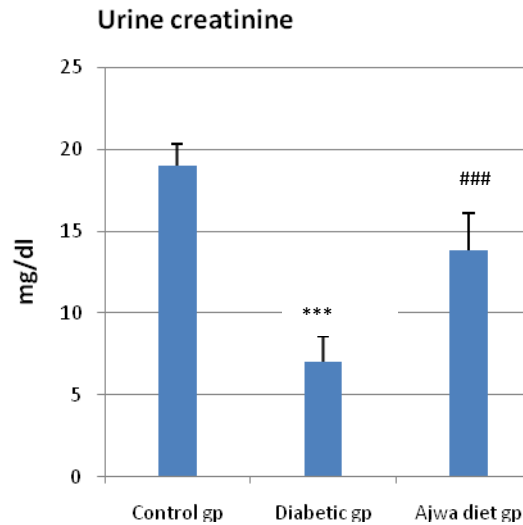
Regarding the renal profile, the levels of both serum urea and creatinine are significantly elevated in diabetic group ($p < 0.001$). However, ajwa date diet significantly ameliorated both of these serum markers compared with diabetic group (0.001) (Table 2).

Table 2. Statistical analysis of serum parameters

Parameter	Control	Diabetic	Diabetic + ajwa diet
Serum urea 0 weeks	31.9±4.8	31.5±3.0	30.3±3.5
Serum urea 4 weeks	29.8±5.2	63.3±9.7	35.5±9.9
Serum urea 6 weeks	31.8±5.5	75.1±11.2	41.3±13.5
Serum creatinine 0 weeks	0.38±0.2	0.35±0.1	0.35±0.1
Serum creatinine 4 weeks	0.36±0.00	0.57±0.10	0.41±0.11
Serum creatinine 6 weeks	0.35±0.1	0.99±0.2	0.49±0.2

Effect of Ajwa date diet on urine biochemical markers for renal functions

Regarding urinary renal profile, urine creatinine and creatinine clearance levels showed marked decrease (p value 0.001) while microalbuminuria levels showed increase in diabetic group. Treatment with ajwa diet improved the urine renal profile as compared to diabetic group (p 0.001).



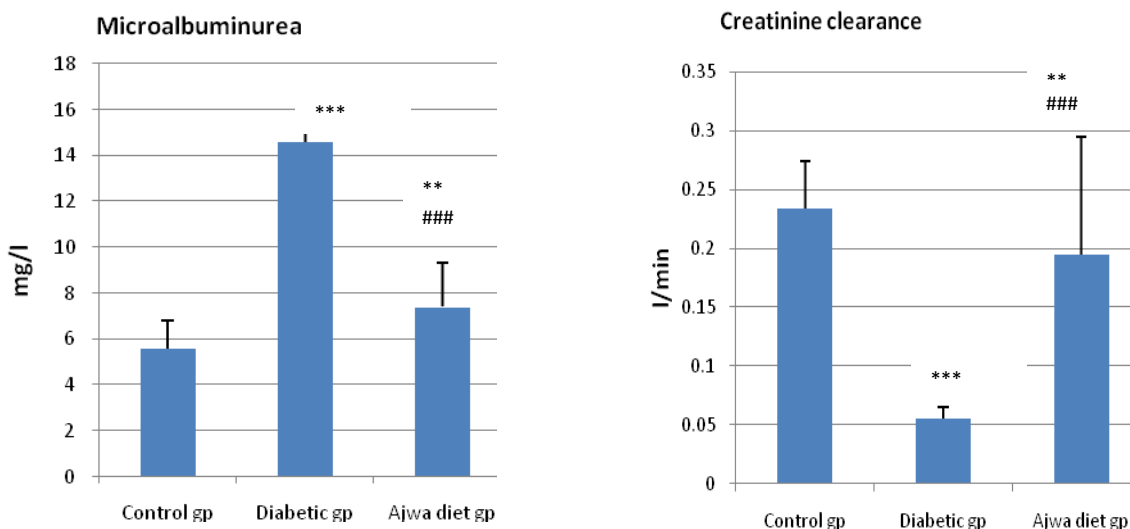


Figure 1. Effects of ajwa date diet on the urinary biochemical markers of alloxan-induced diabetic rats. Data are articulated as mean±SEM; *p0.05 compared with control, **p0.01 compared with control, ***p0.001 compared with control, #p0.05 compared with the diabetic group, ##p0.01 compared with the diabetic group, ###p0.01 compared with the diabetic group.

DISCUSSION:

Traditional benefits of ajwa especially antidiabetic benefits have been utilized by people since many years but still there are only few studies to probe its antihyperglycemic potential and its beneficial effects on diabetic complications.

Only one recent study [15] has demonstrated that date (Hayani) seed suspension has hypoglycemic as well as nephroprotective effect in streptozotocin induced diabetic rats and this effect may be attributed to ameliorated oxidative stress through efficient antioxidant effects and potential of restoring defending enzymes of the body.

The present study was accomplished to investigate the effect of oral administration of Ajwa date on early diabetic complications distressing alloxan - induced diabetic rats.

In the current study, a marked decrease in weight and growth were noted in groups treated with alloxan after 6 weeks in contrast to normal control rats. These results are in line with past studies which proved that intense prolonged hyperglycemia leads to muscle wasting and weight loss occurs through loss of tissue protein [18]. Treatment with Ajwa date diet depicted significant growth improvement and weight gain in comparison to rats of diabetic group.

This improvement in weight could be justified by tremendous glycemic control achieved by Ajwa diet as shown in our results. Our results are in agreement to Abdelaziz [15] who confirmed that Hayani date

seed aqueous suspension significantly reduces hyperglycemia (51%) and improved the weight of diabetic rats. Earlier work by El-foul also established the hypoglycemic potential of aqueous seed extract of “Sukkary date” in diabetic rats along with insulin in a 4 weeks study. This effect may be ascribed to aggravated insulin secretion by beta cells [13,14].

Most severe complication of diabetes is nephropathy and researchers have reported that progressive proteinuria causes gradual declining of kidney function parameters which is the major risk factor for progressive renal impairment [19].

Treatment with Ajwa date diet in diabetic rats ameliorated the serum parameters of kidney damage like urea, creatinine, microalbuminuria and improved the urine creatinine and creatinine clearance levels in alloxan treated diabetic rats suggesting that Ajwa date intake may lessen the diabetes persuaded kidney injury.

Our results are again in accordance to research by Abdelaziz [15] in which researchers found that seed suspension of “Hayani date” has improved renal functions in 4 weeks time advocating the reduction in diabetes provoked renal damage.

Diabetes mellitus is characterized by increased oxidative stress in all tissues. In oxidative stress, free radicals emerge in the body which injures all tissue through increasing lipid peroxidation and also increase insulin resistance by enhancing metabolic processes, proinflammatory cytokines and decreasing

defensive enzymes [3].

An increasing number of researches have shown that *P. dactylifera* has significant amount of antioxidants. Date fruit and seeds both are good source of antioxidants, minerals, flavonoids and best absorbable phenols [21]. Ferulic acid, gallic acid, cinnamic acid, sinapic acid and p-coumaric acids are the main phenols and present in about 8.36 mg GAE/100 g fresh fruit [22]. Polyphenols and flavonoids play the main role as antioxidants in dates seeds [23]. The preventive effects of polyphenolic compound against the diabetic complications have been reported previously [24][25].

Ajwa date seed ethanolic extract contain about 3932.3mg GAE/100g of phenols and total flavonoids were found to be 2956.2 mg QEC/100g. in 80% acetic extract [26]. Ajwa date seed has highest amount of flavonoids including rutin & quercetin [27]. Rutin is major flavonoid present in Ajwa seed [27] and it effectively reduced the increased levels of TBARS and hydroperoxides in diabetic rats [28]. In addition, quercetin has also shown improvement in hyperglycemia when given alone and along with insulin in diabetic rats [29] and attenuated nephropathy in diabetic rats [30].

P. dactylifera seeds have also shown an increase in anti oxidative enzymes like glutathione S-transferase, catalase, superoxide dismutase in kidneys with diabetic stress by decreasing glycation of enzymes and free radical scavenging property [15].

Strong antioxidant effects of Ajwa date have been explored in few studies. Khalid reported that Ajwa date fruit has extracted highest amount of DPPH (96.3%) and ABTS (86.2%) scavenging activity [31]. Water extract of Ajwa fruit showed the highest inhibition of lipid peroxidation by approx. 65% [6][11]. Ajwa seed extract prevented the depletion of essential antioxidants including superoxide dismutase, carnitine acetyltransferase [32].

Ajwa seed extract has 74µg/ml of gallic acid equivalents and good radical scavenging activity in DPPH (84.4%), lipid peroxidation (71.1%) ABTS (26.9%) assays [33]. In cellular reactions, polyphenols act as reducing agents and their antioxidant activity is due to their ability to suppress free radicals, inhibition of lipid peroxidation, protein oxidation, and delaying the depletion of defending antioxidant enzymes of the body [6].

In view of that, our findings concerning the preventive effects of Ajwa date against the diabetic complications may be ascribed to the presence of the

forementioned antioxidant phytoelement.

CONCLUSION:

Current study displays that Ajwa date (*Phoenix dactylefera*) possesses significant anti-hyperglycemic and nephroprotective activities in rat model of alloxan-induced diabetic nephropathy, validating its traditional use in diabetes. The data displayed that Ajwa diet significantly ameliorated fasting blood glucose, serum urea, creatinine and improved body weight, urinary creatinine, creatinine clearance. Further studies are required for the identification and isolation of active compounds responsible for anti-hyperglycemic and nephroprotective effect.

Conflict of Interest:

The authors declare no conflict of interests

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