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Original Research Article

A double-blinded, randomized, placebo-controlled study evaluating the impact of dates vinegar consumption on blood biochemical and hematological parameters in patients with type 2 diabetes

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Abstract

Purpose: *To determine the effects of dates vinegar on blood biochemical and hematological parameters in type 2 diabetic subjects.*
Methods: *Current research focused on fifty-five subjects having blood sugar more than126 mg/dL. Participants ingested dates vinegar (20 mL) daily into their normal diets for a period of 10 weeks. Glycated hemoglobin (HbA1c), fasting blood sugar (FBS), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine (Cr), urea, complete blood count (CBC), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), potassium and folate levels were analyzed before, after 5 weeks and after the experiment*
Results: *Dates vinegar improved the blood concentrations of HbA1c (6.80 ±2.34 to 6.17 ± 2.14 (%)), FBS (171.43 ±36.74 to 147.56 ± 38.86 mg/dL,p=0.001), TC (218.10 ± 16.9 to 191.14 ± 14.23 mg/dL, p<0.001), ALT (24.94 ± 5.03 to 21.88±5.08 IU/L, p=0.002) and ALP (264.32± 45.26 to 257.30 ±44.21 IU/L) and folate (34.6 ± 6.6 to 41.7 ± 6.5 nmol/ L,p<0.001).*
Conclusion: *Dates vinegar significantly improved the total cholesterol.The other blood biochemical and hematological factors were also improved however; the improvements were not significant.*

Keywords: Dates vinegar, diabetes, glycated hemoglobin, hyperlipidemia

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INTRODUCTION

Diabetes mellitus (DM) is a universally emergent health complication and is one of the five main causes of mortality and morbidity in many parts of the world [1]. Globally, more than 171 million people were affected by diabetes in 2000 and this figure is projected to reach 366 million by 2030 [2]. Impaired Insulin resistance, insulin secretion and hepatic glucose over-creation are

possibly related causes of diabetes [3]. Insulin resistance do not merely play a critical role in diabetic problems, but also in dyslipidemia, atherosclerosis and hypertension [4]. Generally, diabetes mellitus is involved in various organ impairment linked disorders including cataract, atherosclerosis, retinopathy, nephropathy and wound restorative impedance [5]. Because of cost of therapy with the various hypoglycemic reagents and insulin commonly used to treat the disease and the unwanted side effects associated with these medications, dietary control is recommended among one of various approaches and techniques required to prevent the diseases.

Results of different studies revealed that some plants and their byproducts are useful in treating chronic diseases such as diabetes, cardiovascular disease and cancer [6]. Acetic acid is considered as main component of vinegar and it is responsible for its biting odor, tart flavor and pungent smell [7,8]. Acetate thiokinase, changes the acetic acid to acetyl-coA and is consequently assimilated as citrate. *In vitro,* the activity of phosphofructokinase is inhibited by citrate but *in vivo,* citrate increase the repletion of glycogen after meticulous exercise [9]. In 1988, it was revealed for first time that vinegar can be used to cure diabetes. Different animal trials showed that consumption of different doses of acetic acid or vinegar produced fluctuating effects from reduction of hypertension and improvement of glycogen repletion to activation of calcium captivation [10,11]. One study showed that white vinegar decreased both insulin levels and postprandial blood glucose [12]. Similarly, another study revealed that intake of apple cider vinegar enhances postprandial insulin sensitivity [13]. Dates vinegar has a variety of flavones and other polyphenols. Dates contain high quantity of anthocyanins, carotenoids and polyphenolic compounds [14]. Extracts of the fruit are used in the prevention of hyperglycemia, hypercholesterolemia, hypertension, and lipoproteins oxidation by reducing the oxidative stress and inflammation on vascular system. The health potentials of dates fruits have been credited to their bioactive compounds, trace elements, vitamin C, tannins, lignins, flavones and other polyphenols especially phenolic acids [15-17].However, no study has explored the beneficial outcomes of dates vinegar consumption against type 2 diabetes.

In this study, the objective was to evaluate the effects of dates vinegar on blood biochemical and hematological parameters in type 2 diabetic subjects.

EXPERIMENTAL

Experimental samples

Red date vinegar was provided by Liyang Bask Vinegar Co., Ltd (Hebei, P.R. China). It contained 38.9 % of total polysaccharides. Spectrophotometric technique used for standardization indicated that it contained heavy metal (< 6 ppm), arsenic (<1 ppm), cadmium (0.1 ppm) and lead (<2.5 ppm).

Subjects and study design

Following approval by the Institutional Review Board of Minhag University Lahore (Pakistan), 60type 2 diabetic patients (fasting blood sugar (FBS)>126 mg/dL, 1 antidiabetic drug/daily), aged 30-60 years, 29 females and 26 males weighing between 55 to 75 kg, who visited an Al-Rashid Clinic Lahore in Pakistan and volunteered to participate in this study were recruited. Those with hepatic, renal, asthmatic or cardiovascular diseases, vinegar intolerance or consumed alcohol were excluded. The patients were randomized into a group (30 patients) that consumed20 ml of dates vinegar with their normal diet preferably in the morning (or before bedtime) or the placebo group (30 patients) that received20 ml of honey diluted with water using a randomization scheme with blocks of 5 patients for 10 weeks. Throughout the trial, the participants consumed foods with similar energy levels, carbohydrates, cholesterol, proteins and fats from the beginning to the end.

Collection of blood and biochemical analyses

The type 2 diabetic patients were exposed to thorough history and clinical evaluation after written informed consent. Blood samples (5 ml each) were collected at baseline, 5 weeks and at 10 weeks, centrifuged at a speed of 3500 rpm for 15 minutes after allowing to clot and the serum obtained was analyzed for both the biochemical and hematological parameters. Biochemistry automated analyzer (Metro lab 2300 PLUS, Vital Scientific B. V., Netherlands), was used to analyze FBS, triglyceride (TG), high density lipoprotein(HDL), urea and creatinine concentrations according to the manufacturer's instruction while LDL concentration was analyzed using Fried Ewald formula [18]:

LDL-C = TC – HDL-C – TG/5 …….. Eq.1

Hematological automated analyzer (Sysmex XS 1000i™, Roche, Basel, Switzerland)) was used

to measure white blood cell (WBC), red blood cell (RBC), mean cell volume (MCV), mean cell hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hematocrit (HCT) and platelets (PLT)[20,21]. HPLC, composed of Rheodyne injector model 7161 (Rheodyne Co., CA, USA), degasser DG- 440 (Phenomenex Co., Torrance, CA, USA), photodiode-array detector Jasco MD-915 (Tokyo, Japan) and an Agilent UV- detector model 1100, was used to analyze folate and HbA1c concentrations [19,20].

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 21.0.0 (SPSS Inc., IBM) was used to analyze the data using one-way analysis of variance (ANOVA). Variations in experimental and placebo groups were determined by the paired t-test. All statistical outcomes with a p value of less than 0.05 were deliberated as statistically significant. The values were expressed as mean ± SD.

RESULTS

Subject characteristics and diet monitoring

Of the 60 patients recruited for this study, five participants (2 in the date vinegar group and 3 in the placebo group) were excluded from the data analyzed because of protocol variance (n=3) or consent withdrawal (n=2) Figure 1. No serious side effects were observed during the trial. The baseline data for the patients are provided Table 1.

Effect of dates vinegar consumption on various blood biochemical factors

As from the (Table 3), it can be seen that fasting blood sugar (FBS**)**, cholesterol and LDL showed statistically significant reduction (P<0.05) in dates vinegar group while folate and HDL significantly increased. , however no significant difference was observed in placebo group. MCH and MCV values decreased, while PLT (P<0.005) enhanced in date vinegar group. Slight variations were also observed in RBC, WBC, hemoglobin, MCHC and HCT (Table 4).

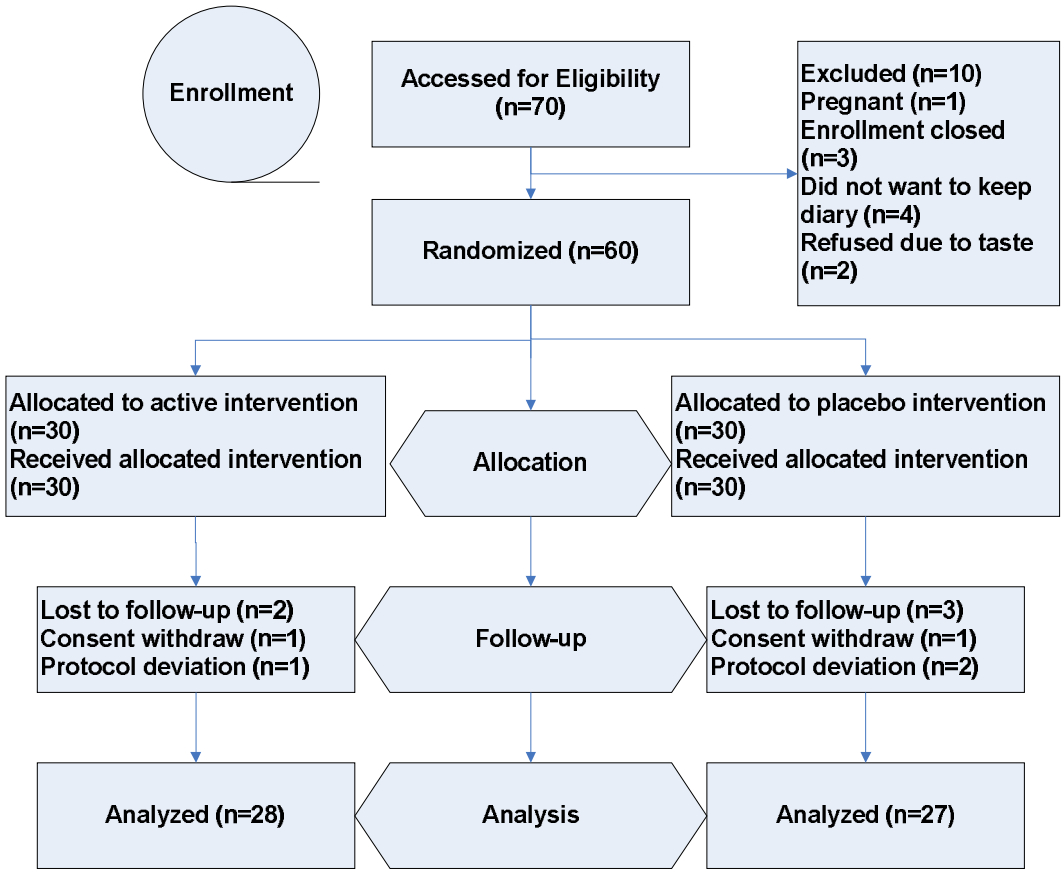

Figure 1: Flow diagram

Table 1: Baseline characteristics of subjects who completed the intervention trial

Variable	Vinegar group (n=28) Mean ± SD	Placebo group (n=27) Mean ± SD	P-value
Age	46.4 ± 1.5	48.6 ± 1.6	0.221
Female/ male (n)	15/13	14/13	0.278
BMI (Kg/m2)	24.2±0.4	23.3± 0.5	0.389
Systolic BP (mmHg)	122.1 ± 1.5	121.0 ± 1.9	0.463
Diastolic BP (mmHg)	75.3± 1.4	76.5 ± 1.6	0.343
Cholesterol (mg/dL)	218.30 ± 3.5	216.28±3.5	0.234
Triglycerides(mg/dL)	198.25±4.4	190.20.1±4.2	0.014
HDL -C (mg/dL)	43.4 ± 4.0	42.5±5.0	0.178
LDL –C (mg/dL)	122.4 ±4.9	118.4±4.8	0.032
Urea (mg/dL)	35.50 ± 5.6	33.48±4.5	0.012
Creatinine(mg/dL)	0.848 ± 0.4	0.845±0.7	0.171
Potassium(mEq/L)	2.98 ± 0.3	2.91 ± 0.7	0.247

Values are expressed as mean ± SD. No significant difference as compared with the initial ($p<0.05$). BMI; body mass index; BP, blood pressure; HDL-C high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol VLDL-C very low-density lipoprotein cholesterol.

Table 2: Mean daily intake of energy and selected nutrients at baseline and after intervention

Nutrients	Vinegar group		Placebo group		P values	
	Before[a]	After[b]	Before[c]	After[d]	ab	cd
Energy (kcal)	1546 ± 39	1457 ± 34	1458 ± 56	1502 ± 29	0.131	0.129
Carbohydrate (g)	254.9 ± 6.6	251.5 ± 5.7	246.7 ± 6.5	249.5 ± 5.4	0.451	0.376
Protein (g)	62.2± 4.3	60.6 ± 4.2	58.7 ± 2.4	56.1 ± 2.3	0.261	0.158
Total fat (g)	39.7 ± 4.6	37.2 ± 4.7	36.8 ± 2.6	36.5 ± 2.7	0.104	0.202
Dietary fibers (g)	17.6 ± 1.3	23.8 ± 1.5 *	17.5 ± 1.4	19.9 ± 1.6	0.001	0.511
Saturated Fat (g)	5.8 ± 0.8	4.4 ± 0.5	3.9 ± 0.5	4.1 ± 0.7	0.418	0.247
Monounsaturated Fat (g)	7.5 ± 0.8	7.1 ± 0.4	6.8 ± 0.5	6.7 ± 0.7	0.382	0.424
Polyunsaturated Fat (g)	4.2 ± 0.6	3.7 ± 0.8	3.5± 0.8	3.9 ± 0.6	0.534	0.304
β-carotene (mg)	2.64± 0.8	3.81±0.7	2.28± 0.6	2.48± 0.4	0.142	0.328
Cholesterol (mg)	218.2 ± 6.7	190.4 ± 6.5*	215.8 ± 5.7	219.3 ± 5.9	0.001	0.217

Intakes of test products were included in the analysis and estimated from three-day food records. Values are expressed as mean±SD. *Significant difference as compared with placebo group.[ab]$P>0.05$; [cd]$P>0.05$.

DISCUSSION

This is first evidence based study that showed that continuous intake of dates vinegar reduces the HbA1c and FBS levels in patients of type 2 diabetes but increased folate levels in blood. In agreement with our findings, Mahmoodi et al. (2011) revealed that white vinegar consumption by type 2 diabetic patients reduced HbA1c and improves various biochemical factors like total cholesterol and LDL as compared to placebo. Similarly, one researcher showed that regular consumption of vinegar reduced the HbA1c (0.16%) concentration in experimental subjects as compared to control [21]. In the small intestine, acetic acid, major component of dates vinegar, stalled the starch molecules digestion completely via blocking the activity of disaccharides and also reduces uptake of glucose through muscle performance. Intake of 0.2 per 100 grams of acetic acid decreased accretion of xylulose-5- phosphate (Xu-5-P) in

Table 3: Effects of dates vinegar consumption on various biochemical factors

	Dates vinegar group			Placebo group		
Variable	**Baseline**	**After 5 weeks**	**After 10 weeks**	**Baseline**	**After 5 weeks**	**After 10 weeks**
HbA1c *(%)*	6.80 ±2.34	6.54 ± 2.31	6.17 ± 2.14	6.55 ± 3.25	6.67 ± 3.65	6.72 ± 4.16
FBS (mg/dL)	171.43 ±3.74	159.36 ± 4.61 *	147.56 ± 3.86 *	164.43 ± 2.64	169.51 ± 2.73	168.65 ± 2.23
Cholesterol(mg/dL)	218.10 ± 3.9	198.12 ± 3.11 *	191.14 ± 3.7*	213.1 ± 4.6	209.3 ± 4.8	211.4 ± 4.9
HDL (mg/dL)	41.7 ± 4.7	44.1 ± 4.6*	47.5 ± 4.5*	40.5 ± 3.5	42.3 ± 3.3	41.4 ± 3.9
LDL(mg/dL)	117.14 ± 3.6	102.16 ± 3.5*	97.15 ± 3.7*	114.16 ± 2.6	118.20 ± 2.2	121.12 ± 2.4
Triglyceride(mg/dL	213.30±4.4	211.21±4.5	207.17±4.7	209.4 ± 5.7	213.1 ± 5.6	214.5 ± 5.8
VLDL(mg/dL)	46.90 ± 3.7	46.10 ± 3.6	45.44 ± 3.5	43.64 ± 3.8	43.62 ± 3.7	44.48 ± 3.9
Urea (mg/dL)	37.11 ± 4.4	35.13 ± 4.4	34.16 ± 4.2	39.86 ± 3.4	38.5 ± 3.3	39.3 ± 3.4
Creatinine (mg/dL)	0.843 ± 3.6	0.841 ± 3.7	0.839± 3.4	0.848 ± 5.6	0.850 ± 5.9	0.849 ± 6.1
Folate (nmol/ L)	34.6 ± 6.6	37.6 ± 6.7*	41.7 ± 6.5*	35.4 ± 5.8	37.6 ± 5.6	38.1 ± 5.7
ALT (IU/L)	24.94 ± 5.03	22.93± 4.08	21.88±5.08	25.76 ± 6.06	24.85 ± 6.04	25.78 ± 6.09
AST (IU/L)	30.86± 4.09	29.44±3.06	28.53±3.08	31.98 ± 4.07	31.99 ± 4.01	31.77 ± 4.00
ALP (IU/L)	264.32 ±5.26	260.36± 4.28	259.30±4.21	267.54 ± 3.32	268.48 ± 3.41	271.24 ± 3.26
Potassium (mEq/ L)	2.98 ± 1.7	2.73 ± 1.8	2.85 ± 1.6	2.91 ± 1.5	2.86 ± 1.3	2.81 ± 1.4

Variables are expressed as mean ± SD. * p< 0.05 when compared with baseline. HDL; High density lipoprotein, LDL; Low density lipoprotein, ALP; Alkaline phosphatase, VLDL; Very low density lipoprotein

Table 4: Effects of dates vinegar on various hematological factors

	Dates Vinegar group			Placebo group		
Variable	**Baseline**	**After 5 weeks**	**After 10 weeks**	**Baseline**	**After 5 weeks**	**After 10 weeks**
WBC(n/ml)	8923.04±1217	9245.25±1085	9515.38±1510	9014.05±1432	9145.1674±1241	9168.1811±1123
RBC (mil/ml)	5.512±0.458	5.524±0.44	5.608±0.42	5.413±0.31	5.418±0.331	5.425±0.32
Hemoglobin (g/dl)	14.11±3.26	14.45±3.31	14.88±3.46	14.25±2.43	14.30±2.52	14.33±2.21
HCT (%)	44.34±4.542	44.84±4.49	45.25±4.51	45.12±4.33	45.74±4.341	45.98±4.36
MCV (fl)	87.11±5.304	84.65±5.43	80.44±5.53	88.04±4.32	88.24±4.344	88.79±4.35
MCH (pg)	26.55±3.5	24.86±3.1	21.45±3.3	25.31± 3.8	25.44 ±3.4	25.02±3.2
MCHC (%)	28.67±1.44	28.88±1.32	29.35±1.43	29.25 ± 1.34	29.41 ±1.25	29.36 ± 1.47
PLT (n/ml)	256076±31584	284742±45264	318307±62581	258934±34273	256831±41156	254365±49187

Variables are expressed as mean ± SD. No significant difference as compared with the baseline (p<0.05)
RBC; Red blood cells, WBC; White blood cells, HCT; Hematocrit, MCHC; Mean cell hemoglobin concentration, MCV; Mean cell volume, MCH; Mean cell hemoglobinPLT; Platelets

liver and activity of phosphofructokinase-1 (PFK-1) in skeletal muscles [9]. Acetic acid also slows down the rate of gastric emptying [22]. Enhancement of free fatty acids in subjects having impaired glucose tolerance, presupposes that insulin resistance connected with enhanced free fatty acids befalls earlier the inception of hyperglycemia [23]. Results of one trial conducted in non-diabetic subjects reveled that reduced glucose exploitation in muscles was connected with severe raise of free fatty acids [24]. Some experiments also showed association among insulin resistance and levels of free fatty acids [25,26]. During the manifestation of insulin resistance, free fatty acids in the form of triglycerides are stored in heart, liver, pancreas

and muscle. Particularly, agents that reduced enhanced levels of free fatty acids, like thiazolidinedione's, have been exposed to up-regulate insulin sensitivity in liver, adipose tissue and muscle. As, outcomes of our study showed that regular consumption of dates vinegar reduces lipid profile parameters hence, we can say that dates vinegar might be involved in improving insulin sensivity by reducing the free fatty acids levels.

High level of fructose and fiber content in dates might be interconnected with reduced level of glycemic index (GI). The results of one study revealed that regular consumption of rutab dates enhanced the GI and suggested that high content of rutab dates hydration affects gastric emptying, insulin secretion or intestinal absorption [27]. Similarly, results of various studies showed that ingestion of dietary fibers applies physiological effects on the small intestine and stomach that curb postprandial glycemic responses, comprising adjourning small bowel passage and modifying myoelectric commotion of gastrointestinal way, suspending gastric emptying lessening the availability of α-amylase to its substrate because of enhanced gut contents viscosity, and decreasing diffusion of glucose via callous water layer gel forming and enhanced viscosity chattels of fibers are primarily accountable for its glycemic effect. Because of reformed levels of incretin, soluble fibers prolonged the carbohydrates absorption in intestine along with enhanced levels of glucagon-like peptide 1 (GLP1) [28-30]. Soluble dietary fibers also affect the uptake mechanisms of glucose via periphery, comprising enhanced skeletal muscle manifestation of the insulin-responsive glucose transporter type 4 (GLUT-4), which increases skeletal muscle upregulation, enhances sensitivity of insulin and regularizes blood glucose [31]. Several fatty acids in humans stimulate the manifestation of peroxisome proliferator-activated receptor-γ (PPARG), which enhances levels of adipocyte GLUT-4 [32]. During metabolic disorders the levels of hepatic enzymes like ALT and AST increased and thus resulted in atherosclerosis [33]. In our study the levels of ALT, AST and ALP reduced at the end of trial in the experimental group. While, the results of one study showed that the activity of liver AST and ALP in the animals treated with the vinegar decreased and elevated, respectively [34].

Current results showed slight variations in the number of RBC, WBC count and its allied indices like Hb, MCHC, MCV, MCH and platelets. Total RBC and Hb along with platelets increased at the end of study. While, results of one study showed that no substantial variations were observed in these variables after ingestion of vinegar [35]. The increase in total RBC and Hb might be due to high content of folate in dates.

In summary, this study indicates that date vinegar improves the concentration of HbA1c, FBS and lipid profile, and/or potentiates the capacity of anti-glycemic remedies in type 2 diabetic subjects. The limitations of this study include several proposed molecular mechanisms through which date vinegar may exert its effect were not measured directly. More studies are required to substantiate these preliminary outcomes. During the trial, neither deformity of kidney or liver functions nor adversative outcomes were noted. As regular consumption of dates vinegar (20 mL) for 10 weeks in diabetic patients was testified not to cause side effects, dates vinegar consumption is supposed to be safe in type 2 diabetic patients.

CONCLUSION

Conclusively based on the present outcomes, it can be decided that dates vinegar is beneficial as a therapeutic agent in diabetes, without producing side effects. Intake of 20 mL of dates vinegar on daily basis was adequate to attain these effects. Dates vinegar might be considered helpful for precluding metabolic syndrome by reducing diabetes and its related complications. However, more experiments are required to discover both its disadvantages and advantages as a tool for directing type 2 diabetes.

DECLARATIONS

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Conflict of interest

The authors declare that they have no conflict of interest with regard to this work.

Authors' contribution

We declare that this work was performed by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All the

authors listed in this manuscript contributed equally, and read and approved the manuscript.

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