Original Article *Internal Medicine*

Medical Journal of Islamic World Academy of Sciences
doi: 10.5505/ias.2017.37888 2017;25(2): 40-49

A Comparative Clinical Study of Unani Formulation (Maghz Tukhm-e-Jamun wa Tukhm-e-Hayat) and Metformin in the Management of Ziabetus Shakari (Type 2 Diabetes Mellitus)

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ABSTRACT

Type 2 diabetes mellitus is a major health concern in the 21st century, which is largely preventable but remains responsible for millions of deaths annually and many life-threatening complications. The present study was conducted to evaluate and compare the efficacy of Withania coagulans *Dunal and* Eugenia jambolana *Lam with that of standard control metformin in managing type 2 diabetes mellitus.*

This was a randomized open study with standard control. A total of 60 diagnosed cases of type 2 diabetes mellitus were randomly allocated in the test (n = 30) and control groups (n = 30). Test drug, a combination of E. jambolana *(6 g in powder form) and oral infusion of* W. coagulans *(10 pieces), and control drug metformin (500 mg) were administered to the participants twice daily for 90 days. The subjective parameters were assessed at every follow-up, blood sugar was recorded at a monthly interval, while hemoglobin A1c, RFT, and lipid profile were recorded at baseline and at the termination of the trial. The study outcome was analyzed using appropriate statistical tests. The test drug showed significant improvement at par to the control drug in subjective (polydipsia, polyphagia, fatigue, and weight loss) and objective (blood sugar, glycated hemoglobin, RFT, serum cholesterol, and serum triglyceride) parameters without any side effects or toxicity. The study inferred that the drug was safe and effective in managing type 2 diabetes mellitus.*

Key words: Eugenia jambolana, type 2 Diabetes mellitus, Withania coagulans, Ziabetus Shakari

INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiology, characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both (1). The cost of diabetes care is high and escalating worldwide. The number of people with diabetes is increasing in every country. Half of the people with diabetes are not aware that they have it, and four out of five people with diabetes live in low- and middle-income countries. Half of the people who die from diabetes are aged less than 60 years (2,3).

According to the World Health Organization, the prevalence of diabetes in adults has increased worldwide, and the number is expected to rise from 135 million in 1995 to 300 million by the year 2025 (4). According to Rao et al., 32 million patients had diabetes in India in 2005, which might increase to 80 million by the year 2030 (5). According to Madras Diabetes Research Foundation, Chennai, this disorder is the most prevalent in South Asia, especially in India, which has earned the unwelcome title of the "Diabetes Capital" of the world with 41 million individuals with diabetes (6). The number of people living with diabetes in India currently is around 69.2 million (7).

This disorder is frequently associated with long-term complications such as atherosclerosis, ischemic heart disease, chronic renal failure, and ketoacidosis. It is a leading cause of morbidity and mortality owing to its complications. Due

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to these complications, diabetes has become a global concern despite tremendous advancements in modern medical science. Several distinct types of diabetes mellitus exist caused by a complex interaction of genetic and environmental factors. Factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The associated metabolic dysregulation causes secondary pathophysiologic changes in multiple organ systems, which imposes a tremendous burden on the individual and the health care system (3).

Ziabetus Shakari is characterized by excessive thirst, excessive urination, (8,9,10) presence of sugar in urine, increased appetite, gradual loss of body weight, and so forth (10,11). Decreased sexual functions and gangrene are noted as complications of Ziabetus Shakari (11). The main causes of Ziabetus Shakari are sue mizaj haar (extreme hot derangement of temperament) and weakness of quwwate maseka (retentive power) of the kidney (8,12) Hararate naria, (11) sue mizaj barid (cold derangement of temperament) of the kidney or whole body, zoafe gurda (weakness of the kidney), and dilatation of ducts and vessels of the kidney (13).

Several antidiabetic agents are already being used to manage diabetes mellitus, such as glibenclamide, gliclazide, glipizide, metformin, and so forth,(14,15) but these drugs are associated with certain side effects. Therefore, search for safe and effective drugs is a hot area of research, particularly in the Unani system of medicine.

Unani scholars have described many effective single and compound antidiabetic drugs in classical texts, but many of them have not yet been explored in terms of scientific parameters. The present study was conducted keeping in view the aforementioned factors.

MATERIALS AND METHODS

This randomized open study with standard control was conducted at Ajmal Khan Tibbiya College Hospital, Aligarh Muslim University, Aligarh, India, for a duration of 18 months from January 2015 to June 2016. Ethical approval was obtained from the Institutional Ethical Committee on 18-12-2014 before the commencement of the trial. Sixty patients diagnosed with type 2 diabetes mellitus who fulfilled the inclusion criteria and gave their voluntary written informed consent were enrolled in the study. The study population was randomly allocated using a simple randomization technique (computer-generated randomization sheet) in 2 groups, 30 in the test group (Group A) and 30 in the control group (Group B) (Figure 1).

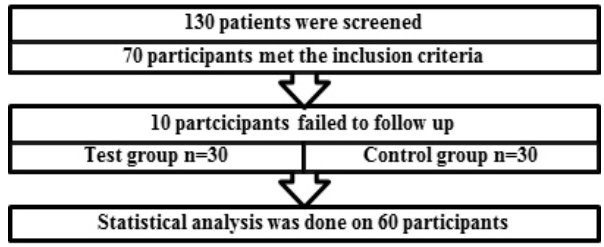

Figure 1: Schematic presentation of the study population.

Patients with type 2 diabetes mellitus of either gender aged 40–60 years meeting the following criteria were included in the study: fasting blood sugar >126 mg/dL, postprandial blood sugar >200 mg/dL, hemoglobin A1c (HbA1c) >7%, and consent to participate in the study and follow the instructions. Exclusion criteria were pregnancy and lactation, malnutrition-related diabetes mellitus, complications of diabetes mellitus (diabetic ketoacidosis, retinopathy, neuropathy, nephropathy, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and liver disease), and impaired organ functions.

The subjective parameters (polyphagia, polyuria, nocturia, chronic fatigue, rapid weight loss, paresthesia, erectile dysfunction, and genital candidiasis) were assessed at every follow-up. The objective parameters were assessed on reduction in blood sugar, glycated hemoglobin, glycosuria, and microalbuminuria. Blood sugar (fasting and postprandial) investigation was done monthly; HbA1c, serum total cholesterol, serum triglyceride, blood urea, and serum creatinine were measured at baseline and after completion of the clinical trial. A total of 70 participants were enrolled, of which 10 failed to report on subsequent visits due to personal reasons and were therefore excluded from the study.

Clinical (signs and symptoms) and biochemical assessments were done at regular intervals during the study. The duration of the study was 90 days, and the follow-up was carried out at the interval of 15 days, that is, on the 0th, 15th, 30th, 45th, 60th, 75th, and 90th days. No adverse effect was noted during the course of the clinical trial. Good clinical practice was followed during the study.

Test Drug (16-24)

Maghz-Tukhm-e-Jamun (Syzygium cumini/Eugenia jambolana) and Tukhm-e-Hayat (Withania coagulans): the single drugs were procured from Dawakhana Ajmal Khan Tibbiya College, and their identification was established by the competent staff of the college and preserved in the departmental seminar room at room temperature. Maghz-Tukhm-e-Jamun was ground into a fine powder and administered at a 6 g dose. Khesanda (infusion) of Tukhm-e-Hayat (10 pieces soaked in 150 mL of water twice a day) was given to the test group for 90 days.

Standard Drug (14,15,25,26,27)

Metformin tablet (500 mg) was purchased from the open market (Glyciphage, Franco-Indian) and administered to the control group twice a day for 90 days.

Both the groups were advised brisk walk for 30 min per day and dietary restriction as per the Indian Council of Medical Research guidelines (28,29).

Statistical Analysis

Objective parameters were analyzed using the paired t test for intragroup comparison and the unpaired t test for intergroup comparison. Subjective parameters were analyzed using the chi-square test.

The result was considered significant at $P < 0.05$.

OBSERVATIONS AND RESULTS

The baseline demographic data is depicted in Table 1. The effect of interventions on the subjective parameters is shown in Table 2. The statistical analysis on objective parameters is given in Tables 3–7.

TABLE 1: Demographic data.

Attribute	Test group (*n*=30)	Control group (*n*=30)
Age		
40–45	10	10
45–50	4	6
50–55	5	4
55–60	11	10
Gender		
Male	11	12
Female	19	18
Diet		
Vegetarian	4	6
Mixed	26	24
*Socio-Economic Status		
Upper	6	5
Middle	16	17
Lower	8	8
Mental Stress		
Positive	10	11
Negative	20	19
Family History of DM		
Positive	12	11
Negative	18	19

*SES: Kuppaswamy Socio-economic Status

DISCUSSION

The present study was conducted to evaluate the efficacy of test drugs in the patients with type 2 diabetes mellitus. A higher prevalence of type 2 diabetes mellitus was found in the age group 50–60 years (50%) in this study. It inferred that the prevalence of the disease was higher in later life. Out of 60 patients, 37 (61.66%) were females and 23 (38.33%) were males. The predominance of female patients may be attributed to lack of exercise, menopause, and central obesity, which are the risk factors for the pathogenesis of type 2 diabetes mellitus (30-33).

Socioeconomically, a majority of cases belong to middle and lower classes in the Indian community. Moreover, mental stress is more common in this population owing to their livelihood-related problems.

According to the dietary pattern, 10 (16.67%) patients were vegetarian and 50 (83.33%) had mixed diet. The probable

Table 2: Effect of drugs on subjective parameters.

Polydipsia	0th day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (*n*=30)							
No. of patients	13	12	12	8	7	4	2
% improved	–	7.69	7.69	38.46	46.15	69.23	84.61
Control group (*n*=30)							
No. of patients	10	10	8	7	5	3	2
% improved	–	–	20	30	50	70	80
$\chi^2 = 0.084$ ($P = 0.772$)							

Polyphagia	0th day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (*n*=30)							
No. of patients	11	10	8	7	5	3	1
% improved	–	9.01	27.27	36.36	63.64	72.73	90.90
Control group (*n*=30)							
No. of patients	12	11	10	8	5	3	3
% improved	–	8.33	16.67	33.33	58.33	75	75
$\chi^2 = 0.207$ ($P = 0.649$)							

Polyuria	0th Day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (*n*=30)							
No. of patients	23	21	18	15	11	5	3
% improved	–	8.67	21.73	34.78	52.14	78.26	86.96
Control group (*n*=30)							
No. of patients	24	22	20	15	11	7	4
% improved	–	8.33	16.67	29.16	54.67	70.83	83.33
$\chi^2 = 0.122$ ($P = 0.727$)							

Nocturia	0th day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (*n*=30)							
No. of patients	25	22	19	16	10	7	3
% improved	–	12	24	36	60	72	88
Control group (*n*=30)							
No. of patients	27	24	21	17	12	8	5
% improved	–	11.11	22.22	37	62.96	70.37	81.48
$\chi^2 = 0.071$ ($P = 0.790$)							

Chronic fatigue	0th day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (*n*=30)							
No. of patients	25	24	22	18	14	9	5
% improved	–	4	12	28	44	64	80
Control group (*n*=30)							
No. of patients	20	17	15	12	9	5	4
% improved	–	15	25	40	55	75	80
$\chi^2 = 0.000$ ($P = 1.000$)							

Table 2: Continue.

Rapid weight loss	0th day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (*n*=30)							
No. of patients	14	14	12	10	9	6	4
% improved	–	–	14.28	28.57	35.71	57.14	71.43
Control group (*n*=30)							
No. of patients	10	10	9	8	7	4	4
% improved	–	–	10	20	30	60	60
$\chi^2 = 0.021$ ($P = 0.884$)							
Paresthesia	0th day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (*n*=30)							
No. of patients	5	5	4	4	3	2	2
% improved	–		20	20	40	60	60
Control group (*n*=30)							
No. of patients	6	6	5	4	4	2	2
% improved	–	–	16.67	33.33	33.33	66.67	66.67
$\chi^2 = 0.052$ ($P = 0.819$)							
Erectile dysfunction	0th day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (*n*=30)							
No. of patients	4	4	4	3	3	2	2
% improved	–	–	–	25	25	50	50
Control group (*n*=30)							
No. of patients	3	3	3	3	2	2	2
% improved	–	–	–	–	33.33	33.33	33.33
$\chi^2 = 0.194$ ($P = 0.659$)							
Genital candidiasis	0th day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (n=30)							
No. of patients	3	3	3	3	2	2	1
% improved	–	–	–	–	33.33	33.33	66.67
Control group (*n*=30)							
No. of patients	5	5	5	4	4	3	3
% improved	–	–	–	20	20	40	40
$\chi^2 = 0.533$ ($P = 0.465$)							

Table 3: Effect of Unani formulation and metformin on fasting blood sugar.

Control group (*n*=30)					Paired *'t'* test
Fasting blood sugar	0th day (mg %)	30th day (mg %)	60th day (mg %)	90th day (mg %)	Intra-group comparison at baseline and 90th day
Mean+SD	161.4±19.17	152.7±20.37	142.6±17.14	129.7±15.22	t = 14.05 P < 0.0001
% of fall	-	5.4	11.65	19.64	
Test group (*n*=30)					
Mean+SD	163.1±28.56	150.13±31.27	147.03±27.2	122.47±20.93	t = 12.67 P < 0.0001
% of fall	-	7.95	9.85	24.91	
	Unpaired *'t'* test		t = 1.531, P = 0.1312		

Table 4: Effect of Unani formulation and metformin on fasting blood sugar.

Control group (*n*=30)					Paired *'t'* test
Postprandial blood sugar	0th day (mg %)	30th day (mg %)	60th day (mg %)	90th day (mg %)	Intra-group comparison at baseline and 90th day
Mean+SD	249.5±49.02	233.37±40.34	221.83±44.09	210±42.02	t = 8.96 P < 0.0001
% of fall	–	6.46	11.09	15.83	
Test group (*n*=30)					
Mean+SD	244.8±40.5	226.47±40.88	216.2±40.14	200.37±38.84	t = 7.36 P < 0.0001
% of fall	–	7.49	11.63	18.14	
	Unpaired *'t'* test		t = 0.9221, P = 0.3603		

Table 5: Effect of Unani formulation and metformin on glycated haemoglobin.

HbA1c	Control group (*n*=30)		Test group (*n*=30)	
	0th day	90th day	0th day	90th day
Mean+SD	8.66±0.87	7.85±0.56	8.42±0.99	7.62±0.89
	Paired *'t'* test t = 9.23, P < 0.0001		Paired *'t'* test t = 7.64, P < 0.0001	
	Unpaired *'t'* test	t = 1.215, P = 0.2294		

Table 6: Effect of Unani formulation and metformin on RFT.

	Control group (*n*=30)		Test group (*n*=30)		Unpaired *t* test
Blood urea	0th day	90th day	0th day	90th day	t = 0.1064 P = 0.1064
Mean±SD	28.83±5.80	27.67±4.36	28.9±4.84	25.9±3.98	
	Paired 't' test t= 2.02, p= 0.0527		Paired 't' test t= 6.35, p< 0.0001		
Serum creatinine					t = 0.8640 P = 0.3911
Mean±SD	0.92±0.08	0.90±0.07	0.92±0.06	0.88±0.05	
	Paired *'t'* test t = 4.62, P < 0.0001		Paired *'t'* test t = 5.96, P < 0.0001		

Table 7: Effect of Unani formulation and metformin on cholesterol and triglycerides.

	Control group (*n*=30)		Test group (*n*=30)		Unpaired *'t'* test
Total cholesterol	0th day	90th day	0th day	90th day	*t* = 0.1479, *P* = 0.8830
Mean + SD	190.87±48.15	177.37±43.24	193.07±40.67	175.9±32.89	
	Paired *'t'* test *t* = 5.67, *P* < 0.0001		Paired *'t'* test *t* = 7.18, *P* < 0.0001		
Serum triglycerides					t=0.5383 p=0.5925
Mean + SD	166.83±46.19	155.03±16.64	173.77±31.34	160.03±28.90	
	Paired *'t'* test *t* = 5.12, *P* < 0.0001		Paired *'t'* test *t* = 4.23, *P* < 0.0001		

Table 8: Effect of Unani formulation and metformin on glycosuria.

Glycosuria	0th day	15th day	30th day	45th day	60th day	75th day	90th day
Test group (n=30)							
No. of patients	30	27	23	15	12	9	3
% improved	–	10	23.33	50	60	70	90
Control group (*n*=30)							
No. of patients	30	30	26	22	17	12	2
% improved	–	–	13.33	26.67	43.33	60	93.33
$\chi^2 = 0.1847$ ($P = 0.6674$)							

Table 9: Effect of Unani formulation and metformin on microalbuminuria.

Microalbuminuria	Control group (*n*=30)		Test group (*n*=30)	
	0th day	90th day	0th day	90th day
No. of patients	5	2	4	2
% improved		60		50
$\chi^2 = 0.03439$ ($P = 0.8529$)				

reason behind a higher prevalence of type 2 diabetes mellitus in nonvegetarians may be the use of smoked meat, less dietary fiber, and cellulose (32).

The study revealed that positive family history was associated with increased prevalence of type 2 diabetes mellitus in the younger population. Genetic predisposition may be a major cause of type 2 diabetes mellitus (32,33).

It was observed that 45 (75%) had a negative history of mental stress and only 15 (25%) had a positive history. This might be attributed to the psychological factors inducing an increment in the levels of growth hormones, adrenaline, noradrenaline, and cortisol, which results in increased rate of glycolysis and gluconeogenesis, and consequently type 2 diabetes mellitus (74).

The study revealed that 48 (80%) of 60 patients had negative history of physical exercise, indicating that type 2 diabetes mellitus was more prevalent in physically inactive individuals. The probable reason was insulin resistance.

Highly significant improvement was observed in subjective parameters such as polydipsia (84.61%), polyphagia (90.90%), polyuria (86.96%), nocturia (88%), rapid weight loss (71.43%), chronic fatigue (80%), genital candidiasis (66.67), erectile dysfunction (50%), and paresthesia/tingling sensation (60%).

The efficacy of Unani formulation on subjective parameters might be due to a reduction in blood sugar levels, as both the drugs exerted anti-hyperglycemic activity synergistically with antioxidant properties inherent in them, especially Jamun (16-24,34-44).

Initially, glycosuria was present in every patient of both groups at baseline; only three patients showed the presence of sugar in the urine at the end of the study, and 50% improvement in microalbuminuria was recorded. The improvement in both the parameters might be due to blood sugar–lowering effect of W. coagulans and E. jambolana. An experiment carried out at the Central Drug Research Institute, Lucknow, showed that oral administration of dried alcoholic extracts of the seeds to patients with diabetes reduced blood sugar level and glycosuria. Fresh seeds were found superior to dried ones in this respect (45).

Fasting and postprandial blood sugar examination was done at monthly intervals depicting a marked reduction in both the levels. The possible mechanism by which Jamun seeds decreased blood sugar level might be the induction of insulin secretion from β-cells of the islets of Langerhans or its release from the bound form (34,36,38,42).

It is evident that Unani formulation has anti-hyperglycemic activity probably due to the glycoside jamboline in E. jambolana seeds, which is reported to be anti-hyperglycemic. It may also be due to ellagitannins including corilagin, 3, 6-hexa hydroxyl diphenoyl glucose and its isomer 4, 6-hexahydroxy diphenoyl glucose, 1-galloylglucose, 3-galloylglucose, gallic acid, and ellagic acid (EA), which exert antidiabetic action. The second probable reason for glycemic control by glycosides jamboline and EA is that these active substances are reported to have the ability to check the conversion of starch into sugar in case of excess production of glucose (39,45).

The mechanism of action of W. coagulans has not been completely explored; however few studies have been carried out in this regard showing its anti-hyperglycemic activity. According to Shukla et al., it might be due to enhanced secretion of insulin from existing β-cells.

The glycated hemoglobin test was performed to check the control of hyperglycemia for a period of 3 months. The test drugs showed significant results. The data conformed to the findings of Shukla et al. that aqueous W. coagulans significantly decreased HbA1c, reflecting the improvement in glycemic status as shown by decreases in FPG and PPPG.(36)

A significant effect on total cholesterol and serum triglyceride levels was reported in the test group ($P < 0.0001$). The observation was completely in accordance with the finding of Saif-ul et al. that this effect was due to the presence of flavonoids, saponins, and glycosides in the extract of E. jambolana seed, which were reported to decrease the activity of enzyme 3HMG-CoA reductase in the liver (42,43). A significant influence was also noted on blood urea and serum creatinine the in test group, implying the nephroprotective effect of the extract supported by Swami et al. (34).

CONCLUSION

The present study revealed that the test drug was safe and effective in managing type 2 diabetes mellitus. The limitations of the study were smaller sample size and limited resources and time. Randomized clinical trials with larger sample size should be conducted to further explore the effects of test drugs in managing type 2 diabetes mellitus..

ACKNOWLEDGEMENT

The authors are thankful to the Vice-Chancellor of Aligarh Muslim University, Aligarh, and Chairman, Department of Moalajat, Ajmal Khan Tibbiya College, Aligarh Muslim University, Aligarh, for providing facilities during the clinical trial.

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