



Effect of *Eugenia Jambolana* on Plasma Glucose, Insulin Sensitivity and HDL-C Levels: Preliminary Results of A Randomized Clinical Trial

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ABSTRACT

To validate scientifically a household remedy of *Eugenia jambolana* seed based drug Madhuhara churna [AVA Trust Regd] in diabetes mellitus, a use based on ethnic preferences. A 6 month parallel designed open labeled randomized, controlled trial was conducted in 30 newly diagnosed type 2 diabetes mellitus. Patients were enrolled to: Group 1 (n = 15) received Madhuhara churna [AVA Trust Regd]; Group 2 (n= 5) received metformin and Group 3 (n=10) were on diet restriction and exercise therapy only. They were followed up each month for 6 months with detailed clinical examination; assessment of compliance to drug intake, diet adherence and exercise; a complete history of adverse events; different parameters to measure the efficacy were done. There was no significant difference in the baseline characteristics of patients in each of the three groups enrolled for study. The results showed a significant decrease in fasting blood glucose at 3rd (152.0 mg/dl ± 22.5 to 140.7 mg/dl ± 26.6, P=0.016) and 6th (152.0 mg/dl ± 22.5 to 134.0 ± 21.3, P=0.043) month, homeostatic model assessment for insulin resistance at 3rd (10.3 ± 4.7 to 6.5 ± 4.1, P=0.027) month and a highly significant rise in high density lipoprotein value at 3rd (39.7 ± 9.6 to 47.3 ± 6.8, P= 0.001) month was seen in group 1 when compared to baseline values. Madhuhara churna [AVA Trust Regd] treatment in type 2 diabetic patients for 6 months has a beneficial effect in improving the glycemic profile in newly diagnosed type 2 diabetics.

Keywords: *Eugenia jambolana*; Fasting blood glucose; Homeostatic model assessment; Glycosylated hemoglobin; Diabetes mellitus

INTRODUCTION

Diabetes mellitus is a syndrome with disordered metabolism and inappropriate hyperglycemia due either to: a deficiency of insulin secretion or a combination of insulin resistance and inadequate insulin secretion to compensate [1]. In the year 2025, there will be an increase in prevalence of diabetes in developed and developing countries by 42% and 170% respectively [2]. Worldwide, various antidiabetic drugs are available for treatment of diabetes; however, challenges in metabolic control and prevention of vascular complications persist globally. Indigenous medications from plant extracts have been advocated by Ayurveda, Yunani, and Siddha prior to the discovery of insulin [3]. Some of the plants widely cultivated and used for treatment of diabetes are *Momordica charantia*, *Eugenia jambolana*, *Gymnema sylvestra*, *Trigonella foenum* and *Petrocampus marsupium* [4]. *Eugenia jambolana* Lam. (Myrtaceae) (syn. *Syzygium cumini* (L.) is commonly called 'black plum'. Parts of the plant used as medicine include fruit, leaf, dried seed and bark. The chemical constituents of *Eugenia jambolana* seed powder include ellagic acid, essential oil, gallic acid and tannic acid. Use of indigenous herbal compounds may simplify the management of diabetes and make it less expensive [5]. Clinical studies conducted previously on the antidiabetic properties of *Eugenia jambolana* seed powder in diabetic patients showed a moderate reduction in blood sugar levels. However, data on the long term efficacy of this herbal preparation in newly diagnosed type 2 diabetic patients from clinical trials is inadequate [3,6]. With this background and to validate the long history associated with the use of *Eugenia jambolana* as a house hold remedy in diabetes, this clinical trial was conducted.

Data obtained from preclinical studies on *E. jambolana* seed based drug Madhuhara churna, Abhinava Vidyatheertha Ayurveda Trust Regd [AVA Trust Regd] in streptozotocin-induced diabetic rats concluded: dose related hypoglycemia and increase in liver glycogen [7].

The primary objective of this clinical trial was to evaluate the pharmacological effects of Madhuhara churna [AVA Trust Regd] as monotherapy on plasma glucose in newly diagnosed type 2 diabetic patients who failed to respond to life style modification - diet control with exercise. The composition of the drug described, as "Madhuhara churna" is a product of *E. jambolana* seed. The secondary objectives were to evaluate: the effects of Madhuhara churna on insulin sensitivity, fasting lipid profile and to assess the safety profile of the drug.

MATERIALS AND METHODS

A single centered, open labeled, randomized parallel designed controlled study conducted in 30 newly diagnosed type 2 diabetes mellitus patients. Patients attending Medicine outpatient department of a tertiary care hospital during the study period of January 2005- August 2007, with symptoms of diabetes and who had not received any medicines for diabetes were screened. Patients diagnosed to be diabetic followed life style modification (restricted caloric intake with exercise) for 4 weeks. At the end of 4 weeks, fasting blood glucose, postprandial blood sugar, glycosylated hemoglobin (HbA_{1c}), lipid profile, fasting insulin levels and safety investigations (hemoglobin percentage, liver function tests, serum urea and serum creatinine) were performed. A total of 30 patients with elevated HbA_{1c} above the reference upper limits of normal for this laboratory (4.8-6%), fasting blood glucose > 126 mg/dl up to 200mg/dl and who provided informed consent to participate in the study were randomly assigned to three groups based on a computer generated randomization list: Group 1 (study group on Madhuhara churna [AVA Trust Regd], n = 15 patients, Group 2 (control group on standard therapy, metformin), n = 5 patients and Group 3 (control group on life style modification only), n = 10 patients. The following were not included in the study: women of childbearing potential who were not on contraceptives or did not have hysterectomy done; simultaneous participation in another clinical trial. The study duration for groups 1 and 2 was 6 months and for group 3 was 3 months as advised by Independent Ethics committee (IEC).

The *E. jambolana* seeds used for conducting the trial were collected in the month of April from the trees grown locally, dried in sunlight and seed powder

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was prepared by [AVA Trust], an Ayurvedic establishment. Specimens of the collected material used were matched with the authenticated voucher specimens; Numbers 124678, 124679 identified and deposited in the Herbarium of the Botanical Survey of India (BSI) in Pune on 13th July 2004 (7). Four batches of Madhuhara churna [AVA Trust Regd] were eluted for the percentages of ellagic acid and gallic acid. The HPTLC analysis report on percentages % (w/w) of ellagic acid were 0.17; 2.772; 1.42; 1.94 and of gallic acid were 0.33; 4.42; 4.39; 4.11.

The study was conducted in compliance with 'Ethical Guidelines for Biomedical Research on Human Subjects ICMR 2000' - conduct of trial with herbal remedies, IEC, Informed Consent regulations and ICH/GCP guidelines. Before initiating the trial, the investigator had taken written and dated approval from the IEC for the following: study protocol and written informed consent form. The IEC advised the study group that the test drug (group 1) be compared with a group that continued with lifestyle modification alone (group 3). Metformin (group 2) was introduced into the study design as a powerful and established antidiabetic 'comparator'.

Patients in: group 1 were instructed to take 5g Madhuhara churna [AVA Trust, Regd] twice daily, half an hour before food without addition of sugar or honey; group 2 received tablet metformin 500 mg dose as titrated by the registered medical physician and group 3 was advised only life style modification which was also continued in groups 1 and 2. At monthly visits patients were followed up with: detailed clinical examination; assessment of compliance to drug intake (including counting of unused sachets); diet adherence and exercise (from a compliance chart provided to each patient), record of adverse events, fasting blood glucose and postprandial plasma glucose report. In addition to this; HbA_{1c}, lipid profile, fasting insulin were done at the end of the 3rd and 6th months. Safety investigations were repeated at the end of the 6th month. Results of these values were compared with baseline values. In the event the clinical investigators felt that significant deterioration of glycemic control occurred, the patient was withdrawn from the study. The primary outcome measure was based on decrease in fasting plasma glucose measured each month over six months and on HbA_{1c} measured at the end of 3rd and 6th months of the study respectively. Secondary outcome measures were based on calculating insulin resistance and fasting lipid profile, measured at the end of 3rd and 6th months. Homeostatic model assessment (HOMA) is a useful surrogate index of insulin resistance in diabetic and nondiabetic subjects. It is calculated by using the formula fasting plasma insulin (the reference upper limits of normal for this laboratory is 2- 25µU/ml) multiplied by fasting glucose (millimol/ml) divided by 22.5. Patient with level >6.8 are considered to have insulin resistance [8]. Wilcoxon Signed Ranks test was used to analyze the association within groups for the primary and secondary end points of efficacy. For groups 1 and 2, baseline values were compared with those at the end of 3rd and 6th month; while for group 3, baseline values were compared with those at the end of the 3rd month. SPSS Version 11.5 for windows was used to analyze the data. P < 0.05 was considered statistically significant. An intention to treat analysis was used.

RESULTS

In group 1 (n = 15) two patients at the end of the 3rd month of follow-up were withdrawn from the study due to uncontrolled fasting plasma glucose levels, in group 2 (n = 5) one patient after the 3rd month was lost to follow-up and in group 3 (n=10) there were no dropouts. The baseline characteristics of patients in each of the three groups enrolled for study were comparable and are summarized in Table 1.

At the beginning of the study, the average fasting blood glucose (mg/dl) level in group 1 was 152.0 ± 22.5; this decreased significantly at the 3rd month to 140.7 ± 26.6 (P=0.016) and at the 6th month to 134.0 ± 21.3 (P=0.043). In group 2 the average fasting blood glucose (mg/dl) level decreased significantly at the 3rd month from 161.4 ± 20.1 to 128.8 ± 16.5 (P=0.043). However, the reduction was not significant at the 6th month. In group 3 there was no significant reduction in average fasting blood glucose levels. Percentage reduction of fasting blood glucose levels at 3rd and 6th in group 1 was 7.4% and 11.8%; in group 2 was 20.2% and 25.3%; in group 3 was 0.1% at 3rd month. In

group 2 there was significant reduction in average postprandial blood glucose (mg/dl) levels at the 3rd month from 270.4 ± 25.4 to 188.0 ± 13.3 (P=0.042). In groups 1 and 3, there was no significant reduction in average postprandial blood glucose levels. The average HbA_{1c} % at the beginning of the study for group 1, group 2, and group 3 was: 8.0 ± 1.3; 9.0 ± 1.3; 7.8 ± 1.4 respectively which reduced significantly to 7.6 ± 0.7 (P=0.042) and 7.3 ± 1 (P=0.026) at the end of 6 months and 3 months in group 2 and group 3 respectively. The reduction in HbA_{1c} level in group 1 at the end of the 6th was not significant. (Table 2, Table 3, Table 4)

Basal values of HOMA-IR for group 1 was 10.3 ± 4.7 which reduced significantly to 6.5 ± 4.1 (P=0.027) at 3rd month, there was also a reduction at 6th month which was not significant (Table 2). There was no significant reduction of HOMA-IR values from baseline to 3rd or 6th month in group 2 and group 3. Serum concentrations of total cholesterol, LDL-C and triglyceride levels did not differ within the group from baseline to 3rd or 6th month in all the three groups. The mean basal HDL-C (mg/dl) values at the beginning of the study for group 1, group 2 and group 3 was: 39.7 ± 9.6, 46.5 ± 5.9 and 40.3 ± 9.9 respectively. A very highly significant rise in HDL-C value to 47.3 ± 6.8 (P= 0.001) at 3rd month was seen in group 1. There was also a rise in HDL-C value in group 2 at the 3rd and 6th month which was not significant (Table 3). Finally there was no significant change in waist: hip ratio, safety parameters, compliance to drug, compliance to diet restriction and exercise in all the three groups from base line to end of the study.

Table 1: Demographic characteristics of patients at baseline

Group	Group 1	Group 2	Group 3
Age (years) (mean±SD)	54.5± 8.7	59.6± 7.3	54.6± 11.8
Sex (Male/Female)	8/7	2/3	6/4
BMI (mean±SD)	24.1± 3.9	25.5± 2.2	25.7± 2.4
Waist:hip ratio (mean±SD)	0.9 ± 0.05	0.9± 0.01	0.9± 0.01

BMI, body mass index = body weight in kilograms divided by height in meters square. BMI: 18.5-24.9 – Normal; 25-29.9 – Over weight; 30-34.9 – Class I obesity; 35-39.9 – Class II obesity; >40 – Class III (extreme) obesity [9]

Table 2: Average levels of different parameters at the beginning, after 3rd and 6th month of study in Group 1

Group 1	(mean ± SD)		P value		
	Baseline	3 month	6month	3 month	6 month
FBS	152 ± 22.5	140.7 ± 26.6	134 ± 21.3	0.016*	0.043*
PPBS	218.9± 87.2	219.6± 56.2	202.9 ± 43.8	0.754	0.424
HbA1c	8 ± 1.3	8 ± 1.43	7.6 ± 0.7	0.95	0.233
HOMA-IR	10.3± 4.7	6.5± 4.1	9.3 ± 8.5	0.027*	0.64
HDL-C	39.7 ± 9.6	47.3 ± 6.8	40.8 ± 10.86	0.001*	0.443

HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high density lipoprotein cholesterol in mg/dl; FBS, fasting blood sugar in mg/dl; PPBS, postprandial blood sugar in mg/dl; HbA1c, glycosylated hemoglobin in %; *P<0.05 when compared with baseline data

Table 3: Average levels of different parameters at the beginning, after 3rd and 6th month of study in Group 2

Group 2	(mean ± SD)		P value		
	Baseline	3 month	6month	3 month	6 month
FBS	161.4 ± 20.1	128.8 ± 16.5	120.5 ± 18.7	0.043*	0.144
PPBS	270.4 ± 25.4	188 ± 13.3	155.8 ± 49.8	0.042*	0.068
HbA1c	9 ± 1.3	7.8 ± 1.4	7.6 ± 0.7	0.08	0.042*
HOMA-IR	8.45 ± 1.5	5.6 ± 1.2	6.3 ± 3.2	0.081	0.35
HDL-C	46.5 ± 5.9	51.1 ± 7.1	51.4 ± 4	0.111	0.3

HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high density lipoprotein cholesterol in mg/dl; FBS, fasting blood sugar in mg/dl; PPBS, postprandial blood sugar in mg/dl; HbA1c, glycosylated hemoglobin in %; *P<0.05 when compared with baseline data

Table 4: Average levels of different parameters at the beginning, after 3rd month of study in Group 3

Group 3	(mean ± SD)		P value 3 month
	Baseline	3 month	
FBS	139 ± 25.9	127.5 ± 11.5	0.345
PPBS	178.5 ± 37.4	179.8 ± 67	0.917
HbA _{1c}	7.8 ± 1.36	7.3 ± 1	0.026 *
HOMA-IR	4.8 ± 1.2	4.8 ± 3	0.993
HDL-C	40.3 ± 9.9	41.3 ± 9.2	0.789

HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high density lipoprotein cholesterol in mg/dl; FBS, fasting blood sugar in mg/dl; PPBS, postprandial blood sugar in mg/dl; HbA_{1c}, glycosylated hemoglobin in %; *P<0.05 when compared with baseline data

DISCUSSION

There is a growing awareness among various 'Health Science bodies' to: preserve the ethnic culture and beliefs associated with intake of herbal remedies for common disorders and to complement modern medicine with patients choice of alternative remedies. There is however paucity of scientific data on complementary therapies from conduct of clinical trial according to GCP guidelines to substantiate these pursuits. The present study made efforts to bridge these gaps. Life style modification is a non pharmacological measure practiced in the management of diabetes mellitus by all patients. The comparison of group 1 versus group 3 hence is justified. Group 2 wherein the dose of metformin was adjustable was introduced for clarity in the analysis of data in the background of an established antidiabetic comparator. The findings of this study in group 1 was a decrease in fasting blood sugar, a decrease in HOMA-IR and an increase in HDL value uniformly seen significantly at the third month. However these beneficial findings do not translate to a decrease in postprandial blood sugar or to a decrease in HbA_{1c} at any point of time during the study. At best the values of postprandial blood sugar and HbA_{1c} were maintained during the study period. The fasting blood sugar is a result of increased hepatic glucose production, which is inhibited by relative low levels of insulin; while higher levels are needed for maximal stimulation of peripheral glucose uptake i.e. to decrease post meal glucose [10]. In this study since only fasting blood sugar has shown a decline but not the postprandial sugar, this implies that Madhuhara churna [AVA Trust, Regd] may be only a weak secretagogue, if at all. Significant fall in fasting blood sugar and HOMA-IR, maintenance of postprandial blood sugar and HbA_{1c} values at third month when compared to baseline also suggest Madhuhara churna [AVA Trust, Regd] may have extrapancreatic action also. This action could be due to its action on liver to decrease glucose release by enhancing glycogen storage, similar to the findings of Sridhar *et al* [7]. The adverse effect profile of *Eugenia jambolana* in studies conducted so far, did not show any major adverse events. Hence it could be used in combination with other oral antidiabetic drugs to reduce insulin resistance. Since Madhuhara churna [AVA Trust, Regd] reduced HDL-C levels it might be a potential agent in reducing the risk of complications like atherosclerosis and cardiovascular disease in diabetic patients.

In type 2 diabetic patients the elevation of glucose and free fatty acid levels lead to generation of reactive oxygen species and oxidative stress [11, 12]. These metabolic complications not only induce late diabetic complications but also lead to insulin resistance, β cell dysfunction and impaired insulin secretion [13]. An antioxidant activity of Madhuhara churna [AVA Trust, Regd] is also a possibility which is worthwhile pursuing.

In this study, though there was a significant fall in fasting plasma glucose from the third month onwards, the HbA_{1c} value at the end of 6 months of therapy remained at almost the same level as the baseline value. This finding is not surprising as in the assessment of glycemic control, HbA_{1c} values provide an indication of the average blood glucose concentration during the preceding pre-prandial glycemia assessed by fasting blood sugar and postprandial glycemia assessed by postprandial blood sugar measured 2 hours after the start of meal. There is insufficient data to determine accurately the relative contributions of the fasting plasma glucose and postprandial plasma glucose to HbA_{1c}. The findings in this study is suggestive of this proposition, as the baseline HbA_{1c} values were maintained during the 6 month study duration and did not rise unlike the postprandial plasma glucose values.

In conclusion, the result showed that Madhuhara churna [AVA Trust, Regd] had a beneficial effect in reducing the glycemic state, insulin resistance and elevating HDL-C levels in patients with type 2 diabetes mellitus. Madhuhara churna [AVA Trust, Regd] could be an effective complementary therapy in patients with newly diagnosed type 2 diabetics with mildly elevated plasma glucose.

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