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ORIGINAL ARTICLE

Effects of a Composite of Tulsi Leaves, Amla, Bitter Gourd, Gurmur Leaves, Jamun Fruit and Seed in Type 2 Diabetic Patients

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ABSTRACT

Traditional treatment applies different herbal principles used as a composite in food, serving as an effective measure against different diseases like diabetes in economically backward rural India lacking in health service infrastructure. The present study intends to observe the effects of a composite of Tulsi (Ocimum Sanctum) leaves, Amla (Emblica Officinalis), Bitter Gourd (Momordica Charantia), Gurmur (Gymnema sylvestre) leaves and Jamun (Syzygium Cumini) fruit and its seed, on mild diabetic patients. 120 patients whose Fasting Blood Sugar values is below 180mg/dl and without any complications of diabetes, and free from other diseases, are screened out of 2607 cases from hospitals at and around Kharagpur by random selection (lottery), divided into two groups of 60 patients each (lottery). The experimental group receives the composite of the above substances mixed with Soybean *Sattu* and used as a breakfast item for three months. The parameters like fasting blood sugar and lipid profile values for both experimental and control groups are measured at monthly intervals and compared statistically. Insulin resistance pictures are calculated. Application of the composite results in reduction of fasting blood sugar, bad cholesterols and Insulin resistance and increase in good cholesterol. Normal distribution method is used to analyse the data. The composite in this study causes beneficial changes in the blood bio-chemic parameters with reduction of Insulin resistance in the patients and needs to be supported by long-term experimentations.

Key Words: Type 2 diabetes [C19.246. 300]+, Composite, Tulsi Leaves, Amla, Bitter Gourd, Gurmur Leaves, Jamun Fruit and Seed

Introduction

India, facing a diabetic explosion, the exact cause being unknown and both genetic and life style factors being blamed, has the worlds Largest diabetic population – about 25 million, and the number is predicted to rise to 35 million by 2010 and to 57 million by 2025 [1]. Rural India is urbanizing rapidly. A recent sample study of Medavakkam town near Chennai, which is a village a decade ago shows that the prevalence of diabetes rise from 2.4 per cent to 5 per cent within five years of urbanization [2]. The Chennai Urban Population Study (CUPS) records in 1997 shows 12 per cent prevalence of diabetes in

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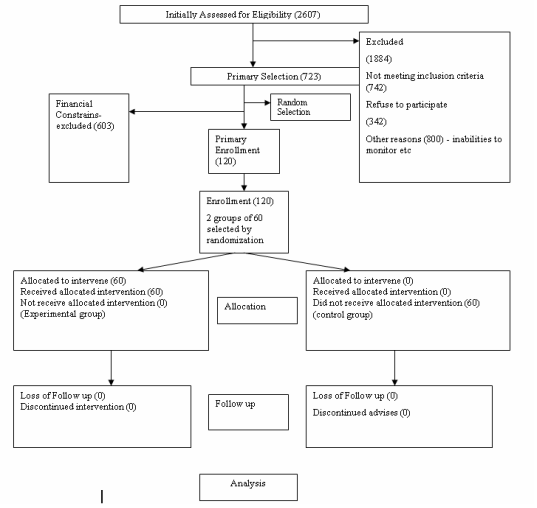
the Chennai population which is 70 per cent higher to what is being reported 14 years ago [3]. The Chennai Urban Rural Epidemiology Study (CURES) records a prevalence of 16% diabetic[4]. This rising trend puts a significant health burden due to diabetes in India [5]. The urbanization tendency of rural India puts the incidence of diabetes with all its complications and mortality on the rise [6],[7]. Rural India lacks development in different sectors including health service infrastructures. Food based control to different diseases can serve as an alternative, particularly if it is economically and socio-culturally viable and acceptable [8]. Different herbal principles or foods are traditionally used in India in treating diabetes and other diseases. Ayurvedic practices recommend Tulsi (Ocimum Sanctum), Amla (Emblica Officinalis), Bitter Gourd (Momordica Charantia), Gurmur (Gymnema sylvestre), and Jamun (Syzygium Cumini) etc. for diabetic patients [9],[10],[11],[12],[13] For every 1-percentage point drop in glycolated haemoglobin (A_1C), e.g. from 9 to 8 percent, there is a 35 percent reduction in the risk for diabetes-related complications and lowering the risk of fatal and nonfatal heart attacks by 18 percent [14]. Different dietary ingredients having anti-diabetic potentials can act in synergism leading to wider range of control in diabetic patients and as such the study is particularly important in rural Indian context in reducing the incidence of diabetes related complications [15]. The composite being used here has added advantages of inducing beneficial changes in blood pressure values [16]. The study thus helps particularly the rural Indian mass in preventing the complications of diabetes.

Materials and Methods

Selection of Subject (Patients):

For the present study, based on the data available in hospitals, 2607 patients suffering from Type 2 diabetes are identified. From these 2607 patients 723 patients are screened based on the following criteria- they do not require drugs until now (fasting blood sugar within140mg/dl), agree to participate and develop diabetes within past 3 years. They are free from any diabetic complications and symptomatically normal. They are also having no signs of any other diseases except the altered bio-chemical parameters due to diabetes. Out of these 723 patients, 120 patients are randomly selected (lottery) mainly based on financial reasons (inadequacy of funds). They are divided into two groups by random selection of 60 patients each, one for experimentation and other for control [Table/Fig 1]. The patients are informed details of the study, including benefits and risk involved, in vernacular. Ethical clearance is obtained from the Institute authority by presenting the matter before the competent committee with a clear understanding that risk process being involved is minimum and all food processes being used in the study are traditional ones and to be used in the traditional route. The research team prior to use will taste food processes being used in the study. It is important that plants and herbal remedies currently in use or mentioned in literature of recognized Traditional System of Medicine is prepared strictly in the same way as described while incorporating GMP norms for standardization. So it may not be necessary to undertake phase I studies. However, it needs to be emphasized that since the substance to be tested is already in use in Indian Systems of Medicine or has been described in their texts, the need for testing its toxicity in animals has been considerably reduced. Neither would any toxicity study be needed for phase II trial unless there are reports suggesting toxicity or when the herbal preparation is to be used for more than 3 months [17]. Different herbal composite are already being tested nationally and internationally and two Ayurvedic doctors are present in the research team. Written consents of the patients are obtained for the study. The patients are not receiving any lipid lowering and anti-hypertensive or any other drug therapies before and during the study.

Table/Fig 1: Consort Flow Chart of Type 2 Diabetes Patients in the Study



Anthropometrical, Clinical and Bio-chemical characters of Volunteers:

Anthropometrical, Clinical and Bio-chemical characters of Volunteers are shown in [Table/Fig 2] below (expressed in Mean ± SD). In the experimental group body weight is 72 ± 3 kg at the beginning and 72± 2 kg at the end while in the control group it is 66 ± 3kg (beginning) and 66± 2 kg at the end. Body mass index in the experimental group is 24.4 ± 3.4 units initially and 24.3 ± 3.3 units finally while in the control group body mass index is 24.5 ± 2.1 units (beginning) and 24.3 ± 1.9 units (end). These variations are due to non-identical conditions prevailing at the time of experimentation. Systolic blood pressure in the experimental group is146 ± 12 mm of Hg (beginning) and 130 ± 14 mm of Hg (end) while in the control group systolic blood pressure is140 ± 14 mm of Hg at the beginning and 138 ± 14 mm of Hg at the end. Diastolic blood pressure in the experimental group is 100 ± 12 mm of Hg (beginning) and 92 ± 8 mm of Hg (end) while in the control group diastolic blood pressure is 94 ± 8 mm of Hg at the beginning and 92± 10 mm of Hg at the end. The exact cause of this is unknown, possibly strict monitoring of diet with a fixed schedule may cause it. The research team strictly monitors the prescribed diet schedule, which consists of 65% of carbohydrates, 15% of fats and 20% of proteins [18].

Clinically both the groups show no abnormality, other than hypertension in both groups. Different bio-chemical and clinical parameters like Liver Function Tests (LFT), Total leukocyte count (TLC), Differential leukocyte count (DLC), Hb, Urea, Creatinine, total proteins, serum electrolytes, urine tests, Electro-cardiograph (ECG), X-ray of chest etc are almost identical and within normal range in both the groups.

Table/Fig 2: Anthropometrical, Clinical and Bio-chemical characters of Volunteers (n=120)

	Experimental Group	Control Group
Age	48.62 ± 4.76 years	47.38 ± 3.78 years
Sex: Males Females	 31 29	 31 29
Weight	72 ± 3kg (beginning) 72± 2 kg (end)	66 ± 3kg (beginning) 66± 2 kg (end)[1]
Body Mass Index (BMI)	24.4 ± 3.4 units 24.3 ± 3.3 units	24.5 ± 2.1 units (beginning) 24.3 ± 1.9 units (end)[1]
Systolic Blood Pressure	146 ± 12 mm of Hg (beginning) 130 ± 14 mm of Hg (end) (p=0.045) (reduction 11%)	140 ± 14 mm of Hg (beginning) 138 ± 14 mm of Hg (end)
Diastolic Blood Pressure	100 ± 12 mm of Hg (beginning) 92 ± 8 mm of Hg (p=0.030) (reduction 8%)	94 ± 8 mm of Hg (beginning) 92± 10 mm of Hg (end)
Mean Pressure	115±8 mm of Hg (beginning) 105±5 mm of Hg (end) (p=0.040) (reduction 9%)	109±10 mm of Hg (beginning) 107±9 mm of Hg (end)
Total Cholesterol	188 ± 8 mg/dl	182± 6 mg/dl
Low Density Lipoprotein Cholesterol	114±6 mg/dl	110 ± 7 mg/dl
High Density Lipoprotein Cholesterol	48±3 mg/dl	45 ± 4 mg/dl
Very Low Density Lipoprotein Cholesterol	28±5 mg/dl	27 ±5 mg/dl
Triglycerides	138±7 mg/dl	135 ± 8 mg/dl
Fasting Blood Sugar	152±7 mg/dl	154 ± 6 mg/dl
SGPT	42±7 iu/L (beginning) 37±5 iu/L (end) (p=0.020) (reduction 11%)	39±5 iu/L (beginning) 39±5 iu/L (end)

[1] This variation may be non-identical conditions prevailing during measurements

Collection of Blood samples:

12 hours fasting values are taken initially and at monthly intervals for three months. Measurement of total cholesterol (TC), high density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC), very low density lipoprotein cholesterol (VLDLC), triglycerides (TG) and fasting blood sugar (FBS) is done by standard methods as depicted by Boehringer Mannheim [19] and by reagents supplied to meet the standard quality at monthly intervals by an indwelling catheter placed in the anti-cubital vein. Serum insulin level is measured at Bio-Technology Department of IIT, Kharagpur.

Equipment Used:

In order to observe the effect of composite on the Type 2 diabetes patients blood samples are being tested for fasting blood sugar (FBS), total cholesterol (TLC), High Density Lipoprotein Cholesterol (HDLC) by using Photometer 4010 of Boehringer, Germany (19). Very Low Density Lipoprotein cholesterol (VLDLC) is being computed as $1/5^{th}$ of Triglyceride value and Low Density Lipoprotein cholesterol (LDLC) is being computed by the difference TLC - (VLDLC + HDLC) (Catalogue no. 400 971; catalogue no. 543 004) (19). Serum insulin values were measured by Elisa method at Bio-technology Department of IIT, Kharagpur using Biorad, Coda Automated EIA Analyzer [20].

Medication-Daily Dose to Patients:

Duration of the study period is three months. During this period the subjects receive a daily dose of a composite comprising of (1) 2.5 g of Ocimum Sanctum leaves powder [10],[21], (2) aqueous extract of Syzygium Cumini is being made by keeping 60 g of the fruit in 300 g of boiling water and being covered and mashed for half an hour and then filtered [10] (3) 10 g of powdered Syzygium Cumini seeds [22],[23], (4) 5 g of Momordica Charantia juice [24], (5) one teaspoon of Emblica Officinalis juice [25],[26], (6) 2 g of Gymnema Sylvestre leaves [27],[28]. The composite assumes a blue green colour and the colour is totally masked by adding 300 g of Soybean *sattu* [8],[17]. Mature dry soybeans approach the FAO Standards for protein and contain about 20% protein and can be used as a protein source in the form of *sattu* with which the desired ingredients can be easily mixed [29],[30]. To this is being added 0.5 g of salt, 10 drops of lemon and a pinch of vanilla scent to mask the taste and odour. All the food varieties are procured from local market after inspection for good quality. For Soybean flour, the quality is being assessed at Food Quality Control Laboratory of Agriculture and Food Engineering Department in IIT at Kharagpur. The composite is used as breakfast item. The other group is not receiving the composite but receiving the soybean *sattu* only of the same amount and is being mixed with 0.5 g of salt, 10 drops of lemon and to mask the taste and odour. Written responses from 20 other independent observers are obtained to see whether the composite or the *sattu* item differs in colour, apparent taste, odour and other physical characters. Both groups are following identical daily routines and life-style patterns including the daily food intake. Weekly diet charts and all aspects of lifestyle patterns are formulated through discussion and agreement with all members of the group under daily monitoring and follow up by members of the research team. Both groups of patients are kept ignorant about who is getting the composite and who is not. No adverse effect is being reported by any of the volunteers except flatulence, nausea and constipation in two volunteers on 18^{th} day of the therapy, and all subside spontaneously on 22^{nd} day. No drop out occur during the study period and all 60 patients of both the groups are kept under surveillance by members of the research team and being requested to report if any untoward symptoms appear and the patients are clearly being instructed that the study will not impose any risk to them and drug therapy or other therapies will start as and when required. All other clinical and biochemical parameters of those two groups of volunteers remain normal during that period and no drugs or other therapies are being necessitated. Technicians not involved in the study test the blood samples for desired parameters, from all members of both the groups. The volunteers are being followed up monthly for bio-chemical parameters (FBS and Lipid profile) and the results are being analyzed statistically. The study is intended to have a desired outcome to induce beneficial changes in diabetes, that is, reduction of blood sugar, bad cholesterols (LDLC and VLDLC) and triglycerides (TG) with increase in good cholesterol (HDLC). Due to economic constraints serum insulin values are being measured at the beginning and at the end of experiment and insulin resistance being calculated.

Statistical Analysis:

Let μ_0 be the average blood level of the desired parameter of the control group. The goal is to test whether μ, the average blood level of the desired parameter of the experimental group is less than μ_0 or not, that is to test

$$H_0 : \mu = \mu_0 \text{ against } H_1 : \mu < \mu_0 .$$

Let $\overline{X}_0$ be the sample mean of the control group and $\overline{X}$ be that of the experimental group. In order to test (H_0, H_1), our test statistic is $t = \dfrac{\overline{X} - \overline{X}_0}{s\sqrt{2/n}}$, where $s = \sqrt{\dfrac{s_1^2 + s_2^2}{2}}$, s_1^2 and s_2^2 being the sample variances of the control group and the experimental group respectively.

It is to be noted here that the above formula has been simplified from the standard one when the sample sizes $n_1$and n_2 are the same. In our present case, n_1=60. It is to be noted that the sample size being very large, the above test statistic t could be well approximated by normal distribution and the p-value for different parameters be calculated, on using the same kind of test statistic with the help of normal probability table. This logic is used in the SPSS statistical package to get the different results.

Results

Clinical, anthropometrical and bio-chemical evaluations of the patients before the study are as follows:

Age- 48.29 ± 4.56 years (Mean ± SD)
Sex- Males 62, Females 58
Weight- 69.3 ± 3.5 kg
BMI- 24.5 ± 3.29

At the end of the study it is being found that volunteers' weight become 69.3 ± 3.2 kg and their BMI is being found to be 24.3 ± 3.1. These variations are statistically insignificant.

As the patients are from diverse socio-cultural backgrounds with varied food-intake, life-styles, socio-cultural beliefs etc, the variations in the initial readings of blood parameters in patients are noted. Clinical parameters are evaluated at the end of the study. All the parameters remain as before except Blood Pressure values, which show decrease in systolic Blood Pressure by 16 mm of Hg, diastolic blood pressure by 8 mm of Hg and mean pressure by 10 mm of Hg. SGPT values in the experimental group increase by 5 units in the 2nd week and it remain stationary after that. Anthropometrical, Clinical and Bio-chemical characters of Volunteers are shown in [Table/Fig 2].

Table/Fig 3: Homeostasis Model Assessment 2 Values (insulin resistance) of Different Groups

Time in months	Group receiving rural diet		Group receiving the composite	
	Range	Mean ±SD	Range	Mean ±SD
0	5.5-6.3	5.9± 0.2	4.5-5.3	4.9± 0.15
3	5.4-6.6	5.8±0.15	3.6-4.2	3.9± 0.1

Results of analysis of blood samples for plasma glucose and lipid profile are being presented in [Table/Fig 3]. A close study of blood biochemical parameters shown in [Table/Fig 3] reveals that whereas there is only negligible changes in patients receiving normal diet – TLC changing from 188±8 to 187±6 while there has been substantially beneficial changes in patients receiving the composite – TLC values being reduced from 182±6 to 168±5. HDLC values in patients receiving normal diet varies from 48±3 to 46±3 while HDLC values show increasing trend in patients receiving the composite from 45±4 to 49±3. LDLC values show marginal changes in patients receiving normal diet from 114±6 to 116±3 whereas in patients receiving the composite LDLC is being reduced from 110±7 to 94±5. VLDLC values are within 28±5 to 28±4 in patients receiving normal diet while VLDLC values are reduced from 27±5 to 22±4 in patients receiving the composite. TG values vary in patients receiving normal diet from 138±7 to 138±5 while in patients receiving the composite TG vales are reduced from 135±8 to 110±7. FBS values in patients receiving normal diet vary from 152±7 to 155±3 while in patients receiving the composite FBS is being reduced from 154±6 to 139±8. HBA_1c values being measured show in experimental group it is being

reduced from 6.5 ± 0.2 to 6.2 ± 0.2 while it remain at 6.4 ± 0.3 in the control group.

Analysis of fasting serum insulin values in the group receiving the composite is 35±6 μiu/ml (initially) and it is 27±4 μiu/ml at the end of study and the corresponding changes in the group receiving normal diet was from 42±6 μiu/ml to 43±5 μiu/ml. Further studies are required to explain the changes. Table 3 show homeostasis model assessment of insulin resistance (HOMA 2-IR) values of the two groups in order to determine insulin sensitivity values of the patients respectively – one receive normal diet and the other receive diet with composite. In the former group mean insulin resistance is 5.9± 0.4 initially and is 5.8± 0.2 after the study. In the other group of patients, mean insulin resistance is 4.9± 0.2 initially to 3.9± 0.6 at the end of the study showing reduction in insulin resistance by the composite.

Discussion

The herbal composite used in the present study shows significant improvement in several biochemical parameters. Thus the composite shows hypoglycemic effect as being revealed by the reduction of fasting blood sugar level from 154 ± 6 to 139±8 (p=0.020). Insulin resistance is also reduced by the composite, a conclusion drawn after comparing the homeostasis model assessment 2 values of experimental and control groups.

Apart from the blood sugar lowering effect, beneficial changes in lipid profile have also been observed. Thus, administering the composite over a period of 3 months leads to an increase of HDLC being accompanied by reduction in TLC, LDLC, VLDLC and TG. The study is done in a closed community, the rural and semi-urban Bengali population, having commonalities in food intake and common life-style patterns. It may be mentioned that the herbal composite used shows no adverse effects or toxic reactions. Our findings reiterate the importance of life style in the genesis and management of diabetes in rural and semi-urban Bengali population. Moisture content of medicinal plants ranged from 11.76 percent in fenugreek seeds to 93.43 percent in Momordica Charantia. Syzygium Cumini seeds contained minimum crude protein (4.16%) while fenugreek seeds were richest source of it (25.8%) followed by Momordica Charantia (20.53%). Ether extractable fat content of medicinal plants ranged from 0.49 to 6.53 percent in Momordica Charantia and fenugreek seeds respectively. Ash content of Momordica Charantia fruit was very high (9.89%) while it was lowest in Syzygium Cumini seeds (21.6%). Crude fibre content of medicinal plants ranged from 1.28 (Syzygium Cumini seeds) to 10.92 percent (Momordica Charantia). Total carbohydrate content ranged from 58.13 in fenugreek seeds to 90.85 percent in Syzygium Cumini seeds [31]. Emblica Officinalis is rich in Tannin and Vitamin C while Ocimum Sanctum contains Eugenol, Luteolin Apigenin. Syzygium Cumini is rich in flavonoids and polyphenolic compounds; Momordica Charantia contains a polypeptide p-insulin similar to bovine insulin in normalizing the blood sugar level, and, therefore, has been used as a folk medicine for diabetes. Gymnema sylvestre contains gymnemic acid and atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules. Gymnemic Acid molecules fill the receptor locations on the taste buds thereby preventing activation of taste buds by sugar molecules present in the food, thus, curbing the sugar craving. Similarly, gymnemic acid molecules fill the receptor location in the absorptive external layers of the intestine thereby preventing the sugar molecules absorption by the intestine, which results in low blood sugar level [32]. Regarding the probable mechanism of such hypoglycemic and lipid lowering effects, the chemical constituents particularly the flavonoids and polyphenolic compounds present in the composite are largely responsible. However, a thorough study is necessary to find out all the active principles in the composite before a definite conclusion can be drawn.

Our findings are being based upon the study, which is limited to a three-month period. As blood samples are drawn from different

patients, having different socio-cultural backgrounds, considering the diversity of Indian population in intake of food, life-styles, socio-cultural beliefs etc, the variations in the readings of different blood parameters in different patients are to be considered before any long-term experimentation on a broader spectrum of people is formulated. Future studies from our laboratory will be aimed towards that direction.

Mitra and Bhattacharya report that diabetogenic nature of rural diet in Bengal and importance of life style in the genesis of diabetes in rural Bengali population [33]. Different workers have found the role of genetic factors in causation of diabetes and the insulin resistance spectrum in Indians [34],[35],[36],[37]. Diet may contribute to the development of diabetes in two ways: quantitatively, by supplying calories and if activity is low by resultant obesity; and qualitatively by the effects of specific food items. Hence, the study is being intended to provide a cheap, effective, easily available throughout the year and socio-culturally acceptable neutraceutical particularly to rural Indian population suffering from diabetes. It shows that it induces beneficial changes not only in biochemic parameters of type 2 diabetes but also reduces insulin resistance. Raised blood pressure is strongly associated with the risk of diabetic complications in type 2 diabetes. Because of the several clinical benefits are being associated with better blood pressure control in these patients. The potential for less human suffering and cost savings, it is important to evaluate the quality of care by observing trends for several years. Reductions of blood pressure values show favourable trends in glycaemic and blood pressure control in recent years [38],[39]. Different observers report hypoglycaemic effects of the different components used in the composite [40],[41],[42],[43],[44]. Tomer et al. [44] and Karen and Gong [27] show the herbal mixtures are useful as dietary supplements. They are especially useful for lowering the glucose level in patients suffering from diabetes mellitus [44],[27]. The composite being used here has added advantages of inducing beneficial changes in blood pressure values [18].

Conclusion

The socio-economic development of rural India is leading to more prevalence of diabetes and diseases being related to Insulin Resistance Syndromes, particularly obesity, dyslipidaemia, hypertension, atherosclerosis, and coronary artery disease. Hence neutraceutical or food-based therapies are more appropriate as it is traditionally and culturally accepted and can reach majority of the population. A composite of different anti-diabetic herbal preparations are tried in the study and is being found to be effective not only in changing the blood bio-chemic parameters but also the overall picture of Insulin resistance. The study needs to be supported by long-term experimentations.

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