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A STUDY ON THE HYPOGLYCEMIC AND HYPOLIPIDEMIC EFFECTS OF AN AYURVEDIC DRUG RAJANYAMALAKADI IN DIABETIC PATIENTS

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ABSTRACT

A study was undertaken for evaluating the hypoglycemic and hypolipidemic effects of an ayurvedic medicine "Rajanyamalakadi" containing Curcuma longa, Emblica officinalis and Salacia oblonga in type II diabetic patients over a period of 3 months. Ethical committee consent for the study was given by the Director, Indian Systems of Medicine, Kerala. A total of 43 patients with established diabetes mellitus as adjudged from clinical features and FBS values, appeared for the camp (Age group 35–75 yrs). An informed consent for the study was obtained from each patient. The clinical proforma was given to each patient to collect data such as height, weight, diet pattern, previous history of illness etc. The ongoing antidiabetic medications were stopped under medical supervision and the patients were provided with 'Rajanyamalakadi' tablets (dose 1-2 tablets each weighing 500mg). The dosage of the drug was decided by the supervising medical officer on a case to case basis, taking note of the clinical conditions and responsiveness of the patients. The patients were monitored for three months, who were divided into 6 groups based on their age and again into two groups, 5 & 6, based on their mean FBS values. ie; Normal Persons, Diabetics of age groups 35-45yrs, 46-55yrs, >55yrs and those with FBS < 145.9 mg% and > 145.9 mg%. The Ayurvedic medicine "Rajanyamalakadi" has showed significant antidiabetic, hypolipidemic and antioxidant effects. In addition to that significant ameliorating effects on the elevated serum AST and ALT activities were also demonstrated by the treatment. The nutraceuticals present in the drug like Terpenoids, Polyphenols, Curcumin etc are responsible for the medicinal effects.

KEY WORDS

Rajanyamalakadi, Antidiabetic, Hypoglycemic, Hypolipidemic, Salacia oblonga, Curcuma longa, Emblica officinalis.

INTRODUCTION

Various studies suggest that approximately 150 million people suffer from diabetes the world over, and that this number may well double by the year 2025 (1). One fifth of the diabetics will be from India. Much of this increase will occur in developing countries and could be due to population growth, ageing, unhealthy diets, obesity and sedentary lifestyles. Paulose et al predict that by 2025 there will be 195 % increase in the number of diabetics in India (2). Oral medication is initiated in Type 2 diabetics when 2 – 3months of diet and exercise alone are unable to achieve or maintain their optimal plasma glucose levels. These drugs are easy to use but they have shown to have adverse effects (2,3). Currently enormous research interest is centered world wide about the search for newer, cheaper, and safer herbal based formulations which can effectively normalize the metabolic derangement underlying the onset of clinical diabetes. Recent scientific investigations have confirmed the efficacy of many of the ayurvedic preparations, some of which are remarkably effective, relatively nontoxic and have substantial documentation of efficacy (2,4).

In this scenario, we took up a challenging study to evaluate the clinical efficacy of an ayurvedic antidiabetic drug

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"Rajanyamalakadi" (Mfd. By Bipha Drug Laboratories, Kottayam).

MATERIALS AND METHODS

Diabetic patients who were willing to participate in the study were invited for a free medical camp at the District Ayurveda Hospital, Ernakulam . An informed consent for the study was obtained from each patient and the patients were given a code number which was found to be helpful through out the course of the study. The clinical proforma was given to each patient to collect data such as height, weight, diet pattern, previous history of illness etc. Diets of all groups consisted of whole wheat chappathi (4-6daily), half a plate unpolished rice or idli with side dishes of potatoes, peas, tomatoes, beans, lean meat, fish and skimmed milk daily as formulated by a dietician for non vegetarians and without meat and fish for vegetarians. The ongoing antidiabetic medications were stopped under medical supervision and were provided "Rajanyamalakadi" tablets.

INGREDIENTS OF THE DRUG

Rajanyamalakadi, contains the time tested antidiabetic extracts from *Salacia oblonga, Curcuma longa* and *Emblica officinalis*. Each Tablet of 500 mg contains: *Salacia oblonga* wall-250 mg, *Curcuma longa* L-125 mg, *Emblica officinalis*-125 mg.

Salacia oblonga: In traditional Indian medicine the root bark of *S.oblonga* is used in gonnorhoea, rheumatism and skin diseases (5,6). Augusti et al (7, 8) isolated an active terpenoid fraction from the root bark of this plant and showed its antidiabetic action in normal and Streptozotocin diabetic rats. The roots and stems of *Salacia reticulata* also contain potent antidiabetic chemical constituents. Mangiferin (9) (a xanthone from the roots) and sulfonium ion derivatives, kotalanol (10) and salacinol(from the roots and stems) (11), have been identified as the antidiabetic principles. Mangiferin also inhibits aldose reductase activity, thereby delaying the onset or progression of diabetic complications. (eg: diabetic neuropathy and nephropathy). It is possible that these components of *S.reticulata* could also be present in *S.oblonga*. However for these studies are warranted. The polyphenol constituents of *S.oblonga*, the catechins, also contribute to the antidiabetic property of the plant (5).

Curcuma longa: The active principles in the rhizome of this plant viz; curcuminoids lower lipid peroxidation by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase at higher levels. Antioxidant properties of curcuma longa is due to curcumin and its three derivatives (demethoxy curcumin, bisdemethoxy curcumin and diacetyl curcumin) (12,13).

Emblica officinalis: Shows pronounced antioxidant properties. The antioxidant and antidiabetic properties have recently been attributed to the tannoid complexes (14), epigallocatechin gallate, emblican a, emblicanin b, punigluconin and pedunculagin. *Emblica officinalis* also shows significant hypolipidemic activity in combination with curcuma longa, it is effective in the long term treatment of diabetes (15). Jose and Kuttan (16) studied the antioxidant activities of *E.officinalis* and its active ingredients are aqueous soluble, but partially extractable with ether and are heat stable. According to many the active components in the *E.officinalis* are ascorbic acid, tannins, trigalloylglucose, flavonoids etc. Polyphenols are ellagic acid and phyllemblic acid (15, 16).

The dosage of the drug was decided by the supervising medical officer on a case to case basis, taking note of the clinical conditions and responsiveness of the patient. A log book was maintained for each of the patients. The patients were monitored for 3 months. The patients were divided into 6 groups based on their age group and also according to the mean FBS values. As control group normal healthy subjects of the age group 35 – 75 were taken. After overnight fasting blood parameters were determined.

The Groups are as follows: Group I -Normal Control Subjects (n=10); Group II - 35-45 yrs (n=15); Group III - 46-55 yrs (n=13); Group IV - > 55 yrs (n=15); Group V - FBS < 145.9 mg/dl (n=21); Group VI - FBS > 145.9 mg/dl (n=22).

Fasting Blood Sugar (FBS) (25), insulin (26), glycosylated haemoglobin (gly Hb) (27), lipid profile (28,29,30,31), free fatty acids (FFA) (32), atherogenic index (33), glutathione reductase (34), Aspartate amino transferase (AST) and Alanine amino transferase (ALT) (35), Blood Urea Nitrogen (BUN) (36) and Creatinine (37) were determined according to standard methods in the venous blood prior and after oral administration of the medicine for a period of 3 months. Their mean values were recorded in the tables. Statistical analysis was done using Software package for social sciences (SPSS) (38, 39). Lowest level of significance was fixed at $P < 0.05$.

RESULTS

Results are given in Tables 1-4. There is a significant reduction in the final values when compared with the initial values of FBS, gly.Hb, total cholesterol, triglycerides, LDL and VLDL

cholesterol and free fatty acids in all groups. Where as there is a significant increase in the levels of HDL cholesterol, insulin and glutathione reductase activity in all treated groups ($p < 0.05$). According to the Tables the percentage decreases of FBS after treatment in each group from II onwards were in the order of 15.5, 16.3, 17.0, 14.0, and 17.3 respectively which are significant also. Similarly percentage decreases of glycosylated hemoglobin values were in the order of 19.2, 24.1, 14.2, 7.5 and 26.2 respectively, percentage fall except that in group V are significant. In the same series total cholesterol values also decreased in terms of percentages as follows 8.0, 12.6, 7.7, 8.0 and 11.3 respectively. Among which the percentage falls except that in group II, IV and V are significant. Similarly percentage decreases of triglyceride values were in the order of 13, 12.7, 12.9, 12.9 and 14.3 respectively which are found to be significant. Similarly percentage decreases of LDL were in the order of 14.8, 22.9, 15.9, 15.8 and 21.9 which are also found to be significant. The percentage decreases of VLDL were in the order of 13.3, 15, 13.1, 13.2 and 6.8. Among which all values except that in group VI are found to be significant. The percentage fall in free fatty acids were in the order of 10.9, 11.5, 10.4, 10.9 and 10.6 respectively which are found to be significant.

Similarly the atherogenic index values decreased in the order of 17.1, 22.9, 19.1, 18.4 and 22.2 % respectively which were also found to be significant. AST values were found to be decreased in the order of 22.6, 27.5, 20.2, 21.3 and 26.6 % respectively which were found to be significant. The ALT values also decreased in the order of 20.7,,28.5,23.5,23.2 and 26.4 % respectively which are found to be significant. The values of BUN were also decreased in the order of 8.1, 10.1, 8.8, 6.5 and 11.2 %respectively. Of these only values of Group III and VI are found to be significant. The Creatinine values were found to be decreased in the order of 10.3, 10.2, 13.2 ,8.3 and 9.6 % respectively, among them all values except that for Group V and Group VI are found to be significant.

The result showed that the drug has significant hypoglycemic and hypolipidemic effects without any observable toxicity in the diabetic patients of all age groups studied. These effects of the drug are due to the active principles contained in its ingredients. There are notable variations in the amelioration of parameters according to initial FBS and age range of the diabetic patients studied.

DISCUSSION

As all these ingredients of the drug viz; *Salacia oblonga, Curcuma longa* and *Emblica officinalis* contain various nutraceuticals such as terpenoids, curcuminoids and polyphenols/flavonoids respectively, they are all endowed with biological effects such as antioxidant, antidiabetic, immunomodulatory and hypolipidemic properties. As per the

Table 1 : Blood/Serum levels of FBS, Insulin and Glycated Hb (Mean ± SD)

		FBS mg/dl	Insulin IU/l	Gly.Hb%
Group I Normal Control Values N=10		87.521±9.44	22.72±6.19	5.50±0.22
Group II NIDDM age group(35-45) N=15	Initial	168.19±56.55	18.3±6.88	8.3±3.7
	Final	142.10±41.74	26.27±5.94	6.71±2.17
		P < 0.01	P < 0.001	P < 0.02
Group III NIDDM age group (46-55) N=13	Initial	148.82±34.61	15.53±6.03	7.754±2.93
	Final	124.53±3.34	23.72±5.41	5.875±1.26
		P < 0.001	P < 0.001	P < 0.01
Group IV NIDDM age group>55 N=15	Initial	148.01±36.03	16.333±6.67	7.267±2.64
	Final	122.953±27.16	24.227±6.35	6.239±1.21
		P < 0.001	P < 0.001	P < 0.05
Combination Group V NIDDM FBS<145.9	Initial	121.39±9.78	17.71±7.10	5.83±1.06
	Final	104.40±15.53	25.08±6.38	5.39±0.52
		P < 0.02	P < 0.001	P < 0.001
Combination Group VI NIDDM FBS>145.9	Initial	171.45±20.58	15.541±6.08	9.53±3.68
	Final	141.87±23.11	24.50±5.94	7.03±2.05
		P < 0.001	P < 0.001	P < 0.001

Level of significance between groups is determined from initial and final values. All values in this table are significant.

Table 2: Serum levels of Cholesterol, triglycerides and other related parameters (Mean ± SD)

		Total Chol. mg/dl	HDL mg/dl	TG mg/dl	LDLmg\dl	VLDL mg/dl	FFA meq/ml
Group I Normal Control Values No=10		172.65±21.93	52.14±11.21	112.55±20.13	98± 6.14	22.51 ±4.03	0.72 ± 0.14
Group II NIDDM	Initial	233±29.24	60.65±11.6	172.85±39.43	139.4±24.63	34.68±7.89	1.293±0.40
age group(35-45) No=15	Final	214.41±28.52	65.19±8.75*	150.37±29.66	118.75±24.84	30.08±5.94	1.151±0.32
		P < 0.001	NS	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Group III NIDDM	Initial	239.84±34.61	58.38±6.73	176.9±39.264	145.89±30.39	36.56±7.90	1.39±0.379
age group (46-55) No=13	Final	209.59±31.05	65.962±5.32	154.415±33.78	112.55±30.26	31.077±6.627	1.226±0.37
		P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Group IV NIDDM	Initial	230.32±29.02	58.62±4.97	165.28+50.01	139.15±22.79	33.12±9.97	1.25±0.39
age group>55 No=15	Final	212.54±21.49	66.69±4.71	143.94±42.20	117.06±13.3	28.78±8.43	1.116±0.34
		P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Combination	Initial	232.39±27.41	59.79±6.26	169.77±39.37	138.43±21.92	34.14±7.77	1.283±0.36
Group V NIDDM FBS<145.9	Final	213.85±25.85	67.58±1.44	147.75±34.92	116.61±21.09	29.65±6.93	1.144±0.32
		P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001
Combination							
Group VI NIDDM FBS>145.9	Initial	237.19±36.7	57.9±6.79	176.69±47.75	146.28±32.15	35.35±9.62	1.314±0.43
	Final	210.46±7.602	56.57±5.9	151.36±36.98	114.3±28.142	32.94±13.54*	1.166±0.38
		P < 0.001	P < 0.001	P < 0.001	P < 0.001	NS	P < 0.001

Level of significance between groups is determined from initial and final values. All values except that with astrics are significant

work of Augusti et al (7,8), *S.oblonga* contains a terpenoid and a polysaccharide with antidiabetic effects. This and similar properties of the *S.oblonga* compounds might have made the drug under study a strong antidiabetic agent. In two previous reports *E.officinalis* extract has been shown to reduce liver injury caused by administration of xenobiotics, to ameliorate conditions of atherosclerosis and diabetes (16,17). Moreover *E.officinalis* extracts are found to reduce the toxicity and clastogenicity induced by heavy metals also (18). *E.officinalis* polyphenols and *C.longa* curcuminoids, with their antioxidant and hypolipidemic properties (14,19) could protect the β–cells of pancreas from oxidative stress and make them properly functional, with the added advantage of modulating the lipid profile. The drug combinations with *Salacia oblonga* and such other plants as above could minimize long term diabetic complications also (20). Hence the drug "Rajanyamalakadi" is a three in one combination of several nutraceuticals and their mechanism of action may be through stimulation of insulin secretion (21), antioxidant (22), hypolipidemic, antidiabetic (23, 24), hepatoprotective (40) and various such other actions as reported by several workers from time to time for curcuma longa and other plant products. The lowering of blood sugar, serum lipids and amelioration of serum insulin level by the biological actions of the various nutraceuticals in the drug might have protected the liver from various stressful conditions also, eg. decrease in the mechanisms of detoxifications, chances of fatty liver, fall in protein and enzyme synthesis etc. A balanced condition of these activities might have helped the treated diabetics to ameliorate the ups and downs of serum parameters such as marker enzymes like ALT, AST and glutathione reductase for liver and heart diseases respectively. We should appreciate the wisdom of Bipha Drug Laboratories Limited for the preparation of this drug for the benefit of type II diabetics who form a major chunk of India's cream society.

Mechanism of action of the neutraceuticals present in the components of the drug as suggested by various workers. As the serum insulin level of the treated patients increased significantly some of these compounds might have acted as insulin secretagogues, viz ; Terpenoids of *S.oblonga* wall and polyphenols of *Emblica officinalis*. Most of the active compounds present in the drugs are antioxidants and they must have protected the cells and increased their sensitivity to glucose and insulin viz ; polyphenols and flavonoids in *E.officinalis*, the terpenoids of *S.oblonga* and curcumin of turmeric. This type of amelioration in diabetic condition of the patients might have improved the synthesis and activities of the enzymes that control carbohydrate, protein and lipid metabolism viz ; antioxidant curcuminoids, terpenoids, polphenols, flavonoids etc in the drug are responsible for this.

Table 3: Serum levels of Atherogenic Index, Glutathione reductase, AST & ALT (Mean ± SD)

		Atherogenic Index	Glut Reductase IU/L	AST IU/L	ALT IU/L
Group I Control Values No=10		3.31±1.28	2.41±0.24	31.69±5.02	34.79±8.56
Group II NIDDM age	Initial	4.009±0.75	2.19±0.48	42.57±14.79	47.84±23.21
group(35-45) No=15	Final	3.28±0.46	2.434±0.41	32.93±7.18	37.95±16.09
		P < 0.001	P < 0.001	P < 0.001	P < 0.01
Group III NIDDM age	Initial	4.06±0.41	2.245±0.44	36.831±11.83	35.054±12.95
group (46-55) No=13	Final	3.13±0.41	2.533±0.33	26.692±6.77	25.049±9.11
		P < 0.001	P < 0.001	P < 0.001	P < 0.001
Group IV NIDDM age	Initial	3.92±0.43	2.021±0.50	32.4±13.84	28.99±8.05
group>55 No=15	Final	3.173±0.26	2.465±0.34	25.87±9.32	22.18±7.14
		P < 0.001	P < 0.001	P < 0.001	P < 0.001
Combination Group V	Initial	3.85±0.46	2.04±0.55	34.68±12.57	37.98±20.31
NIDDM FBS<145.9	Final	3.14±0.39	2.37±0.38	27.30±7.49	29.18±13.68
		P < 0.001	P < 0.001	P < 0.001	P < 0.001
Combination Group VI	Initial	4.10±0.55	2.168±0.35	40.38±16.89	36.18±16.49
NIDDM FBS>145.9	Final	3.194±0.38	2.52±0.33	29.62±10.14	26.63±3.37
		P < 0.001	P < 0.001	P < 0.001	P < 0.001

Level of significance is determined between initial and final values. All values in this table are significant.

As a combined effect of the above actions for three months, diabetes was controlled in the patients with accompanying improvement in all its aspects of the blood parameters.

Table 4 : Blood/Serum levels of Urea nitrogen & Creatinine (Mean ± SD)

		BUN mg/dl	Creatinine mg/dL
Group I Control Values No=10		13.07±3.28	0.98±0.20
Group II NIDDM age	Initial	14.87±2.69	1.02±0.19
group(35-45) No=15	Final	13.67±2.42	0.915±0.14
		P < 0.001	P < 0.001
Group III NIDDM age	Initial	15.76±2.982	1.077±0.18
group (46-55) No=13	Final	14.169±2.16	0.967±0.17
		P < 0.001	P < 0.001
Group IV NIDDM	Initial	15.406±2.90	1.056±0.18
age group>55	Final	14.06±2.27	0.921±0.13
No=15		P < 0.001	P < 0.001
Combination	Initial	14.07±2.07	0.964±0.19
Group V NIDDM	Final	13.15±1.93	0.881 ± 0.16
FBS<145.9		P < 0.001	P < 0.001
Combination	Initial	16.67±2.80	1.135±0.11
Group VI NIDDM	Final	14.81±2.27	1.032±0.26*
FBS>145.9		P < 0.001	NS

Level of significance is determined between initial and final values. All values except that with astrics are significant.

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