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Research Article

Antihyperglycemic and Antihyperlipidemic Activities of New Polyherbal Formulations

K. Sirisha*, J. Shivani.

Vaagdevi College of Pharmacy, Ram Nagar, Hanamkonda, Warangal,

Andhra Pradesh, India- 506001,

ABSTRACT

In the ayurvedic system of medicine, several plants are said to be useful for the treatment of metabolic disorders like diabetes mellitus. Plants represent a great source of drugs for the management of diabetes mellitus [DM]. The polyherbal products available in the market are mostly comprised of crude drug powders made into dosage form. Further, the existing antidiabetic polyherbal formulations containing *Momordica* suffer from bitter taste. The objective of present study was to develop tablet formulations with the standardized extracts of *Momordica charantia*, *Cinnamomum cassia* and *Stevia rebaudiana* with a view to improve the palatability of such polyherbal formulations using natural sweetening agents *Cinnamon, Stevia* etc which also increase patient compliance. The study examined the acute toxicity, antihyperglycaemic and antihyperlipidaemic effects of the prepared poly-herbal formulations (formulation-1 and formulation-2), a mixture of *Momordica charantia* and *Cinnamomum cassia* standardized extracts and stevioside powder. A significant increase in the body weight was observed in the diabetic groups treated with both formulations. There was a significant reduction ($p<0.001$) in the plasma glucose, total cholesterol (TC), triglycerides (TG) and low density lipoprotein (LDL)-cholesterol levels and significant increase ($p<0.001$) in high density lipoprotein (HDL)–cholesterol in the treated diabetic group compared to the control. The results showed that Formulation-2 had potent antihyperglycaemic and antihyperlipidaemic activities when compared with the marketed herbal formulation.

Key words: Polyherbal formulation, Diabetic, Glucose, Momordica, Tablets.

INTRODUCTION

Diabetes mellitus (DM) is a major global metabolic disorder of current century. This pandemic is characterized by hyperglycemia occurring due to deficient insulin secretion and also to factors opposing the tissue effects of insulin or both[1]. Approximately 6.6% of the world's population suffers from diabetes. According to the International Diabetes Federation (IDF), the global prevalence of the disease has increased from 30 million people in 1985 to 285 million in 2009. IDF predicts if the current rate of growth continues unchecked, the total number will exceed 435 million in 2030[2]. Even though different types of oral hypoglycemic agents are available along with insulin for the treatment of DM, there is increasing demand by patients for natural products with antidiabetic activity, which may be due to their fewer side effects[3].The use of phytotherapy to treat human diseases has its roots in pre-historical times. Indigenous communities have long used plant extracts to treat illness including diabetes[4]. Major formulations used in ayurveda are based on herbs. Formulation-1 and formulation-2 are combination of three medicinal plants namely karela (*Momordica charantia),* dalchini (*Cinnamomum cassia)* and sweet leaf (*Stevia rebaudiana),* which are known to possess antidiabetic effect and have been used in the indigenous system of medicine to treat diabetes mellitus. The present study is aimed to assess the antihyperglycemic and antihyperlipidaemic activities of these two new polyherbal formulations.

MATERIALS AND METHODS

Drugs, chemicals and reagents: In the present investigation standardized extracts of *Momordica* (Total bitters ≥ 3%) and *Cinnamomum cassia* (Total

polyphenols ≥ 10%) were procured from Natural Remedies Pvt.Ltd. Bangalore. Stevioside powder was purchased from ASR Agri Exports Pvt. Ltd. Hyderabad. Alloxan monohydrate was purchased from Sigma-Aldrich (St Louis, MO, USA). Marketed formulation (Glucostat, manufactured by Atrimed) was obtained from local Ayurvedic store (Table 1). Biochemical kits were purchased from Excel diagnostics Pvt. Ltd. Hyderabad, India. All other chemicals used were of analytical grade, supplied by Vaagdevi College of Pharmacy, Warangal (A.P), India.

Preparation of polyherbal formulation: Standardized extracts of momordica, cinnamon, stevioside powder and microcrystalline cellulose (MCC) were weighed accurately and passed through sieve # 40 and blended for 20 min. A 5% solution of PVP in isopropyl alcohol was added to the blended mass until dough like mixture was formed. It was passed through mesh no. 16 to prepare granules and dried at 50^0C for 1 hr 30 minutes in a hot air oven. Dried granules were passed through mesh no.18[5]. The polyherbal formulations of standardized extracts (*momordica* and *cinnamon*) and stevioside were formulated into tablet form using different excipients by wet granulation method.

Evaluation of tablets[6]

Weight variation test: Ten tablets were selected randomly from each formulation and weighed individually to check for weight variation. A little variation is allowed in the weight of a tablet by the U.S Pharmacopoeia. In the total formulation the tablets weight is more than 324 mg, hence a 5% maximum difference was allowed.

Friability test: The friability of tablets was determined using Roche friabilator (Toshiba, India). It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by,

$$F = \frac{W_{final} - W_{initial}}{W_{initial}} \times 100$$

% friability of tablets less than 1% are considered acceptable.

Hardness test: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Five tablets were selected at random from each batch to perform this test. Monsanto hardness tester (Merck) was used to measure the hardness. Tablet was placed between spindle and anvil of the tester and the calibrated length adjusted to zero. The knob was then screwed to apply a diametric compression force on the tablet and the position on the calibrated length at which the tablet broke was recorded. A mean hardness was calculated for each batch and thus their standard deviations were calculated[7].

Disintegration test: The disintegration time of tablets was determined according to the method described in the British Pharmacopoeia 1998. Six tablets were placed in each compartment of the disintegration apparatus, with water thermostated at 37 ± 10^0 C as the medium. The tablets were considered to have passed the test after the 6 tablets passed through the mesh of the apparatus in 15 minutes[8].

***Stability testing*:** Prepared tablet formulations are tightly packed in plastic container for three months. Signs of degradation of tablets viz., Appearance (Cracking, chipping, mottling), Friability, Hardness and colour were observed and reported..

Test Animals*:* Wistar strain of albino rats (175±25g body weight), obtained from Teena Enterprises, Hyderabad, India were housed in standard polypropylene cages, and maintained under standard laboratory conditions (12:12 hr light and dark cycle); at an ambient temperature of 25±5^0C. Feed and water were provided *ad libitum* to all the animals. The experiments were planned after the approval of Institution Animal Ethical Committee (IAEC), Vaagdevi College of Pharmacy, Warangal (A.P), India (1047/ac/07/CPCSEA, dated: 24/04/2007).

Acute toxicity test: The toxicity study was conducted as per the official protocol OECD 420 guidelines. Single dose treatment of F1 and F2 (2g/kg body weight) was done to normal animals and the general observations such as skin and fur color, alteration in the color of eyes, mucous membrane, behavior, salivation, sleep, body weight and incidences of tremors, coma, diarrhea, lethargy are recorded up to 2 weeks[9].

Oral glucose tolerance test: Normal rats were fasted overnight and randomly divided into four groups of 6 rats each. Group I served as control, which received vehicle (distilled water 1ml/kg p.o), group II, III and IV were treated with 200mg/kg of marketed formulation, formulation-1 and formulation-2 respectively. Thirty minutes later, glucose (2g/kg) was administered orally to each rat. Blood samples were taken from the retro-orbital plexus at 0, 30, 60,

90, and 120 min after glucose treatment under mild ether anesthesia for estimation of glucose[10].

Induction of experimental diabetes: Overnight fasted animals were weighed and marked for individual identification. Rats were injected alloxan monohydrate with ice cold saline at a dose of 120mg/kg body weight intraperitoneally[9,11]. Normal control rats were injected with saline only. After one hour of alloxan administration the animals were given feed *ad libitum*. A 5% dextrose solution was given in feeding bottle for a day to overcome the early hypoglycemic phase[12]. Blood samples were collected before the administration of alloxan and after 5 days of alloxan administration[13]. The diabetic rats (blood glucose level > 250mg/dl) were separated and included in the study.

Experimental Design: Diabetic rats were divided into 5 groups of 6 animals each. Group I and II served as normal and diabetic control respectively and received vehicle (distilled water 1ml/kg). Group III, IV and V received 200mg/kg of marketed formulation, Formulation-1 and Formulation-2 respectively.

Biochemical Estimation: It is a single dose study, blood samples were collected at 0, 1, 2, 4, 6 and 24hr from retro orbital plexus after administration of test drugs and vehicle. Glucose levels were estimated using GOD-POD method.

Sub-acute study: It is a multi-dose long term study; the same animals were continued with the same dose of vehicle, marketed formulation, formulation-1 and formulation-2 once daily for 14 days. Blood samples were collected from retro orbital plexus 4hr after administration of test drugs and vehicle on 1, 7 and 14th day. Glucose levels and lipid levels were estimated using biochemical kits[14].

Measurement of body weight: It has been reported that induction of diabetes with alloxan is associated with the characteristic loss of body weight, which is due to increased muscle wasting, loss of tissue proteins, decreased rate of glucose utilization and impaired carbohydrate metabolism. Body weight is periodically checked before and on 1, 7 and 14th day of treatment with formulations.

Statistical analysis: Statistical analysis was carried out using Graph Pad PRISM software (version 6.03). The data were expressed as mean ±SD. The data of oral glucose tolerance test, antihyperglycemic activity and antihyperlipidemic activity were analyzed by one way ANOVA followed by Dunnet's multiple comparison tests. A 'P' value <0.05 was considered statistically significant.

RESULTS

Formulation-1 and Formulation-2 were prepared by wet granulation method. The physical properties of tablet were determined and the results of the uniformity of weight, hardness and friability of the tablets are given in Table 2. The low friability indicates that the herbal tablets are compact and hard. There were no changes in physical properties and the tablets were found to be stable up to 90 days

***Acute toxicity studies*:** Both formulations did not alter the physical and general behavioral pattern even up to 2 weeks .The observations with vehicle-control group also revealed non-toxic effect on general pattern of behavior in control condition.

***Oral glucose tolerance test*:** The blood glucose levels of the normal rats reached peak 60 min after oral administration of glucose (2g/kg b. wt) and gradually decreased to 119.75mg/dL in 120 min (Table 3). Formulation-1 and Formulation-2 produced significant ($p<0.01$) hypoglycemic activity in normal rats, which could be compared to Marketed Formulation. Formulation-2 produced potent hypoglycemic activity than Formulation-1 and Marketed Formulation (200mg/kg b. wt).

***Antihyperglycemic activity in alloxan induced diabetic rats*:** A single dose (200mg/kg b. wt) administration of both the formulations after induction of diabetes showed a significant reduction ($p<0.01$) in serum glucose levels at 4th hour. Maximum reduction in glucose levels from 352mg/dl to 100 mg/dl was seen at 4th hr after administration of Formulation-2 (Table 4).

On repeated administration of Formulation-1 and Formulation-2 for 14 days, a significant ($p<0.01$) and sustained decrease in serum glucose levels was observed at a dose of 200mg/kg as compared to the diabetic control group. A more significant decrease ($p<0.001$) in serum glucose levels was observed with the administration of Formulation-2 (200mg/kg b. wt) represented in table 5.

***Effect on body weight in alloxan induced diabetic rats*:** The change in body weight of animals in different groups was shown in table 6. Normal vehicle control animals showed increase in body weight on 7th and 14th day but diabetic control rats showed significant reduction in body weight, which was reversed by Formulation-1 and Formulation-2 (200mg/kg b. wt) during 14 day study. Animals treated with marketed formulation also prevented reduction in body weight.

***Antihyperlipidemic activity in alloxan induced diabetic rats*:** The results of Formulation-1, Formulation-2 and marketed formulation on the serum lipid levels were presented in tables 7 to 11. There was significant ($p<0.01$) decrease in TG, LDL and TC levels while significant ($p<0.01$) increase in HDL-cholesterol level was observed in all diabetic rats. In contrast, the untreated diabetic rats showed significant increase in TG, LDL and TC levels and significant decrease in HDL-cholesterol level. Formulation-2 showed more pronounced antihyperlipidemic activity ($p<0.001$) than Formulation-1 and marketed formulation.

DISCUSSION

In the present study the polyherbal formulations prepared were found to have good physical properties and improved the palatability and patient compliance. The blood glucose level in alloxan treated rats was significantly increased as compared to normal rats. The groups treated with Formulation-1, Formulation-2 and marketed formulation showed significant reduction in glucose levels as compared to the rats treated with alloxan alone on 7^{th} and 14^{th} day of treatment and in fasted glucose loaded rats, thus exhibiting antihyperglycemic activity. The reduced glucose levels suggested that both the formulations might either increase glucose uptake into muscles and adipose tissues through potentiating effects of insulin by increasing the pancreatic secretion of insulin from existing beta cells or by its release from the bound form.

Previously it has been reported that plants such as *Momordica charantia, Cinnamomum cassia, Stevia rebaudiana* show antihyperglycemic activity[15-17]. The significant antihyperglycemic activity of Formulation-1 and Formulation-2 may be attributed to the presence of above mentioned plants.

The loss of body weight and increase in food and fluid intake in diabetic rats as compared to that of control rats could be due to emaciation of skeletal muscle, dehydration and catabolism of fats and proteins[18]. The difference in body weights observed during the period of treatment of the rats treated with Formulation-1, Formulation-2 and marketed formulations were less compared to the diabetic control. Decreased fasting blood glucose could improve body weight in alloxan induced diabetic rats. Further, it is well known that in uncontrolled diabetes mellitus, there will be increase in the serum cholesterol, TG, LDL, VLDL and decrease in HDL which contribute to coronary artery disease[19]. In the present study, in diabetic control group, there was marked increase in total cholesterol, total lipid and TG, while significant decrease in HDL cholesterol level was observed. Both the formulations and marketed formulation reversed these lipid levels.

The abnormal high concentration of serum lipids in diabetes is mainly due to the increase in the mobilization of free fatty acids from the peripheral depots. Administration of polyherbal formulations for 14 days to diabetic rats decreased the levels of serum cholesterol, TG, LDL and VLDL. Treatment with polyherbal formulations also elevated HDL cholesterol levels[20].

Formulation-1 and Formulation-2 consists of important medicinal plants used in Indian system of traditional medicine. *Momordica charantia*, a major constituent of polyherbal formulations, has been found to increase HDL cholesterol and decrease total cholesterol and triglycerides in circulation. *Cinnamomum cassia* is reported to reduce the total cholesterol level in circulation[21]. The selected ingredients present in these formulations contribute to the antihyperlipidemic activity.

CONCLUSION

Standardized extracts of *Momordica charantia* (≥3% bitter principle), *Cinnamomum cassia* (≥10% total phenols) and stevioside from *Stevia rebaudiana* were used to prepare polyherbal tablet formulations F-1 and F-2. The usage of natural sweetening agents like *Cinnamon, Stevia* with *Momordica* improved the palatability of the formulations F-1 and F-2. Furthermore both the formulations exhibited significant antihyperglycemic and antihyperlipidaemic activity at 200mg/kg body weight dose and F-1 was found to be equipotent and F-2 was more potent than the marketed formulation (200mg/kg b. wt) because of the synergistic effect amongst the selected herbs, which has to be studied further.

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Table 1: Composition of Formulation-1 and Formulation-2 and Marketed formulation

Formulation 1 (F-1)	Formulation 2 (F-2)	Marketed Formulation/500 mg
Momordica (3 % bitter principle) - 200mg	Momordica (3 % bitter principle) - 200mg	Gymnema sylvestre – 125mg
Cinnamon - 150mg	Cinnamon - 150mg	Momordica - 125mg
Stevia - 50mg	Stevia - 150mg	Pterocarpus marsupium-100mg
MCC PH 101 - 20mg	MCC PH 101 - 20mg	Salacia reticulate - 75mg
PVP (Povidone K 25) - 5%	PVP - 5% (Povidone K 25)	Emblica officinalis - 75mg
Aerosil - 3mg	Aerosil - 3mg	
Magnesium stearate - 3mg	Magnesium stearate - 3mg	
Talc - 3mg	Talc - 3mg	

Table 2: Post compression parameters data for granules of Formulation-1 and Formulation-2

Batch	Hardness (kg/cm^2)	Friability (%)	Weight variation (%)	Disintegration (min)
Formulation-1	3.52±0.25	0.51±0.04	431.9±2.96	10.18±0.46
Formulation-2	3.44±0.28	0.53±0.05	532.1±3.57	10.33±0.57

Table 3: Effect of Formulation-1 and Formulation-2 on OGTT in normal rats

Treatment	0 min	30 min	60 min	90 min	120 min
Normal	87.5±3.41	184±6.32	195±8.98	144.75±9.91	119.75±8.73
Marketed Formulation (200mg/kg)	85.75±7.13	132.93±6.44*	150.57±6.44*	121.27±5.74*	101.66±2.95*
Formulation-1 (200mg/kg)	87.35±7.40	143.32±11.69*	125.91±5.74**	110.68±5.25*	94.02±4.77*
Formulation-2 (200mg/kg)	89.02±3.38	135.96±5.15*	118.88±4.01**	101.71±2.88**	78.35±4.90**

All values are expressed as mean ±SD. n=6: *p<0.05, **p<0.01 and ***p<0.001 when compared todiabetic control group. Data was analyzed by one-way ANOVA followed by Dunnet's test for multiple comparisons

Table 4: Effect of Formulation-1 and Formulation-2 on blood glucose levels of alloxan induced diabetic rats in acute study

Treatment	Blood glucose levels(mg/dL)					
	0 hr	1 hr	2 hr	4hr	6 hr	24 hr
Normal control	85.10±11.52	85.18± 10.32	85.62±8.52	81.84±9.40	82.81±12.97	85.22±8.27
Diabetic control	278±15.87	271.4±15.94	277.81±13.72	280.10±15.40	278.18±9.63	286.4±10.88
Marketed formulation (200mg/kg)	328.88±16.77	282.92±13.14	212.95±7.73*	167.32±10.85**	194.66±7.05**	331.03±17.76
Formulation-1 (200mg/kg)	278±15.87	233.47±22.13*	175.21±11.05*	131.44±5.13**	187.40±4.94**	288.33±11.06
Formulation-2 (200mg/kg)	352.21±18.95	233.77±13.2*	192.51±12.01*	100.25±9.06***	184.44±13.50**	357.14±22.45

All values are expressed as mean ±SD. n=6: *p<0.05, **p<0.01 and ***p<0.001 when compared to diabetic control group. Data was analyzed by one-way ANOVA followed by Dunnet's test for multiple comparisons

Table 5: Effect of Formulation-1 and Formulation-2 on blood glucose levels of alloxan induced diabetic rats in sub-acute study

Treatment	Blood glucose levels in mg/dL		
	First day	After 7 days	After 14 days
Normal control	85.18±11.56	89.99±16.66	91±14.52
Diabetic control	264.88±8.14	276.11±10.77	281.19±9.67
Marketed formulation (200mg/kg)	328.88±16.77**	257.7±13.87**	168.88±16.77**
Formulation-1 (200mg/kg)	278±15.87	233.33±17.63*	146.66±6.66**
Formulation-2 (200mg/kg)	352.21±18.95**	208.88±13.87***	119.99±13.33***

All values are expressed as mean ±SD. n=6: *p<0.05, **p<0.01 and ***p<0.001 when compared to diabetic control group. Data was analyzed by one-way ANOVA followed by Dunnet's test for multiple comparisons.

Table 6: Effect of Formulation-1 and Formulation-2 on body weight in alloxan induced diabetic rats

Treatment	Body weight (gm)		
	First day	After 7 days	After 14 days
Normal control	180±13.22	211.66±12.58	220±13.22
Diabetic control	148.33±12.58	135±10	123.33±7.63
Marketed formulation (200mg/kg)	163.33±12.58	178.33±12.58**	221.66±20.20**
Formulation-1 (200mg/kg)	160±5	191.66±10.40**	238.33±10.40**
Formulation-2 (200mg/kg)	163.33±8.49	211.66±10.27***	268.33±10.27***

All values are expressed as mean ±SD, n=6: *p<0.05, **p<0.01 and ***p<0.001 when compared to diabetic control group. Data was analyzed by one-way ANOVA followed by Dunnet's test for multiple comparisons.

Table 7: Effect on Serum cholesterol level in alloxan induced diabetic rats

Treatment	Serum cholesterol level in mg/dL		
	First day	After 7 days	After 14 days
Normal control	148.57±8.03	143.79±6.26	140.14±5.95
Diabetic control	277.80±9.08	278.48±9.87	282.59±8.54
Marketed formulation (200mg/kg)	266.3±12.95	206.65±10.76**	166.77±11.27**
Formulation-1 (200mg/kg)	274.01±9.84	212.1±11.68**	163.29±6.95**
Formulation-2 (200mg/kg)	276.65±10.54	204.47±8.80***	157.47±7.58***

All values are expressed as mean ±SD, n=6: *p<0.05, **p<0.01 and ***p<0.001 when compared to diabetic control group. Data was analyzed by one-way ANOVA followed by Dunnet's test for multiple comparisons

Table 8: Effect of Formulation-1 and Formulation-2 on serum triglycerides level in alloxan induced diabetic rats

Treatment	Serum Triglycerides level in mg/dL		
	First day	After 7 days	After 14 days
Normal control	82.40±6.16	85.14±5.73	81.07±7.16
Diabetic control	191.81±3.85	194.56±3.32	186.06±6.81
Marketed formulation (200mg/kg)	185.95±5.72	127.95±6.53**	114.77±5.93**
Formulation-1 (200mg/kg)	188.62±8.78	116.44±8.61**	101.51±7.43**
Formulation-2 (200mg/kg)	190.18±5.64	106.84±10.86**	85.32±5.89***

All values are expressed as mean ±SD, n=6: *p<0.05, **p<0.01 and ***p<0.001 when compared to diabetic control group. Data was analyzed by one-way ANOVA followed by Dunnet's test for multiple comparisons

Table 9: Effect of Formulation-1 and Formulation-2 on serum HDL-cholesterol level in alloxan induced diabetic rats

Treatment	Serum HDL level in mg/dL		
	First day	After 7 days	After 14 days
Normal control	55.92±3.39	57.40±7.15	55.33±7.70
Diabetic control	30.33±1.79	29.55±5.45	30.41±5.79
Marketed formulation (200mg/kg)	32.36±2.34	38.95±5.59	47.21±3.77**
Formulation-1 (200mg/kg)	36.92±6.26	42.29±5.22	48.81±3.15**
Formulation-2 (200mg/kg)	31.14±2.97	47.32±7.75*	66.51±5.37***

All values are expressed as mean ±SD, n=6: *p<0.05, **p<0.01 and ***p<0.001 when compared to diabetic control group. Data was analyzed by one-way ANOVA followed by Dunnet's test for multiple comparisons

Table 10: Effect of Formulation-1 and Formulation-2 on serum LDL-cholesterol level in alloxan induced diabetic rats

Treatment	Serum LDL level in mg/dL		
	First day	After 7 days	After 14 days
Normal control	76.17±8.53	69.36±14.54	68.42±15.01
Diabetic control	207.12±8.10	210.02±4.16	214.97±2.06
Marketed formulation (200mg/kg)	196.75±10.95	142.11±5.91**	96.60±15.45**
Formulation-1 (200mg/kg)	199.36±3.61	146.52±13.54**	93.27±9.51**
Formulation-2 (200mg/kg)	207.47±9.46	135.78±9.10***	73.90±1.80***

Table 11: Effect of Formulation-1 and Formulation-2 on serum VLDL-cholesterol level in alloxan induced diabetic rats

Treatment	Serum VLDL level in mg/dL		
	First day	After 7 days	After 14 days
Normal control	16.47±1.23	17.02±1.14	16.38±1.44
Diabetic control	38.35±0.76	38.90±0.66	37.20±1.36
Marketed formulation (200mg/kg)	37.18±1.14	25.58±1.30**	22.95±1.19**
Formulation-1 (200mg/kg)	37.72±1.75	23.28±1.72**	20.3±1.48**
Formulation-2 (200mg/kg)	38.03±1.7	21.36±2.17***	17.06±1.17***

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