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RESEARCH ARTICLE

ANTIHYPERLIPIDEMIC ACTIVITY OF METHANOLIC EXTRACT OF DIACURE *A* POLYHERBAL FORMULATION

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ABSTRACT

The aim of this study was to investigate the effects of methanolic extract of *Diacure a Polyherbal Formulation* for antihyperlipidemic effects in Streptozotocin induced diabetic rats. Its effect was compared with that of glibenclamide, a reference antidiabetic drug. White albino male rats were administered With Diacure a Polyherbal Formulation (100mg /kg body wt) orally for 30 days. At the end of 30 days, the serum lipid metabolites such as total cholesterol, triglycerides, HDL, LDL, free fatty acid, phospholipids and lipid peroxides were determined.In order to determine the HDL, LDL, fatty acid, Phospho lipid and lipase content in liver were estimated in control, Streptozotocin, extract treated and glibenclamide treated rats. Oral administration of Diacure a Polyherbal Formulation for 30 days resulted in significant reduction in blood glucose level, lipid profiles of serum and liver of plant treated rats where compared with untreated diabetic rats. The effects produced by the extract were comparable to that of glibenclamide. In conclusion the Diacure a Polyherbal Formulation showed significant antihyperglycemic and antihyperlipidaemic effect in Streptozotocin, induced diabetic rats.

INTRODUCTION

Diabetes Mellitus, a leading non communicable disease with multiple etiologies, affects more than 100 million people worldwide and is considered as one of the five leading causes of death in the world (Zimmet, 1999). The number of diabetic people is expected to rise from present estimate of 150 million to 230 million in 2025 (Iraj *et al.,* 2009). Diabetes mellitus is characterised by an increased concentration of blood glucose due to defects in insulin secretion, insulin action both resulting impaired metabolism of glucose and other energy yielding fuels such as lipids and proteins (Scheen , 1997). Experimental diabetes in animals has provided considerable insight into the physiological and biochemical derangement of the diabetic state. Many of these derangements have been characterised in hyperglycemic animals. Significant changes in structure and lipid metabolism occurs in diabetes (Sochar *et al.,* 1985). In these cases the structural changes are clearly oxidative in nature and are associated with development of vascular disease in diabetes (Baynes and Thrope, 1999). Liver, an insulin dependent tissue that plays a vital role in glucose and lipid homeostasis and it is severely affected during diabetes (Seifter and England, 1982).Liver and Kidney participates in the uptake, oxidation and metabolic conversion of free fatty acids, synthesis of cholesterol, phospholipids and triglycerides. During diabetes, a profound alteration in the concentration and composition of lipids occurs. Despite the great strides that have been made in understanding and management of diabetes, the disease and disease related complications are increasing unabated (Tiwari and Madhusudhana, 2002) Elevated levels of plasma triglycerol and reduced concentration of HDL Cholesterol have been strongly associated with the appearance of small dense LDL particles either in diabetic or non-diabetic individuals (Assumpta *et al.,* 1997). Oxidative stress play an important role in the chronic complication of IDDM. Hyperglycemia is involved in the generation of oxygen free radicals (Lee *et al.,* 2002). Biological oxidants are compounds that protect biological systems against the potentially harmful effects of processes or reactions that can cause excessive oxidations (Krinsky, 1992). Medicinal plants play an important role in

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the management of diabetes mellitus especially in developing countries where resources are meager. Many studies have confirmed the benefits of medicined plants with hypoglycemic effects in the management of diabetes mellitus. The effects of these plants may delay the development of diabetic complications and correct the metabolic abnormalities. Moreover, during the past few years some of the new bioactive drugs isolated from hypoglycemic plants showed antidiabetic activity with more efficency than oral hypoglycemic agents used in the clinical theraphy (Bnouham *et al.,* 2006). More than 400 plants with glucose lowering effect are known (Ernst, 1997). Also a number of plants have a hypolipidemic effect (Sharma *et al.,* 2003). However there is little information about plants with both hypoglycemic and hypolipidemic effects (Subash Babu *et al.,* 2006). The present study conclude that diacure a polyherbal Formulation methanolic extract has potential antihyperglycemic and antihyperlipidemic activity.

MATERIALS AND METHODS

Drugs and Chemicals

Streptozotocin was purchased from Ponmani Chemical Pvt., Ltd., Trichy. All other chemicals and reagents used were of analytical grade.

Plant Material

The fresh plant materials were collected from perambalur, Tamil Nadu, India. The plant was identified, authenticated and the voucher specimen has been kept in our laboratory for future reference. The respective plant parts as given in table below were shade dried, powdered and passed through a 40 mesh sieve, and kept in a well closed container for further extraction.

Preparation of plant extract

500g of dried, powdered plant material diacure, a polyherbal formulation a combination of 11 medicinal plants are mixed 1:1 ratio,the medicinal plants are listed in the table given below, were extracted successively with methanol using soxhelt apparatus. The residual extract was suspended in water for overnight and filtered. The filtrate was dried and was stored at 4^0C until used. A known volume of the residual extract is suspended in distilled water and was orally administrated to the animals during the experimental period.

Table showing the Diacure a polyherbal formulation combination of 11 medicinal plants.

S.NO	Name of the plant	Common name	Family	Part of the plant used
1	Syzigium cumini	Jamun	Myrtaceae	Seed
2	Azardiricta indica	Neem	Meliaceae	Leaves
3	Ocimum tenuiflorum	Tulsi	Lamiaceae	Leaves
4	Abitulon indicum	Tuthi	Malvaceae	Leaves
5	Cassia auriculata	Cassia	Ceasalpinaceae	Flowers
6	Ficus bengalensis	Aalam	Moraceae	Seed
7	Tinospora cardifolia	Seendal	Convolvulaceae	Root
8	Phyllanthus emblica	Nelli	Euphorbiaceae	Seed
9	Trigonella foena graceum	Fenugreek	Leguminasae	Seed
10	Curcuma longa	Turmeric	Zingiberaceae	Rhizome
11	Phyllanthus niruri	Keelanelli	Euphorbiaceae	leaves

As coted by Bnouham,M., Ziyyat,A., Mekhfi,H., Tahri,A., Legssyer, A., (2006).

Animals

Male albino rats of the wistar strain weighing about 175-210g were used for this study. The rats were 10-12 weeks of age at the time of this study. They were acclimatised to the animal house conditions atleast for one week before carrying out any experimental work. The rats were fed ad libitum with normal pellet (Hindustan Lever Ltd., Bangalore, India) and Water. The experiments were designed and conducted in accordance with the ethical norms approved by ministry of social justice and empowerment, government of India and International Animal ethics committee Guidelines for the investigation of experimental pain conscious animals.

Induction of diabetes mellitus

Diabetes was induced by a single IP injection of 55 mg/kg body weight of streptozotocin. After 72 hours of streptozotocin injection, the diabetic rats (glucose level >250mg / dL) were separated and used for the study (Perfumi, M and Tacconi, 1996).

Experimental design

The method described by Pari and Satheesh (2004) was adopted. In the experiment a total of 30 rats (18 diabetic surviving rats and 12 normal rats) were used. The rats were divided into 5 groups (6 rats / group) after the induction of streptozotocin - diabetes.

Group I : Normal untreated rats
Group II: Normal rats were given MEt 100mg/kg body weight in aqueous solution daily for 30 days.
Group III: Diabetic control
Group IV: Diabetic rats were given MEt 100mg/kg body weight in aqueous solution daily for 30 days.
Group V: Diabetic rats were given glibenclamide 600µg/kg body weight (Pari and Uma, 1999) in aqueous solution daily for 30 days.

On completion of 30 days of experimental period, the 18 hour fasted rats were anaesthetised and sacrificed by cervical dislocation. Blood was collected with anticoaglulant was used for serum separation.

Biochemical estimation

Blood glucose was determined by the method of sasaki et al., (1972) using O- toluidine reagent. Insulin content was assayed by using RIA Kit (for rats) supplied by Linco Research Inc. (Stat Dianostics, Mumbai). Total Cholesterol was estimated by Parekh and Jung (1970) method. Triglyceride was estimated by the method of Rice (1970). Lipoproteins (HDL and LDL) were fractionated by dual precipitation techniques (Burstein and Scholnick, 1972). Free fatty acid content was estimated by Hron & Menahan (1981) method. Phospholipid was estimated by the method of Bartlette (1959) by digestion with perchloric acid and phosphorus liberated was estimated by the method of Fiske and subbarow (1925). The level of lipid peroxides was asayed by the method of Ohkawa et al., (1979). Lipase activity was determined by kit method (Pointe scientific, inc, USA).

Statistical Analysis

The values are expressed as mean ± SD for Six rats in each group. All other data were analysed with SPSS/15.0 students software. Hypothesis testing method included one way analysis of variance (ANOVA) followed by post hoc testing performed with least significant difference (LSD) test. The 'P' value of less than 0.05 was considered to indicate statistical significance.

Table 1. Serum glucose, Insulin and Cholesterol content in control and experimental rats in each group.

Groups	Glucose (mg/dl)	Insulin (IU/L)	Cholesterol (mg/dL)
Control	97.22 ± 1.9	94.6 ± 0.87	166.7 ± 5.45
Normal + MEt	99.05 ± 1.6[a]	92.7 ± 0.61[a]	169.0 ± 4.70[a]
Diabetic control	257.88 ± 2.8[b]	59.5 ± 0.70[b]	345.8 ± 13.04[b]
Diabetic +MEt	106.05 ± 2.0[c]	91.2 ± 1.06[c]	209.70 ± 5.80[c]
Diabetic + glibenclamide	108.26 ± 3.7[d]	91.81 ± 3.40[d]	209.40 ± 8.90[d]

values are given as mean ± SD of 6 rats from each group. Values are statistically significant * P<0.05.

a Normal + MEt rats were compared with normal rats.
b Diabetic rats were compared with normal rats.
c MEt treated diabetic rats were compared with diabetic rats and glibenclamide treated diabetic rats.
d Glibenclamide treated diabetic rats were compared with diabetic rats.

Table-1 shows that the amount of glucose insulin and cholesterol in control and experimental group. The amount of glucose and cholesterol was significantly increased and the insulin level was decreased in streptozotocin induced diabetic rats. However the level of glucose, Insulin and cholesterol was returned to near normal concentrations in diabetic rats treated with MEt and glibenclamide.

Table 2. Serum Triglycerides, LDL and HDL level in control and experimental animals

Groups	Triglycerides (mg/dL)	LDL (mg/dL)	HDL (mg/dL)
Control	104.51 ± 5.31	93.86 ± 7.08	68.40 ± 3.66
Normal + MEt	105.03 ± 5.03[a]	94.73 ± 5.04[a]	67.86 ± 4.61[a]
Diabetic control	186.85 ± 4.46[b]	182.11 ± 3.63[b]	21.71 ± 2.11[b]
Diabetic + MEt	120.38 ± 3.50[c]	103.96 ± 7.87[c]	64.01 ± 2.44[c]
Diabetic + glibenclamide	115.60 ± 4.22[d]	115.01 ±10.09[d]	68.98 ± 2.91[d]

values are given as mean ± SD of 6 rats from each group. Values are statistically significant * P<0.05.

a Normal + MEt rats were compared with normal rats.
b Diabetic rats were compared with normal rats.
c MEt treated diabetic rats were compared with diabetic rats and glibenclamide treated diabetic rats.
d Glibenclamide treated diabetic rats were compared with diabetic rats.

The amount of triglycerides and LDL was increased and HDL content was decreased in streptozotocin induced diabetic rats. However the level of triglycerides, LDL and HDL was revert back in its normal level with the treatment of MEt and glibenclamide.

Table 3. Serum Free fatty acids, phospholipid and lipid peroxidation level in the control and experimental group

Groups	FFA (mg/dL)	Phospholipid (mg/dL)	Lipid peroxidation[#]
Control	11.03 ± 0.63	161.45 ± 6.38	24.7 ± 4.3
Normal + MEt	12.05 ± 0.55[a]	161.7 ± 5.83[a]	22.3 ± 3.1[a]
Diabetic control	24.05 ± 1.1[b]	243.3 ± 9.2[b]	40.9 ± 6.1[b]
Diabetic + MEt	14.31 ± 0.66[c]	194.81 ± 4.72[c]	31.2 ± 2.3[c]
Diabetic + glibenclamide	13.68 ± 1.12[d]	189.95 ± 2.79[d]	31.9 ± 5.8[d]

values are given as mean ± SD of 6 rats from each group. Values are statistically significant * P<0.05. # µmoles of MDA liberated / mg protein.

a Normal + MEt rats were compared with normal rats.
b Diabetic rats were compared with normal rats.
c MEt treated diabetic rats were compared with diabetic rats and glibenclamide treated diabetic rats.
d Glibenclamide treated diabetic rats were compared with diabetic rats.

Table-3 shows that the amount of FFA, Phospholipid and LPO in control and experimental animals. The amount of FFA, Phospholipid and LPO was increased in streptozotocin induced a diabetic rats. Treatment with MEt and glibenclamide to alloxan induced diabetic rats reduces the level of FFA, Phospholipid and LPO.

Table 4. LDL, HDL and FFA content in liver of control and experimental rats.

Groups	LDL (mg/dL)	HDL (mg/dL)	FFA (mg/dL)
Control	68.26 ± 1.4	42.16 ± 1.46	8.38 ± 1.09
Normal + MEt	70.43 ± 1.61[a]	41.43 ± 1.05[a]	8.03 ± 0.64[a]
Diabetic control	145.51 ± 1.39[b]	24.9 ± 1.15[b]	4.4 ± 0.56[b]
Diabetic + MEt	75.1 ± 1.08[c]	39.63 ± 1.38[c]	7.8 ± 0.81[c]
Diabetic + glibenclamide	73.33 ± 1.26[d]	42.73 ± 1.99[d]	8.38 ± 0.88[d]

values are given as mean ± SD of 6 rats from each group. Values are statistically significant * P<0.05.

a Normal + MEt rats were compared with normal rats.
b Diabetic rats were compared with normal rats.
c MEt treated diabetic rats were compared with diabetic rats and glibenclamide treated diabetic rats.
d Glibenclamide treated diabetic rats were compared with diabetic rats.

Table 4 shows that the amount of LDL, HDL and FFA in liver of control and experimental rats. The level LDL and FFA were increased and HDL level was decreased in the streptozotocin induced diabetic rats. Whereas the amount of LDL, FFA and HDL were revert back in its normal level with the treatment of MEt and glibenclamide.

Table 5. Phospholipid and Lipase content in the liver of control and experimental rats

Groups	PHospholipid (mg/dL)	Lipase (IU/L)
Control	166.16 ± 2.02	0.74 ± 0.04
Normal + MEt	170.08 ± 2.22[a]	0.75 ± 0.03[a]
Diabetic control	293.05 ± 2.09[b]	0.17 ± 0.02[b]
Diabetic + MEt	159.6 ± 4.02[c]	0.70 ± 0.04[c]
Diabetic + glibenclamide	165.35 ± 2.33[d]	0.71 ± 0.02[d]

values are given as mean ± SD of 6 rats from each group. Values are statistically significant * P<0.05.

a Normal + MEt rats were compared with normal rats.
b Diabetic rats were compared with normal rats.
c MEt treated diabetic rats were compared with diabetic rats and glibenclamide treated diabetic rats.
d Glibenclamide treated diabetic rats were compared with diabetic rats.

Table 5 shows that the level of phospholipid & lipase in the liver of control and experimental rats. Phospholipid content was increased and lipase level was decreased in the streptozotocin induced diabetic rats. Whereas the phospholipid and lipase content was return back its normal level with the treatment of MEt and glibenclamide.

DISCUSSION

Hyperglycemia and hyperlipidaemia are important characteristics of diabetes mellitus; an endocrine disorder is one of the most common chronic diseases worldwide. Streptozotocin, a β-cytotoxin, induces diabetes mellitus by damaging the insulin secreting β-cells of the pancreas, resulting in decreased endogenous insulin release. streptozotocin administered rats become hyperglcaemic in a short period of time, followed by hepatic glucose over production. (Milagro and Martinez, 2000). Diabetes is associated with profound alterations in the plasma lipids and lipoprotein profile and with increased risk of coronary heart disease (Betterridge, 2002). The liver and other some tissues participates in the uptake, oxidation and metabolic conversion of free fatty acids, synthesis of cholesterol and phospholipid secretion of specific classes of plasma proteins (Brown et al., 1993).

The aim of the present work is to explore the scientific basis of the utility of the methanolic extract of Diacure a polyherbal formulation for correction of hyperglycemia and hyperlipidemia in diabetes mellitus. It was evident from the results that MEt reduced the blood glucose level in streptozotocin induced diabetic rats. The antihyperglycaemic effect of MEt could be linked to more than one mechanism. The possible mechanism includes the stimulation of β-cells and subsequent release of insulin and activation of the insulin receptors. The plants antihyperglycaemic action may be by potentiation of pancreatic secretion of insulin, which was clearly evidenced by the increased level of insulin in diabetic rats treated with MEt. In this context, a number of other plants have also been reported to have antihyperglycemic and insulin release stimulatory effect (Kaleem *et al.,* 2006). An increase in serum cholesterol, triglycerides and LDL were observed in streptozotocin induced diabetic rats, but in MEt treated streptozotocin induced rats there is a reduction of cholestrol, triglycerides and LDL. These reductions could be beneficial in preventing diabetic complications as well as improving lipid metabolism in diabetes (Cho *et al.,* 2002). The level of HDL and FFA in serum was decreased in streptozotocin induced diabetic rats and these levels were increased with the treatment of MEt. Rajagopal and Sasikala (2008) reported that HDL and FFA were increased with the treatment of Nymphaea Stellata in streptozotocin induced diabetic rats. The marker hyperlipidemia that characterises the diabetic state may therefore be regarded as a consequence of the uninhibited action of lipolytic hormones on the fat depots (al - Shamaony *et al.,* 1994). Excess of fatty acids in plasma produced by streptozotocin promotes the liver conversion of some fatty acids to phospholipids and cholestrol. These two substances, along with excess of TG formed in the liver, may be discharged into lipoproteins in the blood (Bopanna *et al.,* 1997). Phospholipid and lipid peroxidation in serum was increased in streptozotocin induced diabetic rats. Whereas these levels were decreased in the treatment with MEt. The important factor determining the level and composition of serum and tissue lipids is LPO associated with cellular membrane studies have reported an increase in hepatic, MDA concentration in STZ induced diabetic rats when compared with the normal rats (Vaiyapuri *et al.,* 2008)

The liver lipid profiles like LDL, HDL, FFA, Phospholipids and lipase content were changed in the alloxan induced diabetic rats, where as the treatment with MEt to alloxan induced diabetic rats shows marked changes as shown in Table 4 and 5. In this context, activation of hormone sensitive lipase (HSL) during insulin deficiency is accompanied by enhanced release of free fatty acids in the plasma produced by the STZ - induced diabetes promotes the conversion of excess fatty acids into phospholipids and cholesterol in the liver, may be discharged into the blood in the form of lipoproteins (Bopanna *et al.,* 1997). It can be concluded from the data, MEt significantly reduces the levels of serum and tissue lipids, which are actively raised in alloxan diabetes rats. MEt has beneficial effect on plasma insulin. However its antihyperlipidemic effect could represent a protective mechanism against the development of atherosclerosis.

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