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Original Article

DIABETIC AMELIORATION BY POLY HERBAL SUPPLEMENT AND EXERCISE: STUDIES ON TYPE – I DIABETIC RAT MODEL

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ABSTRACT:Ayurvedic remedies for diabetes are usually mixed formulations containing blood sugar lowering herbs in combination with immunomodulators, diuretics and detoxicants, with the rationale behind such formulations being provided by modern research. The plants for the present study were selected on the basis of their anti-diabetic property, as these plants are consumed by the local people for treatment of diabetes as also supported by literature survey. Plants like Annona squamosa(Annonaceae), Cassia fistula, Coccinia indica, Mangifera indica, Ocimum sanctum, Lagerstroemia losflos-reginee, and Murraya koenigii used in the present study have been known to have same blood glucose lowering effect in diabetic animals and, some of them have an anti-lipidemic and cholesterol lowering effects too. To this effect, adult albino rats were made diabetic (DC) by a single i.p injection of alloxan (120 mg / kg body weight). Animals having blood glucose level of 300 mg / dl or higher were considered diabetic. Control and experimental animals were supplemented with the extract (PE) subjected to swimming exercise(s) of 30 minutes duration for 15 days. Animals were sacrificed on the 16th day and various parameters related to glycaemic status and carbohydrate metabolism were evaluated. The results of the present study showed significant favorable effect of S+PE in non-diabetic as well as diabetic rats. In terms of glycaemic regulation, neither PE nor PE+S showed any significant effect either on fasting or fed glycaemic level in non-diabetic animals while, both were equally effective in minimizing diabetic hyperglycaemia to the same extent. In DC animals, both PE and S+PE improved the insulin status. There was increased hepatic and muscle glycogen contents in both NC and DC animals treated with PE or also subjected to exercise. The increased tissue glycogen load and glucose clearance from blood are paralleled by significant decrement in tissue glycogen phosphorylase activity. There was decrement in cytosolic GLUT 4 level in NC.PE and NC.S+PE animals and significant increment in expression in DC.PE and DC.S+PE animals over that of the low level in DC animals. Overall, the present study provides support and evidence for consideration of a therapeutic approach combining the beneficial effects of a polyherbal preparation in association with adaptive physical activity for effective management of diabetic complications.

Keywords: Diabetes, Herbal extract, Alloxan, Exercise.

INTRODUCTION

Diabetes is a universal metabolic disorder, with an increasing global trend and of particular concern to India, which is fast developing into the world capital of this malady. Insulin insufficiency and hyperglycaemia, though the primary launching pads for the many other secondary consequences like metabolic derangement, oxidative stress,

hyperlipidemia etc, contribute to many other manifestations affecting the cardiovascular system, kidney, retina, nerve, lens and skin. Overall, quality of life suffers and longevity gets curtailed [1]. Multiple foci of insulin sensitive function such as glycogenesis, glycogenolysis, gluconeogenesis, glucose uptake and transport are all impaired.

Many valuable sources of knowledge are available in different cultures, dealing with medication for various diseases and disorders from ancient times and, one such rich source is "Ayurveda". There are many medicinal preparations and, recommendations for preparation, given in literature and, many of these recommendations make use of natural herbs with no side effects to the individuals. Since the information is too old, there arises the need to revive these recommendations carefully by making use of modern scientific techniques; these recommendations may lead to the development of some of the key areas of science such as nutraceuticals and cosmaceuticals [2]. Significance of selection of plants based on the Ayurvedic approach for medication of diabetics have been described and discussed [3] and in fact, there are number of published articles in support of the many indigenous preparations from different medicinal plants for treatment of diabetes.

Few of these preparations have been successfully tested with their active ingredients [4, 5]. Significance of lifestyle management, which includes control of diet and controlled exercise for efficient management of diabetes, has also been discussed. It is suggested by the experts of diet and health from American Diabetes Association (ADA) that, there is no single dietary rule to control diabetes, and the recommendations need to be made on the basis of the individual's health which varies from person to person [6]. The present study involves a polyherbal aqueous extract (PE), using leaves and seed of different plants like *Annona squamosa (Annonaceae), Cassia fistula, Coccinia indica, Mangifera indica, Ocimum sanctum, Lagerstroemia flos-reginee*, and *Murraya koenigii*. The plants used in the present study have blood glucose lowering effect in diabetic animals and, some of them also have an anti-lipidemic and cholesterol lowering effects. Biochemical evaluation of antidiabetogenic properties of some of these plants have been carried out in streptozotocin-induced diabetic rats [7]. A major objective of selecting these plants is that, they are commonly available with minimal or no cost of procurance and hence very cost effective. Ayurvedic remedies for diabetes are usually mixed formulations containing blood sugar lowering herbs in combination with immunomodulators, diuretics and detoxicants. The rationale behind such formulations is provided by modern research, which documents that immune processes play a predominant role in the destruction of beta cells and that free radicals feature predominantly in the progression of the disease and its secondary complications [2].

The present study was designed with the objective of elucidating the therapeutic efficacy of the poly herbal extract (PE) in combination with swimming exercise in rats rendered diabetic by evaluating mechanisms of glucoregulation. Swimming exercise was incorporated along with PE supplementation as, exercise has been known to have beneficial effects in diabetes management and in fact, swimming exercise has been recorded to have favorable effects in alloxan induced diabetic rats in terms of diabetic manifestations [3].

MATERIALS AND METHODS

Details of plants selected for the study: Seeds of *Cassia fistula(Fabaceae),* and leaves of *Langerstromia flos reginee (Lythraceae), Murraya koenigii(Rutaceae), Annona squamosa (Annonaceae), Ocimum sanctum(Lamiaceae), Coccinia indica(Cucurbitaceae) and Mangifera indica(Anacardiaceae)* were used for the preparation of a polyherbal extract. The plant material after collection was identified by Prof. M. Daniel (Head, Department of Botany, M.S.University of Baroda, Vadodara).

Preparation of polyherbal extract (PE): Equal amount (250 grams) of fresh leaves/seeds was plucked and separated from the twigs. Leaves were chopped into small pieces and shade dried and then ground in a mixer along with the seeds of *Cassia fistula* which were dried separately to get a powder mixture. The powder was extracted with distilled water using soxhelt at boiling temperature (100º C) up to 10 h; a dark brown coloured extract was obtained. This dark brown extract was cooled and filtered to remove the residue. The extract was concentrated on rotavapour under reduced pressure and then dried to

get a powder. The dried powder was diluted with saline in required proportion for the study. The PE was administered to non-diabetic and diabetic animals by oral gavage.

Swimming protocol for exercise: Animals were subjected to swimming exercise and were made to swim in a tank with a dimension (150X90X70) (length X breath X height), filled with water to a depth of 30–45 cm, once per day between 08:30 and 9:00 hrs. Animals were acclimatized by making them to swim for 5 days prior to the commencement of the experimental schedule. The acclimatized animals were divided into different experimental groups and were subjected to swimming exercise for 15 days for 30min.

Experimental animals: Female *Wistar* rats (200–250 g) were housed in the departmental animal house under controlled room temperature (21 ± 2 ºC). The animals were provided with rat chow and water *ad libitum.* The rat chow was purchased from M/s Pranav Agro Ltd., Baroda. The experiments were carried out after the approval of Animal Ethical Committee of Department of Zoology, The M.S. University of Baroda, Vadodara (Approval No. 827/ ac/04/ CPCSEA), and CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) guidelines were followed strictly.

Induction of Type I diabetes: Diabetes was induced in experimental rats by single intraperitonial injection of alloxan (120 mg/kg body weight) dissolved in 0.1 M Citrate buffer, pH 4.5. Diabetes was confirmed in animals after seven days of alloxan administration, and blood samples were collected form retro-orbital sinus and analyzed for glucose levels. Animals having fasting blood glucose levels higher than 300 mg/dl were considered for experiments.

Biochemical analysis: At the end of a 15 day treatment schedule, the rats were sacrificed by cervical dislocation after an overnight fast. Liver, Muscle and Kidney were excised out and stored at -80^{o} for further analysis. Glucose (assayed using Kit purchased from Agappe Diagnostics), and Insulin (assayed using Rat Insulin ELISA kit from MERCODIA, Sweden), were assayed using the above kits. Protein by Lowry *et al.* [8] (1951). Glycogen by Seifter *et al*, [9](1950). Glycogen phoshphorylase by Cahill. [10] (1957), Glucose-6-phosphatase by Harper [11] (1973), were assayed.

GLUT 4 expression in muscle tissue: Western Blot: Cytosolic fractions were prepared from skeletal muscles (gastrocnemius) from both control and test animals as described by dombrowski *et al* [12] (1996). Briefly stated, 100 mg of muscle was homogenized in an ice-cold homogenization buffer (1:10 w/v) containing 25 mmol l^{-1} 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 20mM b-glycerophosphate, 2 mmol l^{-1} ethylenediaminetetraacetic acid (EDTA), 250 mmol l^{-1} sucrose, 3.3 mg l^{-1} leupeptin, 3.3 mg l^{-1} aprotinin, 100 mg l^{-1} trypsin inhibitor and 1 mmol l^{-1} PMSF at pH 7.4 using a polytron-equipped homogenizer at a precise low setting on ice. The resulting homogenate was centrifuged at 1300Xg for 10 min at 4^{0} C. The supernatant was saved and the pellet was resuspended in a homogenization buffer and again spun at 1300Xg for 10 min at 4^{0} C and, the supernatant of this spin was combined with the first one and again spun at 9000Xg for 10 min at 4^{0} C. The resulting supernatant was further centrifuged at 1,90,000Xg for 1 h (Preparative Ultracentrifuge, Hitachi, Japan). The resultant supernatant was saved, and sampled as a cytosolic fraction for GLUT4 protein analysis. Protein concentration was further determined by the method of Lowry *et al* [8].

Separation of Proteins: Briefly, each sample (25 mg) was subjected to heat denaturation at 96^{0}C for 5 min with Laemmli buffer. The proteins were resolved by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE) on 10% polyacrylamide gels as described by Laemmli. [13], and then electrophoretically transferred to polyvinylidene difluoride (PVDF) membrane (Amersham Biosciences, UK). The membrane was blocked with phosphate-buffered saline plus 0.3% Tween-20 (PBST) containing 10% non-fat dry milk for 2 h and then incubated with anti–GLUT-4 (1:2000; Santa Cruz Biotechnology, USA), and b-actin (1:2000; Santa Cruz Biotechnology, USA) primary antibodies overnight. After three washes with PBST, the membrane was re-blocked and incubated with secondary antibody (horseradish peroxidase–conjugated donkey anti-rabbit IgG; 1:5000; Sigma, St. Louis, MO, USA) for 2 h at room temperature. The blots were then rinsed in Tris buffered saline with 0.05% Tween 20 and immunoreactive bands were detected by the

Enhanced Chemiluminescence Reagents (ECL; Amersham Biosciences, UK). Images were captured with a ChemiDoc TM XRS system (Bio-Rad Laboratories, CA, USA). Later, the membranes were incubated in stripping buffer (50 ml containing 62.5 mmol l^{-1} Tris–HCl (pH: 6.8), 1 g SDS and 0.34 ml b mercaptoethanol) at 55^0C for 40 min. After this, the membrane was reprobed using a b-actin antibody (1:2000). All protein bands were quantified (using Quantity one software system, Bio-Rad) and normalized against internal control b-actin.

Oral Glucose Tolerance Test (OGTT): At the end of treatment schedule, animals were fasted overnight and glucose tolerance test was done by feeding them orally with a glucose solution at a dose of 2g/kg body weight. Blood was collected from the retro orbital sinus at 0min, 30min, 60min, 90min, and 120min after glucose load. Serum was separated and, glucose was estimated in all the collected samples to get a tolerance curve for all the experimental groups.

Insulin Response Test (IRT): Response to insulin was checked by injecting Insulin to the rats at a dose of 1U/kg body weight intraperitoneally (i.p) in the fed state, a day following the completion of treatment and blood was collected at 0, 30, 60, 90, and 120 min from the retro orbital sinus under mild ether anesthesia . Serum was separated and used to estimate glucose level and, an insulin response curve was drawn to evaluate the results.

STATISTICAL ANALYSIS

Statistical evaluation of the data was done by one way ANOVA followed by Bonferroni's Multiple comparison test. The results are expressed as mean ± S.E.M using Graph Pad Prism version 3.0 for Windows, Graph Pad Software, San Diego, CA/USA.

RESULTS:

Glycaemic changes and Insulin levels (Table 1)

Non diabetic control rats supplemented with poly herbal extract (PE) has shown significant decrease in fasting serum glucose level with no apparent change in the fed state. Diabetic rats have shown significant hyperglycaemia in both fasted and fed states. However, supplementation with PE together with S showed significant anti hyperglycaemic effect with the decrement in fasted state being greater than the fed state on a percentage basis. The serum insulin titres have shown a decrement with both PE and S+DE in NC animals. Diabetic animals have shown a still lower significant decrement: Both PE and S+PE tended to increase the levels significantly though still significantly lower than in NC

OGTT (Fig 1, 2 and Table 2)

The glucose tolerance curves show an intermediary position for DC+PE and DC.S+PE animals. The area under curve also shows significant decrease in DC+PE and DC.S+PE animals in that order. The relative glucose elevation and clearance rates and the E/C ratio seem to suggest no apparent change in NC groups of animals though, NC+PE animals show a higher E/C value due to poor clearance. Diabetic animals show a significantly high E/C ratio with a higher elevation rate and poor clearance rate. Diabetic animals treated with PE or PE+S have shown significant decrement in E/C ratio essentially due to significant improvement in clearance rates in the order S+PE>PE. PE + S

IRT (Fig 3, 4 and Table 3)

The insulin response curves and the area under curve show no significant difference in any of the NC groups, while DC animals show higher positioning of the insulin response curve and greater area under curve. The insulin response curves show an intermediary position for DC+PE and DC.S+PE animals with the position of the latter being much lower. The area under curves also shows significant decrease in the order DC+S+PE > DC+PE. In terms of glucose clearance and elevation rates, where NC groups do not show much change, the DC+PE and DC+S+PE animals show increasing rates of clearance in that order.

Carbohydrate Metabolism (Figure 5, 6 and Table 4)

The tissue glycogen load of both liver and muscle was significantly lower in diabetic rats in conjunction with significantly increased phosphorylase hepatic glucose 6 phosphatase activities. Diabetic rats treated with PE or also subjected to S have shown significant increase in tissue glycogen contents with concomitant decrease in phosphorylase and G6Pase activities. These changes were greater in S+PE than in PE.

Table 1: Levels of Fasting, Fed Serum Glucose (mg/dl) and serum insulin levels in Exercised and Extract treated Non-Diabetic and Diabetic Rats

GROUPS	FASTING	FED	INSULIN
NC	93.97 ± 3.50	113.36 ± 3.18	0.349 ± 0.013
NC+PE	99.59 ± 5.187	110.12 ± 5.38	0.25 ± 0.00578 [c]
NC+S+PE	88.55 ± 8.064	140 ± 7.16 [b]	0.245 ± 0.006 [c]
DC	443.33 ± 31.21 [c]	655.33 ± 17.69 [c]	0.164 ± 0.013 [c]
DC+PE	201.25 ± 12.071 [@]	570.3 ± 14.18 [#]	0.170 ± 0.00334
DC+S+PE	159 ± 9.57 [@]	602 ± 2.57	0.185 ± 0.00334 [*]

Data are expressed as Mean±SE

NC = Non Diabetic Control, NC+PE = Non Diabetic Control+Polyherbal Extract, NC+S+PE = Non Diabetic Control+Swimming+Polyherbal Extract, DC= Diabetic Control, DC+PE = Diabetic Control + Polyherbal Extarct and DC+S+E = Diabetic Control+ Swimming +Polyherbal Extract

a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, ○) p< 0.005 •) p< 0.0005 compared to DC

Table 2 : Rates of glucose elevation and clearance for OGTT in exercised and extract treated diabetic and non diabetic rats.

ORAL GLUCOSE TOLERANCE TEST			
GROUPS	**RATE OF ELEVATION**	**RATE OF CLEARANCE**	**E/C Ratio**
NC	1.21	0.50	2.42
NC+PE	0.88	0.23	3.82
NC+S+PE	0.85	0.35	2.42
DC	9.13	1.07	8.53
DC+PE	6.85	1.23	5.56
DC+S+PE	6.5	2.21	2.94

Table 3: Rates of glucose clearance and elevation for IRT in exercised and extract treated diabetic and non diabetic rats.

INSULIN RESPONSE TEST		
GROUPS	**RATE OF CLEARANCE**	**RATE OF ELEVATION**
NC	2.1	0.56
NC+PE	1.13	1.244
NC+S+PE	1.16	0.94
DC	2.4	0
DC+PE	3.10	0.63
DC+S+PE	4.23	0

Table 4: Tissue Protein and Glycogen contents (mg/100 mg tissue) in Control and Treated Rats

	PROTEIN			GLYCOGEN	
Groups	Liver	Muscle	Kidney	Liver	Muscle
NC	16.39±1.24	9.76±1.42	10.39±1.10	2.18±0.10	0.93±0.035
NC+PE	17.57±0.042	9.94±0.0057	10.81±0.0120	2.41±0.0057[c]	1.53±0.0088[c]
NC+S+PE	13.90±0.0437[a]	5.50±0.0033[c]	10.043±0.0057	2.55±0.10[c]	1.63±0.0033[c]
DC	10.63±0.88	3.32±0.73	6.93±1.58	1.79±0.061	0.58±0.050
DC+PE	16.89±0.0033[@]	6.23±0.054[@]	10.49±0.0088[#]	1.84±0.008	0.65±0.0057
DC+S+PE	16.65±0.0033[@]	6.48±0.13[@]	11.89±0.015[@]	2.16±0.0057[@]	0.82±0.0038[@]

Data are expressed as Mean±SE

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a) $p<0.05$, b) $p< 0.025$ c) $p<0.01$, d) $p< 0.005$, e) $p< 0.0005$ compared to NC and *) $p< 0.05$ #) $p< 0.025$ @) $p< 0.01$, ○) $p< 0.005$ •) $p< 0.0005$ compared to DC

Tissue Protein content (Table 4)

Diabetic animals have shown maximal reduction in tissue protein contents though NC.S+PE also show some. Both PE and S+PE diabetic animals showed significant reversal of protein contents to NC levels.

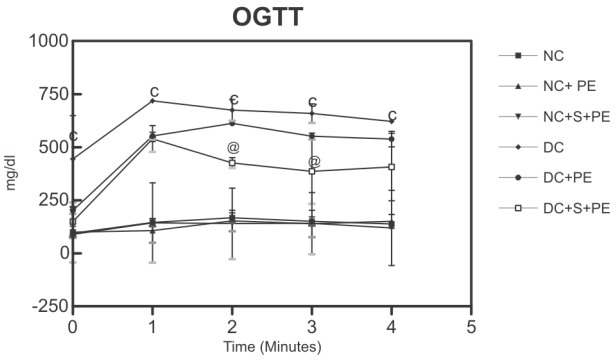
Immunoblot Analysis (Fig 7 and 8)

Immunoblot analysis for cytosolic GLUT 4 has shown significantly greater decrement in DC animals. Treatment with PE or treatment and exercise (S+PE) has shown an opposite picture of significant decrement in NC animals and increment in DC animals.

DISCUSSION

The present study undertaken to evaluate the efficacy of a poly-herbal extract (PE) prepared of seven plants of common use or, availability and, a combination of PE and swimming exercise (S), has shown significant favorable effect of both in non-diabetic as well as diabetic rats. In terms of glycaemic regulation, neither PE nor PE+S showed any significant effect either on fasting or fed glycaemic level in non-diabetic animals while, both were equally effective in minimizing diabetic hyperglycaemia to the same extent. Though both, DC.PE and DC.S+PE have shown similar average glycaemic level, the fasting glycaemic level is much better in DC.S+PE. This is well reflected in the observed significantly greater glucose clearance rate under GTT (2.21mg/min in DC.S+PE v/s 1.23mg/min in DC.PE). This would suggest either an increased insulin release upon glucose challenge and/or increased insulin sensitivity. The purported increased insulin sensitivity finds justification in the recorded greater glucose clearance in DC.S+PE animals during IRT (4.23 mg/min in DC.S+PE v/s 3.10 mg/min in DC.PE). In this context, two of the plants used in the present PE, *Coccinia indica* and *Occimum sanctum* have shown improved glucose tolerance in diabetic rats [5, 14] and even, *Annona squamosa* and *Murraya koenigii*, constituents of the present PE, have reported hypoglycaemic/anti-hyperglycaemic effect in diabetic animals [15, 16, 17, 18]. The relatively better insulin recovery from the diabetic low in DC.S+PE animals also subscribe to the possibility of greater β cell rejuvenation and increased secretion of insulin. The maintenance of glycaemic level in NC.E and NC.S+PE animals despite reduced insulin titers, is indicative of higher insulin sensitivity. However, in DC animals, both PE and S+PE improve insulin status and hence, their influence on glycaemic regulation in DC animals could be accredited to both a quantitative and qualitative effect of insulin. The reports of Kaleem *et al*. [17] of improvement in plasma insulin level and glucose on treatment with *Annona sqamosa* extract in streptozotocin induced diabetic rats and of Vinuthan *et al*. [19] of probable insulin synthesis and secretion from the β cells of

Fig. 1: Serum glucose levels in response to oral glucose tolerance test (OGTT) within a time range of 0 to 120 minutes in all the experimental groups.



Data are expressed as Mean±SE

NC = Non Diabetic Control, NC+PE = Non Diabetic Control+Polyherbal Extract, NC+S+PE = Non Diabetic Control+Swimming+Polyherbal Extract, DC= Diabetic Control, DC+PE = Diabetic Control + Polyherbal Extarct and DC+S+E = Diabetic Control+ Swimming +Polyherbal Extract

a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01,) p< 0.005) p< 0.0005 compared to DC

Fig. 3: Serum glucose levels in response to insulin administration (IRT) within a time range of 0 to 120 minutes of all the experimental groups

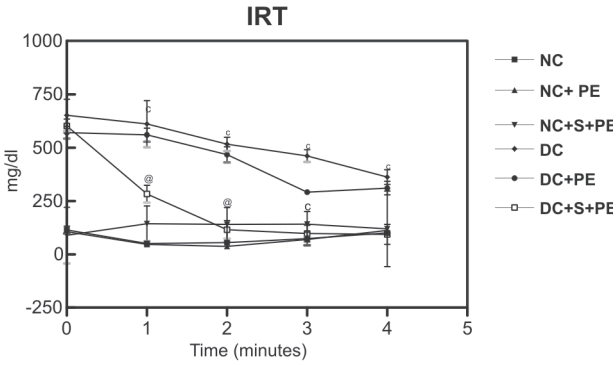


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Fig. 2: Area under curve for OGTT in all experimental groups

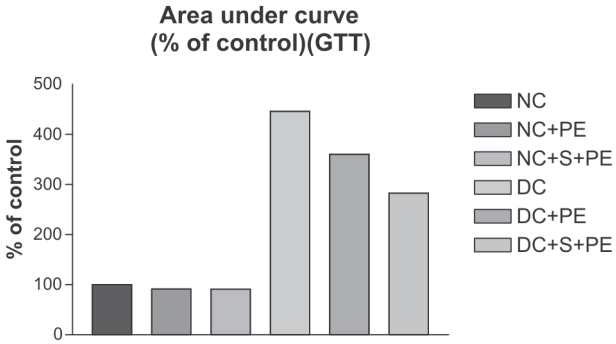

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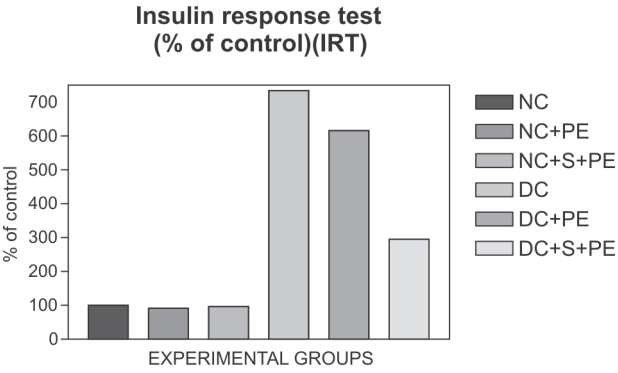
Fig. 4: Area under curve for IRT in all experimental groups



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pancreatic islets by the extract of *Murraya Koenigii* leaves in diabetic rats provide adequate support to the present contention. The greater insulin sensitivity and better glucoregulation shown by S+PE in DC animals is further well reflected in the recorded significant decrement in hepatic G6pase activity. Apparently, both PE and S+PE are potent in decreasing G6pase activity in both NC and DC animals. The appreciable decrement in G6pase activity seen in DC.S+PE> DC.PE animals, alluding to decreased gluconeogenesis, is well substantiated

Fig. 5: Hepatic and muscle glycogen phosphorylase activity in control and treated rats.

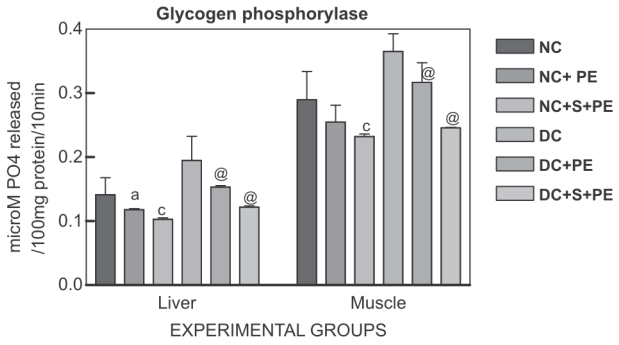

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Fig. 6: Hepatic Glucose-6-phosphatase activity in all the experimental groups.

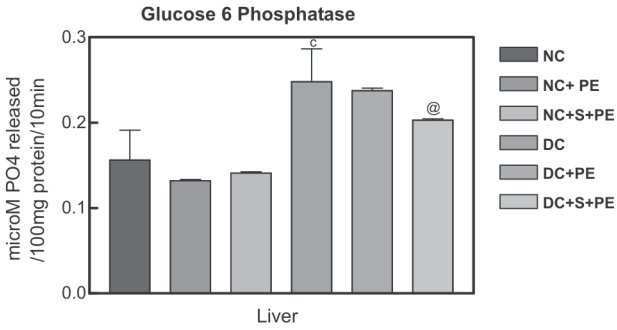

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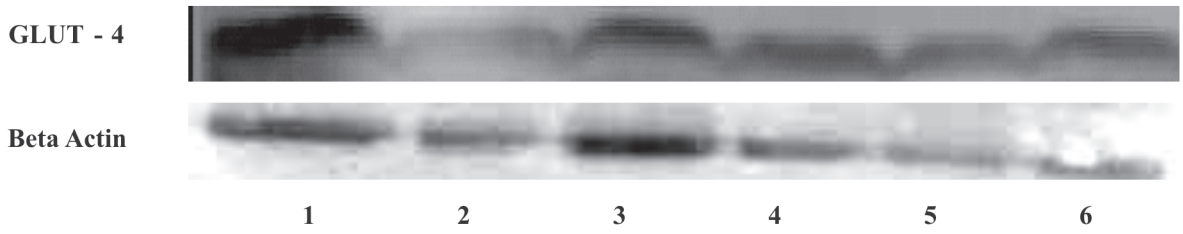
Fig. 7: Immunoblot analysis of Glut-4 protein expression.

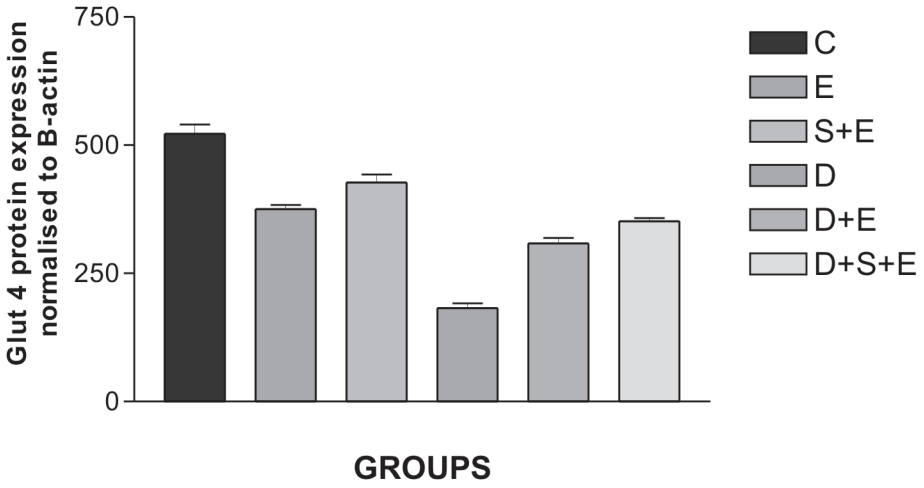


1 : Control, 2 : Diabetic, 3 : Swimming + Extract, 4 : Extract, 5 : Diabetic + Extract, 6 : Diabetic + Swim + Extract

by the presently observed increased tissue protein content in these animals. Another possible mechanism contributing to glycaemic regulation in NC and DC rats by PE or S+PE could be by reduced intestinal absorption, an effect of Mangifera *indica*, a constituent of PE, as has been indicated by the few studies on the hypoglycaemic and anti-hyperglycaemic effects of M.indica extract [20, 21, 22].

Increased hepatic and muscle glycogen contents in both NC and DC animals either treated with PE or also subjected to exercise are well co-relatable with the above discussed greater glucose clearance. The increased tissue glycogen load and glucose clearance from blood are paralleled by significant decrement in tissue glycogen phosphorylase activity. The present set of observations is in consonance with the idea that, PE and S+PE improve glycaemic status and carbohydrate metabolism deranged by diabetes, by way of increased glycogenesis and decreased gluconeogenesis. Interestingly, two of the plants in the PE extract, *Murraya koeingii* [23] and *Coccinia Indica* [24], have been shown to act by increasing glycogenesis and decreasing gluconeogenesis. These favourable changes in carbohydrate metabolism induced by PE and S+PE in diabetic animals and, to a certain extent even in non diabetic animals, bespeak of heightened glucose uptake into peripheral tissues. Experimental support to this is provided by the herein observed changes in cytosolic GLUT 4 expression. Whereas the decrement in cytosolic GLUT 4 level in NC.PE and NC.S+PE animals is indicative of increased membrane translocation, the significant increment in GLUT 4 expression seen in DC.PE and DC.S+PE animals over that of the low level in DC

Fig. 8: Semi quantification analysis of Glut-4 protein using scanning densitometry. Signals of Glut-4 in immunoblot were quantified arbitrarily. Bars represent means of ± S.E. of independent experiments and a representative immunoblot is shown here.



Data are expressed as Mean±SE

NC = Non Diabetic Control, NC+PE = Non Diabetic Control+Polyherbal Extract, NC+S+PE = Non Diabetic Control+Swimming+Polyherbal Extract, DC= Diabetic Control, DC+PE = Diabetic Control + Polyherbal Extarct and DC+S+E = Diabetic Control+ Swimming +Polyherbal Extract a) $p<0.05$, b) $p< 0.025$ c) $p<0.01$, d) $p< 0.005$, e) $p< 0.0005$ compared to NC and *) $p< 0.05$ #) $p< 0.025$ @) $p< 0.01$,) $p< 0.005$) $p< 0.0005$ compared to DC

animals, is suggestive of increased synthesis of GLUT 4 protein through transcriptional and translational activation. Apparently, PE promotes increased glucose uptake which is further potentiated by the additive effect of exercise, providing support to the actions of PE and S+PE on the molecular mechanisms contributing to insulin dependent or independent glucose uptake. The ability of S to up regulate GLUT 4 expression has already been reported [3]. It is pertinent to note that ellagitannin, an active principle of *Lagerstroemia speciosa* (a constituent of the present PE), has been reported to promote insulin like glucose uptake [25].

Overall, the present study provides support and evidence for consideration of a therapeutic approach combining the beneficial effects of a polyherbal preparation in association with adaptive physical activity for effective management of diabetic dysregulation of carbohydrate metabolism in Type-I-diabetes.

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