Research Article

Evaluation of Antidiabetic and Hypolipidemic Potential of *Drynaria quercifolia* Linn Rhizome in Streptozotocin Induced Diabetic Rats

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ABSTRACT

Traditional medicines from plants play an important role in the management of Diabetes Mellitus. Diabetes is a metabolic disorder critically affecting the population of both developed and developing countries. Recently, there has been a resurgent interest in the herbal treatments of diabetes. The present study has been designed to determine the Antidiabetic and Hypolipidemic potential of *Drynaria quercifolia* Linn. Rhizome in Streptozotocin induced diabetic rats. Glibenclamide (5mg/kg) was used as reference standard for the activity comparison. Ethanolic and chloroform extract of *Drynaria quercifolia* Linn. Rhizome in a dose of 400mg/kg used for the antidiabetic and hypolipidemic study. Fasting blood glucose level and lipid profile parameters were measured, from this result it was concluded that both extract has significant antidiabetic and hypolipidemic property. Histopathological study also revealed our findings.

Keywords: Diabetes, Hypolipidemic, Streptozotocin.

INTRODUCTION

Diabetes mellitus is a complex and a multifarious group of disorders that disturbs the metabolism of carbohydrates, fats and proteins. It results from shortage or lack of insulin secretion or reduced sensitivity of the tissue to insulin. Hyperglycemia and hyperlipidemia, as the most common features of DM, contribute to the development of micro vascular and macro vascular complications, which cause the morbidity and mortality.[1] Diabetes Mellitus is a global health crisis, which has been persistently affecting the humanity, irrespective of the socioeconomic profile and geographic location of the population. According to an estimate, one person detected with diabetes every 5 seconds somewhere in the world, while someone dies of it every 10 seconds. Currently India has the highest number of diabetes patients and India has called as the diabetic capital of the world.[2]

According to the International Diabetes Federation, diabetes is one of the most challenging health problems in the 21st century. Diabetes Mellitus estimated to be the 20th leading cause of burden of disease in the world in 2010, accounting for 1.4% of total years lived with disability, around the same percentage as respiratory infections or malignant neoplasm.[3] Global prevalence of diabetes mellitus is rapidly increased because of population aging, urbanization and associated life style changes.[4] The highest number of deaths due to diabetes is in countries with the largest numbers of people with diabetes India, China, United States of America, and the Russian Federation.

Diabetes is the most prevalent disease in the world affecting 25% of population and afflicts 150 million people and, which is expected to touch 300 million marks by 2025.[5] Recent reports have estimated an increase in these figures with the global prevalence reaching up to 66%, representing 285 million people in 2010, and by 2030 it will rise up globally 78% (438 million people).[2]

Traditional medicines from plants play an important role in the management of Diabetes Mellitus.[6] More than 1123 species of plants used experimentally to treat symptoms of diabetes mellitus. These are very large and widely distributed families; the phylogenetic distance between even these selected groups is a good indication of the varied nature of the active constituents. Therefore, it is necessary to learn more about particular groups of hypoglycemic natural products, and their mechanism of action before this method of drug discovery can be successfully employed.[7]

Nowadays, the agents used as the main means of diabetes treatment are synthetic drugs and insulin. However, these drugs usually come with considerable side effects such as hypoglycemia, drug resistance, dropsy and weight gain. In contrast, hundreds of traditional folk medicine has demonstrated potential for the treatment of diabetes with less tolerability and side effects. Thus, there is an increasing need to search natural antidiabetic agents from traditional medicine.[1]

Drynaria quercifolia Linn. (Polypodiaceae) is locally known as Matilpanna, pannakizhangu in Kerala. Traditionally, the fronds of plant are reported to be used by tribal communities of Tamil Nadu and Kerala in treatment of diverse ailments including typhoid fever, chronic jaundice, anti-inflammatory agent, as a poultice and antifertility agent, and antipyretic agent. The whole plant is used to treat chest and skin diseases, and is also anthelmintic, expectorant and tonic. Various phytoconstituents like 3,4-dihydroxybenzoic acid friedelin, epifriedelinol, *β*-amyrin, *β*-sitosterol and *β*-sitosterol 3-*β*-D-glucopyranoside has

been isolated from the plant.[8] Although the plant is traditionally used for treatment for diabetes mellitus in the folk medicine healers of Bangladesh, there are no systematic scientific reports in the modern literature regarding the usefulness of the plant and its phytoconstituents as a antidiabetic agent. Hence, to scientifically validate this ethnopharmacological relevance, antidiabetic and hypolipidemic potential of *Drynaria quercifolia* rhizomes was studied STZ induced diabetic rats.

MATERIALS AND METHODS

Plant material

The fresh and matured plants of *Drynaria quercifolia* were collected from different areas of Idukki district, Kerala in the month of March, and authenticated by Dr. Raju Thomas, Department Head of Botany, Baselius College, Kottayam. Voucher specimens were kept in our library with reference number UCP/MGU/RIMSR/ 2013/HERB 12, for future reference. After the authentication, fresh rhizomes were collected, cleaned thoroughly with distilled water and cut into small pieces and dried under shade. The shade-dried rhizomes were pulverized in a mechanical grinder to obtain coarse powder.

Chemicals

STZ and Glibenclamide (Spectrum reagent & chemicals, Kochi), sodium citrate (Nice chemicals Pvt. limited).

Experimental animals

Female Wistar rats weighing 150-200 gm obtained from the animal house of University College of Pharmacy, Regional Institute of Medical Sciences, Puthuppally, and housed in polycarbonate cages. Before the starting of the experiment, animals were acclimatized to the laboratory conditions for a period of 2 weeks prior to the treatment. They are maintained an ambient temperature (25±2^{o}C) and relative humidity (40-60%), with 12/12 h of light/dark cycle. They were fed on standard pellet and water given *ad libitum*. Institute Animal Ethical Committee (IAEC No: 1702/OP/C/13/CPCSEA) approved the study and all the experiments were carried out by following the guidelines of CPCSEA, India.[9]

Sequential Extraction of the Drug *Drynaria quercifolia* rhizome

The method based on the extraction of active constituents present in the drug using various solvents ranging from non-polar to polar by cold maceration. The solvents used are petroleum ether, chloroform, ethanol and water. The material subjected to successive extraction with solvents in their ascending order of polarity. In this process the substance, which is soluble in a solvent with particular range of polarity were extracted in the solvent and remaining marc further extracted with next solvent. The macerates were concentrated under reduced pressure on rotary evaporator at 40^{0} c for further use.[10, 11]

Preliminary phytochemical screening

The different rhizome extracts of *Drynaria quercifolia* was analysed for the presence of flavonoids, alkaloids, glycosides, steroids, phenols, vitamins, saponins, terpenoid, proteins, cardiac glycosides and tannins according to standard methods.[12, 13]

Acute toxicity study

Acute toxicity study was performed for the extracts to ascertain safe dose by the acute oral toxic class method by the Organization of Economic Cooperation and Development (OECD) 423 guidelines.

Oral glucose tolerance test

Oral glucose tolerance test were performed in overnight fasted (18h) normal rats. Rats were divided into five groups (n=6). Control animals received an equal volume of the vehicle (CMC solution). Group 2 rats were given Glibenclamide orally at a dose level 5mg/kg body weight. Rat in-group 3, 4 received orally DQCE and DQEE in doses of 400 mg/kg body weight, respectively. Glucose (2g/kg; p.o) was fed 30 min from the administration of extract. Blood were withdrawn from the tail vein at 30, 60, 90 and 120 min of extract administration and plasma glucose level was estimated.[14,15]

Experimental Induction of Diabetes in Rats

Diabetes mellitus was induced in overnight fasted adult Wistar albino rats weighing (170± 5) g by single intra peritoneal injection of freshly prepared STZ at a dose of 40 mg/kg in 0.1 m citrate buffer (PH= 4.5). After four days of STZ administration blood glucose level was estimated. Rats with blood glucose level above 200mg/dl considered diabetic and included in the study.[16]

Experimental design for screening

In this experiment, total 30 rats (6 normal; 24 STZ diabetic surviving rats) were use. The rats were dividing into five groups of six rats each.

Group 1: Normal control rats received vehicle solution (1% w/v CMC)

Group 2: diabetic control rats received vehicle solution (1% w/v CMC)

Group 3: diabetic rats treated with DQCE at the dose of 400mg/kg. b.w

Group 4: diabetic rats treated with DQEE at the dose of 400mg/kg.b.w

Group 5: diabetic rats treated with Glibenclamide at a dose of 5mg/kg.b.w

The vehicles and drugs were administered orally using intra gastric tube daily for three weeks. After three weeks of treatment, animals were sacrificed by cervical decapitation.[17]

Blood sample collection

Glucose estimation

For detecting fasting blood glucose levels blood samples were collected from tail vein and determined by glucose oxidase method on 1st, 7th, 14th and 21st day by using commercially available glucose estimating strips (one touch horizon glucometer, Johnson& Johnson).[18]

Lipid profile evaluation

For detecting lipid profile, blood samples were collected by cardiac puncture and transferred into empty fresh centrifuge tubes. Care was taken during collection and transferring of blood samples to prevent haemolysis. The collected blood samples were immediately centrifuged at 2000 rpm for 15 mints (Remi centrifuge, Mumbai). The serum separated was collect in fresh serum tubes and stored in 200^0C after tightly capped. Biochemical parameters notably total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) levels and high-density lipoprotein (HDL) level in blood serum were measured (Abdel Aziz M T *et al*, 2012). VLDL-C and LDL-C were calculated as per Friedwald's equation.[19]

$$VLDL = TG/5$$

$$LDL = TC - (HDL + VLDL)$$

Effect on body weight in STZ induced diabetic rats

During the study period of 21 days, the rats were weighing once in every week and Mean changes in body weight were calculated.

Histological studies

After blood sampling for the biochemical analysis, the animals were sacrificed, quickly dissected. Small slices of pancreas were taken and fixed in 10% formalin. The specimens were dehydrated in ascending grades of ethanol, cleared in xylene and embedded in paraffin wax. Sections of 6µ m thickness were stained with haematoxylin and eosin and subjected to microscopical examinations.[20]

Statistical analysis

The collected data on different parameters from each subject analyzed using standard statistical techniques. Data was analyzed by one way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. All values were expressed as mean ± SD. Data was computed for statistical analysis using Graph Pad Prism software. P values < 0.05 were considered as statistically significant.

RESULTS AND DISCUSSION

Phytochemical screening

The results of phytochemical screening shows that the chloroform and ethanolic extracts of *Drynaria quercifolia* Linn. Rhizomes possess the maximum number of constituents thus these two extracts were selected for further studies. The qualitative analysis of chloroform extracts of *Drynaria quercifolia* Linn. rhizome shows the presence of phytoconstituents like Carbohydrates, Steroids, Flavonoids, Tannins and Phenolic compounds. The ethanolic extracts of *Drynaria quercifolia* Linn. rhizome shows the presence of Carbohydrates, Cardiac glycosides, Steroids, Flavonoids, Tannins and Phenolic compounds.

Table 1: Physical appearance and yield of different extracts of powdered *Drynaria quercifolia* Linn. rhizome

Solvents used	Color and consistency	Percentage yield
Pet ether	light brown color, viscous and sticky	3.12%
Chloroform	brownish black color and sticky	8.72%
Ethanol	brown color and sticky	10.67%
Distilled water	dark brown color and non sticky	7.33%

Acute toxicity study

No mortality and no signs of toxicity found even after administration of a limit dose of 2000 mg kg. body weight of extract; hence, 1/5th of the dose(400mg/kg) were taken as effective dose for further screening studies as per OECD guidelines 423 (Annexure- 2D).

Oral glucose tolerance test

Oral glucose tolerance test was performed in normal rats and after the administration of 2g/kg glucose; blood glucose level was measured at 30, 60, 90 and 120 mint. Standard drug Glibenclamide (5 mg/kg) produced most significant reduction in the plasma glucose level at 60, 90, and 120 min after oral glucose administration. DQEC at a dose of 400mg/kg produced most significant reduction in blood glucose level at 60 and 90 minutes. DQEE at a dose of 400mg/kg produced most significant reduction in blood glucose level at 30, 60 and 90 minutes. From this result showed that the two extracts have significant reduction (P<0.01) in blood glucose level in OGTT.

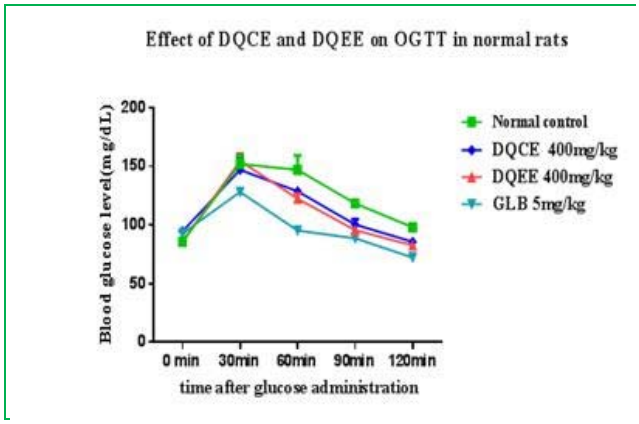

Figure 1: Effect of *Drynaria quercifolia* on Oral glucose tolerance test in normal rats.

Table 2: Effect of ethanolic and chloroform extracts of *Drynaria quercifolia* Linn rhizome on oral glucose tolerance test in normal rats

Treatment Group	Blood Glucose Level (mg/dl) after glucose (2g/kg) treatment at periods				
	0 minute	30 minute	60 minute	90 minute	120 minute
1% CMC	85.67±2.52	152±7	147±12.12	118.83±3.51	98±1
GLB 5mg/kg	93±3.06	128±3.61**	95.33±2.52**	88.67±4.04**	72.33±3**
DQEC 400 mg/kg	87.33±3.05	134.3±4.9**	111.33±14.15	87.33±2.08**	85.66±1.52
DQEE 400 mg/kg	85±1	120±5**	98.33±10.69**	93.33±5.68**	85.66±2.08

Values are presented as mean ± SD by one-way Analysis of Variance (ANOVA) followed by Dunnett's multiple comparisons, n=6, ***P*<0.01, when groups compared with diabetic control.

Table 3: Effect of ethanolic and chloroform extracts of *Drynaria quercifolia* Linn rhizome in fasting blood glucose level in STZ induced diabetic rats

Groups	Blood glucose level (mg/dl)			
	1st DAY	7th DAY	14th DAY	21st DAY
Normal	95.33±7.53	95±2.53	93±390	90±3.23
Diabetic control	384.25±23.56	417.2±13.65	453.25±16.94	533±39.18
GLB 5mg/kg	379.75±30.40	314.25±10.18**	229.5±11.82**	95.75±12.84**
DQCE 400mg/kg	392±28.417	384±19.322	285±20.897**	166.6±17.67**
DQEE 400mg/kg	395.25±19.67	346±32.17**	226.25±19.19**	116.25±15.47**

Values are presented as mean ± SD by one-way Analysis of Variance (ANOVA) followed by Dunnett's multiple comparison test, n=6,***P*<0.01, when groups compared with diabetic control.

Table 4: Effect of chloroform and ethanolic extracts of *Drynaria quercifolia* on body weight on STZ induced diabetic rats

Groups	Body weight (gm)			
	1st DAY	7th DAY	14th DAY	21st DAY
Normal	118.330±12.571	121.670±6.831	120.833±7.360	120.830±6.46
Diabetic control	113.75± 7.50	107.5±8.66	101.25±6.29	96.25±7.50
GLB 5mg/kg	110.5±5.77	111.25±5.77	117.50±2.88*	122.50±2.84**
DQCE 400mg/kg	116±10.247	115±10	117±10.368*	121±7.416**
DQEE 400mg/kg	121±8.216	123±10.368*	125±7.906**	130±7.906**

Values are presented as mean ± SD by one-way Analysis of Variance (ANOVA) followed by Dunnett's multiple comparisons test, n=6, *P <0.05,**P< 0.01, when groups compared with diabetic control.

Table 5: Effect of chloroform and ethanolic extracts of *Drynaria quercifolia* on lipid profile in STZ induced diabetic rats

Groups	Lipid profile (mg/dl)				
	HDL	LDL	TC	TG	VLDL
Normal	41.6±1.410	22±5.958	76.5±2.58	65.6±6	13.6±1.140
Diabetic control	25±1.789	131.5±1.87	188.83±3.54	165.33±2.33	31.166±1.42
GLB 5mg/kg	46.83±1.4**	27.83±1.4**	88.5±3.271**	76.33±1.86**	14.16±0.75**
DQCE 400mg/kg	40.83±0.75**	51.83±1.7**	117.66±4.22**	120.66±7.36**	24.5±1.049**
DQEE 400mg/kg	47.33±1.63**	35±2.828**	99.66±5.82**	89.85±5.08**	17.1±0.754**

Values are presented as mean ± SD by one-way Analysis of Variance (ANOVA) followed by Dunnett's multiple comparisons test, n=6, **P<0.01, when groups compared with diabetic control.

Effect of extracts on fasting blood glucose level

Presence of high fasting blood glucose level indicated the induction of diabetes. Both treated groups showed extremely significant decrease in blood glucose level when compared with diabetic control rats. The initial blood glucose level of DQEC and DQEE were 395.25±19.670 and 392±28.417 mg/dl respectively. After 14th day both extracts showed consistent reduction in blood glucose level (226.25±19.19, 285±20.897) and marked reduction in 21st day (116.25±15.478, 166.6±17.67). However, DQEE has shown maximum effect than DQEC. In standard group initial blood glucose level was 379.758±30.40 mg/dl and the last day was 95.75±12.84 mg/dl, which showed that the standard drug

produce maximum hypoglycaemic effect, and statistical analysis were extremely significant (*P*<0.01) and slightly higher than test group. Untreated diabetic rats showed increase in blood glucose level throughout the study period.

The hypoglycemic activity of DQEC and DQEE may be due to its protective action against STZ mediated damage to the pancreatic beta cells and possibly because of regeneration of damaged beta cell or increased insulin release or secretion.

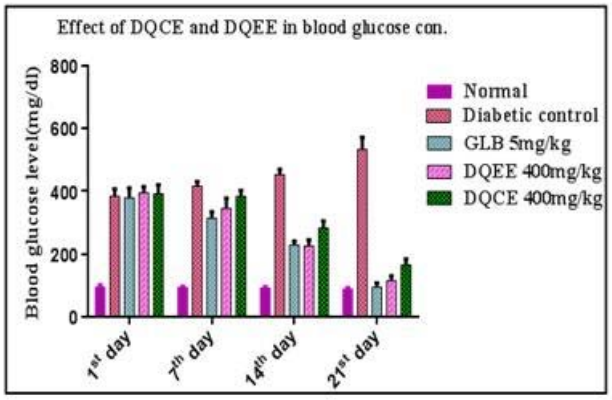

Figure 2: Effect of ethanolic and chloroform extracts of *Drynaria quercifolia* Linn. rhizome in fasting blood glucose level in STZ induced diabetic rats.

Effect of *Drynaria quercifolia* on body weight on STZ induced diabetic rats.

Body weights of the diabetic untreated control group decreased from 113.75±7.50 to 96.25±7.50 after 21 days. In standard drug group, the initial body weight was 105±5.77 and after 3 weeks of treatment was 122.50±2.89, which significant (*P*<0.01) when compared with diabetic control groups. The initial body weight of DQEC and DQEE were 116±10.247, 121±8.216 respectively and after 21 days of treatment the body weight was gained to 121±7.416 (p< 0.01) and 130±7.906 (*P*<0.01) respectively which is significant when compared with control groups. When compared between two different extracts DQEE gained more weight than DQEC group.

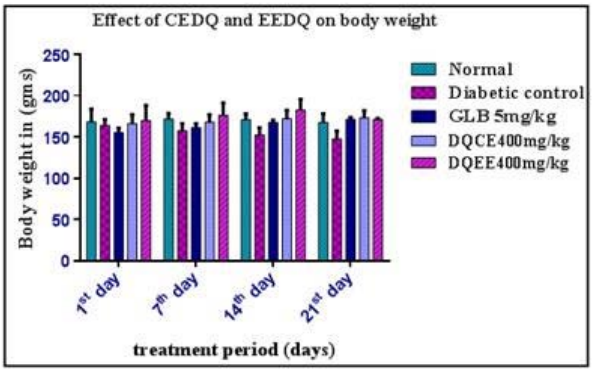

Figure 3: Effect of chloroform and ethanolic extracts of *Drynaria quercifolia* on body weight on STZ induced diabetic rats.

The ability of these test extracts to restore body weight seems to be a result of its ability to reduce diabetes by increased glucose metabolism.[17] The above effect in diabetic rats may be due to its preventive action on pancreatic beta cells destruction by STZ, which improves insulin levels, stabilization of blood glucose in diabetic rats and there by inhibition of muscle wasting by the reversal of gluconeogenesis.[21] The ability of the Drynaria quercifolia rhizome extract to protect the body weight loss seems to be due to its antidiabetic activity.

Effect of *Drynaria quercifolia* on lipid profile in STZ induced diabetic rats

The plasma lipid profiles i.e. total cholesterol, triglycerides, and lipoprotein values were shown in Table 5. The levels of plasma total cholesterol (TC), triglycerides (TG) and low density lipoprotein (LDL-C) were significantly increased, whereas levels of high density lipoprotein (HDL-C) were significantly decreased in diabetic rats as compared to control rats. Administration of test extracts to diabetic rats, reversed plasma lipid profile near normal values showed that treatment with *Drynaria quercifolia* significantly improved the lipid profile in diabetic animals (*P*<0.01). The effect of DQEE (400mg/kg; p.o) was more significant than that of DQEC (400mg/kg; p.o) and was comparable with that of Glibenclamide (5mg/kg).

The altered lipid profiles were reaches to near normal level after the treatment of both extracts of DQ and Glibenclamide in STZ induced diabetic rats. This lipid lowering action may be due to proper stabilization of glucose level and increase in insulin level after the administration of test extracts, which may normalize the disturbed lipid metabolism in diabetic rats. Therefore, hypolipidemic effect of DQEC and DQEE in diabetic rats supports its ability to prevent the CVD associated with diabetes.

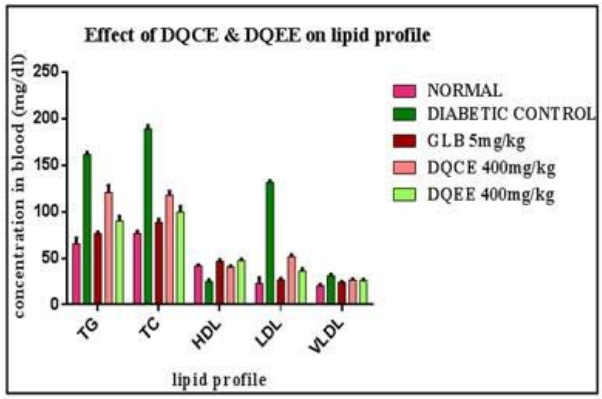

Figure 4: Effect of chloroform and ethanolic extracts of *Drynaria quercifolia* on lipid profile in STZ induced diabetic rats.

Histological examination of pancreas

In the present study, histopathological examination of pancreas of STZ induced diabetic rats' revealed destruction of beta cells and reticular changes of islet as evidence of fibrosis and destroy pancreas partially. The

histopathological study of diabetic treated group indicated increased volume density of islets and increased percentage of beta cells, in the diabetic rats that received the extracts, which may be a sign of regeneration. Signs of regeneration of ß cells, potentiation of insulin secretion from surviving ß cells of the islets of Langerhans and decrease of blood glucose have been reported following consumption of some plant extracts.[23] *Drynaria quercifolia* rhizome extract may have some chemical components that exert regenerative effects on ß cells, stimulate these cells to produce more insulin (pancreatotrophic action) or may have some insulin-like substances. Induction of regenerative stimulus in diabetic state triggers pancreatic regenerative processes, thereby restoring functional activities of the pancreas.

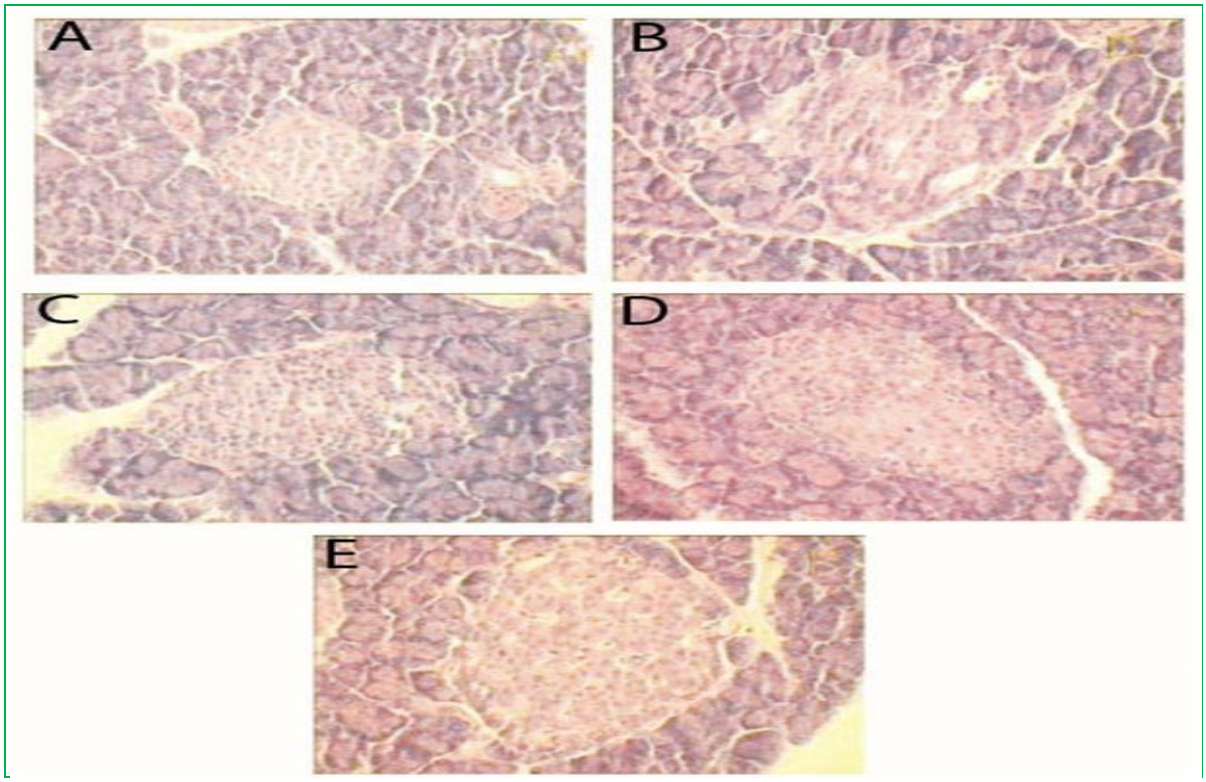

Figure 5: Histological examination of pancreas

Group A (Normal control): Normal histology in normal rats; **Group B** (Diabetic control): Hematoxylin-eosin section showed pancreatic acini, small atrophic islet cells; **Group C** (Standard group- GLB 5mg/kg): Glibenclamide treated rats pancreas showed absence of dilation and prominent hyperplastic islets; **Group D** (DQEC 400mg/kg): Diabetic rats treated with DQEC 400mg/kg showed mild expansion and absence of dilation; **Group D** (DQEC 400mg/kg): Diabetic rats treated with DQEE at a dose of 400mg/kg showed moderate pancreatic islets showed prominent hyperplasic islets.

CONCLUSION

Based on these results, it was clear that the chloroform and ethanolic extract of *Drynaria quercifolia* possesses antidiabetic and hypolipidemic activity in experimental animal models, which support the traditional uses of *Drynaria quercifolia* Linn rhizome. However, detailed studies were required to determine the exact nature and mechanism of action of the phytochemical compounds responsible for the antihyperglycemic and hypolipidemic effects of *Drynaria quercifolia* Linn rhizome.

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