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Article

Ameliorating effect of *Malva Neglecta* on hyperglycemia and hyperlipidemia in diabetic rats

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The plant, *Malva neglecta* wallr., is widely consumed for medicinal and nutritional purposes. The current study was carried out to assess the hypoglycemic and antihyperlipidemic potential of aqueous methanolic extract of *M. neglecta*. Chemical evaluation of the extract was performed by high pressure liquid chromatography. Oral glucose tolerance test (OGTT) was done in diabetic rats pre-exposed to 250, 500 and 750 mg/kg plant extract via the oral route. For hypoglycemic and biochemical study, the same therapy was administered to alloxan induced diabetic rats for 14 days. The standard control group received Glibenclamide (5 mg/kg). Ferulic acid, *p*-coumaric acid and other phenolic acids were detected and estimated in the extract. Administration of the plant extract significantly reduced blood glucose level in diabetic rats subjected to OGTT. The plant extract lowered the fasting blood glucose and alpha amylase, and prevented the damage to pancreas. It also corrected dyslipidemia in diabetic animals following 14 days therapy. Hence, this experimental study establishes the fact that *M. neglecta* exhibited significant antidiabetic and antihyperlipidemic activities in alloxan induced diabetic rats.

Keywords: Antidiabetic. Malva neglecta. Alloxan. Hypolipidemic. Alpha amylase.

INTRODUCTION

Diabetes Mellitus (DM) is associated with hyperglycemia owing to reduced production of insulin or inability of the body to utilize insulin (Association, 2014). Progression of DM is associated with various complications. Micro-vascular complications include neuropathy, nephropathy and retinopathy, whereas peripheral and coronary artery diseases are the macro-vascular alterations caused by DM (Fowler, 2008). The prevalence of DM is increasing steadily even in low- and middle-income countries. It is suggested to be the 7th major cause of death globally with the prevalence of 4.7-8.5% during 1980 to 2014 (Organization, 2016). A previous study has shown that 592 million people would be affected by DM up to the year 2035 (Guariguata *et al*., 2014). Unhealthy lifestyle and diet, inadequate health care services and large-scale urbanization are major risk factors that increase the occurrence of DM in developing countries (Kaveeshwar, Cornwall 2014; Akhtar *et al*., 2016a).

An impairment of carbohydrate metabolism accelerates the process of lipolysis that culminates in hyperlipidemia. It increases the risk of atherosclerosis and causes oxidative stress that culminates in cardiovascular complications. The DM causes an increase in triglycerides and low-density lipoproteins (m) (Alamgeer *et al*., 2017). Insulin resistance develops due to altered metabolism of lipids. A rigorous metabolic control is required to avoid and delay the complications of DM. Risk of hypoglycemia restricts the extensive insulin use for acquiring euglycemia (Mehmood *et al*,. 2016). The current pharmacological

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therapies, comprising of exogenous insulin and oral hypoglycemic agents are unable to establish glycemic homeostasis without adverse effects (Tiwari, Rao, 2002). The DM also exerts substantial economic burden in developing countries (Organization, 2016). These facts prompt the exploration for anti-diabetic activity of medicinal plants and their phytochemicals which may be beneficial for DM complications (Tiwari, Rao 2002; Akhtar *et al*., 2016b).

The plant *Malva neglecta* wallr. (Family: Malvaceae) is locally known as "Sonchal". It is used as a traditional therapy for respiratory, urinary, inflammatory and digestive system disorders (Gürbüz *et al*., 2005). It is also used traditionally as anti-diabetic agent (Yaseen *et al*., 2015). Pharmacologically, it exhibits antiulcer, antibacterial and oxygen radical scavenging activities (Dalar *et al*., 2012). The presence of different chemical constituents, including tannic acid, quercetin, *p*-coumaric acid, quinic acid, malic acid, salicylic acid, rutin, hesperidin, vanillin, coumarin and luteolin has been reported from *M. neglecta* (Haşimi *et al*., 2017).

The plant has not been validated for the ethnobotanical claim of antidiabetic action. Furthermore, the antioxidant activity and presence of phenolic and flavonoids also suggested possible hypoglycemic and hypolipidemic potential of the plant. The current study was designed to evaluate the antidiabetic and the hypolipidemic potential of aqueous methanolic extract of *M. neglecta*.

MATERIAL AND METHODS

Alloxan monohydrate and analytical grade compounds for high pressure liquid chromatography (HPLC) analysis (Sigma-Aldrich Co. USA), methanol, acetonitrile, HPLC grade (Merck Pharmaceutical Private Limited), Glibenclamide (Sanofi-Aventis Pakistan Limited), normal saline (Medipak Limited®, Pakistan) and glucometer Accu-Chek® Performa (Roche Diabetes Care) were utilized in the study.

Plant collection and extraction

The whole plant *M. neglecta* was collected from the fields of the University of Agriculture (UAF), Pakistan during Jan-Feb, 2017. The plant material was identified by a taxonomist from the same univversity and the plant sample was deposited to the herbarium for future reference (Ref. No. 10495). The whole plant was washed, shade dried and coarsely powdered. The plant powder was macerated with an aqueous methanolic solution (70:30) for seven days. The plant powder and solvent ratio was 1:5. The filtrate was separated, pooled and dried with a rotary evaporator to acquire crude extract of dark green color. The extract was stored in amber colored air tight containers at 2-8 ºC (Ahmed *et al*., 2017).

Estimation of phenolic and flavonoid compounds

A quantitative analysis was performed for determining phenolic and flavonoid compounds in *M. neglecta* extract. The sample preparation was carried out by dissolving 50 mg plant extract in 40 mL double distilled water and methanol (2:3) solution through shaking for 5 min. Then, 10 mL, 6 M HCl was added. The solution was heated in an oven for about 2 h at 90 ºC followed by filtration through 0.2 µm syringe filter. Then the sample was subjected to HPLC (Shimadzu, Japan). Phenolic and flavonoid compounds were identified by using Shim-Pack C18 column by reverse phase HPLC technique. The mobile phase comprised of two gradients, 1 and 2. Gradients 1 comprised of water: acetic acid (94:6) at pH 2.27. Gradient 2 consisted of acetonitrile only. Gradient 2 flow rate was 1 mL/min for 0-15 min = 15%, 15-30 min at 45% and 30-45 min at 100%. The detection of phytochemicals was carried out with a UV-Vis detector attached to the HPLC at 280 nm wave length (Saleem *et al*., 2019).

Experimental animals

Wistar rats of 200-250 g weight were used in the study. The animals were acclimatized to laboratory conditions at room temperature (25 ºC with a variation of 2 ºC) in an equal duration of day and night cycle. Animals were fed with standard chow diet. Animal study was approved by the Institutional Review Committee, GC University Faisalabad. Guidelines of the National institute of health were carefully followed regarding the care of animals (NIH publication no. 85-23).

Induction of diabetes

Diabetes was induced in rats by administering 150 mg/kg alloxan through intra-peritoneal route (Ahmed *et al*., 2010). To avoid the initial hypoglycemia in alloxan treated rats, 10% w/v glucose solution was administered. The fasting blood glucose level was checked 48 h post alloxan administration. Diabetic animals with more than 200 mg/dL fasting blood glucose were used in the study.

Animal groups

The animals were divided into 6 groups, each comprising of 6 rats. Normal control (NC) group received normal saline. Diabetic control (DC) group received normal saline only. Diabetic standard therapy (PC) group received 5 mg/kg glibenclamide. Other groups received plant extract either of 250 (MN250), 500 (MN500) and 750 mg/kg (MN750) plant extract (Kumar *et al*., 2012).

Evaluation through OGTT

The hypoglycemic effect of the plant extract was evaluated through OGTT in diabetic rats. The rats, fasting for overnight, were fed with 2 g/kg glucose 1/2 hour after the specified dosing regimen indicated in animal groups (Miura *et al*., 2001). Blood samples were drawn from rat tail. The blood glucose level was determined just prior to glucose administration and 30, 60 and 120 min from the tail vein for estimation of glucose level (Fatima *et al*., 2019).

Evaluation of hypoglycemic activity after multiple dosing

All rat groups were subjected to daily therapy for 14 days. Animal weight and blood glucose level were monitored at 0, 1, 3, 5, 7, 10 and 14th day. After two-week therapy, rat blood samples were collected in coagulation tubes by heart puncture under chloroform anesthesia. The blood was used to determine biochemical parameters such as total cholesterol, high density lipoproteins (HDL), triglycerides and serum alpha amylase (Kumar *et al*., 2012).

Histopathological study

The pancreas was removed and preserved in 10% formaldehyde. The slides of pancreatic tissues were prepared with microtome and fixed in paraffin (Akhtar *et al*., 2018). These were then stained with hematoxylin & eosin, and subjected to histopathological examination under a light microscope (Sharif *et al*., 2016).

Statistical analysis

The data were stated in the form of standard error of mean (Mean ± SEM). Results of blood glucose level in OGTT and 14 days study were analyzed by repeated measures two-way analysis of variance (ANOVA) followed by Duncan range comparison test. However, results of the, body weight lipid profile and α- Amylase were analyzed by one-way ANOVA followed by the same post-hoc test. The difference was considered significant at $P < 0.05$.

RESULTS

Chemical Analysis

Evaluation of *M. neglecta* extract through HPLC showed the occurrence of compounds such as quercetin, gallic acid, ferulic acid, *p*-coumaric acid and sinapic acid. The most abundant phytochemical was ferulic acid followed by sinapic acid and para-coumaric acid. The quantities of phytochemicals detected in plant extract are shown in Table I.

TABLE I – Retention time, percentage area and quantities of phytochemicals in *M. neglecta* extract

Compounds detected	Retention time (minutes)	% Area	Quantity (ppm)
Quercetin	2.84	0.1	0.0744
Gallic acid	4.7	1.9	0.8143
p-coumaric acid	17.673	12.1	1.9114
Ferulic acid	22.24	7.5	6.5814
Sinapic acid	26.013	14.8	2.3368

Effect on OGTT

Administration of glucose solution significantly increased the blood glucose level in disease control group compared to that of normal control. The extract of *M. neglecta* exhibited a significant decrease in blood glucose level as compared to untreated diabetic rats after 120 min. The normo-glycemic effect of all the doses of plant extract was evident as shown in Figure 1.

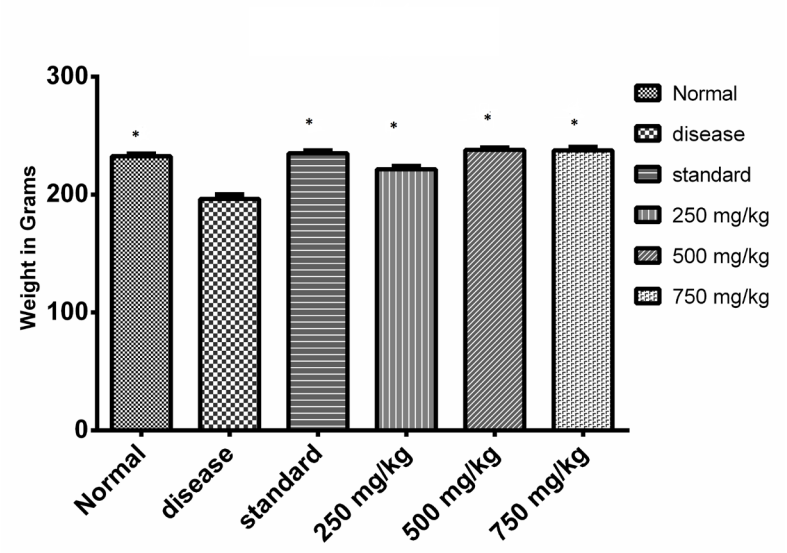

FIGURE 1 – Effect of *M. neglecta* extract pretreatment on blood glucose level (mg/dL) in Oral glucose tolerance test Where the values of blood glucose level were significantly different to disease control ($p<0.05$) at 120 min.

Effect on fasting blood glucose level

Administration of alloxan caused severe hyperglycemia in Wistar rats. Treatment with different doses of the plant extract exhibited a decline in fasting blood glucose level in comparison to the disease control group after two weeks therapy as evidenced in Table II. Fasting blood glucose was markedly higher in extract treated groups than the normal control group which improved gradually.

TABLE II – Fasting blood glucose level (mg/dL) in diabetic rats exposed to *M. neglecta* extracts

Treatment	Day 0	Day 1	Day3	Day 5	Day 7	Day 10	Day 14
Normal control (NC)	102.6 ± 3.58*	112.4 ± 6.60*	111.4 ± 9.30*	123.2 ± 11.0*	113.2 ± 6.82*	113.6 ± 5.81*	108.6 ± 14.1*
Disease control (DC)	407.6 ± 59.16	459.0 ± 39.1	470.6 ± 35.8	432.4 ± 24.57	398.8 ± 6.29	377.8 ± 12.9	385.0 ± 12.3
Standard therapy (PC)	428.8 ± 45.16	372.6 ± 25.25	220.6 ± 4.01*	209.6 ± 4.02*	184.2 ± 2.59*	169.2 ± 7.09*	179.2 ± 7.68*
Plant extract 250 mg/kg	356.8 ± 73.07	359.6 ± 21.95	262.2 ± 35.26*	265.2 ± 42.16*	205.00 ± 29.00*	179.8 ± 29.33*	179.4 ± 23.54*

(continuing)

TABLE II – Fasting blood glucose level (mg/dL) in diabetic rats exposed to *M. neglecta* extracts

Treatment	Day 0	Day 1	Day3	Day 5	Day 7	Day 10	Day 14
Plant extract 500 mg/kg	372.2 ± 10.33	325.4 ± 27.37*	303.0 ± 16.7*	251.8 ± 12.58*	213.6 ± 13.4*	208.00 ± 12.43*	178.6 ± 16.31*
Plant extract 750 mg/kg	426.0 ± 72.21	307.0 ± 56.08*	240.4 ± 70.94*	209.4 ± 36.52*	197.2 ± 34.68*	119.0 ± 18.4	113.2 ± 17.07*

Where * showed Where * showed significantly different at $p<0.05$ compared to untreated disease control. Data were expressed as Mean ± SEM, (n=6)

Effect on body weight

A decline in body weight of untreated diabetic animals was evident during the course of the experiment. The animals treated with the extract showed a marked increase ($p<0.05$) in body weight than disease control rats. The effect of treatment with the plant extract on diabetic rats is shown in Figure 2.

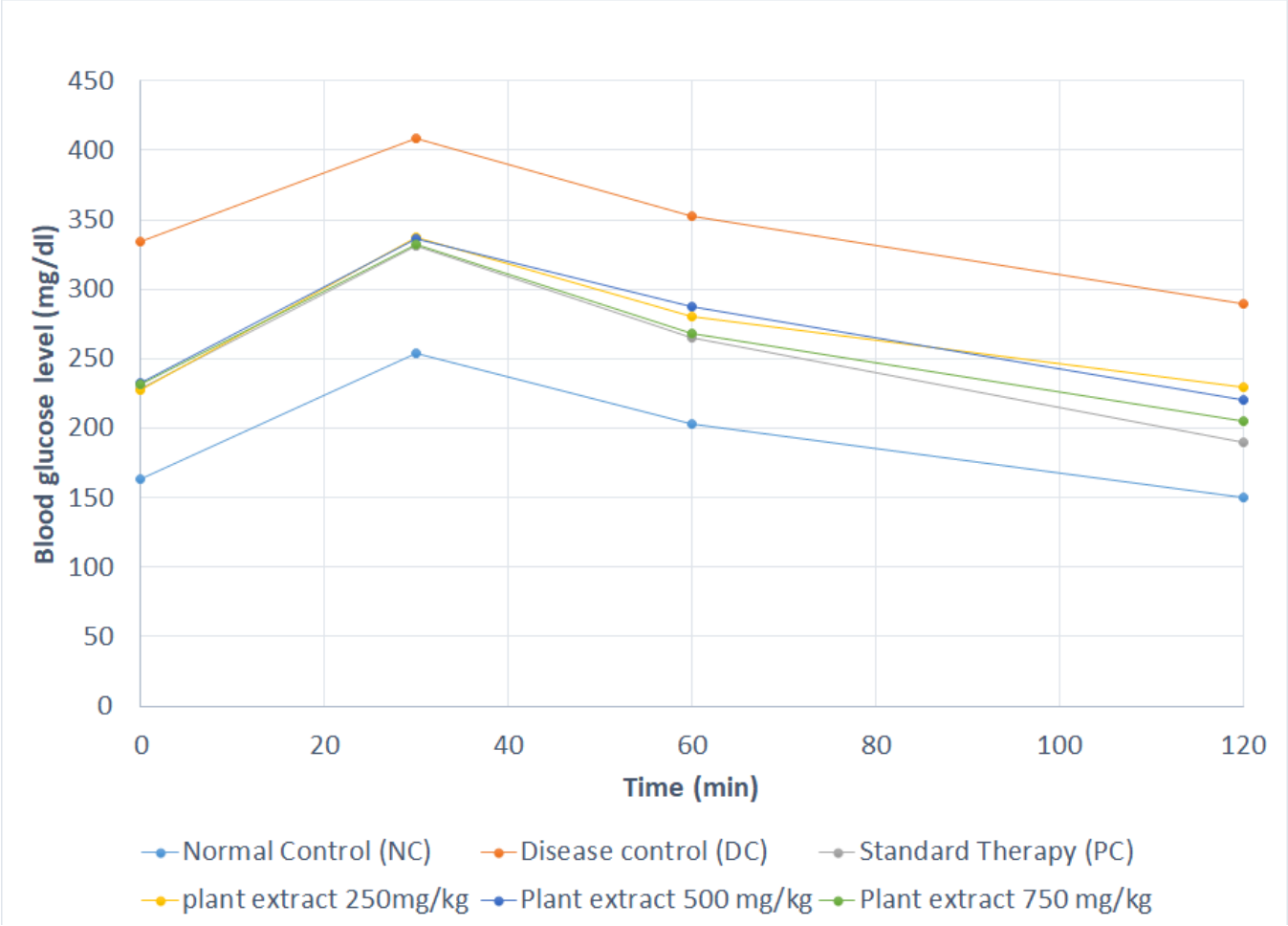

FIGURE 2 – The average weight of treated and untreated diabetic rats during 14 days therapy.
Where * showed significantly different at $p<0.05$ as compared to untreated disease control.

Effect on lipid profile and α-amylase

An elevated level of cholesterol, triglycerides and α-amylase was observed in disease control group as compared to normal control. It was also revealed that the HDL was significantly lower in disease control group than the normal control. Furthermore, it was revealed that the decline in cholesterol, alpha-amylase and triglycerides while a surge in HDL were observed in the extract treated diabetic animals. The effect of plant extract on total cholesterol, triglycerides and α- amylase in diabetic rats is shown in Table III.

TABLE II – Effect of *M. neglecta* on lipid profile and α-amylase

Treatment	Total cholesterol (mg/dL)	Triglycerides (mg/dL)	High density lipoprotein (mg/dL)	α- Amylase (U/L)
Normal control (NC)	79.66 ± 3.75*	70.66 ± 11.79*	56.33 ± 3.52*	698.33 ± 69.36*
Disease control (DC)	177.6 ± 14.42	212.33 ± 12.34	34.33 ± 3.52	1882.6 ± 52.71
Standard therapy (PC)	68.0 ± 6.24*	82.66 ± 8.41*	75.30 ± 3.48	943.33 ± 42.55*
Plant extract 250 mg/kg	87.0 ± 4.16*	100.0 ± 4.36*	59.0 ± 4.16*	1368.0 ± 115.04*
Plant extract 500 mg/kg	73.33 ± 5.60*	73.66 ± 5.04*	63.67 ± 9.96*	1122.3±84.42[a]
Plant extract 750 mg/kg	51.67 ± 185*	55.33 ± 3.48*	79.3 ± 0.8*	904.66 ± 48.02*

Where * showed significantly different at $p<0.05$ compared to untreated disease control.

Histopathological findings

Histopathological observations revealed that the non-diabetic rats had a normal proportion of acinar and islet cells. The beta cells in the islets of Langerhans were enclosed in a fine shell entrenched within the acinar cells. Untreated rats showed congestion and slight vacuolization of islets of Langerhans. Glibenclamide treated diabetic rats showed mild abnormal septa and congestion of blood vessels. Rats treated with 250 mg/kg dose of the extract showed normal acinar cell and severe infiltration of eosinophils in and around the islets. Rats treated with 500 mg/kg extract also showed the infiltration of eosinophils in islets. It was further found that the proportion of islet cells present in diabetic rats treated with 750 mg/kg plant extract was higher than non-diabetic rats. Histopathological changes in plant extract treated diabetic rats are shown in Figure 3.

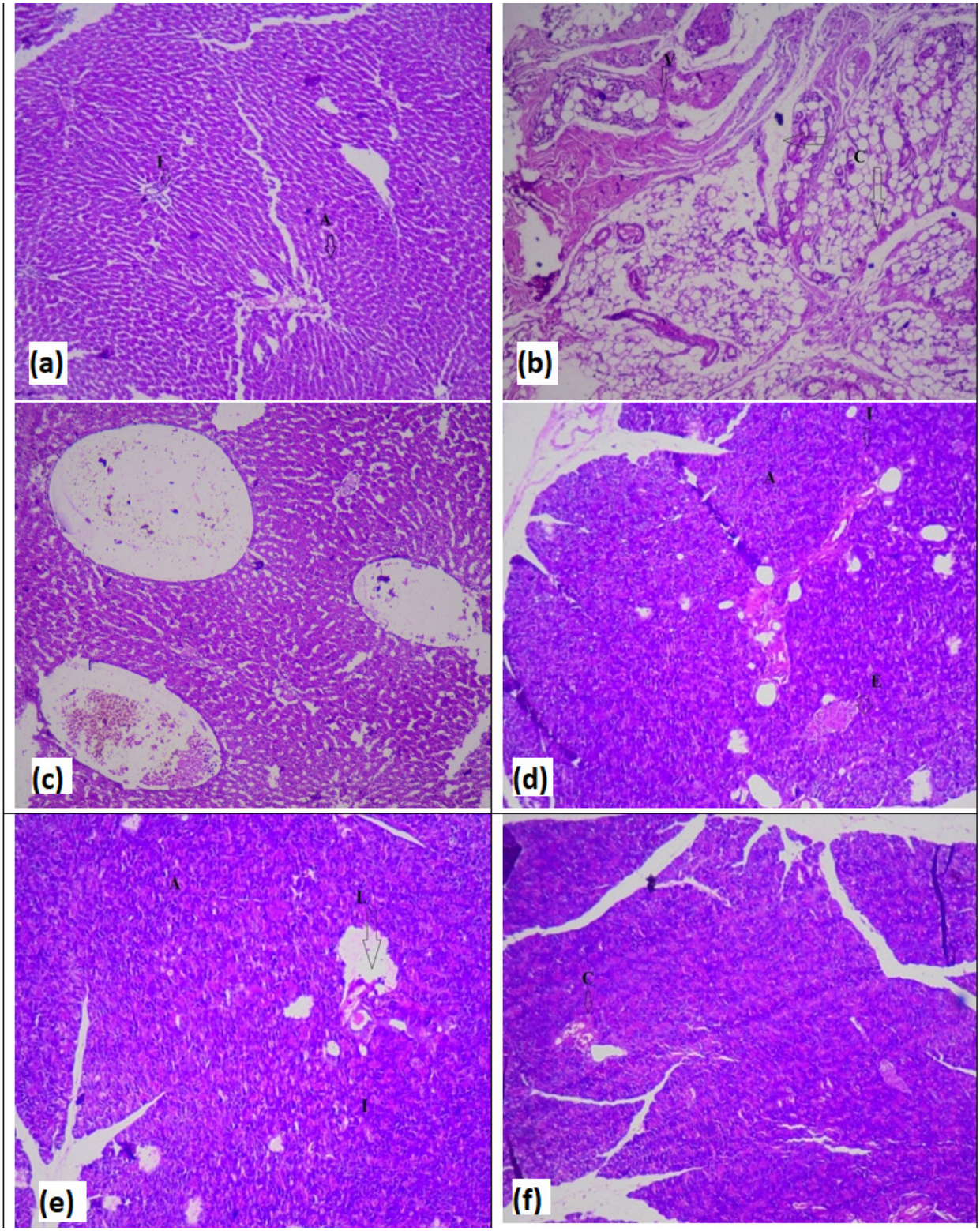

FIGURE 3 – Histopathological examination of pancreatic tissues (a) Photomicrograph of normal control rats showed normal acinar and islet cells of the pancreas (b) Photomicrograph of untreated diabetic rats showed showing congestion and slight vacuolization of islets of Langerhans cells (c) Photomicrograph of Glibenclamide treated diabetic rats showing mild abnormal septa (s) and congestion in the blood vessels (d) Pancreas of rats treated with 250 mg/kg plant extract showing normal acinar cells and heavy infiltration of eosinophils in and around islet cells (e) Pancreas of rats treated with 500 mg/kg extract showing normal acinar cells and the infiltration of eosinophils in islets (f) Photomicrograph of diabetic rats treated with 750 mg/kg plant extract showing the presence of islet cells in smaller amount than untreated diabetic rats.

DISCUSSION

The DM patients require proper glycemic control to prevent the complications so as to improve the quality of life. Insulin release from the pancreas is mainly responsible for maintaining glycemic control in the body (Edem *et al*., 2009). Alloxan is a glucose analogue that is toxic to pancreatic β-cells and readily destroys them. It damages β-cells through oxidative stress that also results in other complications of diabetes (Sabir *et al*., 2018). The current investigation showed the ameliorating effect of *M. neglecta* extract on fasting blood glucose level and damage to islets of Langerhans in alloxan induced diabetic rats. The plant extract also exhibited a preventive effect against diabetic complications such as weight reduction and hyperlipidemia.

The current investigation indicated that the blood glucose lowering effect of *M. neglecta* extract was reliant on the dose as well as phytoconstituents. Damage prevention to insulin secreting islets was also dependent upon the dose of extract. In the present research findings, there was a dose dependent decrease in fasting blood glucose level of diabetic rats with the most pronounced effect exerted by the extract at 750 mg/kg dose. It also prevented some diabetic complications including weight reduction and hyperlipidemia. The hypoglycemic effect of *M. neglecta* extract may be due to an increased production of insulin by some β-cells that survived or recovered from exposure to plant extract. Chemical evaluation of *M. neglecta* extract confirmed the presence of pharmacologically active ingredients predominantly ferulic acid, quercetin, gallic acid, *p*-coumaric acid and sinapic acid. Various studies have shown anti-diabetic activity of quercetin, gallic acid and ferulic acid. These phytochemicals mainly increase insulin secretion through recovery of pancreatic β-cells and enhance skeletal muscle glucose uptake (Eid *et al*., 2010). The highest dose (750 mg/kg) of the plant extract exhibited higher antidiabetic potential as compared with glibenclamide treated animals or those treated with 250 and 500 mg/kg/day extract. A fasting blood glucose level observed with 750 mg/kg/day extract was comparable to that normal control rats following 14 days therapy.

Normally DM is associated with deregulation of lipid metabolism which occurs due to insulin deficiency or resistance. Insulin prevents the breakdown of fat by inhibiting intracellular lipase that is responsible for hydrolyzing triglycerides to fatty acids and increase cholesterol and triglycerides in the blood (Sah *et al*., 2011). Hypercholesterolemia is also the result of insulin depletion due to metabolic abnormalities (Sud *et al*., 2017). In current study, *M. neglecta* extract corrected the dyslipidemia in diabetic rats similar to Glibenclamide. Treatment with the extract showed a decrease in triglyceride and total cholesterol level and an enhancement in HDL than disease control rats. Previous studies have shown that treatment with quercetin decreased serum triglycerides and total cholesterol (Eid, Haddad, 2017). Gallic acid was reported to decrease insulin resistance via activation of peroxisome proliferation activated receptor (Adefegha *et al*., 2015). Gallic acid also lowered cholesterol, triglycerides and low-density lipoproteins and enhanced the release of insulin through regeneration of β-cells (Latha, Daisy, 2011). Therefore, it can safely be assumed that the antihyperlipidemic action *M. neglecta* extract was partly due to the presence of quercetin and gallic acid.

A possible therapeutic strategy to manage DM is to decrease the activity of alpha amylase or glucosidase, which cause high postprandial blood glucose level. However, a high level of alpha glucosidase activity in blood could be due to pancreas damage (Fatima *et al*., 2019). This study found the inhibition of serum alpha amylase in extract treated rats. Therefore, the other possible mechanism behind the antidiabetic effect of the plant was through protection of pancreas in diabetic rats. It can be proposed that *M. neglecta* extract may be effective against a postprandial rise in serum glucose level as evidenced by OGGT in diabetic rats.

CONCLUSION

The *Malva neglecta* exhibited a significant antidiabetic potential in alloxan induced diabetic rats. The current experimental study showed that the aqueous methanolic extract of *Malva Neglecta* had substantial potential to manage hyperglycemia in diabetic rats and prevented diabetic complications such as dyslipidemia and weight loss. Thus, the plant should be considered as a source for the separation of novel antidiabetic agents and used as a nutraceutical.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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