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Formulation of an Antidiabetic Herbal Capsule from Isolated Compounds of Ethanolic Extract of *Dregea Volubilis* and *Leptadenia Reticulata*

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GJMR-B Classification: *NLMC Code: WB 330*

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Keywords: diabetes mellitus, polyphenolic compound, herbal formulation.

I. Introduction

Medicinal plants are commonly known for their therapeutic value and free from side effects. Keeping this in view, the development of anti diabetic drug from the natural plants being a major thrust area has drawn the attention of the researchers in the field of natural product research because synthetic drugs may cause unwanted side effects. The rational design of novel drugs from traditional medicine offers new prospects in modern healthcare. However, a scientific proof of the anti-diabetic activity of medicinal plants and phytopharmaceuticals with fewer side effects is still lacking. *Dregea volubilis* and *Leptadenia reticulate* belongs to the family of Asclepiadaceae which is widely used in Indian traditional medicines. In our previous study, isolated fractions of Dv-1 from ETDV [1] and Lr-1 from ETLR [2] showed promising hypoglycaemic activity and the compound has been confirmed by GC-MS and spectral analysis. The spectral analysis showed that the compounds are polyphenolic in nature. Isolated fractions Dv-1 from ETDV and Lr-1 from ETLR were combined and given a trivial name DVLR which would be used for further studies. In herbal medicine, plant based formulations are used to alleviate the diseases. But the most important challenges faced by these formulations arise because of their lack of complete evaluation. So evaluation is necessary to ensure the quality and the purity of the herbal product. It is very important to establish a system of evaluation for every plant medicine in the market, since the scope for variation in different batches of medicine is enormous. Nutrition is the provision, to cells and organisms, of the materials necessary (in the form of food) to support life. A poor diet can have an injurious impact on health, causing deficiency diseases. Herbal nutritional supplements provide essential nutrients that are not present or present in less amount in diet [3, 4]. Hence we formulate the DVLR capsules and the study was carried out for its anti-diabetic effect of STZ induced diabetic rats.

II. Material and Methods

a) Formulation and Evaluation of Capsules

Description and size of capsules are summarized in Table 1. 9el size of capsule purchased from capsule suppliers, Torpac, Fairfield, USA. Capsule especially made for administration of rats.

b) Preformulation studies

Preformulation studies were carried out for the investigation of physicochemical characteristics of a drug substance alone and in combination with excipients. The overall objective of preformulation testing was to generate information which will be useful in developing a stable dosage form.

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i. *Angle of Repose*

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 g of sample powder (DV and LR isolated fraction was mixed in 1:1 ratio) is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula:

$\tan \theta = h/r$ Where, h is height of the heap and r is radius of the heap.

ii. *Bulk Density*

A known quantity of powder was poured into the measuring cylinder carefully. The powder was levelled (DV and LR isolated fraction was mixed in 1:1 ratio) without compacting, if necessary and read the unsettled apparent volume, V_o, to the nearest graduated unit. Bulk density was calculated, in gm per ml, by the following formula.

Bulk density = Bulk Mass/ Bulk Volume.

c) Filling of Capsule

i. *Hand Operated Hard Gelatin Capsule Filling Machine*

The empty capsules are filled into the loading tray which is placed over the bed. By opening the handle, the bodies of the capsules are locked and caps separated in the loading tray itself, which is then removed by operating the lever. The weighed amount of the drug was mixed with sufficient quantity of excipients to be filled in the capsules and placed in powder tray already kept in position over the bed. The powders are spreaded with the help of a powder spreader so as to fill the bodies of the capsules uniformly to get 200 capsules. The excess of the powder is collected on the platform of the powder tray. Lowered the pin plate and moved it downward so as to press the powder in the bodies. The powder tray is removed and placed the caps on the holding tray in position. The caps are pressed with the help of plate with rubber top and operated the lever to unlock the cap and body of the capsules. The loading tray is removed and the filled capsules are collected in a tray.

d) Quality Control Parameters for Capsule

i. *Formulation of Capsule*

Each formulated capsule contains equivalent to 50 mg of DVLR and exicipients 30 mg which was priorly grounded which are summarized in Table 2.

ii. *Determination of Moisture Content*

The test was performed by using KF instrument by Electro Lab. The sample prepared by mixing together the content of four capsules. For low water concentrations (< 0.1 %), the utilization of a titrant with a factor of less than 5 mg/mL recommended. An alternative to the direct volumetric titration are both the external extraction as well as the KF oven technique: during external extraction the sample is dissolved, During analysis by the KF oven technique the water released by heating the sample to an appropriate temperature and then transferred into a volumetric cell [5].

iii. *Determination of pH*

The pH value of a solution was determined potentiometrically by means of a glass electrode, a reference electrode and a digital pH meter. The pH meter was operated according the manufacturer's instructions. First the apparatus was calibrated using buffer of 4, 9 and 7 pH. One empty capsule was taken and dissolved in 100 ml demineralized water. The electrodes were immersed in the solution and the pH was measured [5].

iv. *Uniformity of Weight*

Twenty filled capsules were randomly selected and weighed to determine the average weight and were compared with individual capsule weight. The percentage weight variation was calculated [5].

e) Dissolution Test for Capsule

The dissolution test was performed for capsule using USP dissolution apparatus 2 by Electro Lab. The 900 ml of the pH - 7.2 phosphate buffer as dissolution medium was introduced into the vessel of the apparatus. For the capsules basket type dissolution apparatus was used. Temperature was maintained at 37.5°C ± 0.5°C[5]. 10 ml of sample was withdrawn at 30, 45, and 60 time interval and replaced by same quantity of fresh buffer solution. The absorbance of samples was measured at 263 nm. The amount of percentage drug release was calculated by using the following formula [6].

$$\text{Concentration (mg)} = \frac{\text{Absorbance / Slope x Dilution factor x Total volume of dissolution bath}}{1000}$$

$$\% \text{ Drug Release} = \frac{\text{Concentration (mg)}}{\text{Labelclaim}} \text{X } 100$$

f) Disintegration Test for Capsule

Disintegration test was performed with the help of the digital microprocessor based disintegration test apparatus by Electro Lab. One capsule was introduced into each tube and added a disc to each tube. The assembly was suspended in the water in a 1000 ml beaker. The volume of water was such that the wire mesh at its highest point is at least 25 mm below the surface of the water, and at its lower point was at least 25 mm above the bottom of the beaker. The apparatus was operated and maintained the temperature at 37.50 ± 0.5°C. The time required to disintegrate all capsules and pass through wire mesh [6].

g) Anti-diabetic Effect of DVLR on Plasma Glucose Concentration and Lipid Profile in STZ induced Diabetic Rats

i. *Induction of Diabetes*

Male Wistar rats each weighing 180–220 g was obtained from Annamalai University at Chidambaram, Tamil Nadu, India. The guidelines of the CPCSEA of the Government of India were followed, and prior permission was granted from the Institutional Animal Ethics Committee (No. 842/CPCSEA). Rodent laboratory chow and water were accessed *ad libitum*, and rats were maintained on a 12 h light/dark cycle in a temperature regulated room (20–25 °C) during the experimental procedures. The fasted rats were injected intravenously with 50 mg/kg of STZ along with High Fat Diet (HFD). The HFD was freshly prepared everyday and the method of preparation is described by Devi, *et al*., 2004 [7]. Control animals were provided with normal pellet chow (Lipton, India). After 3 days on high fat diet, animals were fasted overnight and diabetes is induced by STZ injection. The STZ was freshly dissolved in citrate buffer (0.01 M, pH 4.5) and kept on ice prior to use. One week after STZ administration, the rats with fasting blood glucose concentrations of over 200 mg/dl were considered to be diabetic and were used in the experiment.

ii. *Effect of DVLR on FBG and the Lipid Profile in Diabetic Rats*

Normal control and diabetic control rats were divided into four groups with six rats in each group. Group I and II are normal control and diabetic control rats received 1 ml of distilled water. Group-III diabetic rats received 50 mg/kg of DVLR. Group IV-diabetic rats received 50 mg/kg metformin. All the groups were treated orally for 21days. The filled capsules were administered by dosing syringe [8].

iii. *Assessment of Liver, Kidney and Pancreas Function*

Blood samples collected from all four groups were allowed to clot at room temperature. Serum was separated by centrifugation at 2500 rpm for 10 minute. The functional state of the liver, kidney and pancreas were assessed by estimating the biochemical parameters of blood serum. After collecting the blood, the animals were sacrificed and their liver, kidney, pancreas was isolated, weighed and preserved in 10% formalin solution for histopathological studies.

h) Histopathological Studies

Histopathology the microscopic study of diseased tissue is an important tool in anatomical pathology, since accurate diagnosis of diabetes and other diseases usually requires histopathological examination of samples [9]. The isolated liver, kidney and pancreas were sliced into 5 mm pieces and fixed in neutral formalin solution (10%) for 3 days and washed in running water for about 12 hour. This was followed by dehydration with alcohol of increasing strength (70, 80 and 90%) for 12 hours each. Final dehydration was carried out using absolute alcohol with 3 changes at 12 minute interval. Cleaning was done by using xylin with changes at 15-20 minute interval. After cleaning, the pieces were subjected to paraffin infiltration in automatic tissue processing unit. The pieces were washed in running water to remove formalin completely.

i) Statistical Analysis

Data are expressed as $x \pm$ SEM. Statistical analysis was performed by one-way analysis of variance (ANOVA). The least significant difference test was used for mean comparisons and $P < 0.05$ was considered to be statistically significant.

III. Results

a) Preformulation studies

The latest developments in the fields of formulation science and technology offer new opportunities for filling liquid and semi-solid formulations in hard gelatin capsules. Hence we formulate the DVLR (trivial name) capsules and the study was carried out for its anti-diabetic effect of STZ induced diabetic rats. In our study an angle of repose of sample powder was found to be 30.88° ± 0.28 (n=3) and Bulk density of powder sample was found to be 0.6675 ± 0.005 (n=3). Empty capsule shell pH was found to be 3.62 and the moisture content of capsule was found to be < 5 % w/w. Filled capsule passed the test for uniformity of weight and DVLR capsules disintegration time was found to be 7 minutes. Percentage release of capsule was observed in Table 3 and Figure 1. From the data dissolution percentage of capsule was found to be 94.17 %.

b) Effect of DVLR on FBG and the lipid profile in diabetic rats

DVLR (50 mg/kg) produced a significant ($P < 0.05$) reduction in FBG as more as metformin in diabetic rats which is summarized in Table 4. Additionally DVLR also caused significant ($P < 0.05$) reduction in the level of triglyceride, cholesterol, LDL and significant ($P < 0.05$) improvement in HDL when compared to normal control

which was summarized in Table 4 and shown in Figure 2 and 3. The changes in mean percentage blood glucose in diabetic control group is 64.15% and DVLR, metformin treated groups are 47.62% and 48.41% respectively when compared to normal control. However the percentage rate of treated groups were decreased in compared to those of diabetic control. The changes in mean percentage of total cholesterol in diabetic control group is 32.08% and DVLR, metformin treated groups are 4.18% and 22.17% respectively. On the other hand, changes in mean percentage of triglyceride diabetic control group is 30.48% and DVLR, metformin treated groups are 5.15% and 25.35% respectively when compared to those of normal control. The changes in mean percentage of LDL in diabetic control group is 42.09% and DVLR, metformin treated groups are 2.80% and 19.78% respectively. On the other hand, changes in mean percentage of HDL in diabetic control group is 41.21% and DVLR, metformin treated groups are 1.12%, 14.5% respectively when compared to those of normal control.

c) Histopathological Studies

i. *Histopathology of Liver*

In histopathology studies of liver (Figure 4) normal control group showed structure of liver with sheets of hepatocytes separated by sinusoids cartial vein & portal tract appears. Diabetic control group showed the structure of liver with cords of hepatocytes and small area of lyphmatous cells in diabetic control animals. DVLR treated group showed the structure of liver with sheets of hepatocytes separated by sinusoids cartial vein & portal tract appear in normal. Metformin treated group showed structure of liver with cords of hepatocytes. No morphological changes were observed.

ii. *Histopathology of Kidney*

In histopathology study of kidney (Figure 5), normal control group showed the structure of kidney with normal glomeruli and renal tubules. Diabetic control group showed the structure of kidney with inflammation of renal tubules and glomeruli. DVLR treated group showed the structure of kidney without inflammation of renal tubules and glomeruli. Metformin treated group showed the structure of kidney without inflammation of renal tubules and glomeruli.

iii. *Histopathology of Pancreas*

In histopathology study of pancreas (Figure 6) normal control group showed the structure of pancreas with the normal numbers and volume of the islets cells. Diabetic control group showed the structure of pancreas with the numbers of islets cells were severely decreased and severely swelled. DVLR treated group showed the structure of pancreas with the numbers of islets cells were moderately decreased and moderately swelled. Metformin treated group showed the structure of pancreas with the numbers of islets cells were slightly decreased and slightly swelled.

IV. Discussion

In recent years, interest in using hard gelatin capsules in developing and manufacturing medicines has increased considerably. This is most probably due to rapid advances in dosage forms for hard gelatin capsules. In tandem with this, the structural foundation of a new technology has been developed and realised in the form of efficient process machinery. The formulation of a rapid release hard gelatin capsule can be largely deduced from the physicochemical properties of the drug active. Usually, active compound simply mixed with the exicipients and directly filled into the capsules. The costly process of granulation and compression can mostly be avoided. The choice available in terms of capsule type, the range of sizes and the capsule's colour or combination of colours, as well as the possibility of printing directly onto the capsule, means that patient compliance, product recognition and product differentiation can be markedly improved. A range of manual, semi-automatic and automatic filling machines are available for the manufacture of hard gelatin capsules. The latest developments in the fields of formulation science and technology offer new opportunities for filling liquid and semi-solid formulations in hard gelatin capsules. In our study empty capsule shell pH was observed as 3.62. Moisture content of capsule was found to be < 5 % w/w which indicates that there are less chances of microbial growth and capsule will not become soft. Filled capsule passed the test for uniformity of weight, all capsules disintegrated within 7 minutes. Percentage release of dissolution of capsule was found to be 94.17%. Administration of STZ caused rapid destruction of pancreatic cells in rats, which led to impaired glucose stimulated and inhibit insulin release, both of which are marked feature of type II diabetes [10]. The blood glucose-lowering effect of plant extracts is generally depends upon the degree of pancreatic β-cell destruction and useful in moderate streptozotocin induced diabetics [11]. Hypertriglyceridemia and hypercholesterolemia are the most common lipid abnormalities in diabetics [12]. In addition, hypertriglyceridemia is a metabolic consequence of hyperinsulinemia, insulin resistance and glucose intolerance [13]. STZ induced diabetic rats also showed the increases in plasma cholesterol and triglyceride concentrations [14], which may contribute to the development and progression of micro vascular and macro vascular complications, including neuropathy, nephropathy, cardiovascular and cerebrovascular diseases. The marked hyperlipidemia (increase in the level of lipid in the body) that characterizes the diabetic state which may be the consequence of the un-inhibited

actions of lipolytic hormones on fat depots [15]. DVLR possesses significant blood glucose lowering and cholesterol lowering activities. For this mechanism DVLR may be acutely stimulates it glucose uptake via activated protein kinase and extracellular signal-related kinase and produced great improvement of the altered lipid profile. It may also participate in the hypolipidemic activity by inactivating hepatic HMG-CoA reductase a key enzyme, in cholesterol synthesis. The improvements in the lipid profile in diabetic animals after treatment with DVLR could be beneficial in preventing diabetic complications, as well as improving lipid metabolism in diabetic patients.

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Table 1: Description and Size of Capsule

Description	Size 9el
Capsule Body Capacity	0.08 ml
Fill Weight (materials with density 1g/ml)	80 mg
External Diameter Maximum	2.65 mm
Length When Locked Maximum	23.2 mm
Weight Empty (Cap & Body) Average	17 mg
Colors Available	Clear & Opaque

Table 2: Quantity of Ingredients in DVLR Capsule

Ingredients	Strength (mg)
DV	25
LR	25
Carboxy methyl cellulose (CMC) Q.S	80

Table 3: Dissolution Study of DVLR Capsule

	DVLR		
	30 minutes %	45 minutes %	60 minutes %
1	65.72	80.17	93.75
2	66.12	82.27	94.17
3	65.10	81.50	92.97
4	64.98	80.97	94.07
5	65.27	82.15	93.10

Table 4: Effect of DVLR on Plasma Glucose Concentration, Cholesterol, Triglyceride, LDL and HDL for 21 days

Treatment	Fasting Blood Glucose (mg/dl)			Cholesterol (mg/dl)	Triglyceride (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
	0 day	10 day	21 day				
Normal control	76.8 ± 4.9	87.9 ± 2.2	98.3 ± 3.9	91.6 ± 5.3	73.6 ± 3.6	83.10 ± 1.5	44.2 ± 0.9
Diabetic control	265.7 ± 3.8	257.6 ± 4.5	248.7 ± 4.4	134.5 ± 3.4	114.6 ± 6.8	143.5 ± 4.7	31.3 ± 3.1
DVLR (50 mg/kg)	263.6 ± 4.7	172.3 ± 5.2	92.2 ± 5.7*	95.6 ± 2.6*	77.6 ± 6.5*	85.5 ± 3.6*	49.7 ± 3.3*
Metformin (50mg/kg)	254.6 ± 4.2	188.8 ± 2.7	93.8 ± 4.8*	117.3 ± 3.4	98.6 ± 4.6	103.6 ± 6.3	38.6 ± 2.3

*n=6. The statistical analysis was carried out using one way ANOVA followed by Dunnett's multiple comparison tests. *P < 0.05, compared to normal control group.*

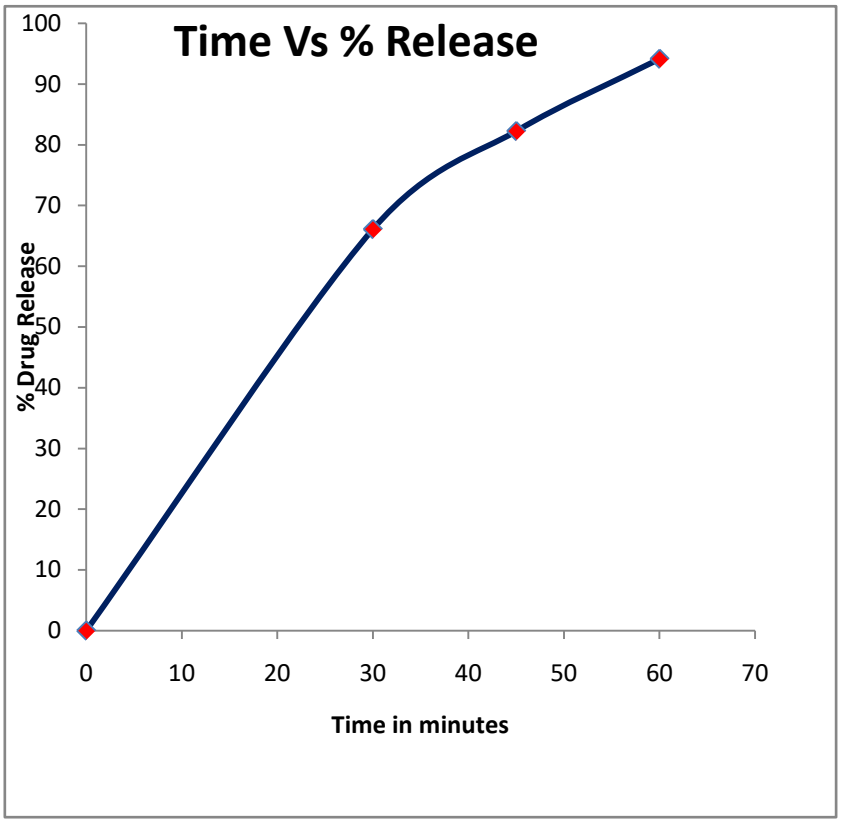


Figure 1: Dissolution profile of DVLR capsule

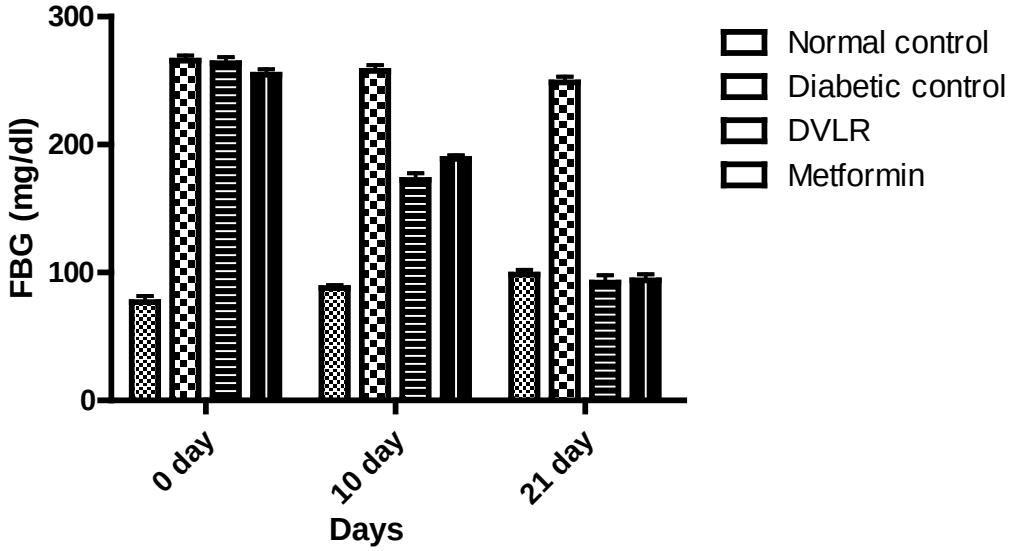


Figure 2: Effect of DVLR on Plasma Glucose Concentration

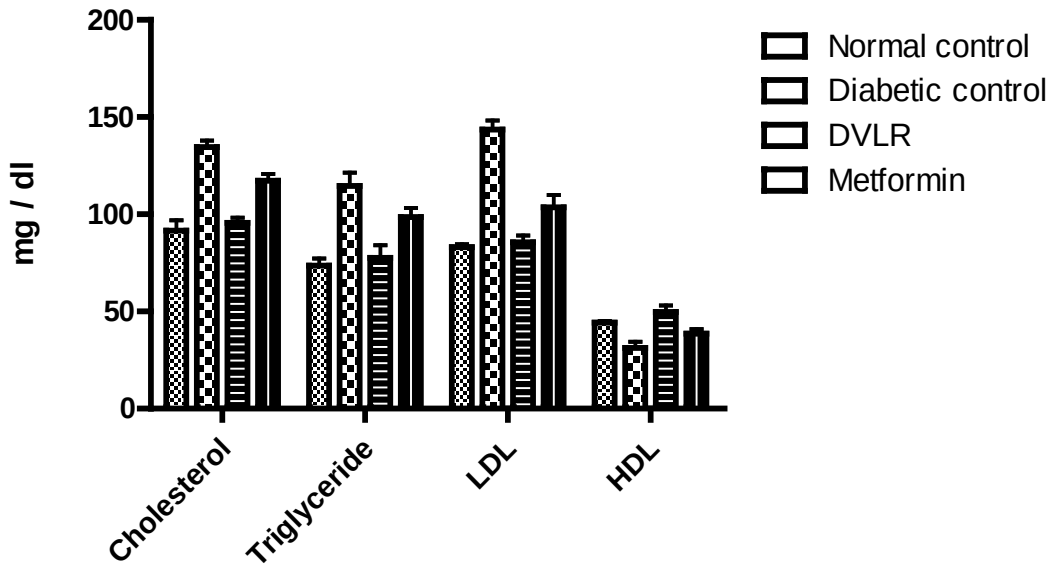
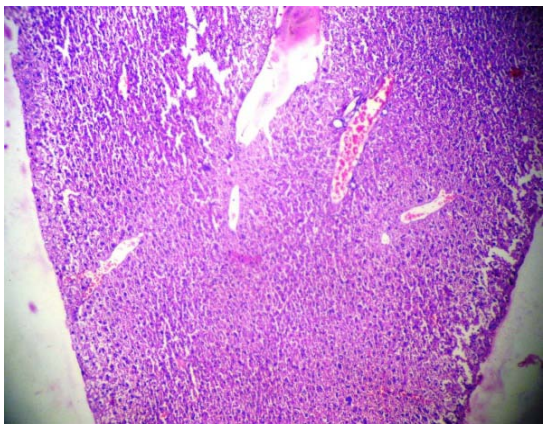
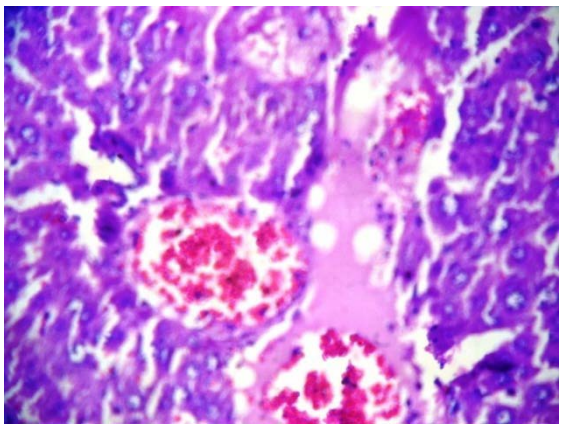


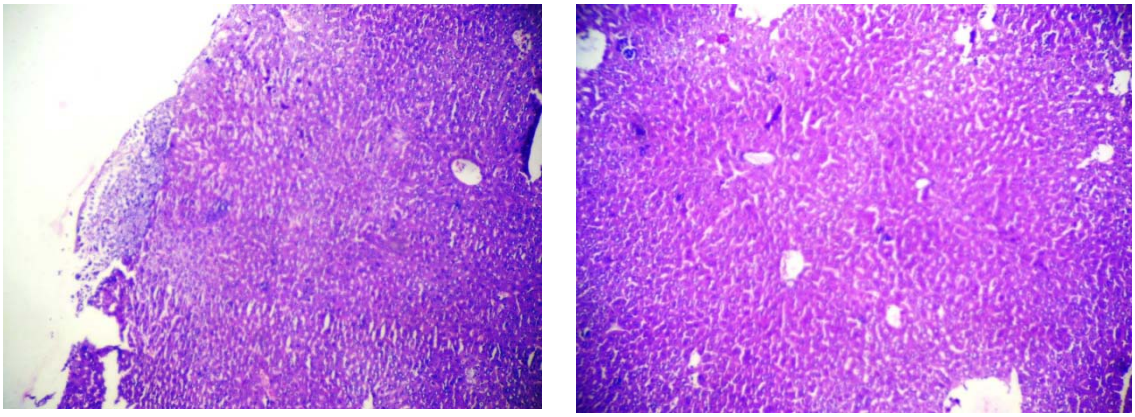
Figure 3: Effect of DVLR on Cholesterol, Triglyceride, LDL and HDL



Normal control

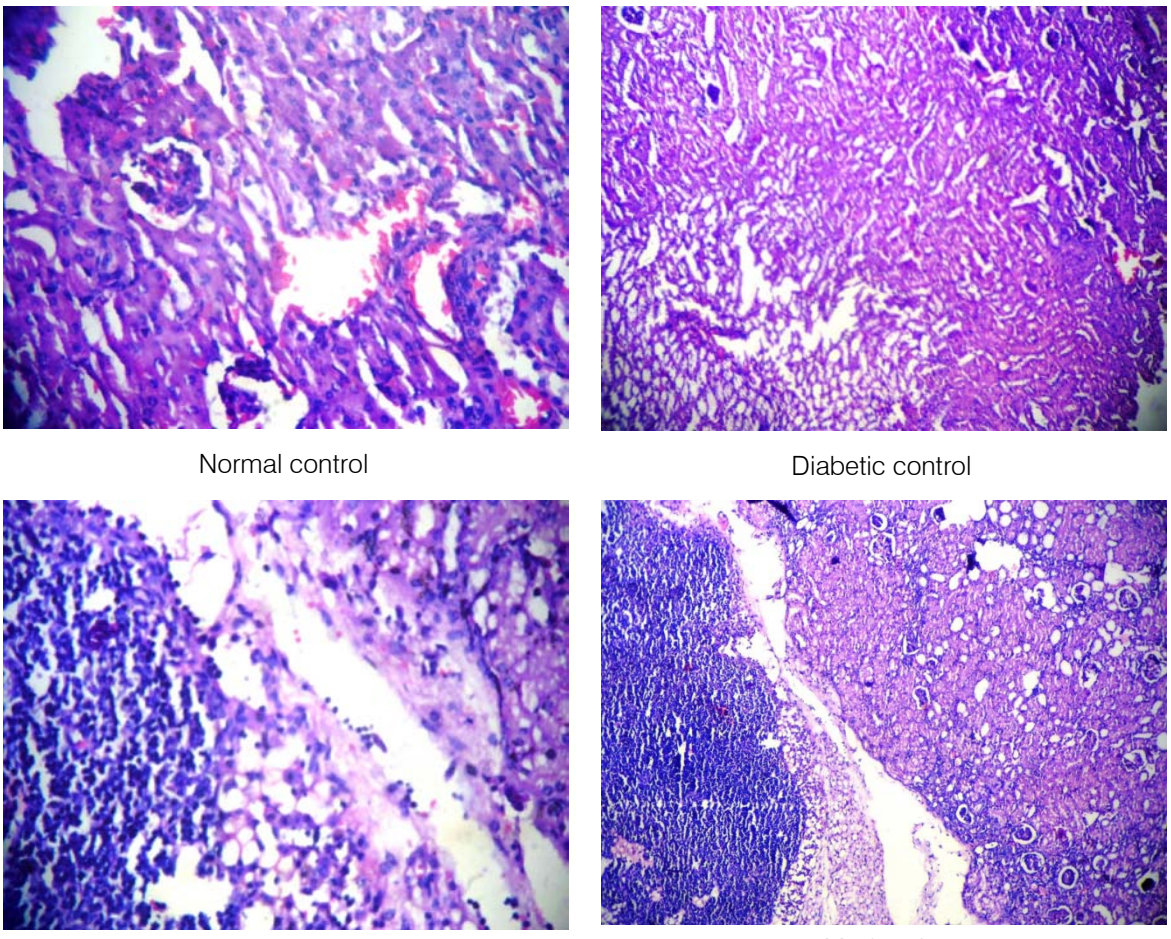


Diabetic control



DVLR Metformin

Figure 4: Histopathology of Liver



Normal control Diabetic control

DVLR Metformin

Figure 5: Histopathology of Kidney

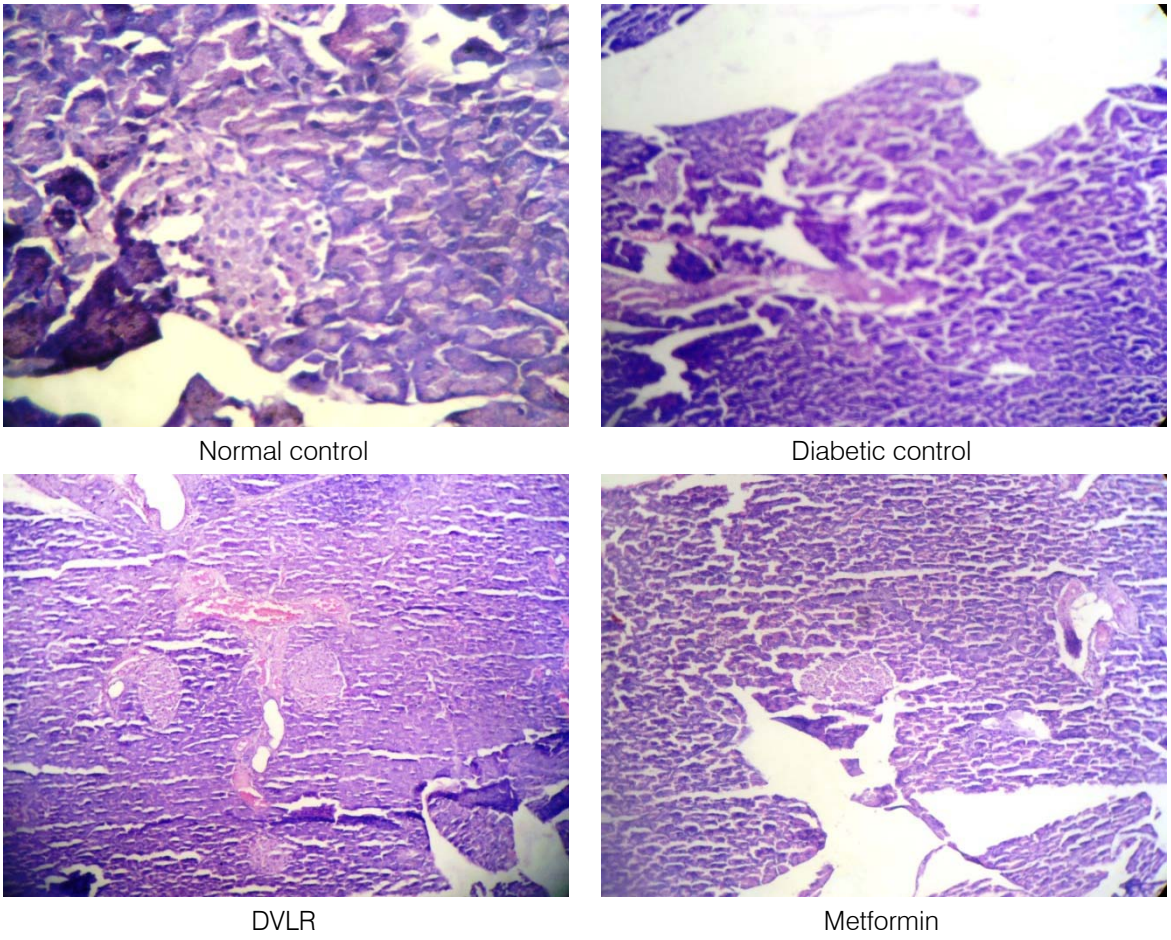


Figure 6: Histopathology of Pancreas