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DIABETIC NEPHROPROTECTIVE ACTIVITY OF HYDRO ALCOHOLIC STEM EXTRACT OF *MORUS ALBA* AND *LANTANA CAMARA* IN STREPTOZOTOCIN INDUCED DIABETIC NEPHROPATHIC IN RATS.

Sundeep K.[1*], Somanathan S. S.[1*] Jerusha Rani V.[1] and Ranganayakulu[1]

[1]Dept of Pharmacology, Sri Padmavathi School of Pharmacy, JNTUA Anantapur (Affliated), Tiruchanoor, Tirupathi.

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***Correspondence for Author**
Dr. Somanathan S. S.
Dept of Pharmacology, Sri Padmavathi School of Pharmacy, JNTUA Anantapur (Affliated), Tiruchanoor, Tirupathi.

ABSTRACT

Herbal drugs have been the predecessors of all medicines. Mankind has been using several herbal medicines to cure several diseases and relieve from physical sufferings. The knowledge of herbal drugs are innovative and critical since the ancient days. The current study objects to evaluate the diabetic Nephro protective activity of hydro alcoholic stem extract of *morus alba* leaf extract and *lantana camara* leaf extract(HAML) in streptozotocin induced diabetic nephropathy in rats by evaluating and assessing parameters like animal body weight, Fasting Blood Glucose(FBG), lipid profiles like Total protein, HDL, LDL, VLDL, Triglycerides, Albumin, blood urea nitrogen **(**BUN), Creatinine, Uric acid and *in-vivo* antioxidant parameters which include SOD, Catalase, GSH, LPO and histopathology of the kidney tissues. The experimental animals were grouped as **1) Normal** -Vehicle treated (normal saline), **2) Disease control** (STZ) **3) Standard** (STZ + Glibenclamide (5mg/kg) and **4) Test-I** (STZ + HAML (100mg/kg.) and **5) Test-II** (STZ + HAML (200mg/kg.). The results have shown an excellent nephroprotection action with the high dose of HAML.

KEY WORDS: Herbal drugs, Nephro protective, lipid profiles, *in-vivo* antioxidant.

1.0 INTRODUCTION

Today in many countries, modern medicines have displaced traditional medicine with many synthetic products even almost 30 % of pharmaceutical ingredients are still obtained from plants directly or indirectly. (Sandhu *et al*, 2005).

Recently an estimation carried out by WHO showed that 80% of people worldwide are using herbal medicines for their primary health care to some extent. The cost of modern medicines along with interest towards herbal medicines have increased the usage of herbal medicines over the past 30 years. Atropine, digoxin, quinine, colchicine, morphine, vincristine and vinblastine are some of the examples of herbal sources. (Gupta *et al*, 2005)

Diabetic nephropathy is a clinical syndrome characterized by albuminuria and irreversible decrease in glomerular filtration rate and arterial hypertension (Deepak parchwani, S.P.Singh 2011) Approximately there are 382 million people suffering from Diabetes worldwide and about 20-30% of these people are suffering from Diabetic nephropathy. The people suffering from Diabetes may increase upto 440 million by 2030. Herbal drugs are being used to treat Diabetic nephropathy along with allopathic medicines(Saud butt *et al*,2010).

Diabetes mainly occurs by increased blood glucose levels due to decreased free insulin in the body or due to insulin resistance. Diabetic nephropathy is caused due to damage of glomeruli because of decreased glomerular filtration rate in the kidneys. Usually Diabetic nephropathy occurs in patients with Diabetes after 5-10 years. Diabetic nephropathy can be controlled by allopathy medicines but side effects are more in long term use of these drugs. So, now-a-days herbal medicines are preferred due to their lesser side effects, safety and low cost(Lakshminarasimmha Gupalli 2015).

Streptozotocin is a well known diabetogenic agent which acts by damaging the β cells in the pancreas to release insulin and increases the blood glucose levels in the body(Szkudelski 2001). It is mostly preferred due to it's lower mortality rate and low dose compared to other diabetogenic agents. It also causes kidney tumours if the animals are kept for long duration studies.

The parameters to be estimated include Body weight (weekly basis), serum parameters include blood glucose(weekly basis), total cholesterol, LDL, HDL, VLDL, triglycerides, total protein, urine parameters include blood urea nitrogen, uric acid, creatinine, total protein and albumin.

Mainly Diabetes occurs due to increased blood glucose levels, increased LDL levels and decreased HDL levels in the body. Main risk factors for Diabetic nephropathy include changes in Blood pressure, weight gain etc. Treatment for Diabetic nephropathy include

sulphonylureas (glibenclamide, gliclazide), biguanides (metformin), α-glucosidase inhibitors(acarbose), thiazolidinediones (pioglitazone), angiotensin converting enzyme inhibitors(captopril, enalapril), angiotensin-II receptor blockers(candesartan, losartan), calcium channel blockers(verapamil) and Diuretics(furosemide, spironolactone).

Some of the plants reported to be effective in diabetic nephropathy include *Anacordium occidentale, Andrographis paniculata, Camellia sinensis, Cinnamomum zeylanicum* etc., Information about herbal plants can be obtained from folklore or traditional medicine system. For systematic pharmacological evaluation, useful herbal medicines are mostly needed to ensure efficacy, safety and therapeutic doses.

The plant ***Morus alba*** belongs to the family *Moraceae* and is used to treat fever, constipation, edema, cough and antidote for snake bite. Earlier work done on this plant include Hepatoprotective, anti-platelet, anti-anxiety, anti-bacterial, anti-stress, anti-diabetic activities etc. (Rajbir kaur2015)

The plant ***Lantana camara*** belongs to the family *Verbenaceae* and is used to treat leprosy, skin itches, chicken pox, measles, rabies etc., Earlier work done on this plant include antibacterial, wound healing, anti-corrosive, anti-ulcer, anti-obesity, anti-spasmodic activities etc.,(**Sanjeeb kalita *et al.*,2012)**

It is reported that these plants have shown potent anti-diabetic activity (leaf extract) but have no scientific evidence that stem extract of these plants show Diabetic Nephro Protective activity.

The present study aims to evaluate the diabetic nephroprotective activity of hydroalcoholic stem extract of *Morus alba* and *Lantana camara* in streptozotocin induced diabetic nephropathy in rats. In our study, the streptozotocin rat model is used to assess the efficacy of hydroalcoholic stem extract of *Morus alba* and *Lantana camara* and focus on biochemical parameters and histopathological studies.

2.0 MATERIALS AND METHODS

2.1 Chemicals

Epinephrine, DTNB, Sucrose, Thiobarbituric acid (TBA), Trichloro acetic Acid, Hydrogen Peroxide, Sodium dihydrogen phosphate, Potassium dihydrogen phosphate, Tris Buffer and

all other reagents used were of analytical grade. Triglycerides, Total cholesterol, Total protein, albumin, Uric acid, creatinine were obtained from Span diagnostics, Gujarat.

2.2 Collection of plant material

The plant material was collected from local area of Tirupathi and authenticated by Dr.B.Sitaram, Professor, Department of Dravyaguna, S.V.Ayurvedic Medical College, Tirupati.

2.3 Preparation of plant extract

The fresh stem part of *Morus alba* and *Lantana camara* were shade dried. The stem parts were grinded to get coarse powder. 250gm of coarse powder of *Morus alba* and *Lantana camara* was subjected to maceration process using hydro alcohol (7:3) as solvent. The extraction was continued for 5 days at room temperature with occasional shaking. Then the extract was filtered, collected and concentrated at 70^{o}C on a heating mantle until a softy mass obtained. It was then thoroughly air dried to remove all the traces of solvent and then was subjected to freeze drying. The obtained plant extract was preserved in cold condition till the end of treatment period.

2.4 Preliminary Phytochemical screening

Standard qualitative screening test of the extract was carried out for various plant constituents. The crude extract was screened for the presence or absence of secondary metabolites using standard procedures (Khandelwal, 2005).

2.5 Instruments

Analytical UV-Visible Spectrophotometer (Analytical Technologies Ltd, Model no: AUV 2060), Electronic Balance (Shimadzu, Model no: DS-852 J), Homogenizer (Ever Shine, Model no: 607), Cooling Centrifuge (Remi, Model no: KKLO-9013). Semi Autoanalyzer (Mispa excel, version: 1.4e)

2.6 Acute toxicity studies (Diener*et al*., 1999)

Acute toxicity study was carried out as per OECD-423 guidelines using female and male wistar strain rats. The rats were fasted overnight and the weight of each rat was recorded just before the experiment. Animals were divided randomly into four groups viz; a control and four groups, each group consisting of two rats. Control group received only the vehicle and other four groups received combination extract of *Morus alba* and *Lantana camara* in a dose

of 5, 50, 300, and 2000 mg/kg through oral route respectively as mentioned in OECD 423 guidelines. Animals were kept under close observation for 4 hours after administering the extract. The behavioral, neurological and autonomical parameters were observed and followed by observation for further 14 days. At the end of the experimental period, the animals were observed for any change in general behaviour, other physical activities and mortality. During the acute toxicity studies, mortality was not found with dose of 2000mg/kg body wt and the safe dose of 100mg/kg body wt and 200mg/kg body wt. were selected.

2.7 Experimental protocol

The experimental animals were divided into **five groups** (n =6)

1) Normal : Vehicle treated (normal saline) to assess the normal parameters.
2) Disease Control : STZ administered to assess the parameters in diseased rats.
3) Standard : STZ + Glibenclamide (5mg/kg) for 28 days to assess the parameters in standard group and compare with disease control.
4) Test-I (low dose) : STZ + HAML (100mg/kg.) for 28 days to assess the activity of test drug at low doses.
5) Test-II (high dose) : STZ + HAML (200mg/kg.) for 28 days to assess the activity of test drug at high doses.

2.8 Induction of diabetic nephropathy

In this method, streptozotocin (60mg/kg) was injected to the experimental rats through intra peritoneal route initially. Animals were treated for 28 days. The blood samples were collected from the retro orbital plexus just before removal of kidneys from rats without any coagulant for the separation of serum. After collecting the blood in micro centrifuge tubes they were kept for 1 hr at room temperature and serum was separated by centrifugation at 2000 rpm for 15 min and stored until analyzed for the estimation of biochemical parameters, then remove the kidneys for *In vivo* anti-oxidant studies and estimation of one kidney of each animal is excised and sent for histopathological studies.

2.9 Parameters measured

To evaluate the diabetic nephro protective activity of stem of *Morus alba* and *Lantana camara* by assessing the parameters like animal body weight, Fasting blood glucose, Glucose tolerance test (GTT), Total protein (Tissue), Albumin, uric acid, BUN, Creatinine, Total protein (Serum), Total cholesterol, HDL, LDL, VLDL, Triglycerides and *in-vivo*

antioxidant parameters which include Catalase, SOD, GSH, LPO of kidney tissue and Histopathology of the kidney tissues (10 X and 40 X).

3.0 STATISTICAL ANALYSIS

All the data was expressed as mean ± S.E.M. Statistical significance between more than two groups was tested using one way ANOVA followed by the Dunnett's test using computer based fitting program (Graph pad prism 5.0). Statistical significance was set accordingly. P value of < 0.05 has been considered as statistical significance level.

4.0. RESULTS AND DISCUSSION

Results of Preliminary Phytochemical Screening of HAML: The plant extract contains Proteins & amino acids, Flavonoids, Phenols, Alkaloids, Saponins, Carbohydrates, Tannins and Sterols**.**

Acute toxicity studies

Acute toxicity studies were performed for the selection of dose. Acute toxicity studies were performed as per OECD-423 guidelines. The rats were fasted overnight, allowed water ad libitum. Animals were divided into four groups, each group consisting of three rats. Hydro alcoholic stem extract of *Morus alba* and *Lantana camara* were received at a dose of 5 mg/kg, 50 mg/kg, 300 mg/kg and 2000 mg/kg for each group. They showed normal behavior, alertness, grooming, touch and pain response. But at the dose of 300mg/kg, they showed jumping. So it was considered to be psychic effect. Also from the above observation it was found that there is no mortality at 2000 mg/kg. Hence it can be considered as a safe dose taking $1/5^{th}$ of its dose as low dose (i.e., 100 mg/kg) and double of its dose as high dose (i.e., 200 mg/kg) for the present study to evaluate the anti-diabetic activity.

Table 1 shows the effect of HAML on body weight in STZ induce diabetic nephropathy rats: The body weights of STZ control animals were gradually decreased(-15.23%) compared to normal control animals(+11.7%) during the treatment days. Glibenclamide (5mg/kg **:** +17.11%), the test drug treated animals showed increase(100Mg/kg **:** +11.16% & 200Mg/kg **:** +10.93%) in body weights compared to STZ control animals gradually (HAML 100mg/kg > HAML 200mg/kg).

Table 2 evidences the effect of HAML on Fasting Blood glucose levels in STZ induce diabetic nephropathy rats: The fasting blood glucose levels were significantly ($p < 0.001$)

increased in STZ control group during 28th days (+14.6% from base line diabetic 272.4mg/dL) than normal control animals. Glibenclamide (-70.82mg/dL from base line diabetic 264.7mg/dL), HAML (100mg/kg : -58.55% from base line diabetic 260.1mg/dL and 200mg/kg : -64.52% from base line diabetic 264.7mg/dL) treated animals showed significant ($p < 0.001$) decrease in fasting blood glucose levels compared to STZ control group on 14th, 21st, 28th day of treatment this is the primary evidence for this study.

Table 3 means that the effect of HAML on oral glucose tolerance test (OGTT): The blood glucose levels in normal animals were increased to maximum at 30mins by the administration of glucose (2gm/kg) and there after showed gradual decrease in blood levels in 60, 90, 120mins. Glibenclamide (5mg/kg *p.o*), HAML 100mg/kg and HAML200mg/kg treated animals showed significant ($p < 0.001$) decrease in glucose levels as that of normal control group. the maximum tolerable group is HAML 200 mg/dL dose than HAML 100mg/dL dose)

Table 4 indicates the effect of HAML on Urine total protein, Albumin, Uric acid, BUN, Creatinine (mg/dl) levels in experimental rats: There was a significant rise in urine Total protein, Albumin, Uric acid, bun, Creatinine (mg/dl) levels in diabetic control animals when compared to normal group. Group of animals treated with Glibenclamide (5mg/kg) showed significant decrease than STZ control group. The test groups at doses of 100 and 200 mg/kg showed significant decrease compared to STZ control animals. The result shows that 200mg/kg is better effect than 100mg/kg dose.

Table 5 Is the Effect of HAML on Serum Total protein, Total cholesterol, HDL, LDL, VLDL, Triglycerides levels in experimental rats: There was a significant decrease in total protein and high density lipoprotein levels in STZ control animals when compared to normal group. Group that was treated with Glibenclamide (5mg/kg) showed significant increase in total protein and high density lipoprotein when compared with STZ control group. The test groups at doses of 100 and 200mg/kg showed significant increase in total protein and high density lipoprotein levels when compared with STZ control group which indicates the loss of good cholesterol and proteins may be due to the free radicals and oxidants production and loss of anti-oxidants in the tissues which results in the serum. The results gives a clear picture in the dose related efficacy ie.,100mg/kg and 200mg/kg are closely produced the effectiveness.

Table 6 Concludes the effect of HAML on Catalase, SOD, GSH, LPO on kidney tissue of experimental rats: The STZ control animals showed significant ($p < 0.05$) reduction in Catalase, SOD, GSH levels compared to normal control animals but LPO shows the incremental level on 28th day. Glibenclamide (5mg/kg), HAML 100mg/kg and 200mg/kg treated animals were showed significant ($p < 0.05$) increase in Catalase, SOD, GSH levels and LPO was decreased.

Histopathology

The histopathology slides of kidneys of STZ control group showed damage in kidney tissue when compared to normal group. Though Glibenclamide (5mg/kg), HAML100mg/kg and HAML 200mg/kg treated animals showed protection against damage of kidneys compared to STZ control group, high dose showed a better tissue texture and development than low dose test drug.

Table 1: Effect of HAML on body weight of experimental rats.

S.No	Groups	Body weight (in gms)					
		0th day	7th day	14th day	21st day	28th day	% change
1	Normal control	148.16 ± 2.12	151.23 ± 3.12	154.01 ± 2.39	159.52 ± 3.92	165.49 ± 3.28	+11.7
2	STZ control	190.12 ± 15.39	185.28 ± 9.49^{a}	180.31 ± 14.49^{a}	169.82 ± 4.96^{a}	161.12± 6.98^{a}	-15.23
3	Standard Glibenclamide 5mg/kg	155.02 ±12.68	164.36 ± 13.58^{b}	170.19 ± 11.22^{b}	176.69 ± 3.26^{b}	181.54 ± 5.21^{b}	+17.11
4	HAML (100mg/kg)	152.12 ± 16.05	155.91 ± 11.25^{b}	161.23 ±12.01^{b}	166.62 ± 10.57^{b}	169.09 ±10.99^{b}	+11.16
5	HAML (200mg/kg)	158.76 ± 5.45	164.34 ±8.71^{b}	167.12 ± 7.41^{b}	173.56 ± 6.92^{b}	176.11 ±10.02^{b}	+10.93

Values were expressed as mean ±SEM. **a-** indicates $p<0.001$when compared with normal group. **b-** indicates $p<0.001$ when compared with STZ control group.

Table 2: Effect of HAML on Fasting Blood glucose levels in experimental rats.

S.No	Groups	Fasting Blood glucose levels (in mg/dl)					
		0th day	7th day	14th day	21st day	28th day	% change
1	Normal control	77.82 ± 1.915	79.82 ± 2.711	79.82 ± 2.711	83.15 ± 2.776	83.98 ± 2.761	+7.92
2	STZ control	272.4 ± 7.982^{a}	273.4 ± 7.015^{a}	286.7 ± 3.617^{a}	300.1 ± 3.702^{a}	312.4 ± 5.815^{a}	+14.68
3	Standard Glibenclamide 5mg/kg	264.7 ± 3.361	191.9 ± 2.916^{b}	131.1 ± 2.233^{b}	90.93 ± 2.162^{b}	77.25 ± 2.152^{b}	-70.82
4	HAML (100mg/kg)	260.1 ± 4.852	222.7 ± 1.789^{b}	180.9 ± 3.159^{b}	143.5 ± 1.760^{b}	107.8 ± 2.794^{b}	-58.55

5	HAML (200mg/kg)	264.7 ± 4.175	206.5 ± 2.028[b]	163.3 ± 2.831[b]	119.9 ± 2.133[b]	93.92 ± 1.656[b]	-64.52

Values were expressed as mean ±SEM. **a**- indicates p<0.001when compared with normal group. **b**- indicates p<0.001 when compared with STZ control group.

Table 3: Effect of HAML on oral glucose tolerance test (OGTT) on experimental rats.

S.No	Groups	Blood glucose levels (in mg/dl)					
		0' min	30 min	60 min	90 min	120 min	Maximum tolerable% (Maximum to 0' minute)
1	Normal control	83.98 ± 2.761	110.52 ± 1.24	**114.49 ± 1.58**	93.89 ± 0.72	88.25 ± 0.85	36.33
2	STZ control	312.4 ± 5.815[a]	319.55 ± 2.09	327.95 ± 1.30	332.55 ± 1.03	**339.55 ± 1.49**	8.69
3	Standard Glibenclamide 5mg/kg	77.25 ± 2.152[b]	**98.66 ± 0.9[c]**	84.45 ± 0.79[c]	80.34 ± 0.41[d]	78.24 ± 0.62[b]	27.72
4	HAML (100mg/kg)	107.8 ± 2.794[b]	118.84 ± 0.29[a]	**122.29 ± 1.25[f]**	117.98 ± 0.42[d]	110.56 ± 0.82[b]	13.44
5	HAML (200mg/kg)	93.92 ± 1.656[b]	**109.26 ± 0.44[c]**	101.02 ± 0.75[d]	98.09 ± 0.59[d]	95.34 ± 0.84[b]	16.33

Values were expressed as mean ±SEM **a** = p < 0.001 when compared with 0 min. **b** = p<0.001 **c** = p < 0.01 and **d** = P<0.01 and **f**= p< 0.05 when compared with 30min.

Table 4: Effect of HAML on Urine Total protein, Albumin, Uric acid, BUN, Creatinine (mg/dl) levels in experimental rats.

S.No	Groups	Total protein (gm/dl)	Albumin (mg/dl)	Uric acid (mg/dl)	BUN (mg/dl)	Creatinine (mg/dl)
1	Normal control	3.448 ± 0.127	0.773 ± 0.03	6.854 ± 0.232	2.428 ± 0.027	0.718 ± 0.04
2	STZ control	5.429 ± 0.245[a]	0.996 ± 0.031[a]	10.38 ± 0.423[a]	5.57 ± 0.276[a]	1.310 ± 0.137[a]
3	Standard (Glibenclamide 5mg/kg *p.o.*)	3.010 ± 0.319[b]	0.4213 ± 0.039[b]	5.821 ± 0.271[b]	2.184 ± 0.104[b]	0.433 ± 0.072[b]
4	HAML (100mg/kg)	3.738 ± 0.245[b]	0.796 ± 0.048d	6.439 ± 0.234[b]	3.228 ± 0.211[b]	0.511 ± 0.04[b]
5	HAML (200mg/kg)	2.583 ± 0.143[b]	0.5413 ± 0.003[b]	5.561 ± 0.272[b]	1.916 ± 0.117[b]	0.246 ± 0.019[b]

Values were expressed as mean ± SEM . **a**- indicates p<0.001when compared with normal group. **b** - indicates p<0.001when compared with STZ control group.

Table 5: Effect of HAML on Serum Total protein, Total cholesterol, HDL, LDL, VLDL, Triglycerides levels in experimental rats.

S.No	Groups	Total protein (gm/dl)	Total cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	Triglycerides (mg/dl)
1	Normal control	7.33 ± 0.05	56.24 ± 1.756	24.29 ± 1.391	28.69 ± 1.09	5.198 ± 0.197	28.17± 1.299
2	STZ control	2.617 ± 0.29[a]	81.04 ± 2.209 [a]	12.59 ±1.342 [a]	46.21 ± 2.519 [a]	12.91 ± 0.512 [a]	57.74 ± 3.34 [a]
3	Standard Glibenclamide 5mg/kg	8.259 ± 0.12[b]	60.76 ± 3.297[d]	22.69 ± 0.61 [b]	30.44 ± 1.204 [b]	6.272 ± 0.722 [b]	32.96 ± 4.15 [b]
4	HAML (100mg/kg)	6.085 ± 0.17 [b]	66.91 ± 2.098 [d]	20.19 ± 0.891 [d]	34.26 ± 3.552 [d]	7.243 ± 0.712 [d]	42.69 ± 2.019 [d]
5	HAML (200mg/kg).	7.59 ± 0.44 [b]	63.28 ± 3.382 [d]	19.18 ± 0.765 [b]	32.79 ± 3.482 [b]	6.949 ± 0.248 [b]	35.09 ± 2.157 [b]

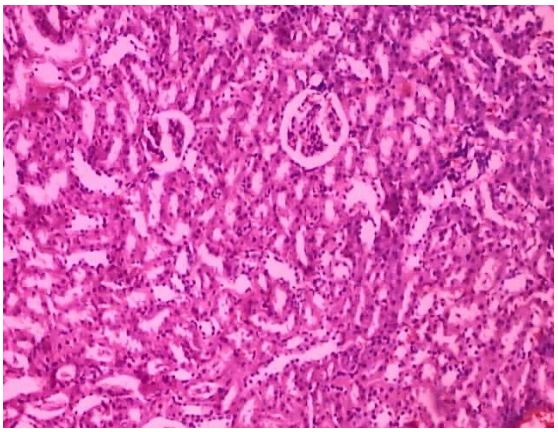
Values were expressed as mean ±SEM . **a** - indicates p<0.001when compared with normal group. **b** - indicates p<0.001, dindicates P<0.01when compared with STZ control group.

Table 6: Effect of HAML on Catalase, SOD, GSH, LPO in experimental rats.

S.No	Groups	Catalase (µM H_2O_2 consumed/mg protein)	SOD (U/mg protein)	GSH (µM of GSH/mg protein)	LPO (nM of MDA/mg protein)
1	Normal control	21.23 ± 0.785	14.66 ± 0.439	18.34 ± 0.42	5.080 ± 0.23
2	STZ control	8.002 ± 0.4904[a]	4.91 ± 0.311[a]	7.280 ± 0.49[a]	13.08 ± 034[a]
3	Standard (Glibenclamide 5mg/kg)	18.51 ± 0.344[b]	13.08 ± 0.34[b]	16.20 ± 0.33[b]	6.298 ± 0.32[b]
4	HAML (100mg/kg)	15.99 ± 0339[b]	11.79 ± 0.319[b]	12.64 ± 043[b]	8.217 ± 023[b]
5	HAML (200mg/kg)	18.09 ± 0.437[b]	12.86 ± 0.264[b]	15.76 ± 0.44[b]	6.197 ± 0.21[b]

Values were expressed as mean ±SEM . **a**- indicates p<0.001when compared with normal group. **b** -indicates p<0.001, dindicates P<0.01when compared with STZ control group.

HISTOPATHOLOGY (10X)



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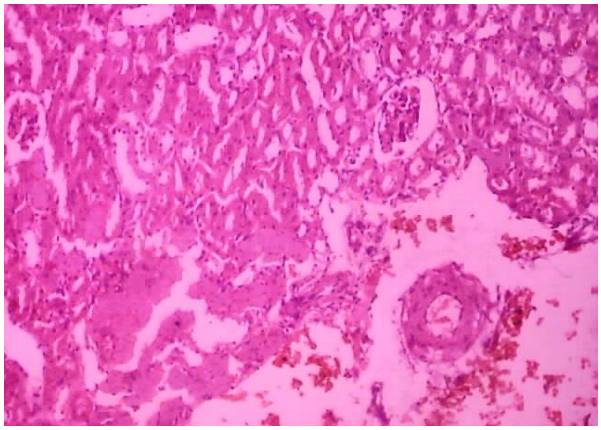

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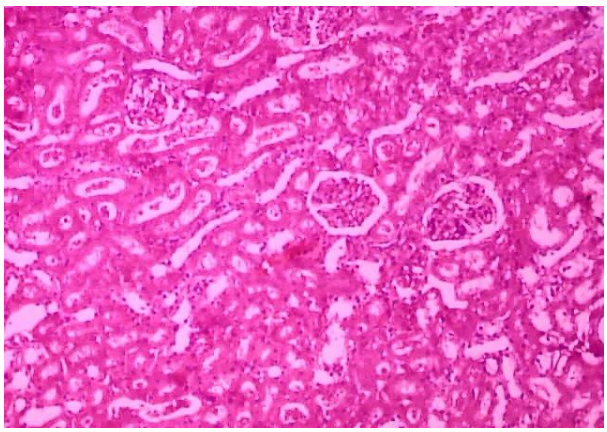

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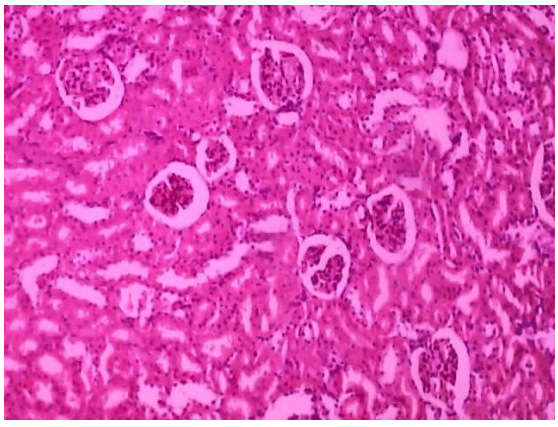

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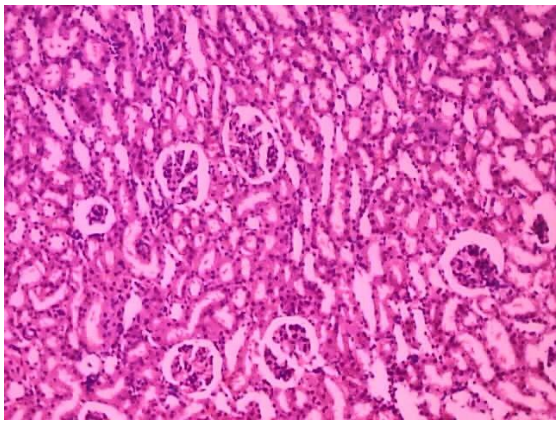

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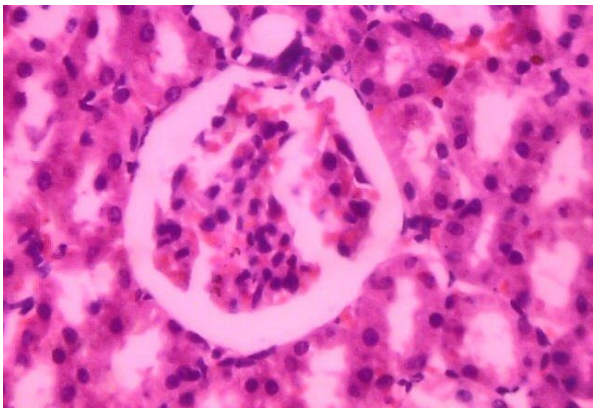

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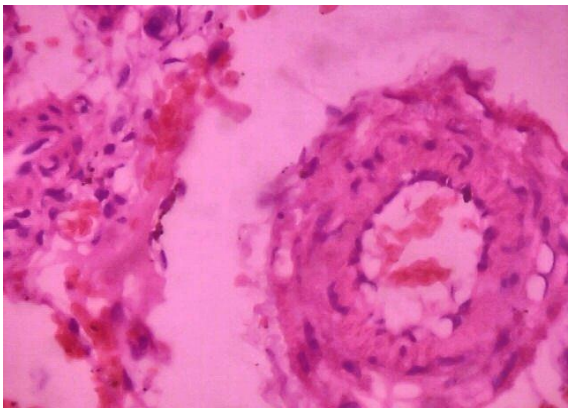

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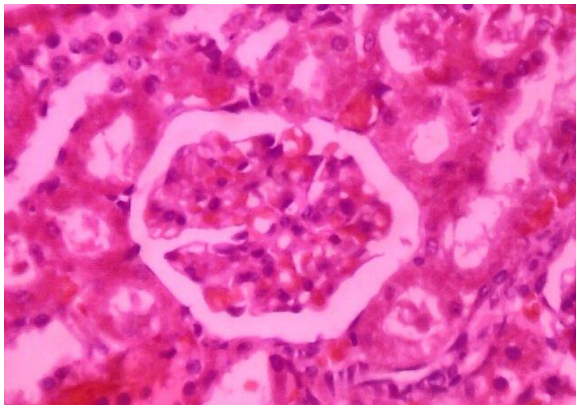

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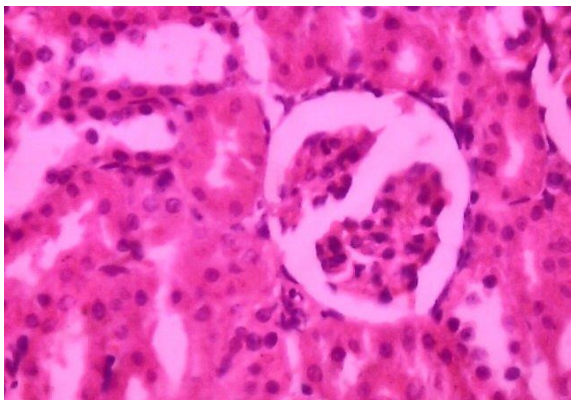
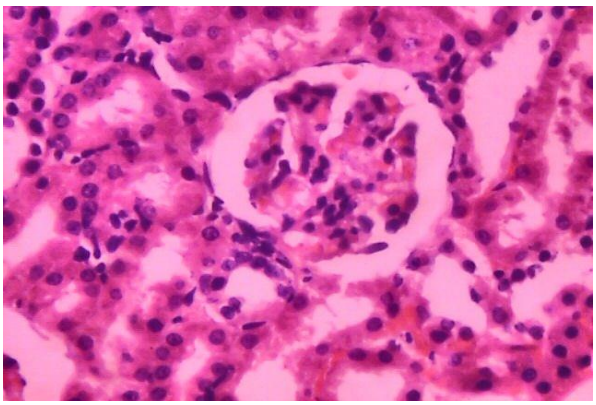


TEST-1



TEST-2

5.0 CONCLUSSION

In the current study administration of hydroalcoholic extract of *Morus alba* and *Lantanacamara* were found to significantly increase serum HDL levels and decrease triglycerides, total protein, LDL, VLDL, blood glucose and decrease urine levels of BUN, Creatinine, total protein, albumin, uric acid levels. In addition histopathology studies of

kidney in *Morusalba* and *Lantana camara* extract treated groups supports the observation. All these results demonstrate significant diabetic nephro-protective activity of *Morus alba* and *Lantanacamara*. Further studies are required to determine the active components that are responsible for its diabetic nephro-protective activity.

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