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Antihypertensive Activity of Methanolic Extract of *Artemisia pallens* Wall in Renal Hypertensive Diabetic Rats

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Abstract

Hypertension and diabetes mellitus are chronic medical conditions that frequently coexist. The aim of the present study is to evaluate the effect of methanolic extract of *Artemisia pallens* Wall in hypertension induced by uninephrectomy in diabetic animals. Albino Wistar rats were used for the study. Diabetes was induced in rats by nicotinamide-STZ. After one week of diabetes induction rats were nephroctemized and animals were divided into seven groups: Sham control, Diabetic nepherectomy control, Glibenclamide treated group (5 mg/kg), Candesartan treated group (10 mg/kg), MEAP treated group (low dose i.e. 100 mg/kg), MEAP treated group (medium dose i.e. 200 mg/kg), MEAP treated group (high dose i.e. 400 mg/kg). The animals received Glibenclamide 5 mg/kg, Candesartan 10 mg/kg and received drug of MEAP 100, 200, 400 mg/kg, per oral respectively for 3 weeks for their respective groups. Treatment of MEAP (200 and 400 mg/kg) significantly decreased systolic blood pressure ($p<0.001$), diastolic blood pressure ($p<0.001$), heart rate ($p<0.001$) and significant increase in contractility index ($p<0.001$) indicating the effect on cardiac contractility. These findings were confirmed in histopathology. MEAP (200 and 400 mg/kg) showed significant ($p<0.001$) reduction in the glucose level showing antihyperglycemic effect.

Keywords: Artemisia pallens Wall; Streptozotocin; Diabetic nephrectomy; Hypertension; Uninephrectomy

Abbreviations

SBP: Systolic Blood Pressure;

DBP: Diastolic Blood Pressure;

DNC: Diabetic Nephrectomy Control;

MEAP: Methanolic Extract of *Artemisia pallens* Wall;

CI: Contractility Index

Introduction

Hypertension and diabetes are chronic medical conditions that regularly exist within the US, it's calculable that ten million persons suffer from diabetes, sixty million from cardiovascular disease and three million from the combination of the two [1].

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There could also be a causative relationship between cardiovascular disease and polygenic disease. fleshiness could also be a causative issue for each cardiovascular disease and ketosis-resistant diabetes mellitus. Those with insulin-dependent diabetes typically become hypertensive solely with the onset of renal disorder aldohexose tolerance, hypoglycaemic agent resistance, and hyperinsulinemia often times occur with essential cardiovascular disease and will be aggravated by hypertension medical care, particularly with diuretics and beta-blockers. Hyperinsulinemia could also be a crucial factor promoting metallic element retention, sympathetic system stimulation and inhibition of the metallic element pump. The unit on cardiovascular disease in polygenic disease has printed a versatile changed version of the stepped-care approach to the treatment of cardiovascular disease in polygenic disease. Management is advanced as a result of polygenic disease is related to involuntary pathology, sexual pathology, symptom, and fluid and solution disorders of these issues are often exacerbated by medicinal drug treatment [2,3].

The incidence and prevalence of sort a pair of polygenic disease area unit increasing its projected that the full range of individuals with polygenic disease can rise from 171 million in 2000 to 366 million by 2030. The amount of adults with cardiovascular disease is foreseen to extend by hour to a complete of one 56 billion folks by 2025 [4,5]. Although great advances have been made in the care of patients with diabetes, it's still long before all patients suffering from diabetes mellitus reach the therapeutic goal and long term damages are confined. In most countries, diabetes is one of the major causes of premature illness and death. Over time it leads to serious damage to many of the body's organ systems induced by macro and micro vascular disease [4-7] .Cardiovascular disease causes the death of at least 50% of people with diabetes, depending on the population.

Cardiovascular diseases account for 12 million deaths, annually worldwide and are known to be number one group of 'killer disease'. Hypertension is one of the leading causes of disability, mortality, and mortality along the populance. It is the most common chronic illness among the world faces. Although it is common, asymptomatic and readily detectable but it can often lead to lethal complication, if left untreated. Because of high incidence and morbidity, various drugs and regimes have been advocated for the control of hypertension [8]. Many new drugs have been introduced which may demonstrate better efficacy but possess side effects. Recently attention has been focused towards herbal and mineral preparations which are traditionally used as potential therapeutic agents in the prevention and management of cardiovascular diseases

Artemisia pallens Walls. ex DC, commonly known as Davana, is an aromatic herb found abundantly in humid habitats in the plains all over India. *Artemisia pallens* is found in Nilgiri hills, and has been used by the tribal people for various ailments. It has been widely used in Indian folk medicine for the treatment of diabetes mellitus. This plant is accredited with antihelmintic, antipyretic and tonic properties and also considered as a good fodder. The oil possesses antispasmodic, antibacterial, antifungal and stimulant properties. The plant has been screened for the antimicrobial, antidiabetic, antinociceptive and wound healing activity [9,10].

Materials and Methods

Experimental research protocol

Albino Wistar rats of either sex weighing between 200 g-250 g were used for the present study. The animals were procured from National Institute of Virology (NIV), Pune. The animals were maintained under standard environmental conditions and were fed with standard pellet diet and water *ad libitum*.

Drugs and chemicals

Candesartan (Aurobindo Pharma Ltd), Streptozotocin, Nicotinamide (Sigma–Aldrich Corporation, USA), Glibenclamide (Hemlin chemicals, Mumbai, Maharashtra, India), Anesthetic ether (Narson Pharma, Mumbai), Urethane (Hi-Media Laboratories Pvt. Ltd, Mumbai, India), Heparin (Gland Pharma Ltd., Mumbai) were used for study.

Collection and authentication of plant

The aerial parts of *Artemisia pallens* Wall was collected from Jejuri, Maharashtra; botanically identified and authenticated by Dr. A.S. Upadhye, Scientist, Plant Drug Authentication Service, Agharkar Research Institute, Pune, India. A voucher specimen was deposited (Voucher specimen No.WP-091) at Agharkar Research Institute, Pune for further reference.

Preparation of crude extract

The aerial parts were shade dried and size reduced to obtain a coarse powder. The weighed quantity (500 g) of powder was cold macerated with 7.5 liters of methanol (99.5%, v/v) for one week with occasional shaking. The macerate was then filtered and the filtrate was evaporated under reduced pressure using vacuum evaporator (Rotava, Equitron Instruments) to obtain a dark green colored extract. This extract was coded as MEAP for further study.

Preparation of drug solution MEAP dose

Weighed quantity of MEAP (100 mg/kg, 200 mg/kg and 400 mg/kg) was dissolved in water. The route of administration was oral by using intra-gastric tube.

Experimental induction of diabetes

Streptozotocin was dissolved in a freshly prepared 0.1 M citrate buffer (pH 4.5) and nicotinamide was dissolved in normal physiological saline. Diabetes was induced in overnight fasted (16 h fasting with free access to water) rats of all the groups except vehicle control by a single intraperitoneal injection of 65 mg/kg of Streptozotocin (STZ), 15 min after the intraperitoneal injection of 110 mg/kg of nicotinamide [10]. The vehicle control group (Group I) was injected with buffer alone. After 72 h, blood was withdrawn by retroorbital puncture under light ether anaesthesia and the blood glucose level was estimated. After 1 week of induction, blood glucose level was estimated again and the fasting blood glucose level more than 200 mg/dL was considered as diabetic.

Experimental induction of hypertension

The rats were anaesthetised with thiopental sodium (35 mg/kg, intraperitoneal) after 1 week of diabetes induction. The abdominal region was shaved and the right kidney removed through a small flank incision. After 3 days of recovery the

nephrectomised rats were divided into six groups of six in each and dosing was started. In the sham group (group I) the right kidney was exposed but not subjected to nephrectomy.

Uninephrectomy in diabetic rats resulted in enlargement of the remaining kidney, which was further increased by the development of diabetes. Uninephrectomy showed an increased glomerular capillary pressure in SHR rats which promoted diabetic glomerular injury. However, interpretation of this model was complex, as it was difficult to dissect the relative contributions of STZ-induced hyperglycaemia and uninephrectomy induced changes in glomerular haemodynamics in the development of renal injury [11].

Experimental design

The rats were randomly divided into seven groups, each containing six rats:

Group I: Sham control (Animals undergone surgery but not nephrectomzied)

Group II: Diabetic nepherectomy control

Group III: Glibenclamide treated group (5 mg/kg)

Group IV: Candesartan treated group (10 mg/kg)

Group V: MEAP treated group (low dose i.e. 100 mg/kg)

Group VI: MEAP treated group (medium dose i.e. 200 mg/kg)

Group VII: MEAP treated group (high dose i.e. 400 mg/kg)

Group I and II received vehicle, group III received Glibenclamide 5 mg/kg, group IV received Candesartan 10 mg/kg and Group V, VI, VII received drug of MEAP 100, 200, 400 mg/kg, per oral respectively for 3 weeks.

Assessment of hemodynamic changes

On last day of study, animals were anaesthetized by urethane (1.25 gm/kg) i.p. The right carotid artery of each rat was cannulated (FIG. 1) for the measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP), contractility index (CI). The cannula was filled with heparinized saline and connected to pressure transducer to record all the parameters mentioned above. After 30 min of stabilization hemodynamic parameters were recorded by eight channel recorder Power lab (AD Instruments, UK) having LABCHART-6 pro software.

FIG. 1**. Cannulation of carotid artery for measurement of ECG parameters.**

Results

Effect of MEAP on serum glucose level in renal hypertension in diabetic rats

Before induction of diabetes the serum glucose level in sham control, diabetic nephrectomy control, glibenclamide, candesartan and MEAP (100, 200 and 400 mg) groups was found to be 73.24 ± 0.25, 73.02 ± 0.01, 72.32 ± 0.25, 72.82 ± 0.01, 72.32 ± 0.25 and 72.90 ± 0.12 mg/dL, respectively. On this day there was no significant difference in serum glucose level between any of the test groups.

There was no significant change in the blood glucose level of the sham control group throughout the experimentation. However, there was a significant increase in the blood glucose level of DNC group on induction of diabetes and nephrectomy which continued to remain high in week 1 and week 3 [12-15]. Treatment with Glibenclamide (5 mg/kg) significantly ($p<0.001$) decreased the blood glucose level from the week 1 to 318.69 mg/dL (30.17% decrease) which continued through week 3 to 275.01 mg/dL (47.66% decrease). On the other hand treatment with MEAP (200 mg/kg) significantly ($p<0.001$) decreased the blood glucose level from week 1 to 409.00 mg/dL (10.38% decrease) which continued through week 3 to 383.62 mg/dL (26.99% decrease) while MEAP (400 mg/kg) significantly ($p<0.01$) decreased the blood glucose level from week 1 to 385.84 mg/dL (15.46% decrease) which continued through week 3 to 328..87 mg/dL (37.41% decrease). However treatment with candesartan and MEAP (100 mg/kg) showed non-significant decrease in serum glucose level compared to DNC on all the tested weeks (FIG. 2).

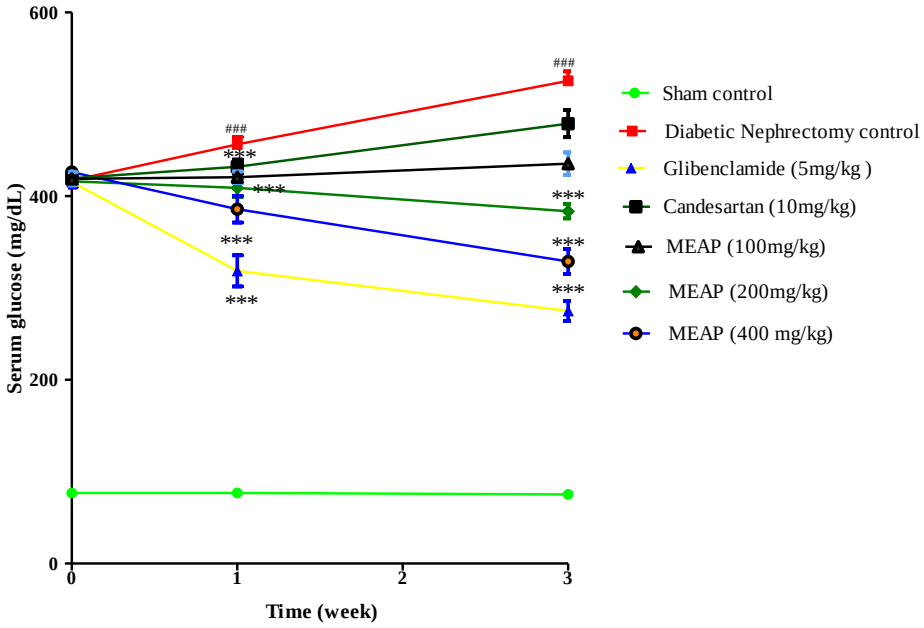

FIG. 2. **Effect of MEAP on serum glucose level in renal hypertension in diabetic rats. Data was analyzed by Two-Way ANOVA followed by Bonferroni's posttests ***p< 0.001 as compared with Diabetic nephrectomy control group and ###p<0.001 as compared with sham control on respective days. DNC-Diabetic Nephrectomy Control, MEAP-Methanolic Extract of *Artemisia pallens* Wall.**

Effect of MEAP on different parameters in renal hypertension in diabetic rats

Heart rate: On week 3 the heart rate in sham group was found to be (328.00 ± 3.02 bpm). There was a significant ($p<0.001$) increase in heart rate (439.00 ± 8.0 bpm) in DNC group (33.84% increase) when compared to sham group. On the other hand treatment with glibenclamide (5 mg/kg) and candesartan (10 mg/kg) significantly ($p<0.001$) decreased the heart rate to 380.00 ± 3.65 bpm (13.43% decrease) and 337.00 ± 7.2 bpm (23.23% decrease), respectively. Treatment with MEAP (100, 200 and 400 mg/kg) decreased the heart rate to 404 ± 7.2 bpm (7.97% decrease), 352.00 ± 7.9 bpm (19.81% decrease) and 359.00 ± 6.6 bpm (18.22% decrease), respectively. This decrease in heart rate with MEAP 200 and 400 mg/kg was significant ($p<0.01$ and $p<0.001$), respectively when compared with DNC (FIG. 3).

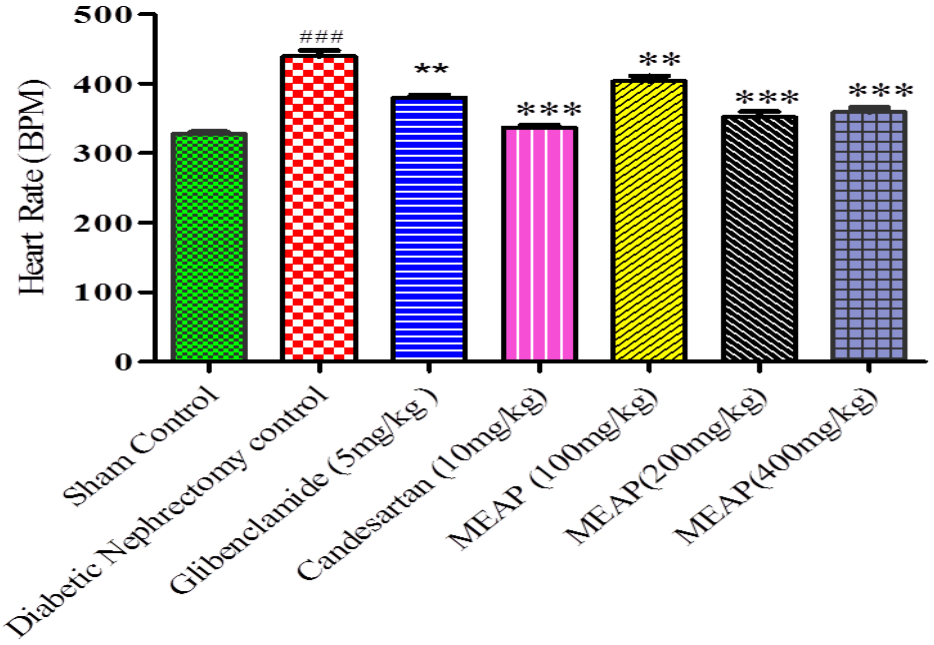

FIG. 3**. Effect of MEAP on Heart rate in renal hypertension in diabetic rats. Values are expressed as mean ± SEM (n=6), Data was analyzed by one way ANOVA followed by Dunnets 't' test. **p<0.01 and ***p<0.001 as compared with DNC, ###p<0.001 as compared with Sham control. DNC-Diabetic Nephrectomy Control, MEAP-Methanolic Extract of *Artemisia pallens* wall.**

Systolic blood pressure: On week 3, the SBP in sham group was found to be (123.00 ± 1.65 mmHg). There was a significant ($p<0.001$) increase in SBP (159.60 ± 4.0 mmHg) in DNC group (29.75% increase) when compared to sham group. On the other hand treatment with glibenclamide (5 mg/kg) and candesartan (10 mg/kg) significantly ($p<0.001$) decreased the SBP to 142.00. ± 1.06 mmHg (10.97% decrease) and 132.75 ± 1.39 mmHg (16.82% decrease), respectively (FIG. 4A). Treatment with MEAP (200 and 400 mg/kg) showed significant ($p<0.001$) decrease in SBP when compared with DNC which was 140.80 ± 1.61 (12.16% decrease) and 137.05 ± 1.08 mmHg (14.04% decrease), respectively. However the decrease in SBP with MEAP 100 mg/kg was non-significant when compared to DNC observed as 154.17 ± 1.39 mmHg (3.40% decrease).

Diastolic blood pressure: On week 3, the DBP in sham group was found to be (111.20 ± 3.25 mmHg). There was a

significant (p<0.001) increase in DBP (135.15 ± 3.24 mmHg) in DNC group (21.58% increase) when compared to sham group. On the other hand treatment with candesartan (10 mg/kg) caused decrease in DBP which was 98.43 ± 2.74 mmHg (27.19% decrease). Treatment with MEAP (200 and 400 mg/kg) showed significant (p<0.01 and p<0.001) decrease in DBP which was 120.07 ± 2.96 mmHg (11.19% decrease) and 110.41 ± 2.06 mmHg (18.33% decrease), respectively (FIG. 4B). However the decrease in DBP with MEAP (100 mg/kg) and glibenclamide (5 mg/kg) were non-significant when compared to DNC.

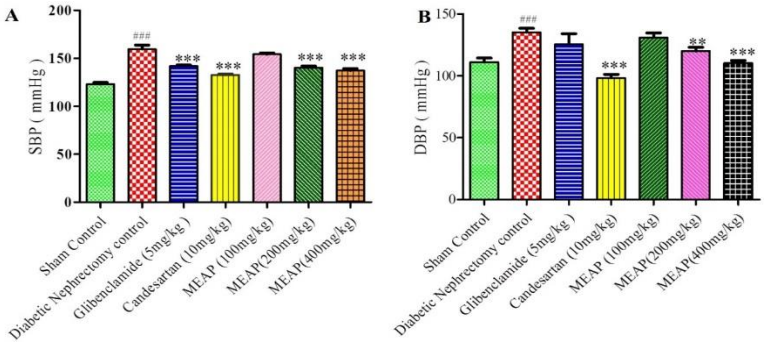

FIG. 4. **Effect of MEAP on Blood pressure in Renal hypertension in diabetic rats. Values are expressed as mean ± SEM (n=6), Data was analyzed by one way ANOVA followed by Dunnets 't' test. **p<0.01 and ***P<0.001 as compared with DNC, ###P<0.01 as compared with Sham control. DNC-Diabetic Nephrectomy Control, MEAP-Methanolic Extract of *Artemisia pallens* Wall.**

Contractility index: On week 3, the contractility index in sham group was found to be (18.55 ± 0.10). There was a significant (p<0.001) decrease in C.I. (8.61 ± 0.10) in DNC group (53.58% decrease) when compared to sham group. On the other hand, treatment with candesartan (10 mg/kg) significantly (p<0.001) increased C.I. by 66.45% (16.49 ± 0.279). However treatment with glibenclamide (5 mg/kg) and MEAP (100 mg/kg) showed non-significant increase in C.I. when compared to DNC. On the contrary, treatment with MEAP (200 and 400 mg/kg) showed significant (p<0.001) increase in C.I. which was 49.01% (12.83 ± 0.46) and 41.92% (13.22 ± 0.34) increase, respectively when compared with DNC (FIG. 5).

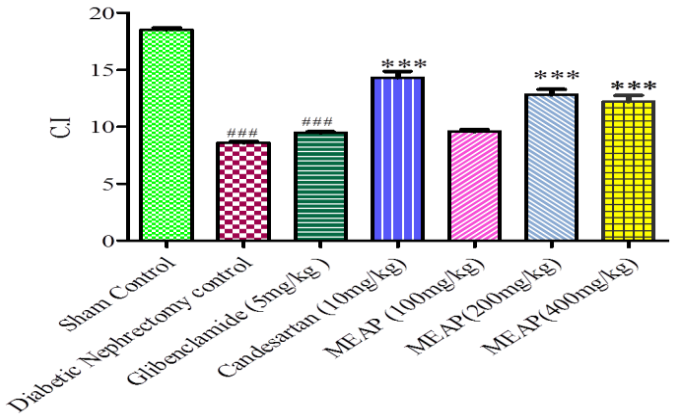

FIG. 5. **Effect of MEAP on Contractility Index in Renal hypertension in diabetic rats. Values are expressed as mean ± SEM (n=6), Data was analyzed by one way ANOVA followed by Dunnets 't' test. ***p<0.001 as compared with DNC,**

###p<0.01 as compared with Sham control. DNC-Diabetic Nephrectomy Control, MEAP-Methanolic Extract of *Artemisia pallens* Wall.

Effect of MEAP on histopathology of kidney in renal hypertension of diabetic rats

The microphotography of the kidney cortex of sham control group animal which was not diabetic and surgery was carried out without Uninephrectomy, showed the normal renal parenchyma with normal histomorphology of glomeruli and renal tubules (FIG. 6A). The kidney of glibenclamide (5 mg/kg) showed mild hemorrhagic foci with tubular swelling of renal tubular epithelium and no accumulation of mononuclear cell were observed. (FIG. 6B). Treatment of Candesartan (10 mg/kg) showed mild hemorrhagic foci with tubular swelling of renal tubular epithelium and no accumulation of mononuclear cell were observed (FIG. 6C). In case of Diabetic nephrectomy control group showed severe pathological changes with interstitial hemorrhages and tubular damage with loss of integrity and disruption of tubules and also accumulation of mononuclear cells were observed (FIG. 6D). Treatment of the test drug at low MEAP (100 mg/kg) showed moderate pathological changes with interstitial hemorrhages and tubular damage with loss of integrity and disruption of tubules and accumulation of mononuclear cell were observed (FIG. 6E). Treatment of test drug at the medium dose MEAP (200 mg/kg) showed moderate hemorrhagic foci with tubular swelling of renal tubular epithelium and no accumulation of mononuclear cell were observed (FIG. 6F). Treatment of test drug at the high dose MEAP (400 mg/kg) showed mild hemorrhagic foci with tubular swelling of renal tubular epithelium and no accumulation of mononuclear cell were observed (FIG. 6G).

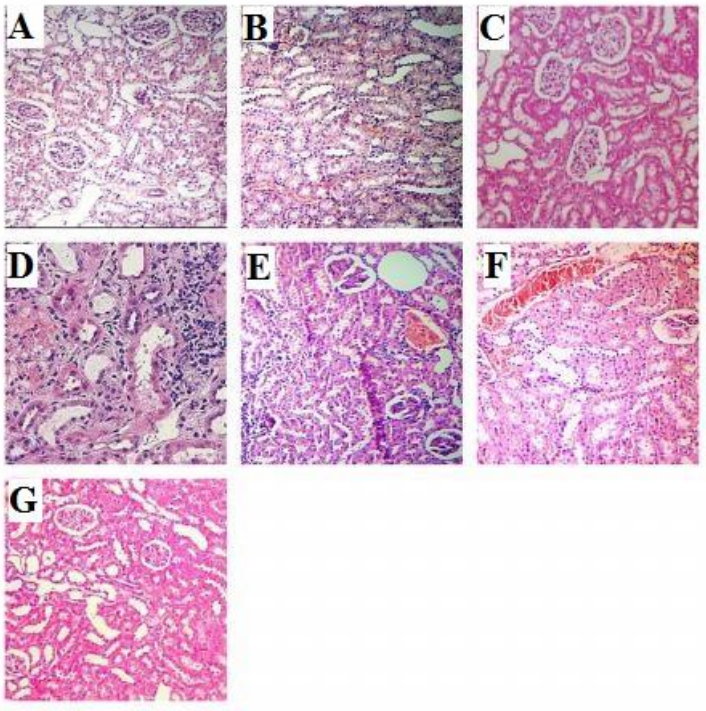

FIG. 6. **Effect of MEAP on histopathology of kidney in renal hypertension of diabetic rats. (A) Sham control: nothing abnormal detected. (B) Glibenclamide (5 mg/kg) showed mild hemorrhagic foci with tubular swelling of renal tubular epithelium. (C) Candesartan (10 mg/kg) showed mild hemorrhagic foci with tubular swelling of renal tubular epithelium. (D) Diabetic Nephrectomy control showed severe pathological changes with interstitial hemorrhages and tubular damage with loss of integrity and disruption of tubules. (E) MEAP (100 mg/kg) showed moderate pathological**

changes with interstitial hemorrhages and tubular damage with loss of integrity and disruption of tubules. (F) MEAP (200 mg/kg) moderate hemorrhagic foci with tubular swelling of renal tubular epithelium. (G) MEAP (400 mg/kg) mild hemorrhagic foci with tubular swelling of renal tubular epithelium.

Discussion

The preset study deals with the effect of methanolic extract of aerial parts of *Artemisia pallens* Wall. in experimentally induced diabetic renal hypertension. The study was based on the findings that MEAP decreases blood glucose level in alloxan induced diabetic rats [16,17]. In the present study, diabetes was induced by injecting nicotinamide-streptozotocin intraperitoneally. Nicotinamide given 15 min before STZ administration causes 40% decrease in pancreatic β-cell mass which resembles human type-2 diabetes [18-21].

Uninephrectomy along with nicotinamide-streptozotocin induced diabetes causes increased activity of renin-angiotensin system which brings about haemodynamic and biochemical changes [22]. Once nephropathy is initiated, it may not only contribute to further blood pressure increase but also enhances the glomerular transmission of the elevated pressures due to renal autoregulatory impairment that seems to develop currently. Hence the model of diabetes mellitus followed by uninephrectomy was selected to study the effect of MEAP on renal hypertension induced by uninephrectomy in diabetic animals. Uninephrectomy induces hypertension by activating renin angiotensin aldosterone system in which angiotensin antagonist like candesartan are proven to be effective hence candesartan (10 mg/kg) was chosen [20] as a standard drug for hypertension.

Sulfonlyurea such as glibenclamide was often used as standard antidiabetic drug to compare the efficacy of the antihyperglycemic agents hence glibenclamide (5 mg/kg) dose was used as a standard for diabetes mellitus [17,19]. In the present study, on induction of diabetes there was a significant increase in the blood glucose level. Uninephrectomy was carried out on all groups except sham control in diabetic animals. On treatment with MEAP (200 and 400 mg/kg) there was a significant decrease in blood glucose level which illustrated the antidiabetic effect of MEAP. However, MEAP (100 mg/kg) failed to decrease the blood glucose level.

In early stages after nephrectomy the RAAS is thought to play critical role in the development of hypertension in this model [11]. RAAS activates angiotensin II which binds with AT1 receptor which in turn increases the release of noradrenaline from sympathetic nerve terminals causing vasoconstriction and increase in rate and force of contraction of the heart. This was evident by the significant increase in heart rate, systolic blood pressure, diastolic blood pressure of diabetic nephrectomy control. There was an increase in the systolic, diastolic blood pressure and there was an increase in heart rate which indicates that there was an increase in sympathetic stimulation which in turn increases the contractility. However, there was a significant decrease in contractility index which may be due to increase in preload which in turn follows Laplace's law and hence decrease in cardiac contractility which is further confirmed by increase in systolic blood pressure which indicate increase in ventricular wall stress. MEAP (200 and 400 mg/kg) significantly decreased the heart rate, systolic blood pressure, diastolic blood pressure, and increase in contractility index. Hence it was found to effective in diabetes induced hypertension.

Conclusions

The results indicated that MEAP possess therapeutic property in restoring the complications of the diabetic renal hypertension.

- Treatment with MEAP (200 and 400 mg/kg) showed significant decrease in serum glucose level when compared to DNC group, whereas the MEAP (100 mg/kg) showed non-significant decrease in serum glucose level when compared to DNC group.
- Treatment with MEAP (200 and 400 mg/kg) showed decreased systolic blood pressure, diastolic blood pressure, when compared to DNC group.
- Treatment with MEAP (200 and 400 mg/kg) showed increased contractility index, when compared to DNC group. Whereas the MEAP (100 mg/kg) showed non-significant increase in contractility index. There is a significant increase in contractility index of MEAP (100, 200 and 400 mg/kg) when compared to sham control group.
- Treatment with MEAP (200 and 400 mg/kg) showed decrease in Heart rate when compared to DNC group. Whereas the MEAP (100 mg/kg) showed non-significant decrease in heart rate.

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