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Antihypertensive and Antihyperlipidemic Activity of Aqueous Methanolic Extract of *Rauwolfia Serpentina* in Albino Rats

Syed Muhammad Ali Shah[1], Syed Ali Raza Naqvi[2], Naveed Munir[3], Sohaib Zafar[2], Muhammad Akram[1], and Jaweria Nisar[1]

Abstract

Rauwolfia serpentina has a wide range of therapeutic effects so this study was planned to explore the antihypertensive and antihyperlipidemic therapeutic responses of *R serpentina* doses using albino rats by measuring the blood pressure, biochemical parameters, and histological architecture of liver and kidney tissues. Thirty albino rats were divided into 5 groups (n = 6) as G1 (normal Control) received normal diet, G2 (positive control) received only 8% NaCl added diet (high salt diet); G3 was given atenolol (standard drug control) 50 mg/kg body weight, G4 and G5 groups were given methanolic plant extract as low dose (100 mg/kg body weight) and high dose (200 mg/Kg body weight) daily along with high salt diet for 4 weeks, respectively. *Rauwolfia serpentina* significantly ($P < .05$) decreased the blood pressure in G4 and G5 groups as compared to G2 and G3. Significant ($P < .05$) impact was reported, on serum lipid profile and serum proteins as well as hepatoprotective and renoprotective potential on studying tissues sections under microscope, in animal groups given herbal extract as compared to control groups. It could be concluded that *R serpentina* has therapeutic effect to manage the hypertension and hypercholesterolemia most probably via protecting the liver and renal architectures.

Keywords

Rauwolfia serpentina, herbal medicine, hypertension, hypercholesterolemia, therapeutic response, different doses

Introduction

Rauwolfia serpentina is used as drug since ancient times. *Rauwolfia serpentina* belongs to family *Apocynaceae*. There were still about 121 chemical substances identified from different medicinal plant which are used throughout the world.[1] *Rauwolfia serpentina* is perceived as Rauwolfia in Hindi, Hindustani Snake Root in English, Amalpori in Malayalam, Chandra in Bengali, and so forth. It is a sage of restorative worth marked in ayurvedic, western arrangement of prescription. Its leaves, seeds, roots, and organic products are used in the cure of numerous disorders. *Rauwolfia serpentina* contains many phytochemical compounds including flavonoids, alkaloids, tannins, and phenols.[2] Flavonoids have a wide range of therapeutic applications and are being utilized for more than one billion years to treat hypertensive activity.[3] *Rauwolfia serpentina* possesses the alkaloid reserpine that is useful agent to treat the blood pressure and other neurological diseases.[4] Reserpine produces its antihypertensive effect by binding to the catecholamine in the nerve cells.[5] Suggestions includes, it leads to depress the central nervous system and peripheral nervous system. Reserpine also activates the parasympathetic system by neurotransmitter substance depletion from the adrenergic neurons.[4,6] The drug *R serpentina* is used to treat

[1] Department of Eastern Medicine, Government College University, Faisalabad, Pakistan
[2] Department of Chemistry, Government College University, Faisalabad, Pakistan
[3] Department of Biochemistry, Government College University, Faisalabad, Pakistan

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Corresponding Authors:
Syed Muhammad Ali Shah, Department of Eastern Medicine, Government College University, Faisalabad 38000, Pakistan.
Emails: smalishahgcuf@gmail.com

Syed Ali Raza Naqvi, Department of Chemistry, Government College University, Faisalabad 38000, Pakistan.
Email: draliraza@gcuf.edu.pk

many neurological disorders including vertigo, insomnia, schizophrenia, and sexual aggression.[6] The drug acts as hypnotic, sedative, antihypertensive, and antihypercholesteremic. Its leaves and root extract can be used to relief stomach pain, liver pain, dysentery, and to expel intestinal worms.[2,7] It is utilized in the management of hypertension, arrhythmia, human promyelocytic leukemia, pneumonia, asthma, AIDS, spleen disorders, and skin illnesses.[6,8,9] The present study was planned to evaluate the *R serpentina* therapeutic potential in the treatment of hypertension and hypercholesterolemia induced in animal model.

Material and Methods

Preparation of Plant Extract

Rauwolfia serpentina roots were bought from local market of Faisalabad and taxonomically authenticated from Department of Botany, Government College University, Faisalabad, Pakistan. To clean or rid the roots of the sample plants of impurities, fresh water and later distilled water were used to rinse them, the roots of the sample plant were dried under a shaded place avoiding direct sunlight. Then dried roots were grinded to make powder and save this powder in a glass jar under temperature 4 °C. Hydro-methanolic (30:70) was used as solvent for the extraction of roots of *R serpentina*. The plant materials were dissolved in extraction solvent at a ratio of 1:10 (wt/vol) and placed for 72 hours at room temperature in a shaker. Then, the mixture was filtered using Whatman filter paper No. 1. The extraction was repeated 3 times and the filtrate was collected in a beaker. Then the filtered extract was concentrated using rotary evaporator at 40 °C under vacuum.[10] Then dry extract was stored in air tight polythene bags until the trial was run.

Experimental Design

Albino rats (n = 30) were used as experimental animals in this study weighing about 130 ± 20.5 g of 10 to 12 weeks of age. All rats were given a standard diet and water ad libitum and before start the trial, rats were acclimatized to handlers for 3 days. This study was approved from ethical review committee for research, Government College University, Faisalabad, Pakistan. The animals were divided randomly, made 5 groups having 6 rats (n = 6) in each group. First group G1 (normal control) received normal diet and water ad libitum, group G2 (positive control) received only 8% sodium chloride (NaCl) added diet (high salt diet), and group G3 was given allopathic drug atenolol (standard drug) orally at dosage 50 mg/kg body weight daily along high salt diet. Groups G4 and G5 were given methanolic plant extract with dosage as low dose (100 mg/kg body weight) and high dose (200 mg/kg body weight) daily along with high salt diet for 4 weeks, respectively.

Measurement of Blood Pressure

Tail-cuff method is noninvasive method used to measure systolic and diastolic blood pressure, heart rate, and temperature. Before blood pressure measurements, rats were kept in scanner for 30 minutes to warm them. Blood pressure was measured at the 0, 7, 15, and 30 days.

Blood Biochemical Parameters and Histopathological Studies

At the end of fourth week samples of blood were collected in clot activator vials by cardiac puncture. The serum was separated by centrifugation at 3000 rpm for 10 minutes. Serum biochemical analysis including total protein was measured by Biuret method, albumin by bromocresol green method[11] and Serum globulin was determined using the formula given below

$$\text{Serum globulin} = \text{Serum total protein} - \text{serum albumin}$$

Albumin/globulin ratio was calculated by dividing the albumin concentration to globulin concentration. Cholesterol in the sample was determined quantitatively by cholesterol oxidase method using the commercially available kit spectrophotometrically.[12] Triglyceride was measured using enzymatic kit method following the protocol of the study by Shephard and Whiting[13] with the help of spectrophotometer. High-density lipoprotein (HDL)–Cholesterol was determined calorimetrically using the procedure described by Friedewald et al,[14] and low-density lipoprotein (LDL)–Cholesterol and very low-density lipoprotein (VLDL)–Cholesterol were calculated using the formulas described by Friedewald et al,[14] given below:

$$\text{LDL} - \text{cholesterol (mg/dL)} = \text{Total cholesterol} - (\text{TG}/5) - \text{HDL} - \text{cholesterol.}$$

Liver and kidney tissues were collected from the sacrifice rats for histopathological examination. The tissue sections were processed to embed in paraffin wax and the slides were prepared by staining with hematoxylin and eosin stain after microtomy and observed under light microscope to note any type of morphological changes in tissues as described in the study by Spencer et al.[15]

Statistical Analysis

All results were presented as mean ± standard error of mean. The obtained data were analyzed statistically using 1-way analysis of variance and Tukey test were used to determine pairwise comparison using statistical Software SPSS 23 (Trial version). P value <.05 was representing the significant difference between groups.

Results

Effect of R serpentina on Hypertension

The mean systolic and diastolic blood pressure were significantly ($P < .05$) decreased in groups G3, G4, and G5 as compared to G2 group throughout the experimental days. Moreover, results revealed that systolic and diastolic blood pressure was significantly ($P < .05$) lower in G4 and G5 group received *R serpentina* extracts as compared to G3 group given

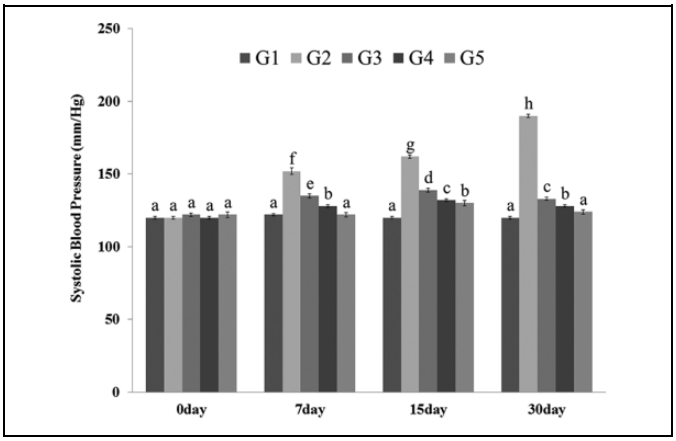

Figure 1. Means ± standard errors of mean of systolic blood pressure in different groups at specific intervals. Alphabets represent the pairwise comparison of groups (Bars bearing different letters are statistically, $P < .05$, differ).

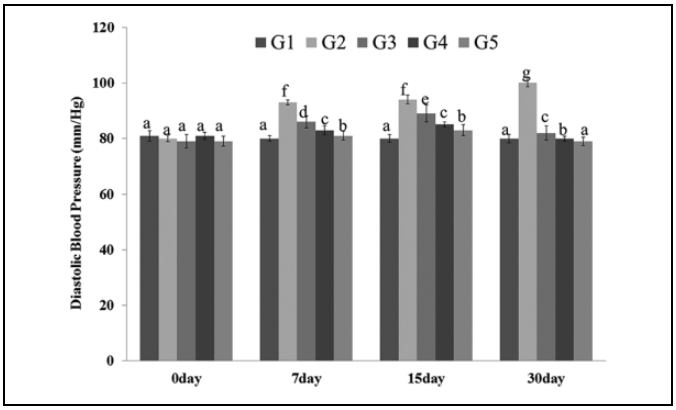

Figure 2. Means ± standard errors of mean of diastolic blood pressure in different groups at specific intervals. Alphabets represent the pairwise comparison of groups (Bars bearing different letters are statistically, $P < .05$, differ).

standard drug (Figures 1 and 2). Further, it was reported that there was a nonsignificant difference between control group (G1) and *R serpentina* treated group (G4 and G5) at the end of the experiment. Results also revealed that blood pressure in G4 and G5 was lower as compared to G3 group but the difference was not significant ($P > .05$) statistically. Pairwise study was also revealed the significance ($P < .05$) difference among different study groups represented by small alphabets (columns share the same letters represent nonsignificant ($P > .05$) difference) for more details please see all figures.

Effect of R serpentina on Blood Biochemical Parameters

The results of present study showed significant ($P < .05$) reduction of total cholesterol (TC) and LDL-Cholesterol levels in G4 and G5 groups on given *R serpentina* extract for 4 weeks in contrast with the G2 group (Figures 3 and 4). High-density lipoprotein–Cholesterol level was significantly increase ($P < .05$) in G3, G4, and G5 groups in contrast with G2 group. It was also determined that *R serpentina* also have significant potential ($P < .05$) to regulate the serum VLDL-Cholesterol and triglyceride levels in G4 and G5 group. Further, the results of serum proteins were also revealed that *R serpentina* extracts induction increase the serum proteins in G4 and G5 but statistical analysis revealed a nonsignificant ($P > .05$) impact among the groups (Figure 5).

Effect of R serpentina on Histopathology of Liver and Kidney

Histologic examination of the section from control group (G1) shows a liver tissue with intact architecture. No altered architecture is seen and the hepatocytes with typical cores, sinusoidal spaces, with Kupffer cells (Figure 6A). While G2 group liver section shows liver tissue with altered architecture, periportal necroinflammatory changes, portal inflammation, mild degenerative changes, congestion, and mild chronic inflammation (Figure 6B). Moreover, liver tissue sections from G3, G4, and G5 groups showed the preventive effect of extract on the architecture of liver and no critical change was reported under microscope (Figure 6C and D). Histological examination of the sections from the kidney comprises of cortex and medulla. There was minor harm of kidneys in G2 group (Figure 7B). There was minimal endothelial swelling and impediment of slim circles in G2 group. There was no critical impact of salt in G4 and G5 (Figure 7C and D).

Discussion

Hypertension is one of the important common global challenge in public health.[16,17] It is the major risk of many diseases including stroke, heart failure, chronic liver failure, coronary artery disease, and retinopathy.[18-21] *Rauwolfia serpentina* contained a wide range of phytochemical constituents such as alkaloids, flavonoids, phenolics, carbohydrates, tannins, and saponins.[22] The most important alkaloids include reserpine, ajmalicine, serpentinine, ajmalimine, ajmaline, rescinnamidine, rescinnamine, reserpiline, serpentine, indobidine, yohimbine, and deserpidine. Reserpine acted as hypotensive agent by depleting the catecholamine and angiotensin-converting enzyme (ACE) is inhibited by rescinnamine to halt the conversion of angiotensin I, resulting in a decrease of plasma angiotensin II then lowering blood pressure. Sodium channel blockage is the major role of ajmaline to show antiarrhythmic effect of *R serpentine*.[22,23] Yohimbine has role in the treatment of erectile dysfunction as it is selective alpha-adrenergic antagonist in blood vessels. Antidiabetic and hypolipidemic potential of *R serpentina* extract is due to the presence of high concentration of phenolic compounds. Antioxidant, anti-inflammatory, and anticancer activities of *R serpentina* are due to the presence of flavonoids.[2] Cholesterol binding ability is due to the presence of saponins.[23]

The present study was conducted to explore the *R serpentina* effect for the management of hypertension and hypercholesterolemia in animal model. The result of the present study showed

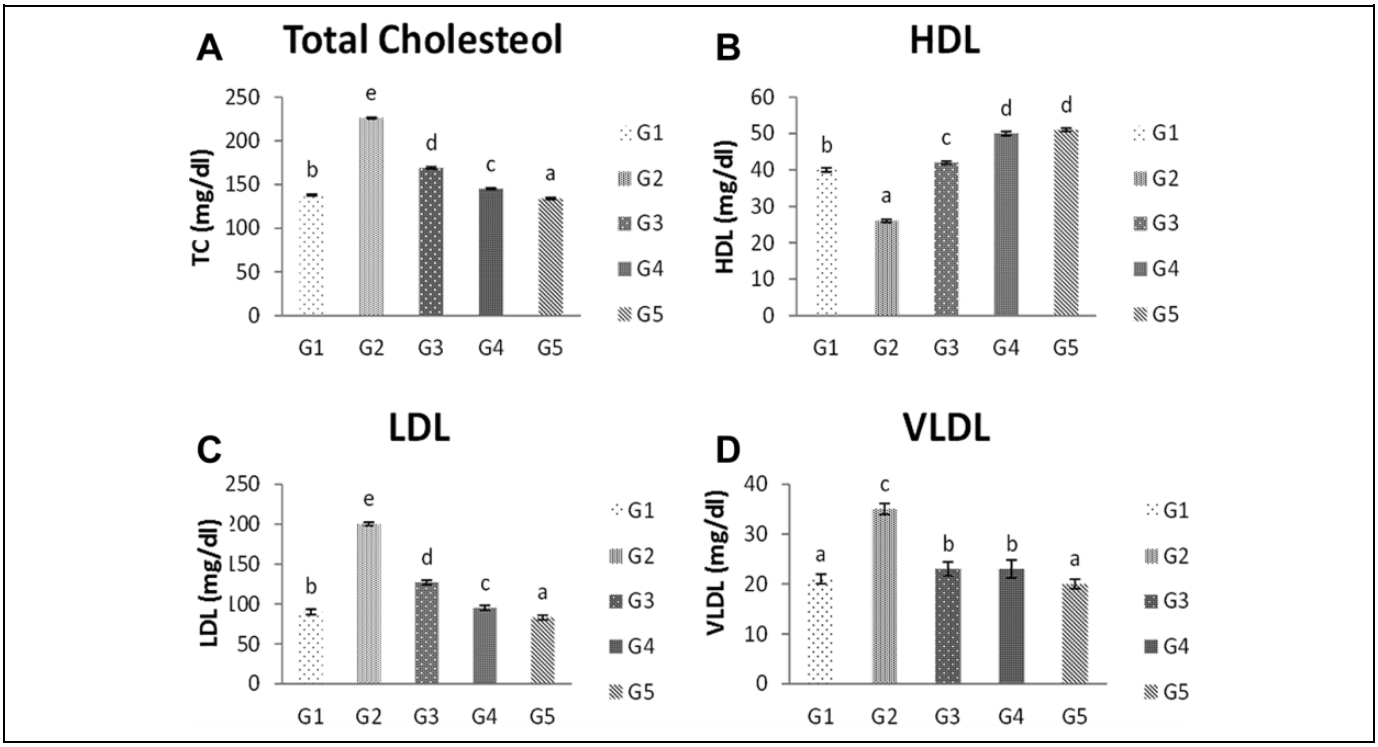

Figure 3. Means ± standard errors of mean of total cholesterol, LDL-Cholesterol, HDL-Cholesterol, and VLDL-Cholesterol in different groups. Alphabets represent the pairwise comparison of groups (Bars bearing different letters are statistically, $P < .05$, differ). HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

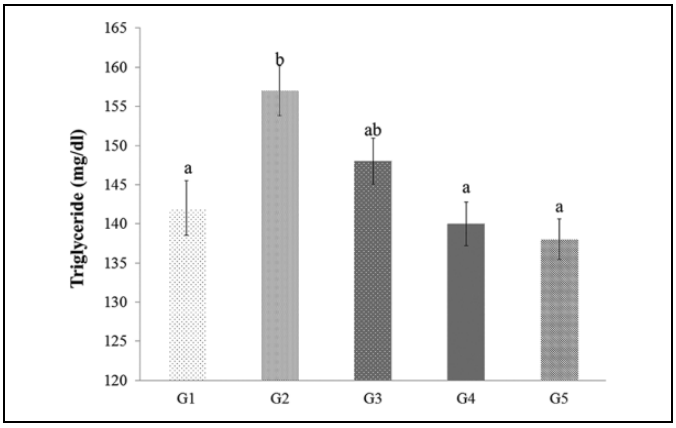

Figure 4. Means ± standard errors of mean of triglyceride in different groups. Alphabets represent the pairwise comparison of groups (Bars bearing different letters are statistically, $P < .05$, differ).

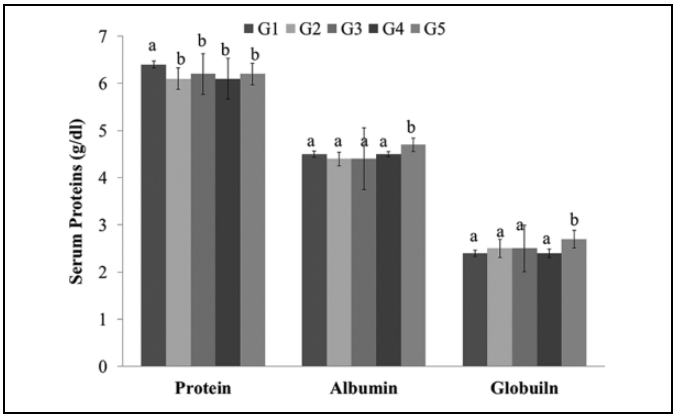

Figure 5. Means ± standard errors of mean of serum total proteins, albumin, and globulin in different groups. Alphabets represent the pairwise comparison of groups (Bars bearing different letters are statistically, $P < .05$, differ).

that *R serpentina* extract showed significant improvement in the blood pressure, lipid profile, and tissues histopathology as compared to the animal group receive the allopathic drug. Ranjini et al investigated the antihypertensive effect of aqueous extract of *R serpentina* leaves along with the *Allium sativum* cloves using animal models as sheep kidney and lung ACE. Hippuryl-hiatdyl-leucine method to measure the activity was used and the level of hippuric acid release was determined. The study revealed significant antihypertensive effect of *R serpentine*.[24]

It was reported that *R serpentina* contain very important alkaloid as reserpine that produces the antihypertensive effect. The researcher Shaman and Perez reported that reserpine at the dose of 0.5 mg/d able to reduce the blood pressure. They described that reserpine significantly declined the systolic and diastolic blood pressure.[25] Globally, day by day, the occurrence of hyperlipidemia is increasing either due to unhealthy lifestyle or the genetic factor involvement.[26] High cholesterol level in the blood is becoming one of the chief causes of mortality due to cardiac arrest worldwide[27] and also has been reported in

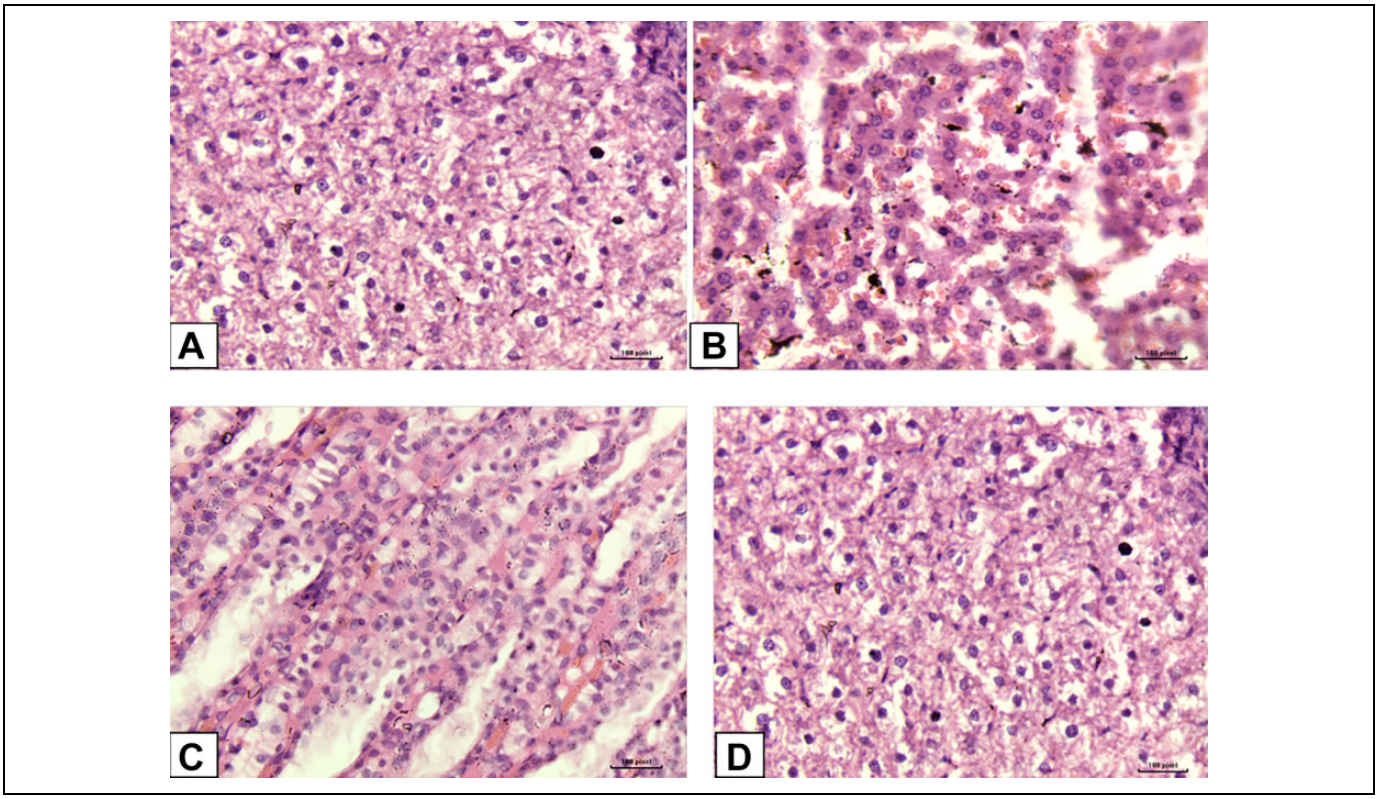

Figure 6. Histopathology of liver tissue (A) represents the histopathology of control group (G1); (B) represents the histopathology of high salt diet group (G2) with histopathological alterations; (C) represents the histopathology of group (G3) with very minute cellular changes treated with atenolol; (D) represents the histopathology of high-dose extract treated group (G5).

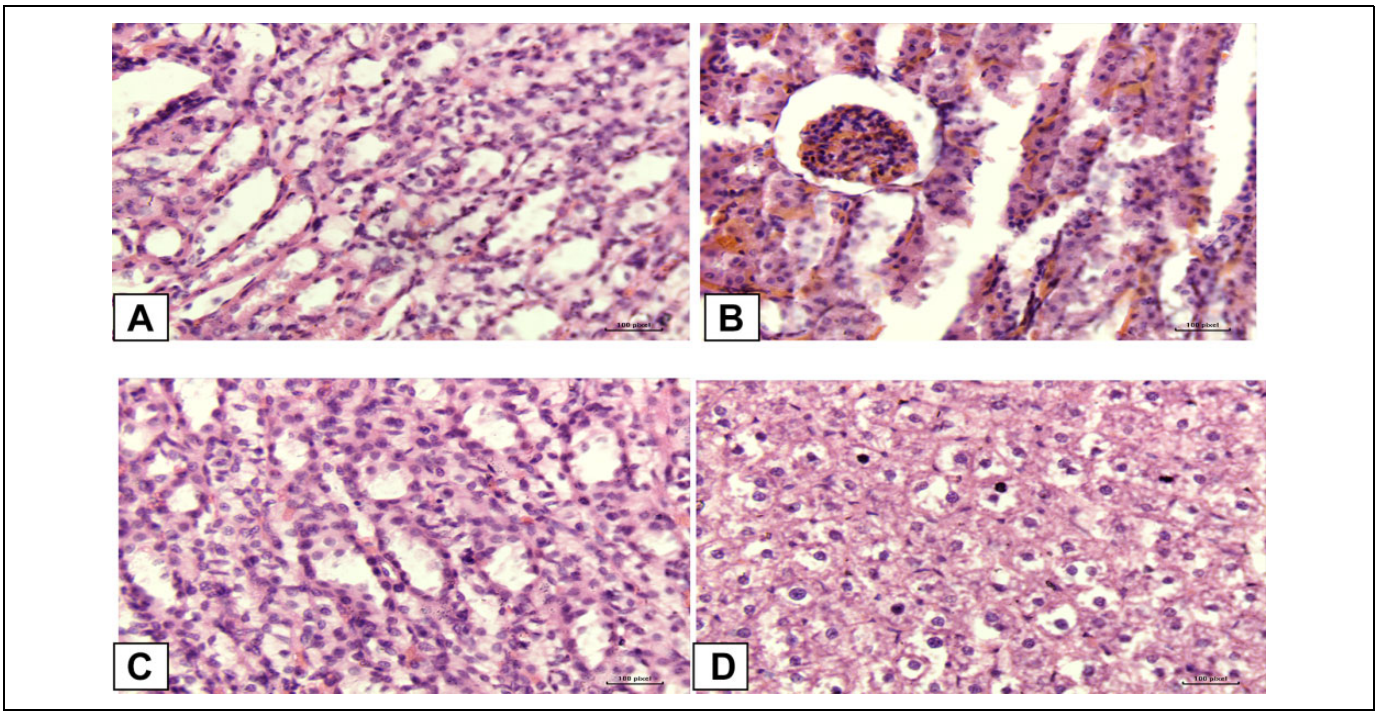

Figure 7. Histopathology of kidney tissue (A) represents the histopathology of control group (G1); (B) represents the histopathology of salt diet group (G2); (C) represents the histopathology of group (G3) treated with atenolol; (D) represents the histopathology of high-dose extract treated group (G5).

Pakistan.[28,29] It was reported that root powder of *R serpentina* significantly reduced the serum lipids including TC, triglycerides (TG), LDL-C, and increased the HDL-C when given to rabbits orally for 12 days. Moreover, it also has hepatoprotective activities investigated by measuring the alanine aminotransferase, and lactate dehydrogenase.[30] It was also reported that methanolic extract of *R serpentina* have antihyperglycemic, antiatherogenic, decreased coronary blockage risk, and cardioprotective indices in alloxan-induced diabetic mice.[31] Recently, Azmi and Qureshi reported the lipid homeostasis effect of *R serpentina*. They reported that the drug significantly improved the lipid profile including TC, LDL, VLDL, HDL, and triglyceride. The results showed that herbal medicine significantly lowered the TC, LDL, VLDL, triglyceride level, and increased the HDL.[32] *Rauwolfia serpentina* effect on kidney was controversial. Many researchers reported the effect of *R serpentina* on liver. Gupta et al demonstrated the hepatoprotective effect of *R serpentina* paracetamol induced damage. They described that *R serpentina* has the hepatoprotective activity due to its antioxidant property.[3,33] In another study, Qureshi et al described the hepatoprotective, hypolipidemic, and hypoglycemic effect of the methanolic extract of the drug in diabetic-induced rats. The results of histopathology of liver in our study also showed the significant improvement between control group and extract-treated group.[34] On the other hand, Mossoba et al described the vulnerable effect of *R serpentina* on kidney specifically proximal tubules of kidney. They explained that the drug produced the harm effects on renal system in vitro.[35] However, the present study reported the no harm effect on kidney tissues. More research has been required to demonstrate the effect of *R serpentina* on kidney.

Conclusion

Although commercially available pharmaceutical products are used for the treatment of wide range of clinical conditions are available in market but the medicinal plants always remained as primary choice due to their safety as well as high efficacy. *Rauwolfia serpentina* is one of the natural herbal medicines with wide spectrum of therapeutic effects. The results of current study also revealed the hypotensive and hypolipidemic effect of methanolic extract of *R serpentina* in albino rats without any damage to liver and kidney. However, further research is required at large scale to isolate the phytochemical constituents responsible for its therapeutic and alongside side effect if any.

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Declaration of Conflicting Interests

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ORCID iD

Syed Muhammad Ali Shah https://orcid.org/0000-0003-3825-5589
Muhammad Akram https://orcid.org/0000-0001-7863-8803

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