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Ravi D Patel

M.V.Sc. Scholar, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A. H., Kamdhenu University, Anand, Gujarat, India

Kamlesh A Sadariya

Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A. H., Kamdhenu University, Anand, Gujarat, India

Darshan R Patel

M.V.Sc. Scholar, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A. H., Kamdhenu University, Anand, Gujarat, India

Vicky M Patel

M.V.Sc. Scholar, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A. H., Kamdhenu University, Anand, Gujarat, India

Vaidehi N Sarvaiya

Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A. H., Kamdhenu University, Anand, Gujarat, India

Shailesh K Bhavsar

Professor & Head, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A. H., Kamdhenu University, Anand, Gujarat, India

Corresponding Author:

Kamlesh A Sadariya

Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A. H., Kamdhenu University, Anand, Gujarat, India

Therapeutic efficacy of bi-herbal extracts of *Coriandrum sativum* and *Murraya koenigii* on chronic kidney disease model in rats

Ravi D Patel, Kamlesh A Sadariya, Darshan R Patel, Vicky M Patel, Vaidehi N Sarvaiya and Shailesh K Bhavsar

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Abstract

Chronic kidney disease (CKD) is an incurable disease that advances over time. The research assesses the bi-herbal extracts of *Coriandrum sativum* and *Murraya koenigii* on adenine-induced CKD in rats. The bi-herbal extracts of *Coriandrum sativum* (CS) and *Murraya koenigii* (MK) were prepared using aqueous and alcoholic solvents, respectively, and their therapeutic efficacy tested at a ratio of 1:1:5 as ascertained by *in vitro* nucleation assay. A total of thirty-six male Sprague-Dawley rats were selected for the study and randomly assigned to six groups (n=6). Group I served as the normal control and was received a standard pelleted diet. Group II was the adenine control group receiving adenine (200 mg/kg b.wt., orally) for 28 days. Therapeutic group III, IV, V and VI were given adenine in a dosage of 200 mg/kg b.wt. Orally once a day for 28 days in order to induce chronic kidney disease (CKD) and after that induction period, the rats were given bi-herbal aqueous and alcoholic extracts of CS and MK leaves orally for 42 days. After CKD induction, groups III and IV were treated with bi-herbal aqueous extracts of CS and MK at 250 mg/kg and 500 mg/kg, respectively, while groups V and VI received bi-herbal alcoholic extracts of CS and MK at the same respective doses for 42 days. Haematology, serum biochemistry, rat uromodulin ELISA, urine analysis and renal ultrasonography were done on the 28th and on day 70th. The experimental rats were assessed for ultrasonographic, gross and histopathological changes in the kidneys of different groups. Administration of bi-herbal aqueous and alcoholic extracts in CKD-induced rats resulted in significant improvements in body weight, feed intake and haemato-biochemical profiles compared to the adenine control group. Renal ultrasonography and histopathological assessments confirmed that both aqueous and alcoholic bi-herbal extracts reduce in kidney-related abnormalities in adenine-induced CKD in rats. The alcoholic extract at 500 mg/kg b.wt. Exhibited the highest therapeutic efficacy, demonstrating marked improvement in renal function and structure. These findings highlight the potential use of these bi-herbal extracts in CKD treatment strategies.

Keywords: Bi-herbal extracts, *Coriandrum sativum*, *Murraya koenigii*, therapeutic efficacy, CKD rats

Introduction

The kidneys are the body's main organs for maintaining homeostasis, eliminating metabolic waste products like urea, creatinine, uric acid and ammonia, regulating extracellular fluid volume, blood pressure and controlling systemic pH (Chew *et al.*, 2011) [3]. Chronic Kidney Disease is usually referred to as simply CKD, a condition characterized by the gradual reduction in a person's kidney function. CKD is diagnosed when structural abnormalities like CKD persist for three or more months. Additionally, CKD is further subclassified into six progressive stages: Stage 1, Stage 2, Stage 3A, Stage 3B, Stage 4, and Stage 5 depending on the results of GFR (glomerular filtration rate) testing (Qaseem *et al.*, 2013) [19].

Animal models, like the rodent adenine diet model, are key in CKD research. This model mimics human CKD with rapid kidney damage, fibrosis, tubular atrophy and vessel calcification, providing insight into stable kidney and cardiovascular disease (Diwan *et al.*, 2018) [4].

Coriandrum sativum L. belongs to the Umbelliferae family. It is commonly known as coriander, dhania in Hindi and dhana in Gujarati (Momin *et al.*, 2012) [13]. It is well-known for having hepatoprotective, diuretic, carminative, digestive and antihelminthic properties.

Flavonoids and polyphenols are the main components of *Coriandrum sativum*, which is a source of phytochemicals with nephroprotective potential (Lakhera *et al.*, 2015) [10].

Murraya koenigii, commonly known as the curry leaf tree, belongs to the genus *Murraya* within the citrus family Rutaceae. It is indigenous to South-East Asia and the Indian subcontinent. The leaves of this plant are widely referred to as "curry leaves" in English, "Mitho Limado" in Gujarati, and "Mitha Neem" in Hindi (Yankuzo *et al.*, 2011) [26]. The plant is also reported to have antitumor (Ito *et al.*, 2006) [9], anti-inflammatory (Muthumani *et al.*, 2009) [16], hypoglycemic (Tembhurne and Sakarkar., 2009) [25], antihyperglycemic (Phatak *et al.*, 2019) [17]. Research involving *Murraya koenigii* leaf extract has demonstrated its ability to support normal kidney function, evidenced by stable urine volume, creatinine, urea, urea nitrogen, total protein, and sodium levels. In rodent models, this extract also protected kidneys from injury caused by temporarily cutting off and then restoring blood flow (ischemia-reperfusion). It appears to work by boosting the organ's antioxidant defenses, tempering excessive myeloperoxidase activity, and preserving the kidney's microscopic structure. A number of rat studies have underscored the positive impact of *Murraya koenigii* extract in managing and mitigating kidney-related disorders. (Punuru *et al.*, 2014) [18]. The present work explored whether using both water and alcohol-based extracts of coriander (*Coriandrum sativum*) and curry leaves (*Murraya koenigii*) could safeguard kidneys in male Sprague-Dawley rats with adenine-induced chronic kidney disease. To evaluate their effects, we tracked changes in blood parameters, serum chemistry and urine composition, performed kidney ultrasound scans and examined tissue samples under a microscope.

Materials and Methods

Experimental Animals

A total of 36 male Sprague-Dawley rats, aged 8-10 weeks, were procured from Zydus Research Centre in Ahmedabad and kept at the Small Animal Facility, Veterinary College, Kamdhenu University, Anand. All experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC/373/VPT/2022) and conducted in accordance with CPCSEA guidelines.

Experimental Design

Group I received a standard diet (control), while Group II was given adenine (200 mg/kg, orally) for 28 days. Groups III, IV, V and VI were therapeutic groups that received adenine (200 mg/kg body weight, orally) once daily for 28 days to induce CKD, followed by oral administration of bi-herbal aqueous and alcoholic extracts of *Coriandrum sativum* and *Murraya koenigii* leaves for the next 42 days. Groups III and IV received bi-herbal aqueous extracts at doses of 250 and 500 mg/kg body weight, respectively, while Groups V and VI were administered bi-herbal alcoholic extracts of *Coriandrum sativum* and *Murraya koenigii* at the same respective doses.

Extraction of Plant Materials and Determination of Ratio: Leaves of *Coriandrum sativum* and *Murraya koenigii* were shade-dried, ground into fine powder, and stored in airtight containers. For aqueous extracts, 100 g of each powder was soaked separately in 1 L of distilled water

with shaking three times daily. Extracts were concentrated using a rotary evaporator at 50-60 °C under reduced pressure, then dried on a hot water bath until solvent evaporation was complete. Alcoholic extracts were prepared by Soxhlet extraction of 100 g of leaf powder with alcohol, concentrated similarly, and dried under the same conditions. All extracts were refrigerated at 4 °C until use. The aqueous and alcoholic extracts of CS and MK were mixed in a 1:1.5 ratio based on in-vitro nucleation assay results.

Observation of Clinical Symptoms and Mortality

Assessment: Throughout the entire experiment, group I to VI rats were daily observed for any abnormal physical or behavioral changes and also for any mortality incidence.

Feed Intake

To quantify feed intake, the amount of feed provided to each cage was measured and the leftover measured weekly throughout the study.

Body Weight

Body weights of animals across all groups I, II, III, IV, V, and VI was recorded one day prior to the start of the experiment (Day 0) and then recorded weekly from the first to the tenth week of the experimental period.

Hematological and Biochemical Assessment of Blood

Samples: Blood was collected on day 28 to confirm chronic kidney disease and 70th days of CKD induction (i.e., 42nd day after treatment). Under light isoflurane anesthesia, blood was collected from each rat by a capillary tube inserted into the retro-orbital plexus. Approximately 1 mL of blood was collected in K₃EDTA-coated test tubes for hematological analysis. The assessed hematological parameters included hemoglobin concentration (g/dL), total leukocyte count (TLC, 10³/μL), total erythrocyte count (TEC, 10⁶/μL), lymphocyte (%), granulocyte (%) and monocyte (%) levels, using an automated hematology analyzer (BC-2800 Vet, Mindray).

Approximately 1.5 mL of blood was also drawn into centrifuge tubes without the use of anticoagulant agents and allowed to clot at room temperature (26 ± 2°C). The clotted samples were centrifuged at 3000 rpm at 10°C for 15 minutes in an Eppendorf 5804 R centrifuge (Germany) to separate the serum, which was stored at -60°C for the estimation of biochemistry. Levels of serum uromodulin were estimated by an ELISA kit (MyBioSource, California, USA; Catalog No. MBS2024146). Other serum biochemistry parameters like creatinine (mg/dL), uric acid (mg/dL), blood urea nitrogen (BUN, mg/dL), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), total protein (g/dL), albumin (g/dL), calcium (mg/dL) and phosphorus (mg/dL) were estimated with the help of commercially available diagnostic kits with the help of a CKK 300 Clinical Chemistry Analyzer (Bangalore, India).

Collection of Urine Sample and Urine Analysis

Urine samples were collected from all experimental rats on the 28th and 70th days of the study. These samples were analyzed for qualitative parameters such as pH and specific gravity, along with biochemical parameters including urinary calcium, phosphorus, total protein and creatinine.

The analyses were performed using a Mindray BS-120 chemistry analyzer.

Ultrasonography

Ultrasonographic evaluations were performed on all experimental rats on day 28th and 70th using the Esaote MyLab40 VET system (Esaote Europe B.V., Philipsweg 1, 6227 AJ Maastricht, Netherlands). Real-time B-mode imaging of the kidneys was carried out using linear transducers with a frequency range of 3.5 to 12 MHz

Pathological Examination: Gross and Histological Findings:

On day 70 of the study, animals from the treatment groups were humanely sacrificed, and vital organs including the kidneys, liver, lungs, spleen and heart were harvested. Any visible pathological alterations were noted. The collected tissues were preserved in 10% neutral buffered formalin and subsequently processed using the paraffin embedding method. Thin sections (5-6 μ m) were prepared using an automated microtome (Leica, Germany) at the Department of Pathology. These tissue sections were then stained with Hematoxylin and Eosin (H&E) and examined under a microscope for histopathological evaluation.

Statistical Analysis

Data from the experiment were subjected to statistical analysis using a completely randomized design. One-way ANOVA was performed through IBM SPSS software (version 26.0) and group differences were deemed statistically significant at $p < 0.05$. To identify specific group differences, Duncan's Multiple Range Test was applied. All values were reported as Mean $\pm$ Standard Error (SE).

Results

This study aimed to assess the therapeutic effects of aqueous and alcoholic bi-herbal extracts of *Coriandrum sativum* (CS) and *Murraya koenigii* (MK) in a rat model of adenine-induced chronic kidney disease (CKD). Findings from multiple evaluations including feed consumption, body weight, hematobiochemical tests, urine analysis,

ultrasonography and histopathological examination are summarized here.

Clinical Monitoring and Assessments

Common and characteristic behavioral indicators offer important insights into the initiation, peak intensity and duration of the test drug's action, as well as the range of pharmacological actions produced. Rats in group I (control) maintained normal behavior throughout the study. In contrast, adenine control rats (Group II) exhibited several observed atypical behaviors comprised signs such as reduced strength, decreased activity, sluggishness, depressive-like symptoms, loose stools, fluid loss, coprophagy, excessive salivation, increased urination, and heightened thirst. Rats in groups III, IV, V and VI, which received bi-herbal extracts following adenine administration, showed some of the behavioral symptoms seen in group II exhibited symptoms including increased thirst, excessive urination and weakness, but their activity levels were relatively higher than those of the adenine control group.

Measurement of Feed Consumption

In the current study, the average feed consumption observed in the adenine control (group II), III, IV, V and VI was significantly less from week 1 to week 4 than the control group. However, after 28th day (4th week), treatment with aqueous and alcoholic bi-herbal extracts of CS and MK in groups III, IV, V and VI for 42 days (10th week) shows significant improvement in feed intake as compared to adenine control demonstrate in Table 1.

Body Weight Measurement

The mean value in the current experiment of body weight in adenine control (group II), III, IV, V and VI was significantly less from week 1 to week 4 than the control group. However, after 28th day (4th week), treatment with CS and MK bi-herbal alcoholic and aqueous extracts in groups III, IV, V and VI for 42 days (10th week) shows significant increase in body weight as compared to the adenine control group shown in Table 2.

Table 1: Effect of bi-herbal aqueous and alcoholic extracts of *Coriandrum sativum* and *Murraya koenigii* on daily feed consumption (g/day) in rats with adenine-induced CKD.

Group	1 st week	2 nd week	3 rd week	4 th week	5 th week	6 th week	7 th week	8 th week	9 th week	10 th week
I	24.59 $\pm$ 0.40 ^b	28.97 $\pm$ 0.98 ^c	27.86 $\pm$ 0.24 ^c	31.12 $\pm$ 1.17 ^b	30.76 $\pm$ 0.8 ^c	31.59 $\pm$ 1.2 ^d	29.88 $\pm$ 1.2 ^d	33.14 $\pm$ 1.72 ^c	29.40 $\pm$ 0.6 ^d	33.75 $\pm$ 1.0 ^d
II	10.12 $\pm$ 0.09 ^a	9.21 $\pm$ 0.07 ^a	8.15 $\pm$ 0.25 ^a	7.88 $\pm$ 0.21 ^a	8.42 $\pm$ 0.14 ^a	9.54 $\pm$ 0.27 ^a	11.02 $\pm$ 0.23 ^a	10.77 $\pm$ 0.32 ^a	11.54 $\pm$ 0.21 ^a	11.84 $\pm$ 0.23 ^a
III	10.64 $\pm$ 1.50 ^a	11.78 $\pm$ 0.07 ^{ab}	12.29 $\pm$ 0.86 ^b	10.26 $\pm$ 0.04 ^a	16.92 $\pm$ 0.7 ^c	18.62 $\pm$ 0.38 ^c	21.50 $\pm$ 0.07 ^c	22.52 $\pm$ 0.34 ^c	22.78 $\pm$ 0.93 ^c	26.86 $\pm$ 0.29 ^c
IV	11.71 $\pm$ 0.29 ^a	10.86 $\pm$ 0.57 ^{ab}	10.50 $\pm$ 0.93 ^{ab}	10.29 $\pm$ 0.43 ^a	15.43 $\pm$ 0.5 ^{ab}	16.07 $\pm$ 0.0 ^b	17.21 $\pm$ 0.6 ^b	16.29 $\pm$ 0.8 ^b	16.71 $\pm$ 0.2 ^b	18.00 $\pm$ 0.1 ^b
V	10.48 $\pm$ 1.37 ^a	10.55 $\pm$ 1.02 ^{ab}	9.59 $\pm$ 1.27 ^{ab}	10.18 $\pm$ 0.96 ^a	15.00 $\pm$ 0.2 ^b	15.00 $\pm$ 0.2 ^b	16.18 $\pm$ 0.3 ^b	16.65 $\pm$ 0.7 ^b	17.17 $\pm$ 0.8 ^b	17.89 $\pm$ 0.6 ^b
VI	12.79 $\pm$ 0.50 ^a	12.14 $\pm$ 0.86 ^b	9.79 $\pm$ 1.07 ^{ab}	8.61 $\pm$ 0.62 ^a	20.00 $\pm$ 0.1 ^c	20.50 $\pm$ 0.36 ^c	22.70 $\pm$ 0.58 ^c	28.07 $\pm$ 0.9 ^d	28.68 $\pm$ 0.4 ^d	32.16 $\pm$ 0.0 ^d

[Data are presented as Mean $\pm$ SEM (n = 6). Mean values within the same column bearing different superscripts (a, b, c, d) are significantly different ($p < 0.05$)]

Table 2: Effect of bi-herbal leaf extracts of *Coriandrum sativum* and *Murraya koenigii* (aqueous and alcoholic) on body weight (g) in rats with adenine-induced chronic kidney disease

Group	0 day	1 st week	2 nd week	3 rd week	4 th week	5 th week	6 th week	7 th week	8 th week	9 th week	10 th week
I	419.66 $\pm$ 19.61	451.50 $\pm$ 13.68 ^d	488.00 $\pm$ 14.22 ^c	523.16 $\pm$ 13.55 ^d	522.83 $\pm$ 15.98 ^b	564.33 $\pm$ 15.39 ^c	582.66 $\pm$ 20.79 ^d	585.33 $\pm$ 19.42 ^d	604.66 $\pm$ 18.47 ^d	595.16 $\pm$ 17.04 ^c	616.6 $\pm$ 15.93 ^c
II	384.66 $\pm$ 12.97	325.50 $\pm$ 16.66 ^{ab}	299.00 $\pm$ 17.94 ^a	295.66 $\pm$ 18.92 ^{ab}	264.33 $\pm$ 17.83 ^a	274.33 $\pm$ 17.15 ^a	280.50 $\pm$ 11.10 ^a	288.16 $\pm$ 13.38 ^a	305.16 $\pm$ 15.85 ^a	325.16 $\pm$ 13.50 ^a	342.6 $\pm$ 10.57 ^a
III	397.66 $\pm$	401.83 $\pm$	393.00 $\pm$	349.50 $\pm$	306.00 $\pm$	350.66 $\pm$	425.66 $\pm$	465.33 $\pm$	470.50 $\pm$	478.66 $\pm$	488.50 $\pm$

	20.65	21.21 ^c	13.66 ^b	13.57 ^c	14.54 ^a	20.18 ^b	11.71 ^c	11.78 ^c	13.10 ^c	20.29 ^b	17.56 ^b
IV	369.66± 12.90	294.33± 14.24 ^a	303.00± 13.78 ^a	282.66± 13.36 ^a	262.16± 13.52 ^a	307.33± 6.10 ^{ab}	339.33± 13.07 ^b	368.00± 18.26 ^b	375.33± 21.37 ^b	359.50± 13.87 ^a	374.5± 15.77 ^a
V	410.33± 20.00	362.33± 20.12 ^{bc}	352.50± 21.84 ^b	318.83± 21.28 ^{abc}	282.16± 19.50 ^a	332.00± 20.89 ^b	353.00± 19.29 ^b	326.50± 19.55 ^{ab}	328.50± 19.38 ^{ab}	346.16± 17.08 ^a	361.3± 13.98 ^a
VI	412.16± 18.74	379.66± 15.02 ^c	385.83± 8.86 ^b	334.16± 7.29 ^{bc}	289.33± 7.56 ^a	355.50± 13.09 ^b	438.00± 18.77 ^c	445.83± 19.20 ^c	462.66± 11.52 ^c	472.83± 15.69 ^b	471.66± 13.85 ^b

[Data are presented as Mean ± SEM (n = 6). Mean values within the same column bearing different superscripts (a, b, c) are significantly different ($p < 0.05$)]

Haematological Analysis

Findings from the hematological analyses in different experimental and control groups on day 28th and 70th of the study have been presented in Table 3. Adenine administration for 28 days in groups II, III, IV, V and VI resulted in significant increase in total granulocyte, leukocyte count, while significant decrease in haemoglobin, total lymphocyte and erythrocyte count. Following CKD induction, groups III, IV, V and VI treated with aqueous and alcoholic bi-herbal leaf extracts of *Coriandrum sativum* and *Murraya koenigii* showed significant improved total erythrocyte count, haemoglobin and lymphocyte, while significantly reduced granulocyte and total leukocyte count as compared to adenine control group II. Notably, pronounced therapeutic effect was observed in rats treated with bi-herbal leaf extracts of *Coriandrum sativum* and *Murraya koenigii* prepared using aqueous and alcoholic solvents @ 250 mg/kg body weight, whereas the alcoholic bi-herbal extracts at 500 mg/kg body weight also demonstrated significant restoration of hematological parameters, closely resembling those of the normal control group.

Serum Biochemistry Analysis

The results of serum biochemistry analysis for the control and various experimental groups on day 28th and 70th of experiment have been presented in Table 4. Adenine administration for 28 days in groups II, III, IV, V and VI resulted in a significant increase uric acid, serum creatinine, BUN, alanine aminotransferase, aspartate aminotransferase

and phosphorus, whereas a significant decrease in serum albumin, total protein, uromodulin and calcium. Following CKD induction, treatment with bi-herbal leaf extracts of *Coriandrum sativum* and *Murraya koenigii* prepared using aqueous and alcoholic solvents significantly reduced uric acid, serum creatinine, BUN, alanine aminotransferase and phosphorus, while significantly improving albumin, calcium, serum uromodulin and total protein as compared to adenine control rats. The result indicated that the bi-herbal aqueous and alcoholic extracts at 250 mg/kg and 250 mg/kg body weight respectively showed greater therapeutic efficacy.

Urine Analysis

Urine analysis findings for various experimental and control groups on day 28th and 70th of experiment have been presented in Table 5. Adenine was administered for 28 days in groups II, III, IV, V and VI resulted in a significant decrease in urine pH, urine creatinine and phosphorus, while significant increase in urine total protein and urine calcium. Following CKD induction, treatment with aqueous and alcoholic bi-herbal extracts of *Coriandrum sativum* and *Murraya koenigii* leaves significantly increased urine creatinine, urine pH and phosphorus, while significantly reduced urine calcium and total protein as compared to adenine control rats. Additionally, bi-herbal aqueous and alcoholic extracts @ 250 and 500 mg/kg b.wt., respectively demonstrated significant therapeutic efficacy in terms of urine parameter restoration.

Table 3: Hematological alterations in adenine-induced CKD rats treated with bi-herbal extracts of *Coriandrum sativum* and *Murraya koenigii*.

Group	Hb (g/dL)		TEC ($\times 10^6/\mu\text{L}$)		TLC ($\times 10^3/\mu\text{L}$)		Lymphocyte (%)		Granulocyte (%)		Monocyte (%)	
	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day
I	14.02± 0.34 ^b	15.12± 0.60 ^c	7.28± 0.42 ^c	7.32± 0.33 ^c	5.50± 0.21 ^b	5.70± 0.65 ^a	73.83± 1.65 ^c	74.65± 1.50 ^c	24.05± 1.70 ^a	22.16± 1.35 ^a	2.11± 0.25	3.18± 0.29
II	10.51± 0.25 ^a	7.82± 0.55 ^a	4.18± 0.44 ^{ab}	3.90± 0.31 ^a	12.64± 0.55 ^a	14.16±0.69 ^c	53.60± 1.43 ^b	54.70± 1.64 ^a	43.84± 1.06 ^b	42.42± 1.42 ^c	2.55± 0.47	2.86± 0.32
III	10.00± 0.14 ^a	14.05± 0.26 ^{bc}	3.80± 0.19 ^a	6.53± 0.29 ^c	13.42± 0.57 ^a	6.66± 0.27 ^a	49.30± 1.69 ^{ab}	71.93± 1.22 ^c	48.63± 1.72 ^{bc}	25.12± 1.21 ^a	2.06± 0.08	2.92± 0.10
IV	10.08± 0.19 ^a	12.64± 0.85 ^b	4.63± 0.35 ^{ab}	5.37± 0.36 ^b	13.03± 0.32 ^a	8.66± 0.51 ^b	46.20± 1.48 ^a	65.38± 1.24 ^b	52.18± 1.50 ^c	31.72± 1.29 ^b	2.04± 0.05	2.89± 0.14
V	10.36± 0.17 ^a	12.57± 0.37 ^b	3.86± 0.14 ^{ab}	5.04± 0.46 ^b	12.28± 0.57 ^a	9.32± 0.73 ^b	47.12± 1.46 ^a	64.19± 1.93 ^b	51.16± 1.20 ^c	32.91± 1.96 ^b	2.04± 0.08	2.90± 0.09
VI	10.34± 0.21 ^a	14.76± 0.49 ^c	4.95± 0.42 ^b	7.17± 0.24 ^c	12.32± 0.34 ^a	6.00± 0.15 ^a	51.30± 1.82 ^{ab}	71.01± 1.79 ^c	47.13± 1.84 ^{bc}	26.08± 1.73 ^a	2.13± 0.04	2.92± 0.11

[Significant differences ($p < 0.05$) between means are indicated by differing superscripts (a, b, c, d) within the column. Hb: hemoglobin TLC: total leukocyte count and TEC: total erythrocyte count]

Table 4: Effect of aqueous and alcoholic bi-Herbal extracts of *Coriandrum sativum* and *Murraya koenigii* on serum biochemical parameters in adenine-induced CKD Rats (Mean $\pm$ SE).

Group	Uromodulin (ng/mL)		Creatinine (mg/dL)		Uric acid (mg/dL)		BUN (mg/dL)		AST (U/L)		ALT (U/L)	
Days	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day
I	19.60 $\pm$ 0.58 ^b	19.03 $\pm$ 0.63 ^d	0.56 $\pm$ 0.05 ^a	0.61 $\pm$ 0.05 ^a	2.38 $\pm$ 0.16 ^a	2.31 $\pm$ 0.15 ^a	23.23 $\pm$ 0.54 ^a	25.60 $\pm$ 0.74 ^a	110.29 $\pm$ 2.08 ^a	116.07 $\pm$ 2.12 ^b	26.23 $\pm$ 0.22 ^a	27.30 $\pm$ 0.25 ^a
II	10.61 $\pm$ 0.34 ^a	10.24 $\pm$ 0.56 ^a	3.40 $\pm$ 0.10 ^{bc}	3.05 $\pm$ 0.09 ^d	5.01 $\pm$ 0.14 ^b	4.90 $\pm$ 0.10 ^d	154.42 $\pm$ 2.53 ^b	121.70 $\pm$ 2.63 ^d	117.84 $\pm$ 2.96 ^b	116.35 $\pm$ 2.51 ^b	51.88 $\pm$ 0.44 ^b	50.78 $\pm$ 0.34 ^c
III	10.65 $\pm$ 0.23 ^a	18.58 $\pm$ 0.30 ^{cd}	3.19 $\pm$ 0.09 ^b	1.020 $\pm$ 0.02 ^c	5.35 $\pm$ 0.13 ^c	2.54 $\pm$ 0.34 ^{ab}	156.74 $\pm$ 1.21 ^b	41.58 $\pm$ 1.42 ^c	120.50 $\pm$ 0.93 ^b	108.44 $\pm$ 1.95 ^a	51.55 $\pm$ 0.41 ^b	35.29 $\pm$ 0.38 ^b
IV	10.52 $\pm$ 0.20 ^a	17.63 $\pm$ 0.48 ^{bc}	3.23 $\pm$ 0.04 ^b	1.18 $\pm$ 0.06 ^c	5.30 $\pm$ 0.11 ^{bc}	3.20 $\pm$ 0.08 ^c	157.38 $\pm$ 1.68 ^b	38.92 $\pm$ 1.42 ^c	123.31 $\pm$ 1.66 ^b	109.46 $\pm$ 1.99 ^{ab}	53.50 $\pm$ 0.51 ^c	35.85 $\pm$ 0.21 ^b
V	10.42 $\pm$ 0.17 ^a	16.65 $\pm$ 0.32 ^b	3.25 $\pm$ 0.04 ^b	1.18 $\pm$ 0.05 ^c	5.23 $\pm$ 0.09 ^{bc}	3.33 $\pm$ 0.06 ^c	155.27 $\pm$ 2.14 ^b	41.40 $\pm$ 0.97 ^c	121.27 $\pm$ 1.60 ^b	114.74 $\pm$ 0.87 ^{bc}	53.46 $\pm$ 0.21 ^c	35.11 $\pm$ 0.25 ^b
VI	10.53 $\pm$ 0.20 ^a	18.82 $\pm$ 0.21 ^{cd}	3.46 $\pm$ 0.06 ^b	0.82 $\pm$ 0.01 ^b	5.37 $\pm$ 0.06 ^c	2.66 $\pm$ 0.12 ^b	157.26 $\pm$ 1.06 ^b	31.72 $\pm$ 0.24 ^b	121.44 $\pm$ 1.22 ^b	114.67 $\pm$ 1.61 ^{bc}	54.41 $\pm$ 0.24 ^c	35.33 $\pm$ 0.14 ^b

Group	Albumin (g/dL)		Total Protein (g/dL)		Calcium (mg/dL)		Phosphorus (mg/dL)	
Days	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day
I	3.68 $\pm$ 0.07 ^b	3.76 $\pm$ 0.06 ^c	6.62 $\pm$ 0.16 ^b	6.49 $\pm$ 0.19 ^b	10.30 $\pm$ 0.27 ^b	10.20 $\pm$ 0.23 ^c	6.83 $\pm$ 0.15 ^a	7.04 $\pm$ 0.17 ^a
II	2.73 $\pm$ 0.12 ^a	2.74 $\pm$ 0.11 ^a	5.58 $\pm$ 0.14 ^a	5.75 $\pm$ 0.08 ^a	7.42 $\pm$ 0.19 ^a	8.27 $\pm$ 0.09 ^a	9.92 $\pm$ 0.26 ^b	9.41 $\pm$ 0.15 ^c
III	2.59 $\pm$ 0.11 ^a	3.61 $\pm$ 0.10 ^{bc}	5.43 $\pm$ 0.04 ^a	6.52 $\pm$ 0.11 ^b	7.85 $\pm$ 0.09 ^a	10.06 $\pm$ 0.23 ^c	11.00 $\pm$ 0.05 ^d	8.74 $\pm$ 0.09 ^b
IV	2.48 $\pm$ 0.10 ^a	3.37 $\pm$ 0.09 ^b	5.45 $\pm$ 0.03 ^a	6.31 $\pm$ 0.04 ^b	7.45 $\pm$ 0.22 ^a	8.85 $\pm$ 0.28 ^{ab}	10.51 $\pm$ 0.08 ^c	8.43 $\pm$ 0.17 ^b
V	2.57 $\pm$ 0.08 ^a	3.38 $\pm$ 0.10 ^b	5.48 $\pm$ 0.04 ^a	6.36 $\pm$ 0.05 ^b	7.57 $\pm$ 0.18 ^a	8.96 $\pm$ 0.62 ^b	10.26 $\pm$ 0.06 ^{bc}	8.44 $\pm$ 0.11 ^b
VI	2.48 $\pm$ 0.07 ^a	3.52 $\pm$ 0.09 ^{bc}	5.51 $\pm$ 0.04 ^a	6.47 $\pm$ 0.09 ^b	7.76 $\pm$ 0.16 ^a	10.10 $\pm$ 0.13 ^c	11.03 $\pm$ 0.04 ^d	8.67 $\pm$ 0.06 ^b

[Significant differences ($p < 0.05$) between means are indicated by differing superscripts (a, b, c, d) within the column. BUN: blood urea nitrogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase]

Table 5: Effect of bi-herbal aqueous and alcoholic extracts of *Coriandrum sativum* and *Murraya koenigii* on urine parameter in adenine-induced CKD rats (Mean $\pm$ SE).

Group	pH		Specific Gravity		Total Protein (g/dL)		Creatinine (mg/dL)		Calcium (mg/dL)		Phosphorus (mg/dL)	
Days	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day	28 th day	70 th day
I	8.25 $\pm$ 0.11 ^b	8.50 $\pm$ 0.18 ^c	1.014 $\pm$ 0.003	1.018 $\pm$ 0.002	7.31 $\pm$ 0.29 ^a	7.41 $\pm$ 0.24 ^a	11.13 $\pm$ 0.23 ^b	11.68 $\pm$ 0.18 ^d	2.28 $\pm$ 0.09 ^a	2.53 $\pm$ 0.12 ^{ab}	2.47 $\pm$ 0.12 ^b	2.59 $\pm$ 0.14 ^b
II	6.16 $\pm$ 0.11 ^a	5.98 $\pm$ 0.18 ^a	1.008 $\pm$ 0.002	1.012 $\pm$ 0.011	25.52 $\pm$ 0.67 ^b	26.54 $\pm$ 0.62 ^c	4.08 $\pm$ 0.21 ^a	5.05 $\pm$ 0.09 ^a	4.74 $\pm$ 0.29 ^b	5.34 $\pm$ 0.32 ^c	1.74 $\pm$ 0.06 ^a	1.37 $\pm$ 0.16 ^a
III	6.58 $\pm$ 0.40 ^a	7.75 $\pm$ 0.21 ^b	1.008 $\pm$ 0.002	1.013 $\pm$ 0.002	27.39 $\pm$ 1.27 ^b	8.49 $\pm$ 0.47 ^a	4.88 $\pm$ 0.35 ^a	11.01 $\pm$ 0.32 ^{cd}	4.80 $\pm$ 0.23 ^b	2.75 $\pm$ 0.13 ^{ab}	1.51 $\pm$ 0.14 ^a	2.37 $\pm$ 0.17 ^b
IV	6.50 $\pm$ 0.38 ^a	7.58 $\pm$ 0.15 ^b	1.010 $\pm$ 0.002	1.013 $\pm$ 0.003	23.91 $\pm$ 1.93 ^b	12.25 $\pm$ 0.35 ^b	5.30 $\pm$ 0.42 ^a	9.47 $\pm$ 0.24 ^b	4.89 $\pm$ 0.14 ^b	3.02 $\pm$ 0.14 ^b	1.63 $\pm$ 0.15 ^a	2.13 $\pm$ 0.11 ^b
V	6.50 $\pm$ 0.31 ^a	7.91 $\pm$ 0.30 ^{bc}	1.009 $\pm$ 0.003	1.015 $\pm$ 0.003	27.54 $\pm$ 0.81 ^b	12.88 $\pm$ 0.63 ^b	4.98 $\pm$ 0.20 ^a	10.14 $\pm$ 0.25 ^b	5.12 $\pm$ 0.12 ^b	3.01 $\pm$ 0.10 ^b	1.51 $\pm$ 0.09 ^a	2.35 $\pm$ 0.16 ^b
VI	6.66 $\pm$ 0.33 ^a	7.66 $\pm$ 0.21 ^b	1.008 $\pm$ 0.002	1.011 $\pm$ 0.001	26.86 $\pm$ 1.11 ^b	7.73 $\pm$ 0.33 ^a	5.09 $\pm$ 0.34 ^a	10.31 $\pm$ 0.38 ^{bc}	4.91 $\pm$ 0.25 ^b	2.39 $\pm$ 0.15 ^a	1.55 $\pm$ 0.09 ^a	2.21 $\pm$ 0.13 ^b

[Significant differences ($p < 0.05$) between means are indicated by differing superscripts (a, b, c, d) within the column]

Ultrasonographic Evaluation of the Kidney

Renal ultrasonography was performed on day 28th and 70th to assess kidney changes in all experimental rats. On day 28, in CKD induced rats, ultrasound examination showed the presence of several areas with increased echogenicity spots at the cortico-medullary junction along with a poorly defined cortico-medullary boundary. The kidneys exhibited parenchymal swelling, a more spherical shape with hypoechoic renal tissue and cortico-medullary junction appeared poorly defined on ultrasound. In contrast, rats in the normal control group showed a clearly defined cortico-medullary junction. Following CKD induction in rats, the treatment with bi-herbal leaf extracts of *Coriandrum sativum* and *Murraya koenigii* obtained using aqueous and hydroalcoholic solvents demonstrated notable effectiveness

in restoring ultrasonographic abnormalities observed in the kidney on day 70th as showed in figure 1.

Histopathological Examination of Kidney

Adenine-induced groups showed pathological alterations including prominent tubular atrophy, cystic enlargement, extensive fibrotic changes, vascular congestion, presence of inflammatory exudates, and tubular degeneration casts on H&E staining. In contrast, groups III, IV, V and VI, which received bi-herbal leaf extracts of *Coriandrum sativum* and *Murraya koenigii* obtained using aqueous and hydroalcoholic solvents alongside adenine, exhibited noticeably fewer histopathological changes compared to the adenine control group. These findings are illustrated in Figures 2 to 7.

Discussion

The present observations on feed consumption were consistent with those reported by Diwan *et al.* (2017) ^[4] that the rats receiving dietary adenine treatment gradually consumed less feed as compared to normal control rats. Li *et al.* (2018) ^[12], Rahman *et al.* (2018) ^[20] also reported that rats with adenine-induced chronic renal failure consumed less food. The present finding were in accordance with Diwan *et al.* (2017) ^[4] reported that adenine diet induced CKD in Wistar rat and there was gradual decrease in their feed consumption. Similarly, Rahman *et al.* (2018) ^[20] and Zhu *et al.* (2018) ^[28] also reported that there was decrease in feed intake of adenine induced chronic kidney disease in rats. The result of present experiment were in accordance with Singh *et al.* (2019) ^[23] reported that administration of *Coriandrum sativum* ethanolic extract at the dose of 200 mg/kg/day for 28 days, after gentamicin induced renal toxicity resulted in a significant increase in feed consumption.

Body weight recorded in the present study were in accordance with the findings of Mori-Kawabe *et al.* (2015) ^[14], Ali *et al.* (2014) ^[1] and Rahman *et al.* (2018) ^[20] reported that significant decrease in body weight following the adenine-induced CKD model in rats. The result of present experiment were in accordance with Singh *et al.* (2019) ^[23] reported that administration of *Coriandrum sativum* ethanolic extract at the dose of 200 mg/kg/day for 28 days, after gentamicin induced renal toxicity resulted in a significant increase in body weight.

The present finding were in accordance with Munoz Abellan *et al.* (2019) ^[15], Chang *et al.* (2017) ^[2] and Ali *et al.* (2014) ^[1] observed low haemoglobin and low erythropoietin (EPO) levels in adenine-treated rats. Ali *et al.* (2014) ^[1] founded that adenine-induced chronic kidney disease caused significant decreases in TEC. Chang *et al.* (2017) ^[2] and Munoz Abellan *et al.* (2019) ^[15] reported founded increase in white blood cell counts after adenine treatment, due to induced inflammation or iron deficiency in rats. The present finding were in accordance with Gehani *et al.* (2019) ^[7] founded that oral administration of *bryophyllum calycinum* and *achyranthes aspera* after adenine-induced chronic disease in rats significant increase in total erythrocyte count and lymphocytes, while significantly decrease in granulocytes and non-significant changes in mean values of monocytes. Similarly, Singh *et al.* (2022) ^[24] also observed significant increase in total erythrocyte count and significantly decrease in total leucocyte count in rats with adenine-induced chronic disease following oral administration of *Bryophyllum calycinum* and *Boerhavia diffusa*. Gomez-Flores *et al.* (2010) ^[8] founded that *Coriandrum sativum* leaf extract stimulated splenic lymphocyte proliferation significantly.

The findings of the present study in accordance with other previously reported studies of Chang *et al.* (2017) ^[2], Rivera-Valdes *et al.* (2017) ^[21], Mori-Kawabe *et al.* (2015) ^[14], Ghelani *et al.* (2019) ^[7], Li *et al.* (2018) ^[12], Zhu *et al.* (2018) ^[28], Zhang *et al.* (2016) ^[27] and Diwan *et al.* (2017) ^[5] for various serum biochemical parameters. Seo *et al.* (2022) ^[22] who founded that serum uromodulin concentrations were significantly lower in dogs with chronic kidney disease (CKD) compared to a control group. The validity and applicability of our most recent discoveries in light of earlier research is increased by this synchronisation. The result of present experiment were in accordance with Kumar *et al.* (2011) founded that after administration of aqueous extract

of *Coriandrum sativum* there was significant decrease serum creatinine in Profenofos-induced nephrotoxicity in Swiss albino mice. Similarly another study Gehani *et al.* (2019) ^[6] investigated that the therapeutic effects of *Bryophyllum clycinum* and *Achyranthes aspera* on adenine-induced CKD in Wistar rats and founded that bi-herbal extracts of both plants, lower mean values of BUN, uric acid, phosphorus and significantly increase the serum total protein in treatment group as compared to the adenine control group. After oral administration of *Bryophyllum calycinum* and *Boerhavia diffusa* in rats with adenine-induced chronic kidney disease there was significantly decrease ALT level (Singh *et al.*, 2022) ^[24].

The present finding were in accordance with Levey *et al.* (2003) ^[11] founded a correlation between chronic kidney disease and a decreased urine pH, suggesting that kidney damage contributes to urine acidification. Munoz Abellan *et al.* (2019) ^[15] observed a mild elevation in urine calcium, phosphorus and urine protein levels in adenine-treated rats at a dose of 200/mg/kg body weight. Ghelani *et al.* (2019) ^[7] observed decrease in urinary creatinine levels in a rat model of adenine-induced chronic kidney disease. The results of present experiment were in accordance with Singh *et al.* (2022) ^[24] observed significant decrease in urine total protein, urine calcium, while significant increase in urine creatinine level in rats with adenine-induced chronic kidney disease following oral administration of *Bryophyllum calycinum* and *Boerhavia diffusa*. Another experimental study revealed that administration of aqueous extract from the stem bark of *Garcinia lucida vesque* (clusiaceae) in adenine-induced chronic kidney disease in rats which causes decrease urine protein level while increase creatinine excretion and creatinine clearance (Sonfack *et al.*, 2021). In contrast to present study Gehani *et al.* (2019) founded significant decrease in urine specific gravity after oral administration of *Bryophyllum calycinum* and *Achyranthes aspera* to rats with adenine-induced chronic kidney disease. The present findings were in accordance with Ali *et al.* (2016) ^[1] investigated the histopathology of adenine induced CKD in rat kidneys, which showed fibrosis, tubular lumen dilatation, and inflammation. The present findings align with Lakhera *et al.* (2015) ^[10] reported that treatment with ethanolic extract of *Coriandrum sativum* @200 and 400 mg/kg reduced renal histological lesions against gentamicin-induced renal damage in rats. Similarly, Yankuzo *et al.* (2011) ^[26] reported that treatment with aqueous extract of *Murraya koenigii* @ 200 and 400 mg/kg reduced renal histological lesions, less matrix expansion and glomerular basement membrane thickening compared to the streptozotocin-induced diabetic male rats.

Conclusion

The aqueous and alcoholic bi-herbal extracts of *Coriandrum sativum* and *Murraya koenigii* leaves in the ratio of 1:1.5 given @ 250 mg/kg and 500 mg/kg b.wt., respectively, orally daily once for 42 days after induction of CKD was demonstrated therapeutic efficacy. This was substantiated by evaluating parameters such as body weight and feed consumption, urine assessment, heamato-biochemical analysis, histopathological evaluation and ultrasonographic examination. Notably, the alcoholic bi-herbal extracts exhibited greater effectiveness in comparison to the aqueous extracts. The findings from this study provide a promising path for future research endeavours in the field of CKD management and treatment.

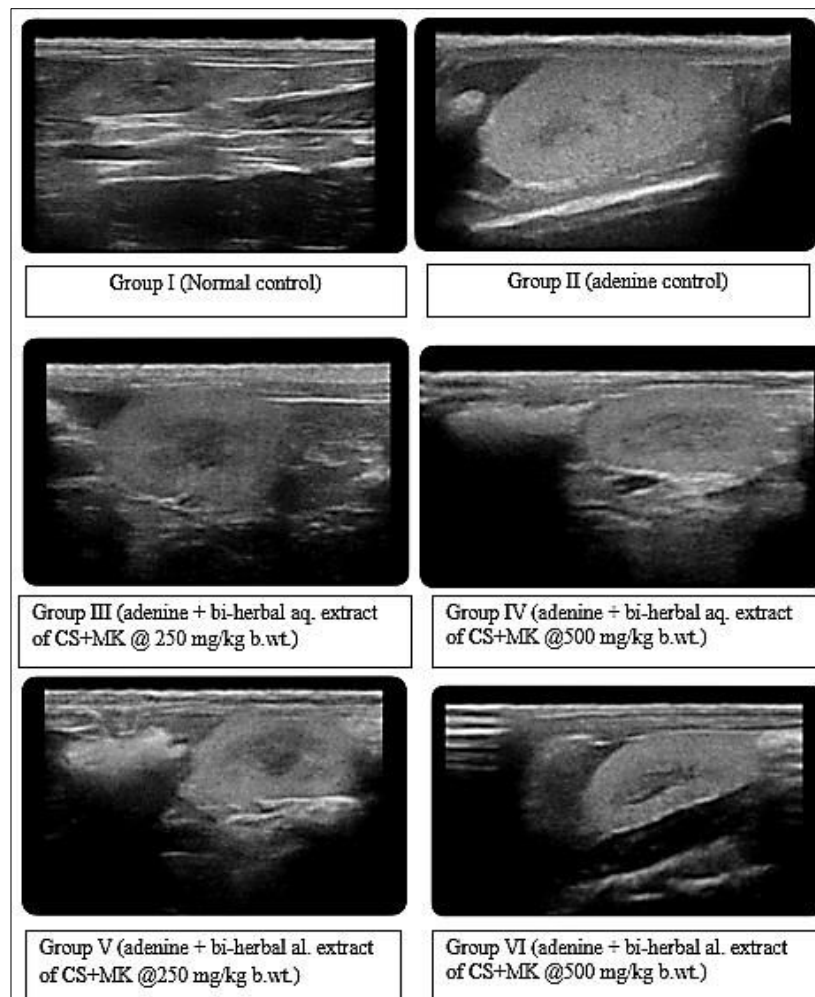


Fig 1: Renal ultrasonography evaluation of the normal and treatment groups in adenine-induced CKD rats.

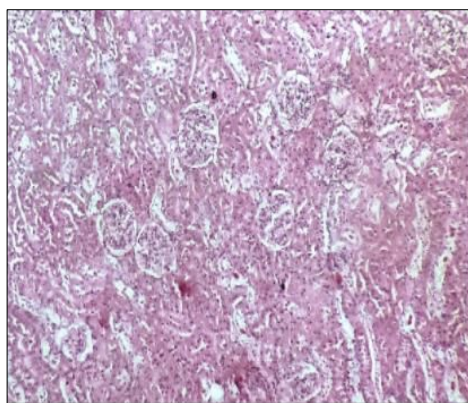


Fig 2: Microphotographs of the kidneys from non-treated rats revealed normal histoarchitecture in group I (Normal control) (H&E, 120X).

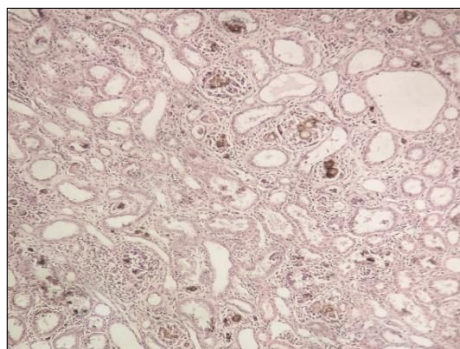


Fig 3: Microphotographs of kidney showed marked tubular atrophy, cystic dilatation, mild fibrosis, infiltration of mononuclear cell congestion, inflammatory exudates and tubular cast in group II (adenine control) (H&E, 120X).

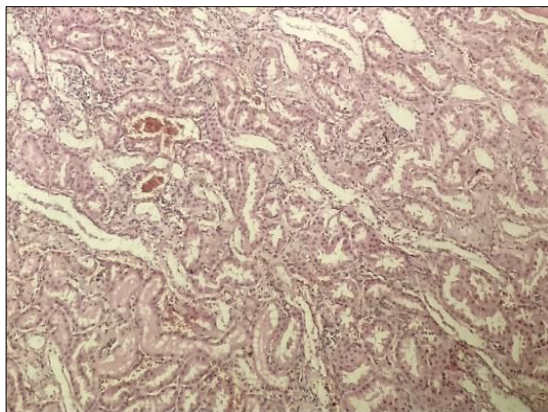


Fig 4: Microphotographs of kidney showed moderate degeneration of tubules and mild infiltration of inflammatory cells in interstitium (H&E, 120X) in group III (Bi-herbal aq. ex. of CS and MK at dose rate of 250 mg/kg b.wt.).

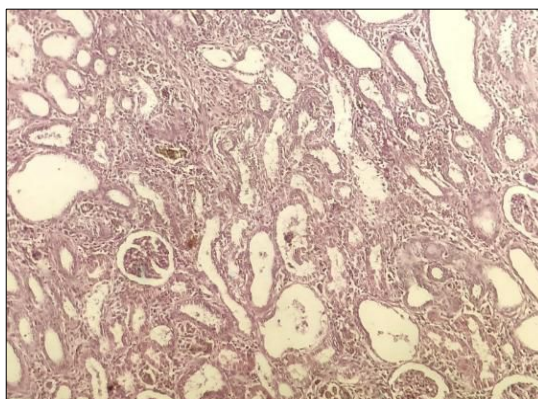


Fig 5: Kidney microphotographs revealed severe tubular dilation with atrophy and marked fibrosis of renal parenchyma in group IV (Bi-herbal aq. ex. of CS and MK at dose rate of 500 mg/kg b.wt.) (H&E, 120X).

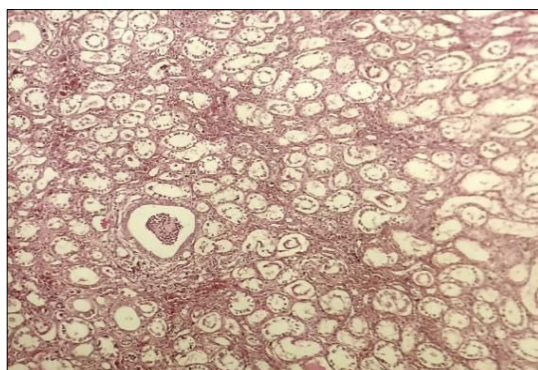


Fig 6: Microphotographs of kidney showed mild inflammatory exudates in lumen with degeneration of tubular epithelial cells and minimal fibrosis in group V (Bi-herbal al. extract of CS and MK at dose rate of 250 mg/kg b.wt. (H&E, 120X).

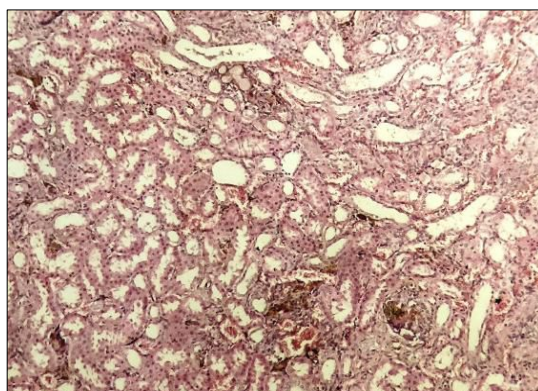


Fig 7: Kidney microphotographs revealed very scanty thickening of interstitium and tubular dilatation in group VI (Bi-herbal al. ex. of CS and MK CS and MK at dose rate of 500 mg/kg b.wt (H&E, 120X).

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