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Original Research Article

MITIGATION OF ARSENIC-INDUCED RENAL TOXICITY THROUGH PACHYPODOL IN QUAILS

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Abstract: *Heavy metals are abiotic toxicants that are non-biodegradable and can be propagated by human activities. Heavy metals can induce hepatotoxicity, immuno-toxicity, hemotoxicity, cardiotoxicity, neurotoxicity, and nephrotoxicity in living things. Arsenic (As) is gradually deposited into renal tissues because of its great affinity for hemoglobin, resulting in renal damage, oxidative stress, DNA, and urinary bladder damage. Pachypodol (4', 5-dihydroxy-3, 3', 7-trimethoxyflavone) is a flavonoid extracted from Pogostemon cablin and is a protective anti-oxidant. To determine renal damage markers in quails treated with arsenic, pachypodol, and a mixture of both, sixteen quails (Coturnix coturnix) were purchased from Bird's Market Jhang Bazar, Faisalabad. Birds were divided into four groups of equal size. Group-I was the control group, group-II was exposed to arsenic, group-III was co-treated with arsenic and pachypodol, and group-IV (positive) was treated with pachypodol. After 30 days, all groups of birds were sacrificed. Blood samples were collected from all groups of birds. In the current experiment, the levels of uric acid, creatinine, biliverdin, and metal accumulation were significantly ($p<0.05$) due to arsenic treatment but normalized as pachypodol administered. The albumin, body weight, and organ weight were observed significantly ($p<0.05$) lowered in arsenic treatment while regaining significantly ($p<0.05$) due to pachypodol treatment. Histopathological and behavioral alterations were also observed. Therefore, current research concluded that pachypodol has ameliorative potential against arsenic-induced renal damage in quails (Coturnix coturnix).*

Keywords: Arsenic Toxicity, Renal Toxicity, Pachypodol, Mitigation, Kidney Damage

Introduction

Heavy metals are noxious substances. They possess greater atomic number and density than water 5g/cm^3 (Bathla and Jain, 2016). Metals like Gold, antimony, iron, and bismuth are used in pharmaceuticals, and silver, ruthenium, and indium are potentially toxic. Literature reported that heavy metals bioaccumulation is continuously increasing and causes lethal effects on life. Zinc, Nickel, Copper, Chromium, Lead, and Cadmium are potentially toxic to living organisms (Nazir et al., 2015).

Heavy metals enter the environment through non-point sources (urban runoff, agricultural runoff) and point sources (plastic, paint, dyes, and battery industries disposal). The burning of fossil fuels and weathering of mountains, rocks, and the earth's crust are leading factors behind the exposure of arsenic into the environment (Khan et al., 2015).

Mercury, aluminum, arsenic, lead, and cadmium are heavy metals that concern public health issues. Heavy metals can enter the body by inhaling contaminated air and drinking contaminated water and food. The mortality can occur through combining chlorides with oxygen. Heavy metals can cause lethal effects on living organisms' growth, immunity, and behavior. The free radicals produced by arsenic, nickel, cobalt, and chromium can cause DNA damage and negative effects on the DNA repair system. The body behaves anomalously to anti-oxidant, enzymatic, and hormonal activities through heavy metals poisoning. Heavy metal toxicity can be reduced through chelating agents (Blanusa et al., 2005).

Arsenic is low in organic (trimethylarsine oxide, dimethyl arsenic acid, and monomethyl arsenic acid) and inorganic (pentavalent and trivalent arsenate) forms in the environment. Volcanic eruptions and agricultural and industrial activities are effective sources of arsenic environmental exposure. Arsenic penetrates the living body through consuming contaminated water, food, soil, and air (Sattar et al., 2016).

Arsenic quickly accumulates in nails, hairs, and renal tissues due to its high affinity for hemoglobin. Maximum arsenic-based poisoning is related to inorganic arsenic forms. Arsenic can induce toxicity in the kidney, liver, lungs, urinary bladder, and skin. Arsenite inhibits the functionality of enzymes that are involved in metabolism. Arsenic is a potential source of genetic toxicity, oxidative stress, DNA, and neuron damage (Flora et al., 2007).

The people of India, Taiwan, Chile, Mexico, and Bangladesh are continuously exposed to groundwater containing arsenic above the threshold set by WHO (10 μgL^{-1}) (Wei et al., 2018; Wu et al., 1989).

The phases linked to arsenic carcinogenesis are chromosomal abnormalities, the production of free radicals, and changes in transcriptional factors. WHO set an arsenic threshold of 10 μgL^{-1} (Hughes, 2002). Arsenic (inorganic) can lead to hypertension, atherosclerosis, and myocardial infarction. Arsenite raises the formation of ROS (H2O2-O2−) by increasing the NADPH oxidase in vascular muscle and endothelium. When reactive oxygen species (ROS) combine with nitric oxide, they form peroxynitrite, a powerful oxidation agent that activates the inflammatory agents comprising cyclooxygenase-2. Excessive formation of ROS like anion radicals, peroxyl radicals, hydrogen

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peroxide, hydroxyl radicals, and nitric oxide causes oxidative stress (Bratovcic, 2020).

Arsenite treatment stimulates the upregulation of monocyte-chemoattractant-protein-(1), heme-oxygenase-(1), and interleukin-(6) (genes of atherosclerosis) (Lee et al., 2005). Arsenic causes VSMCs to proliferate and migrate by altering focal adhesion proteins. Arsenic promotes inflammation and atherosclerosis through activating nuclear-f kappa B, tumor necrosis factor α, prostacyclin, and leukotriene-E-4. Arsenic promotes neurogenic blood vessel inflammation by stimulating the expression of neurokinin 1 (endothelial) and substance (P) (Chen et al., 2007).

The receptors of N, Methyl D, and aspartate in the brain are suppressed by metabolites of arsenic, resulting in neurobehavioral problems and memory deficits. During urination, arsenic (As) deposits in the kidney, affecting the efficiency of the nephron (Li et al., 2010). The stimulation of MAPK and HO-1 is increased through arsenic-encouraged oxidative stress, contributing to kidney damage by regulating numerous transcriptional factors (trn- factor 2, activator-protein-1, and Elk-1). Renal failure caused by arsenic poisoning is marked by severe nephrosis and the formation of a cast due to elevated blood creatinine and urea. Renal and hepatic tissues are principal sites for arsenic poisoning, with the liver containing the highest possible concentration of arsenic (Nandi et al., 2006).

Flavonoid is a broad class of naturally occurring phenolic chemicals in the whole plant kingdom. Flavonoids are chelating agents for metal ions and can potentially engulf free radicals, which may mitigate arsenic-based toxicity. Flavonoids protect against oxidative stress, arthritis, aging cancer, and respiratory and cardiovascular abnormalities. Flavonoid ameliorates cancer, diabetes, ulcer, inflammation, cytotoxicity, and renal damage (Tiwari and Husain, 2017). Biochanin, silibinin, and naringenin can mollify arsenic-dependent poisoning in nephritic and hepatic tissues (Milton and Muthumani, 2012).

Patchouli extracts have excellent health-promoting properties that help organs to work properly. The chemicals extracted from patchouli have been proven to fight against ulcers and gastrointestinal problems. Patchouli-based extracts treat atherosclerosis by restricting adipogenesis. They also alleviate neural damage induced by ischemia-reperfusion (Wu et al., 2019).

Pachypodol (4′ 5-dihydroxy 3-3′,7-trimethoxyflavone) is a flavonoid extracted from plant *Pogostemon cablin*, showing an anti-oxidant property. Patchouli (*Pogostemon cablin*) exhibits analgesic, antimicrobial, anti-inflammatory, anti-oxidant, gastro-protective, and antiviral activities. The protective role of pachypodol depends upon its anti-oxidant properties. Pachypodol is antithetical to cancer, poliovirus, allergy, and cytotoxicity. Pachypodol shows cytoprotective characteristics through controlling nuclear factor erythroid-2, related factor-2 (Nrf-2) dependent ERK circuit, and anti-oxidant capabilities. The Nrf-2-dependent ERK cascade regulates the cell cycle, and when it is disrupted, neurological deterioration occurs (Zhang et al., 2021).

Methodology

Model animal

The quails are medium-sized ground-living game birds. Quails fall under the Galliformes order and the Phasianidae family of birds. Quails have significant economic relevance worldwide compared to domestic species like turkey and chicken because of their smaller dietary and homing requirements. Due to their low fatality ratio and high meat and egg market value, Quail rearing is a profitable business. As they make their way south from the north, quails arrive in Sindh approximately in the middle of August, and from there, they disperse to other Pakistani provinces (Zahid et al., 2018).

Animals

This experiment was required with sixteen quails (*Coturnix coturnix*) weighing between 110±10 grams. All birds were confined at the University of Agriculture's birdhouse station in Faisalabad for 30 days. All birds were acclimatized before the trial. The birds were distributed into four categories (Four quails in each group) and kept in wooden cages at 20 to 22 degrees Celsius. The birds were facilitated with safe drinking water, regular food intake, and 12 hours of light and 12 hours of dark intervals.

Ethics

This study followed strict accordance and recommendations in the leisure and care guidance animals in the animal house, University of Agriculture, Faisalabad. Animal studies were conducted according to the Ethical Control Guidelines during experiments. Every effort was made to minimize the suffering of birds. All procedures were carried out following the animal ethics committee of the University of Agriculture, Faisalabad.

Chemicals used

This experiment used arsenic and pachypodol purchased from Sigma-Aldrich, Germany. The doses of pachypodol and arsenic (sodium arsenite) used in the present investigation were based on previous studies (Khan et al., 2013; Zhang et al., 2021).

Preparation of arsenic stock solution

To make the solution, 1428 mg of arsenic was dissolved in 100 ml of purified water. This stock solution was prepared at 50 milligrams per kilogram of arsenic per bird.

Preparation of pachypodol stock solution

To make the solution, 340.8 mg of pachypodol was dissolved in 100 ml of purified water. This stock solution was prepared at 10 milligrams per kilogram of pachypodol per bird.

Experimental design

For this experiment, 16 quails of 110±10 grams were divided into four equal groups.

Group I was marked as a control group. All the birds in this group received tap water and commercial feed chaw at the libitum under aerated and clean environment at room temperature (25-30 "C).

Group II was tagged as an arsenic group. All birds in this group received 50 milligrams per kilogram of body weight per day per bird of arsenic for 30 days.

Group III was labeled as the arsenic and pachypodol co-treated dosage group. All birds in this group received gavages of 50 mg per kg of body weight of arsenic and 10 mg per kg of BW of pachypodol per bird daily for 30 days.

Group IV was designated as a positive group. All birds in this group received gavages of 10 mg per kg BW of pachypodol per bird daily for 30 days.

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Figure: Showing experimental design of birds

Administration

For the period of 30 days, 0.41 ml of arsenic stock solution, which contains 5.95 mg of arsenic, and 0.41 ml of pachypodol stock solution, which contains 1.42 mg of pachypodol were given daily through oral gavages to each designated bird.

Figure: Showing administration of dose

The symptoms of mortality and toxicity were recorded when the concentrations of these chemicals were given during the experiment. The initial weight and behavior of the animal were noticed at the start of this experiment.

Estimation of body weight gain

Before slaughtering of birds, final body weight gain was recorded.

Gain in weight of body = Final body weight - Initial body weight

Slaughtering

The weight of the quails was recorded, and then all quails were sacrificed at the end of the experiment. Blood was collected in EDTA tubes for the estimation of biochemical parameters.

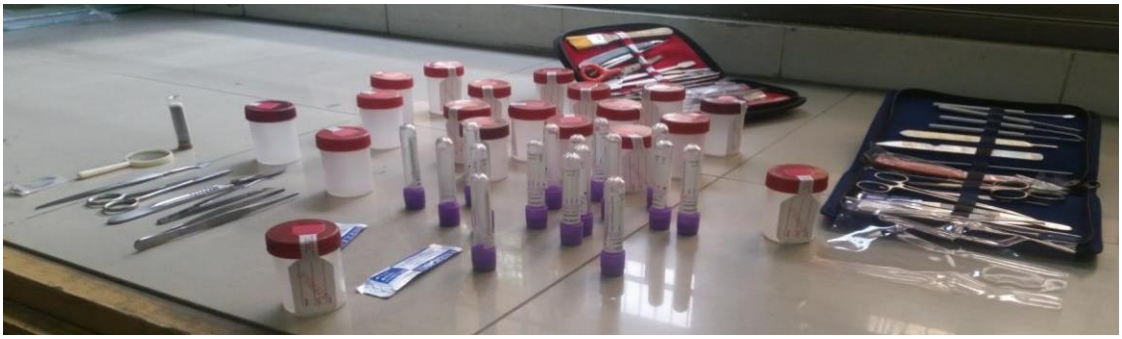

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Figure: Showing slaughtering of quails

Removal of kidney

After dissection of Quails, kidneys were removed and examined.

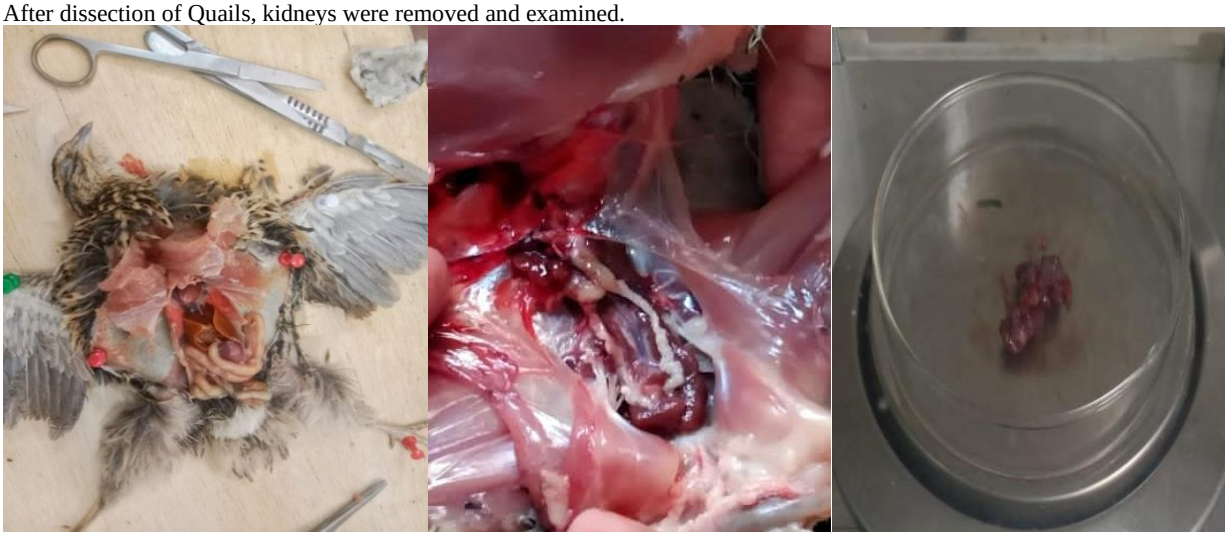

Figure: Showing dissection and removal of the kidney

Organ weight

The kidneys were collected, weighed, and grossly examined, and their comparative weight was also determined.

Testing through blood sample

Blood samples were delivered to the laboratory to analyze the level of albumin, uric acid, creatinine and biliverdin in the blood to determine the kidney's health.

Preparation of serum

Yakubu et al. (2005) estimate the method of serum preparation. Firstly, blood was collected from the jugular vein of the Quail into EDTA tubes. The tubes contain serum gel used for the proper separation of serum. The blood samples were centrifuged for 5 minutes at 13000 rpm to separate serum from blood cells. The separated serum was transformed into 1.5ml Eppendorf tubes. This serum was used to test various biochemical assays within 12 h.

Biochemical analysis of Serum

1) Creatinine in serum (Jaffe Method)
2) Albumin (Bromocresol green dye)
3) Uric acid (Uricase method)
4) Biliveredin (BVR analysis)

Estimation of Behavioral changes in quails

The Quail's behavior was observed right from the start of this experiment. Behavioral variations were detected from the start to the end of the trial.

Figure: Showing behavior of the quails

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A microtome was used to slice tissues into slices as small as 3 microns (Histo-line MR 2258). Paraffin-waxed ribbons of tissue pieces were immersed in warm water for some time before being applied to the slide (containing glycerine and albumin). Tissue-filled slides were heated in the oven overnight at 37 degrees Celsius. For three minutes, the slides were submerged in xylene cleaning fluid. Soak the slide in a downward succession of ethanol-alcohol for 1 to 2 minutes. Hematoxylin was applied to the slides to stain for 3 to 5 minutes. Coverslips were placed on slides through Canada balsam and examined under an efficient light microscope. Images were taken, and histological alterations were observed compared with the control (Mahboob et al., 2020).

Metals Estimation

Birds were slaughtered, and kidneys were collected. The kidney samples were kept in an oven with an air circulatory system overnight at 60 ^{o}C for proper drying. The samples were ground through porcelain mortar to make homogenized powder. The samples (weight 1 gram of each) were put in the 150 mL Erlenmeyer flasks, and 10 mL nitric acid HNO_3 (65%) was poured into each flask and left to digest overnight slowly. Perchloric acid $HClO_4$ 5 mL (70%) was 70% was poured into each sample. In 1st step, digestion continued, and even dark fumes vanished. In 2nd step, digestion was continued. Even a light yellow color appeared. A hot plate was used for digestion at 200 ^{o}C. To achieve the sample volume of 25 mL, distilled water was poured into each sample in polyethylene tubes. The reference samples were likewise made and evaluated. The filter papers with pore size 0.45 µm were used to filter the samples. A Shimadzu AA 680 flame atomic absorption spectrophotometer was used to measure heavy-metal concentrations (Alipour et al., 2016).

3.18. Statistical analysis

The data was expressed as Mean ± SEM and was calculated by one-way variance of analysis ANOVA through Tukey's test. The degree of significance was established at $p<0.05$ (Inkielewicz-Stepniak et al., 2012).

RESULTS

Body Weight Gain

Mean ± SEM body weight of quails in administered and control birds groups indicated significant variations at ($p < 0.05$).

Table 1: Mean ± SEM presenting weight of Quail's body (g) in administered and untreated groups for 30 days of treatment

Groups	Initial	Final weight	Total body weight
Control	109.25±3.84	142.5±1.55	33.25±3.82^{a}
Arsenic Treated	110.75±4.35	129.5±3.23	18.75±1.31^{b}
Arsenic + Pachypodol Treated	112±3.92	144.75±1.93	32.75±3.92^{a}
Pachypodol Treated	113.5±2.53	147.5±4.11	34±3.54^{a}

Data is presented as Mean ± SEM.

Kidney weight Mean, ± SEM organ weight of quails in treated and untreated bird groups, exhibited significant distinctions at ($p < 0.05$).

Table 2: Mean ± SEM displaying the weight of Quail's kidney (g) in reference and dosage groups after treatment of 30 days

Groups	Kidney weight (g)
Control	0.86±0.03^{a}
Arsenic Treated	0.49±0.07^{b}
Arsenic + Pachypodol Treated	0.82±0.05^{a}
Pachypodol Treated	0.92±0.12^{a}

Observations are stated as mean ± SEM.

Effect of Arsenic and Pachypodol on levels of Albumin, Uric Acid, Creatinine, Biliverdin, and arsenic accumulations in Quail's kidney

Levels of albumin, uric acid, creatinine, biliverdin, and arsenic accumulations in control, arsenic, arsenic, and pachypodol co-treated, and pachypodol (positive) dosage-treated groups are presented in Table 4.3, 4,5 & 6.

Table 3: Mean ± SEM exhibiting the Albumin level in the kidney of treated and untreated groups after treatment of 30 days

Groups (n=4/groups)	Albumin Level (mg/dL)
Control	2.03±0.17^{a}
Arsenic Treated	0.95±0.10^{b}
Arsenic + Pachypodol Treated	1.66±0.16^{a}
Pachypodol Treated	1.76±0.10^{a}

Data is stated as mean ± SEM

Table `4: Mean ± SEM presenting the Uric acid level in the kidney of reference and administered groups after treatment of 30 days

Groups (n=4/groups)	Uric acid Level (mg/dL)
Control	4.48±0.65^{b}
Arsenic Treated	8.8±0.85^{a}
Arsenic + Pachypodol Treated	4.98±1.33^{b}
Pachypodol Treated	3.75±0.52^{b}

Observations are presented as mean ± SEM.

Table 5: Mean ± SEM illustrating Creatinine level in the kidney of dose administered and control groups after treatment of 30 days

Groups (n=4/groups)	Creatinine Level (mg/dL)
Control	0.85±0.22^{b}
Arsenic Treated	1.83±0.15^{a}
Arsenic + Pachypodol Treated	0.85±0.16^{b}
Pachypodol Treated	0.73±0.24^{b}

Data is stated as mean ± SEM

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Table 6: Mean ± SEM exhibiting Biliverdin level in the kidney of administered and reference groups after treatment of 30 days

Groups (n=4/groups)	Biliverdin Level (µmol/L)
Control	14.23±0.91[b]
Arsenic Treated	24.48±1.47[a]
Arsenic + Pachypodol Treated	13.69±1.34[b]
Pachypodol Treated	13.08±1.53[b]

Observations are presented as mean ± SEM

Table 7: Mean ± SEM illustrating Arsenic concentration in the kidneys of treated and non-treated groups after treatment of 30 days

Groups (n=3/groups)	Arsenic Level (ppm)
Control	0.25±0.01[b]
Arsenic Treated	3.48±0.18[a]
Arsenic + Pachypodol Treated	0.35±0.02[b]
Pachypodol Treated	0.23±0.02[b]

Data is stated as mean ± SEM

Table 8: Remarks of Behavioral alterations in administered and reference groups in the range of 0 to 4 for 30 days overall score range

Weeks	Range	Control	Arsenic Treatment	Arsenic + Pachypodol Dosage	Pachypodol Treatment
1st week	20	5	4	4	5
2nd week	20	9	7	8	9
3rd week	20	11	9	10	13
4th week	20	15	8	11	17
Grand Total	**80**	**40**	**28**	**33**	**44**

Table 9: Histopathological partial quantitative recording of kidney tissues in reference and exposed quails after trial of 30 days

Groups	Control	Arsenic	Arsenic+ Pachypodol	Pachypodol
Tubular degeneration	*	***	**	*
Distance in Glomerulus	*	***	**	*
Expansion of tubules	*	***	**	*
Necrosis of tubules	*	***	**	*
Vacuole formation	*	***	**	*
Hemorrhage	*	***	**	*

Assessment was completed as follows: none (*), moderate (**), Severe (***)

Discussion

Heavy metals are potentially toxic to living systems with a density higher than 5g/cm^3 (Bathla and Jain, 2016). Arsenic can induce toxicity in the kidney, liver, lungs, urinary bladder, and skin. Arsenite inhibits the functions of enzymes that are involved in metabolism. Arsenic is a potential source of oxidative stress, which may cause genetic toxicity and neuronal impairment. Arsenic causes an increase in oxidative stress, resulting in circulatory impairment and decreasing nitric-oxide synthase activation in endothelial tissues (Jindal et al., 2008). Pachypodol shows cytoprotective characteristics through controlling nuclear-factor-erythroid-2, related factor 2 (Nrf-2) dependent ERK circuit, and anti-oxidant capabilities. The Nrf-2-dependent ERK cascade regulates the cell cycle, and when it is disrupted, it can cause neurological deterioration (Zhang et al., 2021).

Arsenic exposure might increase leptin levels encoded by the ob gene and produced by adipocytes. Leptin binds to LepRb (leptin receptor) and activates intracellular Janus kinase 2 (JAK2), which phosphorylates STAT3 then suppresses AgRP gene (neuropeptide agouti-related peptide) and induces expression of Pomc gene (neuropeptide proopiomelanocortin) with inhibiting activity on appetite and reduction of body weight (Handali and Rezaei, 2021).

Milton and Muthumani (2012) performed an experiment in which a significant drop ($p < 0.05$) in the weight of rat kidney was detected when treated with arsenic, while retention of kidney weight when treated with flavonoid (silibinin). Ahangarpour et al. (2018) had a severe effect on the level of total albumin that was statistically ($p < 0.05$) decreased in male mice. Arsenic changes T4 stimulation. Arsenic lowered albumin levels in plasma. Lower albumin could be due to podocyte apoptosis induced by oxidative stress derived from NADPH oxidase following stimulation by angiotensin II and cytokines.

The creatinine extents were significantly ($p < 0.05$) elevated in the arsenic dosage group. Arsenic-produced free oxygen radicals induce necrosis of tubules, which results in permeability enhancement of tubules, leading to reduced excretion and elevated retention of uric acid and creatinine due to the defuse back of nitrogenous waste (Narayana et al., 2001). It could result as arsenic induces the HMOX1 gene in HEK293 and PRCC cells, which encodes heme oxygenase 1, an essential enzyme in heme catabolism, and cleaves heme to form biliverdin. Heme oxygenase activity is induced by oxidative stress. HMOX1 gene expression was upregulated through arsenic exposure, ultimately increasing biliverdin levels in the body (Zheng et al., 2003). Histological inspection in the present investigation summarized that Arsenic treatment resulted in desquamation, the basal membrane enlargement, the tubules' necrosis, and the degradation of tubules. Milton and Muthumani (2012) interpreted similar outcomes in rats. This might be related to the buildup of free radicals. The enhanced generation of peroxidation of lipids and related reactive oxygen species leads to impairment in membrane stability and other pathologic alterations in renal tissue of arsenic drunken Quail.

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Metal content (arsenic) significantly ($p < 0.05$) uplifted in an arsenic-exposed group in distinction with the control group (Bera et al., 2011). Our work is in line with the work of Sinha et al. (2008). Chronic exposure to arsenic can cause a higher buildup of arsenic in the kidneys due to their participation in biomethylation and removal of arsenic metabolites (Dopp et al., 2004).

Schulz et al. (2002) observed convergent behavioral changes due to arsenic. It might be attributed to behavioral alterations when an individual brain accumulates arsenic when it crosses the blood-brain barrier, which explains the animal's malfunctioning neurological system. Birds were shown to have abnormalities in several of the brain's key neurotransmitter networks. Dopamine pathway neuronal transmission may affect the hypo-activity observed in the induced groups. Arsenic and pachypodol lead to behavioral variations in quails. The arsenic and pachypodol may cause alterations in feed uptake and foamy poop, crowing, mating, and alertness populations who are on the ground is also part of this study.

Conclusion

It is concluded from the current study that nephrotoxicity induced by arsenic is due to oxidative stress (lipid peroxidation), disturbance in metabolic machinery, and injury to proximal tubules, which leads to necrosis of epithelial cells of tubules in renal tissues. Tubular injury, which ultimately results in seep-back of metabolic excrements, leads to a deteriorated state of health. Renal tissues are highly involved in arsenic bio-methylation, resulting in more arsenic accumulation chances. The mitigative role could be due to flavonoids' ability to protect anti-oxidant, anti-apoptotic, SH group enzyme, and metal chelating efficacy that reduces NADPH oxidase stimulation and hyper-activation of Nrf2 in the kidney. It could be due to flavonoid's ability to enhance the activity of ɣ-glutamylcysteine synthetase and demonstrated simultaneous escalation in the intracellular glutathione level that can reduce the arsenic level and its damages. Pachypodol, due to its properties, including anti-oxidant and antithetical to cancer, poliovirus, allergy, and cytotoxicity, resulted as protective against arsenic-based nephrotoxicity in quails. Therefore, current research concluded that pachypodol contains ameliorative potential against arsenic-induced renal damage in quails (*Coturnix coturnix*).

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department Concerned.

Consent for publication
Approved

Funding
Not applicable

Conflict of interest

The authors declared absence of conflict of interest.

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