ABSTRACT: Boswellic acids, derived from the *Boswellia serrata* plant, have been demonstrated to have anti-inflammatory properties in experimental animal models. The present study was aimed to evaluate the uro-protective effect of boswellic acids in rats with cyclophosphamide-induced cystitis. Interstitial cystitis was induced by cyclophosphamide (CYP). In order to analyze the reduction of the urothelial damage, the bladder weight, the nociception response, and the Evans blue dye extravasation from the bladder were evaluated. To investigate the involvement of lipid peroxidation and enzymatic antioxidants CAT, SOD, and GPX and MPO and NO were evaluated. IL-6 and TNF-α were measured by the ELISA immunoassay technique. The results showed that pretreatment with boswellic acids significantly reduced urothelial damage which was accompanied by a decrease in the activity of MDA, CPO, and NO levels and prevention of the depletion of CAT, SOD, and GPX. The levels of IL-6 and TNF-α were dramatically reduced by boswellic acids. Histopathological findings revealed a considerable reduction in cellular infiltration, edema, epithelial denudation, and bleeding. Our findings showed that boswellic acids, by their antioxidant and anti-inflammatory properties, negate the detrimental effects of cyclophosphamide on the bladder, suggesting boswellic acids as promising therapeutic alternatives for cystitis.

1. INTRODUCTION

Cyclophosphamide (CYP) is the first line drug in treating large granular lymphocyte leukemia and breast cancer. Patients who have received conventional chemotherapy treatments which contain oxazaphosphorine alkylating drugs such as CYP have experienced interstitial cystitis (IC). The direct interaction of the uroepithelium with acrolein, the urotoxic byproduct of CYP, is the mechanistic explanation of CYP-induced IC. Some mediators, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and nitric oxide (NO), have been found to have a significant role in the pathophysiology of IC. IC has also been related to ailments like fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and lupus, so it might be a symptom of a widespread problem. The treatment goal should be to alleviate the discomfort of interstitial cystitis, which is often generic and empiric. Initiatives have been devoted to mitigate the adverse effects of CYP on the bladder mucosa using various medications. Despite the fact that mesna (2-mercaptoethanesulfonate Na) is the most regularly utilized agent to prevent CYP-induced IC, nonsteroidal anti-inflammatory drugs, corticosteroids, and nitric oxide synthase inhibitors have been proven to protect rats from CYP-induced cystitis across many investigations.

The preference of natural remedies to treat IC is becoming more popular, and several studies have demonstrated that extracts of medicinal plants or isolated components can alleviate cystitis in rodents caused by cyclophosphamide. Boswellic acids, a group of pentacyclic triterpene compounds, are isolated from *Boswellia serrata* Roxb. ex Colebr. and *Boswellia carteri* Birdw. (*Buraceace*). *Boswellia serrata* L., (Indian frankincense) is a vital Indian medicinal plant that has historically been used to treat inflammatory conditions. In current medicine and pharmacology, antiarthritic, anti-inflammatory, antihyperlipidemic, antiatherosclerotic, analgesic, and hepatoprotective activities of *B. serrata* are well documented. It has the characteristic properties of an antiseptic, analgesic, nephroprotective, tranquilizer, and expectorant. Numerous studies have been shown that it has a potential effect in managing inflammatory disorders like edema, arthritis, asthma, bowel disease, cancer, and carcinomas. Boswellic acids have shown anti-inflammatory potential in various inflammatory conditions (Ammon, 2016).

Received: December 26, 2021
Accepted: April 4, 2022
Published: April 14, 2022
The basic reason for this exploratory study was to investigate the uroprotective potential of boswellic acids and to illustrate their mechanism(s) underlying against cyclophosphamide induced interstitial cystitis rat model.

2. MATERIALS AND METHODS

2.1. Chemicals Used. All the chemicals used were of analytical grade. Both cyclophosphamide and mesna (Sigma-Aldrich) were obtained from the Oncology Department, Doctors Hospital Lahore, Lahore, and CYP was reconstituted with 0.9% normal saline to make an injectable solution. Boswellic acids (97%) was obtained from Yuantai Biological Technology (China).

2.2. Animals Used. This study concluded 30 female rats (Sprague–Dawley, 250 ± 10 g). These animals were purchased from the “animal house” at the University of Veterinary and Animal Sciences, Lahore, and then kept for 12 h in a light/dark cycle along with free access to food and water with sustained temperature (21 ± 3 °C). The study was conducted with the approval from Institutional Research Ethics Committee of Faculty of Pharmacy (IREC-2020-30), The University of Lahore, Lahore, Pakistan.

2.3. Cyclophosphamide-Induced Interstitial Cystitis. The rats were injected CYP (150 mg/kg solution prepared in 0.9% normal saline) once a day intraperitoneal on days 1, 4, and 7 for the induction of interstitial cystitis. On the eighth day, rats were sacrificed and utilized for study purposes.

2.4. Study Design. Female rats were divided into five groups (n = 5) after a 10-day habituation period. Group I, control; received 0.9% normal saline on first, fourth, and seventh day intraperitoneal. Group II, disease control; received CYP (150 mg/kg) by intraperitoneal injection on first, fourth and seventh day. Group III, mesna (standard drug treatment): they had been administered mesna (40 mg/kg) orally 1 h before CYP. Groups IV and V, Boswellic acids (100 and 200 mg/kg) treated: administered boswellic acids in 100 and 200 mg/kg doses orally 1 h before CYP intraperitoneal injection on first, fourth, and seventh day.

2.5. Collection of Blood Samples and Urinary Bladder. On the eighth day, all experimental rats were sacrificed, and blood samples were collected and allowed to coagulate for half an hour at 37 °C in sterile centrifuge tubes. After centrifugation, the serum was extracted and stored at −20 °C and used in determining oxidative stress biomarkers malondialdehyde (MDA), protein carbonyl content (PCO), nitric oxide (NO), glutathione peroxide (GPX), superoxide dismutase (SOD), catalase, TNF-α, and IL-6 levels (31). The urinary bladders or tissues were excised abruptly and immersed in physiological formalin solution for histopathological examinations.

2.6. Assessment of Nociception. Prior to behavioral testing, the rats were placed individually in observation boxes and acclimatized for 30 min. The following behavioral changes were assessed: (1) activity (walking, climbing, and grooming); (2) immobilization; and (3) visceral pain-related behaviors (“cries”). Additionally, the behavioral changes were graded on the following scale: 0 indicates normal; 1 indicates a piloerection; 2 indicates a vigorous piloerection; 3 indicates difficult breathing; 4 indicates abdominal licking; and 5 indicates abdominal stretching and contraction.14 After CYP injection, the rats were examined for 2 min, every 30 min for a total of 4 h, to score the nociceptive responses. An open-field test was conducted at the conclusion of 4-h observation session. The rats were placed in a box divided into nine squares for 10 min, and the number of squares crossed with the four paws used as a locomotor activity index.15

2.7. Macroscopic Analyses. Following the rats having been euthanized, an explorative laparotomy was performed, and the animal’s bladder was removed, drained, and weighed. Bladder edema was reported as an increase in bladder wet weight, expressed in milligrams.16 Gray’s criteria was followed for the gross examination of hemorrhage and edema of urinary bladders. All bladders were excised and transacted at the bladder neck. The following categories showed the acuteness of edema as (3+) severe, (2+) moderate, (1+) mild, or (0) absent edema, which were all considered. When fluid was visible both externally and internally in the bladder walls, the edema was considered severe. When the edema was restricted to the inner mucosa, it was classed as moderate; when there were only minimal edematogenic signals then mild edema was considered. The bladders were also examined for hemorrhage and classified into four categories based on the presence of (3+) intravesical clots, (2+) mucosal hematomas, (1+) bladder vessel dilatation, and (0) for the normal aspect.15

2.8. Evaluation of Vascular Protein Leakage by the Evans Blue Dye Technique. The rats were given an intraperitoneal injection of CYP along with intravenous infusion of Evans blue dye (25 mg/kg), 30 min before execution.17 After execution, the bladders were excised, dissected, and cultured for dye extraction in incubator at 56 °C for 6 h (overnight) in vials containing formamide solution (1 mL/bladder). By measuring the absorbance at 600 nm and comparing it to the standard curve of Evans blue dye μg/bladder, the concentration of extracted dye was determined.16

2.9. Biochemical Parameters. 2.9.1. Malondialdehyde Assay. The reaction mixture contained 100 μL of serum and 1 mL of 0.67% thiobarbituric acid (TBA), and a clear solution was formed. Then 500 μL 20% trichloroacetic acid (TCA) was added, making the solution milky, and then the solution was incubated for 20 min at 100 °C and centrifuged at 3000 rpm for 20 min. Supernatant absorbance value was determined at 532 nm. MDA levels were assessed by molar extinction coefficient 1.56 × 105 M−1 cm−1 and the values were indicated as unit of μmol/mL.34

2.9.2. Protein Carbonyl Content Assay. First, 200 μL of sample was taken into the Eppendorf, and then we added 300 μL of 10 mM solution of dinitrophenylhydrazine (DNPH) (dissolved into 2 M HCl). After that the sample with DNPH was incubated at room temperature for 30 min. A yellow or orange color appeared in the Eppendorf. Then solution was centrifuged at 3000 rpm for 20 min. Supernatant was discarded and washed the pellet with 1 mL ethanol. After washing with 1.5 mL of 6 M guanidine hydrochloride was added and mixed it well. The Eppendorf tube was incubated at 90 °C for 15 min; centrifugation was done for 5 min. The supernatant absorbance was read at 370 nm. Serum plus HCl was used as the blank.53

2.9.3. Catalase Analysis. Catalase activity was assessed by taking a 50 μL sample and 500 μL of 20 mM hydrogen peroxide in the test tube, which was mixed thoroughly with the help of vortex. Bubbles formed in the test tube. Then sample solution incubated for 3 min at 37 °C, and after incubation 2000 μL of 32.4 mmol/L ammonium molybdate was added into the test tube which stopped the reaction, as seen by the yellow color appearance in the test tube. The test tube that contained
550 μL of distilled water and 2000 μL of ammonium molybdate was used as the blank. The absorbance was taken at 374 nm and measured as KU.\textsuperscript{18}

2.9.4. Superoxide Dismutase, GPX, NO, IL-6 and TNF-α Assays. For determination of superoxide dismutase, GPX, NO, IL-6, and TNF-α levels, commercially available kits (SolarBio Kits, China) were used. The procedure was followed as per the manufacturer’s protocols.

2.10. Histopathological Studies. After being weighing and microtomized, bladders were preserved in formalin solution (10%), diaphanized, and embedded in paraffin; these were stained with haematoxylin and eosin (H&E) and assessed in an optical microscope by two trained clinical analysts through blind inspection, each specimen was examined by a pathologist who was unaware of the treatment and took into consideration the existence and severity of edema, tissue damage, and hemorrhage.\textsuperscript{16}

2.11. Statistical Analysis. The data were expressed as mean ± SEM. The data acquired from various groups were statistically analyzed by one-way analysis of variance (ANOVA) followed by Tukey’s multiple comparison tests using Graph Pad Prism version 8.4.2. \(P \leq 0.05\) was considered as significant statistically.

3. RESULTS

3.1. Effect of Boswellic Acids on Nociception. After seventh day trial, 9 square boxes were made and rats were put in one by one to check the number of squares crossed by each rat. The assessment of nociception was observed for 10 min by counting the no. of squares crossed. The number of boxes crossed by rats treated with CYP was less (10.75 ± 1.5) in relation to the control group (60.5 ± 1.84), and this number was noticeably increased in mesna (40 mg/kg) and boswellic acids (100 mg/kg and 200 mg/kg) treated groups (\(P < 0.01\) compared to the control group, \(P < 0.05\) compared to diseased control group, \(P < 0.01\) compared to diseased control group; \(n = 5\)) in cyclophosphamide induced cystitis (Figure 1a).

3.2. Macroscopic Analysis. 3.2.1. Effect of Boswellic Acids on Bladder Weight. The administration of CYP, induced hemorrhage and edema of urinary bladder which could be verified by increase in bladder weight. It was observed that rats treated with CYP (150 mg/kg) had an increased (97%) bladder weight than the control group. However, groups pretreated with mesna (40 mg/kg) and boswellic acids (100 and 200 mg/kg) presented inhibition of increase in bladder weight, respectively (Table 1).

3.2.2. Effect of Boswellic Acids on Edema and Hemorrhage. The rats treated with CYP (150 mg/kg) presented edema and hemorrhage of urinary bladder prominently when compared with the control group. However, these morpho-

| groups | bladder weight (mg) (mean ± SEM) | edema | hemorrhage |
|--------|---------------------------------|-------|------------|
| control | 8.00 ± 0.05 | 0 | 0 |
| diseased control (CYP 150 mg/kg) | 16.62 ± 0.52\textsuperscript{b} | 3+ | 3+ |
| mesna treated (40 mg/kg) | 11.56 ± 0.19\textsuperscript{b} | 2+ | 1+ |
| boswellic acids treated (250 mg/kg) | 10.98 ± 0.46\textsuperscript{c} | 1+ | 2+ |
| boswellic acids treated (500 mg/kg) | 9.39 ± 0.24\textsuperscript{c} | 1+ | 1+ |

\(a\)Control, diseased control (CYP 150 mg/kg), standard drug (mesna 40 mg/kg), and boswellic acids (100 mg/kg and 200 mg/kg) treated groups. \(P < 0.01\) compared to the control group, and \(P < 0.05\) compared to the diseased control group. \(P < 0.01\) compared to the diseased control group; \(n = 5\) in cyclophosphamide-induced cystitis.
logical changes were markedly reduced in mesna (40 mg/kg) and boswellic acids (100 and 200 mg/kg) treated rats, respectively (Table 1).

3.2.3. Effect of Boswellic Acids on Vascular Permeability. Vascular protein leakage was evaluated by Evan blue dye extravasation permeability. The optical density of extracted dye was measured on spectrophotometer at 600 nm. It was observed that Evans blue dye concentration (vascular permeability) has been significantly elevated (0.68 ± 0.004) in diseased control group contrasted to control group (0.17 ± 0.002) and decreased (0.45 ± 0.015, 0.32 ± 0.013) remarkably in boswellic acids (100 and 200 mg/kg) treated group of rats respectively (Figure 1).

3.3. Biochemical Parameters. 3.3.1. Effect of Boswellic Acids on Malondialdehyde. The administration of cyclophosphamide significantly increased the levels of MDA. Pretreatment with boswellic acids was able to prevent this increase presenting that boswellic acids were capable to reduce oxidative stress (Figure 1c).

3.3.2. Effect of Boswellic Acids on Carboxyl Protein Content. An enhanced (0.008) carbonyl protein content was detected in diseased control group (CYP 150 mg/kg) balanced to control group. In mesna (40 mg/kg) and boswellic acid (100 mg/kg and 200 mg/kg) treated group of rats, carbonyl protein content levels were gradually dropped (0.006 ± 0.0002, 0.006 ± 0.0002, 0.004 ± 0.0001) as shown in Figure 1c.

3.3.3. Effect of Boswellic Acids on Catalase Activity. There was a sharp drop off (29.09 ± 1.67) noticed in the levels of catalase enzyme in diseased control group in relation to control group (78.00 ± 3.33), while in mesna (40 mg/kg) and boswellic acids (100 and 200 mg/kg) treated group catalase levels were increased (46.90 ± 2.21, 53.68 ± 2.45, 65.27 ± 2.88) significantly (Figure 1d).

3.3.4. Effect of Boswellic Acids on Superoxide Dismutase (SOD). A decrease (5.51 ± 0.19) in superoxide dismutase activity by cyclophosphamide induced oxidative stress was significant as compared with control group (11.6 ± 0.008). CYP-treated rats showed a remarkable improvement (10.81 ± 0.06) in SOD activity when boswellic acids were preadministered (Figure 2a).

3.3.5. Effect of Boswellic Acids on Glutathione Peroxide. Glutathione peroxide level dropped (379.94 ± 9.86) in diseased control group when compared to control group (810.90 ± 12.00), while in mesna (40 mg/kg) and boswellic acids (100 and 200 mg/kg) treated group, there was a significant increase (712.79 ± 10.34, 1046.85 ± 10.79, 1113.72 ± 8.81) in GPX levels (Figure 2b).

3.3.6. Effect of Boswellic Acids on Nitric Oxide. The administration of cyclophosphamide induced a significant increase (65.54 ± 1.38) in nitric oxide level when compared with control group (20.00 ± 0.71). Pretreatment with boswellic acids was able to significantly attenuate (29.99 ± 1.66) this increase in the diseased group (Figure 2c).

3.3.7. Effect of Boswellic Acids on Interleukin-6 and Tumor Necrosis Factor-α. It was observed that IL-6 and TNF-α levels in the diseased control group rose (88.92 ± 1.38, 28 ± 2.35) in comparison with the control group (23.15 ± 1.07, 12 ± 0.82), and these were notably reduced (62.44 ± 1.68, 51.70 ± 1.23, 38 ± 1.20, 22 ± 0.4, 20.25 ± 0.25, 18.5 ± 0.28) in mesna (40 mg/kg) and boswellic acids (100 and 200 mg/kg) treated groups (Figure 2d and 2e).

3.4. Histopathological Studies. Urinary bladder tissues were assessed for histopathological studies. The isolated bladder was stained with H&E to observe morphological changes. Bladders from the control group represented normal intact cells with no inflammation while in the diseased control group inflammation and severe edema were found. Pretreat-
pharmacological induced cystitis. Boswellic acids are natural substances with determined the role of boswellic acids in cyclophosphamide-regard, the protocols designed in the present study aimed to oxidative stress generated by acrolein, the inflammatory process (with an emphasis on edema), and bleeding, which emphasizes the overall clinical aspect of this illness. In this study, the protocols designed in the present study aimed to determine the role of boswellic acids in cyclophosphamide-induced cystitis. Boswellic acids are natural substances with pharmacological effects which include antioxidant and anti-inflammatory activities.

Several investigations in experimental animals have demonstrated that various medicinal herbs or isolated substances can protect against interstitial cystitis caused by CYP. Curcumin, tertiarnid, spirulina, Phyllanthus niruri, alpha phellandrene, Ipomea obscura, and the inner bark of Caesalpinia pyrhamidalis have all been proven to be effective antioxidants in the treatment of CYP-induced IC.

The current investigation found that pretreatment with boswellic acid reduced CYP-induced severe urinary bladder toxicity (represented by nociception, increased bladder weight, and vascular permeability). Assessment of nociception exhibited an increase in behavioral changes including activity like walking and climbing, immobility, and behaviors symptomatic of visceral pain (“crises”). For this locomotor activity, the rats were put in a container with portions of 9 squares, the number of squares crossed was counted for 10 min. Pain crisis induced by cyclophosphamide injection was averted significantly by an oral pretreatment with boswellic acids (100 mg/kg and 200 mg/kg). Previous studies exhibited an analgesic effect in some models. In this line, investigations have demonstrated that extracts or chemicals extracted from herbal medicines can attenuate cystitis in rodents caused by oxazophorines.

Evans blue dye was applied to describe the degree of bladder tissue edema because this fluorescent material adheres to serum albumin with a greater affinity, and this complex has commonly been used to experimentally explore the degree of capillary leakage that accompanies inflammatory reaction, consisting of a relatively inexpensive, reliable, and convenient method, and which can be adapted to appraise leakage in a variety of experimental pathological conditions. The outcomes of the Evans blue dye assessment of the growth of IC showed that boswellic acids at doses of 100 and 200 mg/kg were able to reduce vascular protein leakage, confirming that boswellic acids have defensive prospects against the development of CYP-induced IC.

![Histopathological studies (H and E staining) of control group (a), diseased control (b), mesna treated (c), boswellic acids (100 mg/kg) treated (d), and Boswellic acids (200 mg/kg) treated (e).](image)

4. DISCUSSION

Cyclophosphamide-induced interstitial cystitis is well characterized, and the etiology of this adverse effect is related to its toxic metabolite (acrolein), which promotes a rupture of the intraluminal membrane, enabling contact with the deeper epithelial layers, which in turn induces displacement of the urothelial cells to develop a typical robust inflammatory process, resulting histologically in subepithelial edema, neutrophil infiltration, hemorrhage, and endothelial tissue destruction. In the pathogenesis of IC, three factors stand out: oxidative stress generated by acrolein, the inflammatory process (with an emphasis on edema), and bleeding, which emphasizes the overall clinical aspect of this illness. In this regard, the protocols designed in the present study aimed to determine the role of boswellic acids in cyclophosphamide-induced cystitis. Boswellic acids are natural substances with pharmacological effects which include antioxidant and anti-inflammatory activities.
Cyclophosphamide administration induced oxidative stress; caused renal damage in rats by glomerular inflammation, epithelial cytosolic vacuolization in cortical tubules, hemorrhagic alterations and interstitial edema in the renal cortex and oxidative damage, as increased kidney malondialdehyde (MDA) levels in serum. MDA level was measured to determine lipid peroxidation. Pretreatment with boswellic acids (100 and 200 mg/kg) showed their capability in reducing oxidative injury including MDA lipid peroxidation in CYP-induced interstitial cystitis by dropping the levels of MDA. These findings were aligned with a previous study.

Protein carbonylation, the most frequent type of ROS-induced protein modification, is considered irreversible and aims to induce protein degradation. The toxicity of cyclophosphamide is mediated by its binding to cellular antioxidants, which led to the depletion of cellular defense mechanisms and perhaps an elevation in protein carbonyl content. The CPO levels in the cyclophosphamide administered rats increased compared to control group rats. Pretreatment with boswellic acids (100 and 200 mg/kg) showed these were capable of reducing oxidative stress in CYP-induced interstitial cystitis by decreasing the levels of carbonyl protein content in cystitis.

GPX and CAT activity were markedly smaller in the CYP group than in the normal group, which is consistent with prior investigations. It has been shown that CYP therapy causes the generation of reactive oxygen species (ROS), which causes oxidative stress harm to the bladder urothelium. Furthermore, acrolein can reduce the concentration of GPX. When compared to the CYP group, boswellic acids dramatically raised the levels of GPX and CAT in the bladder. The activities of glutathione reductase and catalase enzymes were boosted by boswellic acids. Because CYP has a pro-oxidant character, it causes oxidative stress by lowering antioxidant enzyme activity. It enhances lipid peroxidation in the body. The pro-inflammatory aspect of CYP intoxication may potentially play a role in the disruption of total redox cycling in bladder tissues.

The importance of NO in HC pathophysiology was underlined. In our investigation, CYP injection resulted in increased levels of NO in bladder tissue than the control. In addition to increased production of inducible nitric oxide synthase, these augmented NO levels could be explained by physiological adaptation processes of the bladder in reaction to acrolein. As a result, overproduction of reactive oxygen and nitrogen species (ROS and RNS) occurs, causing damage to the bladder wall. NO levels were dramatically reduced after boswellic acid treatment, which is consistent with prior research showing that boswellic acid reduces nitrogen species formation. Because of its potential to scavenge NO, boswellic acid was found to reduce NO synthesis and iNOS overexpression. Furthermore, multiple experimental studies have shown that inhibiting iNOS is useful in the treatment of CYP-induced cystitis.

In this work, boswellic acid decreased the release of inflammatory cytokines like IL-6 and TNF-α in a dose-dependent manner. It has been reported previously that TNF-α participates actively in IC induced by CYP. Boswellic acid’s cytokine inhibitory impact may have helped to bladder architectural protection and reduced inflammatory infiltration. As a result, the organ protection activity in CYP-induced cystitis could be attributed to suppression of pro-inflammatory cytokines.

CYP caused bladder inflammation in the mucosa and submucosa which resulted in vascular injury and subsequent hemorrhage, as well as mucosal perforation, according to our findings. Multiple investigations in rats revealed similar bladder alterations after CYP treatment. As with other plant extracts, boswellic acid treatment dramatically reversed these histological alterations in the bladder. This impact could be attributed by boswellic acid’s potential to lower oxidative stress and inflammation while also speeding up healing.

5. CONCLUSION

It is concluded that boswellic acids possessed a powerful uroprotective effect by lowering urinary bladder weight, Evans blue dye concentration, MDA, CPO, NO, IL-6, and TNF-α, and increasing CAT, GPX, and SOD activities. It is suggested that boswellic acids have indeed been proposed as a potential uroprotective agent versus cyclophosphamide-induced interstitial cystitis. More clinical research is intended to explain the benefits and potential mechanism of uroprotection of boswellic acids.

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Author Contributions

I. Anjum proposed the concept, validated methodology, performed results analysis while M. Fatima was involved in the data collection and A. Abdullah and S. Z. Abid performed the histopathological analysis and wrote the initial manuscript. M. N. H. Malik reperformed and confirmed the statistical analysis. All the authors finally read and approved the contents.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are thankful to the University of Veterinary and Animal Sciences, Lahore, for providing facilities to complete this research project.

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