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Chronic Oral Administration of *Phyllanthus niruri* Extract Is Well Tolerated in Sheep: Hematological, Biochemical, and Histopathological Evidence

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Abstract

Phytogenic additives are increasingly explored as alternatives to synthetic feed additives in ruminant production, yet chronic organ-level safety evidence in sheep remains scarce. *Phyllanthus niruri* is widely reported to possess antioxidant, anti-inflammatory, and hepatoprotective activities, but its long-term safety in small ruminants has not been established. This study evaluated hematological indices, serum biomarkers of hepatic and renal function, and liver–kidney histopathology following eight weeks of oral supplementation with *P. niruri* extract in sheep. Twenty-four healthy male sheep (6–8 months) were randomly assigned to four groups (n = 6): control (0.5% CMC-Na) and extract-treated groups (5%, 10%, or 20% w/v), administered once daily at 1 mL/kg body weight. Hematology and serum biochemistry (AST, ALT, GGT, BUN, creatinine) were assessed at baseline and week 8, and tissues were examined histologically at study end. Total leukocyte counts increased significantly in all extract-treated groups; however, animals showed no clinical abnormalities and no histological evidence of inflammation. Other hematological indices and all serum hepatic and renal biomarkers remained within physiological limits with no adverse deviations. Histopathological evaluation revealed preserved hepatic and renal architecture without degeneration, necrosis, congestion, or tubular damage. Overall, chronic oral supplementation with *P.*

niruri extract (5–20%) for eight weeks was well tolerated in sheep, supporting its safety as a candidate phyto-genic additive, while further immunological profiling is warranted to clarify the leukocyte response.

Keywords : *Phyllanthus niruri*; sheep; phyto-genic feed additive; hematology; liver enzymes; kidney function

Introduction

Small ruminants, particularly sheep, remain essential to livestock production systems in tropical and subtropical regions, where climate variability, seasonal feed scarcity, and disease pressure continue to limit productivity and animal health (Thornton and Herrero 2022; Sejian et al. 2023). In these environments, inadequate nutrition and compromised immune status frequently contribute to reduced performance and increased susceptibility to infectious diseases, highlighting the need for sustainable nutritional strategies that support physiological resilience.

In response to global restrictions on antibiotic growth promoters and rising concerns regarding antimicrobial resistance, phyto-genic feed additives (PFAs) have gained increasing attention as natural alternatives in animal nutrition (Gadde et al. 2023; Wang et al. 2024). These additives, derived from herbs, spices, and plant extracts, contain diverse bioactive compounds such as flavonoids, phenolics, and terpenoids that may exert antimicrobial, antioxidant, and immunomodulatory effects (Franz et al. 2021; Animut et al. 2022). Recent reviews emphasize that PFAs can positively influence animal health and productivity, although their biological effects are highly dependent on dose, duration, and species-specific metabolism (Cieslak et al. 2023).

In ruminants, phyto-genic compounds have been reported to modulate rumen fermentation, nutrient utilization, and metabolic homeostasis, with potential implications for immune function and organ health (Patra et al. 2022; Joch et al. 2023). However, emerging toxicological evidence indicates that certain plant-derived secondary metabolites may induce hepatic or renal stress when administered chronically or at high concentrations, underscoring the importance of comprehensive safety assessments prior to long-term application (Teschke et al. 2022; Lala et al. 2024). Consequently, organ-level safety evaluation has become a critical requirement in the responsible development of phyto-genic additives for livestock.

Phyllanthus niruri L. is a tropical medicinal plant that has attracted renewed scientific interest due to its reported antioxidant, anti-inflammatory, and hepatoprotective properties. Recent phytochemical and pharmacological studies have confirmed the presence of lignans, flavonoids, tannins, and polyphenolic compounds that contribute to its biological activity (Rani et al. 2024; Arshad et al. 2025). Experimental investigations using in vitro and rodent models demonstrate that *P. niruri* extracts can attenuate oxidative stress,

regulate inflammatory signaling pathways, and protect hepatic and renal tissues from chemically induced injury (Londhe et al. 2021; Arshad et al. 2025). Despite these findings, data derived from monogastric models cannot be directly extrapolated to ruminants.

Ruminant species present a distinct physiological context due to the presence of rumen microbial fermentation, which can substantially alter the bioavailability, metabolism, and biological activity of phytochemical compounds (Patra et al. 2022; Cieslak et al. 2023). As a result, phytochemical additives that appear safe in non-ruminant models may exhibit different efficacy or toxicity profiles in sheep. Although *P. niruri* supplementation has been associated with enhanced immune responses in poultry and other monogastric species, evidence regarding its chronic safety in ruminants remains scarce (Hidanah et al. 2022; Pasaribu et al. 2023).

To date, no study has comprehensively evaluated the long-term safety of oral *Phyllanthus niruri* extract supplementation in sheep by integrating hematological parameters, serum biochemical markers of hepatic and renal function, and histopathological examination of target organs. Therefore, the present study aimed to assess the chronic safety of *P. niruri* extract administered orally to sheep by combining hematological, biochemical, and histopathological endpoints. This work provides contemporary, species-specific evidence to support the safe application of *P. niruri* as a phytochemical additive in tropical small ruminant production systems.

Materials and Methods

Ethical approval

All experimental procedures involving animals were reviewed and approved by the Animal Care and Use Committee (ACUC) of the Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia (Approval No. 2.KEH.129.08.2023). The study was conducted in accordance with national regulations governing animal research and followed the ARRIVE 2.0 guidelines to ensure animal welfare throughout the experiment.

Animals and housing

Twenty-four clinically healthy male local sheep (*Ovis aries*), aged 6–8 months and weighing 18–22 kg, were used in this study. Animals were acclimatized for 14 days before the start of the experiment. Sheep were housed individually in raised pens (1.5 × 1.5 m) under natural tropical environmental conditions (ambient temperature 26–30 °C; relative humidity 65–80%) with a 12-h light–dark cycle. All animals received a standardized basal diet consisting of fresh forage and commercial concentrate formulated to meet maintenance requirements, and clean drinking water was provided *ad libitum*.

Experimental design and treatments

After acclimatization, sheep were randomly allocated into four experimental groups (n = 6 per group). The control group received 0.5% sodium carboxymethyl cellulose (CMC-Na), while treatment groups received *Phyllanthus niruri* extract at concentrations of 5%, 10%, or 20% (w/v). All preparations were administered orally once daily at a dose of 1 mL/kg body weight for eight consecutive weeks. Body weight was recorded weekly to allow accurate dose adjustment. Animals were observed daily for general health status and behavioral changes throughout the experimental period.

Preparation of *Phyllanthus niruri* extract

Fresh whole plants of *Phyllanthus niruri* were collected, washed thoroughly, and air-dried at 25 ± 2 °C. The dried plant material was ground into a fine powder and extracted by maceration in 70% methanol for 72 h with periodic agitation. The extract was filtered and concentrated under reduced pressure using a rotary evaporator at 40 °C. The resulting crude extract was stored at 4 °C until use and reconstituted in 0.5% CMC-Na to obtain working concentrations of 5%, 10%, and 20% (w/v).

Clinical monitoring

Throughout the eight-week treatment period, animals were monitored daily for clinical signs of adverse effects, including changes in appetite, behavior, locomotion, respiratory condition, and fecal consistency. Any abnormalities observed were recorded to identify potential treatment-related effects.

Blood sampling

Blood samples were collected from the jugular vein at baseline (week 0) and at the end of the treatment period (week 8). Samples for hematological analysis were collected into EDTA-coated tubes, whereas samples for biochemical analysis were collected into plain tubes and centrifuged at 3000 rpm for 15 min to obtain serum. Serum samples were stored at -80 °C until analysis.

Hematological analysis

Hematological parameters, including total leukocyte count, erythrocyte count, hemoglobin concentration, hematocrit, platelet count, and lymphocyte percentage, were analyzed using an automated hematology analyzer (Mindray BC-3200, Shenzhen, China) according to the manufacturer's instructions.

Biochemical analysis

Serum biochemical markers of hepatic and renal function were determined using an automated chemistry analyzer (Horiba Pentra C200, Horiba, France). The parameters assessed included aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), and

creatinine. All assays were performed using validated commercial kits, and each sample was analyzed in duplicate.

Tissue collection and histopathological examination

At the end of the experimental period, animals were humanely euthanized following sedation using intravenous sodium pentobarbital. Liver and kidney tissues were collected immediately, fixed in 10% neutral-buffered formalin for at least 48 h, and processed using standard histological procedures. Tissue sections (4–5 μm) were prepared and stained with hematoxylin and eosin (H&E).

Histopathological evaluation was performed by a veterinary pathologist blinded to treatment allocation. Liver sections were examined for hepatocellular degeneration, necrosis, congestion, and inflammatory infiltration, while kidney sections were assessed for tubular degeneration, tubular necrosis, glomerular alterations, and vascular congestion. Lesions were scored semi-quantitatively on a scale from 0 (absent) to 4 (severe).

Statistical analysis

Data are presented as mean $\pm$ standard deviation (SD). Normality of data distribution was assessed using the Shapiro–Wilk test. Hematological and biochemical parameters were analyzed using repeated-measures analysis of variance (ANOVA), with time as the within-subject factor and treatment as the between-subject factor. When significant effects were detected, Bonferroni post hoc tests were applied. Histopathological scores were analyzed using the Kruskal–Wallis test followed by Dunn’s multiple comparison test. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 25.0 (IBM Corp., USA).

Results

Hematological profile

Administration of *Phyllanthus niruri* extract resulted in a marked increase in total leukocyte counts in all treated groups compared with the control group (Table 1; Fig. 1). Mean leukocyte values ranged from 42.34 to 54.72 $\times 10^3/\mu\text{L}$ in extract-treated sheep, whereas the control group exhibited a mean value of 9.22 $\times 10^3/\mu\text{L}$. The increase in leukocyte count was statistically significant ($p < 0.05$) across all extract concentrations.

In contrast, other hematological parameters, including erythrocyte count, hemoglobin concentration, hematocrit, lymphocyte percentage, and platelet count, did not differ significantly among treatment groups ($p > 0.05$). All measured values remained within physiological ranges, and no abnormal hematological patterns were observed during the experimental period.

Serum biochemical markers

Serum biochemical markers of hepatic and renal function are presented in Table 2; Fig. 2. No significant differences were observed among groups for aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), or creatinine ($p > 0.05$). Minor variations were noted across treatments; however, all values remained within reference ranges for healthy sheep.

Gamma-glutamyl transferase (GGT) activity differed significantly among groups ($p < 0.05$), with lower mean values observed in extract-treated sheep compared with the control group. Despite this variation, GGT levels in all groups were within normal physiological limits.

Histopathological findings

Histopathological examination of liver tissues revealed preserved hepatic architecture in all experimental groups (Table 3; Fig. 3). Hepatocytes exhibited normal morphology, with intact cellular arrangement and well-defined sinusoidal spaces. No evidence of hepatocellular degeneration, necrosis, congestion, or inflammatory infiltration was observed in either control or treated animals. Semi-quantitative scoring confirmed the absence of significant treatment-related hepatic lesions ($p > 0.05$).

Similarly, kidney tissues from all groups displayed normal histological features (Table 4; Fig. 4). Glomeruli appeared intact with normal Bowman's spaces, and renal tubules showed no signs of degeneration, necrosis, or vascular congestion. Histopathological scores for renal parameters did not differ significantly among groups ($p > 0.05$), indicating preserved renal structural integrity following chronic supplementation with *P. niruri* extract.

Discussion

The present study provides a comprehensive evaluation of the chronic safety of oral *Phyllanthus niruri* extract supplementation in sheep by integrating hematological parameters, serum biochemical markers of hepatic and renal function, and histopathological examination of target organs. Phytogetic feed additives have long been investigated as alternatives to synthetic growth promoters due to their bioactive properties (Franz et al. 2010), and recent reviews have emphasized the importance of species-specific safety validation in ruminants under chronic exposure conditions (Animut et al. 2022; Cieslak et al. 2023; Wang et al. 2024). Within this context, the absence of adverse hematological, biochemical, or histopathological alterations observed in the present study indicates that *P. niruri* extract was well tolerated at the tested doses.

A prominent finding of this study was the significant increase in total leukocyte counts in all extract-treated groups. Increases in leukocyte counts following phytogetic supplementation have been reported previously and are often interpreted as indicators of immune activation rather than pathological inflammation when not accompanied by clinical abnormalities or tissue damage (Franz et al. 2010; Animut et al. 2022). More recent assessments suggest that phytochemicals such as flavonoids and polyphenols can stimulate leukopoiesis and innate immune responses without inducing inflammatory lesions, provided that dosing remains within tolerable limits (Cieslak et al. 2023; Wang et al. 2024). In the present study, leukocytosis was not associated with alterations in erythrocyte indices, platelet counts, or histopathological evidence of inflammation, supporting the interpretation of a non-pathological, immunomodulatory response. Nevertheless, the lack of differential leukocyte counts and cytokine measurements limits mechanistic inference and should be addressed in future studies.

Serum biochemical analyses further supported the absence of hepatic and renal toxicity. Activities of AST and ALT remained stable across treatment groups and within physiological ranges, indicating preserved hepatocellular integrity. Earlier work on herbal safety has highlighted that stable aminotransferase activities are indicative of the absence of hepatocellular injury during phytogetic exposure (Teschke and Eickhoff 2015). More recent toxicological evaluations reinforce that chronic supplementation with plant-derived compounds does not necessarily impair liver function when administered at appropriate doses and durations (Lala et al. 2021; Lala et al. 2024). In the present study, gamma-glutamyl transferase activity was lower in extract-treated animals compared with controls, although all values remained within normal limits, suggesting that *P. niruri* extract did not impose hepatobiliary stress.

Renal biomarkers, including blood urea nitrogen and creatinine, also remained unaffected by treatment, indicating preserved renal excretory function. Earlier studies on phytogetic safety have demonstrated that the absence of changes in these markers reflects maintained glomerular filtration and tubular integrity (Teschke and Eickhoff 2015). Recent ruminant-focused investigations further confirm that chronic exposure to plant bioactive compounds does not adversely affect renal biochemical indices when supported by normal histopathological findings (Patra et al. 2022; Joch et al. 2023). These observations are consistent with the renal safety profile observed in the present study.

Histopathological examination provided direct morphological confirmation of the biochemical results. Liver and kidney tissues from all experimental groups exhibited preserved architecture, with no evidence of degeneration, necrosis, congestion, or inflammatory infiltration. The importance of histopathological evaluation in safety assessment has been emphasized previously, as microscopic lesions may precede detectable changes in

serum biomarkers (Lala et al. 2021). Recent reviews underscore that the concordance of normal histology and stable biochemical parameters represents a robust indicator of organ-level safety in phytogetic studies (Cieslak et al. 2023; Lala et al. 2024).

From an applied perspective, these findings are particularly relevant for tropical small ruminant production systems, where phytogetic additives are increasingly explored to support animal health and reduce reliance on antimicrobial inputs. Ruminant species present a unique physiological context due to rumen microbial fermentation, which can alter the bioavailability and metabolism of phytochemicals and necessitates species-specific safety evaluation (Patra et al. 2022; Cieslak et al. 2023). It should be noted that the dosing regimen employed in the present study reflects oral administration of a standardized extract (1 mL/kg body weight) and should not be directly extrapolated to dietary inclusion rates without further feed-based evaluation. Additionally, the relatively short experimental duration and the absence of oxidative stress markers, immune mediators, and performance outcomes represent limitations that should be addressed in future research.

In conclusion, chronic oral administration of *Phyllanthus niruri* extract at concentrations of 5–20% for eight weeks did not adversely affect hematological stability, hepatic or renal biochemical function, or liver and kidney histological integrity in sheep. The observed leukocytosis, occurring in the absence of clinical or pathological abnormalities, is consistent with a potential immunomodulatory response rather than toxicity. Collectively, these findings provide ruminant-specific, organ-level safety evidence supporting the tolerability of *P. niruri* extract and establish a contemporary safety reference for its further development as a phytogetic additive in tropical small ruminant production systems.

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Competing interests

The authors declare that they have no relevant financial or non-financial interests to disclose.

Ethics approval

All experimental procedures involving animals were reviewed and approved by the Animal Care and Use Committee (ACUC) of the Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia (Approval No. 2.KEH.129.08.2023). The study was conducted in accordance with national guidelines for animal research and complied with the ARRIVE 2.0 recommendations.

Consent to participate

Not applicable. This study did not involve human participants.

Consent to publish

Not applicable. This study did not contain any individual human data.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Author contributions

Emy Koestanti Sabdoningrum: Conceptualization, investigation, writing—original draft.

Sri Hidanah: Conceptualization, validation, investigation.

Nazri Nayan: Formal analysis, validation.

Ira Sari Yudaniayanti: Validation, investigation.

Soeharsono Soeharsono: Statistical analysis.

Lita Rakhma Yustinasari: Writing—review and editing.

Raihan Ario Saputro: Blood sample collection.

Mira Audrea: Tissue sample collection.

Supriyadi: Supervision, resources.

All authors read and approved the final manuscript.

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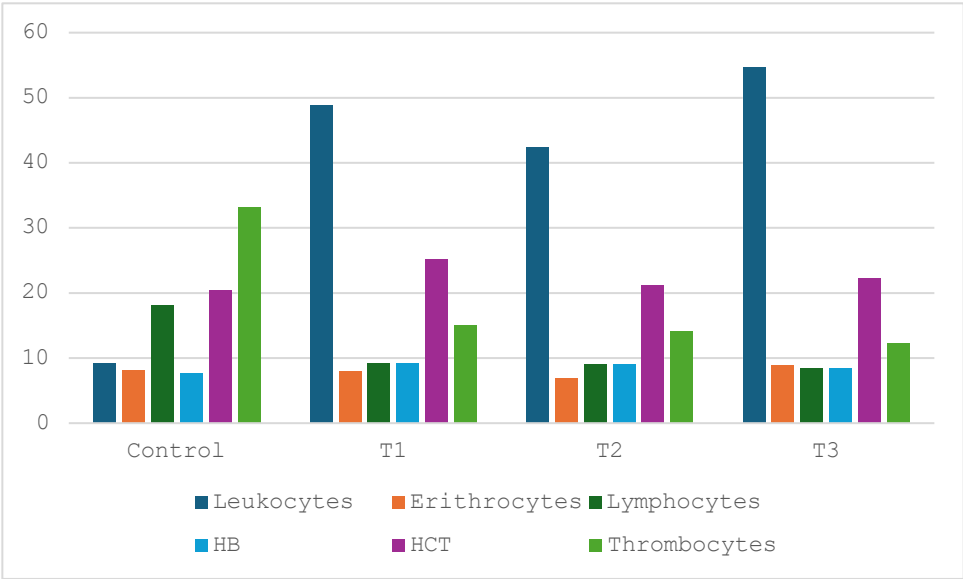
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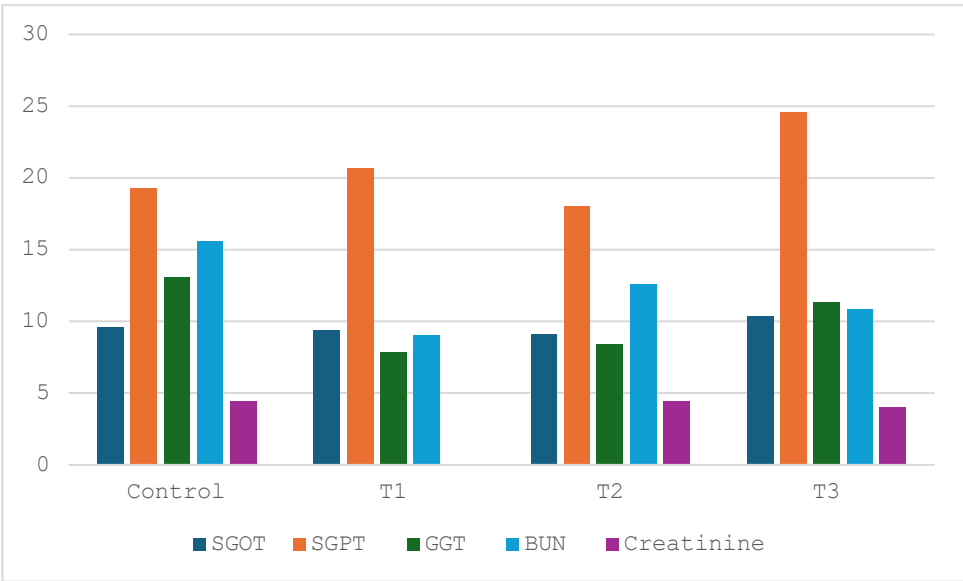
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Figure



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Figure 1. Blood profile results in sheep administered with *Phyllanthus niruri*. extract as a feed additive



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Figure 2. Biochemical results in sheep administered with *Phyllanthus niruri* extract as a feed additive.

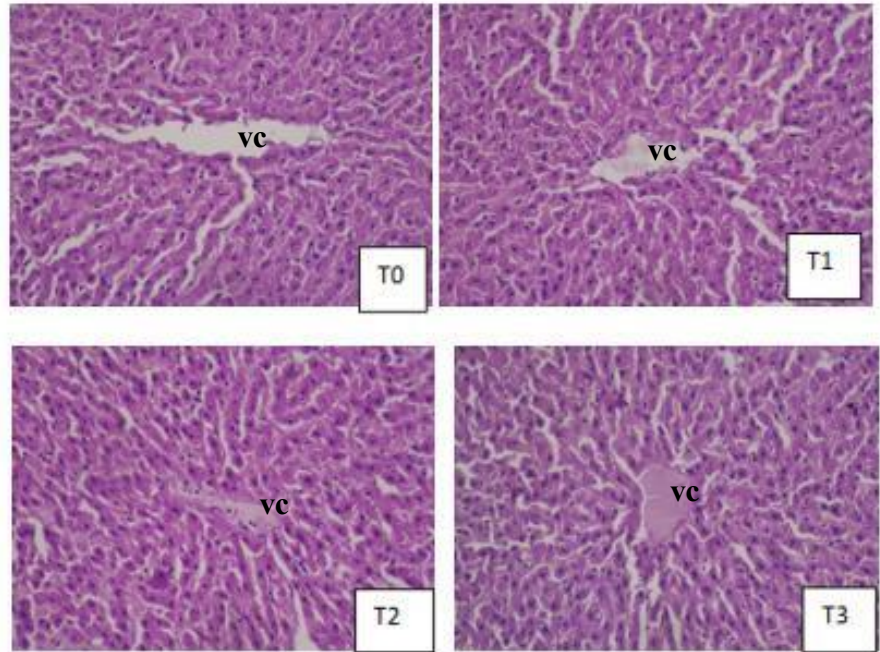


Figure 3. Microscopic examination of sheep liver samples after administration of *Phyllanthus niruri* extract as a feed additive showed no significant morphological changes (HE, 200x). VC, vena centralis.

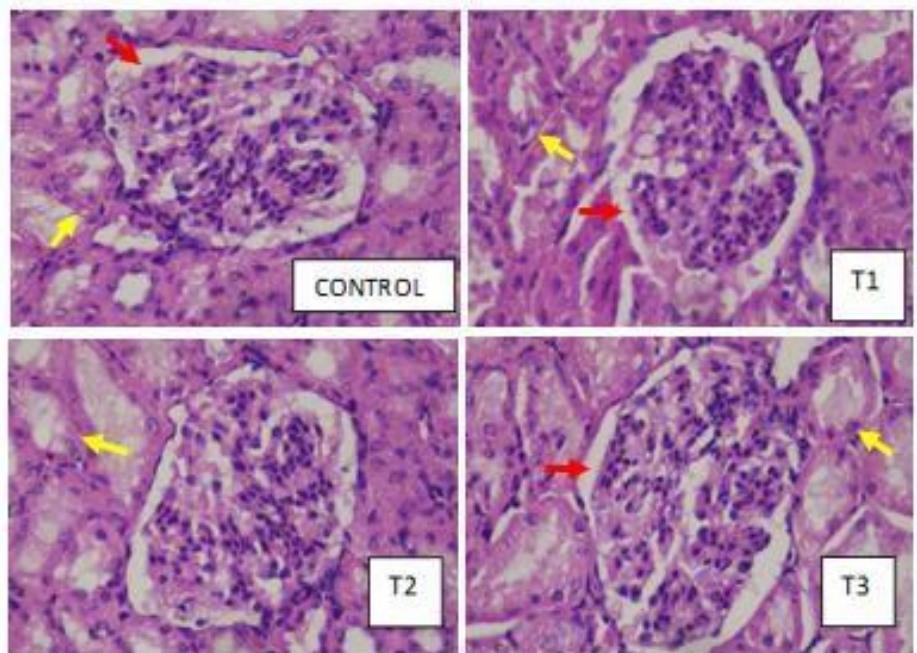


Figure 4. Microscopic examination of sheep kidney samples after administration of *Phyllanthus niruri* extract as a feed additive showed no significant morphological changes. The spaces within Bowman's capsules are indicated by red arrows. Proximal tubules are indicated by yellow arrows (HE, 400x).

Table

Table 1. Hematological parameters of sheep administered *Phyllanthus niruri* extract

Group	Leukocytes (10 ³ /μL)	Erythrocytes (10 ⁶ /μL)	Lymphocytes (%)	Hb (g/dL)	HCT (%)	Platelets (10 ³ /μL)
Control	9.22 ^a ± 12.34	8.18 ^a ± 1.23	18.18 ^a ± 20.32	7.64 ^a ± 4.45	20.38 ^a ± 12.01	3315.35 ^a ± 1903.96
T1 (5%)	48.80 ^b ± 16.23	8.02 ^a ± 1.95	9.18 ^a ± 1.10	9.18 ^a ± 1.10	25.20 ^a ± 6.80	1496.60 ^a ± 1499.71
T2 (10%)	42.34 ^b ± 18.06	6.84 ^a ± 0.93	9.06 ^a ± 1.72	9.06 ^a ± 1.72	21.16 ^a ± 2.98	1418.20 ^a ± 1951.21
T3 (20%)	54.72 ^b ± 13.42	8.91 ^a ± 1.12	8.36 ^a ± 4.72	8.36 ^a ± 4.72	22.22 ^a ± 12.85	1227.20 ^a ± 1685.61

Different superscripts (a,b) indicate significant differences among groups (p

< 0.05). Hb = hemoglobin; HCT = hematocrit.

Table 2. Serum biochemical markers of sheep administered *Phyllanthus niruri* extract

Group	AST (IU/L)	ALT (IU/L)	GGT (IU/L)	BUN (mg/dL)	Creatinine (mg/dL)
Control	95.88 ^a ± 23.44	19.28 ^{ab} ± 6.35	130.82 ^b ± 30.24	15.60 ^a ± 8.04	0.44 ^a ± 0.05
T1 (5%)	93.86 ^a ± 10.42	20.64 ^{ab} ± 2.20	78.44 ^a ± 14.79	9.00 ^a ± 2.12	0.44 ^a ± 0.05
T2 (10%)	90.98 ^a ± 7.61	18.04 ^a ± 3.38	84.11 ^a ± 25.01	12.60 ^a ± 4.44	0.44 ^a ± 0.05
T3 (20%)	103.52 ^a ± 15.84	24.60 ^b ± 1.30	113.36 ^{ab} ± 2.68	10.80 ^a ± 2.68	0.40 ^a ± 0.07

Different superscripts (a,b) indicate significant differences among groups (p

< 0.05). ALT = alanine aminotransferase; AST = aspartate aminotransferase;

GGT = gamma-glutamyl transferase; BUN = blood urea nitrogen.

Table 3. Liver histopathological scores (mean rank ± SD)

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Group	Degeneration	Necrosis	Congestion
Control	0.13 ^a ± 0.48	0.13 ^a ± 0.05	0.15 ^a ± 0.05
T1 (5%)	0.13 ^a ± 0.09	0.15 ^a ± 0.10	0.15 ^a ± 0.10
T2 (10%)	0.20 ^a ± 0.08	0.20 ^a ± 0.08	0.15 ^a ± 0.05
T3 (20%)	0.25 ^a ± 0.05	0.30 ^a ± 0.06	0.15 ^a ± 0.05

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Values represent mean rank ± SD; same superscript (a) indicates no significant difference (p > 0.05).

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Table 4. Kidney histopathological scores (mean rank ± SD)

Group	Degeneration	Necrosis	Congestion
Control	0.18 ^a ± 0.03	0.25 ^a ± 0.05	0.03 ^a ± 0.03
T1 (5%)	0.30 ^a ± 0.06	0.35 ^a ± 0.05	0.05 ^a ± 0.03
T2 (10%)	0.23 ^a ± 0.06	0.25 ^a ± 0.05	0.03 ^a ± 0.03
T3 (20%)	0.30 ^a ± 0.06	0.35 ^a ± 0.05	0.03 ^a ± 0.03

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Values represent mean rank ± SD; same superscript (a) indicates no significant difference (p > 0.05).

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