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Coleus amboinicus Lour. Leaf Extract Has No Effects on the Biochemical Markers but Improves the Liver Histopathological Scores of Septic Rat Model

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Abstract

Coleus amboinicus Lour. is a herbal plant with immunoregulatory effects due to the polyphenols it contains. This research aims to determine the effects of *Coleus amboinicus* Lour. leaf extract on the biochemical markers and the liver histopathological scores of septic rat model. We used 28 *Rattus norvegicus* rats for the study and divided them into 4 groups consisting of 7 rats each: control (healthy rats without treatment), group 1 (septic rats treated with antibiotics), group 2 (septic rats treated with antibiotics and 250 mg/kg body weight of *Coleus amboinicus* Lour. leaf extract), and group 3 (septic rats treated with antibiotics and 500 mg/kg body weight of *Coleus amboinicus* Lour. leaf extract). We measured the serum glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine levels, as well as the liver histopathological scores, to assess the improvement. Results showed a decrease in the serum glucose, AST, ALT, urea, and creatinine levels of the rat groups given *Coleus amboinicus* Lour. leaf extract compared to the rat group given only antibiotics, though the decrease was not significant ($p = 0.393$; $p = 0.064$; $p = 0.961$; $p = 0.288$; $p = 0.119$, respectively). However, there was a significant decrease in the liver histopathological scores of the rat groups given *Coleus amboinicus* Lour. leaf extract compared to the rat group given only antibiotics ($p = 0.003$). To conclude, *Coleus amboinicus* Lour. leaf extract administration has no significant effect on the biochemical markers but improves the liver histopathological scores in septic rat model.

Keywords: Coleus amboinicus Lour, Herbal, Histopathology, Organ dysfunction, Sepsis.

Introduction

Sepsis is one of the global health challenges and contributes to half of hospital deaths, above stroke and myocardial infarction.[1] In sepsis, the dysregulated immune response to infection can lead to multiple organ dysfunction, causing death. Each organ dysfunction adds to the risk of death. Currently, the definition of sepsis emphasizes the presence of organ dysfunction.[2,3]

A decrease in renal function is often found in sepsis.[4] Up to 60% of septic patients are affected by acute kidney injury (AKI).[5] However, the association between organ dysfunction and mortality in sepsis

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depends on the affected organ. A retrospective analysis conducted in Catalonia shows that although hepatic failure is a less frequent organ dysfunction in sepsis, it is associated with a high mortality rate.[1]

Intravenous broad-spectrum antibiotics have been the standard therapy for sepsis.[6] However, there is a lack of supportive therapy for sepsis-associated organ dysfunction. Current supportive therapy consists of supplemental oxygen, mechanical ventilation, and dialysis.[7] Meanwhile, extracorporeal liver assist devices are not considered a standardized organ support measure for liver dysfunction.[1] Therefore, there is a need for effective supportive therapy.

Herbal plants have been used as a co-treatment with antibiotics in sepsis. Administering XueBiJing, a Chinese herbal medicine, has been shown to alleviate liver and renal injury in rats with its immunoregulatory effect.[8] Similarly, ginger has been reported to attenuate organ injury and enhance survival rate in septic mice through immunoregulatory mechanisms.[9]

Coleus amboinicus Lour. or *Plectranthus amboinicus* Lour. Spreng is a herbal plant known for its therapeutic properties and has been widely used in folk medicines.[10] The polyphenols within the leaves possess immunoregulatory effects.[11,12] A study showed that *Coleus amboinicus* Lour. extract inhibited the proinflammatory mediators in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells and the edema-paw tissue of mice.[13]

Although *Coleus amboinicus* Lour. is known for its immunoregulatory effects, its potential in alleviating organ dysfunction has yet to be clearly studied. Therefore, we aim to determine the effects of *Coleus amboinicus* Lour. leaf extract on the blood glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, and creatinine levels, as well as the liver histopathology of septic rat model.

Materials and Methods

Preparation and Phytochemical Screening of the Extract

We obtained *Coleus amboinicus* Lour. from Tanah Karo Berastagi, Medan, North Sumatra, and identified the specimen in the pharmacy laboratory of Universitas Sumatera Utara (USU) faculty of pharmacy. We made the extract from dry powder via maceration with 70% ethanol, which was then soaked for 6 hours while stirred. After keeping the macerate in place for 18 hours, we performed a centrifugation to separate the powder from the solvent. This process was repeated at least once, with the solvent volume halved from the volume of the initial dilution. The macerate was later evaporated with a low-pressure vacuum or a rotary evaporator until it produced a thick extract.[14] Lastly, we used standardized methods to examine the presence of alkaloid, flavonoid, glycoside, saponin, tannin, and triterpenoid.[13-16]

To indicate the presence of alkaloid compounds, a total of 0.5 g of simplicia powder plus 1 mL of 2 N HCL and 9 mL of distilled water were blanched for two minutes, sprayed, and filtered. The filtrate was then processed with the following steps[14]:

- Three drops of filtrate were added to two drops of Mayer reagent solution, creating a white, lumpy precipitate.
- Three drops of filtrate were added with two drops of Bouchardat's reagent solution, creating a black-brown precipitate.
- Two drops of Dragendorff's reagent solution were added to the filtrate. The presence of alkaloid compounds was indicated by a red or orange precipitate.

To indicate the presence of flavonoid, 1 mL of the solution was evaporated. The remainder was dissolved in 1 mL of 95% ethanol, plus 0.1 g of magnesium powder and ten drops of concentrated hydrochloric acid. A positive result for flavonoid was indicated by red-orange to purple-red color.[14]

Experimental Animal Model

This study is approved by Health Research Ethics Committee of USU (No. 711/2021). We used *Rattus norvegicus* rats for the study from the pharmacology laboratory of USU faculty of medicine, with the following inclusion criteria: male, healthy, aged 10-12 weeks, and weighing 200-300 grams. We excluded the rats that died during the study. Using the Federer formula with adjustments to the expectation of attrition, the sample was 28 rats in total. The rats were divided into 4 groups consisting of 7 rats in each group:

- Control: Healthy rats
- Group 1: Septic rats treated with antibiotics

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- Group 2: Septic rats treated with antibiotics on the first three days and 250 mg/kg body weight of *Coleus amboinicus* Lour. leaf extract throughout the study
- Group 3: Septic rats treated with antibiotics on the first three days and 500 mg/kg body weight of *Coleus amboinicus* Lour. leaf extract throughout the study

The antibiotics used were 25 mg/kg body weight of intraperitoneal imipenem cilastatin. Each rat was placed in a cage with a 12 h light/dark cycle at a temperature of 27 ± 5°C. Before the experiment, the rats received the same standard laboratory treatment and feed for a week.

For the sepsis induction, we used fecal slurry at a dose of 1 g/kg body weight of the rats. The feces were suspended in saline to a concentration of 90 mg/ml and kept in place for 24 hours at 4°C. The suspension was injected into the right lower quadrant of the abdomen using a 21 G cannula.[17] To ensure that the severity was the same across the septic rat groups, we performed measurements with Murine Sepsis Score (MSS), in which rats with MSS of less than 3 or more than 21 were excluded from the research.[18]

At the end of the eighth day of observation, the rats were euthanized via cardiac puncture using a 27 G needle and 3 mL syringe. The rats were anesthetized with 10-12.5 mg/kg xylazine and 80-100 mg/kg ketamine during the euthanasia.

Serum Test

The blood collected during the cardiac puncture was centrifuged to separate the serum and stored at -80 °C. Serum glucose (mg/dL), AST (U/L), ALT (U/L), urea (mg/dL), and creatinine (mg/dL) levels were measured in the laboratory using EDTA serum. The spectrophotometer wavelengths were as follows: 500 nm for glucose, 340 nm for AST and ALT, 578 nm for urea, and 510 nm for creatinine).

Histopathological Examination of the Liver

After the euthanasia, we collected the liver of the rats via post-mortem laparotomy. The organs were fixated using a neutral 10% formalin buffer solution for 24 hours and then cut and dehydrated with 70%, 80%, and 90% alcohol for 2 hours. We later dehydrated the tissues again with absolute alcohol I and II for 2 hours. Next, we clarified the tissues with xylol for 3 minutes. They were then immersed in paraffin and cut with a microtome at 6-8 mm thickness. Hematoxylin-Eosin (H&E) staining was performed on the slides for histopathological examination.

A pathologist who is blind to the experimental conditions examined sections of tissue. Based on a past study, we used the Scheuer system to score the histopathological damage of the liver.[19]

Statistical Analysis

The statistical analysis was performed using Statistical Package for the Social Studies (SPSS). We analyzed the differences in creatinine and AST levels in all groups with ANOVA test. Meanwhile, the serum glucose, urea, and ALT levels, as well as the histopathological scores in all groups, were analyzed with Kruskall-Wallis test. $p < 0.05$ indicates significance.

Results and Discussion

The results of phytochemical screening showed that the *Coleus amboinicus* Lour. leaf extract contained alkaloids, flavonoids, glycosides, saponins, and triterpenoids. These molecules offer anti-inflammatory and immunoregulatory effects. In particular, the polyphenol compound within *Coleus amboinicus* Lour. leaves, flavonoid, is best known for its therapeutic potential.[11,12] Flavonoid exerts anti-inflammatory effects by modulating nuclear factor kappa beta (NF-κB) through affecting IκB kinase (IKK) activation, thereby reducing the production of proinflammatory cytokines. It is also capable of blocking tumor necrosis factor (TNF)-α release through modulation of mitogen-activated protein kinases (MAPK) pathway. Another anti-inflammatory mechanism of this compound is reducing the release of arachidonic acid, prostaglandin, and leukotriene.[11]

To assess the therapeutic potential of *Coleus amboinicus* Lour. leaf extract in sepsis, we assessed the serum glucose levels of the rats. Hyperglycemia is often found in sepsis, particularly in the early proinflammatory stage. The body produces catecholamine in response to the stress, inhibiting insulin secretion and glucose uptake and causing increased blood glucose levels.[20,21] Hyperglycemia contributes to further liver dysfunction through

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Kupffer cell activation. These liver macrophages release chemokines and inflammatory cytokines, causing the recruitment of various immune cells to the damaged site and the amplification of inflammation.[22]

In line with this, we found an increase in serum glucose levels of group 1 compared to the control group, which is shown in Fig. 1. Meanwhile, the serum glucose levels of group 2 and 3 showed a decrease compared to group 1, although not significant, with $p > 0.05$ ($p = 0.393$). This suggests that the extract reduced the inflammatory response and thus decreased the stress response. Moreover, flavonoids have been reported to stimulate insulin production.[23]

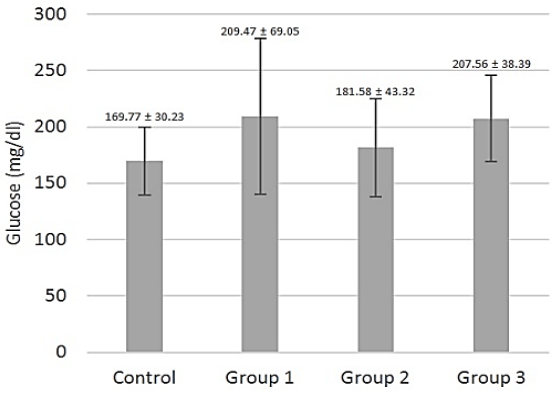

Figure 1. Serum glucose levels of all rat groups

We also examined the AST and ALT levels in the rats' serum to assess the effect of *Coleus amboinicus* Lour. leaf extract on liver damage. Due to their abundance in hepatocytes, AST and ALT are associated with hepatocellular integrity. Both enzymes are released from the hepatocytes to the bloodstream during hepatocellular injury.[24] As such, increased serum AST and ALT levels indicate liver injury.[25] Liver injury has also been reported to correlate with elevated inflammatory markers and cytokine levels.[26]

This is in line with our study, in which group 1 showed an increase in serum AST and ALT levels compared to the control group, which is shown in Fig. 2. Group 2 and group 3 showed lower levels of serum AST and ALT compared to group 1, though the decrease was not significant, with $p > 0.05$ ($p = 0.064$; $p = 0.961$). As inflammation causes liver injury in sepsis, this suggests that the extract alleviates the injury directly by regulating inflammation and indirectly by reducing serum glucose levels.[27] This is supported by our histopathological findings, in which the liver tissues of the rat groups treated with *Coleus amboinicus* Lour. leaf extract showed a decrease in the number of inflammatory cells, as shown in Fig. 3. The mean of the liver histopathological scores was significantly decreased in group 2 and 3 compared to group 1, as shown in Fig. 4, with $p < 0.05$ ($p = 0.003$).

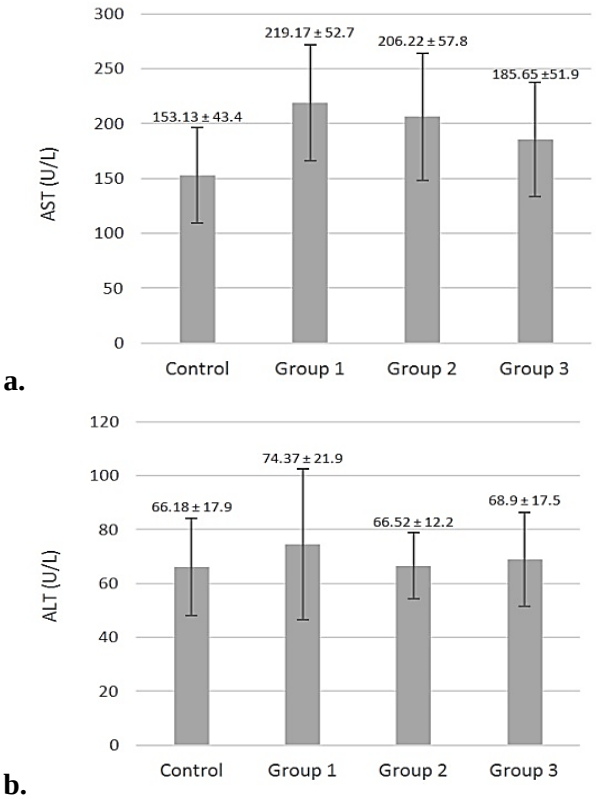

Figure 2. Serum (a) AST and (b) ALT levels of all rat groups

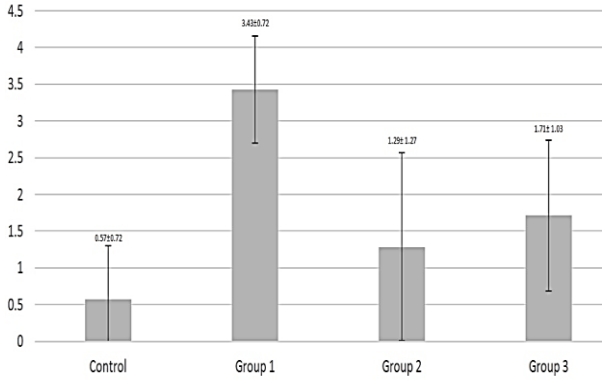

Figure 3. Liver histopathological scores of all rat groups

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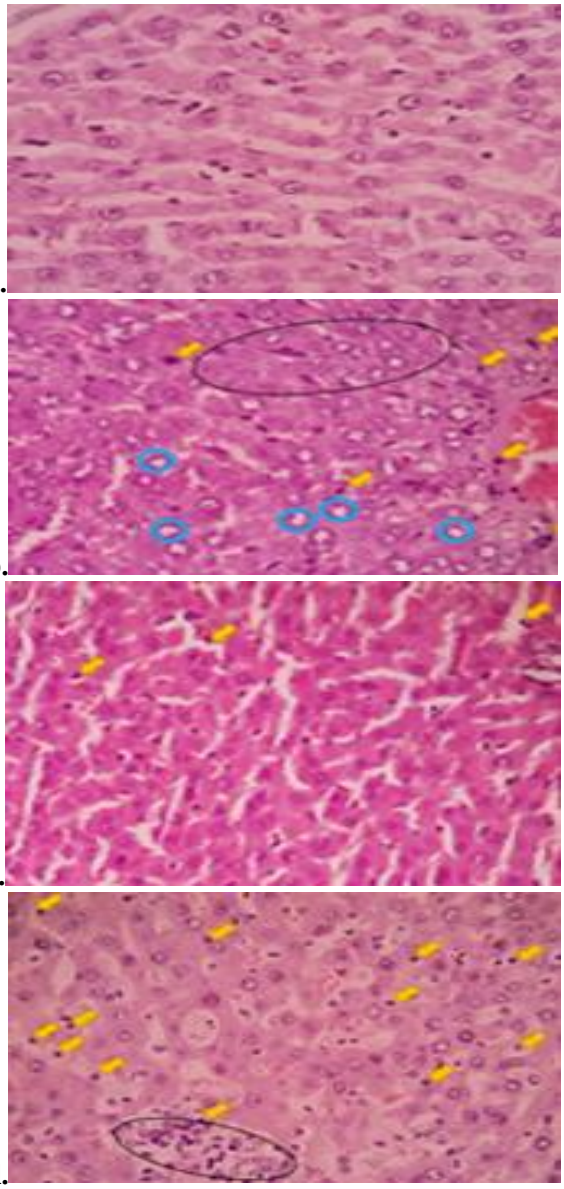

Figure 4. The liver histopathological examination of all rat groups (H&E-stained), (a) in control, (b) in group 1, (c) in group 2, and (d) in group 3. Yellow arrows indicate lymphocytic inflammatory cells. Blue circles indicate necrotic cells. Black circles indicate deformed cells and inflammatory cell clusters.

Lastly, we examined the urea and creatinine levels in the rats' serum to assess the effect of *Coleus amboinicus* Lour. leaf extract on kidney damage. Kidney injury occurs in sepsis due to the inflammatory response to infection, which leads to pyroptosis.[28] The inflammation also triggers an adaptive response of the tubular epithelial cells, which consists of cell function downregulation to decrease energy expenditure and ensure cell survival. However, this leads to reduced kidney function and increased serum urea and creatinine levels.[29, 30]

In line with this, we found an increase in serum urea and creatinine levels of group 1 compared to the control group. Meanwhile, the serum urea and creatinine levels of group 2 and 3 showed a decrease compared to group 1 as shown in Fig. 5, although not significant, with $p > 0.05$ ($p = 0.288$; $p = 0.119$). The attenuation of the inflammatory response by *Coleus amboinicus* Lour. leaf extract inhibits the adaptive response of the tubular epithelial cells, resulting in the preservation of kidney function and a decrease in the serum urea and creatinine levels of the rats.[31]

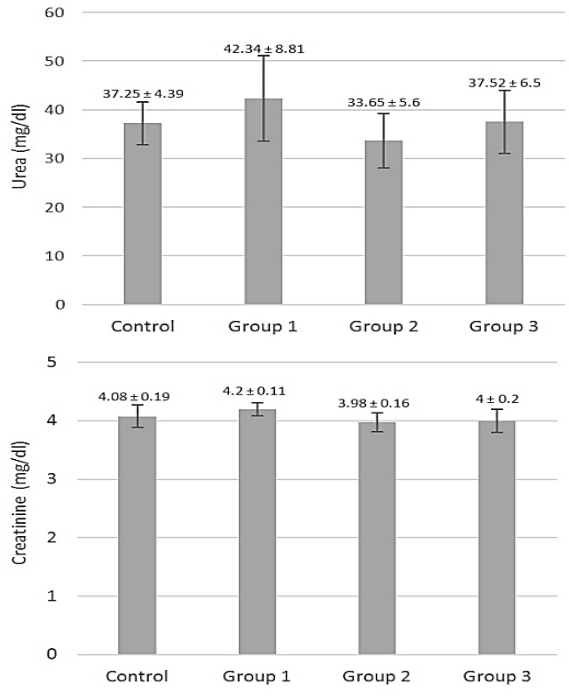

Figure 5. Serum (a) urea and (b) creatinine levels of all rat groups

Interestingly, the rat group given 250 mg/kg body weight of *Coleus amboinicus* Lour. leaf extract showed a more consistent improvement compared to the rat group given 500 mg/kg body weight of *Coleus amboinicus* Lour. leaf extract. This is similar to a past study that evaluated the antiinflammatory effect of *Coleus amboinicus* Lour. leaf extract in carrageenan-induced rat paw edema. The rat group given 250 mg/kg body weight of *Coleus amboinicus* Lour. leaf extract showed a higher percentage of reduction in the edema compared to the rat group given 350 mg/kg body weight of *Coleus amboinicus* Lour. leaf extract.[12] A possible mechanism is the excessive immunosuppression in higher doses, which leads to the release of damage-associated

molecular patterns (DAMPs) such as histones and neutrophil extracellular traps (NETs). These DAMPs impair microcirculation and cause coagulation, leading to disseminated intravascular coagulation (DIC) and further organ injury. The further organ injury will, in turn, release more DAMPs, resulting in a vicious cycle of immunosuppression via immune senescence and organ injury.[32, 33]

The limitation of this study is the short duration of observation. We designed the study with other inflammatory studies in mind, in which one week of observation is sufficient. Future studies with longer observation duration are recommended.

Conclusion

Coleus amboinicus Lour. leaf extract administration has no significant effect on the biochemical markers but improves the liver histopathology scores in septic rat model. However, we recommend a lower dose as it shows more consistency in the improvements. It is also worth noting that only the liver histopathological scores showed a significant reduction upon administration of the leaf extract, suggesting that histopathological improvements occur faster than biomarker improvements.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- The authors have signed an animal welfare statement.
- Ethical Clearance: The project was approved by the local ethical committee at Universitas Sumatera Utara.
- No human studies are present in the manuscript.
- No potentially identified images or data are present in the manuscript.

Authors' Contribution Statement

M.I.S. designed the study. R.L.K. and Y.S.P. performed the experiments and gathered the data. S.S. analyzed the data. M.I.S. wrote the paper with input from all authors. All authors have read and approved the final version of the manuscript.

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مستخلص أوراق كوليوس أمبوينيكوس لور ليس له أي تأثير على العلامات البيوكيميائية ولكنه يحسن النتائج التشريحية المرضية للكبد في نموذج الفئران الإنتانية

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[2] قسم الأحياء الدقيقة، كلية الطب، جامعة سومطرة أوتارا، ميدان، إندونيسيا.
[3] قسم الصيدلة والعلاج، كلية الطب، جامعة سومطرة أوتارا، ميدان، إندونيسيا.
[4] قسم التشريح، كلية الطب، جامعة سومطرة أوتارا، ميدان، إندونيسيا.

الخلاصة

كوليوس أمبوينيكوس لور. هو نبات عشبي له تأثيرات مناعية بسبب احتوائه على مادة البوليفينول. يهدف هذا البحث إلى تحديد تأثيرات مستخلص اوراق نبات Coleus amboinicus Lour على العلامات البيوكيميائية والنتائج النسيجية المرضية للكبد لنموذج الجرذ الإنتاني. استخدمنا في الدراسة 28 فأرًا من نوع Rattus norvegicus وقسمناها إلى 4 مجموعات تتكون كل منها من 7 فئران: مجموعة الضابطة (فئران سليمة دون علاج)، المجموعة 1 (فئران مصابة بالعدوى تعامل بالمضادات الحيوية)، المجموعة 2 (فئران مصابة بالعدوى تعامل بالمضادات الحيوية و250 ملجم). /كجم من وزن الجسم لمستخلص أوراق نبات Coleus amboinicus Lour والمجموعة الثالثة (الفئران المعالجة بالمضادات الحيوية و500 ملجم/كجم من وزن الجسم لمستخلص أوراق Coleus amboinicus Lour). قمنا بقياس مستوى الجلوكوز في الدم، AST، ALT، اليوريا، ومستويات الكرياتينين، بالإضافة إلى درجات التشريح المرضي للكبد، لتقييم التحسن. أظهرت النتائج انخفاضًا في مستويات الجلوكوز في الدم وAST وALT واليوريا والكرياتينين في مجموعات الفئران التي أعطيت Coleus amboinicus Lour.مستخلص أوراق مقارنة بمجموعة الفئران التي أعطيت المضادات الحيوية فقط، على الرغم من أن الانخفاض لم يكن كبيرا (ع = 0.393؛ ع = 0.064؛ ع = 0.961؛ ع = 0.288؛ ع = 0.119، على التوالي). ومع ذلك، كان هناك انخفاض كبير في درجات التشريح المرضي للكبد في مجموعات الفئران التي أعطيت كوليوس أمبوينيكوس لور. مستخلص الأوراق مقارنة بمجموعة الفئران التي أعطيت المضادات الحيوية فقط (ع = 0.003). في الختام، ليس لاستخدام مستخلص الأوراق أي تأثير معنوي على المؤشرات البيوكيميائية، ولكنه يحسن النتائج التشريحية المرضية للكبد في نموذج الفئران الإنتانية.

الكلمات المفتاحية: القوليوس أمبوينيكوس لور.، عشبي، التشريح المرضي، خلل الأعضاء، الإنتان.