Journal of Natural Sciences and Mathematics Research
J. Nat. Scien. & Math. Res. Vol. 11 No. 1 (2025) 23-28
ISSN: 2460-4453 (Online); 2614-6487 (Printed)
Available online at http://journal.walisongo.ac.id/index.php/jnsmr

Evaluation of *Paederia foetida* L. Extract on Liver Weight Alterations in an *Escherichia coli* Sepsis Mouse Model

Lisa Savitri[1]*, Elfred Rinaldo Kasimo[1], and Rochmad Krissanjaya[1]
[1] Medical Laboratory Technology Study Program (D.IV), Universitas Kadiri, Kediri, East Java, Indonesia.

* Corresponding author's e-mail: lisasavitri@unik-kediri.ac.id

ABSTRACT
Sepsis is a critical medical condition caused by a systemic immune response to infection and is often associated with severe organ dysfunction and high mortality. Bacterial sepsis, including cases triggered by *Escherichia coli*, can damage host tissues as the immune response becomes dysregulated. Infections involving *E. coli* in the digestive tract have become increasingly common. Among the affected organs, the liver plays a key role in metabolic regulation and host defense during sepsis. This study investigated the effect of *Paederia foetida* L. leaf extract on liver weight in a murine sepsis model. Introducing *E. coli* induces systemic infection and establishes the sepsis model, a commonly used approach in experimental studies to mimic the clinical features of sepsis. After acclimation, mice received treatments for 14 days across several groups: a normal control (N), a negative control (K–) given distilled water, a positive control (K+) given ciprofloxacin, and three treatment groups receiving *P. foetida* extract at 100 mg/kg BW (P1), 300 mg/kg BW (P2), and 500 mg/kg BW (P3). The analysis revealed significant differences among groups, with the highest mean liver weight recorded in P1 (1.3750 ± 0.3932). Liver abnormalities included enlargement, increased organ mass, swelling, and thickening of one liver lobe, which may reflect heightened hepatic workload during infection and toxin clearance. Interestingly, the normal group showed greater liver weight than several treatment groups, possibly due to fatty accumulation within hepatic tissue, which can influence overall organ mass.

Keywords:
Paederia foetida extract; liver weight; mice; sepsis; *Escherichia coli*

Introduction

Sepsis is a critical medical emergency, namely a widespread immune response to infection that can lead to severe organ dysfunction and death (Gyawali et al., 2019). Diarrheal diseases and lower respiratory tract infections were identified as major contributors to global sepsis cases and related deaths in 2017, with diarrheal diseases alone accounting for an estimated 9.2 to 15 million cases annually. Among the pathogens associated with sepsis, *Escherichia coli* plays a significant role and remains a common Gram-negative bacterium isolated from bloodstream infections (Lawn et al., 2017; Stoll et al., 2011; Mora-Rillo et al., 2015). Infections caused by *E. coli* have been increasing as a source of digestive tract disorders (Silaban, 2021), and many strains carry beta-lactamase genes that contribute to resistance against several antibiotic classes, including extended-spectrum cephalosporins and aztreonam (Paterson & Bonomo, 2005). The body's response to infection determines the severity of sepsis, where dysregulated immune activation can cause tissues and organ damage (Singer et al., 2016).

A key factor in the pathogenesis of Gram-negative bacterial sepsis is Lipopolysaccharide (LPS), a major component of the outer membrane. After release into the bloodstream, LPS binds circulating proteins and interacts with receptors on macrophages, lymphocytes, monocytes, and other cells of the reticuloendothelial system. This interaction triggers the release of cytokines and activates complement and coagulation pathways, contributing to clinical manifestations such as fever, leukopenia, hypoglycemia, hypotension, shock, intravascular coagulation, and organ failure

(Brooks et al., 2003). The process of bacterial translocation, in which microorganisms migrate from the gut to mesenteric lymph nodes and organs such as the liver and spleen, also contributes to the progression of sepsis (Alexander et al., 1990). Dysregulated apoptosis, especially the delayed death of neutrophils, intensifies inflammation and promotes Multiple Organ Dysfunction Syndrome (MODS).

The liver plays a central role in metabolic regulation and host defense during sepsis. It filters and eliminates bacteria, endotoxins, vasoactive substances, and inflammatory mediators, while producing cytokines, bioactive lipids, and acute-phase proteins. Hepatic dysfunction may appear early, often related to reduced organ perfusion, and can worsen as sepsis progresses, leading to both structural and functional impairments. These changes can contribute to further release of endotoxins and inflammatory molecules, perpetuating multi-organ damage (Sumantri, 2012).

Paederia foetida L., known as sembukan leaf in East Java, has been used in traditional medicine for centuries to treat digestive disorders including diarrhoea. The plant contains secondary metabolites, including alkaloids, saponins, tannins, and flavonoids, which provide antioxidant, antimicrobial, anticancer, anti-insect, antitumor, and immunomodulating effects (Savitri & Kasimo, 2022). Previous studies have shown that plant extracts rich in flavonoids can reduce inflammation, modulate immune responses, and protect organs during systemic infection. However, research specifically examining the effects of *P. foetida* on sepsis-related liver changes remains limited. The novelty of this study lies in evaluating whether *P. foetida* extract can influence liver weight in a murine sepsis model induced by *E. coli*, offering new insight into its potential protective role against hepatic alterations during sepsis.

Methods

Mice that had been adapted received treatment for 14 days with the following variations: 1) group 1 as normal control (N), namely mice that were not given gastric tube, 2) group 2 as negative control (K-), namely mice given distilled water with volume 0.5 mL, 3) group 3 as positive control (K+), i.e. mice were given ciprofloxacin at a dose of 500 mg/kgBW with a volume of 0.26 mL, 4) group 4 as treatment 1 (P1), i.e. mice were given 100 mg/kgBW *P. foetida* extract with a volume of 0.5 mL, 5) group 5 as treatment 2 (P2), namely mice were given 300 mg/kgBW *P. foetida* extract with a volume of 0.5 mL, 6) group 6 as a treatment 3 (P3), namely mice given 500 mg/kgBW *P. foetida* extract with a volume of 0.5 mL.

The treated mice were injected with *E. coli* into their peritoneum at a dose of $1x10^5$ CFU/mL. Exposure to septic polymicrobials triggers apoptotic events in the liver of mice within 24 hours, thus allowing the killing of the animals within that time. The death of mice within 24 hours requires immediate surgery to remove the liver to prevent autolysis.. The organ slices taken were in the middle, left and right edges.

After euthanasia, the liver is removed carefully and weighed using a balance, generating data in the form of liver weights. These liver weight data were subjected to statistical analysis using One-Way ANOVA at a 95% confidence level (α=0.05). If the ANOVA results showed statistical significance, further analysis was conducted using Tukey's HSD post hoc test at a confidence level of 95% (α=0.05). SPSS 23.0 software for Windows was used to perform statistical analysis.

Results and Discussions

The findings from the conducted research indicate that the treatment group with the highest mean value and standard deviation is P1, with a recorded value of 1.3750 ± 0.3932 g. On the other hand, the treatment group with the lowest mean value and standard deviation is K+, with a value of 1.1400 ± 0.1639. Table 1 and Picture present the mean values and standard deviations for all the treatment groups.

Table 1. The Mean and Standard Deviation of the Treatment Group

Groups	Number of Observations (n)	Mean±SD (g)
N	6	1.2067±0.1695
K-	6	1.3617±0.2049
K+	6	1.1400±0.1639
P1	6	1.3750±0.3932
P2	6	1.1967±0.2068
P3	6	1.1733±0.1687

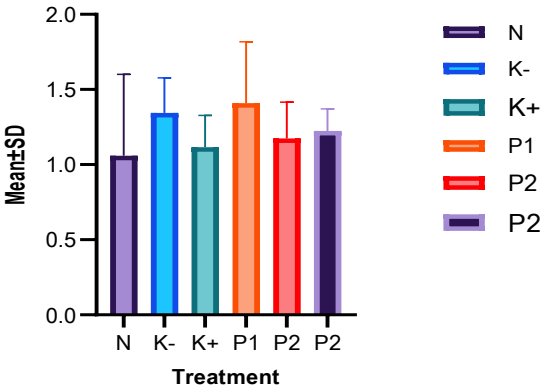

Figure 1. The Graph of Mean and Standard Deviation of the Treatment Group

The gathered data were subjected to statistical analysis using One-Way Single Analysis of Variance (One Way ANOVA) at a 95% confidence level (α = 0.05) (Figure 1). If the ANOVA calculation demonstrates statistical significance, the following analysis should use the Least Significant Difference (LSD) test at a 95% confidence level (α = 0.05). Table 2 shows the results of statistical analysis using SPSS 23.0 software for Windows.

Table 2. ANOVA One-Way

Source of Variation	Sum of Squares	Mean Square	Variance	F
Between Groups	1.6886	0.3377	0.0185	8.5350
Within Groups (Error)	0.9337	0.1556		
Total	2.6223			

The analysis using One Way ANOVA indicated a significant difference among the treatment groups, with an F-ratio value and p-value of 0.0005. The calculation of the standard deviation for each group shows the variability within it. Post hoc analysis using Tukey's HSD test identified several significant differences between the groups. Specifically, a significant difference was observed between group N and group P1 (p = 0.0369), indicating that the average liver value in group N differed significantly from that in group P1.

Furthermore, the analysis revealed significant differences between the K-group and the K+, K-P2, K-P3, and K+-K+ groups, with p-values of less than 0.05, which suggests significant variations in mean liver values among these groups. Similarly, the K+ group showed significant differences in mean liver values compared to the P2, P3, and K+-P2 groups, with p-values of less than 0.05. The analysis revealed no significant differences between the N group and the K- and K+ groups. Likewise, there were no significant differences between the K- group and the P1 and P2 groups, as well as between the K+ group and the P1 and P3 groups. In conclusion, there are significant differences in liver data 1-6 among the groups. Further analysis provides a more comprehensive understanding of these differences within each group.

The liver is one of the organs in the body that functions as a detoxification tool, making it highly susceptible to toxic substances. Previous research stated that red calliandra leaf extract

contains compounds that can damage liver cells, including alkaloids, saponins, and caffeic acid (Onyeama et al., 2012; Moharram et al., 2006). The presence of the same compounds in *P. foetida* leaf extract indicates a risk of liver cell damage.

A related study using neem (*Azadirachta indica*) leaf extract by Kupradinun et al. (2012) reported that neem may produce adverse effects, including structural damage to the liver and kidneys. Sitaswi et al. (2018) showed that the ethanol extract of neem leaves can increase liver weight, while Ghimeray et al. (2009) found that neem leaf extract at 200 g/kg body weight caused weight loss accompanied by weakness, anorexia, and histopathological abnormalities. In addition, Omotayo et al. (2012) demonstrated that the ethanol extract of neem bark increased the ratio of liver weight to body weight in rats. Although the phytochemical composition of neem differs from that of *Paederia foetida* L., neem is an appropriate reference because both plants contain diverse secondary metabolites that can modify hepatic function and morphology. Prior studies have shown that plant-derived bioactive compounds, particularly flavonoids, alkaloids, and saponins, can exert either hepatoprotective or hepatotoxic effects, depending on concentration, extraction method, and metabolic interaction within the liver (Subramoniam, 2016; Jaeschke et al., 2014). Research on neem, therefore provides a comparative framework for understanding the possible spectrum of liver responses to botanical extracts, helping contextualize whether the changes observed in liver weight following *P. foetida* extract administration fall within typical responses to phytochemical exposure or indicate a distinct biological effect.

The toxicology of alkaloids, saponins, and caffeic acid to organs remains a topic of debate, as several studies on these compounds have shown benefits to the body. However, other studies have shown that these three compounds can damage cells and tissues and even cause death in experimental animals. Pyrrolizidine alkaloids can cause liver enlargement (hepatomegaly) (Hanafi, 2023). According to Irfai (2013), an increase in the size and weight of the liver, accompanied by swelling and thickening in one of the liver lobules, is a sign of liver abnormalities. Additionally, the liver will work harder to prevent these toxic substances from damaging the body, and as a result, the liver's weight will increase. According to Anggraini (2008), if fat degeneration occurs in the liver, it will result in weight gain in the liver. In this study, the liver in the treatment group was heavier than that in control; additionally, fatty degeneration also occurred. Fatty substances in liver tissue can lead to weight gain and impact the overall weight of the liver.

Conclusion

The study's results revealed significant differences between the treatment groups. A more in-depth analysis of each group provides further explanation on this matter. The highest mean and standard deviation values were 100 mg/kg BW with a volume of 0.5 mL for 14 days, namely 1.3750 ± 0.3932. An increase liver size and weight indicates liver abnormalities, accompanied by swelling and thickening of one of the liver lobules. In addition, the liver will work harder to prevent these toxic substances from damaging the body, resulting inl increased weight of the liver. Additionally, liver fat degeneration can lead to an increase in liver weight. In this study, the liver in the normal group was heavier than in the treatment group. The increase in weight that occurs is caused by fatty substances found in the tissues, which can affect the total weight of the liver.

Acknowledgments

Acknowledgements to the Academic Directorate of Vocational Higher Education, Directorate General of Vocational Education, Ministry of Education, Culture, Research and Technology for providing funding for this research.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

Anggraini, D. R. (2008). *Gambaran makroskopis dan mikroskopis hati dan ginjal mencit akibat pemberian plumbum asetat* (Tesis sarjana kedokteran). Universitas Sumatra Utara.

Brooks, G. F., Butel, J., & Morse, A. S. (2003). *Medical microbiology* (22nd ed.). McGraw-Hill.

Ghimeray, A. K., Jin, C. W., Ghimire, B. K., & Cho, D. H. (2009). Antioxidant activity and quantitative estimation of azadirachtin and nimbin in *Azadirachta indica* A. Juss grown in foothills of Nepal. *African Journal of Biotechnology, 8*(13).

Guntur, A. H. (2006). *SIRS & sepsis: Imunologi, diagnosis, penatalaksanaan*. Sebelas Maret University Press.

Gu, M. J., Ahn, Y., Lee, Y. R., Yoo, G., Kim, Y., Choi, I., Ha, S. K., & Kim, D. (2024). *Coriandrum sativum* L. leaf extract ameliorates metabolic dysfunction-associated steatotic liver disease by modulating the AMPK pathway in high-fat-fed C57BL/6 mice. *Nutrients, 16*(23), 4165. https://doi.org/10.3390/nu16234165

Gyawali, B., Ramakrishna, K., & Dhamoon, A. S. (2019). Sepsis: The evolution in definition, pathophysiology, and management. *SAGE Open Medicine, 7*, 2050312119835043. https://doi.org/10.1177/2050312119835043

Hanafi, M. (2023). *Alkaloid sebagai obat modern dan dalam tanaman obat*. Diakses dari http://mhanafi123.wordpress.com/2012/09/18/alkaloid-sebagai-obatmoderen-dan dalam-tanamanobat

He, X., Hao, P., Wang, Y., Wu, C., Yin, W., Shahid, M. A., Wu, R., Zhou, J., Chen, J., Ai, J., & Ju, J. (2023). *Swertia bimaculata* moderates liver damage in mice by regulating intestinal microbiota. *Ecotoxicology and Environmental Safety, 263*, 115223. https://doi.org/10.1016/j.ecoenv.2023.115223

Irfai, I. (2013). *Efektifitas pemberian kenikir (Cosmos caudatus Kunth.) terhadap bobot karkas, organ pencernaan, hati, dan kolesterol daging ayam kampung* (Skripsi). Institut Pertanian Bogor.

Jaeschke, H., McGill, M. R., & Ramachandran, A. (2012). Oxidant stress, mitochondria, and cell death mechanisms in drug-induced liver injury: Lessons learned from acetaminophen hepatotoxicity. *Drug Metabolism Reviews, 44*(1), 88–106. https://doi.org/10.3109/03602532.2011.602688

Kupradinun, P., Tepsuwan, A., Tanthasri, N., Meesiripan, N., Tunsakul, S., Tompat, W., Jarratwisarutporn, Y., & Kusamran, W. R. (2013). Toxicity testing of flowers of neem tree (*Azadirachta indica* A. Juss). *Thai Journal of Veterinary Medicine, 40*(1), 47–55. https://doi.org/10.56808/2985-1130.2206

Lawn, J. E., Bianchi-Jassir, F., Russell, N. J., Kohli-Lynch, M., Tann, C. J., Hall, J., et al. (2017). Group B streptococcal disease worldwide for pregnant women, stillbirths, and children. *Clinical Infectious Diseases, 65*(Suppl 2), S89–S99.

Moharram, F. A., Marzouk, M. S. A., Ibrahim, M. T., & Marby, T. J. (2006). Antioxidant galloylated flavanol glycosides from *Calliandra haematocephala*. *Natural Product Research, 20*, 927 934.

Mohamed, A. M., Azeem, N. H. A., Ashour, A. A., & Ragab, E. A. (2021). Neem leaf (*Azadirachta indica* A. Juss) ethanolic extract affects liver and kidney function in rats. *International Journal of Environmental Research and Public Health, 18*(8), 4325. https://doi.org/10.3390/ijerph18084325

Mora-Rillo, M., Fernández-Romero, N., Navarro-San Francisco, C., Díez-Sebastián, J., Romero Gómez, M. P., Fernández, F. A., et al. (2015). Impact of virulence genes on sepsis severity and survival in *Escherichia coli* bacteremia. *Virulence, 6*(1), 93–100.

Naowaboot, J., Nanna, U., Chularojmontri, L., Songtavisin, T., Tingpej, P., Sattaponpan, C., Jansom, C., & Wattanapitayakul, S. K. (2021). *Mentha cordifolia* leaf extract improves hepatic glucose and lipid metabolism in obese mice fed a high-fat diet. *Preventive Nutrition and Food Science, 26*(2), 157–165. https://doi.org/10.3746/pnf.2021.26.2.157

Omotayo, A., Ashafa, T., Orekayo, L. O., & Yakubu, M. T. (2012). Toxicity profile of ethanolic extract of *Azadirachta indica* stem bark in male Wistar rats. *Asian Pacific Journal of Tropical Biomedicine, 2*(10), 810–817.

Onyeama, H. P., Ibekwe, H. A., Ofemile, P. Y., Peter, A., Ahmed, M. S., & Nwagbo, P. O. (2012). Screening and acute toxicity studies of *Calliandra portoricensis* used in the treatment of snake bite in Southeastern Nigeria. *Vom Journal of Veterinary Science, 9*, 17–24.

Paterson, D. L., & Bonomo, R. A. (2005). Extended-spectrum β-lactamases. *Clinical Microbiology Reviews, 18*, 657–686.

Poo, C. L., Lau, M. S., Nasir, N. L. M., Nik Zainuddin, N. A. S., Rahman, M. R. A. A., Mustapha Kamal, S. K., Awang, N., & Muhammad, H. (2024). Hepatoprotective mechanisms of herbal preparations through gut microbiota modulation: A scoping review. *Current Issues in Molecular Biology, 46*, 11460–11502. https://doi.org/10.3390/cimb46100682

Savitri, L., & Kasimo, E. R. (2022). Efek preventif ekstrak daun kentut (*Paederia foetida* L.) terhadap kadar interleukin-6 pada mencit model sepsis yang diinduksi *Escherichia coli*. *Indonesian Journal of Natural Science Education, 5*(2), 38–43. https://doi.org/10.31002/nse.v5i2.2778

Silaban, H. (2021). The effect of ethanol extract of *Paederia foetida* L. leaves on the growth of *Escherichia coli*. *Journal of Drug Delivery and Therapeutics, 11*(6), 61–67.

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., et al. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA, 315*(8), 801–810.

Sitasiwi, A. J., & Mardiati, S. M. (2018). Effect of ethanolic neem (*Azadirachta indica*) leaf extract as an herbal contraceptive on hepato-somatic index of male mice (Unpublished report). Universitas Diponegoro.

Stoll, B. J., Hansen, N. I., Sanchez, P. J., Faix, R. G., Poindexter, B. B., Van Meurs, K. P., et al. (2011). Early-onset neonatal sepsis: Group B streptococcal and *E. coli* disease burden. *Pediatrics, 127*(5), 817–826.

Sumantri, Sunarsih, E. S., Hakim, L., & Sugiyanto. (2012). Protective effect of *Brassica oleracea* var. *Botrytis* L. against theophylline-induced hepatocellular abnormalities in rats. *Univera Medicina, 31*(1), 12–19.