BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 14, Number 1, April 2025 | Pages: 363-368 | DOI: 10.14421/biomedich.2025.141.363-368 ISSN 2540-9328 (online)

Protective Role of *Paederia foetida* L. Against Hepatic Inflammatory Response in a Mice Model of *Escherichia coli*-Induced Sepsis

Lisa Savitri[1,3,4,*], Maria Do Carmo Da Costa Freitas[1], Fendy Prasetyawan[2], Yuneka Saristiana[2], Konradus Klala Mebung[1], Cornelia Amanda[1]

[1]Department of Medical Laboratory Technology, Faculty of Health Sciences, Kadiri University, Jalan Selomangleng No. 1, Kediri, East Java, Indonesia
[2]Department of Pharmacist Professional Education, Faculty of Health Sciences, Kadiri University, Jalan Selomangleng No. 1, Kediri, East Java, Indonesia
[3]Department of Biology, Faculty of Science and Technology, Universitas Airlangga, Surabaya, Indonesia
[4]Bioinformatics Research Center, Indonesian Institute of Bioinformatics, Malang, Indonesia.

Corresponding author*
lisasavitri@unik-kediri.ac.id

Manuscript received: 01 May, 2025. Revision accepted: 27 June, 2025. Published: 04 July, 2025.

Abstract

Sepsis is a severe medical condition characterized by a systemic immune response to infection, often leading to multi-organ failure and death if not treated effectively. This study aimed to investigate the antiseptic properties of *Paederia foetida* leaf extract in male mice induced with sepsis using *Escherichia coli*. A total of 24 mice were divided into six groups: a normal group (no treatment), a negative control group (distilled water), a positive control group (ciprofloxacin), and three treatment groups receiving *P. foetida* leaf extract at doses of 100, 300, and 500 mg/kg BW. After 15 days of oral administration, liver tissue samples were analyzed for IL-6 expression, a pro-inflammatory cytokine associated with sepsis. The results revealed a significant reduction in IL-6 expression in the treatment groups, particularly at the 500 mg/kg BW dose. This dose showed the most effective anti-inflammatory response, with IL-6 expression levels comparable to those of the positive control group treated with ciprofloxacin. However, the 100 mg/kg BW dose demonstrated minimal effects, similar to the negative control. These findings suggest that *P. foetida* leaf extract, especially at higher doses, has potential as an anti-inflammatory agent in sepsis management. The bioactive compounds in the extract, including flavonoids, alkaloids, and terpenoids, likely contribute to its efficacy. This study provides preliminary evidence supporting the use of *P. foetida* as a potential herbal alternative for managing sepsis, but further clinical research is necessary to confirm its therapeutic potential.

Keywords: sepsis; *Paederia foetida*; IL-6; anti-inflammatory; *Escherichia coli*.

Abbreviations: Interleukin-6 (IL-6), Body Weight (BW), Randomized Complete Design (RCD), Systemic Inflammatory Response Syndrome (SIRS), Disseminated Intravascular Coagulation (DIC), World Health Organization (WHO), Analysis of Variance (ANOVA), Least Significant Difference (LSD), Immunohistochemistry (IHC), Nuclear Factor kappa B (NF-κB), Mitogen-Activated Protein Kinase (MAPK), Cyclooxygenase (COX), Lipoxygenase (LOX), Phospholipase A2 (PLA2), Superoxide Dismutase (SOD)

INTRODUCTION

Sepsis is a critical medical condition characterized by a systemic immune response to infection, which may progress to multi-organ failure and fatality (Turnip et al., 2022). It reflects the body's overwhelming reaction to an infectious agent and can escalate into severe sepsis or septic shock. Severe sepsis entails organ dysfunction, driven by systemic inflammation and a procoagulant response, while septic shock involves persistent hypotension despite adequate fluid therapy (Singer et al., 2016).

Complications of sepsis include systemic inflammatory response syndrome (SIRS), which involves cytokine release such as interleukin-6 (IL-6), as well as disseminated intravascular coagulation (DIC), septic shock, and multiple organ dysfunction including liver failure (Ministry of Health, 2017). In 2017, the WHO reported 48.9 million global sepsis cases with 11 million deaths—accounting for nearly 20% of global mortality. Approximately 20 million cases and 2.9 million deaths occurred in children under five. Most sepsis-related deaths (85%) occurred in low- and middle-income countries (WHO, 2020). In Indonesia, sepsis incidence remains high (30.29%) with mortality ranging from 11.56% to 49%. At Abdul Wahab Sjahranie Hospital, there were 312 sepsis cases from 2018 to 2020, 69 of which were pediatric. Sepsis ranked among the top ten causes of death in the hospital (Verdure et al., 2021).

The sepsis pathophysiology involves complex inflammatory and anti-inflammatory responses, humoral and cellular reactions, and vascular dysfunction (Kaukonen et al., 2015). Genetic polymorphisms in IL-6 have been associated with varying susceptibility to

sepsis, septic shock, and mortality (Tischendorf et al., 2007). Gram-negative bacteria, particularly *Escherichia coli*, are the predominant pathogens (60–70%), while Gram-positive bacteria account for 20–40%. Fungi, viruses, and protozoa are less common causes (Ministry of Health, 2017).

Severe sepsis can result from local infections, not necessarily requiring bacteremia, due to systemic effects of bacterial toxins. Blood cultures are positive in only 20–40% of severe cases, increasing to 40–70% in septic shock. Gram-negative and Gram-positive bacteria constitute most isolates, with the remainder comprising fungi and mixed infections (Clarias et al., 2018).

Effective antimicrobial therapy depends on the rapid identification of the causative agent. Empirical broad-spectrum antibiotics should be initiated immediately, followed by de-escalation based on culture results and clinical response. Recommended options include anti-pseudomonal quinolones (e.g., ciprofloxacin, levofloxacin) and aminoglycosides. Even bacteriostatic antibiotics may be appropriate depending on the infection type (Ministry of Health, 2017).

Due to the adverse effects of conventional antibiotics, many people turn to herbal remedies, which remain popular in rural areas due to accessibility and affordability. *P. foetida* L., commonly known as "daun kentut," is traditionally used for anti-inflammatory properties (Silaban, 2021). Other plant-based options include mangosteen rind (*Garcinia mangostana*), known for xanthones that exhibit antibacterial and anti-inflammatory activity (Syahruna et al., 2020; Dewi et al., 2014).

P. foetida leaves contain a variety of bioactive compounds, including alkaloids (α-, β-paederine), flavanols, friedelin, β-sitosterol, campesterol, triterpenoid saponins, gallotannins, and essential oils (Salamah & Halim, 2021). The anti-inflammatory effect, particularly in sepsis models, is believed to stem from saponins, flavonoids, and volatile oils. Saponins may interact with lipid membranes, affecting prostaglandin production and inflammatory pathways (Savitri & Kasimo, 2022). These secondary metabolites also exhibit pharmacological functions such as antioxidant, antimicrobial, anticancer, insecticidal, antitumor, and immunomodulatory activities (Das et al., 2018).

MATERIALS AND METHODS

This experimental study utilized a Randomized Complete Design (RCD) to assess the antiseptic activity of *P. foetida* leaf extract on male white mice (*Mus musculus*). A total of 24 male Balb/c strain mice, aged 3–4 weeks and weighing 30–40 g, were randomly assigned to six groups (n = 4 per group). Group I (Normal) received no treatment, Group II (Negative Control) was treated with distilled water (aquades), and Group III (Positive Control) received ciprofloxacin (500 mg/kg BW). Groups IV–VI received *P. foetida* leaf extract at 100, 300, and 500 mg/kg BW, respectively. All mice in Groups II–VI were intraperitoneally injected with *E. coli*, while Group I received no bacterial injection.

The study was conducted in two different locations. The treatment of mice took place in the Pharmacy Laboratory of Universitas Kadiri, while histological analysis was performed in the Anatomical Pathology Laboratory of Universitas Brawijaya, Malang. Male Balb/c mice were selected as the experimental subjects due to their reproductive characteristics, ease of handling, and similarities to humans in anatomy, physiology, and genetics (Mutiarahmi et al., 2021). The sample size was calculated using Federer's formula, which determined a minimum of 4 subjects per group. The sampling method followed a Randomized Complete Design (RCD), ensuring that all mice had an equal chance of being assigned to any group.

Inclusion criteria for the study were as follows: male mice, aged approximately 1 month, with a body weight of 18–40 g, and in good health during the study period. Mice with poor appetite, declining health, or signs of illness during acclimatization were excluded from the study. The independent variable in this study was the dose of *P. foetida* leaf extract, while the dependent variable was the IL-6 expression in liver tissue. The study controlled for various factors, including the inclusion criteria, housing conditions, and the method of extract administration (oral gavage).

The *P. foetida* leaf extract used in this study was obtained through maceration. For histological analysis, liver tissue was stained using an immunohistochemistry (IHC) kit, with IL-6 expression indicated by brown staining in the tissue sections. Mice were induced with sepsis by intraperitoneal injection of *E. coli*. After 15 days of oral administration of the extract, the mice were euthanized by cervical dislocation, and liver tissue was collected and fixed in 10% formalin for further examination.

Data analysis was performed using One-Way ANOVA, following tests for normality (Shapiro-Wilk) and homogeneity (Levene's Test). If the data met normality and homogeneity assumptions ($p > 0.05$), Post Hoc LSD or Duncan tests were used to analyze group differences. If data were not normally distributed, the Kruskal-Wallis test was used, followed by Mann-Whitney U tests for pairwise comparisons when significant differences were observed.

RESULTS AND DISCUSSION

In this study, the average IL-6 expression values in the liver of mice for each group were as follows: the normal group had 7.09% ± 0.06; the positive control group had 26.36% ± 0.02; the negative control group had 72.60% ± 0.05; treatment group I (100 mg/kg BW) had 71.04% ± 0.04; treatment group II (300 mg/kg BW) had 62.22% ±

0.02; and treatment group III (500 mg/kg BW) had 40.92% ± 0.01. Statistical analysis using One-Way ANOVA revealed a significance value of 0.000 (p-value < 0.005), indicating a significant difference between the groups. According to the Duncan test table, the optimal dose order was as follows: (1) normal group; (2) positive control group; (3) treatment group III (500 mg/kg BW); (4) treatment group II (300 mg/kg BW); (5) treatment group I (100 mg/kg BW); and (6) negative control group.

The normal group **(Fig. 1)** had the lowest average IL-6 expression compared to the other groups, at 7.09% ± 0.06. This result is attributed to the fact that the normal group was not injected with *E. coli*, and thus did not experience sepsis. Groups II through VI were injected with *E. coli*, causing sepsis in these mice. Group II **(Fig. 2)** was the most effective in treating sepsis compared to the other five groups, as it was the positive control group treated with ciprofloxacin. Ciprofloxacin, an antibiotic in the fluoroquinolone class, treats gram-negative bacterial infections, including *E. coli* (Thai et al., 2023). In sepsis, ciprofloxacin works by inhibiting the enzymes DNA gyrase and topoisomerase IV, which are essential for bacterial DNA replication. Inhibition of these enzymes prevents bacterial replication, halting the spread of infection (Roberts et al., 2019). Ciprofloxacin also inhibits protein synthesis in bacterial cells by blocking ribosomal activity, which is crucial for protein production, further aiding in stopping bacterial infections (Demirtas et al., 2012).

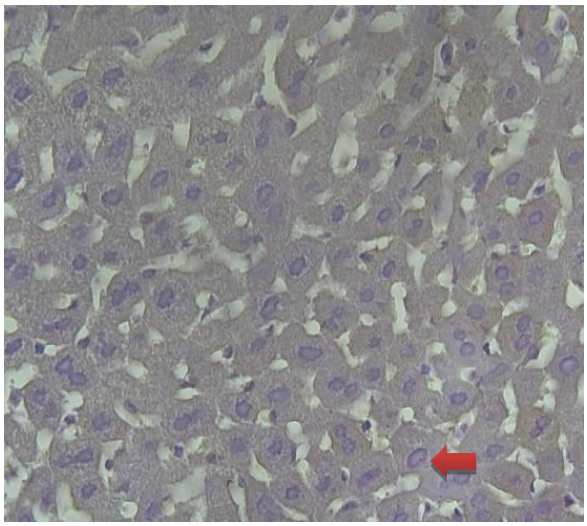

Figure 1. Non-Expressed Hepatocytes in The Liver of Mice At 40× Magnification (Cell Cytoplasm Appears Purple as Indicated by The Arrow) in The Normal Group.

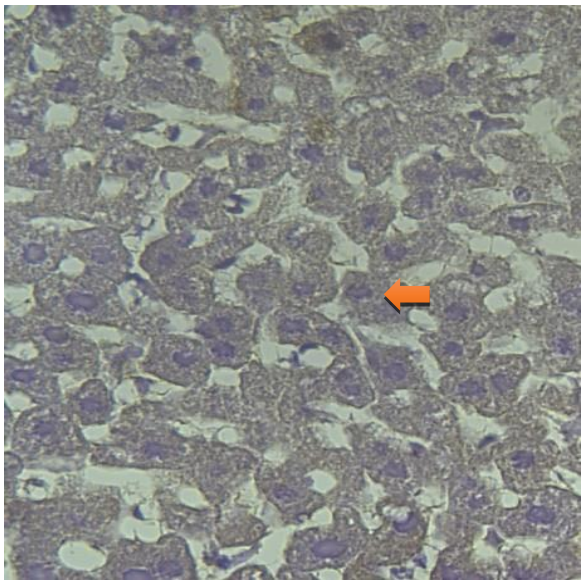

Figure **2.** IL-6 Expression in Hepatocytes of Mice Liver Injected with *E. coli* at 40× Magnification (Cell Cytoplasm Appears Brown as Indicated by The Arrow) in The Positive Control Group.

In the treatment groups receiving *P. foetida* leaf extract, including group I (100 mg/kg BW) **(Fig. 3)**, group II (300 mg/kg BW) **(Fig. 4)**, and group III (500 mg/kg BW) **(Fig. 5)**, the most effective dose for preventing IL-6 expression in the liver of sepsis mice was found to be 500 mg/kg BW. The statistical analysis, using ANOVA with a 95% confidence level, showed significant differences in the doses of *P. foetida* leaf extract for preventing IL-6 expression. Post hoc LSD and Duncan tests indicated that the negative control group and group I (100 mg/kg BW) exhibited similar antiseptic effects. This result suggests that the 100 mg/kg BW dose was less effective as an antiseptic because it showed the same effect as the negative control group. It is suspected that the low dose of 100 mg/kg BW was insufficient to manage inflammation in the *E. coli*-induced sepsis model.

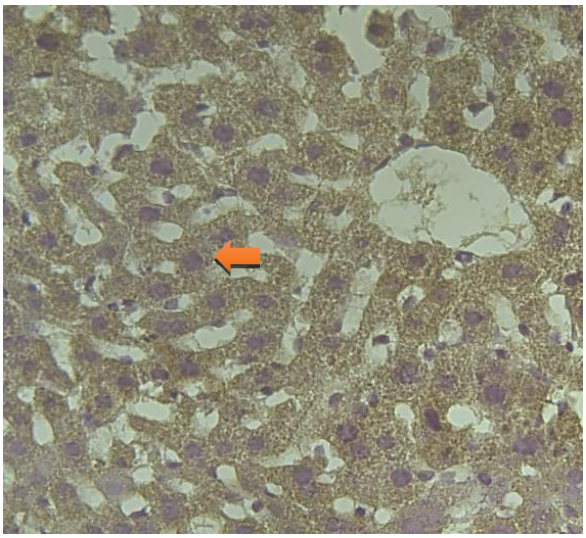

Figure 3. IL-6 Expression in Hepatocytes of Mice Liver Injected with *E. coli* at 40× Magnification (Cell Cytoplasm Appears Brown as Indicated by The Arrow) in Treatment Group I (100 mg/kg BW).

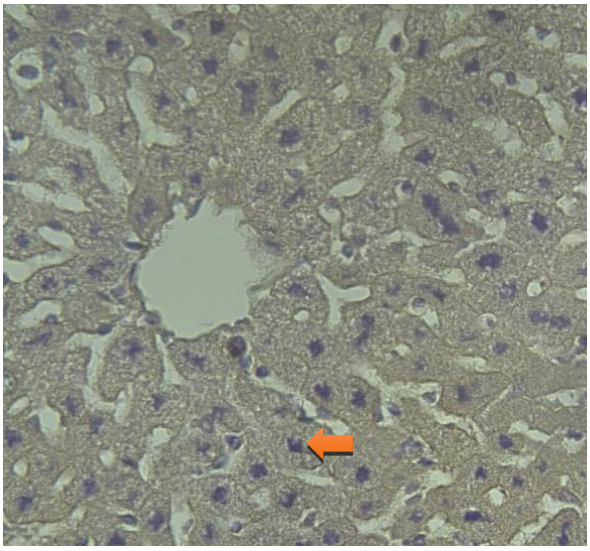

Figure 4. IL-6 Expression in Hepatocytes of Mice Liver Injected with *E. coli* at 40× Magnification (Cell Cytoplasm Appears Brown as Indicated by The Arrow) in Treatment Group II (300 mg/kg BW).

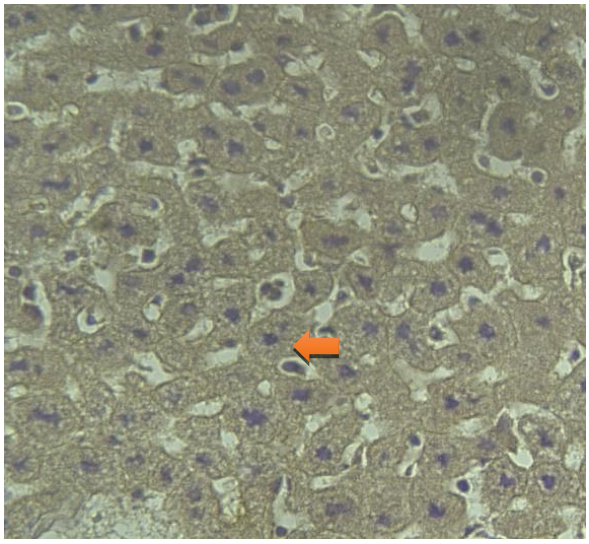

Figure 5. IL-6 Expression in Hepatocytes of Mice Liver Injected with *E. coli* at 40× Magnification (Cell Cytoplasm Appears Brown as Indicated by The Arrow) in Treatment Group III (500 mg/kg BW).

P. foetida leaves are known for their anti-inflammatory properties. The anti-inflammatory mechanism in sepsis in this study is likely due to various secondary metabolite compounds found in the leaves, including flavonoids, alkaloids, phenolic acids, and terpenoids (Rosanti, 2016). These compounds are thought to help prevent IL-6 expression, a pro-inflammatory cytokine involved in inflammation. During inflammation, caused by infection, injury, or chronic disease, immune cells release IL-6 into the surrounding environment. IL-6 then interacts with its receptors on various cell types, including immune cells, endothelial cells, and other tissues (Tanaka et al., 2014).

Flavonoids in *P. foetida* leaves are believed to possess anti-inflammatory properties that inhibit the release of pro-inflammatory cytokines like IL-6. Flavonoids can block the NF-κB signaling pathway, a major pathway regulating pro-inflammatory cytokine release. By inhibiting NF-κB activation, flavonoids prevent the migration of proteins involved in cytokine gene transcription, including IL-6 (Ginwala et al., 2019). Furthermore, flavonoids can block MAPK signaling pathways such as ERK, JNK, and p38, which are involved in pro-inflammatory cytokine gene expression. By inhibiting MAPK activation, flavonoids can reduce IL-6 production. Additionally, flavonoids can inhibit cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, which are involved in the production of inflammatory mediators like prostaglandins and leukotrienes, both of which stimulate IL-6 production (Maleki et al., 2019).

Apart from flavonoids, phenolic acids in *P. foetida* leaves have strong antioxidant properties that can help protect cells from oxidative damage and oxidative stress associated with inflammation. Phenolic acids neutralize free radicals involved in oxidative stress by donating electrons or hydrogen atoms, thereby preventing cellular damage. Additionally, phenolic acids stimulate the production of endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase, which eliminate free radicals and prevent oxidative damage (Maleki et al., 2019). Phenolic acids can also inhibit the activation of transcription factors like NF-κB and AP-1, which regulate pro-inflammatory cytokine gene expression, thereby reducing pro-inflammatory cytokine production and alleviating inflammation (Lopez et al., 2022).

Alkaloids present in *P. foetida* leaves also inhibit inflammatory mediator production by blocking the release of arachidonic acid, which is essential for synthesizing prostaglandins and leukotrienes. Alkaloids achieve this by inhibiting the enzyme phospholipase A2 (PLA2), which releases arachidonic acid from cell membrane phospholipids (Lopez et al., 2022). Alkaloids can also inhibit cellular receptor expression and transcription factors activating pro-inflammatory immune cells, such as macrophages and T-cells. By inhibiting these processes, alkaloids reduce the production of pro-inflammatory cytokines like IL-6.

Terpenoids in *P. foetida* leaves can also influence inflammatory responses by inhibiting proteolytic enzymes like elastase and collagenase, which are involved in extracellular matrix degradation and tissue damage during inflammation. Terpenoids may interact directly with proteolytic enzymes, inhibiting their catalytic activity and potentially increasing the expression of protease inhibitors, thus preventing tissue damage (Gallily et al., 2018).

The findings of this study are consistent with previous research by Savitri and Kasimo (2022), which also demonstrated that the dose of 500 mg/kg BW of *P. foetida* leaf extract was the most effective in reducing IL-6 levels. However, there were differences between this study and theirs, particularly with the 100 mg/kg BW and

300 mg/kg BW doses. In their study, significant differences in IL-6 reduction were observed between these doses, while in this study, no significant difference was found between the 100 mg/kg BW and 300 mg/kg BW doses.

The anti-inflammatory effects in sepsis are believed to be attributed to compounds such as saponins, flavonoids, and essential oils in *P. foetida* leaves. These compounds may inhibit the synthesis of inflammatory mediators like prostaglandins and leukotrienes, which trigger IL-6 production and contribute to the inflammatory response. Further clinical studies are needed to confirm these effects and develop *P. foetida* as a phytopharmaceutical alternative therapy in preventing IL-6 expression in sepsis.

CONCLUSIONS

In conclusion, sepsis is a life-threatening condition characterized by a systemic immune response to infection, which can lead to multi-organ failure and death if not appropriately managed. The study demonstrated that *P. foetida* leaf extract, particularly at a dose of 500 mg/kg BW, shows significant anti-inflammatory effects in sepsis, as evidenced by the reduction in IL-6 expression in the liver tissue of mice. This suggests that the leaf extract may be a potential therapeutic agent for managing inflammation associated with sepsis. While the lowest dose (100 mg/kg BW) showed minimal effectiveness, the higher doses (300 mg/kg and 500 mg/kg BW) exhibited a marked reduction in IL-6 levels, indicating a dose-dependent response. The anti-inflammatory properties of the extract are likely due to its bioactive compounds, including flavonoids, alkaloids, and terpenoids, which work by modulating inflammatory pathways such as NF-κB and MAPK. Although the results of this study are promising, further clinical research is required to confirm the potential of Paederia foetida as a phytopharmaceutical alternative for sepsis management, especially in areas with limited access to conventional antibiotics.

Acknowledgements: Thank you to the Laboratory of Medical Laboratory Technology, Kadiri University, and the Laboratory of Pathological Anatomy, Brawijaya University, Malang, for their support during the completion of this research.

Authors' Contributions: Lisa Savitri designed the study, analyzed the data, and wrote the manuscript. All authors wrote the manuscript and approved the final version of the manuscript.

Competing Interests: The authors declare that there are no competing interests.

Funding: The authors declare that there are no funding.

REFERENCES

Allung, C. M. (2019). Identifikasi Bakteri Escherichia Coli Penghasil Extended Spectrum Beta – Lactamase (ESBL) di Ruang Nicu Rumah Sakit Umum Naibonat Tahun 2019. *Karya Tulis Ilmiah*, 1–48.

Azmi, F. (2016). Anatomi dan Histolofi Hepar. JURNAL KEDOKTERAN, 1(2), 147–154.

Clarias, L., Pada, E., & Tnf-, D. A. N. E. (2018). Hewan Model Mus Musculus Yang Diinfeksi Escherichia coli Dilihat Dari Histopatologi Skripsi Sebagai Salah Satu Syarat Memperoleh Gelar Sarjana Kedokteran Hewan.

Das, K., Dang, R., Sivaraman, G., & Ellath, R. P. (2018). Phytochemical Screening for Various Secondary Metabolites, Antioxidant, and Anthelmintic Activity of Coscinium fenestratum Fruit Pulp: A New Biosource for Novel Drug Discovery. *Turkish Journal of Pharmaceutical Sciences*, 15(2), 156. https://doi.org/10.4274/TJPS.54376

Demirtas, A., Yildirim, Y. E., Sofikerim, M., Kaya, E. G., Akinsal, E. C., Tombul, S. T., Ekmekcioglu, O., & Gulmez, I. (2012). Comparison of infection and urosepsis rates of ciprofloxacin and ceftriaxone prophylaxis before percutaneous nephrolithotomy: a prospective and randomised study. *The Scientific World Journal*, 20(12), 1–6. https://doi.org/10.1100/2012/916381

Dewi, I. D. A. D., Astuti, K., & Warditiani, N. (2014). Identifikasi Kandungan Kimia Ekstrak Kulit Buah Manggis (Garcinia mangostana L.). *Jurnal Farmasi Udayana*, 2(4), 13–18.

Gallily, R., Yekhtin, Z., & Hanuš, L. O. (2018). The Anti-Inflammatory Properties of Terpenoids from Cannabis. *Cannabis and Cannabinoid Research*, 3(1), 292. https://doi.org/10.1089/CAN.2018.0014

Ghozali, I. (2009). Aplikasi Analisis Multivariate Dengan Program SPSS (4th ed.). Universitas Diponegoro.

Ginwala, R., Bhavsar, R., Chigbu, D. G. I., Jain, P., & Khan, Z. K. (2019). Potential Role of Flavonoids in Treating Chronic Inflammatory Diseases with a Special Focus on the Anti-Inflammatory Activity of Apigenin. *Antioxidants*, 8(2), 1–28. https://doi.org/10.3390/ANTIOX8020035

Irvan, I., Febyan, F., & Suparto, S. (2018). Sepsis dan Tata Laksana Berdasar Guideline Terbaru. *JAI (Jurnal Anestesiologi Indonesia)*, 10(1), 62–73. https://doi.org/10.14710/JAI.V10I1.20715

Kaukonen, K.-M., Bailey, M., Pilcher, D., Cooper, D. J., & Bellomo, R. (2015). Systemic inflammatory response syndrome criteria in defining severe sepsis. *The New England Journal of Medicine*, 372(17), 1629–1638. https://doi.org/10.1056/NEJMOA1415236

Kemenkes. (2017). Pedoman Nasional Pelayanan Kedokteran Tata Laksana Sepsis. 342, 1–14.

Kuswoyo, N. H., & Natadidjaja, R. I. (2019). Korelasi antara kadar procalcitonin dengan serum transaminase pada pasien sepsis: sebuah studi pendahuluan. *Jurnal Biomedika Dan Kesehatan*, 2(1), 15–19. https://doi.org/10.18051/jbiomedkes.2019.v2.15-19

Lopez, C. A. V., Valencia-Espinosa, I., González-Sánchez, F. A., Sánchez-López, A. L., Garcia-Amezquita, L. E., & Garcia-Varela, R. (2022). Antioxidant, Anti-Inflammatory and Cytotoxic Activity of Phenolic Compound Family Extracted from Raspberries (Rubus idaeus): A General Review.

Antioxidants 2022, Vol. 11, Page 1192, 11(6), 1199. https://doi.org/10.3390/ANTIOX11061192

Maleki, S. J., Crespo, J. F., & Cabanillas, B. (2019). Anti-inflammatory effects of flavonoids. *Food Chemistry*, 299(160), 1145–1156. https://doi.org/10.1016/J.FOODCHEM.2019.125124

Maulina, M. (2018). Histopatologi Hepar. In JURNAL KEDOKTERAN (Issue 2). Unimal Press.

Mutiarahmi, C. N., Hartady, T., & Lesmana, R. (2021). Kajian Pustaka: Penggunaan Mencit Sebagai Hewan Coba di Laboratorium yang Mengacu pada Prinsip Kesejahteraan Hewan. *Indonesia Medicus Veterinus*, 10(1), 134–145. https://doi.org/10.19087/IMV.2021.10.1.134

Purwanto, D. S., & Astrawinata, D. A. W. (2018). Mekanisme Kompleks Sepsis dan Syok Septik. *Jurnal Biomedik:JBM*, 10(3), 143–151. https://doi.org/10.35790/JBM.10.3.2018.21979

Rahayu, W. P., Nurjanah, S., & Komalasari, E. (2018). Escherihia Coli: Patogenitas, Analisis dan Kajian Risiko. IPB Press.

Roberts, J. A., Alobaid, A. S., Wallis, S. C., Perner, A., Lipman, J., & Sjövall, F. (2019). Defining optimal dosing of ciprofloxacin in patients with septic shock. *The Journal of Antimicrobial Chemotherapy*, 74(6), 1662–1669. https://doi.org/10.1093/JAC/DKZ069

Silaban, H. (2021). The Effect of Various Concentrations of Ethanol Extract of the Leaves of Paederia foetida L. on the Growth of Escherichia Coli Bacteria. *Journal of Drug Delivery and Therapeutics*, 11(6), 61–67. https://doi.org/10.22270/JDDT.V11I6.5037

Singer, M., Deutschman, C. S., Seymour, C., & Shankar-Hari, M. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, 315(8), 810. https://doi.org/10.1001/JAMA.2016.0287

Sugiyono. (2018). Metode Penelitian Kuantitatif, Kualitatif dan R & D. Alfabeta.

Suprayogi, E., Sudarsono, & Harijanto, E. (2018). Sepsis dengan Disfungsi Multi Organ. *Journal Anesthesia & Critical Care*, 36(1), 9–18.

Surahmaida, S., & Handrianto, P. (2018). Analisis Kandungan Kimia Daun Dan Batang Sembukan (Paederia Foetida) Dengan Menggunakan 2 Pelarut Yang Berbeda. *Journal Pharmasci (Journal of Pharmacy and Science)*, 3(2), 23–27. https://doi.org/10.53342/PHARMASCI.V3I2.112

WHO. (2020). Laporan Global Tentang Epidemiologi Dan Beban Sepsis.

WHO. (2021). Sepsis. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/sepsis