VOLUME 10 NOMOR 2 DESEMBER 2023 ISSN 2548 – 611X

JURNAL
BIOTEKNOLOGI & BIOSAINS INDONESIA

Homepage Jurnal: http://ejournal.brin.go.id/JBBI/index

ANALYSIS OF KIDNEY HISTOPATHOLOGY IN SEPSIS MODEL OF MICE (MUS MUSCULUS) WITH PREVENTIVE TREATMENT OF LEAF EXTRACT FROM 'DAUN KENTUT' PLANT (PAEDERIA FOETIDA L.) AGAINST ESCHERICHIA COLI INFECTION

Analisis Histopatologi Ginjal Mencit (*Mus musculus*) Model Sepsis dengan Perlakuan Preventif Ekstrak Daun Kentut (*Paederia foetida* L.) terhadap Infeksi *Escherichia coli*

Lisa Savitri[1]*, Elfred Rinaldo Kasimo[1], Rochmad Krissanjaya[1], Datin An Nisa Sukmawati[2], Syntia Tanu Juwita[1], Akbar Nur Kholis[1], Yosep Mosse[1]

[1]Department of Medical Laboratory Technology, Faculty of Health Sciences, Kadiri University, Jalan Selomangleng No. 1, Kediri, East Java, Indonesia

[2]Department of Pharmacy, Faculty of Health Sciences, Kadiri University, Jalan Selomangleng No. 1, Kediri, East Java, Indonesia

*Email: lisasavitri@unik-kediri.ac.id

ABSTRACT

Sepsis is a critical health concern characterized by organ dysfunction due to uncontrolled host reactions to infections. The prevalence of microorganisms causing sepsis varies, with Gram-positive bacteria and fungal sepsis gaining significance. Sepsis often leads to acute kidney injury (AKI), and its association with sepsis is known as sepsis-associated AKI (SA-AKI). The "Daun Kentut" plant, known for its diverse bioactive compounds, has shown potential in combating inflammation and oxidative stress. In this study, histopathological changes in mouse kidneys induced by Escherichia coli were investigated. Hemorrhage was the primary change observed. Dehydration caused by E. coli infection potentially led to kidney injury through hormonal responses. The plant extract's anti-inflammatory potential, attributed to compounds like saponins and flavonoids, was also explored. The study emphasizes the need for understanding sepsis-related kidney damage and suggests possible preventive strategies using natural compounds.

Keywords: *kidney, histopathology, sepsis, daun kentut, Escherichia coli*

ABSTRAK

Sepsis adalah masalah kesehatan yang kritis yang ditandai dengan disfungsi organ akibat reaksi tidak terkendali inang terhadap infeksi. Prevalensi mikroorganisme penyebab sepsis bervariasi, dengan bakteri Gram-positif dan sepsis jamur semakin penting. Sepsis sering menyebabkan cedera ginjal akut (CGA), dan asosiasinya dengan sepsis dikenal sebagai cedera ginjal terkait sepsis (CGTS). Tanaman "Daun Kentut", dikenal dengan senyawa bioaktif beragamnya, telah menunjukkan potensi dalam mengatasi peradangan dan stres oksidatif. Dalam penelitian ini, perubahan histopatologis pada ginjal tikus yang diinduksi oleh *Escherichia coli* diselidiki. Perdarahan adalah perubahan utama yang diamati. Dehidrasi yang disebabkan oleh infeksi *E. coli* berpotensi menyebabkan cedera ginjal melalui respons hormon. Potensi antiinflamasi ekstrak tanaman, yang dikaitkan dengan senyawa seperti saponin dan flavonoid, juga dieksplorasi. Studi ini menekankan perlunya memahami kerusakan ginjal yang terkait dengan sepsis dan menyarankan strategi pencegahan yang mungkin dengan menggunakan senyawa alami.

Kata Kunci: ginjal, histopatologi, sepsis, daun kentut, *Escherichia coli*

***Received**: 18 December 2023* ***Accepted**: 19 December 2023* ***Published**: 29 December 2023*

INTRODUCTION

Sepsis is characterized as a severe malfunction of organs triggered by an uncontrolled reaction of the host to an infection. Septic shock can be regarded as a subgroup of sepsis where underlying disturbances in circulation, cells, and metabolism further elevate the likelihood of death compared to sepsis on its own (Singer et al., 2016). This information prompted the World Health Organization (WHO) to designate sepsis as a critical concern for global health (WHO, 2020).

The prevalence of detectable microorganisms in cases of sepsis/septic shock has fluctuated over time, currently displaying a higher occurrence of Gram-positive bacteria and an elevated clinical and epidemiological significance of fungal sepsis. In the category of Gram-positive bacteria, the most frequently encountered culprits include *Staphylococcus aureus* and *Streptococcus pneumoniae*, while within the realm of Gram-negative bacteria, the prevailing species are Escherichia coli, Klebsiella, and Pseudomonas spp. Concerning fungal infections linked to this condition, Candida spp. takes on a predominant role, often being identifiable in patients who are immunosuppressed or undergoing long-term treatment involving chemotherapeutic and immunosuppressive medications, particularly in those with compromised immune systems or undergoing prolonged chemotherapy and immunosuppression protocols (Angus et al., 2013).

Sepsis is a frequent contributor to severe medical conditions and is linked to significant levels of illness and death (Finfer and Machado, 2016; Vincent et al., 2006; Chiu and Legrand, 2021), frequently coinciding with the development of acute kidney injury (AKI). In the presence of sepsis, the occurrence of AKI is labeled as sepsis-associated acute kidney injury (SA-AKI) (Poston and Konyer, 2019; Peerapornratana et al., 2019). The relationship between sepsis and AKI has been the subject of previous investigations (Bagshaw et al., 2008; Bagshaw et al, 2007). Nevertheless, the absence of an easily replicable and universally agreed-upon definition has constrained the comprehensibility of the existing body of knowledge.

Plants offer an inexhaustible reservoir of natural products that yield novel pharmaceuticals, primarily encompassing antioxidant and anticancer agents. *Paederia foetida* L., locally referred to as "daun kentut" in Indonesia, is an aromatic perennial climbing plant commonly utilized as a leafy vegetable, either consumed in its raw state or steamed. This plant contains various phytochemicals, including steroids, saponins, alkaloids, flavonoids, vitamin C, and volatile oils (Mazumder et al. 2018; Patel 2017; Rosli et al. 2013). Furthermore, extracts derived from this plant have been extensively investigated for their biological activities, such as antibacterial and antibiofilm effects (Priyanto et al. 2022), antifungal properties (Morshed et al. 2012), antihyperlipidemic, antihyperglycemic, and antioxidant effects (Kumar et al. 2014), anti-melanogenic potential (Chung et al. 2021), chemoprotective abilities (Li et al. 2021), and cytotoxic actions on human prostate cancer cells (Pradhan et al. 2019).

In a previous study, extracts of fresh and dried *P. foetida* leaves (obtained from Malaysia) demonstrated noteworthy antioxidant activity, reaching levels of 68% and 76%, respectively, which correlated with their total phenolic content (Osman et al. 2009). Additionally, its methanolic extract exhibited antioxidant activity with IC50 values ranging from 538.97 to 859.20 µg/ml. Furthermore, a preventive test of *P. foetida* leaves (obtained from Malaysia) on interleukin-6 (IL-6) levels in a mouse sepsis model induced by *Escherichia coli* revealed that the 500 mg/kgBW dose was the most effective in reducing IL-6 levels (Savitri and Kasimo, 2022). However, variations in plant growth locations and extraction techniques might lead to variations in the composition and solubility of active constituents.

MATERIALS AND METHODS

Location and Time

The study was carried out from June to August 2023 at the Medical Laboratory Technology Laboratory, Kadiri University, for the maintenance and surgery of mice, and at the Anatomy Pathology Laboratory, Brawijaya University, for the preparation of specimens and tissue analysis.

Materials

Disposable 1 mL syringe, disposable 3 mL syringe, disposable 5 mL syringe, 35 cm feeding tube, 60 mL urine container, micropipette, freezer, rotary microtome or sliding microtome, brush, water bath, glass slides, Eppendorf 1500 µL pipette, blue tips, yellow tips, white 10 µL tips, oven, digital scale, surgical board, surgical instrument set (including scissors, tweezers, and lancets), gloves, tissues, mask, binocular light microscope, and microscope camera.

The materials used in this research include: 24 male Balb/c strain mice aged 4-8 weeks with a weight of 20-30 grams obtained from the Veterinary Center Surabaya, East Java, *Paederia foetida* leaf extract from Materia Medika Batu, East Java, ciprofloxacin, clinical isolate (wild type) of *E. coli* with a dose of $1x10^5$ CFU/mL from Nano Laboratory, physiological saline solution (PZ) (pyrogen-free aqua pro injection), mouse feed, wood powder (kawol), methanol, Giemsa stain, distilled water, 37% formaldehyde solution (H_2CO), formalin buffer, sodium hydrogen phosphate dibasic (Na_2HPO_4) 6.5 grams, distilled water 900 mL, 37-40% formaldehyde, 80% ethanol, 95% ethanol, absolute ethanol, xylene, clearing solution, paraffin, and poly-L-lysine.

Method

Male mice were weighed and placed in standard polypropylene cages with wood powder bedding for a two-week acclimatization period. Bedding was changed daily. Softened feed, weighing approximately 90 grams per cage (containing 6 mice), was provided ad libitum, along with water. Feed and water were replenished daily. After two weeks of acclimatization, mice were divided into six treatment groups.

Acclimatized mice were subjected to a 14-day treatment regimen as follows: 1) Group 1 served as the normal control (N), receiving no gastric intubation; 2) Group 2 acted as the negative control (K-), receiving 0.5 mL of distilled water; 3) Group 3 was the positive control (K+), administered ciprofloxacin at 500 mg/kgBW (0.26 mL); 4) Group 4 was treated with 100 mg/gBW dose of *Paederia foetida* leaf extract (P1); 5) Group 5 received 300 mg/gBW dose of the leaf extract (P2); 6) Group 6 was treated with 500 mg/gBW dose of the extract (P3).

Mice subjected to treatment were intraperitoneally injected with *E. coli* at a dose of $1x10^5$ CFU/mL. After 24 hours of polymicrobial sepsis exposure, mice showed signs of apoptosis in the spleen. If mice died before 24 hours, immediate surgery was performed to extract the kidneys to prevent autolysis. Kidney samples were taken from the middle, left, and right regions.

Kidney tissue was fixed in formalin buffer to preserve cellular morphology, prevent autolysis, and inhibit bacterial or fungal growth. Tissue was embedded in paraffin blocks, sectioned (4-6 microns) using a rotary or sliding microtome, placed on a water bath, adhered to object glass coated with tissue adhesive, air-dried at room temperature, and oven-dried overnight. Histopathological examination of mice kidneys involved hematoxylin and eosin (HE) staining. Tubules, glomeruli, and other potentially affected areas were observed for necrosis or apoptosis.

RESULTS AND DISCUSSION

The results of histopathological changes in the kidney organs of mice are presented in Table 1 and Figure 1. The observations reveal the histopathological features of kidney tubular cell damage due to *Escherichia coli* induction. The highest mean score for histopathological changes in the mouse kidney is hemorrhage, which is 5.683 ± 4.998.

Table 1. Mean and SD Values of Mice Kidney Histopathology in Sepsis Model with Preventive Treatment of Leaf Extract from 'Daun Kentut' Plant (*Paederia foetida* L.) against *E. coli* Infection

Types of Damage	Mean	SD
Hemorrhage	5,683	4,998
Karyorrhexis	2,900	2,941
Karyolysis	1,917	2,045

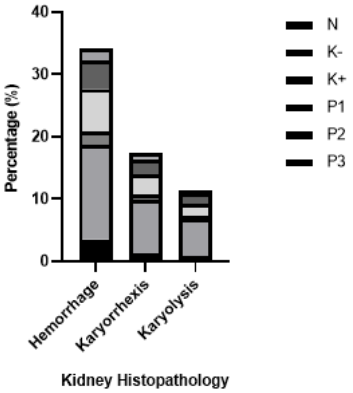

Figure 1. Data of Mice Kidney Histopathology in Sepsis Model with Preventive Treatment of Leaf Extract from 'Daun Kentut' Plant (*Paederia foetida* L.) against *E. coli* Infection

Based on the conducted research, it is shown that even under normal conditions, there is evidence of damage, although no treatment is given as seen in Figure 2. This can occur due to the experimental animals not being specific pathogen-free (SPF), so it is possible that the experimental animals have already experienced pathological disturbances not expected in the kidney organs due to factors outside of the treatment (Berata et al., 2011).

According to Cotran et al. (2007), this can also occur due to the physiological process of apoptosis experienced by normal cells. Naturally, cells in the body undergo aging and cell death, which in the process of regeneration will be replaced by new cells. Changes in the form of hemorrhage are observed in the histopathological appearance of all treatments. Hemorrhage is a condition characterized by blood escaping from blood vessels due to damage to their walls, which pathologically is marked by the presence of red blood cells outside the blood vessels or within the tissue. The causes of hemorrhage are varied, including trauma, infectious agents, vitamin C deficiency, and exposure to toxic substances.

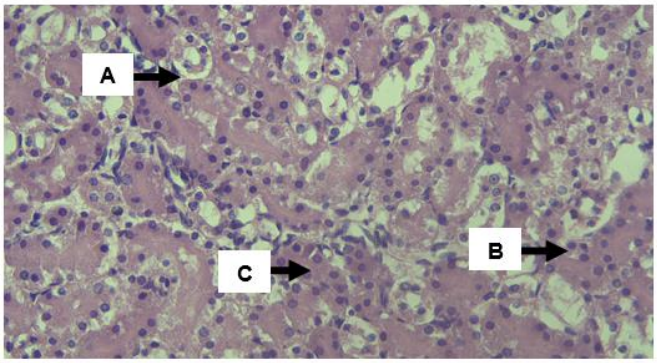

Figure 2. The Histopathological View of Mice Kidney Under Normal Treatment (N) Reveals The Presence of (a) Karyorrhexis, (b) Karyolysis in The Proximal Tubules, and (c) Deposition of Protein in The Tubular Lumen (HE Stain, 400x Magnification)

Injection of *E. coli* can lead to histopathological changes in mouse kidneys, as observed in Figures 3-7. This is suspected to be due to *E. coli* infection, which can cause diarrhea and subsequently lead to dehydration. This is supported by the study by Bongers et al. (2018), which indicates that dehydration can stimulate the secretion of arginine vasopressin (AVP) and the renin-angiotensin-aldosterone system (RAAS), subsequently promoting the reabsorption of water and sodium by the kidney. Increased renal sodium absorption, which requires additional energy, coupled with decreased renal perfusion, can lead to kidney injury. This dehydration prompts mice's bodies to adapt in order to maintain normal metabolic processes.

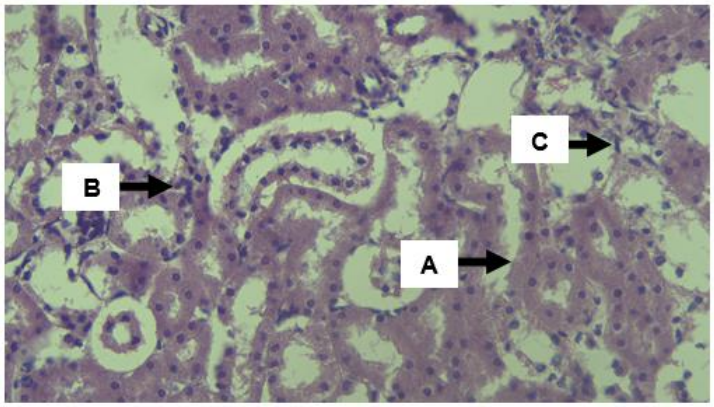

Figure 3. The Histopathological View of Mice Kidney Under Negative Control Treatment (K-) Reveals The Presenc of (a) Karyorrhexis, (b) Karyolysis in The Proximal Tubules, and (c) Deposition of Protein in The Tubula Lumen (HE Stain, 400x Magnification)

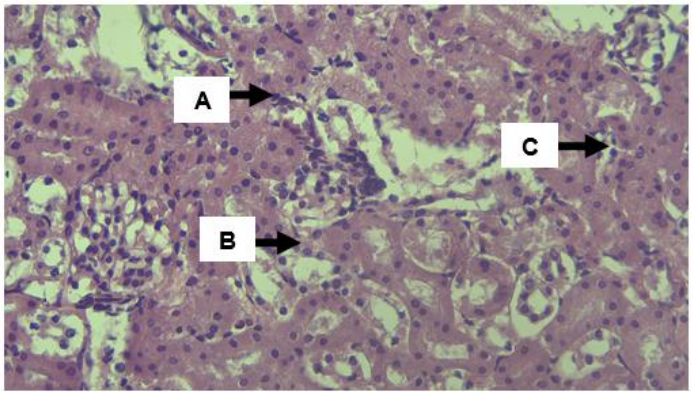

Figure 4. The Histopathological View of Mice Kidney Under Positive Control Treatment (K+) Reveals The Presence of (a) Karyorrhexis, (b) Karyolysis in The Proximal Tubules, and (c) Deposition of Protein in The Tubula Lumen (HE Stain, 400x Magnification)

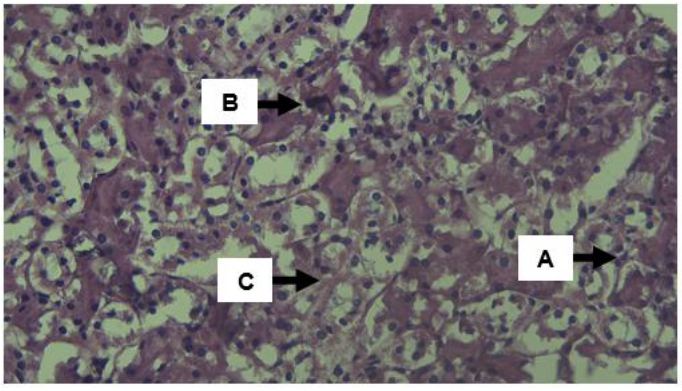

Figure 5. The Histopathological View of Mice Kidney Under Treatment 1 (P1) Reveals The Presence of (a) Karyo rhexis, (b) Karyolysis in The Proximal Tubules, and (c) Deposition of Protein in The Tubular Lumen (HE Stain, 400x Magnification)

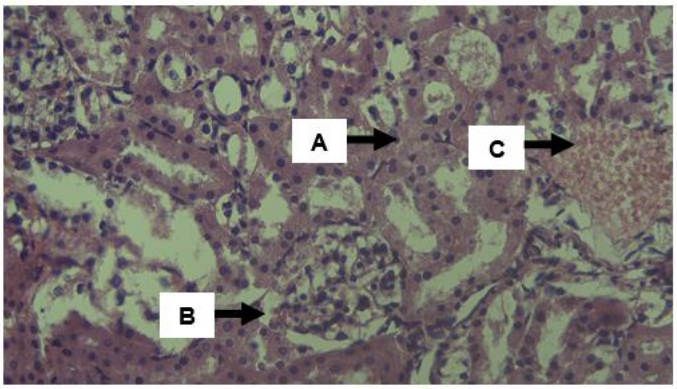

Figure 6. The Histopathological View of Mice Kidney Under Treatment 2 (P2) Reveals The Presence of (a) Karyo rhexis, (b) Karyolysis in The Proximal Tubules, and (c) Deposition of Protein in The Tubular Lumen (HE Stain, 400x Magnification)

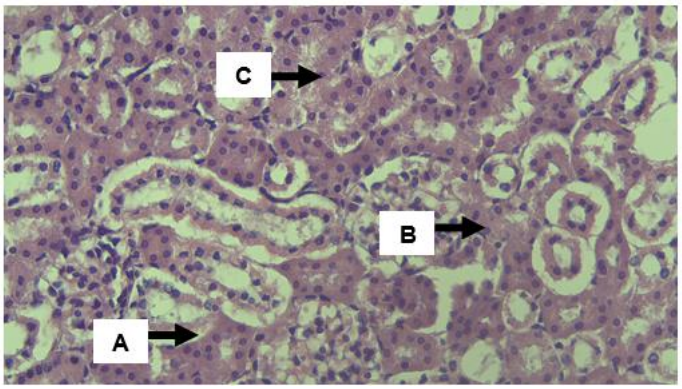

Figure 7. The Histopathological View of Mice Kidney Under Treatment 3 (P3) Reveals The Presence of (a) Karyo rhexis, (b) Karyolysis in The Proximal Tubules, and (c) Deposition of Protein in The Tubular Lumen (HE Stain, 400x Magnification)

According to Habibah et al. (2018), the animal body undergoes physiological stress when adapting to achieve new conditions in order to maintain normal metabolism. Szende and Suba (2000) added that a significant amount of adaptation is followed by observable structural changes at the micro level, yet these changes represent a normal growth pattern in tissues. Inability to adapt to environmental changes leads to structural damage to cells. Structural damage to kidney cells is caused by conditions of dehydration induced by *E. coli* injection. Dehydration triggers the activation of the aldose reductase pathway in the kidney cortex, which in turn produces fructose. Subsequently, fructose is metabolized into fructose-1-phosphate, but during this process, there's intracellular ATP consumption, leading to intracellular phosphate depletion, AMP deaminase activation, uric acid formation, oxidative stress, and cytokine production. It's this oxidative stress that interacts with membrane components, disrupting membrane permeability, cell membrane integrity, and causing damage (Roncal-Jimenez et al., 2015).

According to Simanjuntak (2007), disrupted membrane permeability causes uncontrolled movement of substances in and out of cells, while disturbances in membrane integrity lead to structural changes that make cells susceptible to lysis. Additionally, the hormone arginine vasopressin (AVP), the effector renin-angiotensin system (RAS), and angiotensin II produced during dehydration play a significant role. These hormones can have a significant impact on arterial pressure, glomerular hemodynamics, and non-hemodynamic renal mechanisms that lead to changes in kidney function and morphology in regulating repeated dehydration (Hilliard et al., 2016).

The potential anti-inflammatory mechanism during sepsis is thought to arise from the presence of saponins, flavonoids, and essential oils found in marigold leaf extract. Among these compounds, the most likely anti-inflammatory action is attributed to saponins, which could interact with various lipid membranes, including phospholipids that serve as precursors for prostaglandins and other inflammation mediators (Savitri and Ihsan, 2020).

Flavonoids, on the other hand, also exhibit anti-inflammatory effects by hindering the functions of COX and/or lipoxygenase enzymes. This inhibition of COX and lipoxygenase pathways subsequently impedes the synthesis of eicosanoids and leukotrienes, which are the end products of these pathways (Savitri, 2022). Furthermore, flavonoids have the capacity to decrease the number of immobile white blood cells and suppress complement activation, leading to reduced adhesion of these cells to the endothelium and ultimately causing diminished inflammatory responses. Flavonoids also play a role in inhibiting the release of histamine, with their anti-inflammatory effect being bolstered by their antihistamine properties (Savitri et al., 2020).

Histamine, a key inflammatory mediator, is released due to an influx of calcium into cells. Flavonoids can hinder the enzyme cAMP phosphodiesterase, elevating cAMP levels within mast cells. This action prevents the entry of calcium into cells, thereby impeding histamine release. Additionally, flavonoids can stabilize Reactive Oxygen Species (ROS) by engaging with reactive radical compounds, rendering these radicals inactive (Savitri et al., 2019).

CONCLUSION

Histopathological changes in mouse kidneys were examined after inducing *Escherichia coli* infection. The observations revealed kidney damage, with hemorrhage being the most prominent change. The research explored the preventive effects of 'Daun Kentut' plant leaf extract against *E. coli* infection in a sepsis model. Hemorrhage, characterized by blood leakage from damaged vessels, was consistently seen. Further investigation focused on *E. coli*-induced kidney changes, highlighting potential injury caused by dehydration from the infection. Dehydration triggered hormonal responses leading to water and sodium reabsorption, potentially damaging the kidneys due to increased energy demand for sodium absorption and reduced renal perfusion. The study also indicated potential anti-inflammatory effects of plant extract compounds like saponins and flavonoids. These compounds could interact with lipid membranes and inhibit inflammation-causing enzymes, suggesting a role in reducing inflammation and oxidative stress.

ACKNOWLEDGEMENT

The author would like to thank the Institute for Research, Development, and Community Service (LP3M) of Kadiri University which has always provided support for writing and publications.

REFERENCES

Angus, D.C.; van der Poll, T. (2013). Severe Sepsis and Septic Shock. N. Engl. J. Med. 2013, 369, 840–851.

Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M et al. (2007). Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephro 2(3):431–439.

Bagshaw SM, George C, Bellomo R, Committee ADM. (2008). Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care 12(2):R47.

Berata IK, Winaya IBO, Adi AAAM, Adnyana IBW. (2011). Patologi Veteriner Umum. Denpasar. Swasta Nulus. Hlm. 106-198.

Bongers CCWG, Alsady M, Nijenhuis T, Tulp ADM, Eijsvogels TMH, Deen PMT, Hopman MTE. (2018). Impact of Acute versus Prolonged Exercise and Dehydration on Kidney Function and Injury. Physiological Reports 6(11): 1-11.

Chiu C, Legrand M. (2021). Epidemiology of sepsis and septic shock. Curr Opin Anaesthesiol 34(2):71–76.

Chung, Y.C., Lee, J.N., Kim, B.S., Hyun, C.G., (2021). Anti-melanogenic effects of Paederia foetida L. extract via MAPK signaling-mediated mid-ownregulation. Cosmetics. 22, 1-10. https://doi.org/10.3390/cosmetics8010022

Cotran RS, Rennke H, Kumar V. (2007). Buku Ajar Patologi. 7th Edition. Jakarta. EGC. Hlm. 795-800.

Finfer S, Machado FR. (2016). The global epidemiology of sepsis. Does it matter that we know so little? Am J Resp Crit Care 193(3):228–230.

Habibah N, Dhyanaputri IGAS, Karta IW, Dewi NNA. (2018). Analisis Kuantitatif Kadar Nitrit dalam Produk Daging Olahan di Wilayah Denpasar Dengan Metode Griess Secara Spektrofotometri. Journal of Natural Sciences and Engineering 2(1): 1-9.

Hilliard LM, Colafella KM, Bulmer LL, Puelles VG, Singh RR, Ow CP, Gaspari T, Drummond GR, Evans RG, Vinh A, Denton KM. (2016). Chronic Recurrent Dehydration Associated with Periodic Water Intake Exacerbates Hypertension and Promotes Renal Damage in Male Spontaneously Hypertensive Rats. Scientific Report 6(1): 1-13.

Kumar, V., Anwar, F., Ahmed, D., Verma, A., Ahmed, A., Damanhouri, Z.A., Mishra, V., Ramteke, P.W., Bhatt, P.C., Mujeeb, M. (2014). Paederia foetida Linn. leaf extract: an antihyperlipidemic, antihyperglycaemic and antioxidant activity. BMC Compl. Altern Med. 14, 1-16. https://doi.org/10.1186/1472-6882-14-76.

Li, N., Zhou, H., Chen, X., Chen, H., Tang, H., Yao, Y., (2021). Potential chemoprotective effect of Paederia foetida Linn on benzyo[a]pyrene induced gastric cancer. Latin American J. Pharm. 40, 834-843.

Mazumder, K., Dey, Z.K., Dey, S., Hossain, M.D.S., Sajon, S.R., Hossain, K.M.D., (2018). Phytochemical screening and evaluation of ant diarrheal mode of action of leaves extracts of Paederia foetida Linn. Int. J. Complement. Altern. Med. 11, 304–309. https://10.15406/ijcam.2018.11.00416

Morshed, H., Islam, Md, S., Parvin, S., Ahmed, M.U., Islam, M.S., Mustofa, A.G.M., Sayeed, M.S.B. (2012). Antimicrobial and cytotoxic activity of the methanol extract of Paederia foetida Linn (Rubiaceae). J. Appl. Pharmaceut. Sci. 2, 77 80.

Osman, H., Rahim, A.A., Isa, N.M., Bakhir, N.M. (2009). Antioxidant activity and phenolic content of Paederia foetida and Syzygium aqueum. Molecules. 14, 970 978. https://10.3390/molecules14030970

Patel, D.K. (2017). Paederia foetida Linn: a potential climbing medicinal herb in Central India. Int. J. Environ. Sci. Nat. Resour. 6, 118–24.

Peerapornratana S, Manrique-Caballero CL, Gomez H, Kellum JA. (2019). Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, preventionand treatment. Kidney Int 96(5):1083–1099.

Poston JT, Koyner JL. (2019). Sepsis associated acute kidney injury. BMJ 364:k4891

Pradhan, N., Parbin, S., Kausar, C., Kar, S., Mawatwal, S., Das, L., Deb, M., Sengupta, D., Dhiman, R., Patra, S.K. (2019). Paederia foetida induces anticancer activity by modulating chromatin modification enzymes and altering pro-inflammatory cytokine gene expression in human prostate cancer cells. Food Chem. Toxicol. 130, 161-173. https://doi.org/10.1016/j.fct.2019.05.016

Priyanto, J.A., Prastya, M.E., Sinarwadi, G.S., Datu'salamah, W., Avelina, T.Y., Yanuar, A.I.A., Azizah, E., Tachrim, Z.P., Mozef, T. (2022). The antibacterial and antibiofilm potential of Paederia foetida Linn. leaves extract. J. Appl. Pharmaceut. Sci. 12, 117-124.

Roncal-Jimenez C, Lanaspa MA, Jensen T, Sanchez-Lozada LG, Johnson RJ. (2015). Mechanism by Which Dehydration May Lead to Chronic Kidney Disease. Annalsof Nutrition and Metabolism 66(3): 10-13.

Rosli, N.H.M., Tajuddin, N.A., Shafie, S. (2013). Preliminary study: vitamin C

in Paederia foetida leaves. The Open Conf. Proceedings J. 4, 9-11.

Savitri, L., Sandhika, W., & Wahyu Widodo, A. D. (2019). Perbedaan Ekspresi Caspase3 pada Limpa Tikus Model Sepsis yang Diinfeksi Escherichia coli ESBL dan dengan yang Diinfeksi Klebsiella pneumoniae Carbapenemase. ProsidingSeminar Nasional Multidisiplin, 2(1), 300–306. Retrieved from https://ejournal.unwaha.ac.id/index php/snami/article/view/705

Savitri, Lisa; Maslikah, Siti & Susilowati,. (2020). Effect of red betel leaf extract (Piper crocatum) against interleukin-1 beta (IL-1β) levels and thickness of feet oedema in Mus musculus (swiss strain) rheumatoid arthritis model. AIP Conference Proceedings. 2231.040012. 10.1063/5.0002562.

Savitri, L. & Ihsan, K. Aktivitas Triterpenoid Kulit Batang Waru Jawa (Hibiscus tiliaceus L.) terhadap Bakteri Escherichia coli. Jurnal Kesehatan Perintis (Perintis's Health Journal), 7 (1) 2020: 41-50.

Savitri, Lisa. (2022). Perbandingan Tingkat Keganasan Bakteri Berdasarkan Lama Waktu Kematian pada Tikus Model Sepsis yang Diinfeksi Escherichia coli ESBL dan Klebsiella pneumoniae Carbapenemase. Quagga: Jurnal Pendidikan dan Biologi. 14. 67-72. 10.25134/quagga.v14i1.5065.

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 (IJNSE), 5 (2): 38-43.

Simanjuntak. (2007). Radikal bebas dari Senyawa Toksik Karbon Tetraklorida. Bina Widya 18(1): 25-31.

Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.-D.; Coopersmith, C.M.; et al. (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis 3). JAMA 2016, 315, 801–810.

Szende B, Suba Z. (2000). Introduction to Histopathology. Hungary. Mediciana Publishing House Co. Hlm. 292.

Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H et al. (2006). Sepsis in European intensive care units and colon; results of the SOAP study and ast. Crit Care Med 34(2):344–353.

WHO. (2020). Global Report on the Epidemiology and Burden of Sepsis: Current Evidence, Identifying Gaps and Future Directions; World Health Organization: Geneva, Switzerland.