

## **BAB 5**

### **KESIMPULAN DAN SARAN**

#### **5.1 Kesimpulan**

1. Pada paru-paru yang diberi senyawa uji asam 2-(3-(klorometil)benzoiloksi)benzoat tidak menunjukkan penurunan derajat inflamasi apabila dibandingkan dengan kontrol positif.
2. Pada hati tidak menunjukkan penurunan derajat inflamasi secara bermakna
3. Senyawa uji asam 2-(3-(klorometil)benzoiloksi)benzoat tidak menunjukkan efek sebagai anti-inflamasi pada organ paru-paru dan hati tikus yang telah diinduksi lipopolisakarida.

#### **5.2 Saran**

1. Perlu dilakukan penelitian mengenai frekuensi dosis dari senyawa asam 2-(3-(klorometil)benzoiloksi)benzoat yang diberikan sebagai terapi anti-inflamasi.
2. Perlu dilakukan penelitian tentang mekanisme kerja dari senyawa asam 2-(3-(klorometil)benzoiloksi)benzoat mempengaruhi ekspresi dan aktivitas *cyclooxygenase* (COX) secara proteomik.
3. Distribusi senyawa ke dalam jaringan beserta efeknya juga perlu dilakukan.
4. Untuk mengamati parameter inflamasi seperti jenis granulosit yang berada dalam jaringan perlu dilakukan pewarnaan spesifik yaitu *immunohistochemistry* (IHC).

## DAFTAR PUSTAKA

- Aniagu, S.O., Nwinyi1, F.C., Akumka, D., Ajoku, G.A., Dzarma, S., Izebe, K.S., Ditse, M., Nwaneri, P.E.C., Wambebe1, C. and Gamaniel, K. 2005, Toxicity Studies in Rats Fed Nature Cure Bitters, *African Journal of Biotechnology*, **4(1)**: 72–78.
- Arwita, K.B.S. 2018, ‘Pengaruh Senyawa Asam 2-(3-(Klorometil)Benzoiloksi)Benzoat pada Lambung, Ginjal dan Hepar Tikus Wistar Betina Sebagai Pelengkap Uji Toksisitas Subkronis’, *Skripsi*, Sarjana Farmasi, Universitas Katolik Widya Mandala Surabaya.
- Badriyah and Purwanto. 2016, The Influence Of Pomelo Juice (*Citrus Maxima Var Nambangan*), Vitamin C And Lycopene Toward Mda Level Of Mouse (*Mus Musculus*) Hepatic Tissue Which Exposure by Ochratoxina, *Journal of Arts Science and Commerce*, **7**: 74–81.
- Balamayooran, G., Batra, S., Fessler, M.B., Happel, K.I. and Jeyaseelan, S. 2010, Translational Review Mechanisms of Neutrophil Accumulation in the Lungs, *American Journal of Respiratory Cell and Molecular Biology*, **43**: 5-16.
- Baranova, I.N., Souza, A.C.P., Bocharov, A.V., Vishnyakova, T.G., Hu, X., Vaisman, B.L., Amar, M.J., Chen, Z., Kost, Y., Remaley, A.T., Patterson, A.P., Yuen, P.S.T., Star, R.A., and Eggerman, T. 2016, Human SR-BI and SR-BII Potentiate Lipopolysaccharide-Induced Inflammation and Acute Liver and Kidney Injury in Mice, *J Immunol*, **196(7)**: 3135–3147.
- Brown, K.A., Brain, S.D., Pearson, J.D., Edgeworth, J.D., Lewis, S.M. and Treacher, D.F. 2005, Neutrophils in Development of Multiple Organ Failure in Sepsis, *The Lancet*, **368**: 157-169.
- Brzóska, M.M., At-marcinkiewicz, B.P.I. and Sawicki, B. 2003, Liver and Kidney Function and Histology in Rats Exposed to Cadmium and Ethanol, *Alcohol and Alcoholism*, **38(1)**: 2–10.
- Caroline, Foe, K., Esar, S.Y., Soewandi, A., Wihadmadyatami, H., Widharna, R.M., Tamayanti, W.D., Kasih, E. and Tjahjono, Y. 2019, Evaluation of Analgesic and Antiplatelet Activity of 2-((3-(chloromethyl)benzoyl)oxy)benzoic acid, *Prostaglandins and Other Lipid Mediators*. **145**: 1-8.

- Cecconi, M., Evans, L., Levy, M. and Rhodes, A. 2018, Sepsis and Septic Shock, *The Lancet*, **392**: 75–87.
- Chian, C.F., Chiang, C.H., Chu, Y.J., Chuang, C.H., Liu, S.L., Jheng Y.H., Zhang, H. and Ryu, J.H. 2012, Apocynin Attenuates Lipopolysaccharide-Induced Lung Injury in An Isolated and Perfused Rat Lung Model, *The Shock*, **38(2)**: 196–202.
- Cornell, S. 2000, *Membrane Structure in Disease and Drug Therapy*, Marcell Dekker, New York.
- Dai, Y. and Ge, J. 2012, Clinical Use of Aspirin in Treatment and Prevention of Cardiovascular Disease, *Thrombosis*, **12**: 1-7.
- Dogan, M.D., Ataoglu, H. and Akarsu, E.S. 2000, Effects of Different Serotypes of *Escherichia coli* Lipopolysaccharides on Body Temperature in Rats, *Life Sciences*, **67(19)**: 2319–2329.
- Eisen, D.P. 2012, Manifold Beneficial Effects of Acetyl Salicylic Acid and Nonsteroidal Anti-Inflammatory Drugs on Sepsis, *Intensive Care Medicine*, **38**: 1249–1257.
- Fajt, V. and Brant, S.G. 2013, ‘Method of Euthanasia’ in Matushek, K., *AVMA Guidelines for the Euthanasia of Animals: 2013 Edition.*, American Veterinary Medical Association, Schaumburg, hal 38.
- Freudenberg, N., Freudenberg, M.A., Guzman, J., Mittermayer, C.H., Bandara, K. and Galanos, C. 1984, Identification of Endotoxin-Positive Cells in The Rat Lung During Shock, *European Journal of Pathology*, **404**: 197–211.
- Fuster, V. and Sweeny, J.M. 2011, Aspirin: A Historical and Contemporary Therapeutic Overview, *Circulation*, **123(7)**: 768–778.
- Galanos, C. and Freudenberg, A. 1993, Bacterial endotoxins Biological Properties and Mechanisms of Action, *Mediators of Inflammation*, **2**: 11–16.
- Glasgow, A.M.A. Small, D., Scott, A., McLean, D., Camper, N., Hamid, U., Hegarty, S., Parekh, D., O’Kane, C., Lundy, F., McNally, P., Elborn, S., McAuley, D., Weldon, S. and Taggart, C. 2015, A Role For Whey Acidic Protein Four-Disulfide-Core 12 (WFDC12) in The Regulation of The Inflammatory Response in The Lung, *Thorax*, **70**: 426–432.

- Grisham, J.W., Nopanitaya, J., Compagn and Nagel, A.E.H. 1975, Scanning Electron Microscopy of Normal Rat Liver: The Surface Structure of Its Cells and Tissue Components, *Journal of Anatomy*, **144**: 295-322.
- Grommes, J. and Soehnlein, O. 2011, Contribution of Neutrophils to Acute Lung Injury, *Molecular Medicine*, **17(3-4)**: 293–307.
- Hamid, U., Krasnodembskaya, A., Fitzgerald, M., Shyamsundar, M., Kissenpfennig, A., Scott, Lefrancais, C., Looney, M., Verghis, R., Scott, J., Simpson, A., McNamee, J., McAuley, D. and Kane, C. 2017, Aspirin Reduces Lipopolysaccharide-Induced Pulmonary Inflammation in Human Models of ARDS, *Thorax*, **72**: 971-980.
- Han, C., Li, G., Lim, K., DeFrances, M.C., Gandhi, C.R. and Wu, T. 2019, Transgenic Expression of Cyclooxygenase-2 in Hepatocytes Accelerates Endotoxin-Induced Acute Liver Failure, *The Journal of Immunology*, **181**: 8027-8035.
- Harry, D.A.H., Anand, R., Holt, S., Davies, S., Marley, R., Fernando, B., Goodier, D. and Moore, K. 1999, Increased Sensitivity to Endotoxemia in The Bile Duct – Ligated Cirrhotic Rat, *Hepatology*, **30(5)**: 1198–1205.
- Hartwigotto, H. 1983, Pharmacokinetic Considerations of Common Analgesics and Antipyretics, *The American Journal of Medicine*, **75(5A)**: 30–37.
- Hollander, C.F., Leeuw, A.M. and Zwieten, M.J. 1985, Anatomy, Histology, and Ultrastructure Embryology, Anatomy, Histology, and Ultrastructure of the Liver, Rat, *Digestive System: Spinger*, 3-9.
- Hung, Y. Fang, S.H., Wang, S.C., Cheng, W.C., Liu, P.L., Su, C.C., Chen, C.S., Huang, M.Y., Hua, K.F., Shen, K.H., Wang, Y.T., Suzuki, K. and Li, C.Y. 2017, Corylin Protects LPS-Induced Sepsis and Attenuates LPS-Induced Inflammatory Response, *Nature*, **7**: 1–11.
- Jessica, M., Caroline, Nathania, Foe, K., Esar, S.Y. 2019, Characterization of Pharmacokinetics of 2-((3-(chloromethyl)benzoyloxy)benzoic Acid in Rats by Using HPLC-DAD Method, *International Journal of Applied Pharmaceutics*, **11(5)**: 1–5.
- Jiang, Z., Meng, Y., Bo, L., Wang, C., Bian, J. and Deng, X. 2018, Sophocarpine Attenuates LPS-Induced Liver Injury and Improves

- Survival of Mice through Suppressing Oxidative Stress, Inflammation, and Apoptosis. *Mediator Inflammation*, **18**: 1-12.
- Kao, S., Su, C.F., Liu, D.D. and Chen, H.I. 2007, Endotoxin-Induced Acute Lung Injury and Organ Dysfunction Are Attenuated by Pentobarbital Anaesthesia, *Clinical and Experimental Pharmacology Physiology*, **34(5-6)**: 480-487.
- Kassim, Mustafa, Marzida M., Nazeah A. and Kamaruddin, M. Y. 2012, Gelam Honey Has A Protective Effect against Lipopolysaccharide (LPS)-Induced Organ Failure, *International Journal of Molecular Sciences*, **13(5)**: 6370–6381.
- Kawada, N. and Parola, M. 2015, 'Interactions of Stellate Cells with Other Non-Parenchyma Cells' in Gandhi, C. R. and Pinzani, M., *Stellate Cells in Health and Disease*, Academic Press, San Francisco, 185-207.
- Khedoe, P.P.S.J., Kleijn, D., Oeveren-Rietdijk, A.M., Plomp, J.J., Boer, H.C., Pel, M., Rensen, P.C.N., Berbeke, J.F.P, and Hiemstra, P.S. 2017, Acute and Chronic Effects of Treatment with Mesenchymal Stromal Cells on LPS-Induced Pulmonary Inflammation, Emphysema and Atherosclerosis Development, *PLoS One*, **12(9)**: 1–21.
- Kumar S., Jyotirmayee K., and Sarangi M. 2013, Thin Layer Chromatography: A Tool of Biotechnology for Isolation of Bioactive Compounds from Medicinal Plant, *International Journal of Pharmaceutical Sciences Review and Research*, **18(1)**:126-132.
- Liu, M.W., Liu, R., Wu, H.Y., Zhang, W., Xia, J., Dong, M.N. Yu, W., Wang, Q., Xie, F.M., Wang, R., Huang, Y.Q., and Qian, C.Y. 2016, Protective Effect of Xuebijing Injection on D-Galactosamine- and Lipopolysaccharide-Induced Acute Liver Injury in Rats through the Regulation of P38 MAPK, MMP-9, and HO-1 Expression by Increasing TIPE2 Expression, *International Journal Of Molecular Medicine* , **38**: 1419–1432.
- Liu, Y. Li, F., Zhang, L., Wu, J., Wang, Y., and Yu, H. 2017, Taurine Alleviates Lipopolysaccharide-Induced Liver Injury by Anti-Inflammation and Antioxidants in Rats, *Molecular Medicine Reports*, **16**: 6512–6517.
- Maas, S.L., Soehnlein, O., and Viola, J.R. 2018, Organ-Specific Mechanisms of Transendothelial Neutrophil Migration in the Lung,

- Liver, Kidney, and Aorta, *Frontiers in Immunology*, **9**: 1–24.
- Mantovani, A., Cassatella, M.A., and Costantini, C. 2011, Neutrophils in The Activation and Regulation of Innate and Adaptive Immunity, *Nature*, **11(8)**: 519–531.
- Maynard, R. and Downes, N. 2019<sup>a</sup>, 'The Lung', in Washington, K., *Anatomy and Histology of the Laboratory Rat in Toxicology and Biomedical Research*. 1<sup>st</sup> ed., Academic Press, London, 129-146.
- Maynard, R. and Downes, N. 2019<sup>b</sup>, 'Liver', in Wahington, K., *Anatomy and Histology of the Laboratory Rat in Toxicology and Biomedical Research*. 1<sup>st</sup> ed., Academic Press, London, 159-168.
- Medzhitov, R. 2008, Origin and Physiological Roles of Inflammation, *Nature*, **454**: 428–435.
- Nair, A.B., and Jacob, S. 2016, A Simple Practice Guide for Dose Conversion between Animals and Human. *Journal of Basic and Clinical Pharmacy*, **7**: 27–31.
- Petrovová, E. and Jr, A.J. 2016, Importance Rat Liver Morphology and Vasculature in Surgical Research, *Medical Science Monitor*, **22**: 4716–4728.
- Prince, P.D., Fischermana, L., Tobllic, J.E., Fraga, C.G., Galleano, M. 2017, LPS-Induced Renal Inflammation Is Prevented by (–) Epicatechin in Rats, *Redox Biology*, **11**: 342–349.
- Putra, A.R. 2017, 'Pengaruh Senyawa Asam 2-(3-(Klorometil)Benzoiloksi)Benzoat terhadap Agregasi Trombosit Dengan Metode Pengujian *Flow Cytometry* dan Uji Waktu Perdarahan pada Mencit', *Skripsi*, Sarjana Farmasi, Universitas Katolik Widya Mandala Surabaya.
- Ramaiah, S.K. and Jaeschke, H. 2007, Role of Neutrophils in The Pathogenesis of Acute Inflammatory, *Toxicologic Pathology*, **35(6)**: 757–766.
- Ricciotti, E. 2012, Prostaglandins and Inflammation, *Arteriosclerosis, Thrombosis, and Vascular Biology*, **31(5)**: 986–1000.
- Stan, F.G. 2018, Comparative Study of The Liver Anatomy in The Rat , Rabbit, Guinea Pig, and Chinchilla, *Veterinary Medicine*, **75**: 32–40.
- Steven, S., Dib, M. and Daiber, A. 2017, Time Response of Oxidative / Nitrosative Stress and Inflammation in LPS-Induced Endotoxaemia

— A Comparative Study of Mice and Rats, *International Journal of Molecular Sciences*, **18**: 1-12.

- Sweetman, S.C. 2009, 'Analgesics Anti-inflammatory Drugs and Antipyretics', *Martindale*, 36<sup>th</sup> ed., The Pharmaceutical Press, London, 20-25.
- Szczeklik, A. 2006, the History of Aspirin : The Discoveries That Changed Contemporary Medicine, *Pontifical Academy of Sciences*, **18**: 175–184.
- Vaez, H., Najafi, M., Toutounchi, N.S., Barar, J., Barzega, A. and Alireza, G. 2016, Metformin Alleviates Lipopolysaccharide-induced Acute Lung Injury through Suppressing Toll-like Receptor 4 Signaling, *Iranian Journal of Allergy, Asthma, and Immunology*, **15**: 498–507.
- Valkhoff, V.E. and Kuipers, E.J. 2012, Best Practice and Research Clinical Gastroenterology Risk Factors for Gastrointestinal Bleeding Associated with Low-Dose Aspirin, *Best Practice & Research Clinical Gastroenterology*, **26(2)**: 125–140.
- Young J.C. 2013, True Melting Point Determination, *Chem. Educator*, **18**: 203-208.
- Yücel, G. Zhao, Z., El-Battrawy, I., Lan, H., Lang, S., Li, X., Buljubasic, F., Zimmermann, W.H., Cyganek, L., Utikal, J., Ravens, U., Wieland, T., Borggreffe, M., Zhou, X.B. and Akin, I. 2017, Lipopolysaccharides Induced Inflammatory Responses and Electrophysiological Dysfunctions in Human-Induced Pluripotent Stem Cell Derived Cardiomyocytes, *Scientific Reports*, **7**: 1–13.