

BAB 5

KESIMPULAN DAN SARAN

5.1. Kesimpulan

Berdasarkan penelitian yang telah dilakukan dan dianalisis data sehingga dapat disimpulkan bahwa :

1. Senyawa uji dosis 27 mg/200 gBB menunjukkan tingkat keparahan tukak dan nekrosis sel yang hampir sama pada organ lambung bila dibanding asam asetilsalisilat.
2. Senyawa uji dosis 9, 18 dan 27 mg/200 gBB menunjukkan tingkat keparahan nekrosis sel yang lebih rendah pada organ ginjal bila dibanding asam asetilsalisilat.
3. Senyawa uji dosis 9, 18 dan 27 mg/200 gBB menunjukkan tingkat keparahan nekrosis sel yang lebih rendah pada organ hepar bila dibanding asam asetilsalisilat.

5.2. Saran

Berdasarkan hasil penelitian, disarankan perlu dilakukan penelitian lebih lanjut untuk pemeriksaan histopatologi lambung, ginjal dan hepar pada pemberian senyawa asam 2-(3-(klorometil)benzoiloksi)benzoat menggunakan metode pewarnaan yang berbeda seperti immunihistokimia untuk memastikan bahwa penelitian ini memberikan hasil yang sama atau setara.

DAFTAR PUSTAKA

- Alisi, A., Feldstein, A.E., Villani, A., Raponi, M. and Nobili, V. 2012, Pediatric nonalcoholic fatty liver disease: a multidisciplinary approach. *Nature Gastroenterology and Hepatology*, **9**(3): 152-161.
- Altinoz, E., Oner, Z., Elbe, H., Cigremis, Y. and Turkoz, Y. 2015, Protective effects of saffron (its active constituent, crocin) on nephropathy in streptozotocin-induced diabetic rats. *Human & experimental toxicology*, **34**(2): 127-134.
- Amoury, R.A., Beatty, E.C., Wood, W.G., Holder, T.M., Aschraft, K.W., Sharp, R.J. and Murphy, J.P. 1988, Histology of the intestine in human gastroschisis relationship to intestinal malfunction: dissolution of the “peel” and its ultrastructural characteristics. *Journal of pediatric surgery*, **23**(10): 950-956.
- Anggraini, N. D. 2014, ‘Uji Toksisitas Subkronis Senyawa Asam 2-(3-(Klorometil)Benzoiloksi)Benzoat Pada Profil Darah dan Urin Mencit (*Mus musculus*)’, *Skripsi*, Sarjana Farmasi, Universitas Katolik Widya Mandala, Surabaya.
- Bismuth, H. 1982, Surgical anatomy and anatomical surgery of the liver. *World journal of surgery*, **6**(1): 3-9.
- Bjorkman, D. 1998, Nonsteroidal anti-inflammatory drug-associated toxicity of the liver, lower gastrointestinal tract and esophagus. *The American journal of medicine*, **105**(5): 17-21.
- Bou-Abboud, C.F., Wayland, H., Paulsen, G. and Guth, P.H. 1988, Microcirculatory stasis precedes tissue necrosis in ethanol-induced gastric mucosal injury in the rat. *Digestive diseases and sciences*, **33**(7): 872-877.
- Chandan, V.S., Shah, S.S., Torbenson, M.S. and Wu, T.T. 2016, Arginase-1 is frequently positive in hepatoid adenocarcinomas. *Human pathology*, **55**: 11-16.
- Critchlow, V., Liebelt, R.A., Bar-Sela, M., Mountcastle, W. and Lipscomb, H.S. 1963, Sex difference in resting pituitary-adrenal function in the rat. *American Journal of Physiology Legacy Content*, **205**(5): 807-815.

- D'Agati, V. 1996, Does aspirin cause acute or chronic renal failure in experimental animals and in humans?. *American journal of kidney diseases*, **28(1)**: 24-29.
- Dewi, C. 2012, 'Uji Toksisitas Akut Senyawa Asam-(3-Klorometil)BenzoilSalisilat dan Asam-(4-Klorometil)BenzoilSalisilat Terhadap Mencit (*Mus musculus L.*)', *Skripsi*, Sarjana Farmasi, Universitas Katolik Widya Mandala, Surabaya.
- D'haens, G.R., Geboes, K., Peeters, M., Baert, F., Penninckx, F. and Rutgeerts, P. 1998, Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology*, **114(2)**: 262-267.
- Dive, C., Gregory, C.D., Phipps, D.J., Evans, D.L., Milner, A.E. and Wyllie, A.H. 1992, Analysis and discrimination of necrosis and apoptosis (programmed cell death) by multiparameter flow cytometry. *Biochimica et Biophysica Acta (BBA) Molecular Cell Research*, **1133(3)**: 275-285.
- Djawa, M. 2015, 'Efek Asam 2-(3-(Klorometil)Benzoil)Benzoat Terhadap Profil Darah, Hepar dan Lambung Pada Tikus Wistar Jantan Sebagai Pelengkap Uji Toksisitas Subkronis', *Skripsi*, Sarjana Farmasi, Universitas Katolik Widya Mandala, Surabaya.
- Farber, J.L. and El-Mofty, S.K. 1975, The biochemical pathology of liver cell necrosis. *The American journal of pathology*, **81(1)**: 237.
- Ferreira, S., H. 1972, Prostaglandins, aspirin-like drugs and analgesia. *Nature New Biol.*, **240**: 200-203.
- Filipe, M.I. 1979, Mucins in the human gastrointestinal epithelium. *Investigative & cell pathology*, **2(3)**: 195.
- Friesner, R. A., Banks, J. L., Murphy, R. B., Halgren, T.A., Klicic, J. J., Mainz, D. T., Repasky, M. P., Knoll, E. H., Shaw, D. E., Shelley, M., Perry, J. K., Francis, P., Shenkin, P. S. 2004, Glide: A new Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy, *J.Med.Chem.*, **47**: 1739- 1749.
- George, S.K., Abolbashari, M., Jackson, J.D., Aboushareb, T., Atala, A. and Yoo, J.J. 2016, Potential Use of Autologous Renal Cells from Diseased Kidneys for the Treatment of Renal Failure. *Plos One*, **11(10)**: 1-18.

- Gershbein, L.L. and Elias, H. 1954, Observations on the anatomy of the rat liver. *The Anatomical Record*, **120**(1): 85-98.
- Ghoshal, N.G. and Bal, H.S. 1989, Comparative morphology of the stomach of some laboratory mammals. *Laboratory animals*, **23**(1): 23.
- Gusdinar, T., Herowati, R., Kartasasmita, R.E. dan Adnyana I.A. 2009, Synthesis and Gastric Ulcer Protective Activity of 46 Chlorinated Quercetin,. *Indonesian Journal of Pharmacy*, **20**(4): 163-169.
- Hirata, T., Ukawa, H., Yamakuni, H., Kato, S. and Takeuchi, K. 1997, Cyclo-oxygenase isozymes in mucosal ulcerogenic and functional responses following barrier disruption in rat stomachs. *British journal of pharmacology*, **122**(3): 447-454.
- Hirsh, J., Dalen, J.E., Fuster, V., Harker, L.B., Patrono, C. and Roth, G. 1995, Aspirin and other platelet-active drugs: the relationship among dose, effectiveness, and side effects. *Chest*, **108**(4): 252.
- Hoffmann, F., Farbenfabriken Of Elberfeld Company. 1989, *Acetyl salicylic acid*. U.S. Patent 644, **077**: 1.
- Ito, S. and Lacy, E.R. 1985, Morphology of rat gastric mucosal damage, defense, and restitution in the presence of luminal ethanol. *Gastroenterology*, **88**(1): 250-260.
- Kammeraad, A. 1942, The development of the gastro-intestinal tract of the rat. I. Histogenesis of the epithelium of the stomach, small intestine and pancreas. *Journal of Morphology*, **70**(2): 326.Kanani, K., Gatoulis, S.C. and Voelker, M. 2015, Influence of differing analgesic formulations of aspirin on pharmacokinetic parameters. *Pharmaceutics*, **7**(3): 188-198.
- Kanter, M., Coskun, O. and Uysal, H. 2006, The antioxidative and antihistaminic effect of *Nigella sativa* and its major constituent, thymoquinone on ethanol induced gastric mucosal damage. *Archives of toxicology*, **80**(4): 217-224.
- Kararli, T.T. 1995, Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. *Biopharmaceutics & drug disposition*, **16**(5): 351-380.
- Kerr, J.F., Wyllie, A.H. and Currie, A.R. 1972, Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *British journal of cancer*, **26**(4): 239.

- Kimberly, R.P. and Plotz, P.H. 1977, Aspirin-induced depression of renal function. *New England Journal of Medicine*, **296**(8): 418-424.
- Kleiner, D.E., Brunt, E.M., Van Natta, M., Behling, C., Contos, M.J., Cummings, O.W., Ferrell, L.D., Liu, Y.C., Torbenson, M.S., Unalp-Arida, A. and Yeh, M. 2005, Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*, **41**(6): 1313-1321.
- Kogure, K., Ishizaki, M., Nemoto, M., Kuwano, H. and Makuuchi, M. 1999, A comparative study of the anatomy of rat and human livers. *Journal of Hepato-Biliary-Pancreatic Sciences*, **6**(2): 171-175.
- Larrey, D. 2000, Drug-induced liver diseases. *Journal of hepatology*, **32**: 77-88.
- Laurence, D.R. and Bacharach, A.L. eds., 1964, *Evaluation of drug activities: pharmacometrics*. Vol. 1, p. 183-205. New York, Academic press.
- Leh, S., Hultström, M., Rosenberger, C. and Iversen, B.M. 2011, Afferent arteriolopathy and glomerular collapse but not segmental sclerosis induce tubular atrophy in old spontaneously hypertensive rats. *Virchows Archiv*, **459**(1): 99-108.
- Lemley, K.V. and Kriz, W. 1991, Anatomy of the renal interstitium. *Kidney international*, **39**(3): 370-381.
- Levy, M. 1974, Aspirin use in patients with major upper gastrointestinal bleeding and peptic-ulcer disease: a report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. *New England Journal of Medicine*, **290**(21): 1158-1162.
- Ligumsky, M., Golanska, E.M., Hansen, D.G. and Kauffman, G.L. 1983, Aspirin can inhibit gastric mucosal cyclo-oxygenase without causing lesions in rat. *Gastroenterology*, **84**(4): 756-761.
- Lindop, G.B.M. and Lever, A.F. 1986, Anatomy of the renin angiotensin system in the normal and pathological kidney. *Histopathology*, **10**(4): 335-362.
- Majno, G. and Joris, I. 1995, Apoptosis, oncosis, and necrosis. An overview of cell death. *The American journal of pathology*, **146**(1): 3.

- Miletić, D., Fučkar, Ž., Šustić, A., Mozetič, V., Štimac, D. and Žauhar, G. 1998, Sonographic measurement of absolute and relative renal length in adults. *Journal of clinical ultrasound*, **26(4)**: 185-189.
- Molland, E.A. 1978, Experimental renal papillary necrosis. *Kidney international*, **13(1)**: 5-14.
- Moore KL dan Agur AMR. 2002, *Anatomi Klinis Dasar*. Jakarta, Hipokrates. Hlm: 54-79.
- Muriel, P. and Escobar, Y. 2003, Kupffer cells are responsible for liver cirrhosis induced by carbon tetrachloride. *Journal of Applied Toxicology*, **23(2)**: 103-108.
- Murray, G., Wyllie, R.G., Hill, G.S., Ramsden, P.W. and Heptinstall, R.H. 1972, Experimental papillary necrosis of the kidney: I. Morphologic and functional data. *The American journal of pathology*, **67(2)**: 285.
- Nanra, R.S. and Kincaid-Smith, P. 1970, Papillary necrosis in rats caused by aspirin and aspirin-containing mixtures. *British medical journal*, **3(5722)**: 559.
- Natalia, O. 2013, 'Pemodelan interaksi turunan potensial asam benzoil salisilat dengan reseptor enzim siklooksigenase-2', *Skripsi*, Sarjana Farmasi, Universitas Katolik Widya Mandala, Surabaya.
- Netter, Frank H. *Atlas OF Human Anatomy* 25th Edition. Jakarta, EGC, 2014.
- OECD. 1995, *Repeated Dose 28 Day Oral Toxicity Study in Rodents In OECD Guidelines for Testing of Chemical*, No 407, Organization for Economic Cooperation and Development, France.
- Owen, D.A. 1986, Normal histology of the stomach. *The American journal of surgical pathology*, **10(1)**: 48-49.51.
- Petrescu, I. and Tarba, C. 1997, Uncoupling effects of diclofenac and aspirin in the perfused liver and isolated hepatic mitochondria of rat. *Biochimica et Biophysica Acta (BBA) ioenergetics*, **1318(3)**: 385-394.

- Pinzani, M., Milani, S., Herbst, H., DeFranco, R., Grappone, C., Gentilini, A., Caligiuri, A., Pellegrini, G., Ngo, D.V., Romanelli, R.G. and Gentilini, P. 1996, Expression of platelet-derived growth factor and its receptors in normal human liver and during active hepatic fibrogenesis. *The American journal of pathology*, **148**(3): 785.
- Piper, D.W. 1980, Mucus: Chemistry and characteristics. *Scientific Foundations of Gastroenterology*. Philadelphia, WB Saunders Co, **33**(6): 333.
- Pradipta, I. 2015, 'Efek senyawa asam 2-(3-(klorometil benzoiloksi)benzoat terhadap aktivitas dan indeks organ tikus wistar jantan sebagai pelengkap uji toksisitas subkronis', *Skripsi*, Sarjana Farmasi, Universitas Katolik Widya Mandala, Surabaya.
- Pratiwi, V. D. 2009, 'Sintesis Asam 3-Klorometilbenzoil Salisilat dan Uji Aktivitas Analgesik pada Mencit (*Mus musculus*)', *Skripsi*, Sarjana Farmasi, Universitas Katolik Widya Mandala, Surabaya.
- Prescott, L.F. 1969, Renal papillary necrosis and aspirin. *Scottish medical journal*, **14**(3): 82.
- Puspitasari, D. A. 2008, 'Gambaran Histopatologi Lambung Tikus Putih (*Rattus norvegicus*) Akibat Pemberian Asam Asetil Salisilat', *Skripsi*, Fakultas Kedokteran Hewan, Institut Pertanian Bogor.
- Rehberg, P.B. 1926, Studies on kidney function: the rate of filtration and reabsorption in the human kidney. *Biochemical Journal*, **20**(3): 447.
- Reinus, J.F. and Simon, D. eds., 2014, *Gastrointestinal anatomy and physiology: the essentials*, John Wiley & Sons.
- Rizzo, D.C. 2001, *Delmar's Fundamentals of Anatomy & Physiology*. USA, Delmar Thomson Learning, 346.
- Rocha, R., Stier Jr, C.T., Kifor, I., Ochoa-Maya, M.R., Rennke, H.G., Williams, G.H. and Adler, G.K. 2000, Aldosterone: a mediator of myocardial necrosis and renal arteriopathy 1. *Endocrinology*, **141**(10): 3871-3878.
- Seleem, H.S., Ghobashy, H.A. and Zolfakar, A.S. 2010, Effect of aspirin versus aspirin and vitamin C on gastric mucosa (Fundus) of adult male albino rats. Histological and Morphometric Study. *Egypt J Histol*, **33**(2): 313-26.

- Smith, R.J., Sabin, C., Gilchrest, H. and Williams, S. 1976, Effect of anti-inflammatory drugs on lysosomes and lysosomal enzymes from rat liver. *Biochemical pharmacology*, **25(19)**: 2171-2177.
- Soekarto T. S. 1981, *Penilaian Organoleptik*. Bogor, Pustaka Bangtepa-IPB.
- Susanti, E. 2016, ‘Gambaran Histopatologi Hati Tikus Putih (*Rattus Novaezelandiae*) Yang Diberi Insektisida Golongan Piretroid (Sipermetrin)’. *Skripsi*, Fakultas Kedokteran, Universitas Makassar.
- Takei, Y., Marzi, I., Kauffman, F.C., Currin, R.T., Lemasters, J.J. and Thurman, R.G. 1990, Increase in survival time of liver transplants by protease inhibitors and a calcium channel blocker, nisoldipine. *Transplantation*, **50(1)**: 14-20
- Takeuchi K, Ukawa H, Konaka A, Kitamura M, Sugawa W. 1998, Effect of Nitric Oxide-Releasing Aspirin Derivate on Gastric Functional and Ulcerogenic Response in Rats: Comparison With Plain Aspirin. *Journal of Pharmacology and Experimental Therapeutics*. **286**: 115-121.
- Taylor, K.J.W., Carpenter, D.A., Hill, C.R. and McCready, V.R. 1976, Gray Scale Ultrasound Imaging: The Anatomy and Pathology of the Liver 1. *Radiology*, **119(2)**: 415-423.
- Tsukamoto, H., French, S.W., Benson, N., Delgado, G., Rao, G.A., Larkin, E.C. and Largman, C. 1985, Severe and progressive steatosis and focal necrosis in rat liver induced by continuous intragastric infusion of ethanol and low fat diet. *Hepatology*, **5(2)**: 224-232.
- Vane, J. R. 1971, Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol.*, **231**: 232-235.
- Wakim, K.G. 1954, Physiology of the liver. *The American journal of medicine*, **16(2)**: 256-271.
- Wallace, J. L. 1997, Nonsteroidal anti inflammatory drugs and Gastroenteropathy. the Second Hundred Years. *Gastroenterology*. 1997, **112**: 1000-1016.
- Watson, A.J. 1995, Necrosis and apoptosis in the gastrointestinal tract. *Gut*, **37(2)**: 165-167.

- Winchester, J.F. 1996, Therapeutic uses of aspirin in renal diseases. *American journal of kidney diseases*, **28(1)**: 20-23.
- Woda, M.K.W. 2016, ‘Efek Asam 2-(4-(Klorometil)Benzoiloksi)Benzoat Terhadap Profil Darah dan Ginjal Pada Tikus Wistar Jantan Sebagai Pelengkap Uji Toksisitas Subkronis’, *Skripsi*, Sarjana Farmasi, Universitas Katolik Widya Mandala, Surabaya.
- Yeomans, N.D., John, D.S. and De Boer, W.G.R.M. 1973, Regeneration of gastric mucosa after aspirin-induced injury in the rat. *The American journal of digestive diseases*, **18(9)**: 773-780.
- Zimmerman, H.J. 1981, Effects of aspirin and acetaminophen on the liver. *Archives of Internal Medicine*, **141(3)**: 333-342.
- Zuraida, R., Rohaeni, E.S. dan Hikmah, Z. 2006, Prospek pengusahaan ayam pedaging pada Kotamadya Banjarbaru, Kalimantan Selatan: kasus di Desa Palam Kecamatan Cempaka, Kota Banjarbaru, Kalimantan Selatan dalam Seminar Nasional Teknologi Peternakan dan Veteriner. *Kalimantan Selatan: Balai Pengkajian Teknologi Pertanian*, Indonesia, 44.