

DAFTAR PUSTAKA

- (CIOMS), C. for I.O. of M.S., 1985. International guiding principles for biomedical research involving animals. pp. 4461–4464.
- Abdel-Salam, O.M.E., Nada, S.A., Salem, N.A., El-Shamarka, M.E.S., Omara, E., 2014. Effect of Cannabis sativa on oxidative stress and organ damage after systemic endotoxin administration in mice. *Comp. Clin. Path.* 23, 1069–1085. <https://doi.org/10.1007/s00580-013-1745-1>
- Abdullah, B.A., Wadi, S.A., Sarhat, E.R., 2017. Histological Study Effects of Paracetamol on Livers and Kidneys of Adult Mice. *J. Tikrit Univ. Agri. Sci* 28–29.
- Ak, T., Gülçin, I., 2008. Antioxidant and radical scavenging properties of curcumin. *Chem. Biol. Interact.* 174, 27–37. <https://doi.org/10.1016/j.cbi.2008.05.003>
- Akhila, J.S., Shyamjith, Deepa, Alwar, M.C., 2007. Acute toxicity studies and determination of median lethal dose. *Curr. Sci.* 93, 917–920.
- Aki, T., Nara, A., Uemura, K., 2012. Cytoplasmic vacuolization during exposure to drugs and other substances. *Cell Biol. Toxicol.* 28, 125–131. <https://doi.org/10.1007/s10565-012-9212-3>
- Akomolafe, S.F., Akinyemi, A.J., Anadozie, S.O., 2014. Phenolic Acids (Gallic and Tannic Acids) Modulate Antioxidant Status and Cisplatin Induced Nephrotoxicity in Rats. *Int. Sch. Res. Not.* 2014, 1–8. <https://doi.org/10.1155/2014/984709>
- Al-snafi, A.E., 2016. Pharmacological importance of Clitoria ternatea – A review. *IOSR J. Pharm.* 6, 68–83.
- Alarkey, D.E.M., 2012. Liver Hypertrophy : A Review of Adaptive (Adverse and Non-adverse) Changes — Conclusions from the 3rd International ESTP Expert Workshop 971–994. <https://doi.org/10.1177/0192623312448935>
- Alebachew, M., Kinfu, Y., Makonnen, E., Bekuretsion, Y., Urga, K., Afework, M., 2014. Toxicological evaluation of methanol leaves extract of Vernonia Bipontini Vatke in blood, liver and kidney tissues of mice. *Afr. Health Sci.* 14, 1012–1024. <https://doi.org/10.4314/ahs.v14i4.33>
- Ashrafunnisa, Pullaiah, T., 2000. Embryology of Clitoria ternatea (Fabaceae). *Plant Biosyst.* 134, 39–43. <https://doi.org/10.1080/11263500012331350325>
- Asri Werdhasari, 2014. Peran Antioksidan Bagi Kesehatan. *J. Biomedik Medisiana Indones.* 3, 59–68.
- Avraham, Y., Zolotarev, O., Grigoriadis, N.C., Pautahidis, T., Magen, I., Vorobiav, L., Zimmer, A., Ilan, Y., Mechoulam, R., Berry, E.M., 2008. Cannabinoids and capsaicin improve liver function following thioacetamide-induced acute injury in mice. *Am. J. Gastroenterol.* 103, 3047–3056. <https://doi.org/10.1111/j.1572-0241.2008.02155.x>
- Bishoyi, A.K., Geetha, K.A., 2013. Polymorphism in flower colour and petal type in Aparajita (Clitoria ternatea). *Open Access J. Med. Aromat. Plants* 3, 12–14.
- Bissell, D.M., Gores, G.J., Laskin, D.L., Hoofnagle, J.H., 2001. Drug-induced liver injury: Mechanisms and test systems. *Hepatology* 33, 1009–1013. <https://doi.org/10.1053/jhep.2001.23505>
- Bonventre, J. V., Vaidya, V.S., Schmouder, R., Feig, P., Dieterle, F., 2010. Next-generation biomarkers for detecting kidney toxicity. *Nat. Biotechnol.* 28, 436–440. <https://doi.org/10.1038/nbt0510-436>
- Brozovic, A., Ambriović-Ristov, A., Osmak, M., 2010. The relationship between cisplatin-Induced reactive oxygen species, glutathione, and BCL-2 and resistance to cisplatin. *Crit. Rev. Toxicol.* 40, 347–359. <https://doi.org/10.3109/10408441003601836>
- Bunchorntavakul, C., Reddy, K.R., 2013. Review article: Herbal and dietary supplement

- hepatotoxicity. *Aliment. Pharmacol. Ther.* 37, 3–17. <https://doi.org/10.1111/apt.12109>
- Cattley, R.C., Cullen, J.M., 2013. Liver and Gall Bladder, Haschek and Rousseaux's Handbook of Toxicologic Pathology. <https://doi.org/10.1016/B978-0-12-415759-0.00045-5>
- Chandra, S., 2019. Evaluation of Methanolic Extract of *Clitoria ternatea* Hepatoprotective & Nephroprotective Activity in Rats. *J. Drug Deliv. Ther.* 9, 313–319. <https://doi.org/10.22270/jddt.v9i4-a.3478>
- Chauhan, N., Rajvaidhya, S., Dubey, B., 2012. Pharmacognostical, phytochemical and pharmacological review on *Clitoria ternatea* for antiasthmatic activity. *Int. J. Pharm. Sci. Res.* 3, 398–404.
- Chauhan, N. s, Shah, K., Gupta, J.K., Mishra, P., 2017. A Review on *Clitoria ternatea*(Linn.): Chemistry and Pharmacology, Medicinal Plants and Its Therapeutic Uses. <https://doi.org/10.4172/978-1-63278-074-4-075>
- Chinedu, E., Arome, D., Ameh, F.S., 2013. A new method for determining acute toxicity in animal models. *Toxicol. Int.* 20, 224–226. <https://doi.org/10.4103/0971-6580.121674>
- Chiu, P.Y., Luk, K.F., Leung, H.Y., Ng, K.M., Ko, K.M., 2008. Schisandrin B stereoisomers protect against hypoxia/reoxygenation-induced apoptosis and inhibit associated changes in Ca²⁺-induced mitochondrial permeability transition and mitochondrial membrane potential in H9c2 cardiomyocytes. *Life Sci.* 82, 1092–1101. <https://doi.org/10.1016/j.lfs.2008.03.006>
- Cho, Y.M., Imai, T., Ito, Y., Takami, S., Hasumura, M., Yamazaki, T., Hirose, M., Nishikawa, A., 2009. A 13-week subchronic toxicity study of dietary administered saponin-rich and isoflavones-containing soybean extract in F344 rats. *Food Chem. Toxicol.* 47, 2150–2156. <https://doi.org/10.1016/j.fct.2009.06.001>
- Craig, E.A., Yan, Z., Zhao, Q.J., 2015. The relationship between chemical-induced kidney weight increases and kidney histopathology in rats. *J. Appl. Toxicol.* 35, 729–736. <https://doi.org/10.1002/jat.3036>
- da Silva, J., Herrmann, S.M., Heuser, V., Peres, W., Possa Marroni, N., González-Gallego, J., Erdtmann, B., 2002. Evaluation of the genotoxic effect of rutin and quercetin by.pdf. *Food Chem. Toxicol.* 40, 941–947.
- Damodaran, T., Tan, B.W.L., Liao, P., Ramanathan, S., Lim, G.K., Hassan, Z., 2018. *Clitoria ternatea* L. root extract ameliorated the cognitive and hippocampal long-term potentiation deficits induced by chronic cerebral hypoperfusion in the rat. *J. Ethnopharmacol.* 224, 381–390. <https://doi.org/10.1016/j.jep.2018.06.020>
- DeLeve, L.D., Ito, Y., Bethea, N.W., McCuskey, M.K., Wang, X., McCuskey, R.S., 2003. Embolization by sinusoidal lining cells obstructs the microcirculation in rat sinusoidal obstruction syndrome. *Am. J. Physiol. - Gastrointest. Liver Physiol.* 284, 1045–1052. <https://doi.org/10.1152/ajpgi.00526.2002>
- Deora, P., Mishra, C., Mavani, P., Asha, R., Rajesh, K.N., 2010. Effective alternative methods of LD50 help to save number of experimental animals. *J. Chem. Pharm. Res.* 2, 450–453.
- Diwan, F.H., Abdel-Hassan, I.A., Mohammed, S.T., 2000. Effect of saponin on mortality and histopathological changes in mice. *East. Mediterr. Heal. J.* 6, 345–351.
- Dutta, S., Sengupta, P., 2016. Men and mice: Relating their ages. *Life Sci.* 152, 244–248. <https://doi.org/10.1016/j.lfs.2015.10.025>
- Edoardo, G., Federica, B., Alberto, F., Paola, C., Domenico, R., Pasquale, B., Lantieri, G., Celle, R., 1999. Progressive Liver Functional Impairment Is Associated with an Increase in AST/ALT Ratio. *Dig. Dis. Sci.* 44, 1249–1253.
- Effendi, M., Darda, R., 2020. Histopatological Description Of Liver And Kidney Of Mice Exposed To The Ethanol Extract Of *Syzygium Myrtifolium*walp Leaves. *Int. J. Eng. Nat. Sci.* 5, 50–56.

- Fakurazi, S., Hairuszah, I., Nanthini, U., 2008. Moringa oleifera Lam prevents acetaminophen induced liver injury through restoration of glutathione level. *Food Chem. Toxicol.* 46, 2611–2615. <https://doi.org/10.1016/j.fct.2008.04.018>
- Falconer, I.R., Hardy, S.J., Humpage, A.R., Froschio, S.M., Tozer, G.J., Hawkins, P.R., 1998. Hepatic and Renal Toxicity of the Blue – Green Alga (Cyanobacterium) *Cylindrospermopsis raciborskii* in Male Swiss Albino Mice 143–150.
- Farber, J.L., 1985. The biochemical pathology of toxic cell death. *Monogr. Pathol.* 19–31.
- Finney, J., 1947. Probit Analysis : A Statistical Treatment of the Sigmoid Response Curve 110, 263–266.
- Foltz, C.J., Ullman-Cullere, M., 1999. Guidelines for Assessing the Health and Condition of Mice. *Lab Anim. (NY)*. 28, 28–32.
- Foo, N., 2002. Cellular Vacuolization and Apoptosis Induced by Hepatitis B Virus Large Surface Protein. *Hepatology* 36, 1400–1407.
- Francis, G., Kerem, Z., Makkar, H.P.S., Becker, K., 2002. The biological action of saponins in animal systems: a review. *Br. J. Nutr.* 88, 587–605. <https://doi.org/10.1079/bjn2002725>
- Frenzel, C., Teschke, R., 2016. Herbal Hepatotoxicity: Clinical characteristics and listing compilation. *Int. J. Mol. Sci.* 17. <https://doi.org/10.3390/ijms17050588>
- Fu, P.P., Xia, Q., Lin, G., Chou, M.W., 2004. Pyrrolizidine Alkaloids - Genotoxicity, Metabolism Enzymes, Metabolic Activation, and Mechanisms. *Drug Metab. Rev.* 36, 1–55. <https://doi.org/10.1081/DMR-120028426>
- Fujisawa, S., Atsumi, T., Ishihara, M., Kadoma, Y., 2004. Activity of Curcumin and Related Compounds 570, 563–569.
- Go, J., Kim, J.-E., Koh, E.-K., Song, S.-H., Seung, J.-E., Park, C.-K., Lee, H.-A., Kim, H.-S., Lee, J.-H., An, B.-S., Yang, S.-Y., Lim, Y., Hwang, D.-Y., 2015. Hepatotoxicity and nephrotoxicity of gallotannin-enriched extract isolated from *Galla Rhois* in ICR mice. *Lab. Anim. Res.* 31, 101. <https://doi.org/10.5625/lar.2015.31.3.101>
- Gollen, B., Mehla, J., Gupta, P., 2018. *Clitoria ternatea* Linn: A Herb with Potential Pharmacological Activities: Future Prospects as Therapeutic Herbal Medicine. *J. Pharmacol. Reports* 3, 1–8.
- Grindley, D.N., Burden, E.H.W.J., Akour, A.A., 1954. The seed oils of *Clitoria ternatea* AND OF *Entada phaseoloides*. *J. Sci. Food Agric.* 5, 278–280. <https://doi.org/10.1002/jsfa.2740050605>
- Grossberg, A.J., Zhu, X., Leininger, G.M., Levasseur, P.R., Braun, T.P., Myers, M.G., Marks, D.L., 2011. Inflammation-induced lethargy is mediated by suppression of orexin neuron activity. *J. Neurosci.* 31, 11376–11386. <https://doi.org/10.1523/JNEUROSCI.2311-11.2011>
- Gründemann, C., Thell, K., Lengen, K., Garcia-Käufer, M., Huang, Y.H., Huber, R., Craik, D.J., Schabbauer, G., Gruber, C.W., 2013. Cyclotides Suppress Human T-Lymphocyte Proliferation by an Interleukin 2-Dependent Mechanism. *PLoS One* 8, 1–12. <https://doi.org/10.1371/journal.pone.0068016>
- Gupta, G.K., Chahal, J., Bhatia, M., 2015. *Clitoria ternatea* (L.): Old and new aspects. *J. Pharm. Res.* 3, 2610–2614.
- Helmi, A., Nelmi, A., Dian, H., Rosalinda, R., 2016. Standarisasi ekstrak etanol Daun *Eugenia cumini* Merr. *J. Sains Tek. Far* 11, 88–93.
- Henics, T., Wheatley, D.N., 1999. Cytoplasmic vacuolation, adaptation and cell death: A view on new perspectives and features. *Biol. Cell* 91, 485–498. [https://doi.org/10.1016/S0248-4900\(00\)88205-2](https://doi.org/10.1016/S0248-4900(00)88205-2)
- Horiguchi, H., Oguma, E., Kayama, F., Sato, M., Fukushima, M., 2001. Dexamethasone Prevents Acute Cadmium-Induced Hepatic Injury but Exacerbates Kidney Dysfunction in Rabbits 234, 225–234. <https://doi.org/10.1006/taap.2001.9218>
- Huang, H. Bin, Jiang, W., Wang, C.Y., Qin, H.Y., Du, B., 2018. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: A systematic review and

- meta-analysis. *Crit. Care* 22, 1–9. <https://doi.org/10.1186/s13054-017-1937-1>
- Hurst, H.E., Martin, M.D., 2017. *Toxicology. Pharmacol. Ther. Dent.* Seventh Ed. 603–620. <https://doi.org/10.1016/B978-0-323-39307-2.00040-0>
- Ingawale, D.K., Mandlik, S.K., Naik, S.R., 2014. Models of hepatotoxicity and the underlying cellular, biochemical and immunological mechanism(s): A critical discussion. *Environ. Toxicol. Pharmacol.* 37, 118–133. <https://doi.org/10.1016/j.etap.2013.08.015>
- Ivanova, N., Gugleva, V., Dobрева, M., Pehlivanov, I., Stefanov, S., Andonova, V., 2016. We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists TOP 1%. Intech i, 13.
- Jackson, S.J., Andrews, N., Ball, D., Bellantuono, I., Gray, J., Hachoumi, L., Holmes, A., Latcham, J., Petrie, A., Potter, P., Rice, A., Ritchie, A., Stewart, M., Strepka, C., Yeoman, M., Chapman, K., 2017. Does age matter? The impact of rodent age on study outcomes. *Lab. Anim.* 51, 160–169. <https://doi.org/10.1177/0023677216653984>
- Ji, Y., Ji, C.F., Yue, L., Xu, H., 2012. Saponins isolated from Asparagus induce apoptosis in human hepatoma cell line HepG2 through a mitochondrial-mediated pathway. *Curr. Oncol.* 19, 1–9. <https://doi.org/10.3747/co.19.1139>
- Joshi, S.S., Shrivastava, R.K., Shrivastava, D.K., 1981. Chemical examination of *Clitoria ternatea* seeds. *J. Am. Oil Chem. Soc.* 58, 714–715. <https://doi.org/10.1007/BF02899459>
- Karta, J., Pandjaitan, M., Rahminiwati, M., 2013. Evaluation of acute oral toxicity of Butterfly Pea Root extract on experimental mice. *Proc. 2013 3rd Int. Conf. Instrumentation, Commun. Inf. Technol., Biomed. Eng. Sci. Technol. Improv. Heal. Safety, Environ., ICICI-BME 2013* 317–323. <https://doi.org/10.1109/ICICI-BME.2013.6698516>
- Khare, C.P., 2007. *Launaea pinnatifida* Cass. *Indian Med. Plants* 1–1. https://doi.org/10.1007/978-0-387-70638-2_887
- Lakshan, S.A.T., Jayanath, N.Y., Abeysekera, W.P.K.M., Abeysekera, W.K.S.M., 2019. A commercial potential blue pea (*Clitoria ternatea* L.) flower extract incorporated beverage having functional properties. *Evidence-based Complement. Altern. Med.* 2019. <https://doi.org/10.1155/2019/2916914>
- Larrey, D., 1997. Hepatotoxicity of herbal remedies. *J. Hepatol.* 26. [https://doi.org/10.1016/s0168-8278\(97\)82333-1](https://doi.org/10.1016/s0168-8278(97)82333-1)
- Lazic, S.E., Semenova, E., Williams, D.P., 2020. Determining organ weight toxicity with Bayesian causal models: Improving on the analysis of relative organ weights. *Sci. Rep.* 10, 1–12. <https://doi.org/10.1038/s41598-020-63465-y>
- Lee, W.J., Kim, H.W., Lee, H.Y., Son, C.G., 2015. Systematic review on herb-induced liver injury in Korea, *Food and Chemical Toxicology*. Elsevier Ltd. <https://doi.org/10.1016/j.fct.2015.06.004>
- Light, J.G., Haidari, W., Feldman, S.R., 2019. Assessing Efficacy and the Speed of Response in Psoriasis Treatment. *J. Dermatolog. Treat.* 30, 523–524. <https://doi.org/10.1080/09546634.2019.1643588>
- Lijon, M.B., Meghla, N.S., Jahedi, E., Rahman, M.A., Hossain, I., 2017. Phytochemistry and Pharmacological Activities of *Clitoria ternatea*. *Int. J. Nat. Soc. Sci.* 4, 1–10.
- Linggam, K., Ramanathan, S., Sasidharan, S., Mansor, S.M., 2012. Toxicity evaluation of methanol extract of *clitoria ternatea* L. Leaf Toxicity of *Clitoria ternatea* Toxicity Study of Methanol Extract of *Clitoria ternatea* L. Leaf Linggam Kamilla • Surash Ramanathan • Sreenivasan Sasidharan • Sharif Mahsufi Mansor Lingg.
- López-Gil, S., Nuño-Lámbarki, N., Chávez-Tapia, N., Uribe, M., Barbero-Becerra, V.J., 2017. Liver toxicity mechanisms of herbs commonly used in Latin America. *Drug Metab. Rev.* 49, 338–356. <https://doi.org/10.1080/03602532.2017.1335750>
- Mhaskar, A. V., Prakash, K., Vishwakarma, K.S., Maheshwari, V.L., 2010. Callus

- induction and antimicrobial activity of seed and callus extracts of *Clitoria ternatea* L. *Curr. Trends Biotechnol. Pharm.* 4, 561–567.
- Michael, B., Yano, B., Sellers, R.S., Perry, R., Morton, D., Roome, N., Johnson, J.K., Schafer, K., 2007a. Evaluation of Organ Weights for Rodent and Non-Rodent Toxicity Studies : A Review of Regulatory Guidelines and a Survey of Current Practices. *Toxicol. Pathol.* 35, 742–750. <https://doi.org/10.1080/01926230701595292>
- Michael, B., Yano, B., Sellers, R.S., Perry, R., Morton, D., Roome, N., Johnson, J.K., Schafer, K., Pitsch, S., 2007b. Evaluation of organ weights for rodent and non-rodent toxicity studies: a review of regulatory guidelines and a survey of current practices. *Toxicol. Pathol.* 35, 742–750. <https://doi.org/10.1080/01926230701595292>
- Miyagawa, M., 2010. Globally harmonized system of classification and labelling of chemicals (GHS) and its implementation in Japan, *Nippon eiseigaku zasshi. Japanese journal of hygiene.* <https://doi.org/10.1265/jjh.65.5>
- Morissette, G., Lodge, R., Marceau, F., 2008. Intense pseudotransport of a cationic drug mediated by vacuolar ATPase: Procainamide-induced autophagic cell vacuolization. *Toxicol. Appl. Pharmacol.* 228, 364–377. <https://doi.org/10.1016/j.taap.2007.12.031>
- Morris, J.B., 2009. Characterization of butterfly pea (*Clitoria ternatea* L.) accessions for morphology, phenology, reproduction and potential nutraceutical, pharmaceutical trait utilization. *Genet. Resour. Crop Evol.* 56, 421–427. <https://doi.org/10.1007/s10722-008-9376-0>
- Mossa, A.T.H., Swelam, E.S., Mohafrash, S.M.M., 2015. Sub-chronic exposure to fipronil induced oxidative stress, biochemical and histopathological changes in the liver and kidney of male albino rats. *Toxicol. Reports* 2, 775–784. <https://doi.org/10.1016/j.toxrep.2015.02.009>
- Mukherjee, P.K., Kumar, V., Kumar, N.S., Heinrich, M., 2008. The Ayurvedic medicine *Clitoria ternatea*-From traditional use to scientific assessment. *J. Ethnopharmacol.* 120, 291–301. <https://doi.org/10.1016/j.jep.2008.09.009>
- Nagahama, M., Itohayashi, Y., Hara, H., Higashihara, M., Fukatani, Y., Takagishi, T., Oda, M., Kobayashi, K., Nakagawa, I., Sakurai, J., 2011. Cellular vacuolation induced by *Clostridium perfringens* epsilon-toxin. *FEBS J.* 278, 3395–3407. <https://doi.org/10.1111/j.1742-4658.2011.08263.x>
- Navarro, V.J., Barnhart, H., Bonkovsky, H.L., Davern, T., Fontana, R.J., Grant, L., Reddy, R.K., 2014. Drug induced liver injury. *Hepatology* 60. <https://doi.org/10.1002/hep.27317>
- Nayak, N.C., Sathar, S.A., Mughal, S., Duttagupta, S., Mathur, M., Chopra, P., 1996. The nature and significance of liver cell vacuolation following hepatocellular injury - an analysis based on observations on rats rendered tolerant to hepatotoxic damage. *Virchows Arch.* 428, 353–365. <https://doi.org/10.1007/BF00202202>
- Neha, S., Rekha, V., 2010. Evaluation of Antimicrobial Potential of Some Medicinal Plants Against Plant and Human Pathogens. *J. Pharm. Res.* 3, 700–702.
- Nithianantham, K., Ping, K.Y., Latha, L.Y., Jothy, S.L., Darah, I., Chen, Y., Chew, A.L., Sasidharan, S., 2013. Evaluation of hepatoprotective effect of methanolic extract of *Clitoria ternatea* (Linn.) flower against acetaminophen-induced liver damage. *Asian Pacific J. Trop. Dis.* 3, 314–319. [https://doi.org/10.1016/S2222-1808\(13\)60075-4](https://doi.org/10.1016/S2222-1808(13)60075-4)
- Nusrat, S., Maheshwari, D.G., 2016. An overview on toxicity testing methods. *Int. J. Pharm. Technol.* 8, 3834–3849.
- Obernier, J.A., Baldwin, R.L., 2006. Establishing an appropriate period of acclimatization following transportation of laboratory animals. *ILAR J.* 47, 364–369. <https://doi.org/10.1093/ilar.47.4.364>
- OECD, 2002. The Organization of Economic Co-operation and Development Guidelines Test No. 423: Acute Oral toxicity - Acute Toxic Class Method, OECD Guidelines for the Testing of Chemicals, Section 4. Oecd 1–14.

- Oguis, G.K., Gilding, E.K., Jackson, M.A., Craik, D.J., 2019. Butterfly pea (*Clitoria ternatea*), a cyclotide-bearing plant with applications in agriculture and medicine. *Front. Plant Sci.* 10, 1–23. <https://doi.org/10.3389/fpls.2019.00645>
- Ohkuma, S., Poole, B., 1981. Cytoplasmic vacuolation of mouse peritoneal macrophages and the uptake into lysosomes of weakly basic substances. *J. Cell Biol.* 90, 656–664. <https://doi.org/10.1083/jcb.90.3.656>
- Ohno, K., Sakurai, T., 2008. Orexin neuronal circuitry: Role in the regulation of sleep and wakefulness. *Front. Neuroendocrinol.* 29, 70–87. <https://doi.org/10.1016/j.yfrne.2007.08.001>
- Organisation for Economic Cooperation and Development, 2001. Test guideline 425: acute oral toxicity - Up-and-Down Procedure. *Guidel. Test. Chem.* 26.
- Panche, A.N., Diwan, A.D., Chandra, S.R., 2016. Flavonoids: An overview. *J. Nutr. Sci.* 5. <https://doi.org/10.1017/jns.2016.41>
- Parasuraman, S., 2011. Toxicological screening. *J. Pharmacol. Pharmacother.* 2, 74–79. <https://doi.org/10.4103/0976-500X.81895>
- Pendbhaje, N.S., Pathan, S.M., Musmade, D.S., 2011. Ethanopharmacology, Pharmacognosy and Phytochemical Profile of *Clitoria Ternatea* Linn: an Overview. *Pharmacologyonline* 175, 166–175.
- Phifer-Rixey, M., Nachman, M.W., 2015. Insights into mammalian biology from the wild house mouse *Mus musculus*. *Elife* 2015, 1–13. <https://doi.org/10.7554/eLife.05959>
- Podolak, I., Galanty, A., Sobolewska, D., 2010. Saponins as cytotoxic agents: A review. *Phytochem. Rev.* 9, 425–474. <https://doi.org/10.1007/s11101-010-9183-z>
- Radenkova-Saeva, J., 2008. Historical development of toxicology. *Acta Medica Bulg.* 35, 47–52.
- Ramaswamy, V., Varghese, N., Simon, A., 2011. An investigation on Cytotoxic and Antioxidant Properties of *Clitoria Ternatea* L. *Int. J. Drug Discov.* 3, 74–77. <https://doi.org/10.9735/0975-4423.3.1.74-77>
- Randhawa, M.A., 2009. Calculation of LD50 values from the method of Miller and Tainter, 1944. *J. Ayub Med. Coll. Abbottabad* 21, 184–185.
- Rodriguez-Fragoso, L., Reyes-Esparza, J., Burchiel, S.W., Herrera-Ruiz, D., Torres, E., 2008. Risks and benefits of commonly used herbal medicines in Mexico. *Toxicol. Appl. Pharmacol.* 227, 125–135. <https://doi.org/10.1016/j.taap.2007.10.005>
- Rogers-Cotrone, T., Burgess, M.P., Hancock, S.H., Hinckley, J., Lowe, K., Ehrich, M.F., Jortner, B.S., 2010. Vacuolation of sensory ganglion neuron cytoplasm in rats with long-term exposure to organophosphates. *Toxicol. Pathol.* 38, 554–559. <https://doi.org/10.1177/0192623310369343>
- Roulet, M., Laurini, R., Rivier, L., Calame, A., 1988. Hepatic veno-occlusive disease in newborn infant of a woman drinking herbal tea.
- Saganuwan, S.A., 2017. Toxicity studies of drugs and chemicals in animals: An overview. *Bulg. J. Vet. Med.* 20, 291–318. <https://doi.org/10.15547/bjvm.983>
- Saganuwan, S.A., 2011. A modified arithmetical method of Reed and Muench for determination of a relatively ideal median lethal dose (LD50). *African J. Pharm. Pharmacol.* 5, 1543–1546. <https://doi.org/10.5897/AJPP11.393>
- Sakurai, T., 2014. The role of orexin in motivated behaviours. *Nat. Rev. Neurosci.* 15, 719–731. <https://doi.org/10.1038/nrn3837>
- Sakurai, T., 2003. Orexin: A link between energy homeostasis and adaptive behaviour. *Curr. Opin. Clin. Nutr. Metab. Care* 6, 353–360. <https://doi.org/10.1097/00075197-200307000-00001>
- Saleem, U., Amin, S., Ahmad, B., Azeem, H., Anwar, F., Mary, S., 2017. Acute oral toxicity evaluation of aqueous ethanolic extract of *Saccharum munja* Roxb. roots in albino mice as per OECD 425 TG. *Toxicol. Reports* 4, 580–585. <https://doi.org/10.1016/j.toxrep.2017.10.005>
- Sarumathy, K., Rajan, M.S.D., Vijay, T., Jayakanthi, J., 2011. Evaluation of

- phytoconstituents, nephro-protective and antioxidant activities of *Clitoria ternatea*. *J. Appl. Pharm. Sci.* 1, 164–172.
- Sasidharan, S., Aravindran, S., Latha, L.Y., Vijenthi, R., Saravanan, D., Amutha, S., 2010. In vitro antioxidant activity and hepatoprotective effects of lentinula edodes against paracetamol-induced hepatotoxicity. *Molecules* 15, 4478–4489. <https://doi.org/10.3390/molecules15064478>
- Schiano, T.D., 2003. Hepatotoxicity and complementary and alternative medicines. *Clin. Liver Dis.* 7, 453–473. [https://doi.org/10.1016/S1089-3261\(03\)00030-8](https://doi.org/10.1016/S1089-3261(03)00030-8)
- Schlager, G., 1968. Kidney weight in mice: Strain differences and genetic determination. *J. Hered.* 59, 171–174. <https://doi.org/10.1093/oxfordjournals.jhered.a107677>
- Shubin, A. V., Demidyuk, I. V., Lunina, N.A., Komissarov, A.A., Roschina, M.P., Leonova, O.G., Kostrov, S. V., 2015. Protease 3C of hepatitis A virus induces vacuolization of lysosomal/endosomal organelles and caspase-independent cell death. *BMC Cell Biol.* 16, 1–18. <https://doi.org/10.1186/s12860-015-0050-z>
- Silva-Santana, G., Aguiar-Alves, F., Esmeraldo da Silva, L., Barreto, M.L., Ribeiro da Silca, J.F.R., Gonçalves, A., Mattos-Guaraldi, A.L., Lenzi-Almeida, K.C., 2019. Compared Anatomy and Histology between *Mus musculus* Mice (Swiss) and *Rattus norvegicus* Rats (Wistar). *Preprints* 87, 1–34. <https://doi.org/10.20944/preprints201907.0306.v1>
- Singhal, P.C., Sharma, P., Sanwal, V., Prasad, A., Kapasi, A., Ranjan, R., Franki, N., Reddy, K., Gibbons, N., 1998. Morphine modulates proliferation of kidney fibroblasts. *Kidney Int.* 53, 350–357. <https://doi.org/10.1046/j.1523-1755.1998.00758.x>
- Sogo, T., Terahara, N., Hisanaga, A., Kumamoto, T., Yamashiro, T., Wu, S., Sakao, K., Hou, D.X., 2015. Anti-inflammatory activity and molecular mechanism of delphinidin 3-sambubioside, a Hibiscus anthocyanin. *BioFactors* 41, 58–65. <https://doi.org/10.1002/biof.1201>
- Sparg, S.G., Light, M.E., Van Staden, J., 2004. Biological activities and distribution of plant saponins. *J. Ethnopharmacol.* 94, 219–243. <https://doi.org/10.1016/j.jep.2004.05.016>
- Stirling, D., 2006. History of toxicology and allied sciences: A bibliographic review and guide to suggested readings. *Int. J. Toxicol.* 25, 261–268. <https://doi.org/10.1080/10915810600746064>
- Taranalli, A.D., Cheeramkuzhy, T.C., 2000. Influence of *Clitoria ternatea* extracts on memory and central cholinergic activity in rats. *Pharm. Biol.* 38, 51–56. [https://doi.org/10.1076/1388-0209\(200001\)3811-BFT051](https://doi.org/10.1076/1388-0209(200001)3811-BFT051)
- Taur, D.J., Taware, S.B., Patil, R.N., Patil, R.Y., Kharya, M.D., 2010. Pharmacognostical and preliminary phytochemical evaluation of *Clitoria ternatea* leaves. *Pharmacogn. J.* 2, 260–265. [https://doi.org/10.1016/S0975-3575\(10\)80114-2](https://doi.org/10.1016/S0975-3575(10)80114-2)
- Tonahi, J., Nuryanti, S., Suherman, S., 2014. Antioksidan dari Daun Sirih Merah (*Piper Crocatum*). *J. Akad. Kim.* 3, 158–164.
- Tsujino, N., Sakurai, T., 2009. Orexin/hypocretin: A neuropeptide at the interface of sleep, energy homeostasis, and reward system. *Pharmacol. Rev.* 61, 162–176. <https://doi.org/10.1124/pr.109.001321>
- Uzkeser, M., 2012. Protective effect of Panax ginseng against N-acetyl-p-aminophenol-induced hepatotoxicity in rats. *African J. Pharm. Pharmacol.* 6, 2634–2642. <https://doi.org/10.5897/ajpp12.658>
- Walum, E., 1998. Acute oral toxicity. *Environ. Health Perspect.* 106, 497–503. <https://doi.org/10.1289/ehp.98106497>
- Wang, X., Kanel, G.C., DeLeve, L.D., 2000. Support of sinusoidal endothelial cell glutathione prevents hepatic veno-occlusive disease in the rat. *Hepatology* 31, 428–434. <https://doi.org/10.1002/hep.510310224>
- Wisløff, H., Uhlig, S., Scheie, E., Loader, J., Wilkins, A., Flåøyen, A., 2008. Toxicity

- testing of saponin-containing *Yucca schidigera* Roetzl. juice in relation to hepato- and nephrotoxicity of *Nartheceum ossifragum* (L.) Huds. *Toxicol* 51, 140–150. <https://doi.org/10.1016/j.toxicol.2007.08.016>
- Witthawaskul, P., Panthong, A., Kanjanapothi, D., Taesothikul, T., Lertprasertsuke, N., 2003. Acute and subacute toxicities of the saponin mixture isolated from *Schefflera leucantha* Viguier. *J. Ethnopharmacol.* 89, 115–121. [https://doi.org/10.1016/S0378-8741\(03\)00273-3](https://doi.org/10.1016/S0378-8741(03)00273-3)
- Wolf, J.C., Wheeler, J.R., 2018. A critical review of histopathological findings associated with endocrine and non-endocrine hepatic toxicity in fish models. *Aquat. Toxicol.* 197, 60–78. <https://doi.org/10.1016/j.aquatox.2018.01.013>
- World Health Organization (WHO), 2002. WHO Traditional Medicine Strategy 2002–2005. World Heal. Organ. Geneva 1–74.
- Yang, C.L., Ma, Y.G., Xue, Y.X., Liu, Y.Y., Xie, H., Qiu, G.R., 2012. Curcumin induces small cell lung cancer NCI-H446 cell apoptosis via the reactive oxygen species-mediated mitochondrial pathway and not the cell death receptor pathway. *DNA Cell Biol.* 31, 139–150. <https://doi.org/10.1089/dna.2011.1300>
- Yoon, M.J., Lee, A.R., Jeong, S.A., Kim, Y., Kim, J.Y., 2014. Release of Ca²⁺ from the endoplasmic reticulum and its subsequent influx into mitochondria trigger celastrol-induced paraptosis in cancer cells. *Oncotarget* 5, 6816–6831.
- Zakaria, Z.A., Rofiee, M.S., Somchit, M.N.S., Zuraini, A., Sulaiman, M.R., Teh, L.K., Salleh, M.Z., Long, K., 2011. Hepatoprotective activity of dried- and fermented-processed virgin coconut oil. *Evidence-based Complement. Altern. Med.* 2011. <https://doi.org/10.1155/2011/142739>
- Zhang, J., Brown, R.P., Shaw, M., Vaidya, V.S., Zhou, Y., Espandiari, P., Sadrieh, N., Stratmeyer, M., Keenan, J., Kilty, C.G., Bonventre, J. V., Goering, P.L., 2008. Immunolocalization of Kim-1, RPA-1, and RPA-2 in Kidney of Gentamicin-, Mercury-, or Chromium-Treated Rats: Relationship to Renal Distributions of iNOS and Nitrotyrosine. *Toxicol. Pathol.* 36, 397–409. <https://doi.org/10.1177/0192623308315832>
- Zheng, K., Liao, C., Li, Y., Fan, X., Fan, L., Xu, H., Kang, Q., Zeng, Y., Wu, X., Wu, H., Liu, L., Xiao, X., Zhang, J., Wang, Y., He, Z., 2016. Gypenoside L, Isolated from *Gynostemma pentaphyllum*, Induces Cytoplasmic Vacuolation Death in Hepatocellular Carcinoma Cells through Reactive-Oxygen-Species-Mediated Unfolded Protein Response. *J. Agric. Food Chem.* 64, 1702–1711. <https://doi.org/10.1021/acs.jafc.5b05668>
- Zhong, R., Chen, Y., Ling, J., Xia, Z., Zhan, Y., Sun, E., Shi, Z., Feng, L., Jia, X., Song, J., Wei, Y., 2019. The Toxicity and Metabolism Properties of Herba Epimedii Flavonoids on Laval and Adult Zebrafish. *Evidence-based Complement. Altern. Med.* 2019. <https://doi.org/10.1155/2019/3745051>
- Zielinski, M.R., Systrom, D.M., Rose, N.R., 2019. Fatigue, sleep, and autoimmune and related disorders. *Front. Immunol.* 10, 1–26. <https://doi.org/10.3389/fimmu.2019.01827>