

DAFTAR PUSTAKA

1. “Obat-obat penyakit serebrovaskular”, dr. Aldy S. Rambe Bag Neurologi, Fakultas Kedokteran USU. 2004
2. “The story of the discovery of heparin and warfarin”, Douglas Wardrop and David Keeling. Oxford Haemophilia and Thrombosis Centre, Oxford Radcliffe Hospitals, Oxford, UK. 2008
3. Campbell, H.A. & Link, K.P. (1941) “Studies on the hemorrhagic sweet clover disease. IV. The isolation and crystallization of the hemmorhaic agent”. *Journal of Biological Chemistry*, 138.
4. Buku ajar toksikologi umum, Dr.rer.nat. I Made Agus Gelgel Wirasuta, M.Si., Apt ; Rasmaya Niruri, S.Si., Apt., Jurusan Farmakologi, UNUD. 2006
5. http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/
6. Wysowski DK, Nourjah P, Swartz L. “Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action”. *Arch Intern Med*. 2007; 167 : 1414–9.
7. Casarett & Doull’s Toxicology: The basic science of poisons Descriptive Animal Toxicity Tests - p25-28. 2013
8. “Efektivitas Antikoagulan Baru Dibandingkan dengan Warfarin dalam Mencegah *Stroke* pada Pasien Atrial Fibrilasi”; Alvin Nursalim, Edwin Setiabudi; *SMF Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Kristen Maranatha.zz*
9. Ansell J, Hirsh J, Hylek E, et al. (2008). "Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition)". *Chest* **133** (6 Suppl): 160S–198S.
10. *Fundamentals of Anatomy and Physiology*, 9th edition; Martini, Nath, Bartholomew; p814-815.

11. Sadler T (2003). *Langman's Medical Embryology* (9th ed. ed.). Lippincott Williams & Wilkins.
12. Moore KL, Persaud TVN (2002). *The Developing Human: Clinically Oriented Embryology* (7th ed.).
13. Weinberger SE (2004). *Principles of Pulmonary Medicine* (4th ed. ed.).
14. Maton, Anthea; Jean Hopkins; Charles William McLaughlin; Susan Johnson; Maryanna Quon Warner; David LaHart; Jill D. Wright (1993). *Human Biology and Health*.
15. Schoenwolf, Gary C.; Bleyl, Steven B.; Brauer, Philip R.; Francis-West, Philippa H. (2009). "Development of the Urogenital system". *Larsen's human embryology* (4th ed.). Philadelphia: Churchill Livingstone/Elsevier. p. 237.
16. Deakin, Barbara Young ... [et al.] ; drawings by Philip J. (2006). *Wheater's functional histology : a text and colour atlas* (5th ed. ed.). [Edinburgh]: Churchill Livingstone/Elsevier.
17. Gartner and Hiatt; (2014). *Color Atlas and Text of Histology* (6th Edition ed.). Baltimore: Lippincott Williams & Wilkins.
18. "Gambaran efek toksik etanol pada sel hati", Hernawati, Jurusan Pendidikan Biologi, FPMIPA Universitas Pendidikan Indonesia.
19. "The MSDS HyperGlossary: Acute toxicity". Diambil dari www.ilpi.com/msds/ref/acutetoxicity.html.
20. IUPAC, *Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book") (1997).
21. Walum E (1998). "Acute oral toxicity". (Environmental Health Perspectives, Vol. 106) **106** (Suppl 2): 497–503.
22. "Fifth Report on the Statistics on the Number of Animals used for Experimental and other Scientific Purposes in the Member States of the European Union", *Commission of the European Communities*, diterbitkan November 2007.

23. Barile F. *Clinical toxicology: principal and mechanisms*. Washington DC : CRC Press; 2005.
24. A Pesticide Information Project of Cooperative Extension Offices of Cornell University, Oregon State University, the University of Idaho, and the University of California at Davis and the Institute for Environmental Toxicology, Michigan State University. 2000
25. Krinke, George J. (June 15, 2000). "History, Strains and Models". *The Laboratory Rat (Handbook of Experimental Animals)*. Gillian R. Bullock (series ed.), Tracie buntun (series ed.). Academic Press. pp. 3–16.
26. "Rules and Guidelines for Nomenclature of Mouse and Rat Strains". Diambil dari <http://www.informatics.jax.org/mgihome/nomen/strains.shtml#oacc>
27. Clause, B. T. (1998). *The Wistar Institute Archives: Rats (Not Mice) and History*, *Mendel Newsletter* February, 1998.
28. "The Wistar Institute:History". The Wistar Institute. 2007.
29. "Research Animal Models". Charles River.
30. "Toksikologi Pestisida dan Penanganan akibat Keracunan Pestisida", Mariana Raini. Puslitbang biomedis dan farmasi. 2007
31. "Human P450 Metabolism of Warfarin", Kaminsky LS, Zhang ZY. New York State Department of Health, Wadsworth Center, USA.
32. "Rat small intestinal cytochromes P450 probed by warfarin metabolism.", Fasco, M J; Silkworth, J B; Dunbar, D A.
33. "The warfarin-sulfinpyrazone interaction: stereochemical considerations." Toon S, Low LK, Gibaldi M, Trager WF, O'Reilly RA, Motley CH, Goulart DA *Clin Pharmacol Ther.* 1986 Jan; 39(1):15-24.
34. Hodgson, E., and J. A. Goldstein. *Metabolism of toxicants: Phase I reactions and pharmacogenetics*. In "*Introduction to Biochemical Toxicology*", 3rd ed., E. Hodgson and R. C. Smart, eds. New York: Wiley, 2001, pp. 67–113.

35. LeBlanc, G. A., and W. A. Dauterman. "Conjugation and elimination of toxicants: In *Introduction to Biochemical Toxicology*", 3rd edn., E. Hodgson and R. C. Smart, eds. New York: Wiley, 2001, pp. 115–135.
36. Oesch, F, and M. Arand. Xenobiotic metabolism. In *Toxicology*", H. Marquardt, S. G. Shafer, R. McClellan, and F. Welsch, eds. New York: Academic Press, 1999, pp. 83–109.
37. Tukey, R. H., and C. P. Strassburg. "Human UDP-glucuronosyltransferases: Metabolism, expression, and disease." *Ann. Rev. Pharmacol. Toxicol.* **40**: 581–616, 2000.
38. Vasiliou, V., A. Pappa, and D. R. Petersen. "Role of aldehyde dehydrogenases in endogenous and xenobiotic metabolism." *Chemico-Biol. Inter.* **129**: 1–19, 2000.
39. Benedetti, M. S. "Biotransformation of xenobiotics by amine oxidases." *Fundam. Clinic. Pharmacol.*
40. "Modulasi CYP1A1 dan GST Serta Ekspresi P53 dan RAS Setelah Induksi 7,12-Dimethyl Benz(α)antrasen (DMBA) dan Pemberian Anti Karsinogenesis *Gynura procumbens* dan *Curcuma zedoaria* Pada Tikus Galur *Sprague dawley*". Iwan Sahrial Hamid, Fak Ked Hewan UNAIR; Edy Meiyanto, Fak Farmasi UGM. 2009.
41. Barthel M, Hapfelmeier S, Quintanilla-Martinez L, Kremer M, Rohde M, Hogardt M, et al. Pretreatment of mice with streptomycin provides a *Salmonella enterica serovar typhimurium* colitis model that allows analysis of both pathogen and host. 1997.
42. Lorraine et al. *Acute Pulmonary Edema*. N Engl J Med. 2005; 353:2788-96.
43. Olson KR, Trickey DN, Miller MA, Yungmann Hile ML. Toxicity, Warfarin and Superwarfarins. *eMedicine, Emergencgy Medicine*. 2009.
44. Diana Haryati Kusumastuti, Dewi Rosalina, Ratna Doemilah, Evelyn Komaratih. Department of Ophthalmology, Faculty of Medicine Airlangga University/Dr. Soetomo General Hospital, Surabaya. Awareness of

Subconjunctival Bleeding on Warfarin Therapy Patient. JOI vol. 7 no. 4
Desember 2010.

Lampiran 1. Biodata Mahasiswa**Identitas**

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Lampiran 2. Ethical Clearance



**KOMISI ETIK PENELITIAN KESEHATAN (KEPK)
FAKULTAS KEDOKTERAN UNIVERSITAS DIPONEGORO
DAN RSUP dr KARIADI SEMARANG**
Sekretariat : Kantor Dekanat FK Undip Lt.3
Jl. Dr. Soetomo 18. Semarang
Telp/Fax. 024-8318350



ETHICAL CLEARANCE
No. 241/EC/FK-RSDK/2015

Komisi Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Diponegoro- RSUP. Dr. Kariadi Semarang, setelah membaca dan menelaah Usulan Penelitian :

Judul : Analisa gambaran post mortem makroskopis dan mikroskopis otak dan hati pada tikus wistar setelah pemberian warfarin LD-50 dan LD-100

Peneliti : **Husein Alaydrus**

Judul : Analisa gambaran post mortem makroskopis paru dan usus halus pada tikus wistar setelah pemberian warfarin LD-50 dan LD-100

Peneliti : **Mada Aji Prakoso**

Pembimbing : dr. Gatot Suharto, SH., Sp.F.,M.Kes & dr. Siti Amarwati, Sp. PA(K)


Penelitian : Dilaksanakan di : Laboratorium Biologi Fakultas Matematika dan Ilmu Pengetahuan Alam Universitas Negeri Semarang, Laboratorium Patologi Anatomi Waspada

Setuju untuk dilaksanakan, dengan memperhatikan prinsip-prinsip yang dinyatakan dalam Deklarasi Helsinki 1975, yang diamended di Seoul 2008 dan Pedoman Nasional Etik Penelitian Kesehatan (PNEPK) Departemen Kesehatan RI 2011

Pada laporan akhir peneliti harus melampirkan cara pemeliharaan & dekapitasi hewan coba dan melaporkan ke KEPK bahwa penelitian sudah selesai dilampiri Abstrak Penelitian.

Semarang, 29 APR 2015

Komisi Etik Penelitian Kesehatan
Fakultas Kedokteran Undip-RS. Dr. Kariadi
Wakil Ketua



Dr. dr. Selamat Budijitno, M.Si.Med, Sp.B, Sp.B(K), Onk, FICS
NIP. 19710807 200812 1 001

Lampiran 3. Ijin Penelitian



**KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN
UNIVERSITAS NEGERI SEMARANG
FAKULTAS MATEMATIKA DAN ILMU PENGETAHUAN ALAM
LABORATORIUM JURUSAN BIOLOGI**

Alamat : Gedung D11 FMIPA UNNES Kampus Sekaran Gunungpati Semarang 50229

Semarang, 23 Maret 2015

Nomor : 310 /UN.3.7.4.5/PP/2015
Lampiran : -
Perihal : -

Yth. Pembantu Dekan I
Fakultas Kedokteran
Universitas Diponegoro

Dengan hormat,

Menjawab Surat saudara nomor 1371/UN7.3.4/DI/PP/2014 tanggal 18 Maret 2015 perihal permohonan ijin penelitian dengan menggunakan hewan percobaan, dalam rangka penyusunan Karya Tulis Ilmiah mahasiswa :

1. Nama : Husein Alaydrus
NIM : 22010111110140
2. Nama : Mada Aji Prakoso
NIM : 22010111130098
3. Nama : Anggoro Adjar Mangestu
NIM : 22010222240185

Judul : Analisa Gambaran Post Mortem Makroskopis Organ Otak, Hati, Paru-paru, Usus Halus, Jantung dan Ginjal pada Tikus Wistar setelah Pemberian Walfarin LD-50 dan LD-100

Dengan ini kami beritahukan bahwa permohonan ijin tersebut dapat kami setujui sesuai peraturan yang berlaku. Adapun pelaksanaannya akan dibantu oleh teknisi kami sdr. Kartika Widya dan Bapak Ngatiman.

Demikian kami sampaikan, terimakasih atas perhatian dan kerjasamanya

Laboratorium Biologi FMIPA Unnes



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LAMPIRAN 4

PERHITUNGAN DOSIS

Tabel 22. Konversi Dosis Pages dan Barnes

Hewan dengan dosis diketahui	Hewan yang Dicari Ekuivalensi Dosisnya							
	Mencit	Tikus	Marmot	Kelinci	Kucing	Kera	Anjing	Manusia
	20g	200g	400g	1,5g	2kg	4kg	12kg	70kg
Mencit	1,0	7,0	12,25	27,8	29,7	64,1	124,2	387,9
Tikus	0,14	1,0	1,74	3,9	4,2	9,2	17,8	56,0
Marmot	0,08	0,57	1,0	2,25	2,4	5,2	10,2	31,5
Kelinci	0,04	0,25	0,44	1,0	1,08	2,4	4,5	14,2
Kucing	0,03	0,23	0,41	0,92	1,0	2,2	4,1	13,0
Kera	0,016	0,11	0,19	0,42	0,45	1,0	1,9	6,1
Anjing	0,08	0,06	0,10	0,22	0,24	0,52	1,0	3,1
Manusia	0,0026	0,018	0,031	0,07	0,076	0,16	0,32	1,0

LAMPIRAN 5

DATA SPESIFIKASI WARFARIN

Warfarin yang digunakan dalam penelitian adalah Simarc® 2. Simarc® 2 bekerja dengan cara menginhibisi beberapa faktor pembekuan. Secara in vivo, obat bekerja menginhibisi faktor VII, IX, X dan II yang terlibat pada proses pembekuan darah. Antikoagulan tidak memiliki efek langsung terhadap thrombus dan tidak memperbaiki jaringan rusak, tetapi lebih ditujukan untuk mencegah terjadinya thrombus lebih lanjut, agar bahaya komplikasi terhindarkan.¹

Komposisi Simarc® 2 : tiap tablet mengandung Warfarin Sodium 2mg

LAMPIRAN 6. Output Statistik

Paru

Case Summaries

Paru

Kelompok	N	Mean	Std. Deviation	Median	Minimum	Maximum
Kontrol	3	.2000	.34641	.0000	.00	.60
LD50	3	1.4667	.11547	1.4000	1.40	1.60
LD100	3	2.2667	1.33167	1.6000	1.40	3.80
Total	9	1.3111	1.13627	1.4000	.00	3.80

Tests of Normality

Kelompok	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Paru Kontrol	.385	3	.	.750	3	.000
LD50	.385	3	.	.750	3	.000
LD100	.358	3	.	.812	3	.144

a. Lilliefors Significance Correction

NPar Tests

Kruskal-Wallis Test

Ranks

Kelompok	N	Mean Rank
Paru Kontrol	3	2.00
LD50	3	5.83
LD100	3	7.17
Total	9	

Test Statistics^{a,b}

	Paru
Chi-Square	6.058
df	2
Asymp. Sig.	.048

a. Kruskal Wallis Test

b. Grouping Variable: Kelompok

NPar Tests**Mann-Whitney Test****Ranks**

	Kelompok	N	Mean Rank	Sum of Ranks
Paru	Kontrol	3	2.00	6.00
	LD50	3	5.00	15.00
	Total	6		

Test Statistics^b

	Paru
Mann-Whitney U	.000
Wilcoxon W	6.000
Z	-2.023
Asymp. Sig. (2-tailed)	.043
Exact Sig. [2*(1-tailed Sig.)]	.100 ^a

a. Not corrected for ties.

b. Grouping Variable: Kelompok

NPar Tests

Mann-Whitney Test

Ranks

	Kelompok	N	Mean Rank	Sum of Ranks
Paru	Kontrol	3	2.00	6.00
	LD100	3	5.00	15.00
	Total	6		

Test Statistics^b

	Paru
Mann-Whitney U	.000
Wilcoxon W	6.000
Z	-1.993
Asy mp. Sig. (2-tailed)	.046
Exact Sig. [2*(1-tailed Sig.)]	.100 ^a

a. Not corrected for ties.

b. Grouping Variable: Kelompok

NPar Tests

Mann-Whitney Test

Ranks

	Kelompok	N	Mean Rank	Sum of Ranks
Paru	LD50	3	2.83	8.50
	LD100	3	4.17	12.50
	Total	6		

Test Statistics^b

	Paru
Mann-Whitney U	2.500
Wilcoxon W	8.500
Z	-.943
Asymp. Sig. (2-tailed)	.346
Exact Sig. [2*(1-tailed Sig.)]	.400 ^a

a. Not corrected for ties.

b. Grouping Variable: Kelompok

Explore**Ukuran paru****Case Summaries**

Ukuran paru

Kelompok	N	Mean	Std. Deviation	Median	Minimum	Maximum
Kontrol	9	5.3511	.47325	5.5400	4.49	6.00
LD50	9	4.3578	1.43857	4.7300	2.08	6.33
LD100	9	4.5244	1.38682	3.9400	3.23	7.29
Total	27	4.7444	1.22203	4.9000	2.08	7.29

Tests of Normality

Kelompok	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Ukuran paru Kontrol	.211	9	.200*	.960	9	.800
LD50	.158	9	.200*	.961	9	.812
LD100	.302	9	.018	.790	9	.016

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Test of Homogeneity of Variance

		Levene Statistic	df1	df2	Sig.
Ukuran paru	Based on Mean	4.325	2	24	.025
	Based on Median	2.000	2	24	.157
	Based on Median and with adjusted df	2.000	2	15.692	.168
	Based on trimmed mean	3.793	2	24	.037

NPar Tests

Kruskal-Wallis Test

Ranks

	Kelompok	N	Mean Rank
Ukuran paru	Kontrol	9	18.44
	LD50	9	11.89
	LD100	9	11.67
	Total	27	

Test Statistics^{a,b}

	Ukuran paru
Chi-Square	4.236
df	2
Asy mp. Sig.	.120

a. Kruskal Wallis Test

b. Grouping Variable: Kelompok

Explore

Berat paru

Case Summaries

Berat paru						
Kelompok	N	Mean	Std. Deviation	Median	Minimum	Maximum
Kontrol	9	1.3844	.08847	1.3500	1.28	1.50
LD50	8	1.1525	.27871	1.1750	.63	1.60
LD100	9	1.4900	.27749	1.4200	1.11	1.96
Total	26	1.3496	.26241	1.3250	.63	1.96

Tests of Normality

Kelompok	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Berat paru Kontrol	.207	9	.200*	.881	9	.160
LD50	.189	8	.200*	.952	8	.733
LD100	.155	9	.200*	.959	9	.783

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Test of Homogeneity of Variance

		Levene Statistic	df 1	df 2	Sig.
Berat paru	Based on Mean	2.856	2	23	.078
	Based on Median	2.176	2	23	.136
	Based on Median and with adjusted df	2.176	2	15.888	.146
	Based on trimmed mean	2.792	2	23	.082

Oneway

ANOVA

Berat paru

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.499	2	.250	4.696	.019
Within Groups	1.222	23	.053		
Total	1.721	25			

Post Hoc Tests

Multiple Comparisons

Dependent Variable: Berat paru

Bonferroni

(I) Kelompok	(J) Kelompok	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Kontrol	LD50	.23194	.11202	.149	-.0573	.5212
	LD100	-.10556	.10868	1.000	-.3862	.1750
LD50	Kontrol	-.23194	.11202	.149	-.5212	.0573
	LD100	-.33750*	.11202	.019	-.6267	-.0483
LD100	Kontrol	.10556	.10868	1.000	-.1750	.3862
	LD50	.33750*	.11202	.019	.0483	.6267

*. The mean difference is significant at the .05 level.

Explore

Usus

Case Summaries

Usus						
Kelompok	N	Mean	Std. Deviation	Median	Minimum	Maximum
Kontrol	3	.1333	.11547	.2000	.00	.20
LD50	3	1.5333	.30551	1.6000	1.20	1.80
LD100	3	2.5333	.46188	2.8000	2.00	2.80
Total	9	1.4000	1.08167	1.6000	.00	2.80

Tests of Normality

Kelompok	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Usus Kontrol	.385	3	.	.750	3	.000
LD50	.253	3	.	.964	3	.637
LD100	.385	3	.	.750	3	.000

a. Lilliefors Significance Correction

NPar Tests

Kruskal-Wallis Test

Ranks

Kelompok	N	Mean Rank
Usus Kontrol	3	2.00
LD50	3	5.00
LD100	3	8.00
Total	9	

Test Statistics^{a,b}

	Usus
Chi-Square	7.322
df	2
Asymp. Sig.	.026

a. Kruskal Wallis Test

b. Grouping Variable: Kelompok

NPar Tests**Mann-Whitney Test****Ranks**

	Kelompok	N	Mean Rank	Sum of Ranks
Usus	Kontrol	3	2.00	6.00
	LD50	3	5.00	15.00
	Total	6		

Test Statistics^b

	Usus
Mann-Whitney U	.000
Wilcoxon W	6.000
Z	-1.993
Asymp. Sig. (2-tailed)	.046
Exact Sig. [2*(1-tailed Sig.)]	.100 ^a

a. Not corrected for ties.

b. Grouping Variable: Kelompok

NPar Tests

Mann-Whitney Test

Ranks

	Kelompok	N	Mean Rank	Sum of Ranks
Usus	Kontrol	3	2.00	6.00
	LD100	3	5.00	15.00
	Total	6		

Test Statistics^b

	Usus
Mann-Whitney U	.000
Wilcoxon W	6.000
Z	-2.023
Asy mp. Sig. (2-tailed)	.043
Exact Sig. [2*(1-tailed Sig.)]	.100 ^a

a. Not corrected for ties.

b. Grouping Variable: Kelompok

NPar Tests

Mann-Whitney Test

Ranks

	Kelompok	N	Mean Rank	Sum of Ranks
Usus	LD50	3	2.00	6.00
	LD100	3	5.00	15.00
	Total	6		

Test Statistics^b

	Usus
Mann-Whitney U	.000
Wilcoxon W	6.000
Z	-1.993
Asymp. Sig. (2-tailed)	.046
Exact Sig. [2*(1-tailed Sig.)]	.100 ^a

a. Not corrected for ties.

b. Grouping Variable: Kelompok