

## DAFTAR PUSTAKA

- Alfikri, F.N., Pujiarti, R., Wibisono, M.G., Hardiyanto, E.B., 2020. Yield, Quality, and Antioxidant Activity of Clove (*Syzygium aromaticum L.*) Bud Oil at the Different Phenological Stages in Young and Mature Trees. *Scientifica (Cairo)*.
- Ali Alzahid, A., 2015. Histopathological study of the toxic doses of Clove Oil "Syzygium aromaticum" on Ovaries of female rabbits". *IOSR J. Agric. Vet. Sci. Ver. I* 8, 2319–2372.
- Asgarpanah, J., Sarabian, S., Ziarati, P., 2014. Essential oil of Nepeta genus (Lamiaceae) from Iran: A review. *J. Essent. Oil Res.* 26, 1–12.
- Ball, P., 2003. Efficacy and Safety of Levofloxacin in the Context of Other Contemporary Fluoroquinolones: A Review. *Curr. Ther. Res. - Clin. Exp.* 64, 646–661.
- Barboza, J.N., da Silva Maia Bezerra Filho, C., Silva, R.O., Medeiros, J.V.R., de Sousa, D.P., 2018. An overview on the anti-inflammatory potential and antioxidant profile of eugenol. *Oxid. Med. Cell. Longev.*
- Benjamin M. Davis, Glen F. Rall, M.J.S., 2017. Pharmacokinetics and Dosing of Levofloxacin in Children Treated for Active or Latent Multidrug-Resistant Tuberculosis, Federated States of Micronesia and Republic of the Marshall Islands. *HHS Public Access. Physiol. Behav.* 176, 139–148.
- Bezerra, D.P., Militão, G.C.G., De Moraes, M.C., De Sousa, D.P., 2017. The dual antioxidant/prooxidant effect of eugenol and its action in cancer development and treatment. *Nutrients* 9, 1–15.
- Bhowmik, D., Kumar, K.P.S., Yadav, A., Srivastava, S., Paswan, S., Dutta, A.S., 2012. Recent Trends in Indian Traditional Herbs Syzygium Aromaticum and its Health Benefits. *J. Pharmacogn. Phytochem.* 1, 6–17.
- Boroumand, N., Samarghandian, S., Hashemy, S.I., 2018. Immunomodulatory, anti-inflammatory, and antioxidant effects of curcumin. *J. HerbMed Pharmacol.* 7, 211–219.
- Boughendjioua, H., 2018. Essential Oil Composition of *Syzygium aromaticum* (L.). *Int. Res. J. Pharm. Med. Sci.* 1, 26–28.

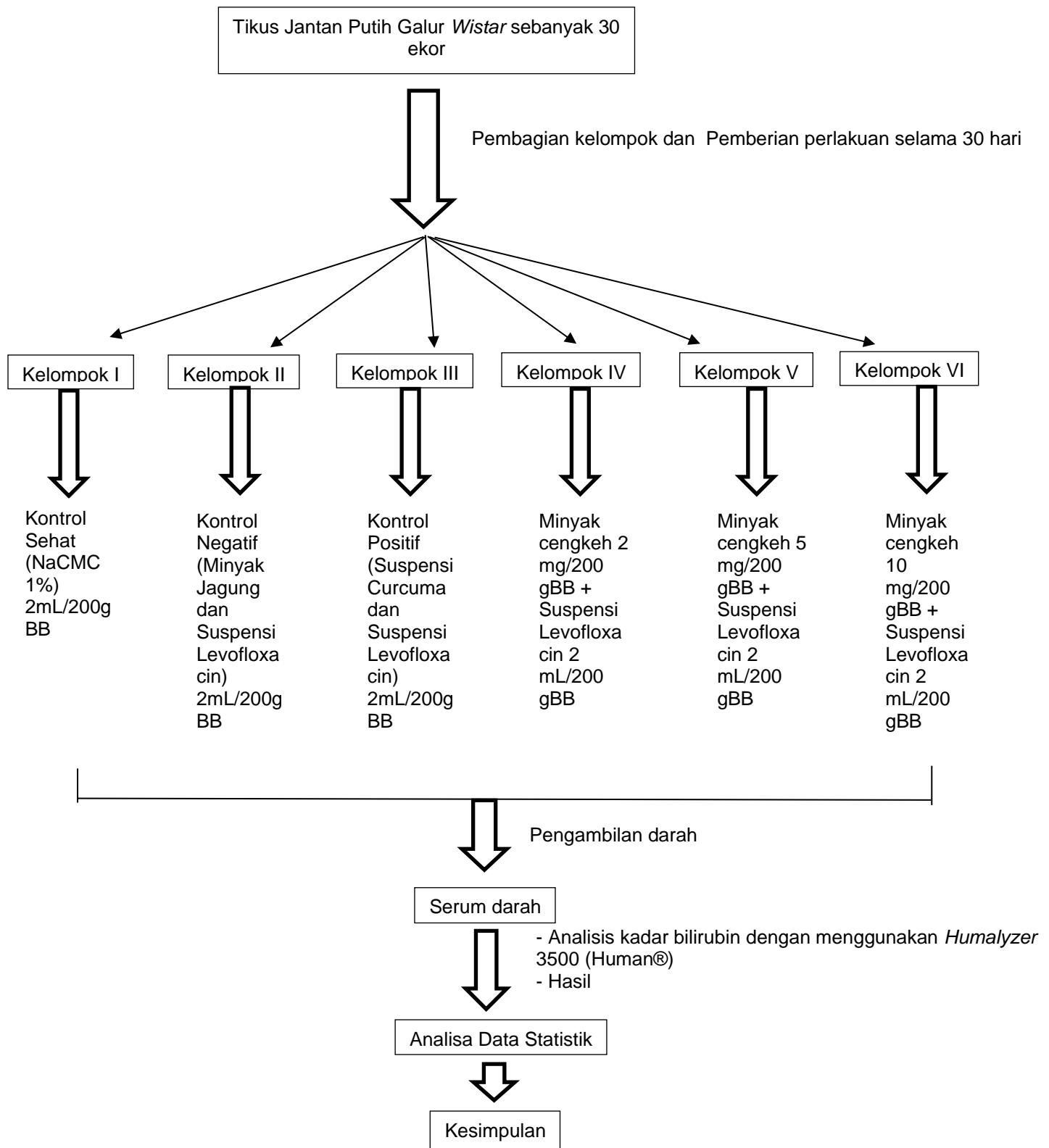
- Charan Raja, M.R., Srinivasan, V., Selvaraj, S., Mahapatra, S.K., 2015. *Pharmaceutica Analytica Acta* Versatile and Synergistic Potential of Eugenol: A Review. *Pharm Anal Acta* 6, 1–6.
- Cortés-Rojas, D.F., de Souza, C.R.F., Oliveira, W.P., 2014. Clove (*Syzygium aromaticum*): A precious spice. *Asian Pac. J. Trop. Biomed.* 4, 90–96.
- DitJen POM DepKes RI. 1979. *Farmakope Indonesia*. Edisi III. DepKes RI. Jakarta
- Eyrisofla, N.V., 2015a. The Study of Levofloxacin Effects on Liver Tissue in Wistar Rat. *J. Liver* 04.
- Gaspar, E.M., 2018. Volatile Composition and Antioxidant Properties of Clove Products. *Biomed. J. Sci. Tech. Res.* 9, 7270–7276.
- Gülçin, I., Elmastaş, M., Aboul-Enein, H.Y., 2012. Antioxidant activity of clove oil - A powerful antioxidant source. *Arab. J. Chem.* 5, 489–499.
- Hariyadi, Mahulette, A.S., Yahya, S., Wachjar, A., 2020. Agromorphologies and physicochemical properties of flower bud, stem and leaf oils in two clove varieties (*Syzygium aromaticum* L. Merr. and Perry.) originated from Ambon Island. *Chiang Mai Univ. J. Nat. Sci.* 19, 516–530.
- Hewlings, S., Kalman, D., 2017. Curcumin: A Review of Its Effects on Human Health. *Foods* 6, 92.
- Kusworo, T.D., Soetrisnanto, D., Widayat, W., Budiyono, B., Utomo, D.P., 2018. Study of polymeric membranes potential for eugenol purification from crude clove leaf oil. *ASEAN J. Chem. Eng.* 18, 81–92.
- Manni, I., Di Rocco, G., Fusco, S., Leone, L., Barbati, S.A., Carapella, C.M., Grassi, C., Piaggio, G., Toletta, G., 2017. Monitoring the response of hyperbilirubinemia in the mouse brain by in vivo bioluminescence imaging. *Int. J. Mol. Sci.* 18.
- Mohammadi Nejad, S., Özgüneş, H., Başaran, N., 2017. Öjenolün Farmakolojik Ve Toksikolojik Özellikleri. *Turkish J. Pharm. Sci.* 14, 201–206.
- Nengsi, S. 2020. Uji Toksisitas Akut Minyak Cengkeh (*Oleum caryophylli*) terhadap Fungsi Hati dan Ginjal Tikus melalui Analisis Biomarker Darah dan Urin. Tesis tidak diterbitkan. Makassar. Fakultas Farmasi Universitas Hasanuddin.

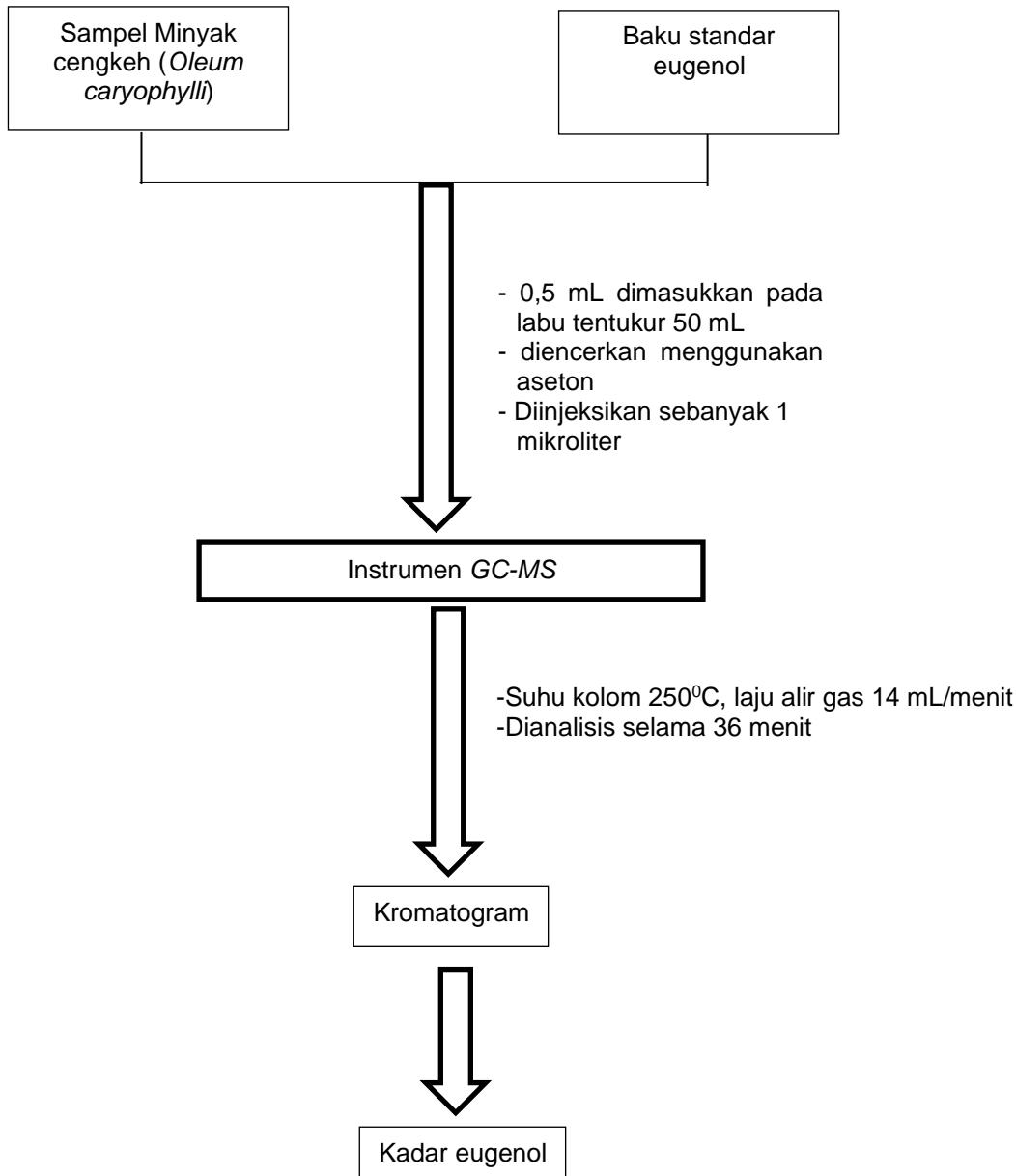
- Ngashangva, L., Bachu, V., Goswami, P., 2019. Development of new methods for determination of bilirubin. *J. Pharm. Biomed. Anal.* 162, 272–285.
- Olayinka, E.T., Ore, A., Ola, O.S., 2015. Influence of Different Doses of Levofloxacin on Antioxidant Defense Systems and Markers of Renal and Hepatic Dysfunctions in Rats. *Adv. Toxicol.* 2015, 1–7.
- Panahi, Y., Fazlolahzadeh, O., Atkin, S.L., Majeed, M., Butler, A.E., Johnston, T.P., Sahebkar, A., 2019. Evidence of curcumin and curcumin analogue effects in skin diseases: A narrative review. *J. Cell. Physiol.* 234, 1165–1178.
- Pramod, K., Ansari, S.H., Ali, J., 2010. Eugenol: A natural compound with versatile pharmacological actions. *Nat. Prod. Commun.* 5, 1999–2006.
- Pranger, A.D., van der Werf, T.S., Kosterink, J.G.W., Alffenaar, J.W.C., 2019. The Role of Fluoroquinolones in the Treatment of Tuberculosis in 2019. *Drugs* 79, 161–171.
- Rathore, S., Mukim, M., Sharma, P., Devi, S., Chandra Nagar, J., Khalid, M., 2020. Curcumin: A Review for Health Benefits Kingdom of Saudi Arabia. *Int. J. Res. Rev.* 7, 1.
- Rifai, A., Firdaus, Soekamto, N.H., 2019. Purification and analysis of patchouli alcohol from patchouli oil by vacuum fractionation distillation. *J. Phys. Conf. Ser.* 1341.
- S Bendre, R., D Rajput, J., 2016. Outlooks on Medicinal Properties of Eugenol and its Synthetic Derivatives. *Nat. Prod. Chem. Res.* 04.
- Safrudin, I., Maimulyanti, A., Prihadi, A.R., 2015. Effect of crushing of clove bud ( *Syzygium aromaticum* ) and distillation rate on main constituents of the essential oil. *Am. J. Essent. Oils Nat. Prod.* 2, 12–15.
- Salehi, B., Martorell, M., Arbiser, J.L., Sureda, A., Martins, N., Maurya, P.K., Sharifi-Rad, M., Kumar, P., Sharifi-Rad, J., 2018. Antioxidants: Positive or negative actors. *Biomolecules* 8, 1–11.
- Schloss, M., Becak, D., Tosto, S.T., Velayati, A., 2018. A case of levofloxacin-induced hepatotoxicity. *Am. J. Case Rep.* 19, 272–276.

- Seyhan, E., Mert, N., Mert, H., 2012. The effect of pepper gas (OC) on some biochemical parameters in rats. *Kafkas Univ. Vet. Fak. Derg.* 18, 259–266.
- Sticova, E., Jirsa, M., 2013. New insights in bilirubin metabolism and their clinical implications. *World J. Gastroenterol.* 19, 6398–6407.
- Swoboda, S., Oberdorfer, K., Klee, F., Hoppe-Tichy, T., von Baum, H., Geiss, H.K., 2003. Tissue and serum concentrations of levofloxacin 500 mg administered intravenously or orally for antibiotic prophylaxis in biliary surgery. *J. Antimicrob. Chemother.* 51, 459–462.
- Waristha, A., Kingkaew, W., Kumthorn, T., 2011. Acute toxicity of clove oil and effects on histopathological changes in gill of siamese fighting Fish betta splendens. *Res. J. Chem. Environ.* 15, 139–144.
- Widayat, Cahyono, B., Hadiyanto, Ngadiwyana, 2014. Improvement of clove oil quality by using adsorption-distillation process. *Res. J. Appl. Sci. Eng. Technol.* 7, 3867–3871.
- Widayat, W., Hadiyanto, H., Cahyono, B., Ngadiwyana, N., 2015. Optimization of Eugenol Extraction from Clove Oil using Response Surface Methodology. *Mod. Appl. Sci.* 9, 68.
- World Health Organization. 2016. *Multi Drug Resistance Tuberculosis*. Swiss:WHO
- Yusuf, P.M. 2018. Pengaruh Pemberian Oral Minyak Cengkeh (*Oleum caryophylli*) terhadap Kadar SGOT dan SGPT Tikus (*Rattus norvegicus*) yang Diinduksi Isoniazid-Rifampisin. Skripsi tidak diterbitkan. Makassar. Fakultas Farmasi. Universitas Hasanuddin.
- Zulfadli F. 2020. Uji Efek Protektif Minyak Cengkeh (*Oleum caryophylli*) terhadap Peningkatan Kadar Laktat Dehidrogenase (LDH) pada Tikus yang Diinduksi Levofloxacin. Skripsi tidak diterbitkan. Makassar. Fakultas Farmasi. Universitas Hasanuddin.

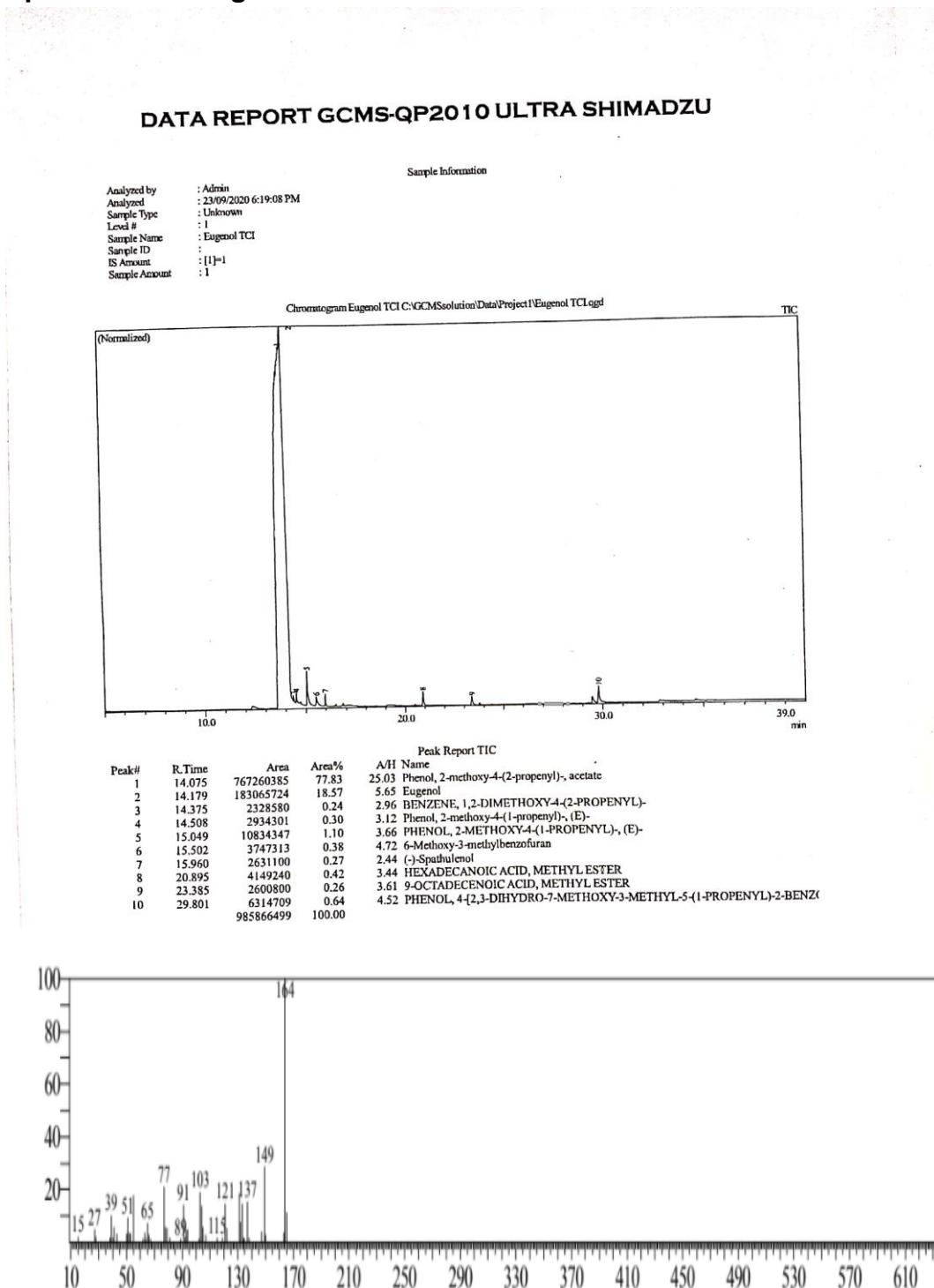
## LAMPIRAN

### Lampiran 1. Skema Kerja Penelitian Skema Kerja Pengukuran Kadar Bilirubin

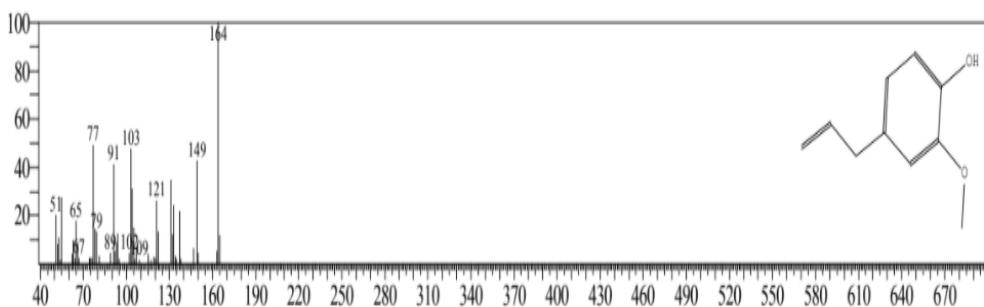
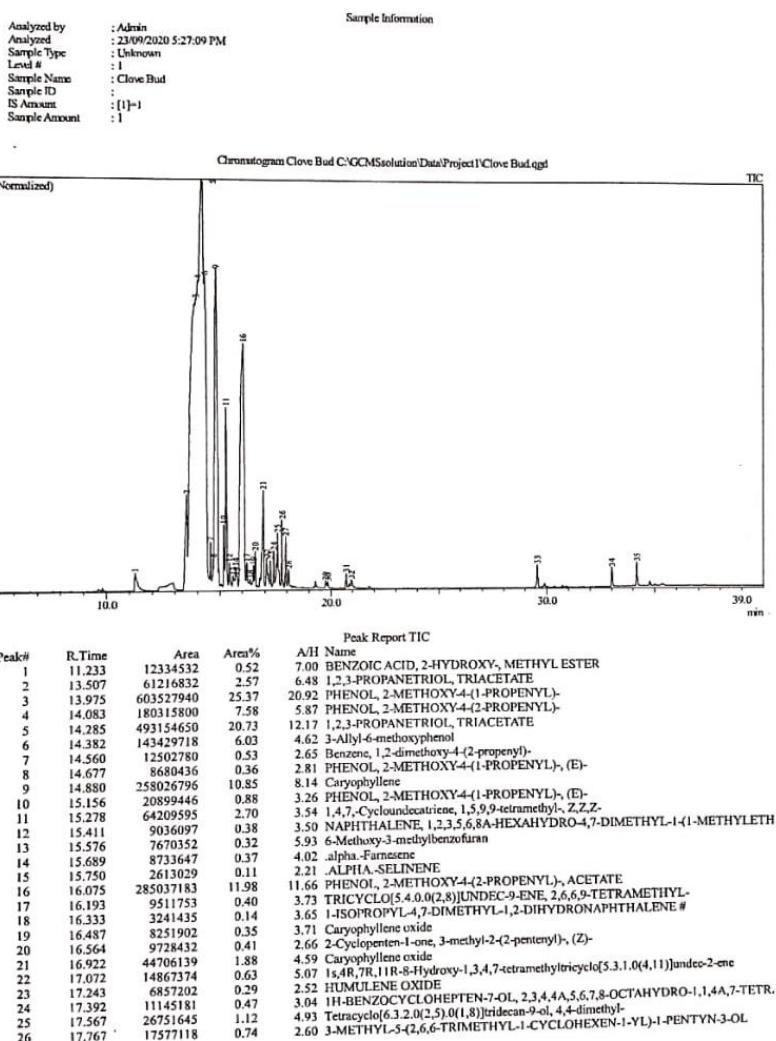


**Skema Kerja Pengukuran Kadar Eugenol**

**Lampiran 2. Spektra Kromatografi Gas Spektroskopi Massa Spektra Baku Eugenol**



### DATA REPORT GCMS-QP2010 ULTRA SHIMADZU



### Lampiran 3. Perhitungan Kadar Eugenol Pada Minyak Cengkeh

$$\frac{\text{AUC Sampel}}{\text{AUC Baku}} = \frac{\text{ppm sampel}}{\text{ppm baku}}$$

$$\frac{783843740}{950326109} = \frac{x \text{ ppm}}{10,660 \text{ ppm}}$$

$$X = \frac{783843740 \times 10,660}{950326109}$$

$$X = 8,792$$

$$\% \text{ Kadar} = \frac{8,792}{10,660} \times 100\%$$

$$= 82,476\%$$

## Lampiran 4. Perhitungan Dosis

### 1. Levofloxacin

Dosis levofloxacin yang akan diamati pada manusia 15 mg/kgBB.

Dosis equivalen Hewan = Dosis Manusia x Faktor Konversi

$$= 15 \text{ mg/Kg} \times 6,2$$

$$= 93 \text{ mg/Kg}$$

$$\text{Untuk tikus 200 g} = 93 \text{ mg/Kg} \times 0.2 \text{ Kg}$$

$$= 18,6 \text{ mg/ 200 gBB/ 2 mL}$$

$$= 232,5 \text{ mg/25 mL}$$

Jumlah serbuk tablet levofloxacin yang ditimbang

$$\begin{aligned} &= \frac{\text{Jumlah yang diinginkan}}{\text{Berat etiket}} \times \text{Berat rata-rata tablet} \\ &= \frac{232,5 \text{ mg}}{500 \text{ mg}} \times 555,56 \text{ mg} = 258,34 \text{ mg} \end{aligned}$$

Ditimbang serbuk tablet 258,34 mg kemudian disuspensikan dalam 25 mL NaCMC 1%

### 2. Minyak Cengkeh

Dosis oral minyak cengkeh pada manusia adalah 250 mg/KgBB sehingga dikonversi sesuai berat tikus 200 gram dan dibagi dalam beberapa kelompok sebagai berikut :

- a. 2 mg/200 gBB;
- b. 5 mg/200 gBB;
- c. 10 mg/200 gBB

### 3. Curcuma® FCT

Setiap tablet curcuma® FCT mengandung ekstrak *Curcuma xanthorrhiza* Rhizome sebanyak 20 mg.

Dosis equivalen Hewan = Dosis Manusia x Faktor Konversi

$$= 60 \text{ mg/Kg} \times 6,2$$

$$= 372 \text{ mg/Kg}$$

$$\text{Untuk tikus } 200 \text{ g} = 372 \text{ mg/Kg} \times 0.2 \text{ Kg}$$

$$= 74,4 \text{ mg/200 gBB/ 2 mL}$$

$$= 930 \text{ mg/25 mL}$$

Jumlah serbuk tablet curcuma® FCT yang ditimbang

$$= \frac{\text{Jumlah yang diinginkan}}{\text{Berat etiket}} \times \text{Berat rata-rata tablet}$$

$$= \frac{930 \text{ mg}}{20 \text{ mg}} \times 414 \text{ mg} = 19251 \text{ mg}$$

Ditimbang serbuk tablet 19251 mg kemudian disuspensikan dalam 25

mL NaCMC 1%

## Lampiran 5. Hasil Data Statistik

One-Sample Kolmogorov-Smirnov Test

		Perlakuan	Bilirubin
N		36	36
Normal Parameters <sup>a,b</sup>	Mean	3.50000	.78564
	Std. Deviation	1.732051	.567524
	Absolute	.140	.114
Most Extreme Differences	Positive	.140	.114
	Negative	-.140	-.089
Kolmogorov-Smirnov Z		.841	.685
Asymp. Sig. (2-tailed)		.480	.736

a. Test distribution is Normal.

b. Calculated from data.

ANOVA					
Bilirubin					
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	6.432	5	1.286	7.971	.000
Within Groups	4.841	30	.161		
Total	11.273	35			

Multiple Comparisons

Dependent Variable: Bilirubin

Tukey HSD

(I) Perlakuan	(J) Perlakuan	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
kontrol sehat	kontrol negatif	-.752000*	.231931	.031	-.45744	-.04656
	kontrol positif	.289333	.231931	.810	-.41611	.99477
	minyak cengkeh 2 mg	.223500	.231931	.926	-.48194	.92894
	minyak cengkeh 5 mg	-.286167	.231931	.817	-.99161	.41927
	minyak cengkeh 10 mg	-.749500*	.231931	.032	-.45494	-.04406
kontrol negatif	kontrol sehat	.752000*	.231931	.031	.04656	1.45744
	kontrol positif	1.041333*	.231931	.001	.33589	1.74677
	minyak cengkeh 2 mg	.975500*	.231931	.003	.27006	1.68094
	minyak cengkeh 5 mg	.465833	.231931	.361	-.23961	1.17127
	minyak cengkeh 10 mg	.002500	.231931	1.000	-.70294	.70794
kontrol positif	kontrol sehat	-.289333	.231931	.810	-.99477	.41611
	kontrol negatif	-1.041333*	.231931	.001	-.174677	-.33589
	minyak cengkeh 2 mg	-.065833	.231931	1.000	-.77127	.63961
	minyak cengkeh 5 mg	-.575500	.231931	.162	-.128094	.12994
	minyak cengkeh 10 mg	-1.038833*	.231931	.001	-.174427	-.33339
minyak cengkeh 2 mg	kontrol sehat	-.223500	.231931	.926	-.92894	.48194
	kontrol negatif	-.975500*	.231931	.003	-.168094	-.27006
	kontrol positif	.065833	.231931	1.000	-.63961	.77127
	minyak cengkeh 5 mg	-.509667	.231931	.269	-.121511	.19577
	minyak cengkeh 10 mg	-.973000*	.231931	.003	-.167844	-.26756
minyak cengkeh 5 mg	kontrol sehat	.286167	.231931	.817	-.41927	.99161
	kontrol negatif	-.465833	.231931	.361	-.117127	.23961
	kontrol positif	.575500	.231931	.162	-.12994	1.28094
	minyak cengkeh 2 mg	.509667	.231931	.269	-.19577	1.21511
	minyak cengkeh 10 mg	-.463333	.231931	.367	-.116877	.24211

minyak cengkeh 5 mg	kontrol sehat	.286167	.231931	.817	-.41927	.99161
	kontrol negatif	-.465833	.231931	.361	-.117127	.23961
	kontrol positif	.575500	.231931	.162	-.12994	1.28094
	minyak cengkeh 2 mg	.509667	.231931	.269	-.19577	1.21511
	minyak cengkeh 10 mg	-.463333	.231931	.367	-.116877	.24211
minyak cengkeh 10 mg	kontrol sehat	.749500*	.231931	.032	.04406	1.45494
	kontrol negatif	-.002500	.231931	1.000	-.70794	.70294
	kontrol positif	1.038833*	.231931	.001	.33339	1.74427
	minyak cengkeh 2 mg	.973000*	.231931	.003	.26756	1.67844
	minyak cengkeh 5 mg	.463333	.231931	.367	-.24211	1.16877

\*: The mean difference is significant at the 0.05 level.

### Bilirubin

Tukey HSD<sup>a</sup>

Perlakuan	N	Subset for alpha = 0.05	
		1	2
kontrol positif	6	.28383	
minyak cengkeh 2 mg	6	.34967	
kontrol sehat	6	.57317	
minyak cengkeh 5 mg	6	.85933	.85933
minyak cengkeh 10 mg	6		1.32267
kontrol negative	6		1.32517
Sig.		.162	.361

Means for groups in homogeneous subsets are displayed.

a. Uses Harmonic Mean Sample Size = 6,000.

**Lampiran 6. Gambar Penelitian**

**Gambar 6. Penyiapan Minyak Cengkeh  
(*Oleum caryophylli*)**

**Gambar 7. Penyiapan Baku Eugenol**



**Gambar 8. Perlakuan Hewan Uji**

**Gambar 9. Penyiapan Minyak Jagung**





Gambar 10. *Humalyzer*



Gambar 11. *Sentrifius*



Gambar 12. *Tikus Penelitian*

## Lampiran 7. Rekomendasi Persetujuan Etik



KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN  
 UNIVERSITAS HASANUDDIN FAKULTAS KEDOKTERAN  
 KOMITE ETIK PENELITIAN KESEHATAN  
 RSPTN UNIVERSITAS HASANUDDIN  
 RSUP Dr. WAHIDIN SUDIROHUSODO MAKASSAR  
 Sekretariat : Lantai 2 Gedung Laboratorium Terpadu  
 JL.PERINTIS KEMERDEKAAN KAMPUS TAMALANREA KM.10 MAKASSAR 90245.



Contact Person: dr. Agussalim Bukhari.,MMed.,PhD.,Sp.GK TELP. 081241850858, 0411 5780103, Fax : 0411-581431

### REKOMENDASI PERSETUJUAN ETIK

Nomor : 796/UN4.6.4.5.31/ PP36/ 2020

Tanggal: 8 Desember 2020

Dengan ini Menyatakan bahwa Protokol dan Dokumen yang Berhubungan Dengan Protokol berikut ini telah mendapatkan Persetujuan Etik :

No Protokol	UH20110631	No Sponsor Protokol	
Peneliti Utama	<b>Novi Febriani</b>	Sponsor	
Judul Peneliti	UJI EFEK PROTEKTIF MINYAK CENGKEH ( <i>Syzygium aromaticum</i> ) TERHADAP PENINGKATAN BILIRUBIN AKIBAT INDUKSI LEVOFLOXACIN PADA TIKUS		
No Versi Protokol	<b>1</b>	Tanggal Versi	06-Nov-20
No Versi PSP		Tanggal Versi	
Tempat Penelitian	<b>Laboratorium Fakultas Farmasi Universitas Hasanuddin Makassar</b>		
Jenis Review	<input type="checkbox"/> Exempted <input checked="" type="checkbox"/> Expedited <input type="checkbox"/> Fullboard Tanggal	Masa Berlaku <b>8 Desember 2020 sampai 8 Desember 2021</b>	Frekuensi review lanjutan
Ketua Komisi Etik Penelitian Kesehatan FKUH	Nama <b>Prof.Dr.dr. Suryani As'ad, M.Sc.,Sp.GK (K)</b>	Tanda tangan	
Sekretaris Komisi Etik Penelitian Kesehatan FKUH	Nama <b>dr. Agussalim Bukhari, M.Med.,Ph.D.,Sp.GK (K)</b>	Tanda tangan	

Kewajiban Peneliti Utama:

- Menyerahkan Amandemen Protokol untuk persetujuan sebelum di implementasikan
- Menyerahkan Laporan SAE ke Komisi Etik dalam 24 Jam dan dilengkapi dalam 7 hari dan Lapor SUSAR dalam 72 Jam setelah Peneliti Utama menerima laporan
- Menyerahkan Laporan Kemajuan (progress report) setiap 6 bulan untuk penelitian resiko tinggi dan setiap setahun untuk penelitian resiko rendah
- Menyerahkan laporan akhir setelah Penelitian berakhir
- Melaporkan penyimpangan dari protokol yang disetujui (protocol deviation / violation)
- Mematuhi semua peraturan yang ditentukan

