

## DAFTAR PUSTAKA

1. Fenny L. Yudiarto, Hasan Sjahrir. Proses Penuaan Otak-Bagaimana Kita Bisa Mencegahnya?. 2011. *Neurona* : 28 (2)
2. Cepelak Ivana, Dodog Slavica, Dodig Daniela Cepelak. Aging, Calorie Restriction and Calorie Restriction Mimetics. *Medical Sciences* 2019; 18-49: 41-50
3. Harianja, E, Widijanti Anik, Arsana Putu Moda. Pengaruh Retriksi Kalori Terhadap Kadar Hidrogen Peroksida dan Kadar Glukosa Darah Pada Tikus Tua. *Indonesian Journal of Clinical Pathology and Medical Laboratory*. 2007; 14: 24-27
4. Gillespie, Zoe E., Pickering Joshua, Eskiw Christopher H. Better Living Thru Chemistry: Caloric Restriction (CR) and CR Mimetics Alter Genome Function to Promote Increased Health and Lifespan. *Frontier in Genome*. 2016; 7: 1-21
5. Lopez-Otin C., Blasco M.A., Partridge L., Serrano M., Kroemer G., The Hallmarks of Aging. *Cell*. 2013; 153: 1194-1217
6. Burch J.B, Augustine A.D, Frieden L.A, et al. Advance in geroscience: Impact on healthspan and chronic disease. *Journal Gerontol. A Biol. Sci. Med. Sci.* 2014; 69: S1-S3
7. Lopez-Lluch Guillermo, Navas Placido. Calorie Restriction as an Intervention in Ageing. *The Journal of Pyhsiology*. 2015;594
8. Longo V.D, Antebi A., Bartke A. et al. Interventions to slow aging in humans: are we ready?. *Aging Cell*. 2015; 14: 497-510
9. Smith Daniel L, Jr. Elam Calvin F., Mattison Julie A., et al. Metformin Supplementation and Life Span in Fischer-344 Rats. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2010; 65A(5): 468-474
10. Lee, S., and Min, K. (2013). Caloric restriction and its mimetics. *BMB Rep*. 46, 181–187. doi: 10.5483/BMBRep.2013.46.4.033
11. X. Yang, H.Kord-Varkaneh, S.Talaei et al. The Influence of metformin on IGF-1 levels in humans: A systematic review and meta-analysis. *Pharmacological Research*. 2020; 151: 104588
12. Samantha M.S, Mitchell S.J, Cabo R, et al. Macronutrients and caloric intake in health and longevity. *Journal of Endocrinology*. 2015; 226 (1) : R17-R28
13. Buschemeyer WC 3rd, Klink JC, Mavropoulos JC, Poulton SH, Demark-Wahnefried W, Hursting SD, et al. Effect of intermittent fasting with or without caloric restriction on prostate cancer growth and survival in SCID mice. *Prostate*. 2010;70:1037–43.
14. Balasubramanian Priya, Howell Porsha R., Anderson Rozalyn M. Aging and Caloric Restriction Research: A Biological Perspective With Translational potential. *Journal EBioMedicine*.2017; 21: 37-44 (DOI: 10.1016/j.ebiom.2017.06.015)
15. Cava E, Fontana L. Will calorie restriction work in humans? *Aging (Albany NY)*. 2013;5:507–14.
16. Balasubramanian Priya, Howell Porsha R., Anderson Rozalyn M. Aging and Caloric Restriction Research: A Biological Perspective With Translational potential. *Journal EBioMedicine*.2017; 21: 37-44 (DOI: 10.1016/j.ebiom.2017.06.015)

17. Di Francesco A., Di Germanio C., Bernier M., et al. A Time to Fast. *Science*. 2018; 362: 6416 : 770-775
18. Heilbronn L.K, Ravussin E. Calorie restriction and aging : review of the literature and implications for studies in humans. *The American Journal of Clinical Nutrition*. 2003; 78 (3): 361-369
19. Redman L.M, Ravussin E. Caloric restriction in Humans: Impact on Physiological, Psychological and Behavioral Outcomes. *Antioxidants & Redox Signaling*. 2011; 12: 275-287
20. H. Shintani, T. Shintani, H. Ashida et al. Calorie restriction mimetics: Upstream-type compounds for modulating glucose metabolism. *Journal Nutrients*. 2018;10(12): 1-17
21. F. Madeo, D. Carmona-Gutierrez, S. Hofer et al. Caloric Restriction Mimetics against Age-Associated Disease: Targets, Mechanisms, and Therapeutic Potential. *Journal Cell Metabolism*. 2019; 29; 3: 592-610
22. N. Barzilai, J. Crandall, S. Kritchevsky et al. Metformin as a Tool to Target Aging. *Journal Cell Metabolism*. 2016; 23; 6: 1060-1065
23. D. van Heemst. Insulin, IGF-1 and longevity. *Journal Aging and Disease*. 2010; 1; 2: 147-157
24. K. Tan, S. Luo., W. Ho, et al. Insulin/IGF-1 receptor signaling enhances biosynthetic activity and fat mobilization in the initial phase of starvation in adult male *C. elegans*. *Cell Metabolism*. 2011; 14 ; 3 : 390-402
25. S. Gubbi, G. Quilpildor, N. Barzilai, et al. 40 years of IGF-1: IGF1: The Jekyll and Hyde of the aging brain. *Journal of Molecular Endocrinology*. 2018; 61; 1: T171-T185
26. Kamus Kedokteran Dorland. 2005. 20<sup>th</sup> ed. Jakarta:EGC
27. Murray RK, Granner DK, Rodwell VW. 2012. *Biokimia Harper*. Jakarta: EGC
28. Sherwood L. 2011. *Fisiologi Manusia dari Sel ke Sistem*. Jakarta : EGC.
29. Andersen M., Winter, L. Animal models in biological and biomedical research-experimental and ethical concerns. *Anais da Academia Brasileira de Ciencias journal*. 2019; 91: 1-14
30. Johnson M. *Laboratory Mice and Rats*. *Mater Methods* 2 : 113
31. Maulana, Indah Fadlul. 2014. Uji Antifertilitas Ekstrak N-Heksana Biji Jarak Pagar (*Jatropha curcas L.*) pada tikus putih jantan (*Rattus norvegicus*) Galur *Sprague Dawley* Secara *In Vivo*. Skripsi. UIN Syarif Hidayatullah Jakarta
32. N. Andreollo.,E. Santos., M.Araujo et al. Rat's age versus human's age: what is the relationship?. *ABCD Arq Bras Cir Dig Journal*. 2012; 25(1) : 49—51
33. Smit JB dan Mangkoewidjojo S. 1988. Tikus Laboratorium (*Rattus norvegicus*). Dalam: *Pemeliharaan, Pembiakan dan Penggunaan Hewan Percobaan di Daerah Tropis*. Jakarta: Penerbit Universitas Indonesia (UI-Press). Hal 37-57
34. Fitria, Laksmindra., Sarto, Mulyatii. Profil Hematologi Tikus (*Rattus norvegicus* Berkenhout, 1769) Galur Wistar Jantan dan Betina Umur 4, 6, dan 8 minggu. *Biogenesis Journal Ilmiah Biologi*. 2014; 2(2): 94-100
35. Arifin Wan Nor, Zahiruddin Wan Mohd. Sample Size Calculation in Animal Studies Using Resource Equation Approach. *Malays J Med Sci*. 2017; 24(5): 101-105.

36. Berryman DE, Christiansen JS, Johannsson G, Thorner MO, Kopchick JJ. Role of the GH/IGF-1 axis in lifespan and healthspan: lessons from animal models. *Growth horm IGF Res.* 2008; 18: 455-471
37. Li P, Sun X, Cai G, Chen X. Insulin-like Growth Factor System and Aging. *J Aging Sci.* 2017; 5: 171
38. Gems D, Partridge L. Genetics of longevity in model organisms: debates and paradigm shifts. *Annu Rev Physiol.* 2013; 75:621-644
39. Solon-Biet SM, J. Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. *J Endocrinol.* 2015; 226(1): R17–R28
40. Stanfel MN, Shamieh LS, Kaeberlein M, Kennedy BK. The TOR pathway comes of age. *Biochim Biophys Acta* 2009;1790:1067-1074
41. Pan H, Finkel T. Key proteins and pathways that regulate lifespan. *J Biol Chem.* 2017;292(16):6452-6460.
42. Ingram DK, Zhu M, Mamczarz J, Zou SG, Lane MA, Roth GS, et al. Calorie restriction mimetics: An emerging research field. *Aging Cell* 2006;5:97-108.
43. Wati, A., Kosman, R., Lizikri, A. Perbandingan Efektivitas Hipoglikemik Obat Metformin Paten Dan Generic Berlogo Berdasarkan Penurunan Kadar Glukosa Darah Mencit (*Mus Musculus*) Jantan Yang Diinduksi Aloksan. *As-Syifaa.*2014; Vol 6 (01) : Hal 91-97
44. Nangoy, B. N., Queljoe, E., Yudistira, A. Uji aktivitas antidiabetes dari ekstrak daun sesewanua (*clerodendron squamatum* Vahl.) terhadap tikus puyih jantan galur wistar (*rattus novergicus* L). *Pharmacon.* 2019; Vol. 8 (4) : hal 774-80
45. Rias Y.A., Sutikno, E. Hubungan antara Berat Badan dengan Kadar Glukosa darah acak pada tikus diabetes mellitus. *Jurnal Wiyata.* 2017; Vol 4 (1): 72-7
46. Kelley, D. E., Kuller, L. H., McKolanis, T. M., Harper, P., Mancino, J., & Kalhan, S. 2004. Effects of moderate weight loss and orlistat on insulin resistance, regional adiposity, and fatty acids in type 2 diabetes. *Diabetes Care*, 27(1), 33-40.
47. Mongi, R., Simbala, H. E. I., Queljoe, E. Uji Aktivitas Penurunan Kadar Glukosa darah Ekstrak Etanol daun pisang Yaki (*Areca vestiaria*) Terhadap Tikus Putih Galur Wistar (*Rattus novergicus*) Yang Diinduksi Aloksan. *Pharmacon.* 2019; Vol 8(2) : hal 449-456
48. Anson RM, Guo Z, De Cabo R, Iyun T, Rios M, Hagepanos A. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie asupan. *PNAS.* 2003; 13(100): 6216-20
49. Salomo H., Busman H., Apriliana E. Pengaruh Pemberian Metformin Dan Ekstrak Daun Teh Hijau Pada Penurunan Berat Badan Tikus Putih (*Rattus novergicus*) Galur Dawley dengan Diet Tinggi Lemak. *Medical Journal of Lampung University.* 2018; Vol.7(2); Hal 65-70
50. Sudoyo, A.W. Setiyohadi B., Alwi L., Simadibrata M., Setiati S., 2009. Ilmu penyakit dalam. Jakarta: departemen ilmu penyakit dalam fakultas kedokteran universitas Indonesia
51. Albu, J., Heilronn, L., Kelley, D. and Smith, S. 2010. Metabolic changes following in patients with type 2 diabetes. *Diabetes.* 2010; 59 : 627-633
52. Mustika, A., Indrawati, R., Sari, G., M. Efek Ekstrak Dau Singawalang (*Petiveria Alliacea*) Dalam Menurunkan Kadar Glukosa Darah Melalui

- Peningkatan Ekspresi AMPK-A1 Pada Tikus Model Diabetes Mellitus. *Jurnal Farmasi Klinik Indonesia*. 2017; Vol. 6 (1) : hal 22-31
53. Tepalla, S., Shankar, A. Association Between Serum IGF-1 and Diabetes Among U.S. Adults. *Diabetes Care*. 2010;33(10):1–3.
  54. Sonntag WE, Cefalu WT, Ingram RL., Bennett SA. Lynch CD, Cooney PT, Thornton PL and Khan AS. Pleiotropic effects of growth hormon and insulin-like growth factor (IGF) in biological aging : inferences from moderate caloric restricted animals. *J Gerontol*. 1999; 54A:B521-B538
  55. Scott A. Is Metformin Effective for Weight Loss?. *Medscape*. 2014. [Online] Available from: <https://www.medscape.com/viewarticle/836254>
  56. Malin K, Kashyap S. Effects of metformin on weight loss: Potential mechanisms. *Curr Opin Endocrinol Diabetes Obes*. 2014 Oct; 21(5):323-9.
  57. Seifarth C, Schehler B, Schneider H. Effectiveness of Metformin on Weight Loss in Non-Diabetic Individuals with Obesity. *Exp Clin Endocrinol Diabetes* 2013; 121: 27-31.
  58. Perry B, Wang Y. Appetite regulation and weight control: the role of gut hormones. *Nutrition & Diabetes*. 2012 Jan 2;2(1);e26
  59. Nakano M, Inui A. Metformin and incretin-based therapies up-regulate central and peripheral Adenosine monophosphoate-activated protein affecting appetite and metabolism. *Indian J Endocrinol Metab*. 2012 Dec; 16(Suppl 3): S529-S531.

## LAMPIRAN

### Lampiran 1. Persetujuan Etik Penelitian



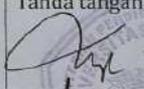
KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN  
UNIVERSITAS HASANUDDIN FAKULTAS KEDOKTERAN  
KOMITE ETIK PENELITIAN KESEHATAN  
RSPTN UNIVERSITAS HASANUDDIN  
RSUP Dr. WAHIDIN SUDIROHUSODO MAKASSAR  
Sekretariat : Lantai 2 Gedung Laboratorium Terpadu  
JL.PERINTIS KEMERDEKAAN KAMPUS TAMALANREA KM.10 MAKASSAR 90245.  
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**REKOMENDASI PERSETUJUAN ETIK**  
Nomor : 701/UN4.6.4.5.31/ PP36/ 2020

Tanggal: 27 Oktober 2020

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

No Protokol	UH20090494		No Sponsor	
Peneliti Utama	<b>dr. Arlina Wiyata Gama, S.Ked</b>		Sponsor	
Judul Peneliti	Perna Metformin sebagai Restriksi Kalori Mimetik Dalam Kadar Gula Darah Dan Kadar Serum IGF-1 Pada Tikus Tua			
No Versi Protokol	<b>2</b>		Tanggal Versi	24 Oktober 2020
No Versi PSP			Tanggal Versi	
Tempat Penelitian	<b>Laboratorium Entomologi FKUH dan Laboratorium HUMRC RS Universitas Hasanuddin Makassar</b>			
Jenis Review	<input type="checkbox"/> Exempted <input checked="" type="checkbox"/> Expedited <input type="checkbox"/> Fullboard Tanggal		Masa Berlaku 27 Oktober 2020 sampai 27 Oktober 2021	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 prokol yang disetujui (protocol deviation / violation)
- Mematuhi semua peraturan yang ditentukan

## Lampiran 2. Tabel Konversi Dosis Hewan

Tabel 12. Konversi dosis antara berbagai jenis hewan dan Manusia  
(Laurence and Bacharach, 1964)

	Mencit 20 gr	Tikus 200 gr	Marmut 400 gr	Kelinci 1,2 kg	Kera 4 kg	Anjing 12 kg	Manusia 70 kg
Mencit 20 gr	1,0	7,0	12,25	27,8	64,1	124,2	387,9
Tikus 200 gr	0,14	1,0	1,74	0,39	9,2	17,8	56,0
Marmut 400 gr	0,08	0,57	1,0	2,25	5,2	10,2	31,5
Kelinci 1,2 kg	0,04	0,25	0,44	1,0	2,4	4,5	14,2
Kera 4 kg	0,016	0,11	0,19	0,42	1,0	1,9	6,1
Anjing 12 kg	0,008	0,06	0,10	0,22	0,52	1,0	3,1
Manusia 70 kg	0,0026	0,018	0,031	0,07	0,16	0,32	1,0

## Lampiran 3. Tabel Maksimum Larutan Sediaan Uji Untuk Hewan

Tabel 13. Volume Maksimum Larutan Sediaan Uji yang Dapat Diberikan pada Beberapa Hewan Uji (RItschel, 1974)

Jenis Hewan Uji	Volume maksimum (ml) sesuai jalur pemberian				
	i.v.	i.m.	i.p.	s.c.	p.o.
Mencit (20-30 gr)	0,5	0,05	1,0	0,5-1,0	1,0
Tikus (200 gr)	1,0	0,1	2-5	2,5	5,0
Hamster (50 gr)	-	0,1	1-2	2,5	2,5
Marmut (250 gr)	-	0,25	2-5	5,0	10,0
Kelinci (2,5 kg)	5-10	0,5	10-20	5-10	20,0
Kucing (3 kg)	5-10	1,0	10-20	5-10	50,0
Anjing (5 kg)	10-20	5,0	20-50	10,0	100,0

## Lampiran 4. Perhitungan Dosis Metformin

Perhitungan dosis Metformin yang akan diberikan pada tikus secara per oral (p.o.)

- Tiap tablet Metformin mengandung 500 mg Metformin-HCl
- Dosis maksimum untuk manusia dewasa = 500 mg – 3000 mg
- Konversi dosis manusia (70 kg) ke dosis untuk hewan uji 'Tikus' dikali 0,018
- Syarat volume maksimum larutan sediaan uji yang diberikan pada hewan uji tikus (200 gr) secara per oral (p.o.) adalah 5,0 ml

a. Berapa dosis Metformin (dalam mg/KgBB) untuk tikus?

- Dosis Metformin untuk tikus (200gr)
 
$$= (500 \text{ mg} - 3000 \text{ mg}) \times 0,018$$

$$= 9 \text{ mg} - 54 \text{ mg}$$
- Menurut FI edisi III, penentuan kadar tablet = 20 tablet, maka diambil tablet metformin, digerus dan ditimbang berat totalnya = 11934 mg
- Berat bahan aktif Metformin-HCl dalam 20 tablet metformin adalah = 500 mg/tab x 20 tab = 10.000 mg
- Dosis Metformin-HCl untuk tikus (200 g) = 9 mg – 54 mg, maka dosis Metformin-HCl yang digunakan 10 mg untuk tikus 200 gr.
- Jadi, dosis (mg/kgBB)  $\rightarrow \frac{10 \text{ mg}}{200 \text{ gr}} = \frac{x}{1 \text{ kg}}$ 

$$x = \frac{10 \text{ mg}}{200 \text{ gr}} \times 1 \text{ kg} = 50 \text{ mg}$$

$$\rightarrow \text{maka, dosis Metformin-HCl} = 50 \text{ mg/kgBB}$$
- Jumlah serbuk metformin yang diambil untuk dosis 50 mg/kgBB

$$\frac{50 \text{ mg/kgBB}}{10.000 \text{ mg}} = \frac{x}{11.934 \text{ mg}}$$

$$x = 59,67 \text{ mg/KgBB} \sim 60 \text{ mg/kgBB}$$

→jadi dalam 60 mg serbuk Metformin mengandung 50 mg Metformin-HCl

b. Berapa jumlah dan volume suspensi Metformin yang diberikan untuk tikus?

- Pembuatan suspensi metformin

Ambil 60 mg serbuk metformin dilarutkan dalam 5 ml suspensi air

- Contoh : BB Tikus = 210 gr

Jumlah serbuk metformin yang diberikan

$$= 60 \text{ mg/kgBB} \times 210 \text{ gr}$$

$$= 12,6 \text{ mg}$$

$$\text{Volume larutan yang diberi} = \frac{12,6 \text{ mg}}{60 \text{ mg/5 ml}} = 0,9 \text{ ml}$$

## Lampiran 5. Komposisi Pakan

Tabel 14. Komposisi Pakan AD II

<b>Bahan-Bahan Campuran</b>	<b>Jumlah (%) dalam 1000 gram</b>
Air	13
Protein	18,5 – 20,5
Lemak	4
Serat	6
Abu	8
Kalsium	0,9
Posfor	0,7
<i>Metabolisme Energy (M.E)</i>	3100 – 3200 Kkal/kg

Tabel 15. Komposisi Pakan Van der Voer

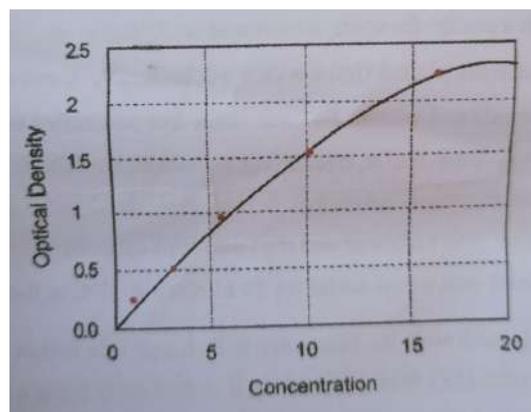
<b>Bahan-Bahan Campuran</b>	<b>Jumlah (%) dalam 1000 gram</b>
Protein	20
Lemak	7
Serat	15-20
Kalsium	1
Fosfor	0,8
Kadar air	12
Karbohidrat	60

## Lampiran 6. Kotak ELISA IGF-1

	1	2	3	4	5	6	7	8	9	10	11	12
A	S <sub>1</sub>	A <sub>3</sub>	B <sub>5</sub>	C <sub>6</sub>	D <sub>7</sub>	B <sub>1</sub>	C <sub>3</sub>	D <sub>5</sub>	A <sub>6</sub>	C <sub>1</sub>	D <sub>3</sub>	S <sub>1</sub>
B	S <sub>2</sub>	A <sub>4</sub>	B <sub>6</sub>	C <sub>7</sub>	A <sub>1</sub>	B <sub>2</sub>	C <sub>4</sub>	D <sub>6</sub>	A <sub>7</sub>	C <sub>2</sub>	D <sub>4</sub>	S <sub>2</sub>
C	S <sub>3</sub>	A <sub>5</sub>	B <sub>7</sub>	D <sub>1</sub>	A <sub>2</sub>	B <sub>4</sub>	C <sub>5</sub>	D <sub>7</sub>	B <sub>1</sub>	C <sub>3</sub>	D <sub>5</sub>	S <sub>3</sub>
D	S <sub>4</sub>	A <sub>6</sub>	C <sub>1</sub>	D <sub>2</sub>	A <sub>3</sub>	B <sub>5</sub>	C <sub>6</sub>	A <sub>1</sub>	B <sub>2</sub>	C <sub>4</sub>	D <sub>6</sub>	S <sub>4</sub>
E	S <sub>5</sub>	A <sub>7</sub>	C <sub>2</sub>	D <sub>3</sub>	A <sub>4</sub>	B <sub>6</sub>	D <sub>1</sub>	A <sub>2</sub>	B <sub>4</sub>	C <sub>5</sub>	D <sub>7</sub>	S <sub>5</sub>
F	Blank	B <sub>1</sub>	C <sub>3</sub>	D <sub>4</sub>	A <sub>5</sub>	B <sub>7</sub>	D <sub>2</sub>	A <sub>3</sub>	B <sub>5</sub>	C <sub>6</sub>		Blank
G	A <sub>1</sub>	B <sub>2</sub>	C <sub>4</sub>	D <sub>5</sub>	A <sub>6</sub>	C <sub>1</sub>	D <sub>3</sub>	A <sub>4</sub>	B <sub>6</sub>	D <sub>1</sub>		
H	A <sub>2</sub>	B <sub>4</sub>	C <sub>5</sub>	D <sub>6</sub>	A <sub>7</sub>	C <sub>2</sub>	D <sub>4</sub>	A <sub>5</sub>	B <sub>7</sub>	D <sub>2</sub>		

Keterangan :

	: Serum darah akhir aklimatisasi (H-0)
	: Serum darah tengah perlakuan (H-15)
	: Serum darah akhir perlakuan (H-30)



Gambar 10. Kurva Standar ELISA

## Lampiran 7. Data Hasil Penelitian

Tabel 16. Data Berat Badan, Kadar Glukosa Darah dan Kadar Serum IGF-1 Tikus Putih Jantan Galur Wistar

Kelompok		Berat Badan (gram)			Kadar Glukosa (mg/dl)			Kadar IGF-1 (ng/ml)		
		Hari 0	Hari 15	Hari 30	Hari 0	Hari 15	Hari 30	Hari 0	Hari 15	Hari 30
Kontrol	1	276	293	314	73	116	112	6,08	7,52	7,76
	2	275	276	292	59	106	123	4,91	5,53	5,99
	3	259	242	269	108	129	158	7,89	7,45	9,77
	4	261	273	298	95	122	129	6,45	7,38	7,48
	5	241	256	276	114	129	157	8,09	8,63	9,78
	6	271	286	295	121	138	172	8,22	9,11	9,56
Resktriksi Kalori	1	306	287	275	117	109	97	10,62	12,28	14,65
	2	308	288	280	123	102	99	8,59	9,25	14,01
	3	303	283	274	92	88	69	13,67	10,99	16,77
	4	290	276	267	105	92	77	9,67	10,38	12,87
	5	291	278	269	118	99	96	10,34	10,57	14,31
	6	272	264	251	111	93	84	9,19	15,23	12,74
Metformin	1	333	325	316	120	108	93	4,77	6,94	8,43
	2	320	314	307	107	98	92	5,56	7,95	8,96
	3	280	273	263	118	110	98	8,56	12,58	12,89
	4	317	302	290	119	116	105	10,12	13,46	14,03
	5	300	280	275	109	121	96	9,44	10,68	13,12
	6	315	304	294	105	98	81	9,71	12,21	13,91

## Lampiran 8. Uji Normalitas dan Uji Homogenitas

Tabel 17. Box's test of Equality of covariance matrices

Box'sM	18.994
F	1.108
df1	12
df2	1.090.385
Sig.	.349

Tabel 18. Uji Normalitas Selisih Perubahan Berat Badan, Kadar Glukosa Darah dan Kadar Serum IGF-1 Tikus Putih Jantan Galur Wistar

Kelompok	Parameter		
	Berat Badan	Kadar Glukosa Darah	Kadar Serum IGF-1
Kontrol (K)	.295	.839	.419
Restriksi (P1)	.340	.789	.824
Metformin (P2)	.721	.371	.828

Keterangan : uji Saphiro-Wilk

Tabel 19. Uji Homogenitas Selisih Perubahan Berat Badan, Kadar Glukosa Darah dan Kadar Serum IGF-1 Tikus Putih Jantan Galur Wistar

Parameter	F	df1	df2	Sig.
Berat Badan	7,434	2	15	.006
Kadar Glukosa Darah	3,803	2	15	.046
Kadar Serum IGF-1	1.647	2	15	.226

Keterangan : Levene's Test of Equality of Error Variances

## Lampiran 9. Uji Univariate MANOVA

## 1. Berat Badan

## Between-Subjects Factors

		Value Label	N
Kelompok	1	Kelompok Kontrol	6
	2	Kelompok Restriksi	6
	3	Kelompok Metformin	6

## Descriptive Statistics

Dependent Variable: Berat\_Badan

Kelompok	Mean	Std. Deviation	N
Kelompok Kontrol	26.83	11.686	6
Kelompok Restriksi	-25.67	4.179	6
Kelompok Metformin	-20.00	5.329	6
Total	-6.28	25.293	18

Levene's Test of Equality of Error Variances<sup>a</sup>

Dependent Variable: Berat\_Badan

F	df1	df2	Sig.
7.434	2	15	.006

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a. Design: Intercept + Kelompok

## Tests of Between-Subjects Effects

Dependent Variable: Berat\_Badan

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	9963.444 <sup>a</sup>	2	4981.722	81.921	.000
Intercept	709.389	1	709.389	11.665	.004
Kelompok	9963.444	2	4981.722	81.921	.000
Error	912.167	15	60.811		
Total	11585.000	18			
Corrected Total	10875.611	17			

a. R Squared = .916 (Adjusted R Squared = .905)

## 2. Kadar Glukosa

### Between-Subjects Factors

		Value Label	N
Kelompok	1	Kelompok Kontrol	6
	2	Kelompok Restriksi	6
	3	Kelompok Metformin	6

### Descriptive Statistics

Dependent Variable: Kadar\_Glukosa\_Darah

Kelompok	Mean	Std. Deviation	N
Kelompok Kontrol	46.83	10.610	6
Kelompok Restriksi	-24.00	3.033	6
Kelompok Metformin	-18.83	5.776	6
Total	1.33	33.858	18

### Levene's Test of Equality of Error Variances<sup>a</sup>

Dependent Variable: Kadar\_Glukosa\_Darah

F	df1	df2	Sig.
3.803	2	15	.046

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a. Design: Intercept + Kelompok

### Tests of Between-Subjects Effects

Dependent Variable: Kadar\_Glukosa\_Darah

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	18712.333 <sup>a</sup>	2	9356.167	180.931	.000
Intercept	32.000	1	32.000	.619	.444
Kelompok	18712.333	2	9356.167	180.931	.000
Error	775.667	15	51.711		
Total	19520.000	18			
Corrected Total	19488.000	17			

a. R Squared = .960 (Adjusted R Squared = .955)

### 3. Kadar Serum IGF-1

#### Between-Subjects Factors

		Value Label	N
Kelompok	1	Kelompok Kontrol	6
	2	Kelompok Restriksi	6
	3	Kelompok Metformin	6

#### Descriptive Statistics

Dependent Variable: Kadar\_IGF1

Kelompok	Mean	Std. Deviation	N
Kelompok Kontrol	1.4500	.35236	6
Kelompok Restriksi	3.8783	.84639	6
Kelompok Metformin	3.8633	.35297	6
Total	3.0639	1.28951	18

#### Levene's Test of Equality of Error Variances<sup>a</sup>

Dependent Variable: Kadar\_IGF1

F	df1	df2	Sig.
1.647	2	15	.226

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.

a. Design: Intercept + Kelompok

#### Tests of Between-Subjects Effects

Dependent Variable: Kadar\_IGF1

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	23.442 <sup>a</sup>	2	11.721	36.434	.000
Intercept	168.973	1	168.973	525.239	.000
Kelompok	23.442	2	11.721	36.434	.000
Error	4.826	15	.322		
Total	197.242	18			
Corrected Total	28.268	17			

a. R Squared = .829 (Adjusted R Squared = .807)

## Lampiran 10. Uji Post Hoc Duncan

**Berat\_Badan**Duncan<sup>a,b</sup>

Kelompok	N	Subset	
		1	2
Kelompok Restriksi	6	-25.67	
Kelompok Metformin	6	-20.00	
Kelompok Kontrol	6		26.83
Sig.		.227	1.000

Means for groups in homogeneous subsets are displayed.

Based on observed means.

The error term is Mean Square(Error) = 60.811.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha =

**Kadar\_Glukosa\_Darah**Duncan<sup>a,b</sup>

Kelompok	N	Subset	
		1	2
Kelompok Restriksi	6	-24.00	
Kelompok Metformin	6	-18.83	
Kelompok Kontrol	6		46.83
Sig.		.232	1.000

Means for groups in homogeneous subsets are displayed.

Based on observed means.

The error term is Mean Square(Error) = 51.711.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha =

**Kadar\_IGF1**Duncan<sup>a,b</sup>

Kelompok	N	Subset	
		1	2
Kelompok Kontrol	6	1.4500	
Kelompok Metformin	6		3.8633
Kelompok Restriksi	6		3.8783
Sig.		1.000	.964

Means for groups in homogeneous subsets are displayed.

Based on observed means.

The error term is Mean Square(Error) = .322.

a. Uses Harmonic Mean Sample Size = 6.000.

b. Alpha =

## Lampiran 11. Uji Korelasi Pearson

		Correlations		
		Berat_Badan	Kadar_Glukosa_Darah	Kadar_IGF1
Berat_Badan	Pearson Correlation	1	.897**	-.886**
	Sig. (2-tailed)		.000	.000
	N	18	18	18
Kadar_Glukosa_Darah	Pearson Correlation	.897**	1	-.894**
	Sig. (2-tailed)	.000		.000
	N	18	18	18
Kadar_IGF1	Pearson Correlation	-.886**	-.894**	1
	Sig. (2-tailed)	.000	.000	
	N	18	18	18

\*\* . Correlation is significant at the 0.01 level (2-tailed).

**Interpretasi tabel korelasi:**

- Ada korelasi berat badan dengan kadar glukosa (sig.<0.05) dengan nilai 0,897 (korelasi kuat positif)
- Ada korelasi berat badan dengan kadar IGF-1 (sig.<0.05) dengan nilai 0,886 (korelasi kuat negatif)
- Ada korelasi kadar glukosa dengan kadar IGF-1 (sig.<0.05) dengan nilai 0,894 (korelasi kuat negatif)

Ada hubungan signifikan antara perubahan berat badan, kadar glukosa darah dan kadar serum IGF-1, penurunan berat badan cenderung menurunkan kadar glukosa namun menaikkan kadar igf- dan penurunan kadar glukosa juga cenderung menaikkan kadar IGF-1

Tabel 20. Interpretasi Nilai Korelasi

No	Besanya r	Interpretasi
1	0.00-0.20	Sangat Lemah
2	0.20-0.40	Lemah
3	0.40-0.70	Cukup
4	0.70-0.90	Kuat
5	0.90-1.00	Sangat Kuat

## Lampiran 12. Uji Regresi Linear Berganda

**1. BERAT BADAN****Descriptive Statistics**

	Mean	Std. Deviation	N
Berat_Badan	-6.28	25.293	18
Kadar_Glukosa_Darah	1.33	33.858	18
Kadar_IGF1	3.0639	1.28951	18

**Correlations**

		Berat_Badan	Kadar_Glukosa_Darah	Kadar_IGF1
Pearson Correlation	Berat_Badan	1.000	.897	-.886
	Kadar_Glukosa_Darah	.897	1.000	-.894
	Kadar_IGF1	-.886	-.894	1.000
Sig. (1-tailed)	Berat_Badan	.	.000	.000
	Kadar_Glukosa_Darah	.000	.	.000
	Kadar_IGF1	.000	.000	.
N	Berat_Badan	18	18	18
	Kadar_Glukosa_Darah	18	18	18
	Kadar_IGF1	18	18	18

**Variables Entered/Removed<sup>a</sup>**

Model	Variables Entered	Variables Removed	Method
1	Kadar_IGF1, Kadar_Glukosa_Darah b	.	Enter

a. Dependent Variable: Berat\_Badan

b. All requested variables entered.

**Model Summary**

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.917 <sup>a</sup>	.840	.819	10.766

a. Predictors: (Constant), Kadar\_IGF1, Kadar\_Glukosa\_Darah

**ANOVA<sup>a</sup>**

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	9137.064	2	4568.532	39.417	.000 <sup>b</sup>
	Residual	1738.547	15	115.903		
	Total	10875.611	17			

a. Dependent Variable: Berat\_Badan

b. Predictors: (Constant), Kadar\_IGF1, Kadar\_Glukosa\_Darah

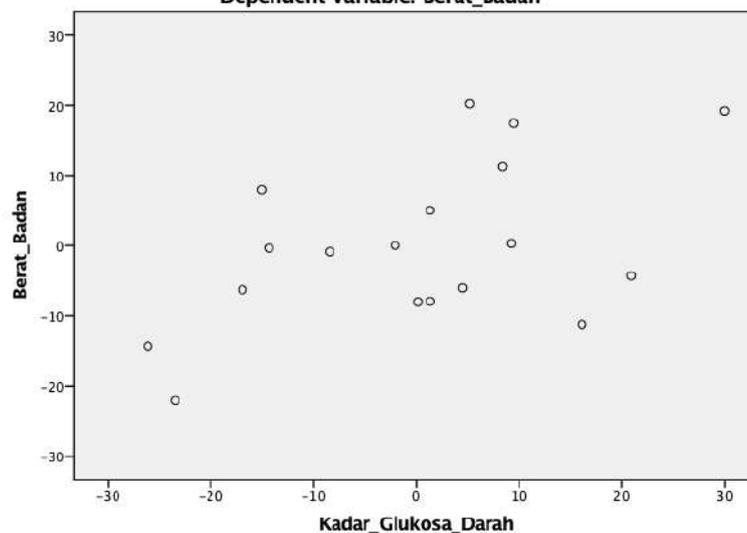
**Coefficients<sup>a</sup>**

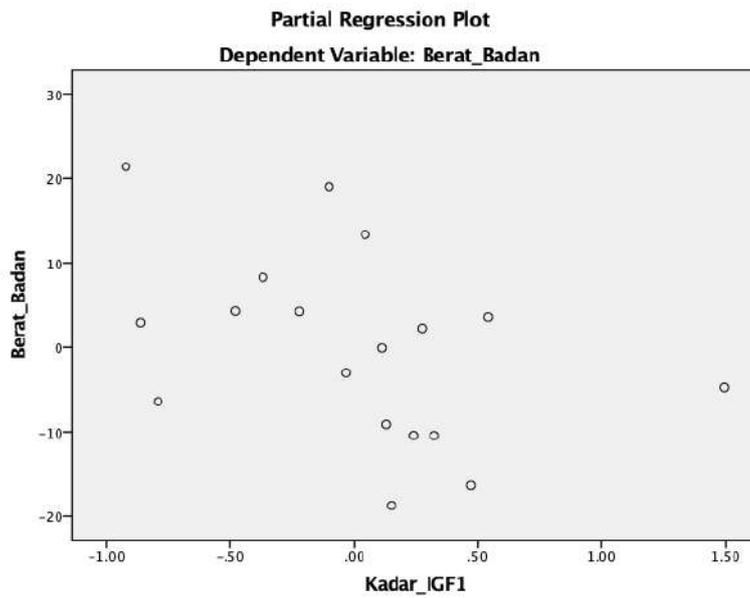
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	18.296	14.270		1.282	.219
	Kadar_Glukosa_Darah	.391	.172	.524	2.276	.038
	Kadar_IGF1	-8.191	4.516	-.418	-1.814	.090

a. Dependent Variable: Berat\_Badan

**Partial Regression Plot**

Dependent Variable: Berat\_Badan





## 2. KADAR GLUKOSA DARAH

### Descriptive Statistics

	Mean	Std. Deviation	N
Kadar_Glukosa_Darah	1.33	33.858	18
Berat_Badan	-6.28	25.293	18
Kadar_IGF1	3.0639	1.28951	18

### Correlations

		Kadar_Glukosa Darah	Berat_Badan	Kadar_IGF1
Pearson Correlation	Kadar_Glukosa_Darah	1.000	.897	-.894
	Berat_Badan	.897	1.000	-.886
	Kadar_IGF1	-.894	-.886	1.000
Sig. (1-tailed)	Kadar_Glukosa_Darah	.	.000	.000
	Berat_Badan	.000	.	.000
	Kadar_IGF1	.000	.000	.
N	Kadar_Glukosa_Darah	18	18	18
	Berat_Badan	18	18	18
	Kadar_IGF1	18	18	18

**Variables Entered/Removed<sup>a</sup>**

Model	Variables Entered	Variables Removed	Method
1	Kadar_IGF1, Berat_Badan <sup>b</sup>	.	Enter

a. Dependent Variable: Kadar\_Glukosa\_Darah

b. All requested variables entered.

**Model Summary**

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.922 <sup>a</sup>	.851	.831	13.933

a. Predictors: (Constant), Kadar\_IGF1, Berat\_Badan

**ANOVA<sup>a</sup>**

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	16575.901	2	8287.950	42.691	.000 <sup>b</sup>
	Residual	2912.099	15	194.140		
	Total	19488.000	17			

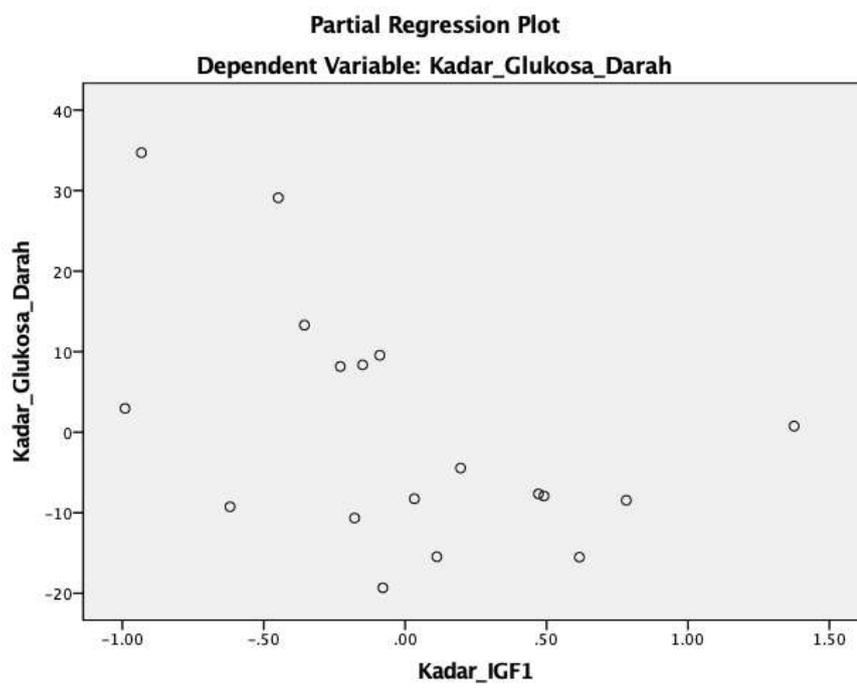
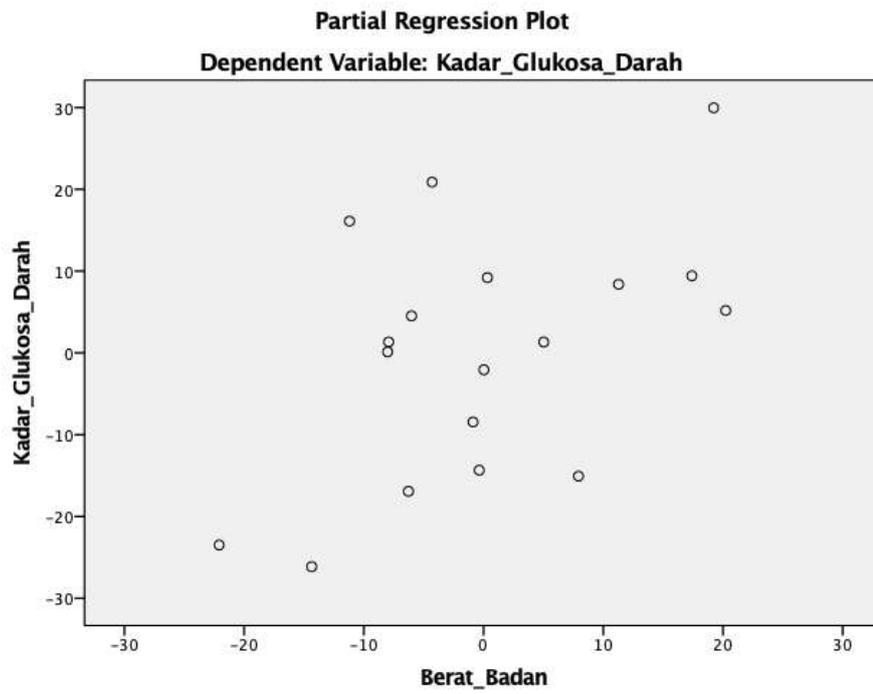
a. Dependent Variable: Kadar\_Glukosa\_Darah

b. Predictors: (Constant), Kadar\_IGF1, Berat\_Badan

**Coefficients<sup>a</sup>**

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	42.446	16.073		2.641	.019
	Berat_Badan	.656	.288	.490	2.276	.038
	Kadar_IGF1	-12.075	5.651	-.460	-2.137	.050

a. Dependent Variable: Kadar\_Glukosa\_Darah



## 3. KADAR IGF-1

## Descriptive Statistics

	Mean	Std. Deviation	N
Kadar_IGF1	3.0639	1.28951	18
Berat_Badan	-6.28	25.293	18
Kadar_Glukosa_Darah	1.33	33.858	18

## Correlations

		Kadar_IGF1	Berat_Badan	Kadar_Glukosa_Darah
Pearson Correlation	Kadar_IGF1	1.000	-.886	-.894
	Berat_Badan	-.886	1.000	.897
	Kadar_Glukosa_Darah	-.894	.897	1.000
Sig. (1-tailed)	Kadar_IGF1	.	.000	.000
	Berat_Badan	.000	.	.000
	Kadar_Glukosa_Darah	.000	.000	.
N	Kadar_IGF1	18	18	18
	Berat_Badan	18	18	18
	Kadar_Glukosa_Darah	18	18	18

Variables Entered/Removed<sup>a</sup>

Model	Variables Entered	Variables Removed	Method
1	Kadar_Glukosa_Darah, Berat_Badan <sup>b</sup>	.	Enter

a. Dependent Variable: Kadar\_IGF1

b. All requested variables entered.

## Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.914 <sup>a</sup>	.835	.813	.55741

a. Predictors: (Constant), Kadar\_Glukosa\_Darah, Berat\_Badan

ANOVA<sup>a</sup>

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	23.607	2	11.804	37.990	.000 <sup>b</sup>
	Residual	4.661	15	.311		
	Total	28.268	17			

a. Dependent Variable: Kadar\_IGF1

b. Predictors: (Constant), Kadar\_Glukosa\_Darah, Berat\_Badan

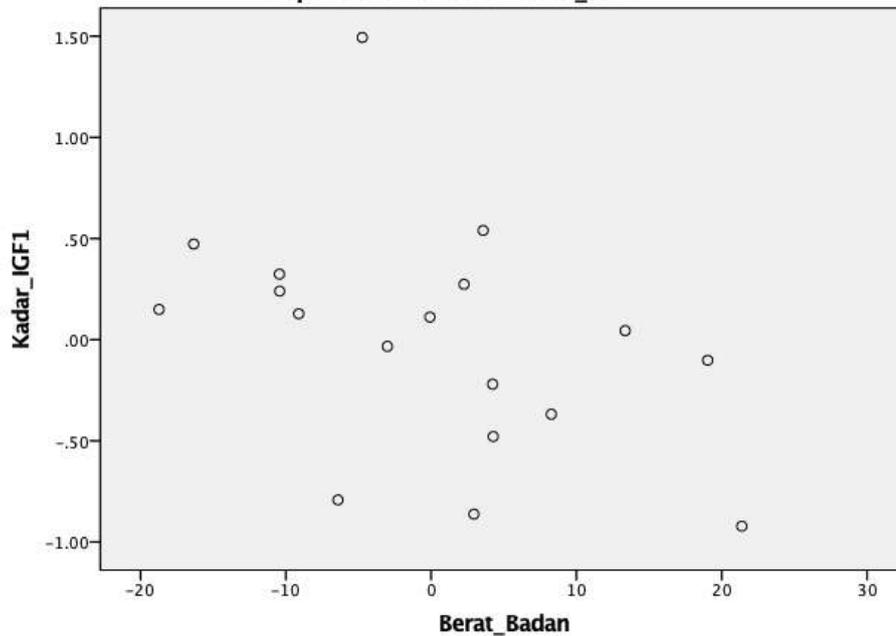
Coefficients<sup>a</sup>

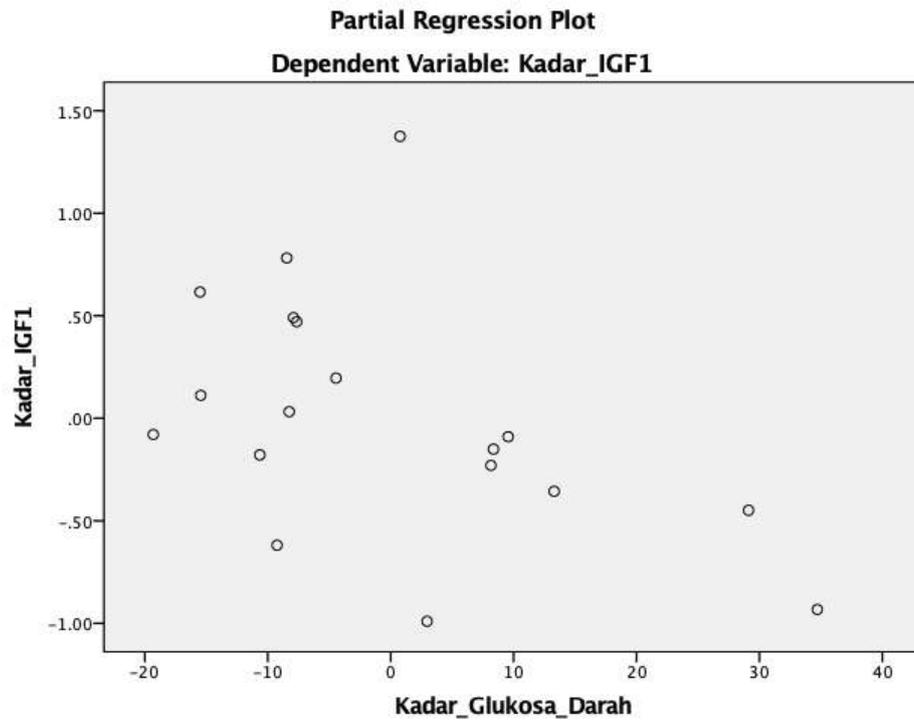
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	2.952	.158		18.733	.000
	Berat_Badan	-.022	.012	-.431	-1.814	.090
	Kadar_Glukosa_Darah	-.019	.009	-.507	-2.137	.050

a. Dependent Variable: Kadar\_IGF1

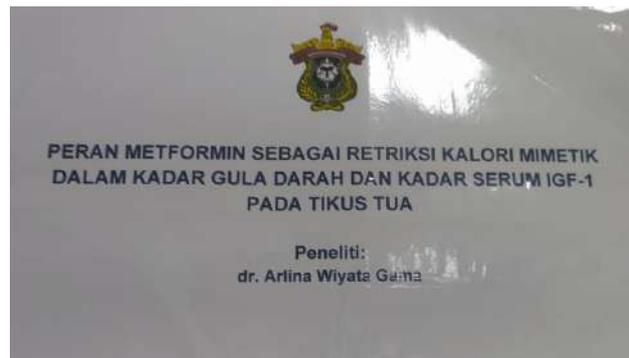
Partial Regression Plot

Dependent Variable: Kadar\_IGF1





## Lampiran 13. Dokumentasi Penelitian



Judul Penelitian yang ditempel di Pintu Laboratorium



Alat dan Bahan untuk Perlakuan pada hewan coba



Workshop Handling pada Hewan Coba



Keadaan Kandang di Laboratorium



**Penimbangan Berat Pakan Hewan**



**Pembuatan Larutan Metformin**



**Sonde Larutan Metformin sesuai dosis pada hewan coba**



**Kondisi ruangan beserta alat dan bahan persiapan pengambilan darah untuk pengukuran kadar glukosa darah dan serum darah hewan coba**



**Tabung berisi darah hewan coba**



**Alat dan Bahan Pengambilan sampel darah hewan coba**



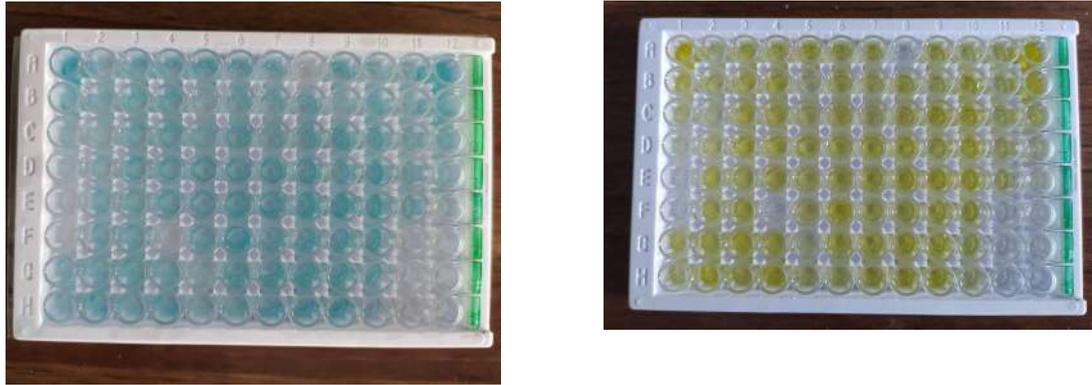
**Serum darah dalam tabung eppendorf untuk pemeriksaan ELISA**



**Reagen ELISA KIT IGF-1**



**Pemeriksaan serum IGF-1 dengan metode ELISA di Laboratorium HUMRC Rumah Sakit UNHAS**



**Perubahan warna pada sampel serum IGF-1**



**Pemeriksaan sampel menggunakan ELISA Reader**