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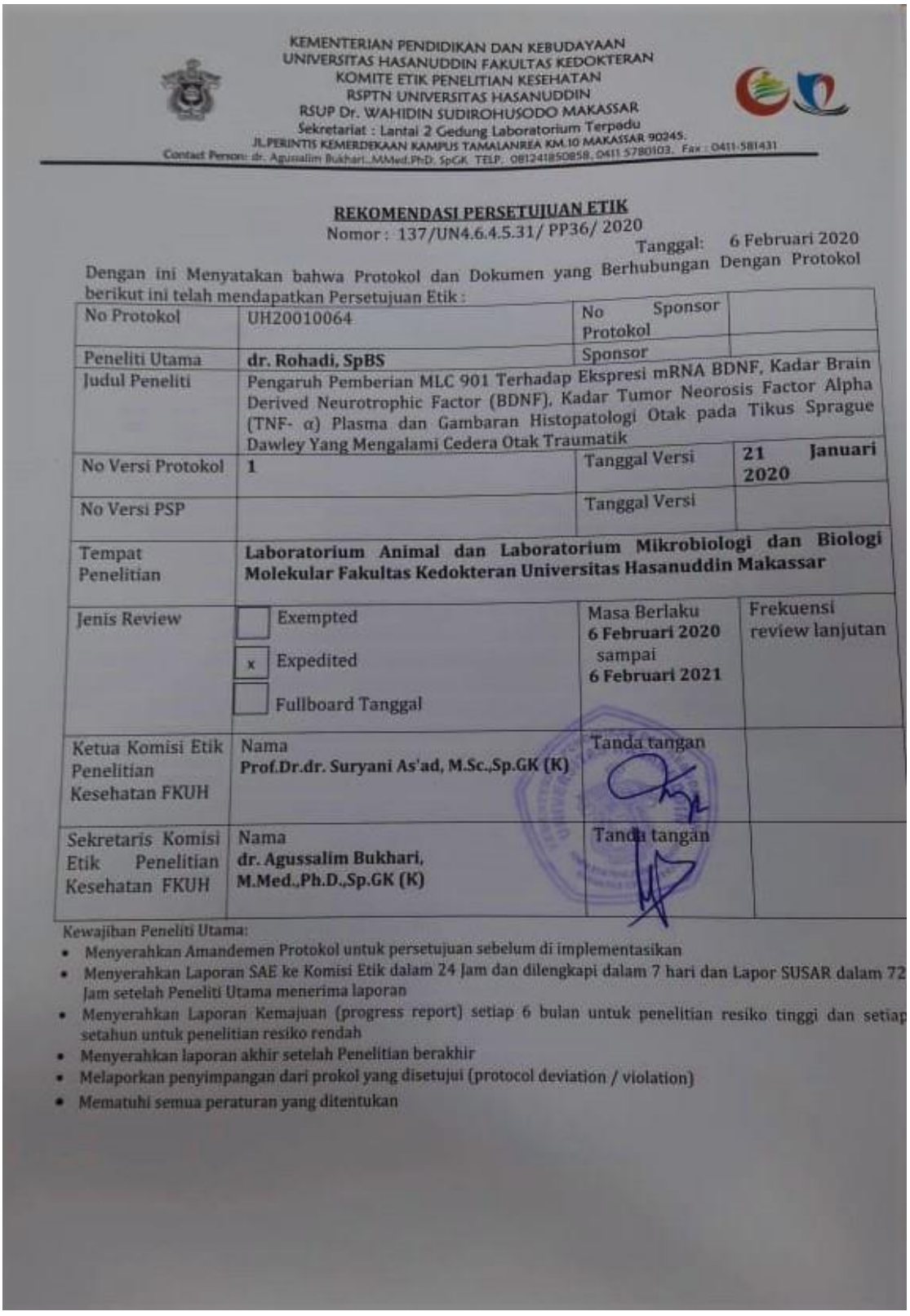
LAMPIRAN

Lampiran 1

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. SpGK. TELP. 081241850858, 0411 5780103, Fax : 0411-581431

REKOMENDASI PERSETUJUAN ETIK
Nomor : 137/UN4.6.4.5.31/ PP36/ 2020
Tanggal: 6 Februari 2020

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

No Protokol	UH20010064	No Sponsor Protokol	
Peneliti Utama	**dr. Rohadi, SpBS**	Sponsor	
Judul Peneliti	Pengaruh Pemberian MLC 901 Terhadap Ekspresi mRNA BDNF, Kadar Brain Derived Neurotrophic Factor (BDNF), Kadar Tumor Neorosis Factor Alpha (TNF- α) Plasma dan Gambaran Histopatologi Otak pada Tikus Sprague Dawley Yang Mengalami Cedera Otak Traumatik		
No Versi Protokol	**1**	Tanggal Versi	**21 Januari 2020**
No Versi PSP		Tanggal Versi	
Tempat Penelitian	**Laboratorium Animal dan Laboratorium Mikrobiologi dan Biologi Molekular Fakultas Kedokteran Universitas Hasanuddin Makassar**		
Jenis Review	[ ] Exempted [x] Expedited [ ] Fullboard Tanggal	Masa Berlaku **6 Februari 2020** sampai **6 Februari 2021**	Frekuensi review lanjutan
Ketua Komisi Etik Penelitian Kesehatan FKUH	Nama **Prof.Dr.dr. Suryani As'ad, M.Sc.,Sp.GK (K)**	Tanda tangan	
Sekretaris Komisi Etik Penelitian Kesehatan FKUH	Nama **dr. Agussalim Bukhari, M.Med.,Ph.D.,Sp.GK (K)**	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

Foto Kegiatan :

1. Aklimatisasi tikus *Sprague Dawley*

2. Pengelompokan tikus Sprague *Dawley* menjadi 2 kelompok

3. Craniotomi

4. Perlakuan cedera otak menggunakan Model Marmarou

5. Penutupan dan penjahitan lapisan otot dan kulit lapis demi lapis

Lampiran 3

- **Hasil pengolahan data penelitian menggunakan SPSS**

Descriptives

	Group			Statistic	Std. Error
Expression of synaptphysin	Placebo	Mean		81.60	6.046
		95% Confidence Interval for Mean	Lower Bound	64.81	
			Upper Bound	98.39	
		5% Trimmed Mean		81.67	
		Median		78.00	
		Variance		182.800	
		Std. Deviation		13.520	
		Minimum		64	
		Maximum		98	
		Range		34	
		Interquartile Range		25	
		Skewness		-.023	.913
		Kurtosis		-1.224	2.000
	MLC901	Mean		118.40	5.455
		95% Confidence Interval for Mean	Lower Bound	103.25	
			Upper Bound	133.55	
		5% Trimmed Mean		118.44	
		Median		120.00	
		Variance		148.800	
		Std. Deviation		12.198	
		Minimum		104	
		Maximum		132	
		Range		28	
		Interquartile Range		24	
		Skewness		-.162	.913
		Kurtosis		-2.501	2.000
BDNFpre	Placebo	Mean		2444.0000	66.12639
		95% Confidence Interval for Mean	Lower Bound	2260.4037	
			Upper Bound	2627.5963	
		5% Trimmed Mean		2441.2222	
		Median		2415.0000	
		Variance		21863.500	
		Std. Deviation		147.86311	
		Minimum		2270.00	
		Maximum		2668.00	
		Range		398.00	
		Interquartile Range		253.50	

		Skewness		.742	.913
		Kurtosis		1.039	2.000
	MLC901	Mean		2357.2000	83.70030
		95% Confidence Interval for Mean	Lower Bound	2124.8107	
			Upper Bound	2589.5893	
		5% Trimmed Mean		2352.7778	
		Median		2307.0000	
		Variance		35028.700	
		Std. Deviation		187.15956	
		Minimum		2162.00	
		Maximum		2632.00	
		Range		470.00	
		Interquartile Range		343.50	
		Skewness		.772	.913
		Kurtosis		-.392	2.000
TNFpre	Placebo	Mean		623.0000	125.62524
		95% Confidence Interval for Mean	Lower Bound	274.2084	
			Upper Bound	971.7916	
		5% Trimmed Mean		616.1667	
		Median		611.0000	
		Variance		78908.500	
		Std. Deviation		280.90657	
		Minimum		319.00	
		Maximum		1050.00	
		Range		731.00	
		Interquartile Range		497.00	
		Skewness		.821	.913
		Kurtosis		.641	2.000
	MLC901	Mean		670.0000	134.74235
		95% Confidence Interval for Mean	Lower Bound	295.8953	
			Upper Bound	1044.1047	
		5% Trimmed Mean		676.5000	
		Median		728.0000	
		Variance		90777.500	
		Std. Deviation		301.29305	
		Minimum		231.00	
		Maximum		992.00	
		Range		761.00	
		Interquartile Range		556.00	
		Skewness		-.693	.913
		Kurtosis		-.397	2.000
BDNFPCRpre	Placebo	Mean		10.24780	.356268

		95% Confidence Interval for Mean	Lower Bound	9.25864	
			Upper Bound	11.23696	
		5% Trimmed Mean		10.25894	
		Median		10.58200	
		Variance		.635	
		Std. Deviation		.796640	
		Minimum		9.206	
		Maximum		11.089	
		Range		1.883	
		Interquartile Range		1.501	
		Skewness		-.514	.913
		Kurtosis		-2.093	2.000
	MLC901	Mean		10.19720	.375602
		95% Confidence Interval for Mean	Lower Bound	9.15436	
			Upper Bound	11.24004	
		5% Trimmed Mean		10.20794	
		Median		10.49000	
		Variance		.705	
		Std. Deviation		.839872	
		Minimum		9.192	
		Maximum		11.009	
		Range		1.817	
		Interquartile Range		1.637	
		Skewness		-.432	.913
		Kurtosis		-2.871	2.000
BDNF30m	Placebo	Mean		721.6000	69.84311
		95% Confidence Interval for Mean	Lower Bound	527.6844	
			Upper Bound	915.5156	
		5% Trimmed Mean		722.3889	
		Median		714.0000	
		Variance		24390.300	
		Std. Deviation		156.17394	
		Minimum		534.00	
		Maximum		895.00	
		Range		361.00	
		Interquartile Range		307.00	
		Skewness		-.037	.913
		Kurtosis		-2.374	2.000
	MLC901	Mean		718.0000	99.31717
		95% Confidence Interval for Mean	Lower Bound	442.2513	
			Upper Bound	993.7487	
		5% Trimmed Mean		711.3889	

		Median		660.0000	
		Variance		49319.500	
		Std. Deviation		222.07994	
		Minimum		497.00	
		Maximum		1058.00	
		Range		561.00	
		Interquartile Range		398.00	
		Skewness		.979	.913
		Kurtosis		.375	2.000
TNF30m	Placebo	Mean		3453.6000	443.99849
		95% Confidence Interval for Mean	Lower Bound	2220.8626	
			Upper Bound	4686.3374	
		5% Trimmed Mean		3447.7778	
		Median		3155.0000	
		Variance		985673.300	
		Std. Deviation		992.81081	
		Minimum		2424.00	
		Maximum		4588.00	
		Range		2164.00	
		Interquartile Range		1944.50	
		Skewness		.330	.913
		Kurtosis		-2.881	2.000
	MLC901	Mean		3564.8000	230.74778
		95% Confidence Interval for Mean	Lower Bound	2924.1414	
			Upper Bound	4205.4586	
		5% Trimmed Mean		3569.6667	
		Median		3536.0000	
		Variance		266222.700	
		Std. Deviation		515.96773	
		Minimum		2834.00	
		Maximum		4208.00	
		Range		1374.00	
		Interquartile Range		921.00	
		Skewness		-.318	.913
		Kurtosis		.195	2.000
BDNFPCR30m	Placebo	Mean		6.00680	.327256
		95% Confidence Interval for Mean	Lower Bound	5.09819	
			Upper Bound	6.91541	
		5% Trimmed Mean		6.00717	
		Median		6.12200	
		Variance		.535	
		Std. Deviation		.731767	

		Minimum		5.149	
		Maximum		6.858	
		Range		1.709	
		Interquartile Range		1.430	
		Skewness		-.129	.913
		Kurtosis		-2.343	2.000
	MLC901	Mean		6.01600	.214696
		95% Confidence Interval for Mean	Lower Bound	5.41991	
			Upper Bound	6.61209	
		5% Trimmed Mean		6.01972	
		Median		6.06500	
		Variance		.230	
		Std. Deviation		.480074	
		Minimum		5.352	
		Maximum		6.613	
		Range		1.261	
		Interquartile Range		.878	
		Skewness		-.288	.913
		Kurtosis		-.259	2.000
BDNF6mg	Placebo	Mean		1778.2000	68.04219
		95% Confidence Interval for Mean	Lower Bound	1589.2846	
			Upper Bound	1967.1154	
		5% Trimmed Mean		1776.7778	
		Median		1764.0000	
		Variance		23148.700	
		Std. Deviation		152.14697	
		Minimum		1601.00	
		Maximum		1981.00	
		Range		380.00	
		Interquartile Range		289.50	
		Skewness		.288	.913
		Kurtosis		-1.288	2.000
	MLC901	Mean		3298.2000	134.60067
		95% Confidence Interval for Mean	Lower Bound	2924.4886	
			Upper Bound	3671.9114	
		5% Trimmed Mean		3303.8333	
		Median		3320.0000	
		Variance		90586.700	
		Std. Deviation		300.97624	
		Minimum		2868.00	
		Maximum		3627.00	
		Range		759.00	

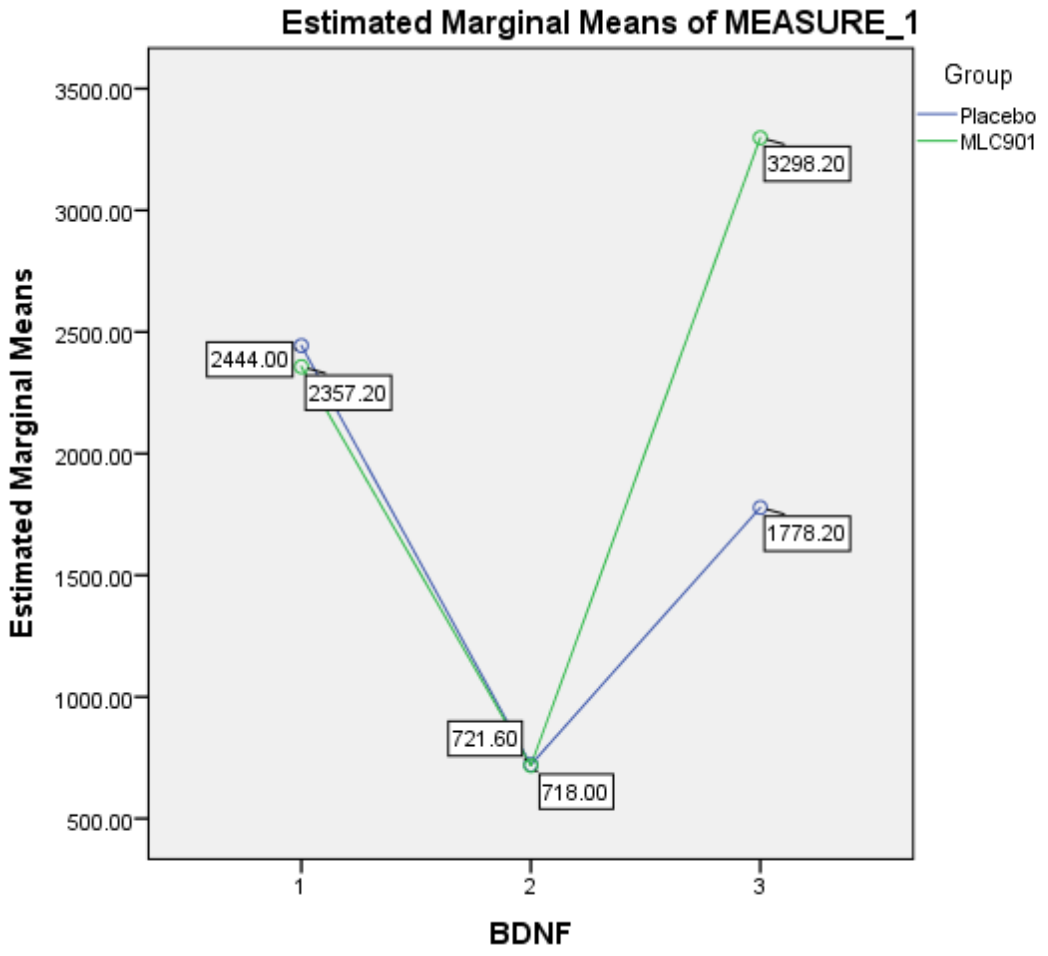
		Interquartile Range		560.50	
		Skewness		-.552	.913
		Kurtosis		-.579	2.000
TNF6mg	Placebo	Mean		1383.4000	177.86248
		95% Confidence Interval for Mean	Lower Bound	889.5746	
			Upper Bound	1877.2254	
		5% Trimmed Mean		1387.9444	
		Median		1401.0000	
		Variance		158175.300	
		Std. Deviation		397.71258	
		Minimum		816.00	
		Maximum		1869.00	
		Range		1053.00	
		Interquartile Range		717.00	
		Skewness		-.405	.913
		Kurtosis		.111	2.000
	MLC901	Mean		2576.6000	133.45209
		95% Confidence Interval for Mean	Lower Bound	2206.0776	
			Upper Bound	2947.1224	
		5% Trimmed Mean		2572.3889	
		Median		2571.0000	
		Variance		89047.300	
		Std. Deviation		298.40794	
		Minimum		2249.00	
		Maximum		2980.00	
		Range		731.00	
		Interquartile Range		570.00	
		Skewness		.339	.913
		Kurtosis		-1.360	2.000
BDNFPCR6mg	Placebo	Mean		9.03720	.196702
		95% Confidence Interval for Mean	Lower Bound	8.49107	
			Upper Bound	9.58333	
		5% Trimmed Mean		9.04222	
		Median		9.06200	
		Variance		.193	
		Std. Deviation		.439839	
		Minimum		8.425	
		Maximum		9.559	
		Range		1.134	
		Interquartile Range		.816	
		Skewness		-.368	.913
		Kurtosis		-.549	2.000

MLC901	Mean		13.86560	.318350
	95% Confidence Interval for Mean	Lower Bound	12.98172	
		Upper Bound	14.74948	
	5% Trimmed Mean		13.85717	
	Median		13.76600	
	Variance		.507	
	Std. Deviation		.711851	
	Minimum		13.034	
	Maximum		14.849	
	Range		1.815	
	Interquartile Range		1.330	
	Skewness		.401	.913
	Kurtosis		-.801	2.000

- **Uji Kadar BDNF, Ekpresi mRNA BDNF dan Kadar TNF alpha**
- **BDNF**

Parameter Estimates

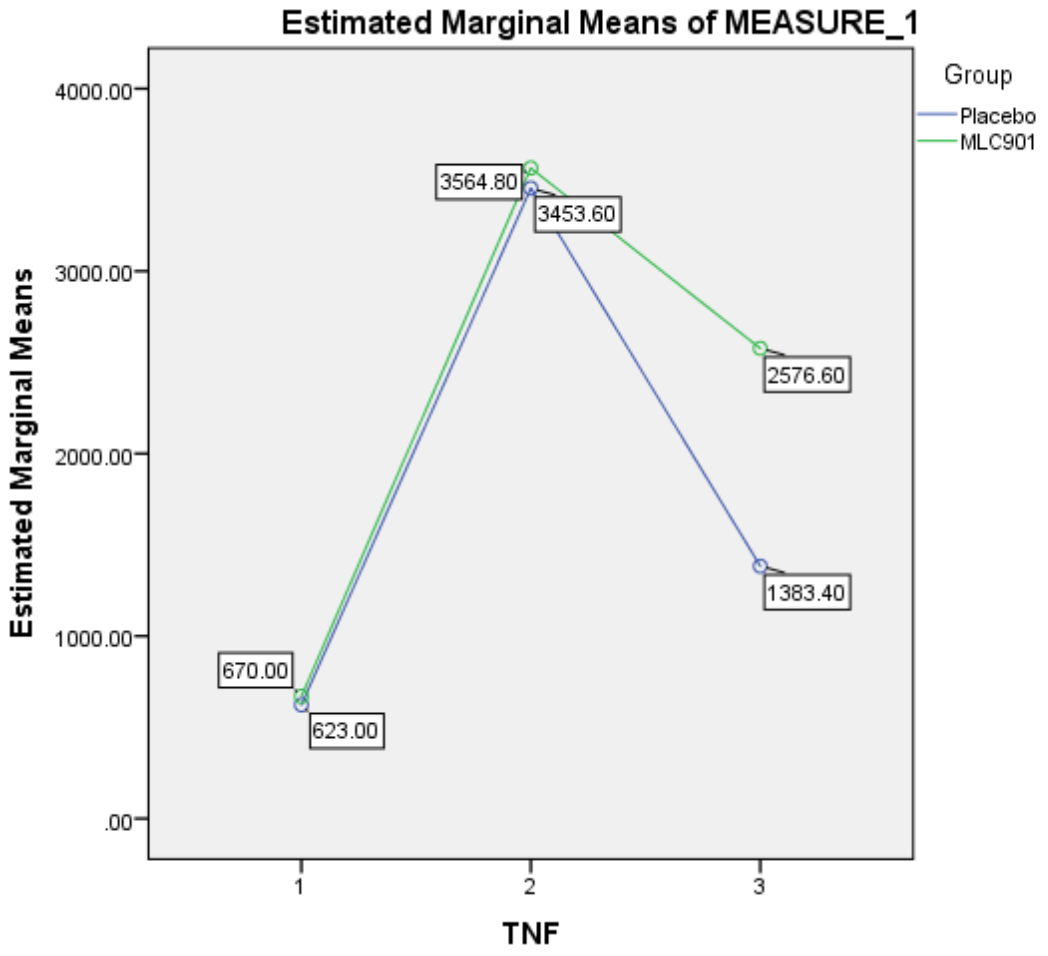
Dependent Variable	Parameter	B	Std. Error	t	Sig.	95% Confidence Interval Lower Bound
BDNFpre	Intercept	2357.200	75.427	31.251	.000	2183.265
	[Group=1.00]	86.800	106.670	.814	.439	-159.181
	[Group=2.00]	0[a]	.	.	.	.
BDNF30m	Intercept	718.000	85.854	8.363	.000	520.019
	[Group=1.00]	3.600	121.416	.030	.977	-276.387
	[Group=2.00]	0[a]	.	.	.	.
BDNF6mg	Intercept	3298.200	106.647	30.926	.000	3052.272
	[Group=1.00]	-1520.000	150.821	-10.078	.000	-1867.795
	[Group=2.00]	0[a]	.	.	.	.



- **TNF alpha**

Parameter Estimates

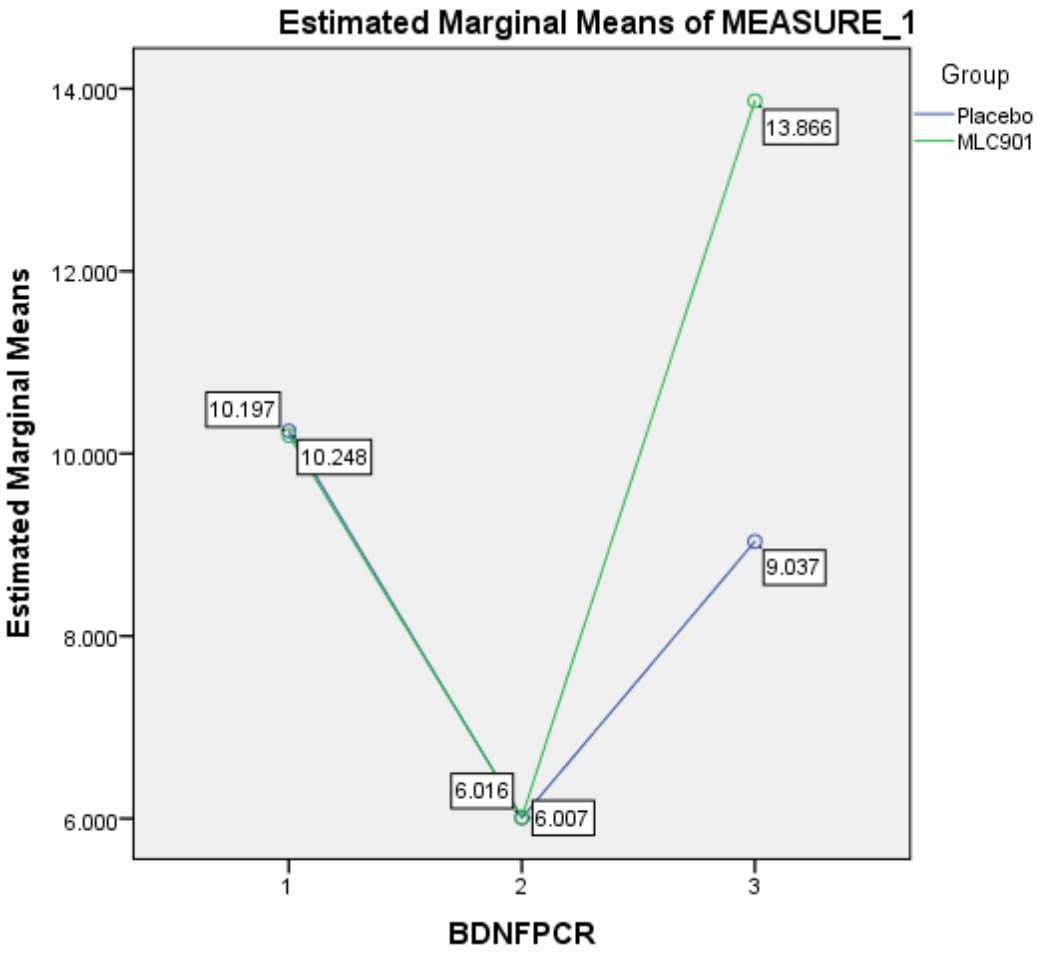
Dependent Variable	Parameter	B	Std. Error	t	Sig.	95% Confidence Interval Lower Bound
TNFpre	Intercept	670.000	130.264	5.143	.001	369.612
	[Group=1.00]	-47.000	184.221	-.255	.805	-471.813
	[Group=2.00]	0[a]	.	.	.	.
TNF30m	Intercept	3564.800	353.821	10.075	.000	2748.886
	[Group=1.00]	-111.200	500.379	-.222	.830	-1265.076
	[Group=2.00]	0[a]	.	.	.	.
TNF6mg	Intercept	2576.600	157.233	16.387	.000	2214.020
	[Group=1.00]	-1193.200	222.361	-5.366	.001	-1705.966
	[Group=2.00]	0[a]	.	.	.	.



- **mRNA BDNF**

Parameter Estimates

Dependent Variable	Parameter	B	Std. Error	t	Sig.	95% Confidence Interval Lower Bound
BDNFPCRpre	Intercept	10.197	.366	27.856	.000	9.353
	[Group=1.00]	.051	.518	.098	.925	-1.143
	[Group=2.00]	0[a]	.	.	.	.
BDNFPCR30m	Intercept	6.016	.277	21.737	.000	5.378
	[Group=1.00]	-.009	.391	-.024	.982	-.912
	[Group=2.00]	0[a]	.	.	.	.
BDNFPCR6mg	Intercept	13.866	.265	52.400	.000	13.255
	[Group=1.00]	-4.828	.374	-12.903	.000	-5.691
	[Group=2.00]	0[a]	.	.	.	.

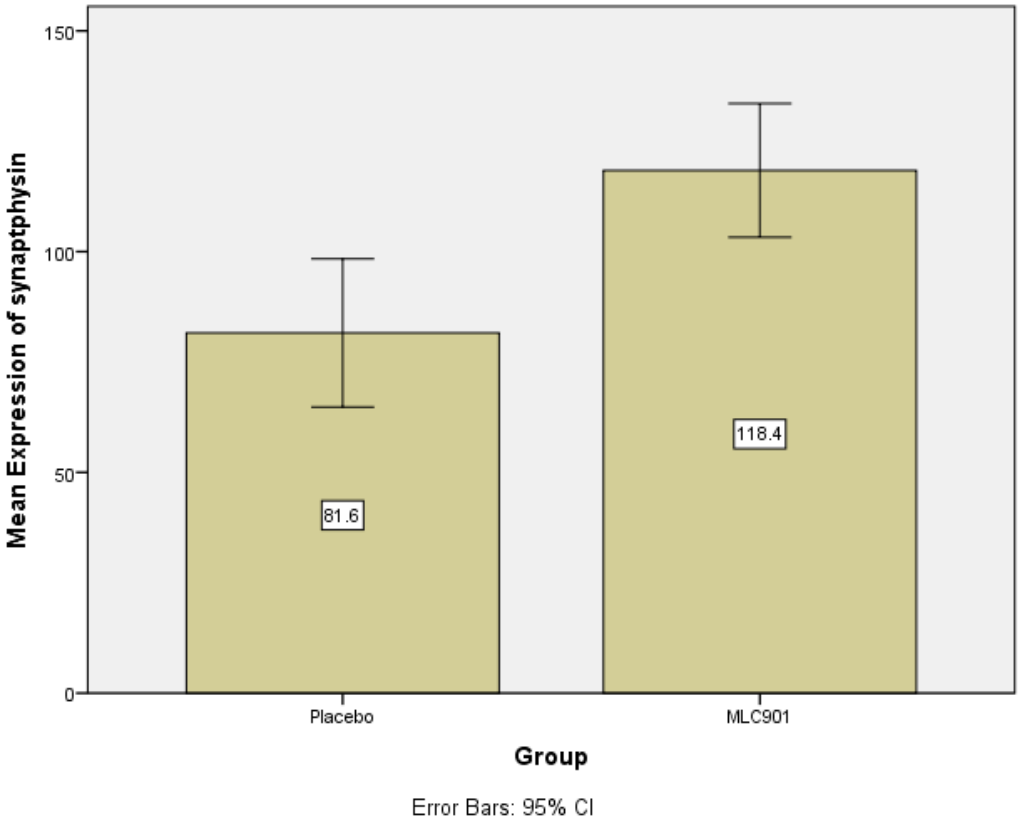


- **Uji Pengaruh MLC 901 terhadap Neurogeneis dengan Penanda Synaptophysin**

Descriptivesa					
	Group			Statistic	Std. Error
Expression of synaptophysin	Placebo	Mean		81.6	6.046
		95% Confidence Interval for Mean	Lower Bound	64.81	
			Upper Bound	98.39	
		5% Trimmed Mean		81.67	
		Median		78	
		Variance		182.8	
		Std. Deviation		13.52	
		Minimum		64	
		Maximum		98	
		Range		34	
		Interquartile Range		25	

		Skewness		-0.023	0.913
		Kurtosis		-1.224	2
	Neuroaid	Mean		118.4	5.455
		95% Confidence Interval for Mean	Lower Bound	103.25	
			Upper Bound	133.55	
		5% Trimmed Mean		118.44	
		Median		120	
		Variance		148.8	
		Std. Deviation		12.198	
		Minimum		104	
		Maximum		132	
		Range		28	
		Interquartile Range		24	

Group Statistics					
	Group	N	Mean	Std. Deviation	Std. Error Mean
Expression of synaptphysin	Placebo	5	81.6	13.52	6.046
	Neuroaid	5	118.4	12.198	5.455



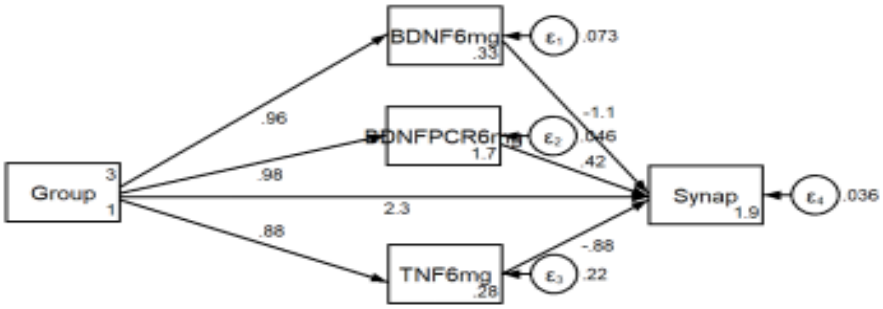
- Uji Korelasi antara Ekspresi Synaptophysin dengan kadar BDNF plasma, ekspresi mRNA BDNF dan kadar TNF-α plasma setelah 6 minggu Pemberian MLC 901

Correlations

		Expression of synaptphysin	BDNF6mg	TNF6mg
Expression of synaptphysin	Pearson Correlation	1	.761*	.576
	Sig. (2-tailed)		.010	.082
	N	10	10	10
BDNF6mg	Pearson Correlation	.761*	1	.818**
	Sig. (2-tailed)	.010		.004
	N	10	10	10
TNF6mg	Pearson Correlation	.576	.818**	1
	Sig. (2-tailed)	.082	.004	
	N	10	10	10
BDNFPCR6mg	Pearson Correlation	.888**	.936**	.824**
	Sig. (2-tailed)	.001	.000	.003
	N	10	10	10

Correlations

		BDNFPCR6mg
Expression of synaptphysin	Pearson Correlation	.888**
	Sig. (2-tailed)	.001
	N	10
BDNF6mg	Pearson Correlation	.936**
	Sig. (2-tailed)	.000
	N	10
TNF6mg	Pearson Correlation	.824**
	Sig. (2-tailed)	.003
	N	10
BDNFPCR6mg	Pearson Correlation	1
	Sig. (2-tailed)	
	N	10

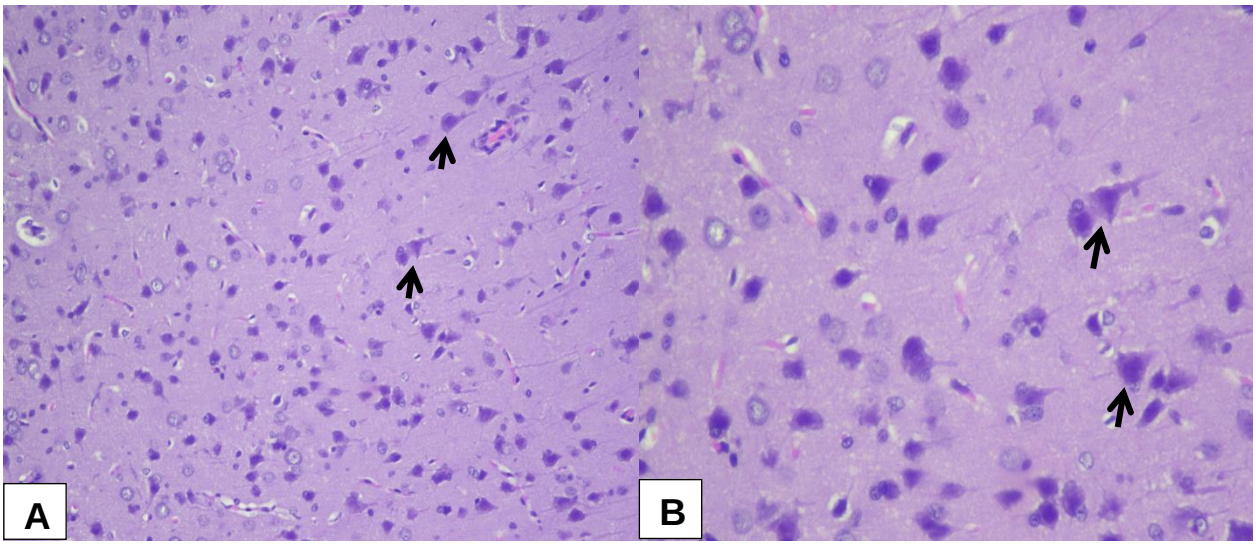



```
. estat teffects, compact standardized nodirect noindirect

Total effects
------------------------------------------------------------------------------
             |                   OIM
             |      Coef.   Std. Err.      z    P>|z|     Std. Coef.
-------------+----------------------------------------------------------------
Structural   |
  BDNF6mg <- |
       Group |        1520   134.8987    11.27   0.000      .9628015
-------------+----------------------------------------------------------------
  BDNFPCR6mg <- |
       Group |      4.8284   .3347095    14.43   0.000      .9768057
-------------+----------------------------------------------------------------
  TNF6mg <-  |
       Group |      1193.2   198.8859     6.00   0.000      .8846331
-------------+----------------------------------------------------------------
  Synap <-   |
     BDNF6mg |    -.031283   .0065673    -4.76   0.000     -1.118724
  BDNFPCR6mg |    3.778883   2.779903     1.36   0.174       .423122
     TNF6mg |    -.028908   .0048421    -5.97   0.000     -.8832336
       Group |        36.8    7.71131     4.77   0.000      .8335947
------------------------------------------------------------------------------

. estat gof, stats(rmsea)

------------------------------------------------------------------------------
Fit statistic          |       Value   Description
-----------------------+------------------------------------------------------
Population error       |
                 RMSEA |           .   Root mean squared error of approximation
 90% CI, lower bound   |       0.000
         upper bound   |           .
               pclose  |           .   Probability RMSEA <= 0.05
------------------------------------------------------------------------------
```

Lampiran 4

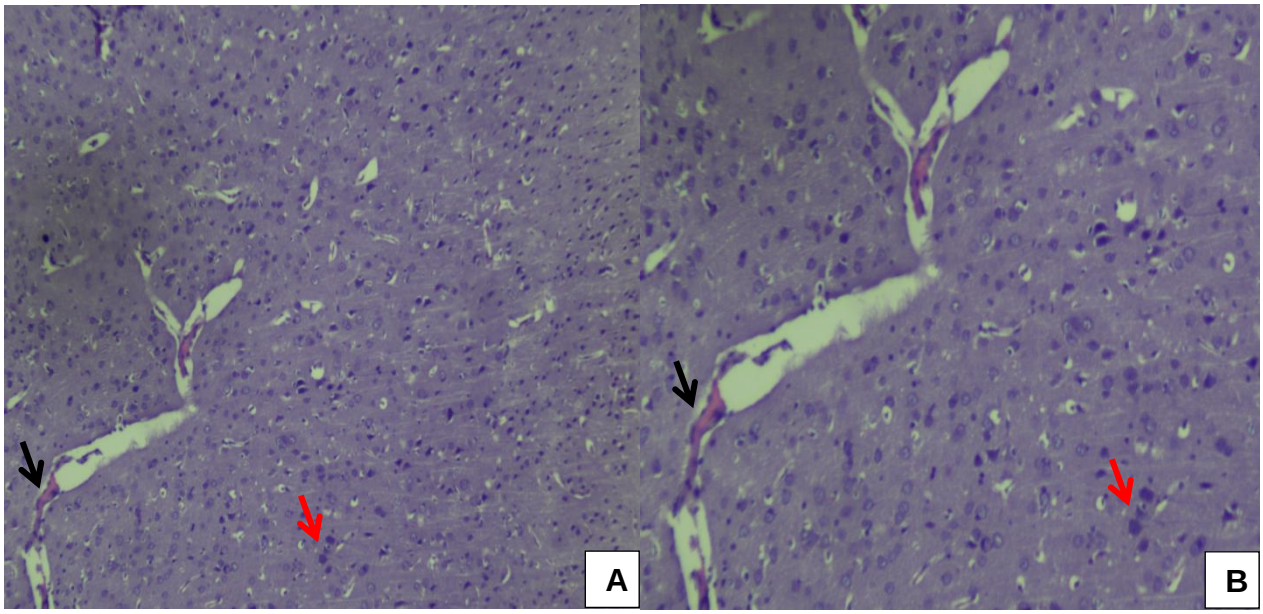
Gambaran Histopatologi

A.* Gambaran histologi normal jaringan otak tikus *Sprague Dawley



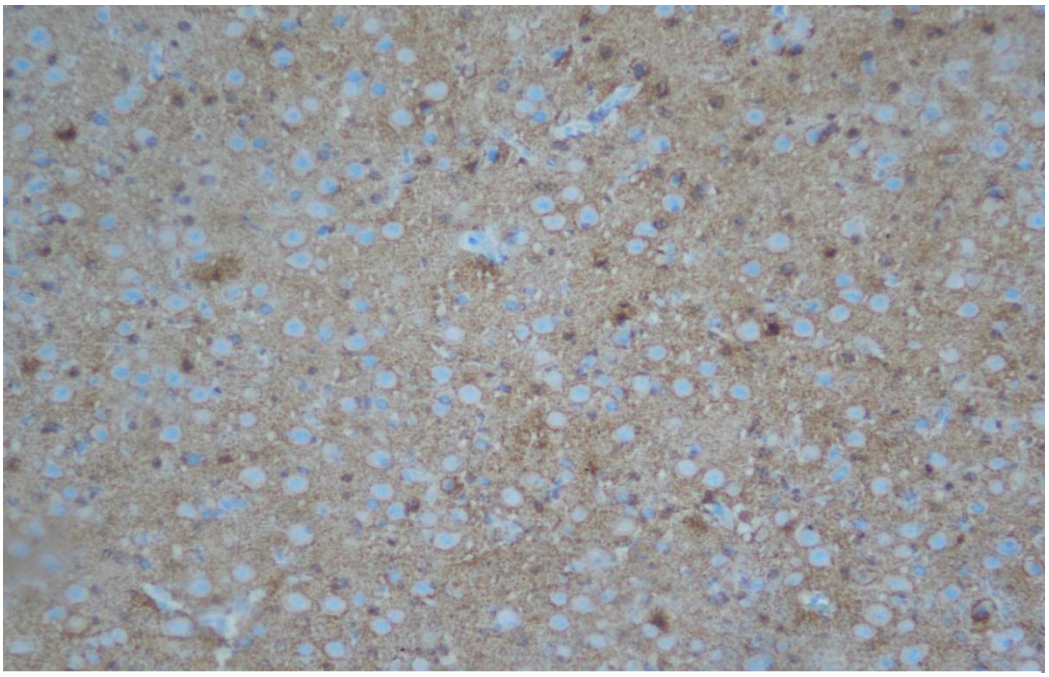
Keterangan : Gambaran histologi jaringan otak tikus normal. Tampak parenkim otak yang terdiri dari sel-sel neuron (panah hitam). Gambar A pembesaran 200 x. Gambar B pembesaran 400 x.

***B.* Gambaran histopatologi jaringan otak tikus *Sprague Dawley* dengan cedera otak**



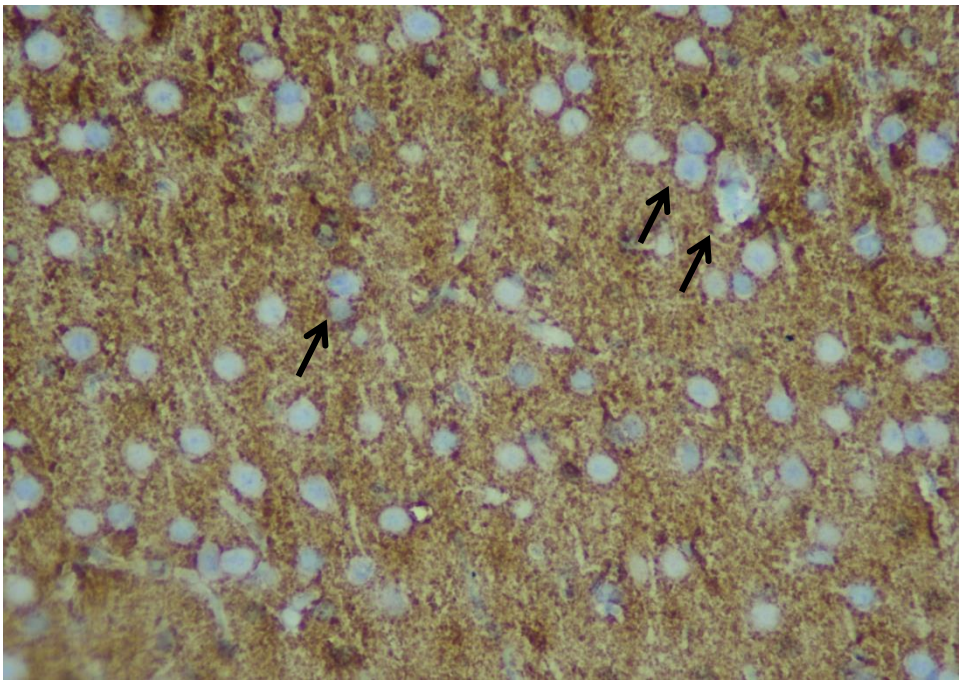
Keterangan : Gambaran histopatologi jaringan otak tikus dengan cedera otak. Tampak parenkim otak dengan sel neuron yang mengalami degenerasi (panah merah) dan area perdarahan (panah hitam). Gambar A pembesaran 100x. Gambar B pembesaran 200x.

C. **Gambaran immunohistokimia normal jaringan otak tikus *Sprague Dawley***



Keterangan : Menunjukan potongan jaringan parenkim otak, terdiri dari sel-sel neuron dan sel granul. Pembesaran 100 x.

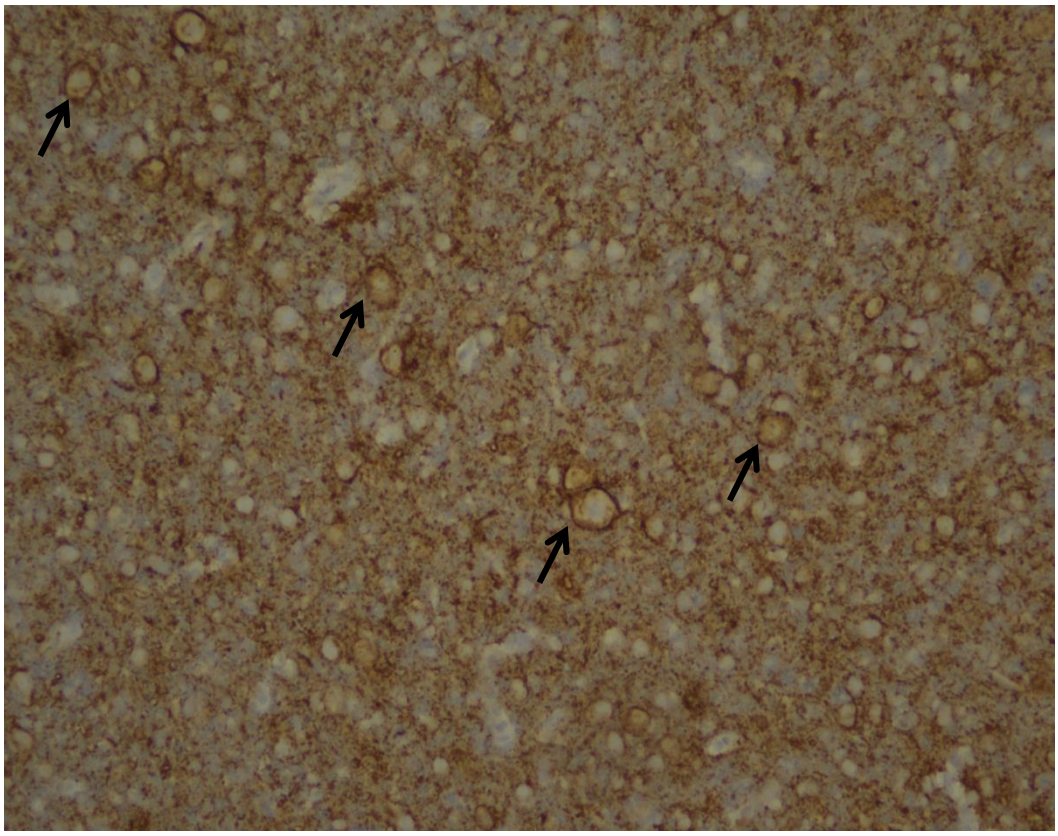
D. **Gambaran immunohistokimia jaringan otak tikus *Sprague Dawley* Model Cedera Otak tanpa pemberian MLC 901**



Keterangan : Pulasan imunohistokimia dengan antibodi *synaptophysin*.

Antibodi *synaptophysin* tidak terpulas pada sitoplasma sel neuron (tanda panah). Tidak ada ikatan antibodi antara *synaptophsyin* dengan sitoplasma sel neuron, sehingga warna sitoplasma tampak tetap biru. Pembesaran 400x.

_E._ Gambaran immunohistokimia jaringan otak tikus _Sprague Dawley_ Model Cedera Otak dengan pemberian MLC 901



Keterangan : Pulasan imunohistokimia dengan antibodi *synaptophysin.* Tampak antibodi *synaptophysin* terpulas pada sitoplasma sel neuron (tanda panah). Terdapat ikatan antibodi antara *synaptophsyin* dengan sitoplasma sel neuron, sehingga warna sitoplasma menjadi cokelat. Pembesaran 400x.