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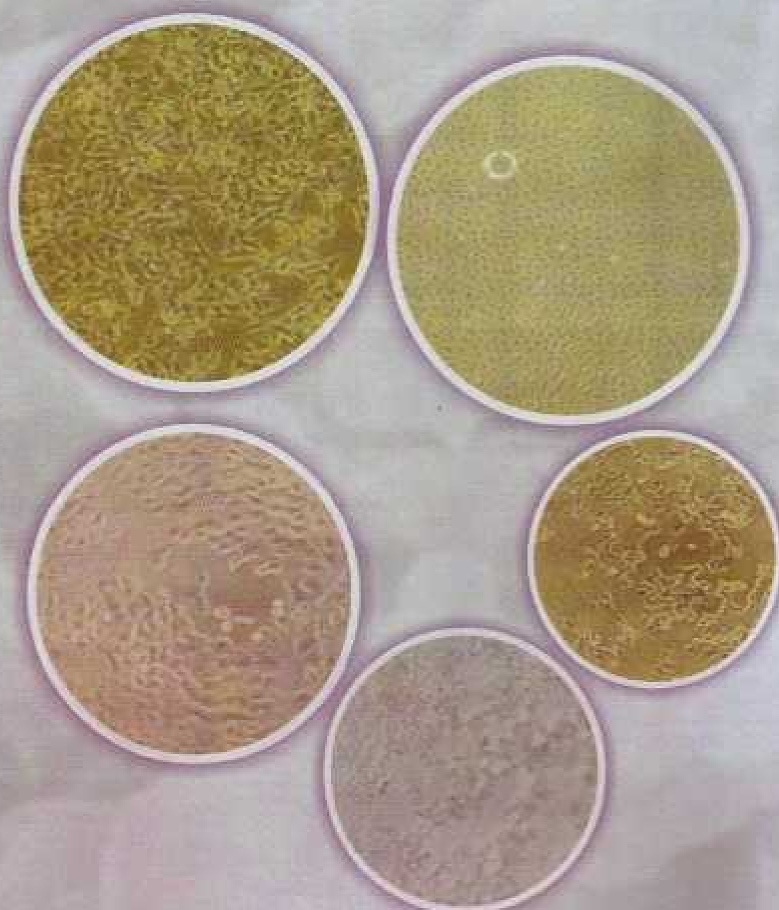

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Aktivitas Antioksidan Kombinasi Ekstrak Jahe Gajah (*Zingiber officinale* Rosc.) dan Zink Berdasarkan Pengukuran MDA, SOD dan Katalase pada Mencit Hiperkolesterolemia dan Hiperglikemia dengan Penginduksi Streptozotosin

Antioxidant Activity of Combination between Ginger Extract (*Zingiber officinale* Rosc.) with Zink Based on MDA, SOD and Catalase Measurements in Hypercholesterolemia and Hyperglycemia Mice with Streptozotocin as Inducer

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Diterima 28 April 2015, Disetujui 24 Juli 2015

Abstrak: Hiperkolesterolemia dan hiperglikemia mampu memicu terjadinya radikal bebas yang berlebih. Untuk mencegah terjadinya radikal bebas, diperlukan pemberian antioksidan. Kombinasi ekstrak jahe gajah (*Zingiber officinalle* Rosc.) yang merupakan tanaman yang memiliki kandungan antioksidan dengan zink diharapkan mampu meningkatkan kemampuan antioksidan untuk melawan radikal bebas yang menyebabkan kerusakan pada organ tubuh. Tujuan penelitian ini adalah mengetahui aktivitas kombinasi ekstrak jahe gajah dan zink berdasarkan pengukuran kadar *malonyldialdehide* (MDA), aktivitas superoksida dismutase (SOD) dan katalase pada mencit hiperkolesterolemia dan hiperglikemia dengan penginduksi streptozotosin. Mencit jantan DDY sebanyak 48 ekor dibagi menjadi 8 kelompok, masing-masing 6 ekor. Kelompok I (normal), kelompok II (negatif), kelompok III (atorvastatin), kelompok IV (ekstrak jahe 37,5mg/kgbb), keblompok V (zink 20mg/kgbb), kelompok VI (ekstrak jahe 37,5mg/kgbb dan zink 20mg/kgbb), kelompok VII (ekstrak jahe 75mg/kgbb dan zink 20mg/kgbb) dan kelompok VIII (ekstrak jahe 150mg/kgbb dan zink 20mg/kgbb). Pengukuran MDA, SOD dan katalase pada hati dan darah mencit menggunakan spektrofotometer UV-Vis. Data yang diperoleh diuji dengan anova satu arah, lalu dilanjutkan dengan uji Tukey. Hasil penelitian menunjukkan bahwa kombinasi pada kelompok VII mampu menurunkan kadar MDA, meningkatkan kadar SOD dan katalase pada mencit jauh lebih baik dibandingkan yang lainnya. Aktivitas antioksidan kelompok VII ini sebanding dengan kontrol positif.

Kata kunci: Antioksidan, kombinasi ekstrak jahe gajah dan zink, MDA, SOD, katalase.

Abstract: Hypercholesterolemia and hyperglycemia were able to trigger the free radicals excess. To prevent this case, antioxidant administration is needed. The combination of ginger extract (*Zingiber officinalle* Rosc.), a plant that contains antioxidants, with zink is expected to improve the ability of antioxidants to fight free radicals that cause damage to the organs. The purpose of this study was to determine antioxidant activity of combination between ginger extract and zink by measuring the levels of malonyldialdehide (MDA), superoxyde dismutase (SOD) and catalase in hypercholesterolemia and

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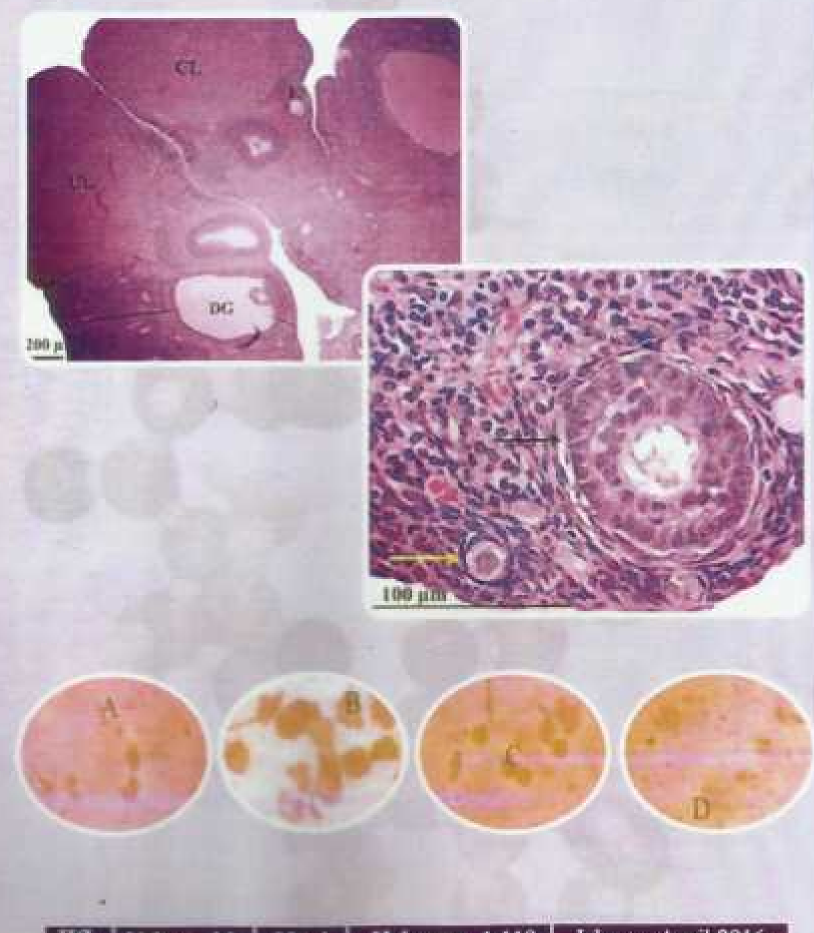

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Antihypertensive and Diuretic Effects of The Ethanol Extract of *Colocasia esculenta* (L.) Schott. Leaves

(Efek Antihipertensi dan Diuretik dari Ekstrak Etanol Daun Talas (*Colocasia esculenta* (L.) Schott.))

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Abstract: *Colocasia esculenta* (L.) Schott (CE) is traditionally used for the treatment of various ailments such as high blood pressure, diarrhea, rheumatic pain, pulmonary congestion, etc. Hence in present study, the effect of ethanol extract of CE leaves (EECE) was evaluated for antihypertensive and diuretic activity in rats. Male Sprague dawley rats were randomly divided into five groups (n=5), and treated as follow: positive control group (hydrochlortiazide 0.2569 mg/ 200 g bw), negative control (NaCl 8%) and EECE (20, 40 and 80 mg/ 200 g bw) was given 14 days. The parameters systole blood pressure (SBP) and diastole blood pressure (DBP) was estimate by Kent Scientific's CODA Non-invasive Blood Pressure on the days 0, 15 and 29. Diuretic activity of EECE was studied based on the volume of urine for 6 hours and measuring the levels of sodium in urine 24 hours. The result of the study showed that EECE 40 mg/ 200 g bw/ day significant ($p<0.05$) decreased in SBP 16.07% and in DBP 13.67%. EECE 40 mg/ 200 g bw/day showed positive diuretic activity and significantly ($p < 0.05$) increased sodium levels in urine. Preliminary phytochemical evaluation revealed the presence of saponins, tannin, triterpenoid and flavonoids in EECE.

Keywords : *Colocasia esculenta*, antihypertensive, diuretic activity, NaCl induced, flavonoids.

Abstrak: Talas (*Colocasia esculenta* (L.) Schott) (CE) secara tradisional digunakan untuk berbagai penyakit seperti tekanan darah tinggi, diare, rematik, gangguan paru-paru dan lain sebagainya. Dalam penelitian ini diteliti aktivitas ekstrak etanol daun talas sebagai antihipertensi dan diuretik pada tikus. Tikus jantan *Sprague dawley* secara acak dibagi menjadi lima kelompok (n=5) dan diberi perlakuan sebagai berikut: kelompok kontrol positif (diberi hidroklorotiazida 0,2569 mg/200 g bb), kontrol negatif (diberi NaCl 8%), 3 kelompok perlakuan masing-masing diberi ekstrak etanol daun talas dengan konsentrasi 20, 40 dan 80 mg/200 g bb selama 14 hari. Parameter berupa tekanan darah sistol dan diastol diukur dengan *Kent Scientific's CODA non-invasive blood pressure* pada hari ke-0, 15 dan 29. Aktivitas diuretik ekstrak etanol daun talas dianalisis berdasarkan volume urin dalam waktu 6 jam dan pengukuran jumlah natrium urin dalam waktu 24 jam. Hasil penelitian menunjukkan bahwa ekstrak etanol daun talas dengan konsentrasi 40 mg/200 g bb/ hari secara signifikan ($p<0,05$) menurunkan tekanan darah sistol sebesar 16,07% dan menurunkan tekanan darah diastol sebesar 13,67%. Ekstrak etanol daun talas 40 mg/ 200 g bb/ hari positif menunjukkan aktivitas diuretik dan secara signifikan meningkatkan kadar natrium dalam urin ($p <0,05$). Evaluasi kandungan fitokimia yang telah dilakukan membuktikan bahwa ekstrak etanol daun talas mengandung saponin, tanin, triterpenoid dan flavonoid.

Keywords : *Colocasia esculenta*, antihipertensi, aktivitas diuretik, induksi NaCl, flavonoid.

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INTRODUCTION

Hypertension is an increase in blood pressure (BP) above normal and permanent, or when systole blood pressure (SBP) is above 140 mmHg and diastole blood pressure (DBP) is above 90 mmHg[1]. Pharmacological therapy for hypertension is using synthetic drugs. Hypertension drugs are use in long term lead to increase cost and side effects.

Medicinal plant which is owned by Indonesia has enough potential to be utilized and developed as raw materials for herbal medicines. Herbal medicines for therapy is also no longer something new to the community. In line with the trend of 'back to nature' that developed among the public at this time, the use of herbal as alternative medicine continues to grow bigger. One of the them which is used as an alternative medicine is taro leaves (*Colocasia esculenta* (L.) Schott.) (CE)[2].

Taro is known as the tuber which can be used as food substitute. All parts of this plant can be used for treatment, including the petiole and leaf. The content of the active compounds in CE is polyphenols. Taro leaves have medicinal properties as diarrhea, arthritis, pulmonary edema[3]. And based on previous research was showed that taro leaf aqueous extract at a dose of 400 mg/ kg bw has efficacy as an antihypertensive and diuretic activity[4].

MATERIALS AND METHOD

MATERIALS. The leaves of *Colocasia esculenta* (CE) were collected from Badan Penelitian Tanaman Rempah dan Obat (BALITTRO), Bogor, Indonesia. The plant specimen was authenticated and herbarium was deposited at Indonesian Institute of Science, Cibinong, Bogor, West Java, Indonesia.

METHOD. Preparation of Ethanol extract of CE leaves (EECE). The leaves were dried under the shade and powdered using a grinder mixer. The powdered material (25 g) was filled in soxhlet apparatus containing 250 mL of ethanol 70%. The obtain filtrate was concentrated and stored in a desiccators till use[5].

Drug and Chemical. Hydrochlorthiazide (HCT) and sodium chloride were obtained from PT. Kimia Farma (Bandung, Indonesia),sodium estimation kit (Research Lab, Indonesia), polysorbat 80, ethanol 70% and other reagents used were purchased from local vendor from Jakarta, Indonesia.

Preparation of Drug Solution. EECE and HCT were powdered and suspended in 1% of polysorbat 80 in distillled water. Sodium Chloride (NaCl) was powdered and dissolved in distillated water. All solutions were prepared freshly and stored in glass bottles.

Preliminary Phytochemical Evaluation of EECE. EECE was subjected for the qualitative analysis by using the standard phytochemical test to evaluate the presence of various phytoconstituens.

Effect of EECE on NaCl 8% induced hypertension in rats. Male *Sprague dawley* rats (3-4 months old, weight between 150 and 200 g) were randomly divided into five groups (n=5) and treated as follows: negative control (NaCl 8% induced); positive control (HCT 0.2569 mg/ 200 g BW); EECE 20, 40, 80 mg/ 200 g bw. NaCl 8% induced given orally 3 mL/ day in rats every day for 28 days to obtain the condition of hypertension. EECE and HCT provided during the last 14 days orally once daily according to the group. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was estimated for each animal on day 0 (zero), 15 and 29. Blood pressure measurements made by the indirect method using a Kent Scientific's CODA non-invasive blood pressure.

Diuretic Activity of EECE in Rats. Diuretic activity was determinate by following methods of Depkes RI[6], with minor modification. Male *Sprague dawley* rats (2-4 month old, weight between 150 and 250 g) were randomly divided into five groups (n=5) and treated as follows: negative control (NaCl 4.5% and tween 80 1%); positive control (HCT 0.514 mg/ 200 g bw); EECE 20, 40, 80 mg/ 200 g bw. The rats were fasted overnight (18 hr) prior to the test. After that, the rats were given an oral loading NaCl 4.5% of 2 mL/ 200 g bw and the treatment according to each group. Immediately after administration, the rats were placed in metabolism cages. Urine volume was collected and calculated at 6 hr and sodium level was estimated using urine 24 hr.

Statistical Analysis. The results were expressed as mean ± S.E.M (n=5). The statistical comparison was carried out by one way ANOVA followed by LSD test. The result were considered statistically significant when $p < 0.05$.

RESULTS AND DISCUSSION

Preliminary Phytochemical Evaluation of EECE. Preliminary phytochemical evaluation revealed the presence of saponins, tannin, triterpenoid and flavonoids in EECE.

Effect of EECE on NaCl 8% Induced Hypertension in Rats. The administration of NaCl 8% in rats for 28 days showed the increasing effect in SBP and DBP (Figure 1 and 2). The treatment with EECE and HCT showed significantly ($p < 0.05$) decrease in SBP and DBP as compared with negative control. EECE (40 mg/ 200 g bw) showed the greatest reduction in SBP of 16.07% and DBP of 13.65% but the effect is still smaller as compared with HCT.

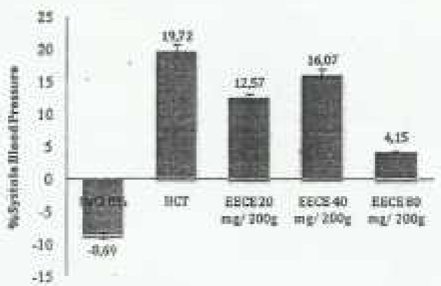

Figure 1. Effect of EECE on systole blood pressure (SBP) in NaCl 8% induced hypertension. Value are expressed as mean ± S.E.M (n=5).

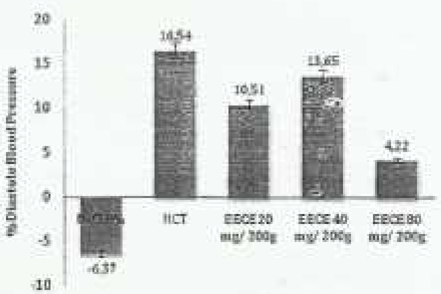

Figure 2. Effect of EECE on diastole blood pressure (DBP) in NaCl 8% induced hypertension. Value are expressed as mean ± S.E.M (n=5).

The administration NaCl 8% for 28 days has been managed to increase blood pressure[7]. NaCl shows hypertensive action through increasing plasma volume, cardiac output and ultimately increase in BP[8]. BP measurements by the indirect method using a Kent Scientific's CODA non-invasive blood pressure. This device is worksby recording systolic and diastolic blood pressure simultaneously through a transducer that is in the tail-cuff[9]. In the present study, the administration of NaCl 8% for 28 day showed increase in SBP and DBP.BP was significantly decreased after the treatment with EECE 20 and 40 mg/ 200 g.

Diuretic Activity of EECE in Rats. The administration of EECE and HCT showed a significant ($p<0.05$) increase in urine volume as compared with negative control group at 6 h (Table 1). Analysis of sodium levels with clinical photometer showed that EECE and HCT significantly ($p<0.05$) increased sodium content in urine 24 h. EECE 40 mg/ 200 g bw showed the greatest diuretic effect 142.50% and sodium levels but the effect is smaller than HCT.

Herbal plants used as diuretic in traditional medicinal system might be useful in the treatment of hypertension. In the present study, EECE at a dose of 40 mg/ 200 g bw showed positive diuretic activity at 6 h, as evident from the diuretic percentage. Furthermore, EECE showed significant increase in sodium content of urine at 24 h but the result revealed the weak diuretic activity of EECE.

The results showed that there was an increase in the activity of the first dose to the second dose. But at the third dose of the extract decreased the activity of diuretics when compared with the second dose. This is possible because the levels of the compounds that are too high, causing a decrease in affinity so that the effects produced are not in accordance with the increasing in dose[10].

The preliminary phytochemical investigations in the present study revealed the presence of flavonoid, saponins, tannins and triterpenoid. The flavonoids isoquercitrin showed inhibition of ACE activity[11]. Flavonoids suspected to have efficacy as a diuretic to stimulate blood flow to the kidneys and lead to the inhibition of tubular reabsorption of water and ions that cause diuretic effect[12]. The result of the present study were suggested that the flavonoids presence in EECE may be responsible for the antihypertensive and weak diuretic effect.

Table1. Effect of EECE on percentage urine volume 6 h and sodium levels in 24 h urine volume. Value are expressed as mean ± S.E.M (n=5).

Treatment	Urine volume 6 h (mL)	Diuretic percentage (%)	Sodium levels (meq/L)
Negative control	1.4±0.32	74.70±11.65	98.48±2.45
HCT	6.1±0.76	240.68±9.56	268.92±7.87
EECE 20mg/ 200g bw	2.44±0.34	91.24±8.06	138.18±3.53
EECE 40mg/ 200 g bw	3.94±0.19	142.50±10.88	161.12±3.87
EECE 80 mg/ 200g bw	2.56±0.51	90.21±9.73	133.23±3.59

CONCLUSION

From this research, it can be conluded that the ethanolic extract of taro leaves (*Colocasia esculenta* (L.) Schott.) (EECE) showed anti hypertensive and diuretic effect. The greatest effect of antihypertensive and diuretic of EECE is 40 mg/ 200g bw, but the effect still lower than HCT. Futher studies are necessary to be performed for the purification, isolation and characterization of the pyhtoconstituens responsible for the anthypertensive and diuretic effect and to explore the exact mechanism of the action.

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SECTORAL VARIATIONS ON TECHNINAL EFFICIENCY AND RETURN TO SCALE IN THE INDONESIAN ECONOMY

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Abstract

This paper discusses on sectoral variations of technical effciency and return to scale in the Indonesian economy. Employing regression analysis of Cobb-Douglas production function, thesecoefficientswere calculated. Nine economic sectors in the Indonesian economy: Agriculture, Mining and Quarying, Manufacturing, Electricity,Gas and Drinking Water, Construction, Trade, Hotel and Restaurant, Transportation and Communication, Finance, Rental and Corporate Services, and Services, were exercised to study the variation of those coefficiens. Sectoral data on gross domestic product, capital stock and employment are those from the years 1967 to 2007 collected from many documents available at the National Statistics Agency. The result shows that the coeffiecients of technical efficiency do vary among sectors. Those sectors in which the coefficients were above that at the national level, experienced decreasing return to scale. On the contrary, those sectors in which the coeffiecients were below that at national level, experienced increasing return to scale.

***Keywords**: Sectoral variation, technical efficiency, returns to scale.*

Abstrak

Paper ini membahas keragaman sektoral dari koefisien efisiensi teknis dan skala hasil dalam perekonomian Indonesia. Menggunakan analisis regressi terhadap fungsi produksi Cobb-Douglas, koefisien-koefisien tersebut telah dihitung. Ada sembilan sektor dalam perekonomian Indonesia dalam kajian ini, meliputi : Pertanian, Pertambangan dan Galian, Industri, Listrik, Gas dan Air Minum, Konstruksi, Perdagangan, Hotel dan Restoran, Angkutan dan Komunikasi, Jasa Keuangan Persewaandan Perusahaan, dan Jasa-jasa. Data produk domestic bruto dan cadangan modal atas harga konstan tahun 2000 serta tenaga kerja dari setiap sector untuk tahun 1967 sampai 2007 diambil dari berbagai terbitan Badan Pusat Statistik. Hasil analisis menunjukkan bahwater dapat keragaman dalam hal koefisien effisiensi teknis dan skala hasil berdasarkan sektor. Sektor-sektor dengan koefisien efisiensi teknis di atas rata-rata nasional mengalami skala hasil yang menurun. Sebaliknya, sektor-sektor dengan koefisien efisiensi teknisnya di bawah rata-rata nasional mengalami skala hasil yang meningkat.

Kata kunci : Keragaman sektoral, efisiensi teknis, skala hasil.

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INTRODUCTION

Since it has been declared its independence on 17 August 1945, the Indonesian economy has been up and down, experiencing booming and recession (Anonymous, 1998, 2004, 2010). Economic cyclesuch as booming, recession, and even crisis do exist in Indonesian economy. Economists have long recognised that technology is a factor of production, and even the most importan factor, given its role in labor quality and the design of capital good. Technological advances play a crucial role in improving productivity and thus the standar of living of a system; economic system (Adams. 2006).

Most economists today agree with the hypotesis that both innovation and technological spilovers are the main engine for explaining productivity growth. Neoclassical economists tend to give all sectors of the economy equal weight for explaining productivity behavior, but structuralist economists argue that manufacturing sector is the main force for explaining the aggregate productivity. Although economic development is basically determined by technical progress, the productive structure of developed economies continues to be much more complex and diversified than that of developing economies. It means that economic development can be understood as a process through which a deep structural change occurs in the economy, in such a way that there is a reallocation of resources from primary sectors (agriculture and mining) to the manufacturing sector, and then as soon as an economy has achieved high level of income per capita, from manufacturing to service sector (Nassif & Feijo, 2013).

Measuring the effect of technology on productivity is a difficult pursuit. It is generally approached through metrics such as Gross Domestic Product, GDP per capita and Total Factor Productivity (TFP). The former two attempt to capture the overall output of a given economy from a macro-environmental perspective. The latter is attempting to measure technologically driven advancement through noting increase in overall output without increases in input. This is done through utilising production function equations and identifying when the output is greater than the supposed input, implying an advance in external technological environment(Boundless, 2016). The technology can be regarded as primary resource in economic development. The level of technology is also an important determinant of economic growth. The rapid rate of growth can be achieved through high level of technology. It was observed that

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innovation or technological progress is the only determinant of economic progress. But if the level of technology becomes constant the process of growth will stops. Thus, it is the technological progress which keeps the economy moving. Inventions and innovations have been largerly responsible for rapid economic growth in developed countries (Debasish, 2016).

In economics, the Cobb-Douglas production function is widely used to represent the relationship of an output to input (Bao Hong, 2008). It was proposed by Knut Wicksell (1851-1926) and tested againts statistical evident by Charles Cobb and Paul Douglas in 1928 (Cobb and Douglas, 1928). From Cobb-Douglas production function, technical efficiency aslo known as total factor productivity, retun to scale, and ouput-capital elasticity as well as output-labor elasticity can easily be calculated by employing regression analysis (Salvator, 1996).

Previous research on technical efficiency, return to scale and output elasticities has been conducted, among others byBiresh K. Sahoo, at all (2014), V. E. Krivonozhko,A. V. Dvorkovich,O. B. Utkin, I. D. Zharkov, M. V. Patrin and A. V. Lyche (2007), Tewodros G. Gebreselasie (2008), Feng, G and Serletis, A (2010), Holyk, S. (2016), Page, John M. Jr (1980),Erkoc, T. E., (2012), Yudistira, D (2004). Measuring Indonesia's sectoral effieciencies has been conducted by Rizaldi Akbar (2015).

Structural transformation process in the Indonesian economy is indicated initially by the dominance of agricultral sector both in output and in employment. The primary sector, namely : Agriculture and Mining-Quarying dominated the Indonesian economy until 1987-1988, but Secondary (Manufacturing) and Tertiary Sectors (Trade, Hotel and Restaurant) have replaced this position after 1999 in term of output. But, in term of employment, data show that during the year of 1967 to 2007, Agriculture has still dominated the Indonesian economy. The reseach reported in this paper aimed to analyzed the sectoral variations of the coefficients of technical efficiency, return to scale and output-capital elasticity as well as output-labor elasticity in the Indonesia economy during the year of 1967 to 2007.

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METHODS

Cobb-Douglas production function, $Q = \gamma K^{\alpha} L^{\beta}$,was employed in this exercise to calculate technical efficiency (γ) return to scale ($\alpha+\beta$), output-capital elasticity (α) and output-labor elasticity (β). This production function was developed and statistically tester by Charles Cobb and Paul Douglas during 1927-1947 (Cobb C.W, and Douglas, P.H., 1928), where:Q = total production (the real value of all good and services produced in a year;K = capital input (the real value of all machinery, equipment, and building;L = labor input (the total number of person-hours worked in a year;γ = technical efficiency in production process, known as total factor productivity;α = output-capital elasticity;β = output-labor elasticity.

Technical efficiency (γ), or total factor productivity (TFP) is the portion of output not explained by the amount of input used in production (Comin, 2006).This is a method of measuring overall productivity of business, industries or economies. Technical efficiency is the effectiveness with which a given set inputs is used to produced an output. A firm or an economy is said to be technically efficient if a firm or an economy is producing the maximum output from the minimum quantity of inputs, such as labor, capital and technoloy. Technical efficiency is related to productive efficiency wich is concern with producing at the lowest point on the short run averaga cost curve. Thus productive effiency required technical efficiency (Pettinger, 2012).

The values of$\alpha$and$\beta$are basically determined by available technology. Output elasticity measure the responsiveness of output to a change in levels either capital or labor used in production. Further more, if$\alpha+\beta = 1$, the production function has constant return to scale, meaning that doubling the usage of capital (K) and labor (L) will also double output (Q).If $\alpha+\beta<1$, return to scale are decreasing and if$\alpha+\beta>1$, return to scale are increasing.

The output elasticity of capital, $E_K = \delta Q/\delta K.K/Q = \alpha Q/K.K/Q = \alpha$. Similarly, the output elasticity of labor, $E_L = \delta Q/\delta L.L/Q = \beta Q/L.L/Q = \beta$ and $E_K + E_L = \alpha + \beta$ = return to scale (Salvator, D., 1996).Converting the production function from $Q = \gamma K^{\alpha} L^{\beta}$in to a logarithms form that is, $\ln Q = \ln\gamma + \alpha \ln K + \beta \ln L$. As this is a linier form, then the coefficiens (γ, αandβ) can easily be estimated by regression analysis (Gasperz, 1996).

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The Cobb-Douglas production function can be estimated either from data for a single firm, industry, region or nation over time using time-series analysis or for a single firm, industry, region or national one point in time using cross-sectional data(Salvator, 1996). Data needed for this exercise were sectoral data on Gross Domestic Product, Capital Stock and Employment. Yearly data on GDP, Capital Stock and Employment were collected from the Central Beurau of Statictics. Fortunately data were available from the year of 1967-2007.

RESULT AND DISCUSSION

Sectoral GDP, Capital Stock and Employment

Figure 1 provides data on GDP (Gross Domestic Product in Billion Rupiah) in the Indonesia economy during 1967 to 2007. In 1967, the GDP in 1967, the early year of Suharto rezim, was Rp417.76 Billion and GDP at the last year (2007) was Rp. 2,686.49 Billion. On average, Indonesian GDP during 30 years grows at 5.11%. It was noted, however, that when multi-dimensionaleconomic crisis (known as monetary crisis or IMF crisis) occurred in 1998, the Indonesian GDP grows at negative (-13.13%), from Rp. 1,555.32 Billion in 1997 to Rp. 1,351.16 Billion in 1998.

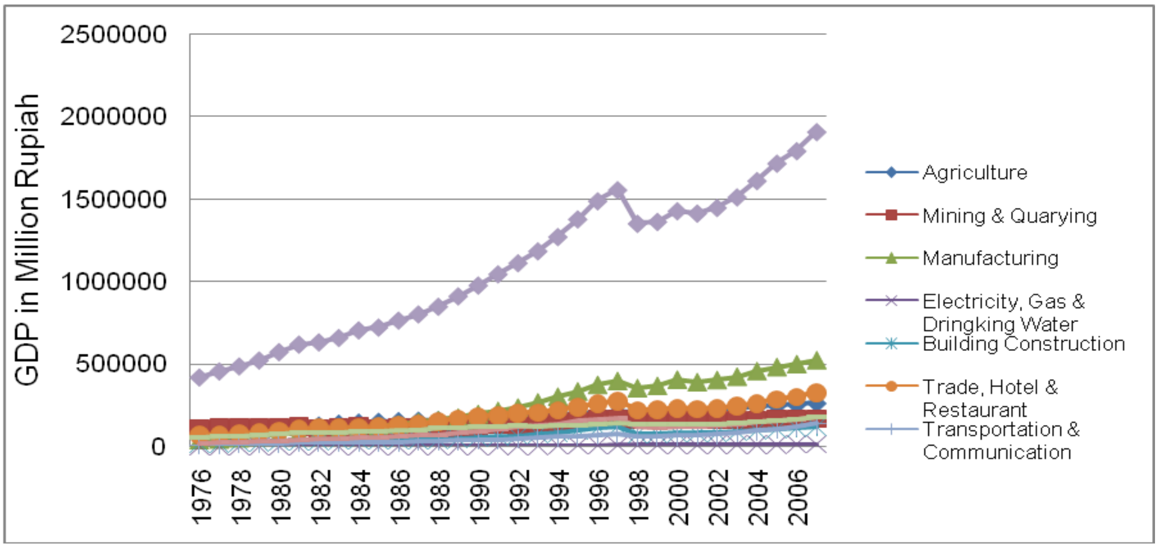

Figure 1. Gross Domestic Product in the Indonesian Economy

Figure 2 provides sectoral GDP in more detail. In 1967, sectoral GDP were dominated by Mining and Quarying (Rp. 105,076 Million) and Agriculture (Rp. 99,642 Million), followed by Trade, Hotel and Restaurant (Rp. 71,104 Million), Services (Rp. 51,468 Million), Manufacturing (Rp. 40,359 Million), Financial, Rental and Corporate

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Services (Rp.20,212 Million), Building Construction (Rp. 16,794 Million), Transportation and Communication (Rp. 12,490 Million) and Electricity, Gas and Drinking Water (Rp. 617 Million). At the year of 2007, sectoral GDP was dominated by Manufacturing (secondary industry) with GDP of Rp. 522,651 Million and followed by Trade, Hotel and Restaurant (Rp. 329,228 Million), Agriculture (Rp. 263,800 Million), Financial, Rental and Corporate Services (Rp. 178,394 Million), Services (Rp. 176,755 Million), Mining and Quarying (Rp. 166,449 Million), Transportation and Communication (Rp. 138,846 Million), Building and Construction (Rp. 118,406 Million), and Electricity, Gas and Drinking Water (Rp. 13,137 Million).

Agriculture GDP grows in average 3.21%, with the lowest growth of 0.03% in the year of 1967 and 0.51% in the year of 2000, and the highest growth of 8.39% in the year of 1982 and 8.37% in the year of 1968. No negatice growth experienced by the sector, even in the time when multidimension of economic crisis in the 1998.Mining and Quarying GDP grows in average 1.63%. This sector experienced many negative growth for instance in the years of 1981 (-10.78%), 1984 (-10.22%), 1987 (-5.71%), 1991 (-2.45%), 1997 (-0.50%), 1998 (-2.57%), 2000 (-3.71%), 2001 (-0.99%), 2002 (1.72%), and 2003 (3.08%).

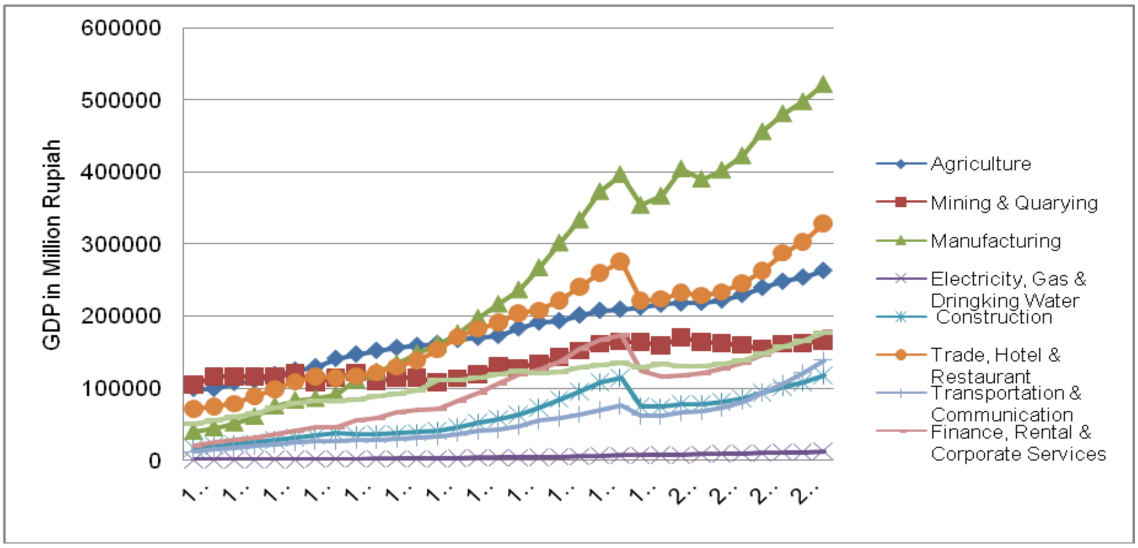

Figure 2. Sectoral Gross Domestic Product in the Indonesia Economy

Manufacturing GDP grows in average 8.81% thesecond highest growth in the Indonesian economy during 30 years period. The highest growth occurred in the year of 1979, still in Oil Boom phase, as 23.92%, as well as in 1983 (22.19%). Some negative growth occurred in the year of 1997, early year of monetary crisis (-10.73%), and the

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year of 2000 (-3.55%).GDP of Electricity, Gas and Drinking Water sector growth in average at 10.67% the highest sectoral GDP growth in Indonesia economy. This sector has the smallest value of GDP among sectors in the Indonesia economy during the period of 30 years. The highest GDP growth of this sector was 31.99% occurred in 1978, in the period of OilBoom. In 1999, this sector experienced negative economic growth, 11.70%.

GDP of Construction sector grows in average at 7% with the highest growth (18.87%) occurred in 1967. This sector experienced with negative GDP growth three time, namely in 1983 (-4.32%), 1997 (-34.67%) and 1998 (-0.95%). Monetary crisis hadvery significant impact on construction sector.In average, the sector of Trade, Hotel and Restaurant grows at 5.24%, the 6th rank in the growth of sectoral GDP. The highest growth occurred in the years of 1978 (12.60%), 1979(10.90%, 1980 (10.66%), 1987 (10.55%) and 1988 (11.64%). Negative growth of GDP occurred in the years of 1982 (-1.06%), 1997 (-9.70%) and 2000 (-1.86%).

Transportation and Communication sector grows in average at 8.32%, the third highest sectoral growth in the Indonesian economy during 1967 to 2007. The highest growth occurred in the years of 1976 (22.99%) and 1978 (17.08%). Negative growth occurred in the year of 1997 (-17.86%).The sector of Financial, Rental and Corporate Services grows in average at 7.7%, with the highest growth occurred in 1976 (26.91%). Negative GDP growth of this sector occurred in years of 1997 (-28.48%) and 1998 (-6.42%), the years when monetary crisis exist.The services sector grows in average at 4.14% which was the highest growth occurred in the year of 1987 (15.10%). Negative growth of this sector occurred in the year of 1982 (-0.05%), 1988 (-0.50%), 1992 (-1.97%), 1997 (-5.10%), and 1999 (-2.44%).

Figure 3 presents sectoral capital stock in the Indonesian economy 1967-2007. In 1967, sectoral capital stock were dominated by Manufacturing (Rp. 22,070 Million), followed by Mining and Quarying (Rp. 20,730 Million), Services (Rp. 15,740 Million), Transportation and Communication (Rp. 12,640 Million), Financial, Rental and Corporate Services (Rp. 8,120 Million), Trade, Hotel and Restaurant (Rp.7,770 Million), Construction (Rp. 6,450 Million), Agriculture (Rp. 4,550 Million) and Electricity, Gas and Drinking Water (Rp. 1,940 Million). At the year of 2007, 30 years later, sectoral capital stock was dominated by Services (Rp. 28,770 Million) and followed by Financial,

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Rental and Corporate Services (Rp. 17,010 Million), Transportation and Communication (Rp. 14,420 Million), Trade, Hotel and Restaurant (Rp. 12,750 Million), Manufacturing (Rp. 10,950 Million), Electricity, Gas and Drinking Water (Rp. 7,820 Million), Agriculture (Rp. 4.510 Million), Mining and Quarying (Rp. 2,770 Million), and Construction (Rp. 1,190 Million).

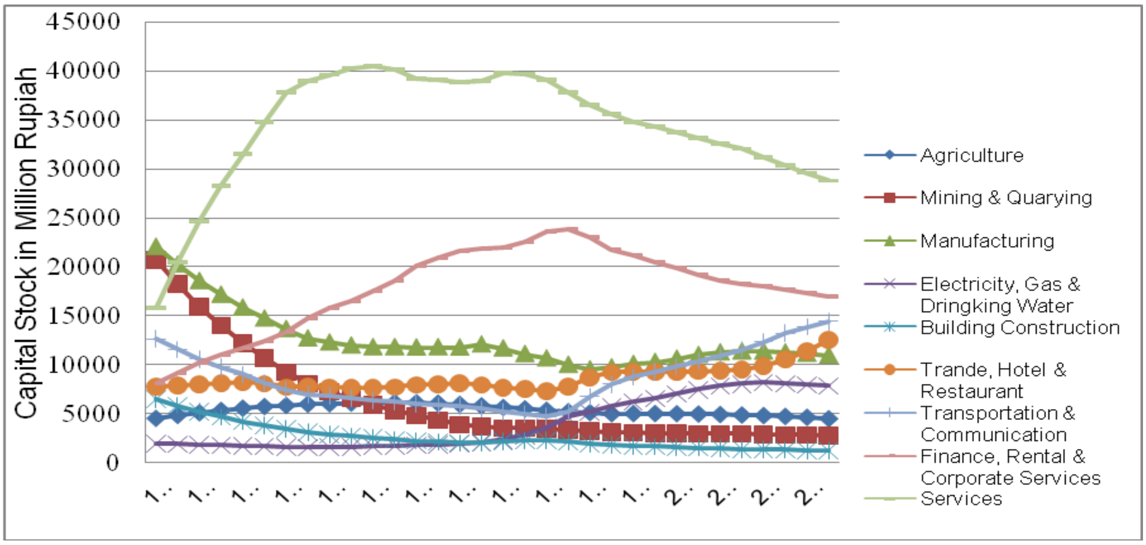

Figure 3. Capital Stock in the Indonesia Economy

Agriculture capital stock grows in average at 0.00%, with the highest growth of 6.59% in the year of 1967. The growth of this sector continually declaine afterward and the growth expereienced negative after the year 1987. Only in the year 1997 and 1998 the growth back to positive growth. After the year of 1998, negative growth occured. Mining and Quarying capital stock experienced negative growth. In average, this sector grows in average at -6.16%. From 30 years period, only 2 years in which this sector had a positive growth in capital stock, namely year : 1992 (0.85%) and 2001(0.00%). Manufacturing capital stock also grows in average at -2.16%. The lowest growth (mean the highest negative growth) occured in the year 1976 (-8.25%). More than a half of the 30 years period experinced negative growth.

There are some more year, though, with positive growth such as : the year of 1988 (0.25%), 1990 (2.63%), 1996 (2.09%), 1997 (3.49%), 1998 (2.08%), 1999 (3.20%), 2000 (3.57%), 2001 (2.45%), and 2002 (0.89%). Capital stock of Electricity, Gas and Drinking Water sector growth in average at 4.93% the highest sectoral capital stock growth in Indonesian economy during 1967-2007. The highest capital stock growth of this sector was 29.69% occurred in 1994. Negative growth experienced by this sector

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were in 1976 to 1982 and during 2004 to 2007. Capital stock of Construction sector grows in average at negative growth (-5.23%). Almost the whole year experienced negative growth, expect in the year of 1990 (3.03%), 1991 (3.43%), 1992 (4.27%) and 1993 (1.82%). In average, capital stock ofHotel and Restaurant grows only at 1.63%). The highest growth occurred in the years of 1995 (12.10%). Negative growth of capital stock of this sector occurred in sveral years, namely: the years of 1980 (-1.46%) 1981(-4.20%), 1983 (-0.64%), 1984 (-0.52%), 1985 (-0.78%), 1990 (-2.09%), 1991 (-3.38%), 1992 (-1.82%) and 1993 (-3.43%).

Transportation and Communication sector grows in average at 0.78%. The highest growth occurred in the years of 1995 (29.17%). More than a half of the study period were negative in growth of capital stock, that was the period of year 1967 to 1994. After 1995, the growth of capital stock of this sector were positive. The sector of Financial, Rental and Corporate Services grows in average at 2.54%, with the highest growth occurred in 1976 (13.18%). Positive growth occured during 1967 to 1994. Meanwhilenegative capital stock growth of this sector occurred during the year 1995 to 2007.

The services sector grows in average at 2.20% which was the highest growth occurred in the year of 1967 (29.48%). Positive growth of this sector occurred during the year 1967 to 1985 and during 1990 to 1991. Negative growth occurred during 1986 to 1989 and during the year of 1992 to 2007.

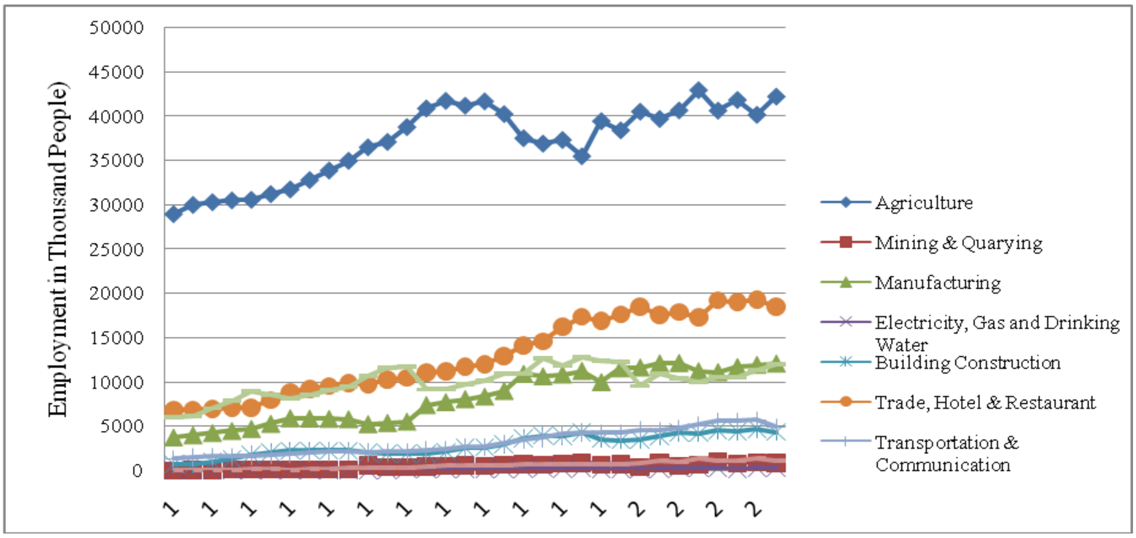

Figure 4. Employment in the Indonesia Economy (1967-2007)

From Figure 4, it is clearly shown that Agriculture has dominated the Indonesia economy in term of employment. It was then followed by Trade, Hotel and

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Restaurant. In 1967, employment in Agriculture sector was 28,879 thousand people. Employment in Trade, Hotel and Restaurant was 6,773 thousand people. In 2007, people work in Agriculture sector was 42,200 thousand, and in Trade, Hotel and Restaurant was 18,441 thousand.

In term of growth in employment, the highest growth was Mining and Quarying (average at 21.08%), followed by Financial, Rental and Corporate Service (average at 18.81%), Electricity, Gas and Drinking Water (average at 11.57%), Construction (average at 7.01%), Transportation and Communication (4.50%), Manufacturing (4.24%), Trade, Hotel and Restaurant (3.39%), Services (2.69%) and Agriculture (1.30%). All sectors experienced with positive and negative growth.

Discussion

Tabel 1 shows the coefficients of technical efficiency (γ)return to scale (α + β), output-capital elasticity (α), and output-labor elasticity (β) in the Indonesian economy during 1967 to 2007 both at national level and sectoral level.

Tabel 1. Coefisiens of Technical Efficiency, Return to Scale, and Ouput Elasticities

Sectoral Analysis	γ	α	β	RTS
National Average	2.775174	0.797882	-0.016258	0.781624
Agriculture	-0.687019	-0.790724	1.987609	1.196886
Mining and Quarrying	5.298335	-0.219114	-0.007185	-0.226299
Manufacturing	4.313086	-0.865074	1.536815	0.671741
Electricity GasDrinking Water	12.040516	2.353230	-2.691094	-0.337864
Construction	4.910134	-1.159027	0.022766	-1.136262
Trade, Hotel & Restaurant	2.487391	-0.214749	1.246332	1.031584
Transportation & Communication	2.717723	-0.157543	1.344240	1.186697
Financial, Rental & Coorp Services	-1.470291	2.236066	-0.102564	2.133502
Services	1.925433	-0.214449	1.530741	1.316292

Technical effiency in Indonesian economy during the year 1967 to 2007 was 2.775174. At sectoral perspective the coefficients of technical efficiency vary among sectors. From 9 economic sectors, 4 sectors had coeffient of thechnical efficiency which were above of that at national level, and other 5 sectors were below that at the national level. The sectors which the coefficient of technical efficiency above of that at national level were : Electricity, Gas and Drinking Water (12.040516), Mining and Quarying (5.298335), Construction (4.910134), and Manufacturing (4.313086). The sectors which the coefficient of technical efficiency below of that at national level were

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: Financial, Rental and Corporate Services (-1.470291), Agriculture (-0.687019), Services (1.925433), Trade, Hotel and Restaurant (2.487391) and Transportation and Communication (2.717723). It means that the technical effiency of 4 sectors earlier were better than that at the national level. Meanwhile the technical efficiency of 5 other sector were worse than that at the national level. These 5 sectors should have get more attention by policy makers, especially those that the values of the coeffient were negative.

At national level, Indonesian economy experienced decreasing return to scale as the coeffient of return to scale which is the summation of coefficient of output-capital elasticity (α) with coefficient of output-labor elasticity (β) less than unity (0.781624). The coeffients of return to scale vary among sectors, where 5 sectors were increasing return to scale and 4 sectors were decreasing return to scale. Five increasing return to scale sectors were : Financial, Rental and Corporate Services (2.133502), Services (1.316292), Agriculture (1.196886), Transportation and Communication (1.186697), and Trade, Hotel and Restaurant (1.031584). These 5 sectors experiencing increasing return to scale were the sectors in which their coeffients of technical efficiency were below of that at the national level. Four decreasing return to scale sectors were : Manufacturing (0.671741), Mining and Quarying (-0.226299), Electricity, Gas, and Drinking Water (-0.337864), and Construction (-1.136262). Again, those sectors that had the coefficient of technical efficiency above that at national level experiencing decreasing return to scale.

The coefficients of output-capital elasticity (α) in the Indonesian economy was 0.797882. Sectoral coeffient of output-capital elasticity vary among sectors. Only two sectors in which coefficient of output-capital elasticity above that of the national average, namely :Electricity, Gas and Drinking Water (2.353230) and Financial, Rental and Corporate Services (2.236066). Seven sectors with the coefficients of output-capital elasticity below that at the national level, namely : Agriculture (-0.790724), Mining and Quarying (-0.219114), Manufacturing (-0.865074), Construction (-1.159027), Trade, Hotel and Restaurant (-0.214749), Transportation and Communication (-0.157543) and Services (-0.214449).

The coefficients of output-labor elasticity (β) in the Indonesian economy was -0.016258. Sectoral coeffient of output-labor elasticity vary among sectors.There were

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five sectors in which coefficient of output-labor elasticity above that of the national average, namely :Agriculture (1.987609), Manufacturing (1.536815), Trade, Hotel and Restaurant (1.246332), Transportation and Communication (1.334240) and Services (1.530741). Four sectors with the coefficients of output-capital elasticity below that at the national level, namely : Mining and Quarying (-0.007185), Electricity, Gas and Drinking Water (-2.691094), Construction (0.022766), and Financial, rental and Corporate Service (-0.102564).

Table 2 presents the Quadrant of Technical Efficiency (Above Versus Below National Average) and Return to Scale (Increasing Versus Decreasing Return to Scale). Four sectors in which the coefficients of technical efficiency were above that at national level also exhibiting decreasing return to scale. Those sectors were: Mining and Quarrying, Manufacturing, Electricity, Gas and Drinking Water and Construction. Other five sectors in which the coefficients of technical efficiency were below that at national level exhibiting increasing return to scale. Those sectors were: Financial, Rental and Corporate Services, Services, Agriculture, Transportation and Communication, and Trade, Hotel and Restaurant.

Table 2. The Quadrant of Technical Efficiency and Return to Scale

Technical Efficiency/ Return to Scale	**Increasing Return to Scale**	**Decreasing Return to Scale**
Above National Average		Mining and Quarrying Manufacturing Electricity, Gas and Drinking Water Construction
Below National Average	Financial, Rental and Corporate Services Services Agriculture Transportation and Communication Trade, Hotel and Restaurant	

CONCLUSION

Sectorally, there were 4 sectors that had coefficient of technical efficiency above of that at national level, namely : Electricity, Gas and Drinking Water, Mining and Quarying, Construction, and Manufacturing.These were the sectors that experienced

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decreasing return to scale. Other five sectors that had the coefficient of technical efficiency below of that at the national level, namely : Financial, Rental and Corporate Services, Agriculture, Services, Trade, Hotel and Restaurant and Transportation and Communication. These were the sectors that had experienced increasing return to scale. There was an inverse relationship between technical efficiency and return to scale.

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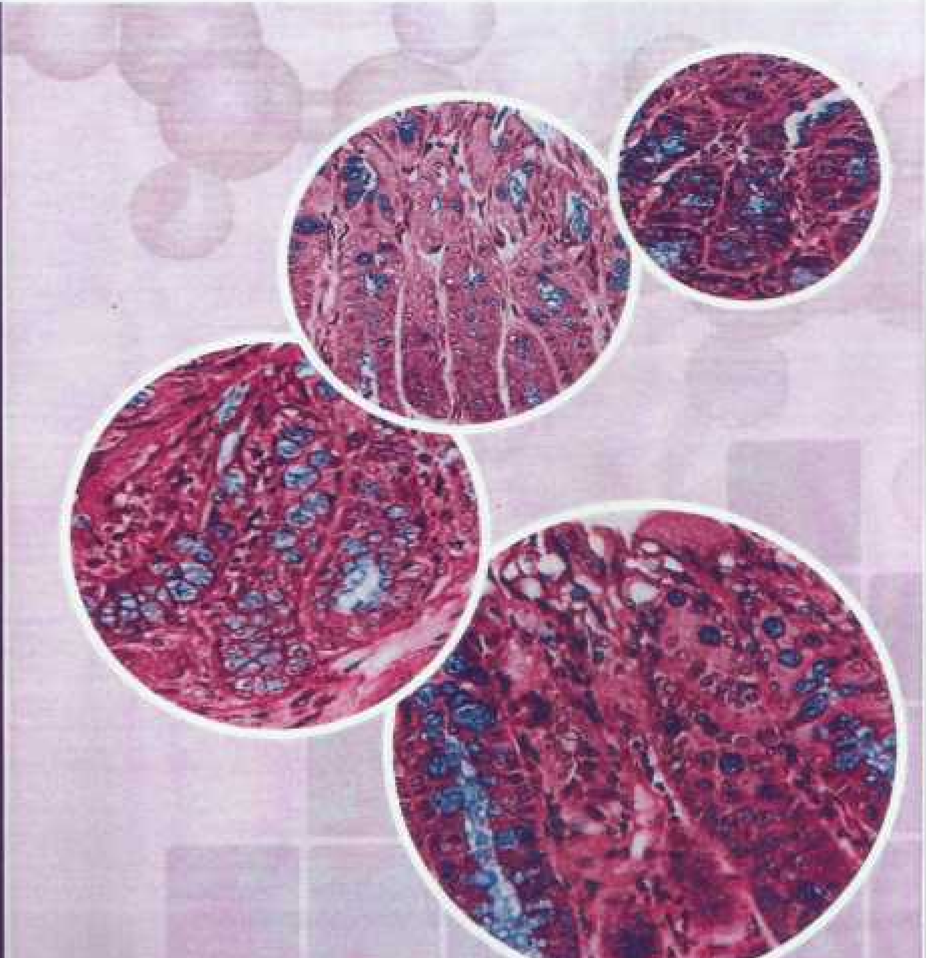

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Perkembangan Anak Tikus (F1) Asal Induk Penerima Asam Valproat sebagai Model Diabetes Mellitus

(Development of Rats Filial (F1) Born From Valproic Acid-Treated Female Rats as a Diabetic Mellitus Model)

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Diterima 24 April 2014, Disetujui 14 Agustus 2014

Abstrak: Untuk melakukan penelitian dan pengembangan obat antidiabetes diperlukan hewan model yang sesuai dengan kondisi diabetes. Tujuan penelitian ini ialah untuk mengembangkan model diabetes yang sesuai kondisi patofisiologi diabetes. Induk tikus yang telah bunting dibagi dalam 2 kelompok, satu kelompok diberi asam valproat 250 mg/kg bb per oral pada kebuntingan hari ke-9 dan kelompok lain sebagai kontrol. Pada umur anak tikus (F1) 8, 16 dan 24 minggu diambil sampel darah untuk dianalisis kadar glukosa, kadar insulin dan trigliserida. Pada waktu yang sama, jaringan pankreas diambil dalam kondisi teranestesi untuk dilakukan immumunohistokimia. Hasil pengukuran kadar glukosa dan histologi pada tikus (F1) umur 8 minggu belum menunjukkan adanya perbedaan yang bermakna dibanding kontrol normal. Pada tikus (F1) umur 16 dan 24 minggu kadar glukosa darah dan konsentrasi insulin serum menunjukkan peningkatan yang signifikan, sedangkan sel yang positif insulin menurun. Dapat diambil kesimpulan pemberian asam valproat pada tikus pada hari ke-9 kebuntingan dapat menghambat fungsi sel β pankreas. Dengan demikian dapat disimpulkan tikus (F1) yang induknya diberi asam valproat pada masa kebuntingan dapat menyebabkan sindrom metabolik yang dimulai pada umur 16 minggu dan berlanjut sampai usia tua.

Kata kunci: asam valproat, sel-β, diabetes mellitus.

Abstract: To do research and development of antidiabetic drugs, animal models of diabetes in accordance with the conditions is required. The aim of this research was to develop a diabetic model that is fit to the pathophysiology of diabetic condition. The pregnant female rats were divided into 2 groups, one group was orally treated by a single dose of valproic acid (250 mg/kg bw) on day 9th of pregnancy and the other was a control. At the ages of 8, 16 and 24 weeks the blood samples of litters (F1) were taken for glucose, insulin and triglyceride determination. At the same time, pancreatic tissues were collected under deep anesthetic condition for immunohistological study. Results of blood glucose concentrations and histological finding of litters (F1) indicated that at the age of 8 weeks both had showed a similar pattern as compared to control. At the ages of 16 and 24 weeks, blood glucose and insulin level showed a significant increase, while positive insulin cells slightly decreased in number. It can be concluded that treating rat with valproic acid on days 9 of gestation will inhibit pancreatic β cells function. There is an indication that F1 of valproic acid treated pregnant mother start showing a metabolic syndrome at 16 weeks and being pronounce by aging.

Keywords: valproic acid, β-cell, diabetes mellitus.

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PENDAHULUAN

KEJADIAN diabetes mellitus pada saat ini banyak dimulai pada usia dewasa dan biasanya ada faktor genetik yang memperkuat. Kondisi ini diawali dengan resistensi insulin yang kemudian akan diikuti oleh penurunan jumlah sel β sehingga sekresi insulin tidak dapat memenuhi kebutuhan[1]. Meskipun upaya penelitian dalam satu dekade dilakukan intensif, dasar genetik dalam peristiwa patogenesis diabetes masih kurang dipahami. Diabetes adalah sindrom multigenik kompleks terutama karena disfungsi sel β pankreas yang berhubungan dengan tingkat resistensi insulin[2].

Hewan model diabetes ada 2 kategori yaitu tipe diabetes karena genetika dan tipe diabetes karena dapatan yang diperoleh dengan induksi diabetagon seperti aloksan ataupun streptozotosin[3]. Untuk model diabetes yang diperoleh dari seleksi perkawinan dan rekayasa genetika tingkat keberhasilannya kurang dari 50% dan memerlukan waktu lama serta biaya yang sangat mahal. Sementara itu, untuk model yang diperoleh dengan induksi diabetagon, kondisi kerusakan sel pada pankreas ada yang bersifat reversibel dan ada yang permanen.Tetapi kerusakan yang permanen menimbulkan kerusakan sel pankreas yang sangat parah. Kondisi ini tidak dapat menggambarkan kejadian diabetes yang diinginkan, karena tidak dihasilkan lagi insulin atau jumlahnya sangat kurang yang lebih identik dengan diabetes tipe 1[4].

Kerusakan sel β pankreas dapat terjadi sejak dimulai organogenesis di rahim, bersamaan dengan perkembangan *neuronal tube* sebagai awal perkembangan sel saraf[5]. Tahapan permulaan organogenesis pankreas bergantung pada interaksi pensinyalan dengan jaringan di sekelilingnya. Inisiasi pertumbuhan organ dan akibat ekspresi marker molekuler pada tahap awal pertumbuhan pankreas selama embriogenesis tikus dari embrionik hari ke-8,5 sampai hari ke-14,5. Perkembangan saluran cerna ventral, termasuk liver dan pankreas ventral, bergantung pada ekspresi endodermal *homeobox gene* Hhex yang mengarahkan proliferasi endoderm ventral dan kontrol transisi morfogenetik sel endodermal epitelial[6].

Pada masa embrional, asam valproat mempunyai kemampuan untuk menghambat deasetilasi histon (inhibitor HDAC). Asam valproat menyebabkan hiperasetilasi histon pada sel kultur dan *in vivo*. Secara *in vitro*, asam valproat menghambat aktivitas HDAC dengan mengikat pusat katalisis dari HDACs dan akibatnya asam valproat menekan differensiasi sel[7]. Pada *stem cell* pemberian asam valproat di hari ke-9 terjadi hambatan pada pengarahan differensiasi sel pankreas[8].

Melihat kronologi pembentukan organ pankreas selama pertumbuhan embrio, maka dapat diprediksi bahwa gangguan pertumbuhan pankreas pada tikus akan menghasilkan kerusakan pada sel β tikus[9]. Oleh karena itu, perlu diinvestigasi kemungkinan pembuatan tikus diabetes dengan menghambat perkembangan sel atau organ pada tahap embrio.

Penelitian ini dirancang untuk mempelajari pengaruh pemberian obat atau senyawa kimia yang dapat mempengaruhi organogenesis, terutama pada perkembangan sel β pankreas. Obat yang dipakai adalah asam valproat yang memiliki mekanisme kerja menghambat deasetilasi histon[7]. Ketika terjadi gangguan perkembangan sel β pankreas maka diharapkan akan menjadi hewan model yang dapat menggambarkan patogenesis diabetes mellitus yang mirip dengan kejadian di manusia.

Tujuan penelitian ini adalah untuk mendapatkan hewan model yang sesuai dengan patofisiologi diabetes dan mampu mengekspresikan gejala klinis diabetes. Dengan pemberian asam valproat pada tikus bunting hari ke-9, diharapkan akan dihasilkan anak tikus (F1) yang mendekati kondisi diabetes.

BAHAN DAN METODE

BAHAN. Tikus yang digunakan adalah tikus putih (*Rattus novergicus* L) galur Sparague-Dawley betina usia 3-4 bulan dan bobot badan 200-300 g sebagai indukan. Bahan induksi adalah asam valproat diberikan pada induk bunting dengan dosis tunggal 250 mg/kg BB per oral pada umur kebuntingan 9 hari. Anak yang di dapat disusukan ke induk hingga masa sapih. Selanjutnya anakan dipisah diberi pakan standar dan air minum ad libitum.

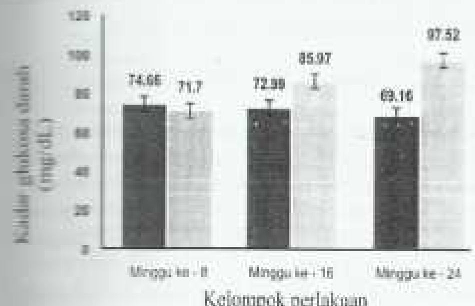
Tahap persiapan untuk kebuntingan induk dengan program *time mating* menyatukan seekor tikus betina estrus dan jantan dalam satu kandang. Hari pertama kebuntingan ditetapkan bila *vaginal plug* terdeteksi keberadaannya pada keesokan harinya.

Induk bunting yang telah diberi asam valproat dipelihara sampai melahirkan dan membesarkan anaknya hingga lepas sapih. Anak yang telah terpisah dari induknya dibesarkan dan dilakukan pengambilan sampel darah dan jaringan pada umur 8, 16 dan 24 minggu untuk pengukuran kadar glukosa, kadar insulin dan kadar trigliserida. Jaringan pankreas digunakan untuk pembuatan sediaan histomorfologi guna melihat perubahan sel endokrin pankreas yaitu sel β dan sel α. Pengambilan sampel darah dan jaringan dilakukan dalam kondisi teranestesi. Jumlah Tikus (F1) untuk kelompok uji 12 ekor.

Pengukuran kadar glukosa menggunakan metode tes kolorimetri enzimatik yaitu *Glucose Kits Based/ GOD-PAP*. Kadar insulin darah pada serum diukur dengan metode ELISA menggunakan *Ultra Sensitive Rat Insulin Immunoassay Kit*. Kadar trigliserida darah diukur menggunakan metode tes kolorimetri enzimatik GPO-PAP dengan *Lipid Clearing Factor* (LCF). Pewarnaan jaringan pankreas secara immunohistokimia menggunakan Ab anti insulin dan Ab anti glukagon, kemudian divisualisasikan dengan diamino benzidin (DAB).

HASIL DAN PEMBAHASAN

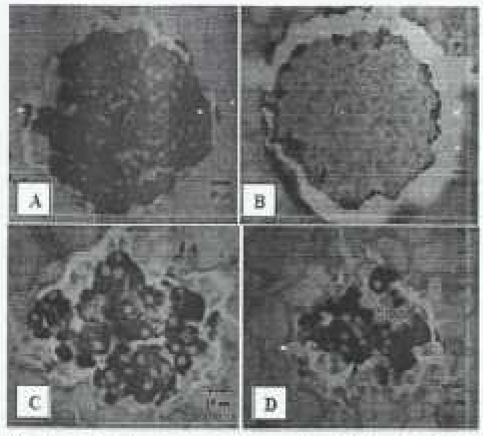
Hasil pengamatan kadar glukosa darah tikus F1 umur 8 minggu dari induk yang diberi asam valproat pada kebuntingan hari ke-9 belum menunjukkan adanya peningkatan kadar glukosa dibandingkan kontrol normal ($p>0,05$). Pada tikus F1 umur 16 minggu ada peningkatan kadar glukosa darah dibandingkan kelompok kontrol normal ($p<0,05$). Pada tikus F1 umur 24 minggu ada peningkatan kadar glukosa darah dibandingkan kelompok kontrol normal ($p<0,05$) (Gambar 1).



Gambar 1. Rata-rata kadar glukosa darah tikus F1 dari induk yang diberi asam valproat 250 mg/kg bb per oral pada minggu ke-8 ($p > 0,05$), ke-16 ($p < 0,05$) dan ke-24 ($p < 0,05$). ■: kontrol normal, ▢: tikus F1 dari induk yang diberi asam valproat.

Pengamatan pulau langerhans pankreas tikus F1 dari induk yang diberi asam valproat pada umur 8 minggu belum menunjukkan adanya perbedaan yang signifikan dibanding kontrol normal dilihat dari hasil reaktivitas imunnya (Gambar 2A dan 2C). Sel-sel yang positif insulin dengan persentase warna cokelat yang hampir sama menunjukkan gambaran sel β yang masih mampu menghasilkan insulin pada usia tikus F1 umur 8 minggu dengan kemampuan yang sama.

Tikus F1 dari induk yang diberi asam valproat pada umur 8 minggu dilihat dari parameter kadar glukosa dan histologi pankreas belum menunjukkan adanya perbedaan yang bermakna jika dibandingkan dengan

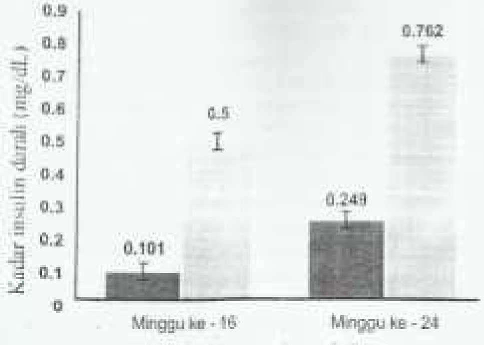


Gambar 2. Hasil pewarnaan immunohistokimia sel endokrin pakreas tikus (F1). A: Sel positif insulin jumlahnya banyak tersebar di tengah secara merata pada kontrol normal. B: Sel positif glukagon jumlahnya sedikit berada di tepi pada kontrol normal. C: Sel endokrin pankreas tikus F1 yang induknya diberi asam valproat pada pengamatan umur 8 minggu, populasi sel yang positif insulin masih dominan disebagian besar pulau Langerhans. D: Sel endokrin pankreas tikus F1 yang induknya diberi asam valproat pada pengamatan umur 16 minggu, terjadi pengurangan populasi sel yang positif insulin.

kontrol normal. Kondisi fisiologi antara tikus F1 yang induknya diberi asam valproat pada masa kehamilan dengan tikus kontrol normal juga menunjukkan tidak adanya perbedaan yang bermakna jika dilihat kadar glukosa darah. Kondisi ini menunjukkan sel β pankreas masih cukup secara jumlah dan kemampuan menghasilkan insulin sehingga kadar glukosa darah masih dapat terkontrol (Gambar 2C).

Hasil pengukuran kadar insulin darah tikus F1 dari induk yang diberi asam valproat pada minggu ke-16 ($p<0,05$) dan 24 ($p<0,05$) menunjukkan adanya peningkatankonsentrasi insulin dalam darah dibanding kontrol normal (Gambar 3). Kondisi ini menunjukkan adanya hiperinsulinemia yang terjadi karena adanya usaha mengontrol kenaikan kadar glukosa darah (Gambar 1). Hasil ini sejalan dengan perubahan histomorfologi sel β yang menunjukkan penurunan immuno reaktivitas sel β terhadap antibodi anti insulin. Kondisi demikian menggambarkan bahwa sel β berusaha melepas hormon insulin ke sirkulasi darah sehingga kadar insulin yang tertinggal dalam sel menurun (Gambar 2D). Peningkatan kadar insulin dalam darah sangat mungkin terkait dengan upaya menjaga nilai kadar glukosa.

Glukosa akan masuk ke dalam sel β pankreas melalui tranporter glukosa (GLUT-2). Glukosa akan mengalami metabolism membentuk ATP. ATP akan menyebabkan menutupnya kanal ion K^+



Gambar 3. Rata-rata kadar insulin tikus F1 dari induk yang diberi asam valproat 250 mg/kg bb per oral pada minggu ke-16 ($p < 0,05$) dan ke-24 ($p < 0,05$), n = 12 ekor. ■ : kontrol normal, □ : tikus F1 dari induk yang diberi asam valproat.

sehingga terjadi depolarisasi pankreas, yang diikuti masuknya Ca^{2+} ke dalam sel β sehingga menyebabkan terjadinya sekresi insulin dari sel β dan menyebabkan meningkatnya konsentrasi insulin pada darah.

Penyerapan glukosa ke dalam sel dimulai dari ditangkapnya insulin oleh reseptor pada membran sel, kemudian kompleks insulin-reseptor akan mengaktifkan ATP-ase membran sehingga memecah ATP menjadi ADP. Kompleks insulin-reseptor ini akan memberi signal untuk mengaktifkan tranporter glukosa (GLUT-4) sehingga siap untuk menerima dan memindahkan glukosa dari luar ke dalam sel[10]. Pada pengamatan pulau langerhans tikus normal, hasil reaktivitas imun sel yang positif insulin menggambarkan sebagian besar sel pulau langerhans pankreas tikus positif insulin (Gambar 2A). Dari hasil reaktivitas imunnya, terlihat bahwa sel yang positif glukagon tampak berderet di bagian tepi pulau Langerhans pankreas (Gambar 2B).

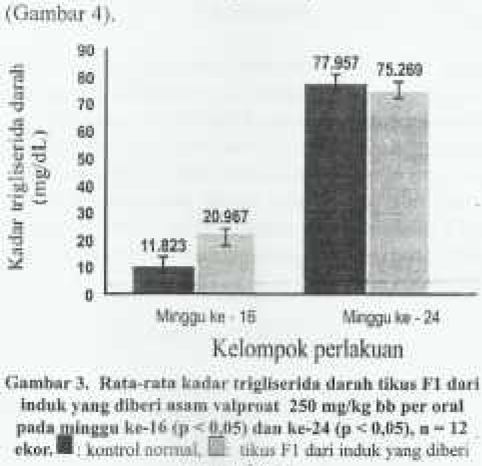
Pewarnaan pada pulau langerhans pankreas tikus F1 umur 16 minggu dari induk yang diberi asam valproat, menunjukkan hasil reaktivitas imun terhadap anti insulin yang menurun. Hal ini terkait dengan ditemukannya sel endokrin dengan warna cokelat pudar yang dibandingkan dengan kontrol normal (Gambar 2D). Lebih dari itu populasi sel yang positif terhadap anti insulin yang kuat tidak sebanyak yang ditemukan pada minggu sebelumnya.

Hasil pengamatan terhadap reaktivitas imun anti glukagon menunjukkan gambaran yang tidak berbeda dari kontrol. Gambaran imunohistokimia sel pankreas yang menghasilkan glukagon menunjukkan bahwa pada kelompok tikus F1 yang induknya diberi asam valproat, sel yang menghasilkan glukagon hanya terdapat pada bagian tepi saja sama dengan kontrol normal[13]. Hal ini menunjukkan bahwa pada kelompok tikus F1 yang induknya diberi asam valproat kerusakan sel pulau langerhans pankreas terjadi pada sel β penghasil insulin. Ada kemungkinan perubahan aktivitas HDAC dapat mempengaruhi faktor transkripsi atau modifikasi histon ekspresi gen yang menginduksi pre-insulin dalam sekresi insulin[14]. Asam valproat mempengaruhi ekspresi gen *cyp3a4* dan gen *mdr1*[15].

Penurunan populasi sel endokrin yang menghasilkan insulin pada tikus F1 umur 16 minggu dapat terjadi karena adanya dua kemungkinan, pertama karena sel-sel β pulau langerhans pankreas tikus sudah tidak mampu menghasilkan insulin atau karena adanya peningkatan sekresi insulin ke darah untuk mengontrol kadar gula darah yang meningkat. Kedua hal ini bisa terjadi bersamaan sehingga kerusakan sel β pankreas akan semakin parah. Hal ini mengindikasikan bahwa tikus F1 mengalami perubahan yang mendekati kondisi kejadian diabetes. Hasil evaluasi parameter glukosa darah, kadar insulin dan gambaran histologis sel endokrin pada umur 16 dan 24 minggu mengindikasikan bahwa metabolism glukosa tikus F1 mulai terganggu pada umur 16 minggu (dewasa).

Kondisi inilah yang biasanya terjadi pada penderita diabetes tipe 2 yang proses kerusakan sel β pankreas awalnya terjadi perlahan, tetapi terus berlangsung sehingga pada saat usia tertentu sel β pankreasnya sudah tidak mampu lagi mensintesis dan mensekresikan hormon insulin.

Pengamatan kadar trigliserida darah tikus F1 pada umur 16 minggu dari induk yang diberi asam valproat menunjukkan adanya peningkatan. Tetapi pada umur 24 minggu tidak menunjukkan perbedaan yang bermakna dibanding kelompok kontrol normal (Gambar 4).



Gambar 3. Rata-rata kadar trigliserida darah tikus F1 dari induk yang diberi asam valproat 250 mg/kg bb per oral pada minggu ke-16 ($p < 0,05$) dan ke-24 ($p < 0,05$), n = 12 ekor. ■ : kontrol normal, □ : tikus F1 dari induk yang diberi asam valproat.

Hipertrigliseridemia merupakan salah satu faktor risiko terjadinya sindrom metabolik[11,12]. Peningkatan kadar trigliserida darah pada tikus F1 umur 16 minggu dapat terjadi karena tidak efektifnya kerja insulin. Salah satu efek insulin adalah untuk merangsang pembentukan lipoprotein lipase (LPL), suatu enzim yang melekat ke sel endotel kapiler di otot dan jaringan adiposa.Insulin seharusnya merangsang sel adiposa untuk mensintesis dan menyekresikan LPL, yang menghidrolisis trigliserida dalam kilomikron VLDL. Pada kondisi hewan percobaan ini, kadar insulin darah tinggi tetapi kadar glukosa darah tetap meningkat. Hal ini menunjukkan kemungkinan terjadinya resistensi inisulin. Sehingga efek insulin dalam merangsang pembentukan LPL juga menurun, yang menyebabkan hidrolisis trigliserida dalam kilomikron dan VLDL berkurang dan menimbulkan hipertrigliseridemia[1].

Asam valproat akan mempengaruhi *Peroxisome Proliferator-Activated Receptors* (PPARs). PPARs adalah ligan faktor transkripsi aktivasi yang memodulasi target ekspresi gen dalam ligan endogen dan eksogen. Mekanismenya melibatkan *reseptor-dependent*, dengan pendekatan *gene silencing*[16]. PPARα dan PPARγ tidak spesifik untuk derivat asam valproat, PPARδ spesifik untuk teratogenik derivat asam valproat, tetapi tidak ada ikatan langsung antara asam valproat dan PPARδ[17]. Hubungan struktur-aktivitas menunjukkan bahwa induksi asam valproat menyebabkan gangguan perkembangan embrio secara *in vivo*. Sifat teratogenik asam valproat mungkin terkait dengan program selularyang kompleks dan regulasi berbagai kegiatan gen. PPARδ memainkan peranan utama dalam mekanisme aksi respons seluler terhadap asam valproat. PPARδ yang diaktifkan secara selektif oleh asam valproat merupakan faktor pembatas dalam pengendalian diferensiasi sel[18].

SIMPULAN

Anak tikus (F1) dari induk yang menerima asam valproat dosis 250 mg/kg bb memperlihatkan gejala klinis diabetes yang ditunjukkan dengan meningkatnya kadar glukosa darah, insulin darah, dan trigliserida darah pada pengamatan umur 16 dan 24 minggu. Pada umur 16 minggu mulai terjadi penurunan populasi sel β pankreas yang menghasilkan insulin.Sehingga dapat dikatakan berpotensi berkembang menjadi tikus diabetes.

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