



Profile of SGPT and SGOT on Male Rats (*Rattus norvegicus*) Hyperglycemic After Giving Insulin Leaf Extract (*Tithonia diversifolia*)

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Abstract

The leaves of insulin (*Tithonia diversifolia* (Hemsl.) A. Gray) are native bush plants from Central America. This plant in Indonesia is often called *paitan* or *kembang bulan*. The aim of this research was to know the profile of SGPT and SGOT of male white rat (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray). This study used 20 male Wistar rats which were divided randomly into 5 groups of treatment. Those were P0 as a group of rats which was not given alloxan and insulin leaf extract, P1 as a group of rats which was given alloxan without insulin leaf extract, P2 as a group of rats which was given alloxan and glibenclamide 2 mg/Body Weight (BW)/day, P3 as a group of rats which was given alloxan and insulin leaf extract 30 mg/BW/day, P4 as a group of rats which was given alloxan and insulin leaf extract 60 mg/BW/day. Each treatment was repeated as many as 4 replications. The results of this study indicated that there was no significant differences in all variables, namely levels of SGPT, SGOT, liver weight, body weight and Hepatosomatic index (HSI), so it can be concluded that giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) of 30 mg/BW/day and 60 mg/BW/day could improve liver function of hyperglycemic male white rats (*R. norvegicus* L.).

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INTRODUCTION

Liver is an organ that plays an important role in detoxification to convert toxic compounds into non-toxic compounds (Chiang, 2014). Liver can be damaged during hyperglycemic conditions due to the increase of blood glucose levels exceeding normal (Sari *et al.*, 2010). It is characterized by the presence of blood glucose more than 126 mg/dL (Prasetyo *et al.*, 2016), which can cause glucose availability in cells decreases so that it can trigger the occurrence of gluconeogenesis in liver cells (Agunbiade *et al.*, 2012). These conditions over a long period of time can lead to increase Reactive Oxygen Species (ROS) compounds that can bind to hepatocyte structures, thereby able to cause hepatocyte damage which is begin with degeneration, up to cellular necrosis (Maulida *et al.*, 2013). Liver damage can be fixed by giving antidiabetic compound. Giving herbal ingredients through oral with specific doses can interfere liver function (Navarro *et al.*, 2017).

The insulin leaf (*Tithonia diversifolia*) is one of the herbs containing the antidiabetic compound, the herb contains the compound of diterpenoid, flavonoid, sesquiterpen, chlorogenic acid and chloric acid derivatives (Passoni *et al.*, 2013). The insulin leaf (*Tithonia diversifolia* (Hemsl.) A. Gray) also contains flavonoids alkaloids, terpenoids, saponins, tannins, and polyphenols (Aman-tie & Sulistyowati, 2015). Flavonoids and sesquiterids contained in the insulin leaf (*Tithonia diversifolia* (Hemsl.) A. Gray) can decrease blood glucose levels and improve hepatocytes and lower levels of Serum Glutamate Pyruvate Transaminase (SGPT) and Serum Glutamate Oxalacetate Transaminase (SGOT). Flavonoids are protective against the destruction of pancreatic β cells as an insulin producer and able to restore the sensitivity of insulin receptors in cells and increase insulin sensitivity (Winarsi *et al.*, 2012). Flavonoid compounds can increase glucose use in peripheral tissues (Jadhav & Puchchakayala, 2012). The antioxidant effects on flavonoids can inhibit the formation of Reactive Oxygen Species (ROS) and trigger the regeneration of β -pancreatic cells (Prasetyo *et al.*, 2016). Sesquiterpene compounds have an effect on glucose metabolism through various mechanisms including in functions such as insulin substitution, inhibiting insulinase activity, increasing insulin secretion from β -pancreatic cells or from insulin sources, and enabling increase regeneration of pancreatic cells (Sasmita *et al.*, 2017).

Serum Glutamate Pyruvate Transaminase (SGPT) and Serum Glutamate Oxalacetate Tran-

saminase (SGOT) are both of the clinical examinations to know the existence of damage to liver organ (Wibowo, 2007). Baroni *et al.*, (2016) states that when hepatocytes are damaged by hyperglycemic, the enzyme GPT (Glutamate Pyruvate Transaminase) and GOT (Glutamate Oxalacetate Transaminase) which are present in the hepatocytes will come out and enter into the blood circulation, thus the levels of SGPT and SGOT is in elevated blood caused by hepatocyte damage. Serum Glutamate Pyruvate Transaminase (SGPT) and Serum Glutamate Oxalacetate Transaminase (SGOT) examinations are indicators of liver impairment (Cahyono, 2009). Liver can be damaged if the amount of Serum Glutamat Pyruvat Transaminase (SGPT) and Serum Glutamat Oxalacetate Transaminase (SGOT) in blood is greater than normal (Aggarwal *et al.*, 2006). Normal levels of SGPT in white rats were 17.5-30.2 U/L and SGOT normal levels in rats were 45.7-80.8 U/L (Gad, 2007). According to the description above, it is necessary to examine further about the appropriate dosage of insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) which can reduce blood glucose levels without damaging liver function and further research on the profile of SGPT and SGOT of male white rats (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray). This study aims to analyze liver function after giving various doses of insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) orally.

METHOD

This Research has been approved by Komisi Etik Penelitian Kesehatan (KEPK) of medicine faculty of Diponegoro University with No. Etichal Clearance 73/EC/H/FK-RSDK/VI/2018. The sample used in this study was male white rat (*Rattus norvegicus* L.) weighing \pm 200 g and the age of mice about 2-3 months.

The sample used in this study was male white rat (*Rattus norvegicus* L.) weighing \pm 200 g and the age of mice about 2-3 months. This study used 20 male Wistar rats divided randomly into 5 groups of treatment. Those were P0 as a group of rats not given alloxan and insulin leaf extract, P1 as a group of rats given alloxan without insulin leaf extract, P2 as a group of rats given alloxan with glibenclamide 2 mg/BW/day, P3 as a group of rats given alloxan with insulin leaf extract 30 mg/BW/day, P4 as a group of rats given alloxan with insulin leaf extract 60 mg/BW/day. Each treatment was repeated as many as 4 replications. The research design used completely randomized

design.

Insulin leaf filtrate (*Tithonia diversifolia* (Hemsl.) A. Gray) was obtained from extraction of 1000 g of leaves in 1 L of aquades for 24 hours. The result filtrate was taken 30 mg and 60 mg then dissolved in 3 ml of aquades as a stock solution (Modified Olukunle *et al.*, 2014). The giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) was taken 0.2 ml from stock solution for 28 days. The other treatment was giving glibenclamide of 2 mg/BW/day. The treatment was done orally. The treatment of rats that would be induced by alloxan was by fasting for 16-18 hours to measure blood glucose levels during fasting. 5% Alloxan monohydrate (Sigma-Aldrich, Belgum) (5g / 100 ml salt solution) at a dose of 150 mg/kg BW by injecting 0.2 ml intraperitoneally (Anwar *et al.*, 2016). Verification after alloxan induction was carried out three days in a row, the aim was to see an increase in blood glucose levels. Alloxan which had played a role was characterized by an increase in blood glucose levels. Test animals with blood glucose levels of more than 126 mg/dl were considered hyperglycemic and selected for further research (Prasetyo *et al.*, 2016).

In this study the variables observed were levels of SGPT, SGOT, liver weight, body weight and Hepatosomatic index (HSI). Observations of SGPT and SGOT were obtained from observations of blood plasma at the end of treatment. The weight of the liver and body weight obtained from weighing at the end of the Hepatosomatic index (HSI) treatment was obtained from the calculation of the liver weight ratio (g) / body weight (g) x 100 (Gupta *et al.*, 2017). The data that had been obtained was analyzed by using analysis of variance (ANOVA) at 95% confidence level with the help of software SPSS version 15.

RESULTS AND DISCUSSION

The resulted analysis of Serum Glutamate Pyruvate Transaminase (SGPT) and Serum Glutamat Oxalacetate Transaminase (SGOT) profile of male white rat (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia*

diversifolia (Hemsl.) A. Gray) for 28 days shows no significant difference ($P>0.05$) between P0 which was a group of rats not given alloxan and insulin leaf extract with other treatments (Table 1).

The Serum Glutamate Pyruvat Transaminase (SGPT) and Serum Glutamate Oxalacetate Transaminase (SGOT) in male white rat (*Rattus norvegicus* L.) hyperglycemic treated with insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) were not significantly different from control, this was probably due to liver damage, it was effected by hyperglycemic conditions, it can be fixed by giving the insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) either with a dose of 30 mg/BW/day or with a dose of 60 mg/BW/day. The condition was in accordance with the statement of Sasmita *et al.*, (2017) that the insulin leaf (*Tithonia diversifolia* (Hemsl.) A. Gray) contains two main components that have antidiabetic or antihyperglycemic roles of flavonoids and sesquiterpenes. Flavonoids are antioxidants that can protect the body against damage caused by Reactive Oxygen Species (ROS), so able to inhibit the occurrence of hyperglycemic. Giving flavonoid compounds can improve hepatocytes, thereby it can decrease levels of SGOT and SGOT in the blood (Yerizel *et al.*, 1998). Insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) contains flavonoid compounds that can regenerate β -pancreatic cells, so that the blood glucose decreases (Abdelmoaty *et al.*, 2010). These compounds can also stimulate peripheral glucose utilization by increasing glycolysis and glycogenesis pathways, which simultaneously depress glycogenolysis and gluconeogenesis pathways. Through this mechanism flavonoids could control blood glucose, so that blood glucose levels decreased. Antioxidants in flavonoids could also donate hydrogen atoms that will oxidize and bind to free radicals, so it becomes a more stable compound. The condition of blood glucose levels decreased until normal circumstances cause the availability of glucose in cells was met so that it could inhibit the occurrence of gluconeogenesis in the liver. The condition can decrease the Reactive Oxygen

Table 1. Average of SGPT and SGOT liver hyperglycemic white male (*Rattus norvegicus* L.) after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray)

Variables	Treatment				
	P0	P1	P2	P3	P4
SGPT(U/L)	69.50 ± 7.54	62.75 ± 7.27	62.75 ± 6.70	63.50 ± 9.03	60.25 ± 9.56
SGOT(U/L)	137.25±17.67	124.75±16.47	126±16.57	126.50±14.38	140±18.42

Description: SGPT and SGOT male white rat (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) did not show significant changes ($P>0.05$).

Species (ROS) compounds that can bind to the hepatocyte structure, so that it can repair hepatocyte and can normalize Serum Glutamate Pyruvate Transaminase (SGPT) and Serum Glutamate Oxalacetate Transaminase (SGOT) levels in the blood (Winarsi *et al.*, 2012). Flavonoids are natural antioxidants that act as antioxidants (Biswas *et al.*, 2011). Sesquiterpene compounds play a role in reducing insensitivity to insulin, and the compound significantly increases glucose metabolism (Zhao *et al.*, 2012). Sesquiterpenes can also inhibit inflammatory factors in cells on hyperglycemic conditions (Wang *et al.*, 2010).

Serum Glutamate Pyruvate Transaminase (SGPT) and Serum Glutamate Oxalacetate Transaminase (SGOT) in the blood are an indicator of liver cell damage. This is in accordance with the opinion Agrawal & Gupta (2013) that SGPT is a specific enzyme in the liver. High levels of SGPT is indication of liver damage, then increasing SGPT significantly is an indication of acute liver damage. Very high cell activity can cause hepatocyte damage which subsequently occurs the release of these enzymes into the bloodstream, so that the levels of SGPT increase (Sarawati, 2015). The activity is used as an indicator of liver function which indicates the increase of activity in liver (Kundu *et al.*, 2012). High SGOT levels and along with the on-site cytoplasm will be released into the blood after hepatocellular damage. Hepatic metabolism was primarily mediated by the cytochrome P450 system. Qodriyati *et al.*, (2016) states that Serum Glutamate Oxalacetate Transaminase (SGOT) levels of less than 300 U/L show no necrosis.

The statistical analysis result of liver weight showed no significant difference ($P > 0.05$) between group P0 and other treatments (Table 2). The condition was suspected that the liver structure was still in normal condition. The liver structure in male white rats (*Rattus norvegicus* L.) hyperglycemic which was allegedly damage had been fixed by giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A Gray) containing flavonoids which are antioxidants that can regenerate

hepatocytes rapidly. That condition was in accordance with the statement of Kio *et al.*, (2018) that hepatocytes have the ability to regenerate quickly to replace damaged hepatocytes replaced with new hepatocytes, so that the metabolic process carried out by the liver continues to run normally. liver is an organ that has rapid regeneration ability. The process of liver regeneration originates from liver parenchymal cells, hepatocyte cells. Hepatocyte cell replication is started from the zone near the portal venous area, then the new hepatocytes proliferate forms a collection of cells. Hepatocyte replication will spread to another zone followed by non-parenchymal cell replication which occurs around 24-72 hours after replicating hepatocyte. then the regenerated endothelial cells enters a collection of hepatocyte cells that has replicated first and then returns the liver as before (Feldman *et al.*, 2010). The ability of the liver to regenerate is very important to protect liver function after injury and during chronic disease (Wang *et al.*, 2012). Liver contains intra-hepatic stem cells that helps hepatocyte replication. Replication of hepatocytes will help regenerate cells so that the growth and development of the liver can be done quickly (Fausto & Campbell, 2003). Hepatocyte replication will make the hepatocytes multiply, then will support liver weight gain. Increasing liver weight usually also occurs due to fatty which is reversible hepatocyte damage and the onset of necrosis, so that it can cause abnormalities in liver weight (Nindya *et al.*, 2011).

The results of statistical analysis of body weight of white male rat (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) showed no significant difference ($P > 0.05$) between P0 groups with other treatments (Table 2). This condition is suspected because glucose could still be used as a source of energy and insulin secreted by the pancreas which is still in normal conditions, so that the body weight of white male rat (*Rattus norvegicus* L.) hyperglycemic was still in the normal range. This condition was in accordance with the statement of Colville and Bassert

Table 2. Average of liver weight and male body weight (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A Gray).

Variables	Treatment				
	P0	P1	P2	P3	P4
LiverWeight (g)	9.76±0.39	10.97±0.60	9.48±0.55	10.06±1.06	9.68±0.68
BodyWeight (g)	218±15.23	232±31.11	213±19.49	215±21.32	206±12.32

Description: liver weight and body weight of male white rats (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A Gray) did not show significant changes ($P > 0.05$).

Table 3. Average of Hepatosomatic index (HSI) of male white rats (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A Gray).

Variables	Treatment				
	P0	P1	P2	P3	P4
Hepatosomatic index (%)	4.46 ± 0.28	4.76 ± 0.41	4.55 ± 0.54	4.86 ± 0.90	4.70 ± 0.35

Description: HSI of male white rats (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) did not show a significant change (P>0.05).

(2008) stating that a decrease in the availability of energy in the body will cause a decrease in body weight because animals cannot synthesize the components of the body perfectly. Flavonoid content of insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) could regenerate pancreatic β cells and help stimulate insulin secretion, so that glucose metabolism could run normally without toxic effects on adipocytes (Dheer & Bhatnagar, 2010). Glucose metabolism always requires insulin to enter the cell which allows the body to convert glucose into energy and then spread throughout the body, so the body weight of male white rats (*Rattus norvegicus* L.) hyperglycemic was still in the normal range. Body weight of normal 3-month-old normal white rats (*R. norvegicus* L.) ranged between 242-244 g (Dharmayudha & Athara, 2013).

Results of statistical analysis of hepatosomatic index (HSI) of male white rats (*Rattus norvegicus* L.) hyperglycemic after giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) showed no significant difference (P>0.05) between P0 which was a group of rats not given alloxan and insulin leaf extract with other treatments (Table 3). This condition is suspected because the hepatosomatic index (HSI) was still in the normal range. The value of hepatosomatic index (HSI) was influenced by body weight and liver weight of male white rats (*Rattus norvegicus* L.) hyperglycemic that were still in the normal range, so that the hepatosomatic index (HSI) was also in the normal range. This condition is in accordance with the statement of Wahyuningtyas *et al.*, (2018) that an increase in the value of the hepatosomatic index (HSI) indicates abnormalities in liver weight and also illustrates that the test material used is suspected not to be toxic because one of the liver functions is to detoxify toxic substances enter the body. The Hepatosomatic Index is a value that describes the amount of toxic compounds that enter and describes the availability of energy in the body (Nunes *et al.*, 2011).

Based on these results, it can be concluded that the giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) could reduce liver damage and had a beneficial effect that was able to

improve the liver function of hyperglycemic male white rats (*Rattus norvegicus* L.)

CONCLUSION

Giving insulin leaf extract (*Tithonia diversifolia* (Hemsl.) A. Gray) of 30 mg/BW/day and 60 mg/BW/day was able to improve the liver function of male white rat (*Rattus norvegicus* L.) hyperglycemic.

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