



## Effect Of Ethanol Extract Of Kenikir (*Cosmos caudatus* Kunth.) Leaves in Blood Glucose, Cholesterol and Histopathology Pancreas of Male White Rats (*Rattus norvegicus*)

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### Abstract

The aim of this study was to investigate the effects extract of Kenikir in male rats parameters blood glucose, cholesterol and histopathological of the pancreas. Thirty rats were divided into six groups, and each group consists of five individuals with the details of groups I, II, and III as control groups and groups IV, V, and VI for the experiments. Group I: normal control was given NaCMC 0,5%; Group II: control negative was given Streptozotocin 30 mg/kgBW i.p, high feed fat 25 g/day, and the positive control was given met form in 45 mg/kgBW, and the experimental groups were each given extract of the kenikir leaves with dose 100 mg/kg BW, 200 mg/kgBW, and 400 mg/kg BW. The results showed that there were secondary metabolites contained in the extract of leaves of kenikir. Giving the extract of kenikir leaves at the dose of 200 mg/kg is effective in lowering the blood glucose levels, extract of leaves of kenikir with the dose of 400 mg/kg is effective to reduce the total cholesterol levels and regenerate pancreatic tissue, and extract of leaves of kenikir with the dose of 100 mg/kg BW did not give any maximum impacts to decrease the blood glucose.

**Keywords:** Cholesterol, diabetic, histopathology, kenikir leaves ethanol extract

### Pengaruh Ekstrak Etanol Daun Kenikir (*Cosmos caudatus* Kunth.) terhadap Glukosa Darah, Kolesterol, dan Histopatologi Pankreas Tikus Putih Jantan (*Rattus norvegicus*)

#### Abstrak

Tujuan dari penelitian ini adalah untuk mengetahui efek ekstrak Kenikir. Pada tikus jantan parameter glukosa darah, kolesterol dan histopatologis pankreas. Tiga puluh tikus dibagi menjadi enam kelompok, dan masing-masing kelompok terdiri dari lima individu dengan rincian kelompok I, II, dan III sebagai kelompok kontrol dan kelompok IV, V, dan VI untuk eksperimen. Kelompok I: kontrol normal diberikan NaCMC 0,5%; Kelompok II: kontrol negatif diberi STZ 30 mg / kgBB ip, lemak pakan tinggi 25 g / hari, dan kontrol positif diberikan dalam bentuk 45 mg / kgBB, dan kelompok eksperimen masing-masing diberi ekstrak daun kenikir dengan dosis 100 mg / kg BB, 200 mg / kgBB, dan 400 mg / kg BB. Hasil penelitian menunjukkan bahwa ada metabolit sekunder yang terkandung dalam ekstrak daun kenikir. Pemberian ekstrak daun kenikir pada dosis 200 mg / kg efektif dalam menurunkan kadar glukosa darah, ekstrak daun kenikir dengan dosis 400 mg / kg efektif menurunkan kadar kolesterol total dan meregenerasi jaringan pankreas, dan ekstrak daun kenikir dengan dosis 100 mg / kg BB tidak memberikan dampak maksimal untuk menurunkan kadar glukosa darah.

**Kata Kunci:** Ekstrak etanol daun kenikir, hiperkolesterolemia, diabetes, histopatologi

## 1. Introduction

The use of medicinal plants in Indonesia has been increasing since 1998 as the result of the Minister of Health, F.A. Moeloek's recommendation to utilize traditional medicine in health care. The development was supported by the society's knowledge about medicinal plants. Indonesia has approximately 30,000 species of plants, and 9,600 species of which are well-known as medicinal plants<sup>1</sup>. Diabetes mellitus is a disease which is today continuously increasing along with the enhancement of prosperity level And the alteration of lifestyle<sup>2</sup>.

Diabetes mellitus causes high morbidity and mortality, mainly due to the vascular complication. It can occur because of the increased of free radical formation through the glucose metabolism as autooxidise of glucose, metabolism of metilglioksal formation, and oxidative Phosphorylation<sup>1,3</sup>. One type of highly reactive free radicals is the hydroxyl radical. The hydroxyl radical is highly toxic because of its ability to diffuse into the transfers subsequently reacting with the lipid membrane to produce the malondialdehyde (MDA) product. Malondialdehyde is the last result of lipid peroxidation that is used as a parameter of oxidative stress levels and risk of complications in diabetes mellitus. In addition, free radicals are also reactive ROS (Reactive oxygen species) that may cause DNA oxidation producing 8 hydroxy-deoksiganosins<sup>4,5</sup>.

Hypercholesterolemia is counted as a condition in which cholesterol in the blood exceeds the normal amount, i.e.  $\geq 240$  mg / dL. Hiperkolesterolemia is closely associated with LDL cholesterol levels in the blood. Hiperkolesterolemia can be caused by genetic factors such as familial hypercholesterolemia and polygenic hypercholesterolemia which is caused by secondary factors as a result of diseases such as diabetes mellitus, nephrotic syndrome, saturated fat diet, obesity and lack of exercise. High blood cholesterol levels increase the risk of some diseases such as cardiovascular disease, hypothyroidism, chronic renal failure, and diabetes mellitus. The increase in diabetes could potentially

leads to hypercholesterolemia with increased LDL due to risk factors of obesity, lack of physical activity, high fat and insulin resistance<sup>6</sup>.

One of the traditional medicinal plants that is efficacious as a medicine diabetic is *C. caudatus* (kenikir). The leaf of kenikir is one of vegetable that is often consumed by Indonesian. The previous introductory study about phytochemicals of kenikir leaves extracted by using ethanol and other solvents showed the existence of active compounds flavonoids, saponins, alkaloids, tannins and polyphenols<sup>4,7</sup>.

The result of a previous using rats study stated that the leaf extract of *C. caudatus* (kenikir) was not merely as anihiperlipidemia, but it had potential as a therapeutic agent of diabetes. The model of test animals used was rodents hyperlipidemia, using High Fat Diet induction, and kenikir leaf extract ethanol 80% dose used in the study was 200 mg / kg<sup>8</sup>.

Previous studies used a dose of 200 mg/kg BW while we used a dose of 100 mg/kg BW, 200 mg/kg BW, and 400 mg/kg BW. Based on the description above, the research was conducted to determine the effect of ethanol extract of *C. caudatus* (kenikir) leaves to the decrease of blood glucose levels to hyper kolesterolemia Wistar rats induced with streptozotocin. This research is expected to be a new source of information for the society so that the ethanol extract of kenikir leaves can be utilized optimally<sup>9</sup>.

## 2. Materials and Methods

### 2.1. Tools

Measuring instrument of glucose (accu check, germany), aluminium foil, mesh sieve 40, stirring rod, blender (Panasonic, japanase), porcelain cup, mouthpiece, chemical glass 1000 ml (agc iwakicte33), measuring glass 100 ml (pyrex), animal test cage, volumetric flask 100 ml, mortar and stamper, oven, pipettetes. Rotary evaporator (heidolph, united kingdom), sonde oral, 3 ml and 5 ml injection spoit (treumo, japanase), glucose strip (accu check), reaction tube, analytical scale (ohaus, england), gram scales, water bath, maceration container, microscope olympus Bx-51

(Japanese), spectrophotometer.

## 2.2. Materials

Kenikir leaves (*C. caudatus* Kunth.), Obtained from Sidera Village, Central Sulawesi; white male rats (wistar), obtained from Bantul Animal Husbandry Farm, Yogyakarta; aquades, 70% alcohol, ammonia, hydrochloric acid, sulphuric acid, buffer citrate, Ethanol 96%, ether, filter paper, duck egg yolk, chloroform, FeCl<sub>3</sub> solution, NaCl 10% solution, pig fat, Na CMC, standard feed, Dragendorff reagent, Lieberman-Burchard reagent, Magnesium P powder, streptozotocin, metformin tablet.

## 2.3. Materials Retrieval and Processing

The materials used were leaves of kenikir obtained from Sidera village, Sigi district, Central Sulawesi. The making of simplisia was prepared including wet sorting and leaching of dried leaves of kenikir conducted by using indirect sunlight. Then, simplicia is separated from foreign material, smoothed and sieved with sieve number 40<sup>6,10</sup>.

## 2.4. Kenikir Leaves Extract

The simplisia powder is extracted by maceration with 96% ethanol solvent, then filtered, concentrated with a rotavapor vacuum, and water bath with temperature 80°C

## 2.5. Na CMC 0.5 %

A-0.5-gram-Sodium carboxyl methyl cellulose (Na CMC) in 100 ml aquadest.

## 2.6. Metformin Suspension

Metformin tablet powder is weighed with the same weight with 360 mg then suspended in Na CMC 0.5% to 100 ml, and shaken until homogeneous<sup>9</sup>.

## 2.7. Test Solution

Metformin suspension and kenikir leaves extract with the dose of 100 mg / kg BW, dose of 200 mg / kg BW, 400 mg / kg are weighted and suspended with NaCMC 0,5%, and the volume is made sufficient with aquadest up to 100 ml.

## 2.8. Test Animal

Test animals used are 30 male white rats (*Rattus norvegicus*) aged 2-3 months, weighing 150-200 grams and divided into 6 groups consisting of 5 rats per group. Rats were adapted in a cage for two weeks in laboratories with sufficiently stamped at normal ambient temperatures and fed with standard feeding and drinking<sup>10</sup>.

## 2.9. Kenikir Leaves Extract Treatment

This study used 30 Rats divided into 6 groups, and each group consisted of 5 rats. The rats then adapted for 2 weeks before getting the treatment to even up the regimen and the food so that they were stressful. Previously, the rats were not fed for 12 hours, and their body weight was measured. Prior to the treatment, the rats were measured to know the first initial blood glucose levels. The feeding in the form of a mixture of standard feed, pigoil and duck egg yolk given for 28 days was taken to obtain the condition of hypercholesterolemic rats, except for healthy control (normal) they were given standard feed.

After induction of high cholesterol feed on day 28, then it was continued with low-dose streptozotocin induction of 30 mg / kg body weight to re-measure the glucose levels on day 35. If the blood glucose level of the rats was > 200 mg / dL, then the rats had diabetes mellitus.

After that, the rats were treated in each group. In group I (normal control) the rats were given standard feed, group II (negative control) was given suspense Na CMC0,5%, group III (positive control) was given Metformin suspension 45 mg / kg BW, group IV was given the extract of kenikir leaves with the dose 100mg / kg BW, group V was given extract of kenikir leaf with the dose 200mg / kg BW, and group VI was given the extract of kenikir leaves dose 400 mg / kg BW in which was given orally for 14 days. After the treatment on day 42 and day 49, the blood glucose level measurement of the rats was re-conducted. Blood glucose measurement data before and after the treatment were recorded and analyzed.

## 2.10. Data analysis

The data obtained were blood glucose levels of rats analyzed statistically by using one way ANOVA method at 95% confidence level. Furthermore, a further test of LSD post tests (statistical methods LSD) was carried out to determine the effective dose. Data processing was done by using SPSS software program<sup>9</sup>.

## 3. Results

### 3.1. Blood Glucose Profile

Profile of blood glucose level measurements of male rats of normal group, pain control, positive control (metformin) And treatment group of ethanol extract kenikir of leaves with the dose 100mg / kg BW, 200 mg / kg BW, and 400mg / kg BW can be seen in Figure 1.

### 3.2. Blood Cholesterol Profile

On day 0 it shows no significant difference in each group marked with  $P > 0,05$  (value  $P = 0,307$ ) On the 35th, 42th and 49th days, there were significant differences in each group marked with  $P < 0.05$  (P values of each group were 0.000, 0,000, 0,000, 0,000 respectively). The data showed in Tabel 1.

### 3.3. Histopatology of Pancreas

The histology of pancreas result are shown on figure 4-6.

## 4. Discussion

### 4.1. Blood Glucose Profile

On day 0, it showed no significant difference in each treatment group marked

with  $P > 0,05$  (P value = 0,167). On days 35, 42 and 49 (has experienced an increase in cholesterol for 1 month) there were significant differences in each treatment group marked with  $P < 0.05$  (P values of each group were (0,000, 0,000, 0,000), respectively).

### 4.2. Blood Cholesterol Profile

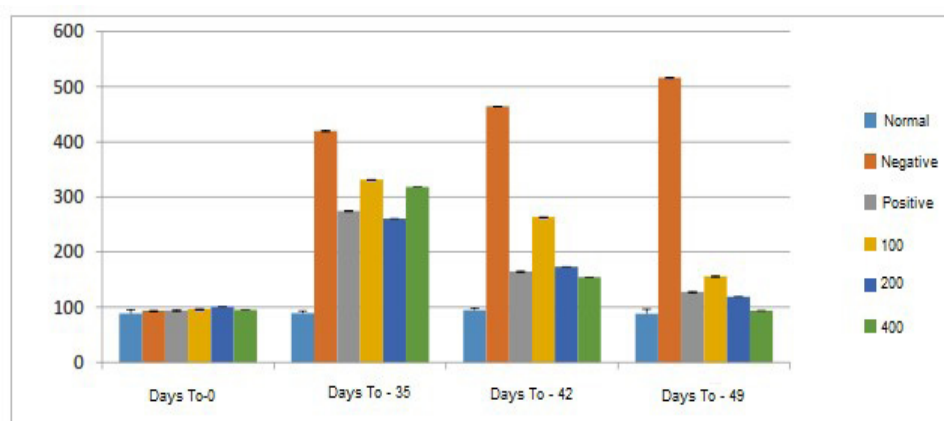
On day 0 it shows no significant difference in each group marked with  $P > 0,05$  (value  $P = 0,307$ ) On the 35th, 42th and 49th days, there were significant differences in each group marked with  $P < 0.05$  (P values of each group were 0.000, 0,000, 0,000, 0,000 respectively).

### 4.3. Histopatology of Pancreas

In the 1st, 2nd and 3rd rats there was a marked difference in each group marked with  $P < 0.05$  (P values of each group were 0.000, 0,000, 0,000, 0,000 respectively).

Kenikir leaves (*C. caudatus*) was used for this research, while the extraction method used was maceration which was conducted by soaking simplicia powder with 96% ethanol. This process was then followed with phytochemical filtering to determine the secondary metabolite contained within the extract. Based on the result of phytochemical extract filtering, *C. caudatus* contains flavonoid, saponin, tannin, polyphenol, and alkaloid.

The result showed the average of  $\leq 200$  mg/dL which was 88.8 – 100.6 mg/dL glucose level in each of the treated group, indicating that all mice were in healthy condition. The next step was to give high-fat food (pork oil



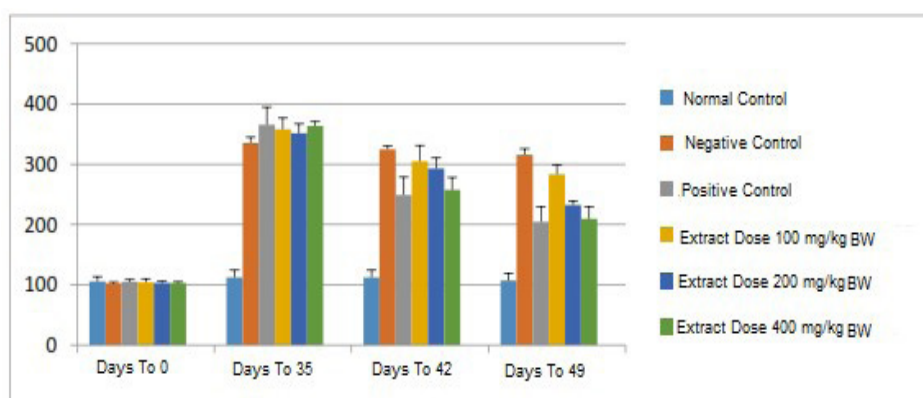
**Figure 1** Profile of Blood Glucose Level

**Table 1** Average Total Cholesterol Level

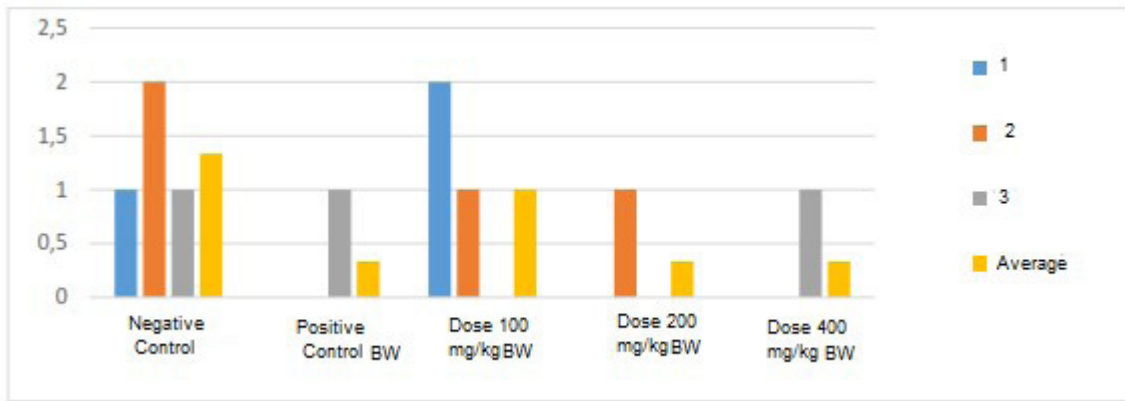
Days-to	Mean $\pm$ SD Total Cholesterol (mg / dL)						P
	Normal Control	Negative Control	Positive Control	Dose 100 mg/kg BW	Dose 200 mg/kg BW	Dose 400 mg/kg BW	
0	105.6 $\pm$ 7.83	102.2 $\pm$ 2.49	105.2 $\pm$ 3.49	104 $\pm$ 5.83	102.8 $\pm$ 2.77	102.8 $\pm$ 2.39	0.307
35	111.8 $\pm$ 12.21	335.4 $\pm$ 9.45	365.4 $\pm$ 29.48	357.8 $\pm$ 18.62	315.4 $\pm$ 15.59	3663.4 $\pm$ 7.02	0.000
45	112 $\pm$ 12.21	324.4 $\pm$ 5.64	249 $\pm$ 29.77	305 $\pm$ 26.22	292.8 $\pm$ 17.81	257.2 $\pm$ 20.69	0.000
49	107 $\pm$ 12.22	315.6 $\pm$ 10.22	204.4 $\pm$ 25.40	283.4 $\pm$ 14.84	232.4 $\pm$ 6.78	209.4 $\pm$ 20.19	0.000

and duck eggs' yolk) for 28 days posterior to the adaptation phase and continued by issuing streptozotocin (stz) by i.p dosage of 30 mg/kg BW. The mice were then left for 7 days to observe the effect of the given hyperglycemia. The blood glucose level was measured on the 35th day. This process provided evidence on how the combination of high-fat food turned the mice hyperglycemic. The administration of streptozotocin (stz) caused insulin resistance by which the lipase-sensitive hormone was activated. This hormone triggered the fragmentation of triglycerides which turned to fat acid, causing free fatty acids and blood cholesterol level to increase. Owing to this condition, the mice experienced diabetes-hypercholesterolemia condition. The high-cholesterol food was halted for 28 days, replaced with standard food. On the 28th day, the mice were given streptozotocin by i.p. The hypercholesterolemia-diabetic tested animal was treated based on their group orally for 14 days. This research was using positive-control comparing medicine which was metformin, a medical substance often used as anti-diabetic treatment suitable for the obese.

The one-way Anova statistic testing on the 42<sup>nd</sup> day showed a significant result with the value of  $P = 0.000$  ( $P < 0.05$ ) indicating significant difference in the entire treated group. This result exhibited the effect of the administration of *C. caudatus* ethanol extract in various dosages, continued with following test of post hoc LSD (method bonferroni) to see the significant difference among the treated groups. The result showed the normal control was not significantly different compared to the positive one and the 400 mg/kg BW dosage group. On the 42<sup>nd</sup> day, the blood glucose level of the mice from positive control group and 40 mg/kg BW dosage group experience a decline nearing the normal value of non-significant difference with normal control. The ill control was not significantly different from the 100 mg/kg BW and 200 mg/kg BW dosage group, showing that both groups were yet to provide prompt effect in reducing the glucose level in blood. The result of Anova one-way statistic test on the 49<sup>th</sup> day showed significant result with value of  $P = 0.000$  ( $P < 0.05$ ) indicating significant difference in the entire treated group.

**Figure 2** Profile of Total Cholesterol Level

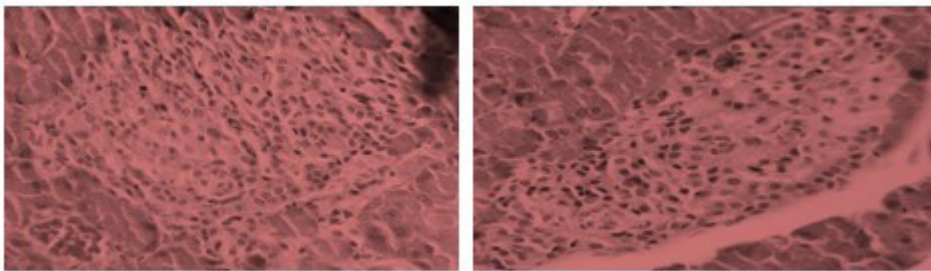




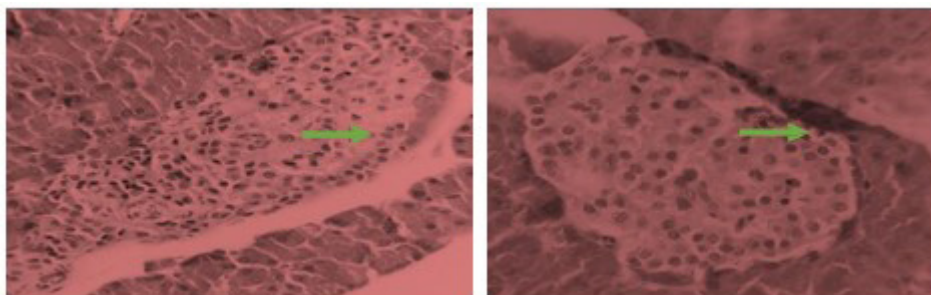
**Figure 3** Scoring of Rat Pancreatic Damage

This result exhibited the effect of the administration of *C. caudatus* ethanol extract in various dosages, continued with following test of post hoc LSD to see the significant difference among the treated groups. The

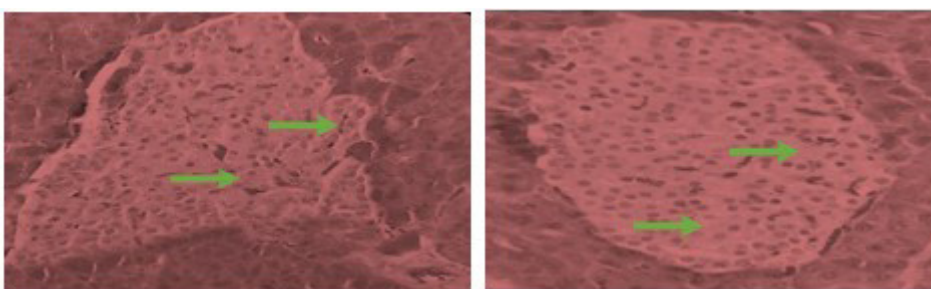
result showed the normal control was not significantly different compared to the positive one, the 200 mg/kg BW dosage group, and the 400 mg/kg BW one. The ill control was significantly different from the rest of the



**Figure 4** Preparations of white rat pancreatic tissue Score 0 (normal) HE Coloring 400X magnification



**Figure 5** Preparations of rat pancreatic tissue score 1 (cytoplasmic degeneration 1-30%) staining HE magnification 400X



**Figure 6** Preparations of rat pancreatic tissue score 2 (cytoplasmic degeneration 30-60%) HE magnification 400X

Information : = Cytoplasmic degeneration

treated group caused by the absence of any treatment. The positive control group was, on the other hand, significantly different with the ill control but otherwise were not compared with the normal control group, 100 mg/kg BW dosage group, 200 mg/kg BW dosage group, and the 400 mg/kg BW dosage group. This showed that the blood glucose level of the 100 mg/kg BW dosage group, 200 mg/kg BW dosage group and the 400 mg/kg BW dosage group was nearing the positive control group. This is due to the concentrated amount of ethanol extract which possessed better capability in reducing the level of glucose in blood.

Based on the statistic result, it was found that the *C. caudatus* extract is effective in reducing the blood glucose level, where the effective dosage which was able to reduce the glucose and cholesterol level in the tested animal's blood was the 400 mg/kg BW dosage. The anticholesterol-diabetic effect of the *C. caudatus* was triggered by the contents of flavonoid, polyphenol, tannin, alkaloid, dan saponin compound. This finding was in accordance to the phytochemical filtering test.

The compound contained within the ethanol extract of the *C. caudatus* played the role in reducing the blood glucose level with flavonoid acting as the anti-oxidant which inhibited the formation of free radicals by neutralizing the increase of Reactive Oxygen Species (ROS) caused by diabetes and was able to regenerate the pancreatic beta cells, addressing the insulin deficiency<sup>1</sup>. According to the previous research, the ethanol extract of the *C. caudatus* contain a total of 55.48% of flavonoid compound and as much as 18.68% of fenolid with the value of IC<sub>50</sub> 19,49 µg/ml<sup>1</sup>. Saponin has the ability to reduce the blood glucose by inhibiting the transportation of glucose within the digestive fluid and triggering insulin secretion in pancreatic beta cells<sup>11</sup>. Tannin also has hypoglycemic activity which boosts the glycogenesis and functions as astringent which shrinks the the epithelium membrane of the small intestines, hence reducing the absorption of the food essence and, as the result, halting the glucose

intake as well as slowing down the rate of glucose increase. The alkaloid could reduce the gluconeogenesis so that the glucose level within the body and the need for insulin are equally decreasing<sup>8,4</sup>.

The *C. caudatus* ethanol extract administered at the dosage of 400 mg/kg BW had a better effect in reducing the cholesterol level. The flavonoid compound was capable in reducing the cholesterol synthesis by hampering the activity of acyltransferase enzyme (ACAT) in HepG2 cells which reduce the cholesterol esterification in the intestines and liver, as well as inhibiting the 3-hydroxy-3-metil-glutaril-CoA enzyme activity, halting the cholesterol synthesis<sup>11</sup>. The saponin could form complex bound which isn't soluble with cholesterol from the food and bonded with the gall acid. The cholesterol within the LDL was carried by HDL towards the liver which then transformed into hydro cholesterol 7 $\alpha$ -. Dual bond reduction then occurred after which the hydroxylation turns into kenodeoksikolat and kolat acid. These compound then entered the small intestines as emulsifier to help digesting the fat and then secreted through the feces. The production of gall acid required cholesterol as its ingredient, and as the gall acid secretion increased, the total level of blood cholesterol would decrease. The tannin could halt the fat absorption within the intestines by reacting with mucosal protein and the intestines epithelium cells. The polyphenol compound worked by slowing down the absorption of trasilglicerole through the inhibition of pancreatic lipase, the increase of cholesterol excretion through the feces, the increase of LDL receptor within the liver, and the halt of apolipoprotein B100 secretion. The alkaloid compound could hamper the pancreatic lipase enzyme activity which increased the fat secretion through feces causing fat absorption by the liver so that it could not be transformed into cholesterol<sup>4</sup>.

Administering the *C. caudatus* ethanol extract at the dosage of 400 mg/kg BW had better effect in regenerating the pancreatic cells of the hypercholerterolemia-diabetic mice. This was due to the difference in gradual dosage administration, by which the active

compound within the *C. caudatus* ethanol extract would also be different at each dosage. This effect was attained by the content of *C. caudatus* extracts active compounds such as flavonoid, polyphenol, tannin, alkaloid and saponin. These compounds acted in regenerating the pancreatic beta cells, due to having antioxidant activity by capturing or neutralizing the free radicals bonded with the OH phenolic group, fixing the damaged tissue. This regeneration process was possible due to the increasing insulin production and GLUT 4 secretion stimulation was able to reach the muscular tissue, adipose and liver which enabled the reduction of malondialdehyde (MDA)<sup>3</sup>. This condition was supported by the natural antioxidant enzymes formed by the body which was the superoxide dismutase (SOD), catalase (CAT), Gluthathion peroxidase (GPx) acting in the first defense line against the free radicals by cleaning them, as detoxification H<sub>2</sub>O<sub>2</sub> and preventing the damage of macromolecule cells component<sup>2</sup>.

## 5. Conclusion

Based on the result of the research, it can be concluded that the *C. caudatus* extract has an effect in the reduction of blood glucose level, total level of the cholesterol as well as regenerating the pancreatic tissue of the hypercholesterolemic male white mice (*R. norvegicus*) which was inducted by streptozotocyn.

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