



## Effects of *Ganoderma lucidum* Extract on Diabetic Rats

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### Abstract

Diabetes mellitus (DM) is a metabolic syndrome which occurs when insulin is insufficiently produced or insulin cannot well serve its function. Diabetes is marked with increase in blood glucose level followed by increase in glycosylated hemoglobin level and decrease in insulin level. This research aims to examining the effect of *Ganoderma lucidum* extract on the blood glucose, insulin and glycosylated hemoglobin (HbA1c) level of diabetic white rat and determining the most effective dose of extract to be a diabetic agent. This research was experimentally conducted by employing Completely Randomized Design (CRD) with 6 treatments and 4 repetitions. The treatment groups consisted of healthy rats group (K1), rats with diabetes as negative control (K2), diabetic rats with the administration of metformin 45 mg/kg BW as the comparison (K3) and diabetic rats with the administration of *G. lucidum* extract with dose of 250, 500 and 1000 mg /kg BW (K4, K5 and K6 respectively). Blood glucose level examination was conducted after the alloxan induction with single dose of 125 mg/kg BW by intraperitoneal injection. The results show that mushroom *G. lucidum* extract administration with dose of 1000 mg/kg BW (K6) is the best dose to be an anti-diabetic agent. The benefit of the research is developing anti-diabetic agent from herbal resources.

### How to Cite

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## INTRODUCTION

Diabetes mellitus (DM) is a metabolic syndrome with 1-8% cases in the world. This disease occurs when insulin is insufficiently produced, or does not well serve its function. DM is marked with hyperglycemia which causes various microvascular or macrovascular complications (Brahmachari, 2011). DM is divided into type 1 DM (insulin dependent DM), which occurs because of damage to  $\beta$  cells of pancreas resulted in lifelong insulin dependency, and type 2 DM (non-insulin dependent DM), which occurs because of insulin resistance, lack of insulin production, or both of those conditions (Dipiro *et al.* 2011).

According to the International Diabetic Federation (IDF, 2015), the number of DM patients continue to increase, there were 415 million DM patients in 2015 and the number is estimated to keep increasing annually. The results of 2013 Basic Health Research showed that there were about 12,191,564 DM patients (Chugh, 2011). The 2015 data of the Health Service of Banyumas Regency identified 1,542 cases of DM type 1 and 563 cases of DM type 2. Diabetes may attack people of any age and of any social and economic background. Lifestyle changes influence the people's habits and diet. Diabetes is one of diseases in Indonesia which needs special attention, since its incidence and prevalence keep increasing (Soegondo *et al.* 2011). Various acute and chronic complications may attack DM patients because of oxidative stress resulted from hyperglycemia, in which steps of medication must be immediately performed in patients with complication.

Therapy for DM is classified into pharmacologic and non-pharmacologic therapies (Dipiro *et al.* 2011), both of which them aim at controlling blood glucose level and preventing any occurrence of complication. Non-pharmacologic therapy constitutes dieting and regular exercise. Pharmacologic therapy constitutes the administration of insulin and oral anti-diabetic medicine (Dipiro *et al.* 2011). DM treatment may be conducted using modern medicines and insulin injection, however, medical treatment is difficultly conducted because of its expensive cost. Diabetes mellitus may also be treated using natural medicine such as by utilizing the macroscopic mushroom with medicinal properties.

Mushroom has important potential, advantage and efficacy. Certain mushroom species have highly efficacious bioactive compound, such as *Ganoderma* (Khastini, 2018). The body of mushroom *Ganoderma lucidum* contains terpenoid, steroid, adenosine, polysaccharide, ergothi-

oneine, flavonoid, alkaloid, saponin, amino acid, mineral, and vitamin (Yue *et al.* 2008).

Terpenoid in *G. lucidum* serves to be antioxidant, in which *G. lucidum*'s hypoglycemic activity is related to increase in insulin hormone. This mushroom is expected to trigger insulin release, decrease blood glucose concentration in vivo and effectively decrease blood glucose level comparable to oral anti-diabetic medicine (Styskal *et al.* 2012). The pre-clinical study conducted by Mao *et al.* (2009) on *G. lucidum* extract administration on rat showed that rat became protected from serious kidney disease resulted from diabetes complication. Triterpenoid also plays the role of aldose reductase inhibitor and  $\alpha$ -glucosidase is useful to inhibit Reactive Oxygen Species (ROS) (Pietta, 2000). Other secondary metabolites like alkaloid, flavonoid, and saponin potentially serve to be anti-diabetic agent.

It is highly important to prove whether *G. lucidum* extract potentially serves to be anti-diabetic agent or not, thus it is also necessary to test it on alloxan-induced diabetic rat. Alloxan causes damage to the  $\beta$  cells of experimental animal's pancreas which then causes the DM.

## METHODS

This research used white rats (*Rattus norvegicus*) as the experimental animal, with criteria as follow: derived from one line (Wistar line), healthy (without any congenital abnormality and with normal random blood glucose level), male, 2-3 weeks old, 200 gram in weight, and had been acclimatized for 7 days before the treatment. The 30 rats were divided into 6 groups, each group consisted of 5 rats.

### *G. lucidum* Sample Preparation

Mushroom *G. lucidum* was randomly selected from 4-5 months old harvested mushrooms, cleaned from dirt, dried in oven at 50°C, and then grinded to produce the *G. lucidum* powder.

### *G. lucidum* Extract

500 g of powder was added into 1250 ml of ethanol 96% until the material was entirely submerged, stirred, and then left tightly closed for 24 hours.

The filtrate was then filtered for separation and stored as filtrate I. The remaining material was then re-filtered using ethanol 96% with the same technique until filtrates II and III were produced. They were then treated using vacuum Rotary Evaporator to remove the liquid, until viscous extract was produced.



**Figure 1.** *G. lucidum* fruitbody



**Figure 2.** Powder of *G. lucidum* (A); *G. lucidum* extract (B)

### Research Protocol

Random blood glucose level check-up was conducted before the treatment. On the first day, the experimental animal groups (excluding healthy control) were intraperitoneally induced with alloxan monohydrate with dose of 125 mg/kg body weight (BW) for one injection to induce DM. The rats' hyperglycemia was then rechecked on the third day. Blood sample was taken through orbital vena. If rat's blood glucose level > 200 mg/dl after 3 (three) days, then it positively had the diabetes. Rats with diabetes were randomly grouped into 6 groups (5 rats in each group). Healthy rats group (K1), rats with diabetes as negative control (K2), diabetic rats with the administration of metformin 45 mg/kg BW as the comparison (K3) and diabetic rats with the administration of *G. lucidum* extract with dose of 250, 500 and 1000 mg/kg BW (K4, K5 and K6 respectively). Stock of test solution were given to experimental animals with curative method for 14 days orally in the morning. Rats' blood sample were taken through orbital vena using capillary tube for blood glucose level, insulin level, and glycosylated hemoglobin (HbA1c) level examination on the fifteenth day after treatment.

### Data Analysis

Data from several tests were then analyzed using SPSS statistical program. Quantitative data were analyzed by one way ANOVA to determine

the effect of *G. lucidum* on blood glucose, insulin and HbA1c level after the treatment.

## RESULTS AND DISCUSSION

Blood glucose level was initially examined (pretest) on the third day after the administration of alloxan with single dose of 125 mg/kg BW. Examination was conducted after three days of induction since alloxan will react more effectively. According to Lenzen (2008), degranulation and loss of  $\beta$  cells of pancreas will be observable 12-48 hours after the induction. However, one more day will be necessary to observe significant increase of blood glucose level.

The increase of blood glucose level of groups K2, K3, K4, K5 and K6 were significantly differs from group K1 after the third day. According to Szkudelski, alloxan is a compound used for DM research by employing experimental animal. Alloxan inside the body enters through Glut-2 pathway until it reaches  $\beta$  cells of pancreas. Alloxan reacts with -SH group in  $\beta$  cells of pancreas resulted in glutathione peptide oxidation inside cells and the formation of dialuric acid which may produce free radicals in the form of hydrogen peroxide ( $H_2O_2$ ) and ROS.  $\beta$  cells of pancreas is sensitive to ROS since they have low antioxidant enzyme. ROS compound causes chain reaction of lipid peroxidation which causes damage to  $\beta$  cells of pancreas. This inhibits glycolysis process and ATP production will decrease. Moreover, insulin secretion was inhibited when ATP decreases. This condition causes decreasing insulin production in the body which causes diabetes condition as marked with hyperglycemia (Lenzen, 2008).

The blood glucose decreases upon *G. lucidum* administration. The posttest blood glucose level of treatment groups K3, K4, K5, and K6 showed a significant difference compared to the negative control (K2). *G. lucidum* extract administration with dose of 1000 mg/kg BW (K6) presented the lowest mean blood glucose level compared to the other groups, with  $140.50 \pm 36.71$  mg/dl and the highest blood glucose level decreasing percentage up to 63.49% (Table 1). The negative control group (K2) had its blood glucose level increasing, representing permanent damage to  $\beta$  cells of pancreas resulted from alloxan induction.

Mushroom *G. lucidum* extract and metformin administration decreases blood glucose level, and for the negative control (K2) the number shows a high increase of blood glucose level because of damage to  $\beta$  cells of pancreas resulted from alloxan induction. Rat's insulin level was

measured upon treatment. This research compared the insulin levels of treatment groups' and healthy rats. The mean insulin level after alloxan induction decreases compared to that of healthy control (K1) (Table 2). This shows that DM condition influences  $\beta$  cells of pancreas, thus insulin produced and secreted by  $\beta$  cells of pancreas decreases. The insulin level of rats with DM after 14 days of observation is presented in Table 2.

Table 2 shows the difference in the mean insulin level of treatment groups after *G. lucidum* extract administration for 14 days. The mean insulin level of group K2 shows the lowest insulin level compared to the group treated with metformin (K3) and *G. lucidum* extract. The mean insulin level of group K2 shows that insulin secreted by  $\beta$  cells of pancreas keeps decreasing since alloxan induction on the cells is still ongoing. Alloxan may influence  $\beta$  cells of pancreas since it produces free radicals resulted from alloxan reduction to dialuric acid (Okamoto *et al.* 2002). The increasing mean insulin level of metformin

group (K3) and *G. lucidum* extract groups (K4, K5, K6) shows that metformin and *G. lucidum* extract are able to inhibit alloxan effect on  $\beta$  cells of pancreas that their mean insulin level values are close to that of healthy control. The group of *G. lucidum* with dose of 1000 mg/kg BW (K6) has its insulin level close to that of the healthy control and is the most effective dose to increase insulin level. *G. lucidum* extract is able to inhibit the effect of free radicals generated by alloxan and influence insulin release from pancreas because of its role as antioxidant (Mohammed, 2007).

Insulin is normally produced by pancreas and in healthy condition, it is spontaneously produced when blood sugar gets high. On the contrary, in DM condition, pancreas does not well serve its function. The bioactive compound in mushroom *G. lucidum* is expected to be able to repair  $\beta$  cells of pancreas, thus  $\beta$  cells of pancreas will be able to produce insulin, and blood sugar level will decrease slowly.

HbA1c examination is one of important

**Table 1.** Blood Glucose Level Decreasing Percentage

| Treatment | Initial Glucose Level (mg/dl) |                 | End Glucose Level (mg/dl) |                  | Blood Glucose Level Decreasing Percentage (%) |                |
|-----------|-------------------------------|-----------------|---------------------------|------------------|---|----------------|
|           | Mean $\pm$ SD                 |                 | Mean $\pm$ SD             |                  | Mean $\pm$ SD                                 |                |
| K1        | 120.50                        | $\pm$ 11.561 a  | 104.00                    | $\pm$ 41.227 a   | -3.913  | $\pm$ 46.82 ab |
| K2        | 423.00                        | $\pm$ 114.83 c  | 576.75                    | $\pm$ 20.320 c   | -40.86  | $\pm$ 60.96 a  |
| K3        | 404.25                        | $\pm$ 108.17 bc | 281.50                    | $\pm$ 149.730 ab | 30.95   | $\pm$ 26.56 bc |
| K4        | 435.75                        | $\pm$ 13.351 c  | 312.00                    | $\pm$ 205.593 b  | 44.27   | $\pm$ 29.06 bc |
| K5        | 311.00                        | $\pm$ 15.535 b  | 203.50                    | $\pm$ 73.510 ab  | 34.95   | $\pm$ 21.19 bc |
| K6        | 384.25                        | $\pm$ 36.945 bc | 140.50                    | $\pm$ 36.711 ab  | 63.49   | $\pm$ 8.43 c   |

Explanation. Numbers followed by the same letter are not significantly different with significance level  $P < 0.05$

**Table 2.** Insulin level and Glycosylated Hemoglobin level (HbA1c) Examination Results

| Treatment | Insulin Level (%) |                   | Glycosylated Hemoglobin Level (HbA1c) (%) |                 |
|-----------|-------------------|-------------------|---|-----------------|
|           | Mean $\pm$ SD     |                   | Mean $\pm$ SD                             |                 |
| K1        | 7.47025           | $\pm$ 1.007258 c  | 5.4500                                    | $\pm$ 0.82664 a |
| K2        | 2.86275           | $\pm$ 0.169995 a  | 11.4500                                   | $\pm$ 2.41730 b |
| K3        | 4.61775           | $\pm$ 0.592475 ab | 7.3250                                    | $\pm$ 2.11877 a |
| K4        | 3.50625           | $\pm$ 0.596476 ab | 8.2250                                    | $\pm$ 2.51843 a |
| K5        | 3.85225           | $\pm$ 0.621951 ab | 7.2500                                    | $\pm$ 1.81200 a |
| K6        | 5.46450           | $\pm$ 3.099690 bc | 6.1250                                    | $\pm$ 0.85000 a |

Explanation. Numbers followed by the same letter are not significantly different with significance level  $P < 0.05$

blood check-ups to evaluate blood sugar control. Based on Figure 2, the HbA1c measurement results show that diabetic rats treated with dose of 1000 mg/kg BW *G. lucidum* has the best outcome compared to the other treatments, in which the HbA1c level value is close to the healthy control (HbA1c level will be declared as normal in value < 7%). HbA1c measurement may become a parameter for the capability of mushroom *G. lucidum* in producing anti-diabetic effect on diabetic rats. This is in line with the results of blood glucose and insulin level measurement. Some researches show close relationship between HbA1c concentration and mean blood glucose level (Begley, 2012; Sultanpur 2010).

*Ganoderma* contains bioactive compound which can synthesize glutathione (GSH). GSH is naturally found in almost all mammal tissues, particularly concentrated in their heart, and potentially serves to be antioxidant (Ratnaningtyas, 2018). Alloxan reduction into dialuric acid and ROS production lead to GSH decrease since alloxan binds -SH group from glutathione which cause decreasing glucokinase enzyme activity, thus inhibiting the glycolysis process. Mushroom *G. lucidum* is expected to contribute H<sup>+</sup> when GSH is inhibited by free radicals, thus glycolysis and phosphorylation processes will be reinitiated to produce ATP. The formed ATP molecules are needed to secrete insulin hormone in order to decrease blood glucose level. Flavonoid contained in *G. lucidum* is able to contribute H<sup>+</sup> (Pietta, 2000). According to Kalaras *et al.* (2017), the terpenoid content in mushroom *G. lucidum* in the form of ganoderic acid is able to strengthen flavonoid's work since it has the OH group. Flavonoid working mechanism in protecting body against the effect of free radicals is by neutralizing oxygen radical and protect cells from lipid peroxidation. Flavonoid is classified as antioxidant since it can catch free radicals by releasing hydrogen atom from its hydroxyl group (Fenglin *et al.* 2011).

Deficiency of incretin especially *glucagon-like-peptide 1* (GLP-1), may occur in DM condition (Sarker, 2015). GLP-1 hormone is an important component in glucose homeostasis maintaining mechanism in gastrointestinal. Incretin is a peptide hormone secreted by gastrointestinal after food is digested, which potentially increases insulin secretion through glucose stimulation. Incretin deficiency disturbs the balance of glucagon and insulin, that glucagon will increase when insulin decreases, consequently blood glucose level also increases (GLP-1 hormone serves to suppress DM).

Insulin production in  $\beta$  cells of pancreas is

also influenced by GLP-1 hormone. GLP-1 hormone will bind GLP-1 receptor in order to secrete insulin from  $\beta$  cells of pancreas. In normal condition, binding of GLP-1 and its receptor occurs very quickly since GLP-1 is immediately broken down by Dipeptidyl peptidase-4 (DPP-4) within 2 minutes, and DPP-4 enzyme is expressed to inactivate GLP-1. In diabetes condition, GLP-1 broken down by DPP-4 is accelerated, resulted in free radicals formation. GLP-1 also gets quickly degraded and cannot bind its receptor, thus insulin hormone cannot be secreted. GLP-1 hormone inactivation disturbs the balance of insulin and glucagon. The role of alkaloid of *G. lucidum* is expected to serve as DPP-4 inhibitor which activates GLP-1, thus GLP-1 in blood circulation will increase and able to rebinds its receptor. This will induce insulin synthesis and prevent the apoptosis as well as increase the sensitivity of  $\beta$  cells of pancreas, which will eventually increase glucose tolerance and improve insulin response.

The other secondary metabolite resulted from *G. lucidum* is saponin that contributes in rejuvenation of  $\beta$  cells of pancreas (Koneri, 2014). Saponin may enter into cell membrane to form more permeable structure. By this way, saponin may inhibit glucose absorption.

Mushroom *G. lucidum* also contains specific antioxidant known as ergothioneine. Ergothioneine is a natural amino acid which is a derivative of thiourea histidine. Ergothioneine in *G. lucidum* body extract is 0.08 mg/g (Lee *et al.* 2009). According to Kalaras (2017). Ergothioneine in some mushroom species, including *G. lucidum*, has the ability to improve GSH synthesis. Ergothioneine is expected to synergize with other bioactive compounds in mushrooms to increase natural antioxidant, which then releases free radical inhibitors.

The results showed that *G. lucidum* can increase insulin level as well as decrease blood glucose and glycosylate hemoglobin (HbA1c) level. The active compound of *G. lucidum* extract act as a natural antioxidant that can increase glutathione to release free radical barrier and increase insulin receptor sensitivity. This research result has benefit in developing the potency of local resources as herbal medicine and this study also provide great benefits for the development of mushroom cultivation industry.

## CONCLUSION

Mushroom *G. lucidum* extract administration may decrease blood glucose level, increase insulin level and decrease glycosylated hemoglobin (HbA1c) level. The dose of *G. lucidum* 1000

mg/kg BW is the most effective dose to decrease blood glucose level with decreasing percentage up to 63.49%, and is able to increase insulin level as well as decrease glycosylated hemoglobin level (HbA1c).

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