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Chicken drumstick mushroom (*Coprinus comatus*) ethanol extract exerts a hypoglycaemic effect in the *Rattus norvegicus* model of diabetes

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ABSTRACT

Coprinus comatus has hypoglycaemic and antioxidant activity, and thus also potential for the treatment of diabetes mellitus (DM). The treatment of DM is prolonged and costly and long-term use of the currently available therapeutics carries a risk of development of side effects. This creates an opportunity for application of traditional medicine. The ideal therapy for DM would not only have an anti-hyperglycaemic effect, but would also enhance antioxidant defences. *C. comatus* contains ergothioneine, a thiol with antioxidant activity.

We assayed the effect of a *C. comatus* ethanol extract on the blood glucose, glycosylated haemoglobin, superoxide dismutase, and plasma insulin levels of male Wistar rats (*Rattus norvegicus*) with alloxan-induced DM, and performed a dose-response analysis. This study used a completely randomised design and a post-test approach, and included a control group.

The *C. comatus* ethanol extract reduced the blood glucose, MDA, and HbA1c levels and increased the plasma insulin level. The 500 mg/kg body weight dose exhibited the greatest efficacy, as it reduced the blood glucose level by 12.33%, HbA1c level by 6.35%, MDA level by 32.6%, and SOD and plasma insulin levels by 10.57%.

1. Introduction

The edible mushroom *Coprinus comatus* is also known as chicken drumstick mushroom, shaggy ink cap, lawyer's wig, shaggy mane and, in Indonesia, as *jamur paha ayam*. Li et al. (2010) reported that a 96% ethanol extract of *C. comatus* fruiting body comprised 4.1% fat, 11.4% phenols, 47.8% polysaccharides, 19.9% protein, 0.6% amino acids, 3.9% nucleic acids, and 7.2% fibre. *C. comatus* has potential as a source of therapeutic agents, in addition to its delicious taste and high level of nutrients (Dai et al., 2009). Also, *C. comatus* has hypoglycaemic (Bailey et al., 1984) and antioxidant (Tsai et al., 2006) activity, and thus shows potential for the treatment of diabetes mellitus (DM).

Worldwide, around 347 million people have DM (Organization, 2006) and more than 80% of deaths due to DM occur in developing countries. Indonesia is the fourth most populous nation in the world (Badawi, 2009), and has around 8.6 million people with DM; this is expected to increase to 21.2 million by 2030 (Wild et al., 2004). Overall, DM is a serious health issue worldwide and must be addressed.

Hyperglycaemia is a major symptom of DM. Reactive oxygen species (ROS) cause lipid peroxidation and membrane damage and are involved in the secondary complications of DM, such as cataracts, neuropathy, and nephropathy. Pancreatic β cells contain relatively low levels of antioxidants, and are thus sensitive to ROS (Grankvist et al., 1981). Antioxidants protect β cells from oxidation by inhibiting lipid peroxidation, and so are important in DM. Liu et al. (2013) reported that *C. comatus* polysaccharide fragments at 1000 mg/kg body weight (BW) significantly reduced the blood glucose level in white rats, whereas *C. comatus* polysaccharide powder at 500 mg/kg BW did not. Therefore, the hypoglycaemic effect of *C. comatus* is not mediated by high-molecular-weight polysaccharides.

We evaluated the hypoglycaemic effect of an ethanol extract of *C. comatus* fruiting bodies by assaying the blood glucose and glycosylated haemoglobin (HbA1c) levels, and the plasma insulin level, of *Rattus novergicus* with alloxan-induced DM.

2. Methods

C. comatus mushrooms were obtained from C.V. Asa Agro Corporation (Cianjur, Indonesia). We used a glucose meter (Gluco Dr.; All Medicus Co., Gyeonggi-do, Korea), insulin enzyme-linked

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immunoassay (ELISA) kit (BT Laboratories, Ipswich, UK), and an HbA1c kit (BioHermes, Beijing, China) in this study, which was conducted in the Faculty of Health Sciences, Department of Pharmacy, Jenderal Soedirman University from February to April 2018. The study used a completely randomised design, a post-test approach, and included a control group.

2.1. Preparation of *C. comatus* ethanol extract and identification of phytochemicals

The *C. comatus* extract was produced by maceration. The mushrooms were cut and dried in an oven at 40–45 °C for 18 h and blended, and 200 g was macerated in ethanol for 2[illegible] in darkness. The macerate was filtered and stored in a clean bottle. The pulp was re-macerated in 96% ethanol using the same procedure. The macerates were combined and concentrated in a rotary evaporator at 40 °C until a thick ethanol extract was obtained. The contents of flavonoids, triterpenoids, saponins, and alkaloids were determined by (Harborne, 1984).

2.2. Animal procedures

The rats were acclimatised to the laboratory conditions for 7 days and fasted for 10–12 h. Next, the rats were intraperitoneally administered alloxan at 200 mg/kg BW in 0.9% NaCl. Following alloxan administration, the rats had access to food and drinking water *ad libitum*. The glucose level in blood obtained from the tail vein was measured on day 3. Rats with a blood glucose level of ≥ 200 mg/dL were classified as hyperglycaemic (Kim et al., 2006).

2.3. Treatments

The rats were divided into four treatment groups and administered the *C. comatus* extract according to Liu et al. (2013): P1 (500 mg/kg BW), P2 (750 mg/kg BW), P3 (1000 mg/kg BW), and KP (positive control; induce by alloxan and treated metformin 45 mg/kg BW), KS (healty control is not induce by alloxan and *C. comatus);* by oral gavage for 14 days. Blood was sampled on day 15 through tby he retro-orbital vein for assay of blood glucose, HbA1c, and superoxide dismutase (SOD) levels, and the plasma insulin level. The data were analysed using SPSS software.

3. Results and discussion

3.1. Extraction and analysis of phytochemical content of the *C. comatus* ethanol extract

Extraction by maceration of 200 g of dried simplicia of *C. comatus* produced 31 g of extract, for a yield of 15.5%. The results of phytochemical screening are shown in Table 1.

3.2. Blood glucose level

The mean blood glucose level of the KS group was 120.50 mg/dL, and that of the KP group was 331.25–423.00 mg/dL. Thus, alloxan increased the blood glucose level. The mean pre- and post-test blood glucose levels are listed in Table 2.

Table 1
Results of the phytochemical screening.

No	Phytochemistry compoud	Reagent	Result
1.	Flavonoid	Mg + HCl + amil alkohol	Red
2.	Triterpenoid	H_2SO_4, CH_3COOH anhidrat	Purple-Black
3.	Alkaloid	Dagendrof	Yellow-Brown
4.	Saponin	Aquadest	Foam

Table 2
Mean pre- and post-test blood glucose levels.

Group	Blood glucose	
	Pre-test	Post-test
	Mean ± SD	Mean ± SD
KS	120.5 ± 11.56 a	121.5 ± 41.23 a
KN	423 ± 114.83 b	576.75 ± 20.32 c
KP	404.25 ± 108.17 b	281.5 ± 149.73 b
P1	331.25 ± 100.57 b	274,75 ± 21.96 b
P2	405.25 ± 87.99 b	189 ± 113.92 ab
P3	344.5 ± 115.81 b	290.5 ± 100.43 b

Note: Lines followed by the same letter do not differ significantly at $p < 0.05$. KS = healthy control; KN = negative control (alloxan 200 mg/kg BW); KP = positive control (metformin 45 mg/kg BW); P1 = *Cc* 500 mg/kg BW; P2 = *Cc* 750 mg/kg BW; P3 = *Cc* 1000 mg/kg BW.

The mean blood glucose level in the KS group before and after treatment was 120.5 ± 11.56 and 121.5 ± 41.23 mg/dL, respectively, thus showing greater stability compared to the other groups. Therefore, the changes in blood glucose levels were due to the treatment administered, and not to environmental factors.

The average decrease in blood glucose level in the KN group was −47.25% (Table 3), suggesting persistent impairment of glucose homeostasis and DM. This was likely due to the effect of alloxan on pancreatic β cells and reduced insulin receptor sensitivity. The decrease in blood glucose level in the KP, P1, P2, and P3 groups shows that metformin and the *C. comatus* extract are capable of modulating glucose homeostasis in the presence of DM.

Administration of metformin or the *C. comatus* extract reduced the blood glucose level in DM rats. This suggests that these agents restore the alloxan-mediated impaired glucose homeostasis, although they do not restore the blood glucose level to within the normal range.

The P2 group exhibited the greatest decrease in blood glucose level, of 50.05% (Table 2). The blood glucose level in the P2 group was 31.03% lower than that in the KP group.

3.3. Glycosylated haemoglobin level

The HbA1c data indicated that total amount of haemoglobin binds with erythrocyte. The mean HbA1c level (Table 4) in the P1 and P2 groups was 6.35% and 5.93%, respectively; this was similar to that in the KS group (5.45%). The KP and P3 groups had a mean HbA1c level of 7.32% and 7.60%, respectively, higher than that of the KN group and indicating moderate DM control (6.1–8.0%). The KN group had the highest HbA1c level (11.45%), indicating uncontrolled/poor DM (> 8%). According to Kusnandar (1983), overall DM control is indicated by an HbA1c level ≤ 7% of total Hb. Therefore, the

Table 3
Mean percentage decreases in blood glucose level.

Group	% Decrease in blood glucose level
	Mean ± SD
KS	12.91 ± 17.53 b
KN	−47.25 ± 54.45 a
KP	31.03 ± 26.64 b
P1	12.33 ± 22.89 b
P2	50.05 ± 34.96 b
P3	8.31 ± 41.46 b

Note: Lines followed by the same letter do not differ significantly at $p < 0.05$. KS = healthy control; KN = negative control (alloxan 200 mg/kg BW); KP = positive control (metformin 45 mg/kg BW); P1 = *Cc* 500 mg/kg BW; P2 = *Cc* 750 mg/kg BW; P3 = *Cc* 1000 mg/kg BW.

Table 4
Post-test (day 15) HbA1c levels.

Group	HbA1c level
	Mean ± SD
KS	5.45 ± 0.83 a
KN	11.45 ± 2.42 b
KP	7.33 ± 2.12 a
P1	6.35 ± 0.87 a
P2	5.93 ± 1.45 a
P3	7.60 ± 1.43 a

Note: Lines followed by the same letter do not differ significantly at $p < 0.05$. KS = healthy control; KN = negative control (alloxan 200 mg/kg BW); KP = positive control (metformin 45 mg/kg BW); P1 = *Cc* 500 mg/kg BW; P2 = *Cc* 750 mg/kg BW; P3 = *Cc* 1000 mg/kg BW.

administration of metformin and 1000 mg/kg BW *C. comatus* extract reduced the HbA1c level, albeit not to within the normal range (< 7%).

The P2 group (750 mg/kg BW) had a mean HbA1c level of 5.925%, which was similar to that of the KS group (5.45%). Indeed, the P2 group also exhibited the greatest decrease in blood glucose level. These results are in agreement with the findings of (Han et al., 2006), who reported that rats given *C. comatus* rich in vanadium (CCRV) extract had an HbA1c level of 7.9%.

The HbA1c level differed significantly between the KN group and the P1, P2, P3, KS, and KP groups. Therefore, under normal conditions, the *C. comatus* extract maintains the HbA1c level. However, the Hb1Ac level did not differ significantly among the P1, P2, P3, KS, and KP groups. Therefore, administration of the *C. comatus* extract at 500 mg/kg BW reduced the HbA1c level to within the normal range (≤ 7%).

3.4. SOD level

Enzymatic antioxidants include SOD, glutathione peroxidase (GPx) and catalase; and non-enzymatic antioxidants include vitamin E (tocopherol), vitamin C, and flavonoids. SOD is an endogenous antioxidant that clears free radicals (Chang et al., 1988), against which it represents the first line of defence (Alvarez et al., 1987; Wahyuningsih, 2016). The pancreas contains the lowest level of SOD among all organs. SOD activity is decreased by alloxan and lipid-peroxidation products (Winarsi et al., 2012).

The blood SOD level on day 6 differed among all of the groups in this study (Table 5), among the P1, P2, and P3 groups ($p < 0.05$). The blood SOD level in the P1, P2, and P3 groups was similar to that in the KS group. This normal rat SOD level, ranging 5.49 ± 1.52 U.mL^{-1} (Astuti, 2016). According to (Moawad, 2007), normal rats have a mean blood SOD level of 70.50 ± 2.16 U.mL^{-1}. In this study, the KN group had the lowest SOD level, likely due to oxidative stress. The *C. comatus* extract increased the SOD level, which was restored to within the normal range by 500 mg/kg $^{-1}$ BW/day extract. The extract-induced increase in the SOD level was likely due to its contents of Cu and Zn, which are cofactors for endogenous SODs, such as CuSOD and CuZnSOD.

C. comatus contains ergothioneine, a glutathione (GSH) precursor. Supplementation with *C. comatus* protects the rat pancreas. Alloxan increases the levels of free radicals, resulting in lipid peroxidase-mediated damage to pancreatic β cells. According to Wu et al. (2004), ergothioneine modulates GSH homeostasis. GSH is the substrate for GPx, which can convert H_2O_2 to H_2O and O_2.

3.5. MDA level

The ability of *C. comatus* as an antioxidant other than based on SOD data is also supported by MDA level examination data. Giving alloxan can increase the level of malondialdehyde (MDA), which the end result of lipid peroxidation. MDA is a parameter that shows the amount of free radicals that enter the body of a rat. Alloxan and glucose are hydrophilic, so they cannot penetrate the bilayer lipids from the plasma membrane. Alloxan is structurally very similar to glucose transport (GLUT2) in the pancreatic beta cell plasma. Alloxan has a redox reaction produce Reactive Oxygen Species (ROS). Increased ROS causes depolarization beta cell membrane and increased Ca^{2+}, so that cytosol activates enzymes such as SOD which causes damage to pancreatic beta cells due to lipid peroxidation. This is indicated by the increase in MDA levels (Lenzen, 2008). Administrating *C. comatus* can reduce MDA levels. This shows that *C. comatus* has the ability as an ROS free radical catcher, so that it has the potential as an antioxidant. Ethanol extract dose 500 mg/kg BW was sufficient enough in reducing MDA level (< 1 nmol.mL^{-1}). MDA data (Table 6) supports SOD activity as an antioxidant.

3.6. Plasma insulin level

The mean plasma insulin level in the KN group was 2.86%, lower than that of the KP (4.26%) and P1–3 groups (10.50–10.76%) (Table 7). Therefore, insulin secretion from pancreatic β cells in rats in the KN group continued to decline due to the effect of alloxan. The increase in the mean plasma insulin level in the KP, P1, P2, and P3 groups suggests that metformin and the *C. comatus* extract inhibited the effect of alloxan on pancreatic β cells and increased their insulin secretion.

The *C. comatus* extract significantly increased ($p < 0.05$) the plasma insulin level. This indicates that the *C. comatus* extract inhibits the effect of alloxan on free-radical levels. Thus, the *C. comatus* extract may restore the disrupted glucose homeostasis in patients with type 2 DM by reducing the blood glucose level and increasing the plasma insulin level.

Ergothioneine acts together with other antioxidants to protect against oxidative stress in mitochondria (Paul and Snyder, 2010), and is responsible for maintaining the GSH level. Therefore, the increase in the plasma insulin level was due not to increased insulin secretion by

Table 5
SOD levels on day 15.

No.	Treatment	Blood SOD level on day 15 (U.mL^{-1})
1.	KN	29.17 ± 1.00^{a}
2.	KP	33.05 ± 2.27^{ab}
3.	P3	37.28 ± 2.60^{bc}
4.	P2	38.32 ± 4.88^{bc}
5.	P1	40.56 ± 7.04^{c}
6.	KS	48.85 ± 4.03^{d}

Note: Lines followed by the same letter do not differ significantly at $p < 0.05$. KS = healthy control; KN = negative control (alloxan 200 mg/kg BW); KP = positive control (metformin 45 mg/kg BW); P1 = *Cc* 500 mg/kg BW; P2 = *Cc* 750 mg/kg BW; P3 = *Cc* 1000 mg/kg BW.

Table 6
MDA levels on day 15.

No.	Treatment	MDA level on day 15 (nmol.mL^{-1})
1.	KN	1.38 ± 0.34^{c}
2.	KP	0.89 ± 0.41^{ab}
3.	P3	0.82 ± 0.22^{a}
4.	P2	0.86 ± 0.39^{a}
5.	P1	0.93 ± 0.40^{ab}
6.	KS	0.72 ± 0.35^{d}

Note: Lines followed by the same letter do not differ significantly at $p < 0.05$. KS = healthy control; KN = negative control (alloxan 200 mg/kg BW); KP = positive control (metformin 45 mg/kg BW); P1 = *Cc* 500 mg/kg BW; P2 = *Cc* 750 mg/kg BW; P3 = *Cc* 1000 mg/kg BW.

Table 7
Post-test (day 15) plasma insulin levels.

Group	Plasma insulin level
	Mean ± SD
KS	7.47 ± 1.01 a
KN	2.86 ± 0.17 d
KP	4.62 ± 0.59 b
P1	10.57 ± 1.07 c
P2	10.76 ± 1.32 c
P3	10.50 ± 1.64 c

Note: Lines followed by the same letter do not differ significantly at $p < 0.05$. KS = healthy control; KN = negative control (alloxan 200 mg/kg BW); KP = positive control (metformin 45 mg/kg BW); P1 = *Cc* dose 500 mg/kg BW; P2 = *Cc* dose 750 mg/kg BW; P3 = *Cc* dose 1000 mg/kg BW.

pancreatic β cells, but to the antioxidant activity of the *C. comatus* extract, which inhibits the effect of alloxan on free-radical levels.

The plasma insulin level differed significantly among the KS, KN, and KP groups, but was similar among the P1, P2, and P3 groups. Thus, all tested extract doses increased the plasma insulin level. Indeed, administration of the *C. comatus* extract resulted in a mean insulin level of 10.50–10.76%, suggesting induction of hyperinsulinemia (plasma insulin level > 7%).

In our next study, we plan to assess the effect of the extract on pancreatic β cells and the activities of other endogenous antioxidants, such as GPx and catalase. Novelty of this research were the fungus used in this study was *C. comatus* native Indonesian isolates from CV Asa Agro Corporation, Cianjur, West Java which had advantages compared to other strains. Usually *C. comatus* grows well in agricultural and plantation waste, rice straw, corn beetle and cotton waste; while the strain used is good for growing in forestry waste, namely sawdust. In addition, the size of the mushroom fruit body is smaller than the other strains, with average a size of 8–12 cm high and 2–3 cm thick.

4. Conclusion

A *C. comatus* ethanol extract reduced blood glucose, MDA, and HbA1c levels in rat, and increased the SOD and plasma insulin levels. An extract dose of 500 mg/kg BW showed the greatest efficacy in terms of reducing the blood glucose, MDA, and HbA1c levels and increasing the SOD and plasma insulin levels.

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