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Effects of powdered young coconut drinks on blood glucose and body weight of diabetic rats

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Abstract

This study aimed to evaluate the effects of powdered young coconut drinks (PYCD) on blood glucose and body weight of diabetic rats model induced with different injection methods and STZ doses. This experimental study examined 18 adult *Sprague Dawley* male rats (250-300 g), divided into three groups: normal control (NC), single intraperitoneal injection STZ 55 mg/kg (SII 55), and multiple intraperitoneal injections STZ 50 mg/kg (MII 50). Diabetics rats with a fasting blood glucose (FBG) level of >200 mg/dL were confirmed 3 days after the STZ injection. The MII 50 functioned as the selected group and was administered with 3500 mg/kg of PYCD in a solid form made from the mixture of coconut water and meat from a hybrid variety using the freeze-drying technology and 0.6 mg/kg of glibenclamide as a standard drug in diabetes mellitus for 45 days. Then, the FBG and body weight were determined. The FBG level of the diabetic group significantly increases ($p<0.05$) unlike that of the NC rats. The result also reveals that MII 50 with a high percentage of animals surviving (100%) is safer than SII 55 with a low surviving rate (50%). The 3500 mg/kg PYCD administration in the solid form has significantly decreased the FBG level and improved the body weight of MII 50 diabetic rats ($p<0.05$). This study concludes that PYCD 3500 mg/kg has a hypoglycemic effect and could maintain the body weight of selected diabetic rats.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic disorders or metabolic syndromes with a high level of morbidity and mortality. Genetic and environmental variables result in complex and progressive issues with varying degrees of insulin resistance and pancreatic β-cell dysfunction (Stumvoll *et al*., 2005). Once β-cells are no longer sufficient to secret insulin that overcomes insulin resistance, deteriorated glucose tolerance or hyperglycemia progresses to type 2 diabetes (T2DM) will occur (Stumvoll *et al*., 2005; Skyler *et al*., 2017). Signs and symptom frequently found in DM conditions are weight loss. Weight loss is an essential parameter in managing DM since weight loss is associated with decreased adipose and muscle tissue (lipid and protein catabolism) for energy production due to frequent urinary output, and excessive glycogen, and glucose conversion (Ene *et al*., 2008).

Several animal models have been produced to research diabetes and test antidiabetic drugs. To produce type 1 diabetes mellitus (T1DM) and T2DM, these models include surgical manipulations (pancreatectomy), diet/nutrient-induced diabetes in animals, and genetic manipulations (spontaneous and transgenic/knockout diabetic animals) in diverse animal species (King, 2012). Furthermore, a diabetogenic agent, such as streptozotocin (STZ), is the most frequent approach that causes diabetes in animals through its pancreatic β-cells toxicity (Lenzen, 2008; Ardiana *et al*., 2018; Gad-Elkareem *et al*., 2019) by triggering random, fast, and permanent necrosis of pancreatic β cells (Szkudelski, 2001). STZ has also been discovered to make peripheral insulin resistant or decrease insulin production in these cells. Such impacts on animals are frequently sufficient to cause noninsulin-dependent diabetes mellitus or T2DM in animals (Szkudelski, 2001). STZ can cause various diabetes symptoms, ranging from moderate to severe ones depending on doses, animal strains, age, route of administration, and injection format (Junod *et al*., 1969; Sakata *et al*., 2012).

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The STZ doses can be injected once or multiply (Furman, 2021). The total of pancreatic-cell necrosis and DM can be created by a single high-dose injection within 48 hrs. The multiple injections can harm some pancreatic cells, trigger an inflammatory response, reduce pancreatic cell function, and lead to insulin insufficiency and hyperglycemia (Furman, 2021). However, multiple injections can harm the pancreas up to 85% (King and Austin, 2017). Thus, multiple STZ injections have fewer harmful consequences than a single high-dose injection with extremely high blood glucose concentrations (Furman, 2021). A single intravenous STZ dose of 55 mg/kg body weight or 60 mg/kg body weight is used to generate T2DM in adult rats (Ardiana *et al*., 2018; Gad-Elkareem *et al*., 2019). The STZ with a larger dose at the birth of 100 mg/kg body weight can also be utilized to create DMT1 mice (Portha *et al*., 1974). As a result, the researchers adjusted their STZ-induced diabetes methods to the specific needs of each study.

Recently, natural nutritious plants, such as *Lannea edulis* (Banda *et al*., 2018), *Dendrophthoe pentandra* (Hasan *et al*., 2018), *Ricinus communis* (Gad-Elkareem *et al*., 2019), *Camellia sinensis* (Ardiana *et al*., 2018), and *Cocos nucifera* (Pinto *et al*., 2015) have been focused on preventing and managing T2DM. *Cocos nucifera* or coconut contains an appropriate quantity of minerals, sugars, amino acids, protein, fatty acids, vitamins, and phenolic acids (Preetha *et al*., 2012; Bhagya *et al*., 2012; Geetha *et al*., 2016; Mahayothee *et al*., 2016). The macronutrients and micronutrients of coconut water are reported to bring hypolipidemic, cardioprotective, and hepatoprotective effects (Prathapan and Rajamohan, 2011) and improve DM conditions due to arginine content (Bhagya *et al*., 2012; Preetha *et al*., 2013). Arginine improves insulin production and sensitivity which have a beneficial effect on DM conditions (Newsholme *et al*., 2006; Hu *et al*., 2017).

Coconuts' composition and health benefits have gained much attention. Unfortunately, coconut water and flesh are highly perishable and should be processed in various methods, such as freeze-drying, to prolong their shelf life and maintain their compositions (Azra *et al*., 2021) and health effects. Previous studies only examined mature coconut water processed by freeze-drying technology to reveal the effects of coconut water on DM conditions (Preetha *et al*., 2012, 2013). This study utilized a new product namely powdered young coconut drink (PYCD) from the mixture of young coconut water and coconut flesh processed by freeze-drying technology previously reported by (Azra *et al*., 2021). Consequently, the goal of this study was to evaluate the effects of PYCD on blood glucose and body weight of STZ-induced diabetic *Sprague Dawley* rats.

2. Materials and methods

2.1 Design, location, and time

This study employed a completely randomized experimental design. This research was conducted from October 2020 to March 2021. PYCD was developed in the Department of Community Nutrition Laboratory and Department of Livestock Technology Laboratory, IPB University, Indonesia. Meanwhile, the assessment of the animal study was conducted at the Veterinary Medical Teaching Hospital, Faculty of Veterinary Medicine, IPB University, Indonesia. All animals in this study were handled and given human care by laboratory animal care guidelines. All protocols for the investigation were approved by the Institute for Research and Community Services, IPB University, No. 184-2020 IPB.

2.2 Materials and tools

A total of 18 adult male *Sprague-Dawley* rats aged 3 -4 months and weighing 250-300 g were acquired from the Non-Ruminants and Animals Laboratory of Hope, Faculty of Animal Science, IPB University, Indonesia. These rats did not receive previous pharmacological treatment. The STZ was purchased from Sigma-Aldrich (Germany). Glibenclamide (5 mg tablet) was obtained from a local pharmacy and was dissolved in distilled water for oral administration. The PYCD was made from a mixture of hybrid coconut water and meat with a maturity age of 6 months from the farm of PT Perkebunan Nusantara (PTPN) VIII of Indonesia using freeze-drying technology (Azra *et al*., 2021).

2.3 Animal care and acclimatization

The rats were housed in individual cages and acclimatized for 14 days in the Veterinary Medical Teaching Hospital of IPB University. They were kept in typical animal house conditions, including a temperature of 26±3°C, relative humidity of 50-60%, as well as 12 hrs of the light-dark cycle (Gad-Elkareem *et al*., 2019). The animals were fed a restricted standard pellet diet (20 g) and had free access to drinking water.

2.4 Selection of STZ dose

For the STZ selection dose, 18 rats were randomly divided into three groups; each group consisted of six rats as required by the resource equation method (Charan and Kantharia, 2013). Group I which consisted of animals did not receive treatment, was kept under the same laboratory conditions, and was regarded as the normal control group (NC). Group II was a diabetic group receiving a single intraperitoneal injection of 55 mg STZ/kg body weight (SII 55). Group III was a diabetic group receiving STZ 50 mg STZ/kg body weight for two consecutive days with multiple

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intraperitoneal injections (MII 50). SII 55 was adopted from a previous study (Gad-Elkareem *et al*., 2019). Meanwhile, the MII 50 was another modified format used to reduce the mortality rate of rats for two consecutive days.

Diabetic induction was prepared by intraperitoneal injections of 55 and 50 mg/kg STZ, which was freshly dissolved in cold citrate buffer solutions of 0.1 M, pH 4.5, and 1 mL (Delli Pizzi *et al*., 2012; Gad-Elkareem *et al*., 2019). An hour after the STZ induction, the animals were orally given 5% (wt/vol) of glucose solution for 12 hrs to prevent hypoglycemia. The fasting blood glucose (FBG) level was estimated before the STZ injection and monitored at the 48th hr and the 72th hr to confirm the DM status. The rats with FBG levels were greater than the 200 mg/dL of diabetic animals; thus, they were included in the study (Banda *et al*., 2018; Barragán-Bonilla *et al*., 2019; Gad-Elkareem *et al*., 2019).

2.5 Selection of powdered young coconut drinks forms and dosages

PYCD was made into four forms with three doses each. Forms 1, 2 and 3 were prepared as a suspension in 2 mL of distilled water, carboxymethyl cellulose (CMC) 0.25%, and CMC 0.5%. Meanwhile, form 4 was served in solid forms. The PYCD doses of each form were 1750 mg/kg, 3500 mg/kg and 7000 mg/kg of body weight. The physical characteristics of PYCD forms, such as texture, solubility and oral convenience, were observed.

2.6 Determination of the effects of powdered young coconut drinks on diabetic rats

After selecting the STZ dose, further experiments were carried out in a diabetic group with a low mortality rate. The selected diabetic group was given a PYCD dose of 3500 mg/kg from the selected form due to the arginine content, which was expected to bring the same effects on DM, as occurring in the previous study (Preetha *et al*., 2013). Moreover, the selected diabetic group received the standard glibenclamide drug with a dose of 0.6 mg/kg dissolved in distilled water via an intragastric tube every morning for 45 days. The PYCD and glibenclamide were administered to three rats in each treatment.

In the one-week interval for 45 days of treatment, all animals from NC and the selected diabetic groups fasted overnight. Moreover, water was not restricted to collect FBG, which was determined from tail blood with a portable glucometer (Accu-Chek Active; Roche, USA). The rats' body weights were measured with a digital balance from the beginning of the experiment and once a week. Body weights were measured simultaneously in the morning (Al-Attar and Alsalmi, 2019).

2.7 Data analysis

Statistical analysis was determined as the mean value ± standard error (SE). The data were analyzed with one-way ANOVA followed by Duncan's multiple range test and t-test. The confidence level was set at 95%. Finally, the data were analyzed using SPSS 21 software.

3. Results and discussion

3.1 Selection of STZ dose

In the first (Day 0) of the FBG level measurement, all of the rat groups had an average FBG level (< 126 mg/dL) without significant differences ($p>0.05$). Thus, all of the acclimatized rats could be involved in the study. The following (Day 3) measurement shows that SII 55 and MII 50 have significantly increased ($p<0.05$) in the FBG level (nearly 3-fold) and biochemically developed a sign of DM as the FBG level of>200 mg/dL. This study indicates that SII 55 and MII 50 can become the groups of rat models of DM. However, after a single injection of 55 mg/kg of STZ had been induced in six rats, the mortality rose (50%) during the three-day treatment and after the STZ administration. In contrast, six rats with multiple injections of 50 mg/kg STZ for two consecutive days have a high survival percentage of 100%. The FBG level of the subjects is presented in Table 1.

Many studies have employed multiple or continuous low-dose injections. The advantage of a single injection is convenience. However, the diabetic model created by this procedure has an unstable diabetic status, and unexpected mortality occurs in around 10–20% of the animals due to the increasing blood glucose and STZ toxicity (Ventura-Sobrevilla *et al*., 2011). On the other hand, multiple injection procedures can achieve hyperglycemia with no or few deaths (Ventura-Sobrevilla *et al*., 2011). In terms of safety, the multiple injection procedures are superior to the single injection model (Sakata *et al*., 2012).

The STZ is a chemical specifically toxic to pancreatic cells. The damage of STZ leads to irreversible cell malfunctions. The STZ has decreased the cell mass of diabetic rats, lowered their pancreatic insulin reserves, impaired insulin secretion in response to glucose stimulation, and increased blood glucose levels (Rossetti *et al*., 1990).

The present study also aims to observe the effects of STZ-induced diabetes and find an association between the reduction in weight in animals. Thus, the body weights of rats in the three groups were monitored during the experimental period. Table 1 shows that the three groups do not have any differences before and after

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Table 1. Effects of STZ doses on FBG levels and body weight of rats

Group	FBG (mg/dL)		Body weight (g)		Mortality rate (%)
	Day 0	Day 3	Day 0	Day 3	
NC	101.6±5.95^{Aa}	106.40±1.4^{Ba}	265.80±11.68^{Aa}	266.40±10.56^{Aa}	0
SII 55	87.60±7.46^{Aa}	374.00±19.47^{Bb}	272.60±6.42^{Aa}	229.00±6.55^{Aa}	50
MII 50	101.2±2.65^{Aa}	303.60±33.76^{Bb}	267.20±17.58^{Aa}	261.20±8.83^{Aa}	0

Values are presented as mean±SD. Values with uppercase superscripts within the same row are statistically significantly different ($p<0.05$) while values with lowercase superscripts within the same column are statistically significantly different ($p<0.05$). NC: normal control, SII: single intraperitoneal injections at 55 STZ dosage, MII 50: multiple intraperitoneal injection at 50 STZ dosage.

3 days (72 hrs) of the STZ injection ($p>0.05$). This result indicates that catabolic metabolism does not persistently cause significant declines in body weight until a three-day injection. This finding agrees with studies demonstrating that STZ causes significant weight loss in rats after 15 days and one-week injections (Cheng *et al*., 2013; Nagarchi *et al*., 2015).

3.2 Selection of powdered young coconut drinks forms and doses

The number of doses in this study (3500 mg/kg PYCD) is expected to bring the same effect as that in the previous study (1000 mg/kg mature coconut water) to improve DM metabolism by considering the arginine content (Preetha *et al*., 2013). The 9.8-11.53 mg of arginine content of PYCD that is administered to 250-300 g of body weight rats is almost equal to 9.36-11.12 mg of mature coconut water. Then, the PYCD dose was split into three dose levels 1750 mg/kg, 3500 mg/kg and 7000 mg/kg. Four PYCD forms are presented in Figure 1.

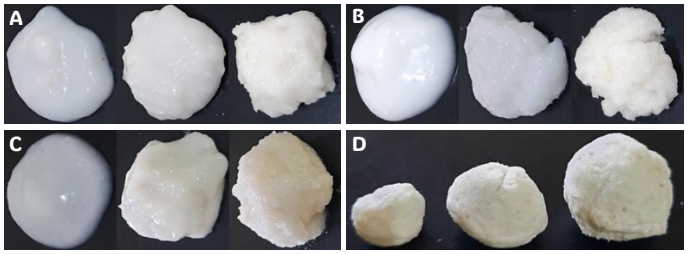

Figure 1.Appearance of PYCD: (A) dissolved in distilled water, (B) dissolved in CMC 0.25%, (C) dissolved in CMC 0.5%, (D) solid form; doses set at (from left to right) 1750 mg/kg, 3500 mg/kg and 7000 mg/kg

It is essential to select an appropriate PYCD form and dose because it will impact the rat's adherence to oral medication and create the safety and efficacy of the intervention products. The PYCD acceptability was compared between liquid forms (dissolved with 2 mL of distilled water, CMC 0.25%, and CMC 0.5%) by gastric gavage route and solid form by oral route. The liquid form needs several additive materials, such as a vehicle. This study used water and CMC as vehicles without any therapeutic and toxic effects (Bampidis *et al*., 2020).

This study has revealed that only the lower dose (1750 mg/kg) of the liquid form of PYCD could be administered to rats easily. Meanwhile, the middle dose (3500 mg/kg) is difficult to pass the tube and causes high stress and even death when administrated to rats. Furthermore, the liquid form of PYCD at a higher dose (7000 mg/kg) is complicated or could not pass the tube. On the other hand, the solid form of PYCD is the most preferred oral administration because it can be administrated efficiently even at all dose levels without causing stress to rats. The PYCD was placed in the cage and left for about ~10 mins to ensure that all solid forms of PYCD were fully consumed.

A previous study denotes that the liquid form of the sample could be delivered directly into the stomach (gastric gavage) to ensure precise and accurate doses for animals; however, because the rats are unable to vomit, an excessive amount of substances administered by gastric gavage may induce discomfort and stress (Turner *et al*., 2011). Therefore, this study used the recommended maximal dose volume of 10 mL/kg body weight (Diehl *et al*., 2001) to avoid dosing accidents liquids by gavage administration. Nevertheless, it was not possible to gauge the administration of the liquid form of PYCD.

Every dose level of PYCD, when dissolved with each solvent in liquid form, constitutes dispersion (suspension), not a solution. They have a thick texture, especially for a higher dose level. Thus, in this study, only the lower dose could be administrated to rats. In contrast, middle and higher doses are complicated to pass through the tube and cause high stress when administrated to rats. The liquid form is problematic because of the rat's difficult administration, tastelessness, risk of choking, and risk of stress.

PYCD by the freeze-drying process has an extremely high porosity, allowing quick water or saliva to penetrate and dissolve within the oral cavity. PYCD fulfils one of the ideal characteristics of a suitable oral drug, promising stability and solubility in water and saliva (Bala *et al*., 2013). Unlike the liquid form, the solid form of PYCD is the most preferred oral

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administration. The advantages of the single unit solid dosage form are convenient dosing, no need for water, safety, no risk of choking, incorporation in high doses, voluntary consumption, rats' improved compliance due to ease of administration, and minimized administration frequency. Moreover, a single unit solid dose could be used when quick action is required. The solid form of PYCD would be easily swallowed and accepted by the rats. Therefore, the solid form of PYCD is recommended for the next intervention procedure.

3.3 Effects of PYCD on FBG and body weight

The effects of 3500 mg/kg PYCD in solid form and glibenclamide at the FBG level in MII 50 diabetic rats as the selected group are presented in Table 2. The present study also reduced FBG levels exhibited by coconut water (Bhagya *et al*., 2012; Preetha *et al*., 2013; Pinto *et al*., 2015). Unlike the 91.20±2.13 mg/dL of NC, the FBG value of MII 50 diabetic rats started to decrease after seven days of administering 3500 mg/kg of PYCD and 0.6 mg/kg of glibenclamide and remained low until 45 days of the administration (113.25±7.52 and 161.25±20.84 mg/dL respectively). However, the value significantly decreased on the 7th and 35th days after the administration of glibenclamide 0.6 mg/kg and PYCD 3500 mg/kg ($p<0.05$). The decrease in FBG level by PYCD is not as drastic as that by glibenclamide, but its effect is continuous or more stable than that of glibenclamide. The FBG level of PYCD could match with glibenclamide after 21 days of administration ($p>0.05$). This finding suggests that PYCD has a hypoglycaemic effect, comparable with glibenclamide, to lower FBG levels and make the levels below the cutoff point of DM (< 200 mg/dL) if PYCD is consumed regularly for a long time. Further research with another treatment, such as the negative control diabetic group, should be conducted to confirm the effect.

The STZ as a diabetogenic agent usually results in weight loss in MII 50 diabetic rats. Unlike NC, the body weight of MII 50 diabetic rats tends to decrease on day seven. Such a condition is probably caused by dehydration, catabolism of fats and proteins under DM conditions, and unavailable carbohydrates as an energy source (Ene *et al*., 2008). PYCD and glibenclamide could prevent weight loss and increase the body weight of MII 50 diabetic rats from day 14 to day 45 of the administration (267.67±10.39 and 273.67±21.31 g respectively). Although the PYCD and glibenclamide have not reached significant NC rat scores (305.60±11.83 g) before the administration ($p>0.05$). Glibenclamide prevents weight loss and starts to gain weight in MII 50 diabetic rats faster than the PYCD. However, glibenclamide and PYCD do not have statistically different effects on increasing body weight on the same day ($p>0.05$) (Table 3).

This study has discovered that the hypoglycaemic effect of PYCD could be linked to coconuts' bioactive components, such as arginine, which significantly provides health benefits. Several preclinical studies of DM have reported that diabetogenic induced by hyperglycemia can be ameliorated by coconut water or its arginine content (Preetha *et al*., 2012, 2013). The arginine content of PYCD has been found to be 17.35 mg/g (Setiawan *et al*., 2022). Another clinical study has also discovered that L-arginine could regulate blood glucose homeostasis by increasing insulin sensitivity and β-cell activity (Monti *et al*., 2012). In addition, the polyphenols in coconut water have a hypoglycemic effect on PYCD by reducing oxidative stress (Bhagya *et al*., 2012). Moreover, the high dietary fiber in PYCD, approximately 17.11 g/100 g, is deducted to improve hyperglycemia because it can reduce insulin resistance in DM conditions (Azra *et al*., 2020).

Body weight loss in diabetic rats is associated with a

Table 2. Effects of PYCD on FBG levels of diabetic rats compared with glibenclamide.

Day	FBG levels (mg/dL)		
	NC	Glibenclamide (0.6 mg/kg bw)	PYCD (3500 mg/kg bw)
Day 0	114.50±6.01^{Ba}	328.67±10.73^{Aa}	325.67±30.88^{Aa}
Day 7	105.80±6.88^{Ba}	181.00±55.60^{ABb}	211.67±29.94^{Aab}
Day 14	89.33±6.35^{Bb}	174.67±18.41^{ABb}	201.33±38.60^{Aab}
Day 21	105.80±7.37^{Aa}	174.33±27.50^{Ab}	225.33±98.61^{Aab}
Day 28	116.60±20.54^{Aa}	163.33±41.36^{Ab}	194.67±76.70^{Aab}
Day 35	94.40±5.75^{Aab}	194.67±70.70^{Ab}	150.25±32.78^{Ab}
Day 42	96.40±4.30^{Aab}	141.33±13.16^{Bb}	158.67±43.44^{Bb}
Day 45	91.20±2.13^{Bab}	161.25±20.84^{Ab}	113.25±7.52^{Bb}

Values are presented as mean±SD. Values with uppercase superscripts within the same row are statistically significantly different ($p<0.05$) while values with lowercase superscripts within the same column are statistically significantly different ($p<0.05$). NC: normal control, SII: single intraperitoneal injections at 55 STZ dosage, MII 50: multiple intraperitoneal injection at 50 STZ dosage.

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Table 3. Effects of PYCD on body weight of diabetic rats compared with glibenclamide

Day	Body weight (g)		
	NC	Glibenclamide (0.6 mg/kg bw)	PYCD (3500 mg/kg bw)
Day 0	272.25±11.03^{Ab}	270.00±6.65^{Aa}	254.67±6.33^{Aa}
Day 7	273.60±6.94^{Ab}	235.00±15.94^{Ba}	248.67±9.82^{ABa}
Day 14	278.80±7.49^{Aab}	254.33±2.02^{Aab}	256.67±7.68^{Aa}
Day 21	286.40±7.77^{Aab}	259.00±10.01^{Aa}	261.00±9.60^{Aa}
Day 28	293.40±8.60^{Aab}	268.00±18.23^{Aa}	262.67±10.86^{Aa}
Day 35	294.40±8.86^{Aab}	277.33±21.40^{Aa}	264.00±11.01^{Aa}
Day 42	300.60±11.84^{Aab}	275.00±20.01^{Aa}	266.33±11.72^{Aa}
Day 45	305.60±11.83^{Aa}	273.67±21.31^{Aa}	267.67±10.39^{Aa}

Values are presented as mean±SD. Values with uppercase superscripts within the same row are statistically significantly different ($p<0.05$) while values with lowercase superscripts within the same column are statistically significantly different ($p<0.05$). NC: normal control, SII: single intraperitoneal injections at 55 STZ dosage, MII 50: multiple intraperitoneal injection at 50 STZ dosage.

decrease in adipose and muscle tissues (lipid and protein catabolism) to produce energy production in insulin deficiency conditions (Ene *et al*., 2008). It is suspected that the PYCD's bioactive compounds, such as arginine, polyphenols, and dietary fiber, could improve insulin productivity and sensitivity to regulate blood glucose homeostasis, increase the use of catabolized fat and protein to produce energy and compensate for weight loss (Bhagya *et al*., 2012; Monti *et al*., 2012; Preetha *et al*., 2013). The improvement in body weight after the administration of coconut products was also supported by several recent studies (Preetha *et al*., 2012; Pinto *et al*., 2015).

4. Conclusion

This study shows that PYCD has a beneficial effect on reducing high FBG and improving body weight. The selected treatment of 3500 mg/kg body weight of PYCD in a solid form could reduce a high FBG level to 113.25±7.52 mg/dL and improve body weight to 267.67±10.39 g in MII 50 diabetic rats. These effects are comparable to glibenclamide as a standard drug for DM. Further, studies are suggested to investigate more treatment groups and more parameters of DM metabolism to ensure the antidiabetic effects of PYCD and confirm the mechanism.

Conflict of interest

The authors declare no conflict of interest.

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