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Mob: +92 300 3008585, Fax: +92 41 8815544
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Research Article
Effect of *Sargassum hystrix* Powder on the Biochemical Profile of Diabetic Wistar Rats

Abdu Rohman Nurfahmi, Amir Husni and Alim Isnansetyo

Department of Fisheries, Faculty of Agriculture, Universitas Gadjah Mada, Jalan Flora Gedung A4 Bulaksumur, 55281 Yogyakarta, Indonesia

Abstract

Objective: This study aimed to determine the effect *Sargassum hystrix* (*S. hystrix*) powder on the levels of glucose, lipid profile and pancreatic profile of diabetic wistar rats. **Methodology:** *S. hystrix* powder (SHP) was made by grinding and sieving to obtain a 120 mesh sized powder. The diabetic rats were administered 450, 600 and 750 mg kg^{-1} doses of SHP orally every day for 15 days. Glucose, lipid profile and weight of rats were measured when in the normal state (baseline) and on days 0 (diabetes), 5, 10 and 15. The histology of the pancreas was observed on the 15th day. **Results:** The 750 mg kg^{-1} dose of SHP was significantly able to reduce the level of preprandial glucose and postprandial glucose and did not have significant differences compared to the positive control. SHP did not affect the level of total cholesterol, triglycerides, HDLc and LDLc. Necrosis was found in all of the streptozotocin-induced rats. **Conclusion:** The SHP has the potential effect that can be beneficial for streptozotocin-induced diabetic rats.

Key words: Blood glucose, necrosis, lipid profile, *Sargassum* sp., diabetes

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Corresponding Author: Amir Husni, Department of Fisheries, Faculty of Agriculture, Universitas Gadjah Mada, Jalan Flora Gedung A4 Bulaksumur, 55281 Yogyakarta, Indonesia

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus is a complex metabolic disorder characterized by hyperglycemia[1]. It is largely classified as insulin-dependent diabetes mellitus (type 1 diabetes) and non-insulin dependent diabetes mellitus (type 2 diabetes). In particular, type 2 diabetes is a growing worldwide health problem. Hyperglycemia plays an important role in type 2 diabetes and complications associated with diseases such as microvascular and macrovascular diseases[2]. Therefore, effective control of blood glucose levels is the key to preventing or reversing diabetic complications and improving the quality of life of diabetic patients.

Globally, an estimated 422 million adults were living with diabetes in 2014 and this number was higher than in 1980, which had approximately 108 million people. Global prevalence (the standard age) of diabetes has nearly doubled since 1980, from 4.78.5% in the adult population and in 2012, diabetes caused 1.5 million deaths[3]. According to the IDF[4], there are an estimated more than half a million children approximately 14 years old living with diabetes type 1. At the end of 2015, diabetes had caused 5.0 million deaths. The increase will continue until 2040 and it is estimated to reach 642 million people living with diabetes.

Currently, the treatment of diabetes is done by injection insulin and using glucose-lowering agents (hypoglycemia) in an oral form such as sulfonylurea, metformin, rosiglitazone, α-glucosidase inhibitors and thiazolidinediones. However, this kind of medication has side effects, such as hypoglycemia, abdominal bloating, weight gain and increased gastrointestinal problems[5]. Therefore, research is now carried out on drug discovery from natural products, especially of plant origin, for treating diabetes[1].

Seaweed is known to have potentially abundant bioactive components for pharmaceutical and biomedical products. Brown seaweed is a plentiful source of potent antioxidant compounds such as several pigments (fucoxanthin, astaxanthin, a carotenoid) and polyphenols (phenolic acids, flavonoids, tannins)[6]. One of the known kinds of brown seaweed is *Sargassum hystrix. S. hystrix* has the highest antioxidant activity compared to other species (*S. polyceratium*, *S. angustifolium*, *S. filipendula*, *S. cinereum*, *S. siliquosum*, *S. mcclurei*)[7]. Extracts of *S. hystrix* have an inhibitory activity of enzymes α-amylase and α-glucosidase in vitro[8] and can lower the glucose levels of a diabetic rat[9]. In addition to pigments and polyphenol compounds, brown seaweed contains polysaccharides such as alginate and fucoidan. The alginate of *S. hystrix* was reportedly able to inhibit the activity of the enzyme α-amylase and α-glucosidase[8] and able to lower glucose levels of a diabetic rat[10]. The objective of this study was to determine the effect of *S. hystrix* powder (SHP) on the levels of glucose, the lipid profile and the pancreatic profile of diabetic wistar rats.

MATERIALS AND METHODS

The main materials used in the study were *Sargassum hystrix* that was obtained from Sepanjang Beach Gunung Kidul Yogyakarta, Indonesia on January, 2016 and a total of 30 wistar rats (2-3 months old) that were obtained from the Integrated Research and Testing Laboratory Universitas Gadjah Mada, Yogyakarta, Indonesia.

Sample preparation: Fresh *S. hystrix* samples were washed and dried at room temperature without light exposure for 7-10 days until the water content reached 11-14%. Dry samples were cut into small pieces, sifted to remove the salt and blended. The obtained powder was sieved to obtain a size of 120 mesh powder of *Sargassum* which did not clog the needle's oral syringe hole when the treatment was given to the rat.

***In vivo* test:** The *in vivo* test was carried out using 30 male wistar rats (10-12 weeks old), which adapted to the environment for 7 days in a temperature of 25±2°C with relative humidity 50±10% and a 12 h cycle of light and dark[11]. Glucose levels of the blood and the lipid profile of the rat were measured. A total of 5 rats were treated with normal saline and the other 25 were induced by streptozotocin. After 48 h, the diabetes mellitus condition was confirmed by glucose levels of the blood if it reached >200 mg dL^{-1}. The rats that had diabetes mellitus were given the treatment. The 25 rats that were induced by streptozotocin and a positive diabetes mellitus rat were given five treatments of the diabetes mellitus commercial drug (positive control), 0.5% CMC-Na (negative control), the powdered *S. hystrix* 450, 600 and 750 mg kg^{-1}. The treatment was carried out for 15 days with daily measurement of the parameters every 5, 10 and 15 days with preprandial (2 h before replenishment of glucose) and postprandial (2 h after replenishment of glucose) systems. Measured parameters were the weight of rat, the glucose level of the blood in preprandial and postprandial state, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDLc) and low-density lipoprotein cholesterol (LDLc) levels and histological pancreas analysis.

Statistical analysis: The study was performed using a completely randomized design (CRD) for *in vivo* tests. Statistical analysis was measured by one-way analysis of variance (ANOVA) with a confidence level of 5%. If the test showed significant differences, there would be a further test with Duncan's multiple range test (DMRT).

RESULTS AND DISCUSSION

Body weight changes of rats: The data of the body weight changes of the rats are presented in Fig. 1. Figure 1 indicates the occurrence of weight loss in all treatments except for the normal control group. The normal control group experienced a positive change in body weight and gained 31.13 g, the negative control group treatment experienced a weight loss of 16.20 g and the positive control group experienced a 10.83 g weight loss. All treatments with powdered *S. hystrix* experienced a weight loss. The treatment at doses of 450, 600 and 750 mg kg^{-1}, resulted in a loss of 3.83, 17.77 and 4.47 g body weight, respectively. The group with the dose of 600 mg kg^{-1} had the highest weight decrease compared to the positive control group and almost the same weight decrease as the negative control group. The treatment with a dose of 450 mg kg^{-1} had the lowest weight loss if compared to the negative control group and almost the same when compared to a dose of 750 mg kg^{-1}.

Preprandial glucose levels: The result based on preprandial blood glucose levels before the induction of streptozotocin (baseline) was classified under normal conditions ranging from 75.10-151.90 mg dL^{-1}. Streptozotocin-induced treatment confirmed the blood glucose levels in plasma at 48 h increased the preprandial glucose levels >200 mg dL^{-1} except for the treatment with powdered *S. hystrix*. Thus, in these conditions, the rat can be categorized as having diabetes mellitus (DM). The initial condition was declared as a day zero (D-0).

Observation on the last day (D-15) showed that all the treatments experienced a decrease of blood glucose levels. The negative control group had a blood glucose level >200 mg mL^{-1} and had significant differences to the normal control group. Blood glucose levels of the treatment with a dose of 450 or 750 mg kg^{-1} and the positive control group were <200 mg mL^{-1}. This condition showed that the glucose levels in blood were normal. It showed that the dose of powdered *S. hystrix* given affected the diabetes mellitus rat as well as the positive control group. The decrease may occur when the antioxidant compound such as polyphenol inhibits the enzyme when the breakdown of carbohydrates into glucose occurs, while the alginate polysaccharide has a role in inhibiting the absorption of glucose in intestines[8]. According to Husni *et al.*[9], ethanolic extract of *S. polycystum* at 450 mg kg^{-1} was able to lower the preprandial glucose levels of diabetic wistar rats. This was also supported by Lailatussifa *et al.*[12] who stated that the ethanolic extract of *S. polycystum* was able to lower the glucose levels of stressed wistar rats. Moreover, Husni *et al.*[10] showed that using sodium alginate from *S. crassifolium* at 600 mg kg^{-1} was also capable of lowering the preprandial glucose levels of diabetic wistar rats. The powdered *S. hystrix* treatment at 750 mg kg^{-1} showed that it was as good as alginate treatment in lowering the glucose levels of diabetic rats.

Postprandial glucose level: The postprandial glucose levels based on Table 1 showed that glucose levels on the baseline after 2 h obtain the glucose intake of 2 g kg^{-1}; it was still in the range of 90.43-119.60 mg dL^{-1}. After all, groups were injected with STZ except the normal control group, which had the highest postprandial glucose levels at 400.21 mg dL^{-1}. This

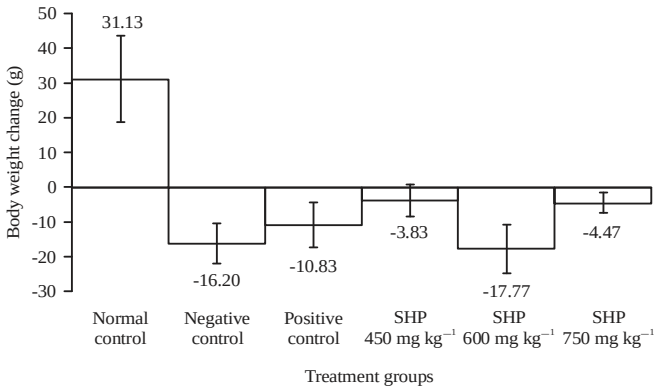

Fig. 1: Changes in body weight of rats after administration of *Sargassum hystrix* powder (SHP) orally for 15 days

Table 1: SHP effect of orally administration for 15 days on preprandial and postprandial glucose levels in wistar rats induced by streptozotocin

	Preprandial glucose (mg dL^{-1})			Postprandial glucose (mg dL^{-1})		
Treatment	Baseline	D-0	D-15	Baseline	D-0	D-15
Normal control	97.10±11.8^{b}	61.97±7.5^{a}	86.60±5.9^{a}	95.53±9.2^{a}	93.70±4.7^{b}	86.40±9.2^{a}
Negative control	93.63±2.8^{b}	345.87±119.1^{b}	267.27±55.3^{b}	119.60±23.5^{a}	400.27±19.9^{a}	283.03±20.2^{b}
Positive control	75.10±2.3^{a}	294.17±97.2^{b}	168.67±65.8^{ab}	90.43±11.4^{a}	226.03±79.3^{a}	201.20±86.2^{ab}
SHP 450 mg kg^{-1}	98.37±2.8^{b}	115.10±17.9^{b}	167.90±8.1^{ab}	108.06±8.5^{a}	195.23±78.4^{a}	119.10±14.1^{ab}
SHP 600 mg kg^{-1}	151.90±12.6^{c}	279.40±107.4^{b}	231.73±136.8^{ab}	115.43±3.8^{a}	302.00±89.9^{a}	186.40±77.4^{ab}
SHP 750 mg kg^{-1}	106.70±3.3^{b}	209.55±15.3^{b}	121.73±24.1^{ab}	113.36±16.6^{a}	330.13±32.1^{a}	89.10±27.9^{a}

Values with different letters in the same column indicate significant difference (p<0.05)

Table 2: SHP effect of oral administration for 15 days on triglyceride levels in wistar rats induced by streptozotocin

	Triglyceride levels (mg dL^{-1})		
Treatment	Baseline	D-0	D-15
Normal control	111.97±12.1^{b}	80.07±5.7^{a}	70.70±7.6^{a}
Negative control	113.30±17.0^{b}	46.77±3.3^{a}	43.27±3.2^{a}
Positive control	117.90±7.3^{b}	83.83±23.4^{a}	66.13±4.6^{a}
SHP 450 mg kg^{-1}	103.20±19.2^{b}	83.50±18.7^{a}	56.70±8.5^{a}
SHP 600 mg kg^{-1}	63.90±9.7^{a}	51.60±10.8^{a}	77.30±29.8^{a}
SHP 750 mg kg^{-1}	80.87±10.2^{b}	86.95±12.0^{a}	45.63±14.9^{a}

Values with different letters in the same column indicate significant difference (p<0.05)

Table 3: SHP effect of orally administration for 15 days on total cholesterol levels in wistar rats induced by streptozotocin

	Total cholesterol levels (mg dL^{-1})		
Treatment	Baseline	D-0	D-15
Normal control	77.87±5.7^{ab}	72.13±6.4^{a}	66.97±3.4^{a}
Negative control	79.57±6.8^{ab}	58.70±9.2^{a}	57.10±8.5^{a}
Positive control	103.50±7.5^{b}	68.30±7.9^{a}	64.03±6.4^{a}
SHP 450 mg kg^{-1}	95.77±9.9^{ab}	71.63±2.1^{a}	66.53±7.0^{a}
SHP 600 mg kg^{-1}	71.30±7.6^{a}	59.70±5.8^{a}	58.90±10.7^{a}
SHP 750 mg kg^{-1}	85.33±5.8^{ab}	65.47±8.1^{a}	58.30±9.2^{a}

Values with different letters in the same column indicate significant difference (p<0.05)

condition showed that the rats were suffering from hyperglycemia. Postprandial hyperglycemia plays an important role in the development of diabetes type 2 and complications associated with this condition, including microvascular and macrovascular disease. Postprandial hyperglycemia is also involved in various metabolic disorders and other diseases, including viral-based diseases and cancer[13].

Data on the last day (D-15) showed that the treatment with the replenishment of SHP did not have significant differences compared to the positive control group. A glucose level for replenishment of SHP treatment at doses of 450, 600 and 750 mg kg^{-1}, respectively, was not significantly different compared to the normal control group. All the replenishment SHP treatments experienced a decrease of the blood glucose level and the levels of glucose were <200 mg dL^{-1}. This indicated the decrease of a postprandial blood glucose level. Therefore, the replenishment of SHP in the diabetic rats can reduce the postprandial glucose levels. According to You *et al.*[14], the florofucofuroeckol A of *Ecklonia cava* capable to lowering the postprandial glucose levels of diabetic rats. The ability of *S. hystrix* to lowering the glucose levels was "Double Inhibition" which was enzymatically by polyphenols and mechanical inhibition by alginate. Polyphenols inhibit the enzymes in the breakdown of carbohydrates into glucose, while the polysaccharide alginate plays a role in intestinal glucose absorption inhibition[8].

Triglyceride levels: Based on Table 2, there were no significant changes in the triglyceride levels of wistar rats. Compared to the baseline condition after STZ was induced (D-0), the triglyceride levels were decreasing both in the normal control group and the treatment group. Triglyceride levels on D-0 of the negative control group decreased from 113.30-46.77 mg dL^{-1}. Variance analysis showed that the level of triglyceride on D-0 was not significantly different among the treatment group (p>0.05). According to Pejic and Lee[15], the normal level of triglyceride in blood is <150 mg dL^{-1} and hypertriglyceridemia will occur if the level of triglyceride in blood is >150 mg dL^{-1}.

The decreasing of triglyceride levels in the tenth day of observation occurred in negative and positive control groups. The replenishment of 450, 600 and 750 mg kg^{-1} of SHP was increasing triglyceride levels. The measurement of triglyceride levels on the last day of observation (D-15) showed that all the treatments were not significantly different from the normal control group. Based on the observation of D-0 to D-15, the replenishment of SHP was not significantly different with all the control groups.

Total cholesterol levels: Total cholesterol levels in all treatments before induction of STZ (baseline) included in normal conditions. Condition after STZ induction (D-0) decreased the total cholesterol levels in the whole observation group (Table 3). Analysis of variance showed that total cholesterol levels in D-0 were not significantly different

Table 4: SHP effect of oral administration for 15 days on HDLc and LDLc levels in wistar rats induced by streptozotocin

	HDLc Levels (mg dL^{-1})			LDLc Levels (mg dL^{-1})		
Treatment	Baseline	D-0	D-15	Baseline	D-0	D-15
Normal control	31.20±3.6^{a}	36.20±5.8^{a}	38.00±3.2^{a}	22.17±0.6^{a}	29.33±1.9^{a}	17.87±4.4^{a}
Negative control	31.73±0.1^{a}	36.53±7.1^{a}	38.23±7.2^{a}	28.03±5.8^{a}	25.03±4.0^{a}	20.97±2.4^{a}
Positive control	38.07±1.7^{a}	40.53±2.5^{a}	36.60±3.5^{a}	34.10±5.0^{a}	20.97±4.5^{a}	24.80±4.7^{a}
SHP 450 mg kg^{-1}	37.03±4.8^{a}	44.03±3.6^{a}	33.83±4.5^{a}	32.27±1.2^{a}	35.13±7.4^{a}	21.53±3.8^{a}
SHP 600 mg kg^{-1}	28.93±2.9^{a}	36.40±3.8^{a}	28.07±3.1^{a}	25.00±6.5^{a}	33.53±7.7^{a}	21.77±3.4^{a}
SHP 750 mg kg^{-1}	37.00±3.4^{a}	39.17±5.7^{a}	29.63±4.2^{a}	28.70±2.7^{a}	30.80±6.5^{a}	20.40±3.1^{a}

Values with different letters in the same column indicate significant difference ($p<0.05$)

between treatments ($p>0.05$). These results indicate that after induction of STZ, there were no significant changes to the cholesterol levels of the rats.

Based on Table 3, it is shown that all groups had relatively similar total cholesterol levels. Husni *et al.*[10] showed no significant difference in total cholesterol levels of replenishment of sodium alginate for both positive and negative control groups. The lipid profiles, such as cholesterol and triglyceride, were done to see how acute the complications of diabetes experienced by rats were. One of the acute complications which is often found in cases of diabetes mellitus is dyslipidemia. Dyslipidemia is a blood lipid metabolism disorder characterized by abnormalities in blood cholesterol levels (hypercholesterolemia), in triglycerides (hypertriglyceridemia), or in a combination of both in plasma[16].

HDLc and LDLc levels: Table 4 shows that HDLc levels throughout treatment have no significant difference from D-0 to D-15; all conditions were in the normal range. D-0, which was after the rats were induced by STZ, showed that the level of HDLc in the blood was increasing. HDLc levels on D-5 showed no significant difference between the treatment replenishment of SHP, the positive control group and the negative control group compared the normal control group. HDLc levels of all treatments were decreased. HDLc levels on D-10 for the treatment of SHP replenishment with doses of 450 or 750 mg kg^{-1} and the positive control group increased. Meanwhile, the levels in the negative control group and the treatment of SHP replenishment with the dose of 600 mg kg^{-1} decreased. However, at the last day (D-15), all the observation groups experienced an increase of HDLc. Based on the research of Husni *et al.*[10] there was no significant difference in HDLc levels of the rats that were suffering from diabetes who were treated using sodium alginate *S. crassifolium*. HDLc levels of wistar rats after replenishment of sodium alginate of *Turbinaria ornata* were not different than those of the normal control group and negative control group[17]. This condition showed that the lipid metabolism of rats was still in a normal condition.

Based on the LDLc levels in Table 4, none of the treatments had a significant difference during the observation of D-0 to D-15. All conditions were in a normal condition. D-5 showed no significant difference between the treatments ($p<0.05$). LDLc levels of the normal controls had higher levels compared to another group. LDLc levels on D-10 for the treatment of SHP replenishment, the positive control group and the negative control group showed the increasing of LDLc levels while the normal control group was decreasing. However, on the last day (D-15), the LDLc levels of all groups were decreased. LDLc levels of D-15 were lower than D-0 and there were no significant differences between all groups. Kim *et al.*[18] showed that *S. yezoense* was able to decrease LDLc levels in the blood of diabetic rats.

Pancreatic necrosis: The results of histological staining of the pancreas in diabetic rats indicated by Fig. 2 show all treatments with STZ-induction experienced cell damage or necrosis. STZ induction is used to make type 1 diabetes and causes degeneration of beta cells in the islets of Langerhans[19]. STZ induction will cause beta cell damage due to the occurrence of DNA alkylation[20]. Chen *et al.*[21] described that on the normal group, Langerhans was round and large, with clear boundaries and a full central particle. However, for the group with the induction of STZ, island state boundaries were not clear and the number of middle particles was reduced.

Based on the results of the histology of the pancreas in Fig. 2, the negative control compared to the positive control has more cell damage. The increasing of the amount of cell damage in the negative control was caused by the absence of drug treatment, while the positive control received the oral addition of glibenclamide, which was predicted to be able to repair cells. The normal control had a normal condition of the cell because it was not STZ induced (non-diabetic). Cell damage also occurred in rats treated with replenishment of SHP at the doses of 450, 600 and 750 mg kg^{-1}. Total damage to cells in the treatment of SHP replenishment of 450 and 600 mg kg^{-1} SHP was higher than that of 750 mg kg^{-1}. The data showed that SHP replenishment at the dose of

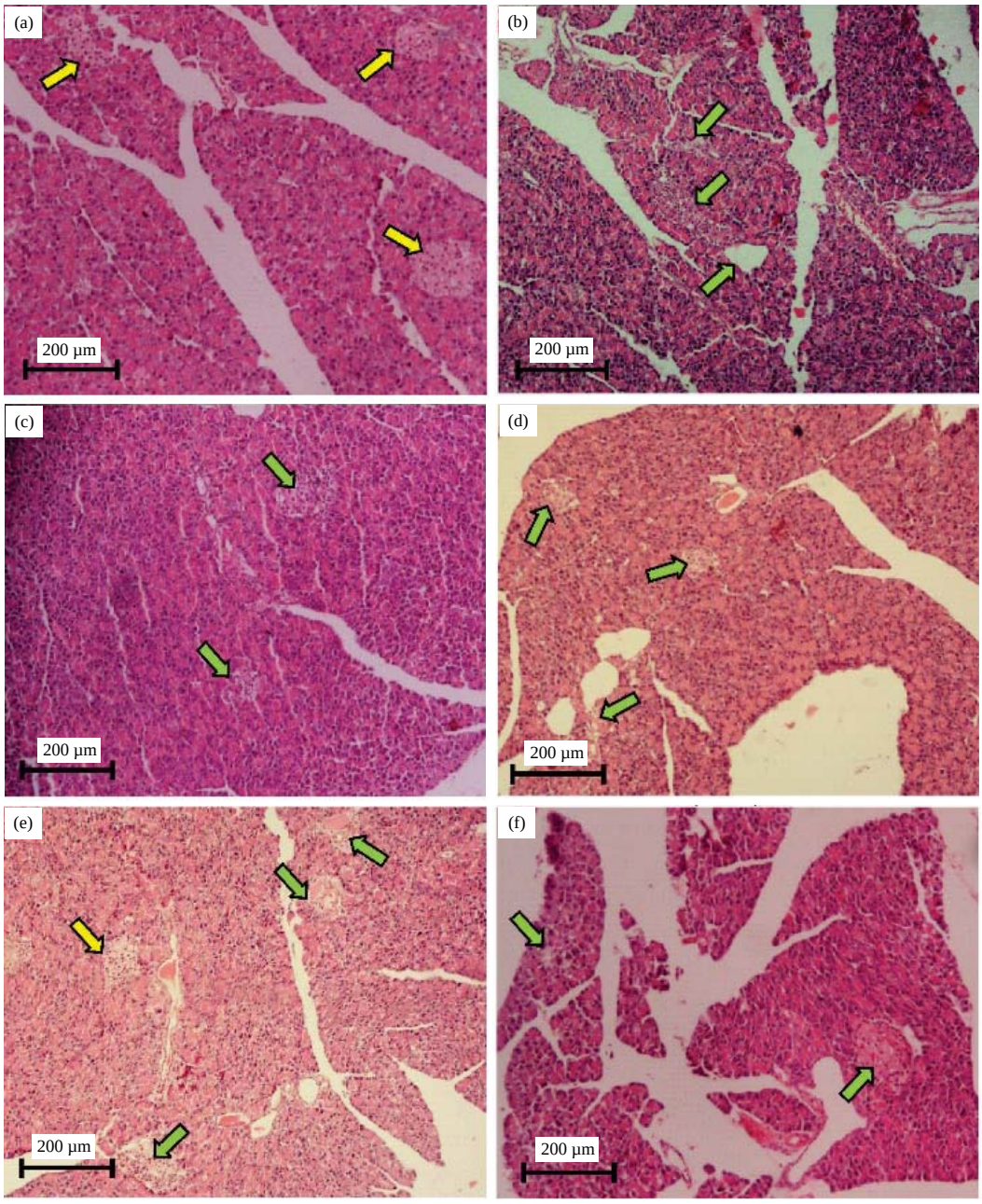

Fig. 2(a-f): Sargassum hystrix powder (SHP) effect of orally administration for 15 days in the pancreatic beta cells of rats induced by streptozotocin

(a) Normal control (-), (b) Negative control (+++), (c) Positive control (++), (d) SHP 450 mg kg^{-1} (+++), (e) SHP 600 mg kg^{-1} (+++) and (f) SHP 750 mg kg^{-1} (+++). $^{-}$No necrosis, $^{++}$Medium necrosis, $^{+++}$Severe necrosis. Normal cells (green arrow) and necrosis (yellow arrow)

750 mg kg^{-1} was able to repair cell damage. Husni *et al.*[9] revealed that the ethanolic extract of *S. polycystum* at a dose of 450 mg kg^{-1} gave the effect of increasing the pancreatic beta cells. Additionally, Husni *et al.*[10] revealed that the extract of sodium alginate of *S. crassifolium* in the dose of 600 mg kg^{-1} had the best ability to reconstruct the destruction of pancreatic cells. Replenishment of SHP 750 mg kg^{-1} with a simple manufacturing process has been able to repair damage to cells of the pancreas.

CONCLUSION

SHP replenishment at 750 mg kg^{-1} could lower preprandial and postprandial glucose levels better than the doses of 450 and 600 mg kg^{-1} and was not different than use of 5 mg kg^{-1} of glibenclamide as a standard drug. SHP replenishment did not affect total cholesterol, triglycerides, HDLc and LDLc of wistar rats induced by streptozotocin. Induction of streptozotocin caused necrosis of pancreatic β cells and the replenishment of SHP dose of 750 mg kg^{-1} had fewer necrotic cells than the treatment with 450 and 600 mg kg^{-1} and had a condition similar to 5 mg kg^{-1} of glibenclamide treatment.

SIGNIFICANCE STATEMENT

This study discovers the potential effect of SHP that can be beneficial for streptozotocin-induced diabetic rats. This study will help the researchers to uncover a critical area of diabetes that many researchers have not been able to explore. Thus, a new theory on the use of SHP may be arrived at.

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