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# Antidiabetic Activity of *Sargassum hystrix* Extracts in Streptozotocin-Induced Diabetic Rats

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**ABSTRACT:** The objective of this research was to determine the potential effects of *Sargassum hystrix* extracts (SHE) on the glucose levels, lipid profile, and pancreas of streptozotocin (STZ)-induced diabetic rats. SHE at 200, 300, and 400 mg/kg was administered orally to STZ-induced diabetic rats once daily for 15 days. Glucose levels, lipid profile, and weight of rats were measured in the normal state and on the 15th day. The histology of the pancreas was observed on the 15th day. The results showed that the preprandial and postprandial glucose levels in the group treated with SHE at 300 mg/kg were significantly reduced compared with those of the diabetes group. Additionally, the levels of triglycerides and cholesterol in the 300 mg/kg SHE group were significantly different from those in the diabetes group. However, the levels of high-density lipoprotein cholesterol and low-density lipoprotein cholesterol across the treatment groups did not have significant differences. Necrosis was found in all STZ-induced rats. SHE at a dose of 300 mg/kg had the best capability to lower the levels of preprandial and postprandial glucose and to prevent necrosis in diabetic rats.

**Keywords:** polyphenol, *Sargassum hystrix*, antihyperglycemia, lipid profile, pancreatic necrosis

## INTRODUCTION

Diabetes mellitus describes a metabolic disorder of multiple etiology that is characterized by chronic hyperglycemia with disturbances in carbohydrate, fat, and protein metabolism resulting from a defect in insulin secretion, insulin action, or both (1). Diabetes is a leading cause of morbidity and mortality for the world's growing population. The International Diabetes Federation has predicted a worldwide increase from 8.3% to 9.9% by the year 2030 (2). Diabetes is associated with major abnormalities in fatty acid metabolism (3). The most common lipid pattern in type 2 diabetes consists of hypertriglyceridemia, high-density lipoprotein cholesterol (HDL-c), and normal plasma concentrations of low-density lipoprotein cholesterol (LDL-c) (4). It is one of the primary threats to human health due to its increased prevalence and associated disabling complications. Additionally, its treatment mainly involves obtaining a sustained reduction in hyperglycemia using oral hypoglycemic agents in addition to injectable insulin. However, the prominent side-effects of such drugs are the main reason for an increasing number of people seeking alternative therapies that may have less severe or no side effects (5).

Some plants from different parts of the world that possess antidiabetic and related beneficial effects have been documented (6). The brown marine alga *Sargassum crassifolium* is an abundant species that is commonly found around the world and is rich in polysaccharides, proteins, peptides, amino acids, lipids, minerals, and some vitamins. Marine algae also have a high content of antioxidants that can be used to ward off the free radicals that increase due to hyperglycemic conditions in patients with diabetes mellitus (7). Several marine algae, such as *Petalonia binghamiae*, *Padina gymnospora*, *Sargassum cystoseria*, and *Spyridia fusiformis*, have hypoglycemic effects in diabetic mammals (8). Marine algae and algal polysaccharides also have hypocholesterolemic effects in mammals (9). Until now, research on the antidiabetic activity of the seaweed *Sargassum hystrix* has not been conducted. The purpose of this study was to evaluate the effects of *S. hystrix* extracts (SHE) on the glucose levels, lipid profile, and pancreas of streptozotocin (STZ)-induced diabetic rats.

## MATERIALS AND METHODS

### Materials

The main material used in this study was the brown sea-

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weed *S. hystrix* obtained from coastal Sepanjang, Gunungkidul, Yogyakarta, Indonesia, in April 2016. The chemical used for extraction of polyphenols was methanol (Merck KGaA, Darmstadt, Germany). All other chemicals used in this study were of analytical grade.

### Extractions of seaweed

Before extraction, seaweed was dried indoors for 4～7 days, then cut into small pieces and powdered using a blender. The ethanolic extract was obtained by extracting the seaweed using the modified method of Zhang et al. (10). Two hundred grams of powdered *Sargassum polycystum* samples were extracted using ethanol 96% (1.875 mL) that had been adjusted to pH 4 using 1 N HCl (±7 mL) at room temperature and stirred for ±4 h. Maceration was then performed for 2×24 h, and the mixture was filtered with Whatman paper No. 1. Then, the filtrate was evaporated in a rotary evaporator (RV 10 basic; IKA-Werke GmbH & Co., Breisgau, Germany; 40～60°C, 135～150 rpm, ±2 h) and freeze-dried. The freeze-dried sample was weighed for yield calculations and stored at a temperature of −20°C.

### Experimental method

Male albino Wistar rats, weighing 106.1～148.6 g were obtained from the Integrated Research and Testing Laboratory at Universitas Gadjah Mada, Yogyakarta, Indonesia. Rats were maintained under the standard condition of 24±2°C at a relative humidity of 40±5% with a 12-h light and 12-h dark cycle and were fed a standard pellet diet with water available *ad libitum*. All animal studies conducted were approved by the Institutional Animal Ethics Committee (IAEC) of the Integrated Research and Testing Laboratory at Universitas Gadjah Mada (Approval No. 305/KEC-LPPT/VIII/2015), Yogyakarta, Indonesia.

Rats were fasted overnight before being injected with STZ. Diabetes mellitus was induced by a single intraperitoneal injection of a freshly prepared solution of STZ [50 mg/kg body weight (b.w.)] in 0.1 M citrate buffer at pH 4.5. Rats were treated with 5% glucose solution orally to combat the early phase of drug-induced hypoglycemia. The blood glucose levels of the rats were measured 48 h after STZ administration (11).

A total of 30 rats were divided into 6 groups as follows: Group 1, normal rats treated with normal saline; Group 2, diabetic rats treated with 0.5% carboxymethyl cellulose-Na; Group 3, diabetic rats treated with 5 mg glibenclamide/kg b.w.; Group 4, diabetic rats treated with SHE 200 mg/kg b.w.; Group 5, diabetic rats treated with SHE 300 mg/kg b.w.; and Group 6, diabetic rats treated with SHE 400 mg/kg b.w. The concentration of SHE was based on the results of a brine shrimp lethality test (data not shown). The rats' body weights were measured every day. On day 15, the rats were anesthetized with anesthetic ether and dissected immediately, and blood was collected in microtubes. Blood was centrifuged at 1,610 *g* for 20 min at 4°C to obtain serum that was collected and stored at −20°C before testing. The blood serum levels were measured to determine the profile of biochemical parameters, including glucose, triglycerides, cholesterol, HDL-c, and LDL-c. The stomach of each animal was opened along the greater curvature and qualitatively examined macroscopically for gastric ulcers. Gastric tissue was stored in a 10% formalin solution before testing for gastric ulceration. Ulceration was analyzed using the method described by Gregory et al. (12).

### Statistical analysis

All data were expressed as the mean±standard deviation (SD) of three determinations. Statistical comparison was performed via one-way analysis of variance (ANOVA) followed by Duncan's multiple range test (DMRT) using SPSS version 8 software (SPSS Inc., Chicago, IL, USA). The values were considered significant when $P<0.05$.

## RESULTS AND DISCUSSION

### *S. hystrix* supplementation has no effect on body weight of STZ-induced diabetic rats

Body weight changes during the whole experiment are shown in Fig. 1. Five groups of diabetic rats had decreased in body weight during the 15 days treatment, but there were no significant ($P\geq0.05$) differences between the groups of rats. Weight loss in the DM rats from baseline to day 15 for the diabetes, glibenclamide, polyphenol 200, 300, and 400 mg/kg groups was 16.2, 10.9, 21.2 16.1, and 14.5 g, respectively. However, in contrast, the control group that did not get the induction of DM by STZ gained weight. Weight gain in the control group continued to increase from day 0 to day 15 by 31.1 g.

Weight loss in the STZ-induced DM rats was due to excess protein tissue destruction, dehydration, and catabolism of fat and protein (13). Additionally, the weight loss of the rats was due to decreased insulin production and was followed by energy reduction (14). The study by Moree et al. (11) showed that weight loss in STZ-induced rats was due to the degradation of protein structures. These protein structures are related to body weight, so their degradation can reduce weight. During relative or absolute insulin deficiency, adenosine triphosphate production, and decreased protein synthesis in all tissues also become factors that cause weight loss. The loss and ineffective utilization of glucose lead to the breakdown of protein and fat. Structural proteins are known to contribute to body weight, and the degradation of these structural proteins reflects the reduction in body weight (15).

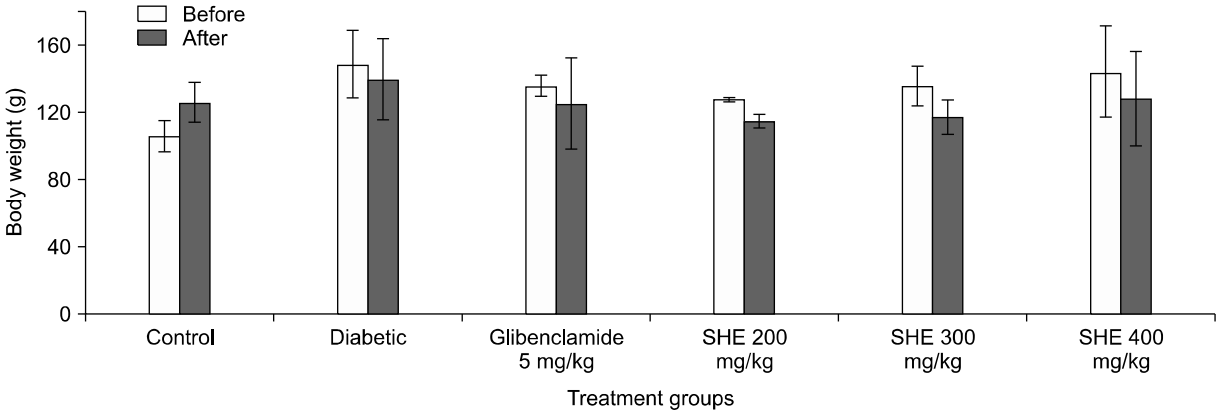


**Fig. 1.** Effects of *Sargassum hystrix* extracts (SHE) and glibenclamide on streptozotocin-induced body weight changes in Wistar rats.

**Table 1.** Effects of *Sargassum hystrix* extracts (SHE) and glibenclamide on streptozotocin-induced biochemical changes in Wistar rats (unit: mg/dL)

| Treatment groups | Preprandial glucose | Postprandial glucose | Triglycerides | Cholesterol | HDL-c | LDL-c |
|---|---|---|---|---|---|---|
| Control | 89.6±11.0$^{a}$ | 75.3±8.1$^{a}$ | 65.3±11.2$^{abc}$ | 83.1±11.3$^{b}$ | 28.8±7.9$^{ns}$ | 30.0±9.9$^{ns}$ |
| Diabetic | 347.8±20.9$^{c}$ | 315.6±19.9$^{c}$ | 45.9±2.6$^{a}$ | 50.2±5.8$^{a}$ | 21.5±2.7 | 21.5±5.1 |
| Glibenclamide 5 mg/kg | 195.6±184.4$^{b}$ | 104.8±25.6$^{a}$ | 46.0±9.5$^{ab}$ | 72.7±17.2$^{ab}$ | 27.1±5.1 | 25.8±4.6 |
| SHE 200 mg/kg | 238.7±174.5$^{bc}$ | 344.9±99.6$^{c}$ | 76.3±34.2$^{bc}$ | 67.8±21.3$^{ab}$ | 25.3±2.7 | 25.9±5.3 |
| SHE 300 mg/kg | 186.4±124.3$^{b}$ | 186.9±84.4$^{b}$ | 91.2±26.6$^{c}$ | 80.4±17.6$^{b}$ | 26.3±8.7 | 32.2±6.8 |
| SHE 400 mg/kg | 215.3±205.4$^{b}$ | 333.8±12.5$^{c}$ | 49.9±8.2$^{ab}$ | 72.3±4.3$^{ab}$ | 28.9±2.7 | 34.1±7.1 |

Different letters (a-c) in the same column indicate significant differences ($P$<0.05).
HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.
$^{ns}$Not significant.

### *S. hystrix* supplementation decreases blood glucose levels in STZ-induced diabetic rats

Rat blood glucose levels are shown in Table 1. Rats given SHE at a dose of 300 mg/kg showed a significant ($P$< 0.05) decrease in blood glucose levels to near levels of the control and glibenclamide-treated rats. Firdaus et al. (7) reported that methanol extracts of the brown algae *Sargassum echinocarpum* at a dose of 450 mg/kg b.w. lowered blood glucose levels of diabetes mellitus rats to below 200 mg/dL. *S. echinocarpum* extracts inhibited α-glucosidase activity and showed insulin-mimetic activities. Lamela et al. (16) also reported that *Sargassum* sp. extracts exerted hypoglycemic properties in normal and diabetic rabbits. Borriello et al. (17) suggested that activation of adenosine monophosphate-activated protein kinase by polyphenols can increase Akt activity, causing glucose transporter 4 to translocate to the cell membrane immediately. The glucose transporter is useful for uptake of glucose in the blood and muscles.

### *S. hystrix* supplementation has no effect on triglyceride levels of STZ-induced diabetic rats

Rats had triglyceride levels in the normal range (45.9～91.2 mg/dL) until day 15 (Table 1). Elevated triglyceride levels occurred in the control, glibenclamide, and SHE 400 mg/kg groups. However, when the triglyceride levels at baseline were compared to those at day 15, there was a decrease across all treatments, but the levels were still within the normal range. Damron (18) stated that the levels of triglycerides in the blood are affected by the digested fat levels from a meal or the amount of fat that enters the body. The feed given to the rats would not have this effect because the feed used was not a high-fat diet, in contrast to Motshakeri et al. (19), who added dietary fat and sugar to the rat feed, which could have caused dyslipidemia.

The STZ-induced rats in this study had triglyceride levels within the normal range. Husni et al. (20) also reported a normal range of triglycerides between 69.6～77.4 mg/dL. However, the administration of Na-alginate from *Turbinaria ornata* was able to lower triglyceride levels on day 15. The administration of SHE in this study can also decrease triglyceride levels at day 15. Moreover, sodium alginate from *S. crassifolium* and *S. polycystum* can decrease triglyceride levels in STZ-induced hyperglyceride rats (21,22).

### *S. hystrix* supplementation has no effect on total cholesterol of STZ-induced diabetic rats

Blood serum total cholesterol levels of rats showed no

significant ($P \geq 0.05$) differences between the diabetic rats and rats that received SHE at 200 and 400 mg/kg and glibenclamide at 5 mg/kg (Table 1). Cholesterol levels in the SHE 300 mg/kg group were significantly different compared to those in the diabetes group. Motshakeri et al. (19) stated that *S. polycystum* ethanol extract could reduce dyslipidemia in type 2 diabetic rats. A decrease in cholesterol levels by *Sargassum wightii* extract was also shown by Mohapatra et al. (23) in type 2 diabetic mice with a high-fat diet and STZ induction. Husni et al. (21) stated that sodium alginate from *S. crassifolium* at a dose of 600 mg/kg could lower cholesterol levels equally well with glibenclamide drugs in STZ-induced rats. The ability of Na-alginate as a reducer of cholesterol in diabetic rats was also obtained from *T. ornata* (20), in contrast to Husni et al. (22), who stated that *S. polycystum* extract had no effect on the cholesterol levels of diabetic rats induced by STZ.

**_S. hystrix_ supplementation has no effect on HDL-c of STZ-induced diabetic rats**

Blood serum levels of HDL-c in Wistar rats showed no significant ($P \geq 0.05$) differences between rats in the control, diabetes, and SHE groups (Table 1). Husni et al. (21) reported that 400 and 600 mg/kg of sodium alginate did not affect HDL-c levels in the STZ-induced rat. However, a dose of 200 mg/kg of sodium alginate could increase HDL-c levels in the rats. *S. polycystum* extracts also increased HDL-c levels to >100 mg/dL (22). The HDL-c levels in alloxan-induced diabetic rats may also increase with alginate administration from *T. ornata* (20).

**_S. hystrix_ supplementation has no effect on LDL-c of STZ-induced diabetic rats**

Blood serum levels of LDL-c in Wistar rats showed no significant ($P \geq 0.05$) differences between the rats in the control, diabetes, and SHE groups (Table 1). Decreased levels of LDL-c on day 15 in the treatment group given

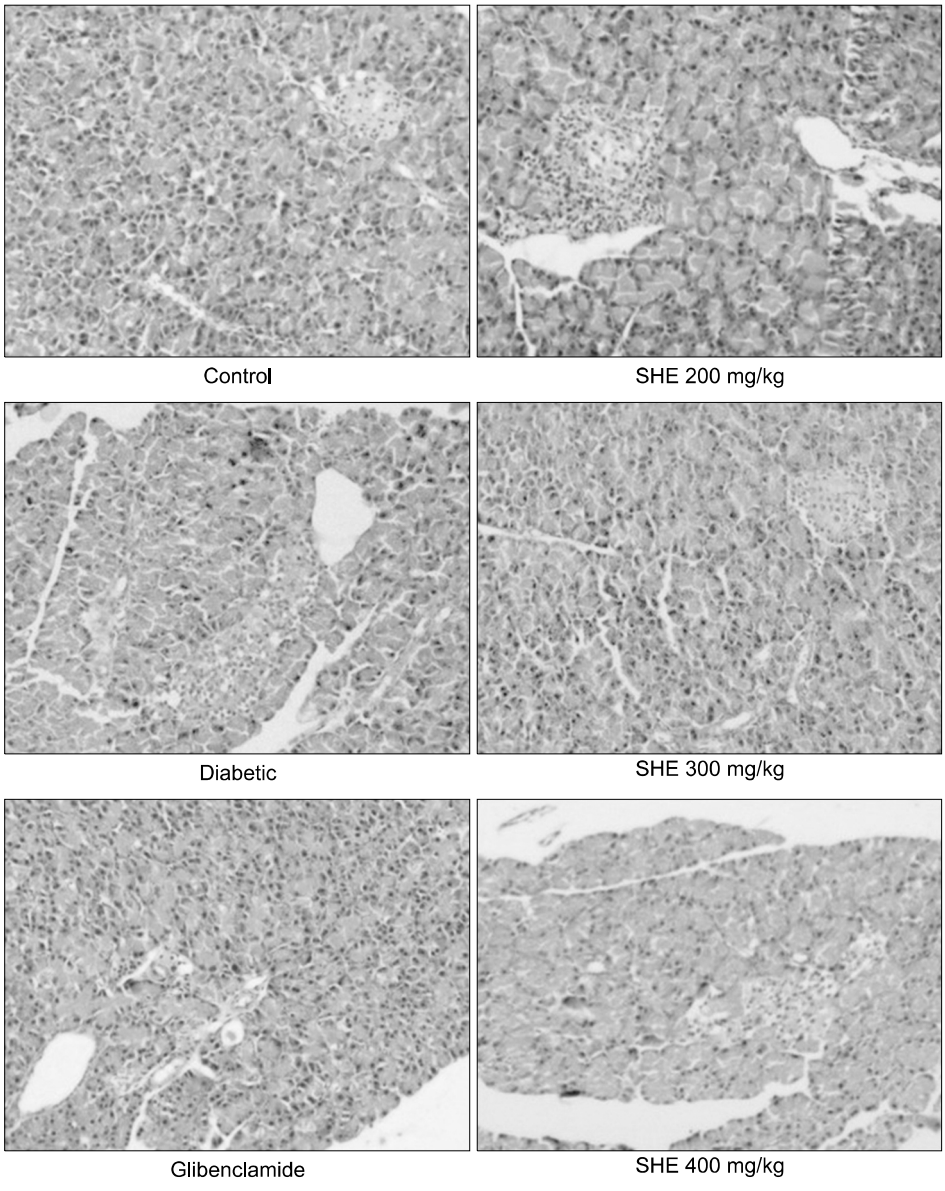


**Fig. 2.** Effects of *Sargassum hystrix* extracts (SHE) and glibenclamide on streptozotocin-induced gastric ulcers in Wistar rats.

*S. hystrix* polyphenols showed that administration of *S. hystrix* polyphenols could lower LDL-c levels as well as glibenclamide. Husni et al. (20,21) also reported that administration of sodium alginate from *S. crassifolium* and *T. ornata* were able to lower LDL-c levels in diabetic rats. The activity of phloroglucinol was also reported to have potential as an antihyperlipidemic agent (24). Phloroglucinol can reduce serum concentrations of fatty acids that lead to decreased LDL concentrations. However, Husni et al. (22) reported an increase in LDL-c levels in the presence of *S. polycystum* extract.

**_S. hystrix_ supplementation was able to prevent cell damage in pancreas of STZ-induced diabetic rats**

The histologic analysis of the diabetic rat pancreas in Fig. 2 shows that STZ induction treated rats have necrosis/cell damage. Motshakeri et al. (25) explained that the STZ-induced rats exhibited small islets of Langerhans including cell degeneration and cell beta reduction. Arya et al. (26) also reported that pancreatic tissue in diabetic rats showed a decrease in the number of Langerhans islands, β cell degeneration, hydropic degeneration, β cell clumping, pyknosis, necrosis, and STZ-induced cell morphology due to some damaged β cells. Based on the results of the histologic analysis, the diabetic group rats had more cellular damage than the glibenclamide group. The increase in the amount of cell damage in the diabetic group was caused by the absence of drug administration, while the group given glibenclamide may have been able to repair cells. The normal control rats had normal cell conditions because they did not receive STZ induction (nondiabetic).

Fig. 3 shows the effect of SHE on the number of normal pancreatic cells of STZ-induced Wistar rats. Pancreatic cells of rats that were not induced by STZ (control) under normal conditions, as well as rats that had been given glibenclamide and SHE 400 mg/kg. The number of normal cells in rats induced by STZ without treatment was 62.50±17.68%, while in the treated rats with SHE 200 and 300 mg/kg the number of normal cells were 75.00±35.36 and 87.50±17.68%, respectively. This suggests that administration of SHE up to 400 mg/kg and glibenclamide at 5 mg/kg may decrease the number of necrotic cells in the pancreas. The result indicated that the cell repair ability of SHE at 400 mg/kg was better than that of SHE at 200 and 300 mg/kg. Motshakeri et al. (25) also reported that *S. polycystum* extracts affected the prevention and repair of pancreatic cell damage. Administration of sodium alginate from *S. crassifolium* (21) and *S. polycystum* extract at 450 mg/kg (22) can also affect the ability to repair necrotic cells.

Diabetic complications can be due to unmanaged diabetes in the long term. Diabetic complications are divided into two types, namely, acute and chronic. Acute complications are triggered by abnormally elevated blood sugar levels, resulting in diabetic ketoacidosis conditions in type 1 and 2 diabetes and hyperosmolar coma in type 2 (27). Hyperglycemic conditions can also cause chronic complications in blood vessels, which usually attack small blood vessels (microvascular) and large blood vessels (macrovascular) (28). Retinopathy, neuropathy, and nephropathy are complications of microvascular diabetes induced by chronic hyperglycemia via several mechanisms, which include the production of end-product advanced glycation processes and the induction of oxidative stress (29). A common complication of macrovascular diabetes is atherosclerosis, where arterial wall narrowing occurs throughout the body as a result of chronic inflammation, and there are arterial wall lesions in the peripheral vascular or coronary system (28).

Diabetic complications can also be caused by damage to the body's defense system, such as oxidative stress, cell membrane damage, DNA damage, and cell death. This study showed that the SHE at 300 mg/kg was able to prevent cell death by repairing pancreatic cell damage in STZ-induced rats; thus, this extract also plays a role in overcoming diabetic complications. Lailatussifa et al. (30) reported that the *S. polycystum* ethanol extract acts as an

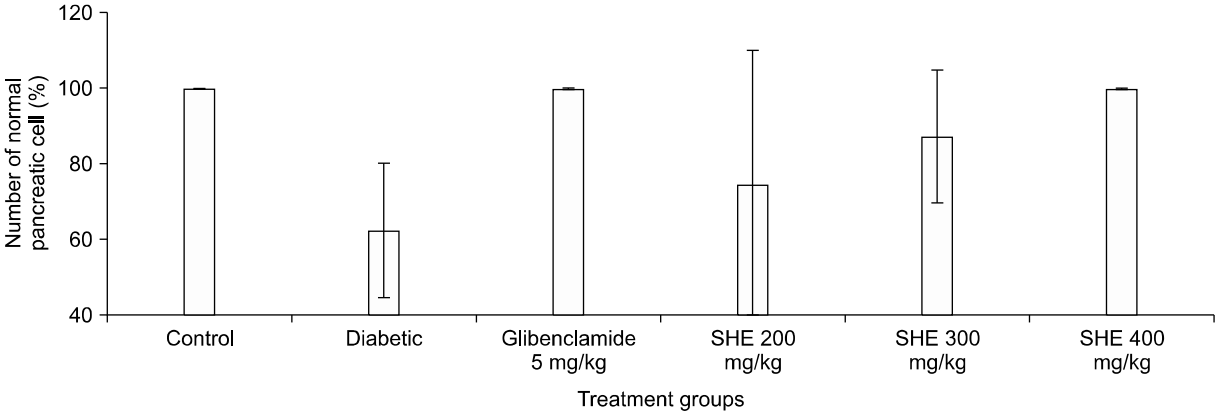


**Fig. 3.** Effects of *Sargassum hystrix* extracts (SHE) and glibenclamide on the number of normal pancreatic cells of streptozotocin-induced Wistar rats.

inhibitor of oxidative stress due to complications of diabetes through the maintenance of gastric mucosal lining. Kidneys in type 2 diabetes in the study by Motshakeri et al. (25) have acute cell swelling, glomerular atrophy, and tubular necrosis, which are characteristics of nephropathy, and may show decreased symptoms of necrosis when administered with *S. polycystum* extract treatment. This shows that the extract of *Sargassum* sp. also plays a role in overcoming the complications of diabetes.

In conclusion, the administration of SHE at a dose of 300 mg/kg was able to decrease the preprandial and postprandial blood glucose levels but did not affect the fat profile of diabetic rats. STZ induction leads to necrosis of pancreatic β cells, and the administration of SHE at 300 ~400 mg/kg could improve necrosis.

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## AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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