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Functionality Screening of Instant Pumpkin Porridge with Cinnamon and Morel Berry Extract for Performance Enhancement of Diabetic Mice's

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Abstract Pumpkin, soybean, cinnamon and morel berry have the potential as functional foods for people with diabetes. Therefore, this research aimed to determine the effect of pumpkin instant porridge formula plus extract on the pancreatic beta-cell repair of the diabetic mice lipid profile induced by alloxan. A total of 7 groups of mice (Mus musculus) strain DDY (Deutschland Denken and Yoken) Japan were grouped as positive control K(+) (diabetic mice), including the group that was given FA porridge (instant porridge group with 120 mg/kg body weight (WB) extract), FB (addition of 240 mg/kg BW extract), FC (addition of 360 mg/kg BW extract), FD (addition of 480 mg/kg BW extract), FE (addition of 600 mg/kg BW extract), and OG Group (Glibenclamide drug). The formula was given for 30 days, starting when the mice had diabetes (fasting blood glucose level ≥126 mg/dL). The histopathological description of the mice pancreas in the instant porridge group improved pancreatic tissue with a decrease in cells undergoing necrosis. The observations of lipid performance also showed a significant effect between several treatments for total and HDL cholesterol levels ($p<0.05$). However, the lipid profile performance of mice with instant porridge did not significantly affect cholesterol levels. The finding indicated that giving pumpkin instant porridge plus cinnamon and morel berry extract can act as a functional food to improve lipid profiles in people with diabetes.

Keywords Diabetes, Dyslipidemia, Functional Instant Porridge, Histopathology, Morel Berry Extract

1. Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia caused by defects in insulin secretion, insulin action or both [1]. In 2015, around 415 million people had diabetes, and this number is expected to rise to 642 million by 2040 [2]. Indonesia's adult population suffering from this disease is around 7 million people. Subsequently, the country was in 7th place with the most diabetes mellitus sufferers in 2010 and is estimated to be ranked 6th globally in 2030 [3].

There had been a decline in pancreatic beta-cell function at the time of the diagnosis of type 2 diabetes [4]. Moreover, dyslipidemia was also frequently found, even with controlled blood sugar levels. The specific characteristics of type 2 diabetes are increased triglycerides, decreased high-density lipoprotein (HDL), and increased low-density lipoprotein (LDL), although total LDL is sometimes normal [5]. Extracts from several plants can control blood

glucose in diabetic conditions at different levels, such as inhibiting glucose absorption from the intestine, increasing insulin secretion from the pancreas and glucose absorption by muscle and adipose tissue, as well as inhibiting the production of hepatocytes [6]. Therefore, there is a possibility to exploit phytochemicals as an effective alternative medicine with limited side effects. The ideal food for diabetic people should contain good and balanced nutritional content, low glycemic index (GI), antioxidant compounds, bioactive components, and dietary fiber [7]. Furthermore, Diabetes mellitus can be controlled by consuming functional foods with bioactive components to positively impact health while considering their sensory value [8].

Jiang and Du and Chang et al. [9,10] reported that pumpkin (Cucurbita moschata, D) could reduce blood glucose levels in diabetic rats induced by streptozotocin, potentially treating type 1 and 2 diabetes or insulin resistance. Soybeans can meet the protein needs of people with diabetes [11]. Meanwhile, cinnamon extracts found polyphenolic compounds, including flavonoids consisting of procyanidins and phenolic components, as well as specific antioxidants such as epicatechin, camphene, eugenol, γ-terpinene, phenol, and tannins. These compounds are useful for fighting oxidants and increasing the potential for insulin activity and glucose and lipid metabolism. Isdadiyanto et al., [12] reported that morel berry (Physalis angulata L.) leaf extract at a 28.5 ml/kg BW dose in mice could improve β pancreatic insulin cells. However, no one has made and analyzed a food formula using the local raw materials mentioned. Hence, using these ingredients in instant food products is expected to optimize the potential of local raw materials [13,14,15]. The development of instant food products aims to make consuming them easier because serving requires a relatively short time. One form of the instant product is porridge in dry form, which is easy to perform by simply adding hot water. In this research, the functional instant porridge of pumpkin plus other local food ingredients described was conducted to examine its effect on the histopathological description of the pancreas and the lipid profile of the experimental diabetic mice (Mus musculus).

2. Materials and Methods

This was experimental research with five different treatments (FA, FB, FC, FD and FE), one drug treatment (Glibenclamide) and one positive control (K^+). The pumpkin and soybean flour were obtained by the local farmer in Padang City, West Sumatra Province. The flours were produced in homemade way where the drying process was conducted by a food dehydrator (Maksindo, FDH16) at 80℃ until the water content was approximately 12%. The cinnamon and morel berry extract were fabricated in the Food Processed Laboratory, Department of Food and Agricultural Product Technology, Andalas University. The extract was made by maceration of ethanol to the dry powder of cinnamon and morel berry with ultrasonic assistance [16]. The extract solution was evaporated using a rotary evaporator (B-ONE, RE-1000VN) until the ethanol was completely removed.

2.1. Instant Porridge Making

The Pumpkin flour was cooked with a 1:4 flour-to-water ratio. It was cooked until gelatinized at a temperature of 60℃ for 10 hours to produce porridge. Similar step was also conducted on soybean flour to make the soybean porridge. These two porridge masses were then homogenized (Ultra Thurrax IKA T 25) with the ratio of (75:25) ratio. On the other hand, the cinnamon extract was mixed with the morel berry extracts with the ratio of (7:3) to produce the final extract that was added to the Pumpkin and soybean porridge. The final porridge was produced as described in table 1. The porridge dan extract was stored in the refrigerator (Sharp, SJ-IS71PGA-BK) and mixed according to the formula prior to experimental daily.

Table 1. Instant porridge formula

Composition	FA	FB	FC	FD	FE
Pumpkin and soybean porridge (g)	100	100	100	100	100
Cinnamon and morel berry extract (mg)	120	240	360	480	600

2.2. Experimental Animal Preparation

All experimental handling procedures were approved by the Committee of Research Ethics of Faculty Medicine Andalas University (Ethics approval number: 195/KEP/FK/2019). In this experiment, 63 male mice (*Mus musculus*) strain DDY (Deutschland Denken and Yoken) Japan (divided into 7 groups, each with n=9), 2-3 months old with 20 – 30 g body weight, were adapted to feed in a new cage for ±7 days. The dose for porridge feed was 126 mg / 20 g body weight of mice. The control treatment was fed by general diet while drug treatment was treated by Glibenclamide. During adaptation, animals were given a standard ration such as pellets (PT. Charoen Pokphand, Medan) in 10 g/head/day and drinking water *ad libitum*.

2.3. Diabetes Induction

The adapted animals fasted for 16 hours before receiving a single intraperitoneal (IP) injection of alloxan monohydrate (SIGMA ALDRICH, Steindhelm) at a concentration of 150 mg/20 g BW. Mice were declared diabetic after checking fasting blood glucose levels which was ≥126 mg/dL. The functional instant porridge effect testing was carried out after the mice had diabetes. The porridge was made daily where the preparation time took time approximately for 2-3 h.

2.4. Histopathological Description of the Pancreas

The histopathological description of the pancreas was conducted by dissecting the test animals. The pancreas was taken, and a histopathological examination was performed with hematoxylin eosin (HE) staining. Histological observations were carried out on liver tissue preparations from experimental mice (Mus musculus) which were fixed using hematoxylin eosin's fixation solution for 4 hours. The observation criteria contain a description of the quality of the liver tissue preparations seen from the cell nuclei, cytoplasm, boundaries between cells and the uniformity of the color of the liver tissue preparations. These results were obtained based on observations using a microscope with a magnification of 10x40. The level of cell damage in pancreatic tissue was grouped based on the score of the necrotic cells. Score 0 indicated that there was no cell necrosis; score 1 indicated that there was less than ¼ of necrotic from pancreatic beta cells; score 2 indicated the necrotic was observed from ¼ to ⅔ of pancreatic beta cells; score 3 indicated the necrotic was observed from ⅔ to ¾ of pancreatic beta cells; and score 4 indicated that there was ¾ of necrotic from total pancreatic beta-cell.

2.5. Measurement of Lipid Profile

Measurement of lipid profile with blood cholesterol levels was determined by the enzymatic method [16] using the Photometer 5010V5+. The blood was taken from the orbital sinus using a micro hematocrit. After being accommodated, it was centrifuged to obtain serum or blood plasma. The measured blood cholesterol levels were total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and triglyceride (TG). To determine total cholesterol (TC) and triglyceride (TG) levels, 10 µL of serum was taken, and 1,000 µL of cholesterol and HDL reagents were added and read on the Photometer. HDL-C determination was conducted by adding 500 µL of reagent to 250 µL of serum, then centrifuged for 10 minutes. The supernatant (100 µL) was taken and 1,000 µL of cholesterol reagent was added and incubated for 10 minutes. The readings were performed on the Photometer, and the LDL-C was determined using Friedewald's equation as follows:

$$\text{LDL-C} = \text{Cholesterol} - \text{HDL-C} + (\text{TG}/5)$$

2.6. Blood Sugar Level Measurement

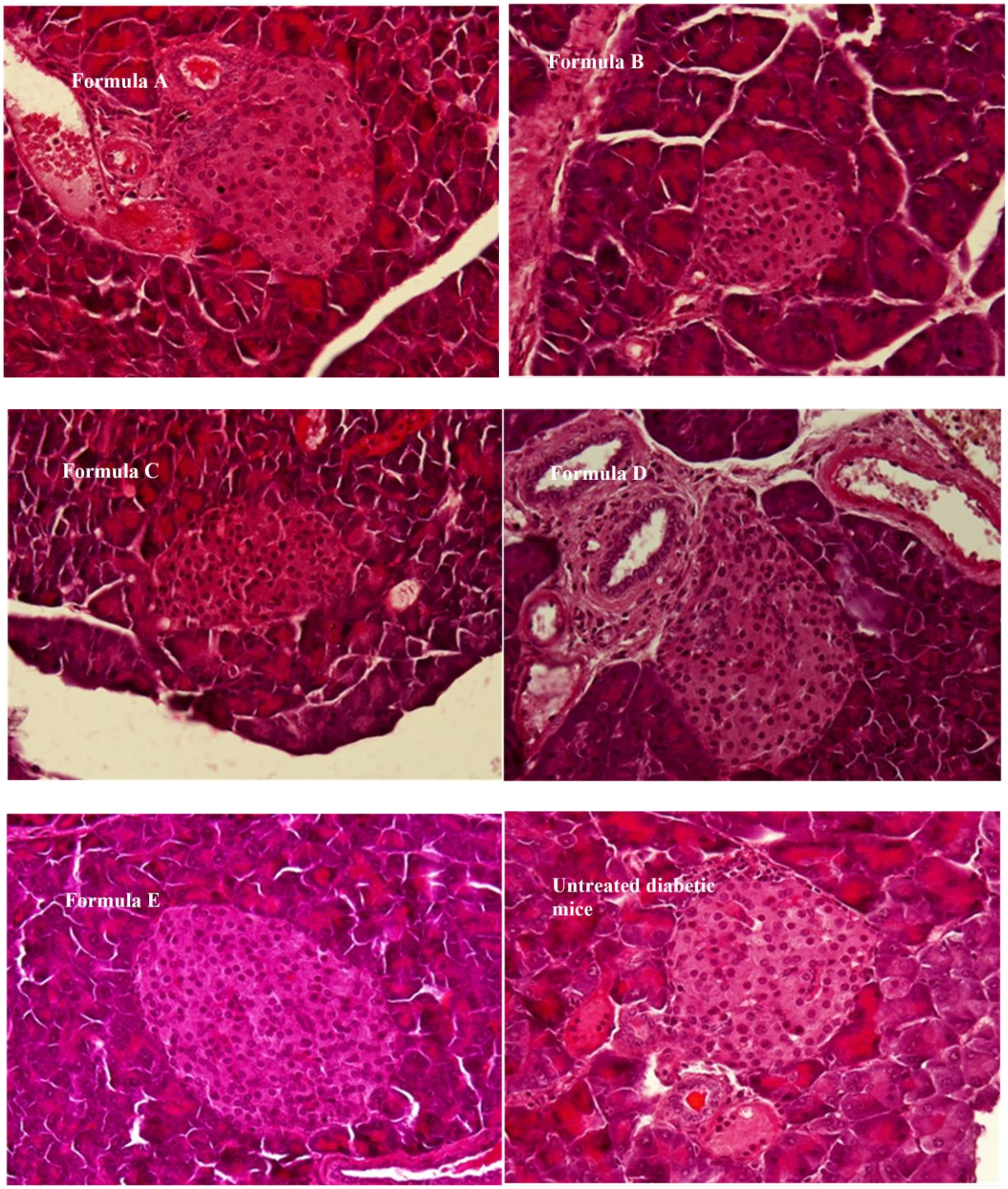
Blood sugar measurements were carried out after the mice had alloxan-induced diabetes and treatment, and the mice were reared and treated daily for 30 days. Observations were made by taking blood and measuring glucose levels on day 0 and the end of the 30th day. Fasting blood glucose measurements were carried out using Blood glucose test strips Easy Touch® following the procedure from the apparatus manufacturer. The blood was taken from the tail of the mice, which had previously been cleaned with 70% alcohol. The blood sample was then placed on the glucometer, and the glucose levels were read on the Gluco DrTM screen after 10 seconds of observation in mg/dL.

2.7. Statistic Analysis

The experiments were conducted at least sevenplicate. The data were statistically analyzed by one-way ANOVA (Analysis of Variance) and further tested with Duncan's New Multiple Range Test to obtain the differences between treatments. Analysis was performed using IBM SPSS Statistics version 25.

3. Results and Discussion

The histopathological observations showed an improvement in pancreatic tissue in the treatment of pumpkin instant porridge plus extract addition which is shown in Figure 1. Figure 1 shows that in the treatment of formulas A to E, most pancreatic islet cells underwent a degeneration process with more eosinophilic cytoplasm. Improvement in pancreatic tissue for the treatment of instant porridge includes endocrine cells that begin to regenerate to a normal shape. Some cells showed necrotic appearance, darkened (pyknotic) (arrowhead), and fuzzy nuclei (karyolysis) (arrow). Necrosis in ß pancreatic cells occurred due to its membrane depolarization after alloxan administration in test mice. It has several stages, starting with the cell nucleus shrinking, called pyknosis. The cell nucleus disintegrates and forms fragments of chromatin material scattered within the cell called karyorexia. The dead cell nucleus can no longer be stained, known as karyolysis [17].


Formula A
Formula B
Formula C
Formula D
Formula E
Untreated diabetic mice

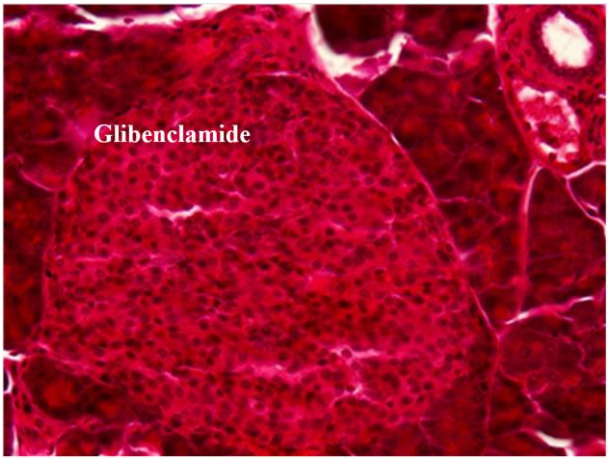


Figure 1. Islets of Langerhans pancreas histology at 400x magnification. (Formula A, B, C, D, untreated mice and Glibenclamide treatments)

The level of cell damage in pancreatic tissue is grouped based on the score of pancreatic cells that experienced necrosis. The percentage of score acquisition can be seen in Table 2. Although there are still some that degenerate, and the number is not more than one positive control (K(+)), which is supported by the data presented in Table 2. The percentage of absence of necrosis (score 0) in formulas A and B administration is more significant than the treatment with Glibenclamide. This shows that the administration of instant porridge, cinnamon, and morel berry extracts can repair endocrine cell damage due to alloxan induction to increase insulin secretion.

Description:

- Score 0 is no pancreatic cell necrosis
- Score 1 is less than ¼ total pancreatic beta cells are necrotic
- Score 2 is ¼ - ⅔ total pancreatic beta cells are necrotic
- Score 3 is ⅔ - ¾ total pancreatic beta-cell necrosis
- Score 4 is ¾ to total pancreatic beta-cell necrosis

The results of data analysis using Oneway Anova in Table 3 show a significant effect between treatments for total cholesterol (TC) and HDL cholesterol levels ($p<0.05$). However, there is no significant effect between treatments for LDL cholesterol and triglyceride levels. Table 3 shows that total cholesterol (TC) and HDL levels significantly differ between FA and FB treatment. However, FA was not significantly different from glibenclamide (OG) treatment. LDL cholesterol and triglyceride (TG) levels also do not differ significantly between treatments. The lipid profile of the diabetes test mice was still in the normal range and not significantly different from the OG treatment group. This shows that the diabetic mice tested were still under controlled conditions and had dyslipidemia disorders. Dyslipidemia is a lipid metabolism disorder characterized by an increase or decrease in the lipid fraction of the plasma. A previous study showed that about 60% of people with diabetes had dyslipidemia [17]. The results of research by Ristić Medić *et al.* [18] showed that the administration of soy-based food products in diabetic patients has the capacity to improve serum lipid profiles and to some extent affect the reduction of glucose levels in patients with type 2 diabetes. That soy product is well tolerated without real side effects. This functional instant porridge is also made from soybean flour. Its flavonoid and isoflavone content allow soybeans to lower cholesterol by inhibiting the activity of the HMG-CoA reductase enzyme. Additionally, Bintari and Parwati [19] proved that yogurt from black soybeans can reduce cholesterol and triglyceride levels in dyslipidemia patients aged 40-55 years.

Table 2. Percentage of necrosis in pancreatic beta cells

Treatment	Percentage of score obtained in the level of pancreatic cell necrosis (%)					Average Area of fhans Island (μm^2)
	0	1	2	3	4	
Formulas A	24.14±0.22	68.97±0.7	6.90±0.01	-	-	8253.89±12
Formulas B	44.44±0.14	50.01±0.3	5.55±0.01	-	-	1181.63±35
Formulas C	20.59±0,21	76.47±0.1	2.94±0.01	-	-	4715.07±23
Formulas D	11.11±0.12	88.89±0.2	-	-	-	3019.61±24
Formulas E	17.86±0.13	82.14±0.2	-	-	-	3212.71±57
Untreated Diabetic mice (K+)	-	16.67±0.1	55.56±0.01	27.78±0.1	-	6341.61±45
Receiving Glibenclamide OG	20.01±0.2	80.01±0.3	-	-	-	3272.72±35

Table 3. Average lipid profile of diabetic mice

Treatment	TC (mg/dL)	HDL (mg/dL) (Mean ± SD)	LDL (mg/dL) (Mean ± SD)	TG (mg/dL)
Formulas A	147.5 ± 4.95^{b}	71.7 ± 4.9^{b}	5.3±2.97	106.7±7.8
Formulas B	65.67 ± 1.16^{a}	49.5 ± 13.4^{a}	20.5±2.97	88.67±11.6
Formulas C	92 ± 12.7^{ab}	62.5 ± 5.0^{b}	17.47±7.5	79.5±13.4
Formulas D	105.7 ± 6.1^{ab}	46 ± 11.4^{a}	39.4±12.8	84.5±3.5
Formulas E	88 ± 4.2^{ab}	55.7 ± 7.5^{ab}	7.7±5.2	157.5±0.7
Untreated	100.3 ± 13.6^{ab}	55.3 ± 14.0^{ab}	19.3±3.5	109±5.7
Received Glibenclamide	110.3 ± 13.6^{ab}	55.3 ± 14.0^{ab}	12.5±2.97	119±2.7

Pumpkin contains carbohydrates consisting of galactose, glucose, arabinose, xylose and glucuronic acid [20,21]. Fu *et al.* [22] reported that pumpkin polysaccharides can reduce blood glucose and lipid levels in diabetic rats. Zhang *et al.* [23] reported that polysaccharides from pumpkin have chemical and pharmacological properties that can increase insulin levels significantly, reduce blood glucose and improve its tolerance. The polysaccharides in soybeans can also suppress postprandial glucose and triglyceride levels, as well as reduce the postprandial insulin-to-glucose ratio [24].

Giving instant porridge decreased blood glucose levels by 63.25% from the initial average blood glucose of 202.67 mg/dL and final glucose after treatment of 67.13 mg/dL. Instant porridge as a functional food has a perfect effect on reducing blood glucose levels. Cinnamon extract also greatly affects the decrease due to its antioxidants, such as cinnamaldehyde and methyl hydroxy chalcone polymer (MHCP), as derivatives of polyphenolic compounds [25] and pure polymer of hydroxy chalcone with activity similar to insulin (insulin-like activity) to stimulate glucose oxidation. The content of flavonoids and tannins in cinnamon functions as an inhibitor of α-glucosidase activity [26]. Cinnamon extracts play a direct role in lipid metabolism to prevent hypercholesterolemia and hypertglycerides, as well as reduce the level of free fatty acids in plasma and increase HDL in subjects with type 2 diabetes mellitus [27].

The α-glucosidase enzyme is responsible for converting carbohydrates into glucose in the small intestine [28]. The inhibition can delay the complex carbohydrate's decomposition to monosaccharides in the intestines. Hence, glucose is released more slowly, and its absorption into the blood is also less rapid, and lower [29,30]. This effect also reduces postprandial blood glucose levels in type 2 diabetes mellitus [28].

Phytochemical screening results showed that its simplicia and water extract from morel berry contains alkaloids, flavonoids, saponins, polyphenols, steroids and triterpenoids, monoterpenoids, and sesquiterpenoids [31,32]. Based on the research by Ahmad et al. [33], morel berry extract identified by GC-MS showed the presence of Nordextromethorphan unsaturated fatty acids and alkaloids. Nordextromethorphan alkaloids are similar to morphine derivative compounds that can cure neuropathic diabetes. The chloroform fraction also contains fatty acids such as Hexanoic acid, Hexadecanoic acid, 9-Octadecenoic acid, Oleic acid, and Octadecanoic acid. The body needs these fatty acids as precursors of the hormone content regulating many complex functions. Oleic acid is an unsaturated fatty acid whose mechanism of action inhibits glucose production and is also an antioxidant that can counteract the free radical's formation in the body. There is a significant correlation between the adipocyte membrane of oleic acid and insulin, which mediates glucose transport.

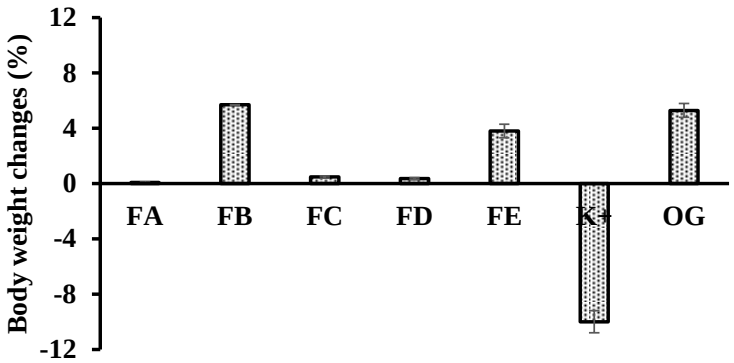


Figure 2. Body weight change of mice (FA=formulas A, FB= formulas B, FC=formulas C, FD= formulas D, FE=formulas E, K+= untreated diabetic mice, OG= received Glibenclamide)

Figure 2 shows the average change in the weight of the mice with different percentages. Many factors, such as stress, influence their weight loss, while weight gain may be caused by the repair of β cells in the pancreas, which have improved to produce insulin. In diabetes, there will be weight loss, and the clinical symptoms include polyphagia, polydipsia, and polyuria. It is caused by insulin deficiency or resistance, affecting fat and protein metabolism [34]**.** Giving instant porridge with the addition of cinnamon and morel berry extracts can increase the weight of the mice along with the decrease in the blood glucose levels of the mice which show a normal decrease. Decreased blood glucose levels, indicating the occurrence of repair of the pancreas in cells to secrete insulin, to convert glucose into energy. Thus, increasing normal appetite. This is in accordance with Guz *et al*. (2001) [35] who reported that the ability to regenerate pancreatic beta cells in hyperglycemic mice depends on the regulation of normal blood glucose levels. In steeping cinnamon powder there is a compound double-linked procyanidin type-A polymerase which has insulin-like activity that can play a role in regulating normal blood sugar levels [36].

4. Conclusions

Based on the results, histopathological observations with HE staining and calculation of the necrosis level indicate an improvement in the pancreas tissue of mice after being given instant porridge with pumpkin, cinnamon and morel berry extracts. The administration in all treatments also showed that the overall formulas were not significantly different from Glibenclamide. The effects of lowering glucose, lipid profile, and weight gain were not significantly different from Glibenclamide drug administration. Therefore, instant porridge products have the potential to be used as food for people with diabetes.

Conflict of Interest

All authors declare no conflict of interest.

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