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ANTIDIABETIC ACTIVITY OF BARLEY PORRIDGE ON POSTPRANDIAL BLOOD GLUCOSE AND HISTOPATHOLOGY OF ALLOXAN-INDUCED DIABETICS RATS

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ABSTRACT

Diabetes mellitus (DM) is a critical global health issue, characterized by high morbidity and mortality rates associated with various complications. In Indonesia, the incidence is projected to reach 28.6 million by 2045, positioning the country among the highest globally. The aim of this study is to evaluate the effects of barley as a food ingredient on blood sugar levels and pancreatic histopathology. The study involved dividing the mice into six groups, with six mice in each group. These groups were: normal control (K), negative control (KN) induced with alloxan 125 mg/kg BW intraperitoneally, positive control (KP) with oral metformin 9 mg/200 g BW, normal barley rats (P1), DM barley rats (P2), and DM rats with mixed food (P3). Phytochemical screening was also conducted on barley porridge to identify the presence of flavonoids, glycosides, alkaloids, and saponins. The KP and P2 groups were more effective in reducing blood sugar levels than the KN and P3 groups. In the Kruskal-Wallis test, there was no significant difference between groups P2 and KP on postprandial blood sugar levels, indicating that barley produced an effect similar to metformin (p-value = 0.0395). Pancreatic histopathology observations showed that groups P2, P3, and KP had the same damage score of 2. Barley demonstrated a comparable antidiabetic effect to metformin, as evidenced by similar results in blood sugar reduction and pancreatic histopathology scores in the P2 and KP groups.

KEYWORDS *Barley, Diabetic, Phytochemicals, Pancreas Histopathology*.

INTRODUCTION

Diabetes Mellitus (DM) occurs due to the failure of pancreatic beta cell activity in the process of insulin production or the body's inability to utilize insulin effectively. (Organization, 2019) DM is a silent killer disease, where the sufferer is unaware that he or she has DM before complications appear (Ahuja et al., 2020; Milita et al., 2021). According to the International Diabetes Federation (IDF), Indonesia will maintain its fifth place in the world in the number of diabetics

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reaching 28.6 million people by 2045, with China, India, Pakistan, and the United States in the top four. (Sun et al., 2022) The incidence of DM has now reached 422 million people with high morbidity and mortality rates from macrovascular and microvascular complications. (Reid et al., 2021)

DM treatment includes medical nutrition therapy, diabetes medication, insulin therapy, alternative medicine, and surgery (Lestari & Zulkarnain, 2021). The recommended medical nutrition therapy in DM patients is a low-sugar and high-fiber diet (Hwalla et al., 2021), one example of a recommended diet is legumes, including barley instead of rice and flour (Minaiyan et al., 2014).

Barley is a grain of the Poaceae family that contains beta-glucan fiber (β-glucan), phenolic acids, flavonoids, phenol amides, Jordan, saponin, and other phytochemicals (Fuse et al., 2020; Idehen et al., 2020) that reduce the risk of cardiovascular disease, type 2 diabetes, obesity and some types of cancer. (Bohl et al., 2024; Shvachko et al., 2021) Several studies prove the effectiveness of barley in lowering blood sugar levels. (Bohl et al., 2024; Ham et al., 2022; Idehen et al., 2020; Shvachko et al., 2021; Sivieri et al., 2022) However, the effect of barley as a food ingredient on blood sugar levels and pancreatic histopathology is unknown. This experiment was conducted to analyze the antidiabetic impact and influence on pancreatic histopathology of barley porridge.

Previous studies have shown that barley consumption has the potential to lower blood sugar levels in diabetics. For example, a study by Minaiyan et al. (2014) found that barley was effective in lowering blood glucose in rats induced with diabetes, while Fuse et al. (2020) observed that barley consumption high in β-glucan could lower blood sugar and postprandial insulin levels in patients with type 2 diabetes. Several other studies have also shown the role of β-glucan and other soluble fiber content in barley to stabilize blood glucose levels by increasing intestinal lumen viscosity and glucose binding.

This study offers innovation by comprehensively examining the antidiabetic effects of barley porridge not only on blood sugar levels but also on pancreatic histopathology. The focus on changes in the cellular structure of the pancreas in alloxan-induced rats provides a new dimension in understanding the mechanism of barley as a natural antidiabetic agent. Thus, this study contributes to a deeper understanding of the effects of barley on pancreatic cell regeneration, which has not been widely discussed in previous studies.

This study aims to examine the effectiveness of barley porridge as an antidiabetic agent in reducing postprandial blood sugar levels and affecting pancreatic histopathology in diabetic-induced rats. In addition, this study aims to evaluate the potential of barley in providing effects equivalent to metformin, so that it can be considered as an alternative nutritional therapy for diabetic patients.

This study is expected to provide new insights for the development of nutritional therapy based on natural ingredients in treating diabetes, especially for people who need natural alternatives to chemical treatments. In addition, the results of this study can also provide a scientific basis for the use of barley as a functional food ingredient that supports pancreatic health, thus contributing to the development of the healthy food industry and herbal medicine.

RESEARCH METHOD

The research was carried out at the Laboratory of the Faculty of Pharmacy, University of North Sumatra, in April-May 2024. The research method applied is an experimental study with a pretest-posttest randomized control group design. This research has met the requirements set by the Health Research Ethics Commission of the Faculty of Medicine, Universitas Prima Indonesia No. 013/KEPK/UNPRI/I1/2024

1. Tool

Pots, spoons, stoves, blenders, 1 mL syringes (ONEMED), scales, GCU 3 in 1 easy touch glucometer and glucose strips, surgical tubs, sample pots, dissecting sets, object glass, cover glass and Olympus CX31 microscope (OLYMPUS, Japan).

2. Material

Acehnese barley seeds, male Wistar rats, aquadest, metformin HCl (HEXAPHARM, Indonesia), standard feed, aloxane, alcohol 70% (MERCK, Indonesia), chloroform (MERCK, Indonesia), NaCl 0.9% (WIDATRA, Indonesia), Hematoxylin dye and eosin dye (MERCK, Indonesia).

3. Procedure

a. Preparation of Barley Porridge

Barley kernels are washed under running water, drained, and weighed in as much as 50 g. Barley seeds are boiled with 700 ml of water until they shrink and then blended until smooth

b. Phytochemical Examination

Barley porridge is checked for active content such as flavonoids, tannins, saponins, glycosides, alkaloids, and steroids/triterpenoids.

c. Preparation of Trial Animals

The sample used was a 2-3 month male Wistar rat with a body weight of 200 - 250 grams obtained from a local farm in Medan. Experimental animals will be acclimatized for seven days. The rats were fed and water ad libtium during the acclimatization process.

The mice were divided into six groups, with each group totaling six heads, namely, the normal control group (N), the positive control (KP) group given metformin 9 mg/200 grams of BB orally, the negative control (KN), the normal mice fed barley (P1), the DM mice fed barley (P2) and the DM mice fed barley mixed with standard feed (P3). Rats were induced with aloxan 125 mg/kg BB intraperitoneally.

d. Treatment of Trial Animals

The intervention was initiated when the postprandial 2-hour blood sugar levels (KGD2PP) of the mice reached □ 200 mg/dl. The intervention was carried out for 28 days, with KGD2PP checks carried out weekly.

e. Preparation of Pancreatic Preparations

The pancreas will be removed and stored in a sterile pot containing 10% formalin buffer. The samples were fixated with formalin and then soaked with liquid paraffin at a temperature of 60□ C at the embedding stage. Next, the process of paraffin blocks three μm thick is carried out and then placed in a water bath with

a temperature of 37□C for 24 hours. Staining was carried out using a solution of hematoxylin and eosin (HE) (Sarfraz et al., 2021) Observation of the pancreatic organ was carried out under a microscope with a magnification of 400x.

f. Pancreatic Histopathology Readings

Parameters used to assess cell damage to the pancreatic organ:

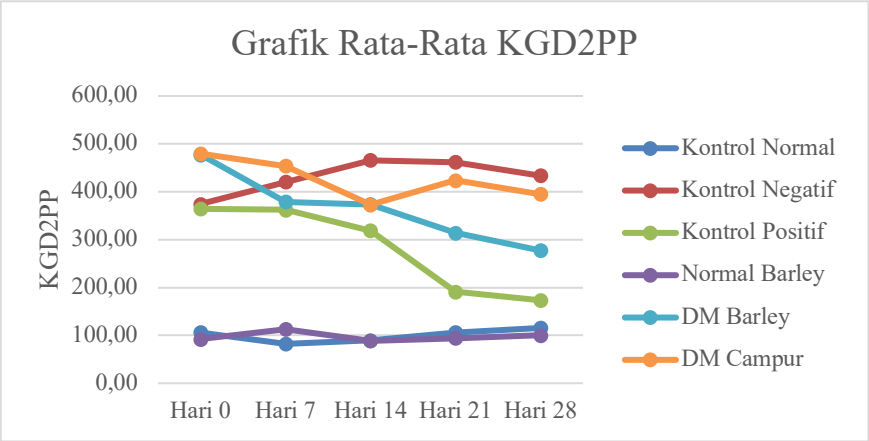

Figure 1. Graphic KDG2PP

1) Score 0: normal cell structure with no change in Langerhans islet boundary.
2) Score 1: normal cell structure with changes in the boundary of the Langerhans island and cell degeneration has occurred.
3) Score 2: cell structure is irregular, the boundary of Langerhans islets is unclear, and there is a decrease in the number of cells without necrosis.
4) Score 3: cell structure is irregular, the boundary of Langerhans islets is unclear, there is a decrease in the number of cells, and most cells have necrosis.
5) Score 4: abnormal cell shape, Langerhans islet organ boundary becomes very unclear, cells are greatly reduced, and almost all cells are necrosis occurs (17)

4. Data Analysis

A normality test with Shapiro-Wilk, a homogeneity test with the Levene Test, a non-parametric test with Kruskal-Wallis, and a follow-up test were carried out to compare the results between experimental groups.

For statistical analysis, several tests were conducted as follows:

a. Normality Test: Shapiro-Wilk was used to test the normality of KGD2PP data to determine whether the data was normally distributed.

b. Homogeneity Test: Levene's test was used to emit homogeneity of data variance between groups. The results of this normality and homogeneity test determine the selection of further statistical tests.

c. Kruskal-Wallis Nonparametric Test: Given that the KGD2PP data was not entirely normally distributed, the Kruskal-Wallis test was used to compare differences in KGD2PP between groups. This test was chosen because it is robust to the assumption of normal distribution and is suitable for small samples, so it is more appropriate in this study which has limited subjects.

d. Further Test: After the Kruskal-Wallis test showed a significant difference between groups, a post-hoc test using Mann-Whitney U was continued to identify significantly different group pairs. This test is relevant because the post-hoc method avoids a higher risk of type I error due to repeated calculations.

RESULT AND DISCUSSION

1. Phytochemical Screening Results

The results of the phytochemical screening of barley porridge can be seen in Table 1

Table 1. Shrine Fitokimia Bubur Barley (Hordeum vulgare)

Active Ingredients	Interpretation
Flavonoid	Positive
Tannins	Negative
Sapronin	Negative
Glikosida	Positive
Alkaloid	Positive
Steroid/ Triterpenoid	Positive

2. Observation Results of KGD2PP

KGD2PP was monitored on day-0, day-7, day-14, day-21 and day-28.

Table 2. Rata-Rata KDG2PP 1

	Day-0	Day-7	Day-14	Day-21	Day-28
K	106,25 ± 13,74	82.25 ± 7.54	89,25 ± 26,16	106,00 ± 14,12	115,50 ± 12,92
KN	374,50 ± 152,12	420,25 ± 125,73	465,50 ± 74,48	461,50 ± 98,08	433,75 ± 112,21
KP	364,25 ± 38,35	362,25 ± 259,11	318,50 ± 89,52	191,00 ± 14,35	173,25 ± 14,01
P1	91.75 ± 7.54	112,75 ± 16,00	88,50 ± 12,92	94.25 ± 9.60	100,25 ± 5,74
P2	477,50 ± 93,65	379,00 ± 71,64	373,50 ± 153,55	314,25 ± 71,36	277,25 ± 58,09
P3	479,50 ± 85,30	453,75 ± 39,81	373,00 ± 75,34	423,50 ± 128,06	395,25 ± 51,18

3. Results of Histopathological Observation of Wistar's Pancreas

Damage and proliferation of pancreatic cells on histopathological examination are assessed by a scoring system.

Table 3. KDG2PP Comparative Further Test Day 28

Group 1	Group 2	P value
K	KN	0,004
	KP	0,355
	P1	0,582

Group 1	Group 2	P value
	P2	0,076
	P3	0,003
KN	K	0,004
	KP	0,051
	P1	0,001
	P2	0,271
	P3	0,960
KP	K	0,355
	KN	0,051
	P1	0,140
	P2	0,395
	P3	0,045
P1	K	0,582
	KN	0,001
	KP	0,140
	P2	0,020
	P3	0,001
P2	K	0,076
	KN	0,271
	KP	0,395
	P1	0,020
	P3	0,250
P3	K	0,003
	KN	0,960
	KP	0,045
	P1	0,001
	P2	0,250

DISCUSSION

The results showed no significant difference between groups K and P1 (value p = 0.582). However, KGD2PP in the P1 group was more stable compared to the normal control group (Figure 1).

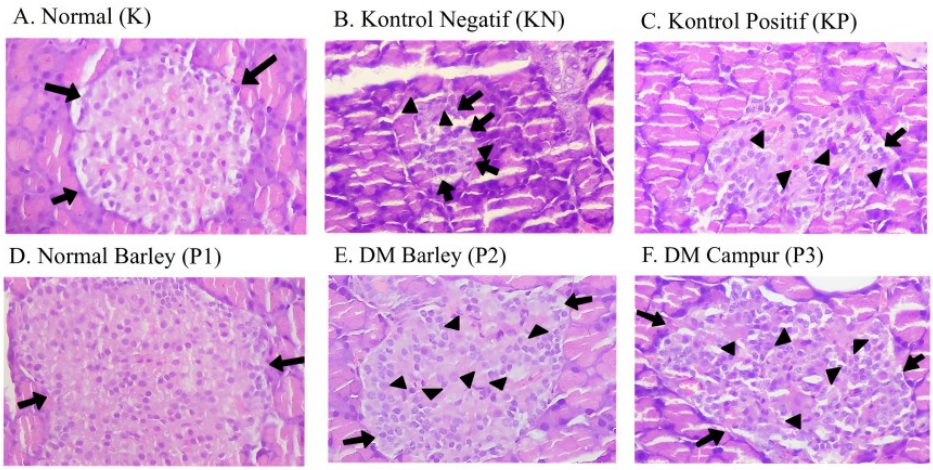

Figure 2. Overview of Pancreatic Histopathology

Caption (400x magnification):

a. A: Score 0 (Arrow: normal Langerhans island) (12.32x12.52 cm)
b. B: Score 4 (Arrow: the number of cells on the island of Langerhans is greatly reduced, the boundary with acini pancreas is unclear; Triangle mark: necrotic cells) (5.63x3.89 cm)
c. D: Score 1 (Arrow: normal Langerhans island) (10.81x15.12 cm)
d. C, E, and F: Score 2 (Arrow: cells on the island of Langerhans decreased, the border with the pancreas acini is away, and the triangular mark: degenerative cells) (C: 13.07x6.75 cm; E: 14.54x12.76 cm; F: 9.84x16.48 cm)

The KP and P2 groups experienced a more significant decrease in KGD2PP than the KN and P3 groups (Figure 1). The KP and P2 groups did not differ significantly (p-value = 0.395). This shows the effect of barley is the same as metformin. This is supported by the results of pancreatic histopathology, where the KP, P2, and P3 groups have the same score of 2.

The histopathological picture in siloxane-induced mice is characterized by changes in cell shape, vacuolization of pancreatic acidosis cells, a decrease in the density of the islands as a whole as well as necrosis. Aloxans induce oxidative stress, which contributes to the damage of these cells through the production of reactive oxygen species (ROS), such as hydrogen peroxide and hydroxyl radicals (Solikhah et al., 2022). It can be seen that the KN group has a relatively smaller cell size compared to the KP, P2, and P3 groups.

The comparison of the P2 and P3 groups was also not significantly different (p-value = 0.250). So, it can be concluded that barley, both pure and blended, can lower KGD2PP with superior pure barley. This is in line with the research of Ham et al. (2022) (Ham et al., 2022), who stated that barley can help lower blood sugar levels because barley is found β - glucan is one of the soluble fibers found in oats, barley, and wheat.

Barley has a low glycemic index, which is < 55, so it is safe for people with diabetes to consume (Boanta et al., 2019). Barley is also famous for its high fiber content, which is around 11-34% of total dietary fiber and 3-20% soluble fiber. The

content that plays a big role in reducing blood sugar and cholesterol levels is β-glucan. (Azam et al., 2019; Ham et al., 2022)

The β-glucan's work is to increase the viscosity of the intestinal lumen. β-glucan will bind to glucose, bile acids, monoglycerides, free fatty acids, and cholesterol so that it will decrease the release of glucose in the intestinal lumen and increase fecal excretion, which leads to a decrease in blood sugar levels. (Pino et al., 2021) This decreases the duration of metabolic transit in the intestines, slowing down the breakdown of glucose and the absorption of carbohydrates in the intestines. (Sivieri et al., 2022)

Based on the phytochemical screening of barley porridge (Hordeum vulgare) (Table 1), it is known that there are flavonoids, glycosides, alkaloids, and steroids/triterpenoids. Barley also contains a variety of other bioactive components such as proanthocyanidins, catechins, phenolic acids, saponins, procyanidin B3, procyanidin C2, prodelphinidin B3, and the alkaloid hordenine. (Bibi & Husain, 2024; Mahajan et al., 2023; Raj et al., 2023) This phytochemical content acts as an antioxidant, anti-inflammatory, and antiproliferative. (Hamany Djande & Dubery, 2024).

Phenolic compounds and flavonoids can increase the enzyme catalase so that it will break down hydrogen peroxide into oxygen and water and have an antioxidant effect that reduces the amount of ROS. The antioxidant effect inhibits cell damage to the pancreas and a decrease in insulin receptors. In addition, antioxidants also reduce apoptosis and promote pancreatic beta-cell regeneration. (PRATAMA et al., 2020)

Anthocyanins, flavonols, and proanthocyanins are the three main forms of flavonoids found as glycoside derivatives such as cyanidin-3-glucoside, penidine-3-glucoside, and delphinidin-3-glucoside. (Raj et al., 2023), which can act as an anti-□-glucosidase agent. (Promyos et al., 2020)

The combination of the alkaloid hordenine and insulin can lower sugar levels by lowering pro-inflammatory cytokines such as IL-1α/β and IL-6 and acting as antioxidants. Barley also contains steroids and triterpenoids in the form of saponins. Saponins affect insulin synthesis through the stimulation of glucose transporter-4 (GLUT-4) and decrease the activity of Glucose 6-phosphate (G6P). (Calderon Guzman et al., 2020)

Hordatin compounds in barley contain a guanide group structure similar to metformin and can bind to the M3 muscarinic receptor which plays a role in the regulation of glucose homeostasis. (Hamany Djande & Dubery, 2024) It is this compound that causes the mechanism of action of barley similar to metformin.

The role of these phytochemical compounds can be proven from histopathological results, which conclude that metformin, barley, and barley mixed with normal feed cause the same effect in regeneration and prevention of pancreatic cell damage with a score of 2.

According to Minaiyan et al. (2014): This study examined the effects of barley (Hordeum vulgare L.) on blood glucose levels in streptozotocin-induced diabetic rats. The results showed that barley was able to significantly lower blood

glucose levels in diabetic rats. This finding strengthens the evidence that barley can act as a natural ingredient to control blood sugar levels in diabetics.

In contrast to Fuse et al. (2020): This clinical study shows the impact of barley with high β-glucan content on postprandial blood sugar levels in patients with type 2 diabetes. The results show that barley can significantly lower sugar and insulin levels. The β-glucan content in barley increases intestinal viscosity and inhibits glucose absorption, thereby controlling blood sugar levels after meals.

Meanwhile, according to Ham et al. (2022): This study examined the effects of barley extract on diabetic rats through the PI3K-Akt-GSK3β pathway. The results show that barley helps regulate glucose metabolism through activation of the insulin signaling pathway, which supports the regeneration of pancreatic beta cells. This study provides a basic understanding of the mechanism of barley in repairing pancreatic damage in diabetic conditions.

This study analyzed the content of β-glucan and other bioactive compounds in barley, which have antioxidant and anti-inflammatory effects. These compounds contribute to a reduced risk of diabetic complications by reducing oxidative stress on pancreatic cells. This study supports the use of barley in the diet to manage the risk of complications in people with diabetes (Shvachko et al., 2021).

This study emphasizes that β-glucan in barley functions as a prebiotic that improves the health of the gut microbiota. These changes in the gut microbiota contribute to better blood glucose control and metabolic health in people with diabetes. This study highlights the additional benefits of barley on digestive health that have an impact on diabetes control (Sivieri et al., 2022).

The above studies provide a scientific basis that barley, with its various bioactive compounds such as β-glucan, flavonoids, alkaloids, and others, has a positive effect on blood sugar control and pancreatic health. Building on these findings, the current study further tested the effects of barley under experimental conditions, particularly in alloxan-induced diabetic rats, to understand the extent to which barley can serve as a safe and effective nutritional therapy.

CONCLUSION

Based on the results of the study, it can be concluded that barley can be used as an addition to food in the treatment of diabetes. Barley can lower KGD2PP and prevent damage to pancreatic tissue in alloxan-induced diabetic mice.

This study shows that barley porridge has the potential as a natural antidiabetic agent that is effective in reducing postprandial blood sugar levels and protecting pancreatic cells from damage in diabetic-induced mice. The results of the observation showed that mice given barley porridge experienced a significant decrease in blood sugar levels, comparable to the effects caused by metformin. In addition, the results of pancreatic histopathology indicated that giving barley helped maintain the cellular structure of the pancreas and reduce cell damage.

These findings support the use of barley as an alternative nutritional therapy for diabetic patients, especially in helping to manage blood sugar levels and prevent

pancreatic damage due to diabetes. With its β-glucan, flavonoid, and alkaloid content, barley plays a role in inhibiting glucose absorption and providing antioxidant and anti-inflammatory effects. Therefore, barley can be considered as an addition to the diet to improve metabolic control in diabetics

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