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Blood Sugar Levels in terms of Differences in Intervention Time Duration for Corncob Ethanol Extract in Male Wistar Rats as a Model Of Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is hyperglycemia due to metabolic dysfunction, with attendant complications of blindness, kidney failure, stroke, and amputation. Diabetes mellitus is a major cause of premature deaths. *Corncob* extract contains antioxidants that enhance pancreatic beta cell structural integrity and activate insulin to respond to glucose. The study evaluated the effectiveness of *corncob* extract administration on blood sugar levels in diabetic male Wistar rats. *The corncob* ethanol extract was administered at 130 mg/kgBW p.o to the diabetic male Wistar rats, and blood sugar levels were measured on days 7,14 and 21. The results indicated that the *corncob* ethanol extract showed a significant reduction in the blood glucose levels of the treated animals, which was highly significant at p-value < 0.05 after 21 days of administration. *Corncob* ethanol extract contains antioxidants that can improve oxidative stress. The longer the consumption time, the better the pancreatic β cell membrane repair. The extract maintained cellular homeostasis and function linked to its antioxidant effects. The extract further prevents membrane damage by inhibiting free radicals implicated in pancreatic beta cell damage, thereby increasing insulin secretion and natural glucose receptors, which impact blood sugar levels reduction.

Keywords: *Corncob* extract, Blood sugar level, Diabetes mellitus.

Introduction

Worldwide estimates in 2019 showed that diabetes mellitus (DM) ranked ninth in terms of causes of mortality and the cause of blindness, kidney failure, stroke, and amputation of the lower limb. DM is reported to be the major cause of premature death.[1] Indonesia contributes the most to DM (diabetes) sufferers in Southeast Asia. The global metabolic disorder of diabetes increases the burden on healthcare providers.[2] Diabetes with insulin resistance results in hyperglycemia, which impairs the metabolism of carbohydrates, protein, and fat.[3] Disorder of fat metabolism resulting in oxidative stress can damage pancreatic *β* cell tissue if not controlled, causing microvascular and macrovascular problems.[4] High levels of ROS contribute to the formation of lipid abnormalities and can trigger cell, tissue, and organ damage.[5] Lipid peroxidase (LPO) plays a role in neurodegenerative events, diabetes, and atherosclerosis.[6]

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First-line therapy is with metformin for patients with type 2 diabetes mellitus.[7] Metformin is a class of biguanide drugs that act by inducing AMP-activated protein kinase (AMPK).[8] However, there are several reports of adverse effects regarding the long-term use of metformin, such as nausea, vomiting, diarrhea, and flatulence.[9] Consuming polyphenols-rich foods can help improve carbohydrate metabolism, increasing pancreatic *β* cell activity and insulin activity in response to glucose. *Corncob* ethanol extract contains polyphenols with potent antioxidant ability.[10] Ethanol (60%) extract of *corncobs* has been shown to possess the highest antioxidant content compared to 20%, 40%, and 80% extract and has good potential for treating diabetes mellitus.[11] The study evaluated the effect of *corncob* ethanol extract on blood sugar levels in diabetic male Wistar rats.

Materials and Methods

Plant collection and preparation

The Bisi-18 *corncobs* used for this study were obtained from UD Bleduq Kelud Pare Kediri Indonesia, and the harvest age was 90-110 days. The c*orn cobs* were cut into small pieces and oven-dried for 4-5 days. They were blended to powder and macerated for 5 days with 60% ethanol in a ratio of 1:10. The macerate was filtered using Whatman No. 42 filter paper, and the filtrate was evaporated to dryness over a water bath. The crude extract obtained was kept in an airtight container and refrigerated at 4°C until further use.

Ethical Approval

This study obtained ethical approval from The Ethics Committee for Health Research of Dr. Moewardi General Hospital with approval Number 1.612/XII/HREC/2022. The study followed standard protocols for the use of experimental animals.

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The antidiabetic screening test was conducted at the Integrated Research and Testing Laboratory, Gajah Mada University, Yogyakarta. Male Wistar rats aged 8 weeks weighing between 150 and 200 g were used for this experiment. The rats were housed in polycarbonate cages with a temperature of 25-28℃ and humidity of 40-60% with bright light. They had free access to water and standard rodent food and were acclimatized for one week. Oral doses of streptozotocin (65 mg/kgBB) and nicotinamide (100 mg/kgBB) were used to induce diabetes in the experimental animals. The experimental animals were divided into three groups: normal group (not diabetic), negative control group (diabetic rats but not treated), and treatment group (diabetic rats given 130 mg/kg BW *corncob* extract intervention). Blood sugar levels of the experimental animals were monitored in a time series on the seventh day, fourteenth day, and twenty-first day post-diabetes induction and treatment with corncob extract. Blood samples were collected from periorbital blood using a photometric examination method.

Statistical Analysis

The data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A p-value ≤ 0.05 is considered statistically significant.

Results and Discussion

The results of the therapeutic potential of corncob ethanol (60%) extract as an antidiabetic agent in streptozotocin (STZ) + nicotinamide (NA) induced diabetes in rats model are presented in Figures 1-4. The blood glucose levels were measured in different groups, including the normal control group, negative control group (STZ and NA-induced diabetes without treatment), and positive control group (STZ and NA-induced diabetes with 130 mg/kg bw corncob treatment). The normal control group exhibited a significantly lower blood glucose level of 191.6 – 122.6 mg/dL than the negative control group, with marked elevated blood glucose levels of 232.3 – 177.7 mg/dL on days 7-21, respectively (Figure 1). From the study results, before the intervention with corncob extract, there was an increase in blood sugar levels in the diabetes mellitus model rats both in the negative control group and the treatment group.

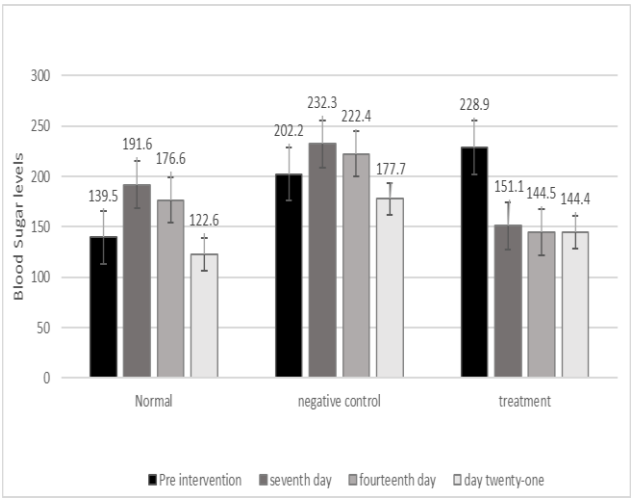

Figure 1. Blood sugar levels in all groups and at all examination times

Notes: Pre-intervention: after induction with streptozotocin and nicotinamide; seventh day: after 7 days of intervention; fourteenth day: after 14 days of intervention; day twenty-one: after 21 days of intervention. Normal: not diabetic; negative control: male diabetic Wistar rats without intervention; Treatment: Diabetic male Wistar rats were given intervention with ethanol extract of corn kernels at a dose of 130 mg/kg BW

The rise in blood sugar levels caused by streptozotocin increases GLUT2 activity, which plays a critical role in glucose transport involving regulation and metabolism in many body tissues with high glucose concentration (liver, kidneys, and nervous system). The rat pancreas is a relatively small organ and is highly sensitive to the cytotoxic activity of streptozotocin.[12] Another opinion states that streptozotocin can cause selective balance disorders in pancreatic β cells, resulting in damage to pancreatic β cells, insulin resistance, and increased blood sugar levels.[13] The administration of nicotinamide combined with streptozotocin is believed to weaken the cytotoxic effect of streptozotocin on pancreatic beta cells such that the pancreas can still respond to glucose stimulation.[14] The diabetes induction process with the combination of streptozotocin and nicotinamide creates a type 2 diabetes mellitus model in which the pancreas can still stimulate insulin release.[14] The effect of streptozotocin on cells causes DNA damage and cytotoxicity by increasing the poly (ADP-ribose) polymerase-1 (PARP-1) activity, resulting in DNA attempting to repair cells by activating NAD+. Loss of NAD+ with subsequent cellular damage.[14] Hyperglycemia resulting from streptozoxin induction is caused by lipid metabolism disorder leading to the generation of Reactive Oxygen Species (ROS).[15] The existence of free radicals in the diabetic animal model causes an increase in oxidative intensity in cells, which becomes increasingly severe. The damage to pancreatic β cells in the negative control group is responsible for the average blood sugar levels of the experimental animals not decreasing to near normal values. The high level of ROS in diabetic animals exacerbates hyperglycemia due to an imbalance between antioxidants and free radicals.

In the normal group (not induced with streptozotocin and nicotinamide), their blood sugar levels increased on the 7th and 14th days (Figure 1), possibly due to psychological stress experienced by the animals during the study. Psychological stress does not only occur in humans but can also be experienced by animals such as vertebrates, worms, and even fish.[16] Stress can cause changes in several hormones, such as cortisol, epinephrine, and norepinephrine. [17] Cortisol contributes to the impaired function of insulin in responding to glucose.[18] Changing the cage, room, and temperature by placing the animals in research cages smaller than the previous ones can cause psychological stress. Psychological stress can increase the need for insulin and could induce insulin resistance. In stressful conditions, the body excretes catecholamines and glucocorticoids.[19] Catecholamines and glucocorticoids during chronic stress may lead to disturbed glucose homeostasis, with eventual hyperglycemic effects.[19] From this discussion, it can be assumed that the experimental rats used in this study experienced increased blood sugar levels due to stress, possibly due to increasing levels of cortisol, epinephrine, and norepinephrine. The mechanism of action of cortisol is the opposite of that of insulin, so high cortisol levels cause an increase in the breakdown of glycogen reserves within the liver, fat tissue, and muscles, resulting in hyperglycemia.

In the treatment group given corncob ethanol extract at 130 mg/kgBW, the diabetic animals' average blood sugar level decreased after the intervention (Figures 2-4). Previous research showed that 60% of corncob ethanol extract contains phenolics and has the best antioxidant capacity compared to 20%, 40%, and 80%.[11] Also, a previous study found that corncob ethanol extract contains polyphenols with antioxidant capabilities. Antioxidants are substances that release hydrogen atoms to ward off free radicals and function to break the chain of activity of free radicals.[20] Antioxidants are divided into 3 groups, namely internal antioxidants like SOD (superoxide dismutase), glutathione peroxidase (GPx), and catalase (KAT). The second type of antioxidant is synthetic antioxidants such as Butyl Hydroxy Toluene (BHT), Butyl Hydroxy Anisole (BHA), Tert Butyl Hydroxy Quinon (TBHQ), and propyl gallate. The third type of antioxidant is natural antioxidants, usually obtained from plant components such as wood, roots, leaves, stems, or flowers.[20] Antioxidants scavenge free radicals and repair damage to pancreatic beta cells[21]. Additionally, antioxidants improve oxidative stress conditions in diabetes mellitus patients[22] and increase insulin secretion by pancreatic β cells.[23] Antioxidants in ethanol extract of corn cobs at a dose of 130 mg/kgBW helped improve the composition of the pancreatic β cells in diabetic animals.

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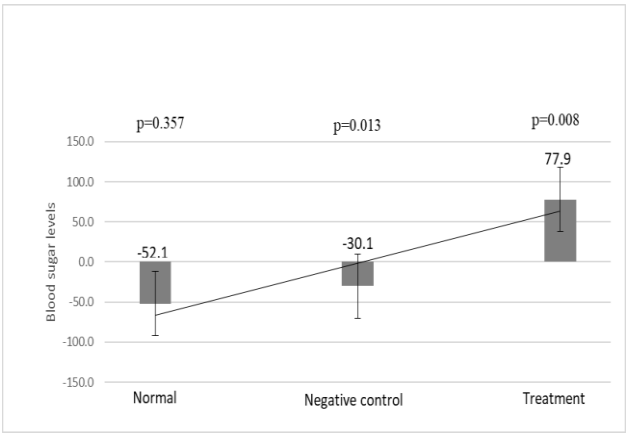

Figure 2. Mean decrease in blood sugar level after 7 days of treatment with 130 mg/kg BW of Corncob extract.

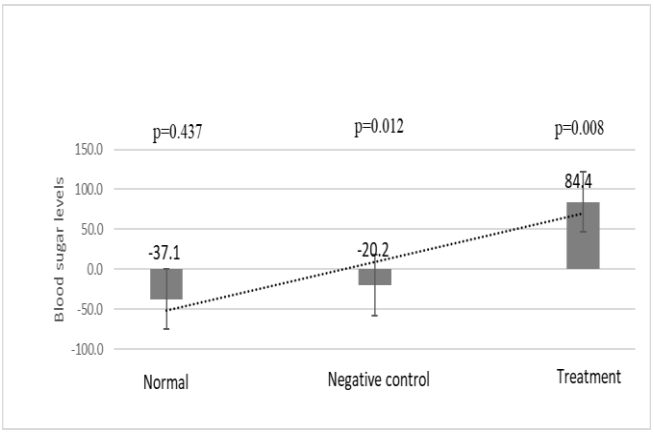

Figure 3. Mean decrease in blood sugar level after 14 days of intervention with 130 mg/kg BW of Corncob extract in the treatment group.

Improvements in the structure of pancreatic β cells trigger insulin excretion in response to glucose. Glucose metabolized due to insulin excretion will be stored in the form of glycogen in the body of the experimental rats. Glycogen storage may have resulted in the average blood sugar levels of the diabetic rats decreasing to near normal.

It was discovered that the average decrease in blood sugar level on the 7th day was seen in the treatment group. Statistical evaluation showed a reduction in blood sugar levels on the seventh day with p=0.015. There was a significant difference in blood sugar levels in the normal group, negative control group and treatment group on the seventh day after the intervention (Figure 2). The normal and negative control groups showed an increase in average blood sugar levels. Further analysis, however, showed that after the 7th day of the intervention, there was no significant reduction in the average blood sugar levels in the normal and negative control groups. There was, however, a significant difference in the blood sugar level reduction between the treatment and the negative control groups. On day 14th of the experiment, there was a significant effect of the extract in lowering the blood sugar level with p=0.012 (Figure 3) and variations in lowering blood sugar levels in all groups. However, after the 14th day of the intervention, there was a significant difference in the average decrease in blood sugar levels between the normal group and the treatment group p=0.008 (Figure 3). There was a notable variation in the mean decrease in blood sugar levels before the intervention and after the intervention from day to day in all groups, p>0.05. The highest average decrease in blood sugar level was observed on day 21 in the treatment group, with p = 0.004 (84.5 mg/dL).

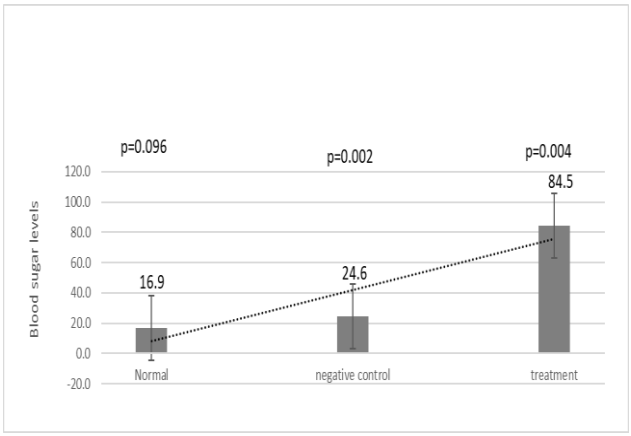

Figure 4. Mean decrease in blood sugar level after 21 days of intervention with 130 mg/kg BW of Corncob extract in the treatment group.

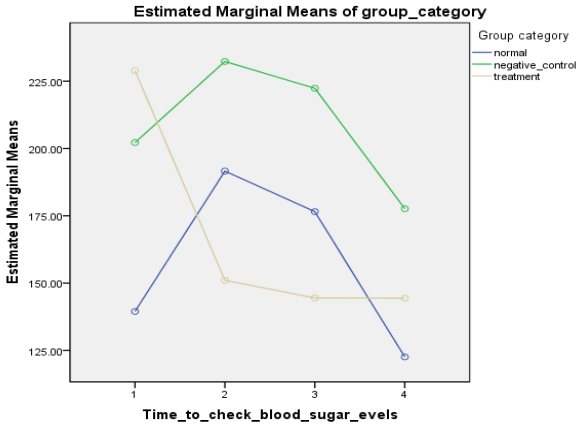

Figure 5. Mean decrease in blood sugar level before and after intervention in all groups based on prolonged intervention period.
Notes: 1: After induction with streptozotocin and nicotinamide; **2:** after 7 days of intervention; **3:** after 14 days of intervention; **4:** after 21 days of intervention. Normal: not diabetic; negative control: male diabetic Wistar rats without intervention; Treatment: Diabetic male Wistar rats were given intervention with ethanol extract of corn kernels at a dose of 130mg/kg BW

In each group, there was a notable variation in the reduction of blood sugar levels after 21 days of intervention. There was a noteworthy distinction in the decrease in blood glucose concentration in the normal group and the treatment group and there was a notable distinction in the average reduction in blood sugar level in the negative control group and the treatment group.

The intervention of 60% corncob ethanol extract at a dose of 130 mg/kgBW in male Wistar rats in the diabetes model on day 21 showed the best blood sugar levels and the most significant decrease in average sugar levels compared to the normal group and the negative control group. The results of the Sphericity Assumed statistical test value of p=0.001 showed that the duration of the intervention of corncob ethanol extract at a dose of 130 mg/kg BW in male Wistar rats as a model of diabetes improved blood sugar levels. *Corncob* ethanol extract contains polyphenols and has natural antioxidant capabilities.[24] Hence, long consumption of corncob extract could improve the functionality of the pancreas, increase its ability to secrete insulin, and reduce the reactive activity of oxidative species, which could be beneficial for those with diabetes.[25] These results suggest that on day 21, there was some

improvement in the pancreatic beta cell integrity in diabetic Wistar rats. In the induction of glucose analogs, cell membranes are repaired so that the insulin produced is able to respond well to glucose. A good response to glucose has an impact on reducing blood sugar levels in the normoglycemia category. Antioxidants in 60% corncob ethanol extract were believed to repair damage to the pancreatic β cell membrane due to streptozotocin injection, causing the average blood sugar level in the treatment group starting on day 7 to decrease and showing that there was a significant difference in the male Wistar rats in the streptozotocin and nicotinamide induced diabetes mellitus model. Antioxidant activity consists of maintaining homeostasis of cell structure and function and preventing membrane damage due to oxidative stress.[5] Antioxidants work by slowing down, blocking or destroying oxidative damage to target molecules.[23] Continuous administration of 60% corn cob ethanol extract has an impact on improving the ability of pancreatic β cells to stimulate insulin excretion with positive response to glucose clearnace.

Conclusion

Several plant extracts have shown potential in reducing hyperglycemia and inhibiting the progression of the disease, which causes damage to major organs of the body such as the eyes, kidneys, and heart, and in some cases, sexual dysfunction. This study showed that the administration of corncob extract (130 mg/kg BW) to the diabetic experimental animals produced a time-dependent reduction in average blood sugar levels in the treatment group, as shown especially on day 21 post-induction. The blood sugar-lowering effects of the extract could be linked to its antioxidant effects due to its rich polyphenolic content and repair of pancreatic β cells, leading to its ability to secrete insulin. Corn cob ethanol extract is a natural antioxidant that can improve and maintain the stability of blood sugar levels in diabetic patients. There is a need for further investigation of the corn cob extract for possible development into a nutraceutical supplement for use by people with diabetes.

Conflict of interest

The authors declare that there is no conflict of interest.

Author's Declaration

The author hereby declares that the work presented in this article is original and that any responsibility for claims relating to the content of this article shall be borne by them.

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