The Effect of Jackfruit (Artocarpus heterophyllus Lam.) Seed Ethanol Extract on Blood Sugar Levels and Anti-Inflammatory Reduction on Wistar Albino Rats Streptozotocin-Induced Gestational Diabetes

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RESEARCH ARTICLE

The Effect of Jackfruit (*Artocarpus heterophyllus Lam.*) Seed Ethanol Extract on Blood Sugar Levels and Anti-Inflammatory Reduction on Wistar Albino Rats Streptozotocin-Induced Gestational Diabetes

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ABSTRACT:
Gestational Diabetes Mellitus is a disorder of carbohydrate tolerance that results in increased blood sugar levels and was first recognised during the second and third trimesters of pregnancy. It is a health problem that has a direct impact on the health of the mother and fetus. The purpose of this study was to analyse the effect of jackfruit (*Artocarpus heterophyllus Lam.*) Seed Ethanol Extract on reducing Blood Sugar Levels and Inflammation in Wistar Albino Rats with Gestational Diabetes Mellitus induced by Streptozotocin. This study used a laboratory experimental research design with a post-test only control group design on Wistar Albino Rats with Gestational Diabetes Mellitus. The sample was obtained by the simple random sampling method. The results showed that the lowest spectrophotometer KGD level was in group C given Streptozotocin 45mg/kg BW + Metformin 45mg/kg BW with a *p* value of 0.003, which means there was a significant difference between groups and the lowest Interleukin-6 level. In group C, they were given Streptozotocin 45mg/kg BW + Metformin 45mg/kg BW with a *p* value of 0.511, meaning there was no significant difference between groups. Jackfruit seed ethanol extract functions as a lowering of blood sugar levels and an anti-inflammatory.

KEYWORDS: Jackfruit Seed Ethanol Extract, Gestational Diabetes Mellitus, Blood Sugar Levels, Anti Inflammation.

INTRODUCTION:

Diabetes Mellitus is a chronic metabolic disorder characterised by high blood sugar levels accompanied by impaired carbohydrate, lipid, and protein metabolism as a result of insulin function insufficiency, which can be caused by impaired insulin production by the beta cells of Langerhans of the pancreas gland or caused by impaired insulin production by the unresponsiveness of the body's cells to insulin.[1]

Diabetes mellitus is one of the causes of high morbidity and mortality, especially in pregnant women, which is often referred to as Gestational Diabetes Mellitus (GDM), mainly due to vascular complications. Gestational Diabetes Mellitus is defined as the glucose

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intolerance of various degrees that is first detected during pregnancy.[2-9] Gestational Diabetes Mellitus occurs due to increased formation of free radicals through glucose metabolism such as glucose auto oxidation, metabolism of methylglyoxal formation, and oxidative phosphorylation. One type of free radical that is highly reactive is the hydroxyl radical, which is highly toxic because of its ability to diffuse to transfer and then react with membrane lipids to produce malondialdehyde (MDA) products.[10]

Gestational Diabetes Mellitus causes blood sugar levels to increase and was first recognised during the second and third trimesters of pregnancy, but is often difficult to find because of the low ability to detect cases. It is rarely known because it is rare for pregnant women to be screened if there are no complaints or indications despite a family history.[12]

Gestational Diabetes Mellitus is one way that the Sustainable Development Goals (SDGs) aim to improve the health of mothers. [13] The prevalence of Gestational Diabetes Mellitus in Indonesia is 1.9–3.6% in general pregnancy, while the prevalence in pregnant women with a family history of DM is 1.5%, of all pregnancies ranging from 1–14% to gestational diabetes mellitus, and the undiagnosed ranged from 10–25%. In fact, approximately 135,000 pregnant women experience gestational diabetes mellitus every year, which is 3–5%.[14]

The impacts that can occur in mothers with gestational diabetes mellitus are preeclampsia, eclampsia, caesarean section, cardiovascular complications, and foetal and maternal death. After the mother has given birth, she can be at risk for recurrent diabetes in the future, and babies born are at high risk for macrosomnia. 15. Based on the data, it was found that the causes of neonatal death were respiratory disorders or abnormalities (35.9%), prematurity (32.4%), sepsis 12%, hypothermia 6.3%, blood disorders/jaundice 5.6%, post-maturity 2.8%, and congenital abnormalities 1.4%.[16]

Treatment of gestational diabetes mellitus can be done by changing diet patterns, maintaining body weight, doing physical activity, and administering anti-diabetic drugs orally or giving insulin. However, long-term use of antidiabetic drugs can cause serious side effects on the body's organs, and the treatment is expensive. One of the treatments is to take metformin.[17]

Traditional alternative medicine has the advantage that it is easy to obtain, economical, and provides relatively low side effects, although in modern medical practise there are still few that have undergone preclinical and clinical trials.[18] Alternatives include jackfruit seeds (*Artocarpus heterophyllus Lam.*) ingredients that can be used as an alternative diabetes treatment. Jackfruit seeds contain compounds such as flavonoids, saponins, alkaloids, terpenoids, steroids, and beta-carotene epoxide compounds that have the potential to lower blood sugar levels by inducing insulin secretion.[19]

The content of flavonoids in jackfruit seeds are insulin mimetic that can stimulate glycogen synthesis and as an insulin secretagogue that stimulates insulin production and has a protective effect on pancreatic cells.[12] Damage that occurs in pancreatic cells can be modelled in a hyperglycemic animal model using streptozotocin (STZ). Streptozotocin is transported to pancreatic cells via the glucose transporter (GLUT2), where it can cause DNA damage by increasing the activity of poly(ADP-ribose) polymerase (PARP-1).[20]

Research that has been done (Sarian, 2017) says that flavonoid compounds have antioxidant and antidiabetic effects. The pharmacological properties of flavonoids are their ability as strong antioxidants, which have been reported to play an important role in reducing diabetes mellitus cases. Treatment of diabetes mellitus can be done with insulin. The dose of insulin used must be adjusted to the patient's blood sugar level. The use of insulin can cause weight gain and hypoglycemia. Because of this, there are a number of medicinal plants with anti-diabetic effects and few side effects, especially for pregnant women.[21]

Insulin resistance is a decrease in tissue response to the effects of insulin on glucose metabolism in the form of a decrease in glucose uptake in muscle and fat tissue. There is no interference with other insulin-dependent processes such as mitogenesis, protein synthesis, and triglyceride formation in fat cells.[22] Measurement of insulin performance and ineffective pancreatic cell function due to insulin resistance can be used to assess the homeostatic model of insulin resistance (HOMA-IR). The two main pathophysiological mechanisms of HOMA-IR are pancreatic cell dysfunction and insulin resistance.[23]

Previous research conducted "Development of Tape Food with Basic Ingredients from Jackfruit Seeds (Concrete) (*Artocarpus heterophyllus Lam.*) combined with Moringa Leaves (*Moringa Oleifera Lam.*) as an Antidiabetic Drug" showed that jackfruit seeds can be processed into tape food and have a texture which is semi-solid, aromatic and has a sweet taste and has a high protein content of 5.57% and can be useful as a type 2 Diabetes Mellitus drug.[24]

Based on the previous research "Potential of Indonesian Plants as Antidiabetics through the Mechanism of Inhibition of -glucosidase Enzymes" and the results

obtained that herbal medicines from plants in Indonesia have the potential as anti-diabetics, one of which is Jackfruit Seed (*Artocarpus heterophyllus Lam*.) macerated using ethanol 70 %.[25]

The study "Activity of 70% Ethanol Extract of Jackfruit Seeds (*Artocarpus heterophyllus Lam*.) in Reducing Blood Sugar Levels of Streptozotocin-Induced Gestational Diabetes Rats" using the Tukey test showed a decrease in blood glucose levels in the test group of jackfruit seed preparation with a dose of 400 mg/kg BW, which is comparable to the positive group given Metformin at 51.37 mg/kgBW.[26]

Based on the explanation above, the researcher is interested in conducting research on "The Effect of Ethanol Extract of Jackfruit (*Artocarpus heterophyllus Lam*.) seeds on Reducing Blood Sugar Levels and Anti-Inflammation in Wistar Streptozotocin-induced Gestational Diabetes Mellitus."

MATERIALS AND METHODS:

This study used a laboratory experimental research design with a post-test only control group design on Wistar White Rats with Gestational Diabetes Mellitus. Samples were obtained by a simple random sampling method. Therefore, experimental animals, experimental sites, and other research materials can be said to be homogeneous, while the Jackfruit Seed *(Artocarpus heterophyllus Lam*.) uses a purposive sampling method. This study will measure the effects of the ethanol extract of Jackfruit seeds (*Artocarpus heterophyllus Lam*.) in antidiabetic and anti-inflammatory treatments.

Each treatment group contained at least 5 Wistar White Rats with Gestational Diabetes Mellitus. The researchers chose to use 5 Wistar White Rats with Gestational Diabetes Mellitus in each group to maintain the mortality of experimental animals with a total of 3 treatment groups with doses of 100, 200, and 400 mg/kgBW/day[19] so that the total number of research samples was 30 tails, which were divided into: group 1, normal control, which was not given any treatment, Group 2, negative control (injected STZ), group 3, positive control (injected STZ) + Metformin, group 4, (injected STZ) treatment with Ethanol Seed Extract of Jackfruit (*Artocarpus heterophyllus Lam*.) dose of 100 mg/kgBW/day, group 5, (injected with STZ)extract treatment of Jackfruit (*Artocarpus heterophyllus Lam*.) seed ethanol at a dose of 400 mg/kgBW/day.

RESULTS:

Blood Sugar Level Check:

The results showed that rats after diabetes induction after treatment of jackfruit seed ethanol extract at weeks 1 to 2 are shown in Table 1.

Table 1. KGD Analysis

Group	Mean
A	104.76±43.699
B	156.41±53.787
C	46.891±13.954
D	153.50±41.197
E	99.866±11.827
F	69.841±36.018
Nilai P	0.003

The lowest spectrophotometer KGD levels were in group C given Streptozotocin 45mg/kg BW + Metformin 45mg/kg BW, which was then followed by Group F given Streptozotocin 45mg/kg BW + ethanol extract of jackfruit seeds 400mg/kg BW with an average KGD 46,891 mg/dl with a standard deviation of 13,954. *p*- value 0.003 which means there is a significant difference between groups. However, group F showed a decrease in KGD, but in group C the decline in KGD was better than group F because metformin had a strong hypoglycemic ability compared to the other groups.

HOMA-IRCheck:

Table 2. HOMA-IR Analysis

Group	Mean
A	3.645±1.874
B	8.283±5.141
C	2.543±2.142
D	4.185±1.974
E	3.651±1.003
F	1.365±0.385
Nilai P	0.026

The highest HOMA-IR was found in the BD group given Streptozotocin 45mg/kg BW with a mean of 8,283 and a standard deviation of 5,141, while the lowest was in the F group given Streptozotocin 45mg/kg BW + jackfruit seed ethanol extract 400mg/kg BW with a mean of 1,365. with a standard deviation of 0.385. *p* - value was 0.026, meaning that there was no significant difference between groups, although statistically it did not show significance, but in group E, insulin resistance decreased compared to other groups receiving extracts or oral hypoglycemic drugs.

Insulin Check:

Table 3.Insulin Analysis

Group	Mean
A	0.749±0.225
B	0.596±0.125
C	0.660±0.050
D	1.347±1.065
E	0.814±0.154
F	0.724±0.280
Nilai P	0.388

The highest insulin levels were found in group D, given Streptozotocin 45mg/kg BW + jackfruit seed ethanol extract 100mg/kg BW, with a mean of 1,347 and a standard deviation of 1,065. The lowest insulin levels

were found in group E, given Streptozotocin 45mg/kg BW + jackfruit seed ethanol extract 200mg/kg BW with a mean of 0.814 and a standard deviation of 0.154 with a *p* value of 0.388, meaning there was no significant difference between groups, but the extract in group D could increase insulin secretion higher than the other groups.

MDA Check:

Table 4. Activity MDA Analysis

Group	Mean
A	0.9521±0.4504
B	0.9182±0.3832
C	0.6610±0.3706
D	0.4285±0.3787
E	0.8205±0.5126
F	0.7158±0.4849
Nilai P	0.568

The highest MDA levels were in group D, given Streptozotocin 45mg/kg BW + ethanol extract of jackfruit seeds 100mg/kg BW, with a mean of 0.4285 and a standard deviation of 0.3787. The lowest MDA level was in group A as a normal control with a mean of 0.9521 and a standard deviation of 0.4504 with a *p* value of 0.568, meaning that there was no significant difference between groups. Group E extract was able to reduce oxidative stress activity better than other groups.

Interleukin-6 Check:

Table 5. Interleukin-6 Analysis

Group	Mean
A	0.031±0.045
B	0.090±0.054
C	0.093±0.012
D	0.166±0.210
E	0.078±0.044
F	0.075±0.054
Nilai P	0.511

The highest levels of Interleukin-6 were in group D given Streptozotocin 45mg/kg BW + jackfruit seed ethanol extract 100mg/kg BW with a mean of 0.166 6 with a standard deviation of 0.210, the lowest levels were in Group C given Streptozotocin 45mg/kg BW + induction Metformin 45mg/kg BW with a mean of 0.093 with a standard deviation of 0.012. *p* value is 0.511 which means there is no significant difference between groups.

DISCUSSION:

Jackfruit seed ethanol extracts 400mg/kg BW was able to reduce KGD and showed a significant difference between groups. These findings indicate that the ethanolic extract of jackfruit seeds contains flavonoids, alkaloids, saponins, steroids and terpenoids. Flavonoid compounds are a group of compounds that can be used to lower blood glucose levels. Although the group given ethanol extract of jackfruit seeds 400mg/kg BW showed a decrease in KGD, the reduction in KGD was better in group F who was given metformin 45 mg/kgBW because Metformin had a strong hypoglycemic ability compared to the other groups.

The lowest insulin levels were found in group E given Streptozotocin 45mg/kg BW + jackfruit seed ethanol extract 200mg/kg BW with a mean of 0.814 and a standard deviation of 0.154 insulin.

Flavonoids are antioxidants that have potential as free radical scavengers, metal chelators, and inhibitors of fat oxidation because they have a structure consisting of a hydroxyl group on the third carbon, has a double bond between the second and third carbons, the position of the fourth carbon has a carbonyl group and polyhydroxylation on the aromatic ring A and B.[27] Some other seed like Cumin (Cuminum cyminum) also have diuretic and antiinflammatery effect.[28]

To assess oxidative stress levels through MDA markers, which were lower in group E given Streptozotocin 45mg/kg BW + jackfruit seed ethanol extract 200mg/kg BW, due to the high antioxidant activity of SOD which can reduce free radicals so that oxidative stress decreases in this group.

The lowest level of Inter Leukin - 6 was in group C which was given Streptozotocin 45mg/kg BW + Metformin 45mg/kg BW with a mean of 0.093 with a standard deviation of 0.012. Jackfruit seed ethanol extract contains triterpenoids where these compounds are related to membrane stability. Triterpenoid compounds from ligustrum have the ability to inhibit the activity of the cyclooxygenase enzyme in converting arachidonic acid into prostaglandins as inflammatory mediators.

CONCLUSION:

Ethanol extract of jackfruit seeds can reduce blood sugar levels with a dose of extract 400mg/kg BW with a *p* value of 0.003 better than the treatment and control groups.

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