Original Research

THE BAJAKAH (*SPATHOLOBUS LITTORALIS HASSK.*) STEM PLANT EXTRACT EFFECT ON THE BLOOD GLUCOSE OF STREPTOZOTOCIN-INDUCED WISTAR MALE RATS

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ABSTRACT

Introduction: Health practitioners have tried to reduce the prevalence of diabetes mellitus, which increases globally every year, but the result has not been optimal yet. Meanwhile, the indigenous people of the Dayak tribe from Borneo Island of Indonesia believe that the Bajakah plant (Spatolobus littoralis Hassk) can treat many diseases, including reducing blood glucose. However, the effect of the Bajakah stem plant extract on blood glucose regulation is still vague. **Aims:** Therefore, our animal-experimental research aimed to test the effect of the Bajakah stem plant extract using streptozotocin-induced Wistar male rats. **Methods**: We grouped the rats into K1, K2 (negative and positive control groups, respectively), P1, P2, and P3 (with additional Bajakah stem extract 50, 100, and 150 mg/kg body weight, respectively), with each group consisted of five rats. We collected blood glucose and insulin level at baseline (T1) and end of the intervention (T2). **Results**: This study found the highest mean $\pm$ standard deviation of insulin level was in the C2 group (5.10$\pm$0.84 µU/mL) and the lowest value in the X3 group (3.65$\pm$0.41 µU/mL). However, we found a significant difference in the blood glucose level at baseline and the end of the intervention (p<0.001). The highest reduction means value on blood glucose level was in the X3 group (T1: 471.40$\pm$89.24 mg/dL; T2: 122.80$\pm$12.50 mg/dL). **Conclusion**: The Bajakah stem plant's extract intervention affects the blood glucose level of Wistar male rats, possibly through the free radical's protection effect on the target cell receptor that binds to insulin and glucose.

Keywords: Antioxidant, Bajakah Extract, Blood Glucose, Diabetes, Target Cell Receptor

INTRODUCTION

The number of people with diabetes aged 20-79 years in the world was 463 million in 2019 and was predicted to reach 700 million in 2045 (International Diabetes Federation, 2019). Diabetes prevalence rises globally yearly, including in low-middle-income countries, for example, Indonesia. The Indonesian basic health research showed that Indonesian adults aged 15 years and older who were diagnosed with diabetes increased from 1.5% in 2013 to 2% in 2018 (Ministry of Health of Republic of Indonesia, 2018). Among the ten highest total global numbers of people with diabetes, Indonesia contributed in the seventh position with a total of around 10.7 million people (International Diabetes Federation, 2019).

The rising diabetes prevalence became a burden for the government and themselves.

Further, diabetes mellitus is a group of metabolic diseases with hyperglycemic characteristics, which happen because of defects in insulin secretion, insulin action, or both. Insulin resistance in muscle and liver cells and pancreatic beta cell failure has been identified as the central damage pathophysiology of Type 2 diabetes. Type 2 diabetes mellitus is caused by decreased insulin levels produced by pancreatic beta cells, which leads to insufficient amounts of binding the glucose circulating in the blood vessels resulting in increased blood glucose levels.

The former researchers suggested the egregious eleven of hyperglycemic pathogenesis are pancreatic beta cell failure, pancreatic alfa cell dysfunction, lipid cell, muscles, liver, brain,

colon/microbiota, small intestine, kidney, gastric, and immune system (Arivazhahan, 2021; Coke et al., 2022; Schwartz et al., 2017). Furthermore, diabetes is classified into four types Type 1 (autoimmune and Idiopathic), Gestational diabetes, Type 2, and specific diabetes type (monogenic diabetic syndrome, exocrine pancreatic disease, because of medicine or chemical substances (Indonesian Society of Endocrinology (PERKENI), 2021). The specific diabetes type may be caused by the free radicals increase in the body that disrupts the target cell receptor, which leads to insulin failure to enter the target cell (insulin resistance) (Rains & Jain, 2011; Schwartz et al., 2017; A. Singh et al., 2022). The oxidative stress mechanism may explain the relationship between the free radical's pathway and diabetes. Moreover, literatures explaining how the decrease in insulin secretion is due to damage to the beta cells of the pancreas from free radicals, which cause insufficient insulin to bind glucose in the blood, is still limited.

On the other hand, people with diabetes are trying to find a cure using medicinal or non-medicinal ways, like herbal ones. For example, the indigenous people from the Dayak tribe of Borneo Island of Indonesia believe that the local plant, called Bajakah or *Spatolobus littoralis Hassk*, can be used as an herbal to treat dysentery, cancer, stop-bleeding, and even can decrease blood glucose level. However, the mechanism of the Bajakah effect on blood glucose is vague. Therefore, we aimed to test the Bajakah plant's extract effect mechanism on the diabetes marker, such as blood glucose, insulin, and HOMA IR using an animal-experimental study.

METHODS
Study Design and Animal Preparation

This study was carried out from December 2021 to January 2022 in Surabaya, Indonesia. This experimental animal study was a completely randomized post-test only with a control group design on white normal male Wistar rats that weighed 150-200 grams and were aged 2-3 months. We included 25 rats without any anatomical defects and never used them in any other research, and let the rats adapt to the research environment, so-called acclimatization, for one week. The research activities were done over five weeks in the Biochemistry laboratory of the Faculty of Medicine and Nutrient Analysis Laboratory of the Public Health Faculty, Airlangga University. These five weeks consisted of one week of acclimatization, two weeks of streptozotocin (STZ) induction, and two weeks of the Bajakah stem extract intervention. Bajakah stem extract preparation was started from the Bajakah stems collected from East Borneo were cut into smaller sizes and weighed 1000 grams. Then, Bajakah stems were extracted using the maceration method with 70% ethanol and shaken for 2-3 hours. The extraction process was 3 x 24-hr and continued to the filtration process. The filtration results were evaporated using 50 degrees Celsius in a rotary evaporator to get the solvent-free viscous extraction. The 1000 grams of dried Bajakah stem can produce 20 grams of Bajakah stem extract.

This study consists of three stages, as shown in Figure 1. Firstly, we randomly grouped the 25 rats into a negative control group, called the C1 group (fed 20 grams of standard diet), which consisted of five rats, and the twenty rats were grouped into the non-negative control group. The standard diet was using BR-1 rat pellets. On day 8, all rats were weighed then the 20 non-C1-group rats went to the STZ-induction stage for 14 days. Secondly, we randomized 20 rats on the same day into C2, X1, X2, and X3 groups on the T1. T1 was the first fasting blood glucose test for all rats on day 23. The positive control group, named the C2 group, was STZ-induced and fed a 20-gram standard diet (BR-1). The intervention groups were X1, X2, and X3 groups, which injected STZ

induction and received 20 grams of the BR-1 diet mixed with Bajakah stem extract for 50, 100, and 150 mg/kg body weight, respectively.

Animal Study Intervention Procedures and Statistical Analysis

Streptozotocin acted as a diabetogenic agent for the effectivity, reproducibility, and stability in the solution before and after animal model injections so that the animal model showed a resemblance to the structural, functional, and biochemical abnormality of Diabetes Mellitus (Goyal et al., 2016). The streptozotocin (STZ) was given to the twenty rats of the non-C1 group. Further, twenty rats were induced weekly with a double dose of 30 mg/kg body weight of STZ for 14 days. After two weeks of STZ induction, we weighed and collected the blood through vena laterals using a glucose kit to test the 4-hour-fasting blood glucose level (Eke & Okpara, 2021). Rats with a blood glucose value test showed ≥ 135 mg/dL were randomized and grouped into four groups (C2, X1, X2, and X3).

Twenty-five Wistar male rats were grouped in C1, C2, X1, X2, and X3 groups, as shown in Figure 1. All rats were fed 20 grams of BR-1 from the beginning to the end of the research, except for the intervention group. The intervention group X1 was given an additional 50 mg/kg body weight of Bajakah stem extract when X2 was given a 100 mg/kg body weight of Bajakah stem extract, and X3 was given an additional 150 mg/kg body weight of Bajakah stem extract for 14 days. Rats were fasted for four hours before being weighed, blood collected (T2), and sacrificed after 14 days of intervention.

In the T2 blood collection, we analyzed the glucose level, insulin, and the HOMA-IR indices' calculation. All the procedures were successfully followed and certified by the ethical committee in the Faculty of Public Health, Airlangga University. The ethic certificate number is 597/HRECC.FODM/XI/2021. This study tested the blood glucose level test between T1 (after STZ-induction) and T2 (after 14-day intervention) using a t-test.
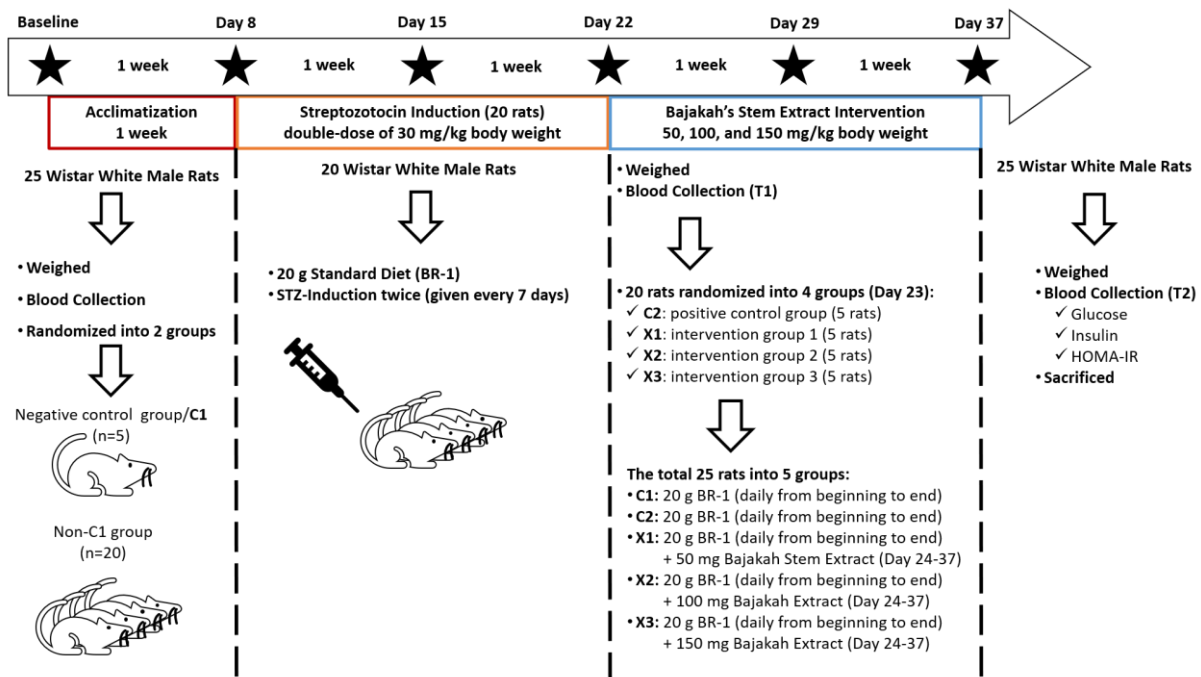

Figure 1. Intervention Process

Further, we tested the mean difference between groups using the Manova and the posthoc Tukey test. All the significance was set to p<0.05.

RESULT

This study data met the normal distribution and homogeneity requirements after being tested using Kolmogorov-Smirnov and Levene tests using SPSS version 23, respectively. The Wistar male rats' normal fasting blood glucose value was less than 135 mg/dL. Table 1 shows that the mean blood glucose value in the C1 group with 101.60±4.16 mg/dL was lower than the mean blood glucose value in the C2 group with 490.60±73.50 mg/dL in T1 blood collection among control groups. Rats in C1 groups met the requirements of fasting blood glucose values.

Further, the lowest mean of blood glucose value among intervention groups in T1 was the X1 group (455.20±61.05 mg/dL), and the highest was the X3 group with 471.40±89.24 mg/dL. Furthermore, in the T2 among control groups, the mean blood glucose value of the C1 group rats with 105.80±5.81 mg/dL was lower than the mean blood glucose value of rats in the C2 group with 480.00±58.46 mg/dL. On the other hand, the lowest mean of blood glucose value among intervention groups in T2 was the X3 group (122.80±12.50 mg/dL), and the highest was the X1 group with 138.40±10.92 mg/dL.

Table 1. Mean and Standard Deviation Blood Glucose of Wistar Male Rats

Group	T1	T2	*p*-value
C1	101.60±4.16	105.80±5.81	0.225
C2	490.60±73.50	480.00±58.46	0.807
X1	455.20±61.05	138.40±10.92	<0.001
X2	464.40±63.14	126.60±14.12	<0.001
X3	471.40±89.24	122.80±12.50	<0.001

The homogeneity data assessment using the Levene test, a variances homogeneity test when the k samples have equal variances, of the blood glucose values after intervention showed a *p*=0.054. Further, we tested the mean difference between T1 and T2 using a t-test and showed a significant difference in X1, X2, and X3 groups (*p*<0.001). This study tested the insulin level and calculated the HOMA-IR value to support the information about the post-intervention effect of insulin resistance. Each group was consisted of five (5) rats and the blood collected after of 4-hour fasting process. T1 was blood collection test after 14-day of STZ induction for C2, X1, X2, and X3 group. T2 was blood collection test after 14-day of additional Bajakah stem extract's intervention. C1 was negative control group (normal diet). C2 was positive control group (STZ induction + normal diet). X1 to X3 were intervention group (STZ induction + normal diet) with additional Bajakah's stem extract 50, 100, and 150 mg/kg body weight, respectively). All values in presented Table 1 and Table 2 were mean ± standard deviation in milligram per deciliters. The p-value was tested using t-test.

Table 2. Insulin and HOMA-IR value of Wistar Rats Post Intervention

Group	Insulin	HOMA-IR
C1	4.43±0.82	1.15±0.21
C2	5.10±0.84	6.02±1.14
X1	4.62±0.60	1.58±0.21
X2	3.76±0.41	1.14±0.12
X3	3.65±0.41	1.14±0.19

Table 2 shows the insulin and HOMA-IR value after 14 days of the Bajakah stem plant's intervention. The highest insulin mean value was in the C2 group, the positive control group in this study. Meanwhile, the lowest insulin mean value was shown in the X3 group, the intervention group with an additional 150 mg/kg body weight of Bajakah extract,

with 3.65±0.41 µU/mL. On the other hand, the HOMA-IR value was calculated using a formula of fasting blood glucose multiplied by fasting-insulin value, then subtracted by a constant number of 405 to define the insulin resistance status of the samples. The highest HOMA-IR value was in the C2 group (6.02±1.14), while the lowest was in the X3 group. The highest HOMA-IR value in the C2 group was due to the STZ induction that the rats received.

Table 3. Manova and Tukey Results Test of Blood Glucose, Insulin, and HOMA-IR between groups at the T2

Group	C1	C2	X1	X2	X3
	Blood Glucose				
C1	-				
C2	<0.001*	-			
X1	0.003*	<0.001*	-		
X2	0.173	<0.001*	0.338	-	
X3	0.075	<0.001*	0.588	0.991	-
	Insulin Level				
C1	-				
C2	0.479	-			
X1	0.988	0.764	-		
X2	0.485	0.026*	0.245	-	
X3	0.344	0.015*	0.158	0.999	-
	HOMA-IR				
C1	-				
C2	<0.001*	-			
X1	0.034*	<0.001*	-		
X2	1.000	<0.001*	0.031*	-	
X3	1.000	<0.001*	0.029*	1.000	-

Further, we also tested the post hoc Tukey test on the mean difference between groups. Table 3 presents that the blood glucose levels between control groups or the comparison between the C2 group and all the intervention groups (i.e., X1, X2, and X3 groups) were significantly different ($p<0.001$). The blood glucose value of the negative control group was significantly different ($p=0.003$) from the one in the X1

group. Furthermore, the insulin mean values were significantly different between the C2 group and the X2 group with $p=0.026$, while between the C2 group and the X3 group it was $p=0.015$. Moreover, the HOMA-IR values were significantly different in all group comparisons, except between the C1 group and the X2 group or the X3 group and between the X2 and X3 groups.

DISCUSSION

This study observed the effect of Bajakah stem extract intervention on the blood glucose, insulin, and HOMA-IR value of 25 Wistar male rats. Bajakah stem extract intervention in the four groups (C2, X1, X2, and X3) showed the expected effect in reducing the blood glucose level between T1 and T2 data collection. The Bajakah is well-known as a functional plant from Borneo Island of Indonesia, which has been used as a herbal remedy. The Bajakah plants are easy to find in the South East Asian forests (Ridder-Numan, 1998). Residents use the roots and stem of Bajakah because they have secondary metabolite compounds and bioactivity as anticancer, antidiabetic, asthma medicine, stroke medicine, and rheumatism (Aulia et al., 2022; Yuniarti et al., 2021; Zannah & Dewi, 2021). Besides, Bajakah also has been used to treat wounds because of its anti-inflammation and antibacterial activity (Ariesanti et al., 2021; Mochtar et al., 2022). Previous researchers who studied the Bajakah found that the plant contains four types of antioxidants (i.e., phenol, flavonoids, saponins, and tannins), and the antioxidant activity score was 8.25 or categorized as high (Arysanti, 2022; Arysanti et al., 2022; Iskandar, 2020).

Flavonoid is one of the active compounds that is important as an antioxidant agent that can bind the free radicals in the body (S. Singh et al., 2022), leading to the success of the insulin receptor working properly and decreasing the blood glucose (Song et al., 2005; Yao et al., 2022). The mechanism of

antioxidants in diabetes treatment may become one of several ways to explain how the 14-day Bajakah intervention can reduce blood glucose.

Most of the people were diagnosed with type 2 diabetes mellitus of which the predisposition factors are varied, such as the genetic heredity factor, the insulin-dominant defect in the pancreatic gland, insulin resistance dominant in the target cells, or insulin resistance with insulin deficiency (Andreadi et al., 2022; Bonnefond & Semple, 2022; DeForest & Majithia, 2022; Indonesian Society of Endocrinology (PERKENI), 2021; Prasad et al., 2022). Diabetes treatment will affect blood insulin levels through either insulin deficiency or insulin resistance mechanisms.

The difference between the control group on the blood glucose was significant because the C1 group did not get any STZ induction, while C2 received the induction that leads to hyperglycemia. Streptozotocin induction is widely used in animal diabetic studies to mimic the acute condition of type 2 diabetes mellitus (Furman, 2015; Kottaisamy et al., 2021). Blood glucose values in the C2 and intervention groups were significantly different because the C2 did not receive any Bajakah extract after STZ induction, meaning that it was a successful intervention in reducing the fasting blood glucose in the body.

In general, glucose works in two ways (i.e., passive diffusion and active transport). Passive diffusion is defined by the glucose entry depending on the difference in glucose concentration between the extracellular medium and inside the cell (intracellular) (Chan et al., 2022). Meanwhile, the active transport way is when insulin acts as a facilitator in specific tissues and accelerates the entry of glucose into cells (Brown, 2000; Lizák et al., 2019; Wright et al., 2007).

Moreover, a receptor is needed by glucose-insulin bonds to enter liver cells, muscle, or other tissue cells. However, most peptide hormone receptors, such as insulin, are on the plasma membrane. The insulin receptor is a glycoprotein component of the plasma membrane (Chen et al., 2019; Cignarelli et al., 2019; Siddle, 2004; Takano et al., 2023). The receptor will bind to insulin on the outer surface of the cell. This bond exhibits a high affinity for insulin and will react in a specific, rapid, saturable, and reversible manner. Thus, the decrease in blood glucose levels can be caused by the entry of insulin and glucose bonds into target cells (especially liver and muscle cells) with the help of receptors found on the surface of the cell plasma membrane (James et al., 2021).

The free radicals increase or the antioxidant decrease leads to oxidative stress and ruins the insulin receptor (Andreadi et al., 2022). Cell receptors are one or a group of nerve cells located on the surface of target cells (intracellular) and function to recognize certain substance stimuli originating from outside or within the body. The way receptors work is to regulate whether elements of substances that the body needs can enter cells through the mechanoreceptor system. In this signaling process, the receptors are supported by proteins (Alipourfard et al., 2019; Berntson & Khalsa, 2021; Chen et al., 2019). The mechanoreceptor system works as an ion door that can be opened or closed due to mechanical stimulation in the form of touch. The increased intake of antioxidants from foods or beverages will decrease the free radicals in the body.

Antioxidants are molecules that can safely interact with free radicals, thereby reducing the number of free radicals in the body before they cause cell damage (Akbari et al., 2022; Fang et al., 2002). Antioxidants can protect the body's cells from the effects and adverse effects of free radicals. The role of flavonoids contained in the Bajakah stem (antioxidants) will directly donate their hydrogen ions so that they can neutralize the toxic effects of free radicals. Thus, the role of antioxidants here is mainly to prevent organ damage and the function of receptors.

Bajakah contains another antioxidant called phenol, which interacts with protein to prevent the alpha-glucosidase enzyme (Cao et al., 2021). Phenol interacts with proteins through the enzymatic activity prevention process by inhibiting the breakdown of carbohydrates into glucose, which decreases glucose absorption into the blood (Barik et al., 2020; Zakłos-Szyda et al., 2019). Moreover, phenol hydrolyzes and reduces the carboxylic acid in the small intestine lumen to prevent blood glucose accumulation with an acceleration of glucose breakdown (Candrarisna & Kurnianto, 2018).

Besides flavonoid and phenols, the saponin in the Bajakah plant, as a natural-glycoside bond to the steroid, works like insulin, prevents lipolysis, increases glucose uptake by adipose-cell, and improves insulin resistance condition (Abdel-Mottaleb et al., 2022; Chen et al., 2018; Luo et al., 2020). Meanwhile, tannin, another of Bajakah's antioxidant compound, works like phenol and postpones glucose absorption, and prevents postprandial hyperglycemia (Huang et al., 2019; Türkan et al., 2019). Our study results supported this phenomenon that the blood glucose values among the intervention groups decreased significantly after 14 days of Bajakah stem extract consumption.

In a normal situation, insulin acts as a signal of hormonal cues in the feeding state. Insulin plays a role in the opening of cell receptors on the cell surface so that glucose can enter the cell (Galli et al., 2023). So, the insulin action mechanism is a transporter that moves blood glucose into cells through receptors on the plasma membrane. Thus, the insulin and glucose bonds in the blood circulation can enter the cell through the receptor gate (Wang et al., 2020). After glucose enters the cell by releasing insulin, then glucose will be metabolized in the cell.

The pancreatic beta cells secrete insulin depending on blood glucose level, ATP-sensitive-K channels, and the pancreatic beta voltage-sensitive calcium channels (Oleson & Corbett, 2020). The suggested optimal fasting insulin cutoff value is 13 µU/mL (Rojas et al., 2012), while, in our study, all the groups' mean insulin values post-4-hour fasting were 3.65-5.10 µU/mL. All rats showed normal-level insulin values at the T2. The Manova test result found significant differences between groups, while Tukey test results were significantly different between C2 and P2 or P3. Therefore, the Bajakah may work through the insulin production mechanism only when the extract dose is >100 mg/kg body weight.

The HOMA-IR calculation provides an overview of insulin resistance, where the bond between glucose and insulin experiences resistance when it enters the target cell (Dobrowolski, 2019; Ostrowski & Dobrowolski, 2014; Tahapary et al., 2022). Homeostasis model assessment of insulin resistance, called HOMA-IR, is an epidemiology investigation application developed to replace the in vivo insulin resistance measurement and an approach to learning the effectivity and insulin receptor function on the target cells (Tahapary et al., 2022). Our study result showed that the HOMA-IR calculation of rats in groups C1, X1, X2, and X3 was less than 1.85, except for the C2 group. Insulin resistance became the main point in diabetes type 2 manifestation wherein an antioxidant substance like flavonoids may reduce the cytokine by decreasing the NF-κB in an inflammation, which leads the GLUT-4 expression (Xu et al., 2018).

Among all the intervention groups, the amount of Bajakah in the X2 group (100 mg/kg body weight) showed the optimal dose that made blood glucose, insulin, and HOMA-IR the range of values close to the negative control group. The X2 group dose is equal to 1.12 grams per day for an adult weighing 70 kg and using the constant variable 56.0. These doses need 56 grams of dried Bajakah stem plant. This study has several limitations. Our study did not use the time-varied approach and

measured the insulin once at the end of the intervention, but the Manova and Tukey test results showed significant results and were in line with the former study results (Arysanti, 2022; Tahapary et al., 2022; Takano et al., 2023). This study used the acute Wistar male rats' condition, which limits the ability to see the Bajakah extract roles on the insulin production and increase in insulin levels in the blood. Thus, further research may test the insulin twice to support the explanation about the insulin mechanism after Bajakah intervention. Our Bajakah stem extract intervention study can be one of the alternative ways for people with diabetes that prefer to consume local herbal products under the supervision of health practitioners.

CONCLUSIONS

In this study, using Wistar strain male rats that had been conditioned as acute cases of diabetes mellitus (STZ induction) and were given Bajakah stem plant extract. it showed that the efficacy of the Bajakah stem extract proved a protective effect on blood glucose levels. Bajakah stem plant extract does not appear to play a role in increasing insulin production but plays a role in inactivating free radicals, so they do not damage cell organs. The form of protection in the receptors process is on the target cell surface, which functions as a "door" to the entry of insulin and glucose bonds because the role of insulin is only as a transporter that moves blood glucose into cells. We suggest that future research may test the Bajakah extract as an additional ingredient in food or beverages so that the organoleptic test can be done.

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