JPPIPA 11(7) (2025)

Jurnal Penelitian Pendidikan IPA

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The Effect of Seaweed Soy Tempe Extract on the Reduction of Blood Sugar Levels in Alloxan Induced Rats (*Mus musculus*)

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Received: May 10, 2025
Revised: June 11, 2025
Accepted: July 25, 2025
Published: July 31, 2025

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DOI: 10.29303/jppipa.v11i7.11307

Abstract: Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia due to impaired insulin secretion or action. This study aimed to examine the antihyperglycemic effect of seaweed soybean tempeh extract in alloxan-induced diabetic mice. A Completely Randomized Design (CRD) was used with 20 healthy male mice (2–3 months old, 25–30 g), divided into five groups: negative control, positive control (metformin), and three treatment groups receiving extract doses of 25, 75, and 125 mg/kg BW. Prior to treatment, mice underwent acclimatization to ensure uniform baseline conditions. Blood glucose levels were measured to assess the effects of the extract. Data were analyzed using ANOVA followed by the Least Significant Difference (LSD) test. The results showed that alloxan effectively induced hyperglycemia by damaging pancreatic beta cells. Administration of seaweed soybean tempeh extract significantly reduced blood glucose levels ($p < 0.05$). The highest dose (125 mg/kg BW) produced the most notable effect, comparable to metformin, while the 75 mg/kg BW dose also demonstrated significant efficacy. Both were significantly more effective than the lowest dose. In conclusion, seaweed soybean tempeh extract has potential as an alternative antihyperglycemic agent, especially at higher doses.

Keywords: Alloxan; Diabetes Mellitus; Seaweed Soy Tempe

Introduction

Glucose is one of the primary sources of energy required by the human body. It is derived from daily food intake, particularly from carbohydrates, but also from fats and proteins (Haryanto et al., 2023; Syaifurrisal et al., 2024). In the human body, glucose undergoes various metabolic processes facilitated by several hormones, including insulin (Zhang et al., 2007; Hongayo, 2011; Bocanegra et al., 2021). The concentration of glucose in the body is referred to as blood glucose level. Normal glucose levels reflect a balance between glucose absorption from the intestines into the bloodstream and the uptake of glucose from the blood into body tissues (Mohapatra, 2016; Yoshari et al., 2023; Faisal et al., 2025). The human body naturally regulates blood glucose levels as part of the homeostatic process. Elevated blood glucose levels are one of the key indicators of diabetes mellitus (Jia et al., 2020; Li et al., 2023).

Diabetes mellitus, commonly referred to as diabetes, is a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both (Kumar et al., 2020). This condition is chronic and is marked by disturbances in the metabolism of carbohydrates, proteins, and fats, often followed by microvascular complications. The prevalence of diabetes mellitus continues to rise and affects populations across all economic levels. According to the World Health Organization (WHO), approximately 150 million people over the age of 20 were diagnosed with diabetes mellitus

How to Cite:
Laenggeng, A. H., Hasanuddin, A., Nuryanti, S., & Trianto, M. (2025). The Effect of Seaweed Soy Tempe Extract on the Reduction of Blood Sugar Levels in Alloxan Induced Rats (Mus musculus). *Jurnal Penelitian Pendidikan IPA*, *11*(7), 402–409. https://doi.org/10.29303/jppipa.v11i7.11307

in 2006, and this number is projected to reach 300 million by 2025 (Hongayo, 2011; Haryanto et al., 2023; Syaifurrisal et al., 2024). In Indonesia alone, an estimated 2.5 million individuals are affected by diabetes mellitus. Therefore, further research into the disease including its symptoms, risk factors, prevention strategies, and effective therapeutic interventions is crucial to curb the rising prevalence of diabetes mellitus (Ratwita et al., 2019; Bocanegra et al., 2021).

Patients with diabetes mellitus require lifelong treatment, necessitating therapies that are both accessible and cost-effective. As a result, increasing attention has been directed toward the development of alternative therapies utilizing traditional medicinal plants and natural food ingredients for the management of diabetes mellitus. Indonesia is rich in plant species that serve as sources of traditional medicine, one of which is seaweed. Seaweed is widely recognized for its diverse bioactive properties. In particular, carrageenan a major polysaccharide component found in marine algae has been reported to possess anticoagulant properties and the potential to stabilize blood glucose levels by slowing the release of glucose into the bloodstream (Zhang et al., 2018; Mantur et al., 2023; Yoshari et al., 2023).

Another food ingredient associated with lowering blood glucose levels is *tempeh*. *Tempeh* is a fermented soybean product produced by cultivating *Rhizopus* spp. mold on soybeans (Bocanegra et al., 2021; Jazilah et al., 2024). It is a common source of plant-based protein in the Indonesian diet. *Tempeh* is classified as a food source that contains both essential and non-essential amino acids, low levels of saturated fat, high concentrations of isoflavones and dietary fiber, a low glycemic index, and is easily digestible (Zhang et al., 2007; Hongayo, 2011; Li et al., 2023).

The components of soybean *tempeh* that contribute to lowering blood glucose levels include protein, isoflavones, dietary fiber, and its low glycemic index. *Tempeh* protein is rich in arginine and glycine, amino acids associated with the regulation of insulin and glucagon secretion by the pancreas (Mohapatra, 2016; Simanjuntak & Gurning, 2020). Its isoflavone content, particularly genistein, has been shown to inhibit α-glucosidase, an enzyme involved in carbohydrate metabolism and linked to various metabolic disorders, including diabetes mellitus. Dietary fiber in *tempeh* also plays a role in glycemic control by slowing the absorption of glucose, thereby contributing to a reduction in blood sugar levels (Jazilah et al., 2024). Furthermore, the low glycemic index of *tempeh* results in a moderate blood glucose response, minimizing postprandial spikes (Bocanegra et al., 2021). This study aims to formulate a novel functional food product by combining soybeans with seaweed to create seaweed soybean *tempeh*. Given the hypoglycemic potential of both ingredients, this research seeks to evaluate the effect of seaweed soybean *tempeh* extract on blood glucose levels in alloxan-induced diabetic mice using varying doses of the extract (Hongayo, 2011; Jia et al., 2020; Mantur et al., 2023).

Method

Time and Place of Research

This research was conducted from March to April 2023 at the Biology Laboratory, Faculty of Teacher Training and Education, Tadulako University.

Research Procedure

Research Design

The study employed a Completely Randomized Design (CRD) to ensure that each experimental unit had an equal chance of receiving any treatment, thereby minimizing bias and increasing the reliability of the results. A total of 20 healthy male mice, aged 2–3 months and weighing between 25–30 grams, were used as experimental subjects. Prior to treatment, all mice underwent a one-week acclimatization period in standard laboratory conditions, including a controlled temperature, 12-hour light/dark cycle, and unrestricted access to food and water. This acclimatization phase was intended to reduce environmental stress and allow the mice to adapt to their new surroundings, ensuring uniform baseline conditions before the intervention began.

Following acclimatization, the mice were randomly assigned to five groups: two control groups and three treatment groups. The positive control group (K^+) received standard treatment to serve as a benchmark, while the negative control group (K^-) received no treatment. The three treatment groups were administered seaweed soybean tempeh extract orally at different dosages: 25 ml/kg body weight/day (P1), 75 ml/kg body weight/day (P2), and 125 ml/kg body weight/day (P3). The extract was freshly prepared and administered consistently throughout the treatment period to ensure dose accuracy and stability. The rationale for using varying doses was to evaluate the potential dose-dependent effects of the extract on the physiological parameters being studied (Figure 1).

The overall experimental procedure and group allocation are illustrated in Figure 1, which provides a visual representation of the study design, including sample grouping, treatment duration, and the timeline of data collection. This design was chosen to facilitate the identification of treatment effects with a high degree of precision, allowing for valid statistical comparisons among groups.

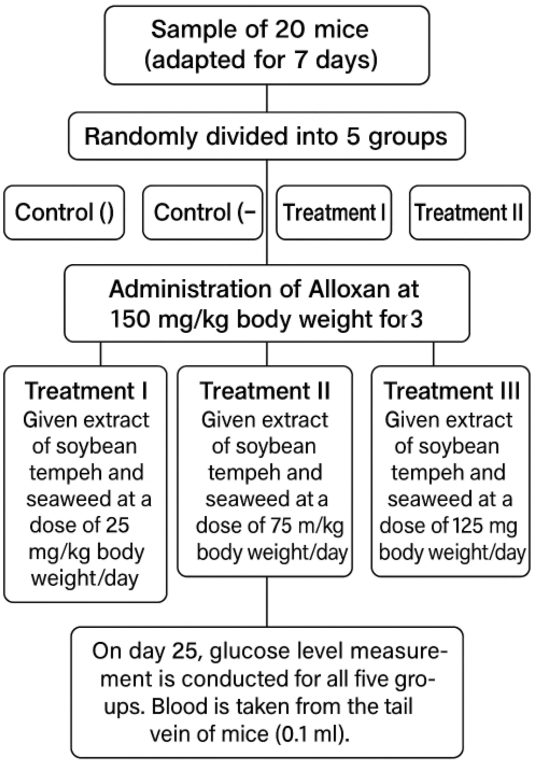

Figure 1. Research design

Acclimatization of Animal Tests

The research subjects were 20 mice, divided into 5 groups, namely the positive control group (K+), negative control group (K-), treatment group I (P1), treatment group II (P2) and treatment group III (P3). The five groups were adapted in the Biology Education Laboratory of Tadulako University for 7 days. On the 8th day, the treatment was carried out.

Preparation of Induction Materials

Alloxan monohydrate powder was diluted using distilled water. Groups of mice were induced by injecting alloxan subcutaneously with a concentration of 150 mg/BB for 3 days before treatment. The administration of alloxan to mice was done once a day.

Preparation of Synthesized Drugs

Based on the conversion table of dose calculation for various test animals of various species and humans, the dose conversion of humans with a body weight of 70 kg to mice with a body weight of 20 grams is 0.0026 (Ngatidjan, 1991). The dose of metformin used for adults is 500 mg/day, thus the dose for 20 gram mice = (500 mg x 0.0026) = 1.3 mg/mice/day.

Preparation of Seaweed Soybean Tempeh Extract

The process of making seaweed soybean tempeh extract is as follows: 1) Making seaweed soybean tempeh starts with weighing 200 grams of seaweed and soaking the seaweed for 48 hours. 2) Then the next day weighing clean dry soybean seeds as much as 2 kg. 3) After weighing the soybeans were washed and then boiled until half cooked approximately 30 minutes. 4) After boiling the soybeans are peeled clean by removing the skin, then soaked for 20 hours. 5) Then after 20 hours soybeans washed thoroughly, steamed again for 45 minutes. 6) Seaweed that has previously been soaked for 48 hours is then blended and then dried. 7) Once dry then mixed with soybeans in a ratio of 80: 20. 8) Furthermore, the soybean and seaweed mixture was given Rhizopus oligosporus yeast and wrapped in plastic with holes. 9) Then fermented for ± 36 hours. 10) After becoming tempeh soybean seaweed then tempeh cut into small pieces and blended. 11) Tempeh that has been blended then sifted into flour powder. 12) Seaweed soybean tempeh powder is then extracted using maceration method.

Administration of Test Materials

In the second week, the experiment began for 14 days. The positive control group (K+) was induced alloxan and given synthetic drugs (Metformin), and the negative control group (K-) was given food and drink and induced alloxan. Treatment group I (P1) was given seaweed soybean tempeh extract at a dose of 25gr/kg BW/day and induced alloxan. Treatment group II (P2) seaweed soybean tempeh extract dose of 75gr/kg BW/day and induced alloxan. Treatment group III (P3) seaweed soybean tempeh extract dose of 125gr/kg BW/day and induced alloxan.

Observation and Examination of Blood Glucose Levels

This experiment was carried out measuring blood glucose using autocheck (a tool for measuring blood sugar levels). The tail end of the mice was cut, then blood was dripped onto the tip of the strips connected to the autocheck, left for 6 seconds then the results will be seen on the screen, where the unit of measurement scale read mg/dl.

Data Analysis

This study was designed using a completely randomized design (CRD). Data were analyzed by ANOVA using SPSS.

Result and Discussion

Blood Sugar Levels of Mice Before and After Alloxan Induction

The average value of the increase in blood sugar levels before and after alloxan induction can be seen in Figure 2. The value of blood sugar levels in mice induced with alloxan in the control (-) increased from 81.5 to 155.75 mg/dl, in the control group (+) from 82.5 to 157.5 mg/dl, in the group of mice (P1) from 85.75 to 160.5

mg/dl, in the group of mice (P2) from 81 to 159.25 mg/dl, and in the group of mice (P3) the increase was from 86.75 to 158.75. This shows that induction using alloxan can increase the blood sugar levels of mice.

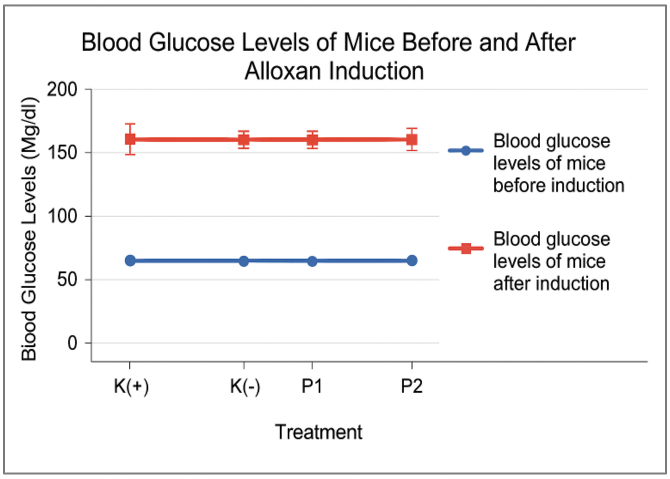

Figure 2. Mean value of blood sugar level increase in mice before and after alloxan induction

Blood Sugar Level of Mice After Administration of Seaweed Soybean Tempeh Extract

The average value of blood sugar after administration of seaweed soybean tempeh extract can be seen in Figure 3. The average value of blood sugar levels after being given treatment in the form of seaweed soybean tempeh extract, including in treatment 1 with a dose of 25 mg / kgBB, from 160.5 to 83 mg / dl, in group P2 with a dose of 75 mg / kgBB, from 159.25 to 72.5 mg / dl, and in P3 with a dose of 125 mg / kgBB, from 158.75 to 70.75 mg / dl. This shows that there is an effect of giving seaweed soybean tempeh extract that can reduce blood sugar levels.

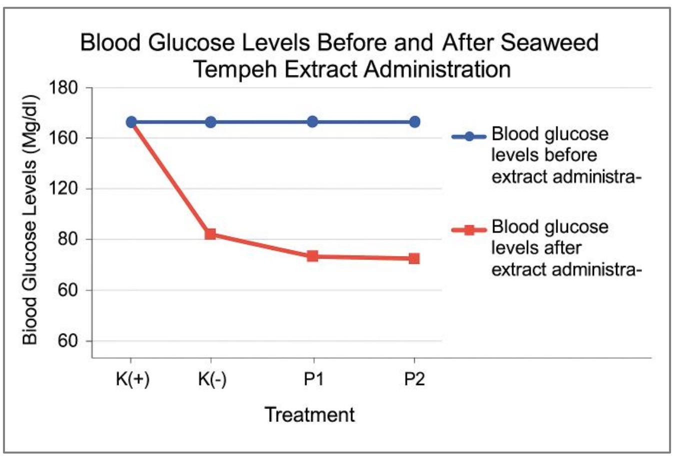

Figure 3. Mean blood sugar level of mice after given seaweed soybean tempeh extract

The results of the comparison of the average blood sugar levels in mice after the administration of alloxan and seaweed soybean tempeh extract can be seen in Figure 4.

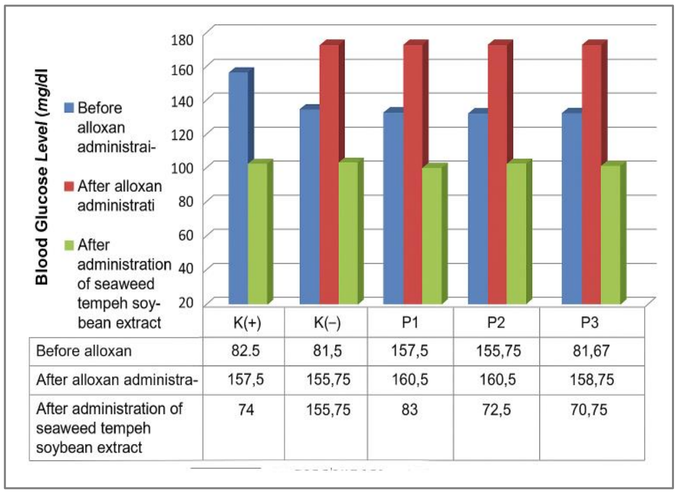

Figure 4. Comparison of the average value of blood sugar levels of mice after being induced by alloxan and treated with Seaweed soybean tempeh extract

The average level of blood glucose in mice in the drug administration group or K (+) which is induced by alloxan and given food and drink and generic drugs (metformin) there is a decrease in the average level of blood sugar which is 74 mg/dl. For K(-) which was induced alloxan and fed and drank had an average blood sugar level of 155.75 mg/dl. The treatment group with the administration of seaweed soybean tempeh extract with different doses including P1 induced alloxan and given seaweed soybean tempeh extract 25 mg/kgBB/day there was a decrease in the average blood sugar level of 83 mg/dl, for P2 induced alloxan and given seaweed soybean tempeh extract 75 mg/kgBB/day there was a decrease in the average blood sugar level of 72.5 mg/dl and for P3 induced alloxan and given seaweed soybean tempeh extract 125 mg/kgBB/day there was a decrease in the average blood sugar level of 70.75 mg/dl.

The calculation data obtained were then tested using ANOVA test to determine whether or not there was an effect of giving seaweed soybean tempeh extract on blood sugar levels of mice. The results of data analysis using ANOVA analysis of variance can be seen in the table of variance in Table 1. Based on Table 1, it is known that sig <0.05 means H0 is rejected and H1 is accepted. The first hypothesis H1 accepted is that there is an effect of giving seaweed soybean tempeh extract on blood sugar levels of mice. Thus, it is known that there is an effect of giving seaweed soybean tempeh extract on reducing blood sugar levels in mice induced with alloxan.

Table 1. Analysis of variance of blood sugar levels in mice

Source of Variance	Df	Mean	F	Sig.
Between Group	4	5297.675	746.151	0.000
Within Group	15	7.100		
Total	19			

Effective Dose of Seaweed Soybean Tempeh Extract in Lowering Blood Sugar Levels

The data that has been obtained is then tested using the BNT test to determine whether or not there is an effective dose in reducing blood sugar levels in mice. The results of data analysis can be seen in Table 2.

Table 2. BNT further test analysis of the effective dose of reducing blood sugar levels of mice

Treatment	N	Sub test for alpha = 0.05	
		1	2
P1	4	70.75	-
P2	4	72.50	-
P3	4	-	83.00
Sig		71..62	1.000

Means for groups in homogeneous subsets are displayed
Uses Haarmonic Mean Sample Size = 4. 000

The experimental animals were induced by alloxan which can increase blood sugar levels, seen from the results of significant measurements of blood sugar levels after alloxan induction in the control group (-) increased from 81.5 to 155.75 mg/dl, this indicates that there is damage to pancreatic beta cells as insulin producers that cause glucose cannot be metabolized properly and accumulated in the blood. The administration of alloxan is a quick way to produce experimental diabetic conditions (Hyperglycemic) in experimental animals because alloxan reacts by damaging the essential substance in the beta cells of the pancreas, causing the reduction of insulin-carrying granules in the beta cells of the pancreas (Cimbiz et al., 2011; Mohapatra, 2016; Kalungia et al., 2018; Bocanegra et al., 2021; Lolok et al., 2023).

Alloxan in the blood binds to GLUT-2 (glucose transporter) which facilitates the entry of alloxan into the cytoplasm of pancreatic beta cells. Inside the beta cells, alloxan causes excessive depolarization of the mitochondria as a result of Ca2- ion influx followed by excessive energy use resulting in energy deficiency in the cells. These two mechanisms cause damage to both the number of cells and the mass of pancreatic cells, resulting in a decrease in insulin release which results in diabetes mellitus (Hongayo, 2011; Solikhah & Solikhah, 2021; Khoirunnisa et al., 2025). Elevated blood sugar levels can be seen by measuring using a blood sugar autocheck. Lolok et al. (2023) explains the normal fasting blood sugar levels of mice 62.8-150 mg/dl. This when compared with the results of research on the control group (-) which has a blood sugar level of 155.75 mg/dl shows a difference that means an increase in blood sugar in mice after alloxan induction.

The test animals used in this study were male white mice (*Mus muscullus*) Male white mice were chosen because they do not have the hormone estrogen which can affect the estrus cycle. In addition, the level of stress in female mice is higher than that of male mice and mice have physiological similarities with humans, are easy to maintain, and are easily available and more economical (Herlina et al., 2018; Jia et al., 2020; Syaifurrisal et al., 2024). The mice used are mice aged about 2-3 months with a weight of 20-40 grams, because at that age the metabolic processes in the mice's body are perfect so as to facilitate research (Zhang et al., 2007; Abdulgani et al., 2014; Akter et al., 2014). A total of 20 mice that have been induced for 3 days to increase blood glucose levels. After that mice will be given treatment in the form of giving seaweed soybean tempeh extract with a ratio of 80% soybeans and 20% seaweed which serves to reduce blood glucose levels so that it can help improve the performance of the pancreas to produce insulin to process glucose as an energy source. The comparison used is taken based on organoleptic tests that have been carried out where at the time of the organoleptic test the most preferred comparison for consumers is the 80:20 ratio. In this study, seaweed soybean tempeh extract was given at different doses, namely doses of 25 mg/kgBB/day, 75 mg/kgBB/day and 125 mg/kgBB/day. In addition, there is also a control treatment (+) which is given a chemical drug, namely metformin at a dose of 1.3 mg as a comparison and control treatment (-) which is only induced by alloxan.

The results of the study of blood sugar levels in the administration of seaweed soybean tempe extract in the P1 group at a dose of 25 mg / kg / day there was a decrease in blood sugar levels from 160.5 mg / dl to 83 mg / dl compared to the control (-) induced alloxan which is 155.75 mg / dl, also after being compared with the control (+) given the chemical drug metformin which is 74 mg/dl. This proves that there is an effect of seaweed soybean tempeh extract on reducing blood sugar levels in mice in the P1 treatment group. The value of blood sugar levels of mice after the administration of seaweed soybean tempe extract in group P2 at a dose of 75 mg / kg / day decreased blood sugar levels from 159.25 mg / dl to 72.5 mg / dl compared to the control (-) induced alloxan which is 155.75 mg / dl, also after being compared with the control (+) given the chemical drug metformin which is 74 mg/dl. This proves that there is an effect of seaweed soybean tempeh extract on reducing blood sugar levels in white mice in the P2 treatment group. The value of blood sugar levels of mice after the administration of seaweed soybean tempe extract in group P3 at a dose of 125 mg / kg / day decreased blood sugar levels from 158.75 mg / dl to 70.75 mg / dl compared to the control (-) induced alloxan which is 155.75 mg / dl, also after being compared with the control (+) given the chemical drug metformin which is 74 mg / dl. This proves that there is an effect of seaweed soybean tempeh extract on reducing blood sugar levels of mice in the P3 treatment group. The control treatment (+) is a treatment that uses chemical drugs in the form of metformin with a dose used in mice that is 1.3 mg can be known that there is a decrease in blood sugar levels from 157.5 mg / dl to 74 mg / dl compared to the control (-) which has a blood sugar level of 155.75 mg / dl can prove that the control treatment (+) there is a decrease in blood sugar levels.

From the results of the BNT further test analysis, it was found that the P3 treatment was not significantly different from the P2 treatment, but P3 and P2 were significantly different from P1. And the best dose that can reduce blood sugar levels in mice is in treatment 3 (P3). The dose in each treatment group has an influence in reducing blood sugar levels in mice but the best dose in reducing blood sugar levels in mice is a dose of 125 mg. (Zhang et al., 2007; Sharma et al., 2013; Ratwita et al., 2019) stated that keragenan derived from Eucheuma cottoni seaweed extract can be used to reduce blood glucose levels in rats that have pancreatic damage due to alloxan induction, giving keragenan can reduce blood sugar levels in rats by 37.55%. According to Yuniarti & Ramadhani (2023), there was a decrease in fasting blood glucose levels by 9.44 mg/dl (8.69%) after giving soybean tempeh for 14 days, because soybean tempeh contains protein and isoplavon that can reduce blood glucose levels. When compared with the results of the study obtained by giving seaweed soybean tempeh extract, the highest decrease in blood sugar levels was in group P1 by 77.5 mg/dl (%). This is because seaweed soybean tempeh contains more nutrients so that it gives the effect of lowering blood sugar levels greater.

The effect of reducing glucose levels in mice in the P1, P2 and P3 treatment groups resulted from the content of seaweed soybean tempeh, namely protein, isoflavones, fiber and keragenan polysaccharide compounds. Soybean tempeh protein is high in arginine and glycine content related to insulin and glucagon secretion from the pancreas. The content of isoflavones in the form of genistein can inhibit α glucosidase which plays a role in several metabolic disorders such as DM (Li et al., 2023; Lolok et al., 2023). Fiber has a hypoglycemic effect because it can slow gastric emptying, change gastric peristalsis, slow glucose diffusion, reduce amylase activity due to increased viscosity of intestinal contents and reduce transit time which results in shortened glucose absorption and affects the increase in insulin secretion (Ratwita et al., 2019; Salem et al., 2020). Eucheuma cottoni seaweed has many properties because seaweed has a large nutritional value, including as a source of protein, carbohydrates, minerals and vitamins that are easily digested and keragenan compounds contained in Eucheuma cottoni seaweed can reduce blood glucose by inhibiting glucose absorption (Mohapatra, 2016; Jia et al., 2020; Li et al., 2023).

The results of the treatment of seaweed soybean tempeh extract 25 mg, 75 mg and 125 mg have different effects in reducing blood sugar levels of mice influenced by the dose of administration of seaweed soybean tempeh extract. Based on research that has been done (Salem et al., 2020; Yoshari et al., 2023) on the effect of seaweed on blood glucose levels and the number of monicits in alloxan-induced Wistar rats, the difference in dose causes differences in the viscosity of the liquid in the gastrointestinal tract, which in turn causes differences in the ability and strength in the binding of glucose by the gel in the gastrointestinal tract, this will cause differences in the rate of absorption of glucose from the gastrointestinal tract to the blood vessels so that the rate of increase in blood glucose levels is affected (Hongayo, 2011; Salem et al., 2020; Yoshari et al., 2023).

Conclusion

This study demonstrated that alloxan induction effectively increased blood sugar levels in mice, confirming its role in damaging pancreatic beta cells and inducing hyperglycemia. Treatment with seaweed soybean tempeh extract at various doses (25 mg/kg BW, 75 mg/kg BW, and 125 mg/kg BW) significantly reduced blood glucose levels in diabetic mice. Among the doses tested, the 125 mg/kg BW dose (P3 group) showed the most substantial glucose-lowering effect, with results comparable to the positive control treated with metformin. The ANOVA test confirmed a significant effect of the extract on blood glucose reduction ($p < 0.05$), and further BNT analysis revealed that the P3 and P2 treatments were similarly effective and both outperformed P1.

Author Contributions

Conceptualization, Abdul Hakim Laenggeng; methodology, Abdul Hakim Laenggeng, Manap Trianto, and Asriani Hasanuddin; formal analysis, Abdul Hakim Laenggeng, Asriani Hasanuddin, and Sitti Nuryanti; writing—original draft preparation, Abdul Hakim Laenggeng, Manap Trianto, and Sitti Nuryanti; writing review and editing, Abdul Hakim Laenggeng and Asriani Hasanuddin.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

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