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Effectiveness of Water Extract of Sea Lada (Ulva Lactuca) from Aceh Waters to Reduce Blood Glucosa Levelsin Diabetic Rats

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ABSTRACT

Diabetes mellitus (DM) is a non-communicable disease characterized by high blood glucose levels caused by damage to the pancreas, which cannot produce insulin. Antidiabetic drugs and insulin injections in the long term have specific side effects, so herbal medicine is considered safer to use. Sea lettuce (*Ulva lactuca*) is one of the herbal medicines that have the potential as an antidiabetic. Methods: Experimental using a completely randomized design. Rats were divided into five groups with three replicates, namely: Kn = normal control, Ka = STZ control, P1 = DM rats + 200 mg/KgBB extract dose, P2 = DM rats + 300 mg/KgBB extract dose, and P3 = DM rats + 400 mg/KgBB extract dose. The stages of this study began with the preparation of tools and materials, phytochemical tests, the preparation of test animals and testing extracts on test animals, and the measurement of blood glucose levels in rats before and after they were given extracts. Blood glucose levels were measured using a glucometer. Data analysis was performed statistically (ANOVA). The results of the phytochemical tests detected were steroids, saponins, and phenols/tannins, while alkaloids, terpenoids, and flavonoids were not. The most effective blood glucose level measurement result is at a dose of 400 mg/KgBB

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Introduction

Diabetes mellitus is a non-communicable disease caused by damage to the pancreas so that it cannot synthesize insulin needed for glucose breakdown. Impaired insulin production will affect blood glucose levels that continue to increase and are not controlled. Although not contagious, diabetes is one of the most dangerous diseases that cause death. Diabetes can cause various disease complications, such as eye damage, vascular disorders, heart disease, kidney failure, and, most fatally, as a cause of death (Thongsom, 2013). The prevalence of diabetes, mainly types 2 diabetes, has increased globally by 30%. The most common complication experienced by people with diabetes is acute heart failure. (Busui, 2022). Hyperglycemia also affects the performance of glands such as the hypothalamus, pituitary gland, gonads, and perigonads. Glands that cannot function properly cause a decrease in the secretion of gonadal steroids such as GnRH, FSH, LH, and testosterone, thus affecting male fertility and reproductive health (Andlip, 2023). Hyperglycemia is the leading cause of various vascular complications through the following mechanisms: activation of the polyol and hexosamine pathways; activation of protein kinase C; increased oxidative stress; increased production of advanced glycation end products; increased synthesis of growth factors, cytokines, and angiotensin II. In addition, diabetic complications are also due to the involvement of epigenetic mechanisms and micro RNAs in pathogenesis (Chiarelli, 2023).

According to the FDI (International Diabetes Federation), people with diabetes aged 20–79 years amounted to approximately 366 million in 2011 and are expected to rise to 522 million people in 2030 (Whiting, DR. 2011). Data compiled by the WHO (2018) shows that there were 2.2 million cases of death caused by diabetes in 2012, making it the seventh leading cause of death worldwide. The age range of people with diabetes is below 70 years. It is estimated that there will be an increase in the number of diabetics by 25% in 2030 and 51% in 2045 (Saeedi, 2019).

Diabetes treatment is still relatively expensive and sometimes has side effects, so herbal plants are starting to be tried as alternative drugs because they have hypoglycemic properties and fewer side effects. Herbal plants are spread throughout Asia but are most abundant in Indonesia, which has 80% of the world's population. There are 2000-7500 species of herbal plants estimated to be distributed in Indonesia. Most people use herbal plants in the form of herbal drinks or herbal medicine. In addition, herbal plants are also used as raw materials for drugs that have been standardized after undergoing research and clinical trials in humans (Zahra, H., 2022). People use herbal plants as antidiabetics by boiling the leaves with water to make herbal medicine (Rinawati, 2019). Researchers have done much research on medicinal plants because their bioactive content gives them biological effects so that they can be used as antioxidants, antibacterials, antidiabetics, anticancer agents, etc. One of the many research projects conducted by researchers today is the potential of herbal plants as antidiabetics (Prisdiani, Y. 2021).

WHO (World Health Organization) states that treatment using natural ingredients has been used by 60% of the population of developed countries (DepKes, RI, 2007). One of the natural ingredients that can potentially be medicinal is sea lettuce (*Ulva lactuca*). *Ulva lactuca* is algae found in marine waters and is usually processed into food ingredients by the community. *Ulva lactuca* is one type that is classified as "Father Seaweed" or a type of green algae that can be consumed and has antioxidant, antifungal, antibacterial, and antitumor content (Arbi et al., 2016). Because it has a high carbohydrate and fat content but a low-fat content, *Ulva lactuca* has the potential as a functional food raw material. Pigments contained in *Ulva lactuca* can also act as antioxidants that inhibit cancer, obesity, and diabetes; these pigments include neoxanthin, antheraxanthin, and vaucheriaxanthin, which have allenic bonds like fucoxanthin (Costa, 2018).

According to some studies, *Ulva lactuca* can be used as an antihyperglycemic in DM disease. The methanol extract of *Ulva lactuca* is proven to reduce hyperglycemia in vitro (Murugesan, S. 2015), and the ethanol extract of *Ulva lactuca* can reduce cholesterol levels in DM rats (Fairuz, 2014) and help restore body weight in diabetic rats who have lost weight (Rinawati, 2020). Ulva lactuca can reduce blood glucose levels by inhibiting the post-prandial glucose absorption process due to its bioactive content's activity (Ditasari, 2022). The oligosaccharide content of *Ulva lactuca* effectively restores blood glucose metabolic processes. It delays brain aging in elderly patients with type 2 DM through the GLP-1/GLP-1R pathway to mobilize communication between the brain and gut (Chen, 2022). *Ulva lactuca* ethanol extract contains alkaloids, steroids, and phenolics/tannins (Zulfadhli, 2018). Research on *Ulva lactuca* using an aqueous extract against hyperglycemia and its phytochemical screening has yet to be carried out, especially in the Aceh area.

Method

Place of Research

his research was conducted at the Laboratory of the Academy of Pharmacy, YPPM Mandiri Banda Aceh, for testing the water extract of *Ulva lactuca* on test rats *in vivo.*

Tools and Materials

The tools used in this study are sonde needles, syringes, cages, weight scales to measure the development of rat body weight during and after treatment, a blood glucose level checker brand called "Easy Touch," and Easy Touch brand blood glucose level measuring strips, distilled water, male rats with an average weight of 200 grams, rat food, and STZ to condition rats into diabetes.

Research Stages

Preparation of sea lettuce extract

After being cleaned of dirt attached to the leaves, *Ulva lactuca* is thoroughly washed and drained. The drying process of *Ulva lactuca* is done by air drying it for several days until it is completely dry and brittle. The powder is made by crushing it in a blender and then sifting it to get a powder that is not too coarse or too fine.

A Phytochemical Test of Sea Lettuce

Water-solvent maceration method for extracting *Ulva lactuca* the juice solution was then evaporated with a vacuum rotary evaporator at 40 °C until a thick extract was obtained. Phytochemical testing was carried out using the Harborne method (1997).

Animal Test Preparation

First, rats were given nicotinamide (NA) solution at a dose of 230 mg/kgBB. After 15 minutes, rats were injected with streptozotocin (STZ) at a dose of 65 mg/kg BB. The STZ required to induce depends on the rats' body weight (BW).

In vivo testing of extracts on test animals

Ulva lactuca water extract was given to test animals *in vivo* using a sonde needle at doses of 200 mg/kg, 300 mg/kg, and 400 mg/kg for 30 days. Every week blood glucose levels were checked every five days.

Research design

This research is experimental with a completely randomized design. The total number of test animals was 25, divided into five treatments with three replicates:

Kn = Normal control (only given food and distilled water).

Ka = STZ control (rats induced by 65 mg STZ)

P1 = DM rats + 200 mg/KgBB extract dose

P2 = DM rats plus a 300 mg/KgBB extract dose.
P3 = DM rats + 400 mg/KgBB extract dose

Parameters observed

1. Blood glucose levels before and after STZ induction

Measuring blood glucose levels before and after STZ induction aims to determine whether STZ has worked perfectly to cause hyperglycemia. Usually, mice will experience an increase in blood glucose on the third day after STZ induction (Saputra, 2028).

2. Glucose levels before and after administration of the extract.

Measuring glucose levels before and after administration of the extract aims to determine whether the administration of *Ulva lactuca* water extract effectively reduces blood glucose levels in DM rats.

Data Analysis

Data analysis was done descriptively in the form of tables and graphs. Data processing and analysis using computer aid Anova analysis were performed for the measurement of blood glucose levels in each group; if there were differences between treatment groups, they were further analyzed by the DMRT (Duncan multiple range test).

Results

Phytochemical Content of Sea Lettuce

Sea lettuce has a thin, sheet-like structure resembling transparent green plastic. In making extracts, sea lettuce must first be cleaned of adhering dirt and then air-dried for several days. After drying, sea lettuce is crushed into powder using a blender and then ready for extraction. The extraction process on sea lettuce is done using water as a solvent. The phytochemical content contained in sea lettuce water extract is as follows:

Table 1: Phytochemical test results of sea lettuce (*Ulva lactuca*) water extract.

Metabolite Content	Reagen	Test Result	Observation Results
Alkaloid	Mayer	-	No white precipitate formed
	Wagner	-	No brown precipitate formed.
	Dragendorff	-	No red precipitate formed
Steroid	Liebermann-Burchard Test	+	Green Color Formed
Terpenoid	Liebermann-Burchard Test	-	There was no red color formed
Saponin	Aquadest	+	Foaming
Flavonoid	Hcl and Mg Metal	-	No Formation Reddish Color
Fenol/Tanin	FeCl3	+	Green Color Formed

Based on the table above, the phytochemical content of sea lettuce water extract is not all detected; of the six metabolite contents that are checked, only three are positive, namely steroids, saponins, and phenols/tannins while alkaloids, terpenoids, and flavonoids are not detected. These results are similar to previous research conducted by Zulfadhli (2018) on the extraction of sea lettuce using ethanol solvents, where the results of phytochemical screening contain alkaloid, steroid, and tannin compounds. Water solvents are polar and are one of the solvents allowed because they meet pharmaceutical-grade requirements and are safe to use (Latifa, 2022). The polarity of the water solvent is because it has a hydroxyl group (Buhang, 2019). Alkaloids are semipolar (Hesturini, 2022), flavonoids are polar (Suryandari, 2022), and terpenoids are nonpolar, so they will not dissolve in polar solvents (Resti, 2022). Although flavonoids are polar, they were not detected in this study. The amount is tiny in *Ulva lactuca*, so water solvents cannot draw it.

Blood Glucose Levels

In this study, rats were divided into the Normal Control group, STZ Control, P1, P2, and P3. The normal control group is a rat test animal only given aquadest without any treatment. This aims to compare the difference between animals that receive treatment and animals that do not. STZ control is a test animal that is always conditioned diabetes as a comparison of the decrease in blood glucose levels in rats treated with *Ulva lactuca* water extract. Group P1 is a diabetic rat given a dose of 200 mg / kgBB, Group P2 is a diabetic rat given a dose of 300 mg / kgBB, and P3 is a diabetic rat group given a dose of 400 mg / kgBB.

The measurement of blood glucose levels starts from day 0 to day 28. Blood sampling is done in 7 days. Measurement of day 0 is a measurement of blood glucose levels carried out after rats are acclimatized and have not received any treatment. Measurement on day 7 is the measurement of blood glucose levels carried out after the test animals were induced by STZ (SZ Control Group, P1, P2, and P3). Day 14, 21, and 28, measurements of glucose levels were taken when the test animals were already in a diabetic state. The results of blood glucose level measurements are presented in the following table:

Table 2: Blood Glucose Level Measurement Results

Treatment	Rat Glucose Level (mg/dl)				
	Day				
	0	7	14	21	28
Normal control (KN)	$80,33 \pm 5,03^{d}$	$80,33 \pm 2,51^{e}$	$79,33 \pm 4,04^{d}$	$79,33 \pm 4,04^{e}$	$80,67 \pm 0,57^{e}$
STZ control (Ka)	$92,33 \pm 4,93^{c}$	$247,33 \pm 2,51^{d}$	$251,00 \pm 1,73^{c}$	$262,00 \pm 2,64^{b}$	$271,00 \pm 7,93^{a}$
Dose 200 mg (P1)	$110,33 \pm 4.50^{a}$	$290,00 \pm 5,00^{b}$	$281,67 \pm 2,88^{a}$	$274,67 \pm 4,50^{a}$	$245,00 \pm 5.00^{b}$
Dose 300 mg (P2)	$106,67 \pm 3,51^{a}$	$301,00 \pm 3,60^{a}$	$268,67 \pm 3,51^{b}$	$230,00 \pm 4,35^{c}$	$216,67 \pm 6.50^{c}$
Dose 400 mg (P3)	$81,33 \pm 1,15^{d}$	$277,67 \pm 3,21^{c}$	$245,00 \pm 8,66^{c}$	$207,00 \pm 8,71^{d}$	$107,00 \pm 7.00^{d}$

Notes: Numbers in the same row followed by the same superscript letter are not significantly different at the 5% test level.

Discussion

The results of measuring blood glucose levels in rat test animals on day 0 are shown in the table above and show no significant difference between treatments. This is because the rats in each treatment are still in a normal state and have not been given any treatment. Although there are differences in glucose levels in each group, they are still normal. The different physiological states of each rat can cause the difference.

The increase in blood glucose levels in STZ-induced rats occurred when measuring day 7, while the

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blood glucose levels of the KN group remained normal. This is because the rats in the KN treatment group were conditioned to be normal and were only used as a comparison. The increase in blood glucose levels in the Ka, P1, and P2 groups is due to the induction of STZ, which has begun to damage the pancreas of rats so that it disrupts insulin secretion, which ultimately causes glucose levels in the blood of rats to increase above normal limits.

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If the glucose level in the test animal exceeds the normal limit, this indicates that the animal is diabetic. According to Port (1995), normal blood glucose levels are 110 mg/dL when fasting or 140 mg/dL 2 hours after eating, whereas diabetes occurs when glucose levels exceed 126 mg/dL when fasting or 200 mg/dL when not fasting. STZ induction can trigger oxidative stress that ultimately disrupts pancreatic performance and causes high glucose levels (hyperglycemia). There are three mechanisms of oxidative stress, as follows: (1) non-enzymatic protein glycation; (2) aldose reductase pathway, which uses the SDH (sorbitol dehydrogenase) enzyme to convert sorbitol to fructose. Sorbitol degradation is slow, so sorbitol accumulates in cells. This causes an increase in osmotic pressure, which ultimately damages cells (3). The change in oxidative status is characterized by changes in endogenous antioxidant activity and increased oxidative damage to biomolecules. To reduce oxidative damage, antioxidants are needed (Setiawan, 2005).

An observation of the effectiveness of *Ulva lactuca* water extract was done after administration of the extract on the 8th day. On day 14, blood glucose levels in the Ka, P1, P2, and P3 groups remained high, but the Ka and P3 groups were not significantly different from the other groups. This data shows that *Ulva lactuca* water extract in the first week has been unable to reduce blood glucose levels to normal in the DM rat group. e normal limit, this indicates that the animal is diabetic. According to Port (1995), normal blood glucose levels are 110 mg/dL when fasting or 140 mg/dL 2 hours after eating, whereas diabetes occurs when glucose levels exceed 126 mg/dL when fasting or 200 mg/dL when not fasting. STZ induction can trigger oxidative stress that ultimately disrupts pancreatic performance and causes high glucose levels (hyperglycemia). There are three mechanisms of oxidative stress, as follows: (1) non-enzymatic protein glycation; (2) aldose reductase pathway, which uses the SDH (sorbitol dehydrogenase) enzyme to convert sorbitol to fructose. Sorbitol degradation is slow, so sorbitol accumulates in cells. This causes an increase in osmotic pressure, which ultimately damages cells (3). The change in oxidative status is characterized by changes in endogenous antioxidant activity and increased oxidative damage to biomolecules. To reduce oxidative damage, antioxidants are needed (Setiawan, 2005).

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The measurement of blood glucose levels at week 21 showed that each treatment group differed significantly. The Ka group experienced an increase in blood glucose levels. Although blood glucose levels in groups P1, P2, and P3 are still classified as hyperglycemia, there is a decrease compared to day 14 measurements.

The measurement of glucose levels on day 28 also showed a significant difference. Group Ka still experienced an increase in glucose levels from 262,00±2,64 mg/kgBB on day 21 to 271,00±7,93. The P1 and P2 groups experienced a decrease in blood glucose levels, but the levels were still high. The P3 group has reached normal limits but is slightly higher than the KN group. The percentage reduction in blood glucose levels can be calculated through the difference between the measurement results on day 7 and day 28. The data is presented in the following table:

Table 3: Percentage reduction in blood glucose levels of diabetic rats

Group	**Decrease in Glucose Blood Glucose Level (%)**
Normal Control (KN)	0%
STZ Control (Ka)	Increast 10%
Dose 200 mg (P1)	16%
Dose 300 mg (P2)	28%
Dose 400 mg (P3)	61%

Based on the table above, the highest percentage decrease in blood glucose levels occurred in the P3 group at a dose of 400 mg/kg BW, as much as 61%, followed by the P2 group by 28%. The lowest percentage decrease was in the P1 group, which was only able to reduce blood glucose levels by 16% after being given *Ulva lactuca* water extract for 21 days. KN did not experience any changes because it was used as a treatment control, while Ka, a diabetic control, experienced an increased blood glucose level of 10%. This is because the rats were diabetic and were not given any treatment. The decrease in blood glucose levels in the group treated with *Ulva lactuca* water extract can be caused by the content of phytochemical compounds that can help regenerate pancreatic cells. According to Tair (2018), *Ulva lactuca* has hypotensive, hypoglycemic, and antiatherogenic properties that can improve or prevent cardiovascular complications because it contains polysaccharides. The polysaccharide content can play a role in improving the antioxidant pathway of diabetic rats that experience complications of neuropathy syndrome (Appu, A., 2022).

The results of phytochemical screening showed that *Ulva lactuca* water extract was positive for steroids, saponins, phenols, and tannins. There may be other phytochemicals besides those mentioned earlier. However, they most likely cannot be attracted by water solvents, or their content is so small that it is not detected during phytochemical screening. Steroids, saponins, and phenol/tanine are antioxidant compounds that can counteract free radicals to repair damage to pancreatic cells to a better or even normal state. The regenerated pancreas causes insulin production to increase so that it can reduce hyperglycemia (Dyahnugra, 2015).

In diabetes, saponins have several functions, including (a) helping improve blood glucose absorption, reducing blood glucose and serum insulin levels, and improving glucose tolerance. (b) help restore weight loss due to diabetes, improve insulin resistance, and help increase the proportion of protein kinase. (c) modulate lipid metabolism, promote adipocyte thermogenesis, restore insulin sensitivity and glucose homeostasis, and reduce inflammation. (d) aid increases insulin secretion. (e) has anti-inflammatory properties and inhibits platelet aggregation. (f) has an activity to reduce plasma glucose and total cholesterol levels (Guzman, D.C., 2020). Saponins can also reduce oxidative stress levels and regulate insulin signaling pathways (Jiang, 2020).

Tannins have hypoglycemic activity by increasing the glycogenesis process. Tannins also function as astringents (chelators), which can wrinkle the epithelial membrane of the small intestine, thereby reducing the absorption of food juice reduced sugar absorption results in a slower rate of blood sugar rise (Suryani, 2013). Furthermore, tannins lower blood glucose levels by delaying intestinal glucose absorption by inhibiting α-amylase and α-glucosidase activity in insulin-sensitive tissues (Tandi, J., 2020). The mechanism of steroid use to reduce blood glucose levels is by helping the pancreas produce and secrete insulin (Munawaroh, 2022). Steroids also act as antioxidants and overcome pancreatic beta-cell damage, the main cause of insulin non-production (Novalinda, 2022). Secondary metabolites in *Ulva lactuca* water extract work together to cause hypoglycemic effects (Pasaribu, 2012).

Conclusion

The chemical compounds contained in the water extract of sea lettuce (*Ulva lactuca*) are steroids, saponins, and phenols/tannins. A water extract of sea lettuce (Ulva lactuca) can reduce glucose levels in diabetic rats, with the most effective dose being 400 mg/kgBB. Further tests must be done with different dose ranges to get a more effective dose. Besides that, it is necessary to add a normal control group given *Ulva lactuca* water extract treatment to see if it affects weight loss and blood glucose levels.

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