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EFFECTIVENESS OF *Sargassum sp* EXTRACT IN REDUCE BLOOD SUGAR LEVELS AND ACCELERATE WOUND HEALING ON THE SKIN OF DIABETES MELLITUS MICE *(Rattus novergicus)*

Martha Kaihena[1], Muhammad Cesar Umagapi[2], Arief Rahman Shabri Kaliky[2], Filep Marfil Tarangi[2], Abdul Mahid Ukratalo[3*]

[1]Department of Biomedical Science, Faculty of Science and Technology, Universitas Pattimura. Jl. Ir. M. Putuhena, Ambon 97233, Indonesia
[2]Department of Medical Education, Faculty of Medicine, Universitas Pattimura. Jl. Ir. M. Putuhena, Ambon 97233, Indonesia
[3]Department of Biology, Faculty of Science and Technology, Universitas Pattimura. Jl. Ir. M. Putuhena, Ambon 97233, Indonesia

**Corresponding Author via E-mail*: abdulalmusaad@gmail.com

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ABSTRACT

Diabetes Mellitus is a metabolic disorder characterised by elevated blood sugar levels beyond normal ranges, resulting from reduced secretion of the hormone insulin by pancreatic β cells and/or impaired insulin action. Diabetes therapy is often overseen by regulating blood glucose levels regularly and preventing or reducing the risk of complications. *Sargassum* sp is a variety of brown seaweed native to Indonesia with possible antioxidant and antidiabetic properties. This study seeks to evaluate the efficacy of *Sargassum* sp extract in lowering blood sugar levels and speeding up wound healing on the skin of diabetic mice. This is an experimental study that uses mice as experimental subjects. The mice were categorised into 5 groups (K-, K+, P1, P2, and P3). Their initial blood sugar levels were recorded, a skin incision was performed, and STZ was administered. When blood sugar levels rise, the K+ group receives metformin; on the other hand, P1, P2, and P3 are administered *Sargassum* sp extract at a specified dosage. The data were examined using ANOVA and SPSS. The analysis revealed that the water content of *Sargassum* sp was 4.32%, and the yield value of the concentrated extract was 8.75%. The ethanol extract of *Sargassum* sp has been revealed to lower blood sugar levels and speed up the wound healing process in mice with diabetes mellitus. The effects observed include decreased blood sugar levels and enhanced wound healing percentage, which are dose-dependent.

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INTRODUCTION

Diabetes mellitus is a metabolic disorder characterised by elevated blood sugar levels resulting from reduced insulin release by pancreatic β cells or insulin resistance (Hancock et al., 2010; Kaihena et al., 2024). The pancreas's endocrine function is performed by Langerhans cells, which secrete glucagon and insulin (Da Silva Xavier, 2018; Ukratalo et al., 2023). Insulin suppresses glucagon secretion and controls blood glucose uptake by cells. Insulin deficiency reduces glucose utilisation by cells and leads to increased glucagon production. This can lead to a persistent rise in blood glucose levels, known as hyperglycemia (Assis & Nobrega, 2022). Diabetes mellitus might lead to acute consequences such as diabetic ulcers due to uncontrolled high glucose levels in the long run. Diabetic ulcers are persistent diabetes-related issues characterised by tissue necrosis and exposed wounds on the skin surface (Baig et al., 2022; Holl et al., 2021). Diabetic individuals with high glucose levels experience prolonged wound recovery in cases of diabetic ulcers. The immune system response slows down, leading to inadequate regulation of blood plasma and extended inflammation (Cohen, 2020; Frydrych et al., 2018).

Diabetes mellitus management often involves maintaining normal blood glucose levels and preventing or reducing the risk of complications (Bowling et al., 2015). Erku et al., (2017) states that diabetes mellitus can be treated using both medication and non-medication methods. Pharmacological treatment involves oral antidiabetics, insulin therapy, or a combination of both. Metformin includes long-term adverse effects such as hypoglycemia and indigestion (Mohammed Alatawi et al., 2022). This facilitates research on natural compounds that are efficacious in diminishing the severity of diabetes.

Sargassum sp is a species of brown seaweed from Indonesia known for its antioxidant properties due to the presence of fucoidan and phenolic components. Brown seaweed commonly contains the phenolic compound phlorotanin, which varies from 0.74% to 5.06% (Apriani & Ariyanti, 2019; Distance B Maatita et al., 2024). *Sargassum* sp. contains steroid chemicals, alkaloids, phenols, flavonoids, saponins, and tannins, which have antioxidant and antidiabetic properties (Herawati & Pudjiastuti, 2021; Ukratalo, 2022). Flavonoids act as antioxidants by inhibiting lipid peroxidation, protecting tissues from oxidative stress and enhancing wound contraction (Zulkefli et al., 2023). Alkaloid chemicals can stimulate fibroblasts to migrate towards the ulcer wound region, promoting faster wound healing. This study aims to evaluate the efficacy of Sargassum sp extract in lowering blood glucose levels and expediting wound healing on the skin of diabetic mice models.

MATERIALS AND METHOD

Materials utilised included *Sargassum* sp, ethanol, aluminium foil, bunsen burner, streptozotocin, citrate *buffer*, metformin, mice feed, rice husk, antiseptic, formalin, and PAM water. The research utilised a variety of instruments including glass, rotary evaporator, digital scales, pisa funnel, syringe, analytical balance, hotplate, coolbox, glucose, Quik-check Hb Haemoglobin testing system, blood sugar stick, haemoglobin stick (*Easy Touch*), mice container, sonde instrument, experimental animal surgical instruments (*scalpel*), tweezers, dissecting set, glass object, incubator, microtome, roll film holder, microscope, digital camera, and IBM SPSS 26.0 software. The data collected on blood sugar levels and wounds on mice skin were examined using IBM SPSS Statistics 25.0 software with the Two-Way Analysis of Variance (ANOVA) test at a 95% confidence level.

Preparation of Test Materials and Extraction

Specimens of *Sargassum* sp were collected from the seas at Metiela Beach, Liang Village, Maluku, Indonesia. Subsequently, the samples were sent to the laboratory for drying. The Sargassum sp seaweed was blended using a blender to obtain simplisia, and the water content was measured. The materials were subsequently extracted using 95% ethanol. The powder was steeped for 24 hours with intermittent stirring and refluxed for 6 hours. The strained reflux was moved to a different flask; the mash was also refluxed similarly. The reflux was condensed using a rotary evaporator until a dense extract of Sargassum sp was acquired (BPOM, 2004). The extracted findings were further analysed for the secondary metabolite content of Sargassum sp. Before treatment, all mice were assessed for baseline glucose levels and anaesthetised with a ketamine solution. To prepare the ketamine solution, mix 3 ml of ketamine with 1 ml of *xylazine* diluted in *aquabidest* to make a 6 ml injection. Administer 0.1 ml of the solution per mouse until they exhibit calm behaviour and only visible abdominal breathing. Once the mice are anaesthetised, their skin is incised with a scapular knife, creating a wound around 1 cm long.

Subsequently, STZ was induced in groups K (-), K (+), P1, P2, and P3. On the seventh day, blood glucose levels were assessed after STZ and compared with those on the first day before STZ administration.

Mice with about ±128128 mg/dL of blood glucose are classified as diabetic. Group K (+) received metformin, P1, P2, and P3 with a specified dose of Sargassum sp extract. The treatment lasted for 7 days. The ultimate blood sugar level was assessed on the 14th day. Furthermore, the researchers observed the incision wounds on the mice.

RESULTS AND DISCUSSION

Water Content and Yield of *Sargassum sp.*

The Sargassum sp grass utilised in this study was collected from Liang village. Figure 1 displays the specific species of Sargassum employed in this investigation.

Figure 1. *Sargassum sp*

The samples were pulverised, assessed for moisture content, and extracted using ethanol solvent. Table 1 displays the findings from measuring Sargassum sp's water content and yield value.

Table 1. Moisture content and yield of *Sargassum sp*

Parameter	Result
Water Content	4,32 %
Yield Concentrated extract	8,75 %

The table 1 indicates that the water content of Sargassum sp was 4.32%, and the yield value of the concentrated extract was 8.75%.

The water content is crucial, following other proximate characteristics like protein, carbohydrate, or fat. The quality and longevity of an ingredient and food safety are influenced by the presence of water (Aganovic et al., 2021). Tournier et al., (2007)) highlighted the importance of water in food ingredients, as it influences their appearance, texture, and flavour. Water content influences metabolic activities, including enzymatic activities, microorganisms, and chemical processes such as rancidity development and non-enzymatic. Gallego et al., (2022) observed that these procedures can alter the meal's organoleptic qualities, appearance, texture, flavour, and nutritional value.

The research findings indicate that the water content of *Sargassum sp* was 4.32%. According to the Indonesian National Standard (SNI 2354-2-2015), the acceptable moisture content range for dried seaweed is between 30% and 50%. The moisture content found in this study falls within this range, meeting the SNI criteria. This study achieved low water content by utilising the seaweed Sargassum sp at the optimal harvest age.

Secondary metabolite content of *Sargassum* sp.

The bioactive chemicals found in Sargassum sp are listed in Table 2.

Table 2. Chemical compound content of *Sargassum sp*.

Compound	Result
Alkaloid	
a. Mayer	+
b. Wanger	+
Flavonoid	+
Tannin	-
Triterpenoid	-
Steroid	+
Saponin	+

Description :

+ : contains compounds (slightly coloured)

- : does not contain compounds

The examination of secondary metabolite chemicals in *Sargassum* sp used phytochemical revealed the presence of alkaloids, flavonoids, steroids, and saponins.

Blood Sugar Level of Mice

Table 3 displays the blood sugar levels measured in positive control mice, negative control mice, and animals treated with 150 mg/kg BW, 300 mg/kg BW, and 450 mg/kg BW.

Table 3. Average blood sugar levels of mice

Treatment	Mean Blood Sugar Level of Mice (mg/dL) ± SD			Mean
	0^{th} Day	7^{th} Day	14^{th} Day	
Negative control	104,67 ± 14,19	266,67 ± 13,32	289,67 ± 11,37	220,33 ± 88,04[a]
Positive control	114,00 ± 12,29	216,67 ± 23,25	117,33 ± 10,21	149,33 ± 52,45[b]
Dose 150 mg/g BW	97,00 ± 7,211	235,67 ± 28,94	206,00 ± 26,89	179,56 ± 66,35[c]
Dose 300 mg/g BW	113,33 ± 6,81	228,67 ± 17,62	165,67 ± 7,51	169,22 ± 51,03[d]
Dose 450 mg/g BW	97,67 ± 16,86	242,00 ± 47,69	155,67 ± 10,79	165,11 ± 68,01[d]
Mean	105,33 ± 12,74[a]	237,93 ± 29,81[b]	186,87 ± 62,01[c]	

Notes: Superscripts with the same letter are not significantly different (P < 0.05).

Table 3 data indicate that on day 0, all treatment groups' average blood sugar levels were within the normal range. By day 7, the mean blood glucose concentration rose to almost 200 mg/dL following the streptozotocin injection. All treatment groups of mice have revealed signs of diabetes. On the 14^{th} day of observation, the blood sugar level increased by 289.67 mg/dL in the control group; on the other hand, in the experimental group (administered metformin), the blood sugar level reduced to 117.33 mg/dL. The average blood sugar levels of mice in the group receiving dosages of 150 mg/kg BW, 300 mg/kg BW, and 450 mg/kg BW were 206.00 mg/dL, 165.67 mg/dL, and 155.67 mg/dL, respectively.

The blood sugar levels of mice in different groups were measured after being administered extract doses of 150 mg/kg BW, 300 mg/kg BW, and 450 mg/kg BW. The difference in drop and percentage decrease was then computed.

Table 4. Difference in Reduction and Percentage of Blood Sugar Level Reduction

Treatment	Difference in Decrease	% Decrease in Blood Sugar Level
Negative control	-56,33	-31,35
Positive control	99,33	45,77
Dose 150 mg/kg BW	29,67	12,64
Dose 300 mg/kg BW	63	12,64
Dose 450 mg/kg BW	86,33	34,68

The study results from Tables 3 and 4 indicate that the average blood sugar levels of mice in the negative control group (injected with STZ; however, not administered medication) are higher than those in the positive control group, which includes DM mice given doses of 150 mg/kg BW, 300 mg/kg BW, and 450 mg/kg BW. The high blood sugar level is due to STZ induced in mice entering the pancreatic β-cells through

Glucose transporter 2 (GLUT2), so that there will be depolarisation in the mitochondria due to incoming Ca2+ ions, followed by excessive energy use resulting in a lack of energy in the cell (Munjiati, 2021). This condition will cause insulin production to be disrupted, resulting in insulin deficiency which will have an impact on all glucose consumed, which cannot be processed, resulting in increased glucose levels in the body.

In addition, blood sugar levels in the positive control group (group of DM mice and given metformin drug), blood sugar levels were lower when compared to the negative control group and the DM mice group and given the extract. This happens because in mice given the drug metformin, it will cause a decrease in glucose production in the liver and increase the sensitivity of muscle and adipose tissue to insulin due to the activation of kinases in AMPK cells through a process mediated by Liver Kinase B1 (LKB1) (Kusuma et al., 2022). Metformin carried by hepatic cells disrupts the activity that occurs in mitochondria and causes a decrease in ATP. Metformin then mediates the binding of LKB1 to AMPK, resulting in the activation of AMPK by LKB1 through the Thr172 phosphorylation process. Activation of AMPK that changes the cell state from anabolic to catabolic causes increased glucose absorption and decreased activity of biosynthetic pathways such as glucose, glycogen, and lipid synthesis in the liver (Ukratalo et al., 2023).

Administrated Sargassum sp extract at a dose of 150 mg/kg BW, 300 mg/kg BW and 450 mg/kg BW can reduce blood sugar levels in mice. The reduction in blood sugar levels following the administration of *Sargassum sp* extract is attributed to its composition of flavonoids, steroids, alkaloids, and saponins. Flavonoids can enhance insulin secretion from pancreatic β cells (Ansari et al., 2022). Cuzzocrea et al., (2006) stated that Peroxisome proliferators-activated receptors (PPAR-α and PPAR-γ) regulate the action. Flavonoids are believed to enhance antioxidant activity by boosting cellular antioxidant enzymes such as Superoxide Dismutase (SOD), Catalase, and Glutathione Peroxidase. This prevents pancreatic β-cell DNA damage induced by DNA alkylation from *streptozotocin* (Rajappa et al., 2019)

Alkaloids, together with flavonoid chemicals, can lower blood glucose levels via various mechanisms such as decreasing glucose production, enhancing glucose transport in the bloodstream, blocking glucose absorption in the intestines, and promoting glycogen synthesis. Alkaloid chemicals can trigger the hypothalamus to increase the secretion of *Growth Hormone Relasing Hormone* (GNRH) in the liver, which helps regulate blood glucose levels by secreting insulin. Consequently, it can induce hypoglycemia and inhibit gluconeogenesis, decreasing blood glucose levels and reducing insulin requirements (Salsabila et al., 2021)

Percent wound healing in diabetic mice

The measures of wounds in mice from different control groups and doses (150 mg/kg BW, 300 mg/kg BW, and 450 mg/kg BW) are presented in Table 5.

Table 5. Mean incision wound healing of DM mice

Treatment	Mean wound healing rate of mice (mg/dL) ± SD			Mean
	Day 0	Day 7	Day 14	
Negative control	1,00 ± 0,00	1,37 ± 0,26	2,05 ± 0,09	1,47 ± 0,92[a]
Positive control	1,00 ± 0,00	1,19 ± 0,11	1,02 ± 0,11	1,07 ± 1,12[b]
Dose 150 mg/kg BW	1,00 ± 0,00	1,30 ± 0,16	1,18 ± 0,07	1,16 ± 1,16[c]
Dose 300 mg/kg BW	1,00 ± 0,00	1,15 ± 0,15	1,04 ± 0,03	1,06 ± 1,07[c]
Dose 450 mg/kg BW	1,00 ± 0,00	1,17 ± 0,08	1,00 ± 0,00	1,06 ± 0,09[c]
Mean	1,00 ± 0,00[a]	1,23 ± 0,15[b]	1,26 ± 0,42[c]	

Table 5 data indicates that incision wounds in diabetic mice healed after receiving *Sargassum* sp extract on the last measurement day. Comparatively, in the group of mice with diabetes, the wound healing rate was 1.18 at 150 mg/kg BW, 1.04 at 300 mg/kg BW, and 1.00 at 450 mg/kg BW. ANOVA results indicate that the extract from *Sargassum sp* significantly reduces incision wounds in diabetic mice. Subsequent testing revealed a substantial difference between groups K- and K +; however, groups P1, P2, and P3 did not significantly differ.

The data revealed in Table 5 indicates that the average rate of wound healing in the group of mice treated with *Saragassum sp* extract is significantly higher than that of the negative control group. This demonstrates a correlation between blood glucose levels and the healing of diabetic ulcers in diabetic mice. Well-controlled blood glucose levels promote good wound healing; on the other hand, high levels can delay healing. The cause is the reduced capacity of blood vessels to constrict and dilate, leading to inadequate blood flow in the tissue and elevated blood glucose levels that promote the growth of anaerobic pathogenic microorganisms. The high viscosity of the blood plasma around the wound creates an ideal habitat for germs to thrive (Yang et al., 2022). The 450 mg/kg BW treatment group exhibited remarkable wound healing due to the maintenance of regulated blood glucose levels.

Wound healing involves a biological process of cell regeneration and tissue repair to recover from harm. This reaction is typical as it is a response to damage to the skin tissue. Wound recovery involves wound surface closure, rapid growth of surface skin cells, collagen contraction, and increased density of connective tissue. The wound recovery process consists of three stages: inflammatory, proliferation, and remodelling. Each phase interacts with the others to ultimately impact the result of wound healing. During the inflammatory phase, blood flow to the wound increases and fibrin is produced to guard against bacterial infection. The proliferation phase involves collagen and connective tissue development by fibroblasts synthesising collagen. Completing the dermis layer marks the end of the wound-healing process. In the remodelling phase, collagen bonds or thick collagen fibres repair the wound, allowing epithelialisation to cover the skin entirely for wound closure (Rodrigues et al., 2019)

Alkaloid chemicals found in *Sargassum sp* extract can stimulate fibroblasts to migrate towards the ulcer wound site, promoting faster wound healing. Flavonoid compounds exhibit antioxidant, antibacterial, and anti-inflammatory effects on wounds in individuals with diabetes mellitus ((Chagas et al., 2022). Flavonoids work as antioxidants by preventing lipid peroxidation, which helps protect tissues from oxidative stress and promotes wound contraction. Tannin components in the extract aid in wound healing by neutralising inflammatory proteins and preventing the excessive production of mucosal secretions (Zulkefli et al., 2023).

Sargassum sp demonstrates promising potential as an herbal medication for individuals with diabetes mellitus based on its effectiveness in detecting blood sugar levels and wound healing in diabetic mice. The relationship is undoubtedly linked to the secondary metabolite chemicals in Sargassum sp extract, which have potential antidiabetic properties.

CONCLUSION

The results and discussion lead to the conclusion that the ethanol extract of *Sargassum sp* can lower blood sugar levels and speed up the healing of incision wounds in diabetic mice. The effective dosage of *Sargassum sp* for lowering blood sugar levels is 450 mg per kilogram of body weight. The effective dose for mice incision wound healing is 300 mg/kg BW.

AUTHORS CONTRIBUTION

M. K contributed to the design of the study, secondary metabolite content assay and review of the manuscript, A. M. U and A.R.S.K conducted the antidiabtes assay, reviewed the data and wrote the manuscript, M. C. U and F.M.T analysed the data and wrote the manuscript.

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