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Identification of Secondary Metabolite Compounds from *Porphyra* sp Extract and Their Potential as Antidiabetic Agents

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Abstract

Aims: *Porphyra* is a type of local seaweed, referred to as *runut* by the community in Wassu Village, Central Maluku Regency, or *sayur laut* in Hukurila Village, Ambon City, Maluku Province, which the locals frequently consume. *Porphyra sp.* contains isoflavones, such as genistein, which has been shown to possess antidiabetic activity by inhibiting the activity of the DPP-4 enzyme.
Study design: This research is pure laboratory experimental research using a completely randomised design with 5 treatments and 3 replicates.
Place and Duration of Study: This research was conducted for three months at the Zoology Laboratory of the Department of Biology at FST Pattimura University.
Methodology: All treatment groups underwent the anti-diabetes test for 14 days. Blood sugar level data were analysed using the Two-Way Analysis of Variance (ANOVA) test at a 95% confidence level.
Results: The results showed that the *Porphyra sp.* extract positively contains flavonoids, triterpenoids, saponins, tannins, and alkaloids. The extract of *Porphyra sp.* also demonstrated the ability to lower blood glucose levels in mice induced with streptozotocin. Extract indicates that *Porphyra sp.* has potential as an effective antidiabetic agent due to the presence of bioactive compounds that may improve glucose metabolism and increase insulin sensitivity.

Conclusion: These findings indicate that *Porphyra sp.*, as a marine natural product, holds significant potential in the development of diabetes therapy.

Keywords: *Porphyra sp.*, diabetes mellitus, secondary metabolites, blood glucose

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Introduction

Indonesia has a marine area of approximately 6,400,000 km² and a coastline extending 110,000 kilometers. Combined with its tropical climate, these conditions make the country highly suitable for cultivating a wide variety of seaweed species [1]. According to Lestari et al. (2020), 555 out of approximately 8,000 seaweed species

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worldwide are able to thrive in Indonesia. The Ministry of Marine Affairs and Fisheries (KKP) reported that Indonesia produced 10.25 million tons of seaweed in 2021, positioning the country as a major global producer [2].

Several economically important seaweed genera are found in Indonesia, including *Eucheuma*, *Gracilaria*, *Gelidium*, *Sargassum*, and *Hypnea*, with some species, such as *Eucheuma cottonii*, already under cultivation [3]. Beyond these commercially recognized species, many types of seaweed have been traditionally used by local communities for generations. For instance, seaweed from the genus *Porphyra* is known locally as *runut* in Wassu Village, Haruku Island (Central Maluku Regency), and as *sa* 49 *ut* in Hukurila Village, Ambon City (Maluku Province). This red algae, belonging to the division Rhodophyta, (attached to rocks in intertidal zones and appears seasonally between June and September during the onset of the eastern monsoon [4].

The tradition of seaweed consumption has been passed down through generations and is believed to have predated foreign contact with the region. According to Loupatty [5], *Porphyra* contains proteins, essential amino acids, and vitamins A, B, and C. Amino acids such as alanine, glutamic acid, and glycine contribute to the characteristic umami flavor of *nori* [6–9].

In traditional medicine, *Porphyra* species are believed to promote digestion, reduce cholesterol, and alleviate fever. Additionally, *Porphyra* has demonstrated various pharmacological properties, including immunomodulatory, anticancer, antihyperlipidemic, and antioxidant activities [10]. According to Anggriany et al. [11], *Porphyra* contains bioactive compounds such as porphyran and AAE. It also contains isoflavones like genistein and daidzein (Santos et al., 2019), with genistein shown to exert antidiabetic effects by inhibiting the dipeptidyl peptidase-4 (DPP-4) enzyme [12–14].

Diabetes mellitus (DM) is a non-communicable disease and a growing global health concern. It is characterized by metabolic dysfunction leading to elevated blood glucose levels (hyperglycemia), which occurs when the body fails to produce sufficient insulin, resulting in impaired glucose regulation [15–17].

According to data from the World Health Organization (WHO) [18], in 2014, approximately 8.5%, or 422 million, adults aged 18 years and older were living with diabetes. In 2019, diabetes directly caused 1.5 million deaths, with about 48% of these occurring in individuals under the age of 70. Additionally, diabetes was a major contributor to 460,000 deaths related to kidney disease. The International Diabetes Federation (IDF), in the 10th edition of the *Diabetes Atlas* published in 2021, reported that the global number of people with diabetes had reached 537 million and is projected to rise to around 643 million by 2030. This number is expected to continue increasing, reaching 783 million by 2045. Diabetes mellitus also affects younger populations, with over 1.2 million children and adolescents under the age of 19 estimated to develop type 1 diabetes each year [19, 20].

According to the same IDF Atlas, the estimated number of individuals with diabetes in Indonesia aged 20 to 79 years was 19,465,000. Considering a total adult population of 179,720,500 in that age group, the prevalence was approximately 10.6%, meaning that about one in every nine adults in Indonesia was affected by diabetes [21]. Meanwhile, data from the 2018 Basic Health Research (Riskesdas) indicated that the prevalence of diagnosed diabetes mellitus among individuals aged 15 years and older was 2.0%. However, based on blood test results for the same group, the prevalence was recorded at 10.9% [22].

The increasing prevalence of diabetes mellitus requires consistent monitoring and control, as the condition significantly raises the risk of complications involving the eyes, heart, kidneys, and brain [23]. The Ministry of Health has also identified diabetes as a leading cause of amputations unrelated to trauma, as well as a major contributor to disability and mortality. According to the IDF, approximately 6.7 million people worldwide died from diabetes in 2021.

Other studies have noted that diabetes treatment can be approached through both pharmacological and non-pharmacological methods. When blood glucose levels cannot be adequately controlled, drug therapy becomes necessary [24]. Non-drug therapy, on the other hand, focuses on minimizing diabetes risk through dietary management, regulation of blood lipids and blood pressure, increased intake of protein and antioxidants, and strict blood glucose monitoring.

The emergence of synthetic chemical-based drugs has marked significant progress in modern medicine. However, traditional plant-based medicine continues to play an important and irreplaceable role [25]. Plants have long been used in traditional medical practices, and natural remedies are increasingly being explored as alternative treatments for diabetes. The use of natural products, both as medicine and food, is expanding in an effort to maximize the potential of these biological resources [26].

As a marine natural resource, seaweed offers numerous health benefits, particularly in the field of medicine, and has potential as an alternative approach for diabetes management [27, 28]. Due to its rich nutritional composition, including polysaccharides, vitamins, minerals, and antioxidants, seaweed is considered a promising candidate for the development of functional products that support diabetes care [29]. Since the consumption of low-sugar foods is a practical strategy for managing diabetes, seaweed may serve as a suitable dietary component by helping to

replace or reduce sugar intake in daily meals. Additionally, seaweed has been shown to enhance insulin sensitivity and regulate glucose metabolism, contributing to the effective control of blood glucose levels [30, 31, 32].

This study aims to identify the secondary metabolite compounds present in *Porphyra* species and evaluate their potential antidiabetic properties.

Research Problem

This study aims to identify the secondary metabolite compounds from *Porphyra sp.* and assess its potential as an antidiabetic agent.

Research Focus

This study will identify secondary metabolite compounds in *Porphyra sp.* and evaluate their activity in lowering blood sugar levels in mice with a diabetes mellitus model

Research Aim and Research Questions

1. To identify the secondary metabolite compounds of the n-hexane extract of *Porphyra sp.*
2. To evaluate the potential of *Porphyra sp.* in lowering blood sugar levels in mice with a diabetes mellitus model.
3. To assess the effective dose of the *Porphyra sp.* extract in lowering blood sugar levels in mice.

Research Methodology

General Background

Diabetes mellitus is a progressive degenerative disease that is increasing in prevalence worldwide and has become a major global health concern. The condition is characterized by insulin resistance and impaired glucose metabolism, which, if left uncontrolled, can lead to serious complications. Conventional treatments typically rely on synthetic drugs, which may cause adverse long-term side effects. Therefore, there is a growing need to explore safer and more effective therapeutic alternatives. One promising source is natural substances, particularly marine algae, which are known to contain bioactive compounds with a variety of health benefits. *Porphyra* species, a type of red algae, contain secondary metabolite compounds such as flavonoids, triterpenoids, saponins, tannins, and alkaloids. These compounds have demonstrated multiple biological activities, including the potential to regulate blood glucose levels.

Sample / Participants / Group

This study utilized male mice as test subjects.

Instrument and Procedures

The brown algae *Porphyra* sp. was collected from Alang Village, Ambon Island. After collection, the sample was cleaned and oven-dried at a temperature of 20–40°C, then ground and extracted using methanol as the solvent. Sixty grams of dried seaweed were extracted with n-hexane using the maceration method for 24 hours. The extract was filtered and concentrated using a rotary vacuum evaporator. Phytochemical screening was conducted to qualitatively identify the presence of flavonoids, steroids/triterpenoids, saponins, tannins, phenols, and alkaloids in the *Porphyra* sp. extract.

The mice underwent a one-week acclimatization period in the Zoology Laboratory of the Department of Biology, Faculty of Science and Technology, Pattimura University, Ambon. Mice exhibiting signs of illness, death, or weight loss exceeding 10% were excluded to ensure uniformity among test subjects.

Twenty male mice were housed individually in cages measuring 21 × 21 cm at the base, with a top area of 18 × 18 cm and a height of 12 cm. Each cage was lined with 0.5–1 cm of rice husk to prevent contamination from waste, which was replaced every three days [29]. The mice were fed AD2 pellets and given tap water in separate containers, both of which were replaced daily.

The dose of streptozotocin (STZ) was calculated as follows:

- The standard dose for a 200 g rat is 40 mg/kg body weight.
- For a 200 g rat: (200 g / 1000 g) × 40 mg = 8 mg.
- The conversion factor from rat to mouse is 0.14.
- For a 20 g mouse: 8 mg × 0.14 = 1.12 mg.
- The average mouse body weight was 25 g: (25 g / 20 g) × 1.12 mg = 1.4 mg.

- The total dose required: 1.4 mg × 16 mice × 3 days = 67.2 mg.
- The solution was prepared by diluting 67.2 mg of STZ in 10 ml of distilled water. Each mouse received 0.25 ml of the solution via intraperitoneal injection for four days [33].

Metformin was administered orally at a dose of 0.4 ml. Baseline blood glucose levels were measured for all mice prior to treatment. STZ was administered to the negative control group (K−), positive control group (K+), and the experimental groups (P1, P2, P3). On day eight, post-induction blood glucose levels were measured. The positive control group (K+) received metformin if hyperglycemia was confirmed. The experimental groups received different doses of *Porphyra* sp. extract: P1 received 150 mg/kg body weight, P2 received 300 mg/kg, and P3 received 450 mg/kg. Treatments were administered for seven consecutive days. Final blood glucose levels were measured on the last day of treatment.

Data Analysis

Blood glucose data were analyzed using IBM SPSS Statistics 24.0 software. A two-way analysis of variance (ANOVA) was performed at a 95% confidence level [34].

Research Results

Phytochemical Testing of Porphyra sp. Extract

The identification of secondary metabolite groups was conducted qualitatively through phytochemical tests to determine the active compounds present in Porphyra sp. extract [35]. The phytochemical screening was performed using the test tube method, where a small sample of the Porphyra sp. extract was added with reagents specific to the compounds to be identified. The results of the phytochemical screening of the Porphyra sp. extract can be seen in Table 1.

Table 1. Results of secondary metabolite testing of *Porphyra sp.* extract

No.	Compound Group	Color/Precipitate Formed	Result
1	Flavonoid	Bluish-green	++
2	Steroid	Red	-
3	Triterpenoid	Bluish-green	+
4	Saponin	Green and foamy	++
5	Tannin	Green	+
6	Phenol	Dark green	-
7	Alkaloid		
a.	Mayer	Yellowish-white precipitate	+
b.	Dragendorff	Orange precipitate	+

Notes:
++ : compound present (color is fairly intense)
+ : compound present (slightly colored)
- : compound absent

The results in Table 1 indicate that *Porphyra sp.* extract contains flavonoids, triterpenoids, saponins, tannins, and alkaloids.

Blood Glucose Levels

Table 2 shows mice's average blood glucose levels in the standard, negative, and positive control groups and those treated with *Porphyra sp.* extract at 150, 300, and 450 mg/kg doses.

Table 2. Average blood glucose levels in mice

Treatment	Average Blood Glucose Level (mg/dL)			Average
	Day 0	Day 7	Day 14	
Normal control	93.33	97.0	112	100,8[a]
Negative control	109.67	212.67	285.55	202,6[b]
Positive control	89	218.0	104	137,0[c]
Dose 250 mg/kg	111	213.33	135	153,1[d]
Dose 300 mg/kg	123	221.0	119.33	154,4[e]
Dose 450 mg/kg	99	211.0	114	141,3[f]

Notes: Groups marked with the same letter are not significantly different (α = 0.05).

The results presented in Table 2 indicate that all treatment groups exhibited normal blood glucose levels at baseline. Following streptozotocin (STZ) induction, blood glucose levels increased across all groups, reaching 212.67 mg/dL in the K− group, 218 mg/dL in the K+ group, 213.33 mg/dL in P1, 221 mg/dL in P2, and 221 mg/dL in P3.

By Day 14, the blood glucose level in the K− group continued to rise, reaching 285.55 mg/dL. In contrast, the K+, P1, P2, and P3 groups demonstrated a reduction in blood glucose levels. The K+ group showed a decrease to 104 mg/dL, corresponding to a reduction of 114 mg/dL. The P1 group declined to 135 mg/dL (a reduction of 78.33 mg/dL), the P2 group to 119.33 mg/dL (a reduction of 101.67 mg/dL), and the P3 group to 114 mg/dL (a reduction of 97 mg/dL).

Analysis of variance (ANOVA) revealed that the administration of *Porphyra* sp. extract significantly influenced blood glucose levels in the type 1 diabetes mellitus model mice. Post-hoc analysis using the Least Significant Difference (LSD) method at a 95% confidence level confirmed that the mean blood glucose levels among all treatment groups were statistically different.

Discussion

Bioactive Compounds of *Porphyra* sp. Extract

Bioactive compounds are phytochemical substances produced through secondary metabolism [36]. This metabolic process generates compounds with specific biological activities, such as alkaloids, terpenoids, flavonoids, tannins, and steroids. Secondary metabolites do not play a direct role in plant growth or development, but they are essential for plant survival in natural environments. The production of secondary metabolites is regulated by factors such as nutrient availability, reduced growth rates, enzyme inactivation, and enzyme induction. Nutrient limitations and decreased growth rates serve as regulatory signals that trigger chemical differentiation through secondary metabolism [37].

The results presented in Table 1 confirm that *Porphyra* sp. extract contains several secondary metabolite compounds, including flavonoids, triterpenoids, saponins, tannins, and alkaloids. Flavonoid identification in the extract was performed using magnesium powder (Mg) and 2 N hydrochloric acid (HCl), which resulted in a bluish-green color change, indicating the presence of flavonoids [38]. Flavonoids belong to the phenolic compound group and are polar due to the presence of multiple hydroxyl groups that are not esterified or bound to sugar molecules [39]. The absence of esterified sugars enables flavonoids to dissolve in polar solvents such as methanol, ethanol, butanol, acetone, and dimethyl sulfoxide [40, 41]. The detection of flavonoids in an n-hexane solvent suggests that these compounds exhibit polarity similar to that of solvents such as ethyl acetate or ethanol [42].

Saponin testing involved hydrolyzing the compound with water. Saponins are triterpene glycosides that exhibit polar characteristics due to their glycosidic bonds [43, 44]. These compounds possess both polar and non-polar groups, giving them surface-active properties. When mixed with water and shaken, saponins undergo hydrolysis and form micelles [45]. These micelles orient polar groups outward and non-polar groups inward, resulting in foam formation [46].

The tannin test was conducted by mixing the extract with distilled water and shaking it until homogeneous. Subsequently, a 1% $FeCl_3$ solution was added, producing a green color change [47, 48]. A positive reaction was observed for *Porphyra* sp. extract when tested with n-hexane solvent. This color change is due to the formation of a complex between Fe ions and tannins [49]. The formation of this complex involves covalent coordination bonds between metal and non-metal atoms [50].

The presence of alkaloids in the *Porphyra* sp. extract was confirmed by the formation of a precipitate after treatment with Mayer's and Dragendorff's reagents. Alkaloids contain nitrogen within a cyclic structure and are bonded to functional groups such as amines, amides, phenols, and methoxyls, which contribute to their semi-polar nature. This semi-polar characteristic allows alkaloids to dissolve more readily in solvents with similar polarity. As a result, alkaloids are soluble in both semi-polar and polar solvents.

Blood Glucose Levels in Mice

Based on the results presented in Table 2, STZ induction in groups K−, K+, P1, P2, and P3 resulted in elevated blood glucose levels. This increase is attributed to the cytotoxic effects of streptozotocin (STZ), which damages pancreatic β-cells and contributes to the onset of diabetes. The cytotoxicity induced by STZ leads to the release of free radicals and the initiation of oxidative stress within the cells [51]. STZ selectively enters and accumulates in pancreatic β-cells through its interaction with glucose transporter 2 (GLUT2) located on the plasma membrane [52, 53]. Other organs that express GLUT2, such as the liver and kidneys, may also be adversely affected by STZ exposure. Typically, β-cell damage occurs within two to four days following STZ administration and is characterized by

pancreatic swelling and degeneration of β-cells in the islets of Langerhans [54]. These pathological changes result in altered insulin secretion, reduced insulin levels, and impaired glucose regulation, ultimately leading to hyperglycemia [55].

The administration of 0.4 ml of metformin effectively reduced blood glucose levels in mice. This effect is achieved through metformin's ability to suppress hepatic glucose production (gluconeogenesis) and improve insulin sensitivity in individuals with diabetes mellitus. Metformin exerts its hypoglycemic effect via non-pancreatic pathways and does not stimulate insulin secretion [56]. Additionally, metformin inhibits endogenous glucose production primarily by reducing gluconeogenesis, with minimal impact on glycogenolysis [57]. The drug also activates AMP-activated protein kinase (AMPK), an enzyme that downregulates key enzymes involved in gluconeogenesis and glycogen synthesis in the liver, while enhancing insulin signaling and glucose uptake in muscle tissue [58, 59]. AMPK is critical in regulating both cellular and systemic energy metabolism, and a decrease in hepatic energy levels can trigger its activation [60]. Metformin also facilitates peripheral glucose utilization by promoting non-oxidative glucose transport to skeletal muscles, thereby reducing blood glucose concentrations.

In this study, the administration of *Porphyra* sp. extract also resulted in a notable reduction in blood glucose levels in mice. On Day 14, the P1 group recorded a blood glucose level of 135 mg/dL, representing a decrease of 78.33 mg/dL. The P2 group had a level of 119.33 mg/dL, with a reduction of 101.67 mg/dL, and the P3 group exhibited a level of 114 mg/dL, reflecting a decrease of 97 mg/dL. This hypoglycemic effect is attributed to the presence of secondary metabolites in the *Porphyra* sp. extract, including flavonoids, triterpenoids, saponins, tannins, and alkaloids.

Flavonoids have been widely recognized for their antidiabetic properties. They inhibit the enzyme α-glucosidase, which plays a key role in carbohydrate metabolism [61]. By blocking this enzyme, flavonoids reduce glucose absorption in the intestine, leading to lower postprandial blood glucose levels. Saponins contribute to antihyperglycemic activity by inhibiting glucose oxidation in the body, thus alleviating symptoms associated with hyperglycemia [62]. Tannins improve glucose and lipid metabolism, preventing the accumulation of these energy substrates in the bloodstream [63]. Tannins also exhibit antioxidant and hypoglycemic effects by modulating glucose production.

Alkaloids are involved in the regeneration of damaged pancreatic β-cells and stimulate insulin secretion, further contributing to glucose regulation. This stimulatory effect is believed to occur through the activation of sympathetic nerves, which enhances insulin release [64–66].

Conclusions and Implications

Based on the research findings, it can be concluded that the *Porphyra sp.* extract contains bioactive compounds, namely flavonoids, triterpenoids, saponins, tannins, and alkaloids. These compounds can potentially lower blood sugar levels in mice, indicating that *Porphyra sp.* could be an effective natural ingredient for developing diabetes therapies.

These findings have significant implications for traditional medicine and drug development from Porphyra sp. ingredients for diabetes therapy as it can reduce blood glucose levels. In addition, Porphyra sp. extract also has the potential to be the raw material for making additional supplements to prevent diabetes. The results of this research also open up opportunities for further research in the aspect of testing the mechanism of action of its bioactive compounds and determining safe doses for long-term consumption.

Suggestions for Future Research

Further research should focus on clinical trials to evaluate the effectiveness of *Porphyra* sp. extract in controlling blood sugar in humans, taking into account the correct dose and potential side effects. In addition, studies on the molecular mechanisms underlying the bioactive activity of flavonoids, triterpenoids, saponins, tannins, and alkaloids in reducing blood sugar levels need to be conducted. Exploration of the synergistic potential between these compounds can also open opportunities for developing safer and more effective natural-based diabetes drugs.

Declarations

Author Contributions

A.M.U and L.A contributed to designing the study, preparing samples and test materials, conducting the study, and preparing the manuscript. E.B and M.N.I contributed to data analysis and curation. M.K contributed to the assay of secondary metabolite compounds and proofread the manuscript.

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Ethical Statement

The use of test animals and the implementation of this research procedure have fulfilled the laws and regulations relating to using test animals in the Republic of Indonesia.

Declaration of interest

The authors declare that this research and the data obtained are not related to any party

Data Sharing statement

Data supporting this study's findings and conclusions can be provided to other parties upon relevant request.

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