In Vitro Inhibitory Activity of the α-Glucosidase Enzyme from *Eucheuma cottonii* Macroalgae Extract

Dewi Kurnia*, Farah Zakiyah, Wempi Budiana, Ivan Andriansyah
Faculty of Pharmacy, Bhakti Kencana University, Jl Soekarno-Hatta No.754 Bandung, West Java, Indonesia
*Email: dewi.kurnia@bku.ac.id

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Abstract

Diabetes mellitus is a metabolic disorder caused by damage to the pancreas, insulin resistance, or other factors. α-glucosidase inhibitors are compounds that can prevent the breakdown of complex carbohydrates into glucose; therefore, they have the potential to be used as therapeutic agents for diabetes. One of the natural marine ingredients that has the potential to act as an antidiabetic is the macroalgae *Eucheuma cottonii*. This research aims to determine the potential of *Eucheuma cottonii* extract in inhibiting the activity of the α-glucosidase enzyme extract using an in vitro approach. *Eucheuma cottonii* was extracted using a multistage maceration method with n-hexane, ethyl acetate, and 70% ethanol as solvents. The extracts were characterized by the TLC method. The α-glucosidase inhibitory activity was tested in vitro using a 405 nm microplate reader. The results of the TLC analysis revealed that the *Eucheuma cottonii* extract contained flavonoids, phenols, alkaloids, steroids, and terpenoids. The α-glucosidase enzyme inhibition activity showed that the IC50 values of the extracts obtained from n-hexane, ethyl acetate, and 70% ethanol were 567.84, 174.32, and 99.57 µg/mL, respectively. At the same time, the IC_{50} of acarbose, used as a comparison, was 64.41 µg/mL. It can be concluded that the *Eucheuma cottonii* extract, when dissolved in 70% ethanol, exhibits strong inhibitory activity against the α-glucosidase enzyme, indicating its potential as an alternative in antidiabetic treatments.

***Keywords**: α-glucosidase, antidiabetic, enzyme inhibitors, Eucheuma cottonii*

How to cite

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Highlights

1. Eucheuma cottoni contains more polar compounds than non-polar compounds. This is shown from the extraction results, namely that the highest extract yield was obtained using ethanol solvent.
2. The combination of organic solvents used as eluents in TLC analysis is more effective because it can separate more types of secondary metabolite compounds compared to previous studies.
3. Base on the results of extract characterization analysis, it is known that the Eucheuma cottonii macroalgae extract contains flavonoids, alkaloids, steroids/terpenoids and phenols.
4. 70% Ethanol extract of Eucheuma cottoni is known to have potential as an antidiabetic. This is indicated by the IC50 value of the extract which is close to the IC50 value of acarbose as a standard comparative drug.
5. The presence of flavonoid and alkaloid compounds is thought to provide an antidiabetic effect in Eucheuma cottoni extract, but this requires further research to prove it.

Introduction

Diabetes mellitus (DM) is a health problem that affects millions of people worldwide, including in Indonesia. According to data from the International Diabetes Federation (IDF) (Thomas et al., 2019), Indonesia has the seventh highest prevalence of diabetes in the world. The most common type of diabetes in Indonesia is type 2 DM, which is diabetes that occurs when the body cannot produce enough insulin needed by the body (DiPiro et al., 2015).

One of the treatments for diabetes is to slow glucose absorption by inhibiting enzymes in the digestive system, such as α-glucosidase. This enzyme accelerates glucose absorption from the small intestine by catalyzing the breakdown of oligosaccharides by hydrolysis into monosaccharides (Permata Yuda et al., 2019). One of the inhibitors that can be used clinically is acarbose, an antidiabetic drug with a mechanism of action that inhibits the activity of the α-glucosidase enzyme. However, the use of this drug has side effects such as nausea, diarrhea, and bloating (Dinicolantonio et al., 2015). Few previous studies on treatments used natural ingredients to avoid these side effects. Therefore, efforts are needed to find α-glucosidase inhibitors that are natural and safer (Ademiluyi & Oboh, 2013).

The use of natural ingredients is an alternative to antidiabetic treatment. Macroalgae as one of the marine resources that has the potential to be developed, both in the food and pharmaceutical industries. Macroalgae are large algae with a body structure of talus and have chlorophyll, carotenoids, and phycocyanin pigments. Macroalgae are also used as agar, a source of alginate and carrageenan. Additionally, macroalgae are a source of bioactive polysaccharides and are widely used in the pharmaceutical field as antioxidants, antitumor, anticancer, antibacterial, antidiabetic, anticoagulant, and antidiabetic (Handayani, 2017; Kurnia et al., 2022; Sambodo, 2019; Sami et al., 2019).

Macroalgae or seaweed have various potentials that can be utilized, one of which is *Eucheuma cottonii*, which is a type of seaweed that lives and develops in coastal areas that receive a steady flow in intertidal and subtidal (Wijayanto et al., 2011). *Eucheuma cottonii*, also known as *Kappaphycus alvarezii*, has the potential to serve as an effective antioxidant and may also exhibit antidiabetic activity in laboratory settings. This is due to various compounds, including phenolic content, flavonoids, saponins, terpenoids, and alkaloids, which all contribute to their antioxidant and antidiabetic properties. (Prasasty et al., 2019). Prasasty's research (2019) showed that in vitro tests of the ethanol extract of *Eucheuma cottonii* showed high α-amylase inhibitory activity. The results of the research conducted by (Nosa et al., 2020) show that the concentration of kappa carrageenan affects the percentage of inhibition of α-glucosidase enzyme activity. Therefore, in this study, the α-glucosidase enzyme inhibition activity of the *Eucheuma cottonii* macroalgae extract was tested to show that the *Eucheuma cottonii* macroalgae has α-glucosidase enzyme inhibition activity so that it can be developed as an alternative treatment for antidiabetic drugs.

Research Methods

Materials

The samples used in this study were *Eucheuma cottonii* macroalgae from Onaria Beach, Tri Dharmayoga village, Ketapang sub-district, South Lampung. Other materials used include $AlCl_3$, $FeCl_3$, H_2SO_4, cytroborate, 70% ethanol, methanol, ethyl acetate, n-hexane, distilled water, chloroform, hydrochloric acid, sodium acetate, Mayer reagent, Dragendroff reagent, $CaCO_3$, NaOH, KH_2PO_4, Na_2CO_3, DMSO, α-glucosidase enzyme (Sigma-Aldrich®), p-

nitrophenyl-α-D-glucopyranoside (*pNPG*) and acarbose.

Instrumentation

While the tools used in this study are measuring cups, dropper pipettes, cups, dark glass bottles, erlenmeyer flasks, beakers, measuring flasks, silica gel F_{254} TLC plates, chambers, UV lamps with 254 and 366 nm wavelength, parchment paper, filter paper, crucible, crucible pliers, furnace, hot plate, stirring rod, spatel, mortar and stemper, micro pipettes of 0.5-10; 10-100 and 100-1.000 µL, analytical balance, incubator, vial bottle, 96-well microplate and multi-well plate reader (ELISA) instrument.

Procedure

1) Sample preparation

A total of 20 kg of *Eucheuma cottonii*i samples were washed and rinsed with clean water to separate sand and other impurities. The samples were chopped and soaked in water, then delicensed by soaking in a $CaCO_3$ solution for 24 hours, followed by soaking in 1 N NaOH for 24 hours. The macroalgae samples were neutralized and washed with hot water to remove NaOH. Next, the samples were dried for 1-3 days until completely dry. The samples were ready to be used for the extraction process (Habibah et al., 2016)

2) Sample characterization

The dried samples were characterized for several parameters, including total ash content, acid-insoluble ash content, water-soluble juice content, ethanol-soluble juice content, and drying shrinkage. All of these parameters were carried out using standardized methods, which refer to the Indonesian Herbal Pharmacopoeia 2017.

3) Extraction

A total of 100 g of dried *Eucheuma cottonii* samples was extracted using the multistage maceration method with three solvents of different polarities: n-hexane, ethyl acetate, and 70% ethanol. The extraction was carried out consecutively for 3 days, with solvent replacement every 24 hours. After that, the crude extract was filtered and concentrated using a rotary evaporator, resulting in the final product obtained from the thick crude extract of *Eucheuma cottonii.* the result of the extract yield value is obtained through calculation with Equation (1). W_1 is the weight of the dry sample, while W_2 is the weight of the crude extract

$$\text{Extract yield (\%)} = \frac{\text{W2 (g)}}{\text{W1 (g)}} \times 100\% \qquad (1)$$

4) Characterization of the crude extract

The extracts obtained were characterized using thin-layer chromatography (TLC) with silica gel F_{254} as the stationary phase and a mixture of several organic solvents as the mobile phase (eluent). The extracts were photographed on the stationary phase and then inserted into the chamber, which had been saturated with the eluent and eluted to the limit mark. The separated TLC plate was dried and sprayed with various spotting agents, namely Dragendroff to determine alkaloid compounds, $FeCl_3$ to determine phenol compounds, Lieberman-Bouchardat to determine steroid/terpenoid compounds, vanillin H_2SO_4 to determine saponin compounds and flavonoid compounds using cytroborate/$AlCl_3$ spotting agents, then observed under UV light 254 and 366 nm wavelength.

5) In vitro inhibition assay for α-glucosidase

The inhibition activity of the α-glucosidase enzyme was carried out according to the journal (Susilowati et al., 2019). The α-glucosidase enzyme used is derived from *Saccharomyces cerevisiae,* and p-nitrophenyl-α-D-glucopyranoside (*pNPG*) was used as

substrate. Optimization of substrate concentration is achieved by dissolving 2 µL DMSO in 48 µL phosphate buffer and 25 µL α-glucosidase enzyme (0.1 Unit/mL), followed by pre-incubation in a 96-well plate at 37 °C for 5 minutes. Then 25 µl of *pNPG* was added to each well, and 25 µl of pNPG with concentrations of 1, 2.5, 5, 10, 15, and 20 mM was incubated again at 37 °C for 15 minutes. The reaction was then stopped by adding 100 µl of 0.2 M Na_2CO_3. Absorbance was determined using a microplate reader at maximum λ. The inhibition testing of α-glucosidase enzyme was carried out after the optimal conditions were obtained; the tests included blank testing, blank control testing, sample testing, standard testing, sample control testing and standard control testing, calculation of the percentage of α-glucosidase enzyme inhibition activity of the -glucosidase enzyme and calculation of the IC_{50} value of α-glucosidase enzyme inhibition activity of the -glucosidase enzyme. The test was carried out three times. The test system was carried out based on Table 1.

Table 1. Procedure for testing the activity of α-glucosidase

Material	Volume (µL)			
	Blank	**Blank Control**	**Sample/Standard**	**Sample Control**
DMSO	2	2	-	-
Buffer Phosphate pH 6.8	48	73	48	73
Enzyme (0.25 Unit/mL)	25	-	25	-
Sample/Standard	-	-	2	2
Incubation at 37°C for 15 minutes				
pNPG Substrate	25	25	25	25
Incubation at 37 ° C for 15 minutes				
Na_2CO_3 (0.2 M)	100	100	100	100
Total Volume	200	200	200	200

After all the test materials were mixed and incubated, the absorption was measured using a microplate reader at a wavelength of 405 nm. The percentage of α-glucosidase enzyme inhibitory activity was calculated using Equation (2), where A_0 is blank absorption, while A_1 is sample absorption. The IC_{50} value was calculated using linear regression (Equation (3)), where the y-axis is the percentage inhibition and the x-axis is the sample concentration. The IC_{50} value calculated was determined using Equation (3).

$$\% \text{ inhibition} = \frac{A0 - A1}{A1} \times 100\% \quad (2)$$

$$y = bx + a \quad (3)$$

$$IC50 = \frac{50 - a}{b} \quad (4)$$

Results and Discussion

The samples used in this study were Eucheuma cotton macroalgae, which belong to the red algae family. They were obtained from Onaria Beach, Tri Dharmayoga Village, Ketapang District, South Lampung. Before being used, a sample was determined at Herbarium Bandungense SITH ITB. The determination result stated that the samples used were true macroalgae, *Eucheuma cottonii*.

Eucheuma cottonii is characterized by its smooth, cylindrical, and cartilaginous

thallus. The branches of the talus can be blunt or pointed and are decorated with nodules and soft spines that serve to protect the gametangia. These branches may be dichotomous or trichotomous (Figure 1). Like higher plants, *Eucheuma cottonii* relies on sunlight for photosynthesis, its primary metabolic process; therefore, successful cultivation must occur at depths where sunlight can penetrate adequately (Anggadiredja et al., 2011).

Figure 1. *Eucheuma cottonii sample*

Before the extraction process, macroalgae samples undergo several stages of preparation, including soaking in $CaCO_3$ and NaOH solutions. The washed and chopped macroalgae were soaked for 24 hours with $CaCO_3$ to neutralize the salt content. Then, we continued with soaking using NaOH for 24 hours, with the aim of damaging the crystal structure that binds cellulose and also breaking down the complex lignocellulose materials in the cell wall. This process is called the delignification process. Next, the sample was dried and then mashed using a grinder. The delignification process and smoothing of the sample aim to simplify and optimize the extraction process, allowing the solvent to extract the compounds contained in the sample properly. This is expected to increase the yield value of the extracted compounds.

Characterization is one of the key parameters in dry sample standardization, which aims to ensure the uniformity of dry sample quality to meet the specified standard. Dry sample characterization testing includes determination of the total ash content, acid-insoluble ash content, water-soluble juice content, ethanol-soluble juice content, and drying shrinkage. The results of the dry sample characterization are presented in Table 2.

Table 2. Characterization of dry *Eucheuma cottonii*

Parameter	Results ($\%^{W}/_{W}$)
Total ash content	17
Acid insoluble ash content	1
Water-soluble content	16
Ethanol-soluble extract content	6
Water Content	7.33

The determination of ash content aims to identify the inorganic compounds that remain after dry samples are combusted. The total ash content provides an

indication of the external and internal mineral content, which may be present in the form of plant tissue or other impurities, such as sand or soil. The determination of the acid-insoluble ash content aims at determining the amount of impurities derived from silicate sand or soil. The small acid-insoluble ash content indicates the lack of impurities in simplicia (S. Handayani & Ruslan Wirasutisna, 2017). The results of the determination of the total ash content and acid insoluble ash were 17% and 1%, respectively. These results show that the samples used contain fewer external and internal minerals.

The determination of juice content aims to quantify the amount of compounds dissolved in organic solvents (nonpolar) and inorganic solvents (polar). Based on the results obtained, the value of the determination of the water-soluble juice content is 16% (w/b), while the value of the ethanol-soluble juice content is 6% (w/b). This shows the high content of polar compounds dissolved in water compared to nonpolar compounds dissolved in ethanol (Cairns, 2003).

The extraction of *Eucheuma cottonii* macroalgae uses a multistage maceration method. This method was chosen due to its simplicity and because it avoids the possibility of decomposition of active substances contained in the sample by temperature influence. Stratified maceration is believed to produce a greater yield of compounds with varying levels of polarity. The results of the extraction are presented in Table 3.

The yield is the value in the manufacture of the product obtained by comparing the weight of the extract produced with the weight of the dry sample powder used (Kemenkes RI, 2017). The higher the yield produced, the higher the content of compounds in the extract. The highest yield was 31.60% in the ethanol extract. This indicates that the compounds contained in *Eucheuma cottonii* macroalgae are predominantly more polar.

Table 3. Yield of *Eucheuma cottonii* extract

Solvent	Extract weight (g)	Yield (%)
n-hexane	28.76	14.38
Ethyl acetate	31.37	15.69
Ethanol-70%	63.19	31.60

The extract was monitored to identify the groups of secondary metabolite compounds it contains, using thin layer chromatography (TLC). This method separates samples based on their polarity levels. The stationary phase used is silica gel F254. In contrast, the mobile phase is used with three developers that have different levels of polarity to observe the chromatogram pattern of compounds from the extract. The nonpolar mobile phase used was a combination of n-hexane: ethyl acetate (7:3) solvent (Figure 2, first sequence); the semipolar mobile phase used chloroform: ethyl acetate (7:3) solvent (Figure 2, second sequence), while the polar mobile phase used ethyl acetate: formic acid: water (8:1:1) solvent (Figure 2, third sequence).). The combination of organic solvents used is more optimal for separating secondary metabolites in the extract. The compounds indicate this was detected more than in previous studies using mobile phases of chloroform-methanol (3:1). The use of this mobile phase only identified the presence of flavonoids (Arsianti et al., 2018). Observations were made visually under UV lamps of 254 and 366 nm, then sprayed with 10% H_2SO_4, $FeCl_3$, Liebermann-Burchard, Dragendorff, and cyroborate spotting agents.

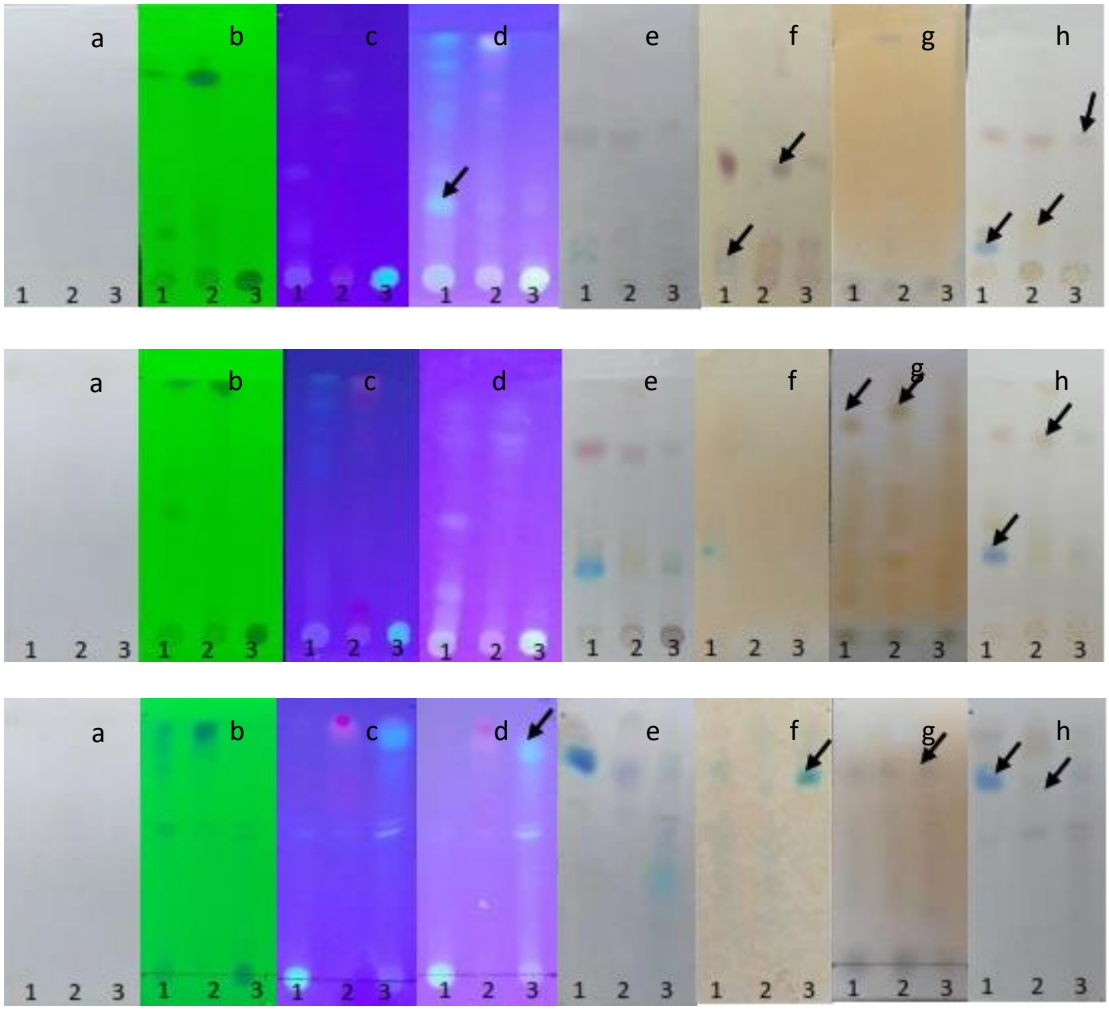

Figure 2. TLC results of *Eucheuma cottonii* extract with the mobile phase n-hexane:ethyl acetate (first sequence), chloroform:ethyl acetate (second sequence), and ethyl acetate:formic acid:water (third sequence). Notes: 1. n-hexane extract; 2. Ethyl acetate extract; 3. Ethanol extract; Monitoring with (a) Visible, (b) UV light at 254 nm, (c) UV light at 366 nm, (d) cytroborate spot appearance at UV 366 nm, (e) H_2SO_4 10%, (f) $FeCl_3$, (g) Dragendorff, (h) Liebermann-Burchard spot appearance.

The results of monitoring the extract under a UV 254 nm lamp showed the appearance of a green fluorescent KLT plate with dark-colored separation spots. Conversely, under UV light at 366 nm, the KLT plate display shows a dark background with fluorescent spots. A summary of the results of the class of compounds identified through extract characterization can be found in Table 4.

Table 4. Characterization extract of *Eucheuma cottonii*

Compound group	Extract		
	n-Hexane	Ethyl Acetate	Ethanol 70%
Flavonoids	+	-	+
Alkaloids	+	+	+
Phenol	+	+	+
Steroids/terpenoids	+	+	+

The α-glucosidase enzyme inhibition activity test method has a working principle in which the α-glucosidase enzyme hydrolyzes the substrate pNPG to glucose and p-nitrophenol, producing a yellow-colored reaction. The inhibitory ability of the sample solution to inhibit the reaction is greater if the yellow color produced is reduced (Yuniarto & Selifiana, 2018). The positive control used was acarbose, which is a commercial antidiabetic drug that works by inhibiting the action of the α-glucosidase enzyme, which is commonly used in the treatment of type 2 diabetes mellitus (Dinicolantonio et al., 2015).

Testing of the α-glucosidase enzyme inhibitory activity of the -glucosidase enzyme of the *Eucheuma cottonii* macroalgae extract was carried out at several sample concentrations. The aim was to determine the effect of increasing the sample concentration on inhibitory activity and obtain the inhibition value. The higher the sample concentration, the greater the inhibition of enzyme activity is expected. The inhibition value obtained was then used to calculate the IC_{50} value. The IC_{50} value can indicate the inhibitory power of the *Eucheuma cottonii*i macroalgae extract sample against the enzyme.

The parameter used to assess α-glucosidase enzyme inhibitory activity is the IC50 value, which represents the concentration that inhibits the α-glucosidase enzyme by 50%. In this test, the absorbance of the sample solution and the absorbance of the control were measured. The IC_{50} value is very active if less than 10 µg/mL, active if less than 100 µg/mL, and inactive if more than 100 µg/mL (Fadhli et al., 2021).

Table 5. Glucosidase inhibition activity

Sample	IC_{50} (µL/mL)
N-hexane extract	567,84 ± 0,66
Ethyl acetate extract	174,32 ± 0,68
70% Ethanol extract	**99,57 ± 0,62**
Acarbose	**64,41 ± 0,48**

Table 5 presents the inhibitory activity of n-hexane, ethyl acetate, and 70% ethanol extracts of *Eucheuma cottonii* macroalgae against the α-glucosidase enzyme, with IC50 values of 567.84 µg/mL, 174.32 µg/mL, and 99.57 µg/mL, respectively. Acarbose, as a comparator, produced an IC_{50} of 64.41 µg/mL. The results show that the ethanol extract of *Eucheuma cottonii* macroalgae has the potential to inhibit the α-glucosidase enzyme because the value of IC_{50} is less than 100 µg/mL (Dwiatmi Dewiyanti et al., 2012). This indicates that the ethanol extract of *Eucheuma cottonii* macroalgae has potential as an alternative antidiabetic agent. The lower the IC_{50} value, the greater the inhibition of the sample against the α-glucosidase enzyme.

Several studies have shown that alkaloid and flavonoid compounds have the ability to inhibit α-glucosidase enzyme activity. Flavonoids are compounds with antidiabetic activity (Febrinda et al., 2013). Based on the results of extract characterization using KLT, compounds containing alkaloids and flavonoids are believed to have α-glucosidase enzyme inhibition activity. However, the type of compound responsible for the macroalgae extract of *Eucheuma cottonii* has not been ascertained on α-glucosidase enzyme inhibition activity.

Conclusions

Based on the results of extract characterization analysis, it is known that the *Eucheuma cottonii* macroalgae extract contains flavonoids, alkaloids, steroids/terpenoids and phenols. The α-glucosidase enzyme inhibition activity of the -glucosidase enzyme using an enzyme concentration of 0.1 U / ml and a substrate concentration of 5 mM shows that of the three macroalgae extracts of *Eucheuma cottonii* that have inhibitory activity against the α-glucosidase enzyme 70% ethanol extract of the -glucosidase enzyme of 70% with an IC_{50} value of

99.57 µg/mL. This result is close to the standard reference value of acarbose. It can be considered active as an antidiabetic, indicating that ethanol extracts have the potential to be developed as an alternative in antidiabetic treatment. The IC_{50} values obtained from the extracts of n-hexane, ethyl acetate, and 70% ethanol of *Eucheuma cottonii* macroalgae are, respectively, 567.84, 174.32, and 99.57 µg/mL. The comparator, acarbose, has an IC_{50} value of 64.41 µg/mL.

Author Contributions

DK designed the research, prepared samples, processed data, and drafted the manuscript. **FZ** performed the extraction and characterization of the extract. **WB** performed the extract activity test. **IA** assisted in drafting and translating the manuscript.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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