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Antidiabetic and Liver Tissue Improvement Potency of Surf Redfish (*Actinopyga mauritiana*) in Alloxan-Induced Diabetic Mice

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Abstract: Long-term hyperglycemia is associated with various organ damage. One of these damages is Non-Alcoholic Fatty Liver Disease (NAFLD). One of the potential natural products that may improve this impact is Surf Redfish. Hence this study aimed to investigate the antidiabetic and liver protection effects of Surf Redfish in some diabetic male Mice. This study was an experimental study that used 25 male mice grouped into control, standard, Surf Redfish Extract-I (100 mg/ kg BW), II (200 mg// kg BW), and III (400 mg/ kg BW). This study evaluated the blood glucose level (before and after induction, third, sixth, ninth, twelfth, and fifteenth days) and histology study of liver tissue. This study showed that the Surf Redfish ethanol extract significantly decreased blood glucose levels every day for fifteen days (P-Value < 0.05). This extract also showed a significant decrease in vacuolated degeneration after fifteen days of extract administration (P-Value). Hence, it can be concluded that the most effective dose of Surf Redfish extracts in this study was 400 mg/ kg BW to decrease blood glucose level and width of vacuolated degeneration after fifteen days of administration.

Keywords: Alloxan; Diabetic; Ethanol; Liver; Surf redfish

Introduction

Long-term hyperglycemia in diabetic patients is associated with various organ damage, especially the eyes, kidneys, nerves, heart, liver, and blood vessels. Various factors affect diabetes mellitus incidence, including genetics, lifestyle, age, and hypertension. (Rohilla & Ali, 2012) Excessive glucose was stored as glycogen in the liver tissue by porta hepatic circulation. When it was required, glycogen was catabolism. However, if the glucose level is too high to store in the liver, it may cause hyperglycemia and worsen early liver tissue damage. Thus, it was obvious that diabetes mellitus may also affect liver tissues. Some studies have reported the accumulation of lipids in the liver tissue. It may also know as Non-Alcoholic Fatty Liver Disease (NAFLD), which showed some clinical presentations including obesity, undernutrition, intestine malabsorption, dyslipidemia, thyroid disease, and metabolic syndrome (Lucchesi et al., 2015; Suherman et al., 2021).

According to the information above, it becomes important to look for novel natural diabetic drugs that can decrease the impact of diabetes and increase the quality of life in diabetic patients. Various herbs in Indonesia have been studied to look for novel diabetic drugs. One of these herbs is Surf Redfish (*Actinopyga mauritiana*). Surf redfish comes from the Holothuroidea family, which is a marine product with high economic value and very popular in the international market. Various products from the family of *Holothuroidea* have been used as a traditional medicine in Chinese medicine for a long time. Furthermore, Surf redfish has been reported to have various health benefits and active compounds. Herliany (2016) reported that Surf redfish had antioxidant, antiprotozoal, inhibiting neoplasm cell growth, wound healing, and antithrombotic activity.

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Moreover, Septiadi et al. (2013) and Abdullah et al. (2018) reported that Surf Redfish also had various vitamins, minerals, and phytochemicals. These vitamins and minerals include calcium, iron, magnesium, zinc, and chondroitin sulfate. On the other hand, the phytochemicals in Surf Redfish include alkaloid, steroid, triterpenoid, and glycoside triterpenoid (saponin) (Herliany et al., 2016; Rasyid et al., 2018; Septiadi et al., 2013). These phytochemicals are important compounds that are responsible for some pharmacological effects. Saponin (glycoside triterpenoid) is an essential compound in surf redfish to offend external obstacles, and this compound is also found in the highest concentration. This compound is commonly found as a secondary metabolite by echinoderms plants, marine sponges, and octocorals, which have some health benefits like antibacterial, antiviral, antidiabetic, and antithrombotic effects (Bahrami & Franco, 2015; Caulier et al., 2013; Fiana & Oktaria, 2016). Thus, this study was performed to investigate the antidiabetic and liver protection effects of Surf Redfish in some diabetic Male Mice.

Method

This experimental study was performed in the Pharmacology and Pharmaceutical Laboratory, Faculty of Pharmacy, Universitas Tjut Nyak Dhien Medan, from February to April 2019. All study protocols have been approved by Health Research Ethics Committee from Universitas Prima Indonesia with No. Letter: 004/ KEPK/ UNPRI/ IX/ 2019.

This study used some materials, including Surf Redfish (*Actinopyga mauritiana*), Sodium Carboxymethyl Cellulose (SCMC), rat pellets, 10% Neutral Buffered Formalin Solution, Normal Saline, paraffin, alcohol, xylol, hematoxylin, and eosin staining powder, distilled water, and Entellan®.

This study used Surf Redfish (*Actinopyga mauritiana*), obtained from a Lamreh Village, Baitussalam District, Nanggroe Aceh Darussalam. Ten kilograms of Surf redfish were washed with distilled water, dried, and weighed. After that, the body content was removed by vertical incision, and the remaining surf redfish body was cut into some small pieces. Hence, it obtained 5.3 kg of clean Surf Redfish (Chiuman et al., 2021; Mutia, 2019).

This clean Surf Redfish was extracted by maceration methods using Pro Analytic Ethanol solution. Finally, the macerate was evaporated by Rotary Evaporator at 40^{o}C to obtain concentrated Surf Redfish ethanol extract (Gulo et al., 2021; Lesmana et al., 2022).

Initially, all mice used in this study were acclimatised for 14 days into the Laboratory settings. This study used 25 mice for the animal trial, weighing 25 grams and aged 2-3 months. These mice fasted for 16-18 hours. After that, these mice were injected with an alloxan monohydrate solution. The blood glucose is also measured after the fasting state. After that, all mice received an injection of 150 mg/ kg BW alloxan monohydrate via intraperitoneal injection, and after 48-72 hours, the blood glucose level was measured. The mice were defined as diabetic mice when the blood glucose level was ≥ 200 mg/ dL (Lesmana et al., 2022; Siregar et al., 2021).

All diabetic mice were grouped into five different groups, including control, standard, Surf Redfish Extract-I, II, and III, which received SCMC suspension 65 mg/ kg BW of metformin, 100 mg/ kg BW, 200 mg/ kgBW, and 400 mg/ kg BW of Surf Redfish Ethanol Extract, respectively (Lesmana et al., 2022) for 14 days. Meanwhile, the blood glucose level was measured on the third, sixth, ninth, twelfth, and fifteenth days.

Blood glucose level was measured by glucometer using vein blood and expressed as mg/ dL, the vein blood was obtained by punction of mice tail for lateral vein blood. Before the punction, the vein tail was disinfected with an alcohol swab.

After 14 days of treatment, all mice were sacrificed by chloroform inhalation and then the liver organ was resected from the abdomen cavity. The liver was then washed with Normal saline solution to remove the blood and fixed into 10% Neutral Buffered Formalin Solution until it was processed for haematoxylin eosin staining. This stained tissue was observed under a light microscope to evaluate the width of vacuolated degeneration in High Power Field (HPF) and expressed as a percentage (%) per HPF (Chiuman et al., 2021; Mutia, 2019; Mutia & Chiuman, 2019).

Blood glucose level and width of vacuolated degeneration were expressed as an average, and the difference was analysed by One Way ANOVA and followed by Post Hoc Test Tukey HSD. Meanwhile, the histology study was reported as histology photographed under a light microscope from a random mouse per treatment group at a magnification of 400 times.

Result and Discussion

The obtained Surf Redfish was identified in Research Center for Oceanography, Indonesian Institutes of Sciences (*Pusat Penelitian Oseanografi Lembaga Ilmu Pengetahuan Indonesia* [LIPI]). The identification reported that the obtained Surf Redfish had the scientific name of *Actinopyga mauritiana*. The phylum, class, ordo, family, and genus of obtained Surf Redfish were Echinodermata, Holothuroidam Holothurii, Holothuriidae, and Acatinopyga, respectively.

This study collected 10.0 kg of Fresh Surf Redfish. All fresh Surf Redfish were washed, and the body contents were removed; thus, 5.0 kg of cleaned Surf Redfish was obtained, which was extracted by maceration methods. This procedure resulted in 625.20 grams of concentrated extract and a yield of 11.79%.

The concentrated Surf Redfish Ethanol Extract underwent phytochemical screening and showed the presence of alkaloids, flavonoids, glycosides, saponin, and steroids. The concentrated Surf Redfish Ethanol Extract was sustained into Sodium Carboxyl Methyl Cellulose Suspension. This suspension was then administrated to alloxan-induced diabetic mice, and the comparison of blood glucose levels was described in Table 1.

Table 1. Comparison of Blood Glucose Levels in All Treatment Groups

Group	Average of Blood Glucose Level (mg/ dL)						
	Before Induction	After Induction	3rd Day	6th Day	9th Day	12th day	15th day
Control	50.5	557.6	529.8	544.8	561.2	579.4	593.0
Standard	52.2	571.8	300.2	241.2	193	152.6	124.6
Surf Redfish Extract-I	50.2	560.4	524.8	506.2	483.4	462.2	428.0
Surf Redfish Extract-II	51.8	572.6	500.2	464.2	419.8	385.5	316.0
Surf Redfish Extract-III	51.8	578.2	344.8	256.0	217.6	181.4	149.2
P-Value	0.604	0.062	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Table 1 shows that all mice before and after induction showed no significant difference in blood glucose levels (P-Value > 0.05). Thus, it showed that all mice had similar blood glucose levels before and after induction. The blood glucose level before and after induction ranged from 50.02-51.80 mg/ dL and 557.6-578.2 mg/ dl, respectively. All mice that received various Surf Redfish Ethanol Extract showed a significantly lower blood glucose level than the control groups after three to fifteen days of administration (P-Value < 0.05). The average blood glucose levels of standard, Surf Redfish-I, II, and III on the third day were 300.3 mg/ dl, 524.8 mg/ dl, 500.2 mg/ dl, and 344.8 mg/ dl, respectively. Meanwhile, these averages decreased on the fifteenth day. The average blood glucose level of standard, Surf Redfish-I, II, and III on the fifteenth day were 124.6 mg/ dl, 428.0 mg/ dl, 316.0 mg/ dl, and 149.2 mg/ dl, respectively. Furthermore, the rate of blood glucose level decreasing as described in Table 2.

Table 2. Rate of Blood Glucose Improvement in All Treatment Groups

Group	3rd day	6th Day	9th Day	12th day	15th day
Standard	43.34	55.73	65.61	73.66	78.99
Surf Redfish Extract-I	0.94	7.09	13.86	20.23	27.82
Surf Redfish Extract-II	5.59	14.79	25.20	33.47	46.71
Surf Redfish Extract-III	34.92	53.01	61.23	68.69	74.84

Table 2 shows that the highest rate of blood glucose level decrease was found in the lowest dose of surf redfish extract (Surf Redfish Extract-I), followed by Surf Redfish Extract-II, III, and the lowest was the standard group. All groups consistently showed a decrease in blood glucose levels every day for fifteen days. At the end of observation, the rate of blood glucose level decreasing of standard, Surf Redfish Extract-I, II, and III were 78.99%, 27.82%, 46.71%, and 74.48%, respectively. Furthermore, this study also evaluated the effect of Surf redfish extract against the liver tissue structure in a diabetic setting, and the liver histology of all mice was shown in Figure 1.

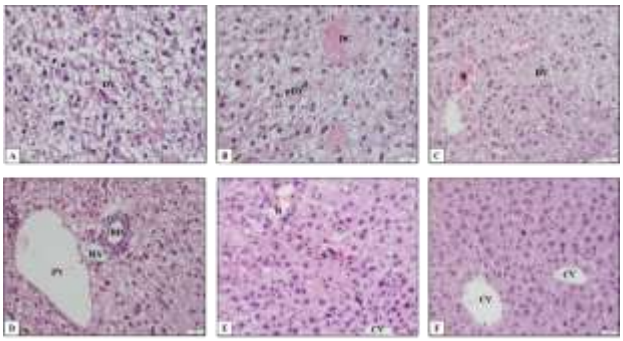

Figure 1. Histology study of liver tissue from (A) Control group, (B) Surf redfish extract-I, (C) Surf redfish extract-II, (D) Surf redfish extract-III (Triad porta area), and (E) Standard group. Meanwhile (F) Histology of normal liver tissue. Stain: haematoxylin and eosin (HE). Magnification: 400x. Abb: BD= bile duct; DC= Congestion; DV= Vacuolated degeneration; CV= Central venous; HA= Hepatic artery; H= Haemorrhage; PV= Portal venous

Figure 1 shows that almost all groups showed various degrees of vacuolated degeneration. The vacuolated degeneration was shown by a 'clear' cell not absorbed staining powder and marked as DV (Vacuolated Degeneration) in the histology section. The width of vacuolated degeneration per high power field determined the severity of vacuolated degeneration. Figure 1 shows that the wideset vacuolated degeneration was the control group, followed by the

Surf Redfish Extract I, II, III, and Standard group. Furthermore, the width of vacuolated degeneration was expressed as a percentage per high power field and described in Table 3.

Table 3. The Width of Vacuolated Degeneration Area in All Treatment Groups

Groups	Vacuolated Degeneration (Percentage per HPF)	P-Value
Control	99.20	
Standard	22.80	
Surf Redfish Extract-I	56.80	< 0.05
Surf Redfish Extract-II	49.60	
Surf Redfish Extract-III	40.00	

Table 3 describes the width of vacuolated degeneration as a percentage, followed by Figure 1. The variation of Surf Redfish extracts significantly affected the width of the vacuolated degeneration area (P-Value< 0.05). The widest vacuolated degeneration was shown in the control group (99.20%), followed by Surf Redfish I (56.80%), II (49.60%), III (40.00%), and the narrowest vacuolated degeneration was shown at the standard group (22.80%).

This study obviously showed that the Surf Redfish ethanol extract has some phytochemicals, including alkaloids, flavonoids, glycosides, saponin, and steroids. This extract also showed a significantly decreased blood glucose level every day for fifteen days. Furthermore, this extract showed significant liver protection from vacuolated degeneration after fifteen days of extract administration.

This study used alloxan to induce diabetic conditions. Alloxan is a widely diabetogenic compound used to induce diabetic conditions in some animal trials. It forms a hydroxyl radical compound that can injure beta cells in pancreatic tissue and lead to a diabetic condition. The dose of alloxan used in this study was 150 mg/ kg BW and increased the blood glucose to 514-578 mg/ dL (Kottaisamy et al., 2021; Vijayaraj et al., 2019).

Prolonged hyperglycaemic conditions may cause various complications. This complication was associated with forming free radicals, especially reactive oxygen species (ROS), that were accumulated in various organs. One of these affected organs is liver tissue, which is shown as Non-Alcoholic Fatty Liver Diseases (NAFLD), ranging from steatosis to cirrhosis (Chiuman et al., 2021).

This study showed that the Surf Redfish significantly improved the NAFLD in diabetic mice. This effect is due to various phytochemical compounds, including alkaloids, flavonoids, glycosides, saponins, and steroids. It showed a similar result to the previous study. The previous study by Moriza et al. reported whether alkaloids, flavonoids, glycosides, saponin, and steroids in Surf Redfish could decrease blood glucose levels and accelerate the incision wound healing process in alloxan-induced diabetic mice (Lesmana et al., 2022).

In a recent study, the most effective dose to improve liver tissue was 400 mg/ kg BW. This improvement was followed by the blood glucose level of all mice receiving the highest Surf Redfish Extract dose (400 mg/ kg BW). Phytochemical contents in Surf Redfish extract are responsible for the antidiabetic and liver improvement effects in diabetic conditions. Flavonoid and saponins have been reported to have antioxidants and antidiabetic effects. Flavonoids and saponin inhibit some enzymes that contribute to the formation of many free radicals.

On the other hand, these compounds also neutralise the free radical compounds formed by the donor proton to the unstable free radical molecule. In addition, saponin also enhances the level of some enzymes that contribute to neutralising free radicals like SOD and CAT. Meanwhile, the flavonoid also has an additional effect, anti-inflammatory effects, by inhibiting cyclooxygenase and lipoxygenase enzymes. Hence, the antidiabetic, antioxidant, and anti-inflammatory effects of Surf Redfish may improve the hyperglycaemic condition and prevent hyperglycaemic-related tissue damage due to oxidative stress (Chiuman et al., 2021, 2022; Sari et al., 2021).

Conclusion

Overall, it can be concluded that the Surf Redfish significantly decrease the blood glucose level, followed by the improvement of vacuolated degeneration in diabetic condition. The decreasing blood glucose level and width of vacuolated degeneration area followed the increased extract dose. The most effective dose of Surf Redfish extract was 400 mg/ kg BW to decrease blood glucose level (74.84%) and width of vacuolated degeneration (40.00%) after fifteen days of administration.

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Author Contributions
Conceptualization: Arma Citra, I Nyoman Ehrich Liester, and Edy Fachrial; Methodology: Arma Citra and Edy Fachrial; Investigation: Arma Citra; Discussion of results: Arma Citra; Writing – Original Draft: Arma Citra; Writing – Review and Editing: I Nyoman Ehrich Liester, Edy Fachrial, Sahna Ferdinand Ginting; Supervision: I Nyoman Ehrich Liester, Edy Fachrial, Sahna Ferdinand Ginting; Approval of the final text: Arma Citra, I Nyoman Ehrich Lister, Edy Fachrial, Sahna Ferdinand Ginting.

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Conflicts of Interest
The authors declare no conflict of interest.

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