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Healthcare In A Pandemic Era: The New Norm

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FACULTY OF MEDICINE AND HEALTH SCIENCES
UNIVERSITI SAINS ISLAM MALAYSIA

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ABSTRACT

Introduction: Hyperglycemia and insulin resistance in uncontrolled diabetics induce the formation of reactive oxygen species (ROS), which is responsible for increased platelet activation. This has the potential for complications of atherosclerosis and cardiovascular disease. Seaweed extract has bioactive content that functions as an antioxidant and can lower blood glucose levels. The bioactive content is influenced by the type of seaweed, location and also the environment. **Objectives:** The purpose of this study was to determine the effect of giving red, brown and green seaweed extracts on the platelet numbers of diabetic mice. **Methodology:** The study was conducted on 6 groups of mice, namely the normal group (without treatment) the negative control group (diabetes), the positive control group (diabetes and metformin), the diabetes group and given red seaweed extract, the diabetes group and given brown seaweed extract and the diabetes group. And given green seaweed extract. The dose of seaweed extract is 10 mg / 20 gr/BB / day and metformin at a dose of 1.3 mg / 20 gr/BB. The platelet count was calculated directly using the Brecher Cronkite method. **Results:** The results showed that the platelet counts in diabetic mice were significantly higher than the normal group and the other groups that were given metformin and seaweed. Diabetic mice given red seaweed showed no significant difference in platelet counts from the positive and normal control groups, while brown and green seaweeds showed lower platelet counts. **Conclusion:** It was concluded that the intake of seaweed extract decreased the platelet count in diabetic mice.

Keywords: seaweed, diabetes, platelets, seaweed extract, anti-oxide

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Effect of Red (*Rhodophyceae*), Brown (*Phaeophyceae*) and Green (*Chlorophyceae*) Seaweed Extracts, On Platelet Counts In Diabetic Mice

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***Abstract*— Introduction:** Hyperglycemia and insulin resistance in uncontrolled diabetics induce the formation of ROS which is responsible for increased platelet activation. This has the potential for complications of arteriosclerosis and cardiovascular disease. Seaweed extract has bioactive content that functions as an antioxidant and is able to lower blood glucose levels. The bioactive content is influenced by the type of seaweed, location and also the environment.

Objectives. The purpose of this study was to determine the effect of giving red, brown and green seaweed extracts on the platelet numbers of diabetic mice.

Methodology: The study was conducted on 6 groups of mice, namely the normal group (without treatment) the negative control group (diabetes), the positive control group (diabetes and metformin), the diabetes group and given red seaweed extract, the diabetes group and given brown seaweed extract and the diabetes group. and given green seaweed extract. The dose of seaweed extract is 10 mg / 20 gr/BB/day and metformin is at a dose of 1.3 mg / 20 gr/BB. The platelet count was calculated directly using the Brecher Cronkite method.

Results. The results showed that the platelet counts in diabetic mice were significantly higher than in the normal group and the other groups that were given metformin and seaweed. Diabetic mice given red seaweed showed no significant difference in platelet counts from the positive and normal control groups, while brown and green seaweeds showed lower platelet counts.

Conclusion(s). It was concluded that the intake of seaweed extract decreased the platelet count in diabetic mice.

Keywords— **seaweed, diabetes, platelets, seaweed extract, anti-oxide.**

I. INTRODUCTION

Diabetus mellitus is a metabolic disease that triggers other diseases, such as cardiovascular, kidney, blindness, injuries resulting in amputation, and is one of the main causes of death. Diabetics are also at high risk for the occurrence of covid 19 and contribute to its severity and death (1). Diabetes has two types, namely 1 and 2. Type 1 diabetes is more often characterized by the destruction of pancreatic beta cells which causes absolute insulin deficiency. Type 2 diabetes is diabetes which affects 90% of diabetics worldwide. This type of diabetes is characterized by insulin resistance or reduced insulin production. The two types can be overlapping conditions, because the development of type 1 will show a phenotype that looks like type 2, giving rise to a new category called multiple diabetes. Type 2 with a long duration of insulin deficiency will display symptoms similar to those of type 1 diabetic patients (2). Diabetes-related mortality is associated with thrombotic events, especially cardiovascular events, usually characterized by hypercoagulation and hypofibrinolysis symptoms (3). Patients with type I diabetes have a 10x risk of developing cardiovascular disease compared to type 2 diabetes sufferers (4). Platelets are an important key in the thrombosis process. Thrombotic dysfunction due to metabolic disorders plays a role in increasing thrombus formation and arterial occlusion, which has the potential to increase the risk of atherothrombosis in diabetic patients with cardiometabolic risk (5). The number of platelets and the mean platelets volume (MPV) are used as markers or indicators of thrombosis and risk factors for microvascular complications associated with cardiovascular disease in diabetics (6) ; (7). In addition, there was a significant increase in platelets in diabetic patients complicated by foot ulcers (8). Hyperglycemia is a major cause of altered platelet responses and oxidative stress which symptoms can be seen in type 1 and 2 diabetes. The changes lead to changes in the platelet phenotype (9).

Seaweed or macroalgae has bioactive content which is widely used for health, cosmetics and food. The seaweed is classified based on their size, characteristic shape and specific pigments. Classification based on pigments, there

are red algae (Rhodophyceae), brown algae (Phaeophyceae) and green algae (Chlorophyceae). Brown algae contains the pigment fucoxanthin. Red algae contain the pigments phycoerythrin and phycocyanin and other pigments in small amounts, namely chlorophyll, carotene and xanthophyll. Green algae contains chlorophyll (10). Seaweed also contains quite high amounts of other bioactive ingredients. The bioactive content is a product of secondary metabolites which have the ability to be anti-aging, antioxidant, antibacterial, anti-inflammatory, antidiabetic and anti-proliferative. The main bioactive components of seaweed are polyphenols, polysaccharides, carotenoids and polysaccharides (11). Supplements containing polyphenols have shown their activity as anti-hyperlipidemic, anti-diabetic, prevent cardiovascular disorders and prevent other metabolic disorders (12). The purpose of this study was to determine the effect of red, brown and green seaweed extracts on platelet volume in diabetic mice.

Equipment and Materials: injection syringe (1 cc / 27 G x ½, Terumo®), blender, freeze dryer, rotary evaporator, centrifuge, glucometer (Autocheck®), blood lanchet. Improved Neubauer counting room, cover glass, microscope, cell counter, Petri dish. Ingredients: standard food, alloxan monohydrate, 0.9% NaCl, red seaweed (Rhodophyceae), brown seaweed (Phaeophyceae), green seaweed (Chlorophyceae), ethanol, filter paper, 1% ammonium oxalat,

Seaweed Extraction

Clean and drained seaweed (red, brown and green), cut into small pieces to make it easier to mash and weigh 1 kg each. Seaweed was mashed using a blender, then dried using a freeze dryer at a temperature of -70ºC for ± 3 days until a dry powder was obtained. The powder was dissolved with ethanol and extracted using an ultrasonic device at a temperature of <50ºC for 3 hours. Filtering using Whatman filter paper and changing ethanol was done every 1 hour 3 times. To separate the filtrate and the residue, a vacuum was used so that the residue was completely dry and the residue was stored if it is used for further extracting. Solvent evaporation was carried out using a rotary evaporator at a temperature of 40 ° C at a speed of 150 rpm to obtain a liquid extract. The liquid extract was thickened using a water bath.

Induction of diabetes in mice

This research procedure is in accordance with research ethical standards and has received approval from the Ethical Commission of the Faculty of Dentistry, University of Jember No.159 / UN25.8 / KEPK / DL / 2018.The condition of diabetes in mice is done by inducing alloxan at a dose of 4.2 mg / 20 gr body weight. Mice are declared diabetic when the blood glucose after fasting exceeds the normal value, which is more than 160 mg / dl. Examination of blood glucose levels was carried out by checking the venous blood droplets in mice using an autocheck. Before checking their blood glucose levels, mice were fasted from food for 8-12 hours (only water was provided).

Treatment of experimental animals

Thirty-six male mice aged 3 months were divided into six groups. The first group (control group), were normal mice that only got saline. The second group was diabetic mice and received saline, while the third group was diabetic mice and were given metformin at a dose of 1.3 mg / 20 g BW / day. The fourth, fifth and sixth groups were diabetic mice which were given brown, red and green seaweed extract. The dose of seaweed is 10 mg / 20 g mice BW / day. Saline, metformin and seaweed were given once a day and given until the mice were sacrificed.

Platelet Volume Examination

Platelet volume is the average number of platelet volumes contained in 10 µL of blood which was calculated using the direct method with the Brecher Cronkite method (Gomes Oliveira et al., 2003). Using blood taken from vena cava orbitalis, and diluted with 1% ammonium oxalate reagent. Dilution of blood samples and reagents. Ammonium oxalat 1% (1: 100), was carefully inserted into the counting room using a micropipette. The filled counting room was placed on a petri dish filled with wet wipes and waited 10 minutes for the platelets to settle. Platelets were counted across the large area in the center of the counting chamber (1 mm2) with a 200x magnification light microscope (Figure 1). The counted platelet count is multiplied by 1000 to produce a platelet count per µl of blood, with a normal reference value of 150,000-400,000 platelets / µl of blood (Gandasoebrate, 2010). The platelet count was counted by diluting 100 times. The calculated area is 1 x 1 mm2 and the room height is 0.1 mm, so the volume is 1 x 1 x 0.1 = 0.1 µl. The platelet count formula uses the formula below:

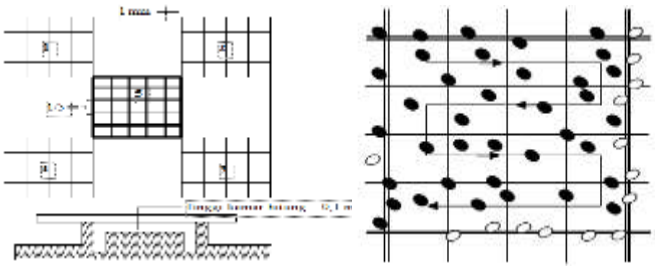
If the number of platelets in the area obtained is N then:

$$\text{MPV} = \frac{\text{calculated platelet volume}}{\text{calculated volume}} \text{ x dilution factor}$$

$$= \frac{\text{N}}{0{,}1\ \mu\text{l}} \text{x } 100$$

$$= 1000\ \text{N}/mm^3$$

The method of counting platelets is that cells touching the top and left lines of the box must be counted, while the cells touching the right and bottom lines on the box are not included in the count.



A B

Figure 1 A. Improved Neubauer counting room. B. counting method (whole round count, blank round is not counted)

Data analysis

The resulting data was subjected to a statistical test with a two-way ANOVA test and then a Tukey HSD test with a 95% confidence level .

III. RESULTS

Mice with diabetes (control -) had the highest mean platelet volume. Diabetic mice given seaweed were significantly lower in platelet volume compared to control (-) (diabetic mice). Low platelet volume also occurred in mice given metformin (control +). In the normal group of mice (without diabetes), they had the lowest platelet volume compared to the other groups. The decrease in platelet volume was lowest in mice treated with green seaweed, although the platelet volume compared to diabetic mice was significantly lower. Tukey HSD analysis showed that there was no significant difference in platelet volume between mice and the brown and red seaweed treatments. The mean platelet volume in both groups was significantly lower than mice treated with metformin. However, when compared with the normal group, the platelet volume was significantly higher (Figure 2 and Table 1).

Figure 2. The mean histogram of platelet volume of normal and diabetic mice fed with seaweed and metformin. Data are presented as mean ± SD. Data for significance differences were analyzed using Two-way ANOVA (P <0.05).

Thrombocyte volume

	Groups	N	Subset 1	2	3	4	5
Tukey HSD[a,b]	Normal	12	2937.50				
	Brown	12		3469.75			
	Red	12		3593.33			
	Metformin	12			3810.66		
	Green	12				4431.66	
	Alloxan	12					6595.75
	Sig.		1.000	.526	1.000	1.000	1.000

Means for groups in homogeneous subsets are displayed. Based on observed means (P<0,05)

Table 1. The results of the analysis using the Tukey HSD test.

Platelet density can be seen in the photo image of each different group. The diabetes group showed a higher density than the other groups (Figure 3).

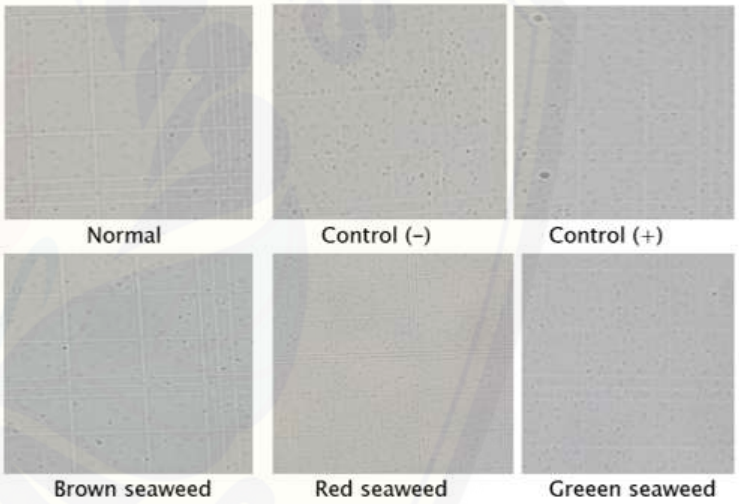


Figure 3. Platelets in the Improved Neubauer count room (200x)

Lamanya hari pemberian rumput laut juga mempengaruhi volume trombosit. Pada hari ke 21 tampak bahwa seluruh kelompok dengan perlakuan rumput laut dan metformin mengalami penurunan volume trombosit yang lebih tinggi dibandingkan pada hari ke 7 dan 14 (Tabel 2).

Table 2: Tukey HSD test based on the length of time given seaweed and metformin

Thrombocyte number				
			Subset	
	Day	N	1	2
Tukey HSD[a,b]	21 days	24	4040.3333	
	14 days	24		4163.6250
	7 days	24		4215.3750
	Sig.		1.000	.569

Means for groups in homogeneous subsets are displayed. Based on observed means. The error term is Mean Square(Error) = 31017,269.

a. Uses Harmonic Mean Sample Size = 24,000. b. Alpha = ,05.

Post-fasting blood glucose levels were significantly higher in diabetic rats compared to the other groups. The seaweed and metformin group showed a significant reduction in blood glucose levels in mice. The green seaweed group had significantly higher blood glucose levels than red and brown seaweed and metformin, but significantly lower than the diabetic mice group (control -) (Figure 4).

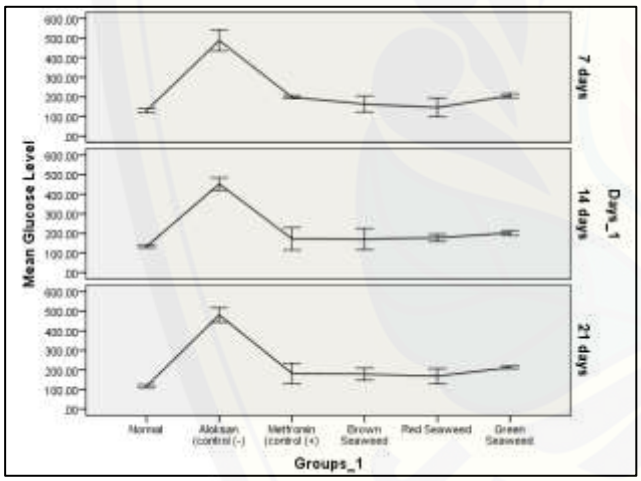


Figure 4. Graph of blood glucose levels in diabetic and mice treated with metformin and seaweed. Data are presented as mean with ± SD. Data analysis used Two Way Anova (P <0.05).

IV. DISCUSSION

The results showed that mice with diabetes had the highest mean platelet volume compared to other groups. Increased platelet volume is associated with hyperglycemia. Mean platelet volume (MPV) reflects changes in platelet stimulation or platelet production rate (13). In accordance with other previous studies that in children with type 1 diabetes there was a change in platelet function (6). Patients with complicated type 2 diabetes had an increased mean platelet volume when compared to uncomplicated diabetes patients and normal patients. The complications seen are retinopathy, nepropathy and also foot lesions. Therefore, it is argued that MPV is closely associated with microvascular and macrovascular complications, although microvascular is more frequently reported.
((14). Changes in peripheral platelet counts due to abnormalities in the main precursor of platelets, namely megakaryocytes. Generally, in newly diagnosed or prediabetic patients peripheral platelets appear to be active. Megakaryocytes are influenced by the presence of cytokines including interleukins 3, 6 and also 11 which cause platelet production to become more reactive. This situation is different in patients with controlled diabetes, who show a decrease in platelet production due to disruption of megakaryocyte function (6).

The mechanism of increasing platelet volume in diabetes due to hyperglycemia conditions triggers the release of S100 calcium binding protein A8 / 9 (S100A8 / A9) by neutrophils that bind to the receptor for advanced glycation end products (RAGE) in Kupffer cells. Thrombopoietin (TPO), which is produced in the liver, triggers the proliferation of megakaryocytes so that platelet production will increase. The platelets released in the circulation by megakaryotic will circulate for 10 days which will eventually be cleared by the reticuloendothelial phagocytosis system. The proliferation and differentiation of megakaryocytes is stimulated by thrombopoitin. This process plays an important role in platelet formation (thrombopoiesis). Some cells produce thrompoieten, namely bone marrow stroma and hepatocytes. The newly released platelets into the blood are larger, contain more mRNA, which is called reticulation, and are more reactive to agonist stimulation than older cells. Highly reactive reticulated platelets are key to understanding the increased risk of CVD and thrombotic events in diabetes (15). The newly formed (young) platelets contain denser granules, appear larger and produce some thromboxane A2. Therefore, the increase in platelet volume is closely related to the amount of platelet aggregation. Larger platelets are more sensitive to platelet stimulants so they are more rapidly recruited to form the thrombus(6). The results of this study differ from other research which show that platelet activation and aggregation occurs due to overreaction to endogenous agonists, so that in diabetic patients, there is a low number of platelets in the circulation. This is due to ineffective thromboiepoysis (16);(16). The causes of platelet dysfunction in diabetics can be caused by several things, namely hyperglycemia, insulin deficiency, metabolic conditions, and other cellular disorders. Hyperglycemia causes platelets to become highly reactive which is indicated by the multiplication of proteins on the surface of the platelet cells. This condition disrupts membrane fluidity and increases platelet adhesion, increases the activity of protein kinase C (a mediator of platelet activation), induces P-selectin expression (surface adhesion protein), and osmotic effects. Insulin deficiency also functions in the occurrence of platelet dysfunction, through the IRS, namely by increasing the concentration of intracellular calcium which causes increased platelet degranulation and aggregation and is independent of IRS, with impaired response to NO and PGI2 (17).

Metformin is the main drug of choice in people with type 2 diabetes. Metformin has been shown to protect the cardiovascular system by reducing blood glucose levels, losing weight, improving hemostasis function, preventing oxidative stress and inhibiting atherosclerosis. (18). Metformin treatment in diabetic patients has shown a reduction in mortality from diabetes. The mechanism of metformin's atheroprotective effect involves inhibition of endothelial leukocyte interactions, smooth muscle cell proliferation, and platelet aggregation (19). Metformin administration in diabetic mice in this study had a major effect on reducing blood glucose levels and platelet volume. This result is in accordance with previous research which shows the same thing. This decrease is because metformin prevents arterial and venous thrombosis by inhibiting platelet activation and preventing extracellular release of mitochondrial DNA (mtDNA). Inhibition of mitochondrial complex I so that it will protect mitochondrial function, reduce platelet activity by inducing mitochondrial hyperpolarization, decrease reactive oxygen species and membrane damage (20).

Polyphenol compounds such as phlorotannin, bromophenol, flavonoids, phenolic terpenoids, and amino acids such as mycosporins are bioactive substances found in seaweed, both red, brown and green. Phlorotannin is the main polyphenol found only in brown seaweed. The phenolic compounds in green and red seaweed are bromophenol, flavonoids, phenolic acids, phenolic terpenoids, and mycosporin-like amino acids. These molecules are considered secondary metabolites, as they are protective agents that are produced in response to different stimuli and are the defense mechanisms of seaweed against herbivores and UV radiation (12). These bioactive substances have been developed as medicines, especially as antidiabetic, anti-inflammatory, antiviral, antithrombotic and so on. Because the content of each type of seaweed is different, it is possible that the extraction effect of each seaweed is also different. The results of this study showed that the treatment of seaweed extract in diabetic mice caused a decrease in blood glucose level and MPV count. In accordance with previous research, the content of grass extract is a factor that plays a role in this reduction. The anti-diabetic mechanism of action by seaweed has been linked to compounds including phlorotannin, fucoxanthin, polyphenols, and polysaccharides that inhibit hepatic gluconeogenesis, and reduce the activity of digestive enzymes such as a-amylase, α-glucosidase, lipase and aldose reductase. This inhibition will reduce the absorption of carbohydrates (21) . The phlorotannin content in seaweed is stated as an antidiabetic because in addition to being able to inhibit the α-amylase and α-glucosidase enzymes it also inhibits the protein tyrosine phosphatase-1B (PTP1B) which can improve insulin sensitivity and provide protection to β-pancreatic cells and adiposity cells against apoptosis, stress. and anti-inflammatory effects through decreasing the different pro-inflammatory mediators (TNF-α, MCP-1, ICAM and leptin), improving AMPK activity and increasing lipid metabolism (22). Therefore, seaweed extract plays a role in preventing nephropathy, blindness, peripheral neuropathy and premature death (21).

Bromophenol (BPs) is a bioactive that can be isolated from red, brown or green seaweed which can inhibit aldose reductase. Aldose reductase is the first enzyme of the polyol pathway, which is responsible for the formation of fructose from glucose and plays an important role in the development of the degenerative complications of diabetes. Bromophenols also have the ability to inhibit thrombin, 3-hydroxy-3-methylglutaril coenzyme A (HMG-CoA) reductase, and phospholipase A2. Thrombin is the main proteinase of the coagulation cascade, which is a target for the treatment of cardiovascular disease. Bromophenol derivatives (2,3-dibromo-4,5-dihydroxyphenyl) -4-bromo-5,6-dihydroxy-1,3-dihydro-isobenzofuran can be isolated from brown algae showed significant inhibition of thrombin inhibitory activity both in vitro and in vivo (23).

Sulphated polysaccharides in brown seaweed also have anticoagulant activity. The anticoagulant ability of seaweed is proven to be used as a medicine for thrombotic disorders. There are reports that there are structural similarities between the sulfated polysaccharides of marine algae and heparin (24). ASP anticoagulant activity was measured using the activated partial thromboplastin clotting time (APTT) test, thrombin time (TT), and prothrombin clotting time (PT). Chemical characterization shows that the sulfated polysaccharides (fucoidan) are negatively charged, which may interact with coagulation factors that are important in the coagulation inhibition process. Fucoidan also binds to P-selectin and increases antithrombotic and hemolytic activity. Therefore sulfated polysaccharide (fucoidan) has high blood anticoagulation activity and significantly prolongs the time before thrombosis and shortens the duration of thrombosis (25).

V. CONCLUSION

It was concluded that high blood glucose levels lead to an increase in MPV. Metformin and seaweed, causing decreased MPV and blood glucose levels. The provision of red and brown seaweed resulted in a higher MPV reduction than green seaweed.

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CERTIFICATE OF ATTENDANCE

This is to certify that

DIDIN ERMA INDAHYANI

has attended the

4th USIM INTERNATIONAL HEALTH E-CONFERENCE

in conjuction with the

3rd INTERNATIONAL CONFERENCE ON MEDICINE AND HEALTH SCIENCES (ICMHS)

Healthcare in Pandemic Era: "The New Norm"

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