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POTENTIAL OF BROCCOLI (*Brassica Oleracea L. Var italica*) EXTRACT AGAINST THE REDUCTION OF MDA LEVELS IN DIABETES MELLITUS TYPE II

Fadilla Ummaiya[1], Widya Hardianti[2], Dyta Putri Aryo[3], Elvina Veronica[4], I Wayan Sugiritama[5]

[1-4]Medical Student of Udayana University, Denpasar, Bali, Indonesia

[5]Udayana University, Bali, Indonesia

Abstract: **Diabetes Mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia and accompanied by various metabolic disorders due to abnormal insulin secretion. Around 90% of DM cases in the world are type 2 of DM and 80% of them are found in developing countries. Indonesia ranks seventh in the country with the most diabetes cases in the world. DM treatment usually expensives and has adverse effects so alternative treatments are needed which are relatively inexpensive, whose properties are not much different from synthetic drugs and are safe for consumption in the long term. Broccoli (Brassica oleracea L. var Italica) is a kind of vegetable that is easy to find and cultivate and contains lots of antioxidants and nutrients. The aim of knowing the potential of broccoli in reducing malondialdehyde (MDA) in patients with type 2 of DM. Methods: The study was derived from various relevant literatures in last 10 years using keywords. Literature from international journals and national journals accessed on PubMed, Garuda, NCBI, and Google Scholar. Results: Antioxidants in extract of broccoli are hepatoprotective and reduce MDA levels in type 2 of DM patients by inhibiting the initiation and propagation of free radical oxidation reactions. Conclusion: Broccoli's extract has the potential to reduce MDA levels in patients with Type 2 of Diabetes Melitus.**

Keywords: **Broccoli, Malondialdehid, Diabetes Mellitus Type 2.**

I. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia and accompanied by various metabolic disorders due to abnormalities in insulin secretion.[1] Peoples are more familiar with the term diabetes mellitus as diabetes.[2] A person is said to have diabetes if the blood glucose level exceeds 200 mg / dl and the person's fasting blood sugar level is greater than 126 mg / dl.[3] In addition, diagnosis of diabetes mellitus can be done by oral glucose tolerance tests. Diabetes mellitus can generally be classified into two types, namely diabetes mellitus type 1 and diabetes mellitus type 2. Diabetes type 1 is diabetes that occurs due to damage the beta cells in the pancreas while diabetes type 2 is diabetes due to insulin resistance.[4] In patients with insulin resistance, the hormone insulin can't work properly so that blood sugar cannot be converted into glycogen. As a result there is a buildup of blood sugar in the blood so that it can cause type 2 of diabetes mellitus.[3] The most common complications of diabetes mellitus type 2 were microvascular complications (57%) followed by complications of diabetic neuropathy (45.6%) and diabetic retinopathy (20.7%), while cases of macrovascular complications were most often found in patients with type 2 of diabetes mellitus is diabetic foot (29.9%) followed by coronary heart disease (29.9%), and cerebrovascular disease (19.4%).[5] The severity of complications of Diabetes mellitus type 2 can be measured by performing kidney function tests. The prognosis of a complication of diabetes mellitus type 2 is said to get worse if the results of renal function tests show a drastic decrease in renal blood flow, glomerular filtration rate, and a drastic increase in urea nitrogen and creatinine levels.[6]

Over the years, diabetes mellitus remains a frightening specter for the countries in the world, including Indonesia. As much as 90% of diabetes mellitus cases in the world are cases of diabetes mellitus type 2.[3] As many as 80% of cases of diabetes mellitus type 2 occur in developing countries.[5] Data from the International Diabetes Federation (IDF) 2015 states that the number of people with diabetes in the world is approximately 415 million peoples and is expected to continue to increase in 2040 to around 642 million (55%).[7] In Indonesia, it is estimated that around 10 million people are positive of diabetes mellitus. This puts Indonesia in the seventh place in the country with the most diabetes sufferers in the world.[1]The prevalence of diabetes mellitus in Indonesia has also increased from 6.9% in 2013 to 8.5% in 2018.[5] Riskesdas in 2018 stated that the number of DM sufferers in Indonesian residents over 15 years of age was 8.5% or the equivalent of 14 million people. The number of DM cases in Indonesia is estimated continue to increase every year. WHO predicts that in 2030 the total population of Indonesia experiencing DM will be around 21.3 million people.[8]

Malondialdehyde or MDA is a marker of oxidative stress that results from in vivo lipid peroxidation reactions and causes tissue damage. Peripheral tissue damage is thought to be due to an increase in free radicals in the body.[9] Research conducted by Rini Kristia to determine blood serum MDA levels in the group with diabetes mellitus type 2 with the normal group, where the average MDA serum level in the diabetes mellitus type 2 group was higher than the normal group. So it can be concluded that there is an increase in serum MDA levels found in people with diabetes mellitus. Increased levels of MDA and enzyme antioxidant activity suggest that diabetics are exposed to oxidative stress through increased lipid peroxidation. The increase in MDA levels in people with diabetes mellitus type 2 was followed by an increase in superoxide dismutase (SOD) activities.[10] The price of diabetes mellitus treatment is not cheap. Based on the research by Rachmawati in 2012 on the analysis of the average total drug price for diabetes mellitus sufferers with complications of kidney problems in various classes of hospitalization at Semen Gresik Hospital during 2011, the average daily drug price was Rp. 1,248,099 (ICU), 1,116,550 (VVIP Class), Rp. 749,038 (Class I), Rp. 566,954 (Class II), Rp. 681,574 (Class III).[11] In addition, the analysis results of the calculation of the average cost of diabetes mellitus based on hospitalization and outpatient treatment at Yogyakarta City Hospital for the period January-June 2014, namely for inpatient Rp. 3,707,654 and Rp. 403,651 for outpatient care.[12]

In addition, diabetes drugs if taken for a certain period of time can cause side effects such as the metformin class, if it taken for a long time will cause anemia due to vitamin B12 deficiency, gastrointestinal disorders such as vomiting, nausea, and kidney damage due to increased creatinine levels in the kidneys.[13] There are about 20-30% of patients who take metformin drugs and experience gastrointestinal adverse effects and 1/ 30,000 patients experience side effects of lactic acidosis.[14] Sodium-glucose cotransporter inhibitor (SGLT2) drugs such as canagliflozin increase the risk of developing ketoacidosis and micosis. The use of insulin injection for a certain period of time can also cause allergies and lipohypertrophy.[13] Because of the side effects experienced by drug users, sometimes there are patients who decide to stop taking DM drugs because they cannot stand the side effects they experience. The percentage of people who decide not to continue treatment is 5%. As a result, their blood sugar becomes uncontrolled and various other complications of DM arise.[15] People are starting to look for alternative treatments that are relatively inexpensive, with properties not much different from synthetic drugs, and safe for long-term consumption. One of them is to use alternative herbal plants.[18] Broccoli (Brassica oleracea L. var italica) is one of the foods that is easily to found, in Indonesia especially Bedugul, Tabanan, Bali.[17] This vegetable contains many vitamins and minerals that are beneficial for the body. Broccoli is known to improve the body's immune system and fight free radicals.[18] Green broccoli is known to decrease MDA and increase SOD. There are no articles that discuss the effect of broccoli extract in reducing MDA levels in diabetes mellitus type 2. Therefore, the authors are interest to discussing literature review articles regarding the potential of broccoli extract on MDA levels in diabetes type 2.

II. METHODOLOGY

The study of literature review method comes from a variety of relevant literature, namely from literature reviews, research articles, and other studies in the last 10 years. The literature comes from both international and national journals which can be accessed at Garuda, PubMed, NCBI, and Google Scholar. In searching for suitable literature, the authors used the keywords broccoli, malondialdehyde, diabetes mellitus type 2, antioxidants, and free radicals. There are 35 articles relevant for this literature review article were used.

III. RESULT AND DISCUSSION

Diabetes Mellitus is a condition in which sufferers have high blood glucose levels because their bodies are unable to produce adequate amounts of insulin or it could be because their bodies are unable to respond the insulin[7]. The main symptoms of diabetes mellitus include polydipsia (excessive thirst), polyphagia (hunger and wanting to eat excessively),

and polyuria (excessive urination). Other complaints include tingling, body weakness, sudden drastic weight loss, itching, erectile dysfunction in men, pruritus vulva in women, and blurred vision.[19] The etiology of diabetes type 2 is still not fully disclosed although lifestyle factors influence the incidence of diabetes melitus type 2. Someone who has a pattern that is low in fiber and high in fat, obesity, or rarely exercise is more at risk of developing type 2 diabetes than others.[20] Diabetes mellitus type 2 is caused by a lack of insulin, where only relatively not absolute insulin deficiency occurs such as diabetes mellitus type 1. In diabetes mellitus type 2, the body is unable to produce enough insulin to meet its needs, this is characterized by a lack of beta cells or peripheral insulin deficiency.[21] The following is the pathogenesis of diabetes mellitus type 2 can be seen in Figure 1.

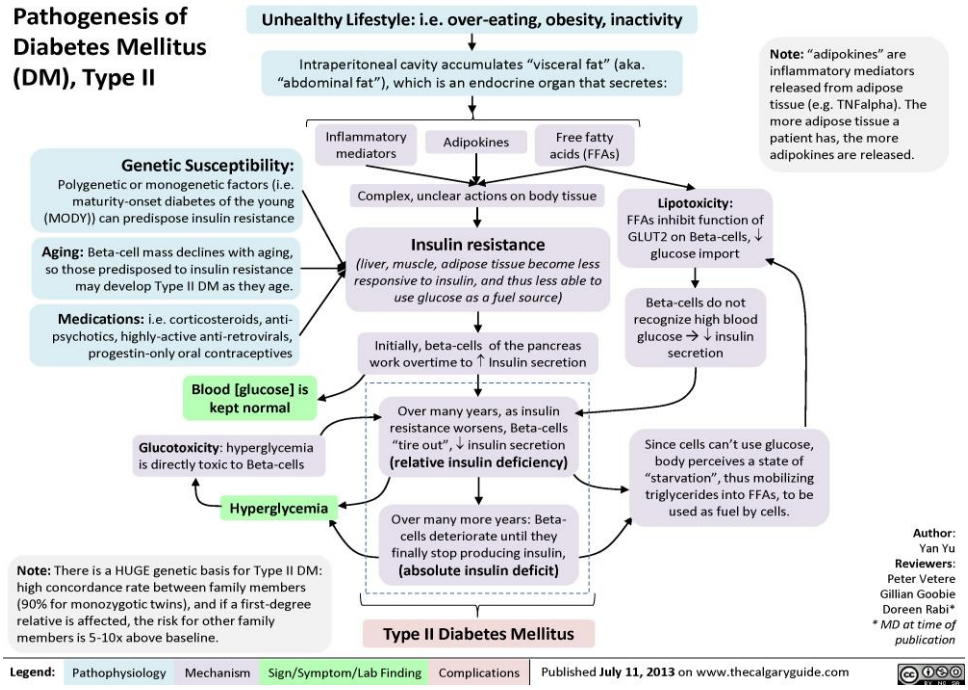

Figure 1: Pathogenesis of DM Type 2.[22]

Diabetes mellitus, both types I and II are characterized by hyperglycemia. Hyperglycemia in diabetes mellitus is involved in the formation of free radicals. Hyperglycemia causes autoxidation of glycation of proteins, glucose and activation of polyol metabolism which can accelerate the formation of reactive oxygen compounds and then increase modification of lipids, DNA, and proteins in various tissues. This results in an imbalance between protective antioxidants and the production of free radicals which eventually leads to oxidative damage or oxidative stress. Then it has a bad impact on the cell membrane which will occur a chain reaction called lipid peroxidation and in the end the fatty acid chain will be broken into various toxic compounds to cells, namely pentane, ethene and Malondialdehyde (MDA).[23] Free radicals are molecular components consisting of unpaired electrons. These unpaired electrons will become very reactive looking for their electronic partners by attacking and binding the electrons of the molecules around them. Its main target is the double bonds of fat found in the cell membrane. If the number of free radicals continues to increase while the number of endogenous antioxidants is constant, the excess free radicals cannot be neutralized and will cause damage and various other diseases, for example diabetes mellitus.[15]

Excessive amounts of free radicals will oxidize and attack the fat components of the cell membrane resulting in fat peroxidation.[25] Along with the increase in free radicals, the peroxidation of cell membrane fats also increases, while the levels of cellular antioxidants will decrease. Fat peroxidation will produce MDA, where an increase in levels of Malondialdehyde (MDA) indicates that there is an increase in fat peroxidation.[26] Malondialdehyde (MDA) is the best and most stable marker of oxidative stress and lipid peroxidation to date. MDA has helped explain the role of oxidation in several diseases which has been used widely in various fields as a clinical marker of lipid peroxidation, which can be found in almost all of the biological fluids. However, the most commonly used research samples are blood (plasma or serum) and urine.[9] Along with the increase in free radicals, the lipid peroxidation of cell membranes also increases which results in the final product in the form of Malondialdehyde (MDA). Based on previous studies, it was reported that superoxide dismutase (SOD) is the front line of defense against free radical compounds and tends to be high in chronic diseases and in diseases that are affected by free radical exposure.[27] The process of free radical lipid peroxidation can be

prevented by administering exogenous antioxidants. In addition, antioxidant compounds can also inhibit inflammatory triggers.[28] One of the natural exogenous antioxidants that has been studied has high antioxidant activity, namely broccoli (Brassica olaracea L. var italica). Flavonoids work as antioxidants by increasing SOD activity.[29] Flavonoids are able to inhibit the lipid peroxidation reaction process with their role as chain breaking antioxidants. The mechanism of action of flavonoids as antioxidants can be direct or indirect. Flavonoids inhibit the oxidation process through inhibiting the initiation and propagation of oxidation reactions from free radicals.[25]

Flavonoids are compounds found in plants and foods that can prevent free radicals and treat diseases such as cancer, antioxidants and inflammation. This is because flavonoids have the ability to methylate through free hydroxyl groups or C atoms which increase metabolic stability and increase membrane transport that occurs in the body.[29] Flavonoids indirectly, namely through several mechanisms in increasing the expression of endogenous antioxidant genes. One of the increasing antioxidant gene expression is through the activation of nuclear related factor 2 (Nrf2) so that the synthesis of endogenous antioxidant enzymes increases genes such as superoxide dismutase (SOD) and MDA genes.[30] Flavonoids are also able to inhibit the absorption of glucose in GLUT 2 compounds and reduce major transporter processes, thereby lowering blood glucose levels and preventing diabetes mellitus. Flavonoids can be found in fruits and vegetables.[3] One example is broccoli.[31] Broccoli is a seasonal plant known for its healthful properties. Broccoli comes from the Mediterranean region.[17] Indonesia is one of the most agrarian countries in the world. About 38% of Indonesia's population make a living as farmers. Many plants cultivated by farmers other than rice. One of them is broccoli (Brassica oleracea L. var. Italica Plenck). Broccoli became known in Indonesia in 1970. In Indonesia, the largest broccoli cultivation center is dominated by areas that are in the highlands with a cool climate such as in Brastagi, Lembang, Bedugul, and Malang.[17] Broccoli grows optimally in temperatures of 130C-200C and with cool humidity. Broccoli is a plant of the cabbage group, has a plant height of 60-90 cm with green stems, basalt-shaped leaves are grayish to greenish, and has thick green broccoli flower buds which are often used as food by human.[31] Broccoli is rich in minerals, vitamins and antioxidants. Raw broccoli contains vitamins A, B1, B2, B3, C, E and K. Broccoli is also contains high levels of folic acid, phosphorus, magnesium, iron, potassium, quercetin, beta carotene, fiber, polyphenols, flavonoids, and calcium. In 100 grams of broccoli, it contains 34 kcal, 188 mg of vitamin C and 64.9 mg of polyphenol antioxidant compounds. The broccoli plant image can be seen in Figure 2.[31]

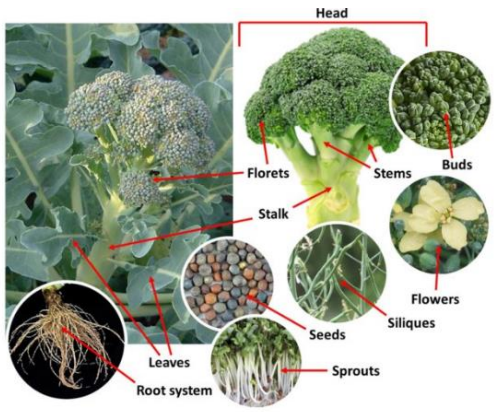

Figure 2: Broccoli Plants.[31]

The IC50 value is an inhibitory concentration value of 50, which indicates the ability of an extract to absorb 50% of the free radical compounds around it. A compound is called to have very strong antioxidants if the IC50 value is below 50 mg / L, strong if the IC50 value is in the 50-100 mg / L range, moderate if the IC50 value is in the 101-150 mg / L range, and weak when the value is IC50 is in the range 150-200 mg / L.[32] Broccoli's extract has an IC50 value of 41.87 mg / L so it is classified as a very strong antioxidant.[33] The antioxidant content in broccoli inhibits the initiation process thus preventing the formation of lipid radicals, preventing the propagation process so that free radicals will not react with PUFAs (through inhibition of oxidation reactions) and indirectly reduce MDA levels to prevent oxidative stress states.[25] The flavonoids in the broccoli's extract provide hydrogen atom donors from the hydroxyl group on the free electrons of the lipids during the initiation stage and the hydroperoxide radicals at the propagation stage so that these radicals become stable and are not toxic. Quercetin contained in broccoli also has the function of preventing the dangers of cell oxidation, lipids and free radical DNA so that it can reduce MDA levels.[29] In addition, the beta carotene content in broccoli is protective against damage to pancreatic β cells. β Carotene is thought to improve the ability of β cells to also trigger

insulisn synthesis and increase the transfer of glucose from blood to adipose and muscle tissue so that it can reduce MDA levels in the blood and also prevent worsening due to complications of DM.[34]

There are several studies have found that broccoli's extract can reduce MDA levels in vivo experimental experiments. One of them was a study conducted by Sielma and friends regarding the effect of administering broccoli ethanol extract at a dose of 250,500,1000 and 2000 mg / kgBB on the liver MDA levels of Wistar rats induced by DMBA in Jember, East Java. DMBA compound or better known as the chemical term 7,12-Dimethylz (a) anthracene is a prototype of PAH (Polycyclic Aromatic Hydrocarbons) which is often found in vehicle's smoke and cigarette's smoke pollutants. In this study, it was found that broccoli extract was proven to be able to provide hepatoprotective effects against DMBA. This hepatoprotective effect is characterized by a decrease of MDA levels in liver to a near normal control. The amount of dose given is directly proportional to the decrease hepatic MDA levels. In addition, the administration of broccoli extract to rats induced by CCI showed a significant decrease, one of which was the MDA level of rat liver tissue, broccoli ethanol extract which had a hepatoprotective effect on histopathological examination. Then the ethanol extract of broccoli with the maceration method has high levels of flavonoids, where quercetin and kaempferol are active substances in flavonoids.[29] Research conducted in 2018 in vivo on mice that were induced with diabetes by being given intraperitonial injection of 70 mg / kg of streptozotocin (STZ). Rats were being diabetic if 72 hours after the injection, the blood sugar of the rats was ≥ 300 mg / dL. The results of the study found that the antioxidants in broccoli extract at a dose of 1ml / mg can reduce levels of free radicals such as MDA, lipid peroxide, and nitric oxide. In addition, broccoli extract can also reduce blood sugar levels.[35]

Similar results were also shown by the research of Kartamiharja and friends in 2011. The research conducted by Kartamiharja et al. Was a study of the difference in the effect of giving organic and non-organic steamed broccoli on MDA levels of male wistar rats induced by alloxan monohydrate, where in the broccoli group organic steamed and steamed non-organic of broccoli is 2100 mg / day, this can reduce plasma MDA levels which are equivalent to the negative group which is a normal experimental animal. This shows that there is no significant difference, this is because the antioxidant components in it, namely flavonoids, vitamin E, vitamin C, β-carotene can reduce plasma MDA levels.[36] Another study found that vitamin C and vitamin E in broccoli extract can regenerate oxidized α-tocopherol and optimize antioxidant performance and protect further joint damage in mice induced with artitis.[37]

An in vivo study conducted by Firi and friends in 2019 found that broccoli extract at a dose of 120 mg / 200 grBB could reduce MDA levels in 36 male Wistar rats exposed to cigarette smoke. Cigarette smoke contains many toxic chemical compounds such as tar, CO, nicotine, lead (Pb), ammonia, acetone, and so on. The collection of toxic compounds will accumulate into free radicals and form oxidative stress and trigger the lipid peroxidation process which damages the surrounding tissue. Antioxidant compounds in broccoli's extract were able to reduce MDA levels from 7.87 nmol / ml in the control group which was only exposed to cigarette smoke to 4 nmol / ml in the group given 120 mg / 200 grBB broccoli extract with p value = 0.002. Comparison of MDA levels in the control group and the treatment group can be seen in Figure.[33]

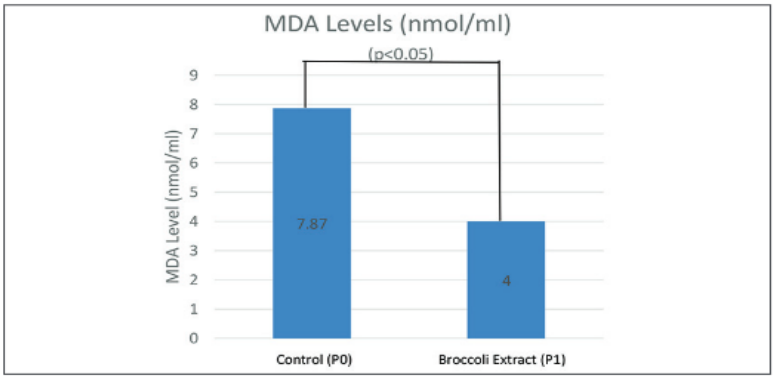

Figure 3: Comparison of MDA levels in the control group and the treatment group given broccoli extract.[33]

Information:

Control Group (P0) : Exposed to cigarette's smoke without being given intervention

Group P1 : Exposed to cigarette's smoke + given broccoli extract 120 mg / 200 gBB one hour before cigarette smoke exposure.

Antioxidants in broccoli such as flavonoids, quercetin, and kaempferol inhibit MDA oxidative stress through the Nrf2-ARE signaling pathway by donating hydrogen atoms to hydroxyl groups and binding metal ions. Antioxidants in broccoli also stimulate the performance of phase II detoxification enzymes, thereby increasing the levels of GST, GPX, which are glutathione levels and protecting cells from the effects of oxidative stress and neutralizing free radical compounds. The vitamin E, C, and beta carotene compounds in broccoli are also able to protect cells from oxidative stress damage and prevent endothelial cell dysfunction.[33]

IV. CONCLUSIONS AND SUGGESTIONS

Patients with diabetes mellitus type 2 can have their MDA levels lowered by broccoli extract (Brassica Oleracea L. Var italic). Further research is needed regarding broccoli extracts related to side effects, the dose of administration and the criteria for patients who can use this treatment method.

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