The Effect of Nutrition Support of Commercial Formula and FortemDia_Tri on Total Cholesterol Level and Blood Pressure in Type 2 Diabetes Mellitus Patients

Abstract—Most people with diabetes mellitus (DM) type 2 have increased lipid prevalence. An increase in cholesterol levels can reach 28% to 34%. High cholesterol levels accompanied by an increase in blood pressure in people with type-2 DM can increase the risk of cardiovascular disease. Proper nutritional support in the patient with type-2 DM is needed in controlling blood sugar along with controlling cholesterol levels and blood pressure. FortemDia_Tri is the development of a liquid dietary modification as nutritional support based on tempeh flour and mung beans as the main source of isoflavones and other ingredients such as skim milk flour, brown rice flour, canola oil, and maltodextrin, which are recommended for type-2 DM patients. Most commercial formulas do not contain isoflavones. The purpose of this research is to determine the effect of nutritional support for commercial formulas and FortemDia_Tri on reducing cholesterol levels and blood pressure in patients with type-2 DM. The sample of this study includes 33 patients with type-2 DM with the sample who neither takes insulin therapy nor consumes cholesterol-lowering drugs. Some samples were divided into 3 groups: control group (P1) given DM dietary education (n=11), P2 group given commercial formula (n = 11), and P3 group given the FortemDia_Tri (n=11). The dosage of commercial formula and FortemDia_Tri was 500 ml and 400 ml/day/person given 2 times/day, respectively. The intervention was done in 5 days. This study is analytical research with a randomized experimental study approach. The research design used is the pretest-posttest control-group design. The data of this research were analyzed with a one-way ANOVA test continued with the posthoc LSD test. After 5 days of treatment, there was a change in the level of total cholesterol of P2 group (-8.91 ± 23.17 mg/dl) with p = 0.231, and P3 group (-40.09 ± 25.04 mg/dl) with p = 0.000). Meanwhile, there was no change in the control group, and there was a significant difference between those groups (p = 0.001). P3 group has reduced more blood pressure than P1 and P2 groups, but the decrease was not different between the groups (p > 0.05). The FortemDia_Tri nutritional support can help reduce cholesterol levels and blood pressure in patients with type-2 DM. Further studies with longer duration and more sample sizes are needed.

Keywords——FortemDia_Tri, Cholesterol, Blood Pressure, Diabetes Mellitus Type 2

I. INTRODUCTION

Diabetes mellitus (DM) is one major health problem and is a serious threat to humans in the world. Indonesia ranked sixth in the world after China, India, U.S., Brazil, and Mexico with 10.3 million people with DM aged 20-79 years, and this number is expected to continue to increase to 16.7 million by 2045 [1]. Type-2 DM is the type of diabetes that has the highest prevalence and continues to increase worldwide [2].

Most people with type-2 DM have an increased lipid prevalence and an increased cholesterol reaching 28% to 34% [3]. High carbohydrate metabolism in patients with diabetes can increase the synthesis of fatty acids in the liver which can increase the change of fat into cholesterol [4]. Increased cholesterol levels are closely related with the severity of atherosclerosis or the emergence of fat in the blood vessels, which is one of the factors in the occurrence of heart and cardiovascular diseases [5]. In addition to an increase in lipid profile, hyperglycemia can damage cells that are unable to reduce glucose transport, which causes non-hyperglycemic diseases such as hypertension and increases the risk of cardiovascular diseases which can lead to death [6].

The American and International Societies of Hypertension recommended a blood pressure target of <140/90 mmHg in patients with DM in 2014. This is in line with the target treatment in type-2 DM patients with hypertension without the cardiovascular disease or risk [7]. There are 39% of patients diagnosed with type-2 DM accompanied by hypertension [8]. Based on the American Diabetes Association (ADA) in 2017, two out of 3 people with DM have high blood pressure [9]. Giving insulin and increasing body weight in diabetic patients causes a hypertensive response thereby increasing blood vessel stiffness, which results in a reduction in arterial distensibility, which is likely to contribute to an increase in systolic blood pressure [10]. Evidence shows that controlled hypertension in diabetic patients can prevent macrovascular complications.
The development of nephropathy and retinopathy can be slowed down by early treatment [8].

The International Macronutrients and Blood Pressure (INTERMAP) study and several other studies show that protein intake, especially vegetable protein and blood pressure, is negatively correlated [11]. Consumption of soy protein and isoflavones can improve vascular function and are cardioprotective [12]. This is due to the ability of isoflavones found in soybeans (genistein, daidzein, and glycitein) that act as estrogen imitators or selective estrogen receptor modulators [13]. Isoflavones also play a positive role in reducing cholesterol levels [14]. Isoflavones are mostly found in soybeans and their processed products [12]. Soy tempeh is a processed soy product as a source of vegetable protein that is easily digested, contains isoflavones, has high fiber, and a low glycemic index [15].

Diet modification combined with pharmacological intervention can be the main approach in controlling DM [16]. If the intake of food in patients with type-2 DM is insufficient, they can be given nutritional support in the form of liquid formula [17]. Nutritional support for DM patients must be given specifically.

Special DM formula generally has a relative high price so that it can increase its maintenance costs. FortemDia_Tri is a processed food specially formulated for diabetic patients that can be used as a meal replacement or liquid food supplement. FortemDia_Tri is based on tempeh flour and mung beans as the main source of isoflavones needed by patients with type-2 DM and is added with other ingredients. FortemDia_Tri is made based on the needs and intake per day of diabetic patients. Made from ingredients recommended for patients with type-2 DM, Dia_Tri is expected to be used as an alternative to nutritional fulfillment and have a positive effect on DM patients. This study aims to determine the effect of nutritional support of commercial formula, FortemDia_Tri on cholesterol level and blood pressure of diabetes mellitus patients in type2.

II. Method

This study is an experiment with a pretest-posttest control-group design conducted in January-February 2020. The population included outpatients with type-2 DM status without severe complications in Landak Public Hospital, West Kalimantan Province in Indonesia. The inclusion criteria are taking anti-diabetic drugs, not using insulin therapy, age >18 years and allowed to consume food orally. The exclusion criteria are ever or being diagnosed with other diseases that can affect the results of this study such as coronary heart, kidney failure, hepatic cirrhosis, stroke, and cancer, and having the previous history of hypoglycemia, hematemesis melena, and allergy or intolerance to soybeans and mungbeans.

The sample size was determined using Murti’s formula (2016) of at least 10 people per group [18]. The subjects were selected by consecutive sampling until a minimum number was met. The subjects were randomized into groups. The subjects of this research were divided into 3 groups: 11 people who were in positive control groups (P1) and they were given DM diet education, 11 people who categorized in treatment groups and they were given commercial formula namely diabetosal (P1), and 11 people who were categorized in treatment groups and they were given FortemDia_Tri (P2). The doses of commercial formulas and FortemDia_Tri were 500 ml and 400 ml / day / person, respectively for morning and eveningsnacks.

FortemDia_Tri is a processed food specially formulated for diabetic patients that can be used as a meal replacement or liquid food supplement. In addition to mung bean and tempeh flour as a source of isoflavones, FortemDia_Tri contains other ingredients recommended for people with type-2 DM such as skim milk flour, brown rice flour, canola oil, and maltodextrin. It is hoped that FortemDia_Tri can be used as an alternative for meeting nutrition and have a positive effect on patients with type-2 DM.

The instruments in this study include anthropometric devices (digital scale, microtoise, LILA and tape), questionnaires, 24-hour food recall forms, informed consent sheets, and educational leaflets. The cholesterol levels were assessed using a chemistry analyzer with the enzymatic colorimetric assay method (GPO-PAP). Blood samples were taken from the veins of the arm twice, before and after intervention, while blood pressure was measured using a digital blood pressure meter. Cholesterol levels were measured at the Landak Public Hospital in West Kalimantan.

The data were analyzed using the SPSS version 20 program. Normality test was conducted to see whether the data were normally distributed by looking at the results of Shapiro Wilk. The statistical analysis was performed using the Paired T-test to see the mean difference in cholesterol and blood pressure if the data were normally distributed. If the data were not normally distributed, the Wilcoxon test was used. The statistical test result is significantly different if p<0.05. The differences in effect after intervention from those three groups were analyzed using One Way ANOVA parametric statistical test and continued with the Post Hoc LSDtest.

All methods in this study were approved by the health research ethics commission of Dr. Moewardi Public Hospital based on the letter of ethics commission with protocol no. 1.395/XII/HREC/2019. All procedures followed were in accordance with the ethical standards of the health research ethics commission of Dr. Moewardi Public Hospital. Moreover, prior to screening and intervention, all subjects had already signed an informedconsent.

III. Result

The characteristics of the subjects in this study include gender, age, profession and education, which can be seen in Table 1 below.

Based on Table 1, there are more female than male subjects. The most age range is the age group of 46-55 years. Regarding to age, this is in line with previous studies which states that age ≥ 45 years have higher opportunity to suffer from type 2 of diabetes than people aged <45 years old [19]. As we get older, the ability of tissues to absorb glucose in the blood decreases [20]. The most profession in the control group is housewife and in the treatment group is civil servant with the most educational status of tertiary institutions. p value >0.05 on each characteristic indicates that gender, age, education, profession of both groups are homogeneous and/or there are no significant differences.
In Table 2, changes in cholesterol levels were apparent after 5 days of treatment. Based on the table above, it can be seen that there was no change in cholesterol level at post-intervention in control group, while in the commercial formula group and FortemDia_Tri, it showed that the total cholesterol level decreased. A statistically significant decrease in cholesterol level was found in the FortemDia_Tri group through the results of paired t-test (p = 0.000), while in the commercial formula group showed that the reduction was not statistically significant (p> 0.05). Based on the One Way Anova test between groups, it showed significant differences between groups (p<0.05).

After getting the results of pre and post intervention, to see how much the effect of treatment on total cholesterol level, the difference value was continued to be analyzed with the Post Hoc test analysis which can be seen in Table 3 below.

The results of Post Hoc test in Table 3 above showed significant differences in the reduction of total cholesterol level between the control group, FortemDia_Tri and the commercial formula group with FortemDia_Tri because they have a significance value of p<0.05.

**TABLE I. THE CHARACTERISTICS OF THE SUBJECTS OF RESEARCH**

| Characteristics of Subjects | P1 | P2 | P3 | P |
|-----------------------------|----|----|----|---|
| Sex                         |    |    |    |   |
| Male                        | 4  | 1  | 30.0| 30.0| 0.066|
| Female                      | 1  | 4  | 36.8| 36.8| 1.000|
| Age                         |    |    |    |   |
| 36-45 years old             | 2  | 26.6| 26.6| 42.9| 0.414|
| 46-55 years old             | 4  | 26.7| 26.7| 46.7| 0.010|
| >55 years old               | 1  | 100 | 0.0 | 0.0 | 0.010|
| Education                   |    |    |    |   |
| No school                   | 1  | 0  | 50.0| 50.0| 1.000|
| Didn't finish elementary school | 2 | 50.0| 25.0| 25.0| 1.000|
| Elementary School           | 1  | 20.0| 0.0 | 20.0| 0.654|
| Junior High School          | 3  | 50.0| 33.3| 16.7| 1.000|
| Senior High School          | 1  | 12.5| 50.0| 37.5| 1.000|
| Profession                  |    |    |    |   |
| Housewife                   | 6  | 42.9| 35.7| 22.8| 0.000|
| Civil servant               | 2  | 25.0| 12.5| 62.5| 0.000|
| Private                     | 2  | 50.0| 50.0| 0.0 | 0.000|
| Entrepreneur                | 1  | 33.3| 0.0 | 66.7| 0.180|
| Farmer                      | 0  | 0.0 | 100.0| 0.0 | 0.000|
| Labour                      | 0  | 0.0 | 0.0 | 100.0| 0.000|
| Staff of A state-owned enterprise | 0 | 0.0 | 100.0| 0.0 | 0.000|

Note: P1 = positive control group which was given DM diet education; P2 = treatment group which was given 2 times of commercial formula (500ml / day); P3 = treatment group that was given education in DM diet and FortemDia_Tri groups (400ml / day) for 5 days.

**TABLE II. THE EFFECTS OF COMMERCIAL FORMULA AND FORTEMDIA_TRI ON THE TOTAL CHOLESTEROL LEVEL IN TYPE-2 DM.**

| Types of Groups | n | Before | After | ΔMean | ΔMean (mg/dL) | p |
|-----------------|---|--------|-------|-------|--------------|---|
| Control         | 11 | 214.63 ± 31.87 | 209.75 ± 37.35 | -4.88 | -0.21|0.91|
| Commercial Formula | 11 | 214.63 ± 31.87 | 209.75 ± 37.35 | -4.88 | -0.21|0.91|
| FortemDia_Tri   | 11 | 214.63 ± 31.87 | 199.64 ± 11.79 | -15.99 | -0.69|0.000|

IV. DISCUSSION

Diabetes mellitus patients with obesity, especially central obesity, can be associated with the incidence of dysmetabolic syndromes (dyslipidemia, hyperglycemia, and hypertension) due to insulin resistance [7]. High carbohydrate metabolism in diabetic patients can increase the synthesis of fatty acids in the liver which can increase changes in fat to cholesterol [4]. Increased cholesterol levels in patients with type-2 diabetes can reach 28% to 34% [3]. The change in glucose to fatty acids increases due to glucose deficiency in cells. Insulin will inhibit the hormone lipase in adipose tissue which will cause free fatty acid levels to increase [21]. Increased chylomicrons and plasma Free Fatty Acid (FFA) can occur in uncontrolled type-2 DM. This increase is mainly due to a decrease in the transport of chylomicrons into the fat depot. Decreased lipoprotein lipase (LPL) activity also plays a role in decreasing this transport. An increase in total cholesterol levels is caused by an increase in VLDL by the liver or expenditure of VLDL and LDL from the circulation [21,22].

The average of total cholesterol of the commercial formula group and FortemDia_Tri is in the slightly high / borderline category (200-239 mg / dL). It is based on the classification of plasma lipid level in PB PERKENI (2019)[7]. The mean of total cholesterol level of each group was 214.63 mg / dL ± 31.07 and 239.73 mg / dL ± 37.42. Most people with type 2 diabetes have an increase in lipid profile, an increase in cholesterol level which can reach 28-34%[3].The total cholesterol level of the control group was 190.27 mg / dL ± 35.13 which was in the category needed, namely (<200) (Table 2). High carbohydrate metabolism in DM patients can increase the synthesis of fatty acid in the liver and can increase fat change into cholesterol [4].

Providing additional nutritional support both in term of commercial formula and FortemDia_Tri to type 2 DM patients can reduce total cholesterol level compared to the control group (Table 2). This is because both of these formulas contain high fiber. This is in line with the research of Bintanah & Handasari (2012) which states that there is a relationship between fiber intake and cholesterol p = 0.002 [23]. The lower the fiber intake the higher the total intervention. The highest decrease was found in the group which given FortemDia_Tri which as much as -10.55mmHg for systolic blood pressure and -6.36mmHg for diastolic blood pressure. Some changes before and after the FortemDia_Tri group were statistically significant (p<0.05). However, based on One Way Anova test between groups, there was no significant difference (p>0.05).
cholesterol level. High fiber foods can influence the transit time in the gastrointestinal by slowing down the rate of emptying of the stomach so that it reduces carbohydrate absorption and increases fermentation of short chain fatty acid [24]. Fiber in the large intestine can be fermented by colon bacteria and can produce short chain fatty acid which can inhibit the mobilization of fatty acid and reduce gluconeogenesis. This will affect the use of glucose by the liver[25].

Cholesterol level in the FortemDia_Tri group were seen more decreased as much as $-40.09 \pm 25.04$ mg / dL ($P = 0.000$) if it is compared with the commercial formula group which only decreased $-8.91$ mm / dL ($P = 0.231$). It was because the influence of tempeh found in FortemDia_Tri. Tempe is used in making FortemDia_Tri because during the fermentation process of making tempe, the protein of Tempe faced hydrolysis into simpler molecules[26] and increases the digestibility of its protein[27]. The findings of Huang et al (2018) suggest that soybean tempeh which fermented by Lactobacillus plantarum and Rhizopusoligosporus is potential to prevent the development of DM because it improves hyperglycemia, hyperlipidemia, and hyperinsulinemia by changing the distribution of bacteria in the intestine[28]. In addition, tempeh itself through the fermentation process increases the degree of unsaturation of fat so that the unsaturated fatty acid in tempeh increases and has the effect in reducing serum cholesterol[29].

The dissimilarity of difference in total cholesterol level between the control group and FortemDia_Tri was statistically significant ($p = 0.001$), as were between the commercial formula group and FortemDia Tri ($p = 0.005$) (Table 3). It shows that the decrease in total cholesterol in the FortemDia-Tri group was better than the control group and commercial formula. Isoflavones play a positive role in reducing cholesterol level[14].

The use of functional food, in this case FortemDia_Tri, is one of the steps of medical nutritional therapy that can increase effectiveness in the management of diets in type-2 DM. Diet modification combined with pharmacological intervention can be the main approach in controlling type-2 DM [16]. Until now, pharmacological interventions of statins have been the first-line medication to reduce cholesterol because they are atherogenic [30]. Statin-type drugs are one of the most-widely-used class of drugs to reduce LDL in the blood by the mechanism of inhibition of enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA-reductase) [31].

Besides increasing cholesterol, the condition of hyperglycemia can damage cells that are not able to reduce glucose transport, which causes non-hyperglycemic diseases such as hypertension [6]. Uncontrolled blood sugar levels in the body can cause various kinds of complications in patients with type-2 diabetes, one of which, that often occurs, is macroangiopathy, which is a complication of large blood vessels that affects changes in blood pressure [32]. The mean systolic blood pressure in the two study groups (Table 4) showed more than 135 mmHg. Blood pressure $\geq 130/85$ mmHg is one of the criteria for metabolic syndrome according to the International Diabetes Federation (IDF) [33]. However, the mean systolic blood pressure and diastolic pre- test in both study groups were in accordance with recommendations from PERKENI (2019) and American and International Societies of Hypertension (2014), which stated a target blood pressure <140/90 mmHg in patients with DM.

Blood pressure becomes a marker that needs to be controlled for DM patients because hypertension is one of the contributors that increases cardiovascular risk for DM[34,35]. Providing education to the subjects of this research before treatment showed a decrease in blood pressure. The decrease occurred in each group after 5 days of treatment both systolic and diastolic blood pressure (Table 4). The group that was supported by FortemDia_Tri reduced the systolic blood pressure by -10.55 mmHg and diastolic - 6.36 mmHg and had a significant effect based on the results of the Wilcoxon test analysis with $p = 0.036$. The control group and commercial formula also experienced a decrease in systolic and diastolic blood pressure but were not statistically significant ($p > 0.05$). Providing additional nutritional support for FortemDia_Tri has been proven to reduce more blood pressure than the control group and commercial formulas. It is because the FortemDia_Tri contains isoflavones which derived from tempe flour and green beans. Welty et al. (2011) found that soy supplementation for hypertensive and non-hypertensive women can significantly reduce systolic and diastolic blood pressure[36]. A research of Dong et al (2011) states that providing supplement with soy isoﬂavones can improve systolic blood and diastolic blood pressure, but the total of its influence depends on the early blood pressure of the participants and the type of control done[37].

Isoflavones can improve vascular function and they are cardioprotective [12]. Isoflavones can prevent the appearance of atherosclerosis which causes hypertension by influencing lipid concentration in blood plasma, acting as an antioxidant, preventing smooth muscle cells from proliferating and migrating, preventing the formation of thrombus (blood clotting in blood vessels) and maintaining normal vascular reactivity. Besides tempeh is a processed soy product which made by fermentation and produces protein peptides, it can inhibit ACE (Angiotensin Converting Enzyme) which has function to prevent hypertension[38]. Inhibition of ACE by bioactive peptides which leads to widening of the arterial wall or vasodilation and continued to reduce blood pressure[39]. Sanjuka and Rai (2016) in their article mentioned that bioactive peptides from soybeans and fermented soybeans have function as antioxidants and ACE-inhibitors and act as antihypertensive agents, and can also become antimicrobial and antidiabetic[40].

The difference in the reduction of systolic and diastolic blood pressure in those three groups was not significant between groups through One Way Anova test ($p > 0.05$), so that further research is needed regarding the dose and duration of FortemDia_Tri administration to improve blood pressure in DM patients to avoid complications. Some evidences of previous research has showed that controlled hypertension in diabetic patients can prevent macrovascular complication, nephropathy development and retinopathy which slowed down by treatment as early as possible[8].
V. CONCLUSION

It can be summed up that the administration of the nutritional support FortemDia_Tri 400 ml/day for 5 days can reduce cholesterol levels and blood pressure in patients with type-2 DM. Future studies are needed by comparing the dose and duration of the FortemDia_Tri intervention to variables related to the target of controlling DM.

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REFERENCES

[1] International Diabetes Federation, “IFD Diabetes Atlas Eight Edition. International Diabetes Federation.” 2017. doi:http://dx.doi.org/10.1016/S0140-6736(16)31679-8.

[2] S. Basu, P. Yoffe, N. Hills and H. L Lustig. “The Relationship of Sugar to Population-Level Diabetes Prevalence: An Ecometric Analysis” of Repeated Cross-Sectional Data”. PLoS One 8 (2). 2013:1–8.

[3] MJ Franz and M. Evert. “Medical Nutrition Therapy for Diabetes Mellitus and Hypoglycemia of Nondiabetic Origin” . pp.586-618, in Mahan, L.K, and Raymond, J.

[4] L. (edt), Krause’s Food and The Nutrition Care Process, Fourthteenth Edition, Elsevier, St. Louis, Missouri. 2017.

[5] S. E Khan, R. L. Hull and K. MUzschmeider. “Mechanisms Linking Obesity to Type 2 Diabetes”. A Nature Research Journal. 2016. 444:840-846.

[6] S.A Pheobe, A.G Goodwill, M. E James, Robert. “Disfunction: International Strategies”. Journal of Inflammation. 2010:7:54.

[7] J. S Skylar, G. L Bakris, E. Bonifacio, T. Darsow, R. H Eckel, L. Groop, et al. “Differentiation of diabetes by pathophysiology, natural history, and prognosis”. Diabetes. 2017. Vol. 66. Feb.241–255.

[8] PERKENI. “Guidelines Programming and Prevention of Adult Type 2 Diabetes Mellitus in Indonesia 2019”. PBI PERKENI. 2019. Jakarta.

[9] I. Laffin Luke and L. Bakris George. “Update on Blood Pressure Goals in Diabetes Mellitus”.CurrCardiol Rep (2015) 17:37 ; 1 DOI10.1007/s11886-015-0591-y.

[10] L.H.deBoer, S.Bangalore, A.Beneto, A.M.Davis, G. C Arthur and J. E Hall. “Textbook of Medical Physiology 11th Edition”. Philadelphia : Elsvier Saunders. 2016.

[11] S. Jonsten, Muthmainnah, Hardjoeno. Lipid Profile for Type 2 Diabetes Mellitus Patients. Indonesian Journal of Clinical Pathology 2013;37(5):319–236.

[12] J. F. Fedacko, R. B. Singh, S. Chaithiraphan, V. Vargova, M. J. Franz and M. Evert. “Medical Nutrition Therapy for Diabetes Mellitus and Hypoglycemia of Nondiabetic Origin”. pp.586-618, in Mahan, L.K, and Raymond, J.

[13] J. A. Kristiansingh, A. Kartini. “Relationships of Isoflavon Intake with a Event of Metabolic Syndrome on Menopause Women”. Journal of Nutrition College. Vol 3. No 4. 2014, pp903-910.

[14] A. Krishnawati, “Soybean as a Functional Food Source”. Food Crop Science and Technology”, vol. 12 no. 1, pp. 57-56,2017.

[15] N. Hamidah, Riyanto and ET Test. “Sensory Quality, Pore Size, Glycemic Index, and Glycemic Loads of Bread Substitution of Cassava Flour (ManihotEsculenta) and Tempe Flour”. Indonesian Nutrition Media. 2019. 14(2):154-163.

[16] A. S. Sanz-Paris, H.J. Alvarez, M.D. Ballesteros-Pomar, “Evidence-Based Recommendations and Expert Consensus on Enteral Nutrition in The Adult Patient with Diabetes Mellitus or Hyperglycemia”. Nutrition. 2017. 41:58–67.

[17] B. Murti. “Principal and Methods of Epidemiological Study 4th Edition”. Master’s Program in Public Health. Surakarta: Graduate Nutrition Media. 2019. 14(2) :154-163.

[18] C. Mensing. “The Art and Science of Diabetes Self-Management Education”. American Association of Diabetes Educators.2015.

[19] A. P. Madara, R.P. J. Kalaitzakis, G.M. Kritikos, P. G. Stavridis, Diabetic Complications. "Epidemiological Risk Factors of type 2 diabetes mellitus and hypertriglyceridemia". Nutrition. 2017. 41:58–67.

[20] S. Jonsten, Muthmainnah, Hardjoeno. Lipid Profile for Type 2 Diabetes Mellitus Patients. Indonesian Journal of Clinical Pathology 2013;37(5):319–236.

[21] T. M. Palimbunga, B.T. Ratag, W.P.P. Kauwung, “Faktor-Faktor Yang BerhubunganDenganKejadian Diabetes MellitusType 2 Di RSU GminPancaKarish Manado”. E-Journal Keperawatan. 2016. 43(2) :1–11.

[22] I. P. Suryaoko. Penyakit Degeneratif. Yogyakarta: Nuha Medika. 2012.

[23] M. Yulistianingsih, A. Kartini. “Relationships of Isoflavon Intake with a Event of Metabolic Syndrome on Menopause Women”. Journal of Nutrition College. Vol 3. No 4. 2014, pp903-910.

[24] S. E Khan, R. L. Hull and K. MUzschmeider. “Mechanisms Linking Obesity to Type 2 Diabetes”. A Nature Research Journal. 2016. 444:840-846.

[25] S.A Pheobe, A.G Goodwill, M. E James, Robert. “Disfunction: International Strategies”. Journal of Inflammation. 2010:7:54.

[26] J. S Skylar, G. L Bakris, E. Bonifacio, T. Darsow, R. H Eckel, L. Groop, et al. “Differentiation of diabetes by pathophysiology, natural history, and prognosis”. Diabetes. 2017. Vol. 66. Feb.241–255.

[27] L.H.deBoer, S.Bangalore, A.Beneto, A.M.Davis, G. C Arthur and J. E Hall. “Textbook of Medical Physiology 11th Edition”. Philadelphia : Elsvier Saunders. 2016.
[41] N. Triandita & N.E. Putri. “Peranan Kedelai dalam Mengendalikan Penyakit Degeneratif”. Teknologi Pengolahan Pertanian. 2019. 1(1):6-17.

[42] R. Norris R and R.J. FitzGerald. “Bioactive Food Peptides in Health and Disease: Antihypertensive Peptides from Food Proteins”. Intech.Croatia.2013.

[43] S. Sanjukta S & A.K. Rai. 2016. Production of Bioactive Peptides During Soybean Fermentation and Their Potential Health Benefits. Trends in Food Science & Technology. 2016.50 :1-10.