The influence of black cumin seed oil therapy with dosage of 1.5 mL/day and 3 mL/day to interleukin21 (IL-21) expression of the patients with metabolic syndrome risk

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The influence of black cumin seed oil therapy with dosage of 1.5 mL/day and 3 mL/day to interleukin-21 (IL-21) expression of the patients with metabolic syndrome risk

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Abstrak. Metabolic syndrome (MS) is a metabolic disorder caused by obesity and insulin resistance. In the state of obesity and insulin resistance occurs increased fat metabolism that causes production reactive oxygen species (ROS) and oxidative stress that makes dysregulation of adipose tissue that decreases antioxidant enzymes and immune system disorders. In diabetes mellitus there is pancreatic β cell damage caused by pro-inflammatory cytokines i.e interleukin-21 (IL-21). Black cumin seed oil (BCSO) contains antioxidants and immunomodulators but has not seen how it affects to IL-21. This study used cross over design to determine the effect of BCSO with dose of 1.5 mL/day and 3 mL/day dose of IL-21 in MS patients. The total subjects 66 of MS patients were divided into 2 groups. Group I was administered 1.5 mL/day and 3 mL/day of BCSO in dosage for 20 days and continued with washing out (BCSO discontinued) for 7 days. On the day 28, group I administrated 3 mL/day of BCSO and group II were given 1.5 mL/day of BCSO during 20 days. Statistical analysis showed that mean value expression of IL-21 were given by BCSO at dose 1.5 mL/day was 5.06±5.48 and BCSO at dose 3 mL/day 4.66±3.63 ($p<0.05$). The result showed that IL-21 expression in patient at risk of MS who received BCSO dose 3 mL/day were lower than those received adose of 1.5 mL/day for 20 days.

Keywords: black cumin seed oil, interleukin-21, metabolic syndrome risk

Introduction

Metabolic syndrome (MS) is a set of abnormalities involving various physiological, biochemical, clinical and metabolic factors that can lead to the development of cardiovascular disease and diabetes mellitus and all-cause mortality risk [1]. Some of the risks causing MS include lifestyle (diet, smoking, physical activity), genetics and socioeconomics [2]. MS in Indonesia is one of the main public health problems such as diabetes mellitus, central obesity, dyslipidemia, and hypertension, which is a component of MS and has an effect on the prevalence of metabolic syndrome. MS case rate in Indonesia reached 23% i.e 26.6% in women and 18.3% in men of productive age, this data is based on the result of basic health research [3].

The pathophysiology of metabolic syndrome is not known for certain, but some literature say that the primary reason is a person's obesity state. Excess fat in the body causes increased fat metabolism

along with reactive oxygen species (ROS) production as well as increased oxidative stress characterized by a balance disorder of oxidation reduction reactions and decreased antioxidant enzymes in both adipose and tissue cells, this situation occurs in hypertension and atherosclerosis [4].

In addition, fat cell enlargement will secrete metabolic products such as pro-inflammatory cytokines, procoagulants, inflammatory peptides and angiotensinogen [5]. Insulin resistance affects type 2 of diabetes and hyperglycemia. A person with diabetes, oxidative stress will inhibit the taking of glucose in muscle cells and fat cells and decrease insulin secretion by pancreatic β cells (type 2 diabetes). This is due to autoimmune disorders mediated by lymphocytes T and activated dendric cells involving inflammatory pathways Thelper1 (Th1), Thelper2 (Th2) and Thelper17 (Th17) and inhibition of T regulators. It is found that the Th17 pathway is involved in the inflammatory process and damage to pancreatic beta cells regulated by interleukin-21, interleukin-23 and interleukin-27. Interleukin-21 is a type 1 of cytokine [6, 7].

BSCO contains antioxidant and immunomodulatory substances which can be used as antidiabetes mellitus [8]. The main content of BSCO is essential oils such as timokuinon that have an effect on the immune system through inhibition of translocation of NF-kB into the nucleus so as to decrease pro-inflammatory cytokines, chemokines, adhesion factors and coagulation factors[8]. In addition, it is known that BSCO can decrease the oxidative stress condition that triggers the synthesis of pro-inflammatory cytokines through adhesion molecules. Interleukin-21 is a pro-inflammatory cytokine that plays a role in pancreatic B cell damage [26] it is not yet known how the effect of BSCO with a dose of 1.5 mL/day and 3 mL/day for 20 days in patients with metabolic syndrome risk.

2. Materials and Methods

This study used cross over design with a total of 66 patients with metabolic syndrome who state willing to follow the study by agreeing inform consent. The inclusion criteria were obesity, blood pressure ≥140/90 mmHg, triglyseride level ≥150 mg/dL or using the drug of methabolic syndrom and 18-70 years old. Exclusion criteria werepregnant and lactating women, tuberculosis and be trought immun disease. But during the course of the study there were 4 patients who were excluded due to side effects such as nausea, vomiting, gastritis, increased blood pressure and decreased kidney function. This research was conducted at Jetis I Public Health Centers, Bantul Regency, Yogyakarta in August 2016 until March 2017. This clinical trial protocol has been reviewed and approved by health research ethics committee of Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta with approval number 279/EP-FKIK-UMY/VIII/2016.

Blood steering patients were taken from vena cubity by analysts in laboratory of the Jetis I Public Health Centers, Bantul Regency, Yogyakarta. Procedures undertaken in the implementation have been reviewed by research ethics committee of Universitas Muhammadiyah Yogyakarta. Blood that has been accommodated in a vacutainer containing anticoagulants is taken to the pharmacology laboratory of Universitas Gadjah Mada (UGM) and ready to be examined with flow cytometer. Here is the scheme of research implementation:

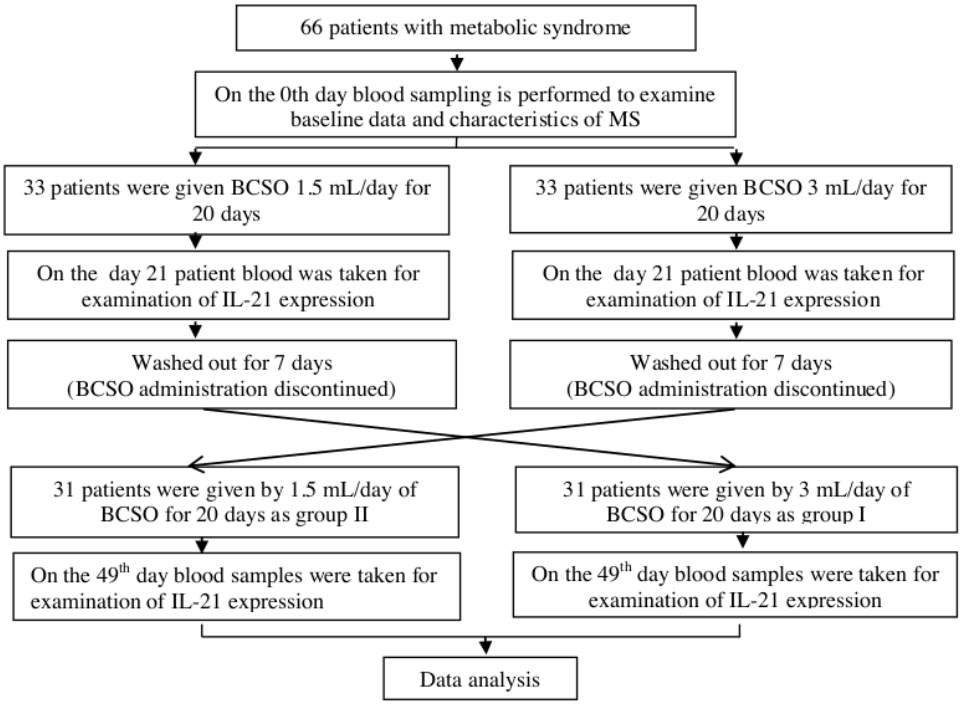

Figure 1. Schematic of research design

3. Results and Discussion

3.1.The characteristics data of patients at risk of metabolic syndrome at Jetis I Public Health Centers, Bantul Regency in 2016

From the previous studies, demographic data and characteristic data of metabolic syndrome as primary outcome and percentage of IL-21 expression as outcome secunder. From the data, statistical test using Chy-Square test and paired T-test sample with 95% confidence level.

This research is conducted at Jetis 1 Public Health Centers, Bantul Regency, Yogyakarta in August 2016 - March 2017. The involved doctors in getting patients who will be joined in the research and obtained a total of 66 patients at risk of metabolic syndrome who have met the inclusion and exclusion criteria. However, during the study there were 4 patients who drop out because they complain the side effects such as nausea, vomiting, gastritis, increased blood pressure and decreased kidney function. The total subjects who followed the study to the end were 62 patients at risk of metabolic syndrome.

Table 1 shows the characteristics of patients at risk of metabolic syndrome. Based on gender, it is known that the metabolic syndrome was mostly suffered by women (78.80%) compared to men (21.20%). Metabolic syndrome was also more prevalent in the age group 51-60 years (42.40%), married status (98.50%), high school education (78.[illegible]%) and employment status (57.60). This result is in line with research conducted before [9] which reported that there was a significant relationship among gender, age, and work with the incidence of metabolic syndrome. Metabolic syndrome is more risky in women than in men. In women there is an excessive accumulation of fat in the adipose tissue that causes hypertriglyceride. Metabolic syndrome in women is also caused by diet, genetics and lack of physical activity than men [9, 10]. Women are more at risk of developing diabetes mellitus due to body mass index (BMI) that is more easily increased and the distribution of body fat easily accumulated due to hormonal processes in the body [11].

Table 1. The characteristics data of patients at risk of metabolic syndrome at Jetis I Public Health Centers in 2016

Characteristics of patients	n=66	Percentage (%)
Gender		
Men	14	21.20
Women	52	78.80
Age		
<41 years old	1	1.50
41-50 years old	20	30.30
51-60 years old	28	42.40
>60 years old	17	25.80
Marital status		
Married	65	98.50
Single	1	1.50
Education		
No school	6	9.10
Elementary-High School	52	78.80
College-Master	8	12.10
Working		
Work	38	57.60
Not working	28	42.40

The incidence of metabolic syndrome is more experienced by age group > 40 years than age < 40 years [9]. Metabolic syndrome occurs as one gets older. This is due to decrease in organ function and metabolic disorders that exist in the body. Diabetes mellitus occurs due to decreased insulin secretion because of the pancreatic β cells damage, insulin resistance, impaired metabolism of carbohydrates, proteins and fats and reduced elasticity of blood vessels may be at risk of hypertension and atherosclerosis leading to the incidence of metabolic syndrome [9, 12, 13]. Metabolic syndrome has a significant relationship with one's marital status [14, 15]. A married person will be faced with a social environment that allows problems and causes unhappiness. Each problem will create psychosocial stress potential that may be at risk of metabolic syndrome [15]. Education and work are two characteristics of metabolic syndrome which has interconnected each other. Education can determine the type of work of a person with different income to meet their daily needs. Lifestyle change can increase the prevalence of diseases such as diabetes, obesity and heart disease which is a factor risk of metabolic syndrome [16]. Job status relates to daily physical activity. In this study, patients with metabolic syndrome are more likely than workers, such as civil servants, entrepreneurs, farmers, fishermen and laborers with mild to severe activity. Physical activity can help lower cholesterol, triglycerides, increase HDL and insulin sensitivity and lower blood pressure which is a risk factor for the incidence of metabolic syndrome and cardiovascular disease complications [12].

Table 2 shows the characteristics data of patients with metabolic syndrome. Metabolic syndrome is more prevalent in patients at risk of metabolic syndrome with prolonged <5 years (59.10%) compared with 5 years of age (40.90%). Patients at risk for metabolic syndrome who participate in this study mostly suffered from diabetes mellitus with complications. Diabetes mellitus is a metabolic disease with characteristics of hyperglycemia due to abnormalities of insulin secretion and become a risk factor for organ damage and dysfunction especially in the eyes, kidneys, nerves, heart and blood vessels.

Table 2. The characteristics data of patients at risk of metabolic syndrome at Jetis I Bantul Public Health Centers in 2016

Characteristics of patients	n=66	Percentage(%)
Characteristics of metabolic syndrome		
DM	10	15.20
Hypertension	1	1.50
Hypertriglyceride	1	1.50
DM+ Hypertension	16	24.20
DM+ Hypercholesterolemia	2	3.00
DM+ Obesity	1	1.50
DM+ Hypertriglyceride	6	9.10
DM+ Dyslipidemia	3	4.50
DM+ Hypertension + Hypertriglyceride	12	18.20
DM+ Hypertension + Hypercholesterolemia	5	7.60
DM+ Hypertension + Obesity	2	3.00
DM+ Hypertension + Dyslipidemia	5	7.60
DM+ Hypertension + Hypertriglyceride + Obesity	2	3.00
Routine Medication		
DM Drug	25	37.90
Hypertension Drug	1	1.50
Dyslipidemia Drug	1	1.50
DM Drug+ Hypertension Drug	33	50.00
DM Drug +Dyslipidemia Drug	3	4.50
DM Drug + Hypertension Drug + Dyslipidemia Drug	3	4.50

3.2. Clinical examination result of patients at risk of metabolic syndrome before and after using BCSO Dose 1.5 mL/day and 3 mL/day

Patients at risk of metabolic syndrome before treatment are examined clinical conditions such as systolic and diastolic blood pressure, pulse rate, body mass index (BMI), using a tool that has been calibrated by the calibration laboratory of Universitas Ahmad Dahlan Yogyakarta. Examination of blood glucose level (BG), triglyceride level (TG) and SGOT and SGPT activity using 5010 spectrophotometer at the laboratory of Jetis I Public Health Centers, Bantul Regency, Yogyakarta. The data were analyzed using repeated measure ANOVA test and continued with Bonferroni test as shown in Table 3.

Table 3. The results of measurement of clinical condition of patients at risk of metabolic syndrome before and after using BCSO dose 1.5 mL/day and 3 mL/day at Jetis I Public Health Centers, Bantul Regency, Yogyakarta in 2016

Clinical Conditions of Patients	Average ± SD, n=62			p Values
	Pretreatment	Dose 1.5 mL/day	Dose 3 mL/day	
SBP(mmHg)	143.06±17.98[a]	137.73±17.66	136.92±17.66	0.00
DBP(mmHg)	80.78±9.25	79.27±13.96	79.95±10.98	0.58
Pulse (x/min)	88.66±13.82[a]	90.69±12.91	92.44±12.15	0.04
BMI (kg/m^2)	24.16±4.13[a]	24.79±4.27	24.35±5.10	0.00
BG (mg/dL)	246.69±109.30[ab]	184.18±89.46	197.77±87.14	0.00
TG (mg/dL)	193.84±114.61[a]	173.42±108.51	158.58±97.87	0.00
SGOT (U/L)	23.00±10.41	21.82±6.47	22.60±9.95	0.63
SGPT (U/L)	22.29±10.81	21.16±7.86	21.03±12.08	0.82

Description: a= there is a significant difference between the measurement before treatment and the dose measurement 3 mL/day; B= there is a significant difference between the measurement before treatment and the dose measurement of 1.5 mL/day.

The results of statistical analysis show that there are significant differences between measurement of systolic blood pressure (SBP), pulse, BMI, BG and TG before and after BCSO administration in patients at risk of metabolic syndrome ($p<0.05$). The results of statistical analysis show that there is no significant difference between diastolic blood pressure (DBP) measurement, SGOT and SGPT activities before and after BCSO administration in patients at risk of metabolic syndrome ($p>0.05$). These results indicate that giving BCSO dose of 1.5 mL/day and 3 mL/day for 20 days can decrease the mean blood pressure value in patients at risk of metabolic syndrome with targeted therapy <140/90 mmHg. This is in line with research conducted which states that the provision of black cumin seed powder can reduce blood pressure during 20 days of administration in patients with metabolic syndrome [18]. Another study mentioned that giving black seeds of cumin seeds for 8 weeks can reduce the blood pressure of cytolic and diastolic without side effects [19]. This study shows that black seeds of cumin seeds for 20 days are able to increase pulse rate and BMI in patients at risk of metabolic syndrome but still within normal limits. According to the American Heart Association (AHA) the normal range of pulse rate is 60-100 x/min and according to the World Health Organization (WHO) the normal value of IMT in patients at risk of metabolic syndrome is <30 kg/ m2. The results of this study stated that the administration of BCSO dose 1.5 mL/day and 3 mL/day for 20 days can reduce blood glucose levels in time and triglycerides in patients at risk of metabolic syndrome. BCSO contains active compounds such as thymoquinone, nigelon and thymol which play a role in lowering blood glucose. Black cumin in adipose cells can stimulate the secretion of insulin produced by pancreatic cells and is shown to have no effect on tissue sensitivity to glucose [20]. Criteria for metabolic syndrome according to International Education DiabetesFederation (IDF) in hypertension, triglycerides >150 mg/dL, HDL for women < 50 mg/dL and men < 40 mg/dL or in treatment of tubercidemia, diagnosed type 2 DM with GDP > 100 mg/dL [21].

Statistical analysis shows that SGOT and SGPT activities in patients at risk of metabolic syndrome decrease after using BCSO dose 1.5 mL/day and 3 mL/day for 20 days but not statistically significant ($p>0,05$). This is because the patients who participate in this study had a mean value of SGOT and SGPT activity in normal limits. The incidence of metabolic syndrome is associated with fatty liver disease or NAFLD. In patients with insulin resistance will experience steatosis due to increased free fatty acids to the liver increased. Oxidative stress and cytokines can cause disruption to the function of cells and liver organ [22]. SGOT and SGPT can be an indicator of liver damage with SGOT values <35 U/L and SGPT <41 U/L.

3.3. Measurements of IL-21 expression in patients at risk of metabolic syndrome given BCSO dosage 1.5 mL/day and 3 mL/day

Measurements of IL-21 expression using a flow cytometer tool in the pharmacology laboratory of the Faculty of Medicine, Universitas Gajah Mada (UGM), Yogyakarta. Data on IL-21 expression measurements in patients at risk of metabolic syndrome given BCSO dose 1.5 mL/day and 3 mL/day for 20 days statistically analyzed using paired T-test as shown in Table 4.

Table 4. The results of IL-21 expression measurements in patients at risk of metabolic syndrome given BCSO dose 1.5 mL/day and 3 mL/day for 20 days

Clinical condition patient	Mean value ± SD		p Value
	Dose 1.5 mL/day (n=62)	Dose 3 mL/day (n=62)	
IL-21	5.06±5.48	4.66±3.63	0.69

The results of statistical analysis shows that the mean value of IL-21 expression in patients at risk of metabolic syndrome who received BCSO dose 3 mL/day was lower than those who received BCSO dose 1.5 mL/day but not statistically significant ($p>0.05$). Several factors that may influence the research results are the possibility of influence from previous treatment before cross over design on BCSO dose 1.5 mL/day and 3 mL/day for 20 days. Physiological conditions of the body and lifestyle

such as lack of exercise, smoking and taking drugs for long periods in patients at risk of metabolic syndrome can also affect the results of the study.

Metabolic syndrome occurs because of insulin resistance. This is due to the disruption of pancreatic β cell function and insulin hypersecretion resulting in insulin resistance, in addition to severe damage to pancreatic β cells that leads to decreased insulin production and hyperglycemia. The deficiency of IL-21 expression in diabetic nonobese mice (NOD) may lead to resistance to insulitis, insulin autoantibody production and the onset of type I diabetes [7]. Excess of IL-21 expression in pancreatic β cells makes of inducing chemokines, inflammatory cytokines such as IL-17A, IL-17F, IFN-gamma, monocyte chemoattractant protein (MCP)-1 and MCP-2. IL-21 is a type I cytokine produced by T-cells and NK cells and is detected in $CD4^+$ and T-helper undergoing differentiation [23].

Giving *Nigela sativa* L. can cause demodulator in pro-inflammatory cytokines produced by T-helper-1 and cytokines. The active substance contained in the BSCO can evoke the immune system with the ability to raise T-helper cell, Tsupressor cells, and NK cells are a product of lymphocytes [24, 25]. T-cells play an important role in inducing inflammation induces makrofaf and secrete inflammatory and pro-inflammatory cytokines in adipose tissue leads to insulin resistance and lead to diabetes mellitus. Inflammatory cytokines would improve insulin resistance through the role of inflammatory signals such as janus kinase (JK) and activation of transcription factors nuclearfactor kappaB (NF-kB). Signaling pathways such as JK and NF-kB may reduce the action of insulin in adipocyte tissue [26, 27].

Black cumin seed can be utilized as an antioxidant and immunomodulator. Hexane extracts of black cumin seeds (*Nigella sativa* L.) can improve macrophage phagocytic activity in DMBA-induced female rats in vitro [8]. Part of the most widely used black cumin seed plant is its oil. Black cumin seed oil contains essential oil content of nonvolatile thymoquinone that is 27.8% [28]. The working mechanism of thymoquinone is by inhibiting non-enzymatic lipid peroxidation in liposomes and has the potential to neutralize free radicals and inhibit the pro-inflammatory cytokines such as interleukin-1β, interleukin-8 and chemokines such as machrophage chemotactic protein (MCP)-1 with the mechanism of action via inhibition of TNF- α which induces activation of transcription factors nuclearfactor kappaB (NF-kB) signaling pathway is involved in IL-21 and inhibiting the translocation of NF-kB into the nucleus [29]. BCSO delivery in the metabolic syndrome will inhibit IL-21 activation by decreasing the deference of T-helper which also produces IL-21 (IL-21R) receptors as well as inhibition of the STAT 3 signaling pathway.

4. Conclusion

IL-21 expressions in patients at risk of metabolic syndrome who received BCSO dose 3 mL/day were lower than those received a dose of 1.5 mL/day for 20 days.

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