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The efficacy of black cumin seed (*Nigella sativa*) oil and hypoglycemic drug combination to reduce HbA1c level in patients with metabolic syndrome risk

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Abstract. Metabolic syndrome is a conditions caused by metabolic abnormalities include central obesity, atherogenic dyslipidemia, hypertension, and insulin resistance. HbA1c examination is required to study the long-term glycemic status and to prevent diabetic complications of metabolic syndrome. The purpose of this study is to determine the efficacy of black cumin seed (*Nigella sativa*) oil and hypoglycemic drug combination to reduce HbA1c level in patients with metabolic syndrome risk. This research performed using an experimental randomized single - blind controlled trial design. A total of 99 outpatients at the Jetis I Public Health Center, Yogyakarta, Indonesia with metabolic syndrome risk were divided into three groups: The control group received placebo and two treatment groups received black seed oil orally at dose of 1.5 mL/day and 3 mL/day, respectively, for 20 days. The clinical conditions such as blood pressure, pulse rate, BMI, blood glucose serum and HbA1c levels were examined on day 0 and 21. The results obtained were analyzed with one-way ANOVA test. The mean of HbA1c levels of all groups before treatment was higher than the normal values and there was no significant difference in HbA1c value on day 0. Administration of 1.5 and 3 mL/day of black seed oil for 20 days decreased ($p<0.05$) HbA1c levels. It can be concluded that administration of black cumin seed oil and hypoglycemic drug combination for 20 days in patients at risk of metabolic syndrome may reduce to HbA1c levels.

Keywords: metabolic syndrome outpatients, black cumin seed oil, HbA1c, clinical test

Introduction

One of the public health problems in Indonesia is metabolic syndrome (MS). MS is a major risk factor for vascular and degenerative diseases, including cancer [1-3]. In Indonesia, MS prevalence varies based on age, gender, and region between 11 and 24.7% [4, 5]. One of the MS diseases, diabetes mellitus, is associated with the complications of various chronic and fatal diseases. Diabetes complications cause 50% and 30% of deaths due to coronary heart disease and kidney failure respectively. Diabetes also causes disability, in which 30% of patients experienced blindness due to retinopathy complications and 10% of them had to undergo leg amputation [6]. Diabetes mellitus is also associated with sudden death incidence in the

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community [7]. Epidemiologically and clinically, it has been demonstrated that angiopathic complication is associated with high hemoglobin A1c (HbA1c) levels.

HbA1c levels considered safe are about 6.5-7%. It is one of the glycosylated proteins to form HbA1c. Glycosylation occurs spontaneously in the circulation and will increase when blood glucose levels are high [2]. HbA1c was the average blood glucose level for 2-3 months [2, 8]. More than 50% of diabetes mellitus patients experience failure to control blood glucose levels that lead to HbA1c levels abnormalities (>7%) [9]. High blood glucose or HbA1c levels causes oxidative stress that damages blood vessels and triggers vascular endothelial death [10, 11]. HbA1c is formed from a bond of glucose with an amide group on the valine amino acid at the end of the Hb globulin beta chain. If this condition is prolonged, *irreversible advanced glycosylation end products* (AGE) will be formed on the walls of blood vessels that may be potentially pathogenic and lead to diabetic complications [12, 13]. Increased AGE results in cellular and tissue oxidative stress, causing damage to tissues and blood vessel cells, especially the endothelium tissue and generating an inflammatory reaction [10, 14].

Oral hypoglycemic drugs (OHOs), which are standard therapy for controlling blood glucose in DM patients, are estimated to be only capable of lowering HbA1c by approximately 0.5-2%, depending on the type of individual OHO drugs [9]. Therefore, it is often necessary for additional or complementary therapies to improve the achievement of ideal HbA1c levels of <7% [8, 15]. It is expected that a combination of high antioxidant food diet and OHOs therapy will lower HbA1c levels [12, 16]. Black cumin seed (*Nigella sativa*) oil (BCSO) has empirically been used as a dietary supplement, antioxidant medicinal ingredients, and immunomodulators. BCSO contains thymoquinone, nigellone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellcine, nigellimine-N-oxide, nigellidine and alpha hedrin which are empirically and laboratorically antioxidative [17]. In preclinical studies, it has been demonstrated that BCSO administration on Danforth's short tail (SD) mice induced by alloxan can prevent damage to the pancreas and the liver by increasing the p53 gene expression [18]. It is safe and well-tolerated in phase 1 trial [19]. BCSO administration as an adjunctive therapy in hyperlipid and hyperglycemic patients at hospital could significantly reduce total cholesterol, LDL and fasting blood glucose levels. However, the effect of BCSO on HbA1c in patients with risk of metabolic syndrome at Public Health Center has never been investigated. Therefore, this study aims to investigate the effect of black cumin seed oil on HbA1c in Public Health Center outpatients with the risk of metabolic syndrome [20].

2. Materials and Methods

This study was a randomized control trial with two dose levels. The number of samples was determined according to the phase 2 clinical trial guidelines, where the sample number was 80-300 volunteers. A total of 99 subjects with metabolic syndrome were divided into three groups, 33 subjects of each which would receive BCSO at dose of 1.5 mL/day and 3 mL/day for 20 days.

Research subjects were outpatients at risk of metabolic syndrome at Jetis I Public Health Center, Bantul, Yogyakarta, Indonesia. The inclusion criteria were male or female patients aged >18 years old, willing to become research volunteers proven by voluntarily signing of informed consent, having been diagnosed with diabetes mellitus or dyslipidemia or hypertension with or without central obesity and having become the outpatient at Jetis 1 Public Health Center at least for three months. Exclusion criteria were drop out volunteers, pregnant women, taking NSAID medications and immunomodulatory supplements, allergic with black cumin seed oil, having a history of chronic kidney disease and cancer, undergoing hyperthyroid and diabetic ulcers therapy and active pulmonary TB patients. For 20 days, groups 1 and 2 were given 1.5 mL/day and 3 mL/day of BCSO soft capsule, respectively, while group 3 acts as a placebo group. This clinical trial research protocol has been reviewed and endorsed by the medical research ethics committee of the Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Indonesia. The selection of prospective research subjects was based on outpatient computer database at the Public Health Center. From the database, it was found that from May

to October 2016, there were 650 patients at risk of metabolic syndrome. The patients' medical records containing information about hypertension, dyslipidemia, or diabetes mellitus with or without obesity were listed and screened to ensure that the medical records data met the inclusion criteria. A total of 120 patients met the criteria, and they were subsequently designated as subject candidates. All prospective subjects were gathered and briefed on general research objectives and benefits and the specific benefits and consequences of participating as research volunteers. Candidates who were willing to participate in the study were required to give consent by signing the informed consent. A total of 112 prospective subjects who have signed then informed consent then underwent physical and laboratory checks. Based on the baseline examination, 13 patients met the exclusion criteria.

The research was conducted at Jetis I Public Health Center, Bantul, Yogyakarta for 10 months from March to December 2016. The research instrument used was a spectrophotometer to measure blood glucose level, while the test material used was BCSO soft capsules containing standardized black cumin seed oil with a composition of: 2.72% thymoquinone and 0.15% caprylic fatty acid, caprat 0.1%, laurat 0.18%, miristat 12.27%, palmitate 0.28%, stearate 7.99%, oleate 0.07%, linoleat 2.85%, eicosanoate 3.15%, eicosenat 0.25%, eicosadienoate 0.03%, arachidonate 0.03%, eicopentanoate 0.03%, behenat 0.06%, docohexanoate 0.04%, 0.02% teracosanoate and placebo in the form of empty capsules.

A total of 99 subjects were divided into three simple randomized groups (with a lottery system). Randomization was done manually by comparison between groups of 1:1:1. Random grouping was done by pharmacist with multiple lot sweepstakes. All subjects were recorded based on sequence number and then divided into three groups: treatment group 1, treatment 2 and placebo group. The drawing was done by taking number 1, 2, and 3. The number obtained by the first drawer acts as the treatment group 1, the number obtained by the second drawer as the treatment group 2, and the number obtained by the last drawer as the treatment group 3. The members of each group were selected using a multiple of 3 of the lottery number obtained. If the first lottery gets the number 1, then the members of the treatment group 1 were 4, 7, 10 and so on until the quota of 33 patients was reached. The same method applied to treatment group 2 and treatment group 3 (placebo).

The treatment given to the subjects was soft capsule (SC) of BCSO with doses of 1.5 and 3 mL/day or placebo. BCSO capsules were prepared by the pharmaceutical industry with *Good Manufacturing Practices* (GMP) certificate. The material was tested to examine the heavy metal content and standardization of the thymoquinone content. The capsule administration was done by doctors at Jetis I Public Health Center. The examination of post-treatment clinical conditions was done also by the doctors every two weeks at Public Health Center. Specifically trained teams were required to make visits to patients' homes twice per week to check blood pressure, pulse, and body mass index, and monitor unexpected reactions and medication compliance. The analysts and research personnel have been trained in the procedures as written in the protocol.

Vital signs, *Random Blood Glucose* (RBG) and HbA1c levels were examined on day 0 (to serve as baseline data) and 21. The peripheral blood was taken from the cubital vein by the previously trained Public Health Center laboratory analyst. From the collected blood, RBS and HbA1c were measured. Blood pressure, pulse and BMI were checked using tools that have been calibrated by the Calibration and Testing Laboratory of Universitas Ahmad Dahlan. RBS and HbA1c measurements were performed by the Public Health Center laboratory with 5010 spectrophotometer. The brief procedure of HbA1c measurement was as follows: 10 µL of blood plasma was put into the reaction tube, and then added with 1 mL of glucose reagent. After 10 minutes, the patients' blood glucose plasma was measured with a 5010 spectrophotometer. The results were then used to calculate the HbA1c value by the following formula:

$$\textbf{HbA1c} = (\textbf{Glucose Plasma} + 77.3) / 35.6$$

Demographic characteristics were presented descriptively. The mean comparison test was performed on the measurement data of blood pressure, pulse, BMI, serum glucose level, and

HbA1c levels day 0 and day 21 with one-way ANOVA using SPSS free edition software (SPSS version 16) with 95% confidence level.

3. Result and Discussion

3.1. *Characteristics of research subjects*

Four hundred and one of diabetes mellitus patients and 615 hypertensive patients who underwent treatment at Jetis I Public Health Center, Bantul, based on the recommendation of the treating physicians, 120 prospective subjects fulfilled the inclusion criteria.

Table 1. Characteristics of research subjects

Characteristics	Treatment Group			p-value
	Placebo group	Group 1	Group 2	
Subjects	n = 33	n = 33	n = 33	
Gender				
Men	9	7	7	0.802
Women	24	26	26	
Age (years)				
≤55 years old	14	14	15	0.582
> 56 years old	19	16	18	
Education				
≤Junior HS	19	21	19	0.999
Senior HS ≤	14	12	14	
Occupation				
Civil servants	1	0	3	0.141
Entrepreneur	5	3	5	
Farmers	4	3	5	
Private Sector	1	2	2	
Labor	5	7	4	
Fishermen	1	0	4	
Unemployed	11	11	5	
etc.	5	7	5	
Marital Status				
Married	32	32	33	0.608
Single	1	1	0	

All prospective subjects were then gathered and briefed and asked to sign the informed consent, but only 112 patients were willing to become research subjects. Demographic and clinical characteristics are presented in table 1 & 2. Table 1 and 2 shows that based on gender, age, education, occupation, marital status and therapy type, there were no differences among groups ($p>0.05$). Most of the subjects were junior high school female graduates and aged over 50 years old.

Most subjects received more than one drug therapy, with most patients receiving a combination therapy of 1 OHO and 1 antihypertensive drugs, followed by patients with a single OHO drug, patients with two OHO drugs, and patients with 2 OHO drugs and 1 antihypertensive medication.

Table 2. Type of drug therapy prescribed by doctors

Type of single and combination therapy for patients at risk of metabolic syndrome	Treatments Group			p-value
	Placebo group (n = 33)	Group 1 (n = 33)	Group 2 (n = 33)	
1 diabetes drug	6	11	6	0.333
1 hypertensive drug	0	0	1	
1 dyslipidemia drug	0	1	0	
2 diabetes drugs	5	6	6	
2 hypertensive drugs	0	1	0	
3 diabetes drugs	0	0	1	
1 diabetes drug +1 hypertensive drug	14	4	7	
1 diabetes drug + 1 dyslipidemia drug	0	1	1	
1 diabetes drug + 2 hypertensive drugs	0	3	1	
2 diabetes drugs + 1 hypertensive drug	5	3	4	
2 diabetes drugs + 1 dyslipidemia drug	1	0	0	
2 diabetes drugs + 2 hypertensive	1	3	3	
3 diabetes drugs + 1 hypertensive drugs	1	0	0	
1 diabetes drug + 1 hypertensive drug + 1 dyslipidemia drug	0	0	1	
1 diabetes drug + 1 hypertensive drug + 2 dyslipidemia drug	0	0	1	
2 diabetes drugs +1 hypertensive drug + 1 dyslipidemia drug	0	0	1	

3.2. *Measurement results of clinical conditions and HbA1c levels on day 0*
Subjects' clinical conditions (blood pressure, pulse rate, BMI, glucose serum level and HbA1c on day 0 (before treatment) are shown in Table 3.

Table 3. Blood pressure, pulse, BMI, serum glucose level and HbA1c on day 0

Vital Signs	Treatment Group			p-value
	Placebo group (n = 33)	Group 1 (n = 33)	Group 2 (n = 33)	
Systolic (mmHg)	142.48± 16.42	141.73±16.84	143.64±18.63	0.903
Diastolic (mmHg)	79.76± 7.005	80.52±9.138	81.09±9.531	0.821
Pulse	89.39± 9.997	89.33±10.764	90.82±11.246	0.816
BMI (Kg/m^2)	24.15± 4.103	23.76±4.346	24.53±3.8	0.749
Serum Glucose Level (mg/dL)	266.93±123.99	233.66±100.94	273.03±126.40	0.070
HbA1c (%)	9,300± 8.057	8.56 ± 2.777	9.34 ± 3.295	0.524

The results of vital signs and HbA1c measurement on day 0 show that there was no significant difference ($p > 0.05$) in blood pressure, pulse, BMI, glucose serum level, and HbA1c levels prior to BCSO administration. Before the treatment, subjects' mean of blood glucose and HbA1c levels exceeded the normal values of RBS with >200 mg/dL and HbA1c with >7%. The mean systolic blood pressure (SBP) also exceeded the normal value with >140 mmHg, but the mean diastolic blood pressure (DBP) was relatively normal with <90 mmHg [8].

3.3. *Measurement results of clinical condition and HbA1c on day 21*
The measurement results of clinical conditions (blood pressure, pulse rate, BMI, blood glucose serum) and HbA1c levels on day 21 are presented in Table 4.

Table 4. Measurement results of clinical conditions and HbA1c levels on day 21

Vital Signs	Treatments Group			p-value
	Placebo group (n = 33)	Group 1 (n = 33)	Group 2 (n = 33)	
Systolic (mmHg)	138.66±13.170	136.10±15.946	139.81±17.662	0.636
Diastolic (mmHg)	75.31±8.476	79.52±17.160	80.87±9.804	0.182
Pulse	89.66±11.085	90.26±10.155	93.87±14.440	0.330
BMI (Kg/m^2)	24.55±4.363	24.04±4.393	25.31±3.881	0.493
Serum glucose level (mg/dL)	270.31±80.324	190.19±88.304	199.61±91.172	0.001
HbA1c (%)	9.60±2.260 [ab]	7.44±2,487 [c]	7.51±2.492	0.001

[a] There was a significant difference between placebo group and group 1
[b] There was a significant difference between the placebo group and group 2
[c] There was no significant difference between group 1 and group 2.

Table 4 shows that after 20 days of BCSO treatment, there was no difference in blood pressure, pulse rate, and BMI between the treatment groups, with significance value of p>0.05. It shows that the BCSO administration can lower blood pressure to the target level defined for patients with diabetes mellitus by the American Diabetes Association (ADA) and the American Heart Association (AHA) [8], i.e. <140/90 mmHg. However, the result has not met the therapeutic target defined by the International Diabetes Mellitus Federation (IDF) (2006) that recommends a blood pressure target of <135/85 mmHg. There has been a decrease in the mean TDS, i.e. TDS <140 mmHg, although not statistically significant (p> 0.05). Research data also shows that there is no change in average pulse in all groups, and the mean pulse is in accordance with the normal target range according to the American Heart Association (60-100x/min). The average BMI in the three groups after the treatment was relatively similar (p>0.05), categorized as non-obese according to the American Heart Association [8]. The results of this study are not entirely consistent with previous studies, which stated that administering black cumin seed extract (BCSE) with a dose of 500 mg for 8 weeks could lower blood pressure in patients with metabolic syndrome [21]. Differences in terms of intervention timing, intervention type, subjects' initial condition, and research setting contribute to the differences in clinical outcomes. Provided an 8-week BCSE intervention for patients with metabolic syndrome in hospitals, whereas this study provided a 20-day BCSO intervention in patients at risk of metabolic syndrome in Public Health Center [21].

The results showed that there was an average decrease of RBS and HbA1c levels after BCSO treatment for 20 days, and there was difference in the average values of RBS and HbA1c levels among three treatment groups (p<0.01). There were significant differences in HbA1c and RBS values between the control group and treatment group 1 and treatment group 2 (p<0.01), but there was no significant difference between treatment group 1 and treatment group 2 (p> 0.05). However, despite a decline in the mean HbA1c value of the treatment groups, the results are not yet capable of reaching the targets defined by the American Diabetes Association (<7%). These results in line with previous studies, which revealed that the administration of BS extract with a dose of 500 mg or BS oil with a dose of 2.5 mL/day for 8 weeks could decrease HbA1c and RBS levels in patients with metabolic syndrome [21] .

BCSO can lower the HbA1c value because it increases insulin production, decreases insulin resistance, stimulates cellular activity, and decreases intestinal insulin absorption [22]. High thymoquinone content in BCSO has antioxidant effect that can decrease oxidative stress to prevent further cell damage [22, 23]. Consumpsion of 2 g/day of black cuminseed combined with oral hypoglycemic drugs can improve the effectiveness of endogenous antioxidant and enzyme therapy [24]. High blood glucose and HbA1c levels have been shown to be associated with increased incidence of death and cardiovascular disease [25]. Furthermore, the antioxidant diet has been shown to inhibit degenerative processes, reduce risk of and death from cardiovascular disease, and prolong life [16, 26-27].

4. Conclusion

Black cumin seed oil treatment with doses of 1.5 and 3 mL/day for 20 days in patients at risk of metabolic syndrome affects HbA1c activity ($p<0.05$) by reducing its level.

Phase III Clinical Trial of BCSO needs to be done in patients at risk of metabolic syndrome with longer administration time as an attempt to obtain phytopharmaca (phytomedicines) for secondary prevention of cardiovascular disease incidence in primary care.

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