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## THE EFFECT OF BLACK CUMIN SEED OIL CONSUMPTION ON CLOTTING TIME, BLEEDING TIME, AND PLATELET COUNTS IN HEALTHY-SMOKER VOLUNTEERS

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### ABSTRACT

**Objective:** The objective of the study was to determine the effect of consumption of black cumin seed oil (BCSO) on platelet count, clotting time (CT), and bleeding time (BT) in healthy-smoker volunteers (HSV).

**Methods:** Participants were 39 healthy male smokers aged 18-66 y. Participants were divided into four groups randomly. The treatment group received BCSO for thirties days in 3x1, 3x2, and 3x3 capsules/day doses. The placebo group received a placebo preparation. We measured CT, BT, and platelet count on day 31. An analysis of the mean difference between CT, BT, and platelet counts was performed using one-way ANOVA.

**Result:** The results showed that the CT, BT, and platelet counts in all groups were within normal. Consumption of BCSO for 30 d did not affect CT, BT, and platelet counts of HSV. The results of the analysis of the mean difference test between groups of CT, BT, and platelet counts indicated that there was no difference with  $p>0.05$ .

**Conclusion:** We concluded that the 30-day BCSO consumption did not affect the CT, BT, and platelet count values in HSV.

**Keywords:** Black cumin seed oil, Hemostasis, Healthy-smoker volunteer, Open-label clinical trial

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### INTRODUCTION

Smoking is one of the public health problems in Indonesia [1]. Cigarettes are addictive, toxic, carcinogenic, and immunosuppressant [2, 3]. Cigarette exposure is associated with an increased incidence of hypertension, diabetes mellitus, cardiac ischemia, stroke, and kidney failure [4-7]. The addictive nature of cigarettes comes from the nicotine they contain. After cigarette smoke is inhaled, nicotine will reach the brain [8, 9]. Smoking is one of the factors that can cause an increase in plasma homocysteine levels and radical reactive in the body [10, 11]. Homocysteine affects several factors involved in the blood clotting cascade, such as decreasing anti-thrombin activity, accelerating thrombus formation, and increasing platelet aggregation [12]. Homocysteine also suppresses natural thrombolysis by reducing tissue plasminogen activator [13]. Homocysteine causes damage to the endothelium [14]. This damage causes a decrease in the production of prostacyclin, which can cause thrombus to form in the vascular system, resulting in thrombosis [11, 15]. Clotting Time (CT) and Bleeding time (BT) are routine examinations to determine the intrinsic and extrinsic coagulation pathways. Platelets are blood cells that are responsible react to bleeding from blood vessel injury by clumping, thereby initiating a blood clot. Platelets in a resting state circulate in the bloodstream. Platelets will undergo rapid deformation at the injury site in the event of a vascular injury, where they roll over, stick together, and collect to stop bleeding with thrombus formation [16, 17]. Smoking habits are associated with coagulation factors malfunctions [18]. Smoking habits are also thought to be related to changes in CT and BT values.

Black cumin (*Nigella sativa* L.) is one of the *Nigella* genus [19]. *Nigella sativa* is useful for increasing stamina and body defense [20], antioxidants and anti-aging [21], anti-infection [22] and prevention of degenerative diseases (cancer, diabetes mellitus, stroke, hypertension) [23]. One of the most important active compounds contained in black cumin is thymoquinone [24]. Thymoquinone is anti-oxidative [25], immunomodulatory, chemopreventive, and anti-inflammatory [26, 27]. Antioxidants can inhibit oxidative stress and reduce the potential for damage to cell structure and function [28]. Tobacco smoking causes oxidative stress [29]. Oxidative stress is a

condition in which the formation of reactive oxygen species (ROS) and long-term antioxidant defense systems is not balanced in the body [30, 31]. Oxidative stress can cause various disorders such as cardiovascular disease, diabetes, rheumatoid arthritis, cancer, and neurodegenerative disorders [32]. Antioxidants are responsible for the body's mechanisms for fighting disease pathologies related to the free radical attack [33]. Thymoquinone and antioxidants agents are believed to play an essential role in the body's defense system against radical reactive and maintain overall body health [34]. Consumption of BCSO is thought to inhibit the increase in platelet counts and normalize CT and BT values in smokers. The purpose of this study was to determine the effect of administration of BCSO for 30 d on the platelet count, clotting time, and bleeding time in healthy-smokers volunteers.

### MATERIALS AND METHODS

#### Types and research design

In this study, the experimental design used was Open-Label Randomized Controlled Trial. Three BCSO dosage ratings were given, namely 3x1; 3x2; and 3x3 capsules/day. We carried out the research protocol following the Declaration of Helsinki, where the research protocol had been reviewed and had obtained ethics worthy statements from the UAD research ethics committee.

#### Materials, tools, and subjects

The research materials included BCSO capsules containing standardized BCSO and placebo preparations. The placebo and BCSO capsules are prepared by the traditional medicine industry certified by the National Agency of Drug and Food Control. The equipment needed in the research includes a weight scale, thermometer, tensimeter, test tube, stopwatch, and hemato analyzer.

Inclusion criteria were healthy volunteers and active smokers. Men aged >18 y and willing to become participants (as evidenced by a willingness to fill and sign the informed consent). Exclusion criteria were volunteer smokers who suffered from chronic diseases, missed medication schedules, and used supplements other than BCSO. Participants who experienced an incidence of side effects to be

excluded from the study. Following phase 1 research guidelines, this study involved 39 participants.

#### Participant recruitment for research procedures

Prospective subjects who meet the inclusion criteria are asked to participate in the study by signing the informed consent after explaining the objectives, benefits, and research procedures and consequences and compensation as participants. Prospective participants who have signed the informed consent are then subjected to a physical examination to determine the clinical condition and physical health status by the Puskesmas doctor.

#### The assignment in the experimental group

Placement of participants into the test group was done randomly using the manual method (coins). Participants were divided into four groups. The pharmacist stores the random numbers were resulting from the randomization process. Group I, namely the control/placebo group, subjects received a soft capsule without BCSO. Group II, III, and IV, the subjects received BCSO capsules at a dose of 3x1, 3x2, and 3x3/day. BCSO is a soft capsule containing BCSO, where one capsule contains 450 mg of BCSO (excluding capsule shell).

#### Implementation of the provision of BCSO and monitoring

Both placebo and BCSO are given for 30 d, which are consumed regularly. Monitoring the condition of the participants is carried out twice a week through direct interviews with residents' houses. Monitoring the participant's situation includes clinical conditions (blood pressure, respiration, temperature, and pulse), complaints, and effects that arise after administration, including side effects and ascertaining the amount of medication remaining and supplementing the case report form (CRF).

#### Data retrieval

On the 31st day, participants/volunteers have collected again for blood sampling for complete blood counts, clinical examination, and education and dissemination on the need for a healthy lifestyle. The researcher presented the first laboratory examination (pre-treatment), providing clinical interpretation and recommendations for follow-up. We sent the blood to Nur Hidayah Hospital for platelet counts using a hemato-analyzer. We determined clotting time using the Lee-white method and bleeding time using the Ivy method.

#### Data analysis

Participant characteristics are presented descriptively in the form of a percentage. We determined the difference in the proportion of demographic and smoking habits characteristics between groups using the chi-square. We performed a mean difference test between groups for the mean of CT, BT, and platelet count using the one-way ANOVA, with a 95% confidence level.

### RESULTS AND DISCUSSION

#### Characteristics of the subject

Based on research conducted on men over 18 y old at PHC Jetis 1 Bantul Yogyakarta (PJ1BY), where BCSO effects on clotting time and bleeding time in smokers. This research was conducted by filling out the nutritional recall form. Respondents have signed informed consent before recruited, and the ethics commission has approved all protocols.

It is known that the Subjects who consumed the BCSO were in the age range <60 y, as many as 39 volunteers. Table 1 showed the demographic characteristics of the Subject. Most of the participants have a junior high school education, with a livelihood as masons and carpenters. Most of the participants smoked less than ten cigarettes/day and had lasted 10-30 y.

**Table 1: Distribution of characteristics of healthy-smoker volunteers (HSV) who consume BCSO in the working area of PJ1BY in september-october 2019**

Characteristic	Placebo	BCSO 3X1	BCSO 3X2	BCSO 3X3	Total	Significance (2-sided)
1. Age						
>60 Y	0	0	2	0	2	0.19
<60 Y	9	9	10	9	37	
Total	9	9	12	9	39	
2. Education						
Elementary	0	0	4	2	6	0.25
Junior High school	2	0	2	1	5	
Senior height school	7	7	5	5	24	
University	0	2	1	1	4	
Total	9	9	12	9	39	
3. Job						
Labor	5	2	6	5	18	0.37
Teacher	0	1	0	0	1	
Students a	0	0	0	1	1	
Retired	0	1	0	0	1	
Farmer	0	0	0	1	1	
private	4	5	6	2	17	
Total	9	9	12	9	39	
4. Smoking habit type						
Cigarette smoking	9	9	11	9	38	0.51
Electrical smoking	0	0	1	0	1	
Total	9	9	12	9	39	
5. Number of stick/day						
<10 stick	5	7	3	3	21	0.29
>10 stick	4	2	6	6	18	
Total	9	9	12	9	39	
6. Duration of smoking (year)						
<10 y	2	4	2	2	10	0.53
10-30 y	7	4	7	5	23	
>30 y	0	1	3	2	6	
Total	9	9	12	9	39	

The clinical conditions [3](#) participants before administering BCSO are presented in table 2. Based on the data in table 2, it is known that the participants' blood pressure, temperature, pulse, BMI, urea,

creatinine, blood sugar, cholesterol, and triglycerides were within normal limits. There was no difference in clinical parameters between test groups ( $p > 0.05$ ).

Table 2: Participants' clinical condition before receiving BCSO, participants were healthy male smokers

Parameter	Experimental groups				Total (n=39)	P
	Placebo (n=9)	BCSO 3x1 (n=9)	BCSO 3x2 (n=12)	BCSO 3x3 (n=9)		
SBP	133.14±17.15	143.14±37.52	140.25±19.71	135.00±9.48	137.97±22.30	0.85
DBP	86.57±8.34	89.29±20.77	86.37±10.47	80.57±7.32	85.72±12.50	0.86
Hearth Rate	83.29±41.19	83.42±40.88	81.13±6.48	83.71±8.64	82.59±8.91	0.52
Temperature	35.28±0.49	35.85±0.69	35.64±0.52	35.86±0.38	35.67±0.65	0.51
BMI	23.57±3.95	22.71±3.30	25.00±5.75	25.71±6.68	24.24±4.95	0.19
Ureum	33.57±11.08	33.54±6.57	28.59±5.79	28.74±4.96	31.11±7.53	0.21
creatinin	1.17±0.20	1.09±0.099	1.04±0.08	1.06±0.11	1.09±0.14	0.76
Blood glucose	131.8±915.60	145.20±53.12	166.80±46.59	131.89±24.84	144.58±40.15	0.14
Triglyceride	172.67±77.59	150.20±76.39	164.70±60.83	188.33±151.63	168.37±93.75	0.53
cholesterol	159.22±41.08	151.30±29.05	152.00±25.56	154.78±26.60	154.18±29.86	0.48

Note: SBP=systolic blood pressure; DBP=diastolic blood pressure; BMI=body mass index; BCSO=black cumin seed oil; Data were given in mean±SD

### BCSO effects on the number of platelets, Clotting time (CT), and bleeding time (BT)

The impact of BCSO consumption for 30 d on platelet count, CT, and BT in healthy volunteers-smokers are presented in table 3.

Average values in healthy humans are: Clotting Time =9-15 min and Bleeding Time=1-5 min. Based on table 3, it is known that the CT, BT, and platelet count values in the four test groups were within normal limits.

The smoking habit of the participants did not affect the CT and BT values and the number of platelets. There was a decrease in platelet count and BT value in the treatment group compared to the placebo group, but it was not statistically significant ( $p>0.05$ ). Consumption of BCSO for 30 d did not affect CT and BT in healthy volunteer smokers in the placebo group with the treatment group. There was no difference in the mean CT and BT between treatment groups ( $p>0.05$ ). Consumption of BCSO for 30 d by healthy volunteer smokers did not affect CT/BT.

Table 3: The average value and standard deviation of clotting time, bleeding time, and number of platelet for healthy smoking volunteers (HSV) who consume BCSO in the work area of PJ1BY for the period September-October 2019

Experimental group (n)	Clotting time	Bleeding time	Platelet count
Placebo (n=9)	10.89±1.05	3.22±0.44	243.22±40.01
BCSO 3X1 (n=9)	11.89±1.61	3.22±0.44	208.33±39.52
BCSO 3X2 (n=12)	10.75±1.71	3.17±0.38	237.75±47.56
BCSO 3X3 (n=9)	10.44±1.66	3.11±0.33	245.44±68.58
Total (n=39)	10.97±1.58	3.18±0.38	236.05±50.43
P	0.31	0.21	0.25

Note: BCSO=black cumin seed oil; capsule of BCSO = 450 mg of BCSO without a shell; One placebo capsule = 450 mg placebo without shell; Data were given in mean±SD

### DISCUSSION

All volunteers are men, mostly as construction workers and casual daily laborers, who have graduated from elementary school education and are in the productive age group (table 1). The clinical and chemical parameters for the participants are in expected value (table 2). The CT and BT of all test groups were within normal limits (table 3). Based on the data in Tables 2 and 3, it is known that the smoking habits of volunteers have not affected the clinical parameters and the CT, BT, and platelet count values. Data from this study are not follow the results of previous studies [35,36]. Research has shown that acute smoking could change the platelet count and induce endothelial damage. The effect of smoking on the clotting time and bleeding time in healthy men was a shortening of clotting time and bleeding time in moderate and heavy smokers [37]. Elkhalfifa's (2018) study, which examined the effect of cigarette smoking on the coagulation screening test and platelet counts in a Sundanese male adults population, that the average prothrombin time (PT) was significantly shorter in smokers when compared to non-smokers [35]. Smoking has been identified as a principal underlying etiology for the occurrence and progression of cardiovascular diseases, inflammatory disorders, and oxidative stress stimulation [38]. Cigarette smoking's crucial role in disrupting platelet activation and aggregation, as well as other coagulation processing components leading to thrombotic formations, has been recently suggested [36]. The pathophysiological effects of cigarette smoking on platelet activation have been recently investigated [10, 39]. Until now, the impact of smoking on the platelets is not clear. Previous research has shown that acute smoking can alter platelet counts and cause endothelial damage [29]; however, in other studies, smoking did not induce platelet aggregation as a result of stimulation by effects such as adenosine diphosphate (ADP), epinephrine, and collagen, has been recently suggested [40]. We

apologize that some of the factors causing the difference in Our results may be include differences in subject characteristics, lifestyle, and smoking intensity. Participants in this study were construction workers with a lot of physical activity and with a mild to the moderate smoking habit. El khalifa's research involved participants with moderate to severe smoking habits [35].

Based on the data in table 3, it is known that the consumption of BCSO for 30 d did not affect the platelet count, CT, and BT values. There was no difference in the number of platelets between the placebo group and the treatment group ( $p>0.05$ ). Based on table 3, it is known that the platelet count, CT, and BT values are within normal limits or in homeostatic conditions [41], and consumption of BCSO for 30 d does not change homeostasis. Based on this evidence, the consumption of BCSO for 30 d did not alter the homeostasis of healthy-smoker volunteers. The results of this study are following previous research data, which proves that consumption of BCSO for 20 in healthy volunteers is safe and can be tolerated [42].

There are several limitations of this study, i.e. (i) we couldn't control the food consumed by the participants, (ii) the number of participants involved was also still limited, and (iii) loose variations in physical activity and lifestyle of participants, so that many confounding factors are difficult to control.

### CONCLUSION

Consumption of black cumin seed oil for 30 d in Healthy-smoker volunteers did not affect the platelet count and the value of clotting time and bleeding time.

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#### AUTHORS CONTRIBUTIONS

All authors discussed the results and contributed to the final manuscript.

#### CONFLICT OF INTERESTS

Authors declare no conflict of interest

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