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The Effect of Black Cumin (*Nigella sativa*) on Hb and VEGF Levels in Lung Cancer Patients Undergoing Chemotherapy at Dr. Saiful Anwar General Hospital, East Java

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ABSTRACT

Background: Studies show that the cytotoxic effect of black cumin seed extract and oil can reduce the viability of lung cancer cells including VEGF and increase the Hb of cancer patients. This study aims to compare Hb and VEGF levels between lung cancer patients undergoing chemotherapy with black cumin (*Nigella sativa*) and those undergoing standard chemotherapy.

Methods: This study used a quantitative approach using the pre-post test control group design method involving 21 lung cancer patients at Dr. Saiful Anwar General Hospital, Malang, who were observed for 9 weeks between August and November 2023. The control group included patients undergoing standard chemotherapy and the treatment group included those undergoing chemotherapy with the addition of black cumin. Examination of Hb and VEGF levels used ELISA.

Results: There were significant pre and post differences between the control and treatment after the 9-week study regarding their Hb and VEGF levels groups with a p-value of 0.021 and a p-value of 0.007, respectively.

Conclusion: The addition of black cumin for 9 weeks plays a role in preventing the decrease in Hb values and reducing VEGF levels in cancer patients receiving standard chemotherapy.

KEYWORDS: Lung cancer, Hb, VEGF, *Nigella sativa*

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I. INTRODUCTION

Cancer is an abnormal growth or malignant tumor characterized by uncontrolled cell proliferation, despite limitations in nutrition and space. This is because cancer cells have unlimited replication potential through upregulation of telomerase expression, which counteracts telomerase erosion.[1] Cancer is the main cause of mortality, with around 2.1 million newly diagnosed cases of lung cancer and 1.8 million deaths in 2018.[2]

Lung cancer, or bronchogenic carcinoma, is a tumor that originates from the lung parenchyma or in the bronchi. The incidence of lung cancer is increasing throughout the world, where, globally, this cancer is the primary cause of cancer-related deaths in men and women. The main cause of the high mortality rate in lung cancer cases is that most diagnoses are delayed and only detected when they reach advanced stages.[3–6]

Vascular endothelial growth factor (VEGF) is a key factor in the angiogenesis process, which is related to the stimulation of proliferation, migration, and invasion of the endothelium. VEGF also influences the increase in vascular permeability, which, in turn, causes the extravasation of plasma proteins into the surrounding tissue and creates new structures for the migration of endothelial cells.[8,9] VEGF is known to directly interact with cancer cells, increasing their growth and metastasis. The levels and expression of VEGF were found to be markedly high in various types of lung cancer. Numerous therapeutic agents targeting VEGF and its receptors have so far shown improvements, albeit non-significant, in clinical trials of subjects with lung cancer.[9–11]

Systemic inflammation and changes in inflammatory status are characteristics often accompanying lung cancer. There is a close relationship between the development of cancer and the patient's clinical, general, and inflammatory

status. In a study involving 257 patients who had undergone lung resection for non-small cell lung cancer (NSCLC), univariate analysis showed risk factors for hemoglobin < 13 g/dL (p = 0.01). The study concluded that preoperative inflammatory status may influence the long-term prognosis of patients developing NSCLC and undergoing surgery.[14]

Black cumin, otherwise known as *Nigella sativa*, has long been used in traditional medicine in various countries and is known to offer plenty of health benefits. Although several studies have demonstrated the potential of black cumin as an anti-cancer agent, to date, not enough evidence shows that black cumin is the therapy of choice for cancer treatment.[15] One of the components in black cumin, thymoquinone, has been studied for its anti-cancer potential. A number of studies highlight that thymoquinone can inhibit the growth of cancer cells in vitro and in vivo and can improve chemotherapy drugs' effectiveness. Thymoquinone works by triggering the death of cancer cells, impeding the formation of new blood vessels that supply nutrients to tumor cells, and suppressing inflammation and oxidative stress.[16] This study aims to substantiate that administering black cumin to lung cancer patients receiving standard chemotherapy will increase their Hb levels and decrease their VEGF levels.

II. METHODS

This study used a quantitative approach with the pre-post test control group design method. This study was conducted from August to November 2023 at Dr. Saiful Anwar General Hospital, Malang, East Java, Indonesia. The minimum sample size required in this study was 7 samples per group. To anticipate patients dropping out of the study, the number of samples was increased to 12 control samples and 9 treatment samples for a total of 21 subjects as the samples. The inclusion criteria for the subjects were > 18 years old, diagnosed with stage IIIB, IVA, and IVB primary lung cancer, and willing to participate in the study and sign informed consent. Meanwhile, the exclusion criteria included primary cancer patients outside the lungs and difficulties in data collection, which resulted in incomplete data.

The procedure for this study is as follows: the subjects were divided into 2 groups, the control group (A) and the treatment group (B). The control group (A) only received lung cancer chemotherapy therapy, while the treatment group (B) received lung cancer chemotherapy therapy with the addition of black cumin (*Nigella sativa*) orally (2 x 500 mg for 9 weeks). Hb and VEGF tests were then carried out, both before starting the initial chemotherapy and nine weeks after the intervention was given.

Statistical tests were carried out through descriptive analysis and bivariate analysis with the help of the Statistical Package for Social Sciences (SPSS) (version 26.0; SPSS Inc., Chicago, Illinois, USA). The tests were conducted using a paired t-test if the data were normally distributed. However, if the data were not normally distributed, the statistical test used the Wilcoxon test, in which a p-value < 0.05 is considered significant.

III. RESULTS

The total subjects included in this study were 21 subjects with the following demographic characteristics (**Table 1**). Out of the 21 subjects taking part in this study, 12 subjects were included in the control group, while the other 9 subjects in the treatment group. The mean (± SD) age of the subjects in this study was 59.14 (± 8.83) years.

Table 1. The demographic characteristics of the subjects

Characteristics	Treatment (n = 9)	Control (n = 12)
Age (years old)		
≤ 60	5 (55.6%)	7 (58.3%)
> 60	4 (44.4%)	5 (41.7%)
Sex		
Male	5 (55.6%)	7 (58.3%)
Female	4 (44.4%)	5 (41.7%)
History of Smoking		
No	6 (66.7%)	5 (41.7%)
Yes	3 (33.3%)	7 (58.3%)
Anatomical Pathology		
SCLC	1 (11.1%)	3 (25.0%)
NSCLC	8 (88.9%)	9 (75.0%)

The normality test results of the control group's data for pre- and post-intervention Hb and pre- and post-intervention VEGF showed normal-normal distribution and normal-normal distribution, respectively. The following Error! Reference source not found. presents the comparison analysis results between pre- and post-intervention in the control group (A). Post-intervention Hb levels are found to be significantly lower than pre-intervention Hb levels (p = 0.009).

Table 2. The result of the comparison analysis pre- and post-intervention in the control group

CONTROL group	**Pre** Mean ± SD	**Post** Mean ± SD	**p-value**
Hemoglobin	11.72 ± 1.35	9.98 ± 1.09	0.009*
VEGF	129275.08 ± 379250.64	10547.83 ± 3509.82	0.583

*** p < 0.05 = significant**

The normality test results of the treatment group's data for pre- and post-intervention Hb and pre- and post-intervention VEGF shows normal-normal distribution and normal-normal distribution, respectively. The following presents the results of the comparison analysis between pre- and post-intervention in the treatment group.

Table 3. The result of the comparison analysis pre- and post-intervention in the treatment group

TREATMENT group	Pre	Post	p-value
	Mean ± SD	Mean ± SD	
Hemoglobin	11.74 ± 1.31	11.06 ± 0.80	0.306
VEGF	7827.56 ± 1284.94	7077.22 ± 1209.57	0.214

*** p < 0.05 = significant**

The results of the comparison test for Hb 1, Hb 2, Hb 3, and Hb 4 between the control group and the treatment group are in Table 4 below. The results of the comparison test for Hb 1, Hb 2, and Hb 3 shows p-value > 0.05, which indicates that there is no significant difference in the Hb 1, Hb 2, and Hb 3 between the control group and the treatment group. The result of the Hb 4 comparison test between the control group and the treatment group shows a p-value of 0.021, which suggests that there is a significant difference in Hb 4 between the control group and the treatment group, in which the average Hb 4 in the treatment group is found to be higher than the Hb 4 in the control group (**Table 4**).

Table 4. The comparison test result for Hb between the control group and the treatment group

	Treatment	Control	p-value
	Mean ± SD	Mean ± SD	
Hemoglobin pre (g/dL)	11.74 ± 1.31	11.72 ± 1.35	0.963
Hemoglobin post 1st cycle (g/dL)	10.88 ± 1.41	10.40 ± 1.93	0.538
Hemoglobin post 2nd cycle (g/dL)	10.78 ± 1.17	10.63 ± 0.97	0.760
Hemoglobin post 3rd cycle (g/dL)	11.06 ± 0.80	9.98 ± 1.09	0.021*

*** p < 0.05 = significant**

The results of the comparison test for VEGF 1 and VEGF 4 between the control group and the treatment group are presented in Error! Reference source not found. below. The result of the comparison test for VEGF 1 shows a p-value > 0.05, which indicates that there is no significant difference in VEGF 1 between the control group and the treatment group. The result of the comparison test for VEGF 4 between the control group and the treatment group shows a p-value of 0.007, which indicates that there is a significant difference in VEGF 4 between the control group and the treatment group, in which the VEGF 4 in the control group is found to be higher than the VEGF 4 in the treatment group.

Table 5. The comparison test result for VEGF between the control group and the treatment group

	Treatment	Control	p-value
	Mean ± SD	Mean ± SD	
VEGF pre (ng/mL)	7748.91 ± 2409.88	129134.12 ± 379300.61	0.73
VEGF post 3rd cycle (ng/mL)	7173.66 ± 1286.56	10851.25 ± 3521.02	0.003*

*** p < 0.05 = significant**

IV. DISCUSSION

Lung cancer is a malignancy originating from the lungs (primary). Primary lung cancer is a malignant tumor originating from the bronchial epithelium.[17] The incidence of and mortality due to lung cancer is closely related to smoking patterns. Ninety percent of lung cancer is caused by smoking habits. Approximately 10–20% of lung cancer cases occur in people who have never smoked, with a much higher incidence in women. This is due to the risk of lung cancer in passive smokers increasing by 20–30%.[3,5] This study found that men suffered more from lung cancer (57.1%), with a history of smoking found in 10 subjects (47.6%). The number of lung cancer cases in Indonesia has increased more than 5-fold in the last 10 years, with the majority of cases presenting at an advanced stage. Patients with lung cancer seeking treatment at Persahabatan Hospital, Indonesia, reached more than 1000 cases in 1 year.[17]

Black cumin (*Nigella sativa*) is an annual flowering plant measuring around 20-90 cm. This herbal plant has been widely used for traditional medicine in the Middle East, Asia, Southern Europe, India, Pakistan, Syria, Saudi Arabia, Turkey, and the Southern Mediterranean. Black cumin has gastroprotective, hepatoprotective, antitumor, antidiabetic, antihypertensive, antioxidant, antifungal, immunomodulatory, anti-inflammatory, analgesic, antiviral, antipyretic, anticancer properties, and so on. Indonesia is one of the countries producing black cumin, which has the potential to be used as a preventive and curative therapeutic modality for various diseases.[18]

Post-intervention Hb levels were found to be significantly lower than pre-intervention Hb levels in the control group (p = 0.009). The results of the comparison test for Hb 4 between the control group and the treatment group showed a p-value of 0.021, which indicated that there was a significant difference in Hb 4 between the control group and the treatment group, where the average Hb 4 in the treatment group was found to be higher than the Hb 4 in the control group. Hb has been reported as a prognostic factor in patients with cancer, where anemia is associated with a poor prognosis. Anemia is associated with shorter survival times

in patients with lung cancer.[22] In the treatment group, Hb levels were found to be significantly higher than in the control group, suggesting the effect of black cumin in patients with lung cancer.

The comparison test results for VEGF after the third chemotherapy between the control group and the treatment group showed a p-value of 0.007, indicating a significant difference in post-third-chemotherapy VEGF between the control group and the treatment group, where VEGF in the control group was found to be higher than VEGF in the treatment group. VEGF plays a role in cancer growth and metastasis directly in target cells, and its expression regulates several cell functions, such as growth, migration, and production of pro-angiogenesis factors.[8] VEGF expression has been shown to increase significantly in lung cancer.[20,21] In this study, administering black cumin is shown to significantly reduce VEGF levels in the treatment group compared to the control group.

The limitation of this study is the relatively small number of samples involved, which was only 21 samples. This study is the first in vivo study, which is why the number of samples is still small. This study may be a basis for subsequent studies that not only assess the effect of black cumin (*Nigella sativa*) but also the effective dose.

CONCLUSIONS

The administration of black cumin for 9 weeks plays a role in suppressing the decline in Hb values and reducing VEGF levels in cancer patients receiving standard chemotherapy.

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