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THE EFFECT OF *OPHIOCEPHALUS STRIATUS* EXTRACTS ON TUMOR NECROSIS FACTOR- α (TNF- α) SERUM IN CANCER CACHEXIA PATIENTSApriani*¹, Dairion Gatot² & Senior Tawarta³^{*1}Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik General Hospital, Medan, Indonesia²Division Hematology-Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik General Hospital, Medan, Indonesia

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Keywords: TNF- α , cancer cachexia, *Ophiocephalus striatus*.**Abstract**

Introduction: One of the most common manifestations of advanced cancer is the development of metabolic symptoms called cancer cachexia. TNF- α hyperexpression has been identified as one of the key cytokine responses involved in cachexia, that continuously results in progressive anorexia and weight loss. In addition, TNF- α appears to affect several cachexia cancer abnormalities: decreased adipose and muscle wasting, and changes in fat and protein metabolism. *Ophiocephalus striatus* extract can be considered as a potential natural support to have anti-inflammatory properties, decrease regulation of both pro-inflammatory cytokine production and acute phase protein responses in cancer patients.

Aim: The objective of this study is to find the effect of *Ophiocephalus striatus* extract supplementation and TNF- α plasma level in patient with cancer cachexia.

Method: This study was an open label study in which all subject knew the purpose of this study and understood the intervention they will get. The design for this study was one group pretest and posttest with inclusion and exclusion criteria to choose the ideal subject for this study. Descriptive statistics analysis used for demographic data and Wilcoxon test used to test numeric variable in study treatment groups before and after treatment and $p < 0.05$ was considered significant. Subjects were treated with supplementation which contains 5000 mg *Ophiocephalus striatus* extract in twice daily 2 weeks period.

Result: The result from this study shows decreased in TNF- α plasma level before (7,83 pg/mL) and after treatment (3,82 pg/mL) with *Ophiocephalus striatus* extract ($p=0.004$). And this study also showed an increase in albumin plasma levels before and after treatment with *Ophiocephalus striatus* extract ($p < 0.001$).

Conclusion: The effect of *Ophiocephalus striatus* extract decreased in TNF- α plasma level and an increase in albumin plasma levels before and after treatment, and statistically significant.

Introduction

Cancer cachexia is a multifactorial syndrome characterized by loss of muscle mass (with or without fat loss) which cannot fully treated with conventional nutrition and causes progressive functional dysfunction.¹ Cancer cachexia usually named by cancer anorexia - cachexia syndrome because anorexia accompanied cachexia sign in cancer patients. This syndrome have some signs which include unintentionally weight loss, anorexia, fatigue, bloating and some others signs such as nausea, dysphagia, and sign of depression with variation in duration and severity.²

Epidemiological data showed that cachexia caused 20% mortality rate in cancer patients and affect 60 – 80% cancer patients.^{3,6} The highest incidence of cahexia is found in patients with cancer of the stomach and pancreas (~ 80%) while the lowest incidence is found in patients with breast cancer and leukemia (~ 40%).^{4,5}

Ophiocephalus striatus extract has lots of benefit. This extract contains amino acid such as glutamic acid, aspartame acid, lisin, and also fatty acid such as palmitate acid, stearate acid, arachidonic acid (omega-6), and docosahexaenoic (omega-3). *Ophiocephalus striatus* extract has high albumin concentration (64.61%) which functioned as amino acid for protein synthesis.⁷ Almost all of these compositions have an anti-inflammatory role.⁸



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Some studies found evidence that people with cancer cachexia are in a state of systemic inflammation. The best known cachexia mediator factor is cytokines (tumor necrosis factor- α (TNF- α)). Specifically, TNF- α hyperexpression has been identified as one of the key cytokine responses involved in cachexia.⁹ TNF- α hyperexpression that continuously results in progressive anorexia and weight loss. In addition, TNF- α appears to affect several cancer cachexia abnormalities: decreased adipose and muscle wasting, and changes in fat and protein metabolism.⁹ This is related to decreased quality of life, poor physical function and indicates a poor prognosis in cancer patients.^{10,11}

Methods

This study used open label study in which all subject knew the purpose of this study and understood the intervention they will get. The design for this study was one group pretest and posttest. This study took place at Department of Internal Medicine in Faculty of Medicine of North Sumatra University satellite hospital from January to Juny 2019. Study population for this study was all cancer patient that has cancer cachexia in H. Adam Malik General Hospital and Department of Internal Medicine in Faculty of Medicine of North Sumatra University satellite hospital. Sampling technique for this study was purposive sampling with inclusion and exclusion criteria. There was 30 subjects included in this study that completed all the inclusion criteria. Inclusion criteria for this study was patient with cancer that had weight loss over 5% for the last 12 months, BMI <20kg/m² and has 3 from 5 criteria listed below:

1. Decrease muscle strength
2. Fatigue
3. Anorexia
4. Low free fatty mass index
5. Biochemical abnormalities such as increase in inflammation marker (CRP, IL-6) anemia (Hb<12g/dL), low albumin serum concentration (<3,2 g/dL).

Exclusion criteria for this study was patient that refuse to join the study, patient that was not fit all the inclusion criteria, Patient > 65 years old and patient that had GFR<15 ml/min/1,73m².

All patient fitted for study and sign the concent included in this study. All subjects in this study had albumin extract supplement treatment which contains 5000 mg *Ophiocephalus striatus* extract. Study subjects had the pills for 2 weeks 2 times a day and before the treatment started, they had themselves educated with nutrition, diet programs, physical activity, and other factors such as stress level, body weight during treatment.

Data analysis

Descriptive statistics analysis used for demographic data and Wilcoxon test used to test numeric variable in study treatment groups before and after treatment. P value <0.05 is said to be significant statistically.

Result

Thirty subjects included in this study were male subjects in majority (20 subjects, 66.70%) and average ages for the subjects was 51.47 years old. Average subjects weight was 45.43 kg and average height was 162.67 cm. Average BMI from all subjects was 17.14 kg/m² (underweight). Most of the subjects has gastrointestinal cancer (14 subjects, 46.7%) followed by lung cancer (6 subjects, 20%), nasopharynx cancer (4 subjects, 13.3%) and Non Hodgkin Lymphoma (2 subjects (6.7%). Twenty five subjects (83.3%) from this study have had routine chemotherapy and 5 other subjects have not had any chemotherapy

Table 1. Study Subjects Characteristics

Characteristic	n = 30	%
Gender		
Male	20	66.7
Female	10	33.3
Age (year)^a	51.47 ± 16.95 ^a	
Antropometry		
Weight (kg) ^a	45.43 ± 5.80 ^a	



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Height (cm) ^a	162.67 ± 5.97 ^a	
BMI (kg/m ²) ^a	17.14 ± 1.66 ^a	
Cancer Classification		
GIT	14	46.7
Lung	6	20
Nasopharynx	4	13.3
NHL	2	6.7
Others	4	13.3
Status Chemotherapy		
Chemotherapy	25	83.3
Non-chemotherapy	5	16.7

^anormal distribution, averageSD

Table 2 below describe blood test result from all subjects before treatment. Hemoglobin result shows anemia in average and serum albumin result shows hypoalbuminemia in average. Other result was normal in average.

Table 2. Subjects laboratorium value

Characteristic	n = 30
Hemoglobin ^a	9.54 ± 1.53
Hematocrit ^a	28.32 ± 4.53
Leucocyte ^b	10320 (2480-29960)
Thrombocyte ^b	307500 (24000-757000)
Ureum ^b	30 (6-133)
Creatinine ^b	0.7 (0.34-3.11)
SGOT ^b	27 (8-175)
SGPT ^b	19 (6-83)
Albumin ^a	2.47 ± 0.43 ^a
D-dimer ^b	586 (100-6231)
Fibrinogen ^b	280 (80-1335)
CRP ^b	1.4 (0.7-2.8)
TNF- α ^b	7.83 (2.72-113.80)

^anormal distribution, average SD

^babnormal distribution, median (min.-max.)

Table 3 shows comparison blood test result before and after treatment and this value further analyzed statistically. There were some changes shows in all parameters from blood result before and after treatment. Highly significant p value shows in TNF- α plasma level changes before and after treatment with p value 0.004. Plotbox diagram also shows decrease in TNF- α plasma level before and after treatment with *Ophiocephalus striatus* extract.

Table 3. Subject Laboratorium value before and after treatment

Parameter	Before (n=30)	After (n=30)	P value
Hemoglobin ^a	9.54 ± 1.53	9.93 ± 1.65	0.177
Hematocrit ^a	28.32 ± 4.53	30.00 ± 5.25	0.127
Leucocyte ^b	10320 (2480-29960)	8760 (2680-31890)	0.820
Thrombocyte ^b	307500 (24000-757000)	342000 (25000-523000)	0.406
Ureum ^b	30 (6-133)	29 (13-133)	0.366
Creatinine ^b	0.77 (0.34-3.11)	0.70 (0.32-2.61)	0.073
SGOT ^b	27 (8-175)	24 (10-64)	0.490
SGPT ^b	19 (6-83)	22 (6-106)	0.147



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CRP ^b	1.4 (0.7-2.8)	1.4 (0.7-2.8)	0.347
Albumin ^a	2.47 ± 0.43	2.92 ± 0.56	<0.001*
TNF-α ^b	7.83 (2.72-113.80)	3.82 (0.52-35.70)	0.004*
BMI ^a	17.14 ± 1.66	17.04 ± 1.74	0.496

^anormal distribution, average SD

^babnormal distribution, median (min.-max.)

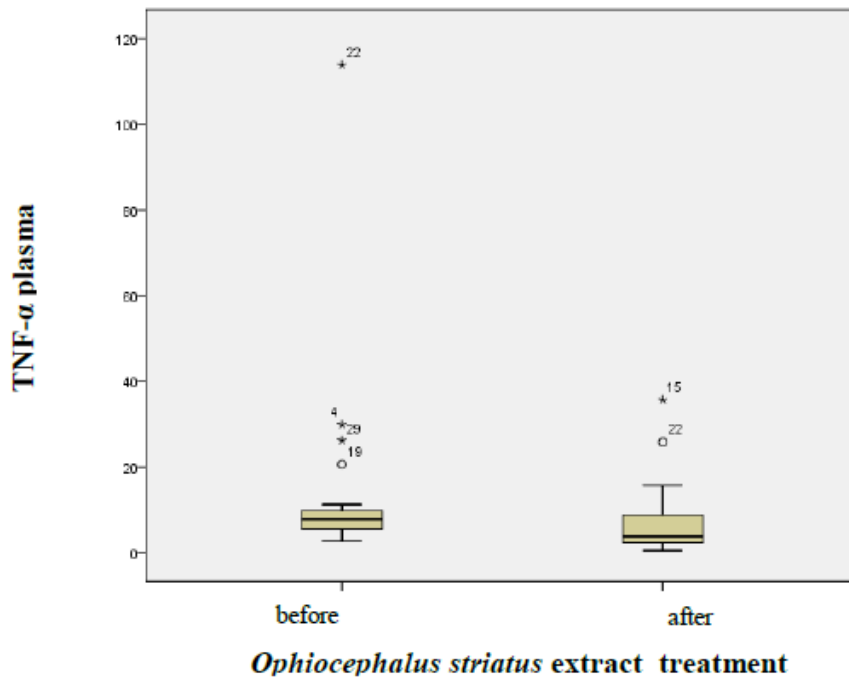


Figure 1. Boxplot Diagram for TNF-α before and after Ophioccephalus striatus extract consumption.

Discussion

Cancer cachexia is more common in male than female. This study showed 66.7% of all subjects with cancer cachexia were male subjects. Other studies also shown the same result. Study from Susanne et al reported 54% subjects with cancer cachexia were male in Netherland.¹² Lei Sun et al study reported 58.5% subjects were male in China.¹³ Average BMI value in this study was 17.14 kg/m² and categorized as underweight. Lei Sun et al study in China reported the same report where 64.8% subjects from the study were underweight.¹³

Raised in hemoglobin level after albumin extract treatment in this study did not show significant result statistically (p value = 0.177). Hematocrit level also showed the same interpretation as hemoglobin. Raised hematocrit level in this study did not show significant result statistically (p value = 0.127).

Renal function test (RFT) before and after treatment from this study did not show significant result statistically with p value = 0.366 from ureum and p value = 0.073 in creatinine level. GFR <15 mL/min/1.73 m² is one of exclusion factor in this study because decrease GFR can cause hypoalbumin state. Patient with chronic kidney disease has higher degradation plasma albumin compare to normal patient. The most common cause for hypoalbumin state in chronic kidney disease patient is chronic asidosis metabolic state and chronic inflammatory state that happen in the same time.¹⁴

Tumor Necrosis Factor-α (TNF-α) plasma level has positive correlation with progressive anorexia and weight loss, decreased adipose and muscle wasting, and changes in fat and protein metabolism, increased acute phase protein responses.¹⁵ This study found decreased in TNF-α plasma level before and after treatment with



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Ophiocephalus striatus extract. Before treatment, TNF- α average plasma level was 7.83 pg/mL and decreased to 3.82 pg/mL after treatment. Wilcoxon test used in this study showed highly significant decrease in TNF- α level statistically with p value 0.004. This study found raised in albumin plasma level before and after treatment with *Ophiocephalus striatus* extract and a statistically significant increase (p <0.001) in serum albumin levels of cancer cachexia patients after administration of *Ophiocephalus striatus* 5000 mg twice a day for two weeks.

Bossola et al. In 2000 found that TNF- α concentrations were consistently and significantly higher in cancer cachexia patients with severe weight loss compared to those with moderate or mild weight loss (p = 0.04).¹⁶ The results of a study conducted by Kemik et al in 2012 found higher serum TNF- α concentrations in cancer cachexia patients compared to controls (p <0.001) and found albumin in cancer cachexia patients lower than controls (p <0.001).¹⁷ Wei et al in 2014, with the administration of fish oil to Ca gaster, the results of the study increased albumin and decreased TNF- α .¹⁸ Weight loss occurs for two main reasons: a) decrease in skeletal muscle mass and b) decrease in adipose tissue, TNF- α is reported to play a role in both of these.¹⁵ Increased TNF- α levels in cachexia correlate with several cancer cachexia parameters associated with poor outcomes.¹⁹ The best known cachexia mediator factor is cytokines (tumor necrosis factor- α (TNF- α). Specifically, TNF- α hyperexpression has been identified as one of the key cytokine responses involved in cachexia.⁹ TNF- α hyperexpression that continuously results in progressive anorexia and weight loss. In addition, TNF- α appears to affect several cachexia cancer abnormalities: decreased adipose and muscle wasting, and changes in fat and protein metabolism.⁹ *Ophiocephalus striatus* extract can be considered as a potential natural support to have anti-inflammatory properties, decrease regulation of both pro-inflammatory cytokine production and acute phase protein responses in cancer patients.²⁰

Conclusion

Based on the results and discussion in this study, it can be concluded that there is a statistically significant decrease of serum TNF- α values before and after administration of *Ophiocephalus striatus* extract in cancer cachexia patients and there was a statistically significant increase in serum albumin levels in cancer cachexia patients after administration of *Ophiocephalus striatus* extract.

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