



## EFFECT OF OPHIOCEPHALUS STRIATUS EXTRACT ON CARNOSINE DIPEPTIDASE-1 PLASMA LEVEL IN CANCER CACHEXIA PATIENTS

**Yan Indra Fajar  
Sitepu**

Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/H. Adam Malik General Hospital Medan, Indonesia

**Dairion Gatot**

Division of Hematology and Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/ H. Adam Malik General Hospital Medan, Indonesia

**Andri Mardia**

Division of Hematology and Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/ H. Adam Malik General Hospital Medan, Indonesia

### ABSTRACT

The objective of this study is to find the association between *Ophiocephalus striatus* extract supplementation and carnosine dipeptidase-1 plasma level in patient with cancer cachexia. 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. Subjects were treated with *vipAlbumin*® supplementation which contains 5000 mg *Ophiocephalus striatus* extract in 2 weeks period. The result from this study shows raised in Carnosine Dipeptidase-1 plasma level before and after treatment with *Ophiocephalus striatus* extract ( $p=0.007$ ).

**KEYWORDS :** *Ophiocephalus striatus* extract, carnosine dipeptidase-1, cancer cachexia.

### 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.<sup>1</sup> 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.<sup>2,3</sup>

Epidemiological data showed that cachexia caused 20% mortality rate in cancer patients and affect 50 – 80% cancer patients.<sup>4</sup> Cancer cachexia incidence rate in Europe is around 1 million people in a year period and 430 thousand people in US each year. Pancreatic cancer (83%), gastric cancer (83%), Esophageal cancer (79%) and head and neck cancer (72%) cause most prevalence in cancer cachexia event.<sup>5</sup>

*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.<sup>6</sup> Carnosine is an anti-aging dipeptide that has antiproliferative and antioxidant activity. Carnosine maintain calcium release, skeletal muscle sensitivity, potentiate heart contractility, and reduce damage such as ischemia in many organs including kidney. Some studies showed that reduce in carnosine dipeptidase-1 concentration in cancer cachexia patients correlates with bad prognosis in patient with cancer cachexia.<sup>4,7</sup>

### 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 July 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,  $BMI < 20 \text{ kg/m}^2$  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 ( $Hb < 12 \text{ g/dL}$ ), low albumin serum concentration ( $< 3.2 \text{ g/dL}$ )

Exclusion criteria for this study was patient that refuse to join the study, patient that was not fit all the inclusion criteria, pregnant woman, patient that had other chronic disease such as diabetes mellitus, coronary heart disease, stroke, thyroid dysfunction, patient that had  $GFR < 15 \text{ ml/min/1.73m}^2$  and patient with proteinuria  $\geq +3$ .

All patient fitted for study and sign the consent included in this study. All subjects in this study had *vipAlbumin*® 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, 61.70%) 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  $17.14 \text{ kg/m}^2$  (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) <sup>a</sup>	51.47 16.95 <sup>a</sup>	
Antropometry		
Weight (kg) <sup>a</sup>	45.43 5.80 <sup>a</sup>	
Height (cm) <sup>a</sup>	162.67 5.97 <sup>a</sup>	
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	17.14 1.66 <sup>a</sup>	
Cancer Classification		
GIT	14	46.7
Lung	6	20
Nasopharynx	4	13.3
NHL	2	6.7
others	4	13.3
Status kemoterapi		
Chemotherapy	25	83.3
Non-chemotherapy	5	16.7

<sup>a</sup>normal distribution, average SD

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 <sup>a</sup>	9.54 1.53
Hematocrit <sup>a</sup>	28.57 4.53
Leucocyte <sup>b</sup>	10320 (2480-29960)
Thrombocyte <sup>a</sup>	309400 159651
Ureum <sup>b</sup>	30 (6-133)
Creatinine <sup>b</sup>	0.7 (0.34-3.11)
SGOT <sup>b</sup>	27 (8-175)
SGPT <sup>b</sup>	19 (6-83)
Albumin <sup>a</sup>	2.47 0.43 <sup>a</sup>
D-dimer <sup>b</sup>	586 (100-6231)
Fibrinogen <sup>b</sup>	280 (80-1335)
CRP <sup>b</sup>	1.4 (0.7-2,8)
Carnosine Dipeptidase-1 <sup>b</sup>	2.21 (1.01-3.51)

<sup>a</sup>normal distribution, average SD

<sup>b</sup>abnormal 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 Carnosine dipeptidase-1 plasma level changes before and after treatment with p value 0.007. Plotbox diagram also shows raised in Carnosine Dipeptidase-1 plasma level before and after treatment with *Ophiocelphalus striatus* extract.

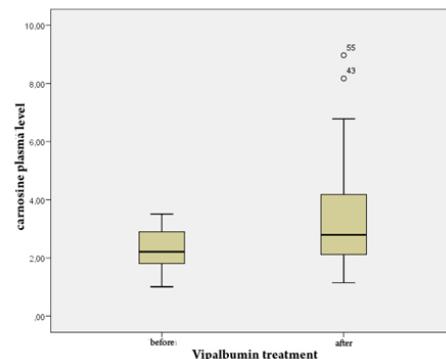
**Table 3. Subject Laboratorium value before and after treatment**

Parameter	Before (n=30)	After (n=30)	P value
Hemoglobin <sup>a</sup>	9.461.51	9.931.65	0.177
Hematocrit <sup>a</sup>	28.324.56	30.00 5.25	0.127
Leucocyte <sup>b</sup>	10320 (2480-29960)	8760 (2680-31890)	0.820

Thrombocyte <sup>b</sup>	307500 (24000-757000)	342000 (25000-523000)	0.406
Ureum <sup>b</sup>	30 (6-133)	29 (13-133)	0.366
Creatinine <sup>b</sup>	0.77 (0.34-3.11)	0.70 (0.32-2.61)	0.073
SGOT <sup>b</sup>	27 (8-175)	24 (10-64)	0.490
SGPT <sup>b</sup>	19 (6-83)	22 (6-106)	0.147
CRP <sup>b</sup>	1.4 (0.7-2.8)	1.4 (0.7-2.8)	0.347
CNDP1 <sup>b</sup>	2.21 (1.01-3.51)	2.8 (1.15-8.97)	0.007*
BMI <sup>a</sup>	17.141.66	17.041.74	0.496

<sup>a</sup>normal distribution, average SD

<sup>b</sup>abnormal distribution, median (min.-max.)



**Figure 1. Boxplot Diagram for carnosine concentration before and after Vipalbumin 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.<sup>8</sup> Lei Sun et al study reported 58.5% subjects were male in China.<sup>9</sup> Average BMI value in this study was 17.14 kg/m<sup>2</sup> and categorized as underweight. Lei Sun et al study in China reported the same report where 64.8% subjects from the study were underweight.<sup>9</sup> US study from Martin et al found BMI less than 18 kg/m<sup>2</sup> and weight loss more than 8 kg in 652 study subjects.<sup>10</sup>

Raised in hemoglobin level after albumin treatment in this study did not show significant result statistically (p value = 0.177). Same finding found in Heirardi et al study in Iran that albumin raised hemoglobin level but did not show any significant result statistically (p value = 0.20).<sup>11</sup> Hematocrit level also showed the same interpretation as hemoglobin. Raised hemoglobin 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 showed insignificant result statistically with p value 0.366 from ureum and p value 0.073 in creatinine level. GFR < 15 mL/min/1.73 m<sup>2</sup> 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 acidosis metabolic state and chronic inflammatory state that happen in the same time.<sup>12</sup>

Carnosine dipeptidase-1 (CNDP1) plasma level has positive correlation with BMI score, fat mass and albumin concentration and correlates negatively with weight loss percentage, PC-SGA score, and lipolysis. Arner et al study found significant correlation between CNDP1 plasma level and BMI score, fat mass, weight loss percentage and lipolysis.<sup>13</sup> This study found raised in CNDP1 plasma level before and after treatment with *Ophiocelphalus striatus* extract. Before treatment, CNDP1 average plasma level was

2.21  $\mu$ g/mL and it raised to 2.8  $\mu$ g/mL after treatment. Wilcoxon test used in this study showed highly significant raised in CNDP1 level statistically with p value 0.007.

Yang et al in Shanghai Traditional Chinese Medicine-Integrated Hospital and First People's Hospital of Benxi on 184 patients with cancer cachexia reported decreased in carnosine level in the early stage of cancer and raised in cachexia patients. ROC analysis shows AUC 0.932 which made high specificity and sensitivity. Carnosine is histidine dipeptide and alanine that has high concentration in skeletal muscle and brain. Some study stated that carnosine supplementation can regulate brain function and raise plasma corticosterone through *hypothalamic-pituitary-adrenal axis*.<sup>14</sup> Letzien et al stated that carnosine potentiated to depress biochemical changes from oxidized protein, glycation and crosslinked. Low level of carnosine dipeptidase-1 also said to be a bad prognostic cancer included weight loss, malnutrition, fat degradation, hypoalbumin state and bad quality of life in patient with gastrointestinal cancer. Lately, carnosine is said to be contributed in body weight regulation.<sup>13,15</sup>

Carnosine has a ergogenic effect in which people with high carnosine level can delayed fatigue when in high intensity exercise. This caused by supplementation  $\beta$ -alanine as a result from carnosine as a pH buffer, calcium stimulator and/or as antioxidant. Other than carnosine ergogenic effect, carnosine may contribute in homeostatic effect to organ except muscle and frailty to some diseases but this fact need more study.<sup>16</sup>

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