INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

THE EFFECT OF OPHIOCEPHALUS STRIATUS EXTRACT ON SERUM LEPTIN LEVEL OF CANCER CACHEXIA PATIENTS

Rury Armayni Siregar*[1], Andri Mardia[2] & Dairion Gatot[3]

*[1]Departement of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/ Haji Adam Malik General Hospital Medan, Indonesia

[2]Hematology-Oncology Division, Departement of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/ Haji Adam Malik General Hospital Medan, Indonesia

[3]Hematology-Oncology Division, Departement of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/ Haji Adam Malik General Hospital Medan, Indonesia

DOI: https://doi.org/10.29121/ijrsm.v8.i1.2021.1

Keywords: Leptin, Cancer Cachexia, Ophiocephalus Striatus.

Abstract

Cancer is a disease caused by the abnormal growth of tissue cells that turn into cancer cells. Cancer can cause severe adverse effects for nutritional status. One of the nutritional problems that need attention in cancer patients is cachexia. The pathophysiology of cancer cahexia is multifactorial and not fully understood. Until now, the inflammation is a common concept raised by several studies on cancer cachexia. Leptin is a hormone produced by adipose tissue and is a member of adipocytokines that play a role in adipose tissue signaling hormones. Leptin plays an important role in signaling that regulates energy homeostasis is both central and peripheral, reduce appetite, adipose tissue mass and body weight. Cork fish or Snakehead (Family Channidae) are known to contain higher protein than other fish species. Cork fish is a potential source of albumin. This study was conducted with the aim to determine the effect of cork fish extract on serum leptin levels in cancer cahexia patients. This study is an open label clinical trial with one group pretest-posttest design. The study was conducted in July - December 2019 at the Haji Adam Malik Hospital in Medan with the approval of the USU FK Research Ethics Commission. Data were analyzed using SPPS program where $p < 0.05$ was considered significant. This study showed that there was a significant difference in the serum leptin levels of the subjects before and after receiving Ophiocephalus striatus extract for two weeks.

Introduction

Cancer is a disease that arises from the abnormal growth of body tissue cells that turn into cancer cells.[1] According to WHO, cancer is a disease characterized by abnormal cell growth which can then attack adjacent parts of the body and / or spread to other organs. Cancer can have detrimental effects on nutritional status.[2] One of the nutritional problems that need attention in cancer patients is cachexia.[3]

Cachexia comes from Greek, namely "kakos" which means "bad" and "hexis" which means "condition", so kaheksia is defined as "bad condition". According to the international consensus in 2011, Cancer cachexia is defined as a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[4] Cachexia is classified as a Patients who have more than 5% loss of stable body weight over the past 6 months, or a bodymass index (BMI) less than 20 kg/m2 and ongoing weight loss of more than 2%, or sarcopenia and ongoing weight loss of more than 2% (for defi nition see panel), but have not entered the refractory stage. Cancer cachexia is a continuum (with three stages of clinical relevance: precachexia, cachexia, and refractory cachexia. [4]

Cachexia occurs in about 15% to 40% of cancer patients and more than 80% of patients with advanced disease which will substantially impact the quality and survival of the affected patient.[5] Of all cancer patients, half had lost weight and one third had lost more than 5% of weight, which is a criterion for cancer cachexia.[6,7] Based on published data it is reported that the prevalence of cachexia in advanced cancer ranges from 60% to 80%, and the overall prevalence of weight loss in cancer patients can increase to 86% in the last 1-2 weeks of life.[7,8] The incidence of weight loss after diagnosis has been shown to vary widely, according to the location of the tumor.[7,9] A landmark study of more than 3,000 patients enrolled in various chemotherapy trials of the eastern cooperative oncology group (ECOG) reported that the greatest incidence of weight loss was seen in patients with solid tumors (eg stomach tumors, pancreatic tumors, lung tumors, tumors colorectal, as well as head and neck tumors). [7,9]

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Cancer cachexia directly contributes to 30% of cancer deaths and more than 50% of cancer patients die from cachexia. [8,10]

Causes of cancer cachexia can be categorized into two groups, namely: primary and secondary cachexia.[11] Primary cachexia is caused by metabolic changes triggered by tumors. The cancer itself produces tumor products that interfere with normal tissue repair. Secondary cachexia is caused by factors that interfere with food intake which will lead to malnutrition including nausea, vomiting, stomatitis, changes in taste and smell such as those caused by chemotherapy, diarrhea, constipation, fatigue and mechanical obstruction such as a tumor covering the esophagus.[11,12]

Clinical cancer cachexia is divided into 3 stages, namely: pre-cachexia, cachexia and refractory cachexia.4 In pre-cachexia early clinical and metabolic signs (such as anorexia and impaired glucose tolerance) can precede accidental weight loss (i.e. %).[4] In patients who experienced stable weight loss of more than 5% over the past 6 months, or body mass index (BMI) <20 kg / m2 and sustained weight loss of more than 2%, or sarcopenia and weight loss persistence of more than 2% but not yet in the refractory stage is classified as cachexia.[4] Whereas in refractory cachexia, cachexia can be clinically refractory due to very advanced cancer or very rapidly progressive cancer that is not responsive to anti-cancer treatment.[4]

The pathophysiology of cancer cachexia is multifactorial and not fully understood.[13] Cancer cachexia is considered as the result of interactions between the host and the tumor is not fully understood.[14,15] Until recently, inflammation was a general concept that has been generated by several studies on cancer cachexia.[16,17] A common feature of advanced cancer is that the immune response fails to eradicate the tumor due to the complexity of immune avoidance mechanisms that limit the protective response of the host. This tumor-host relationship precipitates chronic systemic inflammation, in which normal adaptive regulatory mechanisms become dysfunctional. This inflammatory state is accompanied by the unprogrammed production of inflammatory mediators (including cytokines) causing abnormalities in the central and peripheral regulatory systems. In animal models, collected data support a role for proinflammatory cytokines, including interleukin (IL) -1β, IL-6, tumor necrosis factor (TNF) -α, and interferon-γ, in the development of cancer cachexia. These cytokines are involved in mediating various systemic effects, including the acute phase response (APR) by the liver, hypermetabolism, acidosis, damage to skeletal muscle protein, and reduced appetite.[18-23] In addition, although not well understood, several factors associated with tumors, such as proteolysis inducing factor (PIF) and lipid mobilizing factor (LMF), are each believed to play a role in decrease muscle tissue and fat.[17,24,25] There are factors that play a role in the pathophysiology of cancer cachexia, such as: tumor factors, host-tumor factors, host factors, anorexia, metabolic changes.Leptin comes from the Greek which means thin.[26,27]

Leptin is a hormone produced by adipose tissue and is a member of adipocytokines that play a role in the signaling hormone of adipose tissue.[23,24] Leptin has an important role in signaling which regulates energy homeostasis, both central and peripheral, reducing appetite, adipose tissue mass and body weight. Leptin also plays a role in other body tissues, such as reproductive organs, breast glands, immune system, kidney, lungs and bones.[25] The main function of leptin is to provide a signal for energy stores in the body to the central nervous system so that the brain can make the necessary adjustments to balance energy intake and expenditure.[31,32] If leptin levels in the brain are low, it increases the activity of oroxygenic signals in the hypothalamus, which stimulates food cravings and suppresses energy expenditure and decreases anorexigenic signals. Meanwhile, neuropeptide Y is the most potent peptide in stimulating food cravings and is associated with other oroxygenic pathways (such as galanine, opioid peptides, melanin-concentrating hormone / MCH, orexin, and agouti-related peptides / AGRP).[33] In cancer cachexia, cytokines may stimulate anorexigenic pathways in the long term. IL-1, IL-6 and TNFα can stimulate leptin release thereby increasing the activity of anorexigenic pathways. In addition, several cytokines can penetrate the blood brain barrier and also inhibit oroxygenic pathways.[33]

Snakehead fish (Family Channidae) is a type of freshwater fish. Snakehead fish are known to contain higher protein than other types of fish.[34,35] Snakehead fish is a potential source of albumin. Health practitioners have used snakehead fish extract as a supplementary food (extra menu) for sufferers indicated by hypoalbuminemia, burns, and diet after surgery. Several studies have shown that snakehead fish extract has a high albumin content and can help heal surgical wounds.[36] Other studies have also reported that the use of snakehead fish as a source of protein can maintain the albumin value of inpatients so that it can help speed up the patient's healing process.[37] Until now there has been no research on the effect of snakehead fish extract on serum leptin levels in cancer cachexia patients.

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

So this research was conducted to determine the effect of ophiocephalus striatus extract on serum leptin levels in cancer cachexia patients.

Method

This study is an open label clinical trial with a one group pretest posttest design. The study was conducted at Haji Adam Malik Genereal Hospital Medan from July 2019 to December 2019 with the approval of the Research Ethics Commission of the Faculty of Medicine, University of North Sumatra. The informed consent was obtained from subjects who were willing to participate in this study.

Patients who have met the criteria as research subjects will be given Ophiocephalus striatus extract for 2 weeks. The research sample was cancer cachexia patients who were treated at the General Hospital of Haji Adam Malik Medan during the study period and met the inclusion and exclusion criteria. The inclusion criteria in this study were: Patients who had been diagnosed with cancer, age ≥ 18 years, patients who met the criteria for cachexia such as weight loss> 5% over the last <12 months; or BMI <20kg / m2, plus 3 of the following 5 criteria such as decreased muscle strength, fatigue, anorexia, low free fat mass index, biochemical abnormalities; increased markers of inflammation (CRP, IL-6), anemia (Hb <12gr / dL), low serum albumin levels (<3,2 g / dL). The exclusion criteria in this study were: Pregnant women, GFR <15, Proteinuria +3, severe systemic diseases such as pulmonary infections, and sepsis, history of other chronic diseases such as diabetes mellitus, coronary heart disease, stroke, thyroid dysfunction, human *immunodeficiency* virus, and chronic kidney disease.

Results

This study was followed by 30 cancer cachexia subjects who had met the inclusion and exclusion criteria. The subjects were given snakehead fish extract (Ophiocephalus striatus) at a dose of 2 x 5000 mg for 2 weeks. Table 1 describes the basic characteristics of the study subjects. The male subject of 20 people (66.7%) and female subjects were 10 people (33.3%). The mean age of the research subjects was 52±17 years. The mean body mass index (BMI) was 17.1±1.66 kg / m2. The most types of cancer in this study were gastrointestinal cancer as many as 14 people (46.7%).

Table – 1 Basic Characteristic Of The Subjects

Characteristic	n=30	%
Gender		
Male	20	66,7
Female	10	33,3
Age (years)[a]	52±17[a]	
Anthropometry		
Weight (kg)[a]	45,4±5,8	
Height (cm)[a]	162,7 ± 6,0	
IMT (kg/m^2)[a]	17,14±1,66	
Upper arm circumference[b] (cm)	26,4 (22,3-27,5)	
Cancer type		
GIT	14	46,7
Lungs	6	20
Nasopharyngeal Carcinoma	4	13,3
NHL	2	6,7
Ovarium	2	6,7
Thyroid	1	3,3
Breast	1	3,3
Chemotherapy status		
Chemotherapy	25	16,7
Non- Chemotherapy	5	83,3

[a]normal distribution; mean±SD
[b]abnormal distribution; median (minimum-maximum)

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Table 2 describes the results of laboratory examinations of research subjects. The mean hemoglobin (Hb) was 9,5±1,5 gr / dL. The mean hematocrit (Ht) was 28,3±4,6%. The median leukocytes were 10320 (2480-29960) / mm3. The median platelet count was 327000 (24000-757000) / mm3. The level of urea was 32 (6-133) mg / dL, creatinine was 0.79 (0.35-3.11) mg / dL. SGOT level were 26 (13-175) u / L and SGPT level were 20 (6-83) u / L. D-dimer level were 586 (100-6231) ng / mL and Fibrinogen level were 280 (80-1335) mg / dL. The mean albumin levels were 2.46±0.46 gr / dL. CRP level of 1.4 (0.7-2.8) mg / dL. The leptin level was 1.39 (0.06-11.86) ng / mL.

Table – 2 The Results Of The Laboratory Examination Of The Subject

Characteristic	n=30
Hemoglobin [a] (gr/dL)	9,5±1,5
Hematocrit[a] (%)	28,3±4,6
Leukocytes[b] (cells/mm^3)	10320 (2480-29960)
Platelets [a] (cells/mm^3)	327000 (24000-757000)
Urea[b] (mg/dL)	32 (6-133)
Creatinine[b] (mg/dL)	0,79 (0,35-3,11)
SGOT[b] (u/L)	26 (13-175)
SGPT[b] (u/L)	20 (6-83)
Albumin[a] (gr/dL)	2,46 ± 0,46
D-dimer[b] (ng/mL)	586 (100-6231)
Fibrinogen[b] (mg/dL)	280 (80-1335)
CRP[b] (mg/L)	1,4 (0,7-2,8)
Leptin[b] (ng/mL)	1,39(0,06-11,86)

[a]normal distribution; mean±SD
[b]abnormal distribution; median (minimum-maximum)

Table 3 shows the comparison of clinical and laboratory parameters before and after therapy. The results showed that there were significant differences in serum albumin and leptin levels before and after receiving Ophiocephalus striatus extract at a dose of 5000 mg twice per day for two weeks (p <0.001).

Table – 3 Clinical And Laboratory Parameters Before And After Administration Of Ophiocephalus Striatus Extract

Parameters	Before (n=30)	After (n=30)	P
Weight[a] (kg)	45,4±5,8	45,5±5,7	0,629
IMT[a] (kg/m^2)	17,14±1,66	17,18±1,63	0,598
Upper arm circumference[b] (cm)	26,4 (22,3-27,5)	26,5 (22,3-27,5)	0,060
Hemoglobin[a] (gr/dL)	9,5±1,5	9,9±1,7	0,177
Hematocrit[a] (%)	28,3±4,6	30,0±5,3	0,127
Leukocytes[b] (sel/mm^3)	10320 (2480-29960)	8760 (2680-31890)	0,820
Platelets[b] (sel/mm^3)	327000 (24000-757000)	342000 (25000-523000)	0,406
Urea[b] (mg/dL)	32 (6-133)	29 (13-133)	0,366
Creatinine[b] (mg/dL)	0,79 (0,35-3,11)	0,70 (0,32-2,61)	0,073
SGOT[b] (u/L)	26 (13-175)	24 (10-64)	0,490
SGPT[b] (u/L)	20 (6-83)	22 (6-106)	0,147
Albumin[a] (gr/dL)	2,46±0,46	2,92±0,56	<0,001**
CRP[b] (mg/L)	1,4 (0,7-2,8)	1,4 (0,7-2,8)	0,347
Leptin[b] (ng/mL)	1,39(0,06-11,86)	0,13 (0,04-10,88)	<0,001**

[a]normal distribution; mean±SD; paired t-test
[b]abnormal distribution; median (minimum-maximum); Wilcoxon
* significant, p<0,05
** very significant, p<0,001

Table 4 shows the differences in albumin and leptin levels before and after therapy in the chemotherapy and non-chemotherapy groups. There were no significant differences in albumin and leptin levels before and after

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

administration of Ophiocephalus striatus extract in the chemotherapy and non-chemotherapy groups (p = 0.403 and 0.338).

Table – 4 Difference Of Albumin And Adiponectin Level Based On Chemotherapy Category

Parameters	Before	After	Δ	P
Albumin (gr/dL)				
Chemotherapy	3,02	3,60	0,58	0,403
Non-Chemotherapy	2,33	2,76	0,43	
Leptin				
Chemotherapy	3,64	3,17	-0,47	0,338

Inpaired t-test

Discussion

The development of science and research has revealed the fact that snakehead fish (Ophiocephalus striatus) have very good nutrition for health. This content consists of high protein content, especially albumin and essential amino acids, fats especially essential fatty acids, minerals especially zinc (Zn) and several vitamins which are very good for health. Snakehead fish has a higher protein content than other types of fish. Protein content of snakehead fish is 25.5% higher than other fish protein. In addition, albumin levels Snakehead fish reached 6.22%.[34]

This study showed an increase in body mass index (BMI) in cancer cachexia patients after administration of Ophiocephalus striatus extract for two weeks from 17.14 ± 1.66 kg / m2 to 17.1 ± 1.63 kg / m2. In addition, there was also an increase in body weight in cancer cachexia patients after receiving Ophiocephalus striatus extract for two weeks from 45.± 5.8 kg to 45.5 ± 5.7 kg. However, statistically the increase in BMI and body weight was not significant (p = 0.598 and 0.629). Previous study conducted by Komang et al at Dr. Saiful Anwar Hospital in Malang on COPD patients with malnutrition, where the results of this study found an increase in BMI from 20 ± 3.570 to 21 ± 3.497 and an increase in body weight from 51.94 kg to 52.84 kg after receiving Ophiocephalus striatus extract for 12 weeks.[38] The increase in BMI is probably due to a decrease in leptin levels, which increases appetite and decreases energy expenditure, resulting in an increase in food intake which causes weight gain followed by an increase in BMI. In this study, an increase in BMI and body weight might achieve better results if the administration of Ophiocephalus striatus extract was longer.

This study showed an increase in serum albumin levels in cancer cachexia patients after administration of Ophiocephalus striatus extract at a dose of 5000 mg twice per day for two weeks. The mean serum albumin level in cancer cachexia patients before receiving Ophiocephalus striatus extract was 2.46 gr / dL and after receiving Ophiocephalus striatus extract increased to 2.92 g / dL. Based on previous studies, it was shown that there were differences in serum albumin levels in patients with nephrotic syndrome who received snakehead fish extract and those who did not. In the group that received snakehead fish extract, albumin levels increased by 0.92 ± 1.105 g / dL compared to those who did not get snakehead fish extract of 0.57 ± 0.422 g / dL.[39] The increase in albumin levels is because snakehead fish are a potential source of albumin. From various studies, it is known that extra snakehead fish can significantly increase albumin levels in cases of albuminemia.

This study showed a decrease in serum leptin levels in cancer cachexia patients after administration of Ophiocephalus striatus extract at dose of 5000 mg twice per day for two weeks. The mean serum leptin level in cancer cachexia patients before receiving Ophiocephalus striatus extract was 1.39 (0.06-11.86) ng / mL and after receiving Ophiocephalus striatus extract decreased to 0.13 (0.04-10 , 88) ng / mL. This study is similar to a study that has been conducted in COPD patients, when compared to before receiving snakehead fish extract, there was a significant decrease in leptin levels (p = 0.000) after receiving snakehead fish extract.[38] The decrease in leptin levels was probably due to the anti-inflammatory effect of snakehead fish extract resulting in a decrease in systemic pro-inflammatory cytokines such as CRP, TNF-α and IL-6 which were positively correlated with decreased circulating leptin and increased levels of anti-inflammatory cytokines such as IL-10 and IL- 1 receptor antagonist. The mechanism regarding the effect of snakehead fish extract on leptin levels is still unknown.

In this study, there were no significant differences in hemoglobin, hematocrit, leukocyte, and platelet levels in cancer cachexia patients before and after administration of Ophiocephalus striatus extract. This is similar to a study conducted by Pettalolo, where there was no significant difference in hemoglobin and leukocyte levels in

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

patients after receiving snakehead fish extract for four weeks. [40] In this study, there were also no significant differences in liver function and kidney function before and after administration of Ophiocephalus striatus extract for two weeks. There were no side effects in the subjects during the study period. This has been proven in previous studies that giving snakehead fish extract for six weeks does not cause side effects in patients. [41]

There are several limitations to this study. The short duration of the study caused the results that were not optimal in the study subjects both in terms of benefits and side effects. Research with a longer time is needed to get more concrete results regarding the effects of Ophiocephalus striatus extract.

Conclusion

There was a decrease in serum leptin levels and an increase in serum albumin levels in cancer cachexia patients after administration of the Ophiocephalus striatus extract at a dose of 5000 mg twice daily for two weeks. There was no significant difference in BMI and body weight in cancer cachexia patients after administration of Ophiocephalus striatus extract.

References

[1] Kementrian Kesehatan RI. Stop Kanker. Jakarta: Pusat Data dan Informasi Kementrian Kesehatan RI; 2015.
[2] Cancer [Internet]. World Health Organization. World Health Organization; [cited 2018Dec10]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer.
[3] Boediwarsono. Terapi Nutrisi Pada Penderita Kanker. Dalam: Naskah Lengkap Surabaya Hematology Oncology Update IV. Medical Care of the Cancer Patient, editor: Boediwarsono, Soegianto, Ami Ashariati, Made Putra Sedana, Ugroseno; 2012. hlm 134-141.
[4] Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011; 12: 489-495.
[5] Berenstein EG, Ortiz Z. Megestrol acetate for the treatment of anorexia-cachexia syndrome (Protocol for a Cochrane Review). The Cochrane Library. 2004;4:1-7.
[6] Martignoni ME, Kunze P, Friess H. Cancer cachexia. Molecular Cancer. 2003;2:1-3.
[7] **Tan BHL et al.,** Cachexia: prevalence and impact in medicine. *Curr Opin Clin Nutr Metab Care* 2008;11(4):400-7.
[8] **Von Haehling S et al.,** Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle* 2010;1:1-5.
[9] **Dewys WD et al.,** Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* 1980;69(4):491-97.
[10] Hopkinson JB, Wright DNM, Foster C. Management of weight loss and anorexia. Ann Oncol. 2008;19(7):vii289-vii293.
[11] Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. CA Cancer J Clin. 2002;52:72-91.
[12] Uomo G, Galluci F, Rabitti PG. Anorexia-cachexia syndrome in pancreatic cancer: recent development in research and management. J Pancreas. 2006;7(2):157-62.
[13] Skipworth RJ, Dahele M, Fearon KC. Diseases associated with cachexia: cancer. In: Hofbauer KG, Anker SD, Inui A, Nicholson JR, editors. Pharmacotherapy of cachexia. 1st ed. Baco Raton, FL: CRC Press; 2006. p. 117–42.
[14] Stewart GD, Skipworth RJ, Fearon KC. Cancer cachexia and fatigue. Clin Med 2006;6:140–3.
[15] Anker SD, Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest. 1999;115:836–847.
[16] MacDonald N, Easson AM, Mazurak VC, et al. Understanding and managing cancer cachexia. J Am Coll Surg. 2003;197:143–161.
[17] O'Riordain MG, Falconer JS, Maingay J, et al. Peripheral blood cells from weight-losing cancer patients control the hepatic acute phase response by a primarily interleukin-6 dependent mechanism. Int J Oncol. 1999;15:823–827.
[18] Zhou W, Jiang ZW, Tian J, et al. Role of NF-kappaB and cytokine in experimental cancer cachexia. World J Gastroenterol. 2003;9:1567–1570.
[19] Wigmore SJ, Fearon KC, Maingay JP, et al. Effect of interleukin-2 on peripheral blood mononuclear cell cytokine production and the hepatic acute phase protein response. Clin Immunol. 2002;104:174–182.

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

[20] Costelli P, Bossola M, Muscaritoli M, et al. Anticytokine treatment prevents the increase in the activity of ATP-ubiquitin- and Ca(2+)-dependent proteolytic systems in the muscle of tumour-bearing rats. Cytokine. 2002;19:1–5.
[21] Llovera M, Garcia-Martinez C, Agell N, et al. TNF can directly induce the expression of ubiquitin-dependent proteolytic system in rat soleus muscles. Biochem Biophys Res Commun. 1997;230:238–241.
[22] Baracos V, Rodemann HP, Dinarello CA, et al. Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1): a mechanism for the increased degradation of muscle proteins during fever. N Engl J Med. 1983;308:553–558.
[23] Todorov P, Cariuk P, McDevitt T, et al. Characterization of a cancer cachectic factor. Nature. 1996;379:739–742.
[24] Todorov PT, McDevitt TM, Meyer DJ, et al. Purification and characterization of a tumor lipid-mobilizing factor. Cancer Res. 1998;58:2353–2358.
[25] Donohue CL, Ryan AM, Reynolds JV. Cancer cachexia: Mechanisms and clinical implications. Gastroenterol Res Pract. 2011; doi:10.155/2011/601434.
[26] M.J Tisdale. Mechanisms of cancer cachexia. Physiological Reviews. 2009; 89(2): 381-410.
[27] Yang R, Barouch LA. Leptin signaling and obesity cardiovascular consequences. Circulation Research Journal of The American Heart Association. 2007;101:545-59.
[28] Brabant G, Muller G, Horn R, Anderwald C, Roden M, Nave H. Hepatic leptin signaling in obesity. The FASEB Journal.2005;19:48-50.
[29] Paracchini V, Pedotti P, Taioli E. Genetics of leptin and obesity. American Journal of Epidemiology. 2005;162(2):101-14.
[30] Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998;395(6704):763–70.
[31] Enriori PJ, Evans AE, Sinnayah P, Jobst EE, Tonelli-Lemos L, Billes SK, et al. Diet-Induced Obesity Causes Severe but Reversible Leptin Resistance in Arcuate Melanocortin Neurons. Cell Metabolism. 2007;5(3):181–94.
[32] Gupta, D., Vashi, P.G., Lammersfeld C.A., Braun, D.P., 2011. Role of Nutritional Status in Predicting theLength of Stay in Cancer: A Systematic Review of the Epidemiological Literature. Cancer Treatment Centers of America _ at Midwestern Regional Medical Center, Zion, Ill., USA, 2011;59:96–106
[33] Carvallo. Studi profil asam amino, albumin dan mineral Zn pada ikan gabus dan Tomang Skripsi, Unibraw. Malang.1998.
[34] A, Mustafa, M. Aris Widodo, Yohanes Kristianto. 2012. Albumin And Zinc Content Of Snakehead Fish (Channa striata) Extract And Its Role In Health. IEESE International Journal of Science and Technology (IJSTE), Vol. 1 No. 2, June 2012,1-8.
[35] Salma, Wa Ode.. Pengaruh Pemberian Kapsul Ikan Gabus Terhadap Kadar Albumin Dan Status Gizi Pada Pasien ODHA (Orang Dengan HIV/AIDS) Di RSU Dr. Wahidin Sudirohusodo Makassar. Program Pascasarjana Universitas Hasanuddin. 2007.
[36] Taslim NA., Penyuluhan Gizi, Pemberian Soy Protein Dan Perbaikan Status Gizi Penderita Tuberkulosis di Makassar. Jurnal Medika Nusantara. Vol. 25. No. 2. www.med.unhas.ac.id. 2004.
[37] Widiasari, Komang Sri Rahayu, Susanthy Djajalaksana, Harun Al Rasyid. Pengaruh Pemberian Ekstrak Ikan Gabus Terhadap Kadar Leptin, Adiponektin dan Skor COPD Assessment Test pada Pasien PPOK Stabil yang Mengalami Muscle Wasting. J Respir Indo Vol. 38 No. 3 Juli 2018.
[38] Kusumawardhani, T. 2004. Pemberian Diet Formula Tepung Ikan Gabus (Ophiocephalus striatus) pada Penderita Sindrom Nerotik. T esis. Program Pendidikan Dokter Spesialis I Bagian Ilmu Kesehatan Anak. Fakultas Kedokteran. Universitas Diponegoro. Semarang.
[39] Sri Rezeki Pettalolo. Suplementasi ekstrak ikan gabus dan vitamin c terhadap kadar hemoglobin, lekosit, limfosit, albumin, dan IMT pada pasien HIV/AIDS. Gizi Indon 2015, 38(1):41-48.
[40] Todorov P, Cariuk P, McDevitt T, et al. Characterization of a cancer cachectic factor. Nature. 1996;379:739–742.