RESEARCH ARTICLE

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Effect of Channa striata Extract Supplementation on Febrile Neutropenia in Acute Myeloid Leukemia Patients Undergoing Chemotherapy: A Randomized Controlled Study

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Abstract

Introduction: Febrile neutropenia is one of the most serious complications in patients with hematological malignancies and chemotherapy. Channa striata is a freshwater fish belonging to the family Channidae. This study aims to determine whether the administration of channa striata extract can increase neutrophil count, neutrophil function and prevent incidence of febrile neutropenia in acute myeloid leukemia (AML) patients receiving chemotherapy. **Method:** A randomized, single-blind, controlled study compared a standard nutrition from hospital with a channa striata extract–supplemented per oral containing 6 grams of channa striata extract in patients with acute myeloid leukemia undergoing intensive chemotherapy. To analyze the effects of channa striata extract on function of neutrophil, Interleukin (IL)-6 and nitric oxide (NO) levels which are the result of neutrophil phagocytosis were assessed. **Results:** A total of 32 AML patients were randomized to receive per oral supplementation of channa striata extract (6 g/day) or nutrition from the hospital during intensive chemotherapy and after chemotherapy. The median onset of neutropenia was 6.1 + 3.37 in the channa striata extract group and 8.8 + 4.59 in the control group (p=0.109). The median duration of neutropenia was 12.8 + 6.20 d in the channa striata group and 17.2 + 11.06 d in the control group (p=0.281), whereas the incidence of febrile neutropenia were 85,7% in the channa striata extract group and 43,8% in the control group with median duration of neutropenic fever were 5.7 + 3.56 and 4.7 + 4.57, respectively. The chi-square test in the IL-6 delta category showed a tendency for IL-6 levels to rise in 61.5% of subjects in the Channa striata group compared to the control group (p=0.182). **Conclusion:** Channa striata extract supplementation did not influence neutropenia onset, duration, neutrophil function, or neutropenic fever in AML patients.

Keywords: Channa striata extract- AML- intensive chemotherapy- febrile neutropenia

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Introduction

Neutropenic fever is a serious and potentially fatal side effect of various forms of chemotherapy, characterized by high morbidity and mortality rates. Neutropenic fever often necessitates decisions to reduce or delay subsequent chemotherapy doses, thereby impacting treatment success [1, 2]. Fever is defined as a single oral temperature measurement > 38.3°C (101°F) or a sustained temperature >38.0°C (100.4°F) over one hour [2]. Neutropenia refers to an absolute neutrophil count (ANC) <500 cells/mm3 or an anticipated decline to <500 cells/mm3 over the next 48 hours.2,3 Neutropenic fever occurs when the ANC is <500 cells/mm3 or expected to decline to < 500 cells/mm3 over the next 48 hours accompanied by fever or clinical signs of sepsis [3, 4].

Patients with cancer may experience decreased ANC due to direct effects on hematopoietic systems from conditions like leukemia or bone marrow metastases or as a result of cytotoxic therapy. The nadir of ANC typically occurs between days 5 to 10 after the last chemotherapy session in most outpatient regimens. Inpatient regimens, particularly those for hematologic malignancies, have a higher propensity for inducing neutropenia [5]. Patients undergoing intensive chemotherapy for acute myeloid leukemia (AML) face a high risk of infection complications. Serious infections are a major cause of morbidity and mortality in this patient group. Vulnerability to infection increases with neutrophil counts < 0.1×10^9/L lasting more than 10 days. Other risk factors include cellular and humoral immune disorders, severe mucositis, bleeding disorders in the skin and mucous membranes,

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and intravenous access, predisposing AML patients to infections [6].

The administration of granulocyte colony-stimulating factor (G-CSF) is costly, prompting research into affordable alternatives that can maintain neutrophil counts and function, thereby preventing neutropenia and enhancing the body's immune response against infections. Traditional efforts to increase neutrophil counts include consuming extracts from snakehead fish (Channa striata). Snakehead fish are freshwater fish abundant in Indonesia and are cost-effective [7]. To date, no studies have evaluated the effects of snakehead fish extract on neutrophil count, neutrophil function (e.g., phagocytosis ability, oxidative metabolism), or cytokine synthesis and secretion during neutrophil phagocytosis in AML patients undergoing chemotherapy. This raises questions about whether supplementation with snakehead fish extract in these patients benefits neutrophil count, function, and ability to prevent neutropenic fever.

The advantages of snakehead fish include high protein and mineral content, such as leucine, isoleucine, valine, tryptophan, phenylalanine, methionine, threonine, lysine, histidine, and essential amino acids like proline, serine, arginine, tyrosine, glycine, alanine, and asparagine, with the highest concentration being glutamine at 2.11% [7, 8]. Several studies demonstrate the effectiveness of glutamine in maintaining neutrophil function, enhancing neutrophil phagocytic function, preserving nutritional status, and preventing oral mucositis [9-14]. Based on the roles of protein and minerals found in snakehead fish as previously described, there is a need for research to investigate the benefits of snakehead fish extract on neutrophil count and function by assessing neutrophil phagocytic ability and its potential in preventing neutropenic fever in patients with AML undergoing chemotherapy.

Materials and Methods

Study design

This study was an experimental randomized controlled trial (RCT) with a single-blind design that investigated the effect of snakehead fish extract supplementation on neutrophil function and the incidence of neutropenic fever in AML patients undergoing intensive chemotherapy. The research was conducted at Dr. Kariadi Hospital in Semarang, from 2017 to 2018. Research ethics approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Diponegoro University / Dr. Kariadi Hospital Semarang. Patients who met the sample criteria were selected as potential research subjects. Before the study began, researchers explained the research objectives, examination procedures, and possible benefits to the research subjects. Subjects who agreed to participate were asked for written consent by signing or thumbprinting an informed consent form.

Inclusion and exclusion criteria

Inclusion criteria were AML patients receiving an intensive chemotherapy regimen of cytarabine for 7 days with an anthracycline for 3 days (3 + 7 protocol), aged 18-60 years, without signs of infection, and willing to participate by providing consent through signing an informed consent form. Exclusion criteria included receiving albumin infusion therapy within 1 month before the study, presence of signs of infection, patients with heart disease, patients with creatinine clearance <30 ml/min, patients with serum glutamic oxaloacetic transaminase (SGOT) > 3 times the upper limit of normal, bilirubin >5 mg/dL, performance status with Eastern Cooperative Oncology Group (ECOG) III or higher, and refusal to participate as respondents.

Administration of Snakehead Fish Extract

Snakehead fish extract was administered in 500 mg capsules, with each dose consisting of 4 capsules (2 grams) given three times daily. Administration started one day before chemotherapy and continued until the patient was discharged from the hospital. The snakehead fish extract capsules were standardized in production to ensure consistent nutritional values (including protein, albumin, and other nutrients) in every batch. Patients in the intervention group received the snakehead fish extract capsules three times a day. They also received nutritional education based on the hospital's standard diet calculated according to the patient's energy requirements. Researchers monitored subjects' compliance with daily consumption of the extract. The control group received a placebo and nutritional education, and the hospital's standard diet was calculated based on the patient's energy requirements.

Randomization

Subjects were then randomly assigned in a single-blinded manner, where only the subjects were unaware of their allocation. The intervention group received snakehead fish extract in the form of 500 mg capsules, standardized in production to ensure consistent nutritional values (including protein, albumin, and other nutrients) in every batch.

Channa (Snakehead Fish) is manufactured by PT Mega Medica Pharmaceuticals. The extract was administered starting one day before chemotherapy, with a dosage of 4 capsules (2 grams) three times daily. They also received nutritional education and the hospital's standard diet was calculated based on the subjects' energy requirements. Meanwhile, the control group received a placebo administered one day before chemotherapy. They also received nutritional education and the hospital's standard diet was calculated based on their energy requirements. The placebo contained saccharum lactis and was packaged identically to the snakehead fish extract capsules. Both groups underwent intensive chemotherapy for AML using the combination of cytarabine for 7 days with an anthracycline for 3 days (3 + 7 protocol) and received Ciprofloxacin 500 mg every 12 hours as a prophylactic antibiotic for neutropenic fever.

Definition

Fever is defined as a single oral temperature measurement >38.3°C (101°F) or a sustained temperature > 38.0°C (100.4°F) over 1 hour. Fever is measured using a mercury thermometer. Neutropenia is an ANC <500 cells/

mm3 or an anticipated decline to <500 cells/mm3 over the next 48 hours. Peripheral blood hematology examinations are conducted using an automatic hematology analyzer (Sysmex XP 100 machine). Complete peripheral blood examinations, total protein levels, and albumin levels are conducted twice weekly until the patient is discharged from the hospital. IL-6 and NO levels are measured twice: at the start of intensive chemotherapy and on day 15 after starting intensive chemotherapy. Neutropenic fever events are identified when the ANC is less than 500 cells/mm³ or is expected to decline below 500 cells/mm³ within the next 48 hours, with daily temperature monitoring.

Laboratorium parameters

Initial interviews containing demographic data and other subject information were conducted at the beginning of the study. Subsequently, clinical and laboratory data were recorded according to the study's baseline data sheet. Laboratory examinations, including complete peripheral blood counts, total protein levels, and albumin levels, were conducted in both groups twice a week until the patients were discharged from the hospital.

Neutrophil Count

The ANC is determined by calculating the absolute number of neutrophils within leukocytes. Peripheral blood hematology was examined using an automatic hematology analyzer (Sysmex XP 100 machine). ANC values are categorized as follows: >1500 mm3 = Normal, 500 - 1500 mm3 = Moderate depletion, <500 mm3 = Severe depletion.

Neutrophil's Ability to Kill Bacteria

IL-6 is a cytokine produced by neutrophils during phagocytosis. It was measured using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

NO Levels

NO levels reflect the oxidative metabolism during neutrophil phagocytosis.

Assessment of neutrophil count involved ANC calculation, while neutrophil function was assessed through IL-6 and NO level measurements at the start of chemotherapy and on day 15 post-chemotherapy. The occurrence of neutropenic fever was assessed based on ANC and patient temperature. Results were recorded on the provided research forms. Once the study's predetermined number of subjects or endpoint duration was reached, statistical analysis was performed, and the research findings were reported.

Statistical Analysis

Data analysis used the mean difference test, to test the equivalence of mean values between the treatment group and the control group given snakehead fish extract, a mean difference test (unpaired T-test or Mann-Whitney test) was conducted. To determine the appropriate mean difference test, the normality of the data was assessed using the Shapiro-Wilk test, as the sample size was less than 50. If the Shapiro-Wilk test indicated normal distribution (p-value>0.05), the t-test was used; if not, the Mann-Whitney test was employed. Proportion Difference Test (Chi-Square) was used for nominal scale data. In this study, the Chi-Square test was used to assess differences in proportions of variables between the treatment group and the control group given snakehead fish extract.

Results

Demographics and Subject Characteristics

From January 2017 to May 2018, screening was conducted on 49 research subjects diagnosed with clinical AML based on the French-American-British (FAB) classification. A total of 32 research subjects met the inclusion criteria and were randomized into a treatment group consisting of 16 research subjects and a control group consisting of 16 research subjects. Thirty-two research subjects underwent intensive chemotherapy, with 16 research subjects receiving snakehead fish extract 2 grams every 8 hours (6 grams/day), standard hospital diet, and nutritional education (treatment group), while 16 research subjects received placebo, standard hospital diet, and nutritional education (control group). The research consort can be seen in Figure 1. Table 1 shows the comparison of subject characteristics between the treatment and control groups (Table 2).

The effect of snakehead fish extract administration on neutrophil count

In the treatment group, there were 3 subjects (18.7%) who had neutropenia before receiving intensive chemotherapy (day -1), whereas in the control group, 2 subjects (12.5%) had neutropenia before receiving intensive chemotherapy and were therefore excluded from statistical analysis. Neutropenia occurred in both the treatment and control groups. Out of 13 subjects in the treatment group, all experienced neutropenia (100%), while out of 14 subjects in the control group, 12 subjects (85.7%) experienced neutropenia. The mean onset of neutropenia occurred earlier in the treatment group compared to the control group (6.1 ± 3.37 days vs 8.8 ± 4.59 days). The incidence and onset of neutropenia did not differ significantly between the treatment and control groups ($p > 0.05$) (Table 3).

Out of 13 subjects in the treatment group who experienced neutropenia, 2 subjects (15.3%) died before recovering from neutropenia. Similarly, out of 12 subjects in the control group who experienced neutropenia, 2 subjects (16.6%) died before recovering from neutropenia, thus they were not included in the statistical analysis of neutropenia duration. The average duration of neutropenia was shorter in the treatment group compared to the control group (12.8 ± 6.20 days vs 17.2 ± 11.06 days). However, the duration of neutropenia did not differ significantly between the treatment and control groups ($p=0.281$) (Table 4).

The Effect of Snakehead Fish Extract on Neutrophil Function, IL-6 Levels, and NO Levels

In the treatment group, there were 3 subjects (18.7%) who died before day 15, while in the control group, there were 2 subjects (12.5%) who died before day 15.

Table 1. Comparison of Subject Characteristics Between Treatment and Control Groups

No	Characteristics	Intervention n=16	Control n=16	p value
1	Age (years), (mean ± SD; min-max)	37.06±12.64; 21-56	36.63±9.22;23-55	0.912 [a]
2	Age., n (%)			
	< 25 years old	5 (31.3%)	1 (6.3%)	0.118 [b]
	25-35 years old	3 (18.8%)	7 (43.8%)	
	>35 years old	8 (50%)	8 (50%)	
3	Gender., n (%)			
	Male	6 (37.5%)	9 (56.3%)	0.479 [b]
	Female	10 (62.5%)	7 (43.8%)	
6	AML Diagnosis., n (%)			
	M1	1 (6.3%)	0 (0)	
	M2	3 (18.8%)	5 (31.3%)	0.612 [b]
	M3	1 (6.3%)	2 (12.5%)	
	M4	6 (37.5%)	7 (43.8%)	
	M5	4 (25.0%)	2 (12.5%)	
	M6	0 (0%)	0 (0%)	
	M7	1 (6.3%)	0 (0%)	
7	Weight (Kg)	61.7 ± 26.84	55.7 ± 9.73	0.748 [a]
8	Height (cm)	151.3 ± 26.97	160.5 ± 7.85	0.264 [a]
9	Body surface area (BSA) (m^2)	1.5 ± 0.13	1.6 ± 0.15	0.777 [a]
10	Body mass index (BMI) (Kg/m^2)	22.3 ± 2.65	21.2 ± 2.44	0.407 [a]

[a], Independent-t test; [b], Mann-whitney; [c], Chi-square

Therefore, IL-6 and NO levels on day 15 could not be assessed and were not included in the statistical analysis. Mann-Whitney U test for delta IL-6 showed no significant difference between the treatment and control groups. The chi-square test for delta IL-6 categories indicated a trend towards increased IL-6 levels in 61.5% of subjects in the treatment group compared to 28.6% in the control group, with a p-value of 0.182. Similarly, the average NO levels decreased in the treatment and control groups, as seen in Table 5. Independent t-test for delta NO showed no significant difference between the treatment and control groups. The chi-square test for delta NO categories indicated a trend towards increased NO levels in 23.1% of patients in the treatment group compared to 38.5% in

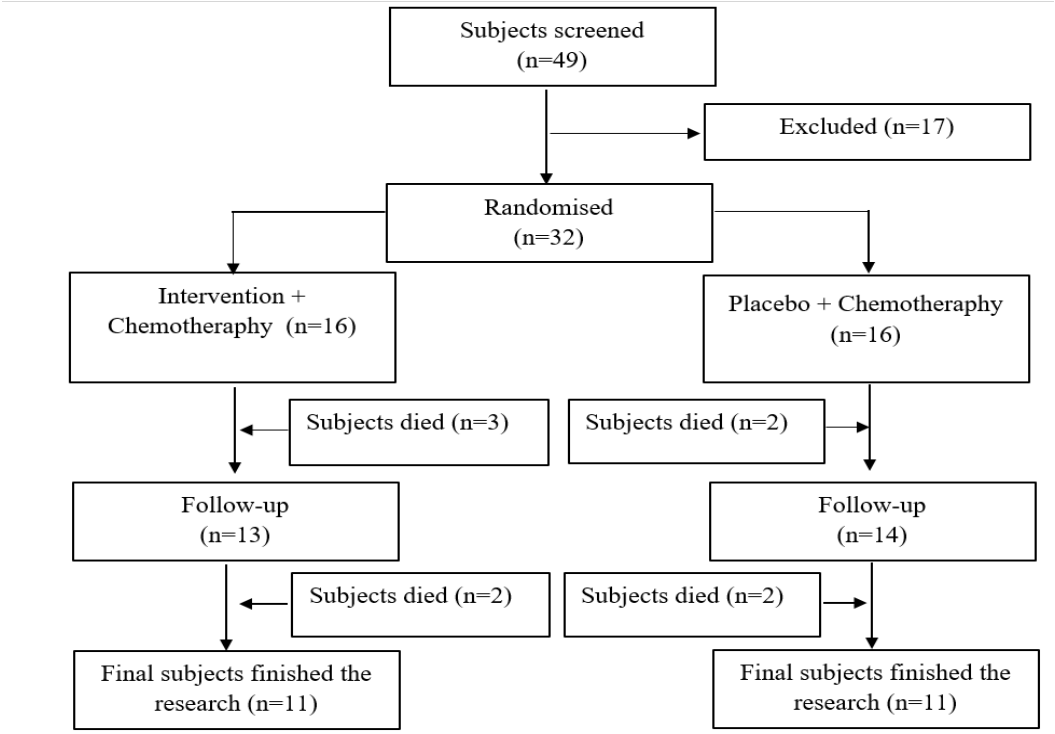

Figure 1. Consort Protocol

Table 2. Laboratory Parameter Data

No	Variable	Mean±SD		p value
		Intervention n=16	Control n=16	
1	Hemoglobin (g/dL)	9.6 ± 1.56	9.3 ± 2.59	0.955 [a]
2	Leucocyte (/µL)	75936.3 ± 85911.29	43928.1 ± 39083.13	0.386 [a]
3	Trombocytes (/µL)	38643.8 ± 25192.67	38375.0 ± 64202.67	0.076 [a]
4	ANC (µL)	10439.3 ± 13667.37	8157.8 ±9932.71	0.792 [a]
5	Ureum (mg/dL)	27.3 ± 13.16	27.4 ± 12.32	0.880 [a]
6	Creatinine (mg/dL)	0.9 ± 0.19	0.8 ±0.27	0.697 [b]
7	Serum Glutamic Oxaloacetic Transaminase (SGOT) (U/L)	35.5 ±16.99	45.19 ±28.90	0.546 [a]
8	Serum Glutamic Pyruvic Transaminase (SGPT) (U/L)	53.2 ±30.27	75.1 ±57.97	0.407 [a]
9	Total bilirubin (mg/dL)	0.8 ± 0.42	0.6 ±0.18	0.485 [a]
10	Direct biliburin (mg/dL)	0.4 ± 0.32	0.2 ±0.10	0.720 [a]
11	Total Protein (g/dL)	7.0 ± 0.99	6.8 ±0.93	0.611 [b]
12	Albumin (g/dL)	3.6 ± 0.58	3.6 ±0.64	0.731 [b]

[a], Mann-whitney; [b], Independent-t test

Table 3. Comparison of Neutropenia Incidence and Onset of Neutropenia Between Treatment and Control Groups

No	Variable	Intervention n=16	Control n=16	p value
1	Neutropenia., n (%)			
	Yes	13 (100%)	12 (85.7 %)	0.481 [a]
	No	0 (0%)	2 (14.3 %)	
2	Onset of neutropenia, (mean ± SD)(days)	6.1 ± 3.37	8.8 ± 4.59	0.109 [b]

[a], Chi-square; [b], Independent-t test

Table 4. Comparison of Neutropenia Duration between Treatment and Control Groups

No	Variable	Mean ± SD (days)		p value
		Intervention n=11	Control n=10	
1	Neutropenia duration	12.8 ± 6.20	17.2 ± 11.06	0.281[a]

[a], Independent-t test

the control group, with a p-value of 0.678 (Table 5).

Discussion

This is the first research in Indonesia conducted to investigate the effect of snakehead fish extract on neutrophil count, neutrophil function, and the incidence of neutropenic fever in AML patients undergoing intensive chemotherapy. The glutamine content in snakehead fish extract should theoretically maintain neutrophil counts

Table 5. Comparison of IL-6 and NO Levels before and after Chemotherapy Between Treatment and Control Groups

No	Variable	Intervention n=13	Control n=14	P –value
1	IL-6 (pg/mL), (mean ± SD)			
	Before chemotheraphy	3.0 ± 1.88	3.3 ± 2.0	0.274 [a]
	After chemotheraphy	2.6 ± 0.56	2.5 ± 0.62	0.690 [b]
	Delta IL-6	-0,3± 1.90	-0,8±2.15	0.224 [a]
2	Delta IL-6., n(%)			
	Up	8 (61.5 %)	4 (28.6 %)	0.182 [c]
	Down	5 (38.5 %)	10 (71.4 %)	
3	NO (µmol/L)(mean ± SD)			
	Before chemotheraphy	60.8 ± 25.73	66.05 ± 28.74	0.620 [b]
	After chemotheraphy	49.8 ± 16.32	41.8 ± 26.11	0.351 [b]
	Delta NO	-10.9 ± 28.05	-24.3 ± 34.10	0.280 [b]
4	Delta NO., n(%)			
	Up	3 (23.1 %)	5 (38.5 %)	0.678 [c]
	Down	10 (76.9 %)	9 (64.3 %)	

[a], Mann-whitney; [b], Independent-t test; [c], Chi-square

in the treatment group longer compared to the control group. Research by Pithon-curi et al. showed that glutamine can protect against neutrophil apoptosis in both mice and humans [9]. The functional parameter of glutamine utilization depends on intracellular NADPH supply. NADPH is required by glutathione reductase and increases reduced glutathione concentration, an antioxidant that enhances immunity and delays apoptosis by stabilizing neutrophil mitochondria [12-14]. The glutamine content in snakehead fish could logically affect biological recovery from neutropenia, although this study does not provide definitive evidence. Glutamine is known as an essential tissue culture medium component for bone marrow. Therefore, it can be imagined that reduced glutamine levels in bone marrow in the control group prolong neutrophil recovery time after intensive chemotherapy.

Administration of snakehead fish, rich in glutamine, would increase glutamine availability to bone marrow precursor cells, thereby accelerating neutrophil count recovery. This study cannot prove the above theory because the bone marrow structure in AML patients is no longer intact, thus affecting neutrophil recovery processes [10-14]. Snakehead fish extract, rich in glutamine, should enhance neutrophil phagocytosis. Glutamine is heavily used by isolated immune system cells like lymphocytes, macrophages, and neutrophils. The addition of glutamine enhances immune cell function such as T cell proliferation, B cell differentiation, macrophage phagocytosis, antigen presentation, cytokine production (IL-1, IL-6, IL-2), neutrophil superoxide production, and apoptosis. The functional parameter of glutamine utilization depends on intracellular NADPH supply. NADPH is required for biosynthesis reactions such as fatty acid synthesis or for producing free radicals such as O2- or nitric oxide (NO) [10-13].

Copper (Cu) content in snakehead fish extract also enhances neutrophil function including migration to infection sites, plays a role in phagocytosis, and kills foreign cells by activating respiratory burst. The Fe content in snakehead fish extract also increases neutrophil activity [15-18]. Results from this study differ from research by Sornsuvit et al., which showed that parenteral glutamine administration can increase neutrophil phagocytosis activity [10]. This difference may be due to the method of glutamine administration; in this study, it was oral whereas Sornsuvit et al. used parenteral administration, which may be more effective than oral administration. In addition, the doses were different; in the Sornsuvit et al. study, the dose was high at 30 g/day and pure glutamine, whereas in this study, snakehead fish extract dose was 6 grams/day [10]. Another difference is that in the Sornsuvit et al. study, the assessment of neutrophil phagocytosis activity was conducted when ANC was above 500/μL, so the assessed neutrophil count was sufficient. In contrast, in this study, an assessment of neutrophil function was done on day 15 regardless of whether ANC had exceeded 500/μL [10].

The research also showed that the duration of neutropenia in the treatment group was faster than in the control group but also not statistically significant. Although statistically insignificant, clinically this is a positive finding of the effect of snakehead fish extract, where administration of snakehead fish extract can shorten the duration of neutropenic fever. The average duration of neutropenic fever in the treatment group was also longer compared to the control group, although not statistically significant. The ability to fight infections in patients receiving snakehead fish extract should be better compared to those who do not receive it, because the addition of snakehead fish extract will increase glutamine, arginine, Zinc (Zn), Copper (Cu), and Fe which can improve the immune system which plays a role in fighting infections [9-18]. This condition can occur in this study possibly because some research subjects who experience neutropenia do not immediately receive positive pressure isolation rooms, or do not receive positive pressure isolation rooms, so the risk of neutropenic fever increases and the duration of neutropenic fever also increases.

Although the minimum sample number was met, some research subjects could not be analyzed to completion because they died before the study ended, which certainly affected the analysis results. Another limitation of the study is that it was conducted at only one hospital center, which may affect the research results. Some patients died, and we did not analyze the causes of death in detail, which is also a limitation of this study. Further research is needed to determine the optimal dose of snakehead fish extract that affects patients and its administration should not be limited to 1 day before chemotherapy so that optimal levels of protein and minerals that play a role in the immune system are achieved. Further research is needed with supervised medication to ensure that research subjects consume snakehead fish extract on time.

In conclusion, Overall, despite the theoretical basis that Channa striata extract, which is rich in nutrients like glutamine, copper, and iron, might enhance immune function and potentially mitigate neutropenia-related complications, the study did not observe these benefits in the context of AML patients undergoing intensive chemotherapy.

These findings highlight the need for further research to better understand the optimal use and potential benefits of dietary supplements like Channa striata extract in cancer treatment settings.

Author Contribution Statement

Budi Setiawan conceptualized the research, designed the study, and oversaw data collection. Eko Adhi Pangarsa handled data analysis, interpretation, and manuscript drafting. Damai Santosa contributed to the literature review and supported data collection. Daniel Rizky conducted statistical analyses and helped interpret the results. Kevin Tandarto edited the manuscript for clarity, while Catharina Suharti managed the project, supervised the research, and provided critical manuscript revisions. All authors approved the final manuscript.

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Ethical approval

This research has been approved by the committee

ethics of Dr. Kariadi General Hospital, Semarang.

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