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Research

Effect of Administration of *Phaleria Macrocarpa* on Liver Function of Nasopharyngeal Carcinoma Patients who Receive Cisplatin Chemotherapy

Adi Januar Akbar, Willy Yusmawan, Farokah, Nur Iman Nugroho

ENT Department of Diponegoro University/ Dr. Kariadi Hospital, Semarang

ABSTRACT

Background: Nasopharyngeal cancer (NPC) is a malignant tumor located in the nasopharynx, which can be treated by Cisplatin, a chemotherapy that has a side effect of increasing the production of Reactive Oxygen Species (ROS) that can damage the liver. We aim to determine the effect of giving *Mahkota Dewa* (*Phaleria macrocarpa*) as an antioxidant on liver function of NPC patients receiving Cisplatin chemotherapy.
Subjects and Method: Forty subjects of stage III and IV Nasopharyngeal Carcinoma patients were divided into treatment and control groups. Subjects will be tested for SGOT SGPT before cisplatin chemotherapy. The treatment group was given *Phaleria macrocarpa* capsules 300 mg/24 hours for 5 weeks since a week before chemotherapy. The control group was given placebo capsules/24 hours for 5 weeks since a week before chemotherapy. The patients received two series of cisplatin chemotherapy with an interval of 3 weeks, then a second blood sample was taken 1 week after the second series of cisplatin chemotherapy.
Results: There was a significant difference in SGOT levels in the post-treatment group of *Phaleria macrocarpa* and control, as well as the difference in the pre- and post- treatment group between the *Phaleria macrocarpa* and control groups. Also, there was a significant difference in SGPT levels in the pre- and post- treatment in the *Phaleria macrocarpa* and control groups.
Conclusion: The administration of *Phaleria macrocarpa* has an effect on decreasing the levels of SGOT and SGPT in NPC patients receiving Cisplatin chemotherapy therapy

Keywords: *Phaleria macrocarpa*, SGOT, SGPT, Nasopharyngeal Carcinoma, Cisplatin

Correspondence:
Adi Januar Akbar. ENT Department of Diponegoro University. Prof. Sudarto Street No. 13, Tembalang, Tembalang Sub-district, Semarang City, Central Java, 50275. Email: diaz17akbarsaleh-@gmail.com. +628161455179..

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BACKGROUND

Nasopharyngeal cancer (NPC) is a malignant tumor that grows in the posterior cavity of the nose (nasopharynx area) and behind the roof of the oral cavity. NPC has special characteristics in terms of epidemiology, histopathological features, clinical characteristics, and biological characteristics (Komite Penanggulangan Kanker Nasional, 2012).

The incidence of NPC in the world is <1 per 100,000 every year. NPC is a tumor that is quite often found in Indonesia. NPC is reported as the 4th most common tumor after cervical, mammae, and skin cancer. The incidence in Indonesia is estimated at 6.2 per 100,000 population and there are about

12,000 new cases every year (Adham et al., 2012). The incidence of NPC in dr. Kariadi as many as 112 cases over a period of five years. NPC also became the most cases in the incidence of head and neck cancer during March-April 2015 at RSUP dr. Kariadi (Widiono et al., 2017).

The risk factors for NPC include genetics, consumption of fish preserved with salt, increased antibody titers to the Epstein-Barr virus, family history of NPC, and class I genotypes of certain leukocyte antigens, neck swelling, and unilateral serous otitis media (KPNK, 2012, 2017). Stages of diagnosis established through endoscopic examination and imaging. Definitive diagnosis is obtained through histopathological examination (Simo et al., 2016).

NPC management options are radiotherapy, chemotherapy, and surgery according to the circumstances of each patient. Chemotherapy is recommended in patients with stage III and IV NPC. The regimen that can be used is cisplatin 100 mg/m^2 (Simo et al., 2016). As a first-generation platinum anti-tumor agent, cisplatin has been widely used as chemotherapy in various malignancies, including head and neck cancer (Rehman and Rather, 2020). Despite its anticancer activity, cisplatin However, the clinical use of this therapy is often limited due to side effects such as hepatotoxicity and nephrotoxicity (Rehman and Rather, 2020). Several previous studies have stated that chemotherapy can cause liver damage (DILI/ Drug Induced Liver Injury). A study by Azad et al. (2018) stated that 82% of patients experienced DILI due to chemotherapy administration.

The mechanism of hepatotoxicity caused by cisplatin is still unknown. Cisplatin is taken up specifically and accumulates in human liver cells, resulting in increased production of Reactive Oxygen Species (ROS). Although the endogenous antioxidant system in the body can prevent the toxic effects of ROS under normal conditions, excessive levels of ROS caused by cisplatin can damage the natural antioxidant defenses of hepatocytes and trigger lipid peroxidation and liver damage. Cisplatin also increases the activity of hepatic inducible nitric oxide synthase (iNOS) and the formation of nitric oxide which will react with O2 to form peroxynitrate, an agent that is toxic to the body's cellular components (Chu et al., 2015).

This study uses *Phaleria macrocarpa* as an antioxidant, better known as "*Mahkota Dewa*". *Phaleria macrocarpa* fruit contains high levels of crude fiber as a potential source of phenolic antioxidants. The main components of fiber are cellulose, hemicellulose, lignin, β-glucan, gums, pectin, and hydrocolloids. These components function as antioxidants. We aim to determine the effect of giving *Mahkota Dewa* (*Phaleria macrocarpa*) as an antioxidant on liver function of NPC patients receiving Cisplatin chemotherapy.

SUBJECTS AND METHOD

1. Study Design

This study was a randomized controlled pre- and post-test trial conducted between June and September 2021 at Dr. Kariadi Hospital Semarang.

2. Population and Sample

We involved patients with NPC who received Cisplastin chemotherapy. They were divided into two groups, which are the treatment group and the control group. The treatment group consisted of patients with NPC who received chemotherapy with cisplatin, vitamin C, *Phaleria macrocarpa,* while the control group consisted of patients with NPC who received chemotherapy with cisplatin, vitamin C, and placebo. The inclusion criteria were patients with NPC stages III and IV, histopathological types of WHO 2 and WHO 3, age of 30-70 years, Hb level >10 gr%,

leukocyte count 3000-11000 cells/mmk, platelets, serum albumin, blood sugar levels, electrolytes, SGOT and SGPT levels, ECOG 1 scale, and negative HBsAg screening results. Exclusion criteria for the study were patients who had previously received radiotherapy or chemotherapy, patients with other malignancies, and patients with severe systemic diseases such as diabetes mellitus and hypertension. The dropout criteria included patients who experienced prolonged time between chemotherapy series, patients with treatment complications or died, patients with worsening general condition during chemotherapy, patients who underwent changes in chemotherapy regimens, and patients who withdrew from the study.

3. Study Variables

The dependent variables were SGOT and SGPT levels before and after cisplatin chemotherapy. The independent variables were the interventions: (1) the treatment group was given *Phaleria macrocarpa* capsules 300 mg/24 hours for 5 weeks starting 1 week before chemotherapy; (2) the control group was given placebo capsules / 24 hours for 5 weeks from 1 week before chemotherapy. The subjects received two series of cisplatin chemotherapy with an interval of three weeks, before a second blood sample was taken one week after the second series of Cisplatin chemotherapy.

4. Operational Definition of Variables

Cisplatin chemotherapy, it is a combined chemotherapy regimen of cisplatin and other regimens. Cisplatin is an alkylating class of chemotherapy that works by activating DNA replication and repair resulting in tumor cell death. Cisplatin chemotherapy was given at a dose of 80 mg/m^2 LPT in 2 hours, followed by hydration of 500 ml of physiological saline solution. Cisplatin chemotherapy was carried out in 2 series of chemotherapy with an interval of 3 weeks.

Phaleria macrocarpa, contains high levels of crude fiber as a potential source of phenolic antioxidants, administered in capsule form at a dose of 300 mg/24 hours, based on previous studies that gave a good response. The time of administration was from 1 week before chemotherapy I to 1 week after chemotherapy II.

SGPT, levels of enzymes that catalyze the transfer of an amino group from alanine to α-ketoglutarate to produce glutamate and pyruvate. Normal levels of SGPT are in the range of 5-10 U/L. Normal levels in men 7-46 U/L; in women 4-35 U/L. It is said to increase when the result is above the normal value.

SGOT, enzymes that catalyze the transfer of an amino group from aspartate to α-ketoglutarate produce oxaloacetate and glutamate. Normal levels in men aged ≤60 years 8 - 20 U/L; male aged >60 years 11 - 26 U/L; female aged ≤60 years 8-20 U/L; female aged >60 years 10-20 U/L. It is said to increase when the result is above the normal value.

5. Study Instruments

To conduct the study, the following instruments were required:

a. *Phaleria macrocarpa* capsules under BPOM number of TR 053348831 with the dose of 300 mg/24 hours for 5 weeks for the intervention group.

b. Vitamin C 100 mg/day for 5 weeks for the intervention and control groups.

c. Patient's medical record to obtain data of the SGOT and SGPT levels.

6. Data Analysis

The subjects' characteristics will be presented descriptively, which consist of gender, age, NPC stage, type of chemotherapy, and the type of drug. We will analyze the association between the intervention and the effect on SGOT and SGPT levels after chemotherapy by conducting a test of different levels of SGOT and SGPT in each group, a test for different levels of SGOT and SGPT before and after chemotherapy in the control group, and

a test for the difference in the increasing average levels of SGOT and SGPT between groups. Data analysis using the mann whitney test, wilcoxon's test and paired t-test.

7. Research Ethics

Subjects who passed the inclusion and exclusion criteria must provided informed consent to participate in the study. They had the rights to reject participation due to any reasons and opted out of the study at any time. Their personal data was confidential. All fees related to this study was under the author's responsibility. This study had received ethical clearance from the Ethical Research Committee of Dr. Kariadi Hospital Semarang with the number of 823/EC/ KEPK-RSDK/2021.

RESULTS

1. Sample Characteristics

Research data collection was carried out from June to September 2021. Research subjects who met the inclusion and exclusion criteria were 40 patients with NPC stage II and IV which was divided into 2 groups, namely the treatment group and the control group. The characteristics of the research subjects are shown in Table 1.

Subjects were dominated by male patients (67.5%) and those aged 30-50 years (52.5%). Most of the subjects had WHO stage III nasopharyngeal cancer (90%) and received *Paclitaxel Cisplatin* chemotherapy (82.5%). The types of intervention, which were *Phaleria macrocarpa* and placebo, was evenly distributed between patients.

2. Bivariate Analysis

The results of data analysis showed that the *Phaleria macrocarpa* group had pre-treatment levels of SGOT around 30.75 ± 17.55 and post-treatment SGOT levels around 25.65 ± 5.72 so that the difference between pre- and post- treatment had SGOT levels around -5.10 ± 16.10. The placebo group had pre-treatment SGOT levels around 49.80 ± 28.24 and post-treatment SGOT levels around 30.75 ± 17.55 so that the differrence between pre and post treatment had SGOT levels around 18.45 ± 28.52.

From the results of the *Saphiro-Wilk* normality test, it was found that the distribution of data was not normal in the *Phaleria macrocarpa* pre-treatment group, control, *Phaleria macrocarpa* post-treatment group, and the difference between pre-treatment and post-treatment *Phaleria macrocarpa* groups, control was 0.002. The data were normally distributed in the post-placebo treatment group of 0.108 (p>0.05).

Mann Whitney Test Result show the significant difference in the post treatment group *Phaleria macrocarpa* and control and the difference in the pre-post treatment group post treatment between the *Phaleria macrocarpa* and control groups. In addition, from the results of the Mann-Whitney test, there were no significant differences between the pre-treatment groups of *Phaleria macrocarpa* and the control group.

The results of data analysis showed that the *Phaleria macrocarpa* group had pre-treatment SGPT levels around 27.15 ± 12.73 and post-treatment SGPT levels around 23.40 ± 5.66 so that the difference between pre and post treatment had SGPT levels around -3.75 ± 8.87. The control group had pre-treatment SGPT levels around 26.55 ± 11.51 and post-treatment SGPT levels around 43.15 ± 21.13 so that the difference between pre and post treatment had SGPT levels around 16.60 ± 20.63.

From the results of the Saphiro-Wilk normality test, it was found that the data distribution was not normal in the *Phaleria macrocarpa* pre-treatment group, and the difference in the *Phaleria macrocarpa* group was 0.008. The data were normally distributed in the pre-treatment control group of 0.212 (p>0.05), the post-treatment group *Phaleria macrocarpa* of 0.983 (p>0.05) and

the post-treatment control group of 0.133 (p>0.05), and the difference between the groups control was 0.129 (p>0.05).

From the results of the paired t test (Table 3), there were significant differences in the pre-treatment post-treatment control group. Meanwhile, from the results of the independent t test, it was found that there was a significant difference in the post treatment group of *Phaleria macrocarpa* and placebo.

From the results of the Mann-Whitney test (Table 3), there was a significant difference in the difference between the *Phaleria macrocarpa* group and the placebo group. From the results of the *Mann-Whitney* test, there were no significant differences between the pre-treatment groups of *Phaleria macrocarpa* and the control group. Meanwhile, from the Wilcoxon test results, there were no significant differences in the pre and post treatment groups of *Phaleria macrocarpa.*

Table 1. Subject Characteristics

Variable	*n*	%
Gender		
Man	27	67.5
Woman	13	32.5
Age		
30 – 50	21	52.5
51 – 70	19	47.5
Stadium		
III	4	10
IV	36	90
WHO		
II	4	10
III	36	90
Types of Chemotherapy		
Paclitaxel Cisplatin	33	82.5
Ifosfamide Mesna Paclitaxel Cisplatin	4	10
Cisplatin 5 FU	3	7.5
Drug Type		
Phaleria macrocarpa	20	50
placebo	20	50

Table 2. Differences in SGOT pre-treatment, post-treatment, and difference

SGOT	Drug Type						p
	Phaleria macrocarpa			Placebo			
	Mean	SD	Median	Mean	SD	Median	
Pre-treatment	30.75	17.55	26	31.35	8.49	28.5	0.083
Post-treatment	25.65	5.72	24.5	49.80	28.24	42	<0.001
p	0.203			0.001			

Table 3. Differences in SGPT pre-treatment, post-treatment, and difference

SGPT	Drug Type						p
	Phaleria macrocarpa			Placebo			
	Mean	SD	Median	Mean	SD	Median	
Pre-treatment	27.15	12.73	25.5	26.55	11.51	30	0.745
Post-treatment	23.40	5.66	23.5	43.15	21.13	38.5	0.001
p	0.061			0.002			

DISCUSSION

Nasopharyngeal carcinoma (NPC) is a carcinoma that arises in the nasopharynx (the area above the throat and behind the nose), which shows evidence of mild microscopic or ultrastructural squamous differentiation (KPKN, 2012, 2017; Wu et al., 2018). NPC itself can get treatment in the form of chemoradiation and chemotherapy. Chemotherapy is given to NPC stages III and IV where one of the chemotherapy regimens is cisplatin (KPKN, 2017).

Cisplatin is an alkylating antitumor drug that can form an electrophilic group from a positive carbon ion, to attack the electron-rich locus of biological macromolecules (Farhat et al, 2014). The way this alkylator works is by forming highly reactive carbonium (alkyl) ions (Santosa et al., 2012). Cisplatin also works by damaging mitochondria, causing ATP decrease and interfere with the work of transport that occurs in the cell. Cisplatin makes the cell cycle stop at the G2 stage which causes apoptosis in cancer cells (Topik, 2014). But this anti-tumor drug has side effects including damaging liver function mainly caused by MTX, 6MP, SFU, DTIC, VP-16, asparaginase, and so on. An increase in bilirubin, ALK affects the excretion of drugs from the anthracycline class (eg adriamycin) and the vinca alkaloids group.

Aspartate aminotransferase or serum glutamic oxaloacetate transaminase (SGOT) is a liver enzyme that helps protein production. This enzyme catalyzes the transfer of an amino group from aspartate to α-ketoglutarate to produce oxaloacetate and glutamate. In this study, it was shown that the use of cisplatin therapy had a negative impact on liver function as indicated by a significant increase in serum SGOT levels in controls between pre and post. treatment.

Alanine aminotransferase or serum glutamic pyruvic transaminase (SGPT) is the most frequently used marker of liver toxicity. SGPT is a liver enzyme that plays an important role in amino acid metabolism and gluconeogenesis. This enzyme catalyzes the transfer of an amino group from alanine to α-ketoglutarate to produce glutamate and pyruvate (Lala et al., 2020). This study also showed that the use of cisplatin therapy had a negative impact on liver function as indicated by a significant increase in serum SGPT levels in controls between pre- and post-treatment.

*Phaleria macrocarpa*or what is often known as the "*Mahkota Dewa*" plant, is widely found in Indonesia. *Phaleria macrocarpa* is classified as a plant that is able to live in various conditions, from lowlands to highlands and has the ability as anticancer through the phytochemicals obtained from its methanol extract (Ahmed et al., 2018). *Phaleria macrocarpa* methanol extract also provides antioxidant effects. The content of Super oxide dismutase / SOD has a role to inhibit the breakdown of superoxide into oxygen and hydrogen peroxide, which are known as free radicals (Alana et al., 2016).

This study shows that the efficacy of *Phaleria macrocarpa* can be used as a therapy to maintain liver function so as not to get the toxic effects of cisplatin therapy. This is indicated by a decrease in SGOT levels in the pre and post treatment groups who received therapy with *Phaleria macrocarpa*, although it was not significant. This is comparable to a very significant decrease in SGPT levels in the pre and post treatment groups who received therapy with *Phaleria macrocarpa*. This is also further proven by the comparison of the levels of SGOT and SGPT in the post-treatment group between the groups receiving *Phaleria macrocarpa* and the control group, where the results are very significant.

Phaleria macrocarpa in several previous studies it was stated that it was successful in providing protection to the liver with the findings of signs of improved liver function (decreased levels of SGOT and SGPT) (OR et al., 2016; Altaf et al., 2013; Nasution et al., 2019). These decrease of liver enzyme processsed through *Phaleria macrocarpa* extract mechanism that can give antioxidant activity in the body. The content of flavonoids and phenolics extracted from *Phaleria macrocarpa* can increase superoxide dismutase (SOD) which is a catalyst to inhibit the change of superoxide into oxygen and hydrogen peroxide so that it acts as an antioxidant so that hydroxyl radicals are not formed which can cause lipid peroxidation in cell membranes (liver) so that they experience Dead. The condition of the liver that is protected from free radicals due to the administration of *Phaleria macrocarpa* extract will show signs of good liver function with SGOT and SGPT enzyme markers in normal or decreased vulnerability (OR et al., 2016; Nasution et al., 2019).

Based on this research, extract from *Phaleria macrocarpa* can be used as an additional therapy option that can be given to patients with nasopharyngeal cancer who are receiving cisplatin chemotherapy so that liver function in these patients does not decrease or have permanent damage due to drug side effects that may cause more severe complications in post-chemotherapeutic patients. However, this research needs further study using different age ranges to show that *Phaleria macrocarpa* is indeed proven to be able to maintain liver function at all ages.

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CONFLICT OF INTEREST

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

Adham M, Kurniawan AN, Muhtadi AI, Roezin A, Hermani B, Gondhowiardjo S, Tan IB, et al. (2012). Nasopharyngeal carcinoma in Indonesia: epidemiology, incidence, signs, and symptoms at presentation. Chin J Cancer. 31(4):185-196. DOI: 10.5732/cjc.011.10328.

Alara OR, Alara JA, Olalere OA. (2016). Review on Phaleria macrocarpa Pharmacological and Phytochemical Properties. Drug Des. 5:134.

Altaf R, Asmawi MB, Dewa A, Sadikun A, Umar M. (2013). Phytochemistry and medicinal properties of *Phaleria macrocarpa* (Scheff.) Boerl. extracts. PharmacognRev. 7(1):73. DOI: 10.4103/0973-7847.112853.

Asrity A, Tsan FY, Ding P, Aris S. (2018). Functional Properties of Phaleria macrocarpa Fruit Flesh at Different ripeness. Int Food Res J. 25(3):1273–80.

Azad A, Chang P, Devuni D, Bichoupan K, Kesar V, Branch AD, Oh WK, et al. (2018). Real World Experience of Drug Induced Liver Injury in Patients Undergoing Chemotherapy. J Clin Gastroenterol Hepatol. 2(3):18. DOI: 10.21767/2575-7733.1000047.

Bouché M, Vincent B, Achard T, Bellemin-Laponnaz S. (2020). N-Heterocyclic Carbene Platinum(IV) as Metallodrug Candidates: Synthesis and 195Pt NMR Chemical Shift Trend. Molecules. 25(14): 3148. Doi: 10.3390/molecules25143148.

Chu NH, Li L, Zhang X, Gu J, Du YD, Cai C, Xiao HP. (2015). Role of Bicyclol in Preventing Drug-Induced Liver Injury in Tuberculosis Patients with Liver Disease. Int J Tuberc Lung Dis. 19(4):475. DOI: 10/5588/ijtld.14.0579.

Farhat, Adham M, Dewi YA, Indrasari SR, editor. (2014). Karsinoma Nasofaring. Penerbit Buku Kedokteran EGC.

Hang Z, Cooper MA, Ziora ZM. (2016). Platinum-Based Anticancer Drugs Encapsulated Liposome and Polymeric Micelle Formulation in Clinical Trials. Bio Chem Comp. 4:1–4. DOI: 10.7243/-2052-9341-4-2.

Komite Penanggulangan Kanker Nasional (2012). Pedoman Nasional Pelayanan Kedokteran Kanker Nasofaring. Kementerian Kesehatan Republik Indonesia.

Komite Penanggulangan Kanker Nasional (2017). Panduan Penatalaksanaan Kanker Nasofaring. Kementerian Kesehatan Republik Indonesia.

Lala V, Goyal A, Bansal P, Al E. (2020). Liver Function Tests. StatPearls.Treasure Isl StatPearls Publ.

Nasution AN, Aziz H, Tjong DH, Zein R. (2019). Effect of *Phaleria macrocarpa* Flesh Fruits Extract on MDA Level, SGOT and SGPT Activity in Serum of Experimental Rats Contaminated by Cd (II) Ion. Open Access Maced J Med Sci. 7(23):3950–3954. DOI: 10.3889/oamjms.2019.786.

Rehman MU, Rather IA. (2019). Myricetin Abrogates Cisplatin-Induced Oxidative Stress, Inflammatory Response, and Goblet Cell Disintegration in Colon of Wistar Rats. Plants (Basel, Switzerland), 9(1), 28. DOI: 10.3390/plants-9010028

Santosa YI, Samiadi D, Aroeman NA, Fianza PI (2012). Pengaruh Alfa Tokoferol pada Efek Ototoksik Sisplatin. MKB,:205–12. DOI: 10.15395/mkb.v44n4.176.

Simo R, Robinson M, Lei M, Sibtain A, Hickey S. Nasopharyngeal carcinoma: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016 May;130(S2): S97-S103. DOI: 10.1017/S0022215116000517.

Topik A (2014). Oxidatively Modified DNA Lesions and Systems for Reparation. Sources, Clinical Significance and Methods of Analysis. Omi Gr United States Am. 53–5.

Widiono KR, Yusmawan W, Naftali Z. (2017). Perbandingan Five Year Survival Rate Penderita Karsinoma Nasofaring pada Modalitas Kemoterapi dan Kemoradiasi. J Kedokt Diponegoro. 6.

Wu L, Li C, Pan L. (2018). Nasopharyngeal carcinoma: A review of current updates. *Experi*mental and therapeutic medicine. *15*(4): 3687–3692. DOI: 10.3892/etm.2018.5878.