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**Research Report**

***Effect Of Administration Of Phaleria Macrocarpa On Liver Function Of Nasopharinal Carcinoma Patients who Receive Cisplatin Chemotherapy***

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# *ABSTRACT*

***Backgrounds:****Nasopharyngeal cancer (NPC) is a malignant tumor located in the nasopharynx, which can be treated in the form of chemotherapy, Cisplatin as one of the chemotherapy which can damage the liver. This study uses Phaleria macrocarpa as an antioxidant.*

***Objectives:****To determine the effect of giving Phaleria macrocarpa on liver function of NPC patients receiving Cisplatin chemotherapy therapy.*

***Methods:****This study used 40 samples in the form of stage III and IV NPC patients who were divided into 2 groups, the treatment and control groups. Samples will be tested for SGOT SGPT before And after a week of chemotherapy. The patient received 2 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 and SGPT levels in post-treatment group of Phaleria macrocarpa.*

***Conclusion:****administration of Phaleria macrocarpa has an effect on decreasing levels of SGOT and SGPT in NPC patients receiving Cisplatin chemotherapy.*

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

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# *ABSTRACT*

***Backgrounds:****Nasopharyngeal cancer (NPC) is a malignant tumor located in the nasopharynx, which can be treated in the form of radiotherapy, chemotherapy, and surgery. Cisplatin as one of the chemotherapy that has a side effect of increasing the production of Reactive Oxygen Species (ROS) which can damage the liver. This study uses Mahkota Dewa (Phaleria macrocarpa) as an antioxidant.*

***Objectives:****To determine the effect of giving Phaleria macrocarpa on liver function of NPC patients receiving Cisplatin chemotherapy therapy.*

***Methods:****This study used 40 samples in the form of stage III and IV Nasopharyngeal Carcinoma patients who were divided into 2 groups, namely the treatment and control groups. Samples 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 5 weeks since a week before chemotherapy. The patient received 2 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:****From this study, there was a significant difference in SGOT levels in thepost-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. Meanwhile, 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***

# PRELIMINARY

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.1

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.2 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.3

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.1,4 neck swelling and unilateral serous otitis media. Stages of diagnosis established through endoscopic examination and imaging. Definitive diagnosis is obtained through histopathological examination.5

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/m2.5 As a first-generation platinum anti-tumor and anti-cancer agent, cisplatin has been widely used as chemotherapy in various malignancies, including head and neck cancer.6 Despite its anti-cancer activity, cisplatin However, the clinical use of this therapy is often limited due to side effects such as hepatotoxicity and nephrotoxicity.6 Several previous studies have stated that chemotherapy can cause liver damage (DILI/Drug Induced Liver Injury). A study by Adiba, et al in 2018, stated that 82% of patients experienced DILI due to chemotherapy administration.7

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.8

 This study uses *Phaleria macrocarpa* as an antioxidant, better known as the ”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. It is hoped that the administration of *Phaleria macrocarpa* can reduce the side effects of giving Cisplatin.

# METHOD

This study was a randomized pre and post test control design with the research subjects being NPC patients who received Cisplatin chemotherapy. The research group was divided into 2 groups, namely the treatment group, namely patients with NPC who received chemotherapy with cisplatin, vitamin C, *Phaleria macrocarpa* and the control group, namely patients with NPC who received chemotherapy with cisplatin, vitamin C, and placebo. The inclusion criteria of the study were patients with NPC stages III and IV, histopathological types WHO 2 and WHO 3, age 30-70 years, Hb level > 10 gr%, leukocytes 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, patients with severe systemic diseases, namely diabetes mellitus, hypertension. The dropout criteria included patients who experienced prolonged time between chemotherapy series, patients with treatment complications or died, patients' general condition worsened during chemotherapy, patients who underwent changes in chemotherapy regimens, and patients who withdrew from the study.

The patient will be carried out SGOT SGPT examination before cisplatin chemotherapy. The treatment group was given *Phaleria macrocarpa* capsules 300 mg/24 hours for 5 weeks starting 1 week before chemotherapy. The control group was given placebo capsules / 24 hours for 5 weeks from 1 week before chemotherapy. The patient received two series of cisplatin chemotherapy with an interval of three weeks, then a second blood sample was taken, one week after the second series of Cisplatin chemotherapy.

Descriptive data was carried out on gender, age, NPC stage, type of chemotherapy, type of drug. Hypothesis testing What was done to prove that the treatment given had an effect on the levels of SGOT and SGPT after cisplatin chemotherapy compared to the control group was 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 difference. increase in average level SGOT and SGPT between groups.

# RESULTS

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.

Demographic data in this study using 40 patients as subjects consisting of 27 male patients (67.5%) and 13 female patients (32.5%). The age of the patients in this study had an age range of 30-50 years totaling 21 patients (52.5%) and an age range of 51-70 years totaling 19 patients (47.55). While the stage of nasopharyngeal cancer in this study based on WHO II was 4 patients (10%), and WHO III was 36 patients (90%). Chemotherapy given in the form of *Paclitaxel Cisplatin* amounted to 33 patients (82.5%), *Ifosfamide Mesna* *Paclitaxel Cisplatin* amounted to 4 patients (10%), and *Cisplatin 5 FU* amounted to 3 patients (7.5%), while the type of drug given was Phaleria Macrocarpa 20 patients (50%), and placebo in 20 patients (50%).

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 difference 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.*

# 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.1,4,9 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.4

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.10 The way this alkylator works is by forming highly reactive carbonium (alkyl) ions.11 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.12 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.15 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.15 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.16 *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.17

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).17,18,19 These decrease of liver enzyme processed 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. 17,19

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 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 in order to show that Phaleria macrocarpa is indeed proven to be able to maintain liver function at all ages.

**Table 1. Characteristics** sample

|  |  |  |
| --- | --- | --- |
| Variable | n | % |
| Gender* Man
* Woman
 | 2713 | 67.532.5 |
| Age* 30 – 50
* 51 – 70
 | 2119 | 52.547.5 |
| Stadium* III
* IV
 | 436 | 1090 |
| WHO* II
* III
 | 436 | 1090 |
| Types of Chemotherapy* Paclitaxel Cisplatin
* Ifosfamide Mesna Paclitaxel Cisplatin
* Cisplatin 5 FU
 | 3343 | 82.5107.5 |
| Drug Type* Phaleria Macrocarpa
* placebo
 | 2020 | 5050 |

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

|  |  |  |
| --- | --- | --- |
| **SGOT** | **Drug Type** | **p** |
| **Phaleria Macrocarpa** | **placebo** |
| Pre-treatment | Mean 30.75 ± 17.55Median 26 (19 – 99) | Mean 31.35 ± 8.49Median 28.5 (21 – 57) | 0.083 |
| Post-treatment | Mean 25.65 ± 5.72Median 24.5 (17 – 35) | Mean 49.80 ± 28.24Median 42 (23 – 148) | <0.001‡\* |
| p | 0.203† | 0.001†\* |  |
| Difference | Mean -5.10 ± 16.10Median -3 (-65 – 14) | Mean 18.45 ± 28.52Median 11.09 (-10 – 121) | <0.001‡\* |

Description: \* Significant (p < 0.05); Mann Whitney; Wilcoxon

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

|  |  |  |
| --- | --- | --- |
| **SGPT** | **Drug Type** | **p** |
| **Phaleria Macrocarpa** | **Control** |  |
| Pre-treatment | Mean 27.15 ± 12.73Median 25.5 (11 – 68) | Mean 26.55 ± 11.51Median 30 (9 – 53) | 0.745‡ |
| Post-treatment | Mean 23.40 ± 5.66Median 23.5 (11 – 35) | Mean 43.15 ± 21.13Median 38.5 (13 – 101) | 0.001§\* |
| p | 0.061† | 0.002¶\* |  |
| Difference | Mean -3.75 ± 8.87Median -3 (-33 – 9) | Mean 16.60 ± 20.63Median 13 (-11 – 71) | <0.001‡\* |

Description: \* Significant (p < 0.05); Mann Whitney; Independent t; Wilcoxon; Paired t

# CONCLUSIONS AND RECOMMENDATIONS

The conclusion of this research is The administration of *Phaleria macrocarpa* had an effect on decreasing the levels of SGOT and SGPT in NPC patients receiving Cisplatin chemotherapy therapy. This study is expected to be a reference for further research regarding the use of Phaleria macrocarpa on the liver function of NPC patients receiving Cisplatin chemotherapy therapy at different age ranges.

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