RESEARCH ARTICLE

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Boosting Antioxidant Defense: The Effect of Astaxantin on Superoxidase Dismutase and Malondialdehyde Reduction in Patients with Head and Neck Cancer Receiving Cisplatin Chemotherapy

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Abstract

Background: Superoxide dismutase (SOD) can be decreased and malondialdehyde (MDA) can be increased in patients with head and neck cancer (HNC) as a result of reactive oxygen species (ROS) brought on by cisplatin. Astaxanthin is one of the external antioxidants required to combat ROS by raising SOD and lowering MDA. The purpose of this study is to demonstrate that astaxanthin can raise SOD and lower MDA in patients with HNC caused by cisplatin. **Methods:** 42 research subjects were randomly assigned to two groups in a double-blind, randomized controlled trial pre-post test design. Astaxanthin 4 mg BID was administered to the treatment group, whereas a single dosage of 500 mg of vitamin C and 250 mg of vitamin E IU was given to the control group. According to the Mann Whitney test, if $p < 0.05$, there is a significant difference in the delta of the decrease in SOD and MDA levels between the astaxanthin and vitamin C & E groups. **Results:** There were 42 research subjects, with a mean age of 48.2 years, a 2:1 male to female ratio, 23 (54.8%) with nasopharyngeal cancer, 32 (76.2%) with stage IV, 14 (33.3%) with cycle IV, 24 (57.1%) with paclitaxel-Cisplatin, 31 (73.8%) with Eastern Cooperative Oncological Group (ECOG) I, and 31 (73.8%) with Normal Body Mass Index. While there was a substantial drop in MDA (p=0.000), there was no significant difference in the delta reduction in SOD (p=0.443). **Conclusion:** Patients with HNC who receive cisplatin chemotherapy can have an increase in SOD and a decrease in MDA after receiving astaxanthin for 21 days.

Keywords: Astaxanthin- SOD- MDA- HNC- cisplatin- ROS

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Introduction

A malignant tumor called head and neck cancer (HNC) develops in the upper aerodigestive tract, which includes the salivary glands, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, and paranasal sinuses [1-3]. HNC accounts for 4% of all malignancies globally and is ranked sixth. The World Health Organization (WHO) estimates that there are 300,000 HNC-related fatalities and 600,000 cases worldwide each year. About 3-5% of all malignancies in the US are HNCs, and they typically affect men over the age of 50 [4-6]. HNC is ranked second in men's top ten malignancies with a 5-year survival rate of less than 50% and fourth in women's top ten cancers, according to the Indonesian Cancer Registration Agency. In March and April of 2015, there were 36 instances of HNC at Dr. Kariadi Hospital in Semarang. Nasopharyngeal cancer was the most common diagnosis, followed by sinonasal and laryngeal cancer. Along with lymphoma, sarcoma, adenocarcinoma, basal cell carcinoma, and melanoma, this kind of squamous cell carcinoma accounts for 95% of all HNCs [7, 8].

Depending on the kind, HNC can be treated with radiation, chemotherapy, surgery, or a combination of these. phases and histology of cancer [9]. One type of chemotherapy involves the use of an alkylating chemical called cisplatin, which is systemic and non-selective, resulting in adverse effects. Because free radicals are produced, apoptosis occurs in both malignant and healthy cells throughout the body. Because this molecule is harmful to the body in excess, it can harm normal cells by decreasing SOD and raising MDA levels in the body [10-12]. This means that in order for the body to combat free radicals and stop cisplatin-induced apoptosis of healthy body cells, exogenous antioxidants must be given in order to raise SOD and lower MDA. Since the body's natural antioxidants cannot fend off free radicals, external antioxidants are required. These exogenous antioxidants

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function by stabilizing free radicals, making up for their deficiency in electrons, and preventing chain reactions brought on by the production of free radicals, which can result in oxidative stress. Antioxidants that are frequently utilized include astaxanthin, lutein, green tea, vitamin C, vitamin E, lycopene, and selenium [13-16].

As an antioxidant alpha carotenoid, astaxanthin can prevent damage to normal cells and break the chain reaction of free radicals. Astaxanthin will bind O2 (singlet oxygen) free radicals, increase the activity of antioxidant enzymes such as SOD, Catalase, and glutathione peroxidase, suppress and inhibit lipid peroxidation through the final product, namely MDA, and inhibit and stop the free radical chain when given to HNC patients undergoing cisplatin chemotherapy. in order to stop normal cells from going through apoptosis [17-19]. Compared to other antioxidants like beta-carotene, lutein, lycopene, and vitamin E, astaxanthin has a number of advantages because of its richly electron-rich carotenoid structure, lack of prooxidation, resistance to autooxidation, and superior ability to neutralize singlet oxygen, break down free radicals, and offer protection. It has little adverse effects and combats oxidative damage and lipid peroxidation [17-19]. According to research by Xue et al. [20], astaxanthin has been tested in vitro as an antioxidant. This means that astaxanthin may be utilized as a potential therapeutic to shield hematopoietic function from bone marrow damage by reducing MDA brought on by radiation exposure in mice and enhancing SOD. In this study, astaxanthin was used as an antioxidant to combat free radicals by raising SOD and lowering MDA in humans (HNC patients undergoing cisplatin chemotherapy).

Research was done to address these issues because astaxanthin has been shown to be effective in combating free radicals and preventing normal cell apoptosis. However, there hasn't been any study done to determine how astaxanthin affects SOD and MDA levels in patients with head and neck cancers undergoing cisplatin chemotherapy. The purpose of the study is to demonstrate that in HNC patients undergoing cisplatin chemotherapy, astaxanthin can increase SOD and reduce MDA.

Materials and Methods

The study was conducted in the GAKY Laboratory, Faculty of Medicine, Diponegoro University, Semarang, and Dr. Kariadi Hospital, Semarang, from March 2022 to March 2023. It was a double-blind, randomized, controlled clinical trial with pre- and post-test designs.

Sample

Inclusion criteria for HNC patients receiving cisplatin treatment by successive sampling: HNC patients taking cisplatin chemotherapy, stage II-IV, age >11- <80 years, ECOG I-III and willing to take part in the research phases by obtaining informed consent. The exclution criteria were patients with hematological malignancies, stomach, liver, or kidney problems, blood transfusions, radiation, or other antioxidant-consuming conditions. Granulocyte Stimulating Factor (GSF) and blood transfusion administration were not included in the study because they may have an indirect impact on blood levels of SOD and MDA by influencing hematopoietic cell activity. This was observed in HNC patients receiving cisplatin. Patients who did not comply with research criteria, had a worsening general condition, had a drug allergy, or showed no interest in continuing the research were excluded from the study. The minimal sample size can be determined by taking the error rate (α) = 5% and power test = 90% [21, 22]. 42 patients were needed as the minimum number of subjects, according to the minimal sample size estimate. Even if the sample size for statistical power in this study was satisfied, a greater sample size might improve generalizability.

Patients who fit the criteria for the study are requested to sign a medical consent form to give their written consent. Patients can withdraw from study at any moment and can refuse to be part in it for any reason. Additionally, patient identity information is kept private. The Dr. Kariadi Hospital in Semarang's Research Ethics Commission granted ethical approval with No. 1066/EC/KEPK-RSDK/2022. The main director of Kariadi Hospital in Semarang granted a research permit letter with the number DP.02.01/I.II/4094/2022.

Intervention Materials

The treatment group received astaxanthin 4 mg twice a day, while the control group received 500 mg of vitamin C and 250 IU of vitamin E once a day. This was the dosage that was followed for the whole 21-day trial period. The aim of this study was to assess the impact of antioxidant supplements on SOD and MDA levels in patients with head and neck cancer who were receiving cisplatin treatment. In comparison to the control group, the results showed that astaxanthin significantly raised SOD and decreased MDA levels. This suggests that astaxanthin may be a useful adjuvant therapy that treating chemotherapy-related oxidative stress in these patients. Antioxidants, specifically vitamins C and E, were administered to the control group; these nutrients have the ability to scavenge free radicals. Free radicals are first attracted to vitamin E, but in order to bind the radicals, vitamin C or ascorbic acid is needed. In patients with HNC, the synergistic antioxidant action of vitamins C and E can increase MDA and reduce SOD levels. When HNC patients are receiving cisplatin therapy, the use of vitamins C and E is less advantageous than astaxanthin because the former is autooxidative, whereas the latter is prooxidant, meaning that after donating electrons, vitamins C and E can become free radicals.

Data collection

Data on age, gender, cancer stage, ECOG, BMI, and kind of Pathological Anatomy (PA) HNC are examples of descriptive data. SOD and MDA levels in study participants were acquired from the outcomes of tests performed with the Elx 800 BioTek Instruments, Inc. ELISA technique.

Processing and analysis of data

Descriptive statistics, the Shapiro-Wilk test for normality, the Levene test for equality of variances, the Wilcoxon and Mann-Whitney U tests, and a significance

level of $p < 0.05$ were used to evaluate the data. The Statistical Package for the Social Sciences 25 (SPSS 25) was used to do the statistical analysis. These assays were used to evaluate the effects on SOD and MDA levels in patients with head and neck cancer receiving cisplatin chemotherapy between the treatment group, which received astaxanthin, and the control group, which received vitamin C and E.

Results

There were 42 research subjects, divided randomly into 2 groups, namely the treatment and control groups to check SOD and MDA levels, one day before cisplatin chemotherapy. The baseline data was showed on Table 1.

Table 2 shows the results of examining the mean + standard deviation; the median (min-max) SOD level in the astaxanthin group before treatment was 76.8 U/mL+56; 61 (6.1-278.9). SOD levels in the vitamin C and E groups before treatment were 66.8 U/mL+33.7; 63.3 (13.3-163.7). The results of the Mann-Whitney test for SOD levels between the astaxanthin and vitamin C & E groups before treatment showed no significant difference, p=0.782 (p>0.05). Examination results mean + standard deviation; median (min-max) MDA level in the astaxanthin group before treatment was 1,438.7 pg/mL+508.4; 1,628 (482-1,998). Before treatment, MDA levels in the vitamin C and E groups were 1,567.7 pg/mL+377.3; 1,628 (710-1,979). The results of the Mann-Whitney test for MDA levels between the astaxanthin and vitamin C and E groups before treatment showed no significant difference, p=0.641 (p >0.05).

Table 3 shows the results of examining the mean + standard deviation; median (min-max) SOD level in the astaxanthin group before treatment was 76.8 U/mL+56; 61 (6.1-278.9) and after treatment was 114 U/mL+113; 88.9 (20.3-566.4). SOD levels in the vitamin C and E groups before treatment were 66.8 U/mL+33.7; 63.3 (13.3-163.7) and after treatment, it was 95.6 U/mL+49.4; 85.3 (38.6-223.7). Delta (difference) mean + standard deviation; median (min-max) SOD levels in the astaxanthin group were 37.1 U/mL+68.5; 23.3 (-47.9-287.5), while in the vitamin C and E group it was -28.8 U/mL+38.8; 15.5 (-29.2-153).

The results of the Mann-Whitney test for SOD levels between the astaxanthin and vitamin C and E groups before treatment showed no significant difference, p=0.782 (p>0.05). The results of the unpaired t-test for SOD levels between the astaxanthin and vitamin C and E groups after treatment also showed no significant difference, p=0.498 (p>0.05). The results of the Mann-Whitney delta test (difference) in SOD levels between the astaxanthin and vitamin C & E groups showed no significant difference, p=0.443 (p>0.05). Table 4 shows the results of examining the mean + standard deviation; median (min-max) MDA level in the astaxanthin group before treatment was 1438.7 pg /mL+508.4; 1,628 (482-1998) and after treatment was 1364.8 pg/mL+408.6; 1,424 (437-1961). MDA levels in the vitamin C and E groups before treatment were 1,567.7 pg /mL+377.3; 1628 (710-1,979) and after treatment was 1,516.1pg/mL+403.8; 1641 (683-1998). Delta (difference) mean + standard deviation; median (min-max) MDA levels in the astaxanthin group were -73.9 pg/mL+139.2; -37 (-412-137), while in the vitamin C and E group it was

Table 1. Characteristics of Research Subject

Characteristics	Group		p value
	Astaxanthinvit (n=21)	C&E (n=21)	
Age(years)			0.732$
11-20	-	1 (4.8)	
21-30	3 (14.3)	-	
31-40	4 (19)	3 (14.3)	
41-50	5 (23.8)	8 (38.1)	
51-60	4 (19)	6 (28.6)	
61-70	5 (23.8)	2 (9.5)	
71-80	-	1 (4.8)	
Gender			0.334*
Male	15 (71.4)	12 (57.1)	
Female	6 (28.6)	9 (42.9)	
AnatomicalofPathology			
Nasopharyngealcancer	14 (66.7)	9 (42.9)	
Sinonasalcancer	3 (14.3)	4 (19)	
Laryngealcancer	-	3 (14.3)	
Tonsillarcancer	1 (4.8)	-	
Nasalcavitycancer	-	1 (4.8)	
Tonguecancer	1 (4.8)	1 (4.8)	
Parotidtonguecancer	-	1 (4.8)	
Neckcancer	2 (9.5)	1 (4.8)	
Pharynxcancer	-	1 (4.8)	
Stadium			0.474$
II	-	-	
III	6 (28.6)	4 (19)	
IV	15 (71.4)	17 (81)	
ChemotheraphyCycle			0.784$
I	5 (23.8)	7 (33.3)	
II	5 (23.8)	4 (19)	
III	-	2 (9.5)	
IV	10 (47.6)	4 (19)	
V	1 (4.8)	3 (14.3)	
VI	-	1(4.8)	
Regimen			0.212*
Cisplatin-5FU	7 (33.3)	11 (52.4)	
Paclitaxel-Cisplatin	14 (66.7)	10 (47.6)	
ECOG			0.101$
I	1 8(85.7)	13 (61.9)	
II	2 (9.5)	7 (33.3)	
III	1 (4.8)	1 (4.8)	
BMI			0.361$
Underweight (<18,5)	4 (19)	3 (14.3)	
Normal (18,5-22,9)	16 (76.2)	15 (71.4)	
Overweight (23-24,9)	1 (4.8)	1 (4.8)	
ObesityI (25-29,9)	-	2 (9.5)	
ObesityII (>30)	-	-	

Description of numbers in the table: amount; percentage; *, x^2 test; $, Mann-Whitney test

Table 2. Results of Initial Examination of SOD & MDA Levels in the Astaxanthin and Group Vitamins C & E

Characteristics	Group		p-value
	Astaxanthin (n=21)	Vit C & E (n=21)	
SOD; U/mL	76. 8±56; 61 (6. 1-278. 9)	66. 8±33. 7; 63. 3 (13. 3-163. 7)	0.782@
MDA; pg/mL	1438. 7±508. 4; 1628 (482-1998)	1567. 7±377. 3; 1628 (710-1979)	0.641@

Description of numbers in the table: mean + standard deviation; median (min-max); @, Mann-Whitney Test

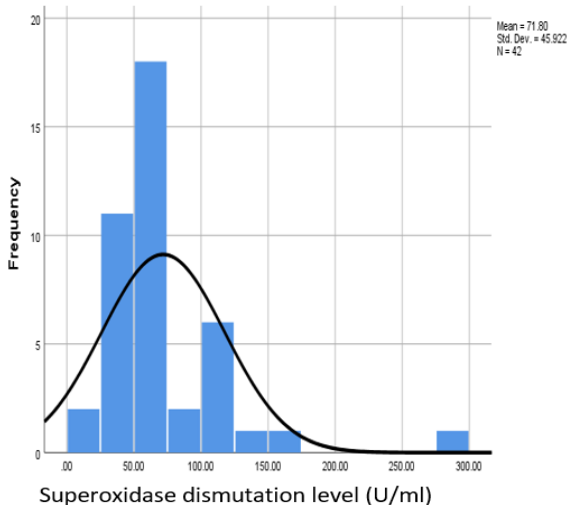

Figure 1. Superoxidase Dismutation Level before Procedure

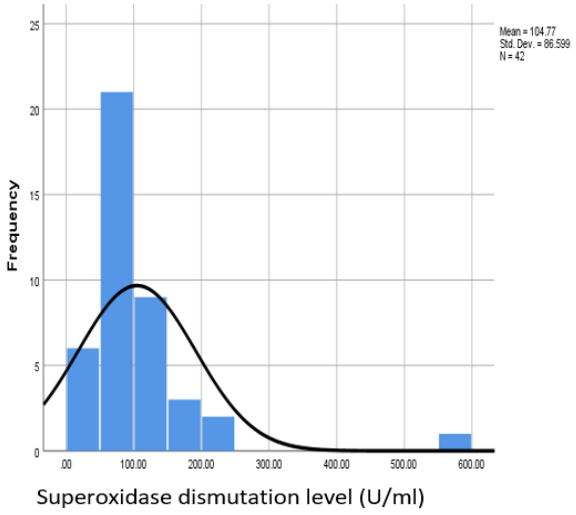

Figure 2. Superoxidase Dismutation Level after Procedure

-51.6 pg/mL+166.1; -64 (-502-435).

The results of the Mann-Whitney test showed that there was no significant difference between the astaxanthin and vitamin C and E groups before treatment, p=0.641 (p>0.05), while the MDA level also did not show a significant difference, p=0.435 (p>0.05). Results of the Mann-Whitney delta test (difference) in MDA levels between the astaxanthin and vitamin C and E groups and E showed a significant difference of p=0.000 (p<0.05).

Table 5 shows the side effects in the astaxanthin group that were found in 3 research subjects before receiving cycle I of cisplatin chemotherapy. Two subjects had nausea and 1 subject had heartburn, while in the vitamin C and E groups no side effects were found, and no patients died during this research.

Discussion

A total of 42 subjects met the inclusion criteria, 42 research subjects, mean age 48.2 years, male and female 2:1, nasopharyngeal cancer 23 (54.8%) subjects, stage IV 32 (76.2%) subjects, IV cycle 14 (33.3%) subjects, Paclitaxel-Cisplatin 24 (57.1%), Eastern Cooperative Oncological Group (ECOG) I 31 (73.8%) subjects and Normal Body Mass Index 31 (73, 8%) subjects (Table 1). Age, gender, type of HNC, stage of HNC, chemotherapy

Table 3. Results of Examination of SOD Levels in the Astaxanthin Group and Vitamins C & E Before and After Treatment

Characteristics	Group		p-value
	Astaxanthin (n=21)	vit C & E (n=21)	
Pre	76.8±56; 61 (6.1-278.9)	66.8±33.7; 63.3 (13.3-163.7)	0.782@
Post	114±113; 88.9 (20.3-566.4)	95.6±49.4; 85.3 (38.6-223.7)	0.498*
Δ	37.1±68.5; 23.3 -47.9-287.5	28.8±38.8; 15.5 -29.2-153	0.443@
p pre vs post	0.000#	0.003$	

Description of numbers in the table: mean + standard deviation; median (min-max); @, Mann-Whitney Test; *, Unpaired t-test; #, Wilcoxon Test; $, Paired t-test

Table 4. Results of Examination of MDA Levels in the Astaxanthin Group and Vitamins C & E Before and After Treatment

Characteristics	Group		p-value
	Astaxanthin (n=21)	vit C & E (n=21)	
Pre	1438.7±508.4; 1628 (482-1998)	1567.7±377.3; 1628 (710-1979)	0.641[@]
Post	1364.8±408.6; 1424 (437-1961)	1516.1±403.8; 1641 (683-1998)	0.435[@]
Δ	-73.9±139.2; -37 (-412-137)	-51.6±166.1; -64 -502-435	0.000[@]
p pre vs post	0.002[#]	0.028[#]	

Description of numbers in the table: mean ± standard deviation; median (min-max); [@], Mann-Whitney Test; [#], Wilcoxon Test

Table 5. Side Effects of Intervention During the Study

Complaint	Astaxanthin (n-21)	vitamin C & E (n=21)
Side Effects = n (%)		-
Nausea	2 (9.5%)	-
Gastritis	1 (4.8%)	-
Die	-	-

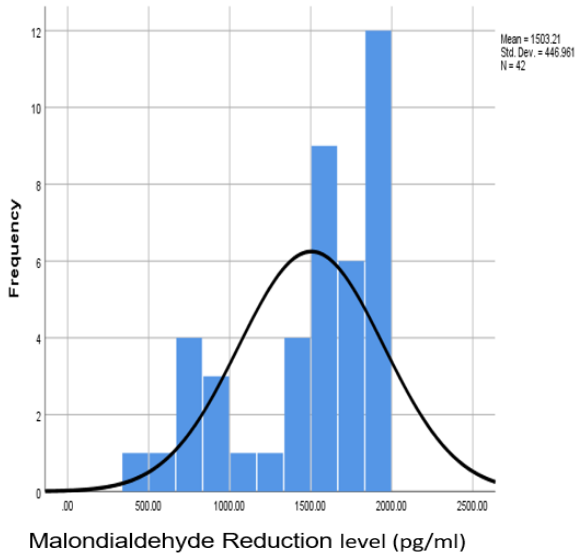

Figure 3. Malondialdehyde Reduction Level before Procedure

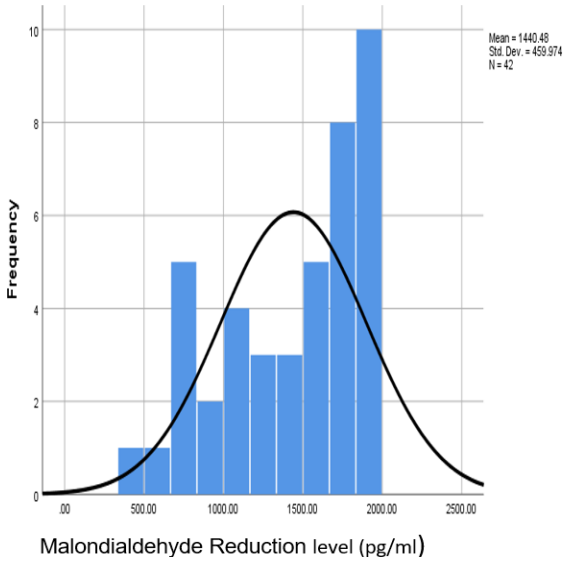

Figure 4. Malondialdehyde Reduction Level after Procedure

cycle, type of PA HNC, ECOG and BMI were tested for differences between the treatment and control groups before therapy. The results showed that there were no significant differences between the treatment and control groups (p>0.05). So this variable does not affect increasing SOD and decreasing MDA. The participants' demographic details (age, gender, type of HNC, stage of HNC, chemotherapy cycle, type of PA HNC, ECOG and BMI) are summed together, but a more thorough examination may be necessary to fully grasp any potential subgroup impacts.

The chemotherapy cycle for HNC patients in the study occurred most frequently in cycle IV, 14 (33.3%) subjects, and the least in cycle VI, 1 (2.4%) subject. The type of chemotherapy regimen used in this study was Cisplatin-5FU for 18 (42.9%) samples and Paclitaxel-Cisplatin for 24 (57.1%) subjects. The research is following the management of HNC chemotherapy at Dr. Kariadi Hospital, Semarang using 3 regimens, namely Cisplatin, Paclitaxel-Cisplatin and Cisplatin-5FU (5-Fluorouracil) and by the NCCN recommendation that Platinum based (cisplatin) as a chemotherapy regimen for HNC [8-12]. Therefore, in this study the effect is more focused, Cisplatin chemotherapy increases SOD and decreases MDA. The combination of cisplatin chemotherapy used in this study was paclitaxel (taxanes group) and 5 FU (Fluorouracil). The average dose of Paclitaxel between the treatment and control groups was the same, namely 175 mg/body surface area. Meanwhile, the average dose of 5 FU (Fluorouracil) between the treatment and control groups was the same, namely 500 mg/body surface area [23, 24].

The reason astaxanthin was selected for this study is that it is an antioxidant with several health benefits. It is said that astaxanthin possesses a higher level of antioxidant activity than other antioxidants including vitamin E, lutein, beta carotene, and lycopene. As an antioxidant, astaxanthin protects against oxidative damage caused by cholesterol and lipid peroxidation by neutralizing singlet oxygen and lipid peroxidation. It

also has a significant ability to digest free radicals. LDL, tissues, cells, and cell membranes. When it comes to binding singlet oxygen, this molecule is 40 times more potent than beta-carotene and 550 times more potent than vitamin E. Astaxanthin is more effective than vitamin E at inhibiting lipid peroxidation. Through a physical mechanism, astaxanthin neutralizes singlet oxygen. The excess energy from singlet oxygen is transferred to carotenoid structures, which are rich in electrons. There, the energy is converted into heat, preventing the formation of new singlet oxygen. Additionally, astaxanthin reacts with other radicals to prevent and stop chain reactions, protecting DNA, fat, and other cell components from damage caused by free radicals [25-27]. Since SOD is the most important antioxidant and can mitigate the consequences of oxidative stress, its levels were measured in HNC patients undergoing cisplatin chemotherapy in this study. This SOD enzyme can catalyze the conversion of superoxide into hydrogen peroxide and oxygen. It also has a typical three-dimensional structure. Superoxide is extremely reactive and can harm other molecules in the body since it is a free radical, a molecule with an unpaired electron. SOD is an enzyme with substantial ramification (branching), which is one of the body's techniques of limiting tissue damage caused by free radicals because of its very vital role [28-31].

Through the accumulation of ROS, cisplatin can enhance the creation of ROS in HNC patients' bodies. This, in turn, can trigger the activation of p38MAPK and c-Jun-N-terminal kinase (JNK), which releases cytochrome-c from mitochondria. Then, by decreasing SOD and raising MDA, cytochrome c will trigger caspase-8, -9, and -3 (intrinsic pathway apoptosis), leading to apoptosis in cancer cells as well as normal body cells [23, 24]. The body will manufacture more SOD as an antioxidant enzyme to combat the free radicals created by cisplatin thanks to the external antioxidants astaxanthin in the treatment group and vitamins C and E in the control group [28-31]. Astaxanthin was administered to the treatment group in this study, while vitamins C and E were given to the control group. Both of these exogenous antioxidants have the ability to halt free radical chain reactions and prevent harm to normal cells. For HNC patients undergoing cisplatin chemotherapy, astaxanthin and vitamins C and E have the ability to bind O2 (singlet oxygen) free radicals, boost the activity of antioxidant enzymes like SOD (superoxide dismutase), and inhibit and stop free radical chains [32-39]. The study found no evidence of a significant difference in delta decrease or mean SOD levels between the treatment and control groups. Given to HNC patients undergoing cisplatin chemotherapy, astaxanthin and vitamins C and E can raise SOD levels because cisplatin produces free radicals. Astaxanthin and vitamins C and E given to HNC sufferers who receive cisplatin chemotherapy can increase SOD levels due to free radicals produced by cisplatin. The antioxidant enzyme SOD is increased, free radicals are broken down, singlet oxygen is neutralized, and oxidative damage is avoided by astaxanthin and vitamins C and E [40-45]. The findings of Wu et al. [46] study demonstrate that astaxanthin can raise SOD and TAC levels while lowering MDA and isoprostane levels. In contrast to the Wu et al. [46] trial, which utilized a dose of 20 mg per day for 21 days, the study used a dose of 2x4 mg per day for the same duration. Therefore, it has been seen that giving HNC patients receiving cisplatin treatment a dose of 2x4 mg per day will raise their SOD levels (Figures 1,2).

Studies demonstrate that astaxanthin, an antioxidant alpha carotenoid, can prevent harm to normal cells and break the chain reaction of free radicals. Astaxanthin will bind O2 (singlet oxygen) free radicals, suppress and inhibit lipid peroxidation through the ultimate product, malondialdehyde (MDA), and inhibit and stop the free radical chain so that MDA can rise in HNC patients following cisplatin chemotherapy. In order to detoxify mitochondrial lipid peroxidation by binding to singlet oxygen, astaxanthin searches for free radicals, or ROS, and inhibits their synthesis. In vitro and in vivo research have shown that astaxanthin, a naturally occurring fat-soluble antioxidant, reduces inflammation. It is stored in cell membranes. Compared to other antioxidants that can regulate the level of ROS, astaxanthin is far more effective at neutralizing the reaction of single-charged oxygen and suppressing lipid peroxidation [32-39].

The findings of the study demonstrate that astaxanthin can lower MDA levels through enzymatic or non-enzymatic mechanisms. MDA is a dialdehyde molecule that is the byproduct of lipid peroxidation in the body. High MDA concentrations are indicative of an oxidation process occurring in human body cell membranes. Since fatty acid chains break down as a result of lipid peroxidation, MDA which is extensively available in circulation becomes hazardous to cells. This MDA is continuously created based on the amount of lipid peroxidation that takes place. It has been demonstrated that astaxanthin administration lowers MDA levels in HNC patients undergoing cisplatin chemotherapy the byproduct of lipid peroxidation [47-51] (Figures 3,4).

This work has practical significance, particularly for cisplatin-treated HNC patients, in terms of reducing MDA and raising SOD to combat cisplatin-induced free radicals. Astaxanthin may work by binding singlet oxygen free radicals and enhancing the oxidative stress pressure that these free radicals cause. The study solely focused on HNC patients who received cisplatin, but the results are consistent with earlier research and the body of literature showing astaxanthin can combat free radicals by raising SOD and lowering MDA [47-51]. During the study, three patients in the astaxanthin group reported experiencing side symptoms such heartburn and nausea. After a thorough analysis of these adverse effects, the patients' conditions remain stable, and they are prescribed antacid tablets. As a result, giving astaxanthin to patients with HNC is generally safe and does not have any negative side effect.

Owing to various research limitations, such as the possibility of research subjects consuming drugs or foods containing other antioxidants, such as the habit of drinking green tea or vegetables, as well as differences in ability, differences in the absorption capacity of food and medicines in HNC patients, and differences in pharmacodynamics and pharmacokinetics for each

HNC patient, the results of this study are not sufficient to explain all the problems. The 21-day trial period might not be long enough to adequately capture how astaxanthin intake affects oxidative stress markers over the long run. Longer-term follow-up evaluations could shed light on the impacts' cumulative and sustainable nature. Reserecher have conquered the constraints posed by the unpredictability of chemotherapy cycles, and the concurrent administration of additional antioxidants would offer a more thorough framework for interpreting the outcomes.

In conclusion, Astaxanthin has been shown to raise SOD and lower MDA levels in patients with HNC receiving cisplatin treatment. This implies that astaxanthin functions as a potent antioxidant supplement that offsets the reactive oxygen species (ROS) produced during cisplatin treatment. Astaxanthin aids in the mitigation of oxidative stress, which is important for controlling the negative effects of chemotherapy and possibly improving outcomes for patients with HNC. It does this by increasing SOD activity and decreasing MDA.

Author Contribution Statement

Yusuf Aminullah: Conceptualization, Methodology, Software, Zulfikar Naftali: Conceptualization, Damai Santosa: Visualization, Investigation: Yan Wisnu Prajoko: final review, Mahalul Azam: methodology, Hardhono Susanto: writing review and editing, Hertanto Wahyu Subagio: Conceptualization, Methodology, analysis data.

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Ethical approval

This study is a component of a doctoral dissertation accepted by Diponegoro University, Semarang's Doctoral Program in Medical and Health Sciences. The Dr. Kariadi Hospital in Semarang's Research Ethics Commission granted ethical approval with No. 1066/EC/KEPK-RSDK/2022. The main director of Kariadi Hospital in Semarang granted a research permit letter with the number DP.02.01/I.II/4094/2022.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest in this study.

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