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Ginkgo Biloba As A Potential Protector Against Cisplatin-Induced Ototoxicity: Expression In Nasopharyngeal Carcinoma

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ABSTRACT

BACKGROUND: Nasopharyngeal carcinoma is a malignancy of the upper aerodigestive tract that has a high death rate. Chemotherapy and radiation therapy are two options for treating nasopharyngeal cancer. Ototoxicity and hearing loss are side effects of platinum-class chemotherapy medications like carboplatin and cisplatin. Because of its antioxidant properties, ginkgo biloba extract may help avoid the negative consequences of cisplatin ototoxicity.
MATERIALS AND METHODS: This study examined a sample of newly diagnosed patients with nasopharyngeal cancer receiving cisplatin treatment at the DR. Moewardi Hospital between July and September 2022. It included a pre- and post-test control group design. The sample was split into two groups: the one that received 60 mg of ginkgo biloba extract twice day for six weeks. Cisplatin treatment without extra extracts was administered to the control group. The NOX-3 levels were examined in order to conduct the examination.
RESULTS: A p-value <0.05 was found when the mean NOX-3 levels in both groups were calculated before and after treatment. The average NOX-3 level in the control group was 2.48 prior to treatment and 3.51 following treatment (p=0.008). The average NOX-3 level in the treatment group was 2.25 prior to treatment and 1.84 following treatment (p=0.045).
CONCLUSION: Blood NOX-3 levels in patients with nasopharyngeal carcinoma treated with ginkgo biloba differed significantly from those in the control group. This demonstrates the benefits of these plants, making them suitable for use in conjunction with cisplatin chemotherapy to avoid hearing loss.

Keywords*: Cisplatin, Ginkgo biloba, Nasopharyngeal carcinoma, NOX-3*

Introduction: Nasopharyngeal cancer (NPC) is a type of cancer that arises from the nasopharyngeal epithelium and is caused by squamous cells. Because of the death it causes, NPC, a cancer of the upper aerodigestive tract, has drawn a lot of interest from around the world (Pieter, 2013). According to international cancer statistics, there were around 84,400 NPC incidences in 2008, with a 51,600 fatality rate (Faisal H, 2015). South China, Southeast Asia, Japan, North Africa, and Central Asia are among the regions with the highest incidence of NPC. In South China, there are 15 to 50 cases of NPC on average for per 100,000 people. More than 71% of new cases of NPC originate in Southeast Asia, making this region an endemic area (Chua et al., 2016). Chemotherapy and radiation therapy are the primary treatments for NPC. Using ionising radiation, radiotherapy treats cancer by killing as many tumour cells as possible while

preserving healthy tissue around the tumour to prevent excessive damage. Patients with NPC may also receive chemotherapy in addition to radiotherapy (Firdaus, 2012). The platinum group is the most often used chemotherapy medication, and it works best when taken in combination. For NPC, platinum-class chemotherapeutic medications such carboplatin and cisplatin are useful treatment plans. However, 60% of patients may have hearing loss as a result of its ototoxic side effects, which leads to social isolation and communication problems. In 2019, Apriliana et al. The most often used chemotherapy medication is cisplatin, also known as cis-diamminedichloroplatinum. Apoptosis, which is brought on by the rise in free radicals in the inner ear caused by cisplatin, is the mechanism by which cisplatin causes ototoxicity. When exposed to cisplatin, NADPH oxidase in outer hair cells produces free radicals. One enzyme that catalyses the production of superoxide radicals is NADPH oxidase. The inner ear produces a specific type of NADPH oxidase called NOX-3, which is a major source of free radical production in the cochlea and may contribute to hearing loss. This process produces free radicals, which in turn cause caspase-mediated apoptosis and mitochondrial death (Sheth, 2017). Ginkgo biloba in the form of an extract with flavonoids has been utilised as an antioxidant thus far to prevent and lessen the harm caused by cisplatin. Ginkgo biloba has been shown in multiple studies to help patients receiving cisplatin treatment avoid sensory-neural hearing loss (Sampaio et al., 2016). The researchers at Dr. Moewardi Hospital planned a study on the impact of ginkgo biloba on NOX-3 expression in cisplatin ototoxicity in patients with nasopharyngeal cancer based on the background information mentioned above.

MATERIALS AND METHODS

Study design

This study was carried out at the DR. Moewardi Hospital between July and September of 2022 as an experimental study with a control group before and after the test.

Picture 1. NOX-3 Reagent

Picture 2. Ginko Biloba Supplements

Picture 3. Blood sample

Participants

Patients with a diagnosis of nasopharyngeal carcinoma arrive at DR. Moewardi Hospital's Otolaryngology Poly. The minimal sample size for this investigation was 18 samples, according to the findings of the sample calculation above (Kothari, 1990 in Bisma, 2013). The complete sampling method, a non-probability sampling methodology, was used to collect the samples.

Criteria for inclusion

1. willing and cooperative as research participants
2. patients between the ages of 25 and 70.
3. NPC patients with new cases using the cisplatin, mesna, and ifosfamide-mesna regimen or the paclitaxel-cisplatin regimen.

Criteria for exclusion

1. NPC patients who have relapsed or cancer patients who have already undergone chemotherapy using a cisplatin regimen.
2. category II patients with a history of pulmonary tuberculosis treatment.
3. Pre-existing hearing loss materials: Information from blood serum and patient medical records from the DR. Moewardi Hospital was used in this investigation.

Image 1. Image 2: NOX-3 Reagent.

Picture 3: Ginkgo Biloba Supplements.

Statistical techniques for blood samples

statistical analyses with SPSS software version 22.

Methods:

Dr. Moewardi Hospital hosted this study in October 2022. This study uses an experimental design with a control group before and after the test. The study's primary data came from a sample of cooperative patients, aged 25–70 years, who met the study's inclusion and exclusion criteria and were diagnosed with new cases of nasopharyngeal carcinoma and treated with either the cisplatin paclitaxel regimen or the cisplatin, mesna, and ifosfamide regimen while they were at Dr. Moewardi Hospital between July and September 2022. Age, sex, smoking history, hearing loss, lumps, and the outcomes of comparing NOX-3 markers before and after treatment were among the details collected about the trial participants. Eighteen samples that satisfied the study's inclusion and exclusion criteria were collected in the allotted time. There were nine samples total—nine in the treatment group and nine in the control group. Tables 1 and 2 present the attributes of the research participants.

Table 1. Characteristics of research subjects in the form of categorical data

Variable	Total	Percentage (%)
Gender		
Male	14	77,8
Female	4	22,2
Age		
25-45 years	5	27.8
46-65 tahun	11	61.1
>65 tahun	2	11.1
Hearing Disorders		
No	8	44,4
Yes	10	55,6
Smoking History		
No	6	33,3
Yes	12	66,7
Lump on Neck		
No	7	38,9
Yes	11	61,1

Table 2. Characteristics of research subjects in the form of continuous data

Variable	Total	Average ± SD
Age	18	52.33 ± 12.46
NOX-3 Pre Treatment	18	2.37 ± 1.23
NOX-3 Post Treatment	18	2.68 ± 2.14

RESULTS

The data distribution analysis was then performed. The distribution of inflammatory marker levels in each study group was ascertained by data distribution analysis. The Shapiro-Wilk test is the chosen normalcy test. The Shapiro-Wilk test's significance level was set at 0.05, meaning that if a p-value > 0.05 was found, the data was considered regularly distributed. The computation results yielded a variety of p-values. While the data in the treatment group were normally distributed in both the pre- and post-treatment periods ($p > 0.05$), the data in the control group did not exhibit a normal distribution ($p < 0.05$).

Table 3. Normality Test

Variable	Saphiro-Wilk	
	P	Information
Control Group		
NOX-3 Pre Perlakuan	0.004	Abnormal
NOX-3 Post Perlakuan	0.002	Abnormal
Treatment Group		
NOX-3 Pre Perlakuan	0.058	Normal
NOX-3 Post Perlakuan	0.201	Normal

A Wilcoxon test and a paired comparative t-test were employed to compare the means of each research group. Based on the findings of the data normalcy test, two distinct tests were used for the comparison analysis. The non-parametric Wilcoxon test was used to analyse research data that was not regularly distributed; a paired t-test was used to analyse normally distributed data. For this comparative test, a significance level of 0.05 is employed. Table 4. displays the comparison analysis's findings. The mean NOX-3 before and after treatment in the two groups is calculated, and the table reveals a p value <0.05, which indicates statistical significance. It can be inferred from the comparison analysis's findings that the mean NOX-3 levels before and after treatment differ. While NOX-3 levels dropped in the treatment group, they rose in the control group. Table 3. Group NOX-3 Pre Perlakuan NOX-3 Post Perlakuan 0.004 0.002 Abnormal Abnormal Treatment Group NOX-3 Pre Perlakuan NOX-3 Post Perlakuan 0.058 0.201 Normal Normal

DISCUSSION

This study examined the impact of ginkgo biloba on NOX-3 expression in cisplatin ototoxicity in patients with nasopharyngeal carcinoma (NPC). The 18 samples in this investigation were split into two treatment groups: one for ginkgo biloba and the other for control. It was discovered that the sample's mean age was 52.33 ± 12.46 years. According to a study by Barata et al. (2014), men were more likely than women to have nasopharyngeal cancer, and the 40–49 age range was the most prevalent. Whitehorn et al. (2014) carried out a comparable study with a sample of 79 (73.8%) males and 28 (26.2%) females, whose average age was 44.4 (14; 75) years. Men are more likely than women to develop nasopharyngeal cancer. These findings are nearly identical to those of studies carried out by numerous other researchers. Cisplatin is used to treat NPC, and this medication is known to produce ototoxic adverse effects. According to Tang et al. (2021), between 22 to 70 percent of patients experienced ototoxicity as a result of cisplatin treatment. Additionally, this study shown that individuals with hearing loss had 10 (55.6%) more characteristics than those without hearing loss. Reactive oxygen species (ROS) generated by NADPH oxidase (NOX) are the cause of hearing loss brought on by cisplatin. This is clear from the research of Mohri et al. (2021), who found that cisplatin treatment in specific cochlear cell types caused apoptosis of the outer hair cells, among other factors, leading to elevated NOX-3 expression. Flavonoids and terpenoids, two significant chemical substances found in the ginkgo biloba plant, have multiple advantageous effects in various treatments, including reducing sensorineural hearing loss in individuals receiving cisplatin treatment for malignant tumours. Because of its antioxidant qualities, this plant can lower ROS and slow down the lipid peroxidation process. Numerous animal cisplatin experiments have demonstrated the autoprotective function of ginkgo biloba. The study's control group and test group had mean NOX-3 levels of 2.48 and 1.84, respectively (Gabriela Achete de Souza et al., 2020). NOX-3 levels rose in the control group ($p = 0.008$) and fell in the treatment group ($p = 0.045$) following the administration of ginkgo biloba in the treatment group and a placebo in the control group. This demonstrates that administering ginkgo biloba to the treatment group had an impact. In an experimental investigation by Wang et al. (2017), rats given ginkgo biloba extract showed a substantial decrease in NOX-3 gene expression. These findings are consistent with the Q research. According to Tang et al. (2021), rats administered this therapy might avoid hearing loss and preserve their hair cells following cisplatin injection. This result supports that of Lin et al. (2007), who found that ginkgo biloba extract can decrease LPS-stimulated NADPH oxidase activity. In that investigation, apocynin, diphenylene iodonium (DPI), and NADPH oxidase inhibitors were used to treat human aortic smooth muscle cells (HASMC). TLR4 mRNA expression was markedly increased by LPS or HO. 30 μM DPI or 100 μM apocynin greatly inhibited this effect, suggesting a connection between ROS generation mediated by NADPH-oxidase and TLR4 expression caused by LPS. LPS-induced NADPH oxidase activation was nearly entirely suppressed by ginkgo biloba extract. It is anticipated to lower the incidence of hearing loss brought on by cisplatin treatment because to the anti-inflammatory properties of ginkgo biloba extract and the demonstrated NOX-3-reducing effect from several previous research. Even though the number of samples has reached the lowest limit based on the number of samples calculation, the study's drawback is the limited number of samples. Only 18 people participated in this study, which was still a limited sample size because it only looked at a small percentage of the current population. Furthermore, the administration

of two 60 mg doses of ginkgo biloba was limited to six weeks. Effects may vary depending on the dosage.

Conclusions:
Based on research findings, ginkgo biloba has been shown to influence NOX-3 expression in cisplatin ototoxicity in patients with nasopharyngeal cancer. In patients with nasopharyngeal cancer, ginkgo biloba lowers NOX-3 levels. Antioxidants, particularly flavonoids, found in ginkgo biloba, have the ability to inhibit apoptosis or lower the prevalence of hearing loss.

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Conflicts of interest
There are no conflicts of interest

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