Jurnal Biologi Tropis

Original Research Paper

Antioxidant Effect in Nasopharyngeal Cancer Histopathology Degree on 40 PPM Formaldehyde-Inducted *Rattus novergicus*

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Article History
Received : February 25th, 2025
Revised : March 10th, 2025
Accepted : March 13th, 2025

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Abstract: Formaldehyde exposure, implicated on the development of nasopharyngeal cancer (NPC), remains a significant concern worldwide, with increasing incidence, morbidity, and mortality cases. This study eager to investigate the antioxidant effect on degree of histopathology from formaldehyde exposure, assessing nasopharyngeal dysplasia progression toward malignancy. *Rattus norvegicus* divided equally into four groups: control, placebo, formaldehyde-induced (40 PPM), and formaldehyde-induced with antioxidant, followed by dysplasia degree examination under light microscope. The result revealed severe dysplasia in the formaldehyde group, indicating non-keratinizing squamous cell carcinoma. Additionally, antioxidant-treated group presented reduced severity, with lower degree of dysplasia. This result is indicating positive improvement of antioxidant effect toward NPC malignancy, supporting previous studies and further confirming genotoxicity and irritability of formaldehyde. Nevertheless, limitations, existed with lack of sample studied and dose-response analysis, were demanding deeper study need to be done.

Keywords: Dysplasia, formaldehyde, histopathologic, nasopharyngeal cancer, *Rattus norvegicus*.

Introduction

Cancer remains one of the leading causes of mortality and morbidity worldwide, particularly nasopharyngeal cancer (NPC) that previously known as lymphoepithelioma. NPC was identified as a specific subtype of head and neck squamous cell carcinoma (HNSCC) with increasing concern globally (Chen et al., 2020). NPC was contributing to total ±133,354 cases and 2.34 million Disability-Adjusted Life Year (DALY) worldwide in 2020, indicating a peak morbidity incidence (Song, Cheng, Li, & Liu, 2022; Yanting Zhang, Rumgay, Li, Cao, & Chen, 2023). In 2020, both NPC mortality and morbidity incidence in South-Eastern Asia emerged as the highest age-standardised incidence rates (AISR) for both male and female, while age-standardised death rates (ASDR) for both gender reached highest between asian region (Yuna Zhang, Gu, Deng, & Shen, 2024). In Indonesia, NPC incidence reached 176,500 cases with third highest mortality rate in 2019 (Yu et al., 2022). These number manifested from heterogenous risk factor, consisting of gender, diet, lifestyle, race, to HLA genes susceptibility (Romdhoni et al., 2023).

Male gender associated with increase risk of developing NPC, supported by three fold higher ASDR and AISR in male globally (Romdhoni et al., 2023; Yanting Zhang et al., 2023). Smoking habit presented a positive correlation to NPC incidence, reinforced by smoking addiction across Indonesian (Romdhoni et al., 2023). Cultural heterogenicity of culture and dish may appeared as risk factor, particularly in salted fish which high in carcinogenic nitrosamine, further culminating NPC incidences (Romdhoni et al., 2023;

Wahidah & Yuliyani, 2023). Moreover, complex interplay between Epstein-Barr virus (EBV) infection and HLA susceptible patient played pivotal cause in NPC incidence (Du, Xiao, Qiu, & Wu, 2019). Ultimately, the incidence of NPC regarding of severe or prolonged formaldehyde exposure (Adamović et al., 2021; Kang et al., 2021).

Frequent formaldehyde exposure is a serious health hazard, ranging from household material, environmental contamination, various spray product, and even occupational specific risk (Adamović et al., 2021; Clausen et al., 2020; Huang et al., 2022; Kang et al., 2021; La Torre, Vitello, Cocchiara, & Della Rocca, 2023a; Qu, Lu, & He, 2017; Salthammer, 2019; Swenberg et al., 2013; Wang, Wang, Xiong, Huang, & Koutrakis, 2022). Furthermore, even formaldehyde toxicity is seasonal dependent, especially in summer with highest toxicity risk (Khoshakhlagh, Ghobakhloo, Al Sulaie, Yazdanirad, & Gruszecka-Kosowska, 2025; Khoshakhlagh, Omer, & Yazdanirad, 2024). This substance proved to induce DNA lesion, mutation, and genetic alteration (Benedict, Kristensen, & Duxin, 2024; Kawanishi, Matsuda, & Yagi, 2014; Li et al., 2021; Nakamura et al., 2017; Swenberg et al., 2013). Numerous studies concur in association of formaldehyde exposure risk to genetic alteration that led to NPC development (Mazurkiewicz, Sak, Nowiński, & Fus-Mazurkiewicz, 2024; Miligi et al., 2020; Möhner, Liu, & Marsh, 2019; Nielsen, Larsen, & Wolkoff, 2017; Niti Wedayani et al., 2023; Wedayani et al., 2024). These facts motivated our priority of interest, necessitating a deeper understanding of its role in development of NPC prognostic and demanding intervention to minimalizing the formaldehyde exposure effect.

Antioxidants are endogenous substance, comprised of enzyme such as superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic molecule like vitamin (Jena, Samal, Bhol, & Duttaroy, 2023). This substance take part in ROS neutralization and cellular redox balance, beside comprimising therapeutic potential in pathological condition (Jena et al., 2023; Kumar et al., 2022; Xiong et al., 2022; P. Zhang et al., 2020). Importantly, antioxidants act in several interplay in cancer development prevention, but its specificity and efficacy remains unknown (Jena et al., 2023; La Torre, Vitello, Cocchiara, & Della Rocca, 2023b; Nitti et al., 2022). Complimenting into that matter, recent study from Zahra et al. (2021) showed double sworded effect of antioxidant dose in cancer therapies, emerging deeper understanding regarding this evidence gap.

As mentioned, histopathological degree examination has given rise to prognostic efficacy and its developing in multivariate approach. Through its comprehensive understanding, complimented with antioxidant intervention, both NPC mortality and morbidity decline from formaldehyde exposure may be concurred. Looking at the importance of these vital purpose, antioxidant effect on nasopharyngeal carcinoma histopathological degree will be the focal point of this research.

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Material and Method

This study was conducted utilizing *Rattus norvegicus* as the experimental model, adhering to spesific inclusion and exclusion criteria. The inclusion criteria comprised: (1) rats aged 2-3 months and (2) rats with healthy conditions characterized by calm movement, absence of wound or defect, thick fur, and clear eyes. The exclusion criteria encompassed: (1) rats that died prior to treatment (2) rats that had previously undergone treatment for another experiment, and (3) rats with anatomical or morphological abnormalities. Forty Rattus norvegicus were allocated into four groups, each consisted of ten rats: (1) control group without any treatment, (2) placebo group, (3) rats inducted with 40 PPM formaldehyde without any antioxidant treatment, and (4) rats inducted with both 40 PPM formaldehyde and antioxidant. The dependent variable was the degree of anatomical pathology, while the independent variable was the formaldehyde induction treatment with and without antioxidants. This research commenced with obtaining ethical clearance, followed by two weeks acclimatization period for experimental animal. Subsequently, all rats of each group underwent their respective treatment for one month and continued with an examination under a light microscope with Hematoxylin and Eosin (H&E) staining by taking a nasopharyngeal biopsy from all rats of each group. The

histopathology degree was divided: (1) first-degree with mild dysplasia, (2) second-degree with moderate dysplasia, (3) third-degree with severe dysplasia, and (4) fourth-degree with very severe dysplasia, based on histological characterization. The derived result from this anatomical pathology analysis will elucidate the association of antioxidant intervention with the histopathological degree of nasopharynx tissue between groups.

Result and Discussion

Histopathological Findings

The nasopharyngeal histopathological of healthy *Rattus norvegicus* revealed all normal findings. This observation result showed absence of any dysplasia characteristic: (1) normal cell size and shape without anisonucleosis, anisocytosis, and squamous cell polymorphism, (2) normal nuclei without hyperchromatic nuclei or even abnormal nuclei number, and (3) normal mitotic activity. **Figure 1**. The nasopharyngeal histopathological revealed in formaldehyde-inducted group with severe dysplasia, third-degree dysplasia. These findings consist of: (1) increase in nuclear/cytoplasmic ratio or anisocytosis, (2) abnormal nucleus with variable shape and size or anisonucleosis and abnormality nuclei count, (3) increase mitotic abnormality.

Table 1. Nasopharyngeal Degree of Healthy and Formaldehyde Induced Group

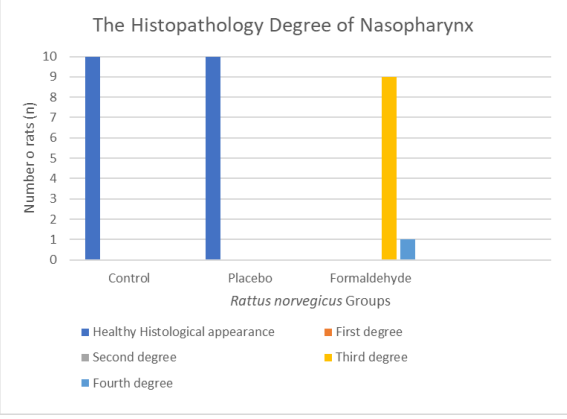

Figure 2. These group fell into a characterization of non-keratinizing squamous cell carcinoma (NKSCC). This NKSCC further specifically categorized as non-keratinizing undifferentiated squamous cell carcinoma based on fifth edition of WHO classification of neck and head tumor. All placebo *Rattus norvegicus* showed no dysplasia degree under histological observation. representing significant result of antioxidant intervention to minimalize the formaldehyde exposure effect in nasopharyngeal carcinoma development.

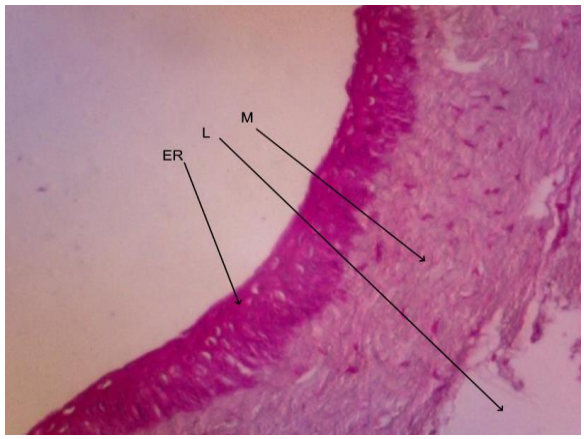

Figure 1. Nasopharyngeal Histology within Control Group

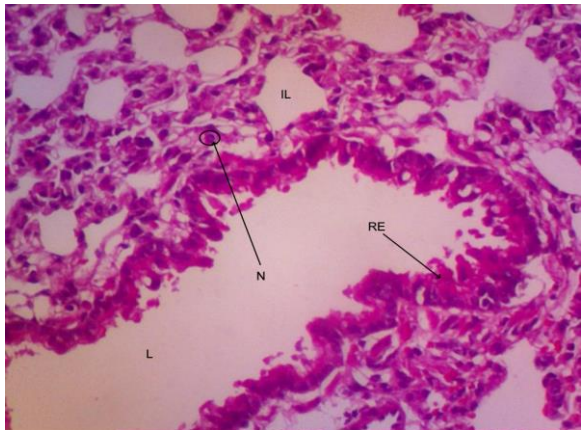

Figure 2. Nasopharyngeal Histology of 40 PPM Formaldehyde-inducted *Rattus norvegicus* group.

Our in vitro study strives to justify the harmful effect of formaldehyde exposure effect on nasopharyngeal carcinoma development. Thus, added clear insight in evidence of NPC histopathological alteration in nasopharynx stratified squamous epithelium cell. Third-degree dysplasia in formaldehyde group presented with many supporting features. In recent case report, histopathological evidence reveals NPC hyperchromatic nuclei by the presence of malignant epithelial cells that exhibit a diffuse and non-keratinizing pattern (Dahbi, Alami, Elmejjabar, & Couhen, 2023). This feature commonly known in

differentiated type of non-keratinizing carcinoma, but also scarcely present in undifferentiated form (Chan, 2017).

This feature was also seen in rare NPC basaloid squamous cell carcinoma with lobular masses and jigsaw-puzzle like appearance (Chan, 2017). Subsequent third-degree histopathological feature, consisting of anisonucleosis, also well known as nucleic atypia, which manifested from nuclear injury due to formaldehyde exposure, appeared as heterogenous nuclei size variation (Monahan et al., 2016). This feature, as well as anisocytosis, also seen in other type of carcinoma, marking a significant histopathological dysplasia appearance of cancer (Alwelaie et al., 2023; Heath, Goicochea, & Staats, 2015; Michal et al., 2018; Tommasi et al., 2023). Overall feature showed abnormalities tumor cell and nuclei with positive association with previous studies (Chan, 2017; Marin et al., 2024).

Formaldehyde Genetic Alteration Effects

Formaldehyde classified as first-class carcinogenic agent according to WHO (Protano et al., 2021). Exogenous formaldehyde exposure exhibit genotoxicity or genetic aberration by DNA linking (Dator et al., 2022; Ghelli, Bellisario, et al., 2020; Leso, Macrini, Russo, & Iavicoli, 2020; Speit, 2002). Formaldehyde also acted as free radical in inducing oxidative stress, increasing ROS production and cellular alteration, including DNA, RNA, and mitochondria, to a greater extent (Ghelli, Buglisi, Bellisario, Santovito, & Bono, 2020). Formaldehyde acted as an irritant for nasopharynx tissue as well (La Torre et al., 2023b). Therefore, this substance participating in NPC development, appeared with degree of dysplasia in formaldehyde-inducted group .

First genetic alteration phenotype was seen in abnormally numerous cells undergo mutation. This feature was seen with many cells in mitosis phase, reflecting its peak rate of proliferation activity (Liu *et al.*, 2022). This abnormally occurring mutation rate was contributing to the development of NPC and its progression to malignancy by altering genetic stability (Liu et al., 2022). This abnormal mitotic rate would give rise to genetic and phenotypic alteration, thus appeared as dysplasia in NPC histopathological observation.

Antioxidant Intervention Effect and Its Future Insight

Subsequently, our study analyzed the antioxidant intervention on the degree of nasopharyngeal carcinoma histopathology, provided an outcome toward minimalizing the effect of formaldehyde exposure. The antioxidant-inducted group showed satisfying results in histopathological degree, with a lower degree of dysplasia. Through examination, seven rats appeared with first-degree dysplasia and three others showed second-degree dysplasia. Thus, the administration of antioxidants mitigated the severity of dysplasia degree, indicating a protective effect against formaldehyde-induced oxidative stress that leads to NPC development. These findings favored the effect of the antioxidant intervention on cancer prevention, filling the evidence gap in its development for cancer therapies (Didier et al., 2023; George & Abrahamse, 2020; Luo et al., 2022).

Study Limitation

Therefore, this study revealed positive correlation between formaldehyde exposure to NPC development according to recent studies available (Mazurkiewicz et al., 2024; Möhner et al., 2019; Nielsen et al., 2017; Niti Wedayani et al., 2023; Wedayani et al., 2024). Additionally, this study presented positive outcome toward antioxidant intervention. However, there were several limitations to this study, especially the dose-response analysis. Another gap is limitation of the given sample in this study. Therefore, deeper study with far bigger population sample needs to be done.

Conclusion

This study demonstrates a clear association between formaldehyde exposure and development of nasopharyngeal carcinoma (NPC) through histopathological alteration feature, particularly the degree of dysplasia of nasopharynx which only falls to non-keratinizing squamous cell carcinoma (NKSCC). Our findings reveal that given formaldehyde exposure leads to dysplasia, manifested from significant genetic, phenotype aberration, and ultimately ROS production. Therefore, this study highlighted antioxidant effeect on overcoming formaldehyde as genotoxic and irritant agent on NPC carcinogenesis. Several limitations must be

addressed in the future research, including the lack of dose-response result and small sample size. Further investigation in subsequent study is crucial to provide comprehensive evaluation based on this matter.

Acknowledgement

We would like to express our sincere gratitude to Dr. dr. Anak Agung Ayu Niti Wedayani, M. Sc. as the Head of Degenerative and Primary Neoplasm Research, for overseeing this study. Our appreciation also goes to dr. Lale Maulin Prihatina, Sp. PA as well as dr. Eka Ari Yuliani, Sp. THT-KL and Sekar Partiwi, SKM., M. Pd. for invaluable insight through this study.

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