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The Effect of Chronic Exposure Between Ascorbic Acid-Based Vape and Tobacco Cigarette Towards Oxidative Stress Level and Tracheal Histopathology in White Rats (Rattus Norvegicus)

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ABSTRACT

Background: Nicotine-based vape has gained popularity as an alternative to cigarette use. Numerous studies have proven the dangers of smoking, including the elevation of oxidative stress and tracheal structure alteration. Ascorbic acid (AA) is a potential nicotine replacement in vape's e-liquid. Publications about AA as nicotine alternative in vape's e-liquid are still scarce.

Objective: This research aimed to analyze the effects of oxidative stress and tracheal histopathology in white rats (Rattus norvegicus) exposed to cigarette smoke and aerosol generated from AA-based e-liquid.

Methods: True experimental research design was conducted using a post-test only control group design approach with 21 white rats (Rattus norvegicus). Rats were randomly distributed into three groups: K1= non-exposed group; K2= exposed to smoke from three cigarettes/day; and K3= exposed with 0.5mL/day of AA-based vape aerosol. The exposure period lasted 12 weeks; then, the blood samples and the trachea were collected after termination. SOD-3 and MDA were measured in blood serum as oxidative stress biomarkers, while goblet cell count and mucosal epithelium thickness were measured through trachea histopathology slide. The data were statistically analyzed using a One-Way ANOVA test, followed by Post Hoc Bonferroni test and Games-Howell test.

Results: Statistical analysis significant result ($p<0.05$) was found in SOD-3 level on K1&K3 and K2&K3, goblet cell count on K1&K3, and mucosal epithelial thickness on K1&K2. MDA level did not show any significant difference between groups. Tracheal histopathology revealed damages, K2 had the highest average of goblet cells (3.93±2.67) and the smallest average mucosal epithelial thickness in K2 (34.65±6.55), likely due to regeneration dysfunction in trachea.

Conclusion: Cigarette smoke exposure and AA-based vape aerosol showed significant differences in SOD-3 level, the number of goblet cells, and mucosal epithelial thickness. MDA level did not show any significant difference. AA as vape e-liquid base alternative is not significantly lower the stress oxidative level and require further investigations.

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1. Introduction

Smoking has become a global challenge for decades. Innovation regarding tobacco cigarette alternatives is currently gaining popularity. One of the alternatives to tobacco cigarettes is an electric cigarette or vape. The marketing jargon of vape is that it is a smoking cessation tool, emphasizing its benefit as a healthier option compared to conventional cigarettes[1]. E-liquid is heated using a vape device, and the aerosol product is inhaled. In 2021, globally, the estimated number of vape users in 48 countries was around 81.9 million[2]. Although the safety of vape usage is still debatable, numerous publications have proven that vaping is still harmful to human health.

Nicotine is a substance that can be found in most e-liquid products and tobacco cigarettes. Nicotine intake is received by nicotinic acetylcholine receptor (nAChR), which regulates cell proliferation and apoptosis. Increasing nAChR activation will lead to uncontrollable cell proliferation and resistance to apoptosis[2], [3] In nicotine-based e-liquid, other substances that get heated along with nicotine, i.e., humectant, flavoring, propylene glycol, and glycerin[4]–[6]. Tobacco cigarette smoke is processed through combustion, which produces carbon monoxide (CO) along with other substances, i.e., tar, chemical additives, etc., which are

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considered carcinogenic substance[7]. Long-term effects of smoking, both using vapes and cigarettes, could increase oxidative stress and respiratory tract inflammation.

Oxidative stress can be caused by the elevation of reactive oxygen species (ROS). ROS is produced from aerobic metabolism in the mitochondria. An excessive amount of ROS can overwhelm the antioxidant defense system, potentially leading to inflammation[8]. Common markers to determine the amount of oxidative stress are superoxide dismutase-3 (SOD-3) and malondialdehyde (MDA). SOD-3 is an extracellular enzyme that can suppress the inflammatory response. SOD-3 was proven to maintain the structure of ECM, decrease oxidative stress burdens in macrophages, and increase lung space[9], [10]. MDA is a lipid peroxide marker that can be used to calculate oxidative stress and redox signaling. Elevation of MDA marks an increase in the intensity of lipid peroxidation. Lipid peroxidation is highly linked to the amount of ROS, whereas lipid peroxidation is susceptible to oxidation by free radicals. MDA is considered a reliable marker of oxidative stress due to its reactivity and toxicity[11]–[13].

Respiratory tract inflammation caused by smoking, whether using a vape or a cigarette, has been proven in numerous studies. The composition in vape that is widely known to cause respiratory tract inflammation is nicotine, propylene glycol, glycerin, flavorings, humectant, and the byproduct from its heating mechanism, which is the aerosol[6]. Meanwhile, harmful components in cigarettes that cause inflammation are nicotine, tar, chemical additives, and the byproduct of the combustion mechanism, which is CO. The trachea is one of the affected organs caused by smoking[14]–[16]. Recorded damages in trachea, including desquamation, reduction of cilia, and increased goblet cells, which leads to mucosal hypersecretion[7], [17]. A damaged trachea would eventually disrupt the nasal mucociliary (NMC) mechanism. The NMC is an innate mechanism that protects the respiratory tract from pathogens, consisting of the mucous layer, airway surface liquid layer, and ciliary epithelium. Harmful ingredients, both in vape and cigarettes, have been proven to affect tracheal histology. The tracheal mucus entraps vape and/or cigarette smoke, later triggering the proliferation of goblet cells. Increasing goblet cells would elevate the expression of mucins (MUC5AC and MUC5B), thereby increasing mucosal thickness. The aforementioned alterations in the trachea would subsequently decrease the effectiveness of NMC[18].

Nicotine is a popular base for e-liquid; however, many studies have already proven the harm of nicotine intake[19]. Many potential chemicals that could replace nicotine as an e-liquid base, such as vitamins, are being explored[20]. Vitamin administration through inhalation is known for its potential to increase the topical effect in the respiratory tract. Ascorbic acid (AA) is one of the most common form of vitamin C, which contain antioxidant property[21]. The antioxidant property of AA could reduce the amount of ROS in the body and prevent lipid peroxidation through electron transfer[22], [23]. Inhaled AA potentially could increase the sinonasal immune system[24]. However, publications regarding the safety and toxicity risk of AA administration through inhalation are still scarce. Thus, further study about the potential of AA as an alternative to nicotine as an e-liquid base is needed.

This research aimed to analyze the comparison between cigarette smoke exposure and ascorbic acid-based vape

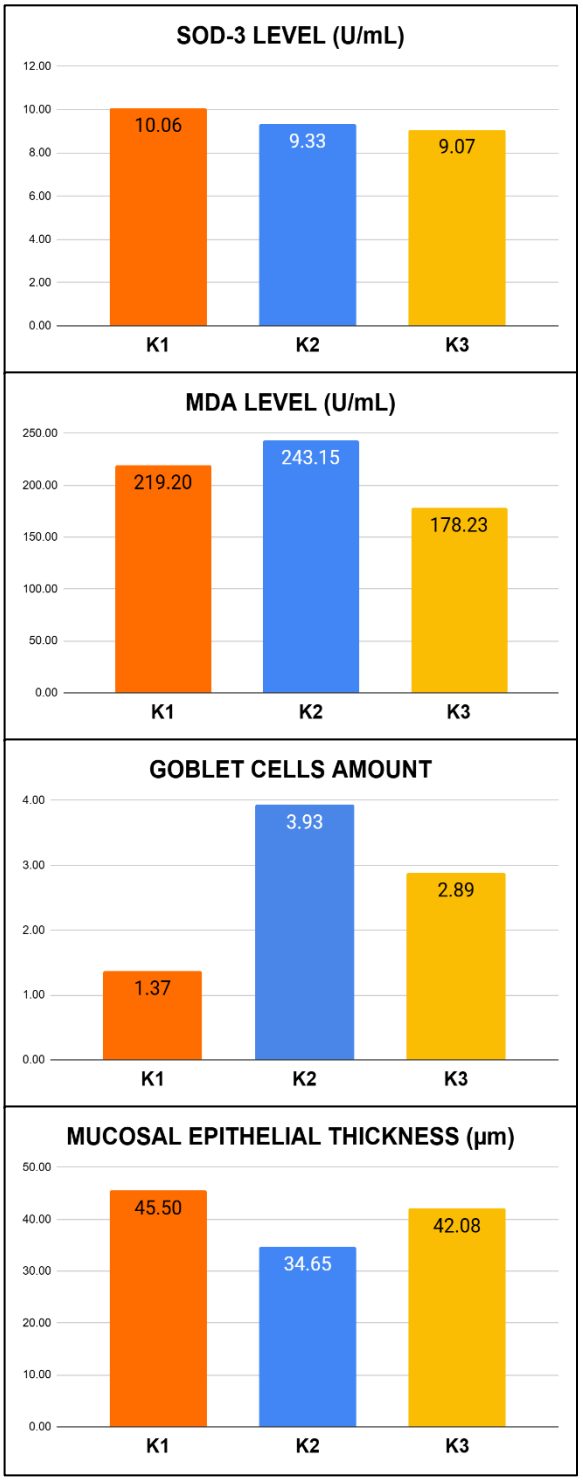


Figure 1. Results of average SOD-3, MDA, goblet cell count, and mucosal epithelial thickness (respectively): K1= control group; K2= cigarette exposure group; and K3= ascorbic acid-base vape exposure group.

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smoke exposure in terms of SOD-3 level, MDA level, and tracheal histopathology in white rats.

2. Methods

This research employed a true experimental study design with a post-test control group design approach. The

treatment administration was conducted in Biology Laboratory at Semarang State University, while the sample analysis was performed in the Faculty of Medicine, Diponegoro University. The subject of this research is eight weeks old 21 white male rats (Rattus norvegicus) outside exclusion criteria were distributed into three groups: group 1 (K1) = control group, no exposure; group 2 (K2) = exposed with cigarette smoke, using three cigarettes/day for 12 weeks; and group 3 (K3) = exposed with ascorbic acid-base vape smoke, using e-liquid as much as 0.5mL/day for 12 weeks. The dosage of cigarettes and e-liquid that are used in this research is equivalent as the dosage of heavy smoking in humans. During the 12-week treatment period, one rat from group 2 (K2) died in the first week.

After 12 weeks, the rats were terminated in order to collect the trachea and blood samples. The trachea was made into a histology slide with H&E staining, later the amount of goblet cells and mucosal epithelium thickness were observed using a light microscope with 400x magnification by an anatomy pathology specialist. The blood sample was collected through retroorbital, then centrifuged to obtain the blood serum for oxidative stress level measurement. The level of SOD-3 and MDA were measured to determine the oxidative stress using an ELISA Kit.

The data were analyzed statistically using IBM SPSS 25 with the One-Way ANOVA method, followed by the Post-Hoc Bonferroni test and Post-Hoc Games-Howell test.

3. Result

Table 1. Post-test One-Way ANOVA test result

Variable	Group	Mean±SD	p
SOD-3	K1	10.06±0.77	0.003*
	K2	9.33±0.10	
	K3	9.07±0.13	
MDA	K1	219.20±83.04	0.371
	K2	243.15±106.00	
	K3	178.23±53.30	
Goblet Cell Count	K1	1.37±0.72	0.040*
	K2	3.93±2.67	
	K3	2.89±1.18	
Mucosal Epithelial Thickness	K1	45.50±7.48	0.035*
	K2	34.65±6.55	
	K3	42.10±6.54	

Notes:
p = One-Way ANOVA test result
* = significant value (p<0.05)

Table 2. Games-Howell Post Hoc test result between the groups of SOD-3 and Goblet Cell Count

Variable	Group	Group	Mean Difference	Sig.
SOD-3	1	2	0.74	0.097
		3	0.99	0.032*
	2	1	-0.74	0.097
		3	0.25	0.006*
	3	1	-0.99	0.032*
		2	-0.25	0.006*
Goblet Cell Count	1	2	-2.56	0.140
		3	-1.51	0.038*
	2	1	2.56	0.140
		3	1.05	0.664
	3	1	1.51	0.038*
		2	-1.05	0.664

Notes:
* = significant value (p<0.05)

Table 3. Bonferroni Post Hoc test result between the groups of Mucosal Epithelial Thickness

Variable	Group	Group	Mean Difference	Sig.
Mucosal Epithelial Thickness	1	2	10.85	0.043*
		3	3.42	645
	2	1	-10.85	0.043*
		3	-7.44	0.150
	3	1	-3.42	0.645
		2	7.44	0.150

Notes:
* = significant value (p<0.05)

The result oxidative stress and tracheal slide measurement can be seen in Figure 1.The Statistical test results can beseen below. One-Way ANOVA test result in Table 1., Games-Howell Post Hoc test result in Table 2., and Bonferroni Post Hoc test result in Table 3.

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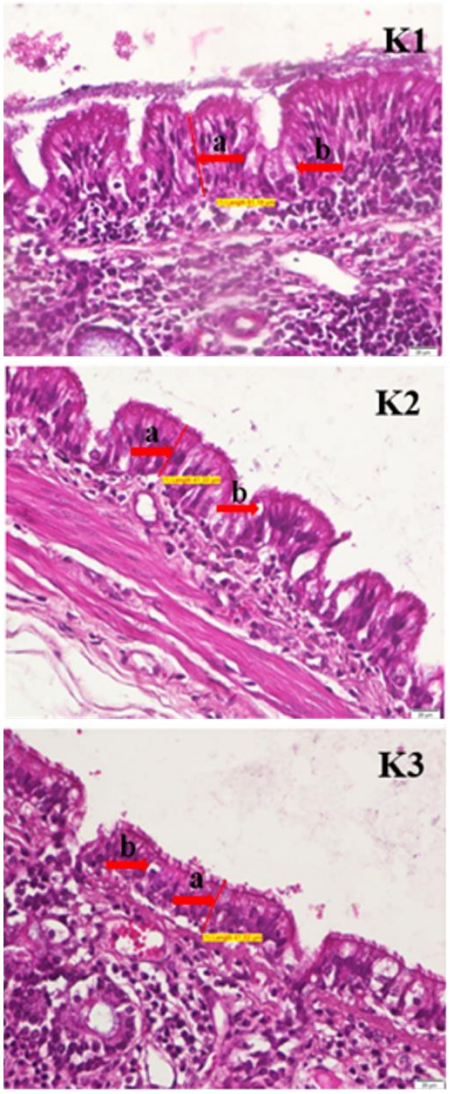


Figure 2. Tracheal histopathology slide of K1= control group, K2= cigarette exposure group, and K3= ascorbic acid-base vape exposure group: a) Trachea Mucosal Epithelial Measurement; and b)

4. Discussion

The highest SOD-3 level was found in K1 (10.06±0.77 ng/mL), followed by K2 (9.33±0.10 ng/mL), and lastly K3 (9.07±0.13 ng/mL).

The SOD-3 level that was found in K3 is lower than K1, which aligns with a previous study, which stated that the SOD-3 level in white rats that were exposed to nicotine-based vape is lower than in non-exposed white rats. Higher SOD-3 levels in blood serum can be caused by increased inflammation due to reactive oxygen species (ROS). Heated e-liquid in vape produced free radicals in the form of aerosols that contain glycerin, propylene glycol, and flavoring that inflamed the upper airway pathway[25], [26].

The low level of SOD-3 in K3 is potentially affected by the impaired antioxidant activity due to chronic inflammation. The aerosol of ascorbic acid in the e-liquid does not act as a precursor for SOD-3 production. Furthermore, imbalanced ROS-level in the body could lead to the declining of antioxidant enzymes, including SODs. Based on the research conducted by Bezerra et al (2023) [28], increased oxidative stress by inflammatory cells in asthmatic patients causing the impairment of SOD activity.

The One-Way ANOVA test showed a significant result ($p<0,05$), followed by the Games-Howell Post-hoc test which indicates a significant difference between K1&K3 and K2&K3. Significant differences in SOD-3 levels in K1 compared to K2 and K3 are likely due to healthier upper airway tissues. The free radical scavenging by SOD-3 in K1 is not affected by the exacerbation due to the impaired upper airway pathway. It is aligned with Sakaguchi et al. (2023)[28], which stated that smoker patients with COPD showed decreased free radical scavenging rate compared to the control non-exposed group.

The highest MDA level was found in K2 (243.15±106.00 ng/mL), followed by K1 (219.20±83.04 ng/mL) and K3 (178.23±53.30 ng/mL).

The MDA level in K2 is higher than K1 and K3, which likely caused by higher free radicals. The combustion mechanism produced CO, nicotine, tar, and other carcinogenic content. It is aligned with publication by Grazioli et al. (2020)[29], which stated that the MDA and 4-hydroxynonenal (HNE) levels in the saliva of the cigarette-smoking group were higher than those in the non-smoking group. Lower MDA level in K3 is suspected due to ascorbic acid content in the e-liquid, which act as antioxidant agent[29], [30].

The One-Way ANOVA test showed no significant result between groups ($p>0,05$). No significant difference of MDA level between groups is potentially caused by the lack of concentration of nicotine in the cigarette and ascorbic acid in e-liquid. Further research with broader range of concentration is required.

The highest goblet cell amount was found in K2 (3.93±2.67), followed by K3 (2.89±1.18), and K1 (1.37±0.72).

The goblet cell amount in K2 is higher than in K1 and K3, which is likely due to higher inflammation. The inhaled carcinogenic and CO content produced by cigarette combustion directly affects the trachea lining, which triggers the production of goblet cells. Other than increasing the production of goblet cells, smoking cigarettes causes epithelial erosion[31], [32]. Publication by Bodas et al. (2021)[33] using human bronchial epithelial cell (HBEC) in BronchiaLlife Epithelial Airway Medium (BLEAM) exposed to 2.5% cigarette smoke extract resulted in increased goblet cell marker (MUC5AC+) compared to the control non-treated group.

The One-Way ANOVA test yielded a significant result ($p<0.05$), followed by the Games-Howell Post-Hoc test, which indicates a significant difference between K1&K3. A Significant difference between K1&K3 is likely due to the aerosols of the heated e-liquid, which still cause inflammation and structural differentiation in tracheal lining. The composition of e-liquid, including propylene glycol, glycerin, and flavoring, has cytotoxic properties. Based on the publication by Kim et al. (2024)[32], e-liquid composition is proven to has cytotoxic properties, which caused several

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health problems such as goblet cell hyperplasia, inflammation, and mucus hyperconcentration. e-liquid composition has been shown to have cytotoxic properties, which can cause several health problems, including goblet cell hyperplasia, inflammation, and mucus hyperconcentration. The amount of goblet cells in K3 is not as high as in K2, which is likely due to the ascorbic acid content acting as an antioxidant property[24]. Goblet cells are part of the epithelial barrier in NMC. Ascorbic acid may potentially maintain the integrity of the nasal mucociliary clearance (NMC) mechanism. The amount of goblet cells within the normal range would be sufficient to produce mucus, which supports the upper airway protection from pathogens[34], [35].

The highest epithelial thickness was found in K1 (45.50±7.48 μm), followed by K3 (42.10±6.54 μm), and lastly K2 (34.65±6.55 μm).

The mucosal epithelial thickness in K1 is higher than in K2 and K3, which is likely due to a healthier epithelial lining. The composition of cigarettes and e-liquid of vapes is known to damage the respiratory epithelial structure. This is inconsistent with previous studies, which stated that the mucosal epithelial thickness in smokers is thicker due to an inflammatory response. Inhaled smokes lead to alteration of respiratory epithelial structure, including mucosal epithelium hypersecretion and hyperplasia[31], [36]. The thinner epithelium in K2 and K3 is potentially caused by chronic exposure. Accumulation of cigarette and vape smokes in long period would eventually incentivized cell deaths, protective barrier dysfunction, and epithelial structural changes[37].

The One-Way ANOVA test result showed a significant difference ($p<0.05$), followed by the Bonferroni Post-Hoc test, which indicated a significant difference between K1&K2. A significant difference between K1&K2 is likely due to the inflammation caused by harmful ingredients in cigarette smoke. Aldehyde, nitride, benzopyrene, and other carcinogenic compounds in cigarette smoke are known to cause health problems, such as chronic obstructive pulmonary disease (COPD). Numerous publications stated that cigarette smoke disrupts bodily function, including ciliated cells, goblet cells, basal cells, and submucosal secretion glands in epithelial structure[38], [39]. The thickness of the mucosal epithelium is a crucial aspect of the NMC mechanism[18]. Chethana et al. (2022)[40] stated that prolonged smoking could cause statis of mucus, which leads to decreased immunity.

5. Conclusion

Based on the results of SOD-3 level, MDA level, the amount of goblet cells, and mucosal epithelium thickness, it can be concluded that both cigarette exposure and vape with ascorbic acid base exposure affected the upper airway pathway compared to healthy control group. There were significant differences between groups in SOD-3 level, the amount of goblet cells, and mucosal epithelium thickness. However, the MDA levels between groups did not show any significant difference. The degree of oxidative stress and tracheal histopathology damages caused by cigarette smoke exposure is higher than that caused by vape with ascorbic acid base exposure. Ascorbic acid as vape base alternative is not significantly lower the stress oxidative level and require further investigations about different concentration of ascorbic acid as an e-liquid base.

Ethical Approval

This study was approved by the Health Research Ethics Commission of the Faculty of Medicine, Diponegoro University, in No. 088/EC-H/KEPK/FK-UNDIP/VIII/2024.

Conflicts of Interest

The authors declare no conflict of interest.

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Author Contributions

Conceptualization, Awal Prasetyo and Udadi Sadhana; methodology, Awal Prasetyo and Udadi Sadhana; software analysis, Levina Athaya Anarizta; validation, Awal Prasetyo and Udadi Sadhana; histopathology slide analysis, Hermawan Istiadi; writing—original draft preparation, Levina Athaya Anarizta; writing—review and editing, Levina Athaya Anarizta, Awal Prasetyo and Udadi Sadhana; supervision, Awal Prasetyo and Udadi Sadhana.

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