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The Effects of Kretek Cigarettes and Ascorbic Acid-based Vape on IL-6, TNF-α Levels, and Pulmonary Histopathology: An Experimental Study on White Rats (*Rattus novergicus*) on Inflammatory Response and Pulmonary Histopathology

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ABSTRACT

Background: Smoking habits remain difficult to break, with 991 million smokers worldwide in 2020. Many have switched to vaping, which is regarded as safer than clove cigarettes. Exposure to cigarette smoke can increase pro-inflammatory cytokines and damage lung tissue.
Objective: This study compared the effects of kretek cigarette smoke and ascorbic acid-based vape smoke on inflammatory response and lung tissue in male white rats (*Rattus norvegicus)*.
Methods: : Twenty-one 8-week-old rats were randomized into three groups: control, exposed to kretek cigarette smoke, and exposed to ascorbic acid-based vape. The kretek cigarette group was exposed to smoke from 3 cigarettes/day, while the vape group received 0.5 ml/day of vape smoke, for 12 weeks. Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) levels were analyzed using ELISA. The perimeter length of the alveolus, the degree of alveolar wall damage, and the extent of inflammatory cell distribution were also examined. Statistical analyses were accomplished using the ANOVA One-Way test, chi square test, and Kruskal-Wallis test.
Results: Cigarette exposure significantly increased IL-6 levels (control: 8.43 ± 0.88 pg/ml; kretek cigarette: 11.45 ± 1.17 pg/ml; ascorbic acid vape: 11.83 ± 1.56 pg/ml; p = 0.000), the degree of alveolar damage (mean rank control: 6.21; kretek cigarette: 14.17; ascorbic acid vape: 11.64; p = 0.001), and the extent of inflammatory cell distribution (mean rank control: 4.00; kretek cigarette: 15.25; ascorbic acid vape: 12.93; p = 0.012). TNF-α levels increased in the kretek cigarette group, while the alveolar perimeter length increased in the ascorbic acid vape group; however, neither parameter was statistically significant (p > 0.05).
Conclusion: Both kretek cigarette smoke and ascorbic acid-based vape smoke induced pulmonary inflammation and structural changes, with significant effects observed in IL-6 levels and histopathological damage, but not in TNF-α levels or alveolar perimeter length. There is a need for better regulation and increased public awareness about the dangers of smoking.

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1. Introduction

Smoking is a common habit that often begins in adolescence and remains difficult to eliminate.[1] Vapes are considered safer than conventional cigarettes, attracting many beginners, but they contain harmful chemicals and metals.[2] In 2025, there were 1299 million smokers worldwide (17.1% of the population over age 15).[3] In Indonesia, 70.2 million adults (34.5%) smoke—58.8 million use kretek cigarettes, 6.2 million use vapes, and the rest use other tobacco products.[4] The high number of smokers poses a serious global health risk, causing over 8 million deaths annually.[5] Despite these dangers, the tobacco industry continues to grow, and its products remain widely accessible.[4] As a result, cigarette smoke exposure affects both active and passive smokers, including 20.3 million indoor workers and 121.6 million adults exposed to smoke in their homes in Indonesia.[4]

There are two main types of cigarettes on the market, clove cigarettes (kretek) and white cigarettes.[6] Kretek, made from a mixture of tobacco and cloves, is the most popular type in Indonesia, consumed by 28.6% of the population in 2021.[4] Cigarettes are also categorized by their method of use, conventional cigarettes (burned) and electronic cigarettes or vapes (heated electronically).[7] Vapes are electronic devices that convert liquid (containing

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nicotine, flavorings, glycerin, and propylene glycol) into aerosol for inhalation.[8] Although considered an alternative to reduce the risks of conventional smoking,[9] vapes still contain nicotine and other harmful substances[10] that can cause respiratory and systemic health problems such as chest pain, shortness of breath, nausea, and lung inflammation.[11,12] Some e-liquid flavors, such as cinnamon, menthol, and strawberry, are cytotoxic, especially when combined with nicotine.[13] In contrast, flavors like chocolate, grape, cola, tobacco, and butterscotch show little to no toxicity.[13] Research has shown that administering ascorbic acid, either intravenously or via inhalation, can reduce oxidative stress caused by vaping and help protect vascular function and mucosal immunity.[14,15]

Damage to the respiratory system, including the lungs, can result from acute or chronic inflammation, marked by increased levels of pro-inflammatory cytokines such as IL-6 and TNF-α. Elevated IL-6 in the serum can serve as an indicator of diseases, including lung cancer, while TNF-α plays a role in inflammation and can act as a biomarker for non- small cell lung cancer.[16,17] A study on nicotine- based vape exposure in rats over 16 weeks showed a significant increase in inflammatory cells (neutrophils, macrophages, eosinophils) in the bronchoalveolar lavage (BAL) fluid compared to unexposed rats.[12] Histopathological examination also revealed inflammatory cell infiltration and increased connective tissue around the bronchioles, indicating pulmonary fibrosis caused by e-cigarette exposure.[12]

Nicotine-based vapes are widely used due to the perception that they are safer than kretek cigarettes. However, both can cause respiratory issues indicated by changes in inflammatory mediators. Research comparing the effects of kretek cigarettes and ascorbic acid-based vapes on inflammation and lung histopathology is limited. This study aims to compare the effects on IL-6 and TNF-α levels, as well as lung tissue morphology in Wistar rats (*Rattus norvegicus*).

2. Methods

Twenty-one male Wistar rats (*Rattus norvegicus*), aged 8 weeks and weighing 150–200 g, were obtained from Bless Mice Semarang. The rats were housed at the Physiology Biology Laboratory of Universitas Semarang. The rats were acclimatized for seven days in group cages with free access to food and water. They were housed in a controlled environment with a temperature of 20–24 °C and a 12-hour light–dark cycle. The smoking exposure cages were specially designed with openings to allow the entry of cigarette and vape smoke, and were equipped with limited air ventilation.

After a 7-day acclimatization period with standard feeding, the rats were randomly divided into three groups (7 rats per group) using simple random sampling. The control group (K1) received standard care, including daily bedding changes, standard feed, and water with no additional intervention. The second group (K2) was exposed to kretek cigarette smoke (3 cigarettes/day), while the third group (K3) was exposed to ascorbic acid-based vape (0.5 mL/day). The exposure doses for both kretek cigarettes and ascorbic acid–based vape were selected based on dose conversion from heavy human smoking exposure, taking into account body weight and inhalation characteristics in rats. Body weight was measured before acclimatization and after the 12-week treatment period.

At the end of the 12-week exposure period, the rats were anesthetized using chloroform. Blood samples of 3–5 mL per rat were collected via the orbital sinus. The blood serum was obtained through centrifugation and analyzed to measure IL-6 and TNF-α levels using the ELISA method. Lung tissue was collected by opening the rat's thoracic cavity. The tissue was then placed in 10% BNF solution for fixation and processed for histopathological examination. The processed tissue was stained with hematoxylin and eosin (H&E) and observed under a light microscope at 100× and 400× magnification. Observations of alveolar perimeter length, the degree of alveolar wall damage, and the number of inflammatory cell distributions were conducted in a blinded manner by an anatomical pathologist.

IL-6 and TNF-α levels were tested for normality using the Shapiro-Wilk test. If the data were normally distributed, analysis was performed using One-Way ANOVA with the Bonferroni post hoc test; if not, the Kruskal-Wallis test with the Mann-Whitney post hoc test was used. Two pathology experts assessed alveolar perimeter, wall damage, and inflammatory cell counts. Ordinal data were analyzed using the chi-square test, or, if the assumptions were not met, the Kruskal-Wallis test with the Mann-Whitney post hoc test. Numerical were tested for normality and homogeneity of variance. If both assumptions were met, a One-Way ANOVA with the Bonferroni post hoc test was applied; if not homogeneous, the Games-Howell test was used. If the data were not normal or homogeneous, the Kruskal-Wallis test with the Mann-Whitney post hoc test was used.

3. Result

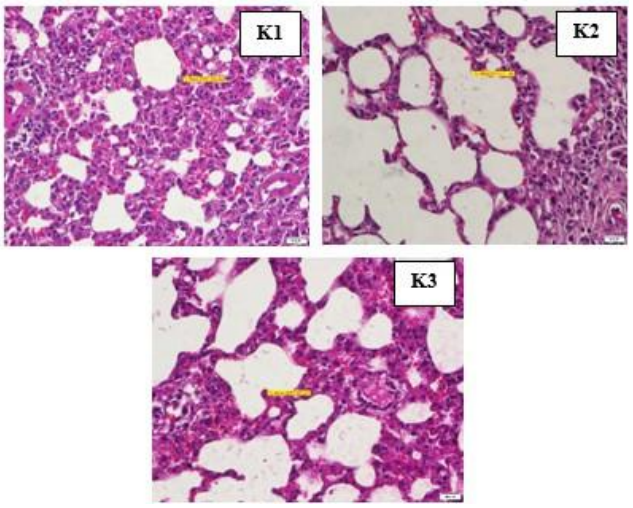


Figure 1. Histopathological features of rat lung tissue stained with Hematoxylin and Eosin (HE), magnification 400×. (K1) negative control, (K2) exposure to kretek cigarette smoke, (K3) exposure to ascorbic acid–based vape smoke.

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Table 1. Shapiro-Wilk normality test on IL-6, TNF-α, and alveolar perimeter length data

Para-meter	Group	Mean ± SD	Median (min-max)	P
IL-6	K1	8,43 ± 0,88	8,73 (7,13-9,64)	0,803*
	K2	11,45 ± 1,17	11,46 (10,26-12,87)	0,149*
	K3	11,83 ± 1,56	11,57 (9,69-13,89)	0,629*
TNF-α	K1	18,76 ± 2,48	19,31 (15,65-22,35)	0,720*
	K2	21,97 ± 4,33	21,29 (17,64-28,98)	0,443*
	K3	18,19 ± 1,62	18,06 (15,65-20,59)	0,970*
The alveolar perimeter length	K1	273,58 ± 45,28	270,09 (225,79-339,67)	0,260*
	K2	221,17 ± 47,64	225,24 (134,29-267,41)	0,225*
	K3	261,61 ± 58,56	276,67 (165,07-324,19)	0,164*

*Shapiro-Wilk test, homogeneous if p > 0.05.

The Shapiro–Wilk normality test on the data for IL-6, TNF-α, and alveolar circumference length in all groups showed p-values greater than 0.05, indicating that the data were normally distributed. The essential requirement for the parametric One-Way ANOVA test is that the data must be normally distributed; therefore, all data were analyzed using One-Way ANOVA.

Table 2. Comparison test using One-Way ANOVA on IL-6, TNF-α, and alveolar perimeter length

Parameter	P
IL-6	0,000*
TNF- α	0,075
The alveolar perimeter length	0,190

*One-Way ANOVA test, significant if p < 0.05

The results of the One-Way ANOVA test showed a significant difference in IL-6 levels among the three treatment groups, whereas no significant differences were found in TNF-α levels and alveolar perimeter length among the three treatment groups. The analysis of IL-6 revealed a significant difference among the three treatment groups; therefore, a Post Hoc Bonferroni test was conducted to determine the differences between the two treatment groups.

Table 3. Post Hoc Bonferroni test on IL-6 levels

Group		Mean Difference	Sig.
K1	K2	-3,04	0,001*
	K3	-3,40	0,000*
K2	K1	3,04	0,001*
	K3	-0,36	1,000
K3	K1	3,40	0,000*
	K2	0,36	1,000

*Post Hoc Bonferroni test, significant if p < 0.05

The results of the Post Hoc Bonferroni test showed a p-value < 0.05 between K1–K2 and K1–K3, indicating a significant difference between the two treatment groups. The p-value > 0.05 for K2–K3 indicates that there was no significant difference between K2 and K3. The control group (K1) had a lower mean value compared to the cigarette group (K2) and the ascorbic acid–based vape group (K3), with a significant difference. The ascorbic acid–based vape group (K3) showed a slightly higher mean IL-6 level compared to the cigarette group (K2), but the difference between these two treatment groups was not significant.

Table 4. Chi-square test on the median degree of alveolar damage

	The degree of alveolar damage					
Group	**No damage**	**<25%**	**26-50%**	**51-75%**	**>75%**	**Total**
K1	4	3	0	0	0	7
K2	0	0	3	3	0	6
K3	0	0	6	1	0	7
Total	4	3	9	4	0	20

*The Chi-square test showed that 12 cells (100%) had an expected count < 5, with the minimum expected count being 0.90.

The results of the Chi-square test showed that more than 20% of the expected counts were less than 5 (EC < 5: 100%). Therefore, the assumptions for the Chi-square test were not met, and the Kruskal–Wallis test was used as an alternative to examine the differences among the three groups. The following table presents the differences among the three groups based on the Kruskal–Wallis test.

Table 5. Non-parametric Kruskal–Wallis test on the median degree of alveolar damage.

Parameter	Group	Mean Rank	p
The median degree of alveolar damage	K1	4,00	0,001*
	K2	15,25	
	K3	12,93	

*Kruskal–Wallis test, significant if p < 0.05

The results of the non-parametric Kruskal–Wallis test on the degree of alveolar damage showed a p-value < 0.05, indicating a significant difference among the three groups. The Kruskal–Wallis analysis was followed by a post hoc Mann–Whitney test to determine the differences between the two groups.

Table 6. Post hoc Mann–Whitney test on the median degree of alveolar damage

Differences between two groups	Sig. (2-*tailed*)
K1-K2	0,002*
K1-K3	0,001*
K2-K3	0,181

*Post hoc Mann–Whitney test, significant if p < 0.05

The results of the post hoc Mann–Whitney test are considered significantly different when the p-value < 0.05. The data showed no significant difference between the kretek cigarette smoke exposure group and the ascorbic acid–based vape smoke exposure group, as the p-value was > 0.05.

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Table 7. Chi-square test on the median degree of pulmonary inflammatory cell distribution

The degree of inflammatory cell distribution				
Group	**0**	**Mild**	**Moderate**	**Total**
K1	5	2	0	7
K2	0	5	1	6
K3	1	6	0	7
Total	6	13	1	20

*The Chi-square test showed that 9 cells (100%) had an expected count < 5, with the minimum expected count being 0.30.

The results of the Chi-square test showed that more than 20% of the expected counts were less than 5 (EC < 5: 100%). Therefore, the assumptions for the Chi-square test were not met, and the Kruskal–Wallis test was used as an alternative to examine the differences among the three groups.

Table 8. Non-parametric Kruskal–Wallis test on the median degree of pulmonary inflammatory cell distribution

Parameter	Group	Mean Rank	p
The median degree of pulmonary inflammatory cell distribution	K1	6,21	0,012 *
	K2	14,17	
	K3	11,64	

*Kruskal–Wallis test, significant if p < 0.05

The results of the non-parametric Kruskal–Wallis test on the degree of pulmonary inflammatory cell distribution showed a p-value < 0.05, indicating a significant difference among the control group (K1), the kretek cigarette treatment group (K2), and the ascorbic acid–based vape treatment group (K3). The Kruskal–Wallis analysis was followed by a post hoc Mann–Whitney test to determine the differences between the two groups.

Table 9. Post hoc Mann–Whitney test on the median degree of pulmonary inflammatory cell distribution

Differences between two groups	Sig. (2-*tailed*)
K1-K2	0,010*
K1-K3	0,037*
K2-K3	0,173

*Post hoc Mann–Whitney test, significant if p < 0.05

The groups of rats exposed to kretek cigarette smoke and ascorbic acid–based vape showed a higher degree of inflammatory cell distribution compared to the control group, with a significant difference (p-value < 0.05). The group of rats exposed to kretek cigarette smoke also exhibited a more severe inflammatory response compared to the ascorbic acid–based vape group; however, the difference between the two groups was not statistically significant (p-value > 0.05).

4. Discussion

Cigarette smoke contains toxic substances that can enter the bloodstream through the alveoli and capillaries, where immune system receptors detect them.[18] This triggers inflammation by activating the expression of inflammatory genes such as IL-6 and TNF-α.[19,20] IL-6 is a potent pro-inflammatory cytokine produced by various cells, including T cells, endothelial cells, activated macrophages, and smooth muscle cells, to support the immune response during infection.[21]

In this study, exposure to both conventional and electronic cigarettes resulted in increased levels of IL-6; however, the increase in IL-6 was not statistically significant in either exposure group. The results showed that IL-6 levels were higher in the ascorbic acid vape group compared to the clove cigarette group. Most non-nicotine vape components consist of proprietary chemical mixtures that may have broad effects on cytotoxicity and cytokine production.[22] Compared to non-users, the use of both vape and clove cigarettes has also been associated with systemic inflammation, marked by elevated inflammatory biomarkers such as IL-6.[23,24] IL-6 is an inflammatory mediator that can be produced by epithelial and smooth muscle cells in response to smoking.[18] In e-cigarette or vape users, IL-6 levels are also elevated compared to non-users.[24] Several studies have shown variations in the effects of electronic cigarettes on IL-6 production, which may be due to differences in the types of cells used, methods of e-cigarette exposure, and brand (flavored vs. unflavored).[25]

Tumor necrosis factor alpha (TNF-α) is one of the key pro-inflammatory cytokines typically secreted by macrophages, lymphocytes, and adipocytes as a response to cell damage caused by infection or malignant transformation.[26,27] This study showed that TNF-α levels increased in the cigarette group compared to the control group, while in the ascorbic acid vape group, the levels were slightly lower than in the control group. Although there was an increase in TNF-α levels in the cigarette group, no statistically significant differences were found among the three groups. TNF-α has been identified as a key cytokine in the response to cigarette exposure, regulating inflammation and promoting neutrophil recruitment through the activation of endothelial cells.[28]

To fully understand the impact of inflammation, it is not sufficient to rely on a single marker alone.[29] Inhalation of foreign substances can also cause lung injury and inflammation aside from cigarette smoking.[30] The severity of lung injury and inflammation is also related to the amount of substance inhaled—the greater the exposure or quantity of foreign material inhaled, the more severe the damage and inflammation.[31]

Lung histopathology was assessed based on alveolar perimeter, the degree of alveolar wall damage, and the level of inflammatory cell distribution. The alveolar perimeter was measured numerically, while the degree of alveolar wall damage and the level of inflammatory cell distribution were measured ordinally.

The alveolar perimeter was highest in the control group, but there were no significant differences among the three groups. An increase in alveolar diameter reflects the loss of alveolar septa and indicates emphysematous lesions, which are a form of Chronic Obstructive Pulmonary Disease (COPD). This enlargement is proportional to the alveolar perimeter and is accompanied by alveolar wall damage.[32] Another study also found alveolar lumen enlargement and wall thickening, accompanied by mild lymphocyte

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infiltration, in the control group.[33] This alveolar enlargement may be caused by various factors, including exposure to dust particles, which can lead to respiratory system disorders.[34]

Rats exposed to kretek cigarette smoke and ascorbic acid-based vape showed more severe alveolar wall damage compared to the control group, with statistically significant differences. However, there was no statistically significant difference between the cigarette and vape exposure groups.

Clove cigarette smoke can increase adenosine and activate the XOR enzyme in the lungs, triggering oxidative stress, endothelial damage, and apoptosis through the p53 pathway.[32] Nicotine has negative effects on the lungs.[35,36] However, several studies suggest that the effects of electronic cigarettes are more influenced by other substances in the liquid or aerosol.[37] Exposure to nicotine-free cigarette smoke also causes structural lung damage, such as alveolar enlargement, inflammatory cell infiltration, and vascular remodeling, resembling emphysema commonly seen in COPD.[29]

Rats exposed to kretek cigarette smoke and ascorbic acid-based vape showed a higher distribution of inflammatory cells compared to the control group, with statistically significant differences. However, there was no statistically significant difference between the cigarette and vape exposure groups.

The histopathological features of the lungs in smokers may include emphysema, arterial wall thickening, increased bronchial tissue, as well as submucosal and adventitial fibrosis.[38] The accumulation of inflammatory cells along the alveolar walls can lead to alveolar wall thickening, disrupting oxygen exchange and potentially affecting blood circulation.[39,40] Although both the control group and the ascorbic acid-based vape exposure group did not contain nicotine, a small number of inflammatory cells were still observed in the lungs of rats in both groups. This suggests that, while nicotine is not the sole cause of lung damage, the levels of propylene glycol (PG) and vegetable glycerin (VG) in e-cigarettes, as well as tar in conventional cigarettes, also contribute to lung injury.[41]

5. Conclusion

Exposure to kretek cigarette smoke containing nicotine and ascorbic acid-based vape without nicotine both significantly increased inflammatory responses and caused lung function damage. Both exposures increased pro-inflammatory cytokines, such as IL-6 and TNF-α, which play crucial roles in the immune response to tissue injury. Although the vape did not contain nicotine, other components in its liquid, such as propylene glycol, glycerin, and flavoring agents, were still capable of triggering inflammation. Lung damage was also indicated by increased alveolar perimeter, alveolar wall damage, and a more widespread distribution of inflammatory cells. These findings reflect alveolar enlargement, tissue degradation, and immune cell infiltration in response to inhaled irritants. Thus, although only kretek cigarettes contained nicotine, the ascorbic acid-based vape still showed similarly harmful effects on lung tissue. This indicates that being nicotine-free does not equate to being risk-free, as other chemical contents can also cause inflammation and lung damage.

Ethical Approval

Ethical clearance was secured from the Health Research Ethics Committee (KEPK) of the Faculty of Medicine, Universitas Diponegoro (Protocol Number 079/EC-H/KEPK/FK-UNDIP/VIII/2024) prior to the commencement of the study.

Conflicts of Interest

There are no conflicts of interest to disclose.

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Author Contributions

Writing-original draft preparation and editing, Dora Maftikhati; Writing-review, Dr. dr. Awal Prasetyo, M.Kes, Sp.THT-BKL, M.M., Dr. dr. Udadi Sadhana, M.Kes, Sp.PA., Subsp. M.S.(K) and dr. Hermawan Istiadi, M.Si.Med., Sp.PA.

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References

1. Almaidah F, Khairunnisa S, Sari IP, Chrisna CD, Firdaus A, Kamiliya ZH, et al. SURVEI FAKTOR PENYEBAB PEROKOK REMAJA MEMPERTAHANKAN PERILAKU MEROKOK. Jurnal Farmasi Komunitas. 2020;8(1).
2. Runtukahu JL, Mamahit DJ, Sugiarso BA. 3D Animation Interactive Learning About The Bad Impacts Of E-Cigarettes (Vape). Jurnal Teknik Informatika. 2021;16(1).
3. WHO global report on trends in prevalence of tobacco use 2000-2025 third edition WHO global report on trends in prevalence of tobacco use 2000-2025, third edition [Internet]. 2019. Available from: http://apps.who.int/bookorders.
4. World Health Organization. Gats|Global Adult Tobacco Survey Fact Sheet Indonesia 2021 Gats Objectives. Fact Sheet Indonesia. 2021;
5. World Health Organization. WHO report on the global tobacco epidemic, 2023: protect people from tobacco smoke. The MPOWER package. 2023.
6. Kemenperindag. Keputusan Menteri Perindustrian dan Perdagangan Republik Indonesia. CWL Publishing Enterprises, Inc, Madison. 2004;
7. Anam F, Sakhatmo T, Hartanto. Remaja indonesia, jauhi rokok! . Hariyadi, editor. Solo: Metagraf; 2019.
8. Masso-Silva JA, Byun MK, Crotty Alexander LE. Acute and chronic effects of vaping electronic devices

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on lung physiology and inflammation. Vol. 22, Current Opinion in Physiology. 2021.
9. Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. Progression to traditional cigarette smoking after electronic cigarette use among us adolescents and young adults. JAMA Pediatr. 2015;169(11).
10. Walton KM, Abrams DB, Bailey WC, Clark D, Connolly GN, Djordjevic M V., et al. NIH electronic cigarette workshop: Developing a research agenda. Vol. 17, Nicotine and Tobacco Research. 2015.
11. Muthumalage T, Lucas JH, Wang Q, Lamb T, McGraw MD, Rahman I. Pulmonary toxicity and inflammatory response of e-cigarette vape cartridges containing medium-chain triglycerides oil and vitamin E acetate: Implications in the pathogenesis of EVALI. Toxics. 2020;8(8).
12. Yoon SH, Song MK, Kim DI, Lee JK, Jung JW, Lee JW, et al. Comparative study of lung toxicity of E-cigarette ingredients to investigate E-cigarette or vaping product associated lung injury. J Hazard Mater. 2023;445.
13. Goenka S, Simon SR. Effects of e-cigarette refill liquid flavorings with and without nicotine on human retinal pigment epithelial cells: A preliminary study. Int J Environ Res Public Health. 2021;18(21).
14. Prasetyo A, Irawati N. Inhalation of Ascorbic Acid Modulates Sinonasal Immune System. In: Ascorbic Acid - Biochemistry and Functions. 2024.
15. Rezk-Hanna M, Seals DR, Rossman MJ, Gupta R, Nettle CO, Means A, et al. Ascorbic acid prevents vascular endothelial dysfunction induced by electronic hookah (Waterpipe) vaping. J Am Heart Assoc. 2021;10(5).
16. Gong K, Guo G, Beckley N, Zhang Y, Yang X, Sharma M, et al. Tumor necrosis factor in lung cancer: Complex roles in biology and resistance to treatment. Vol. 23, Neoplasia (United States). 2021.
17. Siagian D, Soeroso NN, Sinaga BYM, Eyanoer PC. Perbedaan kadar serum interleukin-6 pada pasien kanker paru dan orang sehat di Medan. Jurnal Respirologi Indonesia. 2021;41(1).
18. Nikniaz L, Ghojazadeh M, Nateghian H, Nikniaz Z, Farhangi MA, Pourmanaf H. The interaction effect of aerobic exercise and vitamin D supplementation on inflammatory factors, anti-inflammatory proteins, and lung function in male smokers: a randomized controlled trial. BMC Sports Sci Med Rehabil. 2021;13(1).
19. Madani A, Alack K, Richter MJ, Krüger K. Immune-regulating effects of exercise on cigarette smoke-induced inflammation. Vol. 11, Journal of Inflammation Research. 2018.
20. Scoditti E, Massaro M, Garbarino S, Toraldo DM. Role of diet in chronic obstructive pulmonary disease prevention and treatment. Vol. 11, Nutrients. 2019.
21. Sarihati IGAD, Cahyani KIS, Arjani IAS, Kurniawan SB, Bekti HS. GAMBARAN KADAR SERUM INTERLEUKIN-6 PADA PEROKOK AKTIF. Meditory : The Journal of Medical Laboratory. 2021;8(2).
22. Clapp PW, Jaspers I. Electronic Cigarettes: Their Constituents and Potential Links to Asthma. Vol. 17, Current Allergy and Asthma Reports. 2017.
23. Singh KP, Lawyer G, Muthumalage T, Maremanda KP, Khan NA, McDonough SR, et al. Systemic biomarkers in electronic cigarette users: Implications for noninvasive assessment of vaping-associated pulmonary injuries. ERJ Open Res. 2019;5(4).
24. Boakye E, Uddin SMI, Osuji N, Meinert J, Obisesan OH, Mirbolouk M, et al. Examining the association of habitual e-cigarette use with inflammation and endothelial dysfunction in young adults: The VAPORS-Endothelial function study. Tob Induc Dis. 2023;21.
25. Gellatly S, Pavelka N, Crue T, Schweitzer KS, Day BJ, Min E, et al. Nicotine-free e-cigarette vapor exposure stimulates Il6 and mucin production in human primary small airway epithelial cells. J Inflamm Res. 2020;13.
26. Beutler B, Cerami A. The biology of cachectin/TNF - A primary mediator of the host response. Vol. 7, Annual Review of Immunology. 1989.
27. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose Expression of Tumor Necrosis Factor-α: Direct Role in Obesity-Linked Insulin Resistance. Science (1979). 1993;259(5091).
28. Churg A, Wang RD, Tai H, Wang X, Xie C, Dai J, et al. Macrophage metalloelastase mediates acute cigarette smoke-induced inflammation via tumor necrosis factor-α release. Am J Respir Crit Care Med. 2003;167(8).
29. Dai Z, Xie B, Jiang C, Peng Y, Lin J, Chen Q, et al. Aerosolized nicotine-free e-liquid base constituents exacerbates mitochondrial dysfunction and endothelial glycocalyx shedding via the AKT/GSK3β-mPTP pathway in lung injury models. Respir Res. 2025 Dec 1;26(1).
30. Dongmei W, Yungjing MU, Qian Z, Pei SHI, Yingying HUOY and W. Construction of animal models of inhalation lung injury: a review. 中国比较医学杂志（英文版） [Internet]. 2019;29(10):126–30. Available from: zgbjyxzzen/article/abstract/201910022
31. Deb U, Lomash V, Raghuvanshi S, Pant SC, Vijayaraghavan R. Effects of 28 days silicon dioxide aerosol exposure on respiratory parameters, blood biochemical variables and lung histopathology in rats. Environ Toxicol Pharmacol. 2012;34(3).
32. Lu Q, Gottlieb E, Rounds S. Effects of cigarette smoke on pulmonary endothelial cells. Vol. 314, American Journal of Physiology - Lung Cellular and Molecular Physiology. 2018.
33. Triantara YA, Almira I, Kusumo SA, Fajar M, Darmawan D, Winarni D. The Comparison Effect of Electrical Cigarrete and Conventional Cigarrete

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Smoke toward White Rat's (Rattus norvegicus) Lung Histopathology. Jurnal Respirologi Indonesia. 2019;39(2).
34. Epler GR. Clinical overview of occupational lung disease. Vol. 30, Radiologic Clinics of North America. 1992.
35. Ahmad S, Zafar I, Mariappan N, Husain M, Wei CC, Vetal N, et al. Acute pulmonary effects of aerosolized nicotine. Am J Physiol Lung Cell Mol Physiol. 2019;316(1).
36. Behar RZ, Wang Y, Talbot P. Comparing the cytotoxicity of electronic cigarette fluids, aerosols and solvents. Tob Control. 2018;27(3).
37. Marques P, Piqueras L, Sanz MJ. An updated overview of e-cigarette impact on human health. Vol. 22, Respiratory Research. 2021.
38. Franks TJ, Galvin JR. Smoking-related "'interstitial'" lung disease. Arch Pathol Lab Med. 2015;139(8).
39. Nurliani A, Santoso HB. EFEK ANTIOKSIDAN EKSTRAK BULBUS BAWANG DAYAK (Eleutherine palmifolia) PADA GAMBARAN HISTOPATOLOGIS PARU-PARU TIKUS YANG DIPAPAR. Bioscientiae. 2012;9.
40. Yunus F. Faal paru dan olahraga. Jurnal Respirologi Indonesia. 1997;17(2):100–5.
41. Joel. Smoking's Impact on the Lungs [Internet]. [cited 2025 Jul 4]. Available from: https://whyquit.com/joel/Joel_02_17_smoke_in_lung.html

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