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THE EFFECT OF TOBACCO CIGARETTE AND ELECTRONIC CIGARETTE EXPOSURE ON BODY MICROBIOTA: A SYSTEMATIC REVIEW IN ANIMAL MODELS

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ABSTRACT
Exposure to tobacco and e-cigarette (vape) smoke is a significant factor affecting health, especially regarding the composition and balance of the body's microbiota. Objective to evaluate the impact of exposure to both types of cigarette smoke on body microbiota, particularly oral, gut and respiratory microbiota. A literature search was conducted following PRISMA guidelines through the Google Scholar, PubMed, and Research Gate databases for the period 2015-2025. A total of 4,257 articles were identified, and after screening, obtained 7 in vivo experimental studies using the PICO method, focusing on the effects of chronic cigarette smoke exposure on microbiota composition, inflammation, and dysbiosis were selected, all conducted on animal models. The analysis showed that exposure to tobacco and e-cigarette smoke caused microbiota dysbiosis, characterized by decreased diversity of commensal microbes and increased prevalence of pathogenic bacteria, such as Porphyromonas gingivalis in the oral microbiota, Proteobacteria in the gut microbiota, and Streptococcus, Fusobacterium, Prevotella, and Haemophilus in the respiratory tract microbiota. The main mechanisms of microbiota disruption involve oxidative stress and chronic inflammation induced by chemical components in cigarette smoke. Exposure to cigarette smoke, both tobacco and e-cigarette, has a significant impact on the body's microbiota, potentially increasing the risk of inflammatory diseases, metabolic disorders, and respiratory tract infections.

Keywords: animal models; dysbiosis; electronic cigarettes; inflammation; microbiota; systemic health; tobacco cigarettes

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INTRODUCTION

Cigarette use, both conventional tobacco cigarettes and e-cigarettes (vapes), remains a widespread habit globally, despite overwhelming evidence of negative health impacts. While e-cigarettes are often considered a safer alternative to conventional cigarettes, their long-term health impacts, particularly on the body's microbiota, are beginning to receive greater attention. The use of tobacco cigarettes and e-cigarettes continues to increase, with a higher prevalence of smoking among adolescents and young adults (Mubarak et al., 2024). The chemical composition of cigarettes, which includes nicotine, aldehydes, heavy metals, and other reactive compounds, can disrupt the body's biological homeostasis, especially in the microbiota. Although tobacco cigarettes and e-cigarettes have different chemical components, both can affect the human microbiota in detrimental ways. Smoking is known to alter the composition of the body's microbiota and increase the prevalence of pathogens, impacting oral, digestive and lung health (Wang et al., 2021). The human microbiota plays an important role in immunity, digestion, and protection against pathogens. However, smoking can cause microbiota imbalance, or dysbiosis, which is associated with various inflammatory and metabolic diseases (Carding et al., 2015). Research shows that smoking can increase the risk of periodontitis, lung cancer, and metabolic diseases (Zhang et al., 2018). In the oral microbiota, both tobacco cigarettes and e-cigarettes can increase the number of pathogenic bacteria such as Fusobacterium and Porphyromonas and reduce the number of commensal bacteria that function to protect the body (Quinones Tavarez et al., 2020).

In addition, smoking also disrupts the balance of the gut microbiota, which affects the body's metabolism and immunological functions (Martinez et al., 2021). Although e-cigarettes contain fewer chemicals, their impact on respiratory microbiota remains significant (Hilty et al., 2020). Smoking affects the microbiota of the gastrointestinal tract, increasing the prevalence of pathogenic bacteria that contribute to metabolic damage and inflammation (Zhang et al., 2020). E-cigarette use is also known to cause dysbiosis in the oral microbiota, which increases inflammation in the gums (Park et al., 2023). Microbiota differences between smokers and non-smokers have been observed, with a greater influence on gut microbiota (Fan et al., 2023). Cigarette smoke exposure has been shown to affect the microbiota of the gastrointestinal tract in humans, impacting the immune system and metabolic health (Laiman et al., 2024; Chopyk et al., 2021). Nonetheless, smoking cessation can lead to restoration of the body's microbiota, suggesting potential improvements following a reduction in exposure to cigarette smoke (Sublette et al., 2020). This systematic review aims to systematically review the effects of tobacco cigarettes and e-cigarettes on the composition and balance of the human microbiota, with a primary focus on the oral and gut microbiota.

METHOD

Literature Search and Screening

This systematic review was conducted based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Electronic searches were conducted on three major databases, namely Google Scholar, PubMed, and Research Gate. Keywords were organized using the PICO framework (Population: tobacco smokers, e-cigarette smokers, non-smokers; Exposure: cigarette smoke and vape aerosol; Outcome: microbiota composition and function) and adapted into MeSH terms. Terms used included: “smoking OR tobacco smoke OR cigarette smoking,” “e-cigarette OR vaping,” “microbiota OR microbiome,” and ‘‘oral OR gut OR lung OR skin.” Boolean AND and OR operators were used to optimize the search strategy and ensure comprehensive study coverage.

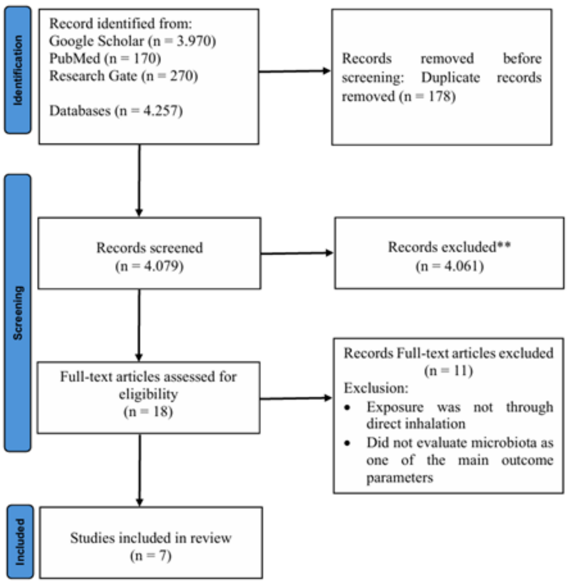
The literature search focused on publications during 2015-2025, both in English and Indonesian. From the initial search results, 4,257 articles were obtained: 3,970 from Google Scholar, 170 from PubMed, and 270 from Research Gate. The screening process began with the removal of 178 duplicate articles, leaving a total of 4,079 articles for further assessment. This process was carried out in three main stages. First, articles were excluded based on their topic, purpose, or methods, particularly if they were not relevant to the focus of microbiota and smoking exposure studies. Second, studies were excluded if they did not follow an in vivo experimental design with animals, or if the microbiota analysis did not utilize culture or sequencing techniques. Lastly, exclusion was based on the population and exposure method, removing studies where the subjects were not active smokers, such as those involving only passive smokers, or if the exposure method was not through direct inhalation, but rather oral or systemic routes.

Selection

The selection process was carried out by applying pre-defined inclusion and exclusion criteria to ensure that only relevant studies were included. Articles that met these criteria were screened based on two main factors: inclusion and exclusion criteria. The inclusion criteria required studies to use an in vivo experimental design with animal models, primarily rats and mice, exposed to tobacco smoke for a clearly specified duration. These studies also had to assess the microbiota in the digestive system, airway, or other organs, using direct inhalation methods via a smoke exposure system. Additionally, the studies needed to report on changes in microbiota composition, inflammation, or dysbiosis resulting from cigarette exposure. The exclusion criteria involved removing studies that did not specify the exposure duration or provided vague details, studies that did not evaluate microbiota as a primary parameter, and studies that used exposure methods other than direct inhalation, such as systemic or oral exposure (including passive smoking). Non-experimental studies, such as literature reviews, case reports, and editorials, were excluded. Additionally, studies that only focused on the effects of cigarette smoke on organs like the lungs or liver, without linking to microbiota alterations, were also excluded.

Data Extraction

After filtering, the data was extracted based on several key details. The animal models used in the studies were Wistar rats and C57BL/6 mice, including both males, females, and ovariectomized specimens. Wistar rats were 5 weeks old at the time of the experiment, with a body weight ranging from 145-155g, while the age of C57BL/6 mice was 12 weeks, although their body weight was not specified and varied depending on the specimen. Regarding cigarette or vape exposure methods, the animals were exposed to active cigarette smoke using standard cigarettes. Mice were exposed for 20 minutes twice a day, while C57BL/6 mice were exposed to cigarette smoke for durations ranging from 4 to 12 weeks. The exposure was conducted using an intraoral active inhalation device for mice and a smoke chamber or exposure system for C57BL/6 mice. The microbiota analysis involved collecting fecal samples, cecal samples, and oral mucosal swabs, with microbiota identification performed using 16S rRNA gene sequencing on an Illumina MiSeq platform. The changes in microbiota were characterized by altered composition in various parts of the gastrointestinal tract and other organs, a decrease in microbiota diversity, and an increase in specific pathogenic bacteria like Desulfovibrio. Additionally, several inflammatory markers, such as IL-6, were found to be elevated in various regions of the body. Tissue changes included damage to lung tissue, showing increased elasticity and emphysema, along with changes in intestinal permeability.



RESULT

Table 1.
Summary of Studies on the Effects of Tobacco Cigarette and Electronic Cigarette Exposure on Body Microbiota in Animal Models

Author	Dose	Route	Findings
Allais et al. (2015)	Chronic smoke exposure for 24 weeks	Inhalation (via exposure system)	Smoke exposure alters gut microbiome and immune factors, and increases inflammation
Tam et al. (2020)	Chronic smoke exposure for 6 months	Inhalation (via smoke exposure system)	Chronic smoke exposure changes gut microbiota and body weight in both male and female mice
Meng et al. (2022)	Chronic smoke exposure for 12 weeks	Inhalation (via smoke exposure system)	Cigarette smoke exposure causes gut microbiota imbalance, liver injury, and lipid metabolism disruptions
Yang et al. (2021)	Chronic smoke exposure for 4 weeks	Inhalation (via exposure system)	Exposure to smoke disrupts cholesterol and bile acid metabolism and induces gut microbiota dysbiosis
Hilty et al. (2020)	Chronic smoke exposure for 6 months	Inhalation (via exposure system)	Smoke exposure causes microbiota shifts in the oropharynx and exacerbates lung damage
Zhang et al. (2018)	Chronic smoke exposure for 2 h/day for 90 days	Inhalation (via smoke exposure system)	Smoking alters microbial diversity in the lower respiratory tract and causes inflammation
Laiman et al. (2024)	Chronic smoke exposure for 20 weeks	Inhalation (via exposure system)	CS exposure significantly affects lung and intestinal microbiomes, correlating with lung function decline

DISCUSSION

Impact of Smoking on Oral Microbiota

Exposure to cigarette smoke and vape aerosols significantly alters the composition of the oral microbiota. Studies show an increase in pathogenic bacteria, such as *Porphyromonas gingivalis*, which is associated with periodontal disease, as well as a decrease in commensal bacteria, such as *Streptococcus* spp. which play a role in maintaining the balance of the oral microbiota (Chattopadhyay et al., 2024). These changes lead to microbiota imbalance or dysbiosis, which in turn contributes to the development of oral diseases, including caries and oral cancer (Leroue et al., 2023). In the study by Wang et al. (2022), both tobacco and vape cigarettes showed an increase in Prevotellaceae and a decrease in Neisseria. This indicates that both types of cigarettes cause microbiota imbalance, albeit by different mechanisms. Other studies have also shown that exposure to cigarette smoke can increase microbial diversity in the oral cavity, but with a predominance of pathogenic bacteria that have the potential to cause periodontal disease.

Impact of Smoking on Gut Microbiota

Not only does cigarette smoke affect the oral microbiota, it also has a significant impact on the gut microbiota. The study by Allais et al. (2015) showed that chronic exposure to cigarette smoke causes an imbalance in the gut microbiota, increasing the number of Proteobacteria and decreasing Firmicutes. These conditions are associated with increased gut permeability, impaired immune response, and risk of inflammatory bowel disease (IBD) (Yan et al., 2021). Tam et al. (2020) found that chronic exposure to cigarette smoke for 6 months caused changes in gut microbiota composition and body weight in male and female mice. This suggests that cigarette smoke-induced microbiota changes may have broader systemic effects. In addition, the study by Meng et al. (2022) showed that exposure to cigarette smoke disrupts cholesterol and bile acid metabolism in the liver, which indirectly affects the gut microbiota, causing dysbiosis that can trigger metabolic disorders such as obesity and diabetes. The study by Yang et al., (2021) also found that exposure to cigarette smoke increased primary bile acid production, which affected the composition of the gut microbiota.

Impact of Smoking on Respiratory Microbiota

Cigarette smoke exposure also affects the microbiota of the respiratory tract. Zhang et al. (2018) found that exposure to cigarette smoke led to a decrease in microbial diversity in the lower airway, with a predominance of pathogenic species. Hilty et al. (2020) confirmed that chronic exposure to cigarette smoke causes dysbiosis in the oropharyngeal microbiota, which increases the risk of respiratory tract infections and inflammation. Laiman et al. (2024) reported that 20 weeks of cigarette smoke exposure caused dysbiosis of the lung and gut microbiota, which correlated with decreased lung function and increased inflammation. These microbiota changes are not only limited to the respiratory tract but also have a systemic impact, affecting lung and gut health.

Mechanisms of Microbiota Disruption by Smoking

The main mechanisms underlying cigarette smoke-induced microbiota disruption involve oxidative stress and chronic inflammation. Chemicals in cigarette smoke cause oxidative stress that damages epithelial cells and microorganisms, triggering an inflammatory response that exacerbates microbiota imbalance. This also increases the risk of degenerative diseases, such as heart disease, diabetes and cancer (Agarwal et al., 2021). In addition, smoking is known to affect the composition of the gut and lung microbiota. Sublette et al. (2020) found that smoking is associated with changes in gut microbiota composition that are linked to increased risk of cardiovascular disease and chronic inflammation, with significant differences between active smokers and former smokers who quit smoking. In another study, Panzer et al. (2018) showed that smoking affects the microbial community in the lungs, particularly in relation to the risk of developing Acute Respiratory Distress Syndrome (ARDS) in critical trauma patients. The microbiota composition of smokers' lungs showed an increased presence of pathogenic microbes such as *Streptococcus, Fusobacterium, Prevotella,* and *Haemophilus* that could potentially worsen lung health conditions. In addition, research by Jetté et al. (2016) revealed that smoking causes a decrease in microbial diversity in laryngeal tissues and increases the proportion of certain pathogenic microbial species, such as *Streptococcus*, which can cause chronic inflammation of the respiratory tract. On the other hand, Li et al. (2021) found that gut microbiota disruption contributes to the development of chronic obstructive pulmonary disease (COPD), where changes in gut microbiota composition were related to the severity of COPD in patients with COPD.

Comparison Between Tobacco and Electric Cigarettes

Both tobacco cigarettes and vapes have negative impacts on the body's microbiota. Although vaping is considered a safer alternative, long-term research is still needed to understand the true impact on the body's microbiota (Wang et al., 2022). More in-depth research from Sublette et al. (2020) showed that both tobacco cigarettes and vapes can cause changes in the gut microbiota that impact systemic health. This primarily occurs through similar mechanisms of oxidative stress and chronic inflammation.

Limitations in Research

Most studies on the impact of smoking on the microbiota have been limited to animal models or conducted in vitro. Although animal models provide important insights into underlying mechanisms, the results are not always directly generalizable to humans (Laiman et al., 2024). In addition, many studies use different methods of exposure to cigarette smoke, either in duration, intensity or type of smoke (tobacco or vape), which may influence the results (Meng et al., 2022). Longitudinal studies in humans using standardized methods and strict controls are needed to understand the long-term impact and possible reversibility of microbiota changes after smoking cessation (Hilty et al., 2020).

Future Research Directions

Further studies focusing on longitudinal studies among humans are essential to understand in more detail the long-term impact of smoking on the body's microbiota, including the microbiota of the mouth, gut and respiratory tract (Wang et al., 2022). Research needs to explore the mechanisms underlying microbiota disruption due to cigarette smoke exposure, including the specific effects of various chemical compounds in cigarette smoke and their role in triggering inflammation or dysbiosis (Agarwal et al., 2021). In addition, future research should explore the potential for microbiota recovery after smoking cessation and evaluate the effectiveness of interventions such as probiotics or dietary changes to restore microbiota balance (Zhang et al., 2018).

CONCLUSION

Exposure to tobacco and e-cigarette (vape) smoke has been shown to have significant impacts on the composition and balance of the body's microbiota, including the oral, gut and respiratory tract microbiota. These impacts include increased prevalence of pathogenic bacteria, decreased diversity of commensal microbes, as well as disruption of microbiota balance (dysbiosis) triggered by oxidative stress and chronic inflammation. The main mechanism underlying this microbiota disruption is related to exposure to harmful chemicals in cigarette smoke, such as nicotine, aldehydes, heavy metals and other reactive compounds, which damage epithelial cells and commensal microorganisms, triggering an exaggerated immune response. Although e-cigarettes contain fewer chemicals than tobacco cigarettes, the potential dysbiosis they cause is similar, especially in the oral and respiratory microbiota. Some studies using animal models have shown similar results, but limitations in the available data, including variations in exposure methods and the use of non-human models, limit the generalizability of results to human populations.

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