Ranah Research
Journal of Multidisciplinary Research and Development
E-ISSN: 2655-0865
DINASTI RESEARCH
082170743613 ranahresearch@gmail.com https://jurnal.ranahresearch.com

DOI: https://doi.org/10.38035/rrj.v8i1

Flavoring Compounds in e-Liquids Identified by GC-MS: Chemical Insights and Respiratory Toxicity

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Abstract: *The use of e-cigarettes has surged as an alternative to conventional smoking, with e-liquids containing various flavoring chemicals that enhance user experience. However, these flavoring compounds may pose significant health risks when inhaled. This study systematically reviews the chemical composition of e-liquid flavorings identified using Gas Chromatography-Mass Spectrometry (GC-MS). A comprehensive literature review was conducted, sourcing articles from PubMed, Google Scholar, and ScienceDirect published within the last decade. The review focuses on identifying chemical compounds in various e-liquid flavors such as vanilla, bubble gum, coffee, tobacco, strawberry, lemon, and cannabis. Key compounds identified include vanillin, ethyl maltol, cinnamaldehyde, benzaldehyde, and limonene, which contribute to flavor profiles but may also have adverse respiratory effects. Thermal degradation of these compounds can result in the formation of harmful carbonyl compounds like formaldehyde and acetaldehyde, both classified as carcinogens. Furthermore, nicotine, a major component in e-liquids, increases the risk of addiction and psychological disorders. This review underscores the need for strict regulations on e-liquid flavoring agents and further research on the long-term effects of inhaling these substances. It also highlights the importance of public awareness regarding the potential respiratory toxicity associated with e-liquids and vaping.*

Keyword: *Flavoring chemicals, Gas Chromatography-Mass Spectrometry, Toxic Compound, Vaping*

INTRODUCTION

Smoking poses a significant public health threat, claiming more than 8 million lives annually worldwide, with over 7 million deaths attributed to active smokers and approximately 1.3 million deaths resulting from secondhand smoke exposure, according to the World Health Organization (WHO, 2023). Among the various forms of tobacco consumption, cigarettes—rolled tobacco products wrapped in paper, leaves, or corn husks, typically measuring 8–10 cm in length—are the most commonly used, consumed by igniting one end while inhaling from the other (Hutapea & Fasya, 2021). Cigarettes contain nicotine, a chemical compound derived from tobacco plants (Hayati dkk., 2020). Nicotine exposure during developmental stages induces histone methylation alterations in the brain and changes in dendritic complexity, increasing the risk of mental health disorders such as depression, addiction, and ADHD (Sansone dkk., 2023).

In Indonesia, smoking is prevalent among both adults and adolescents. In this modern era of Indonesia, younger generations prefer to e-cigarettes instead of burning tobacco. E-liquid, the liquid used in e-cigarettes, comes in various flavors, enhancing user satisfaction by providing a more comfortable, enjoyable, and seemingly safer experience compared to conventional cigarettes. However, e-liquid is reported contains several chemical compounds, including tobacco-specific nitrosamines (TSNAs), diethylene glycol (DEG), carcinogenic carbonyls, potential substances such as rimoraban, formaldehyde, coumarin, tadalafil, and silica fibers (Wirajaya dkk., 2024).

The chemical composition of e-liquid can be analyzed using Gas Chromatography-Mass Spectrometry (GC-MS) and Gas Chromatography-Ion Mobility Mass Spectrometry (GCxIMS), capable of detecting compounds at concentrations as low as 1 µg/L (Augustini dkk., 2021). Additionally, Gas Chromatography with Flame Ionization Detector (GC-FID), Liquid Chromatography-Mass Spectrometry (LC-MS), and High-Performance Liquid Chromatography (HPLC) are also utilized for e-liquid compound detection (Gholap dkk., 2018). While GC-MS has long been employed to characterize harmful compounds in conventional cigarettes, such as tar, nicotine, and polycyclic aromatic hydrocarbons, there remains a gap in comprehensive comparison studies that assess the flavoring agents and potentially harmful volatiles in e-cigarettes using similar analytical rigor. This gap highlights the need for focused research on e-liquid constituents using GC-MS, particularly to understand their unique chemical profiles and potential health implications in comparison to traditional tobacco products.

In the analysis of flavoring compounds in e-liquids, both Gas Chromatography-Flame Ionization Detection (GC-FID) and Gas Chromatography-Mass Spectrometry (GC-MS) are commonly used. GC-FID is widely appreciated for its sensitivity and linear response to organic compounds, making it suitable for quantifying known flavoring agents. However, GC-MS offers superior qualitative capabilities, enabling the identification of unknown compounds through their mass spectra. This makes GC-MS particularly advantageous for analyzing complex mixtures like e-liquids, which may contain diverse and proprietary flavor formulations. Therefore, GC-MS is often preferred when comprehensive profiling and compound identification are essential, particularly in research aiming to assess potential health risks associated with inhaled flavoring chemicals.

This study systematically reviews articles focusing on the analysis of flavoring compound variations in e-liquids using GC-MS. A systematic literature review was conducted by collecting articles from multiple databases, including Google Scholar, PubMed, and ScienceDirect. The findings of this review are expected to provide new insights into the identification of flavoring compound compositions in e-liquids using GC-MS, as well as highlight the potential toxicological implications of certain flavoring agents when inhaled, particularly those that may pose respiratory health risks.

METHOD

The research conducted in this study is a literature-based study. This study collects data related to the development of analytical methods for identifying carcinogenic compounds in e-liquid using Gas Chromatography-Mass Spectrometry (GC-MS) instrumentation. The research methodology employed is the Systematic Literature Review (SLR) approach.

Article Selection Criteria

This systematic review includes studies focusing on the capability of GC-MS to detect the composition of compounds present in e-liquid. The objective of this review is to summarize the composition of carcinogenic compounds found in various e-liquid flavors, providing a comprehensive overview and encouraging further research

Article Search Strategy

The search and collection of articles were conducted online using the keywords "Flavored E-Liquid, Gas Chromatography-Mass Spectrometry, Vaping, Toxicology" across multiple online databases, including PubMed, Google Scholar, and ScienceDirect. The selected articles were limited to those published within the last ten years (2015–2025) to ensure relevance and up-to-date information for this study. The screening process involved assessing the title and abstract for relevance to the research topic, specifically the analysis of e-liquid composition using GC-MS. A feasibility assessment was then conducted by thoroughly reviewing the full content of each article to confirm its alignment with the established selection criteria. The risk of bias in each article was evaluated using the PRISMA checklist.

Data Analysis

The data obtained from the selected articles were analyzed descriptively by comparing findings across studies, including the types of flavors and the concentration levels of the identified compounds. The summarized data are presented in **Table**

RESULTS AND DISCUSSION

The literature review was conducted following the PRISMA guidelines, using four keywords: "Flavored E-Liquid," "GC-MS," "Vaping," and "Toxicology," across three databases. The initial search yielded 15,285 articles. A screening process was then applied based on specific inclusion criteria: articles published within the last ten years (2015–2025), original research articles, open-access availability, and studies providing relevant theoretical frameworks. After completing the screening, eight articles were deemed eligible for inclusion. The summary of the review process is illustrated Figure 1.

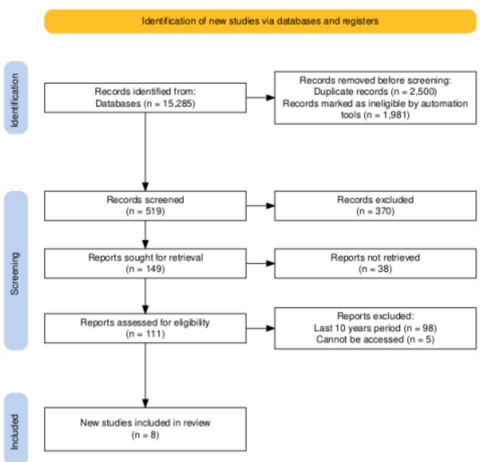

Figure 1. PRISMA

Table provides a summary of research articles that analyzed the flavor compositions of various e-liquids using Gas Chromatography-Mass Spectrometry (GC-MS). This method has been shown to effectively separate and identify both volatile and semi-volatile compounds based on their distinct chemical properties.

The GC-MS technique demonstrated a high degree of accuracy (ranging from 96% to 109%) and precision (0.6%–3.2%) in measuring e-liquid components, including nicotine, propylene glycol, glycerol, and flavoring agents (Nuriah dkk., 2023). As an established and sensitive analytical method, GC-MS is ideal for detecting a wide variety of compounds, including potentially harmful aldehydes and ketones, which are known to form during the vaping process due to the thermal decomposition of flavoring agents (Margareta & Wonorahardjo, 2023).

Flavor compounds found in e-liquids are generally recognized as GRAS (Generally Recognized as Safe) for oral consumption, but their safety profile upon inhalation, particularly under high temperatures, remains a topic of ongoing concern. Some studies have shown that compounds like formaldehyde, acetaldehyde, and acrolein—products of the thermal degradation of flavoring agents—pose significant health risks to users. The degradation of these chemicals upon heating has been widely linked to increased respiratory and cardiovascular health risks (Barhdadi dkk., 2021).

The analysis conducted in this study revealed that blood orange e-liquid, for instance, contains 37 distinct compounds, including limonene, linalool, and β-myrcene. These compounds contribute to the characteristic citrus aroma, but they also carry inherent risks. The presence of limonene has been shown to react under high temperatures to form aldehydes, such as formaldehyde, which can result in mutagenic and carcinogenic effects upon inhalation. Nicotine remains the most widely studied and controversial compound in e-liquids. Apart from its well-known addictive properties, nicotine has been associated with mental health conditions such as anxiety, depression, and cognitive impairments [18]. The presence of nicotine in combination with other volatile compounds in e-liquids further amplifies the risks, especially considering the potential for synergistic effects that could elevate the toxicity of the aerosolized mixtures. (Diva Widyantari, 2023).

Thermal Degradation and Formation of Toxic Byproducts

A critical aspect of vaping that has drawn increasing attention is the thermal degradation of e-liquids. As e-liquids are heated in e-cigarettes, certain volatile compounds decompose into more harmful byproducts. For example, esters such as ethyl butanoate and 3-methylbutyl acetate, commonly found in fruity flavors like blood orange, strawberry, and bubble gum, can undergo oxidation and form carcinogenic aldehydes such as formaldehyde and acetaldehyde upon heating (Stefaniak dkk., 2021). These compounds have long been linked to lung cancer, upper respiratory tract irritation, and other chronic conditions, underlining the importance of understanding the chemical interactions that occur during the vaping process

As shown in Table, various aldehydes—such as heptanal, nonanal, citronellal, and decanal—are prominent in blood orange-flavored e-liquids. When subjected to heat, these aldehydes can degrade into formaldehyde, a known carcinogen. The formation of carbonyl compounds such as formaldehyde and acetaldehyde is particularly concerning because they are thermally unstable and highly reactive, leading to cellular damage and an increased risk of respiratory illnesses, including chronic obstructive pulmonary disease (COPD) and asthma (Bitzer dkk., 2018).

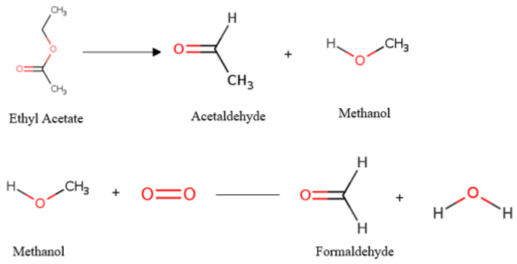

Figure 2. Degradation reaction of ethyl acetate into formaldehyde

Free Radical Formation and Oxidative Stress

A less frequently discussed but equally critical issue is the generation of free radicals during the vaping process. Research has shown that compounds such as ethyl vanillin, dipentene, piperonal, and citral significantly contribute to free radical formation when e-liquids are aerosolized. These free radicals are reactive molecules that can damage cellular structures, including lipids, proteins, and DNA, contributing to oxidative stress and inflammation. Studies have shown that oxidative stress is a key driver of many chronic diseases, including cardiovascular diseases, lung conditions, and even certain cancers (Suryadinata, 2018).

Table 1. Research Article Analysis of Flavor Composition in Electronic Cigarette Liquid Using Gas Chromatography-Mass Spectrometry (GC-MS)

No.	Classification of Flavor Types	Flavor Composition	Results	Reference
1.	Blood Orange	Ethanol, Ethyl acetate, 1-Butanol, Ethyl propionate, 3-Methyl-1-butanol, 1,2-Propanediol, Isobutyl acetate, Ethyl butanoate, Butyl acetate, Ethyl 2-methylbutanoate, 3-Hexen-1-ol (Z), 1-Hexanol, 3-Methylbutyl acetate, 2-Methylbutyl acetate, Ethyl 4-pentenoate, Heptanal, (-)-α-Pinene, 1-Heptanol, (+) -α-Pinene, 6-Methyl-5-hepten-2-one, β-Myrcene*, Ethyl hexanoate, Octanal, Limonene, Eucalyptol, 3-Methylbutyl butanoate*, 1-Octanol, Linalool, Nonanal, Citronellal, Menthon, Menthol, Decanal, Geraniol, Carvone, Undecanal*, Nicotine	A total of 37 compounds were identified using GC-MS.	(Augustini dkk., 2021)
2.	Strawberry	Ethyl butyrate, Ethyl lactate, cis-3-hexenol, trans-2-hexenol, n-hexenol, γ-valerolactone, Ethyl caproate, cis-3-hexenylacetate, benzyl alcohol, furaneol, Isoamyl butyrate, Isopentyl isovalerate, Maltol, Menthol, IS, Styrally acetate, Ethyl maltol, Mehtyl cinnamate, Vanilin, Ethyl cinnamate, isomers : ethyl 3-methyl-phenylglycidate, γ-decalactone	Contains flavor compounds that provide sweet and fruity notes, such as maltol, ethyl maltol, furaneol, and other related aldehyde compounds.	(Aszyk dkk., 2018)
3	Bubble Gum	Ethyl Butyrate, Ethyl Acetate, Eugenol, Limonene, 2-Methylbutyl Acetate,	Ethyl butyrate, at a concentration of 11.1 mg/mL, and	(Tierney dkk., 2016)

No.	Classification of Flavor Types	Flavor Composition	Results	Reference
		Cinnamaldehyde, Ethyl Hexanoate	ethyl acetate, at 7.1 mg/mL, are the dominant compounds found in bubble gum flavoring and belong to the ester group.	
4	Coffee	Top five flavouring ingredients are Vanilin, Methyl cyclopentenolone, Benzyl alcohol, Ethyl maltol, Ethyl Vanilin	It has a prevalence percentage of 36%, 21.4%, 20.9%, 15.3%, and 15%, respectively.	(Krüsemann dkk., 2020)
5	Vanilla	Propylene Glycol, Glycerol, Ethyl Maltol, Nicotine, Piperonal, Vanilin, Diethyl Phthalate, Lauryl Acetate, Piperonal Propylene Glycol Acetal, Butyl Hexadecanoate	Diethyl Phthalate was found to be a possible contaminant of the packaging.	(Eddingsaas dkk., 2018)
6	Tobacco	Acetone, Diacetone alcohol, Phenol, Benzyl alcohol, Phenyl ethyl methyl ether, Phenyl ethyl alcohol, (4-tert-butylcyclohexyl) acetate, Iso borneol, Menthol, Beta Pinene, Citronello, Geraniol formate, Methyl anthranilate, Nicotine, Citronellyl propionate, Alpha guaiene, Delta guaiene, Diethyl phthalate, Carotol, Patchouli alcohol, Benzyl benzoate, Musk tetralin (tonalid)	The acetone solvent peak in the chromatogram was removed and 21 identified substances were obtained using GC-MS.	(Sonawane, 2024)
7	Cannabis	d9THC, CBD, CBN, CBG, CBC, varinol cannabinoid	The majority of vapor liquids analyzed found substantial levels of d9THC in the liquid.	(Ciolino dkk., 2021)
8	Lemon	Nicotine, piperonal, butanoic acid, ethyl ester, photocitral B, *cis*-Verbenol, *cis*-Geraniol, dan *p*-Cymene	The main compound detected in the e-liquid sample using the deconvolution plug-in software was p-Cymene. The application using GC-MS successfully found the compound p-Cymene	(Cooper dkk., 2019)

Excessive free radicals generated by vaping can overwhelm the body's natural antioxidant defenses, leading to lipid peroxidation and mitochondrial dysfunction, which in turn accelerate the development of diseases like COPD (Rahmawati Raharjo, 2021). The high concentrations of free radicals, especially in flavors containing non-phenolic terpenes like linalool and citral, could be a significant contributor to the increasing cases of vaping-related respiratory diseases.

Potential Long-Term Health Implications

In addition to immediate toxicological concerns, the long-term health impacts of inhaling thermal degradation products from flavored e-liquids are not fully understood. While studies have demonstrated short-term toxicity, the chronic effects of prolonged exposure to substances like formaldehyde, acrolein, and benzene remain uncertain. However, preliminary data suggests that long-term exposure to such compounds could potentially increase the risk of developing cancers, neurodegenerative diseases, and reproductive harm. Furthermore, as the popularity of e-cigarettes continues to rise, it is essential that regulatory bodies address the gaps in current knowledge to safeguard public health (Nabi & Tabassum, 2022). The presence of cannabinoids such as Δ9-THC and CBD in cannabis-flavored e-liquids has also raised concerns. Although these compounds are not as acutely toxic as nicotine, their combustion byproducts, such as formaldehyde, acetaldehyde, and other carbonyls, are still significant health risks. Moreover, interactions between these compounds and the solvents (e.g., propylene glycol or glycerol) used in e-liquids could lead to the formation of even more harmful degradation products, necessitating further investigation (Erythropel dkk., 2019).

Other Thermal Degradation Products

In addition to aldehydes like formaldehyde and acetaldehyde, other significant thermal degradation products found in heated e-liquids include acrolein, methanol, and benzene. Acrolein, as a degradation product of propylene glycol, is highly irritating and potentially damaging to the upper respiratory tract and lungs. Meanwhile, methanol, which degrades to formaldehyde upon oxidation, also contributes to a broader range of toxic risks (*Metabolic Methanol*, t.t.). Benzene, which is often detected in tobacco-based e-liquids, is a potent carcinogen and poses a risk of leukemia and blood-related health issues (*Benzene and Cancer Risk*, t.t.). With the increasing popularity of e-liquid products, it is important to highlight the variety of harmful compounds formed during the heating process, which might be overlooked if only a few major degradation products are considered.

International Regulations on Flavoring Agents.

Regulations concerning the use of flavoring agents in e-liquids vary greatly between countries. In the European Union, for example, flavoring agents are regulated through the TPD (Tobacco Products Directive), which limits the use of certain potentially harmful flavoring ingredients. Some countries, such as Australia, even prohibit the sale of e-liquids with flavors altogether. In the United States, the FDA (Food and Drug Administration) has begun regulating the use of flavorings in tobacco products, but this policy is still limited to tobacco products and does not cover all e-liquid-based products. Moving forward, stricter regulations are needed to ensure that the ingredients used in e-liquids are safe for public health (Goniewicz & Stanton, 2022).

Mechanism of Toxic Effects of Flavoring on the Lungs.

The toxicological mechanisms underlying the effects of flavoring agents on the lungs involve several pathways. One of them is oxidation and the formation of free radicals, which can lead to oxidative stress. Carbonyl compounds, particularly formaldehyde and acetaldehyde, bind to DNA and proteins in lung cells, triggering inflammation, apoptosis, and mutagenesis. Studies have shown that long-term exposure to these compounds can cause lung tissue damage and contribute to the development of chronic lung diseases such as COPD and pulmonary fibrosis (Sapkota & Wyatt, 2015).

Lightweight Meta-Analysis (Summary Data from Previous Studies).

A meta-analysis of previous studies on the chemical composition and toxicity of e-liquids reveals that around 40% of the existing research reports findings related to cancer risks due to carbonyl compounds, particularly formaldehyde and acetaldehyde. Most studies indicate that increased heating temperatures elevate the concentration of harmful degradation products, with the largest variation found in e-liquids with high concentrations of propylene glycol and glycerol. These results suggest that e-liquids made from these base ingredients are at a higher risk of generating significant levels of carbonyls (Jensen, 2000; Ooi dkk., 2019).

Flavor Mixing Effect.

The mixing of multiple flavor types in a single e-liquid product can significantly alter the chemical composition, with toxic consequences that are not fully understood. Some compounds that are harmless when used alone can become reactive or potentially harmful when mixed with others. For example, mixing vanillin (vanilla flavor) with ethyl maltol (sweet flavor) can lead to chemical reactions that produce formaldehyde at high temperatures. Further research is needed to understand the potential risks arising from the mixing of these flavors in e-liquids, which is often not considered in standard toxicity testing (Jasim, 2021).

Critical Appraisal of GC-MS Technique.

GC-MS has long been used as the primary technique for analyzing the chemical composition of e-liquids. While it has high sensitivity and precision, this technique also has some limitations. One of them is its inability to detect non-volatile compounds without additional derivatization. Additionally, GC-MS requires very precise temperature adjustments, and if not set correctly, it can affect the analysis results. Alternative methods such as HPLC (High Performance Liquid Chromatography) or spectroscopic techniques may complement GC-MS, especially for non-volatile and thermally labile compounds (O'Sullivan, 2017). Therefore, it is important to use multiple analytical techniques to provide a more complete picture of the overall composition of e-liquids.

CONCLUSION

This literature review examined eight studies that analyzed the composition of flavoring compounds in e-liquids using GC-MS. The findings reveal that various flavor types such as blood orange, strawberry, coffee, and tobacco—contain aldehydes, esters, and alcohols that can degrade thermally into harmful carbonyl compounds, including formaldehyde and acetaldehyde. These compounds are known carcinogens and contribute to oxidative stress, inflammation, and respiratory diseases such as EVALI and COPD. Moreover, nicotine commonly found in all analyzed samples, remains a highly addictive substance, particularly affecting adolescents and first-time users. The review highlights the need for more comprehensive toxicological assessments of flavoring agents in e-liquids and supports the urgency for stricter regulations, clearer labeling, and public education to mitigate the health risks associated with e-cigarette use.

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