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REVIEW PAPER

Literature review: analysis of flavor composition in e-liquid using gc-ms and its potential respiratory health effects

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Abstract: The use of electronic cigarettes (e-cigarettes) has increased substantially in recent years as an alternative to conventional tobacco smoking. E-liquids, the core component of these devices, are formulated with various flavoring chemicals to enhance user experience. However, these flavoring agents may pose potential health risks when inhaled. This study aims to systematically review the chemical constituents of e-liquid flavorings identified using Gas Chromatography–Mass Spectrometry (GC-MS). A comprehensive literature search was conducted through PubMed, Google Scholar, and ScienceDirect databases, focusing on articles published within the past ten years. The analysis concentrated on identifying chemical compounds present in a range of e-liquid flavors, including vanilla, bubble gum, coffee, tobacco, strawberry, lemon, and cannabis. The findings indicate that e-liquids commonly contain compounds such as vanillin, ethyl maltol, cinnamaldehyde, benzaldehyde, and limonene. While these substances are generally recognized for their aromatic and flavor-enhancing properties, several have been associated with adverse respiratory effects. Upon heating, these flavoring compounds undergo thermal degradation, producing harmful carbonyl derivatives such as formaldehyde and acetaldehyde. Both compounds are classified as human carcinogens by the International Agency for Research on Cancer (IARC). Nicotine, frequently present in e-liquids, contributes to addictive behavior and is associated with increased risks of psychological disorders. Additionally, certain studies have reported the presence of diethyl phthalate, likely introduced through contamination from packaging materials. This review highlights the critical need for stricter regulation of flavoring agents in e-liquids to mitigate their potential toxicological impact. Standardized testing and safety evaluations should be mandated prior to product approval. Furthermore, more rigorous scientific investigations are required to assess the long-term health effects of chronic exposure to inhaled flavoring chemicals. The study also underscores the importance of raising public awareness regarding the potential dangers of vaping and supports the development of comprehensive policies to control the chemical composition of e-cigarette products.

Keywords: Gas Chromatography-Mass Spectrometry; Flavoring chemicals; Vaping; Toxic Compound

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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 [1]. 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 [2]. Cigarettes contain nicotine, a chemical compound derived from tobacco plants [3]. 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 [4].

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 [5].

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 [6]. 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 [7]. 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.

MATERIALS AND METHODS

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 1**.

RESULTS AND DISCUSSION

The literature review was conducted using the PRISMA method, based on four keywords from three databases covering the last ten-year period. The keyword search "Flavored E-Liquid, GC-MS, Vaping, Toxicology" across three databases yielded 15,285 articles. A screening process was then performed by applying the following selection criteria: articles published within the last ten years (2015–2025), research articles, open-access publications, and studies containing relevant theoretical foundations. After completing the screening process, eight articles were selected as they were deemed relevant to this study. The summary of this review is presented in **Figure 1**.

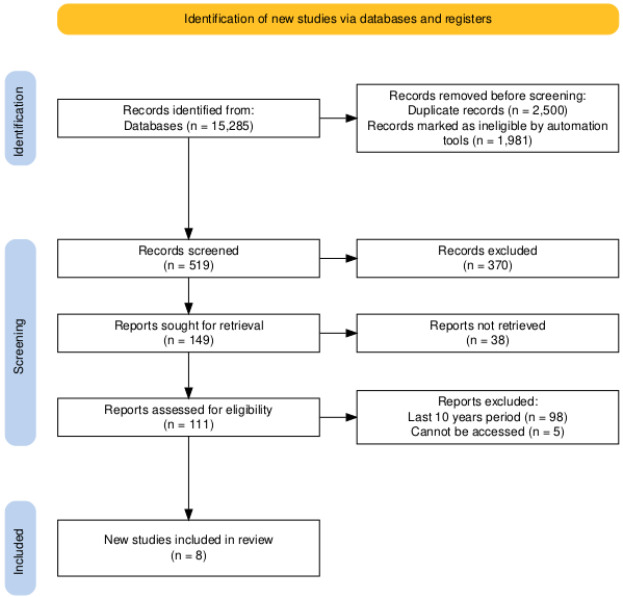

Figure 1. PRISMA

Table 1 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 [8]. 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 [9].

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 [10].

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 [11]. 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

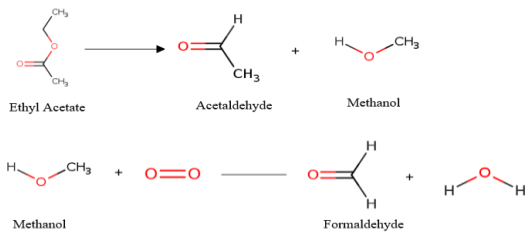

Figure 2. Degradation reaction of ethyl acetate into formaldehyde

The degradation of ester compounds, such as ethyl acetate commonly found in e-liquid flavorings results in bond cleavage, forming alcohol and carboxylic acid derivatives such as acetaldehyde and methanol. Oxidized methanol can subsequently form

formaldehyde, a highly toxic compound. Prolonged exposure to formaldehyde (15 days) has been shown to induce oxidative stress, cause DNA damage in bone marrow, and increase inflammatory markers in the respiratory tract by up to ten times higher than conventional cigarettes [12].

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.	[6]
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.	[13]
3	Bubble Gum	Ethyl Butyrate, Ethyl Acetate, Eugenol, Limonene, 2-Methylbutyl Acetate, Cinnamaldehyde, Ethyl Hexanoate	Ethyl butyrate, at a concentration of 11.1 mg/mL, and ethyl acetate, at 7.1 mg/mL, are the dominant compounds	[14]

			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.	[15]
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.	[16]
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.	[17]

7	Cannabis	d9THC, CBD, CBN, CBG, CBC, varinol cannabinoid	The majority of vapor liquids analyzed found substantial levels of d9THC in the liquid.	[18]
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	[19]

Table 2. Identified Carbonyl Compounds in E-Liquid Flavors and Their Toxicological Risks

Carbonyl Compound	Type	Found in Flavor	Toxicological Notes
Heptanal	Aldehyde	Blood Orange	May degrade into formaldehyde when heated
Octanal	Aldehyde	Blood Orange	Known respiratory irritant
Nonanal	Aldehyde	Blood Orange	Reactive with biological macromolecules
Citronellal	Aldehyde	Blood Orange	Allergenic and irritant potential
Decanal	Aldehyde	Blood Orange	Can release formaldehyde upon degradation
Menthon	Ketone	Blood Orange	Volatile, may cause respiratory irritation
6-Methyl-5-hepten-2-one	Ketone	Blood Orange	Thermally unstable volatile ketone
Vanillin	Aromatic Aldehyde	Strawberry, Coffee, Vanilla	May degrade to formaldehyde under heat
Cinnamaldehyde	Aromatic Aldehyde	Bubble Gum	Reactive compound, toxic to airway cells
Benzyl alcohol *(precursor)*	Alcohol (oxidizable)	Strawberry, Coffee, Tobacco	Can oxidize into benzaldehyde → formaldehyde
Maltol / Ethyl maltol	Furanone derivative	Strawberry, Coffee, Vanilla	Potential precursor to carbonyl volatiles
Acetone	Ketone	Tobacco	Volatile irritant, may harm mucosa
Diacetone alcohol	Ketone	Tobacco	Heat-sensitive, risk of formaldehyde release

Several compounds found in e-liquids pose toxicological risks that may endanger e-cigarette users. This study compares the composition of various e-liquid flavorings using GC-MS analysis. The flavors analyzed include blood orange, strawberry, bubble gum, coffee, vanilla, tobacco, cannabis, and lemon. Blood orange flavoring contains 37 identified compounds, with limonene, linalool and β-myrcene being the key components contributing to its citrus aroma. Nicotine in e-liquid has psychological effects that lead to addiction and an increased risk of mental health disorders such as stress, anxiety, and depression. Additionally, heating e-liquids in e-cigarettes can result in the thermal degradation of certain compounds, producing toxic byproducts. Ester and alcohol compounds, such as ethyl butanoate and 3-methylbutyl acetate, undergo oxidation upon heating, forming formaldehyde and acetaldehyde, both classified as carcinogens. Formaldehyde, a Group 1 carcinogen, increases the risk of cancer by 5 to 15 times. E-cigarette use has been linked to e-cigarette or vaping product use-associated lung injury (EVALI), chronic obstructive pulmonary disease (COPD), bronchiolitis obliterans (popcorn lung), and lung cancer [20].

These findings emphasize the need for comprehensive toxicological evaluation of flavoring agents used in e-liquids, especially those rich in aldehydes and other carbonyl compounds. Strawberry-flavored e-liquids contain flavoring compounds that contribute to sweet and fruity notes, such as maltol, ethyl maltol, furaneol, and related aldehydes. These aldehydes undergo thermal decomposition, generating formaldehyde and acetaldehyde, which are carcinogenic. Bubble gum flavoring contains ethyl butyrate (11.1 mg/mL) and ethyl acetate (7.1 mg/mL), which are the

dominant ester compounds. Coffee and vanilla-flavored e-liquids contain vanillin and ethyl maltol, which contribute to their sweet sensory effects. The reaction between aldehydes and propylene glycol in e-liquids has the potential to form toxicological compounds [10]. Tobacco-derived e-liquids induce oxidative stress, inflammation, DNA damage, and increased cell death in lung cells [21]. Cannabis-flavored e-liquids contain active compounds derived from Cannabis sativa, including Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), and cannabichromene (CBC). Δ9-THC is a semi-solid, hydrophobic compound, typically mixed with diluents such as vitamin E acetate (VEA) or propylene glycol (PG) in e-liquids. When heated to the vaporization temperature of cannabis e-liquids, acetaldehyde and formaldehyde may form [11]. Flavoring contains p-cymene as a dominant compound, identified using GC-MS.

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 [22]. 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 [23].

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 [24].

CONCLUSION

This literature review examined eight studies that analyzed the composition of flavoring compounds in e-liquids using GC-MS. 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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