Metabolic Profiling of E-Cigarettes and Conventional Cigarettes Through Metabolomics Techniques

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Abstract

E-cigarettes are battery-operated devices that generate vapor by heating a liquid, eliminating the combustion process in traditional cigarettes. Although considered a safer alternative, their health effects remain unclear. This study examines metabolic profiles of e-cigarette users versus non-smokers using ^{1}H-NMR-based metabolomics. Urine samples from 30 males (15 e-cigarette users and 15 non-smokers) were analyzed. PLS-DA identified distinct metabolic differences, with significant variations in putrescine, guanine, succinic acid, and syringic acid. Pathway enrichment analysis revealed disruptions in oxidative stress, energy metabolism, and inflammation-related pathways, including glutathione, tryptophan, and purine metabolism, indicating potential health risks. These findings highlight metabolic changes linked to e-cigarette use and emphasize the need for further research on their long-term effects.

Keywords**:** *e-cigarettes, vaping, ^{1}H-NMR-based metabolomics, metabolites*

1. Introduction

Electronic cigarettes (e-cigarettes) are battery-powered devices that heat a liquid to produce vapor, avoiding combustion like traditional cigarettes. This has led users to believe that they are less harmful. However, e-cigarettes can still negatively impact health, potentially contributing to respiratory, cardiovascular, and other diseases (Abuse, 2024). E-cigarettes contain nicotine and other chemicals that may have acute and chronic health effects. Many users believe they are safer than traditional cigarettes. While studies indicate that e-cigarettes contain fewer toxic and carcinogenic substances than regular cigarettes, data on their acute and chronic safety—particularly in Thailand—remain limited. Nicotine is addictive and harmful, contributing to issues like high blood pressure and adverse effects on adolescent brain development. Research on nicotine absorption has shown that a single puff of an e-cigarette rapidly increases nicotine levels in the brain, reaching 50% of the peak concentration within 27 seconds. This absorption rate is similar to that of traditional cigarettes, potentially reinforcing addiction (Marsot & Simon, 2016). Studies report that peak plasma nicotine concentrations (C_{max}) from e-cigarettes range between 13.9 and 16.3 ng/mL, comparable to those of conventional cigarettes. The time to reach peak concentration (T_{max}) ranges from 70 to 75 minutes. Moreover, cotinine levels, a nicotine metabolite, after e-cigarette use are similar to those from traditional cigarettes. Excessive vapor from e-cigarettes contains various chemicals, including nicotine lactate, nicotine benzoate, acetone, acetaldehyde, formaldehyde, and propylene glycol (Pinto et al., 2022), suggesting their use may not be as safe as often claimed (Vandelaer, 2023).

E-cigarettes are currently prohibited under Thai law through multiple regulations. The Ministry of Commerce's Announcement in 2014 designated baraku, electronic baraku, and e-cigarettes as prohibited imports (Parinyarux P, 2022). Additionally, the Consumer Protection Board's Order No. 9/2015 bans the sale and provision of baraku, electronic baraku, e-cigarettes, baraku substances, and e-cigarette liquids (Kennedy et al., 2017). Further legal restrictions come from the Customs Act B.E. 2560 (2017), which regulates the import and taxation of restricted goods, and the Tobacco Products Control Act B.E. 2560 (2017),

which prohibits using e-cigarettes and nicotine-containing products in designated non-smoking areas (C., 2018). Despite these legal prohibitions, data on e-cigarette usage in Thailand may not accurately reflect the real situation. According to the 2018 Thailand Tobacco Consumption Report, only 1,714 individuals, accounting for 0.02% of the population, were recorded as users of electronic smoking devices. However, this is considered significantly lower than the actual number of users. A 2019 study on smoking behavior among university students in Thailand found that among 422 smokers, 65.2% were e-cigarette users, suggesting a much higher prevalence than officially reported statistics to indicate. The health effects of e-cigarettes remain a topic of ongoing debate (Boonpen, 2019). In Thailand, there is a lack of academic studies assessing their long-term health impacts and safety. Additionally, research on the effectiveness of e-cigarettes as a smoking cessation aid remains controversial, with conflicting conclusions across different studies. The World Health Organization (WHO) has stated that e-cigarettes pose health risks to both users and bystanders (Vandelaer, 2023). Due to the lack of clear evidence regarding their effectiveness in smoking cessation, WHO does not recommend e-cigarettes as a tool to quit smoking. Although e-cigarettes are legally banned in Thailand, their actual prevalence is likely higher than reported. The lack of conclusive research on their health effects and smoking cessation efficacy raises concerns among policymakers and health professionals. Further academic studies and comprehensive regulatory frameworks are essential to address the uncertainties surrounding e-cigarette use in Thailand (Boonpen, 2019).

Metabolomics is the study of metabolites within cells and their metabolic profiles, providing insights into biochemical processes within the body. This field helps identify enzyme abnormalities, specific biomarkers for organs, and mechanisms of toxicity. For instance, metabolomics has been used to analyze 1,620 unique metabolites from eight organs, including the brain, liver, heart, and lungs, to study metabolic alterations in diabetic mice (Srivastava, 2019). Currently, there is a lack of acute and chronic safety data on e-cigarettes, especially regarding their metabolic impact. This study aims to investigate the metabolic profiles of e-cigarette users compared to healthy non-smokers using ^{1}H-NMR-based metabolomics techniques. By analyzing metabolic patterns, the study identifies key biomarkers and predicts the effects of e-cigarettes on the body's metabolic processes. This information could contribute to understanding the health risks associated with smoking and provide a foundation for future research (Kotsombat, n.d.). Currently, there is a lack of academic data on the long-term health effects and safety of e-cigarette use, particularly regarding the metabolic profiles of e-cigarette smokers (Lenski et al., 2024). This study aims to investigate the metabolic profiles of e-cigarettes using metabolomics techniques. The analysis will compare metabolic patterns among two groups: healthy non-smokers and e-cigarette smokers. The findings from this study might help identify key biomarkers associated with e-cigarette smoking. Additionally, the study aims to predict how e-cigarette smoking influences metabolic alterations in the body. Given the current uncertainties regarding the health impacts of e-cigarette use, metabolomics techniques can help fill the gap in knowledge by providing a deeper understanding of the biochemical changes associated with smoking.

2. Objectives

To investigate the metabolic profiles of e-cigarette users compared to healthy non-smokers using ^{1}H-NMR-based metabolomics techniques, and analyze metabolic alterations, identify result-related pathways and diseases.

3. Materials and Methods

3.1 Reagents

Methanol, chloroform, deuterium oxide (D_2O), and 3-(trimethylsilyl)-[2, 2, 3, 3-d4]-1-propionate sodium salt (TSP) were purchased from Sigma-Aldrich (St. Louis, MO, USA). All chemicals used were of analytical grade.

3.2 Ethical approval and informed consent

The study was conducted following the Declaration of Helsinki and was approved by the Institutional Review Board (Human Ethics Committee) of the Faculty of Medicine, Chiang Mai University,

Thailand. The ethics approval reference number is No. 282/2024 (Study code: FOR-2567-0336). Before enrollment, written informed consent was acquired from all participants, and the study results were reported anonymously.

3.3 Study design, setting, and population

This is a cross-sectional study. The study population consists of two groups: individuals who currently use e-cigarettes and healthy non-smokers with no history of exposure to any tobacco products (control group). E-cigarette users must have a smoking history of at least three months and be Thai nationals aged 20 years or older. Sampling will be conducted using the snowball or chain sampling technique (Parinyarux P, 2022). The first participant will be identified through inquiries with individuals experienced in e-cigarette use residing in northern Thailand. Each participant will be asked to recommend at least two other individuals with similar e-cigarette vaping experiences. This process will continue until a sample size of approximately 15 participants in each group is achieved.

3.4 Sample preparation

Urine samples were mixed with acetonitrile (1:1) for 10 minutes and then centrifuged at 4000 RPM. The supernatant was lyophilized and reconstituted in 0.6 mL of 0.1 M TSP in D2O. Metabolite concentrations were analyzed using 500 MHz Nuclear Magnetic Resonance (NMR), following a previously optimized method to minimize water resonance interference (Tajai et al., 2024).

3.5 Acquisition parameters

The proton NMR spectra were obtained using a Bruker AVANCE 500 MHz spectrometer (Bruker, Bremen, Germany) configured with a Carr–Purcell–Meiboom–Gill (CPMG, RD—90°, (t—180°), n—acquire) pulse sequence for ^{1}H-NMR analysis. Measurements were performed at 27 °C with water suppression achieved through pre-saturation. The experimental setup included 16 scans, a 1-second relaxation delay, a 3.95-second acquisition time, an 8278.146 Hz spectral window, a 0.126 Hz resolution for free induction decay (FID), and a dwell time (D.W.) of 60.40 µs. A 90° pulse sequence with 16 signal averages (NSAs) was used. Baseline and phase adjustments were performed using TopSpin 4.0.7 software. The spectra were analyzed for metabolite profiling, spanning a chemical shift range of 0 to 12 ppm, and normalized to the total integrated area. Metabolite resonances were identified using human metabolomic databases (Dona AC, 2016). TSP served as an internal standard, facilitating the quantification of 24 energy-related metabolites across all samples.

3.6 Internal standard (I.S.)

Due to its unique chemical properties, TSP was chosen as the internal standard (I.S.). Its uniform chemical environment, with all 14 protons being equivalent, ensures a consistent signal at 0 ppm when measured at 500 MHz. Moreover, the TSP signal arises from a region with stronger magnetic field intensity than other protons. Additionally, TSP is chemically stable and inert, and its low boiling point in organic solvents allows for efficient extraction from samples.

3.7 ^{1}H-NMR spectroscopy

The NMR tube was used to measure the chemical composition by recording the proton NMR spectrum with a Bruker AVANCE 500 MHz spectrometer (Bruker, Bremen, Germany) employing the Carr-Purcell-Meiboom-Gill (CPMG, -RD-90°-(t-180°-t)n-acquire) sequence with a 90° pulse. The chemical composition analysis was conducted using Bruker TopSpin software version 4.0.7, and the resulting chromatograms were analyzed with MestReNova.

3.8 Chemical Composition Identification and Quantification

The identification of individual chemical compounds was performed using the Metabolomic Human Database (HMDB). The identification process utilized parameters such as cluster midpoint values, peak order

(coupling type), the number of hydrogen atoms (H's), atomic numbers, and coupling constants (*J*). The coupling constant represents the distance between split peaks caused by neighboring proton coupling (spin-spin coupling). The compatibility of each compound with the database was determined based on matching criteria. For example, the chemical shift of the cluster midpoint for each compound must differ by no more than 0.02, and the number of observed peaks must be consistent.
The concentration of each chemical compound was calculated using an equation adapted and referenced from the research by Jaikang et al. (2024).

$$C_A = \frac{I_A}{I_{TSP}} \times \frac{H_{TSP}}{H_A} \times C_{TSP}$$

Where: C_A = Concentration of the compound (μM)
I_A = Intensity of the compound of interest
I_{TSP} = Intensity of TSP
H_{TSP} = Number of hydrogen atoms in TSP
H_A = Number of hydrogen atoms in the compound of interest
C_{TSP} = Concentration of TSP (μM)

3.9 Data Analysis

Metabolic profiling, along with statistical methods such as principal component analysis (PCA) or cluster analysis, will be employed to analyze relationships and compare metabolic differences between sample groups. These methods provide insights into the metabolic processes of living organisms or biological systems under specific conditions. The goal is to predict metabolic changes and the breakdown of metabolites in living organisms. If significant changes in metabolic pathways are observed, the area under the Receiver Operating Characteristic (ROC) curve will be analyzed to identify specific biomarkers by MetaboAnalyst (version 6.0, http://www.metaboanalyst.ca/MetaboAnalyst, accessed on March 1, 2024). Pathway enrichment and analysis, along with the evaluation of alterations in the metabolic profiling of e-cigarettes, were performed using MetaboAnalyst. This process included the use of heatmaps and Pearson correlation coefficient calculations to explore metabolic changes. Key metabolites identified as potential biomarkers were further assessed through univariate ROC curve analysis, with 95% confidence intervals calculated for each individual biomarker. Additionally, demographic data were presented as frequencies (n, %) and means ± standard deviation (SD).

4. Results and Discussion

4.1 Demographic Data

Thirty male participants were divided into two groups: e-cigarette users (n=15) and the control group (n=15). The e-cigarette user group had an average age of 29 ± 6 years, while the control group had an average age of 27 ± 4 years. Duration of exposure for the e-cigarette user group had an average age of 4 ± 3 years.

4.2 Determination of differences in urine metabolites between e-cigarettes and control using ^{1}H-NMR

A 500 MHz ^{1}H-NMR spectrum of the urine sample obtained from participants is illustrated in Figure 1 The chromatogram overlay highlights the urine samples collected from one individual in the e-cigarette user group and one individual in the control group. Untargeted metabolomics analysis screened the metabolites in urine samples, detecting 189 metabolites in both the e-cigarette user and control groups. Identification of metabolites was achieved by referencing the Human Metabolome Database (HMDB, https://hmdb.ca/), accessed on October 15, 2024.

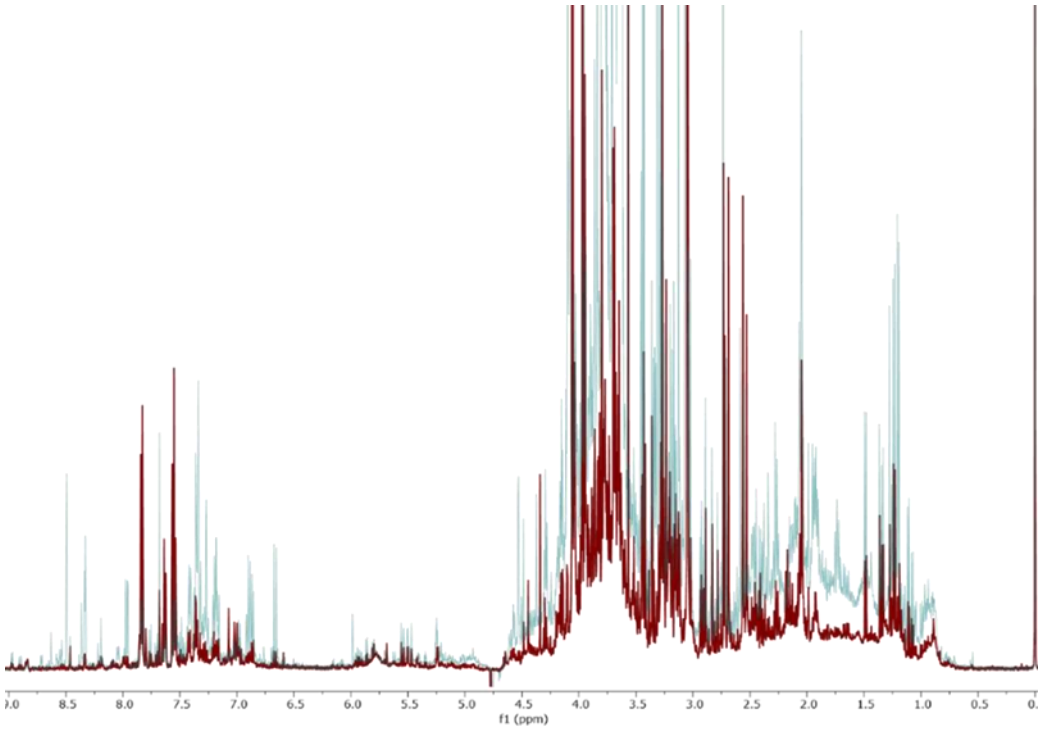


Figure 1 Results of ^{1}H-NMR-Based Metabolomics Analysis. The 500 MHz ^{1}H-NMR spectra of urine obtained from one individual in the e-cigarette user group and one individual in the control group are presented. The spectral overlay reveals distinct metabolic profiling differences between the e-cigarette user group and the control group, when the e-cigarette user group (depicted in red) and those obtained from the control group (depicted in blue).

The Partial Least Squares Discriminant Analysis (PLS-DA) score plot (Figure 2A) shows a clear separation between the two groups: the e-cigarette user group (group 1, depicted in green) and the control group (group 2, depicted in red), highlighting a distinct difference in their metabolic profiles. The VIP score plot (Figure 2B) ranks the metabolites selected by the PLS-DA model for each component, with the top 10 metabolites being: putrescine, guanine, succinic acid, 5-hydroxy-L-tryptophan, leucine, 2-methylhippuric acid, Sumiki's acid, isobutyrylglycine, syringic acid, and homoveratric acid. Multivariate Exploratory ROC Analysis, based on cross-validation (CV) performance across all models and runs (Figure 2C, D), evaluates the model's diagnostic accuracy. The area under the curve (AUC) of 0.927 demonstrates a strong ability to differentiate between the two groups, with a 95% Confidence Interval [CI] of 0.7–1.00.

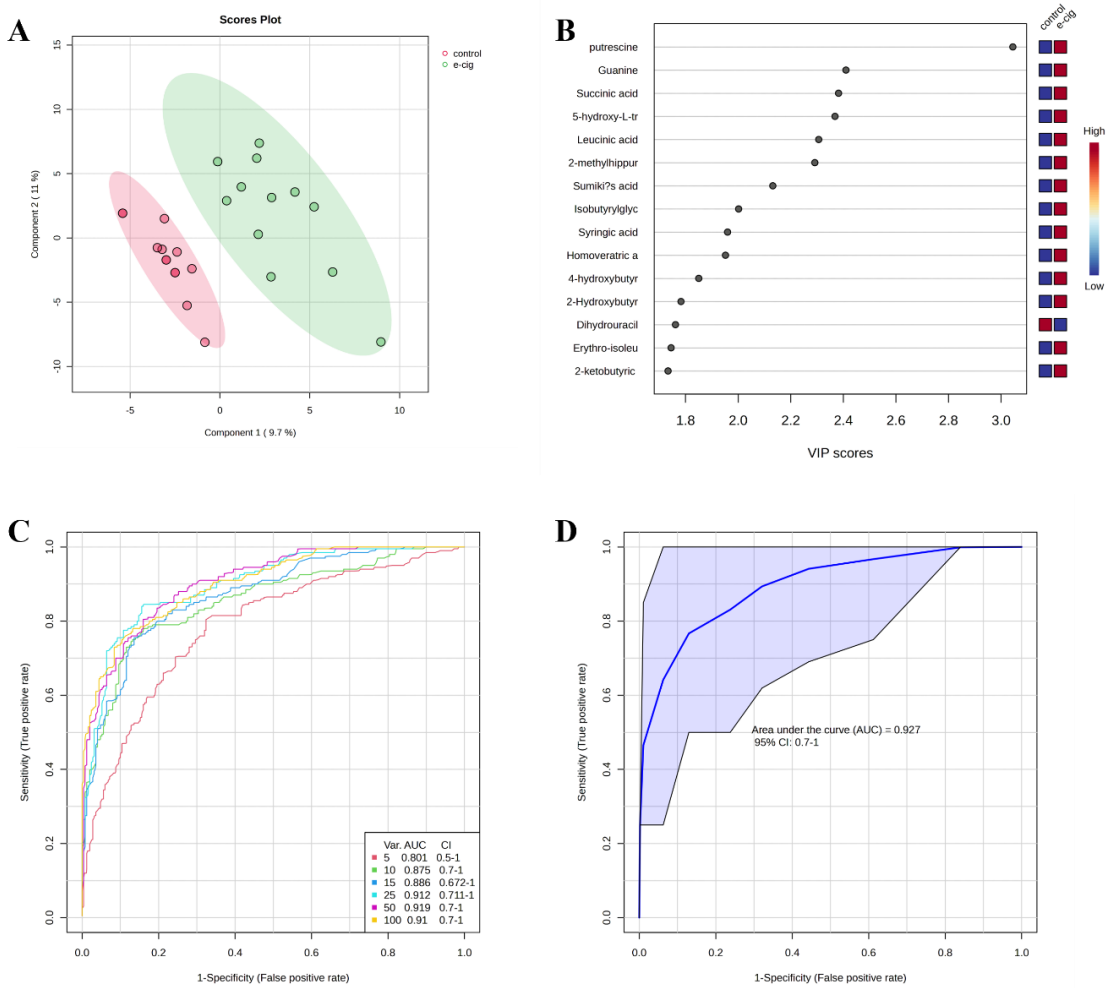


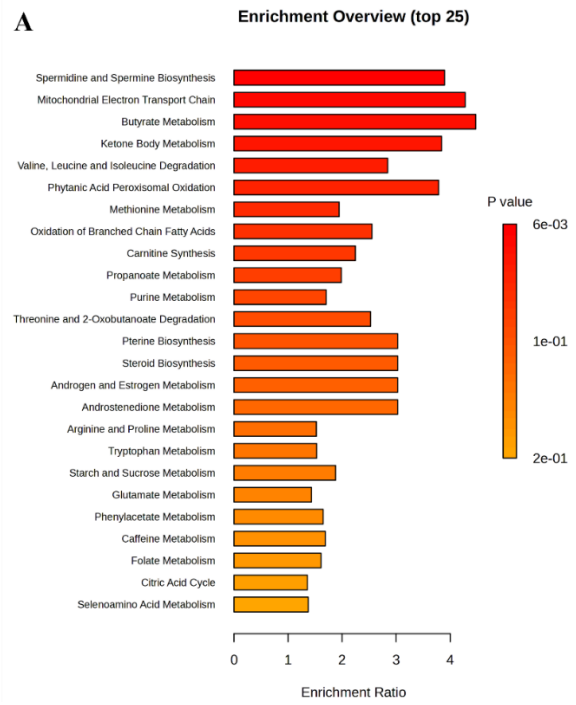
Figure 2 (A) The Partial Least Squares Discriminant Analysis (PLS-DA) scores plot demonstrates a notable separation between the two groups: the e-cigarette user group (group 1, shown in green) and the control (group 2, shown in red). (B) The VIP score plot ranks each component's metabolites selected by the PLS-DA model. (C) Multivariate Exploratory Receiver Operating Characteristic (ROC) Analysis, which is based on cross-validation (CV) performance averaged across all models and CV runs, assesses the model's diagnostic accuracy. (D) The area under the curve (AUC) of 0.927 indicates a strong ability to differentiate between the two groups (95% Confidence Interval [CI]: 0.7–1.00).

4.3 Analysis of related pathways and diseases

Pathway enrichment analysis was conducted using MetaboAnalyst (version 6.0) to map metabolites within specific metabolic pathways and disease signatures, utilizing the Small Molecule Pathway Database (SMPDB) and urine disease signatures. This analysis incorporated 99 metabolite sets aligned with normal human metabolic pathways and 385 metabolite sets reported in human urine. The top 25 enriched metabolite sets, shown in Figure 3A, were ranked by their Enrichment Ratio based on SMPDB. Metabolic disruptions were identified between the e-cigarette group and the control group. Figure 3A highlights the metabolic pathways most affected in e-cigarette users, revealing significant changes in oxidative stress, energy metabolism, and inflammation-related pathways. Notably, e-cigarette use impacts spermidine and spermine biosynthesis, which is linked to oxidative stress. Additionally, similar to traditional cigarette smoke, e-cigarettes have been shown to disrupt mitochondrial respiratory chain function and interfere with the

tricarboxylic acid (TCA) cycle, affecting energy metabolism (Lenski et al., 2024). Another key pathway influenced by e-cigarette use is butyrate metabolism, which plays a crucial role in gut health and inflammation (Zaparte et al., 2024). These alterations suggest that e-cigarette use may contribute to mitochondrial dysfunction, metabolic stress, and increased inflammation, which could have long-term health consequences. Additionally, Figure 3B ranks diseases by enrichment ratio based on the urine disease signatures database, with leukemia emerging as the top-associated condition. Putrescine plays a crucial role in cell growth and is found at elevated levels in the urine of cancer patients, including those with leukemia (Mohsin Amin, 2021). Previous studies indicate that spermine (Spm) levels are significantly increased across all leukemia types, while the spermidine/spermine (Spd/Spm) ratio is markedly decreased, particularly in acute promyelocytic leukemia, acute monocytic leukemia, and acute monomyelocytic leukemia. These findings suggest that erythrocyte polyamine levels could serve as valuable biomarkers for leukemia diagnosis and prognosis (Lenski et al., 2024)

The pathway analysis results presented in Figure 4, conducted using MetaboAnalyst version 6.0, were based on -log10(p) values and pathway impact scores. Figure 4 shows that e-cigarette users experience significant metabolic disruptions, particularly in pathways related to energy metabolism, oxidative stress, cardiovascular health, and inflammation. Key affected pathways include propanoate metabolism (energy balance), tryptophan metabolism (neurological and immune function), arginine and proline metabolism (vascular health), branched-chain amino acid metabolism (muscle and protein balance), glutathione metabolism (oxidative stress defense) and purine metabolism (DNA synthesis and inflammation). These changes suggest increased oxidative stress, potential cardiovascular risks, metabolic imbalances, and immune dysfunction in e-cigarette users. Our findings are consistent with several studies on e-cigarettes conducted in humans, *in vivo*, and *in vitro* models, which have shown that e-cig exposure disrupts multiple metabolic pathways. These include glycolysis, the TCA cycle, amino acid metabolism, beta-oxidation, phospholipid and sphingolipid metabolism, and antioxidant metabolism (Lenski et al., 2024)



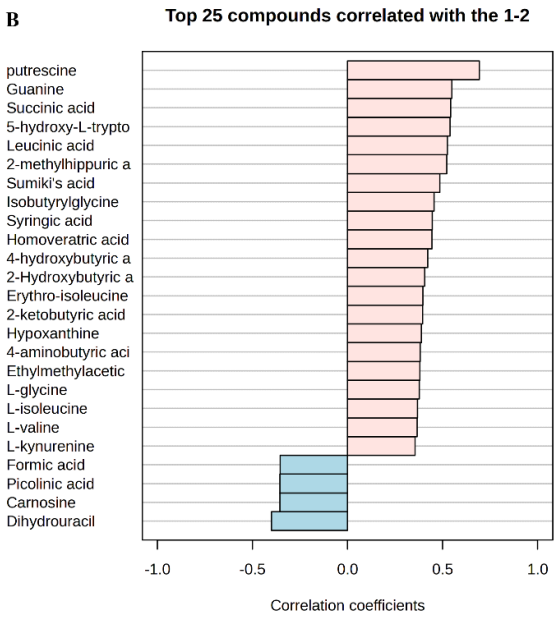


Figure 3 (A) Pathway enrichment analysis maps metabolites to specific pathways using chemical structures. The top 25 enriched metabolite sets are ranked by Enrichment Ratio based on chemical structures and SMPDB. (B) The top 25 metabolite sets are ranked by enrichment ratio and statistical significance (log10(p)). Larger dots indicate higher enrichment, while the color gradient (yellow to red) represents significance, with red being the most significant. Disrupted pathways include leukemia metabolism, lung cancer-related changes, malnutrition, and amino acid metabolism disorders, highlighting significant metabolic alterations in e-cigarette users compared to controls.

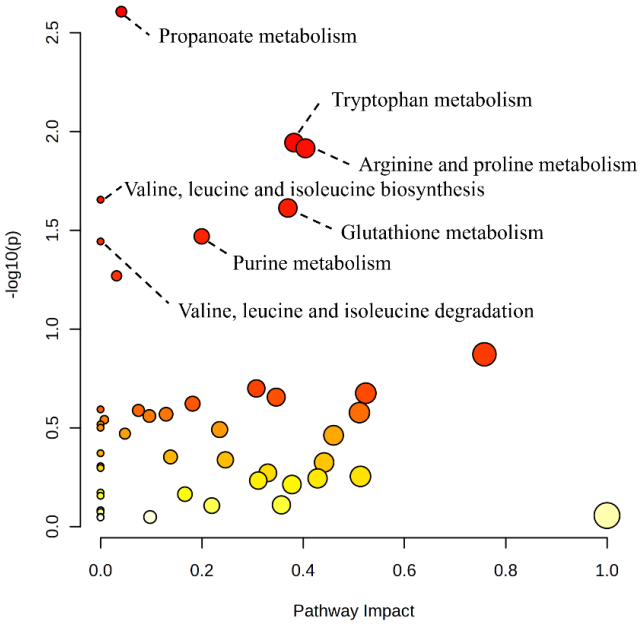


Figure 4 Pathway analysis identified significantly disrupted metabolic pathways, including propanoate, tryptophan, arginine and proline metabolism, as well as glutathione and purine metabolism. These results align with pathway enrichment analysis, confirming notable metabolic alterations in e-cigarette users compared to controls.

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3.4 Alterations in metabolic profiles in the e-cigarette group and the control group

The heatmaps (Figure 5A) demonstrate the differences in metabolite abundance between the e-cigarette group and the control group, highlighting metabolites with either increasing or decreasing trends during the interaction. In these heatmaps, columns represent individual samples from the e-cigarette and control groups, while rows show the top 25 metabolites ranked by their correlation coefficients. The color scale, ranging from red to blue, visualizes the normalized metabolite intensities, where red indicates higher intensities and blue signifies lower intensities. To further explore the metabolic changes, Pearson correlation coefficients were calculated to examine the relationships among metabolites, revealing distinct patterns for the e-cigarette and control groups. These correlations are shown in the bar graph (Figure 5B), which is consistent with the trends observed in the heatmap. Overall, the data indicates significant changes in metabolite profiles, with the e-cigarette group showing noticeable metabolic alterations. Future studies should include larger sample sizes and be conducted across multiple centers to enhance generalizability. In addition, future studies might explore the metabolomic profiling of individuals exposed to secondhand e-cigarette smoke to better understand its potential health effects compared to e-cigarette vapers. The application of 1H-NMR metabolomic analysis holds promise for providing valuable insights into these interactions, as demonstrated by the success of previous investigations (Tajai et al., 2024).

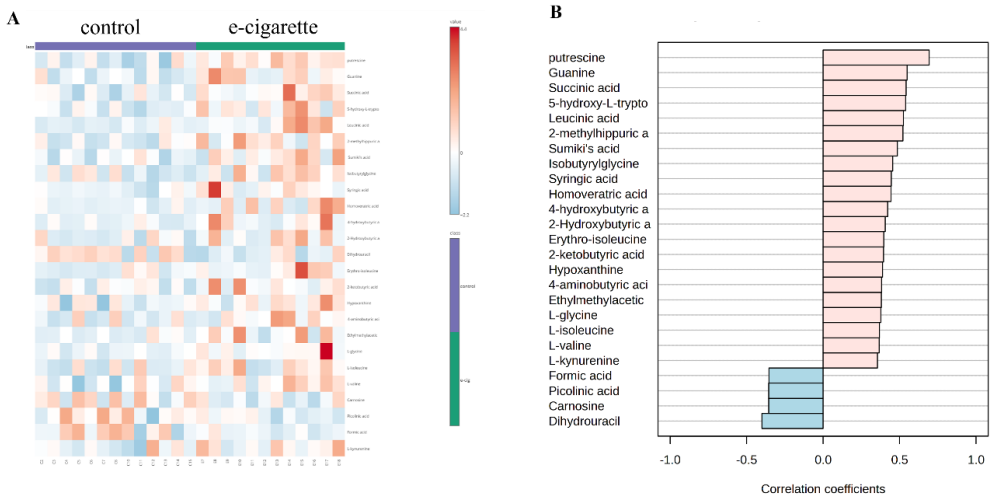

Figure 5. (A) Heatmaps show metabolite differences between e-cigarette users and controls, with columns representing samples and rows displaying the top 25 metabolites ranked by correlation. Colors range from red (high) to blue (low) based on normalized intensities. (B) A bar graph illustrates metabolic alterations, with Pearson correlation coefficients revealing distinct patterns consistent with heatmap trends.

5. Conclusion

In conclusion, the metabolomics analysis of urine samples reveals significant metabolic disruptions in e-cigarette users compared to the control group. The distinct separation observed in the PLS-DA plot, along with the high AUC value of 0.927 in the ROC analysis, underscores the strong differentiation between the two groups. Key metabolic alterations include increased oxidative stress, mitochondrial dysfunction, and inflammatory responses, as evidenced by changes in pathways such as glutathione metabolism, purine metabolism, and energy production pathways. Heatmap and correlation analyses further confirm these metabolic imbalances, highlighting specific metabolites that are significantly altered in e-cigarette users. These findings suggest that e-cigarette use may contribute to metabolic stress, cardiovascular risks, immune dysfunction, or even cancer, potentially leading to severe health consequences. The application of ^{1}H-NMR metabolomic analysis holds promise for providing valuable insights into these interactions, as demonstrated by the success of previous investigations (Tajai et al., 2024)

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