Pharmaciana
Vol.14, No.3, Nov 2024, Page.299-308
ISSN: 2088 4559; e-ISSN: 2477 0256
DOI: 10.12928/pharmaciana.v14i3.30005

Nicotine-free vape liquids containing essential oils of peppermint, lavender, and tangerine: safety and efficacy profile

Rahmad Aji Prasetya[1,3*], Djamilah Arifiyana[2], Zain Budi Syulthoni[4]
[1]Department of Pharmacy Practice, Akademi Farmasi Surabaya
[2]Department of Pharmaceutical Sciences, Akademi Farmasi Surabaya
Jl. Ketintang Madya No.81, Surabaya, Indonesia
[3]Faculty of Mathematics and Natural Sciences, Universitas Negeri Surabaya
Komplek Universitas Negeri Surabaya Gedung C5-C6,
Jl. Ketintang Selatan, Surabaya, Indonesia
[4]Psychiatrist, Medical Doctor Profession Education Study Program, Faculty of Medicine and Health,
Institut Teknologi Sepuluh Nopember
Gedung Fakultas Kedokteran dan Kesehatan, Kampus ITS Sukolilo, Surabaya, Indonesia

Submitted: 06-09-2024 ***Reviewed: 13-11-2024*** ***Accepted: 18-11-2024***

ABSTRACT

Despite low nicotine levels, cigarettes and vape liquids can cause addiction, which makes quitting smoking difficult owing to withdrawal syndrome. Hence, we created a nicotine-free liquid vape using essential oils (EOs) like peppermint (*Mentha piperita*), lavender (*Lavandula latifolia*), and tangerine (*Citrus reticulata*) to substitute the nicotine in inducing relaxation without addiction. Thus, this study aimed to examine (1) the safety profile of this nicotine-free liquid vape by observing chemical characteristics using gas chromatography-mass spectrometry (GC-MS) and (2) its efficacy in reducing short-term anxiety in healthy volunteers who had previously used nicotine vape. The most complicated vape liquid formula (F4), containing propylene glycol, vegetable glycerin, with those three EOs, was injected into GC-MS, and the mass spectra were compared to the Wiley mass spectral library to identify the compound name. For the efficacy test, subjects who met inclusion criteria and fulfilled informed consent were randomly assigned to five groups (four groups received test liquids formula (F1-F4) while one group received placebo). Before and after using the vape liquid, subjects were asked to complete the State-Trait Anxiety Inventory (STAI) questionnaire to assess its anxiety-reduction effects. The result showed that nicotine-free vape liquids containing three EOs did not show any foreign substances that had never been encountered before, which means our product is safer than nicotine-containing vape liquids. This safety was also supported by all study subjects who did not report any adverse effects. The efficacy test showed that subjects who used vape liquids with essential oils (F1-F4) experienced a significant decrease in heart rate and systolic blood pressure. At the same time, 50% had a lower post-test STAI score, indicating a decrease in anxiety, although it was not statistically significant.

Keywords: vape liquids, *Mentha spicata*, *Lavandula latifolia*, *Citrus reticulata*, anxiety, GC-MS

Corresponding author:
Rahmad Aji Prasetya
Faculty of Mathematics and Natural Sciences, Universitas Negeri Surabaya
Komplek Universitas Negeri Surabaya Gedung C5-C6
Jl. Ketintang Selatan, Surabaya, Indonesia
Email: rahmadprasetya@unesa.ac.id

INTRODUCTION

The current trend in Indonesia shows a noticeable rise in the number of active smokers over time. According to data from the 2021 Global Adult Tobacco Survey (GATS) initiated by the Ministry of Health, the population of adult smokers rose from 60.3 million in 2011 to 69.1 million in 2021 (Kemenkes RI., 2022). Moreover, Indonesia holds the highest number of smokers in the Southeast Asia region, as stated in The Tobacco Control Atlas ASEAN Region 4th Edition (Drope et al., 2018). The World Health Organization (WHO) implements multiple strategies to combat the tobacco epidemic. One of these strategies involves substituting traditional tobacco cigarettes with electronic cigarettes, also known as the Electronic Nicotine Delivery System (ENDS) or vape. By utilizing this particular cigarette variant, individuals can effectively regulate their nicotine use, enabling active smokers to quit smoking (Bullen et al., 2013). Conversely, in Indonesia, vape utilization is experiencing a significant rise. According to the 2018 National Basic Health Research (Riskesdas) data, the prevalence of e-cigarette usage among the Indonesian population was 2.8%. The highest proportion of e-cigarette users was found in the 10-14 year age group, with a rate of 10.6%, followed closely by 15-19 year olds at 10.5% (Badan Penelitian dan Pengembangan Kesehatan, 2019). This indicates that nicotine exposure and addiction are increasing among young people.

Nicotine, found in both tobacco cigarettes and vape, is an active compound that induces a feeling of relaxation but is also highly addictive. Nicotine has been demonstrated to cause heart diseases through oxidative stress, fibrosis, and inflammation, in addition to the risks associated with dependency. Nicotine exerts persistent effects on the brain and central nervous system in several organs, which potentially causes stroke (Moheimani et al., 2017; Ramalingam et al., 2021). Particularly in pregnant women, nicotine may hamper blood circulation to the fetus, posing a risk to fetal development and potentially leading to adverse outcomes upon birth, such as disabilities or growth retardation (Rodrigues et al., 2022). Regardless of the low nicotine levels in cigarettes or vape liquids, they can still lead to addiction due to the interaction between nicotine and nicotine cholinergic receptors in the brain. As a result, users may develop tolerance and require higher doses of nicotine over time (Hall et al., 2015). Furthermore, those who are dependent or addicted to nicotine have significant challenges when attempting to suddenly cease smoking due to withdrawal syndrome, characterized by symptoms such as agitation, anxiety, and potential psychological disorders (McLaughlin et al., 2015). Therefore, it necessitates a method for reducing the symptoms of drug withdrawal in individuals seeking to overcome nicotine addiction.

Recently, we developed a nicotine-free liquid vape containing essential oils (EOs) like peppermint (*Mentha piperita*), lavender (*Lavandula latifolia*), and tangerine (*Citrus reticulata*). This vape liquid has been formulated and rigorously tested to ensure it meets quality standards regarding homogeneity, compatibility, viscosity, and acceptability (Prasetya & Imtihani, 2023). The addition of essential oil is expected to function as a substitute for nicotine, inducing a sense of relaxation without the risk of addiction. In other applications, these EOs have been proven to relax patients in several conditions. For instance, studies conducted on patients following abdominal surgery or endoscopic procedures demonstrated that peppermint EO can effectively alleviate both pain and anxiety (Akbari et al., 2019). Lavender and citrus oils possess the capacity to relieve symptoms of anxiety, enhance mood, optimize sleep quality, augment cognitive capacities, and aid in the reduction of blood pressure, discomfort, and muscular spasms in both adults and children (Beyliklioğlu & Arslan, 2019; Koulivand et al., 2013). However, there is no study examining their efficacy in reducing anxiety in the form of vape liquid. In terms of safety, vaping is comparatively less hazardous than smoking traditional tobacco cigarettes; nonetheless, it can still have adverse effects (Mcneill et al., 2015). One factor contributing to this is the release of aldehyde molecules when propylene glycol and glycerin are heated (Mcneill et al., 2015). Hence, this study aimed to (1) examine the safety profile of this nicotine-free liquid vape by observing the chemical characteristics using gas chromatography-mass spectrometry and (2) investigate, for the first time, its efficacy in reducing short-term anxiety among several volunteers who had previously used nicotine vape.

MATERIALS AND METHOD

Materials

This study began with the preparation of vape liquid ingredients such as propylene glycol (PG) and vegetable glycerin (VG) (pharmaceutical grade), 100% pure peppermint, tangerine, and lavender EOs (PT. Syailendra Bumi Investama), vanilla essence, and sucralose (food grade). A hand mixer (Philips) was used to make the liquid. Gas Chromatography-Mass Spectroscopy (GC-MS) analysis was performed using GC-MS QP-2010 Shimadzu with Rtx-5MS capillary column for pure EOs analysis. For vape liquid analysis, ISQ™ 7610 Single Quadrupole Thermo Scientific GC-MS with TriPlus™ RSH SMART Autosampler and the 5% phenyl phase Thermo Scientific™ TraceGOLD™ TG-5MS column were used.

Methods

Vape liquids preparation and formulation

All ingredients mentioned above were mixed directly with a hand mixer to make a liquid based on the formulas stated in Table 1. Each liquid was made for single use with a volume of approximately 10.5 mL.

Table 1. Nicotine-free vape liquids formula

Ingredients	F1	F2	F3	F4	Control
Propylene glycol	7 mL	7 mL	7 mL	7 mL	7 mL
Vegetable glycerin	3 mL	3 mL	3 mL	3 mL	3 mL
EO lavender	15 µL	-		8 µL	-
EO peppermint	-	15 µL	-	8 µL	-
EO tangerine	-	-	15 µL	8 µL	-
Vanilla essence	0.4 mL	0.4 mL	0.4 mL	0.4 mL	0.4 mL
Sucralose	0.3 mg	0.3 mg	0.3 mg	1 mg	0.3 mg

Vape liquid compound characterization

In this study, three EOs and the most complex formula (F4) sample were characterized and analyzed for their compound content using GC-MS. The operating conditions used for pure EOs analysis were an injector temperature of 250°C and an oven temperature of 50°C (2.0 min hold), 10°C/min to 240 °C (10 min hold). The pressure is set at 8.8 Psi, and the capillary column is used. Helium gas is used for the gas carrier with a flow rate of 1.0 mL/min. Meanwhile, the headspace sampling technique was used for vape liquid analysis. A liquid sample (1 mL) was placed in a crimp-closed headspace vial with a magnetic bi-metal cap and a toped silicone septum. The sample was first agitated for 2-3 minutes with a temperature of 250°C before being injected through an autosampler. The operating conditions for GC were almost the same as the EO analysis except for the carrier gas flow rate of 0.5 mL/min. After the sample is injected and analyzed by gas chromatography, it is then analyzed using mass spectrometry. Subsequent identification was performed by comparing their recorded mass spectra with those contained in the Wiley mass spectral library of the GC-MS data system.

Efficacy examination of vape liquids in reducing anxiety levels

This first stage clinical trial was an experimental pre-post randomized controlled study. Ethical approval for this study was obtained from the University of Muhammadiyah Lamongan Ethics Committee for Medical Research with certificate number 337/EC/KEPK-S2/10/2023. The subject's criteria included adult males/females aged 18 years and older, had vaped nicotine liquids at least six

months before, and were currently healthy with no history of asthma or other chronic respiratory disorders. Subjects who were willing (filling out informed consent) and met the inclusion criteria were randomly divided into five groups. Group 1 received a vape liquid product according to F1, Group 2 received F2, Group 3 received F3, Group 4 received F4, and Group 5 received negative control (placebo). The provision of vape liquid products was carried out in a double-blind manner to maintain the objectivity of the effectiveness measurement. Before and after data collection, a general practitioner will check subjects' vital signs, like temperature, blood pressure, heart rate, and SpO2, to ensure their health condition. To reduce the risk of allergies, subjects will be asked to drip vape liquid on the skin of the arm before use. If there was an allergic reaction, such as itching or redness, the subject could switch to another formula or be excluded from the study. Following the allergy check, subjects were allowed to use the assigned formula of vape liquids for around 10-15 minutes using their own devices, either mods or pods. To examine the efficacy of the vape liquid in producing a sense of relaxation and reducing anxiety levels, subjects were asked to fill out the State-Trait Anxiety Inventory (STAI) questionnaire before and after using the vape. STAI questionnaire is a tool utilized to assess both actual state anxiety and persistent trait anxiety. The scale assessment for state anxiety comprises 20 items that enquire about subjects' emotions, such as tension, dread, worry, and restlessness. The trait scale comprises 20 items designed to assess anxiety as a characteristic. The STAI questionnaire consists of four Likert scales for each item, and higher scores indicate greater anxiety (Beyliklioğlu & Arslan, 2019). In this work, we utilized a translated version of the STAI in Bahasa Indonesia that has undergone rigorous testing to establish its validity and reliability (Khoiriyah, 2021).

Data Analysis

The statistical analysis was determined by paired t-test and Wilcoxon test (for paired data that did not pass the normality test) to determine significant differences between pre and post-data. Meanwhile, unless stated otherwise, the Kruskal-Wallis test was used to examine group differences. Data analysis and visualization were performed using GraphPad Prism version 8.0.1 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com; $p<0.05$ was considered significant.

RESULT AND DISCUSSION

Nicotine-free vape liquid compound characterization

The GC-MS examination of the compound content in F4 vape liquid containing three essential oils revealed 37 peaks on the chromatogram with concentrations higher than 0.01% (Figure 1). The main compounds (relative percentage >3%) found in the vape liquid were (R)-(-)-2-amino-1-propanol (peak #1&2), D-limonene (peak #13), eucalyptol (peak #14), linalool (peak #18), cyclohexanone (peak #23&25), levomenthol (peak #26), and linalyl acetate (peak #31). The complete list of the identified components is shown in Table 2. The first and second peaks were identified as (R)-(-)-2-Amino-1-propanol, which was probably formed by the pyrolysis mechanism of propylene glycol and glycerol. Further decomposition and oxidation of PG and VG due to thermal conditions yielded several compounds such as acetone, propanoic acid, and butanoic acid (peak #4, 6, and 8, respectively), which accounted for around 12% of vape liquid composition in total (Li et al., 2021; Liang et al., 2022).

By using the headspace sampling technique, the sample was first heated and turned into aerosol before being auto-injected. This method successfully separated the liquid components from the 3 EOs used in the nicotine-free vape liquid (F4). For instance, compounds found in this study, such as ß-myrcene, 3-octanol, o-cymene, D-limonene, trans-linalool oxide, linalool, limonene oxide, trans-, 1,2-dihydro linalool, terpinene-4-ol, a-Terpineol, and linalyl acetate, have been proven contained in lavender as stated by Dong et al. (2020). Our finding about compounds commonly found in peppermint was also in line with Shahbazi's (2015) study, including ß-myrcene, limonene, menthone (Cyclohexanone,5-methyl-2-(1-methyl ethyl)-, cis-) and its derivate, levomenthol, and pulegone. Meanwhile, compounds like eucalyptol, linalool, a-terpineol, sabinene (Bicyclo[3.1.0] hexane,4-methylene-1-(1-methylethyl)-),

octacosane, heptacosane were commonly contained in tangerine or citrus essential oils (Mahmood et al., 2017; Yabalak et al., 2022).

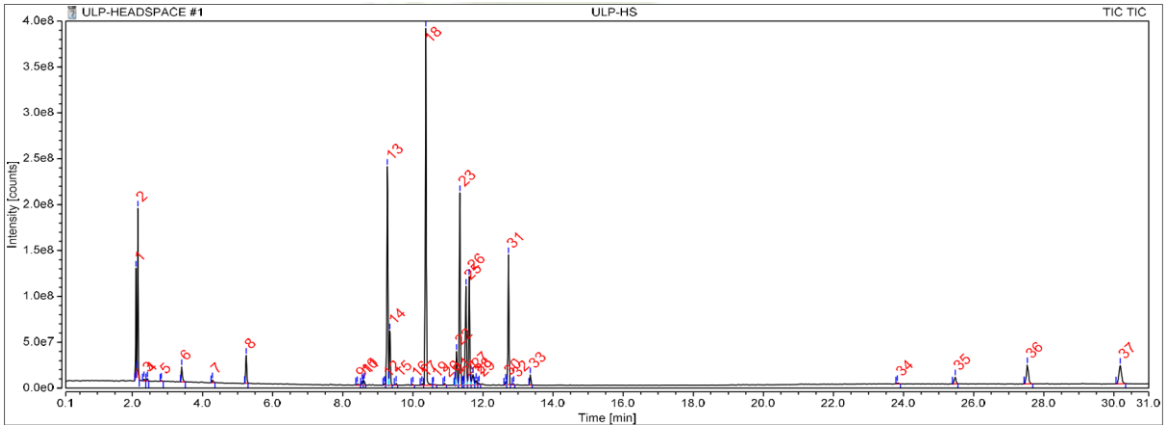

Figure 1. Chromatogram of GC analysis of nicotine-free vape liquid formula with 3 EOs (F4)

Table 2. Identified compounds of nicotine-free vape liquid formula with 3 EOs (F4) by GC-MS

Peak number	Retention time	Compound name	SI	Prob. (%)	Relative area (%)
1	2.100	(R)-(-)-2-Amino-1-propanol	79.2	91.34	3.40
2	2.155	(R)-(-)-2-Amino-1-propanol	80.3	49.15	5.47
3	2.332	Propanamide, 2-hydroxy-	72.2	88.12	0.16
4	2.427	Acetone	60.2	29.73	0.16
5	2.821	L-Alanine, N-acetyl-	56.8	39.39	0.09
6	3.406	Propanoic acid, 2-oxo-	73.4	29.56	1.16
7	4.280	Propanamide, 2-hydroxy-	67.8	55.63	0.22
8	5.246	Butanoic acid, ethyl ester	90.2	94.91	1.77
9	8.419	Bicyclo[3.1.0]hexane, 4-methylene-1-(1-methylethyl)-	68.7	18.00	0.13
10	8.562	ß-Myrcene	77.2	31.24	0.25
11	8.613	3-Octanol	74.4	61.36	0.28
12	9.195	o-Cymene	71.0	28.86	0.12
13	9.273	D-Limonene	93.1	37.45	13.79
14	9.345	Eucalyptol	93.0	82.50	3.53
15	9.521	a-Pinene	71.7	12.47	0.13
16	10.001	trans-Linalool oxide (furanoid)	65.8	19.44	0.08
17	10.259	Cyclohexene, 1-methyl-4-(1-methylethylidene)-	64.2	5.67	0.15
18	10.372	Linalool	92.6	70.69	22.13
19	10.583	Limonene oxide, trans-	67.2	18.44	0.10
20	10.906	1,2-Dihydrolinalool	67.9	22.15	0.12
21	11.205	Isopulegol	83.4	31.03	0.18
22	11.249	Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl-, (1S)-	91.9	43.42	2.47
23	11.341	Cyclohexanone, 5-methyl-2-(1-methylethyl)-, cis-	94.1	44.43	12.44
24	11.433	endo-Borneol	69.0	27.79	0.14
25	11.514	Cyclohexanone, 5-methyl-2-(1-methylethyl)-, cis-	90.1	43.64	7.68
26	11.606	Levomenthol	94.8	44.83	7.22

Peak number	Retention time	Compound name	SI	Prob. (%)	Relative area (%)
27	11.715	Terpinen-4-ol	80.9	33.75	1.12
28	11.804	Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1a,2a,5a)-	78.2	19.95	0.33
29	11.892	a-Terpineol	67.0	5.34	0.14
30	12.647	Pulegone	74.9	28.19	0.24
31	12.729	Linalyl acetate	89.6	22.14	7.56
32	12.875	2-Cyclohexen-1-one, 3-methyl-6-(1-methylethyl)-	69.2	56.57	0.09
33	13.354	Cyclohexanol, 5-methyl-2-(1-methylethyl)-, acetate	85.3	27.92	0.64
34	23.826	Digitoxin	58.0	11.41	0.14
35	25.472	Dotriacontane	76.4	15.41	0.82
36	27.530	Octacosane	83.3	10.89	2.57
37	30.180	Heptacosane	82.8	9.69	2.98
				Total	100

*SI = Similarity Index

The results of GC-MS analysis on pure peppermint EO without solvents (Figure 2) showed the presence of menthone (peak #4), L-(-)-menthol (peak #5, 6, and 8), limonene (peak #2), beta-pinene (peak #1), and pulegone (peak #7) compounds with similarity index of 98, 99, 94, 90, and 92, respectively. Likewise, the mixture of lavender and tangerine EOs (Figure 3) has been proven to contain compounds similar to previous results, including limonene (peak #1), linalool (peak #2), camphor (peak #3), and linalyl acetate (peak #4) with similarity index of 96, 97, 93, and 97, respectively. Taken together, both compound analysis results of nicotine-free vape liquid and pure EOs used as raw materials did not show any foreign substances that had never been encountered before. This indicates that our product has a better safety level than nicotine-containing vape liquids available on the market.

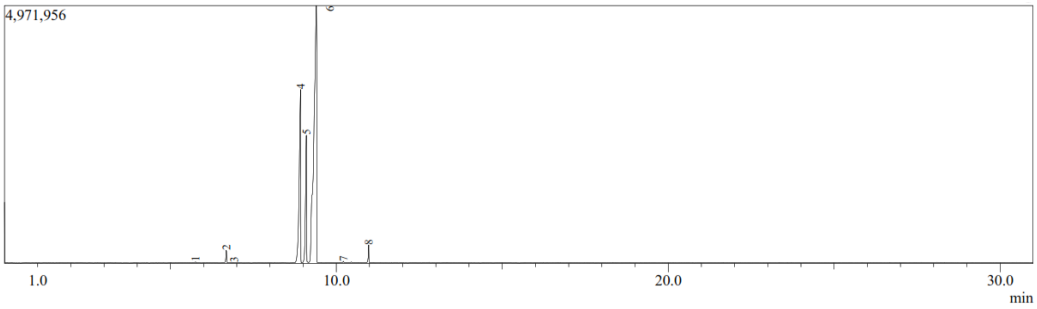

Figure 2. Chromatogram of GC analysis of EO peppermint

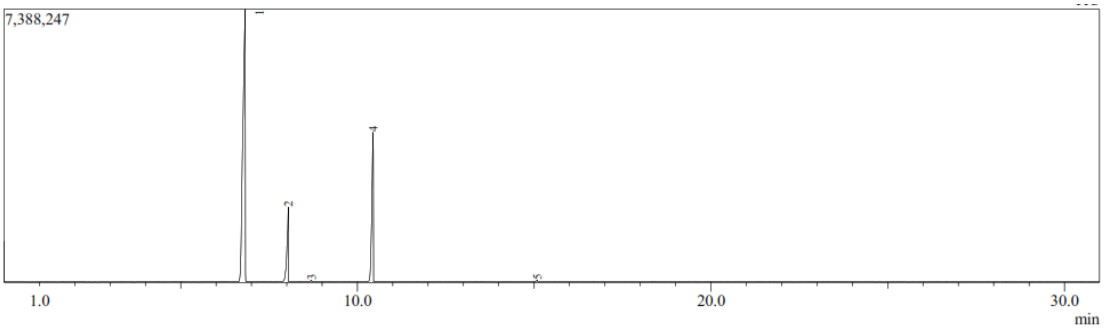

Figure 3. Chromatogram of GC analysis of mixed EOs lavender and tangerine

Efficacy examination of vape liquids in reducing anxiety levels

There were 32 participants who signed up voluntarily, but only 30 were eligible and randomized to 5 groups equally (6 participants in each group). Most of them were students with an average age of 22 years old and used pods (83.3%) as their vaping devices. There was actually one female who enrolled in this study, but she did not pass the health screening due to a history of asthma (Table 3). Then, the result of the efficacy examination showed that 50% of subjects who used vape liquid containing essential oils (F1-F4) experienced a decrease in anxiety levels, as indicated by a lower post-test STAI score. Unfortunately, statistical analysis revealed no significant difference in STAI scores, both between before and after using nicotine-free vape liquid and between the control and test vape liquid (F1-F4). The full results can be seen in Figure 4.

Table 3. Sociodemographic data of the subjects (n=30)

Variable	Frequency	%
Gender		
Male	30	100
Female	0	0
Age (year)		
18-24	26	86.7
25-37	4	13.3
Occupation		
Student	24	80
Private employee	5	16.7
Entrepreneur	1	3.3
Type of vape device		
Mods	25	83.3
Pods	5	16.7

The absence of a significant change in the anxiety levels of the subjects could be caused by several things, including the relatively short treatment so that it did not have a significant impact. The typical user of an electronic cigarette vaped between 60 and 90 puffs in a day (Yingst et al., 2020). The subjects in this study only used vape for ten minutes or about ten to fifteen puffs. In another study related to interventions for reducing stress and anxiety, a decrease in anxiety levels was only observed after the treatment was administered for at least four weeks (Ponzo et al., 2020). The interaction between the treatment subjects during data collection can also affect the anxiety levels of the research subjects. The emotions of the subjects can be influenced by others during data collection. This is in line with a study on the influence of emotional contamination on a social group (Herrando & Constantinides, 2021). In this study, a decrease in anxiety levels was still observed, although it was not statistically significant. This decrease aligns with the findings of other studies that used essential oils such as lavender and peppermint in inhalers, which can reduce anxiety levels in patients in the Intensive Care Unit (ICU) (Karimzadeh et al., 2021).

Table 4 depicted that subjects who vaped with liquid containing essential oil(s) experienced a significant ($p<0.001$) decrease in heart rate and systolic blood pressure but not in diastolic blood pressure. Meanwhile, the control group also showed a decrease in those parameters but not significant ($p>0.05$). This was in line with a study using lavender as inhaled aromatherapy for patients before angiography (Ziyaeifard et al., 2017). Furthermore, regarding acceptability, the subjects said the vape liquid products they tried were well-accepted. Besides, no side effects were experienced by all of the research subjects when using this nicotine-free vape liquid, such as allergic reactions, shortness of breath, or a burning sensation in the respiratory tract.

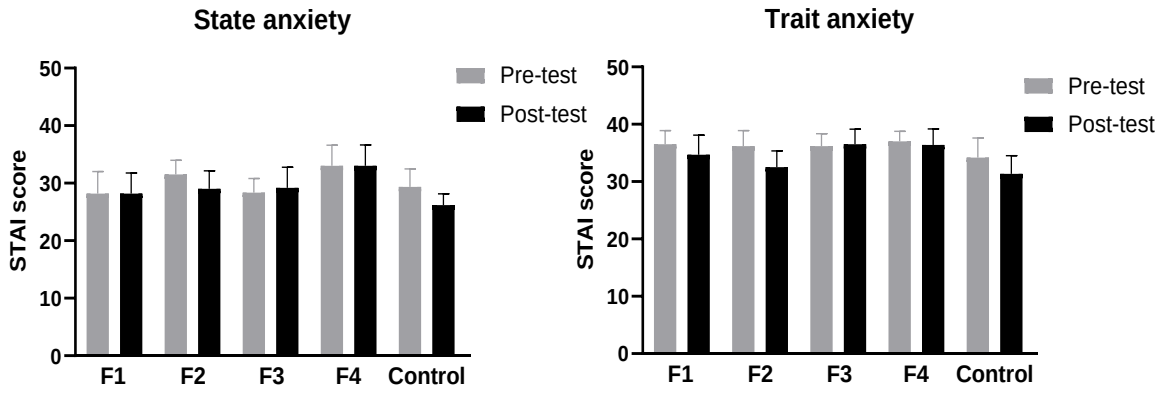

Figure 4. State anxiety (left) and trait anxiety (right) score differences between groups according to the STAI questionnaire. Data are presented in average ± standard error of the mean (SEM)

Table 4. Hemodynamic monitoring data of the subjects

Variables		Control group (n=6) ± SEM	F1-F4 groups (n=24) ± SEM	p-value*
Heart rate (beat/min)	pre-test	91.00±3.31	94.46±2.58	0.55
	post-test	87.67±4.33	87.92±2.85	0.65
	p-value	0.26	**0.0009*** **	
Blood pressure				
Systole (mmHg)	pre-test	119.80±5.05	117.1±3.38	0.75
	post-test	115.20±7.91	109.5±2.38	0.60
	p-value	0.54	**0.0009*** **	
Diastole (mmHg)	pre-test	74.67±5.91	73.83±2.18	0.48
	post-test	80.83±8.92	71.00±1.74	0.39
	p-value	0.32	0.10	

*p-value was analyzed between control and treatment (F1-F4) groups using the Mann-Whitney test
***p<0.001

However, this study has limitations, such as a small sample size in each group and the protocol for measuring anxiety levels. Further examination of liquid vape efficacy should be performed for a longer duration to see whether the liquid can produce relaxed feelings and lessen nicotine addiction. The procedure for measuring anxiety could be improved by allowing each subject to use the liquid without communicating with others to avoid emotional contamination and bias when fulfilling the questionnaire.

CONCLUSION

To conclude, we reported the safety profile for the first time based on the results of GC-MS analysis, which proved that no foreign compounds were found in a nicotine-free vape liquid as it contained in other commercial vape liquids. This safety is also supported by all study subjects who did not report any adverse effects. Regarding the efficacy of this liquid, it can be said that some subjects experienced lower anxiety levels, indicated by lower scores on the post-test STAI questionnaire, though not significant, and decreased heart rate and systolic blood pressure.

ACKNOWLEDGEMENT

This research received funding from the Akademi Farmasi Surabaya's internal research scheme and the Directorate of Vocational Education, Ministry of Education, Culture, Research, and Technology through the Junior Lecturer Research (PDP) Scheme 2024.

REFERENCES

Akbari, F., Rezaei, M., & Khatony, A. (2019). Effect of peppermint essence on the pain and anxiety caused by intravenous catheterization In cardiac patients: a randomized controlled trial. *Journal of Pain Research*, *12*, 2933. https://doi.org/10.2147/JPR.S226312

Badan Penelitian dan Pengembangan Kesehatan. (2019). *Laporan Nasional Riskesdas 2018*.

Beyliklioğlu, A., & Arslan, S. (2019). Effect of Lavender oil on the anxiety of patients before breast Surgery. *Journal of PeriAnesthesia Nursing*, *34*(3), 587–593. https://doi.org/10.1016/J.JOPAN.2018.10.002

Bullen, C., Howe, C., Laugesen, M., McRobbie, H., Parag, V., Williman, J., & Walker, N. (2013). Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet (London, England)*, *382*(9905), 1629–1637. https://doi.org/10.1016/S0140-6736(13)61842-5

Dong, G., Bai, X., Aimila, A., Aisa, H., & Maiwulanjiang, M. (2020). Study on Lavender Essential Oil Chemical Compositions by GC-MS and Improved pGC. *Molecules*, *25*(14), 3166. https://doi.org/10.3390/molecules25143166

Drope, J., Schluger, N., Cahn, Z., Drope, J., Hamill, S., Islami, F., Liber, A., Nargis, N., & Stoklosa, M. (2018). The tobacco atlas. sixth edition. consumption. In *American Cancer Society and Vital Strategies* (Issue March).

Hall, F. S., Der-Avakian, A., Gould, T. J., Markou, A., Shoaib, M., & Young, J. W. (2015). Negative affective states and cognitive impairments in nicotine dependence. *Neuroscience & Biobehavioral Reviews*, *58*, 168–185. https://doi.org/10.1016/J.NEUBIOREV.2015.06.004

Herrando, C., & Constantinides, E. (2021). Emotional contagion: a brief overview and future directions. *Frontiers in Psychology*, *12*. https://doi.org/10.3389/fpsyg.2021.712606

Karimzadeh, Z., Azizzadeh Forouzi, M., Rahiminezhad, E., Ahmadinejad, M., & Dehghan, M. (2021). The effects of Lavender and Citrus aurantium on anxiety and agitation of the conscious patients in intensive care units: a parallel randomized placebo-controlled trial. *BioMed Research International*, *2021*, 1–8. https://doi.org/10.1155/2021/5565956

Kemenkes RI. (2022). *Perokok dewasa di Indonesia meningkat dalam sepuluh tahun terakhir - badan kebijakan pembangunan kesehatan*. 3 Juni.

Khoiriyah, S. N. (2021). Perbedaan tingkat kecemasan mahasiswa Lulusan SMA dam MA dalam Menghadapi Pelajaran Bahasa Arab pada Fakultas Ushuluddin dan Humaniora UIN Walisongo Semarang Angkatan 2018. In *Skripsi*. Universitas Islam Negeri Walisongo Semarang.

Koulivand, P. H., Ghadiri, M. K., & Gorji, A. (2013). Lavender and the nervous system. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 1–10. https://doi.org/10.1155/2013/681304

Li, Y., Burns, A. E., Tran, L. N., Abellar, K. A., Poindexter, M., Li, X., Madl, A. K., Pinkerton, K. E., & Nguyen, T. B. (2021). Impact of e-liquid composition, coil temperature, and puff topography on the aerosol chemistry of electronic cigarettes. *Chemical Research in Toxicology*, *34*(6), 1640–1654. https://doi.org/10.1021/acs.chemrestox.1c00070

Liang, J., Zhang, D., Cao, Y., Xue, K., Xia, Y., & Qi, Z. (2022). Insight into pyrolysis mechanism of 1,2-propylene glycol: based on density functional theory and wavefunction analysis. *Journal of Molecular Graphics and Modelling*, *116*, 108277. https://doi.org/10.1016/j.jmgm.2022.108277

Mahmood, R., Ahmad, S., Jaskani, M. J., & Ahmad, R. (2017). Topographicallocation of orchards modulates the biochemical composition of essential oils in citrus fruit peel. *Pakistan Journal of Agricultural Sciences*, *54*(3), 635–643. https://doi.org/10.21162/PAKJAS/17.6417

McLaughlin, I., Dani, J. A., & De Biasi, M. (2015). Nicotine Withdrawal. In *Current Topics in Behavioral Neurosciences* (Vol. 24, pp. 99–123). Springer, Cham. https://doi.org/10.1007/978-3-319-13482-6_4

Mcneill, A., Brose, L. S., Calder, R., Hitchman, S. C., Hajek, P., & H, M. (2015). E-cigarettes : an evidence update A report commissioned by Public Health England. In *Public Health England*. Public Health England.

Moheimani, R. S., Bhetraratana, M., Peters, K. M., Yang, B. K., Yin, F., Gornbein, J., Araujo, J. A., & Middlekauff, H. R. (2017). Sympathomimetic effects of acute e-cigarette use: role of nicotine and non-nicotine constituents. *Journal of the American Heart Association*, *6*(9). https://doi.org/10.1161/JAHA.117.006579

Ponzo, S., Morelli, D., Kawadler, J. M., Hemmings, N. R., Bird, G., & Plans, D. (2020). Efficacy of the digital therapeutic mobile app bioBase to reduce stress and improve mental well-being among university students: randomized controlled trial. *JMIR MHealth and UHealth*, *8*(4), e17767. https://doi.org/10.2196/17767

Prasetya, R. A., & Imtihani, H. N. (2023). Formulasi dan evaluasi Likuid Vape tanpa Nikotin dengan Kandungan Minyak Atsiri Pepermin (Mentha spicata), Jeruk (Citrus reticulata) dan Lavender (Lavandula angustifolia). *Journal of Herbal, Clinical and Pharmaceutical Science (HERCLIPS)*, *5*(01), 34. https://doi.org/10.30587/herclips.v5i01.6380

Ramalingam, A., Budin, S. B., Mohd Fauzi, N., Ritchie, R. H., & Zainalabidin, S. (2021). Targeting mitochondrial reactive oxygen species-mediated oxidative stress attenuates nicotine-induced cardiac remodeling and dysfunction. *Scientific Reports*, *11*(1), 13845. https://doi.org/10.1038/s41598-021-93234-4

Rodrigues, V. da S. T., Miranda, R. A., Soares, P. N., Peixoto, T. C., de Oliveira, E., Manhães, A. C., de Moura, E. G., & Lisboa, P. C. (2022). Neonatal nicotine exposure changes insulin status in fat depots: sex-related differences. *Journal of Developmental Origins of Health and Disease*, *13*(2), 252–262. https://doi.org/10.1017/S2040174421000131

Shahbazi, Y. (2015). Chemical composition and in vitro antibacterial activity of Mentha spicata essential oil against common food-borne Pathogenic Bacteria. *Journal of Pathogens*, *2015*, 1–5. https://doi.org/10.1155/2015/916305

Yabalak, E., Erdoğan Eliuz, E. A., & Nazlı, M. D. (2022). Evaluation of Citrus reticulata essential oil: Chemical composition and antibacterial effectiveness incorporated gelatin on E. coli and S. aureus. *International Journal of Environmental Health Research*, *32*(6), 1261–1270. https://doi.org/10.1080/09603123.2021.1872059

Yingst, J., Foulds, J., Veldheer, S., Cobb, C. O., Yen, M. S., Hrabovsky, S., Allen, S. I., Bullen, C., & Eissenberg, T. (2020). Measurement of electronic cigarette frequency of use among smokers participating in a randomized controlled trial. *Nicotine and Tobacco Research*, *22*(5), 699–704. https://doi.org/10.1093/ntr/nty233

Ziyaeifard, M., Azarfarin, R., Faritous, Z., Dehdashtian, E., Baghestani, ; Amir, Ziyaeifard, P., & Yousefi, Z. (2017). Evaluation of lavender oil inhalation effects on blood pressure and heart rate in patients undergoing coronary Angiography. *Iranian Heart Journal*, *18*(4), 29–33.