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SURAT KETERANGAN

Nomor: 1551/UNUSA-LPPM/Adm.I/VIII/2022

Lembaga Penelitian dan Pengabdian Kepada Masyarakat (LPPM) Universitas Nahdlatul Ulama Surabaya menerangkan telah selesai melakukan pemeriksaan duplikasi dengan membandingkan artikel-artikel lain menggunakan perangkat lunak **Turnitin** pada tanggal 16 Agustus 2022.

Judul	: Toxicology properties of commercial anti-mosquitos and their effects on carboxyhemoglobin and malondialdehyde levels
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No. Pemeriksaan	: 2022.08.18.555

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Submission date: 12-Aug-2022 05:42PM (UTC+0700)
Submission ID: 1881717015
File name: FINAL_Fullpaper_EQM.docx (71.45K)
Word count: 3682
Character count: 21787

Toxicology properties of commercial anti-mosquitos and their effects on carboxyhemoglobin and malondialdehyde levels

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Abstract

Exposure of carbon monoxide (CO) released by insect repellent has a negative impact on health by forming carboxyhemoglobin (CO-Hb) as a trigger for oxidative stress in the human body. Therefore, the objective of the study was to investigate the effect of commercial anti-mosquitos on CO-Hb and malondialdehyde (MDA) levels in the blood. Effect of electric spray, coils, and electric mats on CO-Hb and MDA levels in blood was evaluated using male Wistar rats (8 hours per day) and monitored for 20 days. The study found that the highest increase in CO-Hb and CO-Hb levels in the blood was observed when exposed to electric spray formula compared to other anti-mosquitos. In addition, the highest increase in MDA levels also occurred when exposed to the

electric spray. Statistical analysis revealed that there was a significant relationship between CO-Hb and MDA levels in the blood (p-value = 0.000). High CO-Hb levels in the blood could stimulate oxidative stress and lead to cell damage in the body.

Keywords: Anti-Mosquito, Carboxyhemoglobin, Malondialdehyde

1. Introduction

People worldwide use insect repellent as protection of mosquito bites that could cause several diseases such as dengue fever, malaria, zika, chikungunya, and yellow fever (Tavares et al., 2018). The insect repellent utilization is quite high across the world, especially in tropical and subtropical regions considering vulnerable environment for mosquitos breeding (Al-Damegh, 2013). Indonesia geographical area is suitable for the life and development of various types of mosquitoes that act as disease vectors. In many areas, heavy rainfall makes it very easy for mosquitoes to breed. Various types of mosquito repellent formulas available in the market consist of sprays, lotions, liquids electric, mats electric, and coils. Prior research related to mosquito repellent formulas use attended by 83 respondents in the Special Capital Region of Jakarta and Depok city, Indonesia, found that they used 32.5% lotion, 26.5% spray, 18.1% spray, 15.7% electricity, and 1.2% fuel. The perceived safety based on the types of mosquitos repellent by respondents were 31% lotion, 30% electric, 15% emulsion spray, and 12% liquid spray (Wahyono & Oktarinda, 2016).

The chemical compounds used in mosquito repellents mostly are pyrethroid, N, N-Diethyl-3-methylbenzamide (DEET), ethyl 3-[acetyl(butyl)amino]propanoate (IR3535), picaridin, and essential oils (Deletre et al., 2019; Elsayed & Hassabo, 2022; Tavares et al., 2018). The pyrethroid

compound type in insect repellent includes deltamethrin (α-cyano pyrethroid with phenoxy benzyl moiety), permethrin (phenoxy benzyl pyrethroid without -cyano group), transfluthrin, dimefluthrin, metofluthrin, and meperfluthrin (polyfluorinated benzyl compounds), and prallethrin (a modified cyclopentadione compound) (Sarkar et al., 2018; Yuan et al., 2019). The previous study revealed dimefluthrin, metofluthrin, and meperfluthrin in insect repellent had higher efficacy defences against mosquitoes (Sarkar et al., 2018). Other research investigated dimefluthrin volatile had multiple and cross-resistance both target-site and metabolic resistant mechanism in mosquitos than volatile of metofluthrin, meperfluthrin, esbiothrin and deltamethrin (Yuan et al., 2019). The dimefluthrin usage in mosquito repellent products in Indonesia reaches around 30.4% (Maksud et al., 2019) due to dimefluthrin having better mosquito control ability than D-allethrin based on knockdown time (Ogoma et al., 2012). Dimefluthrin is a pyrethroid group with a broad spectrum, active in sodium channel modulators which will cause the sodium gate to be more sensitive to stimuli that paralyze mosquitoes (Du et al., 2016).

Insect repellent exposure, especially mosquito coils, can produce pollutants in the form of carbon monoxide (CO) which can bind hemoglobin (Hb) in the blood to form carboxyhemoglobin (CO-Hb) which leads to the Hb function inhibition in distributing oxygen to all body cells. As a result, body tissues not obtained an adequate supply of oxygen (O_2) (Mao et al., 2021). This condition promotes oxidative stress in the body, causing increased levels of Malondialdehyde (MDA) in blood serum (Flores et al., 2017). MDA is a product of membrane phospholipid catabolism which is a sign of oxidative stress (Andini et al., 2021). The macrophages release heme oxygenase and oxygen-dependent cysteine transporters as protection against reactive oxygen species (ROS) during oxidative stress (Duvigneau et al., 2019). However, prolonged insect repellent pollutant exposure in the body lead to biological health impact (Handore et al., 2019;

Madhubabu & Yenugu, 2012, 2017; Syafiuddin et al., 2017). Therefore, this study aimed to investigate the effect of mosquito repellent on electric mats, electric liquids, and coils containing dimefluthrin in various concentrations in serum MDA and CO-Hb levels.

2. Materials and Methods

2.1 Materials

The study was an experimental study. The samples were 2–3-month-old Wistar rats and weighing 150 gr-250 gr. Among 30 male rats were divided into 3 groups randomly, namely E which was exposed to anti-mosquito electric spray containing 0.610% dimefluthrin, C which was exposed to anti-mosquito coils containing 0.031% dimefluthrin, and M which was given anti-mosquito electric mats exposure containing 0.566% dimefluthrin. Each group was exposed at daytime for 20 days (8 hours per day). This study had approved ethical clearance through No. 062/EC/KEPK/UNUSA/2021.

The equipment was used in this study were a digital balance, cage made of wire, rat feeder set, drinking bottles during the treatment and intervention process. Blood sampling was conducted by using a 2cc Terumo syringe. The serum preparation was carried out by using a centrifuge and a centrifuge tube. Meanwhile, the tools used for CO-Hb and MDA were Thermo Scientific UV-VIS Spectrophotometer and cuvette.

This study utilized several materials such as husks, water, and rat feed. Intervention activities used an exposure of insect repellent included electric spray, coils, and electric mats. Solution for CO-Hb test using ammonium hydroxide (NH_4OH) and sodium dithionite ($Na_2S_2O_4$), while the solutions for the MDA test included 50% glacial acetic acid, acid solution, 20% trichloroacetic acid (TCA), and 0.67% thiobarbituric acid (TBA) solution.

2.2 Carboxyhemoglobin (CO-Hb) Assay

The CO-Hb level test was performed using the Hinsberg-Lang method. As the preparation of samples, 20 ml of 0.1% NH_4OH solution was put into an Erlenmeyer and 10 L of blood sample was added and homogenized (sample). Afterwards, 4 ml samples were taken and put into 2 test tubes, namely R (Reagent) and SR (Sample Reagent). Twenty (20) mg Na_2S_2O4 was added in the RS tube and homogenized. The R and SR tubes were incubated at 37°C for 8 minutes and the absorbance R and RS was measured with a spectrophotometer at a wavelength of 414.2 nm. The carboxyhemoglobin (CO-Hb) levels calculation using the following equation.

$$COHb\ Levels = \frac{\Delta A}{\Delta\ Ar\ Hb}\ x\ 6{,}08\% \quad \text{..... (1)}$$

Where Δ A is the reagent absorbance , Δ Ar is the standard sample absorbance and 6.08 is the conversion factor for percent CO saturation in Hb (Wimpy & Harningsih, 2019).

2.3 MDA Assay

In this experiment, the MDA assay was conducted based on the proposed method by Wulandari et al (2020) and Andini et al (2020). Serum MDA levels were measured in several steps such as 0.3 mL serum of P1, P2, and P3 were added 1.0 mL of 20% TCA serum and 1.0 mL of 1% TBA serum in 50% glacial acetic acid, then incubated for 45 minutes at 95°C and allowed to cool down for 15 minutes. The sample solution reagent was centrifuged at 1000 rpm. Subsequently, the supernatant was separated and absorbance was measured using a spectrophotometer with a wavelength of 532 nm. The MDA level was acquired after determining the standard curve and calculating it according to the resulting equation (Andini et al., 2020).

116 2.4 Statistical Analysis

117 The CO-Hb levels, increase in CO-Hb and MDA levels were analyzed using the One-Way
118 ANOVA test for parametric data and Kruskal Wallis test for non-parametric data (Ostertagova et
119 al., 2014)(Van Hecke, 2010). To determine the significant difference between one group and
120 another, the Post Hoc test for parametric data and the Mann Whitney test for non-parametric data
121 was used (Vickers, 2005). The correlation of CO-Hb and MDA levels used the Spearman test for
122 non-parametric data.

123

124 **3. Results and Discussion**

125 3.1 The effect of anti-mosquitos on CO-Hb

126 The highest levels of CO-Hb in the blood due to insect repellent exposure occurred in 0.100
127 % electric fluid, then coils and electric mats at the same level of 0.059%. Based on the CO-Hb
128 levels increase in the blood, electric spray exposure increased CO-Hb up to 2.858%, while coils
129 were 1.696% and electric mats were 1.681% (table 1). The result showed that exposure to electric
130 spray potentially increases CO-Hb levels in comparison to coils and electric mats. Based on one-
131 way Anova statistical analysis obtained significant differences in CO-Hb levels and enhancement
132 of CO-Hb in all exposure groups. Further analysis was conducted to determine the significant
133 differences of each group by using a post hoc test. The test showed that electric spray with higher
134 dimefluthrin content had significant differences on CO-Hb levels compared to coils and electric
135 mats, but coils and electric mats had no significant differences (table 2 and table 3). Therefore,
136 electric spray exposure had a significant effect in CO-Hb levels in blood.

137 CO can interfere the oxygen-carrying by Hb to vital organs and tissues, causing stress that
138 lead to organ's malfunction and failure (Chen et al., 2021; Röhrig, 2016). Lack of oxygen would

increase Hb levels in the blood as the body's adjustment to low levels of oxygen bound to Hb because CO has a stronger affinity for Hb. CO enters the body through the respiratory system diffuses together with O_2 through the alveolus membrane. Both dissolved in the blood, CO combines with hemoglobin to form CO-Hb. The CO and Hb binding occur at the same rate as for O_2 and CO. But CO binds to Hb 245 times stronger than O_2. Therefore, CO and O_2 compete for binding to hemoglobin. CO binds longer than oxygen, which easy to break away from hemoglobin (Dewanti, 2018). The hemoglobin desaturation and a lack of oxygen supply condition to all body tissues promote the mechanism for increasing Hb (Röhrig, 2016). Therefore, CO activates the oxygen site in Hb, interferes the oxygen, and initiates calcification or thickening of blood vessel walls. Thus, CO decreases capacity, increases blood viscosity, facilitates blood clotting, increases blood hemoglobin levels (Chan et al., 2013; Röhrig, 2016).

3.2 The effect of anti-mosquitos on MDA

The MDA results assay showed that the highest serum MDA levels occurred in rats with electric spray exposure at 221.380 ng L^{-1}, followed by mat exposure at 75.548 ng L^{-1} and electric coils at 73.365 ng L^{-1}. These results showed that electric spray had a greater effect on increasing serum MDA levels in the exposure group. Statistical data analysis obtained significant differences in MDA levels in all exposure groups (table 4). Furthermore, the Mann Whitney test showed that electric spray had a significant difference, while in the coil and electric mat group had no significant difference (table 5). Therefore, dimefluthrin compounds in mosquito repellent not only affect the CO-Hb levels, but also MDA levels in blood.

Oxidative stress is an imbalance condition of free radicals such as ROS and nitrous oxide systems (NOS) against anti-oxidants that causes the cell and tissue damage. ROS activity can be

measured by determining MDA. During oxidative stress, macrophages secrete oxygen-dependent heme oxygenase and cysteine transporters to protect against ROS. Free radicals in the body can damage cells such as hyperplasia conditions or abnormal cell growth. The CO and Hb bond is stronger that could not easily be broken by antioxidants (Dewanti, 2018; Flores et al., 2017). CO is a toxic pollutant that enhancing cell damage to oxidative stress and inflammation (Boehm et al., 2018). Numerous cases of morbidity and mortality in toxicological cases are caused by carbon monoxide poisoning (COP) (Kavakli et al., 2010).

3.3 The relationship between CO-Hb and MDA

The relationship between CO-Hb and MDA levels in the blood was shown to have a significant correlation based on statistical analysis using Spearman's test with p-value = 0.000 respectively (table 6). The study results proved a linear relationship between CO-Hb and MDA levels in the blood (Abass et al., 2017)(Flores et al., 2017). These results identify that an increase in CO-Hb levels was followed by MDA levels increase in the blood and vice versa. Those continuous condition could affect the body state because of oxidative stress in the body.

Insecticides contain both toxic and active substances. The various active substances in these insecticides are not only felt by insects that are targeted but also impacted on animals and humans exposed to. Mosquito repellent as an insecticide can poison the body in several ways, namely ingested, inhaled, exposed to the skin or eyes. One of the insect repellent compounds is dimefluthrin. Dimefluthrin compound in mosquito repellent has direct effect on CO-Hb and MDA levels in blood. The use of insect repellent impacted on air quality. The insect repellent exposure in the form of CO gas can bind Hb in the blood with high affinity to form CO-Hb (Setiawan et al., 2020). High levels of CO-Hb in the blood can trigger damage to the lungs such as chronic

obstructive pulmonary disease, bronchial asthma, and acute pneumonia (Liu et al., 2011). An increase in CO-Hb in the blood will lead the formation of oxidative stress due to antioxidants and oxidants imbalance that can trigger persistent inflammation and impacted on organ health (Teksam et al., 2019). This study found that CO-Hb and MDA levels have a significant relationship and proved that free radicals increase in the blood will promote oxidative stress in blood.

4. Conclusion

Dimefluthrin compound in the mosquito repellent formula has a significant relationship to CO-Hb and MDA levels in the blood. The highest dimefluthrin compound in the electric fluid had CO-Hb levels of 0.100±0.042% and increase in CO-Hb of 2.858±1.211%. Meanwhile, MDA levels were also found in the electric spray exposure group of 221.380 ± 126,855 ng L^{-1}. Further studies are needed to confirm the effects of oxidative stress because of anti-mosquito exposure on cellular damage.

Acknowledgments

We would like to thank Institute of Research and Community Service, Universitas Nahdlatul Ulama Surabaya, which has supported and assisted through research grants No. 161.3/UNUSA/Adm-LPPM/III/2021.

Conflicts of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. CO-Hb levels in blood in rats after being exposed to insect repellent

Group	**N**	**Mean ± SD**		**One-Way Anova Test**	
		CO-Hb (%)	Increase in CO-Hb (%)	CO-Hb	Increase in CO-Hb

Electric spray (E)	10	0.100±0.042	2.858±1.211		
Coils (C)	10	0.059±0.032	1.696±0.927	0.019*	0.021*
Electric Mats (M)	10	0.059±0.029	1.681±0.843		

320 *significant p-value<0.05

321

322 Table 2. The Post hoc test results of CO-Hb increase after being exposed to insect repellent.

Group	Electric spray (E)	Coils (C)	Electric Mats (M)
Electric spray (E)		0.015*	0.013*
Coils (C)			0.960
Electric Mats (M)			

323 *significant p-value<0.05

324

325 Table 3. The post hoc results increase in CO-Hb levels

Group	Electric spray (E)	Coils (C)	Electric Mats (M)
Electric spray (E)		0.016	0.014*
Coils (C)			0.974
Electric Mats (M)			

326 *significant p-value<0.005

327

328 Table 4. The MDA serum levels analysis

Group	N	Mean ±SD (ng L^{-1})	Kruskal Wallis Test
Electric spray (E)	10	221.380±126.855	
Coils (C)	10	73.365±16.519	0.005*

Electric Mats (M)	10	75.548±32.179

*significant p-value<0.05

Table 5. The results of Mann Whitney test of MDA test

Group	**Electric spray (E)**	**Coils (C)**	**Electric Mats (M)**
Electric spray (E)		0.010*	0.003*
Coils (C)			0.650
Electric Mats (M)			

*significant p-value<0.05

Table 6. The results of CO-Hb and Serum MDA levels correlation test

Group	**N**	**Spearman Test**	
		CO-Hb and MDA	**Increase in CO-Hb and MDA**
Electric spray (E)	10		
Coils (C)	10	0.000	0.000
Electric Mats (M)	10		

*significant p-value<0.05

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