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ETHANOL EXTRACT OF ONION PEEL EFFECTIVELY REDUCES MALONDIALDEHYDE (MDA) LEVELS OF WISTAR RAT PLASMA INDUCED BY DIAZINON

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ABSTRAK

Diazinon merupakan pestisida organofosfat yang umum digunakan oleh petani. Penggunaan diazinon dapat meninggalkan residu pada produk pertanian. Konsumsi produk tersebut dalam jangka panjang akan mengakibatkan gangguan kesehatan melalui mekanisme stres oksidatif. Kulit bawang merah (Allium cepa L.) memiliki kandungan tinggi flavonoid yang yang dapat menetralisir stres oksidatif. Penelitian ini bertujuan menentukan efektivitas ekstrak etanol kulit bawang merah (EKBM) dalam menurunkan kadar malondialdehid (MDA) plasma tikus Wistar yang diinduksi diazinon. Metode penelitian ini adalah true experimental dengan rancangan penelitian posttest-only control group design secara in vivo, yang menggunakan 28 sampel yang dibagi berdasarkan teknik simple random sampling menjadi 7 kelompok, yaitu kelompok kontrol (K0), kelompok diazinon (K1), kelompok EKBM P1 (300 mg/kgBB), P2 (600 mg/kgBB/hari), P3 (900 mg/kgBB/hari), P4 (1200 mg/kgBB/hari), dan P5 (2400 mg/kgBB/hari). Pemeriksaan kadar MDA plasma dilakukan dengan metode TBARS. EKBM pada dosis 300 mg/kgBB/hari, 600 mg/kgBB/hari, 900 mg/kgBB/hari, 1200 mg/kgBB/hari, dan 2400 mg/kgBB/hari dapat menurunkan kadar MDA plasma tikus Wistar yang diinduksi diazinon secara signifikan ($p<0,05$) dan kadar MDA plasma EKBM dosis 2400mg/kgBB/hari tidak berbeda signifikan dengan kelompok kontrol yang menunjukkan bahwa EKBM dosis 2400mg/kgBB/hari dapat menetralisir peningkatan kadar MDA plasma tikus Wistar yang diinduksi diazinon. EKBM efektif menurunkan kadar MDA plasma tikus Wistar yang diinduksi diazinon.

ABSTRACT

Ethanol Extract of Onion Peel Effectively Reduces Malondialdehyde (MDA) Levels of Wistar Rat Plasma Induced by Diazinon. Diazinon is an organophosphate pesticide commonly used by farmers. The use of diazinon can leave residues on agricultural products. Consumption of these products in the long term will cause health problems through oxidative stress mechanisms. Onion skin (Allium et al.) has a high content of flavonoids, which can neutralize oxidative stress. This study aims to determine the effectiveness of onion peel ethanol extract (OPEE) in reducing the plasma MDA level in diazinon-induced Wistar rats. Method This study is true experimental with a posttest-only control group design in vivo, using 28 samples divided based on a simple random sampling technique into four groups, i.e. the control group (K0), diazinon group (K1), OPEE groups P1 (300 mg/kgBW), P2 (600 mg/kgBW), P3 (900 mg/kgBW), P4 (1200 mg/kgBW), and P5 (2400 mg/kg BW). The examination of plasma MDA levels was carried out using the TBARS method. OPEE at doses of 300 mg/kgBW/day, 600 mg/kgBW/day, 900 mg/kgBW/day, 1200 mg/kgBW/day, and 2400 mg/kgBW/day significantly reduced the plasma MDA levels in diazinon-induced Wistar rats ($p<0.05$). The plasma MDA level in the OPEE group at a dose of 2400mg/kgBW/day was not significantly different from the control group, indicating that OPEE at a dose of 2400mg/kgBW/day could neutralize the increase of plasma MDA level in diazinon-induced Wistar rat. OPEE is effective in reducing the plasma MDA level in diazinon-induced Wistar rats.

INTRODUCTION

Indonesia is an agricultural country where 35.3% of the population works as farmers.[1] It is recorded that around 3,247 types of pesticides are used in the agricultural sector to control plant pest organisms (OPT).[2] The pesticides that are often used are the organophosphate group because there is little residue left in the environment and lower resistance in insects compared to other groups of pesticides.[3] Uncontrolled use of organophosphates can cause poisoning and organ damage. Farmers often use the diazinon group of organophosphates.[4] Diazinon leaves residue on plants, so it has the potential for human consumption. Diazinon that enters the body is metabolized into the active compound diazoxon, which causes the accumulation of reactive oxygen species (ROS).[5] Reactive oxygen species are reactive species that contain oxygen elements that are capable of causing damage to biomolecules.[6] The reactive nature of ROS causes disturbances in the balance of oxidants and antioxidants called oxidative stress, resulting in lipid peroxidation. One of the products produced by lipid peroxidation is malondialdehyde (MDA).[7]

Administration of diazinon caused intoxication in the form of an increase in blood plasma MDA levels in male Wistar rats,[8] which indicates cell damage due to free radicals. This is also supported by research conducted by,[9] where exposure to insecticides in Wistar rats caused an increase in plasma MDA. Antioxidant compounds have been proven to stop, inhibit, and reduce organ damage at the cellular and tissue level.[10] One type of compound that has high antioxidant activity is flavonoids.

Red onion skin has a 3-5 times higher flavonoid content than the tuber.[11] So far, shallot skins have only been used as household waste. Based on the high antioxidant levels of shallot skin, it is necessary to research the use of shallot skin waste as a daily antioxidant intake in preventing health problems due to pesticide exposure, in this case, diazinon. Therefore, this research was conducted to determine the effectiveness of red onion peel ethanol extract in reducing diazinon-induced plasma MDA of Wistar rats. The difference with previous research is that this study aims to determine the antioxidant effect of EKBM on oxidative stress in Wistar rats exposed to diazinon by measuring MDA levels.

METHOD

This type of research was carried out in a proper experimental manner with an in vivo posttest-only control design, which was approved by the Research Ethics Committee of the Faculty of Medicine, Jember University, with number 1.579/H25.1.11/KE/2022. This research was conducted in September – December 2021 at the Pharmacology Laboratory, Animal House, and Biochemistry Laboratory, Faculty of Medicine, Jember University. The experimental unit must meet the following criteria: healthy male Wistar strain Rattur norvegicus rats characterized by active movement and aged 2-3 months and weighing 100-250 grams. Researchers also excluded sick experimental units that were characterized by weak or inactive movements during the process of taking experimental units. Apart from that, experimental units will drop out if they get sick and die during the acclimatization period, which is characterized by diarrhea.

The extract is made by soaking shallot skin in 2% salt water and then washing it using running water. Next, it is dried in the sun in the morning and evening; then, when the shallot skin is dry, it is crushed using a blender. The extract was made using the maceration method using 96% ethanol solvent. EKBM is made by soaking 600 grams of shallot skin powder in 96% ethanol until the volume

reaches 3 liters for 24 hours. The extraction process was carried out three times using a new solvent. The resulting extract was filtered using Whatman No. Filter paper. 2 separate the filtrate and residue. The filtrate obtained was concentrated using a rotary evaporator.

The experimental unit was divided into seven groups, namely the control group (K0), which was given corn oil for seven days and continued with 3% DMSO for seven days; the diazinon group (K1) which was given corn oil for seven days and continued with diazinon for seven days, and 5 OPEE group was given diazinon for seven days and continued with OPEE at various doses (300 mg/kgBW/day, 600 mg/kgBW/day, 900 mg/kgBW/day, 1200 mg/kgBW/day, and 2400 mg/kgBW/day). The number of experimental units used was determined using the Federer method, so 28 mice were used as experimental units.

Plasma MDA levels are measured using the Thiobarbituric Acid Reactive Substances (TBARS) method, which can produce pink due to oxidative stress. Plasma MDA data was converted to a standard graph measured by 1,1,3,3-tetraethoxypropane (TEP) in µM/mL units. The MDA levels obtained were then analyzed using the one way ANOVA comparison test, and post hoc tests were continued using the Tukey HSD test.

RESULTS

The average results of plasma MDA can be seen in Table 1. The average results and standard deviation of MDA obtained by the K0 group were 3.05+ 0.2, K1 was 17.54 + 0.81 , P1 was 9.52 + 0, 44 , P2 is 8.29 + 0.19 , P3 is 6.99 + 0.21 . P4 is 6.5 + 0.23 and P5 of 3.16 + 0.14. The Diazinon group given diazinon and DMSO had the highest average plasma MDA level, 17.54 µM/mL. Meanwhile, the Control group, which received corn oil and DMSO, had the lowest average plasma MDA level, namely 3.05 µM/mL, and the OPEE group, which had the lowest plasma MDA level, was the P5 group, namely 3.16 µM/mL.

Table 1. Mean plasma MDA levels

Group	Plasma MDA levels (µM/mL)	Standard Deviation
K is normal	3,05	0,2
K Diazinon	17,54	0,81
OPEE dose 1	9,52	0,44
OPEE dose 2	8,29	0,19
OPEE dose 3	6,99	0,21
OPEE dose 4	6,5	0,23
OPEE dose 5	3,16	0,14

DISCUSSION

Hasil Uji *Post Hoc Tukey HSD*

i \ j	K0	K1	P1	P2	P3	P4	P5
K0	X	(-14,49) p=0,000*	(-6,471) p=0,000*	(-5,237) p=0,000*	(-3,940) p=0,000*	(-3,449) p=0,000*	(-0,111) p=1,000
K1		X	(8,022) p=0,000*	(9,256) p=0,000*	(10,553) p=0,000*	(11,044) p=0,000*	(14,382) p=0,000*
P1			X	(1,233) p=0,003*	(2,531) p=0,000*	(3,022) p=0,000*	(6,360) p=0,000*
P2				X	(1,297) p=0,002*	(1,788) p=0,000*	(5,126) p=0,000*
P3					X	(0,490) p=0,562	(3,829) p=0,000*
P4						X	(3,338) p=0,000*
P5							X

i-j = beda rerata
p < 0,05 signifikan (*)
p > 0,05 tidak signifikan

Figure 1. Tukey HSD Post Hoc Test Results

The study results showed a significant difference (p=0.000) between the control group (without diazinon administration) and the diazinon exposure group. These results show that giving diazinon to male Wistar rats orally at 40 mg/kgBW/day for seven days increased plasma MDA levels. This is in line with research stated that oral administration of diazinon at a dose of 40 mg/KgBW induces oxidative stress, which is characterized by an increase in plasma MDA levels (Figure 1). [12, 13]

Oxidative stress due to diazinon exposure occurs when the liver metabolizes diazinon. Diazinon is toxic mainly when metabolized to diazoxon. Diazoxon inhibits the action of the ACHE enzyme so that it can cause systemic pathological effects.[14,15] Apart from that, the results of diazinon metabolism also form free radicals. Diazinon metabolism is divided into two phases; phase I occurs when cytochrome P450 (CYP) enzymes oxidize diazinon in the liver, which produces active molecules in the form of oxon-organophosphate and free sulfur (S) atoms[16]. In phase II or hydrolysis, oxono-organophosphate is hydrolyzed by the enzymes paraoxonase (PON) and carboxylesterase (CE), producing diazoxon with a leaving group in the form of diethyl.[16, 17] Diethyl is a very active molecule because it has a hydroxyl radical group (-OH), which is why it is called a free radical.[16]

The reactive properties of diethyl trigger the interaction of diethyl with lipids, nucleic acids, proteins, and DNA, thereby producing ROS.[7,18,19] The reactive oxygen species formed then cause lipid peroxidation by binding to hydrogen ions from polyunsaturated fatty acid (PUFA) bonds. Breaking PUFA bonds induces platelet microsomes to produce large amounts of MDA,[7,20,21] Malondialdehyde reduces the activity of intracellular antioxidants such as glutathione, catalase, superoxide dismutase, glucose-6-phosphate dehydrogenase, and glutathione S-transferase, which will further increase the production of free radicals.[7,19,22,21] Continuous accumulation of free radicals causes oxidative stress, which results in the body losing the ability to regenerate back to its original shape (resilience) and the ability to maintain homeostasis (allostasis).[23, 24] Increased MDA levels are often used as a biomarker of oxidative stress in the body.[2,25] This is because MDA production is related to increased lipid peroxidation due to the accumulation of free radicals.[7,20,21] Measuring MDA levels in plasma is highly accurate because it increases simultaneously with the ongoing oxidative stress process.[2] In this study, an increase in plasma MDA levels in male Wistar rats indicated oxidative stress due to exposure to diazinon.

Based on the results of data analysis, a significant difference (p=0.000) was found between the diazinon group and all OPEE groups. These results prove that administering OPEE at doses of 300 mg/KgBW/day, 600 mg/KgBW/day, 900 mg/KgBW/day, 1200 mg/KgBW/day, and 2400 mg/KgBW/day can significantly reduce plasma MDA levels. . This shows that administration of OPEE can reduce oxidative stress induced by diazinon exposure. This is in line with research conducted by [26] and [27] which states that OPEE has a high antioxidant effect so that it can reduce oxidative stress caused by free radicals. OPEE has antioxidant activity of 65.94 ± 0.55% with a total flavonoid content reaching 26.12 ± 0.7 mg/QE/g.[27]

The significant difference in plasma MDA levels (p=0.000) when administering OPEE at doses of 300 mg/KgBW/day, 600 mg/KgBW/day, and 2400 mg/KgBW/day indicates differences in the ability to reduce plasma MDA levels at each dose. Giving OPEE 900 mg/KgBW/day and 1200 mg/KgBW/day, there was no significant difference in plasma MDA levels between the two (p=0.562); this shows that there is no difference in the effect of reducing plasma MDA when giving OPEE 600 mg/KgBW/day and 900 mg/KgBW/day. The results of the analysis also showed that there was a significant difference (p=0.000) between the control group and the group given OPEE 300 mg/KgBB/day, 600 mg/KgBB/day, 900 mg/KgBB/day, and 1200 mg/KgBB/day. This means that administering OPEE at these four doses has not been able to neutralize plasma MDA levels. In contrast to the results of data analysis between the control group and the group given OPEE 2400 mg/KgBW/day, there was no significant difference (p=1,000). This proves that administering OPEE at 2400 mg/KgBW can neutralize plasma MDA levels.

The antioxidant effect of OPEE is mediated by the high flavonoid content (quercetin type) in shallot skin. [11,28] Flavonoids act as antioxidants by activating superoxide dismutase and catalase, inhibiting cell apoptosis caused by ROS, improving endothelial function, inhibiting the formation of low-density lipoprotein, and neutralizing free radicals.[29,30] Flavonoids neutralize free radicals by giving electrons to the free radicals so that they become a more stable form. Stable free radicals do not efficiently bind with other molecules, so they do not cause biomolecular or structural damage to cells.[31] Flavonoids can also increase the expression of NrF2, a transcription factor for forming antioxidants and detoxification enzymes. Expression of NrF2 can increase the production of the enzymes catalase, superoxide dismutase (SOD), glutathione (GSH) reductase, quinone oxidoreductase, glutamate cysteine ligase, GSH S-transferase, and other detoxification enzymes.[32,33,34] Increasing the activity of the SOD and CAT enzymes functions to catalyze ROS to become a more stable form, as well as GSH, which helps protect cells from ROS by acting as an electron donor.[35]

CONCLUSION

Based on the research results, it was concluded that the administration of onion peel ethanol extract was effective in reducing Wistar rat plasma MDA levels induced by diazinon. A decrease in plasma MDA levels occurred with administration of OPEE at a dose of 300 mg/KgBW/day, 600 mg/KgBW/day, 900 KgBW/day, 1200 mg/KgBW/day, and a decrease in MDA levels to nearly normal at a dose of 2400 mg/KgBW/day.

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