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EFFECT OF GIVING MATOA FRUIT PEEL EXTRACT ON LEVELS OF SUPEROXIDE DISMUTASE (SOD), MALONDIALDEHYDE (MDA) AND HISTOLOGICAL FEATURES OF THE LUNGS OF RATS GIVEN CIGARETTE SMOKE EXPOSURE

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ABSTRACT

The matoa plant (*Pometia pinnata*) is known as a medicinal plant that has high antioxidant activity. Cigarette smoke produces free radicals and causes oxidative stress, a condition where the number of free radicals in the body exceeds the capacity to neutralize them. The aim of this study was to evaluate the levels of malondialdehyde (MDA), superoxide dismutase (SOD) and histopathological features of rat's lung exposed to cigarette smoke and matoa peels extract. The research method uses laboratory experimental studies using rats as research subjects. The design used was Randomized Posttest Only with Control Group Design. 24 male white rats of the wistar strain were divided into 6 groups: normal, negative control, positive control, and group I, II, III were given matoa peels extract 3, 6, and 12 mg/kgBW respectively and exposure to cigarette smoke for 14 days. After 14 days, MDA, SOD and histopathological picture of the rats' lungs will be compared based on the group. Data analysis was carried out using a one-way ANOVA test. The results showed that matoa peels extract could reduce MDA levels and increase SOD activity in rats exposed to cigarette smoke (p value <0.05). Group that is given matoa peels extract 12 mg/kgBW can reduce lung tissue damage.

Keywords: Cigarette smoke, Histopathology of lungs, Matoa peels extract, MDA, SOD

INTRODUCTION

The raw material for cigarettes is tobacco. The cigarette industry in Indonesia poses a dilemma because cigarettes are a source of state revenue through payment of state taxes through excise which are quite large in value, besides that the cigarette industry provides jobs for many people. However, smoking has a dark side because it causes an unhealthy lifestyle and various diseases that cause losses to the country (Direktorat P2PTM, 2018).

Since 1700, cigarettes have existed in Indonesia and have grown rapidly to become one of the largest cigarette producers in the world (Gwyer, 1976). The World Health Organization

says Indonesia is in third place for the total number of smokers worldwide. Smokers are threatened with various health problems, from chronic disease, cancer to death because cigarettes contain harmful compounds such as nicotine, tar, lead carbon monoxide, etc. Not only active smokers but passive smokers, namely people who inhale cigarette smoke indirectly are also threatened with health problems, even the risk of lung cancer for passive smokers is higher because active smokers have filters on their cigarettes while passive smokers have no filters (Wulandari, 2016).

Cigarettes can cause various diseases because of the harmful substances contained in them (Rahman et al., 2014). Cigarette smoke contains toxic substances that have the ability to cause inflammation and free radicals (Milnerowicz et al., 2015). Having unpaired electrons outside their orbitals, free radicals bind to and attack the electrons of nearby molecules, resulting in repeated chain reactions (Sundaram Sanjay & Shukla, 2021). Highly reactive free radicals contained in cigarette smoke thus oxidize the surrounding tissue. Cigarette radicals enter the lungs through the airways. After that, they spread throughout the body through the bloodstream and eventually reach the heart. Free radicals can cause excessive oxidation resulting in damage to proteins, nucleic acids, fats, and DNA cells, which can cause cognitive impairment, cataracts, damage to macromolecules and cancer which causes cell death, even so the body requires a certain amount of free radicals within certain limits for physiological processes (Irianti & Nuranto, 2021).

Superoxide dismutase (SOD), which is an enzymatic antioxidant and other antioxidants used by the body to neutralize free radicals. If too many free radicals enter the body, then the body's enzymes cannot absorb all the effects of free radicals. This is what causes oxidative stress and reactive oxygen species (ROS). Oxidative stress is a condition in which the body has an amount of free radicals that exceeds its capacity to neutralize them. Free radicals enter the plasma membrane, which is made of proteins and lipids. Lipid peroxidation is caused by oxidative stress, which causes disruption of ion distribution and increased membrane permeability, resulting in damage to organ function and in cells. The product of lipid peroxidation, malondialdehyde (MDA), produced by prolonged use of cigarettes can cause a systemic oxidant-antioxidant imbalance (Wulandari, 2016).

Oxidative stress causes inflammation and lung damage. In a previous study, histopathological images of the lungs of rats exposed to cigarette smoke showed that alveolar macrophages covered the alveoli and resulted in greater lung tissue damage. In the non-smoker

group, macroscopically normal lung alveoli; no destruction or breakdown of alveolar macrophages; and alveolar macrophages do not cover the alveoli (Triana et al., 2013).

With their ability to neutralize free radicals, antioxidants can prevent free radicals from smoking. The antioxidant category consists of synthetic antioxidants and natural antioxidants. Matoa fruit is one of the fruits richest in antioxidants. Matoa fruit, also known as Pometia pinnata, is a fruit typical of the Papua region. This fruit has a taste similar to rambutan or longan. As a traditional medicine, matoa fruit is known to contain tannins, saponins and flavonoids, which are natural antioxidants. Matoa bears fruit from September to October, resulting in a lot of unused and unutilized fruit peels that become waste (Andriani et al., 2020).

In previous studies, green and red matoa peels showed higher antioxidant activity than some other matoa species. The content of tannins, saponins and alkaloids, is thought to be responsible for the antioxidant activity of the ethanol extract of green and red matoa peel (Rahmah et al., 2021)

Previous studies have shown that matoa peel, a plant that contains antioxidants, can help prevent oxidative damage. Therefore, studies need to be conducted to see the effect of matoa peel extract on SOD activity, MDA levels, and histopathological images of lungs caused by exposure to cigarette smoke. Matoa fruit skin has the ability to prevent oxidative stress, and this research can help reduce the amount of matoa's peel that is not used so that it does not become waste (Irawan et al., 2017).

METHODS

Materials and Equipment

Materials: Matoa peel extract, methanol, aquades, male white rats from *Wistar* strain, vitamin C, cigarette smoke, SOD kit, pellet, alcohol, hematoxylin eosin. The matoa sample comes from the matoa tree in Java and is available on the market. Equipment: Smoking chamber 66,5 cm x 45 cm x 40 cm, cage 36 cm x 28 cm x 12 cm, spectrophotometer, rotary evaporators, scale, blender, test tube, sieve, water bath, micropipette, volumetric flask, beaker.

Production of Matoa Peel Extract

The production of Matoa fruit peel extract was carried out, the extract was prepared by maceration method with 96% methanol solvent. The peel of the matoa fruit is initially dried in the sun for 3 days. After dry, it will be blended to be a dry powder and macerated for 1 day using 96% methanol at room temperature at ratio 1:10. Whatman paper No. 1 is used to filter

the resulting suspension. Rotary evaporator is used to evaporate the collected filtrate to form a paste. After the matoa peel extract is prepared, a *diphenyl-1-picrylhydrazyl* (DPPH) test will be carried out to determine the antioxidant power and phytochemical screening of the matoa peel extract.

Antioxidant Screening

a. Producing 0.5 mM (200 ppm) DPPH solution

   Weigh 10 mg of DPPH powder mixed with methanol to 50 mL. A DPPH solution with a concentration of 200 ppm was collected.

b. Maximum Absorption Wavelength Measurement DPPH (High Density Pulse Pressure)

   Pipette 1 mL of the standard dpph solution. Put 5 milliliters into a measuring flask, methanol is added up to the mark until a solution with a concentration of 40 ppm is produced. The maximum wavelength was measured with a UV-Vis spectrophotometer (400 nm–800 nm). 516 nm is the highest observed wavelength.

c. Producing Extract Test Solutions

   Weigh 10 mg of condensed extract and mix with methanol up to 10 mL. A solution that has a concentration of 1000 ppm is prepared. Taken from a 1000 ppm extract solution in doses of 0.025 mL, 0.05 mL, 0.075 mL, 0.1 mL, and 0.125 mL. Then, at each concentration, 1 milliliter of DPPH solution with a concentration of 200 ppm was added, and methanol was added up to the mark (5 mL measured flask). After that, concentrations of 5–10, 15–20 ppm were obtained. The absorbance was measured after 30 minutes of incubation using a UV-Vis spectrophotometer as before.

d. Identify DPPH Free Radical Trapping Methods

   The free radical entrapment process of the test sample is calculated to find percentage of antioxidant activity by the following formula: (Wulandari, 2016; Hasan, 2022)

$$\text{DPPH scavenging effect (\%)Inhibition} = \frac{(A_0 - A_1)}{A_0}\ x\ 100\%$$

   Where A_0: the absorbance of control; A_1: the absorbance of sample.

e. Finding the IC_{50} Value

   Calculating IC_{50} is used to calculate the results of the DPPH trapping method from the calculation results of plant extracts that can trigger 50% of the DPPH damping activity. If the extract experiences damping, the dark purple test sample changes to yellow when

DPPH is added. In the regression equation, the sample concentration (ppm) is described as the abscissa (X-axis) and the percent damping activity value is described as the ordinary (Y-axis).

Experimental Animal Groups

This study used a laboratory experimental study with a completely randomized design using rats as research subjects. The research design used was the Randomized Posttest Only with Control Group Design. White rat (*Rattus novergicus*) Wistar strain, male, 2 months old, healthy, body weight 150-200 grams, and not anatomically disabled. The rats used consisted of 24 rats, divided into 6 groups each consisting of 4 rats and exposed to 3 cigarettes/day for 14 days.

The normal group (KN) was not exposed to cigarette smoke and was only given standard feed, the negative control (K-) was exposed to cigarette smoke and only given standard feed, the positive control (K+) was exposed to cigarette smoke and given vitamin C 1 mg/KgBB, the treatment group I (P1), II (P2), III (P3) were given matoa peel extract with doses of 3, 6, and 12 mg/kgBW respectively and exposure to cigarette smoke (Table 1).

Table 1. Experimental Animal Groups

Group	Treatment
Normal group (KN)	Not exposed to cigarette smoke + standard feed
Negative control (K-)	Exposed to cigarette smoke + standard feed
Positive control (K+)	Exposed to cigarette smoke + standard feed + Vitamin C 1 mg/kgBW
Group 1 (P1)	Exposed to cigarette smoke + standard feed + Matoa peel extract 3 mg/kgBW
Group 2 (P2)	Exposed to cigarette smoke + standard feed + Matoa peel extract 6 mg/kgBW
Group 3 (P3)	Exposed to cigarette smoke + standard feed + Matoa peel extract 12 mg/kgBW

After the 14th day, rat blood serum was taken from the orbital sinus to examine MDA levels measured using spectrophotometry with a wavelength of 545 nm, SOD levels were measured using spectrophotometry with a wavelength of 450 nm, histological preparations of

lung organs were made, representatives of each group were assessed for degree lung damage based on Hansel & Barnes criteria in Table 2 (Wilyansi, 2018)

Table 2. Degree of lung damage based on Hansel & Barnes Criteria (Wilyansi, 2018)

Criteria	Description	Score
Normal	There is no histological damage	0
Mild damage	Pulmonary alveoli damage >0%-<30% of the entire visual field	1
Moderate damage	Pulmonary alveolar damage> 30% -60% of the entire visual field	2
Severe damage	Pulmonary alveoli damage >60% of the entire visual field	3

RESULTS AND DISCUSSION

The methanol extract of matoa peel that has been obtained was then subjected to phytochemical screening to assess its phytochemical content qualitatively and quantitatively. The qualitative measurement of the antioxidant content in matoa peel extract was carried out using chemical reaction method and the color change was observed, the results are shown in table 3. Qualitatively from the color change, the methanol extract of matoa peel contains phytochemicals in the form of flavonoids, tannins, glycosides, and saponins. The hydrogen atom of the phenolic compound will be donated to DPPH resulting in color change. This potential or effect as a flavonoid or phenolic antioxidant is due its ability to overcome oxidative stress and reactive oxygen species. Flavonoids, an example of exogenous antioxidants, have the ability to prevent cell damage caused by oxidative stress. By donating hydrogen ions, flavonoids prevent the formation of free radicals, which eliminates the harmful effects of free radicals. In addition, the expression of endogenous antioxidant genes is enhanced, which increases the genes responsible for the manufacture of endogenous antioxidant enzymes. Flavonoids have the ability to prevent redox reactions that can produce free radicals by stopping the xanthine oxidase and NADPH oxidase enzymes (Parwata, 2015).

Table 3. Phytochemical Screening of Matoa Peel Extract

Phytochemicals	Results
Flavonoid	+
Saponin	+
Alkaloid	-

Glycosides	+
Tanin	+
Steroid/Triterpenoid	-

The principle of the DPPH method is that the hydrogen electron donation occuring from the matoa peel extract test solution to DPPH will cause a decrease in the absorbance value of DPPH. The color change indicates the presence of antioxidant activity in extract test solution. The advantages of the DPPH method include: simple, fast, and does not use a lot of chemical reagents (Agustiarini & Wijaya, 2022). Spectrophotometer is used to measure the levels of flavonoids of matoa peel extract quantitatively. Based on Table 4, the antioxidant activity of the methanol extract of matoa peel increased from the lowest concentration 5 mg/L of 18,38% to the highest concentration 25 mg/L of 90,16%. Thus, it can be determined that the concentration of the methanol extract of the matoa peel which produces the highest antioxidant activity is at 25 mg/L. Increased inhibition percentage also informs the increase in the concentration of the extract used. The increase in the percentage of inhibition along with the increase in the concentration of the methanol extract of matoa peel is due to the increasing number of antioxidant compounds in the matoa peel extract which can counteract DPPH free radicals (Tristantini et al., 2016)

Table 4. Antioxidant Screening for Matoa Peel Extract

No.	Concentration (mg/L)	Absorbance				Antioxidant Activity (%)
		n_1	n_2	n_3	Mean	
1	0	1.159($A_{control}$)			1,159($A_{control}$)	-
2	5	0.952	0.948	0.938	0.946	18.380
3	10	0.714	0.710	0.711	0.712	38.570
4	15	0.520	0.519	0.512	0.517	55.390
5	20	0.310	0.311	0.315	0.312	73.080
6	25	0.117	0.112	0.112	0.114	90.160

The maximum absorption wavelength determines the antioxidant levels in the matoa peel extract at 516 nm. The resulting linear regression equation is y = 3.61x + 0.8053 with an R^2 value of 0.9992 as seen in Figure 1. From this equation, the IC_{50} is determined and the value is 13.6273 ppm. The main factor used to determine the antioxidant activity of an extract is IC_{50}

(Inhibitory Concentration). The lower the IC_{50} value, the greater the antioxidant activity (Fauziah et al., 2021). If the IC_{50} value of a compound is below 50 ppm it is considered a very strong antioxidant, 50-100 ppm is a strong antioxidant, 100-150 ppm is a moderate antioxidant, and 151-200 ppm is a weak antioxidant (Tristantini et al., 2016). Matoa peel extract was tested and has an IC_{50} value of 13.6273 ppm which is classified as very strong antioxidant activity.

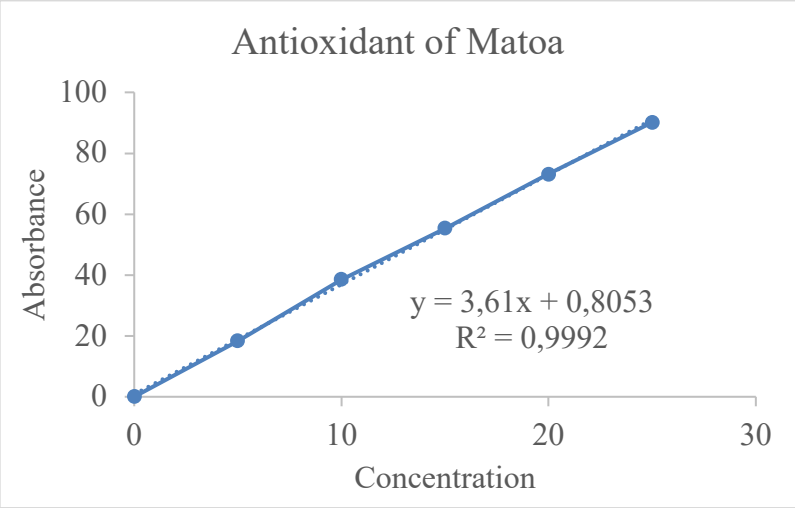

Figure 1. Curve of Antioxidant of Matoa

MDA Level Examination Results

The results can be seen in Figure 2. The One Way ANOVA statistical test showed sig = 0.000 ($p < 0.05$) so the results of this study were significant, matoa peel extract had an effect on blood plasma MDA levels of rats exposed to cigarette smoke. The results showed that administration of matoa peel extract with increasing doses was able to significantly ($P<0.05$) reduce MDA levels in the blood of rats. Decline MDA levels began to occur at doses of 3 mg/kgBW up to 12 mg/kgBW which showed a significant difference ($P<0.05$) in the resulting MDA levels.

KN or the normal group without exposure to cigarette smoke, it can be seen that the normal limit of MDA in normal circumstances without exposure to cigarette smoke, the result is the lowest MDA level. In K-, namely the negative control group exposed to cigarette smoke and standard feed, MDA levels were found to be the highest compared to other groups.

This shows that without exposure to cigarette smoke, the body has the highest antioxidant activity. Antioxidants can improve body health, whereas exposure to cigarette smoke will disrupt SOD activity and increase free radicals in the body marked by increased MDA, although given exogenous antioxidants such as vitamin C and matoa peel extract, the

results of oxidative stress biomarkers and antioxidant activity are not as good as without exposure cigarette smoke at all. These results are in line with previous studies that acute exposure to cigarette smoke can increase MDA levels in blood plasma (Adyttia, 2014). In addition, several previous studies also stated that cigarette smoke is a source of free radicals and therefore can increase MDA levels in the body (Hardi, 2014; Nasution, 2016). The body produces free radicals gradually under normal conditions. Oxidative instability, or oxidative stress, occurs when free radicals outweigh the capabilities of endogenous antioxidants. Excessive lipid peroxidation is caused by oxidative stress. MDA is a product of lipid peroxidation, and MDA levels will increase if there is an increase in lipid peroxidation in the body.

K+, namely the group exposed to cigarette smoke and getting positive control of vitamin C, low MDA levels were almost similar to KN. This study used a positive control, vitamin C, to compare the antioxidant activity of the test materials. Previous studies have shown that vitamin C, as an antioxidant, has the ability to prevent important oxidative damage, such as lipid peroxidation induced by cigarette smoke exposure, and also has the ability to reduce MDA levels in dimethoate-stimulated rats, and can increase SOD enzymatic antioxidant activity as in this research. Vitamin C is also easy to find and affordable. The results showed that blood plasma MDA levels that were given vitamin C decreased when compared to negative controls. This is due to the ability of vitamin C to capture oxygen by transferring hydrogen atoms to oxygen. As a result, oxygen is no longer available for the formation of free radicals (Wulandari, 2016)

In P1 and P2, namely treatment with 3 and 6 mg/kgBW matoa fruit peel extract which was also given exposure to cigarette smoke, MDA levels were lower than K-. At P3, namely the treatment with matoa peel extract 12 mg/kgBW which was also exposed to cigarette smoke, MDA levels were lower than P1 and P2, but not as low as K+. In the phytochemical and antioxidant screening examination of matoa peel extract, it was shown that matoa peel extract has strong antioxidant levels containing natural antioxidants of flavonoids, tannins, glycosides, and saponins so that they have the ability to neutralize free radicals. The function of antioxidants is to provide hydrogen atoms to radicals which are also known as free radical scavengers. An example of free radicals used as a variable in this study is cigarette smoke (Wulandari, 2016)

Based on data on average levels of MDA in blood plasma in Figure 2, it is known that at a dose of 3 mg/kgBW, matoa peel extract has lower antioxidant activity compared to a dose of 12 mg/kgBW. The greatest decrease in MDA levels occurred in the 12 mg/kgBW matoa peel

extract treatment group. This shows that the increasing the dose of matoa peel extract, the greater the amount of antioxidant compounds contained so that it will be more effective in reducing MDA levels in blood plasma.

In this study, the ability of matoa peel extract to reduce MDA levels and increase SOD activity was lower, compared to positive controls given vitamin C. This may be due to the dose of matoa peel extract in this study which was too low, so that the antioxidant activity produced was lower than vitamin C. Types of preparations, different types of fruit, maturity level and different drying processes can also affect the antioxidant content.

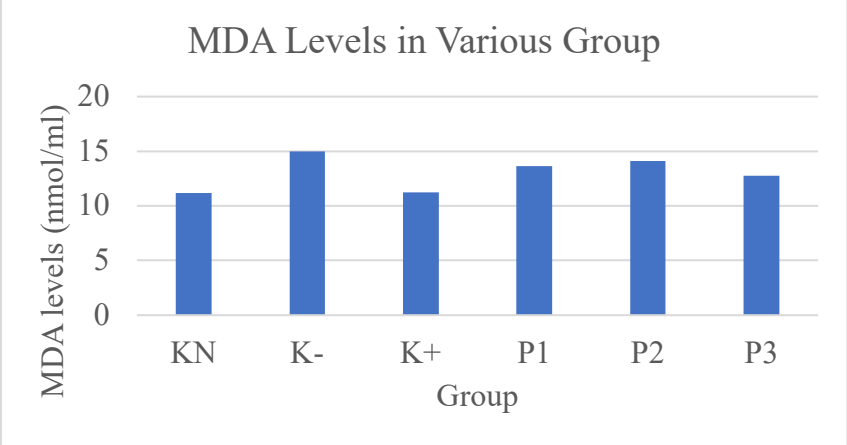

Figure 2. Graph of Average MDA Levels in Various Treatments

SOD Level Examination Results

The results can be seen in Figure 3. The One Way ANOVA statistical test showed sig = 0.000 ($p < 0.05$) so the results of this study were significant, matoa peel extract had an effect on SOD activity in blood plasma of rats exposed to cigarette smoke.

In the KN or the normal group without exposure to cigarette smoke, it can be seen that the normal limits of SOD activity in normal circumstances without exposure to cigarette smoke, the result is the highest SOD activity. In K-, namely the negative control group exposed to cigarette smoke and standard feed, SOD activity was found to be the lowest compared to the other groups. In K+, namely the group exposed to cigarette smoke and getting positive control of vitamin C, SOD activity was higher than K-. At P1, P2 and P3, i.e. treatment with matoa peel extract 3, 6, 12 mg/kgBW which was also exposed to cigarette smoke, SOD activity was higher than K-, but not as high as K+. The highest increase in SOD was seen in the positive control of vitamin C. Increasing the dose of matoa rind extract in the treatment also increased SOD.

This is because vitamin C and matoa peel extract contain antioxidants which can neutralize free radicals obtained from cigarette smoke (Wulandari, 2016). As shown by the decrease in SOD activity in the negative treatment and also the increase in MDA levels in rats, exposure to cigarette smoke causes free radicals. In accordance with previous studies, cigarette smoke produces superoxide radicals ($O_2 \cdot$), namely free radicals that are ready to attack the body so that there will be more free radicals in the body. Therefore, to neutralize it, an enzymatic antioxidant, one of which is SOD, which was measured in this study, will convert two oxygen molecules into H_2O_2 and oxygen. When the amount of reactive oxygen continues to increase to create new free radicals, SOD activity will be disrupted because SOD will continue to be used to neutralize it. As a result, the amount of SOD enzymatic antioxidants will decrease which can be measured by the percentage of reduced SOD activity. Hence, make endogenous oxidants and antioxidants become unbalanced. Without the intake of secondary antioxidants from food, cellular antioxidants cannot function independently. Therefore, in order for the body to be able to spur the function of antioxidant enzymes, it is necessary to consume foods that are rich in antioxidants (Rochmah et al., 2017)

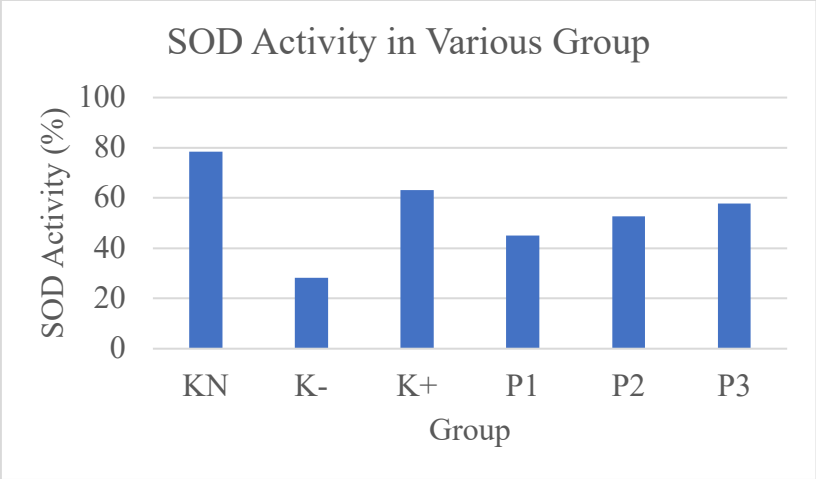

Figure 3. Graph of Average Activity of SOD Various Treatments

Histopathological Results

Examination of the description of lung tissue damage based on Hansel and Barnes criteria assessed the presence of septal destruction, inflammatory cell infiltration and pulmonary edema, then divided into several categories of mild, moderate and severe damage. The histopathological results showed that KN who were not exposed to cigarette smoke did not have lung tissue damage. Damage to lung tissue that occurred was severe damage in the group of rats exposed to cigarette smoke and standard feed or K- showing septal destruction,

inflammatory cell infiltration and pulmonary edema that was more severe and extensive than in other treatments K+, P1, P2 and P3. In the K+ group that was given vitamin C, the damage was reduced to moderate damage. The description of lung tissue damage P1 and P2 is also categorized as severe damage the same as K-. At P3 lung tissue damage is reduced to the same as K+ which is moderate damage.

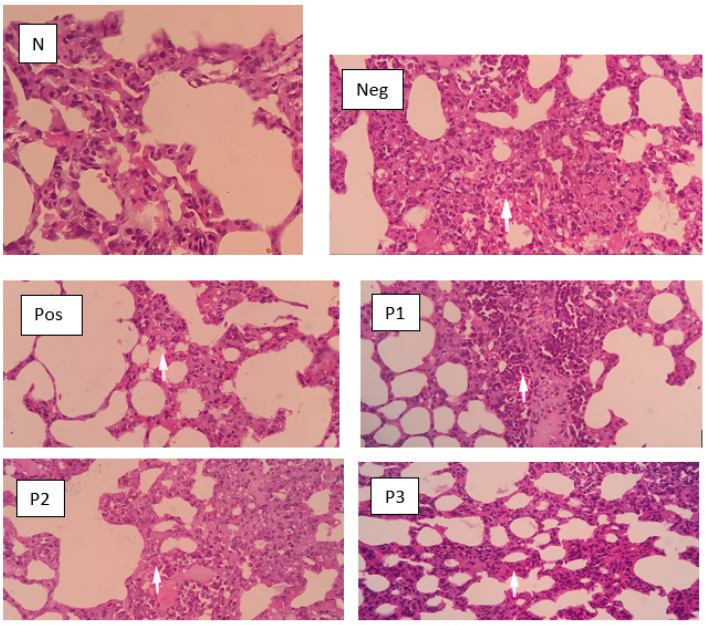

Figure 4. Description of Treatment N=Normal, Neg= Negative Control, Pos= Positive Control, P1= Group 1, P2= Group 2, P3= Group 3

Lung damage occurs due to inflammation that can damage the respiratory tract epithelium by activating target cells there. Microvascular leakage, mucus hypersecretion, eosinophils released during inflammation, and reactive free radicals are some of the inflammatory mediators that can damage the membranes that form epithelial cells. The release of inflammatory mediators, namely leukotrienes, histamine and bradykinin, causes the endothelial cells to contract which in turn causes the extravasation of macromolecules. According to Barnes, macromolecular extravasation is the term used to describe microvascular leakage at the end of capillary venules. This causes epithelial shedding and thickening of the submucosa, leading to airway edema. After inflammatory cells are activated and inflammatory mediators are released, the inflammatory process will produce free radicals that damage the body and attack the respiratory tract epithelium (Herdiani & Putri, 2018).

CONCLUSION

Matoa peel extract contains strong antioxidants and contains several chemical compounds in the form of flavonoids, tannins, glycosides, and saponins. Matoa peel extract can reduce MDA levels and increase blood plasma SOD activity of rats exposed to cigarette smoke. Administration of matoa peel extract 12 mg/kgBB was most effective in increasing SOD activity and reducing blood plasma MDA levels of rats exposed to cigarette smoke and reducing lung tissue damage.

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