International Journal of Ecophysiology
Journal homepage: https://ijoep.usu.ac.id

The Effect Of Durian Skin Extract (*Durio zibethinus* Murr.) On Histological Features Of The Lungs Rats (*Rattus norvegicus*) Induce 7,12-Dimetylbenz (A) Anthracene (Dmba)

Syafruddin Ilyas[*1] , Jernih Nurani Hulu[1]
[1]*Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara. Jl. Dr. T. Mansur No.9, Padang Bulan, Medan Baru, Medan 2024, North Sumatra 20155, Indonesia. Tel./Fax.: 061-8223564*
[*]Corresponding Author: syafruddin6@usu.ac.id

ARTICLE INFO

Article history:
Received 30 January 2024
Revised 15 February 2024
Accepted 28 February 2024
Available online
https://talenta.usu.ac.id/ijoep

E-ISSN: 2656-0674

How to cite:
Ilyas, S., Hulu, J.N. (2024). The Effect Of Durian Skin Extract (*Durio zibethinus* Murr.) On Histological Features Of The Lungs Rats (*Rattus norvegicus*) Induce 7,12-Dimetylbenz (A) Anthracene (Dmba). *International Journal of Ecophysiology*, 6(1), 85-93.

10.32734/ijoep.v6i1.15993

ABSTRACT

Durian peel extract is one of the raw materials for herbal medicine that contains large amounts of flavonoids, such as flavones and flavanols, which function as antiproliferative and antioxidant. The research was conducted from September 2022 to March 2023 which aimed to analyzed the effect of durian peel extract on the morphological and histological of rat lung induced by 7.12-Dimethylbenz (α) Anthracene (DMBA). The samples used were 24 male rats (Rattus norvegicus) with a weight ranging from 150 to 200 grams. This method of the study used a Completely Randomized Design consisting of six treatments and four replications. Each treatment group was divided into a negative control (normal); positive control (DMBA 10 mg/kgBW); P1 (DMBA 10 mg/kgBW + methotrexate 9 mg/kgBW), P2 (DMBA 10 mg/kgBW + durian peel extract 150 mg/kgBW); P3 (DMBA 10 mg/kgBW + durian peel extract 300 mg/kgBW), and P4 (DMBA 10 mg/kgBW + durian peel extract 450 mg/kgBW). The results of this research showed that durian peel extract had significant ($p<0.05$) to improved the morphological damage (color, texture, weight, and volume) as well as its histology from the degeneration, inflammation, congestion, and necrosis, it was also had significant affect on the alveolar membrane, alveolar lumen and alveolar connections of the rat lung that induced by 7,12-Dimethylbenz (α) Anthracene (DMBA).
Keyword: 7,12-Dimethylbenz (α) Anthracene, Durio zibethinus Murr., histology, lung.

ABSTRAK

Ekstrak kulit durian merupakan salah satu bahan baku obat herbal yang mengandung flavonoid dalam jumlah besar yakni flavon dan flavonol yang berfungsi sebagai antiproliferatif dan antioksidan. Penelitian ini telah dilakukan pada bulan September 2022 hingga Maret 2023 yang bertujuan untuk menganalisis pengaruh ekstrak kulit durian terhadap morfologi dan histologi paru-paru tikus yang diinduksi 7,12-Dimetilbenz (α) Antrasen. Sampel yang digunakan yaitu tikus jantan (Rattus norvegicus) berjumlah 24 ekor dengan berat berkisar 150-200 gram. Penelitian menggunakan metode Rancangan Acak Lengkap yang terdiri dari enam perlakuan dan empat ulangan. Masing-masing kelompok perlakuan dibagi menjadi kontrol negatif (normal), kontrol positif (DMBA 10 mg/kgBB), P1 (DMBA 10 mg/kgBB + metotreksat 9 mg/kgBB), P2: (DMBA 10 mg/kgBB + ekstrak kulit durian 150 mg/kgBB), P3 (DMBA 10 mg/kgBB + ekstrak kulit durian 300 mg/kgBB) dan P4 (DMBA 10 mg/kgBB + ekstrak kulit durian 450 mg/kgBB). Hasil penelitian menunjukkan bahwa secara signifikan ($p<0,05$) pemberian ekstrak kulit durian dosis 450 mg/kgBB dapat memperbaiki kerusakan morfologi (warna, tekstur, berat dan volume), histologi (membran alveolus, lumen alveolus dan hubungan antar alveolus) serta mengurangi tingkat kerusakan sel degenerasi, inflamasi, kongesti dan nekrosis pada paru-paru tikus yang diinduksi 7,12-Dimetilbenz (α) Antrasen (DMBA).
Keyword: 7,12-Dimetilbenz (α) Antrasen, Durio zibethinus Murr., Histologi, Paru-paru.

1. Introduction

The incidence of cancer in the world at the end of 2020 reached 19.2 million with 9.9 million deaths, so it is estimated that the number of cancer patients in 2030 will be 26 million and 17 million of them can die. The data shows that cancer ranks second as a cause of death worldwide with a prevalence of 13% after cardiovascular disease. The most common types of cancer found generally in men are lung, prostate, colorectal, stomach and liver cancer, while breast, cervical and thyroid cancer often occur in women [1]. Based on statistical data obtained, the number of cancer prevalence in Indonesia is 1.79% [2]. The high prevalence of cancer can be caused by genetic factors, sex, age, chemicals, drugs and immunological nutrition [3].

Cancer is a disease caused by abnormal proliferation of body tissue cells with damaged mechanisms. Cancer cells grow rapidly, uncontrollably and infiltrate (invasive) in the tissues of an organ, then spread (metastasize) to other organ tissues so as to inhibit the growth of biologically normal cells. Under normal conditions, cancer cells come from the division of cells that have died and damaged, vice versa Cancer cells cause unnecessary buildup of new cells due to continuous division under abnormal conditions. Excessive buildup of abnormal cells can damage normal tissue in certain organs rapidly in the body [4].

7,12-Dimethylbenz (α) Anthracene (DMBA) belongs to chemicals from the Polycyclic Aromatic Hydrocarbon (PAH) group [5]. DMBA has mutagenic, teratogenic, carcinogenic, cytotoxic and immunosuppressive properties. DMBA is produced through a natural and incomplete combustion process in tar combustion from cigarette smoke, wood burning smoke and gas combustion smoke [6]. The resulting DMBA can enter if injected through the skin (subcutaneous) and further accumulates in vital organs in the body, namely the kidneys, liver, heart and lungs [7]. The entry of DMBA will form a receptor bond with the Aryl Hydrocarbon Receptor (AHR). AHR is an important receptor in the process of binding DMBA with the nitrogenous base malonialdehyde so that it can damage DNA (Kleiner et al., 2002). DMBA binding with AHR activates enzymes in the liver with the help of cytochrome P450 to form DMBA 5,6-dihydrodiol and 7,12-epoxid which play an important role in generating DNA adducts that cause early cancer [8].

Induction of carcinogenesis using DMBA is highly specific for the creation of models of breast, lung, skin and mouse liver cancer. Each male wistar rat (Rattus norvegicus) experimentally induced using a single dose of DMBA as much as 4.2 mg / day for 30 days can trigger cancer in mouse lung cells [9]. According to [10], cancer induction using DMBA involves free radical reactions or Reactive Oxygen Species (ROS) and lipid peroxidation so as to damage the structure of the alveoli and damaged cells causing inflammation (inflammation) in mouse lung cells.

The lungs are respiratory organs that function as a place of oxygen and carbon dioxide metabolism, so it is easier to experience interference due to particles, toxic substances and pathogenic microorganisms transported by the blood [11]. Blood is generally highest distributed in lung tissue, followed by liver, kidneys, heart, brain, fat and bone. The large blood supply in lung tissue causes a drug and carcinogen-induced chemicals to be distributed quickly [12].

Cancer in general can be treated through surgery, agent chemotherapy and radiotherapy. In long-term chemotherapy exposure, the drug causes various physiological complications and some cancer cells can be resistant to certain chemotherapy drugs [13]. In addition to inhibiting the proliferation of cancer cells, the treatment carried out has side effects that are not good for normal cells. Methotrexate drugs have toxic side effects, namely hair loss, bone marrow suppression, drug resistance, gastrointestinal lesions, neurological dysfunction and cardiac toxicity.

Durian bark is one of the herbal medicinal raw materials that has been studied to have anticancer, anticardiovascular, antidiabetic pharmacological effects [14], antioxidant [15], antibacterial [16], antiobesity [14] and antihypertensive [17]. In the bark of Durio zibethinus Murr. there are secondary metabolite compounds namely flavonoids, phenolics, alkaloids, steroids, saponins and a little terpenoid [18]. The largest number of flavonoid compounds in durian skin are flavones and flavonols that function as antiproliferatives and antioxidants. Flavonoids as antiproliferatives are able to prevent apoptosis, deactivate the cancer cell cycle through the mechanism of inhibition of topoisomerase and cytochrome P450 enzymes and stimulate the activation of the enzyme gluthatione S-transferase to eliminate and destroy toxic substances in the body [19]. Other flavonoids in durian skin are catechins and quercetin [20]. Quercetin inhibits the proliferation of prostate,

lung, liver, breast and cervical cancer cells [21]. Based on the description above, a study has been conducted to describe and analyze the effect of durian bark extract (Durio zibethinus Murr.) on histological features of rat lungs (Rattus norvegicus) induced by 7,12-Dimethylbenz (α) Anthracene (DMBA).

2. Method

2.1 Materials

The materials used in this study were male wistar rats aged 10-12 weeks as many as 24 heads, feed, wood husks, drinking water, Dimethylbenz (α) Antrasen (DMBA), durian fruit peel extract, corn oil, CMC-Na, Hematoxylin-Eosin coloring, formalin, xylol, paraffin, aluminum foil, gloves, ethanol, stratified alcohol, label paper, physiological NaCl, *whattman filter paper* and tissues.

2.2 Making Durian Fruit Skin Extract

Durian peel extract is made using the extraction method. Durian skin is dried using an oven and then cut into small pieces. The cut skin is smoothed using a blender. The results obtained are in the form of powder and then macerated with 70% ethanol solvent and placed on a shaker for 2 hours. The resulting solution extract can be filtered and concentrated with a rotary evaporator vacuum at 40 °C so that a thick extract is obtained. Phytochemical screening tests on viscous extracts are carried out to determine the chemical compounds contained in the skin of durian fruit [22].

2.3 Cancer Induction in Experimental Animals

DMBA-induced male rats were rats of the positive control treatment group (K+), treatment groups P1, P2, P3 and P4. The positive control group (K+), P1, P2, P3 and P4 were induced by DMBA at a dose of 10 mg/kgBB dissolved in corn oil and injected subcutaneously into the nape of rats every 2 days 10 times for 3 weeks. DMBA injected every 2 days as much as 10 times with a dose of 10 mg / kg BB causes damage at the cellular level, namely hydropic and parenchymatous degeneration, dilated sinusoids, necrosis and congestion (blood clots in the central vein) [23].

2.4 Durian Skin Extract

Durian peel extract was given to rats of groups P2, P3 and P4 after DMBA induction. The extract was administered orally using a sonde daily for 3 weeks. Durian peel extract was given to the P2 group with a dose concentration of 150 mg / kg BB, in the P3 group with a dose concentration of 300 mg / kg BB and in the P4 group with a dose concentration of 450 mg / kg BB.

2.5 Organ Harvesting and Preparation

According to [24], the process of making preparations until they are ready to be observed, can begin with the stages of fixation, dehydration, purification, dealcoholization, infiltration, EmbeddingCutting Affixing, deparafinization, staining and Mounting.

3. Result and Discussion

3.1 Rat Lung Weight

Data on lung weight and the results of its analysis can be seen in appendix 3. ANOVA results showed that administration of durian bark extract had a significant effect on lung weight ($p<0.05$). Analysis results *post hoc Duncan* presented in histogram form in Figure 3.1.

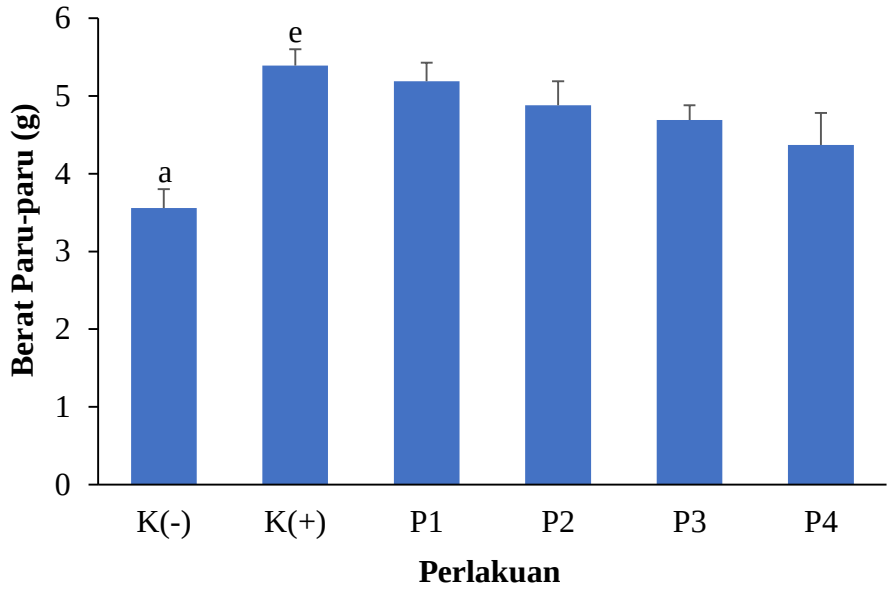


Figure 1. Average Lung Weight of Rats. K(-): negative control (normal), K(+): positive control (DMBA 10 mg/kgBB), P1: (DMBA 10 mg/kgBB + methotrexate 9 mg/kgBB), P2: (DMBA 10 mg/kgBB + durian bark extract 150 mg/kgBB), P3: (DMBA 10 mg/kgBB + durian bark extract 300 mg/kgBB) and P4: (DMBA 10 mg/kgBB + durian bark extract 450 mg/kgBB). Description: letters *Superscript* The difference in each treatment showed a marked difference (P<0.05).

Based on the results of the post hoc test in figure 4.1, it can be seen that the DMBA-induced K(+) treatment group has a higher average lung weight of 5.39 g, while the methotrexate-induced treatment group and durian bark extract doses of 150 mg / kg BB, 300 mg / kg BB and 450 mg / kg BB decreased with an average lung weight of P1 (5.19 g), P2 (4.88 g), P3 (4.69 g), P4 (4.37 g) and the K(-) treatment group had the lowest average lung weight of 3.56 g. Increased lung weight in K(+) treatment group rats can occur because the DMBA carcinogen has entered, accumulated, accumulated and is continuously toxic to lung organs. According to [25], toxic materials can inhibit oxygen exchange, reduce the surface area of the lungs and cause wrinkles in part or all of the lung lobes.

3.2 Rat Lung Volume

Lung volume data and the results of their analysis can be seen in appendix 4. ANOVA results showed that the administration of durian bark extract had a significant effect on lung volume ($p < 0.05$). Analysis results *post hoc Duncan* presented in histogram form in Figure 3.2.

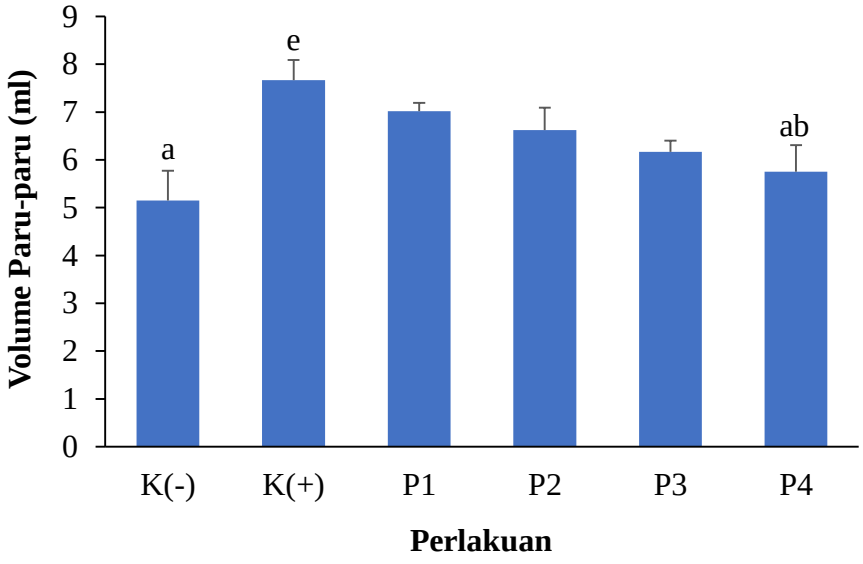


Figure 2. Average Lung Volume of Rats. K(-): negative control (normal), K(+): positive control (DMBA 10 mg/kgBB), P1: (DMBA 10 mg/kgBB + methotrexate 9 mg/kgBB), P2: (DMBA 10 mg/kgBB + durian bark

extract 150 mg/kgBB), P3: (DMBA 10 mg/kgBB + durian bark extract 300 mg/kgBB) and P4: (DMBA 10 mg/kgBB + durian bark extract 450 mg/kgBB). Description: letters *Superscript* The difference in each treatment showed a marked difference (P<0.05).

Based on the results of the post hoc test in figure 3.2, it can be seen that the DMBA-induced K(+) treatment group had a higher average lung volume of 7.67 ml, while the methotrexate-induced treatment group and durian bark extract doses of 150 mg/kgBB, 300 mg/kgBB and 450 mg/kgBB decreased with an average lung volume, namely P1 (7 ml), P2 (6.62 ml), P3 (6.17 ml) and P4 (5.75 ml). The K(-) treatment group had the lowest average lung volume of 5.15 ml. The increase in lung volume in the K(+) treatment group occurred because the alveolus had swollen (enlarged) and filled with blood. Swelling of the alveolus due to DMBA induction can cause turbidity and tissue density that inhibits circulatory function in the lungs of mice. According to [26], alveolar damage due to DMBA induction results in the formation of atypical alveolar hyperplasia and is characterized by lung organs having an increasing diameter and weight.

3.3 Color and Texture Morphology of Rat Lungs

The results of observations on the morphology of color and surface texture of rat lung surfaces (Rattus norvegicus) induced 7,12-Dimethylbenz (α) Anthracene (DMBA) and have been given durian bark extract from the entire treatment group can be seen in Table 3.1

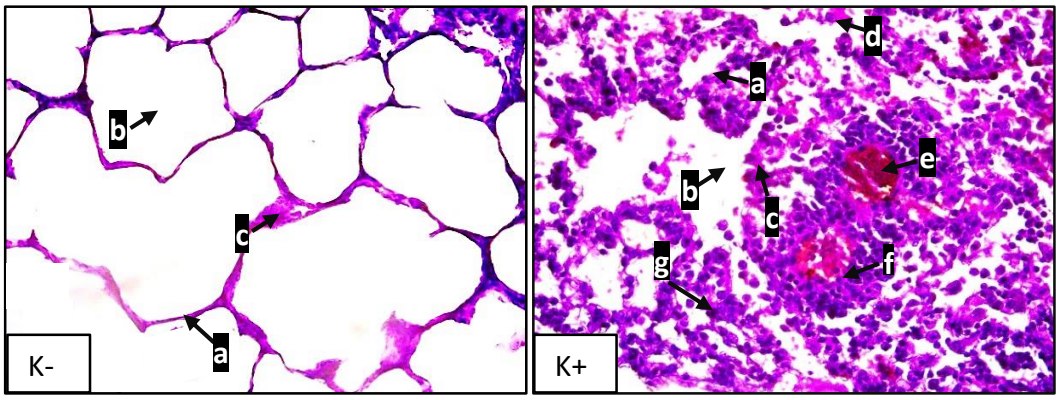
Tabel 3.1 Average Morphological Scores of Color and Texture of Rat Lungs

Treatment	Rat Lung Morphology Score
	Mean±SD
K-	0.00±0.00a
K+	3.75±0.50C
P1	3.25±0.95bc
P2	3.00±0.81bc
P3	2.25±0.50b
P4	0.75±0.95a

Based on table 3.1, normal values were obtained in the K(-) treatment group with pink lungs and chewy texture. The K(+) group has the highest abnormal values and the lungs are blackish-red with a more pronounced texture. Groups P1, P2 and P3 have abnormally lower values, the lungs are pale red, partially blackish-red with a supple and slightly spotted texture. In the P4 group, the lowest abnormal value was obtained and close to normal values with a chewy and spotless texture. This is because the substances contained in durian bark extract play a very good role in improving the morphology, color, and texture of the surface of the lungs of mice that have been damaged. According to [1], morphological characteristics in normal mouse lungs are pink, smooth texture (chewy), shiny and spotless.

3.4 Histological Features of Rat Lungs

The results of observations of DMBA-induced rat lung histology preparations and durian bark extract were obtained through the Olympus CX 23 binocular microscope with the help of Amscope Digital Camera FMA050. The histological picture of the lungs of the rats obtained can be seen in Figure 3.4.



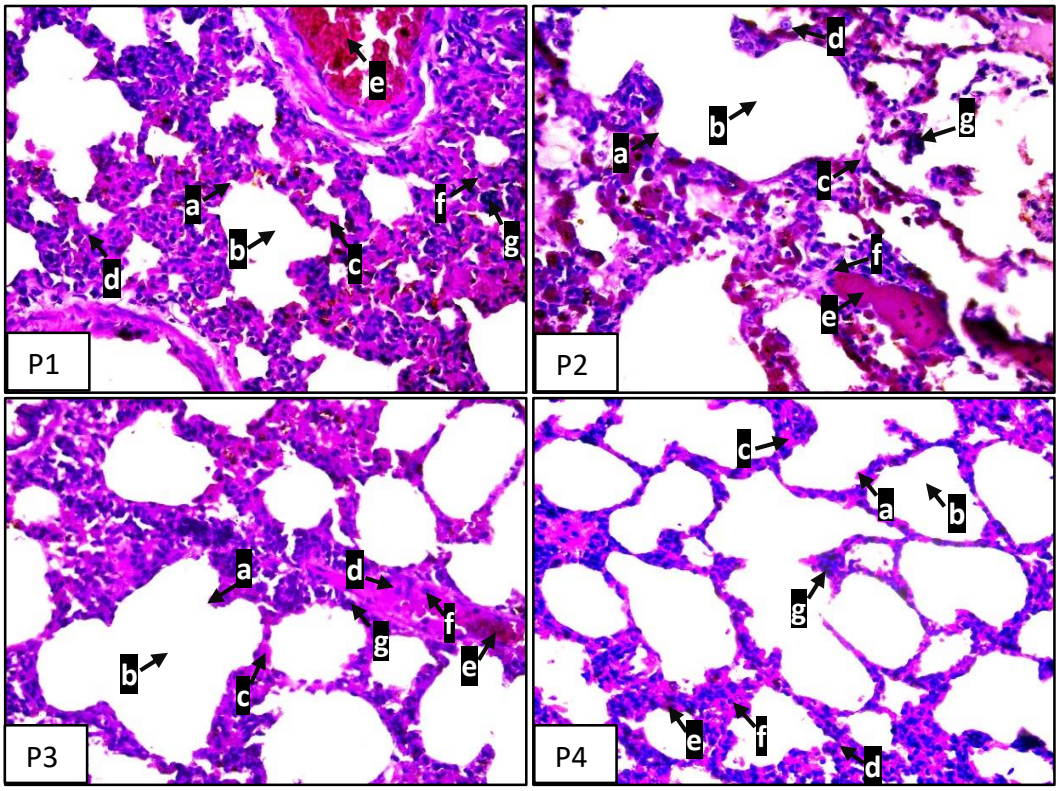


Figure 3.4. Histological Description of Rat Lungs at 400 times Magnification with HE Staining. K(-): negative control (normal), K(+): positive control (DMBA), P1: (DMBA + methotrexate), P2: (DMBA + durian bark extract 150 mg/kgBB), P3: (DMBA + durian bark extract 300 mg/kgBB) and P4: (DMBA + durian bark extract 450 mg/kgBB). Description: (A) alveolar membrane, (B) alveolar lumen, (C) relationship between alveolus, (D) degeneration, (E) congestion, (F) inflammation and (g) necrosis.

Observational data on lung cells and the results of their analysis can be seen in appendix 6. The results of the analysis with *Kruskal Wallis* showed that the administration of durian bark extract had a significant effect on lung cells ($p < 0.05$). The results of *Duncan's post hoc* analysis of all treatment groups are presented in the form of average scores in Table 3.2.

Table 3.2 Average Rat Lungs Cell Damage Score

Treatment	Degeneration	Congestion	Inflammatory	Necrosis
K-	0.00±0.00a	0.00±0.00a	0.00±0.00a	0.00±0.00a
K+	7.10±0.84e	8.35±2.53e	11.95±3.11s	16.45±2.50e
P1	5.20±0.93s	6.30±2.02s	9.50±2.31cd	14.40±1.03de
P2	3.60±0.63C	4.80±1.41cd	7.50±0.95C	12.45±0.80s
P3	2.45±0.66b	3.15±0.86bc	3.90±0.60b	8.55±1.65C
P4	1.50±0.25b	2.25±0.77ab	1.20±0.16a	6.15±2.10b

In table 3.2 it can be seen that the K- group did not find significant damage because it was not DMBA induced, while the P1, P2 and P3 groups showed little damage to lung cells, but the P4 group was the treatment that had the lowest histopathology score value and tended to increase better than the P2 and P3 treatment groups. Cell abnormalities in the P2, P3 and P4 treatment groups were still found in relatively small amounts because the double dose of durian bark extract increased its ability to significantly reduce cell abnormalities back to normal conditions compared to the DMBA control group that was not given drugs and extracts. States that flavonoids and polyphenols are able to improve the histopathology of rat lungs. Flavonoids as one of the classes of reducing compounds that accommodate hydroxy radicals and superoxides so as to protect membrane lipids against reactions that damage tissue due to free radicals. Flavonoids have phenolic hydroxyl (OH) groups that are important in their molecular structure. The reaction of OH groups by flavonoids plays an important role in inhibiting the growth and proliferation of cancer cells [27].

3.5 Histophatology Scoring of Rat Lungs Alveolus

The results of the analysis with Kruskal Wallis showed that the administration of durian bark extract had a significant effect on the histological picture of the lung alveolus ($p < 0.05$). The results of Duncan's post hoc analysis of all treatment groups are presented in the form of average scores in Table 3.3.

Table 3.3 Average Histopathology Scores of Alveolar Lung of Rats.

Treatment	Membrane Alveolus	Lumen Alveolus	Relationships between Alveolus
K-	1.00±0.00a	1.10±0.11a	1.05±0.10a
K+	3.00±0.00s	2.95±0.10s	2.80±0.23s
P1	2.85±0.19cd	2.80±0.16cd	2.70±0.25s
P2	2.55±0.41C	2.65±0.19C	2.30±0.25C
P3	2.05±0.10b	2.10±0.25b	1.60±0.36b
P4	1.25±0.10a	1.30±0.25a	1.10±0.20a

Changes in lung histology based on table 3.3 show that the K(-) treatment group has a close relationship between alveolus, there is no damage to the membrane and lumen of the alveolus. In contrast after administration of durian bark extract in the P2 and P3 groups which had scores close to the P4 group which had the lowest average lung alveolus score. This happens because flavonoids of durian bark extract have the potential to repair damage and increase the ability of epithelial cells in the basement membrane to protect the alveolus from exposure to the carcinogen DMBA. Flavonoids balance antiproteases with proteases in alveolar tissue, inhibiting the work of proteases so as to improve alveolar lumen dilation, damage to alveolar membranes and relationships between alveolus in rat lung tissue [28].

The results of [29], showed that microscopically normal lungs have a structure characterized by the presence of normal cells in the epithelium that makes up the alveolar membrane, the endothelium contains cells that are clearly visible around the alveolus, the lumen of the alveolus is rounded, the relationship between alveolus is tight and no proliferation is found in the alveolar epithelium. In abnormal lungs, epithelial cells that make up the alveolar membrane are no longer nucleated, endothelial cells are also not found, the lumen of the alveolus appears dilated and the relationship between the alveolus is very tenuous.

4. Conclusion

The morphology (color, weight, texture and volume) of the lungs of mice induced by 7,12-Dimethylbenz (α) Anthracene (DMBA) improved significantly ($p<0.05$) after administration of durian fruit peel extract (Durio zibethinus Murr.) and also Durian (Durio zibethinus Murr.) rind extract with the highest dose, namely 450 mg/kgBW, significantly ($p<0.05$) can repair damage to the alveolar membrane, alveolar lumen and connections between alveoli and reduce the number of cells experiencing degeneration, congestion, inflammation and necrosis in rat lungs.

References

[1] H. Sung *et al.*, "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.," *Ca Cancer J Clin*, vol. 71, no. 3, pp. 209–249, 2021.

[2] R. Kemenkes, "Hasil Riset Kesehatan Dasar Tahun 2018," *Kementrian Kesehat. RI*, vol. 53, no. 9, pp. 1689–1699, 2018.

[3] A. Sirait, "Faktor Risiko Tumor/Kanker Rongga Mulut dan Tenggorokan di Indonesia (Analisis Riskesdas 2007)," *Media Penelit. dan Pengemb. Kesehat.*, vol. 23, no. 3, pp. 122–129, 2013.

[4] Y. Mangan, *Solusi Sehat Mencegah dan Mengatasi Kanker*. Jakarta: PT. Agro Media Pustaka, 2009.

[5] A. Rundle *et al.*, "The Relationship between Genetic Damage from Polycyclic Aromatic Hydrocarbons in Breast Tissue and Breast Cancer," *Carcinogenesis*, vol. 2, no. 7, pp. 1281–1289, 2000.

[6] J. Kim, E. Lee, D. Kim, B. Yu, and H. Chung, . "Kaempferol Modulates Pro-Inflammatory NF-kappaB Activation by Suppressing Advanced Glycation Endproduct-Induced NADPH Oxidase," *Off. J. Am. Aging Assoc.*, vol. 32, no. 2, pp. 197–208, 2010.

[7] M. Silitonga, E. Gultom, and M. Nugrahalia, "The Effect of (Plectranthus amboinicus) Lour Spreng Ethanolic Extract on Relative Organ, Body Weights Changes, and Hematology Profile in Wistar Rats Treated with 7, 12-Dimethylbenz (α) Anthracene," *J. Phys. Conf. Ser.*, vol. 1462, no. 1, pp. 1–8, 2020.

[8] F. Girolami *et al.*, "Time-Dependent Acetyl Salicylic Acid Effects on Liver CYP1A and Antioxidant Enzymes in Rat Model of 7,12-Dimethylbenz (α) Anthracene-Induced Mammary," *Carcinogenesis*, vol. 181, no. 2, pp. 87–92, 2008.

[9] A. Fudholi, E. Meiyanto, I. Donatus, A. Nurrochmad, A. Hakim, and R. Murwanti, "Efek Penghambatan terhadap Pertumbuhan Tumor Paru dan Uji Ketoksikan Akut Ekstrak Kapsul Chang Sheuw Tian Ran Ling Yao pada Mencit (Mus musculus) dan Tikus (Ratus tanezumi). Jurnal Biologi Indonesia," *J. Biol. Indones.*, vol. 5, no. 1, pp. 1–21, 2017.
[10] M. Lauretta, Muhartono, and A. Wahyuni, "Pengaruh Pemberian Ekstrak Etanol Mahkota Dewa terhadap Gambaran Histopatologi Paru Tikus Putih yang Diinduksi 7,12-Dimethylbenz (α) Anthracene (DMBA)," *J. Major.*, vol. 3, no. 3, pp. 114–123, 2014.
[11] A. Guyton, *Buku Ajar Fisiologi Kedokteran*, 11th ed. Jakarta: EGC, 2007.
[12] L. Shergel, S. Wu-Pong, and B. Andrew, *Biofarmasetika dan Farmakokinetika Terapan*, Kelima. Surabaya, 2012.
[13] I. Das and T. Saha, "Effect of Garlic on Lipid Peroxidation and Antioxidation Enzymes in DMBA-Induced Skin Carcinoma," *Nutrition*, vol. 25, no. 4, pp. 59–71, 2009.
[14] H. Leontowicz *et al.*, "Durian (Durio zibethinus Murr.) Cultivars as Nutritional Supplementation to Rat's Diets," *Toxicol*, vol. 46, no. 2, pp. 581–589, 2008.
[15] A. Ang, C. Nalda, and S. Sabejon, "Brine Shrimp Lethality and Antioxidant Activity of the Leaf, Rind and Seed Ethanolic Extracts of Durio zibethinus L.," *Asian J. Biol Life Sci.*, vol. 7, no. 3, pp. 105–111, 2018.
[16] N. Dhuha, H. Haeria, and W. Sinta, "Potensi Fraksi Kulit Buah Durian (Durio zibethinus Murr.) terhadap Bakteri Escherhicia coli dan Staphylococcus aureus," *J. Farm. UIN Alauddin Makassar*, vol. 7, no. 1, pp. 51–57, 2019.
[17] K. Kumar, R. Kasiviswanath, and A. Ramesh, "Hypoglycemic and Antihyperglycemic Effect of (Gmelina asiatica LINN.) in Normal and in Alloxan Induced Diabetic Rats," *Biol. Pharm. Bull.*, vol. 28, no. 4, pp. 729–723, 2005.
[18] R. Courtney, J. Sirdaarta, B. Matthews, and I. Cock, "Tannin Components and Inhibitory Activity of Kakadu Plum Leaf Extracts Against Microbial Triggers of Autoimmune Inflammatory Diseases," *Pharmacogn. J.*, vol. 7, no. 1, pp. 18–31, 2016.
[19] W. Ren, Z. Qiao, H. Wang, L. Zhu, and L. Zhang, "Flavonoids: Promising Anticancer Agent," *Med. Res. Rev.*, vol. 23, no. 4, pp. 19–34, 2003.
[20] V. Dembitsky *et al.*, "The Multiple Nutrition Properties of Some Exotic Fruits: Biological Activity and Active Metabolites," *Food Res. Int.*, vol. 44, no. 7, pp. 1671–1701, 2011.
[21] Y. Liu *et al.*, "Effects of Quercetin on Proliferation and Migration of Human Glioblastoma U251 Cells," *Biomed. Pharmacother.*, vol. 92, no. 1, pp. 33–38, 2017.
[22] E. Anggreini and K. Anam, "Identifikasi Kandungan Kimia dan Uji Aktivitas Antimikroba Kulit Durian (Durio zibethinus Murr.)," *J. Kim. Sains dan Apl.*, vol. 19, no. 3, pp. 87–93, 2016.
[23] M. Restuati and P. Nasution, "Pengaruh Ekstrak Etanol Daun Buas Buas (Premna pubescens Blume.) terhadap Gambaran Histopatologi Hati pada Tikus Putih (Rattus novergicus) yang Diinduksi Kanker 7,12-Dimetilbenz (α) Antrasena (DMBA)," *J. Biosains*, vol. 5, no. 2, pp. 76–82, 2019.
[24] N. Harijati, S. Setijono, I. Serafinah, and Aris, *Mikroteknik Dasar*. Malang: UB Press, 2017.
[25] T. Hayu and A. Soekanto, "Pengaruh Pemaparan Uap Anti Nyamuk Elektrik yang Mengandung Allethrin terhadap Berat dan Warna Paru-Paru Tikus," *J. Ilm. Kedokt. Wijaya Kusuma*, vol. 5, no. 1, pp. 26–36, 2018.
[26] S. Hecht, P. Kenney, M. Wang, and P. Upadhyaya, "Benzyl Isothiocyanate: An Effective Inhibitor of Polycyclic Aromatic Hydrocarbon Tumorigenesis in A/J Mouse Lung," *Cancer Lett.*, vol. 187, no. 2, pp. 87–94, 2002.
[27] L. Nurani, "Uji Sitotoksitas dan Antiproliferatif Sel Kanker Payudara T47D dan Sel Vero Biji (Nigella sativa L.)," *J. Ilm. Kefarmasian*, vol. 9, no. 1, pp. 60–69, 2012.
[28] L. Manuella *et al.*, "Mate Tea Ameliorates Emphysema in Cigarette Smoke-Exposed Mice," *Exp. Lung Res.*, vol. 37, no. 4, pp. 246–257, 2011.
[29] A. Marianti, "Aktivitas Antioksidan Jus Tomat pada Pencegahan Kerusakan Jaringan Paru-Paru Mencit yang Dipapar Asap Rokok (Genetic Diversity of Banana with B Genom Using Microsatelite Marker)," *Biosaintifika J. Biol. Biol. Educ.*, vol. 1, no. 1, pp. 1–10, 2009.