

# The Activity Test of Dewandaru Fruit (*Eugenia uniflora* L.) in Trachea of Male Mice (*Mus musculus* L.) Which Exposed to Cigarette Smoke

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**Abstract:** Smoking has a serious negative impact on health because cigarettes contain harmful chemical compounds. To combat these negative effects, using natural antioxidants such as Dewandaru fruit has become the research focus. Dewandaru contains high antioxidants, namely flavonoids, anthocyanins, saponins, and tannins, which can fight free radicals in the body. The trachea is an air channel between the larynx and bronchi. To identify the activity test of dewandaru fruit (*Eugenia uniflora* L.) in the trachea of male mice (*Mus musculus* L.) exposed to cigarette smoke. This study employed true experimental design with *post-test only control group design, probability sampling*. The data were analyzed by using *Shapiro Wilk* and followed by the *ANOVA* test and *Duncan's test*. The finding showed that administering a Dewandaru fruit filter could maintain the histopathology of the male mice trachea exposed to cigarette smoke ( $P < 0.05$ ). Dewandaru fruit filter (*Eugenia uniflora* L.) has activity in the trachea exposed to cigarette smoke among male mice. Using a Dewandaru fruit filter also affects the presence of cilia, goblet cells, epithelial height, and lumen diameter in the trachea of male mice.

**Keywords:** Dewandaru Fruit Filter (*Eugenia uniflora* L.); Male Mice (*Mus musculus* L.); Trachea.

## Introduction

Cigarette smoking is one of the most detrimental behaviours, one of which is for health because it can cause various diseases and even death; for the people of Indonesia, cigarettes are a necessity of life. Smoking habit is the biggest cause of death, which is very difficult to avoid, especially in the respiratory organs, cancer of the mouth, oesophagus, pharynx, larynx, lung, pancreas, and bladder [1].

Cigarette smoking is a major risk factor in causing various respiratory diseases. The lungs, nasal cavity and trachea are also at risk of being affected by cigarette smoke. Lung diseases caused by cigarette smoke include emphysema, chronic bronchitis and chronic obstructive pulmonary disease (COPD). Cigarette smoke can cause damage to respiratory organs, including the mouth, trachea, lungs, skin, brain, heart and bone joints. In the trachea, the damage caused by cigarette smoke is in the form of a reduced number of cilia in the ciliated pseudocomplex epithelium and changes in the height of pseudocomplex epithelial cells. Cigarette smoke can exacerbate pathological conditions, including inflammation, proteolysis and oxidative stress. Oxidative stress shifts the balance of oxidants and antioxidants in favour of oxidants. The body can compensate for oxidative stress with the presence of antioxidants.

The trachea is a respiratory conduit between the larynx and bronchi in the form of a semiflexible and semicollapsed reed located in the ventral part of the neck, extending from the larynx to the chest cavity. Histopathologically, the trachea has several layers, namely the mucosal layer (cylindrical epithelium with

many ciliated rows and lamina propria), submucosa layer (glandular tip area), cartilage ring, muscle layer, (Muculus transversus trachealis), and adventitia [2].

If it enters the body, the nicotine content in cigarette smoke will increase free radicals. Nicotine will disrupt the mitochondrial respiratory chain, causing an increase in superoxide anion and hydrogen peroxide. Superoxide anions will later be converted into hydrogen peroxide ( $H_2O_2$ ) and hydroxyl radicals (OH), which eventually cause fat peroxidation in cell membranes and damage cells. The continuous increase in free radicals entering the body will cause oxidative stress. Continuous oxidative stress will cause DNA damage that leads to genetic mutations, inflammation and fibrosis of the liver, and cell damage, resulting in various diseases.

Free radicals are molecules with one or more unpaired electrons in their outer orbit that are relatively unstable. Radicals can cause various diseases, including lipids, proteins, carbohydrates and DNA. These free radicals can trigger chronic diseases such as lipids, proteins, carbohydrates, DNA, chronic, acute, cancer, premature ageing, etc. Preventing the negative effects of free radicals requires foods containing antioxidants, such as Dewandaru Fruit [3]. Free radicals in cigarette smoke reduce the antioxidant defence mechanism in the body, causing oxidative stress and forming lipid peroxidation. It can cause damage to cell structure and function, leading to disruption of organ systems, one of which is the trachea.

In Indonesia, there are many natural plants and fruits whose antioxidant content is quite high besides being used as medicine, such as Dewandaru Fruit (*Eugenia uniflora* L.) contains many flavonoid compounds, of which 96.7% of dewandaru fruit

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antioxidant activity is obtained from flavonoid compounds that can protect the gastric mucosa, and can treat the trachea [4]. Dewandaru fruit has a high antioxidant content that can capture several free radicals in cigarette smoke, while dewandaru fruit contains vitamin C, anthocyanins, saponins, flavonoids, and tannins. Dewandaru fruit as a biofilter is expected to capture more free radicals contained in cigarette smoke. Therefore, the author is interested in examining the activity test of dewandaru fruit filter (*Eugenia uniflora* L.) as a free radical scavenger against cigarette smoke exposure in the trachea of male mice (*Mus musculus* L.).

**Research Method**

**Making Dewandaru Decoction**

The material used is Dewandaru Fruit (*Eugenia uniflora* L.), as much as 500 grams. The dewandaru fruit is cleaned using clean running water, then the dewandaru fruit that has been washed clean is put into a pot and added 400mL of water, then boiled by turning on low heat and cooking until half the initial volume.

**Cigarette smoke exposure**

Cigarette smoke exposure is carried out in a glass tub measuring 40 x 25 x 20 cm, and two holes are made, one hole to insert the cigarette into the cage and the other hole as ventilation. The base of the cigarette was connected to an aerator hose equal to the diameter of the cigarette to keep the cigarette lit. Each exposure used one clove cigarette per head daily and was conducted for 36 days.

**Dewandaru Fruit Filter on Clove Cigarettes**

Clove cigarette filters were filled with Dewandaru fruit decoction as much as 0.8mL/filter. The result of Dewandaru fruit decoction water was put into a glass beaker as much as 5mL, then 8 clove cigarette filters were inserted into the glass beaker that already contained Dewandaru fruit decoction water and allowed to stand for 24 hours. Cigarette smoke exposure from Dewandaru fruit filters was carried out in a glass tub measuring 40 x 25 x 20 cm, and two holes were made, one hole to insert Dewandaru fruit filter cigarettes into the glass tub and the other for ventilation. The base of the cigarette was connected to an aerator hose equal to the diameter of the cigarette to keep the cigarette lit. Each exposure used one clove cigarette whose filter was filled with 0.8ml of Dewandaru fruit decoction per head per day and was carried out for 36 days.

Twenty-seven male mice (*Mus musculus* L.) with a body weight of 25-30gr were used in this study, and there were three treatments. Group K0 was fed and drinking water, and Group P1 mice in glass tubes were given one cigarette clove daily for 5 minutes. Group P2 mice were given one clove cigarette/day of clove cigarettes for 5 minutes. Clove cigarettes given to mice already contain dewandaru fruit filters with a dose of 0.8mL.

**Surgery**

On the 37th day, adult male mice are ready to be

dissected and seen trachea. After dissecting the trachea, it is inserted into a glass container containing a fixative solution, namely buffered formalin, to preserve the tracheal organs so as not to change their shape and function. Tracheal organs are then made preparations to be observed.

**Data Analysis**

The research method was carried out with a true experimental research design in the laboratory with a post-test-only control group design and probability sampling. The data obtained were analyzed with Shapiro Wilk followed by the ANOVA and Duncan tests.

**Result and Discussion**

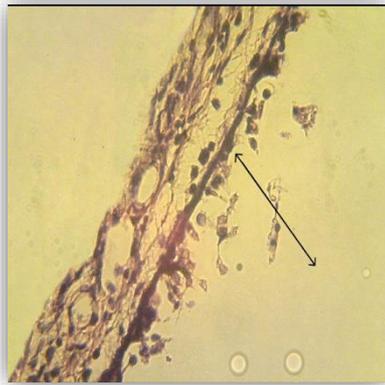
**Presence of Cilia**

Based on observations that have been made descriptively comparative using a microscope with a magnification of 400 times, it shows that exposure to cigarette smoke causes a decrease in the presence of cilia on the surface of the tracheal epithelium of male mice.

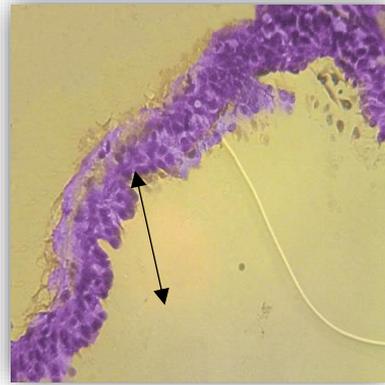
**Table 1.** Presence of cilia on the epithelial pseudocomplex cilia.

Variable	Repetition	Scoring
Control	1	+
	2	++
	3	+++
	4	++
	5	+++
	6	++
	7	++
	8	+++
	9	++
Cigarette(P1)	1	+
	2	+
	3	+
	4	-
	5	++
	6	+
	7	-
	8	-
	9	+
Dewandaru (P2)	1	+++
	2	++
	3	+
	4	+
	5	++
	6	+++
	7	++
	8	++
	9	++

Description:  
 (-) No cilia (0-25%)  
 (+) There are few cilia (26-50%)  
 (++) There are many cilia (76-100%)  
 (+++) There are very many cilia (76-100%)



**Figure 1.** No cilia



**Figure 2.** Multiple cilia

**Epithelium Height**

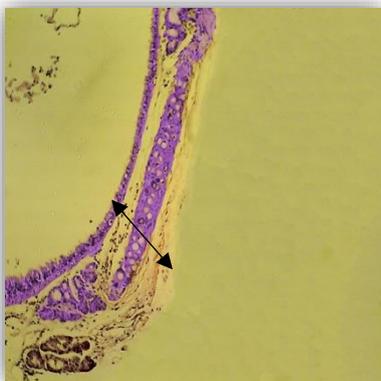
The results of observations that have been made show that dewandaru fruit decoction can maintain the height of the tracheal epithelium from exposure to cigarette smoke, as seen in the picture below.



**Figure 3.** Height of Epithelium  
Magnification Microscope 400x

**Number of Goblet Cells**

The results of observations that have been made show that dewandaru fruit decoction can maintain the number of goblet cells from exposure to cigarette smoke, as can be seen in the picture below.



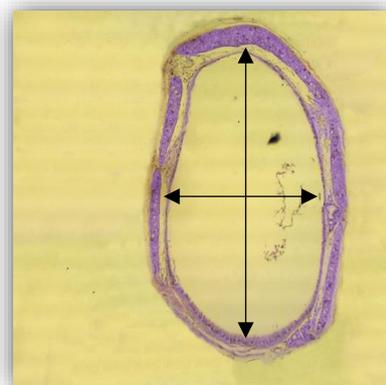
**Figure 4.** Number of Goblet Cells 400x  
Microscope Magnification

**Lumen Diameter**

**Table 2.** The mean and standard deviation of the histology structure of the trachea of adult mice (*Mus musculus*) in controls and treatments after being exposed to cigarette smoke and dewandaru decoction for 36 days.

Group	Lume diameter	epithelial height	Variabel Goblet Cell
K0	1093.78±42.47	567.54±22.27	3.44±0.38
K1	488.61±48.21	265.71±11.76	8.78±0.43
K2	1172.10±68.90	509.59±33.02	3.78±0.72

The results of observations that have been made show that dewandaru fruit decoction can maintain the diameter of the tracheal lumen from exposure to cigarette smoke, as seen in the picture below.



**Figure 5.** Lumen Diameter of 400x  
Microscope Magnification

The results showed that the dewandaru fruit was able to maintain the number of goblet cells; goblet cells are a special type of epithelial cell that secretes intraepithelial mucus; besides that, the function of goblet cells is to secrete mucus and make a protective mucus layer. The study showed that goblet cells were successfully maintained in male mice exposed to cigarette smoke tracheal respiratory tract for 36 days. The content of free radicals contained in cigarette smoke which is very much will cause an imbalance between the amount of oxidants or free radicals in the body and the amount of antibodies available in the body. This unbalanced state is

a state called oxidative stress [5].

Cigarette smoke exposure can cause an increase in ROS (Reactive Oxygen Species) levels, causing changes in the histological structure of the trachea in the form of an increase in the number of goblet cells. The results of statistical tests using One Way ANOVA showed significantly different results ( $P < 0.05$ ) between control and cigarette smoke exposure [6].

Cigarette smoke exposure can cause damage to the histological structure of the trachea, such as reducing cilia contained in the ciliated pseudocomplex epithelium, hyperplasia of goblet cells, shortening epithelial height, narrowing the diameter of the tracheal lumen. Cigarettes are wrapped tobacco products from *Nicotiana tobacco* and *Nicotiana rustica* plants. Cigarette smoke exposure can cause an inflammatory response in the respiratory tract and also exacerbate pathological conditions, namely inflammation, proteolysis and oxidative stress. The body can compensate for oxidative stress with antioxidants. Antioxidants can be found in herbal plants, namely dewandaru fruit [7].

The treatment given to dewandaru fruit decoction is similar to the control because dewandaru fruit does not have toxic properties to tracheal cells. In the research that has been done, exposure to cigarette smoke causes a decrease in the presence of cilia on the surface of the ciliated pseudocomplex epithelium in the trachea. It is thought to be due to dust particles entering and sticking to the cilia due to exposure to cigarette smoke. Furthermore, macrophages will phagocytize the particles attached to the cilia. Particles contained in cigarette smoke stick to the cilia and will damage the structure of the cilia. Cilia that have been damaged by exposure to cigarette smoke will then be phagocytized by macrophages. Exposure to cigarette smoke has a negative impact and is very dangerous for the health of the body, such as the occurrence of oxidative stress. Increased free radicals in the body can cause oxidative stress. Cilia in the pseudocomplex epithelium of the cigarette smoke exposure treatment group and dewandaru fruit extract were more in number compared to the group given exposure to cigarette smoke alone. This is because the dewandaru fruit contains active compounds such as flavonoids, which are derivatives of antioxidants [8].

The average number of goblet cells in the P3 group was more than the K0 and P1 groups but less than the P2 group. In addition to the increase in the number of goblet cells, damage or inflammation caused by the content of free radicals in cigarettes can also affect the decrease in the presence of cilia in the tracheal epithelium. In the inflammatory process, pro-inflammatory factors are released that can affect the process of formation and regeneration of cilia, known as ciliogenesis, which is the process by which cilia grow slender on the cell surface; continuous disturbances in the epithelium will result in a decrease in the presence of cilia [9].

Reducing cilia in the ciliated pseudocomplex epithelium can cause suppression or shortening of the tracheal epithelium. Suppression or shortening of the tracheal epithelium was observed microscopically, and each treatment was average. After being observed and analyzed with the One Way ANOVA test, it showed

significantly different results ( $P < 0.05$ ) between the control group and the treatment given cigarette smoke exposure and cigarette smoke exposure treatment and dewandaru fruit extract, while the administration of dewandaru fruit extract did not show significantly different results from the control group ( $P > 0.05$ ) [10].

Cigarette smoke exposure in male mice for 36 days causes damage to the tracheal structure in mice, especially in high epithelial mice. Observations were made on the tracheal epithelial tissue of mice exposed to cigarette smoke. Cigarette smoke exposure is proven to damage tracheal epithelial tissue. Epithelial tissue is a tissue that forms a layer that covers the surface of the body and lines body cavities [12].

Cigarette smoke treatment causes a reduction in epithelial height and is significantly different compared to the control. It is suspected that the dewandaru fruit filter can reduce the attack of free radicals caused by exposure to cigarette smoke [13]. The group given exposure to cigarette smoke experienced shortening of the epithelium. The shortened tracheal epithelium is caused by the loss of cilia on the surface of the epithelium due to the influence of cigarette smoke exposure. Continuous exposure can cause an imbalance between antioxidants and free radicals in the body, causing oxidative stress [14]. An increase in free radicals in the body can cause lipid peroxidation of macromolecules in tracheal epithelial cells. Macromolecular damage caused by free radicals is most susceptible to unsaturated fatty acids in cell membranes, which will impact the average height of the tracheal epithelium [15].

Based on research that has been done on male mice (*Mus musculus*), namely the observation of lumen diameter, it shows that dewandaru fruit decoction can maintain the diameter of the tracheal lumen in male mice (*Mus musculus*) from cigarette smoke that has been done for 36 days. In addition, smoke from clove cigarettes is a source of free radicals. High exposure to free radicals in the body exceeds what can be compensated, resulting in oxidative stress [16]. Oxidative stress is an imbalance between the systemic manifestation of free radicals in the form of ROS and the body system's ability to neutralize and repair damage caused by free radicals. If exposure to free radicals occurs continuously, it can cause the formation of lipid peroxides, which can damage endothelial cell membranes [17]. Based on the explanation above, it can be interpreted that clove cigarette smoke can cause lipid peroxides and an increase in low-density lipoprotein (LDL). An increase in LDL makes it easier for LDL to adhere to dysfunctional endothelial cells. Then LDL is oxidized and causes atherosclerosis plaque, an accumulation of fat, macrophages, and smooth muscle in the tunica intima and tunica media, which are the walls or layers of blood vessels [16].

In the control group K and group P3, the average value of tracheal epithelium height was higher than the group given exposure to cigarette smoke. It is because the antioxidant content in dewandaru fruit is very important for the body that experiences oxidative stress and can protect cells from free radical attacks by donating one of its electrons to compounds that are oxidants so that the

activity of these oxidant compounds can be inhibited [18-19].

Antioxidants are compounds that can counteract free radicals and have an important role in the health of the body. Antioxidants are thought to protect cells from free radicals by converting superoxide ions (O<sub>2</sub><sup>-</sup>) from the environment into hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) assisted by the enzyme peroxide dismutase (SOD) with the addition of hydrogen ions [20][21]. Hydrogen peroxide is then decomposed into water with the help of the enzyme catalase. The catalase enzyme can use one H<sub>2</sub>O<sub>2</sub> molecule as an electron donor substrate and one acceptor substrate so that 2 H<sub>2</sub>O<sub>2</sub> molecules become 2 H<sub>2</sub>O and O<sub>2</sub>. If the H<sub>2</sub>O<sub>2</sub> molecule is not converted into H<sub>2</sub>O, it can form reactive hydroxyl radicals (OH) [22]. Hydroxyl radicals (OH) will be more reactive if they react with transition metals (Fe<sup>2+</sup> or Cu<sup>+</sup>) and can cause damage to cells, especially to cell membranes, through lipid peroxidation reactions, protein oxidation and DNA oxidation [23-24].

## Conclusion

Based on the results of the research that has been conducted, it can be concluded that Dewandaru fruit filter (*Eugenia uniflora* L.) inhibits free radicals in the trachea of male mice (*Mus musculus* L.) exposed to cigarette smoke. Dewandaru fruit filter has activity on the presence of cilia, goblet cells, epithelial height and diameter of the tracheal lumen of male mice (*Mus musculus* L.).

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