

EFFECT OF BANGKAL LEAF EXTRACT (*Nauclea subdita*) ON THE LUNGS OF TEST ANIMALS EXPOSED TO FOREST FIRE SMOKE : LITERATURE REVIEW

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Abstract

Forest fires occur almost every year in Indonesia, especially during the extreme dry season. The smoke from forest fires causes health problems in the community, especially problems with the respiratory tract. To determine the effect of bangkal leaf extract as an antioxidant on test animals exposed to forest fire smoke to support the government in reducing the incidence of Upper Respiratory Tract Infection (URTI) due to forest and land fires. Writing articles with the Literature Review design, a literature search, both national and international, through journal sites indexed by SINTA and SCOPUS. There were 383 scientific articles found and then screened so that 12 scientific papers were selected to do a literature review. Leaf extract of the bangkal plant can be used as an antioxidant because it contains flavonoid compounds. After being tested for the leaves of the bangkal plant's antioxidant, the results showed IC₅₀ 79.62 ppm with ethanol solvent and IC₅₀ 10 ppm with methanol solvent. This indicates that the leaves of the bangkal plant have an intensity as an antioxidant. The effect was tested by a histopathological test on the lungs of the test animals. The dose of flavonoids used as antioxidants to scavenge free radicals in the body is 500 - 1000 mg/day. The study shows that the extract of bangkal leaf can be useful as a treatment URTI because it contains flavonoids that can be used as antioxidants.

Keyword : Antioxidant, Bangkal leaf, Flavonoids, URTI, Forest fire, Free radical

Introduction

Indonesia forest fires in 2019 at least of 942,484 Ha, occurring in 33 provinces with Banten Province as the smallest area of forest fires (9.00 Ha) and Central Kalimantan Province having the largest forest fire (134,227 Ha) (BNPB, 2019). Forest fire smoke causes visibility problems and causes health problems for residents in respiratory problems. Chronis that appear are coughing, wheezing and shortness of breath, low-grade fever, sore throat, mild headache, cyanosis due to lack of oxygen. These indicate the presence of disease that attacks the respiratory tract, Upper Respiratory Tract Infection (URTI).

Upper Respiratory Tract Infection (URTI) is an infection caused by microorganisms that attack the nose, trachea (breathing tubes) or lungs. The infection can spread throughout the respiratory system and deprive the body of oxygen, which can lead to death. Upper Respiratory Tract Infection (URTI) can be cured with antioxidants. Antioxidants can be found in flavonoid compounds found in plants,

either plants containing high flavonoid compounds is Bangkal leaf. Bangkal leaf that has a function as medicinal plants and cosmetic ingredients. This plant can be found in Kalimantan where its habitat is in wetlands (river banks, flood plains, or freshwater swamps). Bangkal leaf usually used are their bark and leaves. Kalimantan's people use bark as a cold powder mixture. A common area for producing cold powder or *pupur Bangkal* is Barabai, Central Hulu Sungai Regency capital (Soendjoto, 2017).

The results of phytochemical screening showed that bark extract in Bangkal leaf contained secondary metabolites of polyphenols, alkaloids, flavonoids, and saponins, while the leaf extract contained polyphenols, alkaloids, flavonoids, and quinones. Antioxidant activity test was carried out using the DPPH method (1,1-diphenyl-2-picrylhydrazyl) at wavelengths of 523.2 nm and 522.6 nm. The comparison compound used was ascorbic acid. Antioxidant test results showed that IC₅₀ values for its bark and leaf extracts were 307.1496 g/mL and 79.62 g/mL. Based on it, bark extract antioxidant intensity of Bangkal leaf is weak (250-500 g/mL) while its leaf extract included in strong intensity (50-100 g/mL). (Wardhani & Akhyar, 2018).

This conducted research by reason of researchers saw many cases that occurred regarding respiratory tract diseases, especially those caused by forest fires and to support the government in suppressing URTI cases in forest fires, researchers tested the effects Bangkal Leaf extract (*Nauclea subdita* Merr.) on the test animals lungs exposed to forest fire smoke as a natural treatment for URTI.

Materials and Method

This study uses a literature review method. Literature review contains a theory description, findings and other research materials obtained from reference materials to be used as basis for research activities (Hasibuan, 2007). Literature sources in this study were traced through journal sites that have been indexed nationally and internationally such as Google Scholar and PubMed using clinical keys or keywords "Antioxidants, Bangkal Leaves, URTI, Forest Fires, and Free Radicals".

The article collection process was carried out by screening from 383 articles, 272 national articles and 111 international articles from different sources, based on criteria determined by articles authors. These criteria for selecting literature include:

1. Inclusion Criteria

- a. Articles relate to research theme
- b. Articles match to keywords
- c. Articles must be indexed nationally or internationally
- d. Source publication year taken is the last 5 years between 2015 and 2020
- e. Article source is in English or Indonesian

2. Exclusion Criteria

- a. Paid articles

- b. The article in a proposal form
- c. The article unmatched the research topic
- d. Source publication year below is 2015

Table 1. Findings of Scientific Articles

<i>Data Based</i>	Finding	Selected Literature
<i>Google Scholar</i>	272	5
<i>PubMed</i>	111	7
TOTAL	383	12

Results and Discussion

This conducted research starting by determining keywords, the search for this scientific article was started by searching for "forest fire smoke and mice's lungs", "bangkal leaves and antioxidants", "antioxidant activity test with smoke-induced lung histopathology test", "effects of fire peat", "antioxidant and wood smoke", "flavonoids for upper respiratory". Search scientific articles using *Google Scholar* and PubMed, scientific articles found as many as 383 articles were then screened with inclusion and exclusion criteria to 111 articles after which the articles were selected again by seeing whether the articles were available in full text or only in form, then 45 articles were found that deserved to be read one by one so that 12 scientific articles were selected for a literature review. So, this literature review contains forest fire smoke means a test antioxidants to see the lungs of test animals effect after being exposed to fire smoke.

Forest fire smoke affects the heart disease and respiratory tract, it can reduce heart and respiratory health. Incidents reported number by Indonesian government in 2015 due to smog from forest and land fires was 19 people died and more than 500,000 people experienced Upper Respiratory Tract Infection (URTI). Report data in Central Kalimantan shows that there was 1 case of death and 25,000 cases of Upper Respiratory Tract Infection (URTI) due to forest and land fires. Research shows that people affected by Upper Respiratory Tract Infection (URTI) have an RR value of 1.14 (1.04 – 1.24) due to exposure to fire smoke, so that people have the potential to be 1.04 – 1.24 times exposed to upper respiratory problems caused by free radicals from forest and land fire smoke. (Uda et al., 2019). Study (Hunter et al., 2016) and (Bønløkke et al., 2015) using forest fire smoke to be exposed directly to humans shows that forest fire smoke contains more harmful particles than urban dust, which can be seen in the following figure: Source (Hunter et al., 2016)

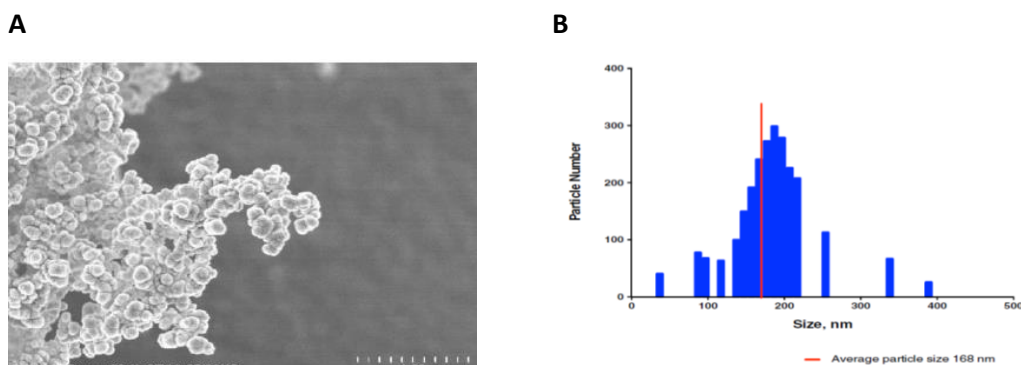


Figure 1. forest smoke particles and average of particle size distribution graph

The smallest particle size of forest fire smoke is 50 nm and the largest is 390 nm, the average particle size of forest fire smoke is 168 nm. Filtered air particles in upper respiratory tract are 5000-3000 nm, in middle respiratory tract are 3000-1000 nm, then in alveoli are 1000-500 nm. (Wardoyo, 2016). Very small particle size of forest fire smoke can enter be in human body through the respiratory tract inasmuch as inflammation in respiratory tract due to very small and sharp particles known as free radicals.

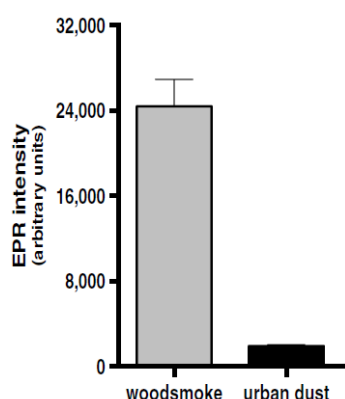


Figure 2. Electron Pragmanetic Resonance (EPR) formation of free radicals

The research results on forest fire smoke after being tested with Electron Pragmanetic Resonance obtained the results of 24,000 free radicals at 100 m particles/ml the effect on body can increase carboxyl hemoglobin from 0.9 ± 0.04 to 1.3 ± 0.04 after exposure to wood smoke ($P < 0.001$). While research by (Bønløkke et al., 2015) looking at forest fire smoke exposure an effect in a short time (3 hours) with 20 subjects divided into 2, viz. being exposed to forest fire smoke directly and exposed to forest fire smoke which was first filtered. The results of this study showed that subjects exposed to fire smoke directly increased IL-1 and IL-6 with a value ($P = 0.03$) (42.8 - 44.8) indicating that exposure result to forest fire smoke could form IL cytokines. -1 and IL-6 of 42.8 - 44.8 times so as some problems in respiratory tract. Other research from (Wulan & Subagio, 2016) showed that forest

fire smoke on pine tree branches contains inorganic compounds such as metal and organic compounds such as carbon which react directly with cells in respiratory tract and produce Reactive Oxygen Species (ROS). Fire smoke belongs to ultrafine particle group, they are air particles could penetrate into the epithelial layer so they can stick to alveolus walls and interact with epithelial cells, the ultrafine particle size is $0.1\mu\text{m}$ (Alessandrini et al., 2011). Forasmuch, it cause effects on the respiratory tract, viz. increasing the inflammatory response and decreasing lung function, inhaled ultrafine particles will become exogenous stimuli which will cause complex reactions in vascularized connective tissue called inflammation. This study directly describes the forest fire smoke from pine tree branches to see how it affects the mice lungs which can be seen in the following picture: Source (Wardoyo, 2016)

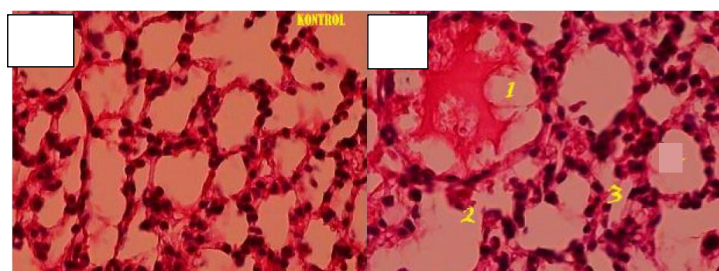


Figure 3. Histology of the lungs of mus musculus mice exposed to smoke

Description: A; mice lungs that were not exposed to smoke, B; mice lungs given biomass combustion smoke (1. Edema; 2. Emphysema; 3. Destruction of alveolar sputum)

The results showed that the mice's lungs histopathological test results in Figure A showed that there was no inflammatory reaction of exposure occurred as a comparison with mice lungs, Figure B shows an inflammatory reaction characterized by ¹ edema due to fluid balance disorders due to an increase in lipid peroxide (LOO^*) and capillary endothelial permeability resulting in plasma proteins leakage that come out together with fluid that collects in the lung tissue, ² emphysema, namely widening from the alveoli, the alveolar ducts and broken boundary wall between alveoli and alveolar ducts, causing widening of alveoli due to cell death in the alveoli walls ³. Destruction of alveolar sputum is damage to alveoli walls defective of protein elastin and epithelial membrane collagen so that alveolar sputum becomes flimsy. After being exposed to ultrafine particles for 10 days stated that forest fire smoke contains harmful ultrafine particles that can trigger an inflammatory response such as neutrophils, eosinophils, basophils, lymphocytes, monocytes, and platelets. Another exposure mechanism to forest fire smoke causes oxidative stress which produces isoprostane, thereby activating IL-6, IL-2 and $\text{TNF-}\alpha$. Ultrafine particle contains organic and inorganic compounds that react directly with cells in the respiratory tract and produce Reactive Oxygen Species (ROS).

Antioxidants are compounds that able to delay, less, and prevent lipid oxidation process. In a special sense, antioxidants are substances wherewith prevent the formation of free radical reactions (peroxides) in lipid oxidation (Jackie Kang Sing Lung, 2018). Study (Sehlstedt et al., 2017) seeing the

natural antioxidant effect of the body after being exposed to forest fire smoke in this study showed that subjects exposed to forest fire smoke had an increase in GSH glutathione levels in bronchial secretions with a value ($P = 0.001$), this indicates that when the body detects foreign substances from wood exposure. Burning will release natural antioxidants to fight these strange substances to reduce the inflammatory reactions occurrence in respiratory tract. Based on it, antioxidants that can be utilized by humans are grouped into three, i.e: human body antioxidants or known as endogenous antioxidants or antioxidant enzymes such as the enzyme Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), and Catalase (CAT). Synthetic antioxidants are widely used in food products.

Flavonoid compounds have antioxidant activity to reduce the cell damage degree by inhibiting the inflammatory mediators release like alveolar macrophages and neutrophils. (Idrus et al., 2016). Flavonoids have the potential to reduce the incidence of Upper Respiratory Tract Infection (URTI) with a $RR = 0.67$ ($0.64 - 0.69$). It can be concluded that flavonoids can reduce upper respiratory tract infections case ($0.64 - 0.69$) times with the research trust interval is 95%. (Somerville et al., 2016). Flavonoid that can be used as an antioxidant is quercetin, it's a flavonoid found in green vegetables, tomatoes, fruits, and vegetables. (Xu & Wang, 2014). Study (Heinz et al., 2016) using quercetin at a dose of 500 mg and 1000 mg/day for Upper Respiratory Tract Infection (URTI) sufferer for 12 weeks. This study showed that subjects taking quercetin 500 mg and 1000 mg for 12 weeks could reduce upper respiratory tract infections with a value ($P = 0.05$), in subjects 45 years and over who consumed quercetin 1000 mg for 12 weeks, the results were physically healthy with a value ($P = 0.02$) with a trust interval of 90%. Researchers believe that flavonoids can reduce the incidence of Upper Respiratory Tract Infection (URTI). Plants that are believed by researchers to contain flavonoids are Bangkal leaf, Bangkal leaf contain polyphenols, alkaloids, flavonoids, steroids and quinones. (Asmiyaarti & Wibowo, 2015; RAA Kusuma Wardhani & Akhyar, 2018)

Bangkal leaf is one of plants with medicinal and cosmetic ingredients, it part often used are bark and leaves. Phytochemical screening results showed that bark extract of Bangkal leaf contained secondary metabolites from polyphenols, alkaloids, saponins, and flavonoids groups. Secondary metabolite compounds contained in leaf extract of Bangkal leaf are polyphenols, alkaloids, quinones, and flavonoids. Flavonoids antioxidant activity from bark and leaf extract of Bangkal leaf was tested, the results showed that the their extract had IC_{50} values of 307.1496 g/mL and 79.62 g/mL with 70% ethanol solvent. Antioxidant intensity seen from the IC_{50} value shows that bark extract of the Bangkal leaf is of weak intensity, while the leaf extract of Bangkal leaf is of strong intensity (50-100 g/mL). (Wardhani & Akhyar, 2018). Other research from (Asmiyaarti & Wibowo, 2015) who tested the Bangkal leaves antioxidants with the DPPH method using methanol extract of Bangkal leaves stated that the it leaves contain alkaloids, flavonoids, polyphenols, and steroids. Researchers believe that Bangkal leaf leaves contain flavonoids and IC_{50} values of 79.62 ppm and IC_{50} of 10 ppm can be used as antioxidants to prevent off free radicals by forest and land fires. The difference in IC_{50} yield of Bangkal leaf leaf extract was due to using different solvents, the results using methanol as solvent

were stronger than ethanol, (Nyoman Citra Suryani, Dewa Gede Mayun Permana, 2017). Tests that can be done to see the antioxidant effect of Bangkal leaves on forest fire smoke through histopathological tests of animals lungs.

Histopathological tests can be done to see the lung damage degree exposed to fire smoke. Histopathological observations of animals lungs included observations of alveolus lumen width, alveolar walls widening, and inflammatory infiltration. Research shows that antioxidants can be used to reduce lung damage degree of test animals due to exposure to cigarette smoke and can be seen through the histopathological tests results of animals lungs with different doses in the following figure: Source (Idrus et al., 2016)

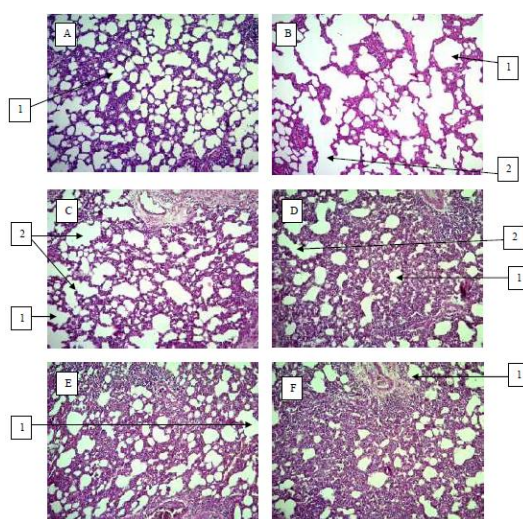


Figure 4. Overview of mouse alveolus lumen parameters

Description: A; smoke-free rat lungs, B; lungs of rats exposed to cigarette smoke without extract, C; the group giving the extract dose of 45 mg/kgbw, D, the group giving the dose of 90 mg/kgbw, E; dose group 180 mg/kgbw, F; vitamin E group (1. Alveolar lumen normal; 2. Alveolar lumen dilation)

This study results in Figure A show that normal mouse lungs without extract and exposure to cigarette smoke were used as a comparison with rats exposed to the extract and vitamin E, Figure B showed that there was 95% damage to alveolar walls, Figure C showed the degree of damage to 76%, Figure B showed damage to the alveolar walls of 95%. D shows 65% damage, E shows 50% damage and F shows 43% damage. So, in test animals without the extract was more severe than in the test animals given extracts containing flavonoids (Idrus et al., 2016). The p value obtained in the study showed a result of 0.01. Researchers believe that test effect of Bangkal leaf leaf extract, they can use the lung histopathological test of the test animals, by looking at lung damage degree of test animals after being given leaf extract various doses of Bangkal leaf with comparison without giving the extract. Other research from (Faturochman, Said Junaidi, 2019) which used orange peel extract as an antioxidant for mouse lungs exposed to cigarette smoke in an analysis with SPSS one way ANOVA test getting a P

value = 0.01 which means orange leaf peel antioxidants can reduce lung damage due to exposure to cigarette smoke at a dose of 25 mg Kg/ BB.

Bangkal leaf extract can be used to treat Upper Respiratory Tract Infection (URTI) due to forest and land fires due to flavonoids presence which can be used as antioxidants. Antioxidant activity of Bangkal leaf leaves can be tested using histopathological tests on animals model with various extract doses.

Conclusion

Bangkal leaf (*Nauclea subdita*) leaves extract contains some active substances such as polyphenols, alkaloids, flavonoids, quinones, and steroids. Bangkal leaves extract can be used as an antioxidant because it contains flavonoid compounds, after being tested for antioxidants in it leaf extract showed IC₅₀ results of 79.62 ppm with 70% ethanol solvent and IC₅₀ value of 10 ppm with methanol solvent. The dose of flavonoids that can be used as antioxidants to capture free radicals in the body is 500-1000 mg / day. Based on these results, it shows that the Bangkal leaves have antioxidant activity to capture free radicals caused by forest fire smoke.

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