

Clinical Trial of Bawang Dayak Leaves Capsules (*Eleutherine americana*) in Active Smokers

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ABSTRACT

Smoking is an unhealthy behavior, particularly for the respiratory system's health due to the free radicals found in cigarette smoke. *Eleutherine americana* or Bawang Dayak has antioxidant properties which can neutralize the harmful free radicals penetrating the body. Additionally, malondialdehyde (MDA) is one of the stress oxidative biomarkers often applied to identify reactive stress. This study was conducted to determine the effect of Malondialdehyde on active smokers who consumed Bawang Dayak Leaves capsules. This study was a pre and post-test design involving 30 smokers who met the inclusion. The participants consumed 1 capsule containing 400 mg Bawang Dayak leaves extract for 7 days. The subject's blood was taken before and after the consumption of the capsules for MDA examination. The results of this study were that the MDA level between before and after Bawang Dayak capsules consumed statistically significant. Moreover, MDA pre and post-test level respectively were 12.074 nmol/ml and 11.869 nmol/ml. The usage of Bawang Dayak leaves capsules for a week can reduce MDA levels and likely has an antioxidant potential for active smokers.

Keywords: active smokers; Bawang Dayak leaves capsules; clinical trials; MDA

INTRODUCTION

Smoking is a behavior that is frequently observed as an issue in contemporary living. After China and India, Indonesia has the third-highest percentage of smokers who vape regularly worldwide (KEMENKES RI, 2013). According to the Tobacco Control Atlas ASEAN Region 4th Edition, Indonesia is in Southeast Asia and has a proportion of smokers aged 25 to 64 years (36.3%), of which up to 66% are men and 6.7% are women (Lian & Dorthea, 2018). Smoking may negatively impact health systems, considering that there may be problems with the heart, stomach, lungs, and throat, as well as an increase in the prognosis of lung cancer and tuberculosis (TB) infection (Rea & Leung, 2018).

Cigarette smoke contains carbon monoxide (3-11%), particulate matter (15-43%), and nicotine (1-9%). More than 4,000 additional constituents have been identified as potential carcinogens, toxicants and irritants. Hydrocarbons, polycyclics, nitrosamines, and heterocyclic aromatic amines found in cigarette smoke are compounds that have carcinogenic effects and induce various cellular cascades including reactions to immunological, mutagenesis, and metabolic changes (Ardiana, 2021). Compounds contained in cigarette smoke are free radical compounds. Free radical compounds can cause

damage to lipid membranes. Damage to the lipid membrane generates cells damaged and results in dead cells (Wang et al., 2019).

Moreover, when the amount of reactive oxygen species (ROS) produced surpasses the host's antioxidant defenses, oxidative stress is the result. The respiratory went up of neutrophils, other phagocytes, and endothelial cells during the inflammatory process resulting in significant production of ROS (De Carvalho et al., 2016). If the inflammation condition combines with oxidative stress, severe damage to cells will occur.

Malondialdehyde (MDA) is a product of lipid peroxidation. MDA levels can be used as a parameter in identifying the level of oxidative stress (Juan et al., 2021; De Carvalho et al., 2016). The application of MDA as a biomarker to assess diseases related to stress oxidative are usual for clinical use, whereas MDA are generally found in plasma sample and as the results of tissue or organ impairment such as cardiovascular, cancer, neurodegenerative diseases, and metabolic diseases (Frijhoff J et al., 2015).

The Bawang Dayak, an herbaceous plant grows in South America, the African continent and also Indonesia. This plant can grow in sulfur soil with an altitude of 600 to 2000 m above sea level. Bawang Dayak plants are used traditionally to treat various diseases such as diabetes therapy, hypertension, stroke, sexual diseases, and cancer (Kamarudin et al., 2021). The main compounds found in Bawang Dayak plants are naphthalene,

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naphthol, and anthraquinone. These compounds have the potential activity of antioxidants (Shi et al., 2018).

When antioxygen has hydrogen atoms that can bind to free radicals to form stable compounds, antioxidants can overthrow free radicals (Vo et al., 2018). Bawang Dayak leaves potentially have the ability to reduce oxidative stress since this plant characterized antioxidant compounds such as flavonoid and phenol. The research conducted by Pratiwi (2013) showed antioxidant activity in the ethanol extract of Bawang Dayak leaves using the DPPH method and obtained an IC50 value of 31.97437 µg/mL. Based on Andiriyani's *in vivo* finding (2014), the Bawang Dayak leaves extract has the potential as an antioxidant against exposure to cigarette smoke by significantly reducing MDA levels starting at a dose of 90 mg/kg BW. The study directly conducting smokers to assess the effect of an antioxidant diminished oxidative stress is still limited. To minimize the harmful effects of smoking, this research was conducted to determine the influence of the ethanol extract of Bawang Dayak leaves in reducing oxidative stress in active smokers through clinical trials.

MATERIALS AND METHODS

Materials

The material used in this study was Bawang Dayak leaves capsules containing 400 mg of Bawang Dayak leaves ethanol extract and 100 mg of Avicel (filler).

Research Subject

The research subjects were subjects who met the inclusion criteria and were given intervention for 7 days. Inclusion criteria for research subjects were active smokers (not the clove cigarettes), aged 17-60 years, male sex, physically and mentally healthy (confirmed by the medical officer), not having a chronic disease and a normal body mass index. Exclusion criteria for research subjects were using antioxidant supplements 1 month before and after the intervention and drinking alcohol.

Research Design

This research is an experimental study, one group only with pre and post-test design. A convenient sampling to recruit 30 participants. Thirty participants as the subject of the study underwent a physical examination including body temperature, blood pressure, and disease history assessment by a medical officer. Three milliliters of blood from participants were carried out before the capsules were taken (pre-test). Subjects were

given Bawang Dayak leaves capsules as an intervention and taken once a day for 7 days after lunch time. After day 7, blood samples from 30 subjects were taken with the same procedure earlier (post-test). The obtained blood was analyzed for blood biochemical parameters and malondialdehyde (MDMA) levels.

A 24-gauge needle was used to extract 2 ml of blood from the cubital vein of the left arm to obtain serum samples. The instantaneous transfer of blood to a simple, sterile bulb followed. After removing the supernatant, it was centrifuged at 3000 rpm for 4-5 minutes. The collected serum was then kept at or below 20°C for further examination. A high absorption compound that is produced as a result of the TBA and MDA reaction can be quickly measured at 531 nm using a spectrophotometer. The concentration of MDA was shown on a typical graph and represented as nmol/ml. Calculations were made for the measurements' mean and standard deviation. (Geetha P et al., 2017; Prijanti A R et al., 2018)

The data were first analyzed via homogeneity using the Levene test and normality test using the Shapiro-Wilk test, then continued by Wilcoxon to test the MDA level differences signification in 95% confidence level. All analyses were carried out using the SPSS software version 22.

Research Ethics

This protocol study was approved by the Ethical Committee of Medicine Faculty, Tanjungpura University. Each participant provided written and informed consent which was approved by committee ethic with the following registration number 6183/UN22.9/PG/2021

RESULTS

Subjects in this study were male active smokers aged 20-65 years. All of the participants are active smokers who have smoked for more than 2 years. The longer a smoker inhales the free radical compounds from cigarettes, the more the respiratory system is damaged (De Carvalho et al., 2016). The subjects work as farmers, private workers, sellers, and unemployed. Their body weight between 36.6 to 96 kg with an average of 64.2 kg and their height is between 155 to 181 cm with an average of 168 cm. There is an association between body mass index and smoking frequency, while inactivity, eating poorly, and alcohol use are all strongly connected with both obesity and smoking characteristics, it may be caused by other lifestyle factors (Kaufman A et al., 2012; Dare S et al., 2015; Carreras-Torres R et al., 2018). Furthermore, the important risk factors for a range

Table I. Characteristics of Subject

Characteristics	n	%
Age (Years)		
21-30	8	26.7
31-40	7	23.3
41-50	8	26.7
51-60	7	23.3
Weight (kg)		
< 50	6	20
51-60	8	26.7
61-70	8	26.7
71-80	4	13.3
> 80	4	13.3
Height (cm)		
151-160	7	23.3
161-170	13	43.3
171-180	9	30
> 180	1	3.3
Job		
Farmer	8	26.7
Private worker	14	46.7
Seller	5	16.7
Unemployed	3	10
Duration of Smoking (year)		
2-10	5	16.7
11-20	8	26.7
21-30	9	30
31-40	7	23.3
> 40	1	3.3

of non-communicable diseases include obesity and tobacco use (WHO, 2014). Characteristics of the subject are shown in Table I.

All of the subjects did not have chronic diseases based on medical doctor assessment. Three participants had gout as their previous problem, meanwhile 2 of 30 participants claimed to have hypertension but during the study there was no report related to increasing blood pressure along the study. All participants also met the inclusion requirements which were verified by medical officer examination for their health status.

MDA levels were tested for normality and homogeneity to be carried out by Shapiro-Wilk statistical tests. Based on the normality and homogeneity tests, MDA levels were not normally distributed but were homogeneous. This is because the p-value < 0.05 ($p = 0.002$), hence, the data is concluded to be not normally distributed. The homogeneity test for MDA levels was $p > 0.05$ ($p = 0.563$), nevertheless the MDA levels were homogeneous. The statistical test that is carried out if the data is not normally distributed is non-parametric, namely the Wilcoxon Signed Rank

Test. Whereby Table II, the average of MDA level before capsules consumed was higher (12.0740 nmol/mL) than the level (11.8693 nmol/mL) after 7 days of consumption. There was a significant difference in the decrease in MDA levels between before and after the Bawang Dayak leaves capsule were taken. The values show that the capsules of Bawang Dayak leaves can reduce MDA levels ($p = 0.000 < 0.05$) (Table II). The decreasing level of MDA was affected possibly by the active component of Bawang Dayak.

DISCUSSION

Bawang Dayak leaves capsules can reduce oxidative stress by reducing MDA levels in active smokers. For the time being, Bawang Dayak leaves capsules were consumed by the respondents there were no reports of unwanted or related effects. The results described in Table III showed that there was no alteration in participants' health status while consuming the capsules, particularly the liver as organ metabolism was not affected by Bawang Dayak Leaf extract capsules.

The increasing levels of MDA can occur due to increased oxidative stress arising from smoking.

Table II. Statistical Analysis of MDA Level (n=30)

Group	Test of Normality (Shapiro-Wilk)	Test of Homogeneity (Levene test)	Mean Std. Error	Mean Level (nmol/mL)	SD	p
Pretest	0.002	0.563	0.6530	12.0740	0.35764	0.000
Posttest	0.022	0.563	0.6065	11.8693	0.33219	0.000

Table III. Blood Biochemical Parameters in Research Subjects

Parameter	Reference Value	Pre-Test	SD	Post-Test	SD	Information	Test of Normality (Shapiro-Wilk)	Bivariate test
Hemoglobin	14.00 – 17.40	15.85	1.01	16.13	1.07	Normal	0.561	0.113 ^a
Leukocytes	5.00 – 10.00	7.61	1.68	7.52	2.15	Normal	0.005	0.266 ^b
Glucose	70.00 – 115.00	94.51	55.28	114.56	60.78	Normal	0.000	0.000 ^b
Cholesterol	< 200.00	206.63	21.61	185.58	28.77	Normal	0.000	0.000 ^a
Urea	13.00 – 45.00	22.52	5.32	21.35	6.54	Normal	0.357	0.090 ^b
SGOT	< 45.00	26.68	4.97	32.19	7.66	Normal	0.003	0.001 ^b
SGPT	< 45.00	23.96	9.18	22.42	9.87	Normal	0.046	0.136 ^b

Notes: a: performed with t-test; b; performed with Wilcoxon test.

Cigarette smoke containing free radical compounds are semiquinones. These free radicals when dissolved in lung fluid and blood plasma can reduce oxygen to superoxide and form hydrogen peroxide. Cigarette smoke also produces ROS which can increase oxidative stress increasing oxidative stress biomarkers such as MDA (Khrisna & Hendriantingtyas, 2016). The excessive free radicals in the body can cause damage to normal tissue. Lipid peroxide in the body occurs as a response to increased oxidative stress which results in the end product MDA (Sirait et al., 2016). MDA is one of the markers initiating in dysfunction of endothelial, and the impairment of respiratory endothelial by smoking (Yilmaz et al., 2020).

Bawang Dayak leaves contain flavonoids and phenolics which function as antioxidants. Likewise, other supplements have anti-inflammatory, anti-oxidant and anti-atherosclerotic properties had claimed they able to reduce the levels of stress oxidative markers after weeks of consumption (Yilmaz M I et al., 2020; Rostami H A A et al., 2022; Farahat M et al., 2016). Effect of supplementing broiler chicken diets with green tea extract on the growth performance, lipid profile, antioxidant status and immune response. *British Poultry Science*, 57(5), 714-722.). Flavonoids work as antioxidants which can stabilize free radicals in the body. Flavonoid structures can donate hydrogen atoms to free

radicals to stabilize them. Flavonoids also produce enzymes that can inhibit the production of free radicals such as xanthine oxidase and lipoxygenase (Caesiro et al., 2019). Phenolic compounds contain hydroxyl groups on aromatic rings so that they can act as donors of hydrogen atoms to free radicals. Phenolic compounds act as a reservoir for O₂⁻ and OH⁻, which protect membrane lipids from damaging oxidation reactions (Dewi et al., 2019).

Many fruits, vegetables, and herbs include secondary metabolites, antioxidant phenols, and flavonoids, which are beneficial in reducing oxidative stress. Phenols and flavonoids can prevent fatty acids from oxidative breakdown. Other onions such *Eleutherine bulbosa* (Mill) and *Allium cepa* (L) have several biological functions, including antibacterial, antifungal, anti-amoebae, antioxidant, anti-inflammatory, and analgesic (Shi et al., 2019; Al-Ansari et al., 2023).

Many of these effects have been related to onions' presence of flavonoid compounds including quercetin and kaempferol. A flavonoid exhibiting potent antioxidant effects is quercetin. Onions nevertheless also contain other phytochemicals, including phenolic and organosulfur compounds, which are often attributed for their purported beneficial effects on health (Setyawan et al., 2020).

In Table III, the average blood glucose level increased significantly (p 0.000 < 0.05) compared

to the value before the Dayak onion capsule intervention was started. The type of test used, random blood sugar, may contribute to this change because it depends on the participant's pre-test diet. In addition, Avicel, as a capsule filler, has a sugar group that can affect the participant's glucose levels. The increase in blood glucose did not exceed normal values. However, other studies have shown that Dayak onions have the effect of lowering glucose levels in pre-clinic and clinical experiments (Febrinda et al., 2014; Andi, 2014; Setyawan et al., 2020). It was likely alpha-glucosidase inhibition and antioxidant activity presented in the ethanolic extracts which contained tannin, phenolic compounds, flavonoids, and triterpenoids. both forms of extracts (Andi, 2014).

The decreasing cholesterol level in this study shares similarities with Saragih et al (2014) and Setyawan et al's (2020) findings. Their participants had lowered glucose and cholesterol levels after consuming Bawang Dayak. According to (Ieyama et al., 2011), Bawang Dayak plants contain eleutherol and eleutherinoside A and B, which have the potential to be used as anticholesterol. Smoking and cholesterol are related in that they influenced each other. Smoking decreases HDL levels in the blood, leading to blood clots more easily. As a result, it exacerbated heart attacks, strokes, and clogged arteries more likely. This behavior raises the risk of thrombosis in a coronary artery that is presently constricted. Additionally, it has been demonstrated to lower HDL levels and raise LDL levels in the blood (Chidozie et al., 2014; Chang, 2012).

Bawang Dayak leaves capsules did not show signs of hepatotoxicity. This can be seen from the SGOT and SGPT values which are still within normal limits. Ethanolic extract of Bawang Dayak was tested on animals for 28 days and showed no significant difference in SGPT and SGOT levels. An amount of 100 mg/kg BW of Bawang Dayak ethanolic extracts could reduce hepatocyte necrosis and hydropic degeneration while also preventing liver tissue inflammation (Andi, 2014). SGPT and SGOT enzymes can reflect liver cell damage. Progressive liver cell damage can make SGOT/SGPT levels rise to three to five times the normal limit (Triyono et al., 2021).

CONCLUSION

Bawang Dayak leaves capsules can reduce MDA levels and can function as an antioxidant supplement for active smokers. Bawang Dayak leaves capsules did not show signs of hepatotoxicity after administration.

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