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Beta vulgaris L. juice Improves Liver Enzymes of Cigarette Exposed Male Wistars

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cigarette smoke, *Beta vulgaris L.* juice (*Beta vulgaris L.*), AST and ALT levels.

ABSTRACT

Cigarette smoke penetrates the body as a free radical that triggers damage caused by oxidative stress. Persistent exposure to cigarette smoke can cause cell and organ injury, including the liver. Biomarkers of ALT and AST may detect liver injury, and free radicals in the body can be reduced by exogenous antioxidants, such as *Beta vulgaris L.*, which has the potential as a potent antioxidant. This study was purposed to identify the effect of *Beta vulgaris L.* on the ALT and AST levels in male Wistar rats treated with cigarette smoke. This research used twenty-four male Wistar rats selected by simple random sampling and divided into 4 groups. This study applied cigarette smoke exposure and *Beta vulgaris L.* juice administration at a dose of 8 mL/kg BW/day and 16 mL/kg BW/day. The outcomes were AST dan ALT levels in the blood. Statistical analysis was conducted using the One Way ANOVA posthoc Bonferroni test. Data of AST and ALT levels are normally distributed (p>0,05) with similar data variance (p>0,05). Analysis of AST level data using Bonferroni's One Way ANOVA posthoc test showed significant differences in AST levels between the groups (p<0.05). The results of the ALT level data test showed a significant difference in ALT levels (p<0.05) between group N and group P1 & P2, group K(-) and group P1 & P2, and between- group P1 and P2. There is no significant difference in ALT levels between group N and K(-) (p>0.05). Administration of *Beta vulgaris L.*. juice affected AST and ALT levels in male Wistar rats exposed to cigarette smoke. The AST and ALT levels of the group given *Beta vulgaris L.* juice at a dose of 16 mL/kg BW/day were lower than those given *Beta vulgaris L.* juice at an 8 mL/kg BW/day.

1. INTRODUCTION

Smoking is one of the health problems in Indonesia. The 2018 Basic Health Research (Riskesdas) data of the Indonesia Ministry of Health, the prevalence of smoking in the Indonesian population aged 10-18 years

increased to 9.1% from 7.2% in 2013 [1]. Cigarettes contain addictive, harmful substances and can directly or indirectly cause health issues. The main toxins in cigarettes include nicotine, tar, carbon monoxide (CO), and various heavy metals [2]. AST is an enzyme usually found in mitochondria in heart muscle, skeletal muscle, kidney, liver, and brain. Typically, ALT is an enzyme found in the cytoplasm of liver cells. These two enzymes will increase if there is any liver damage. AST is an enzyme usually found in mitochondria in heart muscle, skeletal muscle, kidney, liver, and brain [3]. The liver is mainly responsible for endogenous and exogenous substrate metabolism in our body, and it plays an essential role in the detoxification and elimination of drugs. Liver injury may be caused by toxic agents, i.e., alcohol consumption, xenobiotics, malnutrition, drugs, anemia, and infections. Underneath usual state, the cell is in the condition of a state of redox balance ort equilibrium state between reducing and oxidizing agents [4]. Hepatotoxic agents can react with the essential cellular components and consequently induce almost all liver lesions. *Beta vulgaris L.* is high in well- identified antioxidant phytochemical compounds, including flavonoids, phenolic compounds, carotenoids, epicatechin, caffeic acid, ascorbic acid and rutin [5- 7]. We aimed to identify the effect of *Beta vulgaris L.* on the ALT and AST levels in male Wistar rats with cigarette smoke treatment.

2. Methodology

2.1 Sample

Beetroots (*Beta vulgaris L.*) were purchased from a fresh vegetable market in Semarang. We kept the *Beta vulgaris L.* at room temperature until processed.

2.2 Preparation of samples

We washed the fruits and peeled them to remove sand, dirt, debris, and debris. The peeled beetroots were then processed.

2.3 Preparation of Beta vulgaris L. juice

Ten grams (10gms) of the peeled beetroot were blended with 50ml of distilled water in an electronic blender (Miyako BL51-G1 electric blender) to get a constant consistency mix. The mixture was poured into a measuring cylinder and added with distilled water to make a total volume of 100 ml, 10g/100ml (10%). The solution was centrifuged using a low-speed centrifuge 12 hole 80-2 for 10mins at 500rpm. The supernatant was collected and stored in plastic tubes. All the supernatants were stored in a refrigerator at 0oC until utilized within twenty-four hours.

2.4 Study flow

This study is a true experimental study with a post-test-only group design with experimental animals in male Wistar rats (*Rattus novergicus L.*), divided into 4 groups. N: Normal group. Rats were given a standard diet without exposure to cigarette smoke and *Beta vulgaris L.* juice for 28 days. K(-): Negative control group. Rats were given a standard diet and exposure to cigarette smoke without *Beta vulgaris L.* juice for 28 days. P1: Treatment group 1. P2: Treatment group 2. X1: Rats were given a standard diet, exposure to cigarette smoke, and *Beta vulgaris L.* juice at a dose of 8 mL/kg BW/day for 28 days. X2: Rats were given a standard diet, exposure to cigarette smoke, and *Beta vulgaris L.* juice at a dose of 16 mL/kg BW/day for 28 days. O N: AST and ALT levels from the standard group O K(-): AST and ALT levels from negative control group O P1: AST and ALT levels from treatment group 1 O P2: AST and ALT levels of the treatment group 2

2.5 Study procedure

Beta vulgaris L. juice was given to rats using a gastric probe at a dose of 8 mL/kg BW and 16 mL/kg BW before cigarette smoke exposure.

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2.6 Beta vulgaris L. Juice Making

The *Beta vulgaris L.* is washed with clean water and cut into several pieces. The tuber pieces are put into the household juice extractor to become *Beta vulgaris L.* juice.

2.7 Measurement of Antioxidant Activity of Bit. Juice

Antioxidant activity was measured using the DPPH method (2,2-diphenyl-1-picrylhydrazyl) on the first day of *Beta vulgaris L.* juice preparation. The DPPH assay was used to predict antioxidant activities by the mechanism in which antioxidants act to inhibit lipid oxidation, scavenging DPPH radical

2.8 Treatment of Experimental Animals

24 male Wistar rats were adapted to be given standard food and drink for 7 days. Randomly divided 24 rats into 4 groups and housed them based on the group so that each cage contained 1 group consisting of 6 rats. Rats were treated according to their groups for 28 days. Cigarette smoke exposure was carried out using a smoking chamber, and *Beta vulgaris L.* juice was administered through a gastric probe. The following are the details of the treatment of each group, namely: Group N: 6 rats were given standard food and drink for 28 days. Group K(-): 6 rats were given standard food and drink and exposure to cigarette smoke at a dose of 2 sticks/day every morning for 28 days.

Group P1: 6 rats were given standard food and drink and exposure to cigarette smoke at a dose of 2 sticks/day every morning for 28 days. Before being exposed to cigarette smoke, rats were given *Beta vulgaris L.* juice at an 8 mL/kg BW/day dose for 28 days.

Group P2: 6 rats were given standard food and drink and exposure to cigarette smoke at a dose of 2 sticks/day every morning for 28 days. Before being exposed to cigarette smoke, rats were given *Beta vulgaris L.* juice at a 16 mL/kg BW/day dose for 28 days.

2.9 ETHICS

The Health Research Ethics Commission (KEPK) Faculty of Medicine, Diponegoro University, approved this study with register no. 92/EC/H/FK-UNDIP/VIII/2021

3. RESULT

This study used 24 male Wistar rats (Rattus novergicus L.) aged 2-3 months with a bodyweight of 150-250 grams. The adaptation course was 7 days. During the study, there were no research samples that dropped out. On day 29, blood samples were taken via a retro-orbital vein. The measurement of AST (aspartate aminotransferase) and ALT (alanine aminotransferase) levels used the IFCC (International Federation of Clinical Chemistry) method without pyridoxal phosphate, using the Diasys reagent kit.

3.1 Analysis of Antioxidant Levels of Beta vulgaris L. Juice

The antioxidant power of *Beta vulgaris L.* juice was measured using the DPPH method (2,2-diphenyl-1-picrylhydrazyl). DPPH measurement results and IC presented in Table 1. Thereafter, we calculated the value of antioxidant using formula $\boldsymbol{y = 0,02x - 1,7062, 50 = 0,02x - 1,7062. x = 2585\ ppm}$ The IC50 result of *Beta vulgaris L.* juice is 2585 ppm, classified as low because the IC50 is more than 200 ppm.

Table 1. DPPH measurement results of Beta vulgaris L. juice

Sample concentration (ppm)	% antioxidant
100	0,30

200	2,52
300	4,01
400	6,23
500	8,46

Our datasheet showed normal distribution. The highest AST mean data was in group K(-) with a mean value of 95.67 ± 3,266. The lowest mean AST was in group N, with a mean value of 42.67 ± 2.733. Test the data homogeneity using the variance test (Levene's Test). The variance test (Levene's test) showed that the data on serum AST levels had the same data variance with p=0.103 (p>0.05).

Hypothesis testing using One Way ANOVA stated that the value of p=<0.001 (p<0.005) revealed that there were at least 2 groups with significantly different mean AST levels. The following data analysis test used Bonferroni's posthoc analysis because of normal data distribution, and the data variance was the same. Table 2 shows the results of Bonferroni's One Way ANOVA posthoc test.

Table 2. AST level data with posthoc Bonferroni

Group	Difference average	CI 95%		*P-value*
		Minimum	Maximum	
N – K(-)	-53,000	-61,63	-44,37	<0,001
N – P1	-39,667	-48,29	-31,04	<0,001
N – P2	-30,000	-38,63	-21,37	<0,001
K(-) – P1	13,333	4,71	21,96	0,001
K(-) – P2	23,000	14,37	31,63	<0,001
P1 – P2	9,667	1,04	18,29	0,022

The ALT data is usually distributed with p>0.05. The highest ALT mean data was in group P1 with a mean value of 109.33 ± 10.463, while the lowest ALT average data was in group K(-) with a mean value of 69.00 ± 8.532. Test the data homogeneity using the variance test (Levene's Test). The variance test (Levene's test) showed that the data on serum ALT levels had the same data variance with p=0.376 (p>0.05). Bonferroni's posthoc analysis results showed significant differences in ALT levels between groups N and P P1 and P2, groups K(-) and groups P1 and P2, and between groups P1 and P2. However, group N and K(-) showed a non-significant difference in ALT levels. Comparative hypothesis testing using the One Way ANOVA test stated that the value of p=<0.001 (p<0.005) indicated at least 2 groups with significantly different mean ALT levels. The posthoc analysis test used Bonferroni's posthoc because of normal data distribution, and the data variance was the same. Bonferroni's One Way ANOVA post-hoc test results can be seen in table 3.

Table 3. AST level data with posthoc Bonferroni

Group	Average difference	CI 95%		*P-value*
		Minimum	Maximum	
N – K(-)	0,667	-15,42	16,75	1,000
N – P1	-39,667	-55,75	-23,58	<0,001
N – P2	-23,000	-39,09	-6,91	0,003
K(-) – P1	-40,333	-56,42	-24,25	<0,001
K(-) – P2	-23,667	-39,75	-7,58	0,002
P1 – P2	16,667	0,58	32,75	0,039

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4. DISCUSSION

Beta vulgaris L., commonly known as beetroot, has been used to treat various diseases, such as constipation, fever, diabetes, cancer, constipation, cancer, diabetes, liver and heart diseases. *Beta vulgaris L.* extract can prevent and repair histological and biochemical transformations in the liver following a hepatotoxic agent [8]. Inflammation is a complex and adaptive physiological reaction toward harmful stimulants and tissue insults associated with various antigens. The antioxidant action of betanin in *Beta vulgaris L.*, with its ability to donate electron has been identified as the main cause of its enormous antioxidant capacity. Moreover, its efficacy in radical scavenging activity also improves activation of Nrf2 signaling and the defense of oxidants [9]. Betaine is a vital methyl group donor that disrupts inflammation through repressing nuclear factor-kappa light chain enhancer of activated B cells (NF-κB) and Akt activation [10].

In this study, AST levels in group K(-) were significantly higher when compared to group N with p=<0.001 (p<0.05). This result shows that exposure to cigarette smoke can trigger oxidative stress and lipid peroxidation. Exposure to cigarette smoke works as an exogenous free radical in this study.

If damaged, the liver will release biomarkers, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Aspartate aminotransferase is a transaminase enzyme, the highest concentration found in the liver and skeletal muscle, and the concentration of AST is lower in all tissues except bone. Under normal circumstances, enzymes are present in the cells that synthesize them. The enzyme will be released into plasma or serum when cell damage occurs [11]. When ROS levels up, the detachment of Nrf2 from the original Kelch-like ECH-associated protein 1 (Keap1) occurs when ROS increases. After that, it will migrate into the nucleus and adhere to the antioxidant responsive element (ARE), stimulating the gene expression of antioxidant and defensive genes. The Nrf2 regulates the adaptive mechanism of cells toward diverse oxidants and electrophiles [12]. Nrf2 could reduce excessive ROS through the antioxidant activity of *Beta vulgaris L.* and activation of Nrf2 [13].

Upregulated mRNA expressions of NF-κB, MAPK1, MAPK3, CYP2E1, and α-SMA decreased in *Beta vulgaris L.* treated group, suggesting the protective effects in hepatotoxicity due to alteration of the liver damage induced by LPS or alcohol [14] *Beta vulgaris L.* and its juice possess significant antioxidant and radical scavenging abilities, positively correlated with the natural antioxidants [15]. The combined use of alcohol and cigarette smoke on the liver or kidneys induces liver, and kidney injuries, both morphology, and biochemically chronically cigarette smokes treated rats. This damage is related to biochemical changes in rats [16]. Cigarette smokers exhibited a substantial cognitive function impairment [17]. In a study, The activity of liver enzymes of smoking and non-smoking participants In a population-based cohort which involved 10,000 individuals aged 35–70 years old from Sheshdeh, showed that smokers had significantly lower ALT ($P < 0.001$), higher AST ($P = 0.0.002$), and higher ALP ($P < 0.001$) [18].

Administration of *Beta vulgaris L.* juice can help endogenous antioxidants maintain and prevent oxidative stress or damage to cellular components. Antioxidants can neutralize free radicals by donating electrons to free radicals not to react/damage cells or DNA. Betanin in *Beta vulgaris L.* may act as an antioxidant because of its high ability to donate electrons to prevent free radicals from damaging cell membranes. Based on an in vitro study, betalain metabolites in the form of betanin and betanidine can reduce the occurrence of lipid membrane oxidation in *Beta vulgaris L.*. and be the most effective in inhibiting lipid peroxidation [19]. This vital mechanism is due to the inactivation of the enzymes involved in the biochemical response (lipoxygenase and cyclooxygenase) [20]. Betalains are formed through proactive steps in beta-beta biosynthesis; these include condensing the beta-chromatin chromophore, balsamic acid, with cyclo-dopa and amino acids or amino acids alone or those involved in the construction of the related aldimine from the red- purple beta and

yellow betaxanthins [21].

Beta vulgaris L. prevents liver injury by attenuating cell apoptosis, oxidative stress, and inflammation. It stimulates the protection of antioxidants, and therefore hepatoxicity could be minimized using *Beta vulgaris L.* juice [22]. A study that examines the influence of *Beta vulgaris L.*-polyphenols on oxidative liver damage in mice fed a high-fat diet (HF) shows that *Beta vulgaris L.* attenuated the harmful effects of a HF diet on lipid metabolism, reduced fasting blood glucose levels, ameliorated cholesterol levels, and reduced GPx and GR activities compared to the HF group [23]. *Beta vulgaris L.* juice has potential hepatoprotective effects on the liver in a dose-dependent manner [24]. *Beta vulgaris L.* has immunomodulatory/antioxidant effects that could help slow the advancement of diabetic complications, owing to down-regulated the expression of hepatic NF- κB versus the untreated diabetic groups in a dose-dependent manner [25].

Upregulated mRNA expressions of MAPK1, NF-κB, MAPK3, α-SMA and CYP2E1, decreased in *Beta vulgaris L.* treated group, suggesting the protective effects in hepatotoxicity due to alteration of the liver damage induced by LPS or alcohol [26]. The demographic location and cultivating process influence the phytochemical components and antioxidant activity of *Beta vulgaris L.* [27]. Free radicals can oxidatively damage mitochondria and regulate gene expression, contributing to fibrosis and perpetuating the chronic inflammatory process [28]. Betalains have a consistent structural characteristic derived from balsamic acid and a radical R1 or R2, where the substituents can be *Beta vulgaris L.* holds approximately 75−95% betacyanins and 5−25% betaxanthins. Falling levels of cytokines, superoxide anion, and nuclear factor kappa B (NF-κB) after initiation of lipopolysaccharide (LPS) occur after betalain treatment [29]. Pigments from red beetroot consist of betacyanins. Namely, betanin and is betanin, an isomer of betanin. A previous study analyzed the content of betalains in the processed beetroot juice and reported that betanin suggests the most plentiful component at 300−600 mg/kg BW, observed by violaxanthin and is betanin. In this study, there was also a statistically significant difference, where ALT levels in group K were significantly lower when compared to group P1 (p=<0.001) and group P2 (p=0.002). In this study, the AST and ALT levels in the P2 group were significantly lower when compared to the P1 group (p=0.022 and p=0.030). It indicates that the levels of AST and ALT are lower with the administration of *Beta vulgaris L.* juice at a dose of 16 mL/kg BW/day compared to the administration of *Beta vulgaris L.* juice at a dose of 8 mL/kg BW/day. ROS and HClO are released from neutrophils, thereby diminishing oxidative stress. Betanins hinder ROS production by neutrophils and decrease the number of penetrating neutrophils [30].

5. CONCLUSION

There is a difference in the effect of giving *Beta vulgaris L.* juice in the group receiving a dose of 16 mL/kg BW/day compared to the group receiving a dose of 8 mL/kg BW/day on ALT and AST levels in male Wistar rats exposed to kretek cigarette smoke. The group receiving a dose of 16 mL/kg BW/day had lower AST and ALT levels than the group receiving a dose of 8 mL/kg BW/day.

AUTHOR CONTRIBUTION

Conceptualization, S.P.S, and P.K.D.; methodology, S.P.S, P.K.D, and A.N.S. validation, S.P.S, P.K.D, E.K.S.L, and A.N.S.; formal analysis, A.N.S.; investigation, S.P.S, P.KD, and A.NS.; data curation, A.N.S.; writing—original draft preparation, A.N.S.; writing—review and editing, A.N.S.; and funding acquisition, S.P.S

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