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Antioxidant Activity Test of Salak Bali Peel Extract (*Salacca zalacca var. amboinensis*) Against Brain Cells of Male Mice (*Mus musculus L.*) Induced by Alloxan

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Abstract: This study aims to test the antioxidant activity of salak Bali peel extract (*Salacca zalacca var. amboinensis*) against brain cells of male mice (*Mus musculus L.*) exposed to alloxan. Free radicals can trigger damage to brain cells through oxidative mechanisms, which contribute to the development of various neurodegenerative diseases that can damage cells in the body. Salak Bali peel extract contains bioactive compounds such as flavonoids, tannins, and polyphenols that are antioxidant-active. This study was conducted using a completely randomized design (CRD) in mice induced by alloxan at a dose of 150 mg/kg BW (group 1), followed by oral administration of salak Bali peel extract at a dose of 4.2 mg/kg BW (group 2) and 8.4 mg/kg BW (group 3) for 35 days. The control group used in this study was alloxan, which was used to compare the treatment results with conditions without intervention so that the effects of the treatment could be identified more clearly. The results of the antioxidant analysis test using the DPPH method showed an IC50 value of the salak Bali peel extract of 45.5 µg/mL, indicating a high antioxidant capacity. Histopathological analysis revealed that administration of salak Bali peel extract could reduce necrosis in the brain tissue of mice induced by alloxan, suggesting a neuroprotective effect. Therefore, salak Bali peel extract has the potential to be a source of natural antioxidants that can be used to prevent brain damage due to oxidative stress and as a therapy for treating neurodegenerative diseases.

Keywords: Alloxan; Antioxidant Activity; Brain Cells; Male Mice; Salak Bali Peel Extract.

Introduction

Free radicals are highly reactive molecules that can damage cells in the body, including cells in the brain. Damage caused by free radicals plays an essential role in various degenerative diseases, including neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [1]. One of the most effective ways to combat the effects of free radicals is to use antioxidant compounds that can neutralize these free radicals. Therefore, studying the potential of antioxidant compounds from various natural sources is essential for developing safer and more effective therapies [2].

Salak Bali (*Salacca zalacca var. amboinensis*) is a snake fruit that grows in Indonesia and is known to contain various bioactive substances, such as flavonoids, tannins, and saponins. These compounds have potential antioxidant activity [3]. Although the peel of salak Bali is often discarded as waste, it contains various compounds that may have health benefits. The bark of salak Bali contains flavonoids, tannins, and other polyphenol compounds known to have antioxidant and anti-inflammatory activity [4]. These compounds can protect brain cells from oxidative damage and inflammation that often cause neurological disorders [5].

The brain is a very complex and essential organ of the human body. Located in the skull, the brain controls all body activities, conscious and unconscious. The brain regulates vital functions such as breathing, heart rate, body movement, and higher cognitive processes such as thinking, learning, and remembering [6]. The brain consists of various cells, such as neurons, glial cells, and endothelial cells, that form the central nervous system. Neurons function to conduct electrical impulses, while glial cells support nerve function and protect the brain from damage [7].

Diseases associated with brain injury, such as stroke, Alzheimer's disease, and diabetes, are often associated with oxidative stress as the primary cause of cell damage [8]. One way to test the ability of compounds to combat this damage is by using an alloxan-induced animal model [9]. Alloxan is known to cause brain cell damage through an oxidative mechanism that resembles oxidative stress in humans [10]. A study found that mice given alloxan experienced increased brain cells damaged by necrosis. However, giving red dragon fruit juice (*Hylocereus polyrhizus*) to diabetic mice showed positive results, namely a decrease in blood glucose levels and a reduction in brain cell damage. This indicates that red dragon fruit juice has the potential to help repair brain tissue damage caused by diabetes [11]. A recent study showed that administering alloxan to mice caused a significant increase in blood glucose levels, which may be implicated in cellular damage in various organs [12].

Research on the potential of salak Bali peel extract as a source of antioxidant compounds is very important, considering the increasing prevalence of degenerative diseases associated with oxidative stress. With its flavonoid, tannin, and other polyphenolic compounds, salak Bali skin

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has the potential to be a safe and effective alternative therapy to combat brain cell damage caused by free radicals. This study aims to test the antioxidant activity of salak Bali peel extract on alloxan-induced male rat brain cells. Using an alloxan-induced male mouse animal model can explore how salak Bali peel extract can reduce oxidative damage to brain cells and protect against other injuries.

Research Methods

Research Design

The research design was a Completely Randomized Design (CRD) with one negative control group and three treatment groups. Before the test animals were given treatment, the test animals were fasted for approximately 24 hours and only given drinking water, after which the mice were induced with alloxan at a dose of 150 mg/kg BW. On the 4th day, the test animals were tested for blood glucose and then given salak Bali peel extract for 35 days once a day orally. On the 36th day, all test animals were terminated by surgery using a dissecting kit to remove the brain organs. A total of 28 mice were randomly divided into 4 groups, each group consisting of 7 mice as follows: Group 1: negative control group (-) is a group induced with alloxan and given distilled water, Group 2: treatment group, is a group induced with alloxan and given salak Bali peel extract at a dose of 4.2 mg/kg BW, Group 3: treatment group, is a group induced with alloxan and given salak Bali peel extract at a dose of 8.4 mg/kg BW, Group 4: treatment group, is a group induced with alloxan and given salak Bali peel extract at a dose of 16.8 mg/kg BW [13].

Preparation Stage

Extract Sample Preparation

Salak Bali samples were obtained from Sibetan Village, Karangasem Regency, Bali. Samples were taken when the fruit was ripe, indicated by sparse scales; the color of the fruit skin was blackish-red and shiny, and the hairs had disappeared; the pointed tip of the fruit skin felt soft when pressed, easily detached from the bunch.

Preparation of Salak Skin Extract

The salak skin is dried using an oven at 30-50C for 6-8 hours, powdered using a blender, and sieved using a sieve with a mesh number of 10. The following process is to extract the sample by maceration using 96% ethanol solvent for 3 days with occasional stirring. After 3 days, the macerate results are filtered using filter paper and then evaporated using a rotary evaporator to obtain a thick extract.

Antioxidant Content Test

Antioxidant capacity analysis was conducted by running a series of gallic acid concentrations of 0, 5, 10, 15, 20, and 25 ppm. Absorbance was read at a wavelength of 517 nm. IC50 analysis was carried out to determine the sample concentration required to inhibit 50% of DPPH free radicals. The addition of compounds suspected of containing antioxidants to DPPH reduces the concentration of DPPH. It reduces the DPPH absorption value compared to the absorption control containing DPPH without adding compounds suspected of containing antioxidants [2].

Research Implementation Stage

Brain Tissue Collection

On the 36th day, the mice were sacrificed, the mice were dislocated at the neck, then surgery was performed on the head, and the brain organ was removed. The isolated brain was soaked in physiological NaCl salt until clean. After that, the brain was inserted into Bouins solution and NaCl fixative solution. The brain organ was made into a paraffin block. Then, the block was sliced with a 3-5 µm thickness using a microtome to obtain the hippocampus section for histopathological analysis with Hematoxylin and Eosin staining [14].

Hematoxilin and Eosin Staining

The staining of histological preparations began with the deparaffinization process into a xylol solution as much as 2x dipping for 30 minutes. The rehydration process to remove xylol involves inserting the preparation into an absolute alcohol solution for 2 minutes, then inserting it again into a 95% to 70% alcohol solution for 1 minute. After rehydration, the preparation was washed with running water, and hematoxylin staining was done for 8 minutes. The next step is washing again with running water for 2 minutes. The eosin staining lasts 2 minutes, and the preparation is washed with running water. After the eosin staining, the histology preparation is dehydrated into a 95% alcohol solution and absolute alcohol twice for 2 minutes. Then, the preparation is soaked using xylol twice for 2 minutes; then, the preparation is covered with a cover glass using permanent adhesive and labeled [15].

Data Analysis

Data was analyzed quantitatively using a computer statistics program (SPSS 22.0 for Windows). The Kolmogorov-Smirnov test was carried out to test the normality of the data; if the data was not standard, the Kruskal-Wallis test was carried out. Leven's Test was carried out to see the homogeneity of variance. The One Way Anova test was carried out to see the treatment's effect. If there are significant results, it is continued with the Duncan multiple range test with a confidence level of 5% ($P < 0.05$).

Results and Discussion

Antioxidant Content Test

The antioxidant content test of Salak Bali skin extract was carried out using IC50 analysis to determine the sample concentration needed to inhibit 50% of DPPH free radicals. Based on the study's results, data was obtained that the salak Bali peel extract contains high antioxidants. The results of the antioxidant content test can be seen in Table 1.

Table 1. Antioxidant Content Test of Salak Bali Peel Extract

Sample	IC50 Value (µg/mL)	Antioxidant Category
Salak Bali Peel Extract	45.5	High

According to the study results, Salak Bali skin has a high IC50 value of 45.5 µg/mL. IC50 is an indicator of antioxidant strength, and these results indicate that Salak Bali skin has a strong ability to ward off DPPH free radicals. A high IC50 value suggests that the salak Bali peel extract can reduce the number of free radicals. DPPH is a free radical molecule that will change color from purple to yellow when it meets antioxidants. This color changes because the DPPH free radicals have been neutralized by electrons provided by antioxidants [16].

Salak Bali skin contains various bioactive compounds, including antioxidants, and is considered waste, even though it has the potential for various health uses. This study aimed to test the antioxidant content of Salak Bali skin using the DPPH (2,2-diphenyl-1-picrylhydrazyl) method to determine the ability of free radical-fighting compounds. The high antioxidant content in Salak Bali skin is thought to be caused by the presence of phenolic, flavonoid, and tannin compounds found in various parts of the plant, including the fruit's skin [17]. These compounds are known for neutralizing free radicals that can cause cell damage and contribute to aging and degenerative diseases. Polyphenols are natural compounds abundant in plants and have strong antioxidant properties. Flavonoids are also included in the polyphenol group and can prevent free radicals that can damage body cells [18]. Salak Bali skin is also rich in these compounds. The outer skin also protects the fruit from ultraviolet rays and pathogens. For this reason, the snake fruit's skin produces protective compounds with antioxidant properties, such as tannins, which protect the skin from oxidative damage. Tannins found in the skin of the snake fruit can bind and neutralize free radicals. Tannins also act as active ingredients that inhibit the growth of cancer cells, improve blood circulation, and positively impact overall body health [19]. In addition to antioxidants, the active ingredients in the skin of the Bali snake fruit also have antibacterial and anti-inflammatory properties. These compounds may contribute to the antioxidant properties of the skin of the snake fruit, which fight inflammation and infection and support body health [20].

The advantage of the skin of the Bali snake fruit as a source of antioxidants lies mainly in the content of bioactive compounds found in the fruit's skin, which is usually thrown away. This opens up opportunities for optimal use of the skin of the Bali snake fruit in the health and cosmetics industry and in the production of nutritional supplements to increase endurance and fight oxidative stress. Based on existing research, many other natural ingredients also show significant antioxidant activity, such as tea leaf extract, pegagan leaves, and various types of leaves [21]. However, the advantage of the skin of the Bali snake fruit is that it is easy to find in tropical areas, especially Bali, one of the main producers of snake fruit. Due to its high antioxidant power, Salak Bali skin can be a more cost-effective and sustainable alternative when developing antioxidant products.

Brain Cell Count Analysis

An analysis of the number of brain cells in male mice given Balinese salak Bali peel extract can be seen in Table 2. The statistical analysis results showed a significant difference ($P<0.05$) between the control and treatment groups.

Table 2. The average number of neuron necrosis

Treatment	Average number of neuron necrosis ± Standard Deviation
Group 1	24.5 ± 4.762a
Group 2	13.7 ± 5.542b
Group 3	8.9± 5.872b

From Table 2, it can be seen that there was a decrease in the number of neuron necrosis cases from group 1 to group 3. This is because the salak Bali peel extract has a high flavonoid and antioxidant content, so it can reduce the number of neuron necrosis. Alloxan-induced brain cell necrosis is a phenomenon of cell damage caused by oxidative stress [22]. Alloxan, which is known to damage pancreatic beta cells in experimental animals, also has the potential to cause oxidative damage to brain cells, which in turn can lead to necrosis or cell death [23]. This process occurs because alloxan increases the production of free radicals that damage membranes.

Alloxan-induced brain cell necrosis is a phenomenon of cell damage caused by oxidative stress [22]. Alloxan, which is known to damage pancreatic beta cells in experimental animals, also has the potential to cause oxidative damage to brain cells, which in turn can lead to necrosis or cell death [23]. This process occurs because alloxan increases the production of free radicals that damage cell membranes and other cellular components and trigger inflammation that worsens the condition of brain tissue [24]. This oxidative stress plays an essential role in the development of various neurodegenerative diseases, including Alzheimer's and Parkinson's disease, which can affect the quality of life [25]. However, administering salak Bali peel extract, rich in antioxidant compounds, such as flavonoids, tannins, and polyphenols, can protect against this damage. These compounds work by neutralizing free radicals produced by oxidative stress, thereby reducing brain cell damage caused by alloxan. Research shows that salak Bali peel extract can inhibit the oxidation process and prevent further damage to alloxan-induced mouse brain cells, which is reflected in decreased necrosis in brain tissue.

The decrease in necrosis in the brains of male mice given salak Bali peel extract can be explained by the antioxidant activity of the flavonoid and tannin compounds in the extract. Flavonoids are known to have the ability to reduce inflammation and protect brain cells from oxidative damage [26]. In addition, tannins bind heavy metals and inhibit the production of pro-oxidative enzymes, thereby reducing oxidative stress [27]. Other relevant studies also support this protective effect. For example, a study showed that flavonoids contained in plant extracts can reduce free radical activity while suppressing apoptosis in brain tissue exposed to neurotoxins [28]. In addition, a study revealed that tannins contained in herbal plant extracts effectively prevent oxidative damage to mice's brains induced by chemical stress, similar to damage caused by alloxan [29].

The combination of flavonoids and tannins from plant extracts can improve brain tissue structure while reducing necrotic areas by increasing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase. These findings strengthen the idea that compounds in Balinese snake fruit skin extract work synergistically to suppress oxidative stress and accelerate the recovery process of damaged brain structures [30]. Based on the results of the study, salak Bali peel extract can repair the brain structure of mice damaged by alloxan by reducing the area of necrosis that usually forms in brain cells damaged by free radicals.

Thus, salak Bali peel extract has excellent potential as a neuroprotective agent that can reduce brain tissue damage and prevent the development of neurodegenerative diseases associated with oxidative stress. These results indicate that natural compounds from the skin of snake fruit can be used as safe and effective therapeutic candidates to overcome brain damage due to oxidative stress, opening up opportunities for further development in treating brain diseases related to oxidative damage.

Conclusion

This study revealed that the skin extract of salak Bali (*Salacca zalacca var. amboinensis*) has significant antioxidant activity potential and can protect brain cells from damage caused by oxidative stress. Testing the antioxidant content using the DPPH method showed that the skin extract of Balinese snake fruit reached a high IC50 value, indicating its strong ability to neutralize free radicals. In addition, administering salak Bali peel extract to male mice induced by alloxan can reduce necrosis in brain tissue, thus indicating a positive neuroprotective effect. This study opens up opportunities to utilize salak Bali skin as a source of natural antioxidants that can be further developed in therapy for brain diseases related to oxidative stress.

Author's Contribution

Anak Agung Istri Mas Padmiswari: Designed the research framework, conducted the research, performed data analysis, and prepared the results and discussion, Nadya Treesna Wulansari: Contributed to data analysis and prepared the results and discussion, Kadek Buja Harditya: Contributed to data analysis and prepared the results and discussion, Sri Dewi Megayanti: Contributed to data analysis and prepared the results and discussion.

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