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The Effect of Andaliman Fruit Extract (*Zanthoxylum acanthopodium DC*) on α-Synuclein Levels in Rotenon-Induced Wistar Rats

Citra Puan Maulidza[1], Binarwan Halim[1*], Linda Chiuman[1], Atika Rimalda Nasution[1], Yohani Theresia[1]

[1] Department of Biomedical Sciences, Faculty of Medicine, Dentistry, and Health Sciences, Universitas Prima Indonesia, Medan, Indonesia.

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Corresponding Author:
Binarwan Halim
binarwanhalim@unprimedn.ac.id

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Abstract: Parkinson's disease is a neurodegenerative disorder characterized by loss of dopamine and formation of α-synuclein aggregates in the substantia nigra pars compacta (SNpc). This study aims to evaluate α-synuclein levels in the plasma of rotenone-induced Wistar rats as a model of Parkinson's disease and the therapeutic effect of Andaliman fruit extract. The design of this study was experimental with 25 male Wistar rats divided into five groups, negative control group (K-, only given distilled water), positive control (K+, induced rotenone 3 mg/kgBB/day for two weeks), and three treatment groups (P1, P2, P3) induced rotenone and given Andaliman extract orally at a dose of 150 mg/kgBB, 300 mg/kgBB, and 450 mg/kgBB respectively for 14 days. Measurement of levels was performed using ELISA on day 14 after induction and day 28 after therapy. The results of one-way ANOVA analysis showed that Andaliman extract significantly reduced α-synuclein levels at all doses compared to the positive control (p=0.000). The decrease in α-synuclein levels indicates the potential of Andaliman fruit extract in reducing Parkinson's disease-related pathology in mouse models.

Keywords: Andaliman fruit; α-synuclein; Plasma; Rotenone

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that affects the extrapyramidal system, primarily due to damage to dopamine-producing neurons in the substantia nigra pars compacta (SNpc) (Abdel-Salam et al., 2014; Alia et al., 2022). The condition is characterized by decreased dopamine levels, which triggers motor symptoms such as tremors, muscle stiffness, and difficulty moving, as well as non-motor symptoms due to an imbalance of other neurotransmitters (Amelia et al., 2020; Betarbet et al., 2000). Aggregation of α-synuclein protein is also a hallmark of PD, where it forms Lewy bodies that damage nerve cells (Borghammer et al., 2021; González-Usigli et al., 2023).Therefore, α-synuclein is an important biomarker in studying PD progression (Chu et al., 2023; Kuncoro et al., 2020; Kurnia et al., 2023).

Various experimental animal approaches have been developed to study Parkinson's disease (PD), one of which is through the induction of neurotoxins such as rotenone (Salsabila et al., 2021). Rotenone is a neurotoxin used to induce PD models due to its ability to mimic the typical pathology of PD (Elmorsy et al., 2023). Rotenone works by inhibiting complex I of the electron transport chain in mitochondria, reducing ATP production, and causing electron leakage that triggers oxidative stress due to increased reactive oxygen species (ROS) (Susilawati, 2021). This mechanism causes damage to dopaminergic neurons and the formation of α-synuclein aggregates, resembling pathology changes in PD (Hidajat et al., 2023).

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The results of literature studies show that high concentrations of antioxidants have the potential to reduce the symptoms of Parkinson's disease (PD) and protect nerve cells from oxidative stress damage (Pratiwi et al., 2021). Nerve cell damage and death in PD can be prevented through inhibition of oxidation reactions, by providing electrons to stabilize free radicals. This process is important to maintain the balance between oxidants and antioxidants in the body (Fikry et al., 2022; Maharani et al., 2024). In line with these findings, interest in herbal-based medicine is increasing as some plants are known to contain natural antioxidants that are neuroprotective (Iznilillah et al., 2023). Antioxidants in plant active ingredients are believed to help protect nerve cells, slow disease progression, and improve patients' quality of life (Herlianto et al., 2023; Winarti et al., 2018).

The andaliman fruit (*Zanthoxylum acanthopodium DC*) is one of the plants that has been widely studied for its health benefits (Dhillon et al., 2024). The medicinal properties of this plant are due to its rich content of bioactive compounds, especially flavonoids which have strong antioxidant properties (Farida et al., 2021; Tanessa et al., 2023). The andaliman fruit is small, 2-3 mm in diameter, green when unripe, red when ripe, and blackened after drying, with each fruit containing one seed. Besides flavonoids, andaliman also contains alkaloids, saponins, and terpenoids, which are known to have benefits such as anti-inflammation, boosting immunity, improving blood circulation, and fighting infection (Syaputri et al., 2022). The combination of active compounds in andaliman provides great potential in supporting health, both through traditional and modern phytochemical-based medicine (Anggraeni, 2020).

Research conducted by Anggraeni (2020) on phytochemical screening aims to identify the class of secondary metabolite chemical compounds contained in andaliman fruit simplisia. The screening results show that andaliman fruit contains various chemical compounds, including alkaloids, glycosides, steroids/triterpenoids, flavonoids, tannins, and saponins (Anggraeni, 2020). Flavonoids contained in andaliman fruit are thought to play an important role as antioxidants, because flavonoids are one of the secondary metabolites that have broad biological activities and function as antidotes to oxidation, including free radicals that can damage cells (Farida et al., 2021). Although there are many studies on the content and benefits of andaliman fruit, until now there has been no data exploring the effect of andaliman fruit extract on α-synuclein levels. Therefore, researchers are interested in conducting further research on the effect of administration of andaliman fruit extract (*Zanthoxylum acanthopodium DC*) on α-synuclein levels in rotenone-induced Wistar male rats, with the hope of providing new insights in the treatment of neurodegeneration-related diseases.

Method

This study used a quantitative experimental approach with a completely randomized design (RAL) as the research design. This design ensures that the treatment of the experimental group is randomized to reduce potential bias in the division of groups and increase objectivity to the effects of the treatment given (Agustin, 2024; Aprinaldi, 2020). The research was conducted at the Laboratory of the Faculty of Veterinary Medicine, Syiah Kuala University, Banda Aceh from February to May 2024. All procedures have received approval from the Prima Indonesia University Health Research Ethics Committee with protocol number 018/KEPK/UNPRI/V/2024, thus ensuring that this study complies with the ethical standards of animal research.

The tools and materials used in this study include gloves, masks, rat cages, rat food and drink containers, ovens, scales, blenders, autoclave sieves, glass vessels, stirring rods, maceration vessels, aluminum foil, test tubes, cotton swabs, rotary evaporators, 1 ml disposable syringes, alcohol swabs, stopwatches, ethanol, and andaliman fruit (*Zanthoxylum acanthopodium DC*). The research procedure began with the extraction of andaliman fruit using maceration method with 70% ethanol (Djrami et al., 2023; Tandi et al., 2017) . A total of 2 kg of andaliman fruit was washed and dried in an oven at 40°C for one week. After drying, the andaliman fruit was pulverized into powder and extracted by maceration method with stirring until homogeneous. The maceration process was followed by evaporation using a vacuum rotary evaporator to produce a solvent-free thick extract (Hyacintha et al., 2024; Safitri, 2020). The thick extract then underwent phytochemical screening to detect secondary metabolites through alkaloid, terpenoid/steroid, flavonoid, tannin, and saponin tests (Zebua et al., 2024).

Phytochemical screening testing was carried out using the method of detecting bioactive compounds in andaliman fruit extract. The alkaloid test was carried out by adding 1 mL of HCl and 3 mL of distilled water to the extract, then the solution was heated for two minutes on a water bath, cooled, and filtered. Next, two drops of Dragendorff reagent were added, and the color change to orange indicated the presence of alkaloid compounds. For the saponin test, 1 mL of extract is mixed with 10 mL of distilled water in a test tube, then shaken. If foam forms that lasts for one minute, then the extract is

positive for saponins (Halim et al., 2024). The tannin test is carried out by adding 2 drops of 5% $FeCl_3$ solution to the extract, and the blackish green color formed indicates the presence of tannin compounds. Finally, the flavonoid test is carried out by adding a little magnesium (Mg) metal powder and a few drops of concentrated HCl to the extract, where the formation of a reddish orange color indicates the presence of flavonoid compounds (Wardani et al., 2024; Windyaswari et al., 2019).

Antioxidant activity test was conducted using DPPH (2,2-diphenyl-2-picrylhydrazyl) method. First, a 40 ppm DPPH solution was made by dissolving 20 mg of DPPH powder in a 100 ml volumetric flask and adding it with ethanol until it reached the maximum volume, then stored in a place protected from direct sunlight at low temperature. For the measurement of the test solution of ethanol extract of andaliman fruit, a master solution with a concentration of 500 ppm (5 mg in 10 ml ethanol) was made, then from the master solution four concentration series were made, namely 50 ppm, 100 ppm, 150 ppm, and 200 ppm. Furthermore, 1 ml of DPPH solution was added to 4 ml of extract test solution at various concentrations and incubated for 30 minutes at 37°C. The color change from dark purple to brilliant yellow indicates the free radical inhibition reaction by the extract. After incubation, the absorbance value of the sample was measured at a wavelength of 517 nm using a UV-Vis spectrophotometer, then the IC50 value and percentage inhibition were calculated to evaluate the antioxidant activity of andaliman fruit extract (Mahral, 2021) .

This study involved 25 male Wistar rats aged 8-10 weeks with an average body weight of 200-250 grams. Before starting the treatment, the rats went through an acclimatization period for 7 days (Hartini et al., 2024). The negative control group (K-) was only given distilled water without any other treatment, while the positive control group (K+) was given rotenone at a dose of 3 mg/kgBB/day intraperitoneally for 14 days. Three treatment groups, namely P1, P2, and P3, were each given rotenone induction and andaliman fruit extract at different doses, namely 150 mg/kgBB, 300 mg/kgBB, and 450 mg/kgBB orally for 14 days. During the treatment period, the condition of the rats was observed daily to record clinical and behavioral responses as parameters of nerve damage and oxidative stress. Randomization was carried out using the lottery method, in which each rat was given a number, then placed into the group according to the number drawn randomly. After the treatment was completed, the data obtained were analyzed using statistical software to test the effectiveness of the treatment and significant differences between groups. The study was systematically designed to ensure valid and reliable results (Halimah & Febriani, 2023).

To measure plasma α-synuclein levels, 1 ml of blood was taken from the lateral vein of the rat tail and placed in an Eppendorf Tube. After that, the serum to be used for testing α-synuclein levels was obtained by centrifuging the blood at 3000 rpm for 10 minutes. Testing of α-synuclein levels was performed using the Enzyme-Linked Immunosorbent Assay (ELISA) technique, using the Mouse SNCa (Synuclein Alpha) Elisa Kit which has a sensitivity of 9.38 pg/ml. The α-synuclein levels in each treatment group I, II, and III, the positive control group, and the negative control group were compared, and the test results were presented in ng/L (Wang et al., 2019).

Data analysis in this study begins with a normality test using Levene's test to ensure normal sample distribution, followed by a homogeneity test using Shapiro-Wilk to evaluate whether the data is homogeneous. If the data is normally distributed and homogeneous, the analysis continues with One Way ANOVA with a significance level of $p < 0.05$ (Arjita et al., 2023) . If the data does not meet the assumptions of normality or homogeneity, data transformation is performed. If after transformation the data is still not normal and homogeneous, the Kruskal-Wallis nonparametric test is used with the same significance level. If the analysis showed significant results, a post hoc test was performed to identify significant differences between the tested groups (Haidir et al., 2022).

The workflow procedure in this research can be seen in the following diagram.

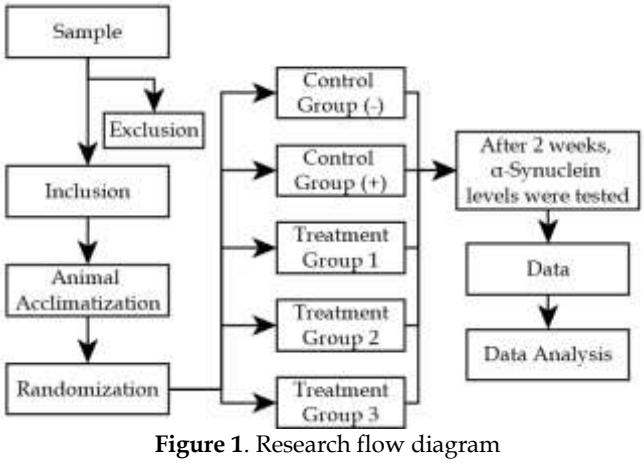

Figure 1. Research flow diagram

Result and Discussion

Phytochemical screening is a qualitative test method carried out as a first step to analyze secondary metabolite compounds in andaliman fruit extract (*Zanthoxylum acanthopodium DC*). The purpose of this screening is to identify the compounds contained in

andaliman fruit extract. The results of phytochemical screening can be seen in Table 1.

Table 1. Phytochemical Screening Results of Andaliman Fruit Extract (*Zanthoxylum acanthopodium DC*)

Secondary metabolite compounds	Reagents	Results
Alkaloids	Bouchardart	+
	Maeyer	+
	Dragendroff	+
	Wagner	+
Steroids and triterpenoids	Salkowsky	+
	Lieberman-burchad	+
Saponins	Aquadest + 96% alcohol	+
Flavonoids	FeCl3 5%	+
	Mg(s) + HCl(p)	+
	10% NaOH	+
	H_2SO_4 (p)	+
Phenolic	FeCl3 1%	+
Tannins	Gelatin + H_2SO_4	+

The table above shows that durian seed extract contains several phytochemical compounds, namely alkaloids, steroids, terpenoids, saponins, flavonoids, phenolics and tannins, which are known to have various benefits in therapeutic activities.

Based on the results of phytochemical screening of andaliman fruit extract (*Zanthoxylum acanthopodium DC*), it can be seen that andaliman fruit extract contains several secondary metabolite compounds, such as alkaloids, steroids, saponins, flavonoids, phenolics and tannins. These compounds are known to have various therapeutic benefits that function as antioxidants and antimicrobials (Sijabat et al., 2021). Several studies have shown that andaliman fruit extract has great potential as a therapeutic agent for various diseases. One of the very strong antioxidant activities, which is produced by the high content of phenols and flavonoids in its extract. This makes it a developmental agent for preventing degenerative diseases associated with oxidative stress, such as heart disease and neurodegenerative disorders. In addition, andaliman extract also has potential as an anti-inflammatory, antimicrobial, and analgesic, which provides added value in the treatment of various inflammatory and infectious diseases. With bioactivity, andaliman fruit extract can be developed into pharmaceutical or nutraceutical products (Lister et al., 2022).

Evaluation of antioxidant activity of Andaliman fruit extract at various concentrations shows the ability of the extract to neutralize free radicals, with higher absorbance values indicating lower antioxidant activity. The results of the antioxidant activity evaluation test can be seen in Figure 1.

The results of the evaluation of antioxidant activity of Andaliman fruit extracts at various concentrations showed a significant positive relationship between extract concentration and percentage inhibition. In the regression analysis, the equation found was y = 0.3672x + 45.168 with R^2 = 0.9842, which shows that the regression model is very good in explaining the variation of data.

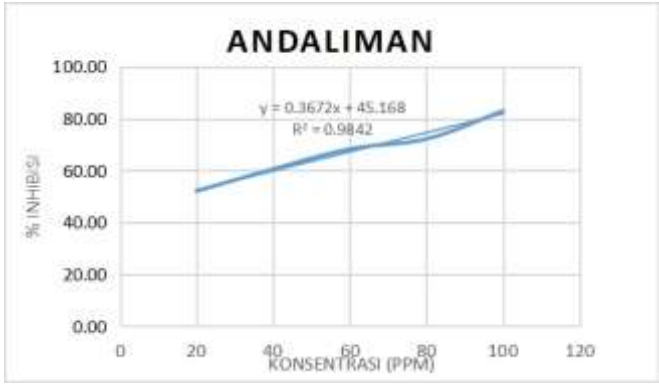

Figure 2. Diagram of antioxidant test results

This indicates that the higher the concentration of the extract, the higher the ability of the extract to inhibit free radicals. This strong antioxidant activity indicates the potential of andaliman fruit extract as a free radical scavenging agent that can reduce oxidative damage to nerve cells, which is associated with neurodegenerative diseases such as Parkinson's disease. This reduction in oxidative damage also has the potential to inhibit the aggregation of α-synuclein, a protein involved in the development of Parkinson's disease. These results are in line with the findings in the study by Maharani et al. 2024, which emphasized the importance of antioxidant-based therapies, such as natural Levodopa from plants, in the treatment of Parkinson's disease (Maharani et al., 2024).

The test results of α-synuclein levels were expressed in ng/L and compared with the values obtained from the negative control group, positive control, and treatment groups I, II, and III. The SNCa Standard curve test results can be seen in Figure 3.

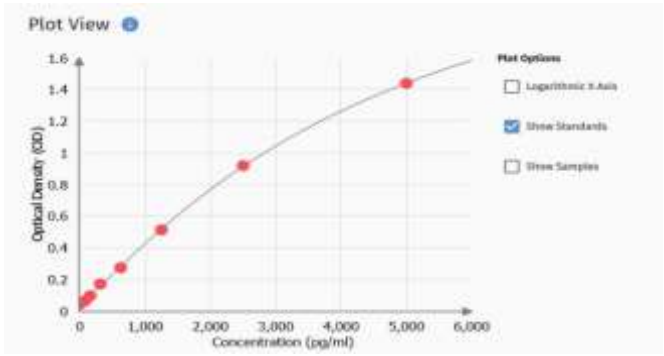

Figure 3. The SNCa standard curve test results

Based on Figure 3, the standard curve used to measure estradiol levels by spectrophotometric method shows the relationship between the optical absorbance (OD) value on the Y-axis and the concentration of estradiol on the X-axis, expressed in units of pg/mL. With an R^2 value of 0.9998 which is almost perfect, the curve illustrates a significant linear relationship between absorbance and estradiol concentration. This confirms that the measurement method has excellent accuracy and precision.

This method has a sensitivity of 28 pg/mL, indicating adequate ability to detect low estradiol levels. This sensitivity is particularly important for identifying small changes in α-synuclein levels due to treatment with andaliman fruit extract. With an R^2 value very close to 1, this method provides high confidence in the measurement results and ensures that the data obtained can be reproduced consistently. The average concentration of α-synuclein protein on day 28 in the KP1, KP2 and KP3 rat groups can be seen in Figure 4.

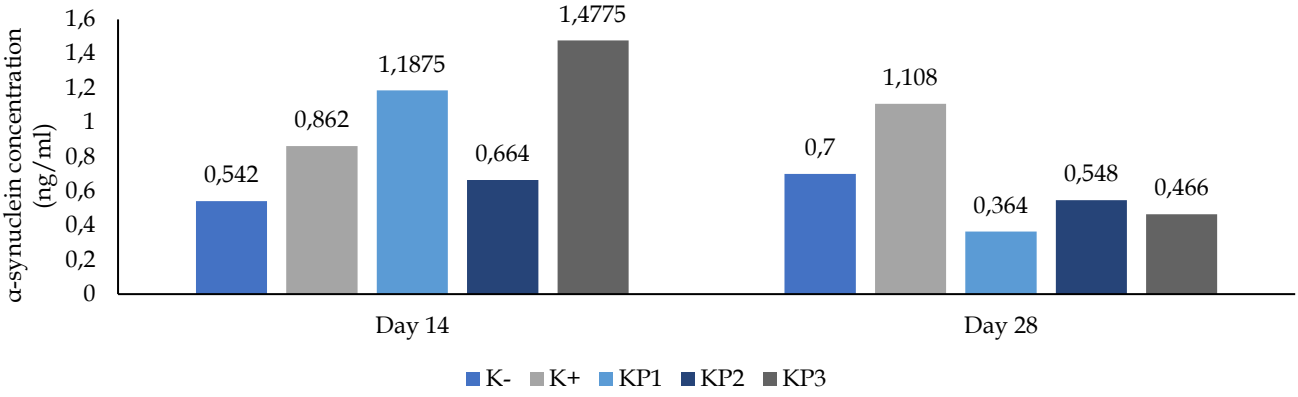

Figure 4. Average concentration of α-synuclein protein on day 28

On the 28th day, the average concentration of α-synuclein protein in the KP1, KP2, and KP3 rat groups showed a significant decrease after being given Andaliman fruit extract, with concentrations of ±0.8235, ±0.116, and ±1.0115 ng/mL, respectively. In contrast, the negative control (K-) and positive control (K+) groups experienced an increase in the average concentration of α-synuclein protein by ±0.158 and ±0.246 ng/mL.

The graphical data also indicates that the administration of Andaliman fruit extract with graded doses produces a significant effect, where a dose of 450 mg/kg is proven to be optimal in reducing α-synuclein concentrations compared to doses of 150 mg/kg and 300 mg/kg. This is consistent with the research of Anggraini et al. (2020) which showed that a daily dose of 300 mg/kg for eight weeks was effective in reducing memory impairment, slowing the aging process, and preventing cognitive decline in aging-induced rats with D-galactose. In addition, a dose of 450 mg/kg also proved to be the most effective in increasing hemoglobin and erythrocytes while reducing leukocytes and platelets after the injection of tartrazine, which is known as a free radical-inducing substance (Anggraeni, 2020).

Based on preliminary analysis, Andaliman fruit extract can be said to be able to reduce α-synuclein protein levels, an indicator associated with Parkinson's disease, if statistical analysis shows significant differences between the treatment and control groups. Although preliminary data supports the effectiveness of this extract, a more in-depth statistical analysis, such as an ANOVA test, is needed to confirm the differences between treatment groups and corroborate the conclusions.

Table 2. Normality Test on Day 14

Tests of normality			
		Shapiro-wilk	
	Statistic	df	Sig.
Negative control + treatment	0.83	5	0.14
Positive control + treatment	0.92	5	0.57
Behavior 1 + treatment	0.78	5	0.06
Behavior 2 + treatment	0.88	5	0.31
Behavior 3 + treatment	0.89	5	0.39

The normality test results show that the significance value for each group is Behavior 1 of 0.06, Behavior 2 of 0.31, Behavior 3 of 0.39, Negative Control of 0.14, and Positive Control of 0.57. All of these significance values are greater than 0.05, indicating that the data is normally distributed. Thus, the data meets the assumption of normality, so it can be used for further parametric statistical analysis.

The results of the Shapiro-Wilk normality test show that the significance value for each group is Behavior 1 at 0.17, Behavior 2 at 0.54, Behavior 3 at 0.29, Negative Control at 0.53, and Positive Control at 0.11. All these values are greater than 0.05, indicating that the data is normally distributed. Thus, these findings indicate that

the data meets the assumption of normality, so it can proceed with parametric statistical analysis to test for differences between groups.

Table 3. Normality Test on Day 28

Tests of normality			
	Shapiro-wilk		
	Statistic	df	Sig.
Negative control + treatment	0.92	5	0.53
Positive control + treatment	0.82	5	0.11
Behavior 1 + treatment	0.84	5	0.17
Behavior 2 + treatment	0.92	5	0.54
Behavior 3 + treatment	0.87	5	0.29

The results of the normality test on days 14 and 28 showed that all treatment groups had a normal distribution, indicating that the assumption of normality had been met at both measurement times. Although there was a slight difference in the resulting significance value (p-value) between the two times, this difference was not significant and did not affect the main conclusion that the data was normally distributed. This positive result of the normality test indicates that the data collected was of sufficient quality to be analyzed using parametric statistical methods.

Table 4. Homogeneity Test

Test of homogeneity of variance					
		Levene statistic	df1	df2	Sig.
Treatment + treatment	Based on mean	1.03	1	48	0.31
	Based on median	0.36	1	48	0.54
	Based on median and with adjusted df	0.36	1	32.61	0.54
	Based on trimmed mean	0.52	1	48	0.47

Based on Table 4, the homogeneity test results in the Based on Mean column show a significance value of 0.31. Since the significance value is greater than 0.05 (0.31 > 0.05), it can be concluded that the samples from the Negative Control, Positive Control, Behavior 1, Behavior 2, and Behavior 3 groups have homogeneous variants.

Table 5. One Way Anova Test

Anova					
	Sum of squares	Df	Mean square	F	Sig.
Between groups	0.44	1	0.44	3.73	0
Within groups	5.65	48	0.11		
Total	6.09	49			

The ANOVA test results show a significance value of 0.00 which is smaller than 0.05 (0.00 < 0.05). This means that the null hypothesis (H0) is rejected and the alternative hypothesis (H1) is accepted. Thus, it can be concluded that the independent variable has a significant influence on the dependent variable. Specifically, the administration of andaliman fruit extract (*Zanthoxylum acanthopodium DC.*) to male Wistar rats after rotenone induction had a significant impact on α-synuclein levels. This finding confirms that treatment with andaliman fruit extract is able to affect α-synuclein levels, which is an important indicator in this study.

Conclusion

An extract of andaliman fruit (*Zanthoxylum acanthopodium DC.*) showed significant potential in reducing α-synuclein levels in rotenone-induced Parkinson's model rats. The strong antioxidant activity with an IC50 value of 13.16 ppm supports the potential claim of this extract. A dose of 450 mg/kg proved to be most effective in reducing α-synuclein levels. Statistical results using One Way ANOVA showed that administration of 70% ethanol extract of andaliman fruit had a significant effect on reducing α-synuclein levels ($p<0.05$). However, therapeutic applications in humans still require further research.

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Author Contributions
Conceptualization, methodology and formal analysis, C.P.M; Investigation, B.H and L.C; writing- original draft preparation, C.P.M; writing-Review and editing, C.P.M, B.H and L.C; Visualization, A.R.N and Y.T. All authors have agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

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