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THE EFFECT OF WHITE DRAGON FRUIT (*HYLOCEREUS UNDATUS*) SIMPLICIA AS A CARDIOPROTECTIVE AGENT IN WHITE RATS (*RATTUS NORVEGICUS*) ADMINISTERED DEXAMETHASONE

Pengaruh Simplisia Buah Naga Putih *(Hylocereus undatus)* Sebagai Kardioprotektor pada Tikus Putih *(Rattus norvegicus)* yang Diberikan Deksametason

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Abstract

Long-term dexamethasone use may induce cardiovascular side effects, such as oxidative stress and myocardial damage, which manifest as degeneration, necrosis, and inflammation. White dragon fruit (*Hylocereus undatus*) contains polyphenols, flavonoids, betalains, and vitamin C, which possess strong antioxidant properties and may have cardioprotective effects. This study aimed to evaluate the effects of white dragon fruit simplicia on cardiac histopathology in dexamethasone-treated rats (*Rattus norvegicus*). Twenty-five Wistar rats were divided into four groups: P0 (negative control), P1 (positive control – dexamethasone 0.13 mg/kg), P2 (dexamethasone + 50% simplicia), and P3 (dexamethasone + 100% simplicia). The treatments were administered orally for 21 days. Cardiac tissue was processed using hematoxylin and eosin staining to assess degenerative, necrotic, and inflammatory changes. Statistical analysis was performed using the Kruskal-Wallis and Mann–Whitney tests. The results of the Mann–Whitney test on the degeneration parameters showed a significant difference between the negative control group (P0) and groups P1, P2, and P3. In the necrosis parameter, the Mann–Whitney test results showed a significant difference between P0 and P1, but no significant difference between P2 and P3. None of the treatment groups showed significant differences in the inflammation parameters ($p > 0.05$). It can be concluded that the administration of white

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Volume 18 No. 3: 527-534
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dragon fruit (*Hylocereus undatus*) simplicia was able to significantly reduce the severity of necrotic lesions, as well as reduce the degree of degeneration, especially at a dose of 100%, but did not have a significant effect on inflammatory lesions in the hearts of white rats (*Rattus norvegicus*) treated with dexamethasone.

Keywords**:** cardiac histopathology, cardioprotection, dexamethasone, *Hylocereus undatus*, oxidative stress

Abstrak

Penggunaan deksametason jangka panjang dapat menyebabkan efek samping serius pada sistem kardiovaskular, termasuk stres oksidatif dan kerusakan jaringan miokard yang tampak sebagai degenerasi, nekrosis, serta peradangan. Buah naga putih *(Hylocereus undatus)* mengandung polifenol, flavonoid, betalain, dan vitamin C yang berperan sebagai antioksidan kuat sehingga berpotensi memberikan efek kardioprotektif. Penelitian ini bertujuan mengevaluasi pengaruh pemberian simplisia buah naga putih terhadap gambaran histopatologi jantung tikus putih (*Rattus norvegicus*) yang diinduksi deksametason. Sebanyak 24 ekor tikus Wistar dibagi menjadi empat kelompok: P0 (Kontrol negatif), P1 (Kontrol positif), P2 (Deksametason 0,13 mg/kgBB + simplisia buah naga putih 50%), P3 (Deksametason 0,13 mg/kgBB + simplisia buah naga putih 100%). Perlakuan diberikan secara oral selama 21 hari. Organ jantung kemudian dibuat preparat histopatologi dengan pewarnaan Hematoksilin-Eosin dan dievaluasi terhadap lesi degeneratif, nekrotik, dan inflamasi. Analisis statistik menggunakan uji Kruskal-Wallis dan Mann-Whitney. Hasil uji Mann–Whitney pada parameter degenerasi menunjukkan adanya perbedaan signifikan antara kelompok kontrol negatif (P0) dengan kelompok P1, P2, dan P3. Pada parameter nekrosis, hasil uji Mann–Whitney menunjukkan adanya perbedaan signifikan antara P0 dengan P1, tetapi tidak berbeda signifikan dengan P2 dan P3. Sedangkan pada parameter peradangan, seluruh kelompok perlakuan tidak menunjukkan perbedaan yang signifikan ($p > 0,05$). Dapat disimpulkan bahwa pemberian simplisia buah naga putih (*Hylocereus undatus*) mampu menurunkan tingkat keparahan lesi nekrosis secara signifikan, serta menurunkan derajat degenerasi terutama pada dosis 100%, tetapi tidak memberikan pengaruh yang signifikan terhadap lesi peradangan pada jantung tikus putih (*Rattus norvegicus*) yang diberikan deksametason.

Kata kunci: deksametason, histopatologi jantung, *Hylocereus undatus*, kardioprotektor, radikal bebas

INTRODUCTION

Dexamethasone, a synthetic corticosteroid, exerts potent anti-inflammatory and immunosuppressive effects, making it commonly used to manage chronic inflammatory conditions, such as arthritis, particularly during the acute phase, which is characterized by severe pain and inflammation. Long-term use of dexamethasone is known to cause systemic side effects, particularly metabolic disturbances in the form of increased serum insulin levels and changes in glucose regulation, which have the potential to worsen a patient's metabolic condition if not controlled properly (Samsuri *et al.*, 2007).

Chronic arthritis is characterized by persistent inflammation, pain, stiffness, swelling, and reduced joint function, all of which require long-term treatment (Di Carlo *et al.*, 2021). In clinical practice, long-term use of glucocorticoids is often unavoidable despite the risk of cardiovascular complications. Dexamethasone can increase vascular sensitivity to vasoconstrictors and cause sodium and water retention in the kidneys, thereby triggering hypertension and increasing the workload of the heart. Additionally, chronic glucocorticoid exposure contributes to dyslipidemia through increased low-density lipoprotein (LDL) levels,

Volume 18 No. 3: 527-534
June 2026
https://doi.org/10.24843/bulvet.2026.v18.i03.p04

decreased high-density lipoprotein (HDL) levels, and triglyceride accumulation, which accelerates atherosclerosis (Setiawan & Suardamana, 2023).

Furthermore, long-term exposure to glucocorticoids triggers oxidative stress due to increased free radical production and a decline in the endogenous antioxidant system. This condition can lead to cardiomyocyte damage, endothelial dysfunction, myocardial fibrosis, and even cardiac cell apoptosis, which ultimately triggers structural and functional changes, such as hypertrophy and diastolic dysfunction. These changes contribute to increased cardiovascular morbidity and mortality in patients with arthritis (Tavares *et al.*, 2024).

With the increasing need for safer adjuvant therapies, natural compounds with antioxidant activity have garnered attention. White dragon fruit (*Hylocereus undatus*) contains various bioactive compounds, such as polyphenols, flavonoids, betalains, and vitamin C, which neutralize free radicals and reduce oxidative stress (Mande *et al.*, 2023). Studies have indicated that dragon fruit from the Hylocereus genus can enhance plasma antioxidant capacity, reduce malondialdehyde (MDA) levels, a biomarker of lipid peroxidation, and improve lipid profiles. These effects have the potential to provide cardiovascular protection and reduce the risk of atherosclerosis in patients undergoing long-term corticosteroid therapy (Nishikito *et al.*, 2023).

RESEARCH METHODS

Ethical Approval for Animal Testing

This study met the ethical requirements for the use of laboratory animals, as evidenced by the issuance of the Animal Testing Ethics Approval Letter, No. B/199/UN14.2.9/PT.01.04/2025.

Research Subjects

The study used 24 female Wistar rats (*Rattus norvegicus*), which were clinically healthy, weighed approximately 100 g, and were 2–3 months old.

Research Design

This study used a completely randomized design (CRD) involving 24 white rats divided into four treatment groups: P0 (negative control), P1 (positive control), P2 (dexamethasone 0.13 mg/kg body weight + 50% white dragon fruit crude extract), and P3 (dexamethasone 0.13 mg/kg body weight + 100% white dragon fruit crude extract). The sample size was calculated using Federer's formula $((t-1)(n-1) \geq 15)$ to ensure statistical validity of the data. On day 22, all rats were euthanized using ether inhalation anesthesia, followed by necropsy to remove the hearts for histopathological preparation.

Research Variables

The research variables in this study were independent, control, and dependent variables. The independent variable was the treatment administered using crude white dragon fruit extract. The control variables included strain, age, sex, body weight, diet, drinking water, environmental conditions, and dexamethasone administration. The dependent variable was the change in the cardiac histopathology.

Data Collection Methods

Data for cardiac histopathological examination were obtained by analyzing the heart tissue of white mice that had been treated according to the study design. Heart samples were processed to prepare histopathological slides using hematoxylin and eosin (H&E) staining. Subsequently, the slides were examined under a light microscope at five microscopic fields of view each to assess changes in cardiac tissue structure, including degenerative lesions, necrosis, and inflammation.

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Pendidikan Tinggi, Riset, dan Teknologi No. 158/E/KPT/2021

Volume 18 No. 3: 527-534
June 2026
https://doi.org/10.24843/bulvet.2026.v18.i03.p04

Heart damage was assessed using a scoring system with scores of 0 (normal), 1 (focal lesions), 2 (multifocal lesions), and 3 (severe lesions). Scoring was based on the extent and severity of heart damage. The scoring values obtained were averaged for each treatment group and used to compare the effectiveness of the treatments across groups.

Data Analysis

Data analysis in this study was performed statistically using the nonparametric Kruskal–Wallis test to determine whether significant differences existed between the treatment groups. If the analysis results indicated a significant difference ($P < 0.05$), the Mann–Whitney test was conducted to determine which groups differed significantly.

RESULTS AND DISCUSSION

Histopathological examinations were performed in five microscopic fields of view at 400 × magnification for each treatment group. The primary focus of the examination was to identify histopathological changes, particularly degeneration, necrosis, and inflammation of the heart. This process was used to evaluate the presence of organ damage in the rats. The results of the histopathological examination are presented in Tables 1 and 2 and Figure 1.

The results of this study indicate that the administration of white dragon fruit (*Hylocereus undatus*) crude extract at varying doses over 21 days to rats treated with 0.13 mg/kg body weight of dexamethasone affected cardiac histopathology, specifically fatty degeneration and necrosis ($P<0.05$). The heart exposed to high-dose glucocorticoids over a long period may experience cellular metabolic disturbances and increased oxidative stress, which affect both the structure and function of myocardial tissue. Dexamethasone increases the formation of reactive oxygen species (ROS) and reduces the activity of the endogenous antioxidant system, leading to redox imbalance within cells. This condition triggers membrane lipid peroxidation, mitochondrial dysfunction, and changes in fatty acid metabolism, ultimately leading to myocardial cell injury (Roy *et al.*, 2009).

In the P0 treatment group (negative control), no histopathological lesions, including fatty degeneration or necrosis, were observed. This is because the physiological condition of the rat heart was normal, with no exposure to oxidative stress caused by dexamethasone treatment. Fatty degeneration lesions were observed in the P1 (positive control), P2, and P3 groups, with the highest average score in the P1 group and the lowest in the group treated with 100% white dragon fruit crude extract (P3).

Fatty degeneration of the myocardium is characterized by the accumulation of intracellular lipids in the cytoplasm of cardiomyocytes due to impaired fatty acid oxidation and mitochondrial dysfunction. Lipid accumulation occurs when lipid uptake and storage exceed the normal mitochondrial oxidative capacity, leading to lipotoxicity, which affects the structure and function of heart cells and triggers oxidative stress and mitochondrial dysfunction (Wende & Abel, 2010).

In the treatment group administered white dragon fruit extract, a decreasing trend in fatty degeneration was observed with increasing dose. Statistically, there was no significant difference between groups P1 and P2 ($P > 0.05$), whereas there was a significant difference between P1 and P3 ($P < 0.05$).

The cardioprotective effects of white dragon fruit (*Hylocereus undatus*) are attributed to its bioactive compounds, which are rich in flavonoids, phenolic compounds, and vitamin C, all of which possess strong antioxidant activity. Phenolic compounds and flavonoids act as free radical scavengers by donating electrons to neutralize reactive oxygen species (ROS), thereby

Terakreditasi Nasional Sinta 4, berdasarkan Keputusan Direktur Jenderal
Pendidikan Tinggi, Riset, dan Teknologi No. 158/E/KPT/2021

Volume 18 No. 3: 527-534
June 2026
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inhibiting lipid peroxidation in cell membranes (Wu *et al.*, 2006). Inhibiting lipid peroxidation is crucial for maintaining cell membrane integrity and mitochondrial function stability, as membrane damage caused by oxidative stress can disrupt myocardial energy metabolism. Additionally, flavonoids enhance the endogenous antioxidant defense system and suppress the formation of toxic lipid metabolites (Kim *et al.*, 2011).

Necrotic lesions were primarily observed in the positive control group (P1) at a statistically significant level ($P < 0.05$) compared to that in the negative control group (P0). In the treatment group administered 50% white dragon fruit crude extract (P2), the degree of necrosis was significantly reduced ($P<0.05$) compared to that in P1. At the 100% dose (P3), there was also a significant reduction in the degree of necrosis ($P<0.05$) compared to that in P1. This finding indicates that a 50% dose is sufficient to suppress necrosis. Necrosis is a form of irreversible cell death characterized by pyknosis, karyorrhexis, and karyolysis, resulting from severe damage to the cell membrane and impaired ATP production (Ayala *et al.*, 2014). Excessive ROS can damage myocardial cell lipids, proteins, and DNA, thereby triggering cell death. Additionally, mitochondrial dysfunction leads to energy production failure, which accelerates necrosis (Ghosh *et al.*, 2012).

The study was conducted over 21 days, ensuring that the duration of dexamethasone exposure was sufficient to cause structural myocardial damage while allowing time for the antioxidant compounds in the dragon fruit to exert their protective effects. The more pronounced efficacy observed at the 100% dose (P3) indicates that a higher concentration of antioxidants is required to counteract the increase in ROS levels caused by dexamethasone. Overall, the results of this study indicate that white dragon fruit extract has cardioprotective potential against dexamethasone-induced myocardial fatty degeneration and necrosis.

CONCLUSIONS AND SUGGESTIONS

Conclusions

Administration of white dragon fruit (*Hylocereus undatus*) extract affects the histopathological findings of the hearts of dexamethasone-induced white mice. This effect was demonstrated by a reduction in the degree of degeneration and necrosis of cardiac muscle cells, although it did not significantly affect the level of inflammation. Differences in the administered doses of the crude extract also influenced the degree of cardiac tissue damage; high doses demonstrated better cardioprotective effects than low doses, particularly in suppressing myocardial necrosis.

Suggestions

Further research is recommended to investigate the potential of white dragon fruit (*Hylocereus undatus*) as a cardioprotective agent in white rats (*Rattus norvegicus*) administered dexamethasone at a wider range of doses and for longer durations. It is also recommended that future studies include additional supporting parameters, such as biomarkers of cardiac damage and oxidative stress, to enable a more comprehensive understanding of the mechanism of action and long-term effects of white dragon fruit extract on cardiac tissue.

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Volume 18 No. 3: 527-534
June 2026
https://doi.org/10.24843/bulvet.2026.v18.i03.p04

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Volume 18 No. 3: 527-534
June 2026
https://doi.org/10.24843/bulvet.2026.v18.i03.p04

Tables

Table 1. Histopathological examination results of rat cardiac tissue in all treatment groups

	Degeneration Score				Necrosis Score				Inflammation Score			
Treatment	0	1	2	3	0	1	2	3	0	1	2	3
P0	6	-	-	-	6	-	-	-	6	-	-	-
P1	-	1	5	-	-	4	2	-	6	-	-	-
P2	-	5	1	-	6	-	-	-	6	-	-	-
P3	1	5	-	-	6	-	-	-	6	-	-	-

Note: P0 (Negative control), P1 (Positive control), P2 (Dexamethasone 0.13 mg/kg BW + 50% white dragon fruit simplicia), P3 (Dexamethasone 0.13 mg/kg BW + 100% white dragon fruit simplicia); Score 0 = No alteration, Score 1 = Focal (mild), Score 2 = Multifocal (moderate), Score 3 = Diffuse (severe).

Table 2. Mean values and significance of histopathological scoring of rat cardiac tissue

Treatment	Mean Lesion Scoring Data and Significance		
	Degeneration	Necrosis	Inflamation
P0	0,00±0,000[a]	0,00±0,000[a]	0,00±0,000[a]
P1	1,83±0,408[b]	1,33±0,516[b]	0,00±0,000[a]
P2	1,17±0,408[b]	0,00±0,000[a]	0,00±0,000[a]
P3	0,83±0,408[c]	0,00±0,000[a]	0,00±0,000[a]
Asymp.Sig	0,000	0,000	1,000

Note: P0 (Negative control), P1 (Positive control), P2 (Dexamethasone 0.13 mg/kg BW + 50% white dragon fruit simplicia), P3 (Dexamethasone 0.13 mg/kg BW + 100% white dragon fruit simplicia); Different superscript letters ([a], [b], [c], [d]) indicate significant differences (P<0.05).

Volume 18 No. 3: 527-534
June 2026
https://doi.org/10.24843/bulvet.2026.v18.i03.p04

Figure

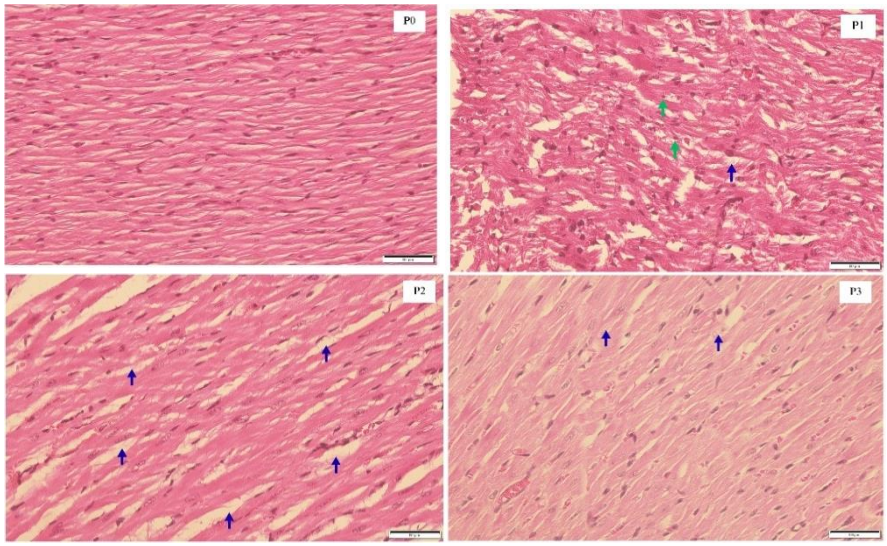

Figure 1. Histopathology of rat (*Rattus norvegicus*) cardiac tissue in each treatment group. (HE, 400×; bar = 50 µm). P0: normal cardiac structure was observed. P1: necrosis (green arrow) and degeneration (blue arrow) were observed. P2: degeneration was observed (blue arrow). P3: decreased degeneration was observed (blue arrow).

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