EGGELEPANTH SKIN ETHANOL EXTRACT MITIGATES AFB1-INDUCED CARDIAC DAMAGE IN RATS: A PROMISING CARDIOPROTECTIVE AGENT

Maydilah Wahyuni Aipina Sari[1], Ali Napiah Nasution[1], Evelyn Angie[1], Sahna Ferdinan[1], Desi Novianti[1], Ikhwanul Hakim Nasution[1], Adi Soekardi[1]

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Abstract

Aflatoxin B1 (AFB1) is a potent mycotoxin that has been shown to induce cardiac damage in rats. In the present study, we investigated the dose-dependent cardioprotective effect of Eggelepanth Skin Ethanol Extract (ESEE) against AFB1-induced cardiac damage in rats, focusing on the cardiac biomarkers lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), and brain natriuretic peptide (BNP). Rats were orally administered AFB1 for 28 days to induce cardiac toxicity, and ESEE was co-administered with AFB1 at doses of 200, 400, and 600 mg/kg body weight. The results showed that AFB1 administration caused a significant increase in the levels of LDH, CK-MB, and BNP, as well as lipid peroxidation and inflammatory cytokines in the heart tissues. However, co-administration of ESEE at all doses significantly reduced the levels of LDH, CK-MB, and BNP, as well as lipid peroxidation and inflammatory cytokines in the AFB1-treated rats. Histological examination of the heart tissues showed that AFB1 caused structural damage and inflammation, which were attenuated by ESEE treatment at all doses. The protective effect of ESEE may be attributed to its antioxidant and anti-inflammatory properties, as demonstrated by the significant reduction in oxidative stress markers and pro-inflammatory cytokines in the ESEE-treated rats. These findings suggest that ESEE may be a promising cardioprotective agent against AFB1-induced cardiac damage in rats, and the dose-dependent effect warrants further investigation..

***Keywords**: ESEE, CK-MB, LDH, BNP, Troponin T, CRP.*

[1]Faculty of Medicine, Prima University of Indonesia

Corresponding Email: alinapiahnasution@unprimdn.ac.id

1. Introduction

Aflatoxin B1 (AFB1) is a potent mycotoxin produced by Aspergillus flavus and Aspergillus parasiticus fungi, and it is commonly found in contaminated food and feed. AFB1 has been implicated in a variety of human diseases, including liver cancer, immune suppression, and neurotoxicity. However, recent studies have also shown that AFB1 can cause cardiac damage in rats. AFB1-induced cardiac injury is believed to be mediated by oxidative stress and inflammation. AFB1 can induce the generation of reactive oxygen species (ROS), leading to lipid peroxidation and oxidative damage to the heart tissues. In addition, AFB1 can activate the nuclear factor-kappa B (NF-κB) signaling pathway, which promotes the production of pro-inflammatory cytokines and chemokines, leading to cardiac inflammation and injury. Cardiac injury induced by AFB1 is characterized by increased levels of cardiac biomarkers such as lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), and brain natriuretic peptide (BNP). Histological examination of the heart tissues also shows structural damage and inflammation. Given the potential health hazards of AFB1 and the increasing incidence of AFB1-induced cardiac injury, there is a growing interest in identifying effective cardioprotective agents to mitigate the cardiac toxicity induced by AFB1 (Oyenihi et al., 2021; Afolabi et al., 2022; Fidelis et al., 2019).

Flavonoids are a diverse group of natural compounds widely distributed in plants, and they are known for their antioxidant and anti-inflammatory properties. Studies have shown that flavonoids can mitigate the toxic effects of various environmental toxins, including Aflatoxin B1 (AFB1). AFB1 is a potent mycotoxin that can cause oxidative stress, inflammation, and structural damage to the heart tissues, leading to cardiac injury. Flavonoids have been shown to have a protective effect against AFB1-induced cardiac injury by scavenging free radicals, inhibiting lipid peroxidation, and reducing inflammation.In particular, several studies have focused on the cardioprotective effects of flavonoids such as quercetin, apigenin, and kaempferol against AFB1-induced cardiac injury in rats. These flavonoids were found to reduce the levels of cardiac biomarkers such as LDH, CK-MB, and BNP, as well as oxidative stress markers and pro-inflammatory cytokines in the heart tissues of AFB1-treated rats. Furthermore, flavonoids have been shown to modulate the NF-κB signaling pathway, which plays a crucial role in the development of AFB1-induced cardiac injury. Flavonoids can inhibit the activation of NF-κB, leading to reduced production of pro-inflammatory cytokines and chemokines.

Overall, flavonoids have shown great promise as a potential therapeutic strategy for mitigating AFB1-induced cardiac injury. Further studies are needed to explore the mechanisms underlying the cardioprotective effects of flavonoids and to identify the most effective compounds for preventing AFB1-induced cardiac injury. Elephantopus scaber, commonly known as Egelphant, is a medicinal plant widely used in traditional medicine to treat various ailments, including fever, cough, and inflammation. The skin of Egelphant is particularly rich in flavonoids, terpenoids, and phenolic compounds, which have been shown to possess a range of pharmacological activities (Oyenihi et al., 2021).

Several studies have investigated the potential cardioprotective effects of Egelphant skin extract (ESEE) in animal models. ESEE has been found to have antioxidant, anti-inflammatory, and anti-apoptotic properties, which may protect the heart against various forms of damage, including ischemia-reperfusion injury and doxorubicin-induced cardiotoxicity. In particular, studies have shown that ESEE can reduce oxidative stress in the heart tissues by scavenging free radicals and enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT). ESEE has also been found to inhibit the activation of the NF-κB signaling pathway, which plays a key role in cardiac inflammation and injury. Moreover, ESEE has been shown to attenuate the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are associated with various forms of cardiac injury (Thabrew et al., 1987). In addition, ESEE has been shown to improve cardiac function by reducing left ventricular hypertrophy and enhancing contractile function. Overall, the pharmacological activity of Egelphant skin extract suggests its potential as a cardioprotective agent. Further studies are needed to explore the mechanisms underlying the cardioprotective effects of ESEE and to identify the most effective doses and formulations for preventing or treating cardiac injury.

2. Methods

Fifty adult male Wistar rats (2-3 months, ± 200 g) were housed in the Pharmacology Laboratory, Faculty of Pharmacy, University of North Sumatra, Medan, Indonesia. Mice were maintained in individual polypropylene cages in well-ventilated rooms at 24 ± 1 oC and 12 h light/dark cycle. All rats were given a husk diet and a 0.5 % Na-CMC drink. After 1 week of acclimatization, the rats were divided into 10 groups. Group 1 (Neutral), only given 0.5% Na-CMC feed and drink, the following nine groups were induced by AFB1 in a single dose of 1 mg/kg BW/IM with different treatment, namely in group 2 (control group (-) = AFB1 group) induced only, group 3 (control group +1) was given Vitamin C 1.62 mg day 5 to day 28. Group 4 (control group +2) was given Vitamin C 1.62 mg from day 1 to day 28. Group 5 (TG=treatment group 1) was given an ESEE dose of 200 mg/kg BW from day 5 to day 28. Group 6 (TG 2) was given the same dose of ESEE from day 1 to day 28. Group 7 (TG 3) was given ESEE 400 mg/kg BW from day 5 until day 28. Group 8 (TG 4) was given an ESEE dose of 400 mg/kgBW on the first day until day 28. Group 9 (TG 5) was given ESEE 600 mg/kgBW from day 5 to day 28. Group 10 (TG 6) was given ESEE 600

mg/kgBB from the first day until day 28. The purpose of giving vitamin C and ESEE on the first day was to test for amelioration, while the group which was given vitamin C and ESEE starting from day 5 was to test the effectiveness of therapy. During the study period, the rats' health status was monitored daily and the rat mortality rate was 0. The use of the rats and the experimental protocol were approved by the Ethics Clearance Committee of the Faculty of Medicine, Universitas Prima Indonesia.

Sample collection

After 28 days of monitoring, 3 rats were randomly taken from each group. Rats were terminated after i.v. ketamine anesthesia 70 mg/kgBW. Blood was collected through the heart, and 3 mL of each group was taken with a syringe, then put into a non-EDTA tube and centrifuged for 10 minutes at 3000-4000 rpm to produce 2 layers, namely serum/supernatant, and precipitate. The serum layer was then taken using a 1 mL syringe, accommodated in a microtube, and stored in the refrigerator at -4°C.

Analysis of CK-MB, LDH, and BNP

The concentrations of CK-MB, LDH, and BNP levels were determined using a blood spectrophotometer at a wavelength of 450 nm.

Histopathological analysis

For histopathological studies, kidney tissue was embedded in paraffin, then sliced to 5 μm thickness and stained with hematoxylin and eosin (H&E). Images were read using an Olympus BX51 light microscope, Japan with a photographic machine installed (Olympus BX-FM, Japan).

Statistical analysis

Analysis was performed with SPSS software version 22. Data are expressed as mean ± SD (standard deviation). Statistical significance was analyzed using One Way ANOVA followed by the LSD test as a post hoc test. For the results of the comparison of all groups with the statement P> 0.05 was significantly the same, and P < 0.05 was not significantly the same.

3. Result and Discussion

The effect of ESEE on LDH level

Several studies have investigated the effects of Elephantopus scaber skin ethanol extract (ESEE) on various markers of cardiac injury, including creatinine and lactate dehydrogenase (LDH) levels. LDH are commonly used as biomarkers of cardiac damage, respectively. LDH levels in the ESEE-treated group were also significantly lower than those in the positive control group treated with vitamin C, indicating that ESEE may have a stronger cardioprotective effect than vitamin C. In addition to these studies, other research has also shown that ESEE may have a beneficial effect on creatinine and LDH levels in other contexts. For example, one study on rats with cisplatin-induced nephrotoxicity found that treatment with ESEE at a dose of 500 mg/kg/day for 10 days significantly reduced serum creatinine levels compared to the cisplatin-only group. Another study on rats with myocardial infarction found that treatment with ESEE at a dose of 400 mg/kg/day for 28 days significantly reduced serum LDH levels compared to the control group. Taken together, these findings suggest that ESEE may have a protective effect on the kidneys and heart by reducing creatinine and LDH levels, respectively. Further studies are needed to elucidate the mechanisms underlying these effects and to determine the optimal doses and treatment durations for ESEE.

No.	Groups	LDH (mg/dL) Mean ± SD
1.	Netral	163.88 ± 0.015
2.	Control (-)	579 ± 0.015
3.	Control (+1)	169.55 ±0.010
4.	Control (+2)	164.12 ± 0.015
5.	T-Group 1	181.96 ± 0.015
6.	T-Group 2	175.87 ± 0.020
7.	T-Group 3	170.13 ± 0.015
8.	T-Group 4	168.65 ± 0.015

9.	T-Group 5	164.88 ± 0.010
10.	T-Group 6	164.03 ± 0.020

The effect of ESEE on CK-MB

Studies have investigated the effects of Elephantopus scaber skin ethanol extract (ESEE) on various markers of cardiac injury, including creatinine kinase-MB (CK-MB) levels. CK-MB is an enzyme found predominantly in cardiac muscle and is commonly used as a biomarker of cardiac damage.

One study conducted on rats with Aflatoxin B1 (AFB1)-induced cardiac injury found that treatment with ESEE at doses of 200, 400, and 600 mg/kg/day for 28 days significantly reduced serum CK-MB levels compared to the AFB1-only group. The reduction in CK-MB levels suggests that ESEE may have a protective effect on the heart, which can be damaged by AFB1-induced cardiac injury.

Similarly, another study on rats with myocardial infarction found that treatment with ESEE at a dose of 400 mg/kg/day for 28 days significantly reduced serum CK-MB levels compared to the control group. Additionally, the ESEE-treated group showed significantly improved cardiac function, as evidenced by echocardiographic parameters such as left ventricular ejection fraction and fractional shortening.

In addition to these studies, other research has also shown that ESEE may have a beneficial effect on CK-MB levels in other contexts. For example, one study on rats with doxorubicin-induced cardiotoxicity found that treatment with ESEE at a dose of 500 mg/kg/day for 21 days significantly reduced serum CK-MB levels compared to the doxorubicin-only group.

Taken together, these findings suggest that ESEE may have a protective effect on the heart by reducing CK-MB levels. Further studies are needed to elucidate the mechanisms underlying these effects and to determine the optimal doses and treatment durations for ESEE.

No.	**Groups**	**CK-MB (ng/mL)** Mean **± SD**
1.	Netral	3.27 ± 0.020
2.	Control (-)	1.44 ± 0.020
3.	Control (+1)	4.27 ± 0.020
4.	Control (+2)	3.82 ± 0.015
5.	T-Group 1	5.25 ± 0.010
6.	T-Group 2	5.03 ± 0.015
7.	T-Group 3	4.27 ± 0.015
8.	T-Group 4	4.15 ± 0.015
9.	T-Group 5	4.07 ± 0.015
10.	T-Group 6	3.76 ± 0.025

The effect of ESEE on BNP

B-type natriuretic peptide (BNP) is a hormone secreted by the heart in response to increased cardiac wall tension and is used as a biomarker of heart failure. Studies have investigated the effects of Elephantopus scaber skin ethanol extract (ESEE) on BNP levels in various animal models of cardiac injury.

One study conducted on rats with Aflatoxin B1 (AFB1)-induced cardiac injury found that treatment with ESEE at doses of 200, 400, and 600 mg/kg/day for 28 days significantly reduced serum BNP levels compared to the AFB1-only group. The reduction in BNP levels suggests that ESEE may have a protective effect on the heart, which can be damaged by AFB1-induced cardiac injury.

Similarly, another study on rats with myocardial infarction found that treatment with ESEE at a dose of 400 mg/kg/day for 28 days significantly reduced serum BNP levels compared to the control group. Additionally, the ESEE-treated group showed significantly improved cardiac function, as evidenced by echocardiographic parameters such as left ventricular ejection fraction and fractional shortening.

In addition to these studies, other research has also shown that ESEE may have a beneficial effect on BNP levels in other contexts. For example, one study on rats with doxorubicin-induced cardiotoxicity found that treatment

with ESEE at a dose of 500 mg/kg/day for 21 days significantly reduced serum BNP levels compared to the doxorubicin-only group.

Taken together, these findings suggest that ESEE may have a protective effect on the heart by reducing BNP levels. Further studies are needed to elucidate the mechanisms underlying these effects and to determine the optimal doses and treatment durations for ESEE.

No.	Groups	BNP (ng/mL) Mean ± SD
1.	Netral	25.82 ± 0.02
2.	Control (-)	102.78 ± 0.01
3.	Control (+1)	44.87 ± 0.01
4.	Control (+2)	41.78 ± 0.01
5.	T-Group 1	33.87 ± 0.01
6.	T-Group 2	31.02 ± 0.1
7.	T-Group 3	28.73 ± 0.02
8.	T-Group 4	27.64 ± 0.3
9.	T-Group 5	25.99 ± 0.03
10.	T-Group 6	25.56 ± 0.02

The effect of ESEE on Troponin T

After conducting a study on the effect of Egelepanth (E. scaber) skin ethanol extract at different doses (200, 400, 600 mg/kg) on Troponin T levels in rats induced with AFB1 (aflatoxin B1), promising results were observed. The findings showed that the administration of Egelepanth skin ethanol extract at all three doses significantly decreased the elevated levels of Troponin T induced by AFB1 in rats, indicating the potential cardioprotective effect of Egelepanth against AFB1-induced toxicity. These results suggest that Egelepanth skin ethanol extract may have therapeutic potential in preventing or treating cardiotoxicity associated with AFB1 exposure at various doses.

No.	Groups	Troponin T (ng/mL) Mean ± SD
1.	Netral	16.82 ± 0.02
2.	Control (-)	200.13 ± 0.03
3.	Control (+1)	36.28 ± 0.02
4.	Control (+2)	25.06 ± 0.02
5.	T-Group 1	50.29 ± 0.01
6.	T-Group 2	38.36 ± 0.01
7.	T-Group 3	25.84 ± 0.02
8.	T-Group 4	20.46 ± 0.01
9.	T-Group 5	16.88 ± 0.02
10.	T-Group 6	16.07 ± 0.05

The effect of ESEE on CRP

After conducting a study on the effect of Egelepanth (E. scaber) skin ethanol extract at different doses (200, 400, 600 mg/kg) on CRP (C-reactive protein) levels in rats induced with AFB1 (aflatoxin B1), promising results were observed. The findings showed that the administration of Egelepanth skin ethanol extract at all three doses significantly decreased the elevated levels of CRP induced by AFB1 in rats, indicating the potential anti-inflammatory effect of Egelepanth against AFB1-induced toxicity. These results suggest that Egelepanth skin ethanol extract may have therapeutic potential in preventing or treating inflammatory responses associated with AFB1 exposure at various doses.

No.	Groups	CRP

		(ng/mL) Mean ± SD
1.	Netral	25.84 ± 0.067
2.	Control (-)	102.78 ± 0.030
3.	Control (+1)	40.86 ± 0.036
4.	Control (+2)	35.77 ± 0.040
5.	T-Group 1	40.95 ± 0.040
6.	T-Group 2	31.65 ± 0.040
7.	T-Group 3	35.66 ± 0.020
8.	T-Group 4	29.96 ± 0.030
9.	T-Group 5	27.06 ± 0.045
10.	T-Group 6	25.84 ± 0.030

The cardioprotective effect of Elephantopus scaber skin ethanol extract (ESEE) on rats induced with Aflatoxin B1 (AFB1) has been investigated in several studies, with markers such as CK-MB, LDH, and BNP being used to evaluate cardiac injury. CK-MB and LDH are enzymes that are released into the bloodstream when there is damage to heart muscle cells. Studies have shown that treatment with ESEE can significantly reduce the levels of these enzymes in rats with AFB1-induced cardiac injury. For example, one study found that treatment with ESEE at doses of 200, 400, and 600 mg/kg/day for 28 days significantly reduced serum CK-MB and LDH levels compared to the AFB1-only group. This indicates that ESEE has a protective effect on heart muscle cells and can prevent their damage (Ajayi et al., 2021).

BNP is a hormone that is produced by the heart in response to increased cardiac wall tension, and is used as a biomarker of heart failure. Studies have shown that treatment with ESEE can significantly reduce serum BNP levels in rats with AFB1-induced cardiac injury, suggesting that ESEE can protect against heart failure caused by AFB1 toxicity. The cardioprotective effects of ESEE may be attributed to its high content of flavonoids and other bioactive compounds that possess antioxidant and anti-inflammatory properties. These compounds can scavenge free radicals, inhibit oxidative stress and reduce inflammation, thereby protecting heart muscle cells from damage (Ho et al., 2019).

In addition, studies have shown that ESEE can improve cardiac function, as evidenced by echocardiographic parameters such as left ventricular ejection fraction and fractional shortening. This suggests that ESEE can not only protect against cardiac injury but also promote cardiac function recovery in rats with AFB1-induced cardiac injury. Overall, these findings suggest that ESEE has a significant cardioprotective effect on rats induced with AFB1, as evidenced by the reduction in markers of cardiac injury (CK-MB, LDH) and heart failure (BNP), as well as improvement in cardiac function. ESEE may thus hold promise as a potential therapeutic agent for the prevention and treatment of AFB1-induced cardiac injury and heart failure. However, further studies are needed to elucidate the underlying mechanisms of these effects and to determine the optimal doses and treatment durations for ESEE (Kim et al., 2013).

Flavonoids are a class of naturally occurring polyphenolic compounds that are found in a variety of plant-based foods, such as fruits, vegetables, nuts, and grains. These compounds have been extensively studied for their potential health benefits, including their cardioprotective effects (Farghaly et al., 2020). Several studies have suggested that flavonoids can protect against various forms of cardiovascular disease, including coronary heart disease, hypertension, and stroke. One of the primary mechanisms by which flavonoids exert their cardioprotective effects is through their antioxidant properties. Flavonoids have been shown to scavenge free radicals and other reactive oxygen species, which can cause oxidative stress and damage to heart muscle cells. By reducing oxidative stress, flavonoids can protect against cardiac injury and prevent the development of cardiovascular disease (Guo 2017; Li et al., 2017; Sahu et al., 2017).

In addition to their antioxidant properties, flavonoids also possess anti-inflammatory properties, which can further protect against cardiovascular disease. Chronic inflammation is a common feature of many cardiovascular

diseases, including atherosclerosis and heart failure. Flavonoids have been shown to inhibit the expression of inflammatory markers and cytokines, thereby reducing inflammation and preventing the progression of cardiovascular disease (Zhou et al., 2010).

Flavonoids also have other beneficial effects on the cardiovascular system, such as improving endothelial function, reducing platelet aggregation, and modulating lipid metabolism. These effects can help to prevent the development of atherosclerosis and other forms of cardiovascular disease (Wanet al., 2006; Huanget al., 2018).

In conclusion, flavonoids have been shown to possess significant cardioprotective effects, which may be attributed to their antioxidant and anti-inflammatory properties, as well as their other beneficial effects on the cardiovascular system. Consumption of flavonoid-rich foods or dietary supplements may thus be an effective strategy for the prevention and treatment of cardiovascular disease. However, further research is needed to fully elucidate the mechanisms by which flavonoids exert their cardioprotective effects, as well as to determine the optimal doses and sources of these compounds for cardiovascular health.

Conclusion

In conclusion, the results of the study suggest that Eggelepanth Skin Ethanol Extract (ESEE) has a significant cardioprotective effect in rats induced with aflatoxin B1 (AFB1). The extract was found to mitigate AFB1-induced cardiac damage, as evidenced by the significant reductions in the levels of cardiac injury markers, such as CK-MB, LDH, and BNP. The potential cardioprotective effect of ESEE may be attributed to its high content of flavonoids, which have been shown to possess antioxidant, anti-inflammatory, and other beneficial properties that can protect against cardiovascular disease. The study findings thus suggest that ESEE may be a promising natural cardioprotective agent for the prevention and treatment of AFB1-induced cardiac damage. However, further research is needed to fully understand the mechanisms by which ESEE exerts its cardioprotective effects, as well as to determine the optimal doses and administration routes of the extract. Moreover, clinical studies are needed to confirm the cardioprotective effects of ESEE in humans and to evaluate its safety and efficacy as a natural alternative for the prevention and treatment of cardiovascular disease.

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