Research Article

Improvement in Cardiac Troponins and Proinflammatory Cytokines Following Dacryodes Edulis Compounds Treatment in Ketamine-Induced Myocardial Injury in Wistar Rats

Odey Paul Anyiom[1], Aniah Julius Akomaye[2], Ajang Cletus Ugbaka[3], Nsikak Michael Umoh[3], Nnenna Williams Afamuefuna[3], Ajagbe Abayomi[1], Oku Michael Effiong[3], Odom Emmanuel Izuchukwu[3], Kumbet Sonny[1], Solomon Abel Y.[1], Abue Andrew Donatus[1]

[1]Department of Human Anatomy, Faculty of Basic Medical sciences, Nile University of Nigeria, Abuja. Nigeria.
[2]Department of Anatomical sciences, Faculty of Basic Medical Sciences, University of Abuja. Nigeria.
[3]Department of Anatomical sciences, Faculty of Basic Medical Sciences, University of Calabar. Nigeria.

ABSTRACT

Aim: To evaluate the cardioprotective effects of Dacryodes edulis compounds on ketamine-induced myocardial injury in Wistar rats by assessing serum troponins and pro-inflammatory cytokines.

Research Design: Experimental, randomized controlled animal study.

Place and Duration: Conducted at the Department of Human Anatomy, Nile University of Nigeria, Abuja, Nigeria, over a period of three months in 2024.

Methodology: Forty-eight male Wistar rats were randomly assigned to eight groups and administered ketamine at doses of 100, 150, and 200 mg/kg to induce myocardial injury. Treatment groups received concomitant oral doses of Dacryodes edulis methanolic extract and its fractions (saponins, alkaloids, flavonoids). Serum levels of cardiac troponins T and I, IL-6, and TNF-α were measured using ELISA kits after 21 days of treatment. Phytochemical analysis of the plant fractions was performed to identify bioactive compounds. Data were analyzed statistically, with $p < 0.05$ considered indicative of significant differences between groups.

Results: Ketamine significantly elevated serum troponins and pro-inflammatory cytokines compared to controls. Treatment with Dacryodes edulis extracts, especially the methanolic and flavonoid-rich fractions, markedly reduced troponin and cytokine levels, approaching those of the control group. Phytochemical analysis revealed high concentrations of flavonoids, saponins, and alkaloids, correlating with observed cardioprotective effects.

Conclusion: Dacryodes edulis compounds exhibit significant cardioprotective effects against ketamine-induced myocardial injury in rats, primarily through their antioxidant and anti-inflammatory properties. These findings suggest its potential as a natural therapeutic agent for mitigating drug-induced cardiac damage, warranting further investigation.

Keywords: Dacryodes edulis, Ketamine-induced myocardial injury, Cardiac troponins, Pro-inflammatory cytokines, Cardioprotection, Phytochemicals.

INTRODUCTION

Cardiovascular diseases (CVDs) remain a major global health challenge, responsible for significant morbidity and mortality worldwide (Di Cesare et al., 2024; World Health Organization, (2025). Myocardial injury, which involves damage to cardiac muscle cells, is a central feature of many CVDs, including myocardial infarction and heart failure (Nekolla et al., 2021). Accurate and timely detection of myocardial injury is crucial for effective management, with cardiac biomarkers such as troponins T and I (cTnT and cTnI) serving as the gold standard due to their high specificity and sensitivity (Zhang et al., 2025). These proteins are released into circulation following cardiac cell injury, thereby serving as reliable indicators of ongoing myocardial damage (Potter et al., 2022.

Alongside troponins, the inflammatory response significantly influences the pathogenesis of myocardial injury (Frangogiannis, 2014). Cytokines like Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) are key mediators that modulate inflammation within the myocardium (Amara et al., 2025). Elevated levels of these cytokines are associated with adverse cardiac remodeling, hypertrophy, fibrosis, and progression to heart failure (Amin et al., 2020; Zhang & Dhalla, 2024). Measuring these cytokines provides valuable insights into the severity of myocardial injury and the inflammatory status, which can inform prognosis and guide therapeutic strategies (Papamichail et al., 2024).

Recently, the recreational use of ketamine, a dissociative anesthetic, has become increasingly prevalent, particularly among youths in Nigeria and other African countries (Joshi & Onajin-Obembe, 2016). While ketamine has legitimate

medical applications, its misuse has been linked to serious adverse effects, including cardiotoxicity (Mladěnka et al., 2018; Odey et al., 2024). The mechanisms involve both indirect sympathomimetic effects, such as increased heart rate and blood pressure—and direct myocardial toxicity (Goddard et al., 2021). The latter is characterized by oxidative stress, inflammation, apoptosis, and structural remodeling of cardiac tissue (Shaikh et al., 2019; Adeyemi et al., 2021). Animal studies have demonstrated that ketamine exposure elevates oxidative stress markers like malondialdehyde (MDA) and pro-inflammatory cytokines such as IL-6 and TNF-α, which contribute to myocardial cell damage and impaired cardiac function (Ince et al., 2025).

Despite these insights, current management strategies for ketamine-induced myocardial injury are largely supportive, with limited options that target the underlying biochemical pathways (Zhang et al., 2023). While cardiac biomarkers such as troponins confirm injury, they do not address the mechanisms involved nor do they provide targeted preventive or therapeutic effects. Consequently, there is a compelling need to explore natural compounds with cardioprotective properties, especially those with antioxidant and anti-inflammatory effects.

Dacryodes edulis (G. Don) H.J. Lam, commonly known as African pear or Safou in Nigeria, is a tropical fruit-bearing tree belonging to the Burseraceae family (Fotouo-M & Dongmo Lekagne, 2022). It is widely distributed across West Africa, including Nigeria, Cameroon, Ghana, and Ivory Coast (Mpemboura et al., 2021). In Nigeria, the tree is locally called Ube (Igbo), Elemi/Apara (Yoruba), Atili (Hausa) and Eben (Ibibio), and simply referred to as Dacryodes or African pear (Duru et al., 201). Traditionally, Dacryodes edulis has been valued for its edible fruit, which is rich in healthy fats, vitamins, and minerals (Fotouo-M & Dongmo Lekagne, 2022). The pulp is consumed fresh, roasted, or processed into various culinary dishes (Morgan & Matthew, 2024). Beyond its nutritional benefits, the tree's leaves, bark, and seeds have been used in folk medicine to treat ailments such as fever, diarrhea, and inflammation (Swana et al., 2023).

Phytochemical analyses of Dacryodes edulis reveal the presence of diverse bioactive compounds, including flavonoids, tannins, phenolic acids, saponins, and terpenoids (Rachel, 2015). These compounds are known for their potent antioxidant, anti-inflammatory, antimicrobial, and analgesic properties (Parham et al., 2020). The antioxidant activity involves scavenging free radicals and reducing oxidative stress, which is crucial in protecting tissues from damage caused by reactive oxygen species (ROS) (Moges et al., 2024). Its anti-inflammatory effects are mediated by the inhibition of pro-inflammatory mediators, thereby reducing cytokine production and inflammation (Okafo et al., 2024). Additionally, studies have demonstrated antimicrobial activity, wound-healing properties, and potential neuroprotective effects (Oyetunji & Adeniyi, 2017).

Although direct research on Dacryodes edulis and its effects on myocardial injury is limited, emerging evidence suggests that its rich phytochemical profile could confer cardioprotective effects by counteracting oxidative stress and inflammation, both of which are major contributors to ketamine-induced myocardial damage. Its ability to modulate cytokine production, decrease lipid peroxidation, and inhibit apoptosis (Swana et al., 2023) positions it as a promising candidate for further investigation.

The existing literature indicates that Dacryodes edulis possesses significant antioxidant and anti-inflammatory properties attributable to its phytochemicals. These properties have been associated with protective effects against oxidative tissue damage and inflammatory processes in various experimental models (Mucha et al., 2021; Kulkarni et al., 2025). Given that ketamine-induced myocardial injury involves oxidative stress, inflammation, and apoptosis, exploring the potential cardioprotective effects of Dacryodes edulis is both relevant and timely. This study aimed to evaluate its capacity to mitigate ketamine-induced myocardial injury by assessing serum levels of troponins and pro-inflammatory cytokines, thereby providing insights into its mechanism of action

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Ketamine hydrochloride (Rotexmedica, Germany) was used as the cardiotoxic agent. Solvents included analytical grade methanol, n-hexane, ethyl acetate, and distilled water (Sigma-Aldrich, USA). High-sensitivity ELISA kits for rat troponin I and T (Elabscience®, UK), supplied with standard proteins, detection antibodies, enzyme conjugates, wash buffers, substrate solutions, and reagents for calibration curves. ELISA kits for rat IL-6 and TNF-α (Elabscience®, UK), including all necessary reagents, standards, and controls. Phosphate-buffered saline (PBS), protease inhibitors (from Sigma-Aldrich), microplate reader capable of measuring optical density at 450 nm.

2.2 Plant Collection and Authentication

Fresh leaves of Dacryodes edulis were harvested from Akamkpa, Cross River State, Nigeria, and authenticated at the Department of Botany, University of Calabar. A voucher specimen was deposited in the institutional herbarium (Voucher No. UC/PCG/DE-002).

2.3 Preparation of Methanolic Extract

The leaves were washed, air-dried at room temperature, and pulverized into powder. Approximately 500 g of powdered material was macerated in 80% methanol (1:5 w/v) for 72 hours with intermittent shaking. The extract was filtered through Whatman No. 1 filter paper, concentrated under reduced pressure at 40°C using a rotary evaporator, and stored at 4°C until use. A portion of this crude extract was used for experimental groups, while the rest underwent phytochemical fractionation.

2.4 Phytochemical Fractionation

The crude methanolic extract was partitioned to obtain specific fractions:

Saponins: Isolated via butanol partitioning and precipitation (Fordos et al., 2015).

Alkaloids: Extracted by acid–base extraction with pH adjustment (Verma et al., 2007).

Flavonoids: Separated through ethyl acetate partitioning and column chromatography (Mujawah et al., 2010).

Fractions were dried and stored at 4°C. The approximate yields from 500 g of powdered leaves were: saponins (30–40%), alkaloids (10–15%), flavonoids (20–25%).

2.5 Experimental Animals

Forty-eight adult male Wistar rats (180–220 g) were housed under standard conditions (12-hour light/dark cycle, 25 ± 2°C, ad libitum access to chow and water). The study was approved by the University of Calabar Research Ethics Committee (Approval No. UC/AREC/025/2024).

2.6 Experimental Design

Rats were randomly assigned into groups:

Group	Treatment
I	Normal control (saline only)
II	Ketamine 100 mg/kg (i.p.)
III	Ketamine 150 mg/kg (i.p.)
IV	Ketamine 200 mg/kg (i.p.)
V	Ketamine 200 mg/kg + Methanolic extract (142 mg/kg, p.o.)
VI	Ketamine 200 mg/kg + Saponin fraction (142 mg/kg, p.o)
VII	Ketamine 200 mg/kg + Alkaloid fraction (192 mg/kg, p.o.)
VIII	Ketamine 200 mg/kg + Flavonoid fraction (164 mg/kg, p.o.)

Doses were selected based on prior literature demonstrating safety and efficacy within this range (Odey et al., 2024). Ketamine was administered daily for 21 days, with plant extracts/fractions given concurrently.

2.7 Sample Collection and Biochemical Assays

On day 22, rats were anesthetized with ketamine (50 mg/kg, i.p.), and blood was collected via cardiac puncture into plain tubes. Blood samples were allowed to clot at room temperature for 30 minutes, then centrifuged at 3000 rpm for 10 minutes to obtain serum, which was stored at -80°C.

Serum Troponin I and T levels: Quantified using high-sensitivity ELISA kits (Elabscience®, UK). Assays were performed according to the manufacturer's instructions. Serum samples were diluted appropriately, added to wells coated with specific antibodies, incubated for the specified times, then washed. Enzyme conjugates and substrate solutions were added sequentially, and absorbance was measured at 450 nm using a microplate reader. Troponin concentrations were calculated from standard calibration curves.

Pro-inflammatory cytokines (IL-6 and TNF-α): Heart tissues were excised, washed in ice-cold PBS, blotted dry, weighed, and homogenized in ice-cold PBS containing protease inhibitors (from Sigma-Aldrich) at a ratio of 1:10 (w/v). The homogenates were centrifuged at 10,000 rpm for 15 minutes at 4°C, and supernatants collected for cytokine analysis. IL-6 and TNF-α levels were measured using ELISA kits (Elabscience®, UK) following the manufacturer's protocols. Absorbance was read at 450 nm, and cytokine concentrations were derived from standard curves.

2.8 Ethical Approval

All procedures conformed to guidelines for animal care and use, with ethical approval granted by the Faculty Animal Research Ethics Committee (FAREC-FBMS), University of Calabar (Approval No. 112ANA1822).

2.8 Ethical approval

All animal experiments were conducted in accordance with the approved institutional and natural guidelines for the care and use of animal. Ethical clearance was obtained from Faculty Animal Research Ethic Committee (FAREC-FBMS), Faculty of Basic Medical Sciences, University of Calabar, Calabar with an issued number: 112ANA1822.

RESULTS AND DISCUSSION

Results

Cardiac Troponin Levels

Ketamine administration at 100 mg/kg, 150 mg/kg, and 200 mg/kg significantly increased serum levels of cardiac troponins T (cTnT) and I (cTnI) compared to the normal control, indicating myocardial injury. The groups treated with Dacryodes edulis extracts, particularly the methanolic extract and its fractions (saponins, alkaloids, flavonoids), showed a significant reduction in troponin levels compared to ketamine-only groups, approaching values closer to the control (Table 2, Fig. 1&2).

Inflammatory Cytokine Levels

Ketamine at various doses elevated serum levels of pro-inflammatory cytokines IL-6 and TNF-α, reflecting heightened inflammation associated with myocardial injury. Treatment with Dacryodes edulis compounds, especially the methanolic extract and flavonoid fraction, significantly lowered these cytokines compared to ketamine-only groups (Table 3, Fig. 3&4).

Phytochemical Composition of Dacryodes edulis

The phytochemical analysis revealed that the 30% methanolic fraction of Dacryodes edulis leaves contains notable amounts of flavonoids (abundantly present), saponins, alkaloids (moderately high), and some phenolic compounds (Table 1).

Discussion

The study demonstrated that ketamine administration at doses of 100 mg/kg, 150 mg/kg, and 200 mg/kg resulted in a significant elevation of serum cardiac troponins T (cTnT) and I (cTnI) compared to the normal control group. This aligns with existing literature indicating that ketamine, especially at higher doses, induces myocardial injury characterized by cardiomyocyte damage and increased release of these sensitive biomarkers (Goddard et al., 2021; Ince et al., 2025). The dose-dependent increase suggests that higher ketamine doses exacerbate myocardial stress and injury, likely via mechanisms involving oxidative stress, inflammation, and apoptosis.

Interestingly, rats receiving Dacryodes edulis extracts, particularly the methanolic extract and its fractions—saponins, alkaloids, and flavonoids—showed a significant reduction in troponin levels compared to the ketamine-only groups. These findings imply a cardioprotective effect, possibly attributable to the bioactive phytochemicals present in the extracts. The decrease in troponin levels approaching those of the control indicates mitigation of myocardial cell injury, supporting the hypothesis that Dacryodes edulis exerts protective effects possibly via antioxidant and anti-inflammatory pathways (Swana et al., 2023).

Ketamine exposure notably elevated serum levels of IL-6 and TNF-α, indicating an enhanced inflammatory response following myocardial injury. Elevated pro-inflammatory cytokines are known to contribute to adverse cardiac remodeling, hypertrophy, and fibrosis (Frangogiannis, 2014; Zhang & Dhalla, 2024). The increase in these cytokines aligns with the proposed mechanism whereby ketamine induces oxidative stress, leading to the activation of inflammatory pathways (Odey et al., 2024).

Treatment with Dacryodes edulis, especially the methanolic extract and flavonoid fraction, significantly lowered IL-6 and TNF-α levels. This suggests that the phytochemicals—particularly flavonoids and saponins—may inhibit pro-inflammatory cytokine production by modulating signaling pathways such as NF-κB, which is central to cytokine gene expression (Okafo et al., 2024). The reduction in cytokines correlates with decreased myocardial inflammation and possibly less tissue remodeling, thereby contributing to the overall cardioprotective effect observed.

Phytochemical analysis indicated that the 30% methanolic fraction of Dacryodes edulis leaves contains significant amounts of flavonoids, saponins, alkaloids, and phenolic compounds. Flavonoids are well-documented for their potent antioxidant properties, scavenging reactive oxygen species (ROS), and reducing lipid peroxidation (Moges et al., 2024). Such activity can prevent oxidative damage to cardiomyocytes, thus decreasing troponin release.

Saponins and alkaloids also possess anti-inflammatory and antioxidant activities. Saponins, for instance, can inhibit inflammatory mediators and stabilize cell membranes, preventing leakage of troponins (Fordos et al., 2015). Alkaloids have been reported to modulate immune responses and possess cardioprotective effects via various mechanisms, including calcium channel modulation and free radical scavenging (Verma et al., 2007).

The combined presence of these phytochemicals in Dacryodes edulis likely contributes synergistically to attenuate ketamine-induced oxidative stress and inflammation, which are key drivers of myocardial injury. The observed reduction in troponin and cytokine levels supports this protective role.

The cardioprotective effects of Dacryodes edulis can be attributed primarily to its antioxidant and anti-inflammatory properties. Oxidative stress plays a pivotal role in ketamine-induced myocardial injury, with increased lipid peroxidation and ROS generation damaging cellular components (Ince et al., 2025). Flavonoids and phenolic acids in the extract can neutralize ROS, thereby preserving cell membrane integrity and preventing leakage of cardiac biomarkers.

Furthermore, the reduction in IL-6 and TNF-α suggests that Dacryodes edulis compounds inhibit inflammatory cascades, which are activated by oxidative stress. By suppressing these cytokines, the extract may prevent downstream effects such as fibroblast activation, fibrosis, and adverse remodeling, ultimately preserving cardiac function (Zhang et al., 2023). Additionally, these phytochemicals may inhibit apoptosis of cardiomyocytes, further preventing tissue damage.

The combined effects of antioxidation, anti-inflammation, and anti-apoptosis highlight the multifaceted cardioprotective potential of Dacryodes edulis (Swana et al., 2023).

The findings from this study underscore the potential of Dacryodes edulis as a natural cardioprotective agent, especially in counteracting chemically or drug-induced myocardial injury. Its rich phytochemical profile, particularly flavonoids, saponins, and alkaloids, offers a promising basis for developing adjunct therapies that mitigate oxidative stress and inflammation, which are common pathways in various cardiac pathologies (Mucha et al., 2021; Kulkarni et al., 2025).

Given the increasing prevalence of ketamine misuse and its associated cardiotoxicity, exploring plant-based remedies with minimal adverse effects is highly relevant. Further studies are warranted to isolate specific bioactive compounds, elucidate their molecular mechanisms, and assess long-term safety and efficacy.

While the results are promising, some limitations need acknowledgment. The study was conducted in an animal model; thus, extrapolation to humans requires caution. Dose optimization, bioavailability, and potential toxicity of the extracts need thorough investigation. Moreover, molecular studies could elucidate specific signaling pathways modulated by Dacryodes edulis phytochemicals.

Future research should also examine the effects of prolonged administration, potential synergistic effects with conventional drugs, and the impact on cardiac function parameters such as ejection fraction and cardiac output through echocardiography.

TABLES & FIGURES

Table 1: Results of Phytochemical Analysis

Constituent	**30% methanol fraction**
Saponin	
Frothing test	+
Emulsifying test	+
Alkaloid	
Wagner's reagent	++
Meyer's reagent	++
Draggendorff's reagent	+
Flavonoids	++++

(-) = Not Present (+) = Present in small concentration. (++) = Present in moderately high concentration. (+++) = Present in high concentration. (++++) = Abundantly Present

Table 2: Comparison of cTnT/TNNT2 and cTnT/TNNT3 concentration among trial groups

Groups	cTnT/TNNT2 (pg/ml)	cTnT/TNNT3 (pg/ml)
A	112.5 ± 2.77	136.7 ± 4.45
B I	109.3 ± 0.58	180.8 ± 2.28*
B II	129.5 ± 0.81^{*,a}	196.0 ± 4.11*
B III	130.6 ± 0.63^{*,a}	185.8 ± 6.25*
C	117.6 ± 1.39^{b,c}	174.9 ± 3.14*
D	120.6 ± 4.53^{a,c}	236.9 ± 4.76^{*,a,b,c,d}
E	117.8 ± 4.20^{b,c}	201.7 ± 4.18^{*,d,e}
F	114.0 ± 2.86^{b,c}	183.1± 7.35$^{*.e}$

scores are presented as Mean ± SEM, n=3
*= markedly dissimilar from A at p<0.05
a= markedly dissimilar from B I at p<0.05
b= markedly dissimilar from B II at p<0.05
c= markedly dissimilar from B III at p<0.05
d= markedly dissimilar from C at p<0.05
e= markedly dissimilar from D at p<0.05

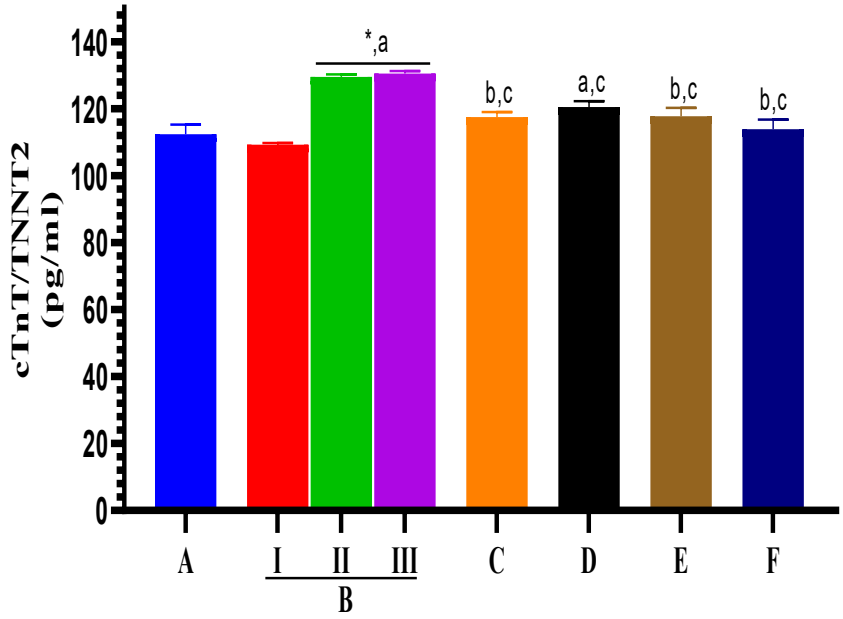

Figure 1: Evaluation of cTnT/TNNT2 concentration among experimental groups
Values are displayed as Mean ± SEM, n=3
*= markedly dissimilar from A at p<0.05
a= markedly dissimilar from B I at p<0.05

b= markedly dissimilar from B II at p<0.05
c= markedly dissimilar from B III at p<0.05

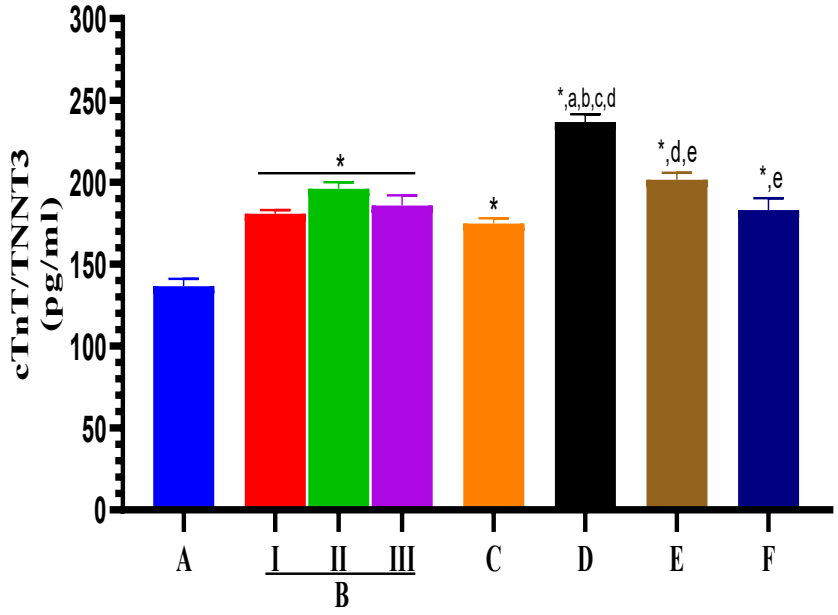

Figure 2: Comparison of cTnT/TNNT3 concentration among experimental groups
Values are presented as Mean ± SEM, n=3
*= markedly dissimilar from A at p<0.05
a= markedly dissimilar from B I at p<0.05
b= markedly dissimilar from B II at p<0.05
c= markedly dissimilar from B III at p<0.05
d= markedly dissimilar from C at p<0.05
e= markedly dissimilar from D at p<0.05

Table 3: Comparison of interleukin-6 and TNF-alpha concentration among experimental groups

Groups	Interleukin-6 (pg/ml)	TNF-Alpha (pg/ml)
A	113.8 ± 1.80	68.10 ± 6.82
B I	135.5 ± 1.97*	106.3 ± 2.34*
B II	148.9 ± 1.89*	95.60 ± 1.91*
B III	154.7 ± 2.01^{*,a}	101.4 ± 1.91*
C	125.6 ± 3.81^{b,c}	77.17 ± 3.74^{a}
D	129.4 ± 2.45^{b,c}	87.46 ± 7.45
E	131.7 ± 5.63^{*,b,c}	92.13 ± 9.01
F	124.0 ± 3.88^{b,c}	79.62 ± 4.62^{a}

Values are displayed as Mean ± SEM, n=3

*= markedly dissimilar from A at p<0.05
a= markedly dissimilar from B I at p<0.05
b= markedly dissimilar from B II at p<0.05
c= markedly dissimilar from B III at p<0.05

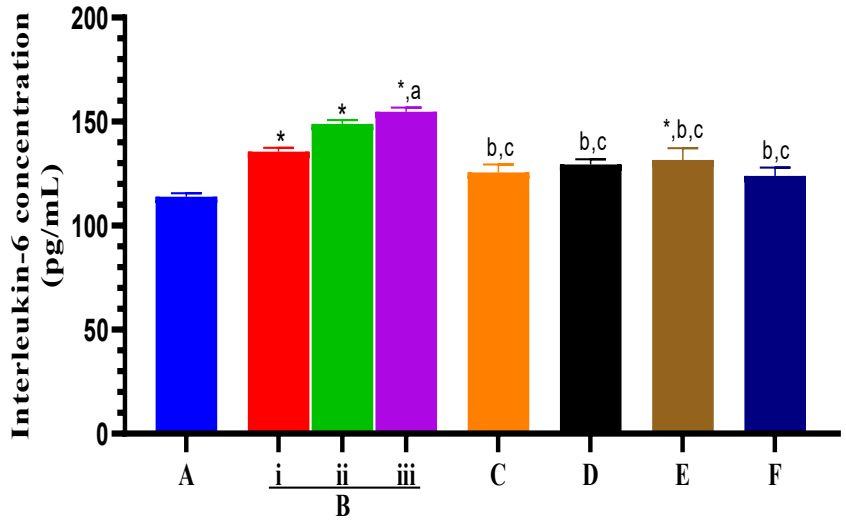

Figure 3: Comparison of interleukin-6 concentration among experimental groups
Values are displayed as Mean ± SEM, n=3
*= markedly dissimilar from A at p<0.05
a= markedly dissimilar from B I at p<0.05
b= markedly dissimilar from B II at p<0.05
c= markedly dissimilar from B III at p<0.05

Analysis of Tumor necrotic factor alpha

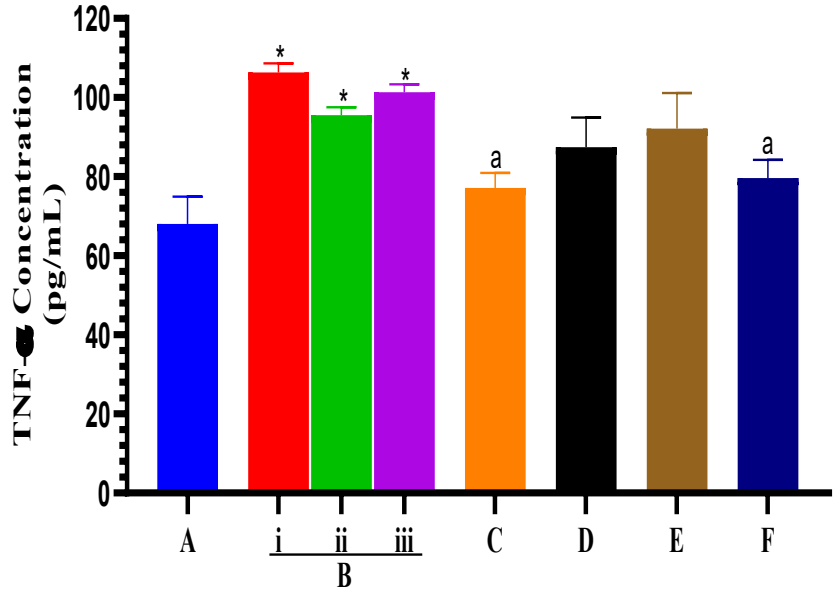

Figure 4: Comparison of TNF-alpha concentration among experimental groups
Values are presented as Mean ± SEM, n=3
*= significantly different from A at p<0.05
a= significantly different from B I at p<0.05

CONCLUSION

This study provides compelling evidence that Dacryodes edulis extracts, particularly the methanolic and flavonoid-rich fractions, confer significant cardioprotective effects against ketamine-induced myocardial injury in rats. The observed reduction in serum troponin levels and pro-inflammatory cytokines such as IL-6 and TNF-α suggests that these plant-derived phytochemicals mitigate oxidative stress and inflammation—key pathways involved in myocardial damage. The presence of bioactive compounds like flavonoids, saponins, and alkaloids likely underpins these protective effects through their antioxidant and anti-inflammatory properties.

These findings support the therapeutic potential of Dacryodes edulis as a natural agent for preventing or attenuating drug-induced cardiotoxicity. Further research is warranted to isolate active constituents, elucidate precise molecular mechanisms, and evaluate its efficacy and safety in clinical settings. Overall, Dacryodes edulis emerges as a promising candidate for developing adjunct therapies aimed at safeguarding cardiac health, particularly in populations at risk of oxidative and inflammatory cardiac injuries.

Animal Ethics Declaration
Animal Research Ethics Committee (FAREC-FBMS), University of Calabar (Approval No. 112ANA1822).

Funding Declaration
No funding

References

1. Di Cesare, M., Perel, P., Taylor, S., Kabudula, C., Bixby, H., Gaziano, T. A., McGhie, D. V., Mwangi, J., Pervan, B., Narula, J., Pineiro, D., & Pinto, F. J. (2024). The heart of the world. Global Heart, 19 (1), 11. https://doi.org/10.5334/gh.1288
2. World Health Organization. (2025, July 31). Cardiovascular diseases (CVDs). Retrieved from https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
3. Nekolla, S. G., Saraste, A., Sager, H., Makowski, M. R., & Schwaiger, M. (2021). Congestive heart failure. In B. D. Ross & S. S. Gambhir (Eds.), Molecular imaging (2nd ed., pp. 1167–1191). Academic Press. https://doi.org/10.1016/B978-0-12-816386-3.00050-8
4. Zhang, N., Wang, Y., Li, F., Zhu, Y., Fu, Z., Jia, M., Zhan, X., & Zhang, W. (2025). Recent advances in monitoring technologies for cardiac troponin I: A pivotal biomarker in cardiovascular diseases. Biomolecules, 15(6), 858. https://doi.org/10.3390/biom15060858
5. Potter JM, Hickman PE, Cullen L. Troponins in myocardial infarction and injury. Aust Prescr. 2022 Apr;45(2):53-57. doi: 10.18773/austprescr.2022.006. Epub 2022 Apr 1. PMID: 35592367; PMCID: PMC9081942.
6. Frangogiannis, N. G. (2014). The inflammatory response in myocardial injury, repair, and remodelling. Nature Reviews Cardiology, 11(5), 255–265. https://doi.org/10.1038/nrcardio.2014.28
7. Amara, M., Stoler, O., & Birati, E. Y. (2025). The role of inflammation in the pathophysiology of heart failure. Cells, 14(14), 1117. https://doi.org/10.3390/cells14141117
8. Amin, M. N., Siddiqui, S. A., Ibrahim, M., Hakim, M. L., Ahammed, M. S., Kabir, A., & Sultana, F. (2020). Inflammatory cytokines in the pathogenesis of cardiovascular disease and cancer. SAGE Open Medicine, 8, 2050312120965752. https://doi.org/10.1177/2050312120965752
9. Zhang, H., & Dhalla, N. S. (2024). The role of pro-inflammatory cytokines in the pathogenesis of cardiovascular disease. International Journal of Molecular Sciences, 25(2), 1082. https://doi.org/10.3390/ijms25021082
10. Papamichail, A., Kourek, C., Briasoulis, A., Xanthopoulos, A., Tsougos, E., Farmakis, D., & Paraskevaidis, I. (2024). Targeting key inflammatory mechanisms underlying heart failure: A comprehensive review. International Journal of Molecular Sciences, 25(1), 510. https://doi.org/10.3390/ijms25010510

11. Joshi, G., & Onajin-Obembe, B. (2016). The role of ketamine in low- and middle-income countries. Anesthesia & Analgesia, 122(1), 1. https://doi.org/10.1213/ANE.0000000000001104
12. Mladěnka, P., Applová, L., Patočka, J., Costa, V. M., Remiao, F., Pourová, J., Mladěnka, A., Karlíčková, J., Jahodář, L., Vopršalová, M., Varner, K. J., & Štěrba, M.; TOX-OER and CARDIOTOX Hradec Králové Researchers and Collaborators. (2018). Comprehensive review of cardiovascular toxicity of drugs and related agents. Medical Research Reviews, 38(4), 1332–1403. https://doi.org/10.1002/med.21476
13. Odey, P., Aniah, J., Okolo, R., Donatus, A., Gbenga, E., Ugbaka, A. C., & Odom, E. (2024). High doses of ketamine inflict myocardial injury and cause changes in the relative body weight to heart of adult albino Wistar rats. Asian Journal of Pharmaceutical and Clinical Research, 17(3), 24-28. https://doi.org/10.22159/ajpcr.2024.v17i3.49464
14. Goddard, K., Sampson, C., Bedy, S. M., Ghadban, R., & Stilley, J. (2021). Effect of ketamine on cardiovascular function during procedural sedation of adults. Cureus, 13(3), e14228. https://doi.org/10.7759/cureus.14228
15. Ince, R., Ozgodek, H. B., Kahramanlar, A. A., Yucel, N., Sarıgül, C., & Suleyman, H. (2025). Relationship between the duration of intravenous ketamine anesthesia and postoperative oxidative stress and inflammatory response in rats. International Journal of Molecular Sciences, 26(19), 9465. https://doi.org/10.3390/ijms26199465
16. Zhang, R., Wang, X., Xie, Z., Cao, T., Jiang, S., & Huang, L. (2023). Lipoxin A4 methyl ester attenuated ketamine-induced neurotoxicity in SH-SY5Y cells via regulating leptin pathway. Toxicology in Vitro, 89, 105581. https://doi.org/10.1016/j.tiv.2023.105581
17. Fotouo-M, H., & Dongmo Lekagne, J. B. (2022). African Pear (Dacoryodes edulis (G.Don) H.J. Lam) physical characteristics, nutritional properties, and postharvest management: A review. Agriculturae Conspectus Scientificus, 87, 1–10.
18. Mpemboura Nsangou, S., Tonfack, L., Mbéguié-A-Mbéguié, D., Temegne Nono, C., Ntsomboh Ntsefong, G., & Youmbi, E. (2021). African plum (Dacryodes edulis [G. Don] H.J. Lam) fruit development indexes clearly defined and phenophases correlated with temperature in the tropics. Journal of Applied Biology & Biotechnology. https://doi.org/10.7324/JABB.2021.9107
19. Duru, F. C., Ochulor, D. O., & Uneanya, G. C. (2017). Evaluation of the physico-chemical characteristics and oxidative/hydrolytic stabilities of oils of African pear (Dacryodes edulis) and bullet pear (Canarium schweinfurthi) fruits. CARD International Journal of Medical Science and Applied Biosciences, 2(2). http://www.casirmediapublishing.com
20. Morgan Ugochukwu Nwaogu, & Matthew Olushola Oluwamukomi. (2024). African pear (Dacryodes edulis) pulp antioxidants and bioactive compounds: Outcome of heat treatment. Food Chemistry Advances, 4, 100653. https://doi.org/10.1016/j.focha.2024.100653
21. Swana, L., Tsakem, B., Tembu, J. V., Teponno, R.. B., Folahan, J.. T., Kalinski,, J.. C., Polyzois,, A., Kamatou,, G., Sandjo,, L.. P., Chamcheu,, J.. C., & Siwe-Noundou,, X. (2023). The genus Dacryodes Vahl.: Ethnobotany, phytochemistry, and biological activities. Pharmaceuticals (Basel), 16(5), 775. https://doi.org/10.3390/ph16050775
22. Rachel, O. (2015). Phytochemical screening and medicinal potentials of the bark of Dacryodes edulis (G. Don) HJ Lam. Journal of Environmental Analytical Chemistry. https://doi.org/10.4172/2380-2391.1000158
23. Parham, S., Kharazi, A. Z., Bakhsheshi-Rad, H. R., Nur, H., Ismail, A. F., Sharif, S., RamaKrishna, S., & Berto, F. (2020). Antioxidant, antimicrobial and antiviral properties of herbal materials. Antioxidants (Basel), 9(12), 1309. https://doi.org/10.3390/antiox9121309
24. Moges, G. W., Manahelohe, G., & Assege, M. (2024). Phenolic, flavonoid contents, antioxidant, and antibacterial activity of selected Eucalyptus species: Review. Biology Medicine & Natural Product Chemistry, 13, 147–157. https://doi.org/10.14421/biomedich.2024.131.147-157
25. Okafo, S. E., Iwetan, B. B., Odiri, O. O., & Nwankwo, L. U. (2024). Anti-inflammatory property of gels formulated using Dacryodes edulis bark ethanol extract. African Journal of Biomedical Research, 25(3), 413–418. https://doi.org/10.4314/
26. Oyetunji, O., & Adeniyi, O. (2017). Antibacterial and antioxidant activities of Dacryodes edulis methanolic leaf extract. Journal of Advances in Medical and Pharmaceutical Sciences, 14, 1–11. https://doi.org/10.9734/JAMPS/2017/33831

27. Swana, L., Tsakem, B., Tembu, J. V., Teponno, R. B., Folahan, J. T., Kalinski, J.-C., Polyzois, A., Kamatou, G., Sandjo, L. P., Chamcheu, J. C., & Siwe-Noundou, X. (2023). The genus Dacryodes Vahl.: Ethnobotany, phytochemistry, and biological activities. Pharmaceuticals, 16(5), 775. https://doi.org/10.3390/ph16050775
28. Mucha, P., Skoczyńska, A., Małecka, M., Hikisz, P., & Budzisz, E. (2021). Overview of the antioxidant and anti-inflammatory activities of selected plant compounds and their metal ions complexes. Molecules, 26(16), 4886. https://doi.org/10.3390/molecules26164886
29. Kulkarni, A., Kulkarni, C. C., Pradeep, S. R., Poyya, J., Kudva, A. K., Radhakrishnan, V., & Khandagale, A. S. (2025). Role of anti-inflammatory and antioxidant properties of natural products in curing cardiovascular diseases. Current Issues in Molecular Biology, 47(11), 955. https://doi.org/10.3390/cimb47110955\
30. Mujawah, A., Mohammed, M., & Ahmed, M. (2010). First isolation of a flavonoid from Juniperus procera using ethyl acetate extract. Arabian Journal of Chemistry, 3, 85–88. https://doi.org/10.1016/j.arabjc.2010.02.003
31. Verma, A., Laakso, I., Seppänen-Laakso, T., Huhtikangas, A., & Riekkola, M. L. (2007). A simplified procedure for indole alkaloid extraction from Catharanthus roseus combined with a semi-synthetic production process for vinblastine. Molecules, 12(7), 1307–1315. https://doi.org/10.3390/12071307
32. Fordos, S. A., Amin, S., Abid, N., Pasha, I., Iqbal Khan, M. K., Amin, A., Gulzar, M., Subtain, M., & Abdi, G. (2025). Saponins: Advances in extraction techniques, functional properties, and industrial applications. Applied Food Research, 5(2), 101146. https://doi.org/10.1016/j.afres.2025.101146