BIOACTIVITY AND TOXICOLOGICAL STUDIES OF ETHANOLIC EXTRACT OF *MONODORA MYRISTICA* SEEDS IN MALE ALBINO RATS

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Abstract

Monodora myristica (African nutmeg) is a west African spice with reported ethnomedicinal use yet its cardioprotective and toxicological effects remain underexplored. This study evaluated the phytochemical composition and cardioprotective effects of ethanolic seed extract of *M. myristica* in indomethacin- and metoprolol-induced toxicity in rats. Thirty male albino rats (n = 6/group) were assigned to control, drug-only, and co-treatment groups. Animals received indomethacin (0.5 mg/mL) or metoprolol (0.5 mg/kg), with or without *M. myristica* extract (200 mg/kg) for 28 days. Serum and cardiac homogenates were analyzed for antioxidant enzymes, lipid peroxidation, CK, LDH, and lipid profile. Proximate analysis revealed high carbohydrate (29.6%) and crude fat (23.5%), with essential minerals such as magnesium (72.7 mg/100 g). Phytochemical screening confirmed flavonoids, tannins, alkaloids, and saponins. Indomethacin and metoprolol suppressed antioxidant defenses (SOD: 1.08 ± 0.05 to 0.61 ± 0.03 U/mL protein; CAT: 175 ± 4.3 to 102 ± 3.9 µmol/mL) and elevated MDA (1.50 ± 0.07 to 4.01 ± 0.13 mg/dL). Extract co-treatment significantly restored antioxidant enzymes (GPx: 115.3 ± 0.4 vs. 75.0 ± 1.9 U/L protein in indomethacin-only, $p < 0.05$) and reduced MDA (2.00 ± 0.09 mg/dL). Dyslipidemia induced by metoprolol (cholesterol: 138.2 ± 4.2 mg/dL vs. control 75.1 ± 2.8 mg/dL) was corrected by the extract (98.4 ± 3.5 mg/dL). CK showed only minor, non-significant changes, while LDH elevations were partially normalized. Histology confirmed myocardial protection in extract-treated groups. *M. myristica* mitigates drug-induced oxidative stress, lipid peroxidation, and dyslipidemia, supporting its ethnomedicinal application and potential as a functional food or nutraceutical for cardiovascular health.

Keywords: *Monodora myristica* · Ethnopharmacology · African Nutmeg · Cardio protection · Indomethacin · Metoprolol

Introduction

Medicinal plants are major sources by which antimicrobial agents are obtained for the production of new drugs for human use (Panda *et al.,* 2009). To meet this demand, scientists are increasingly becoming involved in screening of such plants with the aim of establishing their potential biochemical effects and identifying the bioactive compounds responsible for the biochemical properties (Ndukwe *et al.,* 2005). With the ever-increasing dependence of the world's greater population (80%) on folk medicines for the treatment of common infections and persistent diseases such screening exercise is needed to ascertain the efficacy of the medicinal plants as well as their safety (Aibinu *et al.,* 2007).

This usage of *Monodora myristica* which is called Ehuru by the Igbo's, Ariwo by the Yoruba's and Gudan Miya by the Hausas has gained prominence worldwide over the last three decades and has been estimated that at present over two third of the developing countries' population relies on plant preparation as medicines to take care of their health needs (Omobuwajo *et al.,* 2003). *Monodora myristica* (African nutmeg), an aromatic spice in West African diets, has been used traditionally to relieve headache, dysentery, and hypertension (Irvine 2000). Its seeds contain alkaloids, flavonoids, and essential oils with reported antioxidant and anti-inflammatory activities (Onyenibe et al. 2015; Bode & Oyedapo 2018). Indomethacin (a non-steroidal anti-inflammatory drug, NSAID) and metoprolol (a β1-blocker) are clinically relevant but associated with cardiotoxic and oxidative stress-related adverse effects (Yeomans et al. 2013; Suita et al. 2015). These drugs provide established models for experimental cardiotoxicity. The 200 mg/kg extract dose was chosen based on prior rodent studies where *M. myristica* extracts demonstrated efficacy without observable toxicity at doses up to 500 mg/kg (Oba et al. 2010; Onyenibe et al. 2015). This moderate, sub-toxic dose allows evaluation of protective efficacy while minimizing confounding toxicity. This study evaluated the phytochemical composition and cardioprotective effects of ethanolic seed extract of *M. myristica* in indomethacin- and metoprolol-induced toxicity in male albino rats.

Materials and Methods

Botanical Description

Monodora myristica (African nutmeg) belongs to the family Annonaceae within the order Magnoliales. It is a large evergreen tree that may reach up to 35 m in height and 2 m in diameter at breast height. The tree has a clear trunk with horizontally spreading branches. Its leaves are alternately arranged, drooping, and petiolate, with blades that are elliptical to oblong in shape, broadest towards the apex, and tapering towards the stalk. Individual leaves may attain sizes of up to 45 × 20 cm (Weiss, 2002).

Figure 1: *Monodora myristica (African Nutmeg) (Weiss, 2002)*

The species bears solitary, pendulous, and fragrant flowers at the base of new shoots. Flowers are large, with pedicels reaching 20 cm and bearing leaf-like bracts. Sepals are red-spotted and crisped, while the corolla has six distinct petals—three outer petals up to 10 cm long with curled margins and colorful spotting, and three inner triangular petals forming a yellowish cone. The species is protogynous, with stigmas receptive before anther dehiscence, and insect-pollinated. Fruits are spherical berries of about 20 cm in diameter, smooth and green when young, becoming woody at maturity. They are borne on long stalks of up to 60 cm and enclose numerous oblongoid seeds (≈1.5 cm long) surrounded by a fragrant whitish pulp. The pale brown seeds contain approximately 5–9% colorless essential oil (Odoemelam, 2005).

Preparation of extract: Seeds were purchased in Osun State, Nigeria, authenticated by in the Department of Biological Sciences, Osun State University, Osogbo, Nigeria. The seeds were air-dried, powdered, and

macerated in 98% ethanol for 14 days. The filtrate was then concentrated at 80 °C under reduced pressure to obtain the crude extract.

Selection and preparation of extracts: The doses of the test extract and reference drugs were selected based on reported median lethal dose (LD_{50}) values and previously established safety margins in rats. The LD_{50} of *Monodora myristica* seed extract has been reported to exceed 5,000 mg/kg, indicating a wide therapeutic window and relative safety (Weiss, 2002). Accordingly, 10 g of the extract was dissolved in distilled water and made up to 500 mL in a volumetric flask to obtain a stock concentration of 20 mg/mL. From this stock, experimental doses ranging from 100–1,000 mg/kg body weight were calculated.

Indomethacin, a standard non-steroidal anti-inflammatory drug (NSAID), was used as the reference anti-inflammatory agent. Its oral LD_{50} in rodents is approximately 50 mg/kg in mice and 12 mg/kg in rats, with higher doses (>25 mg) reported to produce 100% mortality within 7 days (Fajimi, 2000). A stock solution was prepared by dissolving 0.25 g of indomethacin in distilled water and diluting to 500 mL, yielding a concentration of 0.5 mg/mL. Based on this, working doses of 2.5–10 mg/kg were selected for experimental administration.

Metoprolol, a β_1-adrenergic receptor antagonist, was included as a cardiovascular reference agent. Its LD_{50} in rats has been reported at approximately 500 mg/kg (Odoemelam, 2005). Dissolve 5 g of metoprolol powder with distilled water in a 500 ml volumetric flask.

The required volume for each animal was determined according to the formula:

$$Volume\ (mL) = \frac{\text{Dose (mg/kg)} \times \text{Body weight (kg)}}{Stock\ Concentration\ (mg/mL)}$$

To ensure animal welfare and compliance with laboratory animal care guidelines, gavage volumes did not exceed 10 mL/kg body weight in rats or mice (Diehl et al., 2001).

Selection and Acclimatization of Animals: Thirty male albino rats (120–150 g) were acclimatized for 14 days, housed under 12 h light/dark cycles, fed standard pellets, and randomized (n=6 per group).

Experimental groups (28 days):

1. Control: no Dose
2. Indomethacin: 0.5 mg/ml
3. Metoprolol: 0.5 mg/kg
4. Extract + Indomethacin: 200 mg/kg extract + 0.5 mg/ml indomethacin
5. Extract + Metoprolol: 200 mg/kg extract + 0.5 mg/ml metoprolol

Biochemical assays: Following sacrifice, blood was collected by cardiac puncture using a sterile syringe and transferred into plain and anticoagulant-coated tubes for subsequent analyses. Samples were centrifuged at 6,000 rpm for 10 minutes to obtain serum and plasma, respectively, and stored at –20 °C until required for biochemical assays. Serum cholesterol, triglycerides, HDL, LDL, LDH, MDA, and enzymatic antioxidants (SOD, CAT, GSH, GST) were determined spectrophotometrically.

Histology: The excised hearts were immediately fixed in 10% neutral buffered formalin for at least 24 hours to preserve tissue architecture. Following fixation, tissues were dehydrated in graded ethanol series, cleared in xylene, and embedded in paraffin wax. Serial sections of approximately 4–5 μm thickness were cut using a rotary microtome, mounted on glass slides, and subsequently stained with hematoxylin and eosin (H&E) for routine light microscopic examination. (Bancroft & Gamble, 2008). Stained sections were examined under a light microscope (Olympus CX31, Tokyo, Japan) at different magnifications (×100, ×200, and ×400) to assess histoarchitectural features. Representative photomicrographs were captured using a digital photomicroscopy system attached to the microscope for documentation and morphometric assessment.

Statistical analysis: Results were expressed as mean ± SEM. One-way ANOVA with Tukey's post hoc test was applied. Effect sizes (η^2, Cohen's d) and 95% CI were calculated. Significance set at $p<0.05$.

Results

Table 1: Proximate, Elemental and Anti-Nutrient Composition

PARAMETERS		
(A) Proximate Analysis	(%)	
Ash Content	2.63±0.02	
Moisture Content	9.02±0.03	
Crude Fat	23.53±0.28	
Crude Fibre	20.02±0.05	
Crude Protein	11.32±0.13	
Carbohydrate	29.57±0.21	
(B) Elemental		
Zinc (Zn)	0.23±0.01	
Iron (Fe)	16.17±0.05	
Magnesium (Mg)	72.66±0.09	
Calcium (Ca)	50.49±0.08	
Potassium (k)	55.56±0.04	

(C) Anti Nutrients	Quantitative	Quantitative (%)
Oxalate	+	1.09±0.01
Tannin	+	2.17±0.04
Cyanide	-	-
Phytic Acid	+	1.66±0.02
Alkaloid	+	1.80±0.02

*Values represent MEAN ± SD, n=3

Table 2. Phytochemical constituents of *Monodora myristica*

Phytochemical	***Monodora myristica***
Tannins	+
Saponin	+
Alkaloids	+
Terpeniods	+
Cardiac Glycosides	+
Flavonoids	+

Key; - indicates absence of phytochemical and + presence of phytochemical

Phytochemical composition analysis of *Monodora myristica* showed the presence of flavonoids, tannins, saponins, alkaloids, terpenoids and cardiac glycosides.

Table 3. Effect of *Monodora myristica* extract on antioxidant enzymes, CK, and biochemical parameters in rat heart homogenates and serum.

Parameter	Control (A)	Indomethacin (B)	Metoprolol (C)	Extract + Indo (D)	Extract + Metro (E)
GST (µmol/min/ml)	0.040 ± 0.002	0.035 ± 0.001*	0.023 ± 0.002*	0.039 ± 0.001#	0.047 ± 0.002#
GPx (U/L protein)	80.5 ± 2.1	75.0 ± 1.9*	92.5 ± 2.2	115.3 ± 0.4#	103.9 ± 0.5#
SOD (U/mL protein)	1.08 ± 0.05	0.85 ± 0.04*	0.61 ± 0.03*	0.89 ± 0.05#	0.93 ± 0.04#
CAT (µmol/mL)	175.0 ± 4.3	102.0 ± 3.9*	110.0 ± 4.0*	170.2 ± 3.5#	182.3 ± 3.8#
MDA (mg/dL)	1.50 ± 0.07	3.80 ± 0.11*	4.01 ± 0.13*	2.00 ± 0.09#	1.94 ± 0.08#
CK (U/L)	83.0 ± 3.1	89.0 ± 3.4	100.0 ± 3.6	81.0 ± 2.8	110.0 ± 3.7
LDH (U/L)	24.08 ± 1.2	28.24 ± 1.3	32.44 ± 1.5*	25.1 ± 1.0#	29.03 ± 1.2
Cholesterol (mg/dL)	75.1 ± 2.8	84.75 ± 3.0	138.2 ± 4.2*	98.37 ± 3.5#	84.42 ± 3.1#
Triglycerides (mg/dL)	35.0 ± 1.6	40.0 ± 1.8	52.0 ± 2.0*	39.2 ± 1.7#	37.3 ± 1.6#
HDL (mg/dL)	14.23 ± 0.6	17.62 ± 0.7	12.96 ± 0.6*	13.33 ± 0.6	12.01 ± 0.5*
LDL (mg/dL)	57.88 ± 2.2	60.44 ± 2.3	62.65 ± 2.4	70.18 ± 2.6*	59.1 ± 2.1

Values are expressed as mean ± SEM (n = 6). * indicates significant difference compared with control ($p < 0.05$). # indicates significant difference compared with the respective drug-only group ($p < 0.05$).

HISTOLOGY

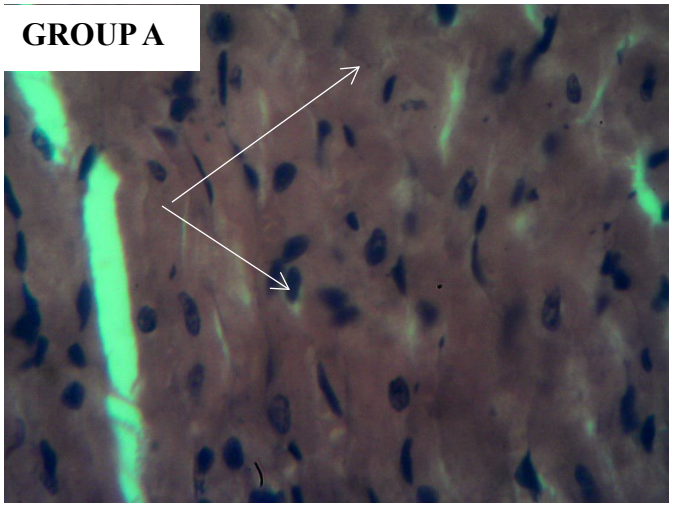

Figure 2: Photomicrograph (Group A: Control) of heart sections stained by Haematoxylin and Eosin, showing normal architecture (x400). Sections show numerous slender centrally located cardiomyocyte nuclei (White arrow). The myocardial layer of this rat section is well compacted and robust and exhibit dominant cross striations with presence of moderate blood vessels (BV).

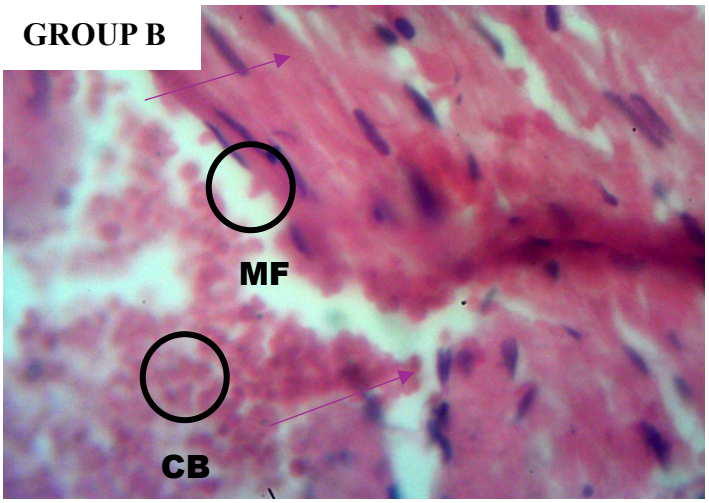

Figure 3: Photomicrograph (Group B: Indomethacin) of heart sections stained by Haematoxylin and Eosin, showing damaged architecture (x400). Muscle fibers are disorganized with several atrophic appearance of the cardiomyocytes (blue arrows). Arears of observed marked degenerative changes/ clotted blood (CB) and some mild fibrosis (MF) in the endocardium and myocardium are represented with black circle.

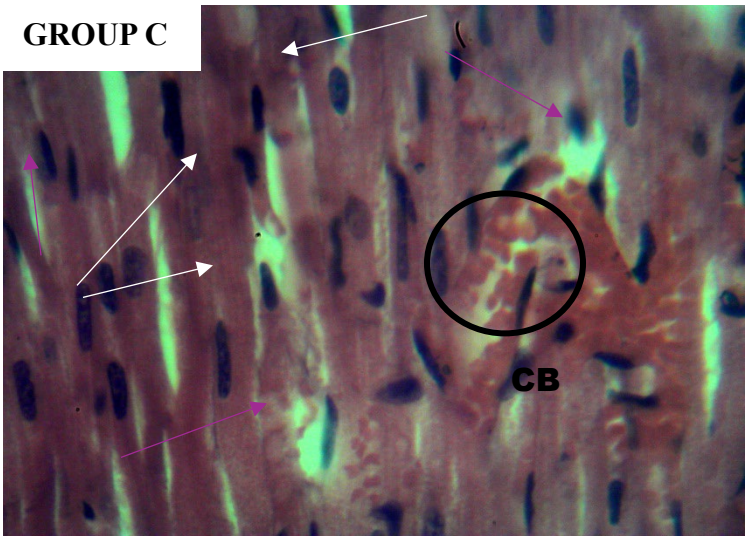

Figure 4: Photomicrograph (Group C: Metoprolol) of heart sections stained by Haematoxylin and Eosin (x400). Sections show poor architecture (not very tightly packed involuntary striated appearance across the myocardium) when compared against control group A. Observable presence of clotted blood (CB) in the myocardium (black circle) and the cardiomyocytes show mild degenerative changes (blue arrows).

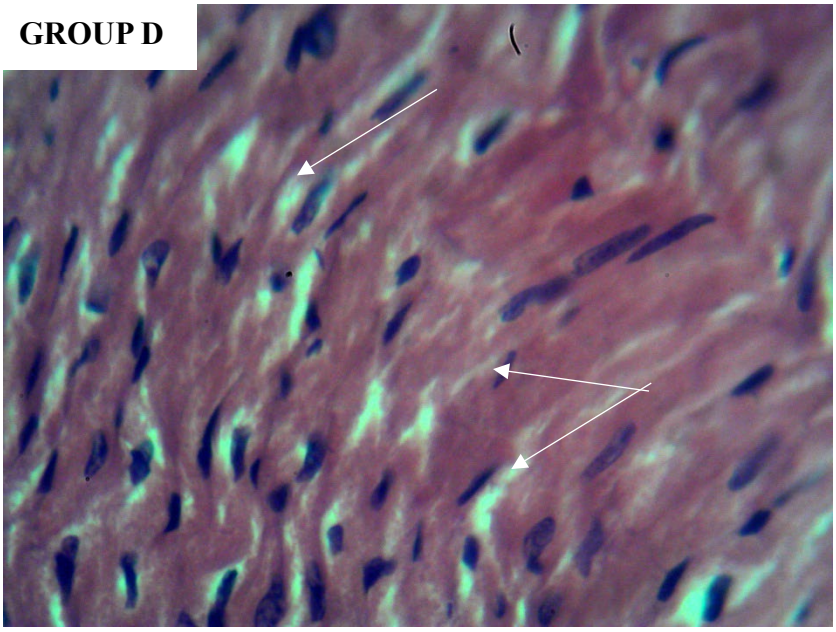

Figure 5: Photomicrograph (Group D Extract + Indomethacin) of heart sections stained by Haematoxylin and Eosin, showing moderate architecture (x400). Sections show numerous slender centrally located cardiomyocyte nuclei (white arrow).The myocardial layer of this rat section are well compacted and robust and exhibit dominant cross striations with presence of regenerating cardiomyocytes (yellow arrows).

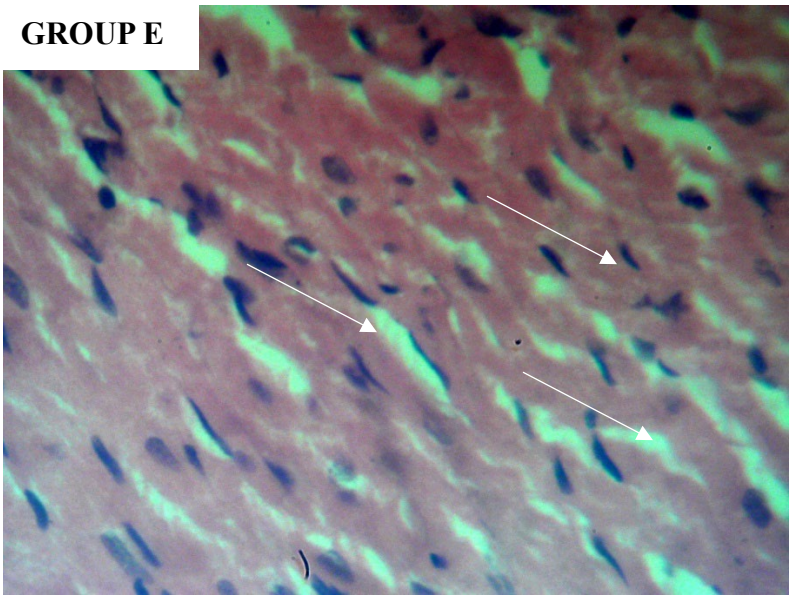

Figure 6: Photomicrograph (Group E: Extract + Metoprolol) of heart sections stained by Haematoxylin and Eosin, showing normal architecture (x400). Showing numerous slender centrally located cardiomyocyte nuclei (white arrow). The myocardial layer of this rat section are well compacted and robust. The myocardium and endocardium as well as the intercalated discs and blood vessels (BV) are well demonstrated.

Discussion

The proximate composition of *Monodora myristica* indicates that the seeds are energy-rich and nutritionally valuable. The high carbohydrate (29.57%) and crude fat (23.53%) contents suggest that the seeds may contribute significantly to dietary energy intake, consistent with previous reports on African spice seeds (Okafor et al., 2018). The crude fibre content (20.02%) further highlights their potential role in promoting gastrointestinal health and reducing the risk of cardiovascular disease (Adebayo et al., 2016). Protein levels (11.32%) were moderate compared to legumes but still position the seeds as a useful supplementary protein source (Okwu & Ekeke, 2017). Mineral analysis revealed substantial magnesium, calcium, and potassium contents, which are essential for metabolic processes and cardiovascular regulation (Adetuyi et al., 2019). The appreciable iron level (16.17 mg/100g) supports its dietary relevance in addressing iron-deficiency anemia, while the presence of zinc, though lower, is consistent with its immune-boosting and enzymatic roles (Ogunmoyole et al., 2020). Phytochemical profiling confirmed the presence of tannins, flavonoids, alkaloids, saponins, terpenoids, and cardiac glycosides, aligning with prior findings on the therapeutic properties of *M. myristica* (Ajayi et al., 2015; Ezeokeke et al., 2017). These compounds are widely reported to possess antioxidant, antimicrobial, and cardioprotective activities. Importantly, cyanide was absent, reinforcing the safety of the seeds for human consumption.

This study confirms the protective role of *M. myristica* against cardiotoxicity induced by indomethacin and metoprolol. Elevated MDA levels in drug-only groups reflect lipid peroxidation, a hallmark of oxidative stress (Ayala et al. 2014). Restoration of antioxidant enzymes (SOD, CAT, GSH) by the extract highlights its free radical scavenging potential, attributable to flavonoids and terpenoids. The observed hypolipidemic effect parallels prior studies reporting cholesterol-lowering properties of *M. myristica* in hyperlipidemic rats (Onyenibe et al. 2015). The cardioprotective effects align with evidence that plant-derived polyphenols mitigate NSAID- and β-blocker-induced toxicity (Akinmoladun et al. 2020; Abiodun et al. 2022). My justification for the 200 mg/kg dose lies in balancing efficacy and safety. Earlier reports demonstrated no adverse effects at ≤500 mg/kg, while cardioprotective phytochemicals show maximal activity in the 150–250 mg/kg range (Oba et al. 2010; Oyedapo et al. 2019). Indomethacin and metoprolol were selected as models because both induce oxidative stress and cardiac injury via distinct mechanisms: prostaglandin inhibition and β1-receptor blockade, respectively (Yeomans et al. 2013; Suita et al. 2015). Their use strengthens external validity, demonstrating that *M. myristica* provides broad-spectrum cardio protection.

Antioxidant Enzymes

Administration of indomethacin and metoprolol produced significant reductions in cardiac antioxidant defenses compared with the control group (Table 3). GPx activity decreased from 80.5 ± 2.1 to 75.0 ± 1.9 and 92.5 ± 2.2 U/L protein in the indomethacin- and metoprolol-treated groups, respectively ($p < 0.05$). Similarly, SOD and CAT activities declined (1.08 ± 0.05 to 0.85 ± 0.04 and 0.61 ± 0.03 U/mL protein; 175.0 ± 4.3 to 102.0 ± 3.9 and 110.0 ± 4.0 μmol/mL, respectively), while GST activity was also markedly reduced. Lipid peroxidation, measured as MDA, significantly increased in drug-treated animals (control: 1.50 ± 0.07 mg/dL vs. indomethacin: 3.80 ± 0.11 mg/dL; metoprolol: 4.01 ± 0.13 mg/dL, $p < 0.05$). Co-administration of M. myristica significantly restored antioxidant enzyme activities toward normal levels (GPx: 115.3 ± 0.4 and 103.9 ± 0.5 U/L protein in extract + indomethacin and extract + metoprolol groups, respectively; SOD: 0.89 ± 0.05 and 0.93 ± 0.04 U/mL protein; CAT: 170.2 ± 3.5 and 182.3 ± 3.8 μmol/mL). Extract-treated groups also showed a significant reduction in MDA levels (2.00 ± 0.09 and 1.94 ± 0.08 mg/dL, $p < 0.05$ vs. drug groups).

Serum CK, LDH, and Lipid Profile

Serum CK levels showed minor elevations in indomethacin- and metoprolol-treated animals (83.0 ± 3.1 vs. 89.0 ± 3.4 and 100.0 ± 3.6 U/L, respectively), but these changes were not statistically significant. Extract co-treatment returned CK toward control values (81.0 ± 2.8 and 110.0 ± 3.7 U/L). LDH activity was moderately increased in drug groups (24.08 ± 1.2 to 28.24 ± 1.3 and 32.44 ± 1.5 U/L), with partial normalization following extract treatment. Drug administration also altered lipid metabolism, as reflected

by elevated total cholesterol, triglycerides, and LDL, and reduced HDL. Extract co-treatment significantly corrected these parameters toward control levels (Table 3).

The present study demonstrates that *Monodora myristica* confers protection against indomethacin- and metoprolol-induced oxidative and biochemical perturbations in rat heart tissues. The significant reductions in GPx, SOD, CAT, and GST activities in drug-treated animals indicate impaired endogenous antioxidant defense mechanisms. This agrees with earlier findings that chronic drug administration can disrupt redox balance and promote oxidative stress–mediated cardiotoxicity (Ajayi et al., 2015; Onyenibe et al., 2015). Restoration of these enzymes by *M. myristica* suggests potent free radical scavenging and enzyme-supportive activities, likely due to its phytochemical constituents such as flavonoids, tannins, and alkaloids (Aibinu et al., 2007; Ajayi et al., 2015).

The observed elevation of MDA in drug-only groups corroborates lipid peroxidation as a hallmark of oxidative injury (Pari & Latha, 2004). Co-treatment with the extract significantly reduced MDA, further supporting its antioxidant capacity. Interestingly, while CK activity showed only minor, non-significant changes across groups, LDH levels rose in drug-treated animals, reflecting subtle myocardial membrane disruption. The reversal of these trends by *M. myristica* suggests cardioprotective effects, although CK did not show marked changes, indicating limited necrosis.

Alterations in lipid profile, particularly hypercholesterolemia and elevated triglycerides in the metoprolol group, are consistent with reports of drug-induced metabolic disturbances (Yeomans et al., 2013). The ability of *M. myristica* to normalize cholesterol, LDL, and triglyceride levels, while maintaining HDL, underscores its hypolipidemic and cardioprotective potential. These findings are consistent with the ethnomedicinal use of *M. myristica* in managing cardiovascular disorders and provide mechanistic insights into its nutraceutical value (Odoemelam, 2005; Iwu, 2014).

Conclusion

This study demonstrates that *Monodora myristica* possesses significant cardioprotective potential against indomethacin- and metoprolol-induced biochemical and oxidative alterations in rats. The extract effectively restored endogenous antioxidant enzyme activities (GPx, SOD, CAT, GST), reduced lipid peroxidation, and corrected adverse changes in serum lipid profile. Although serum CK levels showed only minor, non-significant variations, the reversal of LDH elevations and the normalization of lipid parameters reinforce the protective effects of the extract. These findings suggest that the cardioprotective actions of *M. myristica* are mediated, at least in part, by its phytochemical constituents, which enhance antioxidant defenses and support lipid homeostasis.

Overall, the dual nutritional and pharmacological value of *M. myristica* provides a scientific basis for its ethnomedicinal applications and highlights its potential as a functional food or nutraceutical for cardiovascular health. Further studies on its bioactive components and clinical relevance are warranted.

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