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Evaluation of the Efficacy of Miira-Cell, a Novel Nutraceutical, in Reducing High-Fat Diet-Induced Hypercholesterolemia in Wistar Rats

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Abstract

Hypercholesterolemia is a major risk factor for cardiovascular diseases, often exacerbated by high-fat diets. Miira-Cell, a novel nutraceutical, has been developed to address this issue. This study evaluates the efficacy of Miira-Cell in mitigating hypercholesterolemia induced by high-fat diet in Wistar rats. Acute toxicity testing showed that Miira-Cell was safe, with an LD50 greater than 5000 mg/kg. Thirty Wistar rats were divided into six groups: normal control, high-fat diet control, and three groups receiving high-fat diets supplemented with low, medium, and high doses of Miira-Cell, respectively. A sixth group received Rosuvastatin as a positive control. After a 14-day treatment period following a 21-day high-fat diet, lipid profiles, liver biomarkers, oxidative stress markers, and cardiac tissue histopathology were assessed. The results showed that Miira-Cell significantly reduced triglycerides, VLDL, and total cholesterol in a dose-dependent manner, similar to Rosuvastatin. Both Miira-Cell and Rosuvastatin also lowered LDL levels. However, all treatment groups showed decreased HDL levels, which may indicate potential effects on HDL metabolism. The Miira-Cell demonstrated hepatoprotective properties by reducing liver enzyme levels and oxidative stress. Histopathological analysis revealed tissue damage in the negative control group, while tissue integrity was preserved in Miira-Cell and Rosuvastatin-treated groups. In conclusion, Miira-Cell shows potential as a therapeutic agent for hypercholesterolemia and associated liver diseases, although further research is necessary to elucidate its mechanisms and clinical applicability.

Keywords: Hypercholesterolemia; Miira-Cell; Nutraceutical; High-fat diet; Lipid profile; Oxidative stress; Hepatoprotection; Rosuvastatin.

INTRODUCTION

Hypercholesterolemia, characterized by elevated serum cholesterol, low-density lipoprotein (LDL), and triglyceride levels, along with a reduction in high-density lipoprotein (HDL), is a major risk factor for atherosclerotic cardiovascular diseases (CVDs) (Abdelnaser, et al., 2023; Aimei et al., 2019). It is associated with conditions such as coronary artery disease, cerebrovascular disease, and peripheral arterial disease, often remaining asymptomatic until complications such as myocardial infarction, ischemic cardiomyopathy, sudden cardiac death, ischemic stroke, erectile dysfunction, and acute limb ischemia occur (Araújo, et al., 2011; Arthur, et al., 1985).

Statins, commonly used hypolipidemic agents, act as HMG-CoA reductase inhibitors to lower total cholesterol, LDL, and triglyceride levels while increasing HDL concentrations (Bergh, et al., 2021). Despite their efficacy, long-term use of statins has been linked to adverse effects, including hepatotoxicity, nephrotoxicity, and myopathy in both humans and animal models (Chang, et al., 2020). Consequently, there is growing interest in natural products as alternative therapies for CVD management (Contreras-Zentella, et al., 2016).

Miira-Cell, a novel nutraceutical developed by Revoobit, Selangor, Malaysia, is marketed as a natural supplement for improving lipid metabolism and overall health. It comprises 13 key bioactive ingredients, including Astaxanthin, Goji berry, Kiwi fruit, Salmon Ovary Peptide, Afa, Soursop, Pomegranate, Bilberry, Apple stem cell, Aquamin, Ashwagandha, Ascorbic acid, and Bee propolis. While limited direct evidence exists on the lipid-lowering effects of Miira-Cell, several of its constituents have demonstrated cholesterol-lowering properties in previous studies (Cronin, et al., 2016; De Souza Zanchet, et al., 2017; Esani., 2014; Friedewald,,et al., 1972; Gidding, et al., 2019; Godea, et al., 2020; Góth, 1991; Hageman, et al., 2023; Herrington, et al., 2016).

This study aims to evaluate the efficacy of Miira-Cell in reducing high-fat diet-induced hypercholesterolemia in

Wistar rats, focusing on its effects on lipid profiles, oxidative stress biomarkers, liver function markers, and histopathological changes in cardiac tissue.

MATERIALS AND METHODS

Experimental Animals

Thirty (30) healthy adult male Wistar rats (150–200 g) were procured from the Animal House, University of Nigeria, Enugu Campus (UNEC). The animals were housed under standard laboratory conditions, maintained at a room temperature of 23 ± 1°C, with a 12-hour light/dark cycle. They were provided with standard rat chow and water *ad libitum* and allowed to acclimatize for 14 days before the experiment.

Drugs and Materials

The nutraceutical Miira-Cell was obtained from *Revoobit SDN BHD, Selangor, Malaysia* (Batch No: 3E1915). Rosuvastatin was purchased from *AstraZeneca, Lagos, Nigeria*.

A high-fat diet was formulated based on the method described by Araújo et al. 2011; Karanchi, et al., 2023), consisting of bovine brain (50%), margarine (20%), and standard rat chow (30%).

Acute Toxicity and Determination of LD_{50}

Acute toxicity testing was conducted using twenty-one (21) male Wistar rats following the method of Lorke 1983; Kishimoto, et al., 2016). The study was carried out in two phases:

- **Phase 1**: Twelve rats were randomly assigned into four groups (n=3) and orally administered 50, 100, 500, and 1000 mg/kg of Miira-Cell, respectively. The animals were observed for signs of toxicity over 24–48 hours.
- **Phase 2**: Nine rats were assigned to three groups (n=3) and administered 1600, 2900, and 5000 mg/kg of Miira-Cell, respectively.

Toxicity signs and mortality were monitored throughout the observation period.

Experimental Design

Following acclimatization, the rats were randomly assigned into six groups (n=5) based on body weight, as shown in Table 1.

Table 1. Experimental Groups and Treatment Protocol.

Group	Treatment
1	Normal diet (control) + distilled water
2	High-fat diet (HFD) only
3	HFD + Miira-Cell (MC) (low dose: 221.4 mg/kg)
4	HFD + MC (medium dose: 442.8 mg/kg)
5	HFD + MC (high dose: 664.2 mg/kg)
6	HFD + Rosuvastatin (10 mg/kg)

The animals in Groups 2–6 were fed the high-fat diet for 21 days to induce hypercholesterolemia. Blood samples were collected via ocular puncture to confirm the induction of hypercholesterolemia.

The respective doses of Miira-Cell were dissolved in 0.4 mL of normal saline and administered intramuscularly for 14 days post-hypercholesterolemia induction. Rosuvastatin was dissolved in normal saline and administered orally for the same duration. The animals continued receiving the high-fat diet and water *ad libitum* throughout the treatment period (Li, 2015).

Blood Sample Collection and Processing

Twenty-four hours after the final drug administration, the animals were anesthetized with mild chloroform, and 5 mL of blood was collected via ocular puncture using capillary tubes. The blood samples were centrifuged at 3000 rpm for 15 minutes, and the serum was stored at **4°C** for biochemical analysis.

Biochemical Analysis

Serum total cholesterol (TC), high-density lipoprotein (HDL), and triglycerides (TG) were analyzed using Randox assay kits (Randox Laboratories, Crumlin, UK). Low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) levels were calculated using the Friedewald equation (Lorke, 1983).

Hepatic biomarkers, including alanine transaminase (ALT) and aspartate transaminase (AST), were measured using the endpoint method described by Reitman and Frankel 1957; Miyazaki, et al., 2017) and analyzed with Randox assay kits.

Oxidative stress biomarkers were assessed as follows:

- **Lipid peroxidation (MDA levels)** were evaluated using the thiobarbituric acid reactive substances (TBARS) method (Nair, et al., 2016).
- **Superoxide dismutase (SOD)** activity was determined following the method of Arthur and Boyne (1985; Ning, et al., 2022).
- **Catalase (CAT)** activity was assessed using the method described by Goth 1991; Pizzino, et al., 2017).

Histological Analysis

After euthanasia, the hearts were excised using sterile dissection instruments. The tissues were washed with normal saline, fixed in 10% buffered formalin, and processed for histological examination.

The preserved tissues were dehydrated using ascending concentrations of ethanol, cleared in xylene, and embedded in paraffin wax. Tissue sections were stained with hematoxylin and eosin (H&E**)** and examined under a light microscope at ×200 magnification for histo-architectural evaluation.

Statistical Analysis

Data were analyzed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Results are expressed as

mean ± standard deviation (SD) (n=5). Comparisons between groups were conducted using one-way analysis of variance (ANOVA), followed by post hoc analysis where applicable. Statistical significance was set at $p < 0.05$.

RESULTS

Acute Toxicity Study

The acute toxicity study was conducted using Lorke's method to determine the lethal dose (LD50) of Miira-Cell. No mortality or signs of toxicity were observed in any of the experimental groups, even at the highest dose of 5000 mg/kg, suggesting the safety of Miira-Cell (Table 2 and Table 3).

Table 2. First Phase of LD50 Test Using Lorke's Method.

S/N	Dose (mg/kg)	Toxicity (X/N)	Symptoms Within 24hrs	Remark
1	Mirra-Cell 50	0/3	None	Safe
2	Mirra-Cell 100	0/3	None	Safe
3	Mirra-Cell 500	0/3	None	Safe
4	Mirra-Cell 1000	0/3	None	Safe

Table 3. Second Phase of LD50 Test Using Lorke's Method.

S/N	Dose (mg/kg)	Toxicity (X/N)	Symptoms Within 24hrs	Remark
1	Mirra-Cell 1600	0/3	None	Safe
2	Mirra-Cell 2900	0/3	None	Safe
3	Mirra-Cell 5000	0/3	None	Safe

Lipid Profile Biomarkers

The effect of Miira-Cell (MC) on lipid profile biomarkers was evaluated in experimental rats. The HFD only group exhibited significantly elevated cholesterol, LDL, VLDL, and TAG levels compared to the control group. Treatment with Miira-Cell at varying doses demonstrated a dose-dependent reduction in these parameters, with the high-dose group showing values closer to the normal control (Table 4).

Table 4. Effect of Miira-Cell on Lipid Profile Biomarkers in Experimental Rats.

Groups	Cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	TAG (mg/dl)
1 Control	36.00 ± 9.20	7.31 ± 8.15	23.84 ± 8.02	4.79 ± 1.24	23.97 ± 6.23
2 HFD only	147.74 ± 7.50*	37.9 ± 5.01*	94.00 ± 2.18*	15.81 ± 0.83*	91.80 ± 4.17*
3 HFD + MC (221.4 mg/kg)	57.46 ± 18.34*	24.1 ± 15.95*	23.95 ± 5.72	9.07 ± 0.54*	45.19 ± 2.65*
4 HFD + MC (442.8 mg/kg)	43.42 ± 7.73	15.90 ± 9.27*	15.97 ± 8.16*	11.65 ± 5.63*	58.24 ± 28.13*
5 HFD + MC (664.2 mg/kg)	26.29 ± 4.51	6.92 ± 2.60	16.25 ± 3.21*	3.14 ± 1.05	15.68 ± 5.25
6 HFD + Rosuvastatin	86.94 ± 13.80*	24.98 ± 14.70*	28.65 ± 18.50	18.25 ± 3.17*	91.25 ± 15.57*

Data are expressed as mean ± SD, n=5. *p<0.05 compared with the normal control group.

Liver Biomarkers (ALT and AST)

The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured to assess liver function. The HFD only group exhibited significantly higher ALT and AST levels, indicating hepatic injury. Miira-Cell treatment led to a reduction in these biomarkers, with the high-dose group showing levels comparable to the normal control (Table 5).

Table 5. Effect of Miira-Cell on Liver Biomarkers in Experimental Rats.

Groups	ALT (U/L)	AST (U/L)
1 Control	22.87 ± 1.93	29.98 ± 3.60
2 HFD only	58.33 ± 6.01*	81.96 ± 39.94*
3 HFD + MC (221.4 mg/kg)	41.42 ± 5.48*	69.48 ± 20.48*
4 HFD + MC (442.8 mg/kg)	28.20 ± 6.24	68.12 ± 25.12*
5 HFD + MC (664.2 mg/kg)	24.65 ± 3.95	65.61 ± 20.99*
6 HFD + Rosuvastatin	30.11 ± 2.79	36.47 ± 3.82

Data are expressed as mean ± SD, n=5. *p<0.05 compared with the normal control group.

Antioxidant Biomarkers (MDA, CAT, and SOD)

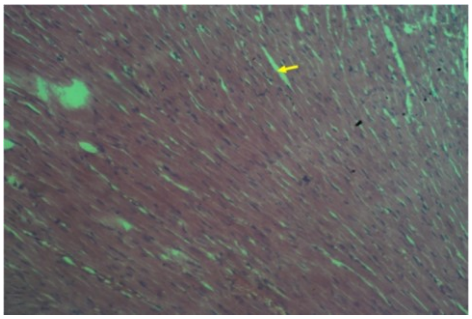
The antioxidant profile of Miira-Cell was assessed by measuring malondialdehyde (MDA), catalase (CAT), and superoxide dismutase (SOD) levels. The HFD group exhibited significantly higher MDA and lower CAT levels, indicating oxidative stress. Miira-Cell administration resulted in a dose-dependent improvement in these biomarkers (Table 6).

Table 6. Effect of Miira-Cell on Antioxidant Biomarkers in Experimental Rats.

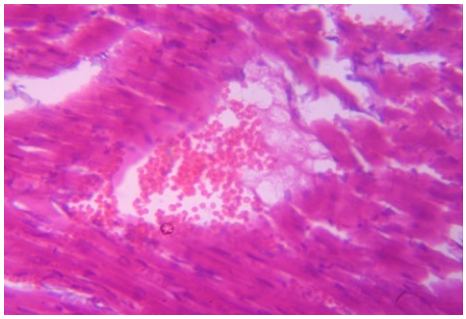
Groups	MDA (mg/dl)	CAT (U/L)	SOD (U/L)
1 Control	0.72 ± 0.14	13.21 ± 0.61	10.84 ± 0.85
2 HFD only	1.58 ± 0.41*	5.04 ± 1.42*	9.27 ± 0.60
3 HFD + MC (221.4 mg/kg)	0.79 ± 0.25	8.90 ± 1.43	11.48 ± 2.12
4 HFD + MC (442.8 mg/kg)	1.05 ± 0.16	8.62 ± 1.89	14.69 ± 0.59*
5 HFD + MC (664.2 mg/kg)	0.98 ± 0.20	10.92 ± 1.70	16.21 ± 0.74*
6 HFD + Rosuvastatin	0.79 ± 0.18	9.84 ± 1.27	9.96 ± 1.36

Data are expressed as mean ± SD, n=5. *p<0.05 compared with the normal control group.

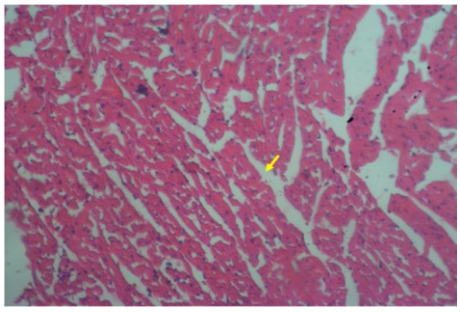
Histological Analysis of the Heart



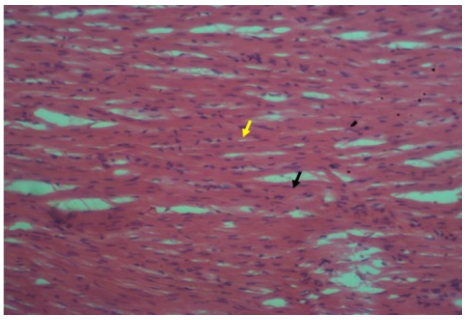
1: Control (H&E X200)



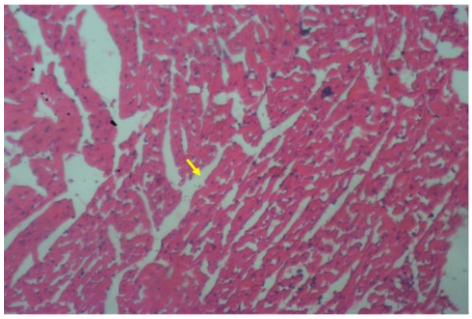
2: HFD only (H&E X400)



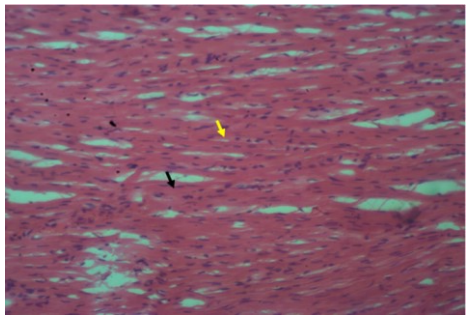
3. HFD + MC (221.4 mg/kg) (H&E X200)



4. HFD + MC (442.8 mg/kg) (H&E X200)



5. HFD + MC (664.2 mg/kg) (H&E X200)



6. HFD + Rosuvastatin (H&E X200)

Figures 1-6. Photomicrographs of heart tissues from experimental rat groups stained with H&E at different magnifications. Figure 1 presents a photomicrograph of normal cardiac muscle tissue, characterized by visible purple-stained nuclei and connective tissue spaces, indicating preserved myocardial architecture. Figure 2 depicts a photomicrograph of cardiac tissue exhibiting moderate structural alterations, including a focal area of myocardial hemorrhage and necrosis, suggesting a moderate pathological effect. Figure 3 shows a photomicrograph of cardiac tissue with mild generalized pyknosis (loss of nuclei), focal myocytolysis, and hypertrophy of connective tissue, indicating early degenerative changes. Figures 4, 5, and 6 display photomicrographs of cardiac muscle tissue with preserved structural integrity, visible purple-stained nuclei, and connective tissue, comparable to control.

DISCUSSION

Hypercholesterolemia is a well-established risk factor for coronary atherosclerosis, contributing to the development of atherosclerotic plaques and subsequent cardiovascular complications such as ischemic heart disease, stroke, and peripheral artery disease (Schwab, and Gruselle, 2020; Tanaka, and Shibasaki, 2019). The present study aimed to evaluate the efficacy of Miira-Cell in modulating lipid profiles, oxidative stress markers, and its hepatoprotective potential. Additionally, the acute toxicity (LD_{50}) of Miira-Cell was assessed to determine its safety profile. The findings from the acute toxicity evaluation indicated no observable toxicity at the highest administered dose of 5000 mg/kg, suggesting an LD_{50} exceeding this threshold.

Analysis of lipid profile parameters revealed significant alterations following treatment with Miira-Cell and Rosuvastatin. The negative control group (high-fat diet only) demonstrated a significant increase in total cholesterol, low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and triglyceride (TAG) levels compared to the normal control group. These findings align with previous reports by Zălar et al. (2022) and Rodrigues et al. (2022), confirming that high-fat diets lead to dyslipidemia and predispose individuals to hypercholesterolemia. However, Miira-Cell administration resulted in a significant reduction in total cholesterol, VLDL, and TAG levels compared to the negative control group, consistent with the hypolipidemic effects reported by Godea et al. (2020). Furthermore, Miira-Cell demonstrated dose-dependent efficacy, with higher doses producing greater reductions in total cholesterol levels. Both Miira-Cell and Rosuvastatin significantly decreased LDL levels, highlighting their effectiveness in reducing atherogenic lipoproteins, as previously observed by Rodrigues et al. (2022). However, reductions in high-density lipoprotein (HDL) levels were noted across all treatment groups, which contradicts prior findings by Zălar et al. (2022) and Rodrigues et al. (2022), necessitating further investigations into the potential effects of Miira-Cell on HDL metabolism.

Hepatocellular integrity was assessed through the measurement of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. The negative control group exhibited significantly elevated ALT and AST levels compared to the normal control group, corroborating previous studies by Zălar et al. (2022) that reported hepatic enzyme elevations following a high-fat diet. The observed increase in these liver enzymes suggests hepatocellular damage, as they leak into circulation upon liver injury (Shweta, and Gotmare, 2023). While ALT is predominantly localized in the liver, AST is found in multiple organs, including the heart and muscles (Silva, et al., 2021). Elevations in ALT are often considered more specific indicators of hepatocellular injury (Okerulu, et al., 2022). Miira-Cell administration significantly reduced ALT and AST levels compared to the negative control group, suggesting its hepatoprotective potential against high-fat diet-induced liver damage, consistent with the findings of Rodrigues et al. (2022) and Ning et al. (2022). Moreover, the dose-dependent reduction in ALT and AST levels further supports the hepatoprotective effects of Miira-Cell.

Oxidative stress plays a crucial role in the pathogenesis of metabolic disorders, including cardiovascular and liver diseases. It results from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms (Ige, et al 2019). In this study, the negative control group exhibited a significant increase in malondialdehyde (MDA) levels, indicating heightened lipid peroxidation and oxidative damage. This was accompanied by a significant reduction in catalase (CAT) and superoxide dismutase (SOD) levels, reflecting impaired antioxidant defenses. These findings are consistent with the oxidative stress profile observed in prior studies by Li et al. (2015) and Zălar et al. (2022). However, Miira-Cell administration led to a gradual reduction in MDA levels, alongside a significant increase in CAT and SOD levels, suggesting its role in mitigating oxidative stress and enhancing antioxidant activity. Notably, Miira-Cell demonstrated comparable antioxidant efficacy to Rosuvastatin, indicating its potential as a nutraceutical intervention for oxidative stress-related metabolic disturbances.

Histological evaluation of cardiac tissue revealed structural alterations in the negative control group, indicating myocardial damage. However, treatment with Miira-Cell and Rosuvastatin mitigated cardiac tissue damage, preserving myocardial integrity. These findings further support the cardioprotective effects of Miira-Cell in hyperlipidemic conditions.

CONCLUSION

The findings of this study demonstrate that Miira-Cell possesses significant hepatoprotective, antioxidant, and lipid-lowering properties, highlighting its potential as a nutraceutical intervention for hypercholesterolemia and liver dysfunction associated with high-fat diet consumption. The observed effects may be attributed to its bioactive constituents, which exhibit strong antioxidant and hypolipidemic properties. The possible mechanisms underlying the effects of Miira-Cell may involve inhibition of LDL oxidation, upregulation of LDL receptor expression, and reduced intestinal cholesterol absorption.

However, the observed reduction in HDL levels raises concerns about its impact on HDL metabolism, warranting further research to elucidate the mechanisms involved. Future studies should focus on identifying the precise molecular mechanisms of Miira-Cell, optimizing dosage regimens, refining its formulation, and assessing

potential synergistic interactions with existing lipid-lowering agents. Additionally, clinical trials are necessary to determine its therapeutic applicability in human subjects, particularly in the management of hypercholesterolemia and metabolic disorders.

Competing Interests: The authors declare that there are no competing interests.

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