Open Access Research Journal of
Life Sciences
Journals home page: https://oarjpublication/journals/oarjls/
ISSN: 2783-025X (Online)

(RESEARCH ARTICLE)

The effects of chronic administration of anti-androgenic agents on cardiac health in adult male Wistar rats

Okwakpam, F. N *, Wopara, I, Igwe. F. U, Amadi, B. A and Ben-Wosu, C. B

Department of Biochemistry, Rivers State University, Nkpolu-Oroworukwo, Port Harcourt, Nigeria.

Open Access Research Journal of Life Sciences, 2025, 09(01), 001-009

Publication history: Received on 11 December 2024; revised on 31 January 2025; accepted on 02 February 2025

Article DOI: https://doi.org/10.53022/oarjls.2025.9.1.0024

Abstract

Background: Antiandrogens such as Flutamide and Bicalutamide are commonly used in treating prostate cancer and other androgen-related conditions. However, their impact on cardiac health remains inadequately explored. This study aims to investigate the cardiovascular effects of these antiandrogens in adult male Wistar rats, focusing on cardiac biomarkers, antioxidant enzyme levels, and oxidative stress indicators.

Methods: Adult male Wistar rats were divided into three groups: a control group and two treatment groups receiving 50 mg/kg Flutamide and 10 mg/kg Bicalutamide, respectively, for 21 days. Body weight changes, heart weight, and serum levels of cardiac biomarkers (LDH, cTn-I, CK-MB) were measured. Oxidative stress was assessed by measuring superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and malondialdehyde (MDA) levels.

Results: Flutamide and Bicalutamide treatment resulted in a significant decrease in relative heart weight, with values of 0.43 ± 0.04 g for Flutamide and 0.45 ± 0.05 g for Bicalutamide compared to 0.61 ± 0.06 g in the control group. Weight gain was also significantly reduced, with percentages of 17.77 ± 0.99% for Flutamide and 12.82 ± 0.91% for Bicalutamide, while the control group had 25.47 ± 0.55%. Elevated cardiac biomarkers were observed, with cTn-I levels of 58.69 ± 0.52 ng/ml for Flutamide and 56.98 ± 0.54 ng/ml for Bicalutamide compared to 52.23 ± 1.72 ng/ml in controls. Additionally, CK-MB levels increased to 29.84 ± 0.47 ng/ml for Flutamide and 31.34 ± 0.52 ng/ml for Bicalutamide from 19.02 ± 1.54 ng/ml in the control group. Antioxidant levels (SOD, CAT, GSH) were significantly reduced, with SOD at 6.17 ± 0.07 U/mg protein for Flutamide and 5.70 ± 0.15 U/mg protein for Bicalutamide, and MDA levels were significantly elevated to 1.88 ± 0.06 U/mg and 1.99 ± 0.52 U/mg, respectively, compared to 0.94 ± 0.06 U/mg in controls.

Conclusion: The findings indicate that Flutamide and Bicalutamide exert significant adverse effects on cardiac health, leading to oxidative stress and myocardial damage. These results calls for careful cardiovascular monitoring and consideration of antioxidant co-therapy during long-term antiandrogen treatment to mitigate potential cardiac risks in patients undergoing such therapies.

Keywords: Flutamide; Bicalutamide; Cardiac biomarkers; Histology; Anti-androgenic agents

1. Introduction

Pharmaceutical agents, commonly referred to as drugs, are chemical compounds that exert specific biological effects on humans or animals, often used in the treatment, mitigation, prevention, or diagnosis of diseases or to enhance physical or mental well-being (Okwakpam et al., 2018). Drugs may be administered for short-term use in acute conditions or on a long-term basis for chronic disorders. Generally, they work by interacting with normal or abnormal physiological processes within biological systems to produce intended therapeutic effects. In some cases, however, the desired

* Corresponding author: Okwakpam, F. N.

biological action may come with adverse side effects that complicate treatment, particularly in the context of long-term therapy.

Bicalutamide, chemically known as 4-Cyano-3-(trifluoromethyl)phenyl-3-(4-fluorophenyl)sulfonyl-2-hydroxy-2-methylpropanamide, is a potent non-steroidal anti-androgen frequently used in combination with luteinizing hormone-releasing hormone (LHRH) agonists to manage symptoms associated with metastatic prostate cancer (Fradet, 2004). Acting purely as an androgen antagonist, bicalutamide blocks androgen receptor (AR) pathways stimulated by adrenal and testicular androgens, effectively curbing the growth of normal and malignant prostatic tissue (Scher et al., 1997; Osguthorpe & Hagler, 2011). Another prominent anti-androgen agent, flutamide, is similarly used in prostate cancer treatment and functions as a competitive AR antagonist. Flutamide, with the chemical structure 2-methyl-N-[4-nitro-3-(trifluoromethyl) phenyl] propanamide, is commonly administered alongside castration therapy to inhibit the progression of metastatic prostate carcinoma (Barqawi et al., 2003; National Institute of Diabetes and Digestive and Kidney Diseases, 2012).

While anti-androgen therapy has proven effective for managing advanced prostate cancer, emerging evidence suggests potential cardiovascular risks, including myocardial infarction and ischemic stroke, associated with prolonged anti-androgen use (Martín-Merino et al., 2011). Cardiovascular diseases (CVDs) remain a leading cause of mortality worldwide, with ischemic heart diseases—particularly acute myocardial infarction (MI)—posing significant health risks despite advancements in medical treatments (Scailteux et al., 2017). Cardiotoxicity in this context can lead to myocardial infarction through necrosis of cardiac cells, which often arises from ischemia resulting from an imbalance between oxygen supply and cardiac demand (Kulkarni et al., 2021).

One approach to identifying and understanding such adverse effects is through cardiac biomarkers, which are molecular indicators found in blood, other body fluids, or tissues that signal normal or abnormal biological processes (Bhatnagar & Jain, 2024). Biomarkers provide valuable insight into disease progression, early diagnosis, and treatment response, and have become increasingly important in cardiovascular research (Wong & Tse, 2021). Given the potential cardiac risks of long-term anti-androgen use, this study investigates the impact of chronic administration of anti-androgenic agents, specifically bicalutamide and flutamide, on cardiac biomarkers in adult male Wistar rats. Through this approach, the study aims to elucidate the effects of these agents on cardiac health, potentially contributing to a broader understanding of their cardiotoxic implications in prostate cancer therapy.

2. Material and methods

2.1. Experimental animals

A total of 15 rats were used for this study. The rats were obtained from the animal house of University of Port Harcourt, Nigeria. They were allowed to acclimatize for 7 days under laboratory conditions with free access to feed and water.

2.2. Experimental design

An experimental research design was adopted, conducted under controlled laboratory conditions with a randomized distribution of animal subjects into distinct treatment groups. The study involved fifteen (15) albino rats, which were randomly assigned to three groups, each comprising five (5) rats. Group 1 served as the control group and was provided with only rat feed and water, ensuring no exposure to the test compounds. Group 2 received a treatment dose of 50 mg/kg of flutamide, an anti-androgenic agent, administered at a consistent rate. Group 3 was treated with 10 mg/kg of bicalutamide, another anti-androgenic compound, administered under similar conditions. The drugs were administered to the rats orally once daily for 21 days.

2.3. Sample collection/preparation

On the last day of the dosage administration the animals were fasted overnight, and weighted. The animals were sacrificed via cervical dislocation, blood samples were collected in plain bottles and heart tissues were harvested and placed in plain bottle.

2.4. Preparation of heart homogenates

One gram of heart tissue was homogenized in 5 ml of phosphate buffer solution using a laboratory mortar and pestle. The homogenate was then centrifuged at 3000 rpm for 10 minutes using a bench centrifuge. After centrifugation, the clear supernatant was carefully transferred into a clean, labelled bottle. This supernatant was subsequently used for the antioxidant assays.

2.5. Determination of antioxidant parameters in heart homogenate

2.5.1 Catalase activity

The method utilized for assessing catalase activity was adapted from Heck et al. (2010). This approach measures catalase activity by monitoring the decomposition of hydrogen peroxide (H_2O_2), which is detected as a decrease in absorbance at 240 nm. The reaction mixture consisted of 13.2 nM H_2O_2 in a 50 mM phosphate buffer (pH 7.0) and 0.1 ml of heart cell homogenate. A control was also prepared, containing only the phosphate buffer and cell homogenate, without H_2O_2. The catalase activity, which was calculated based on the breakdown of H_2O_2, was expressed as micromoles of H_2O_2 decomposed per minute per gram of tissue.

2.6. Superoxide dismutase (SOD) activity

The SOD activity assay was based on the inhibition of nitroblue tetrazolium (NBT) reduction. This reaction occurs when riboflavin, in the presence of oxygen and methionine, generates superoxide ions, which are measured as an absorbance change at 560 nm. The reaction mixture consisted of 1.9 ml of phosphate buffer (pH 7.8), methionine, NBT, and riboflavin, with serum added to bring the final volume to 3 ml. The illumination process was performed for 10 minutes in an aluminum foil-lined box using a 15W fluorescent lamp. The control solution lacked the enzyme source. SOD activity was calculated as the enzyme concentration required to inhibit the NBT reduction by 50%.

2.7. Lipid peroxidation (Malondialdehyde - MDA) levels

Lipid peroxidation levels were determined by measuring malondialdehyde (MDA) as an indicator of oxidative damage. MDA, a by-product of lipid degradation, reacts with thiobarbituric acid (TBA) to form a red or pink complex that absorbs at 532 nm. For the analysis, 0.1 ml of serum was combined with 0.9 ml of water, followed by the addition of 0.5 ml each of 25% trichloroacetic acid (TCA) and 1% TBA in 0.3% NaOH. This mixture was heated for 40 minutes at 95°C, cooled, and then 0.1 ml of 20% sodium dodecyl sulfate (SDS) was added. Absorbance was measured at 532 nm, with MDA levels reported in mg/dl.

2.8. Glutathione peroxidase (GPx) activity

The assay for glutathione peroxidase (GPx) activity was based on the reduction of NADPH to NADP+, observed as a decrease in absorbance at 340 nm. To each well, 120 µl of assay buffer, 50 µl of co-substrate mixture, and varying control or sample conditions were added. For the positive control wells, 100 µl of assay buffer, 50 µl of co-substrate mixture, and 20 µl of diluted GPx control were used. For the sample wells, 100 µl of assay buffer, 50 µl of co-substrate mixture, and 20 µl of the sample were added. Each reaction was initiated by adding 20 µl of cumene hydroperoxide, and absorbance at 340 nm was measured over time using a plate reader. GPx activity was calculated in units/mg protein.

2.9. Histological examination

The heart tissues were transferred into 10% chloroform and trimmed to a thickness of 2 mm to 4 mm, facilitating the penetration of the fixative. The processing of the tissues followed standard methods outlined by Baker (1945) and Isirima and Uahomo (2023). These included stages of fixation, dehydration, clearing, impregnation, embedding, sectioning, and staining with hematoxylin and eosin (H&E), concluding with the mounting of the sections.

2.10. Statistical Analysis of data

The generated data were analysed by comparing the value for the different treatment groups with the values for the control. The one-way analysis of variance was used to determine if there was a statistically significant difference among the experimental groups. The result was said to be statistically significant at a p value <0.05. The values was expressed as mean ± standard error of mean (S.E.M).

2.11. Ethical considerations

Ethical considerations for this study were rigorously upheld to ensure the welfare of the animals and compliance with research standards. Ethical approval was obtained from the Institutional Animal Care and Use Committee (IACUC) of the Rivers State University prior to the study. Adult male Wistar rats were housed in a controlled environment with adequate space, food, and water. The study adhered to the 3Rs principle: Reduction, Replacement, and Refinement, minimizing the number of animals used while ensuring high-quality data. Pain and distress were minimized through careful monitoring and appropriate interventions, with all procedures performed by trained personnel to ensure humane treatment. Humane euthanasia was conducted at the study's conclusion, following accepted guidelines to

prevent suffering. The research team committed to transparency and integrity, ensuring findings would be reported honestly and accurately. By upholding these ethical principles

3. Results

After a 21-day treatment period, Tables 1 to 4 shows the effects of Flutamide and Bicalutamide on the body weight, heart weight, cardiac biomarkers, and oxidative stress biomarkers of adult male Wistar rats. In Table 1, rats in the control group exhibited a weight gain of 40.76 ± 1.20g (25.47 ± 0.55%), while those treated with 50 mg/kg of Flutamide showed a significantly lower weight gain of 29.33 ± 1.86g (17.77 ± 0.99%), and rats treated with 10 mg/kg Bicalutamide had a further reduced weight gain of 22.33 ± 0.66g (12.82 ± 0.91%), indicating that Flutamide and Bicalutamide treatments may lead to reduced body weight increment over time. In Table 2, the percentage of relative heart weight in the control group was 0.30 ± 0.0026g, while the Flutamide-treated group showed a reduced percentage at 0.22 ± 0.0008g, and the Bicalutamide group similarly displayed 0.23 ± 0.0008g. Although the final body and heart weights showed no significant differences across groups, the reduced relative organ weight suggests a possible organ weight suppression effect from both drugs.

Table 3 reveals that cardiac biomarkers, specifically CK-MB and troponin-T, were significantly elevated in the treatment groups. CK-MB levels in the control group were 19.02 ± 1.54 ng/ml, whereas they increased to 29.84 ± 0.47 ng/ml and 31.34 ± 0.52 ng/ml in the Flutamide and Bicalutamide groups, respectively. Similarly, troponin-T levels rose from 52.23 ± 1.72 ng/ml in the control to 58.69 ± 0.52 ng/ml in the Flutamide group and 56.98 ± 0.54 ng/ml in the Bicalutamide group. LDH levels, however, showed no significant variation, with values around 304.3 ± 12.45 U/L across all groups. These elevated CK-MB and troponin-T levels suggest potential cardiotoxicity due to the treatments. Table 4 indicates that oxidative stress biomarkers were significantly affected by Flutamide and Bicalutamide. In treated groups, the SOD levels were notably reduced from 8.57 ± 0.16 U/mg protein in the control to 6.17 ± 0.07 U/mg protein and 5.70 ± 0.15 U/mg protein in the Flutamide and Bicalutamide groups, respectively. CAT activity decreased from 14.59 ± 0.60 U/mg protein in the control to 10.17 ± 0.13 U/mg protein with Flutamide and 9.08 ± 0.68 U/mg protein with Bicalutamide. GSH levels also diminished from 26.60 ± 0.64 U/mg protein in the control to 15.85 ± 1.53 U/mg protein (Flutamide) and 14.76 ± 0.35 U/mg protein (Bicalutamide). Meanwhile, MDA levels, indicative of lipid peroxidation, significantly increased from 0.94 ± 0.06 U/mg in the control to 1.88 ± 0.06 U/mg and 1.99 ± 0.52 U/mg in Flutamide and Bicalutamide groups, respectively. These changes reflect increased oxidative stress and impaired antioxidant defenses in treated rats' heart tissues.

Table 1 Effect of Flutamide and Bicalutamide on Body Weight of Adult Male Wistar Rats

Groups	Initial Body Weight (g)	Weight Gain (g)	Percentage Weight Gain (g)
Control	159.7 ± 2.60[a]	40.76 ± 1.20[a]	25.47 ± 0.55[a]
50 mg/kg Flutamide	165.0 ± 2.08[a]	29.33 ± 1.86[b]	17.77 ± 0.99[b]
10 mg/kg Bicalutamide	175.3 ± 1.80[a]	22.33 ± 0.66[b]	12.82 ± 0.91[b]

Values are expressed as Mean ± standard error of mean (SEM). Values with the same superscript down the column are not significantly different at ($p < 0.05$).

Table 2 Effect of Flutamide and Bicalutamide on Percentage Mean heart Weight (g) of Adult Male Wistar Rats.

Groups	Final Weight(g)	Organ Weight (g)	% Relative Organ Weight
Control	200.3 ± 3.53[a]	0.61± 0.06[a]	0.30 ± 0.0026[a]
50 mg/kg Flutamide	194.3 ± 3.53[a]	0.43± 0.04[a]	0.22± 0.0008[b]
10 mg/kg Bicalutamide	197.7 ± 7.21[a]	0.45± 0.05[a]	0.23± 0.0008[b]

Values are expressed as Mean ± Standard error of mean (SEM). Values with the same superscript down the column are not significantly different at ($p<0.05$).

Table 3 Effect of Flutamide and Bicalutamide on Cardiac Biomarkers of Adult Male Wistar Rats

Groups	LDH (U/L)	TROPONIN (ng/ml)	CK-MB (ng/ml)
Control	304.3 ± 12.45[a]	52.23± 1.72[a]	19.02 ± 1.54[a]
50 mg/kg Flutamide	312.3 ± 7.17[a]	58.69± 0.52[b]	29.84 ± 0.47[b]
10 mg/kg Bicalutamide	309.3 ± 8.69[a]	56.98± 0.54[b]	31.34 ± 0.52[b]

Values are expressed as Mean ± Standard error of mean (SEM). Values with the same superscript down column are not significantly different at ($p<0.05$).

Table 4 Effect of Flutamide and Bicalutamide on Oxidative Stress Biomarkers of Adult Male Wistar Rats

Groups	**SOD U/ mg Protein**	**CAT U/ mg Protein**	**GSH U/mg Protein**	**MDA U/mg**
Control	8.57 ± 0.16[a]	14.59 ± 0.60[a]	26.60 ± 0.64[a]	0.94 ± 0.06[a]
50 mg/kg Flutamide	6.17±0.07[b]	10.17± 0.13[b]	15.85 ± 1.53[b]	1.88 ± 0.06[b]
10 mg/kg Bicalutamide	5.70± 0.15[b]	9.08 ± 0.68[b]	14.76 ± 0.35[b]	1.99 ± 0.52[b]

Values are expressed as Mean ± Standard error of mean (SEM). Values with the same superscript within a column are not significantly different at ($p<0.05$)

3.1. Results of histological examination of the heart

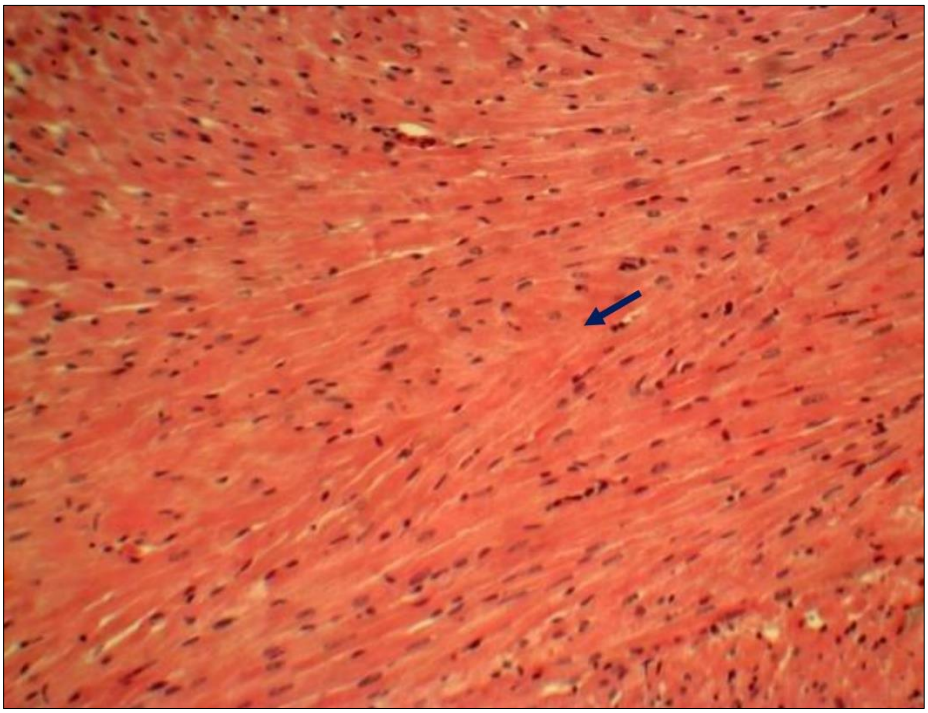

Figure 1 Photomicrograph of the heart of control group rats showing normal histology of the heart H & Ex 160.

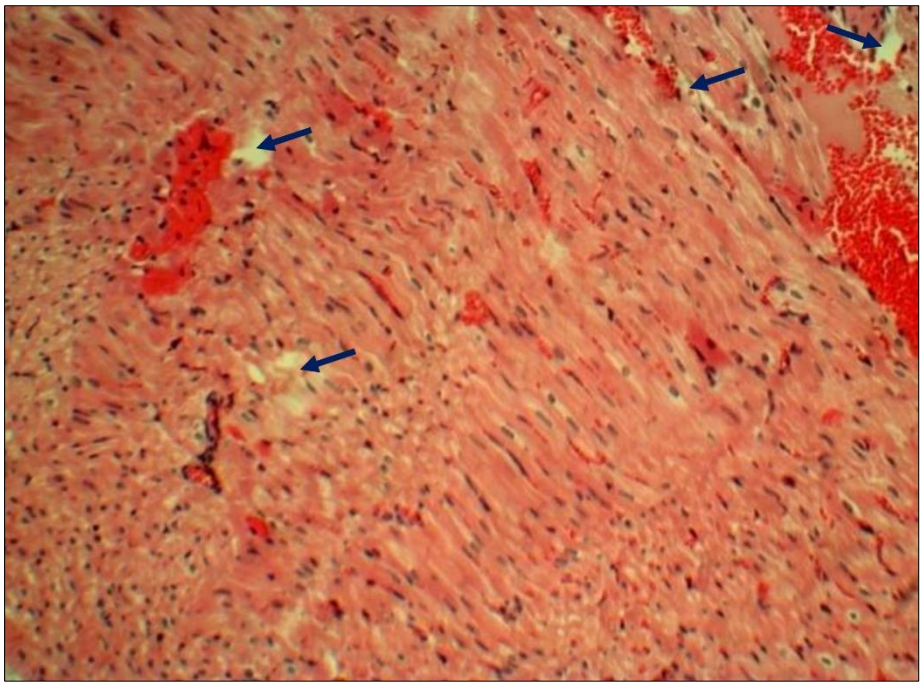

Figure 2 Photomicrography of the heart of 50mg/lg Flutamide group rats showing heart with mild multifocal areas of Zenker's necrosis of the cardiomyocytes (arrow). The affected cardiomyocytes appear hypereosinophilic with pyknotic nuclei. H&Ex 200.

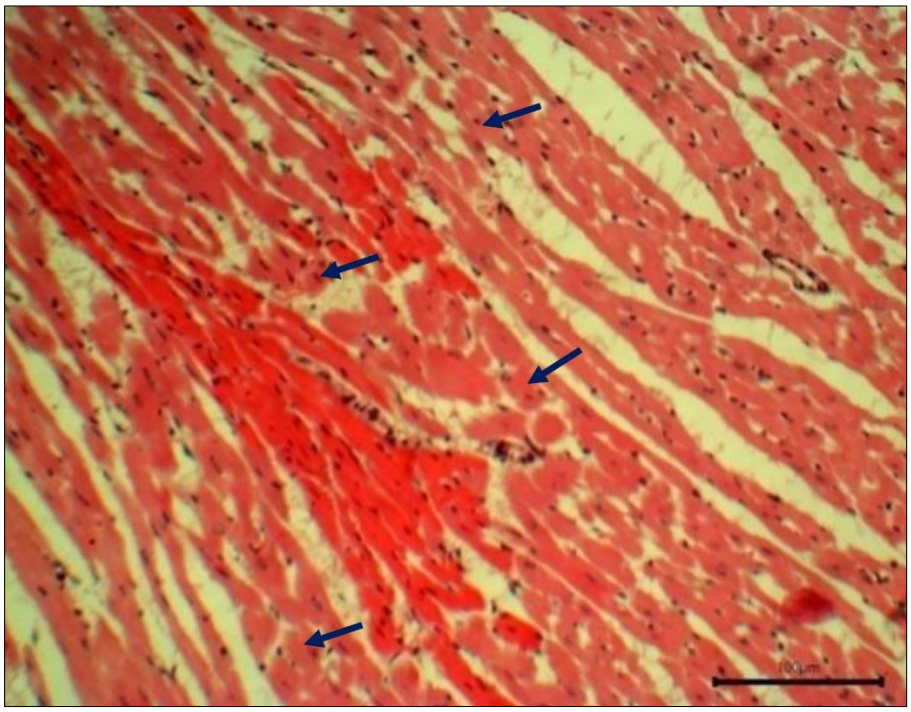

Figure 3 Photomicrograph of the heart of 10mg/kg bicalutamide administered group rats showing moderate to marked multifocal areas of Zenker's necrosis of the cardiomyocytes (arrow). The affected cardiomyocytes appear hyper eosinophilic with pyknotic nuclei

4. Discussion

The study examined the effects of Flutamide and Bicalutamide on various health parameters in adult male Wistar rats, including body weight, relative heart weight, cardiac biomarkers, oxidative stress markers, and heart histology, to assess potential cardiotoxic impacts of these antiandrogen treatments. The findings provided valuable insights into how these drugs may alter physiological and biochemical conditions associated with cardiac health.

Initially, both drugs led to a noticeable reduction in relative heart weight in treated rats. The observed reduction in heart weight might indicate an underlying mechanism of tissue and muscle mass loss influenced by antiandrogen treatment. This is consistent with the findings of Khurhid et al. (2014), who documented decreased organ weights in adult Wistar rats upon similar treatments. Antiandrogens like Flutamide and Bicalutamide could disrupt the normal anabolic signalling in cardiac muscle, leading to a reduction in cellular growth or maintenance. Over time, this may manifest as a lowered relative heart weight, which could contribute to compromised cardiac function under stress or physical demands.

The LDH levels showed no significant differences between treated and control groups, which suggests that Flutamide and Bicalutamide did not cause widespread tissue damage that typically releases LDH into circulation. LDH is abundant in tissues like the heart, liver, and muscles, and elevated levels are often seen in response to cellular damage or necrosis. The absence of significant changes in LDH levels implies that, while the treatments may cause specific cardiac effects, they do not produce extensive tissue destruction across major organs in the body, thus providing a perspective on the selective nature of any potential cardiotoxicity associated with these antiandrogens.

In contrast, cardiac troponin I (cTn-I) levels significantly increased in both treated groups. This rise in cTn-I, a highly specific marker for myocardial injury, suggests that both Flutamide and Bicalutamide may indeed damage cardiac muscle cells, possibly through oxidative stress or a direct toxic effect on cardiac myocytes. Cardiac troponins, particularly cTn-I and cTn-T, are extremely sensitive markers for myocardial injury, which makes them invaluable in clinical diagnostics for identifying heart muscle damage, as highlighted by Ndem and David (2017). Since troponins are typically undetectable in healthy individuals or present only in trace amounts, the detected increase in treated groups implies some level of myocardial stress or injury, which could escalate into more significant cardiovascular problems over prolonged use.

Further supporting this, the levels of CK-MB, another cardiac marker, also rose significantly in both drug-treated groups. CK-MB is an enzyme primarily present in cardiac tissue, and its release into circulation is closely linked with myocardial injury or energy metabolism disruption within cardiac muscle. Tiwari et al. (2008) found that CK-MB levels increase during myocardial ischemia, and its presence in circulation aligns with acute myocardial injury. The significant rise in CK-MB seen here suggests that both Flutamide and Bicalutamide may impair the energy supply chain in cardiac cells or contribute to cellular stress in the heart muscle, likely by affecting mitochondrial function or cellular metabolism.

In terms of oxidative stress markers, both Flutamide and Bicalutamide significantly decreased SOD levels, a vital antioxidant enzyme. SOD plays a critical role in reducing oxidative stress by converting harmful superoxide radicals into less reactive forms. The reduced SOD activity in treated rats implies that the antioxidant defenses in these animals were compromised, which could make the cardiac cells more vulnerable to oxidative damage. Lower SOD levels have been linked to various cardiovascular conditions, including hypertension and heart failure, as shown by Kumar et al. (2020). By lowering SOD, these drugs may inadvertently make the heart more susceptible to oxidative stress-related damage, which could further lead to inflammation and structural deterioration.

The CAT levels also showed a reduction in the treated groups, highlighting another area where antioxidant defense was weakened. Catalase is essential in breaking down hydrogen peroxide, a potentially harmful byproduct of cellular metabolism, into harmless water and oxygen. Reduced CAT activity implies that hydrogen peroxide is not adequately neutralized, thereby increasing the risk of oxidative stress and tissue damage. This decline aligns with findings by Al-Abrash et al. (2000), who noted associations between low catalase activity and cardiovascular diseases. The simultaneous decrease in both SOD and CAT activities suggests a substantial oxidative imbalance, making the cardiac tissues particularly susceptible to oxidative stress and possible lipid peroxidation.

A similar trend was observed in GSH levels, which also dropped significantly in treated rats. GSH is another crucial antioxidant that plays a central role in protecting cells from oxidative stress. Reduced levels of GSH are commonly associated with oxidative stress and have been implicated in diseases such as cardiovascular disorders and cancer, as discussed by Serru et al. (2001). The lowered GSH levels here indicate that the Flutamide and Bicalutamide treatments may compromise cellular defense mechanisms, possibly by affecting the synthesis or regeneration of GSH. This

depletion, combined with reduced SOD and CAT activities, creates a scenario of elevated oxidative stress, which can progressively damage cell membranes, proteins, and even DNA in cardiac cells.

The MDA levels, which serve as a marker for lipid peroxidation, were significantly higher in treated rats compared to controls. MDA is a byproduct of lipid peroxidation, an indication of oxidative damage to cell membranes. The observed increase in MDA levels aligns with findings by Selvakumar et al. (2012) and reinforces the idea that antiandrogen treatments may contribute to oxidative stress. Elevated MDA levels suggest that the lipid bilayers of cellular membranes are undergoing peroxidation, which can compromise cell integrity and function. This finding supports previous research that links MDA to oxidative stress and cellular damage, emphasizing the need for close monitoring of patients on long-term antiandrogen therapy.

Histological examination of cardiac tissues further supported the biochemical findings. The treated rats exhibited significant alterations in cardiac architecture, showing mild to moderate areas of Zenker's necrosis in the heart tissue. This form of necrosis is marked by hypereosinophilic cells with pyknotic nuclei, reflecting cell death and structural compromise within cardiac tissue. Such changes indicate that Flutamide and Bicalutamide may indeed have a direct toxic effect on cardiac cells, leading to necrosis. Zenker's necrosis is generally associated with severe metabolic disturbances or toxic injury, suggesting that these drugs may interfere with energy metabolism or induce oxidative stress severe enough to cause irreversible cellular damage.

5. Conclusion

This study provides compelling evidence that Flutamide and Bicalutamide treatment exerts multiple deleterious effects on cardiac health, evident through reduced heart weight, elevated cardiac biomarkers, compromised antioxidant defenses, and heightened lipid peroxidation. These findings showcase the associated cardiotoxicity risk of long-term antiandrogen therapy, where oxidative stress and myocardial injury appear to be central mechanisms of damage. The chronic administration of Flutamide and Bicalutamide likely contributes to cardiac hypertrophy and oxidative damage, exacerbated by an upsurge in reactive oxygen species (ROS) that suppresses key antioxidant enzymes and non-enzymatic peptides, including glutathione. This highlights an urgent need for careful monitoring and consideration of antioxidant co-therapy to mitigate potential cardiovascular risks during extended antiandrogen treatment, particularly in vulnerable populations.

Compliance with ethical standards

Acknowledgement

Author acknowledges the research assistance received from the laboratory technologists in ensuring this research study was a success.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Ethical approval was obtained for this study and was carried out in accordance with the guidelines for the care and use of animals and in compliance with the Rivers State University Research Ethics Committee's fundamental principles for animal-based research.

References

[1] Al-Abrash, A. S., Al-Quobaili, F. A., & Al-Akhras, G. N. (2000). Catalase Evaluation in different Human Diseases Associated with Oxidative Stress. Saudi Medical Journal, 21(9), 826 – 830.

[2] Baker, J. R. (1945). Cytological technique (2nd ed.). London: Methuen.

[3] Barqawi, A., Akduman, B., Abouelfadel, Z., Robischon, M., & Crawford, E. D. (2003). The use of flutamide as a single antiandrogen treatment for hormone-refractory prostate cancer. BJU international, 92(7), 695–698. https://doi.org/10.1046/j.1464-410x.2003.04479.x

[4] Bhatnagar, S., & Jain, M. (2024). Unveiling the Role of Biomarkers in Cardiovascular Risk Assessment and Prognosis. Cureus, 16(1), e51874. https://doi.org/10.7759/cureus.51874

[5] Fradet, Y. (2004). Bicalutamide (Casodex) in the Treatment of Prostate Cancer. Expert Review of Anticancer Therapy, 4, 37 – 48.

[6] Heck, D. E., Shakarjian, M., Kim, H. D., Laskin, J. D., & Vetrano, A. M. (2010). Mechanisms of oxidant generation by catalase. Annals of the New York Academy of Sciences, 1203, 120–125. https://doi.org/10.1111/j.1749-6632.2010.05603.x

[7] Isirima, J. C., & Uahomo, P. O. (2023). *Acalypha wilkesiana* exhibits antihyperglycemic potentials and ameliorates damages to pancreas and spleen of diabetic rat model. Saudi Journal of Biomedical Research, 8(7), 83–94.

[8] Khurshed, A., Hamid, S. & Niaz, A. (2014). Effect of Bicalutamide, an Antiandrogen on Testicular Weight in Adult Rats. Park Armed Forces Medical Journal 64, 204 – 207.

[9] Kulkarni, A. A., Rubin, N., Tholkes, A., Shah, S., Ryan, C. J., Lutsey, P. L., Prizment, A., & Rao, A. (2021). Risk for stroke and myocardial infarction with abiraterone versus enzalutamide in metastatic prostate cancer patients. ESMO open, 6(5), 100261. https://doi.org/10.1016/j.esmoop.2021.100261

[10] Kumar, A., Khusboo, R., Pandey, R., Sharma, B. (2020). Modulation of Superoxide Dimutase Activity of Mercury, Lead, and Arsenic. Biological Trace Element 196, 654 – 661.

[11] Martín-Merino, E., Johansson, S., Morris, T., & García Rodríguez, L. A. (2011). Androgen deprivation therapy and the risk of coronary heart disease and heart failure in patients with prostate cancer: a nested case-control study in UK primary care. Drug safety, 34(11), 1061–1077. https://doi.org/10.2165/11594540-000000000-00000

[12] National Institute of Diabetes and Digestive and Kidney Diseases. (2012). LiverTox: Clinical and research information on drug-induced liver injury. Flutamide. https://www.ncbi.nlm.nih.gov/books/NBK548908/ (Updated March 15, 2023)

[13] Ndem, J. I., & David I. J. (2011). Cardiac Troponin 1: Evaluation of a Biomarker of the Diagnosis of Heart Disease in Dog. Journal of Small Animal Practice 46, 139 – 145.

[14] Okwakpam, F. N., Omeodu, S. I., Uwakwe, A. A. (2018). The Effects of Diazepam on Selected Blood Enzymes Activity and Prostate Specific Antigen of Adult Male Wistar Rats. Am. J. Biomed. Sci. 2018,10(3),157-166; https://doi.org/10.5099/aj180300157

[15] Osguthorpe, D. J., & Hagler, A. T. (2011). Mechanism of androgen receptor antagonism by bicalutamide in the treatment of prostate cancer. Biochemistry, 50(19), 4105–4113. https://doi.org/10.1021/bi102059z

[16] Scailteux, L. M., Vincendeau, S., Balusson, F., Leclercq, C., Happe, A., Le Nautout, B., Polard, E., Nowak, E., & Oger, E. (2017). Androgen deprivation therapy and cardiovascular risk: No meaningful difference between GnRH antagonist and agonists-a nationwide population-based cohort study based on 2010-2013 French Health Insurance data. European journal of cancer (Oxford, England: 1990), 77, 99–108. https://doi.org/10.1016/j.ejca.2017.03.002

[17] Scher, H. I., Liebertz, C., Kelly, W. K., Mazumdar, M., Brett, C., Schwartz, L., Kolvenbag, G., Shapiro, L., & Schwartz, M. (1997). Bicalutamide for advanced prostate cancer: the natural versus treated history of disease. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 15(8), 2928–2938. https://doi.org/10.1200/JCO.1997.15.8.2928

[18] Selvakumar, C., Maheshwari, U. Suganthi, Archana (2012). Oxidant-Antioxidant Disturbance: Journal of Stress Physiological Biochemistry 8(1), 172 – 181.

[19] Serru, V., Baudin, B., Ziegler, F., David, J. P., Cals, M. J., Yaubourdolle, M. & Mario, N. (2001). Quantification of Reduced and Oxidized Glutathione in whole Blood Samples by Capillary Electrophoresis. Clinical Chemistry, 47, 1321 – 1324.

[20] Tiwari, M., Hamalatha, T., Ganesan, K., Manohar, B. M., Balachandra, C., Variramuthu, S., Subramaniam, S., & Puvanakrishman, R. (2008). Myocardial Ischemia and Reperfusion Injury in Rats. Lysosomal Hydrolases and Matrix Metalloprotinases Mediated Cellular Damage. Molecular and Cellular Biochemistry, 312, 81.

[21] Wong, Y.-K., & Tse, H.-F. (2021). Circulating biomarkers for cardiovascular disease risk prediction in patients with cardiovascular disease. Frontiers in Cardiovascular Medicine, 8, Article 713191. https://doi.org/10.3389/fcvm.2021.713191