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The Protective Role of Gilaburu in Amiodarone-Induced Testicular Damage: Immunohistochemical Evaluation via the TNF-α Pathway

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Abstract

Objective
This study aimed to investigate the protective effects of Gilaburu (GL) in mitigating testicular damage induced by the antiarrhythmic drug Amiodarone (AD) in rats.

Material and Methods
Rats were randomly assigned to four groups: Group Control: received no treatment. Group Amiodarone (AD): received AD (100 mg/kg, intraperitoneally). Group Amiodarone + Gilaburu (GL): received both AD (100 mg/kg, intraperitoneally) and GL (100 mg/kg, orally). Group Gilaburu: received GL alone (100 mg/kg, orally). Following a 10-day experimental period, the animals were euthanized. The left testis was harvested for histological and immunohistochemical examinations, while the right testis and epididymis were collected for testicular weight measurement, sperm isolation, count, and motility analysis.

Results
AD administration results in significant testicular damage, as evidenced by histopathological alterations such as irregularly shaped seminiferous tubules, a reduced number of spermatogenic cells, degeneration, and pyknotic nuclei. The highest testicular weight, sperm count, progressive motility, and total motility values were recorded in the control group, whereas the GL group exhibited values comparable to those of the control, with no statistically significant difference observed between them. In contrast, the AD and AD+GL groups demonstrated significant reductions in histopathological analysis, Tumor necrosis factor (TNF-α) stainings, spermiogram analysis ($p < 0.05$). However, the co-administration of GL with AD mitigated these adverse effects, reducing testicular damage.

Conclusion
The findings of this study indicate that Gilaburu has a protective effect against AD-induced testicular damage, potentially attributed to its potent antioxidant properties.

Keywords: Amiodarone; gilaburu, testis; TNF- α; immunohistochemical analysis

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Introduction

Amiodarone (AD) is a benzofuran derivative characterized by a phenol moiety with two covalently bound iodine atoms (1,2). It is recognized as the longest-acting and most broad-spectrum antiarrhythmic drug, extensively utilized for treating arrhythmias in patients with heart failure (1,3-7). In addition to being highly favoured clinically, AD administration has also been associated with side effects such as hepatic dysfunction, pulmonary complications, thyroid abnormalities, and urogenital disorders (2). In certain cases, these adverse effects may necessitate the discontinuation of treatment. The likelihood of side effects tends to increase with higher doses and prolonged exposure. However, administrating lower doses has been shown to mitigate toxicity while maintaining clinical effectiveness (5, 8). In most tissues commonly affected by the drug's side effects, amiodarone toxicity is believed to be partially attributable to the sequestration of the drug and its metabolite (7, 9).

While pharmacological interventions are designed to target the affected organs, they may inadvertently exert detrimental effects on other organs, potentially resulting in additional health complications during the recovery process. This scenario often encourages patients to seek alternative treatments rather than relying on conventional pharmaceuticals, including herbal remedies, which are perceived to have fewer adverse effects.

Plants and their derived pure chemicals have been used in the treatment of various diseases. Among such natural alternatives, GL (Viburnum opulus L.) is a plant endemic to the Kayseri province in Turkey, recognized for its potent antioxidant properties. It contains compounds such as proteins, ellagic acid, organic acids like catechin, quercetin, ferulic acid, phenolic compounds, sugars, and essential vitamins (10). The red, cluster-shaped fruit is harvested in the autumn and can be consumed either in its raw form or as a juice extract (11-13).

Gilaburu has been traditionally utilized for centuries in the treatment of a wide range of ailments, including circulatory, respiratory, reproductive, and digestive disorders. Its flavonoid composition endows it with notable antiproliferative, antiallergic, antiviral, and anti-inflammatory properties. As a result, it is widely employed in managing conditions such as rheumatism, hypertension, diabetes, and urinary incontinence (11-13).

The scientific literature on GL remains limited, specifically investigating its effects on testicular health. In the present study, the therapeutic potential of GL as an antioxidant, believed to have both preventive and curative effects against AD-induced testicular toxicity, was evaluated through immunohistochemical analysis of the TNF-α pathway which is a cytokine that mediates many of the metabolic responses after tissue injury and regulating different cellular processes pertinent to spermatogenesis (14).

Material and Method

This experimental study was evaluated based on quantitative results.

Experimental Desing

This study utilized a total of 32 male Wistar rats, each weighing between 300 and 350 grams, which were randomly assigned to four groups. The animals were housed under standardized laboratory conditions, including controlled humidity, a 12-hour light/dark cycle, and a temperature of 25°C for 10 days. They were granted continuous ad libitum access to food and water for the entire duration of the experiment.

The dosage of AD (Cordarone / 3 ml I.V, Sanofı Aventıs) was established as 100 mg/kg, based on existing literature (15). The dose was calculated based on the body weight of each rat and administered intraperitoneally at a consistent time during the study. GL (Viburnum Plus, Talex Pharma) powder extract was prepared at a concentration of 100 mg/kg, dissolved in 10 ml of physiological saline, and administered via oral gavage. The dosage and administration method were determined with established guidelines for dosage calculation and stock solution preparation in experimental animal studies (7, 11). The animals were randomly assigned to four groups; Group I (Control) received no treatment. Group II (AD) was administered AD at a dosage of 100 mg/kg, intraperitoneal injection. Group III (AD + GL) received the same dose of AD (100 mg/kg, intraperitoneally) along with GL (100 mg/kg, orally). Group IV (GL) was administered only GL (100 mg/kg, orally).

At the conclusion end of the experimental period, the rats were humanely euthanized under anesthesia, which was induced by intraperitoneal administration of xylazine (10 mg/kg) and ketamine (90 mg/kg) (Ketamine HCl Ketasol 10%, 10 ml RICHTER Pharma-xylazine HCl, Rompun 2%, BAYER). Following euthanasia, the testicular tissues were harvested and fixed in 10% neutral buffered formalin for subsequent histological analysis. Tissue sections were subjected to histological evaluation using hematoxylin-eosin (H-E)

staining and immunohistochemical analysis targeting TNF-α. Additionally, the right testicular tissues were weighed, and the epididymis was processed for sperm isolation, enumeration, and motility assessment.

Histochemical Analyses

Testicular tissue samples were washed in water overnight, followed by sequential dehydration in ethanol and clearance in xylene. Subsequently, the tissues were embedded in paraffin. The paraffin-embedded samples were sectioned at a thickness of 4 µm. The sections were treated with three different xylol series for 30 min each to remove the paraffin from the sections. Afterwards, the tissues were rehydrated by putting them through a series of alcohols, from high grade to low grade. Subsequently, routine hematoxylin-eosin (H-E) staining was performed. After staining was completed, the sections were put through a series of alcohols for full tissue dehydration. Then, entellan was dripped on the xylol-polished tissues, the coverslips were glued, and the sections were evaluated under a microscope. Histopathological evaluation was conducted under a photomicroscope (Olympus CX21 FS), and findings were systematically graded according to the scoring system established by Refaiy et al (16, 17). Histopathological findings were graded and evaluated with a photomicroscope by using the semi-quantitative method according to as follows:

(-) (negative score): No structural changes

(+) (1 positive score): Light structural changes

(++) (2 positive score): Middle structural changes

(+++) (3 positive score): Serious structural changes

Immunohistochemical Analyses

Polyclonal TNF-α primary antibody (rabbit anti-TNF-α antibody, Abcam, ab220210, Cambridge, USA) was used for immunohistochemical examination. The primary antibody was diluted 1:100 in antibody dilution fluids. For immunohistochemical staining, the sections were deparaffinized and rehydrated by treating with xylol and alcohols as described in the histopathology method. The sections were then washed in water for 10 min and incubated in hydrogen peroxide, were then boiled in citrate buffer solution. After this, the sections were washed with phosphate buffer saline (PBS). Afterwards, a series of sections were incubated separately with the primary antibody. This step was carried out at +4 °C overnight. All the sections were then washed in PBS, then biotinylated serum was dripped onto the tissues. Subsequently, they were stained with freshly prepared DAB (3,3 diaminobenzidine) chromogen to make the reaction visible. The sections were then counterstained using hematoxylin. Then, they were dehydrated with alcohols and placed in xylol, dripped with entellan, and covered with coverslips. Sections were scored from 0 to 3 according to the density of staining (0, absence of staining; 1, light; 2, middle; and 3, intense) (16, 17).

(-,) (0 negative score): No immune staining,

(+) (1 positive score): Light immune staining,

(++) (2 positive score): Middle immune staining,

(+++) (3 positive score): Intense immune staining.

Testis weight, Sperm Isolation, Count, and Motility

The right testes of each group were weighed. The epididymis from the same group was meticulously dissected using scissors and a needle, then placed in 2 mL of Tris stock solution (trizma base, citric acid, D fructose, SIGMA) (18) at 37°C and incubated for 10–12 minutes in a petri dish. Following incubation, 1 mL of the solution was collected for sperm analysis. Sperm count and motility were assessed using an IX70 inverted microscope with a Macler chamber (Olympus, Tokyo, Japan) (19).

Statistical Analyses

Mann-Whitney U test were conducted as described in (20, 21) via SPSS 18 software for all analyses. All findings were considered significant at $p<0.05$.

Results

Histochemical Results

Hematoxylin and eosin (H&E) staining of testicular tissue sections revealed a significant difference between the control and experimental groups (Group AD and AD+G) ($p<0.05$). While the testicular tissues in the control group exhibited a normal histological structure (Fig. 1A-D), those in Group AD and AD+GL demonstrated notable histopathological alterations, including irregularly shaped seminiferous tubules, a reduced number of spermatogenic cells, degeneration, and pyknotic nuclei. It was observed that these histopathological abnormalities were attenuated in Group AD+GL following GL administration ($p<0.05$) (Fig.1 B-C). Structural changes were assessed using the semi-qualitative grading method (17), Table 1.

Immunohistochemical Results

Immunohistochemical analysis revealed that TNF-α staining was weak in the Control Group and GL Group

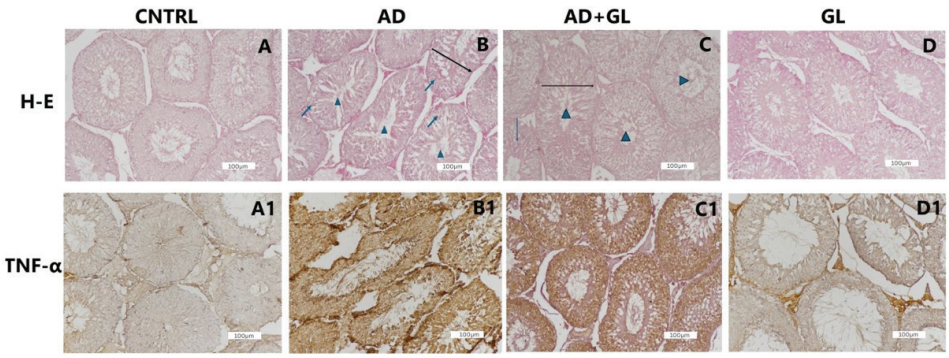

Figure 1

Histochemical (H&E) and immunohistochemical (TNF-α) staining of testicular tissues from control and experimental groups.
A-D: Histochemical staining results. B-C: Seminiferous tubules appear irregular (black arrows), with fewer spermatogenic cells (blue triangles), degeneration, and pyknotic nuclei (blue arrows).
A1-D1: Immunohistochemical staining results. B1: Positive staining for TNF-α, X20.

Table 1 Evaluation of Histopathological Findings Between All Groups

Histopathological Findings	CNTRL Group	AD Group	AD+GL Group	GL Group
Irregularly Shaped Seminiferous Tubules	-/+	+++	++/+++	-/+
A Reduced Number of Spermatogenic Cells	-	+++	++	-/+
Degeneration	-	++	+/-	-
Pyknotic Nuclei	-/+	++	+	-
Mononuclear Cell Infiltration	-/+	+/++	+	-/+

Values were presented as means ± S.D. The relationships between groups and results of immunohistochemical degress were assessed by Mann-Whitney U.
CNTRL: Control, AD: Amiodarone, GL: Gilaburu. (-) (negative score): No structural changes, (+) (1 positive score): Light structural changes, (++) (2 positive score): Middle structural changes, (+++) (3 positive score): Serious structural changes.

Table 2 TNF- α Marking Degrees Between All Groups

TNF- α	CNTRL Group	AD Group	AD+GL Group	GL Group
	-/+	++	+/++	-/+

Values were presented as means ± S.D. The relationships between groups and results of immunohistochemical degress were assessed by Mann-Whitney U.
CNTRL: Control, AD: Amiodarone, GL: Gilaburu, TNF- α: Tumor Necrosis Factor Alpha,
(-) (negative score): No immune staining, (+) (1 positive score): Light immune staining, (++) (2 positive score): Middle immune staining, (+++) (3 positive score): Intense immune staining.

Table 3 Statistical Analysis Results of Testis Weight, Sperm Isolation, Count, and Motility Among Groups.

	CNTRL Group	AD Group	AD+GL Group	GL Group	P value
Parameters	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	
Testis Weight (g)	3.69 ± 0.47[a]	2.60 ± 0.54[b]	2.79 ± 0.52[c]	3.56 ± 0.37[a]	0.0040
Sperm Count (x10^{6}ml)	17.88 ± 3.68[a]	9.13 ± 8.33[b]	13.88 ± 4.45[c]	17.12 ± 4.09[a]	0.0031
Progressive Motility (%)	32.62 ± 4.96[a]	10.00 ± 2.28[b]	16.12 ± 2.64[c]	32.75 ± 7.03[a]	0.0010
Non- Progressive Motility (%)	18.62 ± 4.34[a]	17.95 ± 3.78[a]	18.01 ± 8.26[a]	18.15 ± 7.05[a]	0.1400
Total Motility	51.25 ± 6.78[a]	25.17 ± 3.54[b]	38.75 ± 7.69[c]	50.50 ± 11.78[a]	0.0056

Values were presented as means ± S.D. The relationships between groups and results of immunohistochemical degress were assessed by Mann-Whitney U. CNTRL: Control, AD: Amiodarone, GL: Gilaburu, TNF- α: Tumor Necrosis Factor Alpha. a, b, c; different characters indicate statistically significant differences in the same column, p<0.05, p<0.001.

(Fig.1 A1-D1). A comparative evaluation between Group AD and AD+GL indicated that receptor staining was highest in Group AD, while a moderate reduction in staining was observed in Group AD+GL (p<0.05) (Fig.1 B1-C1), Table 2.

Testis Weight, Sperm Isolation, Count, and Motility Results

The control group exhibited the highest testicular weight, sperm count, progressive motility, and total motility values. While these parameters in the GL group were comparable to those of the control group, a significant decline was observed in the AD group, with an even more pronounced reduction in the AD+GL group substantial decrease was detected in the AD group (p <0.05). However, the evaluation of non-progressive motility did not reveal a significant difference, p = 0.14, Table 3.

Discussion

Amiodarone exerts significant effects on molecular processes, and multiple studies have explored its impact on various organs (3). In recent years, the GL plant (Viburnum opulus) has gained increasing attention (7, 11, 12). However, no studies to date have specifically examined the effects of GL on amiodarone-induced testicular damage.

Tabuu et al. investigated the impact of AD by administering varying doses (20–200 mg/kg) of AD to female rats and reported a dose-dependent induction of ovarian damage (3). In the present study, administration of 100 mg/kg AD resulted in testicular tissue damage. Similarly, Sakr et al. induced testicular damage using amiodarone (AD, 18 mg/kg) and examined the protective effects of grapefruit juice (27 mL/kg). Their histological and molecular analyses indicated a reduction in testicular damage in the groups that received grapefruit juice (5). In another study, Kagan et al. evaluated the effects of low-dose (20 mg/kg) and high-dose (200 mg/kg) AD administration on testicular tissue damage and apoptosis in rats. Following a 14-day period, histopathological analyses revealed severe testicular damage, with the highest degree of deterioration observed in the high-dose group, followed by the low-dose group. Moreover, immunohistochemical staining for caspase-3 and caspase-8 confirmed the presence of apoptosis, which was most pronounced in the high-dose group, followed by the low-dose group (22) Consistently, in the present study, administration of a single dose of AD (100 mg/kg) (15) led to detectable testicular tissue damage, confirming the deleterious effects of AD on testicular health.

Furthermore, immunohistochemical staining for TNF-α revealed increased expression in the AD-treated groups, indicating an inflammatory response associated with AD exposure. Additionally, Altun et al. demonstrated that the GL plant exerted hepatoprotective effects in rats by stabilizing elevated glucose levels and reducing them. They attributed this effect to the bioactive compounds present in the extract, such as glycosides and polyphenols (13).

Sarıözkan et al. investigated the effects of GL (100 mg/kg) on testicular damage induced by docetaxel and paclitaxel, reporting significant histological and cytological alterations, including increased Bax pro-apoptotic immunopositive cell scores in testicular and spermatozoa tissues. Their findings indicated that GL supplementation alleviated taxane-induced damage to the reproductive system in male rats (11). Similarly, in the present study, the administration of 100 mg/kg GL was found to mitigate tissue damage. The results demonstrated that GL exerted a protective effect by reducing histopathological alterations, preserving testicular weight, and improving sperm count, progressive motility, and total motility values. Since no previous studies have specifically investigated the effects of GL on testicular weight, sperm count, progressive motility, and total motility in the context of AD-induced toxicity, direct comparisons with existing literature were not possible.

Haiyu et al. observed that AD significantly reduced the survival rate of atrial myocytes, markedly decreased superoxide dismutase (SOD) activity, and increased the rates of cell apoptosis rates, as well as the levels of IL-1β, IL-6, malondialdehyde (MDA), and TNF-α (23). In a study conducted by Lu et al., administration of AD at doses ranging from 0 to 400 mg/kg did not elevate serum TNF-α levels in rats treated with AD alone. However, a significant increase in serum TNF-α concentration was observed in rats treated with LPS. These findings suggest that the elevated TNF-α levels in AD/LPS co-treated rats were not solely due to an additive effect. Instead, amiodarone AD likely potentiated TNF-α production or impaired its clearance when induced by LPS (2). In the present study, TNF-α was similarly investigated in the context of AD-induced testicular damage. However, it was assessed through positive staining via immunohistochemical analysis in tissue samples. The results confirmed that AD alone induced significant testicular damage.

In this study, testicular damage was induced solely by AD. Immunohistochemical analysis for TNF-α, a key mediator of accurate inflammation, revealed positive staining, indicating the presence of an inflammatory response. The pronounced TNF-α staining observed in the AD group confirmed AD-induced inflammation. Conversely, the reduced staining in the AD+GL group suggests that GL mitigates the inflammation. These immunohistochemical findings validated the toxic effects of AD, aligning with previously reported literature.

Gilaburu, an endemic plant of Turkey, has been extensively studied for its diverse activities in the literature and is gaining increasing recognition in the health sector. The absence of prior research investigating the effects of GL fruit extract on amiodarone-induced testicular toxicity underscores the significance of this study.

Based on the histological, immunohistochemical, and spermiogram parameters evaluated in this study, the findings suggest that incorporating GL into the diet, with careful consideration of appropriate dosage, may offer potential health benefits.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Ethical Approval

Ethical approval was obtained from the Süleyman Demirel University Animal Experiments Ethics Committee of (HADYEK) on 15.09.2022, 06/69, and all procedures were carried out in strict accordance with established ethical guidelines.

Consent to Participate and Publish

Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials

The data supporting the findings of this study are available from the authors upon reasonable request.

Artificial Intelligence Statement

The authors declare that they have not used any generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Authors Contributions

MÖ: Conceptualization, Formal Analysis, Investigation, Validation, Visualization, Writing-Original Draft.

NK: Data Curation, Investigation, Methodology.

DUK: Investigation, Writing-Original Draft

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