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Effect Of Terminalia Arjuna On Amiodarone Induced Body And Liver Weight Dysregulation.

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Abstract

Background: Amiodarone, a class III antiarrhythmic drug, is known to cause hepatotoxicity through mitochondrial dysfunction, phospholipids, and accumulation of toxic metabolites. Although several herbal agents show hepatoprotective potential, the protective effects of *Terminalia arjuna* against amiodarone-induced liver injury have not been fully explored. **Objective:** To evaluate the effect of amiodarone on liver morphology and to determine the hepatoprotective potential of Terminalia arjuna at two different doses. **Methods:** Thirty-two male Wistar rats were randomized into four groups: control, amiodarone-treated (70 mg/kg/day), and two treatment groups receiving amiodarone plus *T.* arjuna aqueous extract at 250 mg/kg/day and 500 mg/kg/day for four weeks. Body weight, liver weight, and liver–body weight index were measured and analyzed using ANOVA and post-hoc comparisons. **Results:** Amiodarone administration significantly increased body weight, liver weight, and liver–body weight index ($p<0.05$), indicating hepatic enlargement and injury. Co-treatment with *T.* arjuna reduced these elevations, with the 500 mg/kg dose showing the most notable improvement, approaching near-normal values. **Conclusion:** Terminalia arjuna exhibits a clear dose-dependent hepatoprotective effect against amiodarone-induced liver injury. Its ability to restore liver weight and liver–body weight index highlights its therapeutic potential as a natural adjunct in managing drug-induced hepatotoxicity.

Introduction

Amiodarone is a class III antiarrhythmic drug used to treat supraventricular and ventricular tachyarrhythmias(Abdul-Hamid et al., 2018).Amiodarone is a multichannel blocker; an alpha and beta adrenergic blocker in cardiac muscles. It is used to treat atrial

fibrillation and even used for prophylactic treatment of atrial fibrillation(Ibrahim Fouad & R. Mousa, 2021). It is orally effective antiarrhythmic drug with a wide range of potential side effect due to long-term administration. The adverse effects of amiodarone are reported in various organs including liver, lungs, thyroid, eyes, nervous system, integumentary system and heart; corneal micro deposit being the most prevalent[3]and pulmonary toxicity being the most fatal adverse effect of amiodarone.(Florek et al., 2023) The main reasons of such wide range of side effects is multifactorial; can be due to its structure, affinity, long term use and long biological half-life.

Amiodarone has a variable absorption rate from 22-86% when given orally, it is a lipophilic drug and its absorption increases if it is taken with fat-rich meals. Due to its affinity for lipids it is accumulated in various cells of body especially adipose tissue. It is also accumulated in highly perfused organs such as skin, liver and lungs(Colunga Biancatelli et al., 2019).Amiodarone is metabolized by liver primarily via its CYP450 enzymes, hence is eliminated from body in bile. Less than 1% also eliminates through the urine. Due to its long half life,it can exert clinical effects for upto 6weeks whereas its pharmacological effects can last upto 1-3 months(Florek et al., 2023).

Hepatocytes bear a specific group of hemoproteins Cytochrome P450 system, it plays a specific role in detoxification around 75 percent of drugs are modified by CYP450.These enzymes reduce lipophilic nature of drug by making it more hydrophilic by either oxidation, reduction or hydrolysis and then conjugation(Zhao et al., 2021).In this process of detoxification, the byproducts accumulate in hepatocytes and damage the cells, and can lead from mild steatosis to cirrhosis.

A study was conducted in Canada in 2024,role of melatonin was established to prevent hepatic injury caused by amiodarone. It was deduced that amiodarone causes liver injury by damaging the mitochondria and increasing the number of reactive oxygen species, this intern leads to cell energy depletion and cell death. Amiodarone was given in the dosage of 70mg/kg. day for 4 weeks and it showed rasie in xanthine oxidase activity and P53 levels. Microscopic changes were also noted along with biochemical changes; hepatocyte degeneration and activation of kupffer cells was noted(Petrović et al., 2024).

Amiodarone when metabolized by liver, form metabolites that accumulate in lysosomes and inhibit enzymes phospholipase A1 and A2,this leads to phospholipidosis and further to steatohepatitis and irreversible liver cirrhosis(González et al., 2022).

A study conducted in Chile in 2023,assessed the hepatoprotective effect of mesenchymal stem cells on amiodarone induced injury, it was inferred that amiodarone causes idiosyncratic DILI(Drug-induced liver injury) i.e non-dose dependent, unpredictable and pathogenesis is also not fully explained. It was deduced that amiodarone affected by inducing mitochondrial dysfunction; beta oxidation impairment and increase number of reactive oxygen species lead to accumulation of free fatty acids and decrease ATP and activation of Caspases which lead to cell death(Huang et al., 2023).

Drugs available to treat liver damage due to drugs can further damage liver, hence various herbal medications are used to treat liver conditions. Herbal medications have also gained popularity due to its safety, cost-effectiveness and and efficacy. Several plants have been proved to either protect liver from damage due to drugs or ameliorate the liver damage casued by different drugs. These are namely Picrorhiza kurroa,Vidakana choornam, Tamra Bhasma and Terminalia Arjuna among others(Valvi et al., 2016).

Terminalia Arjuna is a traditional herbal medicine known for its cardiotonic effects. The main constituents of Terminalia Arjuna are triterpenoids, flavonoids, saponins, alkaloids, phytosterol, tannins and phenolic compounds(Kannappan et al., 2020). Arjunolic acid (AA) is an oleanane triterpenoid found mainly in the heartwood of T.

arjuna(Toppo et al., 2018).The cardioprotective,renoprotective,antidiabetic,anti-inflammatory,anti-diabetic and anti cancer effects of T.Arjuna are already established(Toppo et al., 2018). It has also known to have anti-bacterial, anti-viral,antiallergic,anti-anaphylactic and wound healing properties(Kumar et al., 2023).Among other effects of T.Arjuna heptoprotective effect has been widely studied and it has been established to alleviate the effects of different hepatotoxin .Alcoholic and non-alcoholic steatosis has been reversed with the use of T.Arjuna bark extract. It has also been seen to attenuate the effect of CCL4,Acetaminophen,cadmium and arsenic(Soni & Singh, 2019).
Few studies have also established the hepatoprotective effect of T.Arjuna, however its effect against amiodarone induced liver injury is yet to be explored.

OBJECTIVES
The objective of the study is to establish
The effect of amiodarone on liver
The protective effect of Terminalia arjuna on amiodarone induced liver damage
The protective effect of Terminalia arjuna on liver when administered in different dose

Materials and methods
Study design
Experimental study

Setting
Anatomy department, Superior University, Lahore

Duration of Study
Sample Size
Sample size of 8 in each group was estimated by using 95% confidence level, 90% power with expected average weight gain by animals in 42 days for Control, TA and AMD groups as 17.5, 14.4 and 19.5 grams respectively. The estimated effect size was 0.78 with error standard deviation of 2.70. (Patil et al, 2015 & Fouad et al 2021)
Power and precision 3.0 software was used (screenshots attached)
Eight Animals for each extra group to be evaluated was added. For 4 groups total sample size will be 32.

Sample Selection
Inclusion Criteria
Wistar rats weighing 150-250 gm
Active/healthy rats
Exclusion Criteria
Female rats
Rats showing any signs of disease at time of selection.
Age more than 12 weeks old

Sampling Technique
Initially, rats were selected through convenient purposive sampling and then were divided into groups through random sampling using lottery method.
Ethical Approval:
Ethical Approval was taken from Ethical Review Board, Superior University.

METHODOLOGY

Animals
Adult male Wistar rats were obtained Post graduate Medical institute, Lahore and kept in the animal facility of Superior university for one week to acclimatize. They were provided free access of tap water and balanced diet.. Room temperature were maintained at 25±2ºC with a 12-hours light/dark circle. Animals were taken care of according to the criteria outlined in the "Guide for the care and use of laboratory Animals".

Administration of Amiodarone
Amiodarone was bought from local chemical market in the form of tablets; each tablet contains 200 mg Amiodarone hydrochloride. It was dissolved in normal saline and a solution was formed in concentration of 20mg/ml and given according to weight of animal in the dose of 70mg/kg/day

Administration of Terminalia Arjuna
The TA bark powder will be purchased from Pansari Store. It was washed, sundried and an aqueous extract was prepared by PCSIR labs, Lahore. It was given according to weight of animal.

Animal Grouping
The experimental period was 5 weeks. After a 1-week acclimatization period, the 32 rats were randomly allocated to four groups (8 rats/group)

Group A: (Normal control)
The animals in this group will receive distilled water by oral route.

Group B: (Disease control)
The animal in this group will be given Amiodarone 70mg/kg/day in a single morning dose for four weeks after 1-week acclimatization.

Group C: (T.Arjuna 250mg/kg treated group)
The animals in this group will be given amiodarone 70 mg/kg/day as a morning along with Aqueous extract of Terminalia arjuna 250mg/kg/day for four weeks.

Group D: (T.Arjuna 500 mg/kg treated group)
The animals in this group will be given amiodarone 70 mg/kg/day as a morning along with Aqueous extract of Terminalia arjuna 500 mg/kg/day for four weeks.

Collection of tissue and blood samples
Rats were euthanized by placing in a chamber with chloroform ether for 5 minutes, till loss of consciousness and breathing. Skin was mopped with spirit swab to ensure aseptic technique and avoid contact of animal hair and organs. After aseptic measured were ensured, rat was pinned on the dissection board in a supine position, with its tail towards the dissector. An incision was made from manubrium to pubic symphysis, sternum was divided to expose the heart. Muscles and peritoneum were excised and abdominal viscera were exposed. After dissection of falciform ligament, liver was separated from the anterior abdominal wall. The hepatic artery, portal vein and bile duct were dissected after exposure. Liver was removed from the body and washed with normal saline. It was placed on a clean towel to wipe off any excess. Each liver was weighed and recorded. Bodies of animals were disposed-off by burying in Superior University, Lahore.

Features analyzed in this study were weekly body weight, liver weight and liver-body weight index.
Statistical analysis was done through SPSS 25.0.Shapiro Wilk test was applied to data, and after it was found to be normal. One way ANOVA was applied to data, post hoc Tukey test was applied for pairwise comparison in between the groups. P value < 0.05 was considered to be significant.

Results

Comparison of body weight across the study groups shows significant differences at all time points, with p value was less than 0.05. On Day 1, Group B had a highest mean weight (202.6 gm), followed by Group A (178.0 gm), Group D (163.2gm) and Group C (156.3 gm) with a p value of 0.001. On Day 28, Group B had the highest weight (266.3gm), followed by Group A (219.1 gm), Group D (223.6 gm) and Group C (183.7 gm), with a p value of 0.01. These results indicate that Group B consistently had the highest mean weight, while Group C had the lowest across all days, with all groups showing significant differences in body weight gain.

Table: 1 Comparison of body weight of rats at day 1, 7, 14, 21 and 28 among study groups A-D

	Group A	**Group B**	**Group C**	**Group D**	**P value**
Weight Day 1(gm)	178.0 +24.0	202.6 + 31.2	156.3+ 6.56	163.2+ 11.9	0.001
Weight Day 28 (gm)	219.1 + 29.7	266.3 + 51.0	183.7+ 19.5	223.6 + 40.02	0.01

One way ANOVA

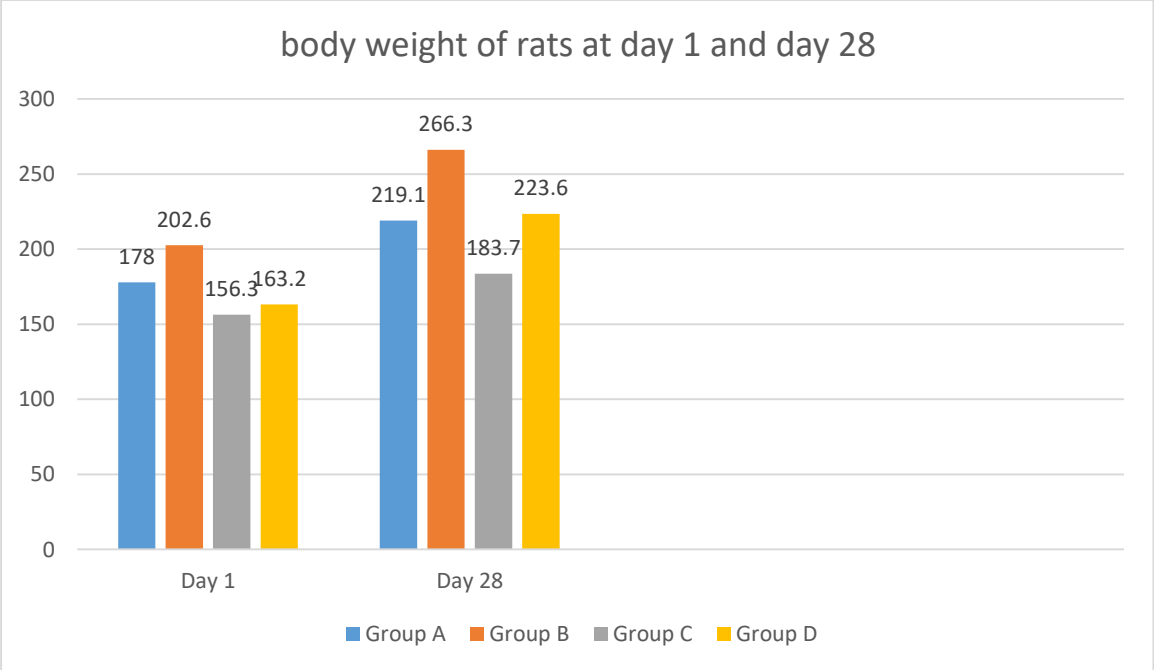

Figure 1: Bar chart showing comparison of body weight at day 1and 28 among study groups.

Pairwise Comparison of Body Weight on Day 1

The pairwise comparison of body weight on Day 1 among the study groups shows varying mean differences and significance levels. Group A compared to Group B, C and D had no significance difference ($p<0.05$) with difference ranging from -24.62 to 21.62. Group B showed significant differences when compared to Group C and D ($p<0.05$), with higher body weights in Group B by 46.25 to 39.37 gm. Group C and D had significant difference when compared to Group B and insignificant difference with another remaining group. Table:2

Table: 2 Pairwise Comparison of paired body weight of rats at day 1 among study groups A-D.

Independent variable	**I group**	**J group**	**Mean Difference (I-J)**	**Sig.**
Weight Day 1	Group A	Group B	-24.62	0.109
		Group C	21.62	0.188
		Group D	14.75	0.503
	Group B	Group A	24.62	0.109
		Group C	46.25	0.001
		Group D	39.37	0.004
	Group C	Group A	-21.62	0.18
		Group B	-46.25	0.001
		Group D	-6.87	0.912
	Group D	Group A	-14.75	0.503
		Group B	-39.37	0.004
		Group C	6.87	0.912

P value <0.05 is considered as statistically significant

Pairwise Comparison of Body Weight on Day 28

The pairwise comparison of body weight on Day 28 among the study groups shows varying mean differences and significance levels. Group A compared to Group B, C and D had no significant difference. Group B compared to Group A, C and D than only significance difference with Group C ($p<0.05$) with difference ranging from 42.75 to 82.62. Group C had only significant difference when compared to Group B and insignificant difference with another remaining group. Table: 3

Table: 3 Pairwise Comparison of paired body weight of rats at day 28 among study groups A-D.

Independent variable	**I group**	**J group**	**Mean Difference (I-J)**	**Sig.**
Weight Day 28	Group A	Group B	-47.25	0.073
		Group C	35.38	0.245
		Group D	-4.50	0.995
	Group B	Group A	47.25	0.073
		Group C	82.62	0.001
		Group D	42.75	0.119

	Group C	Group A	-35.38	0.245
		Group B	-82.62	0.001
		Group D	-39.88	0.160
	Group D	Group A	4.50	0.995
		Group B	-42.75	0.119
		Group C	39.88	0.160

P value <0.05 is considered as statistically significant

Weight of liver of rats

Comparison of weight of liver of rat across the study groups shows significant difference, with p value was less than 0.05. Group B also had a highest liver mean weight (13.37), followed by Group D (8.12), Group C (7.0) and Group A (6.62). Table 4 and fig: 2.

Table 4
Weight of liver of Rats among study groups A-D (gm)

	Group A	**Group B**	**Group C**	**Group D**	**P value**
Liver Weight	6.62+ 0.91	13.37+3.25	7.0+1.41	8.12+1.45	0.001

One way ANOVA

P value < 0.05 is considered statistically significant

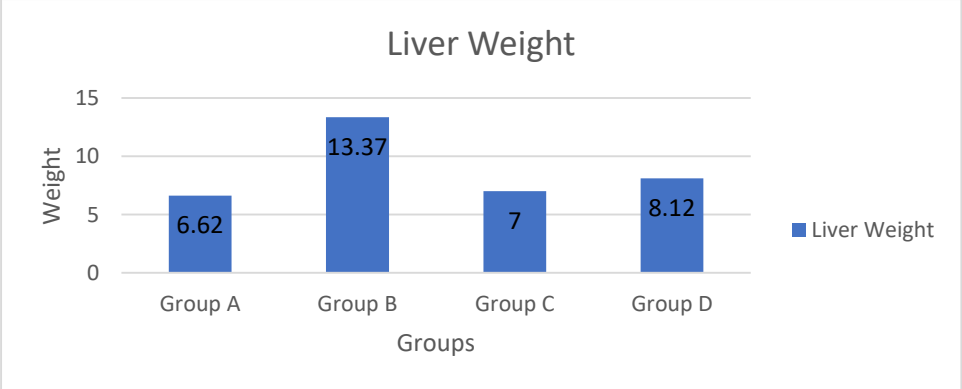

Figure 2. Bar chart showing comparison of Liver weight among study groups

The pairwise comparison of liver weight shows significant differences between Group A and B, Group B and C and Group B and D (p<0.0%) with Group B having higher liver weight than the other groups. No significant difference was found between Group A and C, Group A and D and Group C and D. Table: 5

Table: 5 Pairwise Comparison of paired liver weight of rats among study groups A-D

Independent variable	**I group**	**J group**	**Mean Difference (I-J)**	**Sig.**
Liver Weight	Group A	Group B	-6.75	0.000
		Group C	-0.38	0.981
		Group D	-1.50	0.438

	Group B	Group A	6.75	0.000
		Group C	6.37	0.000
		Group D	5.25	0.000
	Group C	Group A	0.38	0.981
		Group B	-6.38	0.000
		Group D	-1.13	0.667
	Group D	Group A	1.50	0.438
		Group B	-5.25	0.000
		Group C	1.13	0.667

P value <0.05 is considered as statistically significant

Liver-body weight index

Liver-body weight index in study groups is found to be significant with a p value of 0.001 , with group B having the highest mean Liver body-weight index followed by group D,group C and then Group A.Table 6 and Fig: 3.

Table: 6

Liver-body weight Index of rats among study groups A-D

	Group A	**Group B**	**Group C**	**Group D**	**P value**
LBW index	3.05+ 0.42	4.98+ 0.41	3.80+ 0.51	3.62+0.17	0.001

One way ANOVA

P value < 0.05 is considered statistically significant

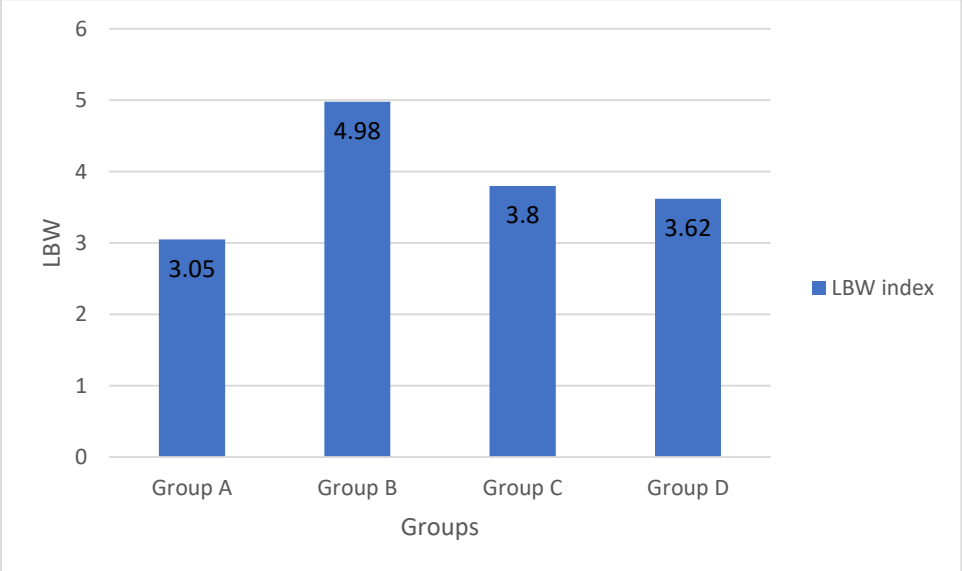

Figure 21. Bar chart showing comparison of LBW among study groups

Pairwise Comparison of paired LBW among study groups were shown in table 7, it shows Group B is significant when compared with Group A,C and D.

Table: 7 Pairwise Comparison of paired liver-body weight index among study groups A-D

Independent variable	I group	J group	Mean Difference (I-J)	Sig.
LBW	Group A	Group B	-1.93	0.000
		Group C	-0.75	0.005
		Group D	-0.58	0.039
	Group B	Group A	1.93	0.000
		Group C	1.19	0.000
		Group D	1.36	0.000
	Group C	Group A	0.75	0.005
		Group B	-1.19	0.000
		Group D	0.18	0.823
	Group D	Group A	0.58	0.039
		Group B	-1.36	0.000
		Group C	-0.18	0.823

P value <0.05 is considered as statistically significant

Discussion

Amiodarone is a potent anti-arrhythmic drug that is being used to treat ventricular tachyarrhythmia, supraventricular tachyarrhythmia, atrial fibrillation and flutter. It has a large volume of distribution and extensive tissue distribution which accounts for a vast range of side effects due to prolonged use of amiodarone. It is excreted through bile. Liver injury is one of the common side effects that arise due to use of amiodarone. Weight gain is a common side effect seen with use of amiodarone. Liver weight and body-weight index are also attenuated due to long term use of amiodarone. Terminalia Arjuna is one such folklore drug used as cardio-protective agent. Its hepatoprotective use has been established as well. No study has explored the use of Terminalia Arjuna in amiodarone induced liver injury. In this study, curative role of TA in AMD induced injury have been positively established.

This present research work exhibits that there is no statistical difference in the weight of animals at the start of experiment among control group A and experimental group B,C and D, p value=0.109(Table.2,Figure.1).By days 7,14 and 21 a significant increase in the weight of rats of Group B is noted compared to group A,C and D. By day 28 the increase in weight is noted with highest weight gain in specimen of Group B, when pairwise comparison is performed, this weight gain is only significant with group C (p value=0.001) (Table.3).The results of the present study are supported by Chakraborty et al.n.d (Chakraborty et al., n.d.)which also observed an increase in body weight of rats due to amiodarone. These findings were attributed to accumulation of amiodarone in adipose tissue and other organs as it is a lipophilic drug. A study conducted by Al shammari et al.2016 showed decrease in the weight of rats when they are administered amiodarone, these findings are inconsistent with findings of this study(Al-Shammari et al., 2016) and (Hubel et al., 2021) that shows that amiodarone leads to metabolic stress and increased lipolysis and leads to decreased body weight.

This study reported that animals receiving amiodarone had liver weight more than the other groups. Liver-body weight index is also significantly increased in group B, (p value=0.001) (Table.6,Figure.3).This hepatomegaly is likely result of lipid accumulation, cellular swelling from hepatocellular injury and phospholipidosis. These observations are consistent with prior established findings with amiodarone induced liver injury as reported by McCarthy et al.2004 (McCarthy et al., 2004).A study explains that between amiodarone and dronedarone amiodarone leads to increase in liver weight along with steatosis(Pop et al., 2024).

Conclusion

The findings of this study clearly establish that amiodarone produces substantial hepatic injury, characterized by measurable increases in body weight, liver weight and liver–body weight index. Intervention with Terminalia Arjuna resulted in marked attenuation of these changes, with restoration of near-normal liver weight and liver-body weight index, in treated groups. Notably, the high-dose T.Arjuna group showed the greatest degree of improvement, highlighting a strong dose-dependent protective effect. Overall, the results indicate that Terminalia Arjuna possesses significant hepatoprotective properties capable of mitigating amiodarone-induced liver toxicity.

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