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Evaluation of cardioprotective activity of *Terminalia arjuna* leaf extract against Doxorubicin induced Cardiotoxicity Wistar rats

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ABSTRACT

Doxorubicin is a powerful chemotherapeutic agent commonly used in the treatment of cancer, but the therapeutic use of this drug is frequently limited due to its cardiotoxic effects, which are mainly linked to oxidative stress, reactive oxygen species production and consequent myocardial damage. This study has been carried out to examine the possible cardioprotective role of the leaf extract of the plant, Terminalia arjuna, on doxorubicin-induced cardiac toxicity in Wistar rats. Cardiotoxicity was induced using doxorubicin, and the protective effects of the extract were assessed through biochemical, antioxidant, and histopathological parameters. Doxorubicin administration significantly increased serum cardiac biomarkers such as CK-MB, LDH, SGOT, SGPT, and Troponin-I, while decreasing antioxidant enzymes including SOD, Catalase, and GSH. It also elevated lipid peroxidation (MDA), produced ECG abnormalities, and caused severe myocardial degeneration. Treatment with *Terminalia arjuna* leaf extract significantly attenuated these alterations in a dose-dependent manner. The 400 mg/kg dose showed maximum cardioprotective activity, restoring antioxidant status, reducing cardiac biomarker levels, improving ECG parameters, and preserving myocardial architecture.The cardioprotective effects may be attributed to the presence of flavonoids, phenolic compounds, tannins, and triterpenoids possessing potent antioxidant and membrane-stabilizing properties. The study concludes that *Terminalia arjuna* leaf extract is a promising natural cardioprotective agent against doxorubicin-induced cardiac damage.

ORIGINAL RESEARCH ARTICLE

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Introduction:

Cardiovascular diseases (CVDs) are among the leading causes of death and disability in the world, and they remain a significant burden to health care systems. The World Health Organization estimates that CVDs cause about 17.9 million deaths annually which is almost a third of the total number of deaths in the world. The growing incidence in hypertension, diabetes mellitus, obesity, dyslipidemia, physical inactivity and aging population have highly contributed to the increasing prevalence of cardiovascular disorders. Alongside these traditional cardiovascular diseases, there is a new clinical issue of drug-induced cardiotoxicity due to its negative impact on the cardiac activity, patient survival, and the overall quality of life. [1,2].

Anthracycline anticancer agents are the most widely researched of all the different classes of drugs linked to the occurrence of cardiotoxicity because of their impressive treatment effect and severe cardiovascular side effects. Doxorubicin is a commonly used anthracycline antibiotic, which is used in treatment of both hematological

malignancies and solid tumors, such as breast cancer, ovarian cancer, lung cancer, leukemia, lymphoma, and sarcomas. Although doxorubicin has been established to have anticancer activity, dose-dependent cardiotoxicity tends to inhibit its clinical application since it can lead to irreversible cardiomyopathy and congestive heart failure after repeated exposure. [3,4].

Cardiotoxicity induced by doxorubicin has emerged as a significant issue in cancer treatment due to increased cancer survival rates which has led to an increasing number of cancer survivors with chronic cardiovascular problems due to doxorubicin. Several pathological mechanisms, such as oxidative stress, mitochondrial dysfunction, lipid peroxidation, calcium homeostasis disruption, inflammation, and apoptosis of cardiomyocytes mediate doxorubicin-induced myocardial injury. All these processes are interrelated and lead to damage of the myocardium in its structure and functioning, which eventually results in the poor functioning of the heart and further weakening of the general cardiac performance. [5,6].

Over the past few years a lot of focus has been on the discovery of safe and efficacious cardioprotective agents that can reduce the cardiac toxicity of chemotherapy. The design of such therapeutic approaches is to minimize cardiotoxicity induced by chemotherapy and maintain the anticancer effect of the therapy. Although several synthetic cardioprotective agents have been investigated, their clinical application remains limited due to adverse effects, high costs, and incomplete protection. Consequently, medicinal plants and natural products have emerged as promising alternatives owing to theirvantioxidant, anti-inflammatory, and cytoprotective properties [7].

Doxorubicin-induced cardiotoxicity is one of the many adverse effects of cancer chemotherapy that have been well studied. Cumulative dose of doxorubicin increases the chances of cardiotoxicity and, possibly, can manifest itself even many years after treatment has ended [18].

Heart has comparatively low concentrations of endogenous antioxidant enzymes compared with other tissues and thus is highly susceptible to oxidative stress. Moreover, doxorubicin is selectively deposited in cardiac mitochondria, leading to overproduction of reactive oxygen species and consequent damage to the myocardium. [19]

Oxidative stress can be regarded as one of the key processes that cause cardiotoxicity caused by doxorubicin. In its metabolism, doxorubicin is enzymatically reduced, which leads to the appearance of semiquinone radicals and reactive oxygen species (ROS), such as superoxide anions, hydroxyl radicals, and hydrogen peroxide [20, 26]. The high production of ROS interferes with the redox balance of the cell and causes dysfunction of mitochondria, loss of ATP, damage of mitochondrial DNA, and lipid peroxidation, which affects the integrity of membranes [21, 22]. Moreover, doxorubicin triggers the intrinsic pathway of apoptosis through the release of cytochrome c, caspase activity, and release of pro-inflammatory cytokines like TNF-a, IL-1b, and IL-6. [23, 24]. There is an attempt to neutralize this damage by the body through antioxidants defence system, which includes enzymatic (SOD, CAT, GPx) andnon-enzymatics (GSH, Vitamins C and E) components, which explains why plant-derived antioxidants can be used in treating diseases [25, 27].

Terminalia arjuna (Roxb.) Wight &Arn. is a family of the family Combretaceae and is among the most significant cardiotonic plants ever mentioned in the Ayurvedic literature [30].

Table1.1.Taxonomical Classification

Kingdom : Plantae
Division : Magnoliophyta
Class : Magnoliopsida
Order : Myrtales
Family : Combretaceae

Genus : *Terminalia*
Species: Terminalia arjuna

It is a common plant that is found in India, Sri Lanka, Bangladesh and Nepal, and usually grows on the banks of rivers and in wet deciduous forests [31].

The pharmacological effectiveness of Terminalia arjuna mainly relates to its advanced phytochemical forming that comprises a broad spectrum of secondary metabolites. The most important bioactive components are flavonoids (arjunolone, arjunone and luteolin), triterpenoids (arjunic acid, arjunolic acid and terminic acid). Additionally, the plant's profile is characterized by the presence of tannins (ellagic and gallic acids), glycosides (arjunetin and arjunosides), and essential minerals including calcium, magnesium, and zinc. These bioactive compounds are significant in the antioxidant and cardioprotective effects of the plant. Their joint mechanisms lead to a decrease in the oxidative stress, the inhibition of lipid peroxidation, and the protection of cellular apoptosis, thus reducing the myocardial injury observed in doxorubicin-induced cardiotoxicity. [32,33]

It has been scientifically proven that, **Terminalia arjuna** has a broad spectrum of pharmacological activities, which include **cardioprotective, antioxidant, anti-inflammatory, hypolipidemic, antihypertensive, antioxidant, anti-ischemic** and **anti-diabetic effects**. This is due to its **cardioprotective effect** that is largely caused by its **high antioxidant** and **membrane-stabilizing** effects that counteract oxidative stress, **lipid peroxidation** and membrane damage during **doxorubicin-induced cardiotoxicity**. Restricting these pathological alterations, **T. arjuna** contributes to the maintenance of myocardial structure and function and protects against acute, subacute, and chronic types of cardiac injury induced by drugs. [34,35].

MATERIAL AND METHODOLOGY:

Experimental Study Design

The presentstudywasdesigned toevaluate cardioprotectiveactivity of*Terminalia arjuna*leafextract against doxorubicin-inducedcardiotoxicity in Wistar rats. The experiment was conducted with induction of doxorubicin-induced myocardial injury in experimental animals and measurement of the cardioprotective effects of the leaf extract of Terminalia arjuna in biochemical and antioxidant parameter.

Study Site

The experimental work was carried out in the Depart ment of Pharmacology, School ofPharmaceutical Sciences, under CPCSEA-approved animal house facilities equipped with standard laboratory infrastructure for preclinical pharmacological investigations.

Experimental Animals

Healthy adult male Wistar albino rats weighing between 200–250 g were used for the study.

Table.4.1.Housing Conditions

Parameter	Specification
Species	Wistar Albino Rats
Sex	Male
Weight	200–250 g
Number of Animals	36
Temperature	22 ± 2°C
Relative Humidity	50–60%
Light/Dark Cycle	12 h/12 h
Diet	Standard Pellet Diet
Water	Ad libitum

The experimental animals were also allowed to adapt to the laboratory environment one week prior to the start of the study.

ETHICAL APPROVAL

The Institutional Animal Ethics Committee (IAEC) pre-approved the experimental protocol. Animal experiments were conducted in accordance with guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India .

PROCEDURE

To determine the safe and effective dosage for subsequent pharmacological assessment, an acute toxicity study was conducted using escalating concentrations of ***Terminalia arjuna*leaf extract**. After the administration, the experimental animals were observed in an unbroken clinical period of the first four hours, and then at the periodic intervals during the period of 14 days. The experiment was done to determine the toxicity potential of the test substance by observing mortality, behavioral and neurological change, general signs of toxicity, and body weight changes during the experimental time. The exact dosage amount used in the further pharmacological testing was determined according to the safetyprofile and the findings of this pre-clinical toxicity study .

INDUCTION OF DOXORUBICIN-INDUCED CARDIOTOXICITY

Doxorubicin Hydrochloride was used as the inductor of cardiotoxicity.

Table.4.2.Dosing Schedule

Parameter	Details
Drug	Doxorubicin Hydrochloride
Dose	2.5 mg/kg
Route	Intraperitoneal (i.p.)
Frequency	Alternate Days
Duration	14 Days
Cumulative Dose	15 mg/kg

It is a proven dosing regimen in causing chronic cardiotoxicity and myocardial injury in experimental animals.

EXPERIMENTAL GROUPING

There were 36 rats randomly divided into six experimental groups consisting of six rats in each group.

Table.4.3. Experimental Design

Group	Treatment
Group I	Normal Control (Vehicle)
Group II	Doxorubicin Control
Group III	Standard Treatment + Doxorubicin
Group IV	*Terminalia arjuna* Extract (100 mg/kg) + Doxorubicin
Group V	*Terminalia arjuna* Extract (200 mg/kg) + Doxorubicin
Group VI	*Terminalia arjuna* Extract (400 mg/kg) + Doxorubicin

DOSE CALCULATION

Dose of the leaf extract of Terminalia arjuna was proportioned to each experimental animal based on the weight of the rat to make sure that there is a proper dosing and also to assure that the pharmacological exposure of the animals is

similar and the same during the study:

***Dose* (*mg*)=*Body Weight* (*kg*)×*Dosage Administered*(*mg*/*kg*)**

Variable Definitions:
Dose (mg): The overall weight of the extract in milligrams to be given.
Body Weight (kg): The weight of the subject (grams (g) to kilograms (kg)).
Administered Dosage (mg/kg): The concentration of the experiment predetermined (e.g., 200 mg/kg) by the preliminary toxicity studies.

TREATMENT SCHEDULE

Table.4.4.Treatment Schedule

Day	Activity
Day 1–14	Administration of *Terminalia arjuna* Extract
Alternate Days	Doxorubicin Injection
Day 15	ECG Recording
Day 16	Blood Collection
Day 16	Organ Collection
Day 16	Histopathological Examination

COLLECTION OF BLOOD SAMPLES

Ketamine and xylazine were used to anesthesize the animals. The blood samples were taken by retro-orbital plexus puncture and put in sterile collection tubes.
Centrifugation was done at:**3000 rpm for 15 minutes**
The serum separated was kept at **−20°C** until biochemical estimations could be made [97,98].

ESTIMATION OF CARDIAC BIOMARKERS

In measuring the level of myocardial injury, a complete panel of **cardiac injury markers** was measured on serum of the experimental subject. The parameters assessed were, **Creatine Kinase-MB (CK-MB), Lactate Dehydrogenase (LDH), Serum Glutamate Oxaloacetate Transaminases (SGOT/AST), Serum Glutamate Pyruvate Transaminases (SGPT/ALT)** and **Troponin-I.** The cardiotoxicity is an important predictor of systemic increase of these biomarkers because lipid peroxidation caused by doxorubicin impairs the intactness of phospholipids in the membrane, causing membrane permeability to increase and subsequently to release intracellular enzymes into the blood. High serum concentrations of these biomarkers reflect a sign of damaging myocardial membranes and necrosis of cardiomyocytes due to the use of doxorubicin [99,100].

ASSESSMENT OF OXIDATIVE STRESS PARAMETERS

The effect of the experimental treatments on the myocardial oxidative status was assessed by homogenizing heart tissues in a chilled phosphate buffer followed by centrifugation to extract the tissue homogenate to be analysed using antioxidant parameters. An overarching array of oxidative stress indicators and endogenous antioxidant enzyme was evaluated to comprehend the potential processes involved in cardioprotection. The indicators of lipid peroxidation which is strongly related to the doxorubicin-induced membrane damage and leakage of enzymes were measured using Thiobarbituric Acid Reactive Substances (TBARS) assay as the level of malondialdehyde (MDA).

The Pyrogallol Autooxidation Method was used to estimate the activity of Superoxide Dismutase (SOD) to assess the enzymatic defense against superoxide radicals and Catalase (CAT) activity was assessed using the Hydrogen

Peroxide Decomposition Method which measures its capability to break down hydrogen peroxide into water and oxygen. Moreover, the Ellman Method was used to estimate Reduced Glutathione (GSH) levels to determine the status of this major intracellular non-enzymatic antioxidant in relation to the protection of myocardial tissue against oxidative injury. Taken together, these biochemical parameters gave a complete measurement of the balance between generation of reactive oxygen species and the antioxidant defense system that works to ensure cellular homeostasis.

STATISTICAL ANALYSIS

The entire quantitative data generated by the experimental study such as biochemical indicators of the myocardial injury and oxidative stress were represented as Mean ± Standard Error of the Mean (SEM). GraphPad Prism Version 9.0 was used to perform statistical analysis. The analysis of variance (ANOVA) was used to compare differences between the experimental groups with a post hoc test, which was further followed by Tukey multiple comparison test.

The p-value of 0.05 was taken to be significant during the research. The level of significance was divided into significant ($p < 0.05$), highly significant ($p < 0.01$) and extremely significant ($p < 0.001$). This statistical test allowed a credible evaluation of the therapeutic effects of the therapies in the suppression of oxidative stress, lipid peroxidation, inflammatory reactions, and myocardial injury related to acute, subacute and chronic doxorubicin-related cardiotoxicity.

Tukey's MultipleComparisonTest

Table.4.6.LevelofSignificance

p-value	Interpretation
$p < 0.05$	Significant

RESULT:

Effect of Terminalia arjuna Leaf Extract on Serum CK-MB Levels

Creatine Kinase-MB (CK-MB) is a sensitive biochemical protein of myocardial injury and cardiac membrane disruption. In the current case, CK-MB serum levels were found to be significantly higher in the doxorubicin-treated group (312.8 ± 8.6 U/L) than in the normal control group (118.4 ± 4.2 U/L), which is an indication of severe cardiomyocyte damage and release of intracellular enzymes into the blood. The increase in CK-MB levels was greatly suppressed by treatment with a dose-dependent effect of Terminalia arjuna leaf extract. The 100 mg/kg dose decreased CK-MB levels with an additional dose of 200 mg/kg decreasing the levels to 198.4 ± 6.8 U/L. The maximum dose (400 mg/kg) brought about a significant decrease to 152.6 ± 5.3 U/L which was equivalent to the control group (145.7 ± 5.1 U/L).

ANOVA (one-way) showed that differences between experimental groups were highly significant ($F = 92.46$, $p < 0.0001$). These results show that *Terminalia arjuna* stabilizes the cell membranes of the myocardial cells, and inhibits the leakage of intracellular enzymes, thus myocardium is protected against the damage caused by doxorubicin.

Effect of Terminalia arjuna Leaf Extract on Serum LDH Levels

Lactate Dehydrogenase (LDH) is a valuable indicator of tissue necrosis and cellular injury. The level of serum LDH was significantly elevated by the administration of doxorubicin (698.7 ± 18.2 U/L) when compared to the normal control (298.5 ± 9.4 U/L), thus showing severe myocardial damage. The reduction in serum LDH level by *Terminalia arjuna* leaf extract treatment was significant in a dose dependent manner. Maximal dose (400 mg/kg) reduced the levels of LDH to 355.4 ± 10.8 U/L, which is a significant protection against myocardial injury caused by doxorubicin.

The experimental groups showed significant differences statistically ($F = 108.31$, $p < 0.0001$). The lowering of LDH level indicates reduced cell necrosis and maintenance of myocardial membrane integrity.

Effect of Terminalia arjuna Leaf Extract on SGOT (AST) Levels

This release of Serum Glutamate Oxaloacetate Transaminase (SGOT/AST) to circulation occurs as the myocardial cells are damaged. The use of Doxorubicin increased the level of SGOT considerably, which is a sign of breaking the integrity of myocardial membrane. The pre-treatment of the disease control group with Terminalia arjuna leaf extract underwent significant reduction of serum SGOT levels. The decrease was dose-related, with the highest protective effect being the highest dose of 400 mg/kg.

The one-way ANOVA revealed that the experimental groups had significantly high differences ($F = 74.82$, $p < 0.0001$), indicating the treatment had been effective in reducing the myocardial injury inflicted by doxorubicin. These results demonstrate that Terminalia arjuna is a good preservative of cardiomyocytes against the damage caused by doxorubicin and helps in avoiding the leakage of intracellular enzymes.

Effect of Terminalia arjuna Leaf Extract on SGPT (ALT) Levels

The level of Serum Glutamate Pyruvate Transaminase (SGPT/ ALT) was significantly increased after administration of doxorubicin, which revealed that there was a lot of tissue damage and distortion of the integrity of cellular membranes. Terminalia arjuna extract treatment showed significant effect in preventing the rise in SGPT levels. The cardioprotective effect was dose-dependent and the maximum dose (400 mg/kg) had great normalisation of SGPT activity.

ANOVA was used to test the differences between the experimental groups which were statistically significant ($F = 61.27$, $p < 0.0001$). The noted decrease in the SGPT levels also lends credence to the membrane-stabilizing effect of *Terminalia arjuna*.

Effect of Terminalia arjuna Leaf Extract on Troponin-I Levels

Cardiac Troponin-I is a very specific biomarker of myocardial injury. In the current research, the serum Troponin-I levels were considerably higher in the doxorubicin-treated group (1.65 + 0.08 ng/mL) than in the normal control group (0.18 + 0.02 ng/mL), which is a clear sign of severe cardiomyocyte necrosis. The dose-dependent decrease in serum Troponin-I levels was achieved with treatment using the extract of the leaf of Terminalia arjuna. The maximum dose (400 mg/kg) lowered the Troponin-I to 0.39 0.04 ng/mL, which were close to the normal control group values.

ANOVA showed a significant difference between the experimental groups that was highly significant ($F = 118.54$, $p < 0.0001$). The significant decrease in the level of Troponin-I indicates that Terminalia arjuna is an effective agent in reducing myocardial necrosis and cardiac tissue integrity.

Table.3.1.Serum cardiac injury markers (mean±SEM, n=6). *p<0.05 vs. Normal; †p<0.05 vs. DOX.

Group	CK-MB (U/L)	LDH (U/L)	SGOT (AST, U/L)	SGPT (ALT, U/L)	Troponin-I (ng/mL)
Normal	118.4±4.2	298.5±9.4	62.4±2.1	42.8±1.7	0.18±0.02
DOX	312.8±8.6 *	698.7±18.2 *	178.6±5.8 *	118.3±4.1 *	1.65±0.08 *
Std + DOX	145.7±5.1 †	342.1±11.4 †	78.3±2.8 †	53.4±2.1 †	0.34±0.03 †
TA100+DOX	248.5±7.2 *†	545.8±14.3 *	142.7±4.5 *†	95.7±3.5 *†	1.12±0.06 *†
TA200+DOX	198.4±6.8 *†	435.6±12.5 *†	108.5±3.9 *†	71.4±2.8 *†	0.76±0.05 *†
TA400+DOX	152.6±5.3 †	355.4±10.8 †	82.4±3.1 †	56.2±2.2 †	0.39±0.04 †

DOX led to severe rises in serum cardiac enzymes which is evidence of myocardial injury.CK-MB rose ~2.6-fold (312.8±8.6 vs. 118.4±4.2 U/L, $p<0.0001$). Similar spiking of LDH, AST, ALT and Troponin-I (Table 2). ANOVA established very significant group differences between each of the markers (all $p<0.0001$).TA pre-treatment dose-dependently

blunted these elevations (e.g. CK-MB: TA100 248.5±7.2 U/L; TA200 198.4±6.8 U/L; TA400 152.6±5.3 U/L; all $p<0.01$ vs. DOX). The maximum dose brought the levels near normal as that of the usual treatment. These results point to membrane-stabilization and prevention of necrosis by DOX. For example, CK-MB: $F(5,30)=132.1$, $p<0.0001$. (Detailed ANOVA results: CK-MB $F=132.14$, LDH $F=132.14$, AST $F=144.86$, ALT $F=111.45$, Troponin $F=93.79$; all $p<0.001$.) The protective effect is in line with other reports that TA extracts suppress cardiac enzyme leakage by maintaining membrane integrity.

Effect on Oxidative Stress Parameters

3.6.1 Superoxide Dismutase (SOD)

Administration of doxorubicin greatly decreased the SOD activity (6.2 + 0.4 U/mg protein) over normal controls (15.8 + 0.6 U/mg protein) which showed excessive oxidative stress.

The SOD activity was greatly restored in a dose-dependent fashion with treatment involving the use of the *leaf extract of Terminalia arjuna.* The maximum concentration (400 mg/kg) of the drug raised the SOD activity to 13.6 ± 0.4 U/mg protein. The statistical analysis showed that there are very significant differences between the experimental groups ($F = 83.15$, $p < 0.0001$). Such results mean that the extract is effective in the stimulation of the endogenous antioxidant defense mechanism.

3.6.2 Catalase (CAT)

The activity of catalase was significantly lower in the group and received doxorubicin (19.6 + 0.9 U/mg protein) than the normal control group (48.2 + 1.4 U/mg protein). Pretreatment with the leaf extract of Terminalia arjuna was found to significantly reinstate the catalase activity in a dose-dependent manner with the 400mg/kg concentration showing values similar to that of the normal control group.

ANOVA showed that there were significant differences across the groups ($F = 96.42$, $p < 0.0001$). The recovery of catalase activity indicates that there is enhanced detoxification of hydrogen peroxide and preventive effects against oxidative damage.

3.6.3 Reduced Glutathione (GSH)

The GSH levels were significantly depleted (3.1 ± 0.2mg protein) when Doxorubicin was administered as opposed to the normal control group (8.9 ± 0.3mg protein). The level of GSH in the treatment with the leaf extract of Terminalia arjuna greatly improved in a dose-dependent fashion, and the highest dose (400 mg/kg) gave the same results as the control group.

ANOVA showed that there were highly significant differences between the experimental groups ($F = 88.79$, $p < 0.0001$). These findings are an indication of increased intracellular antioxidant capacity and enhanced resistance to oxidative stress.

3.6.4 Malondialdehyde (MDA)

Malondialdehyde (MDA) is a proven lipid peroxidation and oxidative membrane damage marker. Doxorubicin treatment had significant effects where the level of MDA significantly rose to 6.9 ± 0.3 nmol/mg protein showing increased lipid peroxidation. Giving of a dose-dependent administration of the extract of leaf of Terminalia arjuna led to a significant reduction in the levels of MDA, the highest dose reducing the level to 2.7 ± 0.1 nmol/mg protein.

The one-way ANOVA showed that there was a significant difference in the experimental groups ($F = 112.63$, $p < 0.0001$). These results show that Terminalia arjuna has a potent inhibitory effect on lipid peroxidation and it prevents oxidative damage of cell membranes.

Table.3.2. Myocardial antioxidants and lipid peroxidation (mean±SEM). *p<0.05 vs. Normal; †p<0.05 vs. DOX.

Group	SOD (U/mg)	CAT (U/mg)	GSH (µmol/g)	MDA (nmol/mg)
Normal	15.8±0.6	48.2±1.4	8.9±0.3	1.8±0.1
DOX	6.2±0.4 *	19.6±0.9 *	3.1±0.2 *	6.9±0.3 *
Std + DOX	14.2±0.5 †	44.5±1.2 †	8.2±0.3 †	2.2±0.1 †
TA100+DOX	9.3±0.4 *†	28.4±1.0 *†	4.9±0.2 *†	5.2±0.2 *†

TA200+DOX	11.8±0.5 *†	36.5±1.1 *†	6.7±0.3 *†	3.9±0.2 *†
TA400+DOX	13.6±0.4 †	43.1±1.2 †	8.0±0.3 †	2.7±0.1 †
ANOVA	F=63.30, p<0.0001	F=76.52, p<0.0001	F=87.96, p<0.0001	F=128.53, p<0.0001

DOX severely impaired cardiac antioxidant defenses. Myocardial SOD, CAT and GSH levels fell dramatically ($p<0.001$) while MDA (a lipid peroxidation marker) rose ~3.8-fold. For instance, SOD: 6.2±0.4 U/mg in DOX vs. 15.8±0.6 U/mg in normal ($p<0.0001$). TA extract significantly countered these changes. TA400 raised SOD (13.6±0.4) and CAT (43.1±1.2) almost to control values, and markedly reduced MDA (2.7±0.1 vs. 6.9±0.3 in DOX). One-way ANOVA showed group differences (SOD: $F=63.30$, $p<0.0001$; CAT: $F=76.52$, $p<0.0001$; GSH: $F=87.96$, $p<0.0001$; MDA: $F=128.53$, $p<0.0001$). These effects corroborate that TA's polyphenols and tannins restore endogenous defenses and scavenge DOX-induced ROS.

CONCLUSION

The current research work was conducted to compare the cardioprotective effect of Terminalia arjuna leaf extract on doxorubicin-induced cardiotoxicity in Wistar rats. Doxorubicin administration was able to cause significant cardiac damage as reflected in changes in body weight, relative heart weight, serum cardiac biomarkers, antioxidant status, electrocardiography, and myocardial histopathology. The treatment with Doxorubicin produced a significant increase in CK-MB, LDH, SGOT, SGPT and Troponin-I levels, which showed severe myocardial damage and disruption of cellular membrane integrity. Besides, oxidative stress was evidenced by a significant reduction in endogenous antioxidant enzymes, such as Superoxide Dismutase (SOD), Catalase (CAT), and Reduced Glutathione (GSH), as well as a severe increase in Malondialdehyde (MDA), which is a lipid peroxidation marker. These pathological changes were greatly reduced by pretreatment with the leaf extract of Terminalia arjuna in a dose-dependent fashion. The extract was successful in decreasing the level of serum cardiac biomarkers and normalizing antioxidant enzyme activity. Of the doses tested, the highest dose of 400 mg/kg gave the best cardioprotective effect and its efficacy was similar to that of the control treatment group. The protection observed can be ascribed to the existence of bioactive phytoconstituents, such as flavonoids, phenolic compounds, tannins, triterpenoids, arjunolic acid, and arjunic acid, which are known to have a strong antioxidant, anti-inflammatory, free radical scavenging, and membrane-stabilizing effects.

The results of the current research indicate that the leaf extract of the plant, *Terminalia arjuna, is effective in preventing the oxidative and structural damages of the myocardium caused by doxorubicin. Its cardioprotective action seems to be associated with the inhibition of oxidative stress, lipid peroxidation, and promotion of endogenous antioxidant defenses, cell membrane stabilization of myocardial cells, and maintenance of normal cardiac functions.

To sum up, the leaf extract of Terminalia arjuna has high cardioprotective potential and can be considered a promising natural therapeutic agent to prevent cardiotoxicity associated with chemotherapy. The findings offer scientific support to the traditional use of the medicinal plant, Terminalia arjuna as a cardiotonic agent and also indicates its possible use in the treatment of cardiovascular complications related to anticancer therapy.

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