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Cardioprotective Activity of *Luffa Acutangula* Fruits Extract on Isoproterenol Induced Myocardial Infarction in Rats

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KEYWORDS

Luffa acutangula fruits; Cardiotoxicity; Isoproterenol; Ethanolic extract.

ABSTRACT:

Introduction: The cardioprotective activity of ethanolic extract of Luffa acutangula fruits was studied in isoproterenol (ISO) induced myocardial infarction using adult male Wistar rats. Exposure of experimental animals to isoproterenol significantly elevated the systolic blood pressure and heart rate and decreased the diastolic blood pressure as compared to control animals. The administration ISO to the cardiac control animals showed an increase in ST segment, prolongation of P waves, QRS complex, and RR interval when compared to normal control animals. Ascorbic acid and various doses of ethanolic extract of Luffa acutangula fruits treatment decreases the ST segment, P waves prolongation, QRS complex, and RR interval. ISO administered rats show increased serum levels of AST, CK and LDH. Administration of ethanolic extract of Luffa acutangula fruits reduced the elevated levels. The animals intoxicated with ISO showed decreased GSH content and an increased MDA content. The treatment of various dosages of ethanolic extract of Luffa acutangula fruits and ascorbic acid significantly reversed the GSH and MDA. In histopathological examination the ISO treated animals exhibited increased infraction, congestion, bleeding, fibrosis, myocyte size and inflammation and rats treated with ascorbic acid and varying doses of ethanolic extract of Luffa acutangula fruits resulted in reduction.

Objectives to evaluate acute toxicity and cardioprotective activity of Luffa acutangula fruits

Methods: The animals were divided into six groups containing six animals each. Group 1 animals received distilled water for 30 days. Group 2 animals administered with distilled water for 30 days and ISO 85 mg/kg on 28th and 29th day. Group 3 animals received Ascorbic acid 20 mg/kg for 30 days and ISO on 28th and 29th day. Group 4, 5 and 6 animals received various doses of EELAF such as 100, 250 and 500 mg/kg respectively for 30 days and ISO on 28th and 29th day. On day 31st animals were anaesthetized using Ketamine 100 mg/kg then those animals were placed in the Biopac. MP-46 instrument

Results: Luffa acutangula fruits 2500 mg/kg was taken as LD50 cutoff value It was observed that the protective effect of test extract at a dose of 500 mg/kg Blood pressure, heart rate, ECG, serum enzymes and biomarker.

Conclusions: In conclusion, antioxidant property and presence of flavonoids and tannins in the EELAF could be the reason for cardioprotective activity against isoproterenol induced myocardial infraction. However, further study is needed to establish the exact mechanism of action of EELAF as Cardioprotective of EELAF.

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1. Introduction Cardiovascular disease (CVD's) are the leading cause of death in both developed and developing countries. Among these, Acute myocardial infarction (MI), is one of the most alarmin values.[1] MI is a condition in which an imbalance between myocardial oxygen supply and demand occurs.[2] Isoproterenol (ISO)-induced myocardial infarction serves as a well standardized model to study the beneficial property of numerous drugs and cardiac function. ISO a synthetic catecholamine and β adrenergic agonist that causes severe stress in myocardium and infarct-like necrosis. ISO induced myocardial injury involves membrane permeability alterations, which brings about the loss of functions and integrity of myocardial membranes.[3]

The use of herbal drugs has been increasing over the past decade. A considerable number of plant-based medicines have been widely used for treatment of various ailments. Hence, interest in the investigation of medicinal plants as potential sources of new drugs is also increasing in recent days. Since ancient times, drugs made from plant sources have been essential in the prevention and treatment of numerous ailments. The use of these herbal remedies in the treatment of human ailments is advantageous. Global demand for plant-derived substances is increasing, and numerous pharmaceutical companies are actively studying the effects of these separated molecules on human health extensively.[4] *Luffa acutangula* (Family: Cucurbitaceae) is a medicinal plant, usually referred as a ridge gourd. India is considered as a primary Centre of origin. The plant is widely cultivated in India, China, Japan, Egypt, and other parts of Africa.

Propagation of this plant is done through seeds and are sown in February–March or June–July.[5] Different ethnic groups in India have made considerable use of various Luffa acutangula components for therapeutic purposes. Jaundice is treated with leaves and fruits powder in Maharashtra and the tribal regions of Madhya Pradesh.[6] A local inhabitant from reserve forest of Mahadevapura (Telangana state) widely uses the fruits for diabetes treatment.[7]

A plant has produced more than 50 chemical substances, the majority of which being flavonoids, anthraquinones, proteins, fatty acids, saponin and triterpene.[8] Hepatoprotective, antiulcer, anticancer, immunomodulatory, antihyperlipidemic, antibacterial, CNS depressing, analgesic, and anti-inflammatory are only a few of the pharmacological effects that crude extracts of medicinal plants and their isolated components have shown Mishra.[9] Previous reports claimed that plant extract and vegetables rich in flavonoids demonstrated to possess significant Cardioprotective property.[10] The fruits of the tittle plant known to contain flavonoids.[11] In context of this the present study has been undertaken for the evaluation of cardioprotective potential of the *Luffa acutangula* fruits extract against isoproterenol mediated cardiotoxicity.

2.Objectives

The following objectives were set for the current study, which aimed to test the ethanolic extract of '*Luffa acutangula* fruits' for the Cardioprotective properties in rats:

To prepare ethanolic extract of *Luffa acutangula* fruits.
To detect the presence of phytoconstituents in crude extract of *Luffa acutangula* fruits.
To study the acute toxicity of the test extract in mice.
To investigate the cardioprotective efficacy of the test extract against ISO mediated cardiotoxicity in experimental rats.

3.Methods

The fruits *of Luffa acutangula* was collected from farmland of Vijayapura and was identified and authenticated. The fruits were shade dried at room temperature and ground to course powder then extracted with ethanol by Soxhlet's extraction method. The extract was concentrated using rotary flash evaporator and percentage yield was found to be 23.89.

Preliminary Phytochemical Test.[12]
Preliminary phytochemical screening of the test extract was carried out for the detection ofphytoconstituents reported in the literature.
The Wistar albino rats of (150-200 g) and Swiss albino mice (20-25g) either sex were used in the experimentation. **IAEC approval No. bldeascop/IAEC/2023/04.**

Acute toxicity study (LD50) [13]
The acute toxicity (LD50) of EELAF was determined according to the OECD guideline number 423. The female albino mice weighing 20-25 g were fasted overnight prior to experiment. The screening doses i.e. 100, 250 and 500 mg/kg body weight were selected for the cardioprotective activity.

Evaluation of *Luffa acutangula* fruits extract for cardioprotective activity against Isoproterenol induced myocardial infarction. [14]

Group 1 -Normal control-Received distilled water.
Group 2 -Cardiac control- ISO 85mg/kg, S.C
Group 3 -Standard- Ascorbic acid 20mg/kg body weight.
Group 4 -EELAF 100 mg/kg body weight.

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Group 5 -EELAF 250 mg/kg body weight.
Group 6 -EELAF 500 mg/kg body weight.
The animals were divided into six groups containing six animals each. Group 1 animals received distilled water for 30 days. Group 2 animals administered with distilled water for 30 days and ISO 85 mg/kg on 28th and 29th day. Group 3 animals received Ascorbic acid 20 mg/kg for 30 days and ISO on 28th and 29th day. Group 4, 5 and 6 animals received various doses of EELAF such as 100, 250 and 500 mg/kg respectively for 30 days and ISO on 28th and 29th day. On day 31st animals were anaesthetized using Ketamine 100 mg/kg then those animals were placed in the Biopac. MP-46 instrument to record electrocardiogram (ECG), Blood pressure (BP), and Heart rate (HR). Immediately after measuring all parameters the blood was withdrawn from retroorbital plexes and was collected in tubes for the estimation of biochemical parameters such as Creatine kinase (CK), Lactate Dehydrogenase (LDH) and Aspartate amino Transferase (AST). Later all the animals were scarified by over dose of ketamine, the heart was dissected out. Half of the heart was used for estimation of MDA and GSH content and remaining half portion was used for histopathological studies.

4. Results

Phytochemical investigation on ethanolic extract of *Luffa acutangula* fruits revealed the presence of alkaloids, flavonoids, phenols and tannins.

1.1. Acute toxicity study

The ethanolic extract of *Luffa acutangula* fruits did not cause any mortality of animals and found to be safe at a dose of 5000 mg/kg. Therefore, 2500 mg/kg was taken as LD_{50} cutoff value as per fixed dose method of OECD guideline number 423.

The screening doses selected for the evaluation of cardioprotective activity of the test extract were:
100 mg/kg - 1/25th dose of LD_{50} cut off value, 2500 mg/kg b.w.
250 mg/kg - 1/10th dose of LD_{50} cut off value, 2500 mg/kg b.w.
500 mg/kg - 1/5th dose of LD_{50} cut off value, 2500 mg/kg b.w.

1.2. Cardioprotective activity

Effect of EELAF on Blood pressure and heart rate:

Exposure of experimental animals to isoproterenol significantly elevated the systolic blood pressure and heart rate and decreased the diastolic blood pressure as compared to normal control animals. The administration different doses of EELAF (100, 250, and 500 mg/kg) attenuated the altered the blood pressure and heart rate when compared the Iso control animals in dose dependent manner. It was observed that the protective effect of test extract at a dose of 500 mg/kg found to be nearer to that of standard drug ascorbic acid. It results were tabulated in table 1.

Effect of EELAF on ECG Pattern:

The administration isoproterenol to the cardiac control animals showed an increase in ST segment, prolongation of P waves, QRS complex, and RR interval when compared to normal control animals. Ascorbic acid and various doses of EELAF treatment decreases the ST segment, P waves prolongation, QRS complex, and RR interval as compared to cardiac control animals.

Effect of EELAF on serum enzymes and biomarker:

Rats intoxicated with Isoproterenol exhibited significant elevation in the serum levels of AST, CK and LDH as compared to normal group. Administration of graded doses of (100, 250 and 500 mg/kg) EELAF significantly reduced the elevated levels of AST, CK, LDH in a dose dependent pattern as compared to cardiac control rats. The results are showed in table 2.

Effect of EELAF on serum enzymes and biomarker:

On comparison of normal control group animals' data with the animals intoxicated with ISO showed a considerable decrease in GSH content and an increase in MDA content. The treatment of various dosages of EELAF and ascorbic acid significantly reversed the GSH and MDA levels in dose dependent manner as compared to cardiac control animals. The results are given in table 3.

Effect of EELAF on histopathology of heart tissue:

The histopathological examination of normal control animals exhibited normal heart structure with free of infractions, congestion, bleeding, fibrosis, inflammation and myocyte size. The isoproterenol treated animals exhibited increased infraction, congestion, bleeding, fibrosis, myocyte size and inflammation compared to normal control animals. In comparison to rats treated with isoproterenol, treatment with ascorbic acid and varying doses of EELAF (100, 250, and 500 mg/kg) resulted in reduction of infraction, congestion, bleeding, fibrosis, myocyte size and inflammation in dose-dependent manner. The pictures of histopathological studies were indicated in figure

5. Discussion

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The present study was designed to carry out the role of EELAF on ISO induced myocardial infraction in experimental animals. The action of ISO on the sarcolemma membrane, stimulation of adenylate cyclase, activation of Na+ and Ca+ channels, excessive Ca+ input, and energy consumption leading to cellular death are likely the causes of the induction of myocardial infarction in experimental animals.

The administration of ISO to the experimental animals caused increased systolic blood pressure due to inotropic and chronotropic effect on heart and decreased in diastolic blood pressure due to vasodilatory effect on blood vessels. The administration of EELAF at various doses decreased the systolic blood pressure and increased diastolic blood pressure. Further the ISO increases the heart rate because the ISO is a beta-adrenergic drug that activates the beta adrenergic receptors including beta 1 and beta 2 adrenergic receptors this increases the heart rate and force of contraction.

Rats given with ISO showed ECG changes was an indication of myocardial infraction.[15] In the present study we observed that an administration of ISO to animals caused a increased ST segment, prolongation of P waves, QRS complex, and RR interval. This could be due to myocardial necrosis, acute ischemic tissue injury, infraction, loss of cell membrane accelerated by ISO.[16] The pre treatment with different doses of EELAF showed a protective effect against ISO mediated myocardial infraction and altered pattern by protecting the cell membrane.

The rats administered with ISO caused a myocardial infraction which was evidenced by marked increase in the levels of serum CK, LDH and AST indicate cardiac muscular damage which may be due to leakage of these enzymes from the heart into blood stream.[17]

CK is an important enzyme in the diagnosis of myocardial injury because the marked abundance of this enzyme in the cardiac tissue and its sensitivity. This enzyme helps in the early detection of Myocardial infraction.[18] In our study also the administration of ISO to the experimental animals caused a increased CK in the serum might be due to cardiac damage induced by ISO. The treatment with different doses of EELAF decreased the serum CK significantly.

The LDH and AST are the cytosolic enzymes, which were essentially present in all the tissues and are involved various metabolic processes. These enzymes found high in concentration in heart. Hence the detection of elevated levels of these enzymes has become an diagnostic criteria for determination of cardiac damage. In the present study, we have observed that an increase in the LDH and AST in iso treated animals which is supported by previous study. Pretreatment of EELAF in experimental rats significantly reduced the levels of serum LDH and AST. This could be due to protective effect of EELAF in myocardium by preventing the leakage of LDH and AST.

The increased level of LPO in the heart tissue is an indication of oxidative damage of the myocardium and is corelated with the increased generation of reactive oxygen species (ROS) as result od auto oxidation by ISO, which is responsible for altering the membrane integrity and decreasing the activity antioxidant defence system.[19] In our study the animals treated with ISO showed significantly elevated levels of MDA, indicating LPO over activity.

However, pretreatment with EELAF significantly decreased the levels of LPO in ISO induced rats and confirmed the protection to the heart tissue may be due to free radicle scavenging activity of EELAF. The oxidative stress induces cardiac damage, which was confirmed by decreased levels of cellular antioxidant enzyme GSH.[20]

The endogenous antioxidant enzymatic defence plays an important role in neutralizing the oxygen free radicle mediated tissue injury.[21] GSH the primary free radicle scavenging enzyme involved in first line cellular defence against oxidative injury by removing the oxygen and hydrogen peroxide before they can interact to form more reactive hydroxyl radicals.[22] In this study, decreased activity of GSH level in the ISO treated rats was observed which may be attributed to the increased generation of ROS. The treatment of EELAF ameliorated level of GSH in the cardiac tissue. In histopathological studies the normal control animals showed normal appearance of heart without any histopathological alterations, but ISO treated animals exhibited increased necrosis, congestion, hemorrhage, fibrosis, size of myocytes and inflammation. The treatment of various doses of EELAF restored the altered pattern of heart compared to ISO treated animals.

Previous studies have asserted that an antioxidant rich medicinal plant extract has cardioprotective properties.[10] The fruits extract from *Luffa acutangula* has also been shown to have antioxidant properties, which may be the cause of the cardioprotective effect shown in this investigation. It has been found that the plant extract contains triterpenoids, flavonoids, and tannins that have strong antioxidant and/or cardioprotective effects.[11] By comparing the results obtained from the present investigation and previous literature, EELAF also exhibited the antioxidant property and presence of flavonoids and tannins this could be the reason for cardioprotective activity against isoproterenol induced myocardial infraction.

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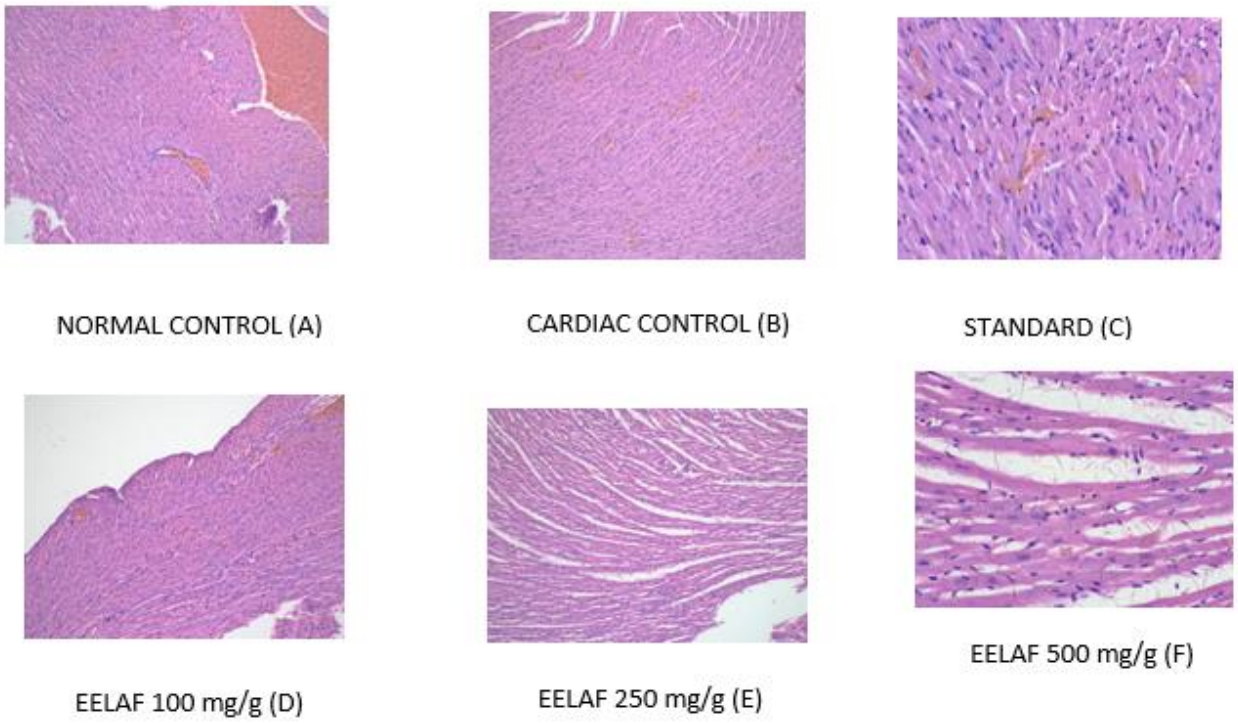

Table 01: Effect of EELAF on Blood Pressure and Heart Rate

Group (n=6)	Treatment	Blood Pressure (mmHg)		Heart Rate Per minute
		Systolic	Diastolic	
I	Normal control	110 ± 8	80 ± 8	390 ± 7.0
II	Cardiac control (ISO)	192 ± 8$^{@}$	105 ± 10$^{@}$	520 ± 5.3$^{@}$
III	Standard (ASC+ISO)	120 ± 9***	90 ± 9***	316 ± 8***
IV	EELAF (100 mg/kg p.o)	150 ± 8*	90 ± 5*	492 ± 8**
V	EELAF (250 mg/kg p.o)	138±2**	106±10*	443± 6**
VI	EELAF (500 mg/kg p.o)	121±8**	135±6*	308 ± 8***

The values are expressed as Mean ± SEM, (n=6), where, @p<0.001, *p< 0.05, ** *p*< 0.01, *** *p*< 0.001 as compared to cardiac control.

Table 02: Effect of EELAF on serum enzyme and biomarker (AST, LDH, CK)

Group (n=6)	Treatment	AST (IU/L)	LDH (IU/L)	CK (IU/L)
I	Normal control	156 ± 1.43	112 ± 2.95	82.3 ± 2.6
II	Cardiac control (ISO)	286.4 ± 2.5$^{@}$	307 ± 3$^{@}$	174.2 ± 1.8$^{@}$
III	Standard (ASC+ISO)	164.5 ± 2.3**	114.8 ± 3.5**	107.0 ± 1.2**
IV	EELAF (100 mg/kg p.o)	265.2 ± 1.9***	285.2 ± 5.1*	85.8 ± 1.7**
V	EELAF (250 mg/kg p.o)	208.8 ± 4.5***	198.4 ± 4.3**	72 ± 2**
VI	EELAF (500 mg/kg p.o)	177.7 ± 3.6***	93.4 ± 1.6**	60.5 ± 1.0**

The values are expressed as Mean ± SEM, (n=6), where, @p<0.001, *p< 0.05,** *p*< 0.01, *** *p*< 0.001 as compared to cardiac control.

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Table 03: Effect of EELAF on tissue GSH and MDA

Group (n=6)	Treatment	GSH (U/mg protein)	MDA (U/mg protein)
I	Normal control	97.15 ± 1.7	15.5 ± 1.3
II	Cardiac control (ISO)	28.2 ± 1.5$^{@}$	62.13 ± 2.3$^{@}$
III	Standard (ASC+ISO)	92.12 ± 1.6***	43.4 ± 1.71***
IV	EELAF (100 mg/kg p.o)	43.2 ± 1.32***	41.8 ± 1.2**
V	EELAF (250 mg/kg p.o)	66.51 ± 1.51***	35.37 ± 1.1**
VI	EELAF (500 mg/kg p.o)	89.84 ± 1.22**	27.43 ± 0.95***

Values are expressed as Mean ± SEM, (n=6), where, @p<0.001, *p<0.05, ** $p< 0.01$, *** $p< 0.001$ as compared to cardiac control.