Effect of *Tinospora cordifolia* (Guduchi) root extract on cardiotoxicity in streptozotocin induced diabetic rats.

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ABSTRACT :

The aim of this study is to explore the effect of *Tinospora cordifolia* (Guduchi) on cardiotoxicity in streptozotocin induced diabetic rats.

All animals were divided into 8 groups of 5 animals each, fed with High fat diet (HFD) except the ones in Sham, NPD and NPD-C-I groups. Food and water intake were monitored daily at the same time during the experimental period. The Food Efficiency Ratio (FER) was calculated during the experiment period. All the animals were pretreated as per the treatment protocol. Streptozotocin; STZ (50mg/ Kg) was administered subcutaneously to induce the diabetes which was confirmed in all the administered groups by testing blood glucose level after 48 hours. Cardiotoxicity was induced by administering isoprenaline (85mg/Kg). Troponin was checked after 4-5 hours of second isoprenaline injection to confirm cardiac damage. At the end of the study the animals were weighed and then sacrificed with high dose of Diethyl ether. Blood samples were collected from retro-orbital plexus and were used for biochemical estimations. The hearts were excised immediately and were weighed. Photomicrographs were taken for gross examination rest of the hearts were kept in 10% Formalin solution for histopathological studies.

Pretreatment with *Tinospora cordifoli*a (200 mg/kg) showed very significant improvement against Streptozotocin induced diabetes ($p< 0.01$) as blood glucose level were found to be decreased when compared to the untreated D-HFD group. The Food efficiency ratio (FER) was found to be significantly increased when compared to D-HFD ($p<0.01$). Significant decrease in the elevated activities of the cardiac marker enzymes, viz, alanine transaminase (ALT) ($p < 0.01$), lactate dehydrogenase (LDH) ($p < 0.01$), creatinine kinase (CK-MB) ($p < 0.01$) and negative troponin test were observed. The observed results were further confirmed by histopathological findings which indicated that *Tinospora cordifolia* (200mg/Kg) shows highly significant reduction in cardiotoxicity and considerable improvement, compactly arranged muscle fibres with minimum interstitial tissue, long spindle shaped vascular nuclei and well marked muscles striations.The findings of this study indicate that *Tinospora cordifola* (Guduchi) root extract exerts potent cardioprotection against isoprenaline induced cardiotoxicity in diabetic rats. This effect is comparable with that of carvedilol and pioglitazone.

Keywords: Cardiac hypertrophy, Diabetes mellitus, Herbal drugs, High fat diet, Isoprenaline, Myocardial infarction.

INTRODUCTION

Cardiotoxicity is the occurrence of heart electrophysiology dysfunction or muscle damage. The heart becomes weaker and is not as efficient in pumping and therefore circulating blood [(1)].

Cardiac troponins are released from myocytes following myocardial damage and loss of membrane integrity. Their significance when diagnosing acute myocardial infarction is immense, e.g., their high sensitivity and specificity for myocardial tissue, the prognostic information they bear, and their role in risk stratification and therapeutic decisions. Toxic insults trigger a series of reactions in cardiac cells leading to measurable changes in myocardial morphology, biochemistry, and physiology. Mild injuries can be repaired; however, severe injuries lead to cell death in

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the form of apoptosis and necrosis. If the cell survives the insults, structural and functional adaptations take place [2].

Myocardial infarction or acute myocardial infarction (AMI) is the medical term for an event commonly known as a heart attack. It happens when blood stops flowing properly to part of the heart and the heart muscle is injured due to not receiving enough oxygen. Usually this is because one of the coronary arteries that supplies blood to the heart develops a blockage due to an unstable build up of white blood cells, cholesterol and fat. MI is usually characterised by symptoms like chest pain that is felt behind the breast bone and sometimes travels to the left arm or the left side of the neck [3, 4].

Streptozotocin is a naturally occurring chemical that is particularly toxic to the insulin-producing beta cells of the pancreas in mammals. It is used in medical research to produce an animal model for Type 1 diabetes in a large dose as well as Type 2 diabetes with multiple low doses. Streptozotocin is a glucosamine-nitrosourea compound. As with other alkylating agents in the nitrosourea class, it is toxic to cells by causing damage to the DNA, though other mechanisms may also contribute. DNA damage induces activation of poly ADP-ribosylation, which is likely more important for diabetes induction than DNA damage itself. Streptozotocin is similar enough to glucose to be transported into the cell by the glucose transport protein GLUT2, but is not recognized by the other glucose transporters [5, 6].

Isoprenaline or isoproterenol is a medication used for the treatment of bradycardia (slow heart rate), heart block, and rarely for asthma. It is a non-selective beta-adrenergic agonist and structurally similar to adrenaline. Isoprenaline has positive inotropic andchronotropic effects on the heart. Isoprenaline can produce an elevated heart rate (tachycardia), which predisposes cardiotoxicity in animal models [7].

T. cordifolia is mentioned in Ayurvedic literature as a constituent of several compound formulations used in general debility, dyspepsia, fever and urinary diseases. In the Ayurvedic system of medicine drug Guduchi or Amrita is mentioned in various classical texts, viz. *Charak, Sushrut* and *Ashtang Hridaya* and other treaties like *Bhava Prakash* and*Dhanvantari Nighantu* under other various names, viz. *Amara, Amritvalli, Chinnarrhuha, Chinnodebha* and *Vatsadani* etc [8].

Although various medicinal properties like antidiabetic, cardioprotective have been reported to be present in *T. cordifolia* but use of this herb in treatment of cardiac problems resulting due to persistent diabetes has not been done extensively. The herb has potent antidiabetic and cardioprotective role and so this work has been done to extensively study this herbal drug further for procurement of two current and major health problems-diabetes and cardiac disorder [9].

METHODS & MATERIALS

Procurement & Authentification of test material:

Dried whole plant of *Tinospora cordifolia* were purchased from the local market of Lucknow. The drug was authenticated by a botanist of National Botanical Research Institute Lucknow. A voucher specimen no NBRI/CIF/407/2013 has been deposited at the herbarium of Faculty of Pharmacy, Integral University, Lucknow, India.

Preparation of extract of test material:

Freshly collected *T.cordifolia* whole plant was dried under shade and the dried material were milled to obtain a coarse powder. The alcoholic extract of the powder were prepared by the process of continuous hot extraction method with Sohxlet apparatus. The solvent was evaporated and dried extract was obtained and used in study.

Drugs and chemicals:

Carvedilol and Pioglitazone were taken as marketed tablets by Sun pharmaceuticals ltd. (Cardivas and Pioglit respectively) procured from local market. Isoprenaline hydrochloride was purchased from Sigma Aldrich Co, St, Louis, USA and streptozotocin was purchased from M.P. Bio medicals ltd. All other chemicals are of analytical grade, purchased from Merck, SD Fine chemicals, Qualigens and Hi media Pharmaceuticals. The enzymatic kits purchased from Span Coget diagnostics and Merck specialities Pvt. Ltd.

Experimental Animals:

Male Sprague dowley (l00-150g) were used for this study. They were housed five each in sanitized polypropylene cages containing paddy husk as bedding under standard laboratory conditions at room temperature (23° C± 2° C) with 12 h light / dark cycle and were randomized into different groups. They had free access to standard pellets as basal diet and water ad libidum. Ethical clearance was obtained from Institutional Animal Ethical Committee (IAEC). The approval no. is IU/Parm/M.Pharm/IAEC/14/02 Faculty of pharmacy Integral University, Dasauli, P.O. Bas-ha Kursi Road; Lucknow – 226026 (U.P).

Experimental protocol:

A total of 40 animals were used, divided into 8 groups containing 5 animals each. All animals were fed with HFD except the ones in Sham, NPD and NPD-C-I groups. Food and water intake were monitored daily at the same time during the experimental period. The Food Efficiency Ratio (FER) was calculated during the experiment period. All the animals were pretreated as per the plan given under treatment protocol. Streptozotocin; STZ (50 mg/kg) was administered subcutaneously on the 4th day of study after 24 hours of fasting in all groups except in Sham and NPD-C-I groups. Diabetes was confirmed in all the administered groups by testing blood glucose level after 48 hours. Cardiotoxicity was induced by administering isoprenaline (85mg /Kg) subcutaneously on 12th and 13th day of study in all groups except Sham. Troponin was checked after 4-5 hours of second isoprenaline injection. The high fat diet was prepared according to the method given in the paper by *Vijaya et al.*[10-17]

***Group I-Sham*:** Rats were administered with normal saline instead of STZ.

***Group II-Diabetic-Normal pellet diet Control (D-NPD)*:** Rats were administered with STZ (50mg/kg i.p.) and fed with NPD throughout the study period (14 days) and isoprenaline (85mg/kg s.c.) administered at the interval of 24 hours on the12th and 13th day of study.

***GroupIII-Diabetic High Fat Diet Control (D-HFD)*:** Rats were administered with STZ (50mg/kg i.p.) and fed with HFD along with NPD throughout the study period (14 days) and isoprenaline (85mg/kg s.c.) administered at the interval of 24 hours on the12th and 13th day of study.

***Group IV-NPD control-Isoprenaline challenged (NPD-C-I)*:** Rats were fed with NPD throughout the study period (14 days) and isoprenaline (85mg/kg s.c.) administered at the interval of 24 hours on the 12th and 13th day of study.

***Group V- Pioglitazone treated (10mg/Kg)*:** Rats were administered with STZ (50mg/kg i.p.) along with *pioglitazone* (0.5 ml/day,p.o.) and fed with HFD + NPD and pretreated throughout the study period (14 days) then isoprenaline (85mg/kg s.c.) administered at the interval of 24 hours on the12th and 13th day of study.

***Group VI- Carvedilol treated (2mg/Kg)*:** Rats were administered with STZ (50mg/kg i.p.) along with *carvedilol* (0.5 ml/day,p.o.) and fed with HFD + NPD and pretreated throughout the study period (14 days) then isoprenaline (85mg/kg s.c.) administered at the interval of 24 hours on the12th and 13th day of study.

***Group VII-Tinospora cordifolia treated (100mg/Kg)*:** Rats were administered with STZ (50mg/kg i.p.) along with *T. cordifolia* extract (0.5 ml/day,p.o.) and fed with HFD + NPD and pretreated throughout the study period (14 days) then isoprenaline (85mg/kg s.c.) administered at the interval of 24 hours on the 12th and 13th day of study.

***Group VIII-Tinospora cordifolia treated (200mg/Kg)*:** Rats were administered with STZ (50mg/kg i.p.) along with *T. cordifolia* extract (0.5 ml/day,p.o.) and fed with HFD + NPD and pretreated throughout the study period (14 days) then isoprenaline (85mg/kg s.c.) administered at the interval of 24 hours on the 12th and 13th day of study.

At the end of the study the animals were weighed and then sacrificed with high dose of Diethyl ether. Blood samples were collected from retro-orbital plexus / cardiac puncture and were allowed to clot for 30 minutes at room temperature. The serum was then separated by centrifugation at 3000 r.p.m at 30 degree celsius for 15 minutes and was used for estimations. The heart was excised immediately and rinsed with normal saline, blotted with filter paper and were weighed. Photomicrographs were taken for gross examination. Rest of the heart was kept in 10% Formalin solution for histopathological studies [18-20].

ESTIMATIONS

Blood glucose level:

Fasting Blood Glucose (FBG) was estimated both at the beginning of the study on day 0 as well as at the end of the study (day 14) by using a Glucometer.

Food Efficiency Ratio (FER):

FER was calculated as: Total body weight/Total food intake during the study period.

Heart weight: body weight ratio:

At the end of the study the animals were weighed and then sacrificed with high dose of Diethyl ether. The heart was excised immediately and rinsed with normal saline, blotted with filter paper and were weighed. Heart weight: body weight ratio was calculated according to the following formula;

$$\text{Heart weight} \times 10^3 / \text{Final body weight}$$

Grading of heart:

Grading of heart was done by observing morphological changes seen with naked eyes according to the following criteria –

Grade 0 = No Lesion

Grade 1 = Inflammation, redness, capillary dilations

Grade 2 = Edema, yellowish ventricle portion

Grade 3 = Atrium & ventricle turns yellow, scar formation

Grade 4 = Diffuse heart, absolute scar formation, increased necrosis portion.

Estimation of Cardiac Marker Enzymes:

The cardiac marker enzyme Troponin was checked by enzymatic kit from Roche diagnostics (after 4-5 hours of second isoprenaline injection), other cardiac marker enzymes like, Alanine Transaminase (ALT) by Span Coget diagnostics' kit & Lactate Dehydrogenase (LDH) and Creatinine Kinase (CK-MB) were also estimated by commercially available kits from Merck Specialities Pvt. Ltd. according to the procedures given in the leaflets provided with kits.

Histopathological Studies:

The myocardial tissue was immediately fixed in 10 % buffered neutral formalin solution. After fixation, tissues were embedded in paraffin and serial sections of 5-6 µm were cut and each section was stained with haematoxylin and eosin. The slides were examined under light microscope and photomicrographs were taken. Histopathological studies were done from RS Diagnostics centre, Lucknow.

STATISTICAL ANALYSIS

Data were expressed as mean ± standard error of mean (SEM, n = 5). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Turkey's t- test with the aid of GraphPad Prism Instat Software (version 5.0, USA). $P < 0.01$ was considered statistically significant.

RESULTS

Blood Glucose level:

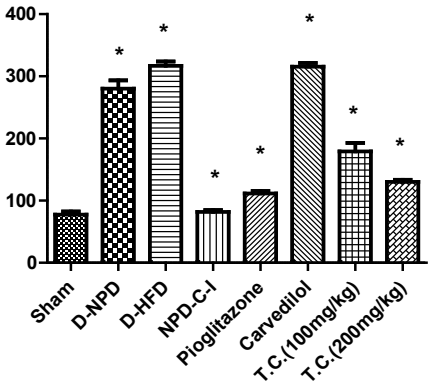

Figure 1: Effect of ethanol extract of *Tinospora cordifolia* on final blood glucose level. [All values are expressed as mean ± SEM for n= 5 animals. *= p<0.01 when D- NPD compared with Sham, D-HFD compared with D-NPD, Pioglitazone and both test extracts compared with D-HFD followed by Tukey's t-test

Food Efficiency ratio (FER):

Groups SNO	Sham	D-NPD	D-HFD	NPD-C-I 85mg/Kg	Pioglitazone 10mg/Kg	Carvidilol 2 mg/kg	*T.cordifolia* 100mg/kg	*T.cordifolia* 200mg/kg
1	5.5	2.21	3.83	4.26	6.74	3.07	4.80	4.87
2	5.6	2.03	3.56	4.37	6.55	3.00	4.34	4.83
3	5.7	1.88	4.21	4.57	7.02	3.54	5.44	5.02
4	6.2	1.85	3.97	4.81	6.96	3.26	5.01	4.70
5	6.7	2.28	4.16	4.70	7.50	3.45	5.38	5.31
Mean*± SEM	5.94 ±0.22	2.05 ±0.07	3.94 ±0.11	4.54±0.10	6.95 ±0.15	3.26 ±0.10	4.99 ±0.20	4.94 ±0.10

Table 1: All values are expressed as ± SEM calculated by one way ANOVA (n=5). *= p<0.01 when D- NPD compared with Sham, D-HFD compared with D-NPD, Pioglitazone and both test extracts compared with D-HFD followed by Tukey's t-test.

Heart weight: Body weight ratio:

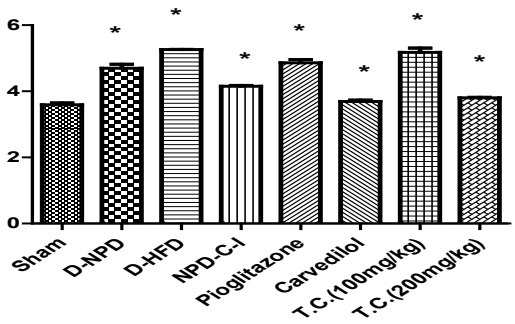

Figure 2: Effect of ethanol extract of *Tinospora cordifolia* on Heart weight: body weight ratio. [All values are expressed as mean ± SEM for n= 5 animals. *= p<0.01 when D- NPD compared with Sham, D-HFD compared with D-NPD, Pioglitazone and both test extracts compared with D-HFD followed by Tukey's t-test]

Assessment and grading of heart:

Groups	Grading of cardiac Damage
Sham	Grade 0
D-NPD	Grade3
D-HFD	Grade 4
Normal-Isoprenaline treated (85mg/Kg)	Grade 3
Pioglitazone (10mg/Kg/day)	Grade 2
Carvidilol (2 mg/kg)	Grade 1
Tinospora cordifolia (100mg/kg)	Grade 3
Tinospora cordifolia (200mg/kg)	Grade 2

Table 2: Grading of hearts

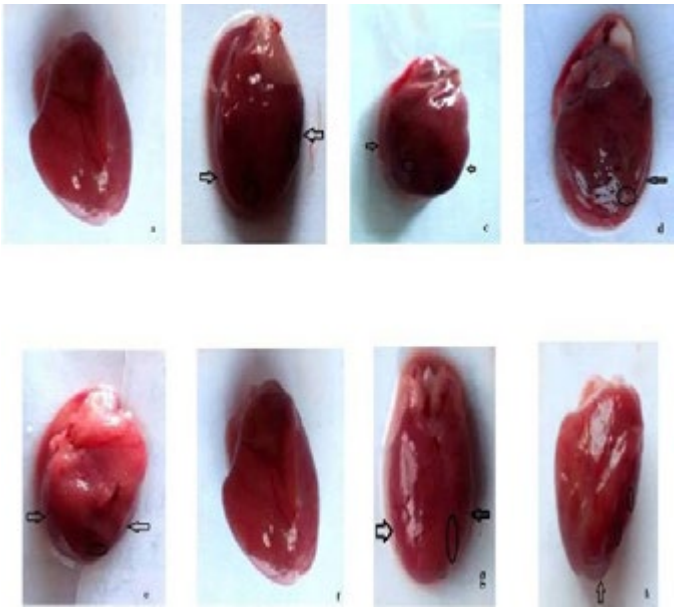

Figure 3: Photomicrographs of assessment and grading of hearts of different experimental group (a) Sham (b) D-NPD (c) D-HFD; (d) NPD-C-I (e) Pioglitazone (10mg/Kg)treated heart (f) Carvedilol (2 mg/kg) treated heart (g) *Tinospora cordifolia* (100 mg/kg) treated heart (h) *Tinospora cordifolia* (200 mg/kg) treated heart.

Effect on cardiac marker enzymes:

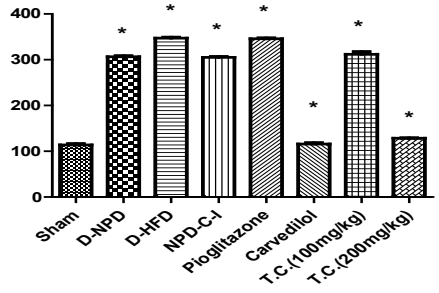

Figure 4.1 Alanine aminotransferase

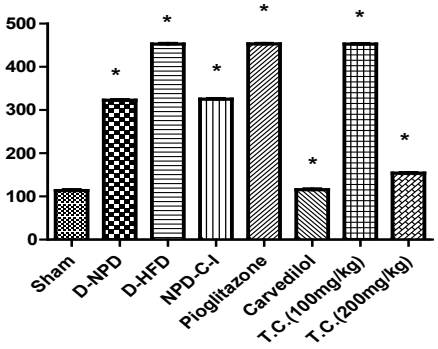

Figure 4.2 Lactate dehydrogenase

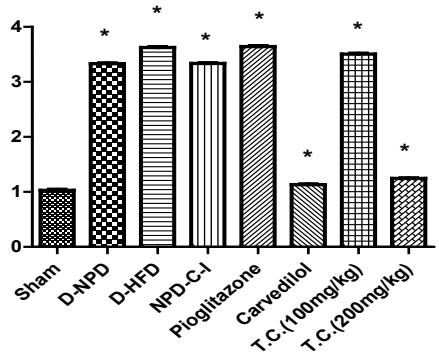

Figure 4.3 Creatinine kinase-Myoglobin

Figure (4.1-4.3): Effect of ethanol extract of *Tinospora cordifolia* on various cardiac marker enzymes(ALT, LDH & CK-MB). All values are expressed as ± SEM (n=5).
*= p<0.01 when D- NPD compared with Sham, D-HFD compared with D-NPD, Carvedilol and both test extracts compared with D-HFD as calculated by one way ANOVA followed by Tukey's t-test.

Groups SNO	Sham	D-NPD	D-HFD	NPD-C-I 85mg/Kg	Pioglitazone 10mg/Kg	Carvidilol 2 mg/kg	*T.cordifolia* 100mg/kg	*T.cordifolia* 200mg/kg
1	-ve	+ve	+ve	+ve	+ve	-ve	+ve	-ve
2	-ve	+ve	+ve	+ve	+ve	-ve	+ve	-ve
3	-ve	+ve	+ve	+ve	+ve	+ve	+ve	-ve
4	-ve	+ve	+ve	+ve	+ve	-ve	+ve	+ve
5	-ve	+ve	+ve	+ve	+ve	-ve	-ve	-ve

Table 3: Effect of *Tinospora cordifolia* pretreatment on cardiac marker enzyme- Troponin in Isoprenaline induced cardiotoxicity
Where +ve means presence of enzyme and –ve means absence of enzyme

Histopathological Studies:

Histopathological studies were done from RS Diagnostics centre, Lucknow. Photomicrographs of rat heart of sham group shows, minimum interstitial tissue, long spindle shaped vascular nuclei, muscle striation well marked, few small blood vessels and minimum fibro fatty tissue. There were no muscular hypertrophy or evidences of necrosis and/or round cell infiltrates in sham. Photomicrograph of rat heart of isoprenaline and streptozotocin treated groups (NPD-C-I, D-NPD and D-HFD) show muscle fibres loosely arranged with fragmentation and increased interstitial tissue, long spindle shaped vascular nuclei with occasional large plump whereas standard drugs and *Tinospora cordifolia* (200mg/kg) treated groups show considerable improvement, compactly arranged muscle fibres with minimum interstitial tissue, long spindle shaped vascular nuclei, muscles striations well marked. H & E stain was used. All photomicrographs were taken on 10 x and 40 x.

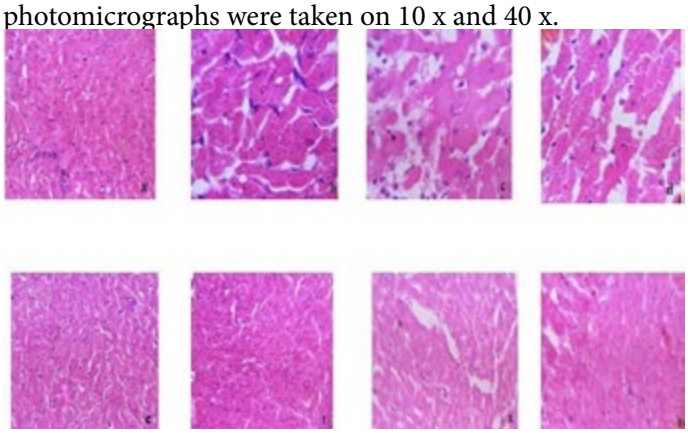

Figure 5 (a- g) Photomicrographs of histopathology of rat's hearts of different group

a. Sham b. D-NPD c. D-HFD d. NPD-C-I e. Carvidilol f. Pioglitazone
g. *Tinospora cordifolia* (100 mg/kg) h. *Tinospora cordifolia*(200 mg/kg)

DISCUSSION

In the traditional Indian medicinal system, there are various herbs and plants that are known to possess cardioprotective and antidiabetic properties but unfortunately have failed to attract much research on them to justify their potential scientifically. One such herb being *Tinospora cordifolia* whose cardio protective and ant diabetic activity, specifically its root and stem extract, needs to be revealed with the help of thorough research [8,9].

The present study was conducted on a 14 day model in which the effect of *Tinospora cordifolia* extract was observed on isoprenaline induced cardiotoxicity in rats that were fed with high fat diet (HFD) and pretreated with STZ for induction of diabetes. STZ in presence of HFD induced potent diabetes and isoprenaline produced cardiotoxicity potently when compared with diabetic –normal pellet diet control (D-NPD) and isoprenaline control (NPD-C-I) groups respectively. Pretreatment with high dose of alcoholic extract of *Tinospora cordifolia* significantly prevented ISO induced myocardial damage/ hypertrophy in STZ induced non genetic type II diabetic rats when compared with 2 standard drugs – Carvedilol and Pioglitazone, which are clearly indicated by various estimations. ISO causes significant damage of myocardium, endocardium, hypertrophy and a significant increase in the levels of serum marker enzymes such as AST, ALT, CK, LDH, and Troponin-I 4-6 hrs after induction. This might be due to the damage in the heart muscle, rendering the leakage of enzymes in to the serum. The biochemical markers that are used widely in detection of myocardial necrosis are CK, LDH and transaminases. CK-MB has greater than 95 % sensitivity and specificity for myocardial injury when measured between 24-36 hrs. Estimation of elevated serum enzymes served a useful guide for necrosis of myocardium [18-25].

Animals were allocated into 8 different groups following two types of dietary regimen; Normal pellet diet (NPD) and High fat diet (HFD) to observe the effects of ISO and STZ in presence of each. One of the groups was given only STZ along with NPD (D-NPD) and the other was given only ISO along with NPD (NPD-C-I), whereas HFD group was administered both STZ followed by ISO to observe the combined effect of all the disease/problem potentiating factors. All the treated groups; both standard and test extracts followed both dietary regimen i.e. NPD as well as HFD. The treated groups were compared with D-HFD. NPD-C-I as well as D-HFD was compared to D-NPD. The Sham served as blank control comparable to all groups [17-20].

Present study shows that STZ elevates blood glucose level drastically in D-HFD due to the presence of all potentiating factors i.e., STZ and HFD. The low dose and high dose of *Tinospora cordifolia* extract (100 mg/kg and 200 mg/kg respectively) showed very significant improvement against Streptozotocin induced diabetes ($p < 0.01$)as blood glucose level were found to be less than the untreated D-HFD group [5,6].

The Food efficiency ratio (FER) is a parameter for assessment of induction of diabetes mellitus. Polyphagia (increased hunger) and polydypsia (increased thirst) which are symptoms of diabetes are assessed by FER. Pioglitazone treated group showed significant increase in FER when

compared to D-HFD (p<0.01) The low dose and high dose of *Tinospora cordifolia* extract (100 mg/kg and 200 mg/kg respectively) also showed significant increase against FER of D-HFD (p< 0.01) however it was not as improved as that of standard (p<0.01) [21,22] .

Isoprenaline induced significant myocardial damage as compared to normal rats as grading shows shifts from grade zero to four .*Tinospora cordifolia* test extract high dose shows more cardioprotective activity compared to streptozotocin damaged group as it shows shift from grade 4 to grade 2 while low dose of test extract shows low cardioprotective activity compared to high dose as it shows shift from grade 4 to grade 3 compared to Streptozotocin damaged group. The heart weight body weight ratio is a very important parameter of cardiac hypertrophy. *Tinospora cordifolia* extract (100 mg/kg) doesn't show significant protective effect (p<0.01) but *Tinospora cordifolia* (200 mg/kg) showed very significant cardioprotection against isoprenaline induced damage (p< 0.01) [7] .

Evaluation of biochemical parameters was done by assessment of various enzymatic factors like Alanine aminotransferase (ALT), Creatinine kinase-myoglobin (CK-MB) and Lactate dehydrogenase (LDH) and the gold marker of cardiac damage i.e., Troponin-T/I. The level of these cardiac marker enzymes were found to be most elevated in diabetic high fat diet group (D-HFD) clearly due to the presence of all potentiating factors i.e., STZ, ISO and HFD. *Tinospora cordifolia* extract (100 mg/kg) doesn't show significant protective effect {(ALT (p<0.01), CK-MB (p<0.01), LDH (p<0.01)} but *Tinospora cordifolia* (200 mg/kg) showed very significant cardioprotection against isoprenaline induced damage in streptozotocin induced diabetes {ALT (p<0.01), CK-MB (p<0.01), LDH (p<0.01)} [21-29]

The cardiotoxic and diabetic groups show positive troponin test whereas the pretreatment groups such as standard drugs and *Tinospora cordifolia* (200 mg/kg) treated groups show significant protection and negative troponin test.

The myocardial damage was also clearly assessed by various cardiac marker enzymes. Isoprenaline causes significant myocardial damage compared to normal rats for various enzymes like ALT (p< 0.01), LDH (p<0.01), CK-MB (p< 0.01), which was clearly seen by various cardiac marker enzymes.

The histopathological reports clearly reveal that ISO along with diabetes causes potent myocardial damage compared to sham and pretreatment group i.e., standard and *Tinospora cordifolia* (200mg/kg) show significant protection against ISO + diabetes induced cardiac damage.The standard drugs and *Tinospora cordifolia* (200mg/kg) treated groups show considerable improvement, compactly arranged muscle fibres with minimum interstitial tissue, long spindle shaped vascular nuclei, muscles striations well marked[27-29] .

All these results were compared and found similar against two clinically established standard drugs Carvidilol (2 mg/kg) and Pioglitazone (10mg/kg).

CONCLUSION

Thus the evaluation of various parameters and comparison of the test extracts with that of standard shows and justifies the significant role of *Tinospora cordifolia* as a cardioprotective drug. The plant extract was found to be not only effective as an antidiabetic but also in cardiotoxicity induced by isoprenaline. The present study concludes with few observations and results. The first aspect of the study is that high fat diet along with STZ induced diabetes is a very suitable, potent and short term model for evaluating the cardiotoxicity in diabetic rats. The second aspect of study is, ISO causes cardiotoxicity more potently in diabetic rats as compared to non diabetic rats which is clearly parallel to the clinical existence. The third aspect of study related to the protective effect of alcoholic extract of *Tinospora cordifolia* which shows potent protection at high dose (200mg/kg) against Isoprenaline-induced cardiotoxicity in STZ induced non-genetic type II diabetic rats which is comparable to clinically established standard drugs i.e., pioglitazone (10mg/kg) and carvedilol (2mg/kg).

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