Int. J. Pharm. Investigation, 2023; 13(1):22-27.
www.jpionline.org

Original Article

Cardioprotective and Hepatoprotective Effects of *Ixora pavetta* and *Tecoma capensis* Leaf Extracts

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ABSTRACT

Background: *Ixora pavetta* and *Tecoma capensis* are two less explored and neglected plants species in medicinal prospective. The flowers bark and root of *I. pavetta* used as a remedy for cough, anaemia, women urinary problems. The bark powder of *Tecoma capensis* useful in treating fever, pneumonia, stomach problems and improve blood clotting. The role of leaves from these plants in medical practices is not yet clearly determined. The present work aimed to examine the potentiality of their leaf extracts in treating cardiovascular and chronic liver diseases. **Materials and Methods:** Solvent extraction method is used to extract the bioactive components. The leaf extracts were tested for the existence of cardiac glycosides. The cardioprotective activity and hepatoprotective activity were done using isoproterenol method and MTT assay respectively. **Results:** The leaf extracts of both plants showed the presence of cardiac glycosides and the leaf extracts of *T. capensis* recorded a high yield of cardiac glycosides. Leaf methanolic extract (200 mg/kg) of *T. capensis* exhibited significant depletion in total cholesterol 108.11 mg/dL, tryglcerides 81.48 mg/dL and LDL cholesterol 93.15 mg/dL in Wistar rats. The *I. pavetta* leaf methanolic extracts recorded moderate protective activity by increasing the concentrations against H_2O_2 pre-stimulated HepG2 cells. **Conclusion:** The extracts of both plants exhibited good cardioprotective activity and hepatoprotective activity. The leaf methanolic extracts of *T. capensis* reported more cardioprotective activity whereas the leaf methanolic extracts of *I. pavetta* showed significant hepatoprotective potentiality.

Keywords: Cardiac glycosides, Bioactive compounds, Cholesterol, Triglycerides, HepG2 cells.

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Received: 10-06-2022;
Revised: 02-09-2022;
Accepted: 12-10-2022.

INTRODUCTION

Heart and liver are the two most important organs of the body. Former acts as the pumping machine to supply oxygen and nutrients to the entire body and later functions to remove the toxins in the blood supply. Diseases of the heart and liver lead to deterioration of life qualitatively and quantitatively.

Risks of cardiac diseases are increasing world widely.[1,2] Around 1/4th of the world populations left their lives due to cardiovascular diseases (CVDs), and it is estimated to be17.9 million people. Of these CVDs deaths, more than 3/4th are from developing countries due to lack of proper medication. The imbalance between coronary blood supply and demand leads to myocardial infarction (MI)[3] (Manzoor 2022) and MI is the major reason for the human death. It happens due to insufficient blood supply to heart tissue, resulting in a condition known as ischemia. The symptoms of cardiovascular diseases (CVD) include hike in total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) cholesterol and reduced concentration of high-density lipoprotein (HDL) cholesterol.[4]

On the other side the loss of lives due to liver damage are also increasing year by year.[5] Liver is considered as the most important organ of the human body and plays prominent role in various biochemical pathways of growth, energy supply followed by reproduction. Apart from this liver also acts as a powerful agent of detoxification and homeostasis.[6-8] Damage to liver tissue results in failure of the metabolic activities followed by increased levels of triglycerides and cholesterol.[9] India alone is victim for 18.3% chronic liver diseases (CLDs) of the world[10] which is comparatively higher than the other Asian countries (WHO).[5,11] The rapid change in eating and drinking habits of the Indian population due to globalization tends the people of India fall for the CLDs such as alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD).[12,13]

Plants are an important source of traditional medicine used to treat various ailments. Around 422,000 flowering plants have been identified globally, of which above 12% are considered as essential for medical use. Often India is considered the Medicinal Garden of the World due to its species richness and diversity.[14,15]

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DOI: 10.5530/223097131566

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Herbal remedies are commonly used as an alternative to allopathic medicine, and they are less harmful than to the synthetic medicines.[16] The usage of medicinal plants against cardiac and liver ailments is increasing in recent trends.[17-19]

Ixora pavetta (Torchwood tree) and *Tecoma capensis* (Cape Honeysuckle) are grows luxuriantly in India. The *I. pavetta* flowers and bark used to treat the coughs and anaemia whereas the fruit and root decoction is used as remedy for the women urinary problems. *Tecoma capensis* bark powder is used to treat fever, pneumonia and stomach problems along with treating bleeding gums to improve blood clotting. There are no reports available on the comparative study of these two medicinal plants. So, an attempt was made to evaluate the biological potentiality of these plants leaf extracts in treating cardiovascular and chronic liver diseases.

MATERIALS AND METHODS

Healthy and fresh plants of *Ixora pavetta* and *Tecoma capensis* growing at Herbal Garden of Acharya Nagarjuna University, Nagarjunanagar, Andhra Pradesh, India are selected for the present study. Acharya Nagarjuna University is located between 16.3818[II] and 80.5329[II] latitudes and longitudes respectively. The study site is having a mean annual rainfall of approximately 906 mm, which mainly occurs between July to October and the mean air temperature ranges from 26.0° to 28.5°C. These plants were identified and authenticated (ANUBH01194, ANUBH01195) by the Plant Taxonomy Laboratory, Faculty of Botany and Microbiology, Acharya Nagarjuna University. The samples were graded and washed with double distilled water. Later the leaf samples were subjected to shade dry followed by grounding and sieving (0.25 mm).

Solvent Extraction

Methanol can readily dissolve the polar organic substances present in the leaf samples and so it was selected for the extraction. Powdered leaf material (150 g) was soxhlet extracted with methanol (80%) for 12-18 hr. The crude leaf methanolic extracts were subjected to evaporation (Vacuum rotary evaporator-model l, R-215; Buchi Labortech Ag) under diminished pressure. The dried samples were stored at 4°C until further use.

Cardiac Glycosides

Cardiac glycosides were determined using standard methods.[20] To the 8 ml of plant extract, 60 ml (H_2O) and 8 ml (12.5% $Pb[C_2H_3O_2]_{2+}$) were added, and thoroughly mixed followed by filtration. To precipitate the excess lead ion, to the 50 ml of the filtrate 8 ml of Na_2HPO_4 (47%) was added and filtered twice. From this purified filtrate 10 ml was treated with 10 ml Baljet reagent. A blank was run with 10 ml DH_2O and 10 ml Baljet reagent. After 1 hr colour intensity was determined calorimetrically at 495 nm. Glycosides content was measured using following formula.

$$\% \text{ Total gly cosides} = \frac{\text{Optical Density}}{77} \times 100$$

Cardio Protective Activity

Cardioprotective activity of the plant extracts was evaluated by Isoproteronol method.[21] Isoproteronol (ISO) is a synthetic catecholamine and β-adrenergic agonist which shows the dreadful impact on the heart muscle and myocardial necrosis. On the other side ISO also causes hike in LDL cholesterol in the blood, which further causes coronary arteries blockage favouring CVD.[22] *Wistar* rats (200-250 g) were used in the current study. The rats were provided with standard laboratory feed and water. Before 5 days of the cardiotoxicity test animals were adapted to the laboratory conditions.

Experimental Design

The *in vivo* cardioprotective activity of plant extracts was evaluated against isoproteronol-induced Cardiotoxicity. Forty-two male *Wistar* rats were divided into 4 groups of 6 animals in each group. The 4th group was again categorized into 4 subgroups' containing 6 rats for each subgroup. And the isoproteronol was administered to the rats as follows (Table 1).

Biochemical Assessment

The levels of serum triglycerides (TGs) and total cholesterol (TC) were determined using Erba Diagnostics (Mumbai) Kit.[23] For determining the high-density lipoprotein cholesterol (HDL) Siemens diagnostics Ltd., India Kit was used.[24] Low-density lipoprotein-cholesterol (LDL) determined according to the formula LDL = TG/5.[25,26]

Histopathological studies

On the 14th day of experiment, rats were subjected to scarification and dissected for hearts. Dissected hearts were washed in ice-cold saline solution. Immediately myocardial tissue fixed in 10% formalin solution. Later fixed myocardial tissues were implant in paraffin wax and serial sections of 4-5 µm thick were prepared.

Table 1: Administration of isoproteronol to the *Wistar* rats.

Group	Treatment	Days
Group-I	Normal saline (0.9% w/v)	14
Group-II	Isoproteronol (3 ml/kg, i.p)	Only on 14th day
Group-III	Verapamil (10 mg/kg)	14
Group-IVa	*I. pavetta* methanolic extract (100 mg/kg)	14
Group-IVb	*I. pavetta* methanolic extract (200 mg/kg)	14
Group-IVc	*T. capensis* methanolic extract (100 mg/kg)	14
Group-IVd	*T. capensis* methanolic extract (200 mg/kg)	14

*On 14th day isoproteronol and plant extracts were given 1 hr before isoproteronol treatment.

Anatomical sections were stained with hematoxylin, eosin and were observed under light microscope.

Hepatoprotective Study by MTT Assay

Hepatoprotective activity of *Ixora pavetta* and *Tecoma capensis* methanolic leaf extracts were evaluated using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium reduction assay assay.[27]

Maintenance of Cell Lines

The HepG2 (Human hepatocellular adenocarcinoma cell line) obtained from NCCS (Pune, India). High Concentrated glucose media mixed with 10% (FBS) 1% (antibiotic) provided with 5% (CO_2), 18-20% (O_2) and 37°C was used to maintain the cell lines. The cells were sub cultured for every 48 hr interval.

Procedure

To the 96 well plate (20,000 cells per well), 200 µl of cell suspension was seeded without the test agent. Cells were left for 24 hr incubation. Toxicity is induced to the cells with 100 uM of H_2O_2 to all the wells except blank, untreated wells and incubated for 4 hr. After incubation period, required concentrations of *I. pavetta* and *T. capensis* methanolic leaf extracts and standard control sylimarin was added and the plates were left for 24 hr incubation in a 5% CO_2 atmosphere at 37°C. Later the medium is provided with MTT reagent to bring a final concentration of 0.5 mg/mL of whole volume. To avoid light exposure plates were wrapped with aluminium foil. Further, plates were subjected to 2-3 hr incubation. Later MTT reagent is removed and added with 100 µl of DMSO. The optical density of five test replicates was measured at 570 nm.

$$\% \text{ Cell viability} = \frac{\text{Absorbance of sample} - \text{Blank}}{\text{Absorbance of untreated} - \text{Blank}}$$

Statistical analysis

Results were statistically analyzed by performing one-way analysis of variance (ANOVA) and the differences between the groups were assessed using Tukey's multiple comparison tests. Data was considered as statistically significant at $p < 0.05$. All the statistics were done using Web Agri Stat Pack, Version-2.0 (WASP-2.0).

RESULTS

Cardiac glycosides

The yield (%) of cardiac glycosides of the *I. pavetta* and *T. capensis* was varied between 1.10±0.54 g/100g to 5.68±0.25 g/100g and 1.78±0.54 g/100g to 6.10±0.54 g/100g respectively. The maximum cardiac glycosides concentration i.e. 5.68±0.25 g/100g extracted with *I. pavetta* leaf methanolic extract in case of *T. capensis* highest cardiac glycosides content 6.10±0.54 g/100 g was reported with leaf methanolic extract.

Cardio protective activity

In present study, isoproterenol and verapamil rats exhibited the enhanced activities of total cholesterol (TC), triglycerides (TGs), low density lipoprotein (LDL) and reduced activity of high density lipoprotein cholesterol (HDL) (Table 2). But verapamil (2 mg/kg) treated rats showed significant increase in HDL-Cholesterol (33.56 mg/dL) (Plate 1). Wistar rats administered with 100 and 200 mg/kg of *T. capensis* and *I. pavetta* methanolic extract reported significant reduction in total cholesterol, tryglcerides and LDL cholesterol mg/dL (Table 2 and Plate 2). But comparatively *I. pavetta* leaf extracts were found to be less significant over *T. capensis* leaf extracts in controlling TC, TGs, LDL and HDL (Table 2 and Plate 3).

In vitro Hepatoprotective activity

Hepato protective activity of leaf methanolic extracts of *I. pavetta* and *T. capensis* examined against H_2O_2 induced HepG2 (Human hepatocellular adenocarcinoma cell line) by MTT assay with positive control as Sylimarin and the percentage of cell viability of test samples on H_2O_2 induced human liver cancer cell line (Plate 4). The % of cell viability is increased on dose dependent manner and confirmed the protective potency on liver cells. The observations suggest that against H_2O_2 pre stimulated HepG2 cells, *I. pavetta* leaf methanolic extracts recorded moderate protective activity by increasing the concentrations (Figure 1). The results confirmed

Table 2: Biochemical assessment of methanolic leaf extracts of *I. pavetta* and *T. capensis*.

Treatment Group	Biochemical Parameters (mg/dL)							
	Total Cholesterol		Triglyceride		HDL-C		LDL-C	
	100 mg/kg	200 mg/kg	100 mg/kg	200 mg/kg	100 mg/kg	200 mg/kg	100 mg/kg	200 mg/kg
Control(Saline) 0.9% w/v	**91.98**	**91.98**	**61.56**	**61.56**	**37.24**	**37.24**	**69.56**	**69.56**
Isoproterenol (2mg/kg)	204.84	204.84	161.28	161.28	26.36	26.36	155.34	155.34
Verpamil (3 mg/kg)	98.22*	98.22*	69.1*	69.1*	33.56*	33.56*	72.76*	72.76*
I. pavetta	129.25	100.12*	97.28	75.46*	31.20	26.77	99.10*	82.36*
T. capensis	140.17	108.11*	100.14	81.48*	30.28	28.74	108.11	93.15*
SEM	107.04	120.65	97.87	89.77	31.72	30.53	100.97	94.63

Values are mean±SEM for six animals in each group; *p<0.05 considered statistically significant as compared to ISO treated group.

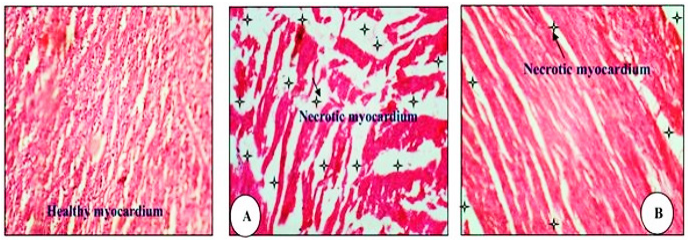

Plate 1: Histopathological nature of healthy myocardium.
A. Isoproterenol treated myocardium B. Verapamil treated myocardium.

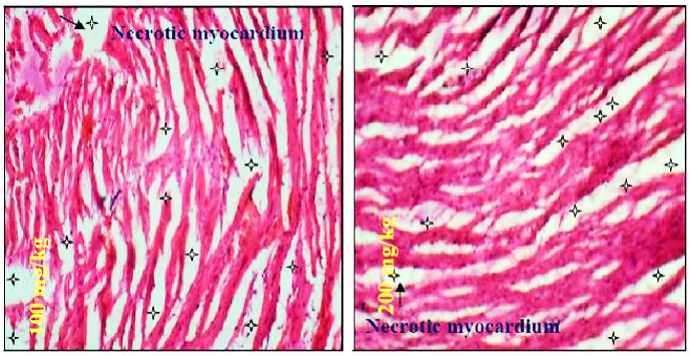

Plate 2: Recovery in myocardium fibril when treated with 100 mg/kg and 200 mg/kg methanolic leaf extract of *T. capensis*.

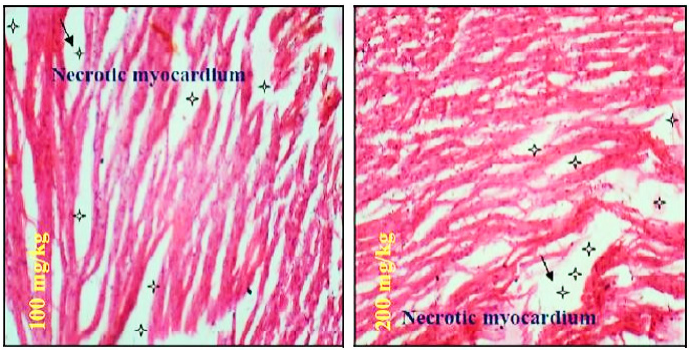

Plate 3: Recovery in myocardium fibril when treated with 100 mg/kg and 200 mg/kg methanolic leaf extract of *I. pavetta*.

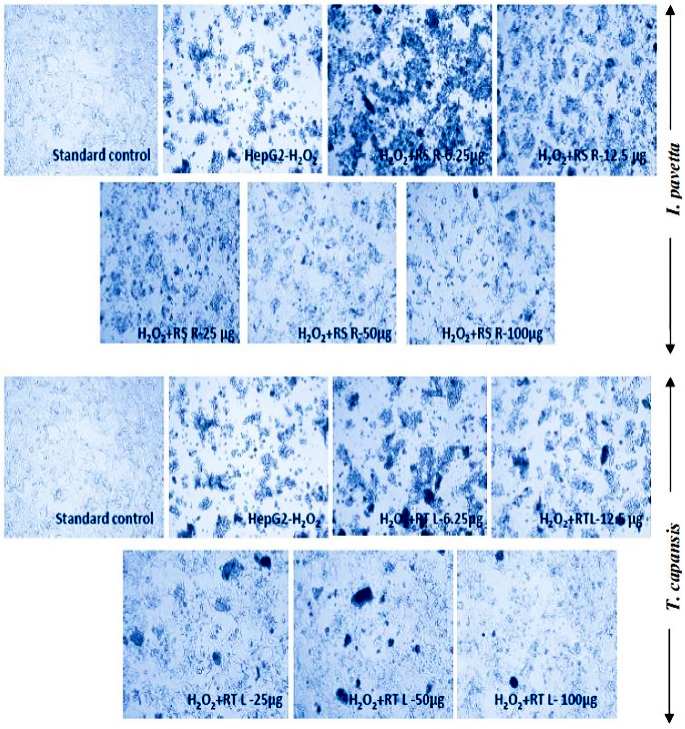

Plate 4: Hepatotoxic potential of *I. pavetta* and *T. capensis* on HepG2 cell line.

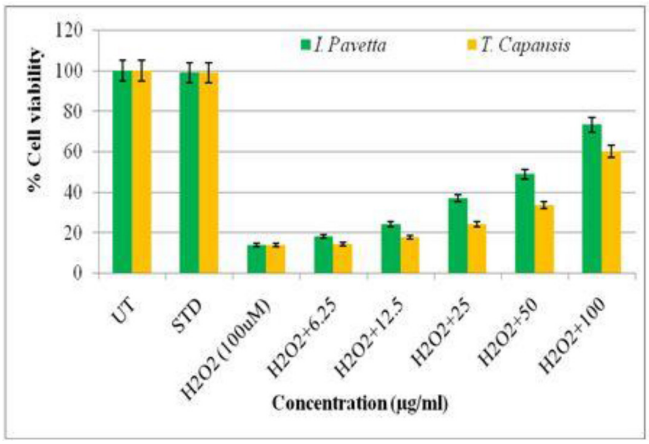

Figure 1: The values are % of cell viability methanolic extracts on H_2O_2 pre stimulated HepG2cell line.

that the *T. capensis* leaf methanolic extract has protective nature against HepG2 cell line by increasing the % of cell viability in a dose dependent manner after incubation of 24 hr.

DISCUSSION

Plants are the basic sources for a number of medicinally important compounds. Cardiac glycosides are one of such compounds. Cardiac glycosides are able to bind selectively with more affinity and inhibit the activity of Na^+, K^+-ATPase. Plants as well as animals generally synthesize cardiac glycosides endogenously, which includes cardenolides, ouabain, digoxin, and a number of bufodienolides. These endogenous cardiac glycosides further regulate blood pressure and natriuresis. Incase inadequate cardiac movement these cardiac glycosides showed enhanced a positive inotropic effect on the heart muscle, results in improved blood circulation.[28,29] The leaf methanolic extracts of the studied plants reported remarkably high amount of cardiac glycosides which indicates their potential role in cardioprotective activity.

The high intake of cholesterol results in increased plasma cholesterol and aortic atherosclerosis.[30] Based on the previous studies we can regulate the CVD through proper diet and drug therapy[31] and focusing on the plant based drugs may evolve in successful control of CVDs.[32,33]

In present study ISO and verapamil administered rats' exhibited prominant reduction in cholesterol content and LDL cholesterol

and significant increase in HDL-Cholesterol with verapamil dose at 2 mg/kg. The results indicated that *T. capensis* (200 mg/kg) reduced the biosynthesis of triglyceride and promotes the cholesterol redistribution. This is in agreement with previous findings,[34] in which leaf extracts of *Vernonia amygdalina* significantly lowered the triglyceride and LDL cholesterol levels in streptozotocin (STZ) induced diabetic rats (Table 2). On the other side low level of HDL-cholesterol is the major problem to the patients of CVD and the close association between HDL-cholesterol and CVD are well established.[35] Hence the increase in HDL-cholesterol is highly needed. In present study, treatment with *T. capensis* triggers the significant raise in plasma HDL-cholesterol, stipulate its prominent role in protecting CVDs. In addition HDL counteracts the LDL oxidation thereby inhibiting the atherogenic effect by reversing the cholesterol pathway.[36] Moreover, HDL impedes the LDL oxidation by transition metal ions, and also stops formation of 12-lipooxygenase-mediated lipid hydroperoxides.[37] The obtained results may confirm the anti-atherogenic activity of the *T. capensis* and *I. pavetta*. Apart from this reduced LDL cholesterol is the crucial factor to reduce the CVD risk.[38] Excess LDL deposited in the walls of blood vessel becomes a prime element of atherosclerotic plaque lesions. Consequently, plasma LDL cholesterol level may be used for monitoring and treating patients with raised blood cholesterol levels. The leaf methanolic extracts of *T. capensis* when administered at a dose of 200 mg/kg reduced the LDL cholesterol levels of the wistar rats. Our results indicated that the leaf methanolic extracts of *T. capensis* lowered levels of plasma and post mitochondrial fraction (PMF) levels of cholesterol including LDL of the treated rats. These results are in agreement with results observed in *Ocimum sanctum*,[39] in *Amaranthus viridis*,[40] in *Rhizophora apiculata*.[41]

In present study, hepatoprotective activity of *I. pavetta* and *T. capensis* methanolic leaf extracts was determined based on the MTT assay in which tetrazolium salt cleaved into blue coloured formazan in the inner membrane of metabolically active mitochondria by leaving the succinate dehydrogenase from tetrazolium salt. And the dye concentration is directly proportional to the number of living cells. In present study the methanolic leaf extracts of studied plants showed protective nature on H_2O_2 pre stimulated HepG2 cell lines by enhancing the percentage of cell viability in dose dependent manner after the incubation period of 2 days.[42] Toxic dose studies of the plant extract lays the foundation for the formulation of any type of herbal remedy.[43] Results revealed that *T. capansis* leaf extracts at 200 µg/ml concentration is more toxic to the HepG2 cells where the percent cell viability is more but not compete with the standard drug silymarin. This percent in cell viability is may be due to the up lift of the cells activity by inhibiting the cell oxidation process. Further it is concluded that the percent cell viability is also due to stabilization of mitochondrial membranes promoted by phytochemicals like phenolic compounds,[44] flavanoids, terpenoids, steroids etc.[45] which upraise the antioxidant defence enzymes of the tissues and thus regulates the oxidative stress. Similar trend of results were observed in *Andrographis paniculata*;[46] in *Cassia roxburghii*;[47] in *Polygonum multiflorum*.[48]

CONCLUSION

The present study on leaf methanolic extracts of *I. pavetta* and *T. capensis* revealed their potential cardio-protective activity by decreasing cholesterol content, triglycerides and LDL cholesterol apart from significant increase in HDL-Cholesterol in wistar rats. The obtained results also showed that the leaf methanolic extracts of the *I. pavetta* and *T. capensis* have good hepatoprotective activity in dose dependent manner on H_2O_2 pre stimulated HepG2 cell lines.

ACKNOWLEDGEMENT

My sincere thank to Plant Physiology and Central Laboratory, Department of Botany and Microbiology, Acharya Nagarjuna University in carrying the phytochemical studies. I wish to extend my thanks to Chalapthi Institute of Pharmaceutical Sciences, Guntur and Synteny Life Sciences Private Ltd., Hyderabad for their help and support in performing biological activities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Suneeta D, Rao YRKVT. Cardioprotective and Hepatoprotective Effects of *Ixora pavetta* and *Tecoma capensis* Leaf Extracts. Int. J. Pharm. Investigation. 2023;13(1):22-7.