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Original article

Terminalia pallida fruit ethanolic extract ameliorates lipids, lipoproteins, lipid metabolism marker enzymes and paraoxonase in isoproterenol-induced myocardial infarcted rats

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ABSTRACT

The present study aimed to evaluate the effect of *Terminalia pallida* fruit ethanolic extract (TpFE) on lipids, lipoproteins, lipid metabolism marker enzymes and paraoxonase (PON) in isoproterenol (ISO)-induced myocardial infarcted rats. PON is an excellent serum antioxidant enzyme which involves in the protection of low density lipoprotein cholesterol (LDL-C) from the process of oxidation for the prevention of cardiovascular diseases. ISO caused a significant increase in the concentration of total cholesterol, triglycerides, LDL-C, very low density lipoprotein cholesterol and lipid peroxidation whereas significant decrease in the concentration of high density lipoprotein cholesterol. ISO administration also significantly decreased the activities of lecithin cholesterol acyl transferase, PON and lipoprotein lipase whereas significantly increased the activity of 3-hydroxy-3-methylglutaryl-coenzyme-A reductase. Oral pretreatment of TpFE at doses 100, 300 and 500 mg/kg body weight (bw) and gallic acid (15 mg/kg bw) for 30 days challenged with concurrent injection of ISO (85 mg/kg bw) on 29th and 30th day significantly attenuated these alterations and restored the levels of lipids, lipoproteins and the activities of lipid metabolizing enzymes. Also TpFE significantly elevated the serum antioxidant enzyme PON. This is the first report revealed that pretreatment with TPFE ameliorated lipid metabolic marker enzymes and increased the antioxidant PON in ISO treated male albino Wistar rats.

1. Introduction

Myocardial infarction (MI) is the necrosis of heart muscle occurs due to the imbalance between myocardial oxygen demand and oxygen supply. Hypercholesterolemia, hyperlipoproteinemia, higher levels of low density lipoprotein cholesterol (LDL-C) and lower levels of high density lipoprotein cholesterol (HDL-C) are the leading risk factors for MI (Khader et al., 2003). Isoproterenol (ISO) is a catecholamine induces stress in heart muscle, leading to the necrosis of myocardium (Sushamakumari et al., 1989). ISO elevates lipids and lipoproteins especially LDL-C in the blood circulation that causes the blockage of arteries favoring cardiovascular diseases (CVD) (Goldstein and Brown, 1984). ISO generates oxygen free radicals which cause MI (Singal et al., 1982). Oxidative stress and oxygen free radicals together lead to the generation of atherosclerotic lesions by the formation of oxidized LDL from LDL, which is the underlying cause of MI (Libby, 2003).

Fruits and vegetables intake play a prominent role in the management of MI. The fruits of *Terminalia pallida* Brandis (*T. pallida*) grow best in the season of monsoon. *T. pallida* is an endemic tree widely distributed in Tirumala hills of Rayalaseema region, Andhra Pradesh, India. *T. pallida* fruits mature in the period of two months that are initially appear in light to dark green and later convert to

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Fig. 1. *Terminalia pallida* fruit.

brown when mature (Solomon Raju et al., 2012). Locally the fruit is known as tellakaraka and used by the tribal people for the remedy of diabetes (Nagaraju and Rao, 1989). *T. pallida* fruits are widely used in the treatment of various maladies such as diarrhea, ulcers, venereal diseases (Kritikar and Basu, 1998), antibacterial and antifungal (Jeevan Ram et al., 2004), skin diseases (Nagaraju and Rao, 1989) and hepatic ailments (Palani et al., 2009) (see Fig. 1).

Paraoxonase (PON) is an important plasma antioxidant enzyme produced by the liver that protects lipoproteins from oxidative modification (Mackness et al., 1993; Aviram et al., 1998). Oxidation of lipoproteins plays a key role in the atherogenic pathogenesis (Steinberg, 1997). Low activity of serum PON has been reported in diseases associated with hypercholesterolemia (Durrington et al., 2001), atherosclerosis and increased prevalence of CVD (Getz and Reardon, 2004). PON shields against CVD by reducing HDL-C peroxidation and protecting plasma membranes from the damage of free radicals (Durrington et al., 2001). Previously, we have reported the cardioprotective effect of HPLC standardized TpFE on cardiac marker enzymes, myocardial lipids, antioxidants and membrane bound ATPases in ISO administered myocardial infarcted rats. In continuation of our research on TpFE, in the present study we assessed the ameliorative effect of TpFE on lipids, lipoproteins, lipid metabolic enzymes and PON in ISO administered myocardial infarcted rats.

2. Materials and methods

2.1. Preparation of T. pallida fruit extract

T. pallida fruits were collected and authenticated by the taxonomist (Authentication Certificate Code: 38609, Department of Botany, Sri Krishnadevaraya University, Anantapuram, India). The fruits were shade dried and grinded with iron mortar & pestle. The coarse powder of the fruits was extracted with absolute ethanol by using Soxhlet apparatus. The extract was concentrated under reduced pressure by using Rotary evaporator. The ethanolic extract of *T. pallida* was preserved in refrigerator for the treatment of animals.

2.2. Animals

Male albino Wistar rats (120 g) were acclimatized for a week to the animal house conditions. The animal house was well maintained with ventilation, temperature at 25 °C and 12/12 h light & dark cycle. Rats were fed with standard pellet diet and water provided *ad libitum*. Animal use was approved by the animal ethical committee of Sri Krishnadevaraya University, Anantapuram (Registered number 470/01/a/CPCSEA), India.

2.3. Experimental protocol

Total 56 rats were used in the experimental study with 8 rats in each group

1. Untreated control rats
2. Pretreatment of rats with TpFE (500 mg/kg bw)
3. Pretreatment of rats with ISO (85 mg/kg bw)
4. Pretreatment of rats with TpFE (100 mg/kg bw) + ISO
5. Pretreatment of rats with TpFE (300 mg/kg bw) + ISO
6. Pretreatment of rats with TpFE (500 mg/kg bw) + ISO
7. Pretreatment of rats with GA (15 mg/kg bw) + ISO

TpFE was solubilized in distilled water and the positive control gallic acid (GA) was solubilized in saline. Both TpFE and GA were orally pretreated to the rats for 30 days by using intragastric tube. ISO was solubilized in distilled water and administered to the rats by subcutaneous injection for last 2 consecutive days. Animals were sacrificed by cervical decapitation. Blood was collected from heart puncture to separate serum and plasma. Tissue samples were separated and refrigerated at −80 °C.

2.4. Biochemical measurements

Lipids and lipoproteins were measured by utilizing the kits of Erba diagnostics Ltd., India. HDL-C was estimated by utilizing the kit of Siemens diagnostics Ltd., India. Very low density lipoprotein-cholesterol (VLDL-C) was calculated as VLDL-C = TG/5, whereas LDL-C was calculated as LDL-C = TC − (HDL-C + VLDL-C). Malondialdehyde (MDA) level was measured to estimate lipid peroxidation (LPO) (Okhawa et al., 1979). Lecithin cholesterol acyl transferase (LCAT) was analyzed by Ngasaki and Akanuma (1977) method. PON activity was assayed by the method of Gan et al. (1991). 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase activity was measured by taking the ratio of HMG-CoA and mevalonate as an index by the method of Venugopal rao and Ramakrishnan (1975). Lipoprotein lipase (LPL) was analyzed by the method of Shirai and Jackson (1982). Protein was measured by Lowry et al. (1951) method.

2.5. Statistical study

Results were analyzed statistically by performing one-way analysis of variance (ANOVA) followed by Duncan's multiple range test. Data considered statistically significant at $p < .05$.

3. Results and discussion

3.1. Effect of TpFE on lipids and lipoproteins

Fig. 2 depicts the effect of TpFE on serum lipids and lipoproteins (TC, TG, HDL-C, VLDL-C and LDL-C) in normal and ISO administered groups. Rats injected with ISO exhibited a significant ($p < .05$) increase in the levels of serum TC, TG, LDL-C and VLDL-C, except HDL-C which showed a significant ($p < .05$) decrease when compared to control rats. Pretreatment with GA (15 mg/kg bw) and TpFE (100, 300, and 500 mg/kg bw) dose dependently decreased serum TC, TG, LDL-C, VLDL-C levels significantly ($p < .05$) and increased serum HDL-C levels significantly ($p < .05$) when

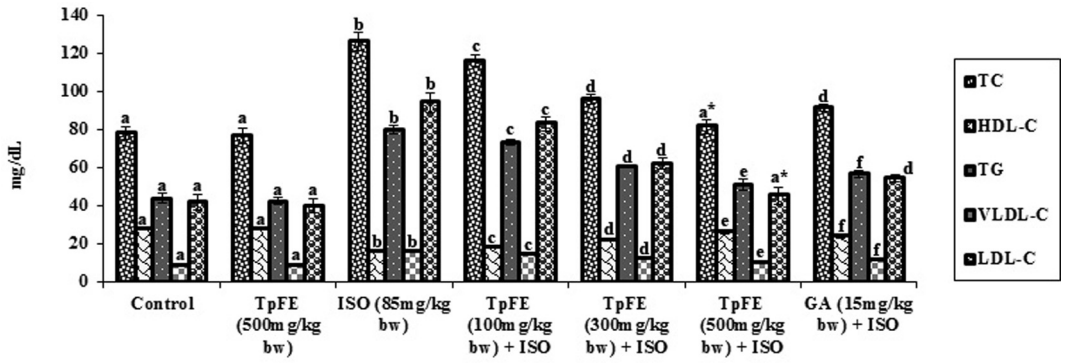

Fig. 2. Effect of *Terminalia pallida* fruit ethanolic extract (TpFE) on lipids and lipoproteins in the serum of untreated and isoproterenol (ISO) administered rats. Individual column is mean ± S.D. (n = 8 rats). Columns with different superscripts (a, b, c, d and e) differ significantly from each other ($p < .05$). *Group is significantly different with TpFE (500 mg/kg bw) treated group.

compared to ISO administered rats. Treatment of TpFE at 500 mg/kg bw in ISO administered rats decreased the serum TC and LDL-C almost to near normal but not significantly ($p < .05$) when compared to the control rats. There is no significant effect with TpFE (500 mg/kg bw) alone treatment on lipid profile when compared to untreated normal rats.

Lipids play a significant role in CVD. Hyperlipidaemia and hypercholesterolaemia are the vital risk factors in the progress of MI. ISO administered MI is allied with elevated levels of circulatory lipids. In this study, ISO administered rats showed significantly increased levels of TC, TGs in serum. The increased level of cholesterol in ISO treated rats is due to increased level of LDL-C taken from the blood circulation (Anandan et al., 2007). Increased level of TGs is the prime risk factor of MI which is associated with cardiovascular disturbances (Sushama Kumari et al., 1990). TpFE treatment ameliorated lipids and lipoproteins with a significant increase in HDL-C levels and a decrease in TC, TGs, LDL-C and VLDL-C levels, which may be due to the hypocholesterolaemic and hypolipidemic activities of TpFE. Our results are in line with earlier reports (Abbas, 2016).

3.2. Effect of TpFE on LPO

Fig. 3 represented the effect of TpFE on serum LPO marker MDA in control and ISO administered rat groups. Rats administered with ISO showed significant ($p < .05$) increase in the level of MDA in serum when compared to control rats. GA (15 mg/kg bw) and TpFE (100, 300 and 500 mg/kg bw) dose dependently decreased the level of MDA significantly ($p < .05$) in serum as compared to ISO alone administered rats. There is no significant effect with TpFE (500 mg/kg bw) alone treatment on LPO.

LPO plays a crucial role in the toxicity of heart and liver (Lakshmi et al., 2005). LPO is an important pathogenic event in myocardial necrosis and accumulation of lipid hydroperoxides which reflects damage of the cardiac constituents (Gutteridge, 1982). The free radicals mediate membrane damage that may increase the level of lipid peroxides in ISO administered MI (Karthikeyan et al., 2007). The present study revealed a significant increase in the level of MDA in the serum of ISO administered rats. TpFE pretreatment to ISO treated rats minimized MDA content, clearly exhibiting that TpFE inhibited the LPO. The inhibition of LPO may be due to the antioxidative and antilipid peroxidative activities of TpFE. This result is in acceptance with previous report of Jagadeesh et al. (2016).

3.3. Effect of TpFE on LCAT

Fig. 4 shows the effect of TpFE on the activity of lipid metabolizing enzyme LCAT in the serum of control and ISO administered rats. ISO treatment significantly ($p < .05$) diminished the activity of LCAT in serum compared to untreated rats. Pretreated group with TpFE (300, and 500 mg/kg bw) and GA (15 mg/kg bw) for 30 days significantly ($p < .05$) increased except the dose 100 mg/kg bw on the activity of LCAT in ISO administered rats when compared to ISO alone treated rats. TpFE at the dose of 500 mg/kg bw in ISO treated rats significantly ($p < .05$) increased the activity of

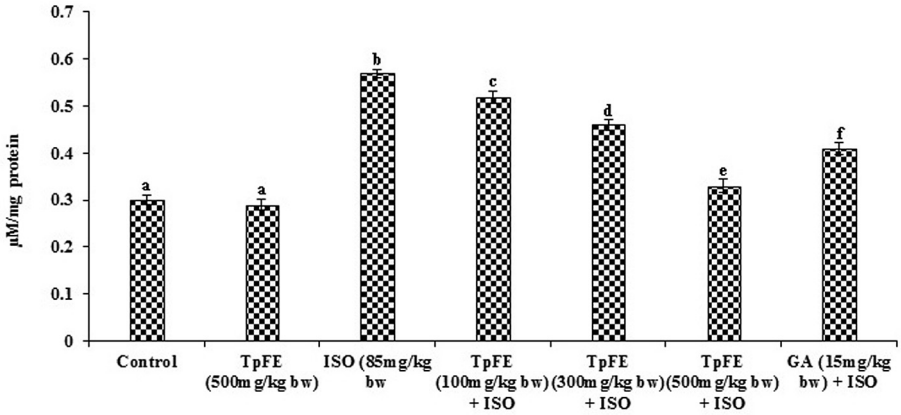

Fig. 3. Effect of *Terminalia pallida* fruit ethanolic extract (TpFE) on the lipid peroxidation in the serum of untreated and isoproterenol (ISO) administered rats. Individual column is mean ± S.D. (n = 8 rats). Columns with different superscripts (a, b, c and d) differ significantly from each other ($p < .05$).

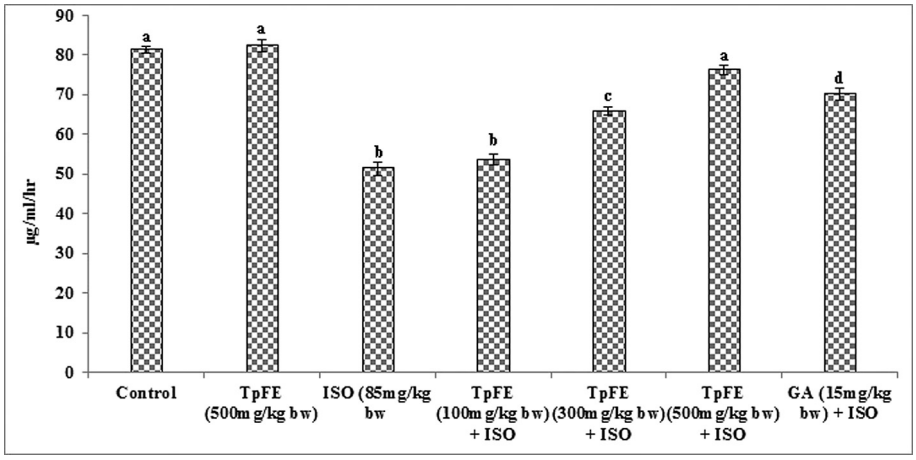

Fig. 4. Effect of *Terminalia pallida* fruit ethanolic extract (TpFE) on Lecithin Cholesterol Acyl Transferase (LCAT) in Serum and Liver of untreated and isoproterenol (ISO) administered rats. Individual column is mean ± S.D. (n = 8 rats). Columns with different superscripts (a, b, c, d, e and f) differ significantly from one another ($p < .05$).

LCAT to near normal compared to the untreated rats. TpFE (500 mg/kg bw) treatment alone did not alter the activity of LCAT.

LCAT involves in the esterification of cholesterol on the surface of HDL, leading to the development of giant HDL particles that protect against MI. Reduced activity of LCAT elevates the content of circulatory lipid profile by preventing the esterification of cholesterol in ISO administered rats which is the high risk of MI (Punithavathi and Prince, 2009). Pretreatment with TpFE elevated the activity of LCAT that enhances the level of HDL-C in ISO treated rats. This noticed raise in LCAT activity may be due to the blockage of LPO in TpFE pretreated ISO administered rats. The result is in agreement with earlier report of Shivaranjani et al. (2017).

3.4. Effect of TpFE on PON enzyme

Data presented in Fig. 5 depicts the effect of TpFE on the activity of serum PON in control and experimental rats. Significant ($p < .05$) decrease in the levels of serum PON was observed in rats administered with ISO as compared to control rats. GA (15 mg/kg bw) and TpFE (100, 300, and 500 mg/kg bw) dose dependent pretreatment for a period of 30 days increased the activity of serum PON significantly ($p < .05$) when compared to ISO alone administered rats. TpFE (500 mg/kg bw) alone treatment showed an improvement of serum PON but not significantly ($p < .05$).

To the best of knowledge, this is the first report exploring the effect of TpFE on the endogenous antioxidant enzyme PON in ISO-induced myocardial necrotic rats. Very limited reports available on PON activity in ISO administered rat models. TpFE treatment has been enhanced PON activity in control and ISO treated groups. The elevated activity of PON may be due to the phenolic compounds present in TpFE. In our previous study, TpFE has been standardized by LC-MS for the presence of phenolic compound GA (Shaik et al., 2012), and it has been reported that GA ameliorated PON activity in ISO-induced MI (Hussain Shaik et al., 2012). The present results are in accordance with Shivaranjani et al. (2017). TpFE may directly elevate serum PON activity because both *in vitro* (Aviram et al., 2004) and *in vivo* (Tas et al., 2005) introduction of antioxidant molecules were shown to preserve PON activity. TpFE may also favorable to PON by its antihypercholesterolaemic, antihyperlipidemic and antioxidant activities. The low concentration and activity of PON have been reported to cause CVD (Ikeda et al., 2009). Hence, the beneficial effect of TpFE on PON has been considered as an important finding.

3.5. Effect of TpFE on HMG-CoA reductase

Table 1 showed the effect of TpFE on HMG-CoA reductase enzyme in plasma, liver tissue and heart tissue of rats. HMG-CoA reductase activity increased significantly ($p < .05$) in plasma, liver and heart of ISO administered rats when compared to control group. TpFE (300, and 500 mg/kg bw) and GA (15 mg/kg bw) pretreatment to ISO administered group revealed significant ($p < .05$)

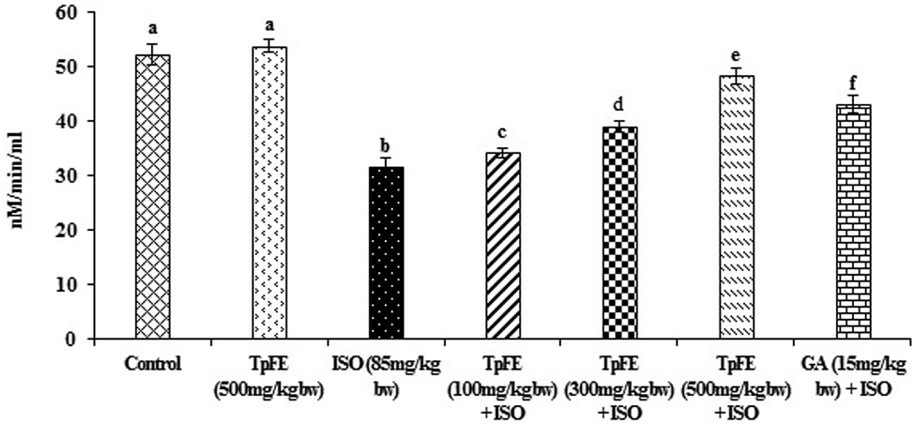

Fig. 5. Effect of *Terminalia pallida* fruit ethanolic extract (TpFE) on the paraoxonase (PON) in the serum of untreated and isoproterenol (ISO) administered rats. Individual column is mean ± S.D. (n = 8 rats). Columns with different superscripts (a, b, c, d and e) differ significantly from each other ($p < .05$).

Table 1
Effect of *Terminalia pallida* fruit ethanolic extract (TpFE) on the hydroxyl methyl glutaryl coenzyme A reductase (HMG CoA-reductase) in Plasma, Liver and Heart of control and isoproterenol (ISO)-induced myocardial infarcted rats.

Group	HMG CoA reductase in plasma (HMG CoA/Mevalonate ratio)	HMG CoA reductase in liver (HMG CoA/Mevalonate ratio)	HMG CoA reductase in heart (HMG CoA/Mevalonate ratio)
Control	3.1 ± 0.3[a]	5.4 ± 0.1[a]	1.3 ± 0.08[a]
TpFE (500 mg/kg bw)	3.2 ± 0.2[a]	5.4 ± 0.2[a]	1.4 ± 0.08[a]
ISO (85 mg/kg bw)	1.1 ± 0.3[b]	2.8 ± 0.1[b]	0.6 ± 0.08[b]
TpFE (100 mg/kg bw) + ISO	1.3 ± 0.1[b]	3.3 ± 0.1[c]	0.6 ± 0.12[b]
TpFE (300 mg/kg bw) + ISO	2.2 ± 0.2[c]	4.0 ± 0.2[d]	0.8 ± 0.12[c*]
TpFE (500 mg/kg bw) + ISO	3.0 ± 0.2[a]	5.1 ± 0.1[a]	1.1 ± 0.12[a$]
GA (15 mg/kg bw) + ISO	2.8 ± 0.4[a]	4.7 ± 0.1[e]	0.9 ± 0.12[d#]

Values are mean ± S.D. (n = 8 rats). Values that do not share a common superscript (a, b, c, d and e) differ significantly from each other ($p < .05$, Duncan's Multiple Range Test).
* Group is not significantly different with TpFE (100 mg/kg bw) + ISO group.
$ Group is significantly different with TpFE (500 mg/kg bw) treated group.
# Group is not significantly different with TpFE (300 mg/kg bw) and (500 mg/kg bw) + ISO groups.

decrease except the dose 100 mg/kg bw on the activity of HMG-CoA reductase in plasma and heart when compared with ISO administered group. TpFE at the dose of 500 mg/kg bw in ISO administered group normalized the activity of HMG-CoA reductase enzyme in plasma and liver when compared to the untreated group. TpFE (500 mg/kg bw) treatment alone did not alter the activity of this enzyme. HMG-CoA/mevalonate in low ratio indicates high activity of HMG-CoA reductase enzyme and vice versa.

HMG-CoA reductase is the rate controlling enzyme in mevalonate pathway or cholesterol biosynthesis. We noticed that HMG-CoA reductase activity is significantly increased in plasma, liver and heart of ISO treated group. The increased HMG-CoA reductase activity directs to accumulate excess amount of cholesterol leading to the formation foam cells, which is a prerequisite step in the progress of atherosclerosis (Berliner and Heinecke, 1996). Cholesterol homeostasis in cells considered as a crucial element in the prevention of CVD such as MI. Our findings clearly show that pretreatment with TpFE regulates cholesterol biosynthesis by inhibiting HMG-CoA reductase enzyme in ISO administered groups. The decreased cholesterol level in TpFE treated rats may be correlated to the decreased HMG-CoA reductase enzyme activity in ISO administered rats. The antioxidative activity of TpFE indirectly assists to reduce the levels of lipid profile, by inhibiting LPO. GA, one of the active compounds of TpFE ameliorated the HMG-CoA reductase in normal and ISO induced MI in male Wistar rats (Hansi and Prince, 2010). These results are in concurrent with Jagadeesh et al. (2016) report.

3.6. Effect of TpFE on LPL

Table 2 depicts the effect of TpFE on the activity of lipid metabolizing enzyme LPL in liver and heart. ISO injected animals significantly ($p < .05$) decreased the activity of LPL in liver and heart tissue when compared to control group. Treatment with TpFE (300, and 500 mg/kg bw) and GA (15 mg/kg bw) showed a significant ($p < .05$) increase except the dose 100 mg/kg bw on the activity of LPL in liver and heart of ISO administered rats when compared to ISO alone treated rats. TpFE (500 mg/kg bw) treatment alone did not exhibit significant influence on the activity of LPL.

Table 2
Effect of *Terminalia pallida* fruit ethanolic extract (TpFE) on Lipoprotein Lipase (LPL) in Liver and Heart of control and isoproterenol (ISO) administered rat groups.

Group	LPL in liver (U/mg protein)	LPL in heart (U/mg protein)
Control	15.3 ± 0.8[a]	22.3 ± 1.4[a]
TpFE (500 mg/kg bw)	15.5 ± 0.5[a]	22.6 ± 0.5[a]
ISO (85 mg/kg bw)	8.1 ± 0.9[b]	9.6 ± 0.9[b]
TpFE (100 mg/kg bw) + ISO	8.7 ± 0.4[b]	9.9 ± 0.5[b]
TpFE (300 mg/kg bw) + ISO	12.3 ± 0.6[c]	16.8 ± 1.3[c]
TpFE (500 mg/kg bw) + ISO	15.1 ± 0.6[a]	21.6 ± 0.8[a]
GA (15 mg/kg bw) + ISO	13.7 ± 0.5[d]	17.2 ± 1.1[c]

Values are mean ± S.D. (n = 8 rats). Values that do not share a common superscript (a, b, c and d) differ significantly from each other ($p < .05$, Duncan's Multiple Range Test).

It has been reported that an increase in LPL is antiatherogenic and a decrease in LPL is atherogenic (Reymer et al., 1995). LPL hydrolyzes triglycerides in plasma lipoproteins such as chylomicrons and VLDL and causes a wide variety of alterations in lipoprotein metabolism. This effect includes the stimulation of the hepatic removal of the lipolyzed lipoproteins, and transfer of surface components of triglyceride-rich lipoproteins to HDL. LPL molecules remain associated with chylomicrons after hydrolysis and, therefore, might assist in their hepatic uptake (Felts et al., 1975). In the present study pretreatment with TpFE enhanced the activity of LPL in ISO administered rats. The results are in agreement with the earlier report of Aman and Balaraman (2012).

4. Conclusion

The conclusion of our study is pretreatment with TpFE dose dependently exhibits ameliorative effects in ISO injected myocardial necrotic rats by modulating lipids, lipoproteins and lipid metabolism marker enzymes. Also, TpFE increased the activity of PON. TpFE at the dose of 500 mg/kg bw effectively ameliorated the activity of antioxidant enzyme PON in ISO administered rats. The possible mechanism of TpFE cardioprotection is due to its antihypercholesterolemic, antihyperlipidemic, and antioxidant actions. *T. pallida* fruit could be used in the therapeutic treatment of cardiovascular ailments.

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