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## Letter to the Editor

### Lipid lowering efficacy of fraxetin, a coumarin derivative on high fat diet-induced hypercholesterolemic rats

Sir,

Hypercholesterolemia is the key risk factor for cardiovascular disorders like coronary heart disease and stroke. Statins or hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors are the widely prescribed drug worldwide (Jukema et al., 2012). However, they have notable side effects such as hyperuricemia, diarrhea, flushing, nausea, myositis, gastric irritation, dyspepsia and gallstones, abnormal liver function and rhabdomyolysis with renal failure, etc. (Durrington, 2003). Hence, the need to discover antihypercholesterolemic drug having better efficacy and lower adverse effects is still felt.

Phytotherapy could be a suitable alternative for the treatment of hyperlipidemia (Liu et al., 2011). A large number of literatures reported that various medicinal plants had lipid lowering effects, for example, *Pterodon emarginatus* (Dal Forno et al., 2019), *Salvia hispanica* (Rodrigues et al., 2018), *Stellaria media* (Khan et al., 2019), *Zingiber officinale* (Bekkouch et al., 2019), *Lagenaria siceraria*, *Commiphora wightii* and *Glycyrrhiza glabra* (Srivastava and Srivastava, 2018).

Coumarin (1,2-benzopyrone) is a natural phenolic compound found in many plants species and green tea (Tejada et al., 2017). Coumarin and some coumarin derivatives viz. esculetin, scoparone, and 4-methylumbelliferone were reported to have lipid lowering effects (Taşdemir et al., 2017). Fraxetin (7, 8-dihydroxy-6-methoxycoumarin), a coumarin derivative widely present in the citrus fruits, tomatoes, vegetables, green tea and natural food products (Thuong et al., 2009) has attracted research interest as antioxidant, anti-diabetic, anti-inflammatory, antiviral, antitumor and neuroprotective agent (Mo et al., 2019; Challa and Prasanna, 2018). This study aimed to investigate the lipid lowering efficacy of fraxetin on high fat diet fed hypercholesterolemic rats.

The male albino Wistar rats ( $180 \pm 20$  g) were procured from the Animal House Facility, Mohamed Sathak A. J. College of Pharmacy, Chennai 119, India.

High fat diet [SKM Egg Products Export (India) Ltd.]

was prepared according to the method of Xie et al., (2005). High fat diet comprised of normal rat feed 84.3%, 5% lard, 10% yolk powder, cholesterol 0.2% and 0.5% (Sisco Research Laboratories Pvt. Ltd., India), bile salt (Central Drug House Pvt. Ltd., India) were fed to the rats for a period of 56 days. The rats with plasma cholesterol  $>250$  mg/dL were used in the present study. The rats were again fed with high fat diet and treatment with fraxetin (25, 50, 75 mg/kg, orally; Sigma Aldrich, USA) and simvastatin (10 mg/kg) was started on the next day after hypercholesterolemia confirmation and this was considered as day 1 of treatment and it was continued for 30 days.

The final body weights were recorded. Other parameters like waist, body mass index and Lee index were determined as previously reported method (Bernardis, 1970). The rats were sacrificed by cervical decapitation under pentobarbitone sodium (60 mg/kg). The levels of total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL-C) were estimated by using biochemical kits (Agappe Diagnostics Pvt. Ltd., India). For the determination of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) cholesterol, Friedewald's formula was used (Friedewald et al., 1972).

Atherogenic index of plasma (AIP), a significant predictor of risk for atherosclerosis was calculated as  $\log$  (TG/HDL-C) (Tan et al., 2004).

Animals fed with HFD had significantly increased in body weight, waist, body mass index and Lee index compared with rats fed with a standard diet ( $p < 0.05$ ). These changes were modulated and brought back to near normal levels on treatment with different concentrations of fraxetin. The reduction in body weight, waist, body mass index and Lee index was observed in all the 4 doses tested. However, the changes are statistically not significant at the dosage of 25 mg/kg while, fraxetin treatment at higher doses i.e. 50 and 75 mg/kg resulted in a significant decrease in the aforesaid parameters (Figure 1A-D).

The plasma levels of total cholesterol, triglyceride, VLDL and LDL cholesterol and atherogenic index were significantly increased, whereas HDL cholesterol was significantly decreased in hypercholesterolemic rats, in comparison to normal control rats. Oral administration of fraxetin significantly reversed all these altered parameters to near normal levels in a dose-dependent manner (Table I).



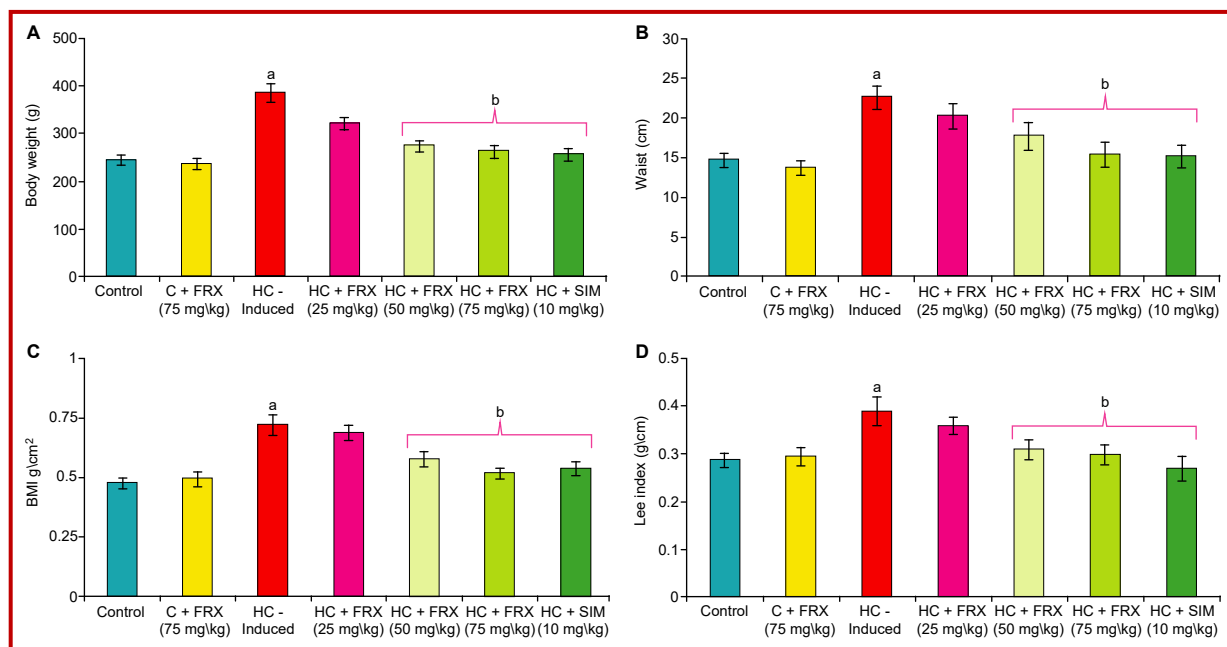


Figure 1: Effect of different concentrations of fraxetin treatment on (A) Body weight (B) waist, (C) BMI and (D) Lee index. Values represented by the mean  $\pm$  SD (n=6); <sup>a</sup>represents significant increase at  $p < 0.05$  when compared to normal control rats while <sup>b</sup>represents significant decrease at  $p < 0.05$  when compared to hypercholesterolemic; C- control; FRX- fraxetin, HC- hypercholesterolemic, SIM- simvastatin

Table I

Dose-dependent effect of fraxetin on the levels of lipid profile in rats

Group	Total cholesterol (mg/dL)	Triglycerides (mg/dL)	VLDL-C (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	AIP
Normal control	126.3 $\pm$ 11.5	62.9 $\pm$ 5.4	12.6 $\pm$ 1.8	67.3 $\pm$ 3.8	46.4 $\pm$ 4.5	-0.0299
Normal control + fraxetin 75 mg/kg	122.8 $\pm$ 13.6	59.7 $\pm$ 4.6	11.9 $\pm$ 2.0	72.9 $\pm$ 2.9	38.0 $\pm$ 4.2	-0.0866
Hypercholesterolemic	368.5 $\pm$ 12.6	153.3 $\pm$ 8.3	30.7 $\pm$ 3.4	45.1 $\pm$ 4.0	292.7 $\pm$ 9.0	0.5312
Hypercholesterolemic + fraxetin 25 mg/kg	298.7 $\pm$ 9.1 <sup>a</sup>	132.4 $\pm$ 5.4 <sup>a</sup>	26.5 $\pm$ 2.3 <sup>a</sup>	49.8 $\pm$ 3.0 <sup>a</sup>	222.4 $\pm$ 6.5 <sup>a</sup>	0.4244 <sup>a</sup>
Hypercholesterolemic + fraxetin 50 mg/kg	237.4 $\pm$ 11.2 <sup>a</sup>	106.4 $\pm$ 6.3 <sup>a</sup>	21.3 $\pm$ 2.7 <sup>a</sup>	56.3 $\pm$ 3.1 <sup>a</sup>	159.9 $\pm$ 5.9 <sup>a</sup>	0.2766 <sup>a</sup>
Hypercholesterolemic + fraxetin 75 mg/kg	192.5 $\pm$ 11.3 <sup>a</sup>	71.3 $\pm$ 4.3 <sup>a</sup>	14.3 $\pm$ 2.5 <sup>a</sup>	61.4 $\pm$ 3.2 <sup>a</sup>	116.9 $\pm$ 5.8 <sup>a</sup>	0.0650 <sup>a</sup>
Hypercholesterolemic + simvastatin 10 mg/kg	184.8 $\pm$ 10.4 <sup>a</sup>	63.6 $\pm$ 4.4 <sup>a</sup>	12.7 $\pm$ 1.7 <sup>a</sup>	65.5 $\pm$ 3.7 <sup>a</sup>	106.6 $\pm$ 5.3 <sup>a</sup>	-0.0126 <sup>a</sup>

The values are mean  $\pm$  SD of 6 animals in each group. AIP- Atherogenic Index of Plasma; <sup>a</sup>The difference between treated and hypercholesterolemic values is significant at  $p < 0.05$

This study highlights the lipid lowering potential of fraxetin at the dose of 75 mg/kg which is comparable to that of simvastatin.

All experiments were conducted according to the ethical norms approved by the CPCSEA and Institutional Animal Ethics Committee (IAEC) Guidelines

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