

EVALUATION OF REVERSAL EFFECTS OF *EUGENIA JAMBOLANA* SEED EXTRACTS AGAINST HIGH-FRUCTOSE DIET-INDUCED INSULIN RESISTANCE IN ALBINO RATS

M.H.R.K GUPATHA BAYYA¹, SACHIDANANDA ADIGA MN^{2*}, NAGENDRA NAYAK IM³, ASITAVA DEB ROY⁴,
SAMPATH KUMAR AK⁵

¹Department of Pharmacology, IQ City Medical College, Durgapur, West Bengal, India. ²Department of Pharmacology, K.S. Hegde Medical Academy, NITTE (Deemed to be University), Mangalore, Karnataka, India. ³Department of Pharmacology, K.S. Hegde Medical Academy, NITTE (Deemed to be University), Mangalore, Karnataka, India. ⁴Department of Pathology, IQ City Medical College, Durgapur, West Bengal, India. ⁵Department of General Medicine, K.S. Hegde Medical Academy, NITTE (Deemed to be University), Mangalore, Karnataka, India.
Email: adigaiscool@yahoo.com

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ABSTRACT

Objective: The objective of this study is to evaluate the reversal effects of aqueous and ethanolic extracts of jamun seeds against high-fructose (HFr) diet-induced insulin resistance (IR) in albino rats.

Methods: Thirty male albino rats were divided into five groups (n=6), and all the group rats except normal control were provided with HFr (60% w/v) to their drinking water daily for 42 days. Group 1 and 2 served as a normal and fructose control. Groups 3, 4, and 5 were supplemented with metformin (MET 500mg/kg p.o) and aqueous and ethanolic extracts of jamun seeds (Jamun seed aqueous extract [JSAE] and Jamun seed ethanolic extract [JSEE] 1000 mg/kg of each p.o), from day 28 to day 42, respectively. Physical (body weights, food, and water intake) and biochemical (glucose, insulin, and lipid) parameters were estimated, and Homeostasis model assessment (HOMA)-IR values were calculated.

Results: HFr diet significantly (p<0.05) increased weight gain and water intake with decreased food intake in rats. HFr-fed rats exhibited a significant (p<0.05) increase in fasting glucose, insulin, and lipid levels along with increased HOMA-IR values and confirms the development of IR. Supplementation with MET, JSAE, and JSEE significantly (p<0.05) restored the physical parameters and reversed fasting glucose and lipid levels in comparison with HFr control. Whereas, only JSAE had significantly reversed the fasting insulin levels in comparison with HFr control. HOMA-IR values were significantly (p<0.05) decreased in both the extract groups of HFr-fed rats, and the results were comparable to MET.

Conclusion: Our study concludes that both aqueous and ethanolic extracts of jamun exhibit a significant reversal effect against HFr diet-induced IR, due to insulin-sensitizing actions at the target tissues.

Keywords: *Eugenia jambolana*, Fructose, Insulin resistance, Hyperglycemia, Hyperlipidemia and Metformin.

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INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia either due to a deficiency of insulin secretion or a decrease in insulin sensitivity and/or both [1]. Type 2 diabetes often characterized by peripheral insulin resistance (IR) and insufficient functional mass of β -cells [1,2]. Persistent hyperglycemia is often associated with long-term complications and had shown a significant impact on the quality of life and as well as on the health-care system [3]. According to the World Health Organization (WHO), the prevalence of type 2 diabetes will increase by up to 300 million by 2025 and could be due to lifestyle changes, consumption of calorie-rich diets, and obesity. India will be a diabetic capital of the world and sharing the global burden by 2025 [4-7].

IR develops due to the decrease in insulin action, insulin-stimulated glucose uptake, and dispose of the target tissues, often observed with hyperglycemia, hyperinsulinemia, and hyperlipidemia. IR is a central pathophysiological feature of type 2 diabetes and associated with dyslipidemia, obesity, hypertension, and atherosclerosis [8]. However, glucose intolerance in IR could be either due to the loss of insulin action or pancreas to induce hyperinsulinemia. IR owes to deregulate carbohydrate and lipid metabolism which are responsible for the oxidative stress that may lead to morbidity and mortality [9].

Fructose consumption has been dramatically increasing in the developed and industrialized nations. It is a lipogenic nutrient and commonly used

as a sweetener in both food and pharmaceutical industries. Fructose is rapidly absorbed from the intestine and transported to the liver through the portal vein. Unlike glucose, fructose uptake and metabolism are not regulated by negative-feedback mechanisms in the liver [10,11]. Hence, long-term high-fructose (HFr) diet intake causes deleterious effects on body weight, glucose, and lipid metabolism, resulting in increased synthesis of fatty acids (FAs) and triglycerides (TGs) which impair insulin sensitivity and which lead to IR [12]. Feeding of rats with HFr diet (>60% of total calories) results in several metabolic abnormalities due to the modification of insulin action and signaling pathways. Therefore, the HFr diet is used as an animal model to induce either type-2 diabetes associated with IR or metabolic syndrome (MetS) [5].

Glitazones and biguanides are insulin-sensitizing agents which are commonly used in the treatment of IR. However, the use of glitazones was associated with several adverse effects such as weight gain, bladder cancer, fractures, and hepatotoxicity [2]. The WHO Expert Committee on Diabetes (1980) had recommended the use of traditional plants to reverse and/or prevent metabolic disorders. They are widely being used because of their effectiveness, less or no side effects, and relatively economical. In response to the pertaining problem, attempts were made to identify the plants that are having insulin-sensitizing as well as antihyperlipidemic effects. Therefore, need of a scientific evaluation of their efficacy in IR animal models may become extremely useful [12,13].

Eugenia jambolana (Family: Myrtaceae) is commonly known as jamun and widely distributed in India and the Asian countries. *E. jambolana* has shown various pharmacological activities which include anti-diarrheal [14], gastric antisecretory [15], antioxidant [16], anti-inflammatory [17], antibacterial [18], anti-HIV [19], and neuropsychopharmacological [20] effects. Pre-clinical and clinical studies have shown that *E. jambolana* seed has anti-diabetic and anti-hyperlipidemic activities [21-23]. According to a review of the literature, there is a lack of scientific work on insulin-sensitizing effects of jamun seed extracts on HFr diet-induced IR model. Hence, the present study was intended to investigate the reversal effects of jamun seed extracts on hyperinsulinemia, hyperglycemia, and hyperlipidemia in HFr diet-induced IR in rats.

METHODS

Experimental animals

Male Wistar Albino rats, initially weighing 240–300 g, were obtained from the animal house and maintained at 22±3°C, humidity of 55±5%, and 12 h/12 h light-dark cycle with free access to food and water *ad libitum*. The experimental protocol (Ref.No: KSHEMA/IAEC/16/2015) was approved by the Institutional Animal Ethics Committee and followed the CPCSEA guidelines. Animal experimentation was carried out only after 1 week of acclimation period. The study had been conducted in the Department of Pharmacology, K.S. Hegde Medical Academy (KSHEMA), Mangalore.

Drugs and chemicals

Fructose was procured from LOBA Chemie, Pvt., Ltd, Bengaluru. Metformin (MET) was supplied in the form of Glycomet Tablets, USV Ltd., Mumbai, and ketamine injection was obtained from Neon Laboratories Ltd., Mumbai, India. Both the glucose and lipid profile kits were purchased from Agappe Diagnostics, Kerala. Serum insulin kit was obtained from RayBio, Delhi. All the other chemicals and reagents used for the experimental purpose were of analytical grade.

Plant extracts

Both the aqueous and ethanolic extracts of *E. jambolana* (batch.no JFE/D26/STD03 and STD04) were obtained from GreenChem, Bengaluru.

Experimental design

Male albino rats were randomly divided into five groups of six rats in each and provided with a standard pellet diet daily. All the rats except normal control received HFr diet (60% w/v) added to their drinking water for 42 days. Group 1 served as a normal control received gum acacia (2%, p.o) and Group 2 served as HFr control received HFr (60% w/v) for 42 days. Groups 3, 4, and 5 received HFr supplementation with Metformin (MET 500 mg/kg) and aqueous and ethanolic extracts of the jamun seed (JSAE and JSEE 1000 mg/kg of each), respectively, orally from day 28 to day 42 (Table 1). Blood samples were collected on days 1 and 42 under ketamine anesthesia from the overnight, fasted rats and centrifuged at 3,000 RPM for 10 min to carry out biochemical estimations.

Biochemical estimations

Blood glucose, total cholesterol (TC), TG, and high-density lipoprotein (HDL) levels (mg/dl) using the kit methods through Semi-Auto analyzer (Star 21 plus), respectively. Serum insulin (μ U/ml) was measured by Enzyme-Linked Immunosorbent Assay (ELISA) method,

using an ELISA reader (Rapid Diagnostics Pvt., Ltd.). The biochemical analysis had been carried out in the Central Research Laboratory, KSHEMA, Mangalore.

Low-density lipoprotein cholesterol (LDL) was calculated according to the Friedewald's equation and very low-density lipoprotein cholesterol (VLDL) with TG/5 equation [24].

Homeostasis model assessment (HOMA)-IR was calculated by using the following equation [25]:

$$\text{HOMA-IR} = \text{Fasting insulin } (\mu\text{U/ml}) \times \text{Fasting glucose (mg/dl)} / 405$$

Determination of physical parameters

Body weights

Weekly changes in their body weight of all group rats were recorded, and the weight gain of each rat was calculated by subtracting day 1 from the day 42 body weight.

Food and water intake

Daily food intake was calculated by deducting the amount of food left in the cage from the amount of food provided to each group, and the weekly average of daily food intake was calculated. Similarly, an average of daily water intake was also recorded.

Statistical analysis

Values are expressed as mean±standard error of the mean. One-way ANOVA followed by Tukey's multiple comparison tests, to assess the statistical significance with GraphPad prism. $p < 0.05$ was considered as statistically significant.

RESULTS

Effect on body weight

At the end of the study, all groups exhibited a significant ($p < 0.05$) increase in their body weight and weight gain in comparison to normal control. Body weight and weight gain in HFr control were significantly ($p < 0.05$) increased from a normal control. Administration of MET significantly ($p < 0.05$) reversed the increased body weight and weight gain as compared to HFr control. However, on HFr dietary supplementation with JSAE and JSEE for 14 days, failed to reverse increased body weight as compared to HFr control. There is no significant difference ($p > 0.05$) in a weight gain of JSAE but exists with JSEE as compared to MET (Figs. 1 and 2).

Effect on food and water intake

Long-term feeding of HFr diet significantly ($p < 0.05$) reduced food intake and increased water intake, in comparison to normal control. The MET significantly reversed ($p < 0.05$) the reduced food intake and increased water intake in comparison to HFr control. Supplementation of HFr diet with JSAE and JSEE also reversed the reduced food intake and increased water intake in comparison to HFr control. Both jamun extracts did not exhibit a significant ($p > 0.05$) difference in food and water intake, except JSAE with MET (Figs 3 and 4).

Effect on fasting glucose and insulin

No significant ($p > 0.05$) difference was observed in the initial fasting glucose and insulin levels in all groups. Fasting glucose and insulin

Table 1: Experimental grouping

Groups.no	Groups (n=6)	Drugs and dosage
Group 1	Normal control	Water (2% gum acacia, p.o)
Group 2	HFr control	HFr (60% w/v+2% gum acacia, p.o)
Group 3	MET	HFr+MET (500 mg/kg+2% gum acacia, p.o)
Group 4	JSAE	HFr+JSAE (1000 mg/kg+2% gum acacia, p.o)
Group 5	JSEE	HFr+JSEE (1000 mg/kg+2% gum acacia, p.o)

MET: Metformin, HFr: High-fructose, JSAE: Jamun seed aqueous extract, JSEE: Jamun seed ethanolic extract

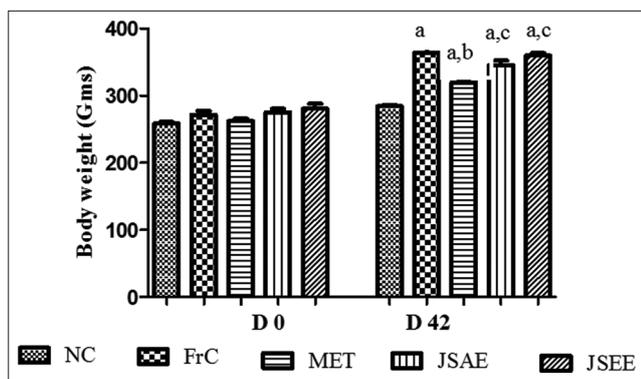


Fig. 1: Effect of aqueous and ethanolic extracts of *E. jambolana* seeds on body weights in high-fructose (HFr) diet-induced insulin resistance rats. Data are expressed as mean±standard error of the mean. a, b, and c mean significantly ($p<0.05$) different as compared with normal control, HFr control, and metformin groups, respectively, on the day 42

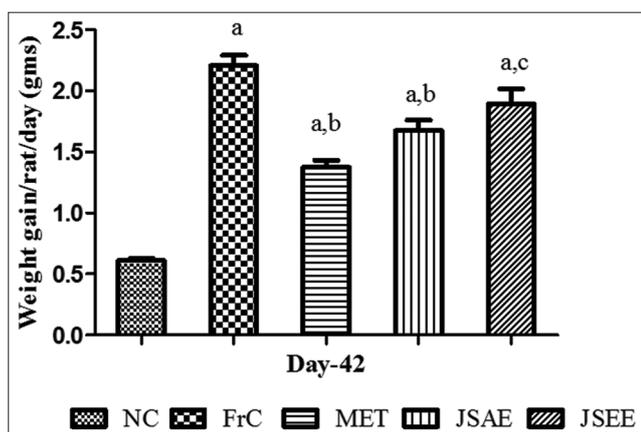


Fig. 2: Effect of aqueous and ethanolic extracts of *E. jambolana* seeds on weight gain in high-fructose (HFr) diet-induced insulin resistance rats. Data are expressed as mean±standard error of the mean. a, b, and c mean significantly ($p<0.05$) different as compared with normal control, HFr control, and metformin groups, respectively, on the day 42

levels were significantly ($p<0.05$) elevated in HFr control as compared to normal control, indicating the establishment of hyperglycemia and hyperinsulinemia of IR in rats. However, administration of MET significantly ($p<0.05$) reversed the fasting glucose and insulin levels as compared to HFr control, and the results were comparable to normal control, concerned with the glucose levels. It was observed that increased fasting glucose levels were significantly ($p<0.05$) reversed by feeding HFr supplementation with JSAE and JSEE, as compared to HFr control, and also exhibit significant ($p<0.05$) differences with normal control and MET group. JSAE has reduced fasting insulin levels as compared to HFr control, and both the extracts exhibit significant differences ($p<0.05$) with normal control and MET group (Table 2).

Effect on IR index

HFr control rats exhibited a significant ($p<0.05$) increase in HOMA-IR values as compared to normal control, due to hyperglycemia and hyperinsulinemia at the end of the experiment. MET significantly ($p<0.05$) reversed increased HOMA-IR values as compared to HFr control and exhibited comparable effects with normal control. Both the jamun extract groups, significantly ($P<0.05$) reversed the elevated HOMA-IR values as compared to HFr control group (Table 2).

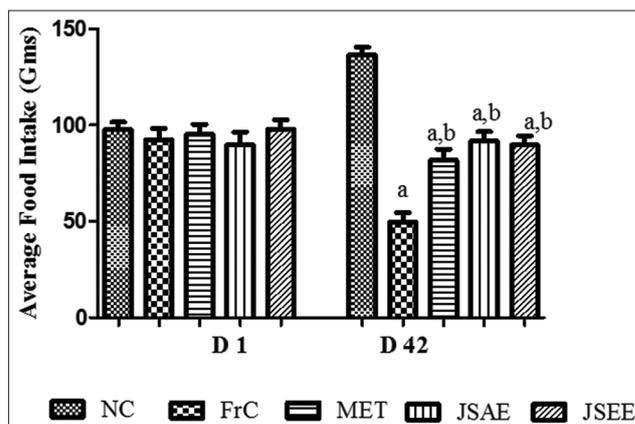


Fig. 3: Effect of aqueous and ethanolic extracts of *E. jambolana* seeds on average food intake in high-fructose (HFr) diet-induced insulin resistance rats. Data are expressed as mean±standard error of the mean. a, b, and c mean significantly ($p<0.05$) different as compared with normal control, HFr control, and metformin groups, respectively, on the day 42

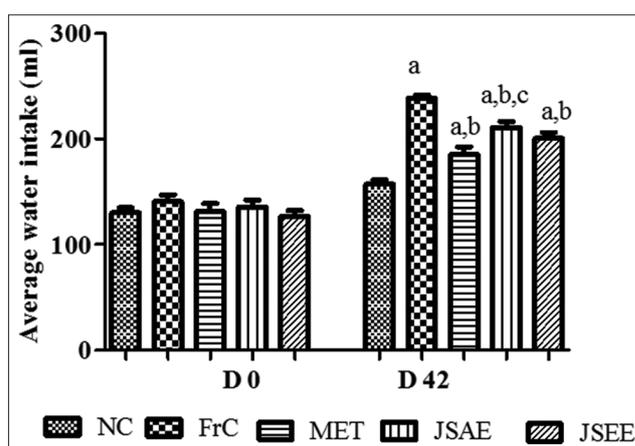


Fig. 4: Effect of aqueous and ethanolic extracts of *E. jambolana* seeds on average water intake in high-fructose (HFr) diet-induced insulin resistance rats. Data are expressed as mean±standard error of the mean. a, b, and c mean significantly ($p<0.05$) different as compared with normal control, HFr control, and metformin groups, respectively, on the day 42

Effect on lipid profile

HFr feeding significantly ($p<0.05$) increased TC, TG, VLDL, and LDL with decreased HDL levels in comparison to normal control and signifies the rise of hyperlipidemia associated with IR in rats. Administration of MET significantly ($p<0.05$) decreased TC, TG, VLDL, and LDL with a significant ($p<0.05$) increase in HDL levels as compared to HFr control and also significantly ($p<0.05$) varies with normal control. HFr supplementation with JSAE and JSEE significantly ($p<0.05$) decreased TC, TG, VLDL, and LDL levels in comparison with HFr control and significantly ($p<0.05$) differed with normal control. However, JSAE but not JSEE significantly ($p<0.05$) restores the HDL levels and varies with normal control. Both extract groups exhibit comparable effects with the MET in reversing lipid abnormalities in HFr-fed rats (Tables 3 and 4).

DISCUSSION

IR is observed before the onset of diabetes and often aggravated by several factors such as genetic, lifestyle, obesity, other diseases, and drugs such as glucocorticoids and protease inhibitors [1]. Fructose intake increases the risk of diabetes, obesity, and non-alcoholic fatty liver disease [12].

Table 2: Effect of aqueous and ethanolic extracts of *E. jambolana* seeds on fasting glucose, insulin, and HOMA-IR in HFr diet-induced IR rats

Groups	Fasting glucose (mg/dl)		Fasting insulin (μ U/L)		HOMA-IR	
	Day 1	Day 42	Day 1	Day 42	Day 1	Day 42
Group 1	98.88 \pm 4.52	113.92 \pm 4.88	25.60 \pm 3.38	28.23 \pm 3.4	6.41 \pm 1.11	8.08 \pm 1.19
Group 2	103.47 \pm 3.68	216.51 \pm 9.36 ^a	33.15 \pm 3.78	123.19 \pm 7.38 ^a	8.62 \pm 1.24	66.65 \pm 6.6 ^a
Group 3	87.02 \pm 6.21	126.21 \pm 5.43 ^b	24.35 \pm 3.51	65.26 \pm 5.26 ^{a,b}	5.48 \pm 1.12	20.61 \pm 2.46 ^b
Group 4	100.32 \pm 4.79	162.19 \pm 6.06 ^{a,b,c}	34.78 \pm 5.09	94.13 \pm 6.32 ^{a,b,c}	8.9 \pm 1.66	38.16 \pm 3.96 ^{a,b,c}
Group 5	95.80 \pm 4.53	170.29 \pm 7.14 ^{a,b,c}	30.73 \pm 4.87	106.19 \pm 4.56 ^{a,c}	7.5 \pm 1.44	45.02 \pm 3.74 ^{a,b,c}

Data are expressed as mean \pm SEM. a, b, and c mean significantly ($p < 0.05$) different as compared with normal control, HFr control, and MET groups respectively on the day 42. *E. jambolana*: *Eugenia jambolana*, HOMA-IR: Homeostasis model assessment-insulin resistance, HFr: High fructose, SEM: Standard error of the mean, MET: Metformin

Table 3: Effect of aqueous and ethanolic extracts of *E. jambolana* seeds on fasting lipid profile (TC, TGs, and HDL) in HFr diet-induced IR rats

Groups	TC		TGs		HDL	
	Day 1	Day 42	Day 1	Day 42	Day 1	Day 42
Group 1	73.35 \pm 2.78	78.2 \pm 2.97	50.7 \pm 4.66	55.93 \pm 2.77	48.07 \pm 2.49	53.7 \pm 2.69
Group 2	71.82 \pm 2.5	179.15 \pm 9.65 ^a	60.97 \pm 4.33	221.42 \pm 7.94 ^a	45.52 \pm 3.72	19.78 \pm 3.36 ^a
Group 3	74.92 \pm 3.72	125.51 \pm 6.2 ^{a,b}	56.68 \pm 4.35	132.37 \pm 4.24 ^{a,b}	47.6 \pm 2.54	34.91 \pm 3.1 ^{a,b}
Group 4	77.09 \pm 4.55	134.88 \pm 5.73 ^{a,b}	51.98 \pm 3.29	147.84 \pm 7.07 ^{a,b}	49.52 \pm 4.09	36.57 \pm 4.2 ^{a,b}
Group 5	69.48 \pm 4.08	146.5 \pm 6.17 ^{a,b}	50.14 \pm 4.12	160.02 \pm 6.87 ^{a,b,c}	44.74 \pm 3.55	31.85 \pm 2.47 ^a

Data are expressed as Mean \pm SEM. a, b, and c mean significantly ($p < 0.05$) different as compared with normal control, HFr control, and MET groups, respectively, on the day 42. *E. jambolana*: *Eugenia jambolana*, HFr: High fructose, IR: Insulin resistance, TC: Total cholesterol, TG's: Triglycerides, HDL: High-density lipoprotein, SEM: Standard error of the mean, MET: Metformin

Table 4: Effect of aqueous and ethanolic extracts of *E. jambolana* seeds on fasting lipid profile (VLDL and LDL) in HFr diet-induced IR rats

Groups	VLDL		LDL	
	Day 1	Day 42	Day 1	Day 42
Group 1	10.14 \pm 0.93	11.19 \pm 0.55	15.13 \pm 1.68	13.31 \pm 1.18
Group 2	12.19 \pm 0.87	44.28 \pm 1.59 ^a	14.11 \pm 1.6	115.09 \pm 8.1 ^a
Group 3	11.34 \pm 0.87	26.47 \pm 0.85 ^{a,b}	15.98 \pm 0.93	64.12 \pm 5.96 ^{a,b}
Group 4	10.4 \pm 0.66	29.57 \pm 1.41 ^{a,b}	17.18 \pm 1.61	68.75 \pm 6.92 ^{a,b}
Group 5	10.03 \pm 0.82	32 \pm 1.37 ^{a,b,c}	14.71 \pm 1.06	82.64 \pm 3.18 ^{a,b}

Data are expressed as Mean \pm SEM. a, b, and c mean significantly ($p < 0.05$) different as compared with normal control, HFr control, and MET groups, respectively, on the day 42. *E. jambolana*: *Eugenia jambolana*, HFr: High fructose, IR: Insulin resistance, VLDL: Very low-density lipoprotein-cholesterol, LDL: Low-density lipoprotein-cholesterol, SEM: Standard error of the mean, MET: Metformin

Our study finding was supported by Mielke *et al.*, who had stated that the HFr diet produces hippocampal IR. HFr diet (60%w/v) was most commonly used to induce hypertriglyceridemia, hyperinsulinemia, and hyperglycemia in hamsters, as reported by de Moura *et al.* and Suga *et al.* Among the various diabetic animal models, HFr diet mimics many symptoms of diabetes. Hence, this model has been used for the screening of effective and safer insulin sensitizers against IR [26-29].

In the present study, male rats were employed because female rats fail to develop IR with the HFr diet, probably due to the protective effects of the sex hormones in them [9,30]. Consumption of HFr diet significantly decreased food intake and increased calorie intake, (through fructose drinking water) promoted fat deposition, and weight gain in rats over a period. Excess calorie intake may be because of HFr that can alter leptin levels, play a significant role in regulating food intake and energy expenditure, thereby increase calorie intake, and encourage weight gain [31]. Both the MET and extracts restored water intake, due to decreased hyperglycemia and blood osmolarity which diminished stimulating effects on the hypothalamus and decreased polydipsia as observed in IR. Supplementation with JSAE extract effectively reduced weight gain in HFr-fed rats by decreasing FA

oxidation, and thereby reducing lipid storage in the tissues. Similarly, both the extracts have improved food intake by ameliorating insulin-sensitizing action and glucose abnormalities.

Hyperglycemia in HFr-fed rats was due to excess hepatic gluconeogenesis as a consequence of IR. Fructose increases the hexosamine pathway for glucose production, plays a crucial role in the development of IR and hyperlipidemia in rats. It does not stimulate insulin secretion directly, but the subsequent hyperglycemia with increased release of glucose-dependent insulin tropic polypeptide and glucose like peptide-1 from the intestine enhances insulin secretion contributes to hyperinsulinemia [6]. Fructose stimulates the β -cells to enhance insulin secretion and decreases insulin extraction by the liver with a delay in insulin clearance from circulation, leading to hyperinsulinemia [32]. The fasting glucose and insulin levels reflect HOMA-IR values and hence used to quantify the IR. A decrease in HOMA-IR values indicates the improvement of IS by reversing glucose and/or insulin concentration in HFr-fed rats [29,33]. In our study, HFr supplementation with MET and jamun extracts significantly reversed HOMA-IR values and exhibits antihyperglycemic effect through their insulin-sensitizing action rather than an increased insulin secretion.

In the liver, fructose increases the rate of *de novo* lipogenesis and TG synthesis. Hence, both TGs and free fatty acids (FFA) enhance the glycogenolysis, successively increase the hepatic glucose levels, and later lead to extrahepatic IR [2,4]. Before phosphofructokinase metabolizes fructose, it gets converted into glycerol and FFAs, which are taken up by the adipose tissue, leading to additional adiposity. The lipogenic nature of fructose increases the synthesis and release of atherogenic lipoproteins. Fructose-induced hyperglycemia also promotes lipid peroxidation and increases oxidative stress, which impairs insulin action at the cellular level. Hypertriglyceridemia and hypercholesterolemia are the most important factors to increase the risk of coronary heart disease [34]. Either increased HDL or decreased oxidized LDL levels will improve endothelial dysfunction by enhancing nitric oxide production and offers protection against atherosclerosis, most commonly seen in IR with obesity [9,27]. Hence, the present investigation demonstrates that both MET and Jamun extracts exhibited antihyperlipidemic effects by decreasing TC, TG, and LDL with an increase in HDL levels except JSEE group. Therefore, jamun extracts can be used to reverse hyperlipidemia in IR patients, according to ATP III guidelines.

CONCLUSION

The promising results have shown that both jamun extracts can mitigate the hyperglycemia, hyperlipidemia, and hyperinsulinemia by improving insulin action at the target tissues, with a decrease in HOMA-IR index in HFr-fed rats. Hence, the study concludes that the reversal effects of jamun extracts were similar to insulin-sensitizing actions of MET and advised as a food supplement in IR patients associated with metabolic abnormalities.

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CONFLICTS OF INTEREST

All authors had declared no conflicts of interests.

AUTHORS' CONTRIBUTION

The present work was carried out with the cooperation between all the authors. The two first authors Mr. B. Gupatha and Dr. S. Adiga were the principal investigators of the experimental study. Dr. Nayak, Dr. Asitava, and Dr. S. Kumar were contributed in the selection of drugs, plants, data analysis, and drafting of the manuscript. All authors reviewed and approved the manuscript for intellectual content.

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