Pharmacogn. Res., 2025; 17(4):1298-1302.
https://www.phcogres.com

Original Article

Modulation of Glucose Homeostasis and Behavioral Parameters by *Passiflora edulis* in a Rodent Model of Metabolic Syndrome Induced by High Fructose Intake

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ABSTRACT

Background: Syndrome X (Metabolic syndrome), commonly associated with high-fructose dietary intake, is characterized by insulin resistance, hyperglycemia, and related neurobehavioral impairments. *Passiflora edulis* Extract (EPE), rich in bioactive compounds, is investigated for its potential therapeutic effects on fructose-induced MS. **Materials and Methods:** A total of five groups were formed using female Wistar rats (200-250 g, *n*=6). Group I served as the control group; Group II was exposed to 20% fructose to induce metabolic syndrome; Groups III to V received fructose along with EPE at 250, 500, and 1000 mg/kg doses, respectively, for a duration of 8 weeks. Biochemical parameters (blood glucose, insulin, HOMA-IR) and behavioral markers (locomotor activity, immobility time, fall time, paw withdrawal time) were recorded. Serum insulin was measured, and HOMA-IR was calculated. **Results:** Chronic fructose intake significantly increased blood glucose, insulin, and HOMA-IR values, indicating metabolic disruption. EPE administration significantly reduced these values in a dose-dependent manner, with the highest efficacy observed at 1000 mg/kg. EPE also improved behavioral outcomes: it increased fall time and locomotor activity, while decreasing immobility time and paw withdrawal time, demonstrating improvements in motor coordination, depressive-like behavior, and pain sensitivity. Effects were more pronounced at higher EPE doses. **Conclusion:** EPE significantly ameliorated both metabolic and neurobehavioral impairments induced by fructose in rats. Its dose-dependent efficacy suggests promising as a plant-based therapeutic for controlling metabolic syndrome and related behavioral dysfunctions.

Keywords: *Passiflora edulis* Extract, Metabolic Syndrome, Fructose, Insulin Resistance, HOMA-IR, Behavioral Markers.

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Received: 14-05-2025;
Revised: 09-07-2025;
Accepted: 23-09-2025.

INTRODUCTION

Metabolic Syndrome (MS) is a growing global health concern characterized by a combination of metabolic abnormalities, comprising visceral fat accumulation, impaired insulin sensitivity, High blood sugar, abnormal lipid profile, and high blood pressure. It significantly elevates the likelihood of type 2 diabetes, cardiovascular diseases, and other chronic conditions.[1] One of the major contributing factors to MS is the excessive consumption of fructose, which has been shown to induce insulin resistance, elevate blood glucose levels, and disrupt lipid metabolism in both humans and animal models.[2,3] In addition to these metabolic disturbances, fructose-induced MS is often associated with neurobehavioral impairments, including reduced locomotor activity, increased depressive-like behavior, altered pain sensitivity, and impaired motor coordination.[4-8]

Natural products and plant-based therapies have gained attention as potential alternatives for managing MS and its associated complications due to their broad pharmacological properties and minimal side effects.[9] *Passiflora edulis*, commonly known as passion fruit, is traditionally used for its anxiolytic, sedative, and antioxidant properties.[10,11] Emerging evidence suggests that *P. edulis* may also possess antidiabetic and neuroprotective effects, though its role in metabolic and behavioral modulation in the context of MS has not been thoroughly investigated.[12-15]

This experimental work evaluates the biological modulation exerted by *P. edulis* Extract (EPE) on both metabolic and behavioral parameters in a rat model of fructose-persuaded MS. Specifically, the study focuses on glucose homeostasis markers-blood glucose, serum insulin, and HOMA-IR-as well as

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DOI: 10.5530/pres.20252369

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behavioral assessments including locomotor activity, immobility time, paw withdrawal latency, and fall time. By addressing both metabolic and neurological outcomes, this research seeks to provide a more comprehensive understanding of the clinical utility of *P. edulis* as a potential treatment modality for MS.

MATERIALS AND METHODS

Drugs and chemicals

Fructose was obtained from a local supplier, and the study employed standard biochemical kits as well as chemicals and reagents of analytical grade quality.

Experimental animals

For this study, female Wistar rats (200-250 g) were acquired from the Zydus Research Centre in Ahmedabad. The rats were accommodated under standardized conditions encompassing with a diurnal cycle with 12 hr of light and 12 hr of darkness, temperature set to 24±1°C and humidity levels between 35% and 60%. Ad libitum access to pellet feed and water for the duration of the study. Before beginning the experiment, the rats underwent a 48-hr acclimatization phase. Approval for the preclinical study was granted by the Institutional Animal Ethics Committee.

Experimental design

Random grouping assigned six rats to each of the five groups to evaluate the effects of EPE on fructose-induced MS. Group I functioned as the normal control and was administered distilled water orally. Group II was given a fructose solution in their drinking water to create the fructose control group. Groups III, IV, and V were fed a fructose diet and administered increasing oral doses of EPE (250, 500, and 1000 mg/kg, respectively) to examine potential dose-dependent effects. All groups except Group I were exposed to a 20% fructose solution to induce MS.[16,17] Treatments were administered daily for a duration of 8 weeks. Behavioral parameters such as locomotor activity, immobility time, paw withdrawal time, and fall time were recorded to assess the neurological and behavioral effects associated with fructose-induced MS.[18-20] These measures were used to evaluate motor function, depressive-like behavior, pain sensitivity, and balance impairments that may have resulted from metabolic disturbances induced by high fructose intake. Blood glucose levels were recorded using a glucometer. Upon conclusion of the experiment, blood was drawn from the retro-orbital sinus of anesthetized rats with glass capillaries for biochemical evaluation. After clotting for 15 min, samples were centrifuged at 5000 rpm for 20 min to separate serum, subsequently stored at -20°C until further examination. Serum insulin levels were measured using ELISA due to its high sensitivity and specificity for detecting insulin concentrations. Following this, HOMA-IR, derived from fasting blood glucose and insulin concentrations, was used to quantify insulin resistance and act as an indicator of metabolic dysfunction.[21]

Statistical analysis

The data are shown as Mean±SEM. Differences among groups were analyzed using one-way ANOVA, complemented by Bonferroni *post hoc* tests as required. Statistical evaluations employed GraphPad Prism software, with significance defined as $p<0.05$.

RESULTS

Impact of EPE on blood glucose, insulin and HOMA-IR against fructose-induced MS

In the present study, chronic intake of fructose caused notable impairments in glucose metabolism, as demonstrated by significantly elevated blood glucose, insulin levels, and HOMA-IR values in the fructose-fed control group when compared to normal controls. Blood glucose levels showed a substantial increase ($p<0.0001$) due to fructose administration. However treatment via oral gavage with EPE at doses of 250, 500, and 1000 mg/kg led to a statistically significant and dose-dependent decrease in glucose levels ($p<0.01$, $p<0.001$, and $p<0.0001$, respectively), indicating that EPE effectively counteracts fructose-induced hyperglycemia. Fructose-fed rats also exhibited significantly increased insulin levels ($p<0.001$), indicating the onset of insulin resistance. Treatment with EPE at doses of 500 mg/kg and 1000 mg/kg meaningfully abridged insulin levels ($p<0.05$ and $p<0.01$, respectively), whereas the 250 mg/kg dose did not show a notable effect, suggesting that improved insulin sensitivity may be more pronounced at higher doses of EPE. Additionally, HOMA-IR scores, a marker of insulin resistance, were significantly elevated in the fructose control group ($p<0.0001$). Administration of EPE at all tested doses resulted in a substantial decline in HOMA-IR ($p<0.01$, $p<0.001$, and $p<0.0001$ for 250, 500, and 1000 mg/kg, respectively), again indicating a dose-dependent improvement in insulin sensitivity. Collectively, these results demonstrate that EPE significantly improves glucose metabolism and reduces insulin resistance in a dose-dependent fashion in a rodent model of fructose-persuaded MS. These findings support the therapeutic potential of EPE in managing metabolic dysfunctions associated with excessive fructose consumption (Figure 1).

Effect of EPE on the neurological and behavioral effects against fructose-induced MS

The results revealed that fructose-fed rats exhibited a substantial decline in fall of time ($p<0.0001$), indicating impaired physical performance likely due to metabolic dysfunction or fatigue, while treatment with EPE at 250, 500, and 1000 mg/kg significantly improved this measure in a dose-dependent fashion ($p<0.01$; $p<0.0001$; $p<0.0001$, correspondingly), suggesting protective effects on motor function. Paw withdrawal time was meaningfully

augmented in fructose-fed rats ($p<0.0001$), reflecting heightened pain sensitivity or hyperalgesia, but EPE treatment at all doses markedly reduced paw withdrawal time ($p<0.0001$), indicating potential pain-relieving and inflammation lowering benefits. Immobility time, a marker of depressive-like behavior, was significantly elevated in fructose control rats ($p<0.0001$), while higher doses of EPE (500 and 1000 mg/kg) considerably declined immobility time ($p<0.05$ and $p<0.01$), suggesting antidepressant-like effects; the lowest dose showed no significant effect. Additionally, locomotor activity was significantly reduced in fructose-fed rats ($p<0.0001$), indicative of lethargy or metabolic impairment, but was significantly increased by EPE at 500 and 1000 mg/kg ($p<0.001$ and $p<0.0001$), with no significant change at 250 mg/kg. Collectively, these findings demonstrate that EPE dose-dependently mitigates fructose-persuaded impairments in motor coordination, pain sensitivity, depressive-like behavior, and physical activity, likely through its metabolic-regulating, neuroprotective, and inflammation lowering properties (Figure 2).

DISCUSSION

The current investigation highlights that long-term consumption of fructose leads to significant disturbances in glucose regulation, as shown by elevated levels of fasting blood glucose, insulin, and HOMA-IR in the fructose-treated control group. These results align with previous research indicating that high fructose intake contributes to the onset of insulin resistance and elevated blood sugar, both of which are central features of MS.[22,23] The marked decline in glucose, insulin, and HOMA-IR values following treatment with EPE points to its promising as a pharmacological agent for enhancing insulin sensitivity and maintaining glucose balance. This supports earlier studies that found polyphenol-rich plant extracts improve insulin signaling pathways and help reduce systemic inflammation.[24,25]

The fact that EPE's effectiveness increased with higher doses-particularly at 500 and 1000 mg/kg-suggests that a greater concentration of bioactive compounds may be required for optimal metabolic benefits. This observation is consistent with the previous findings, it was reported dose-dependent enhancements in insulin sensitivity when using polyphenol-rich plant extracts in fructose-fed animals.[26] Additionally, the restoration of HOMA-IR values supports Severeyn *et al.*, (2019) who highlighted the usefulness of HOMA-IR in identifying insulin resistance and evaluating responses to treatment.[21]

Beyond improvements in metabolic parameters, the study also shows that EPE provides notable benefits for neurobehavioral health. Enhanced physical performance, as reflected in longer fall of time and improved locomotor activity, may result from better energy metabolism and reduced fatigue. These effects align with earlier studies that link insulin resistance and inflammation to neuromuscular decline and lower physical activity in models of MS.[27-29]

In addition, the observed reduction in paw withdrawal time suggests that EPE possesses pain-relieving and inflammation lowering properties. Previous studies have associated fructose-induced hyperalgesia with elevated oxidative stress and inflammatory cytokines,[30] which may be mitigated by the antioxidant components of EPE. The reduction in immobility time in the forced swim test, especially at higher doses, implies antidepressant-like effects. These results align with findings from Ali *et al.*, (1998) who demonstrated that plant-based compounds

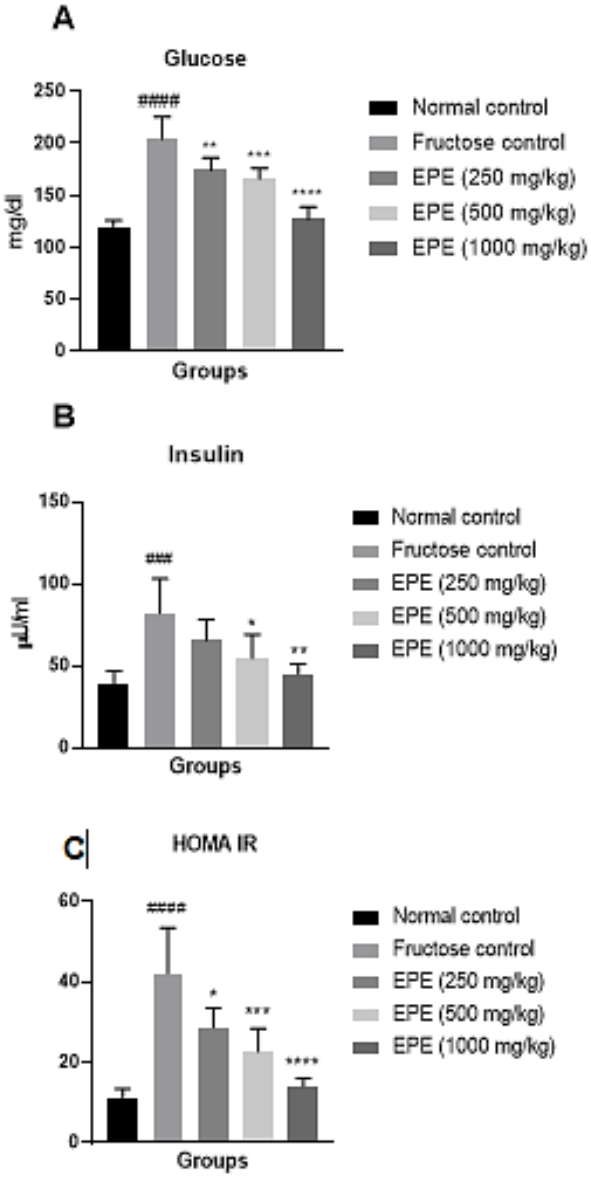

Figure 1: Effect of EPE on blood glucose, insulin levels, and HOMA-IR in fructose-persuaded MS. Values are stated as mean±SEM; $n=6$, $^{###}p<0.001$, $^{####}p<0.0001$ relative to normal control; $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, $^{****}p<0.0001$ relative to fructose control.

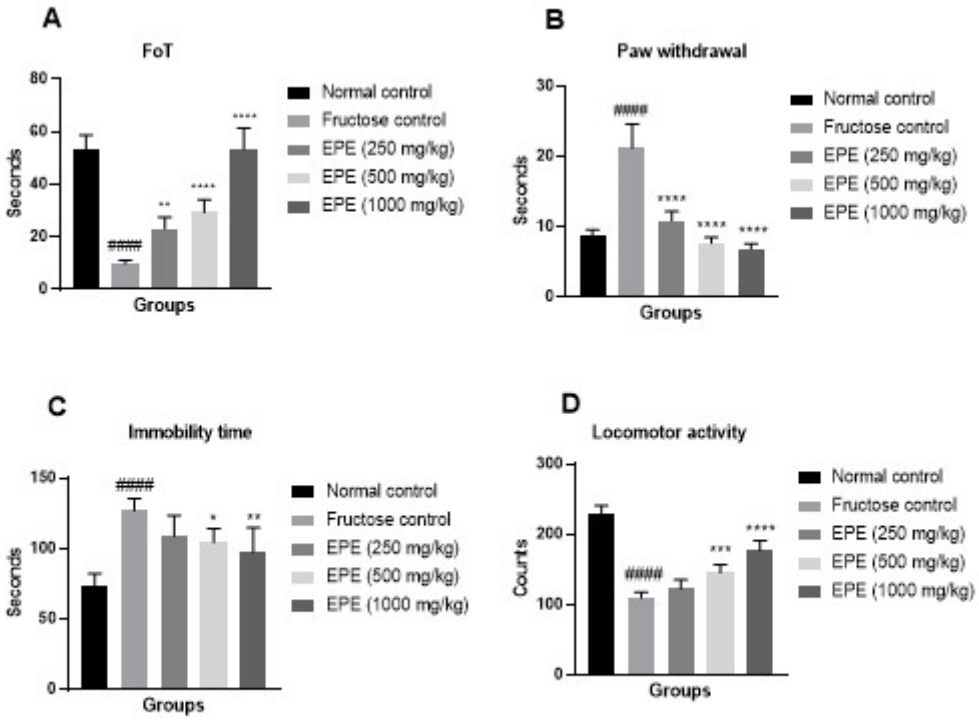

Figure 2: Effect of EPE on neurological and behavioral impairments in fructose-persuaded MS. Values are stated as mean±SEM; n=6, $^{\#\#\#\#}p$<0.0001 relative to normal control; $^{*}p$<0.05, $^{**}p$<0.01, $^{***}p$<0.001, $^{****}p$<0.0001 relative to fructose control.

could reverse depression-like behaviors by regulating oxidative stress and inflammation in the brain.[31]

CONCLUSION

The present study provides compelling evidence that EPE exerts significant protective effects against fructose-induced metabolic syndrome in a dose-dependent manner. Chronic fructose intake led to marked disruptions in glucose metabolism, including elevated blood glucose, insulin levels, and HOMA-IR scores, indicative of insulin resistance. EPE treatment at doses of 250, 500, and 1000 mg/kg significantly improved these metabolic parameters, with the higher doses demonstrating more pronounced effects, suggesting enhanced insulin sensitivity and better glycemic control. In addition to its metabolic benefits, EPE also mitigated a range of fructose-induced neurobehavioral disturbances. These included impaired motor coordination, increased pain sensitivity (hyperalgesia), depressive-like behaviors, and reduced physical activity. EPE administration effectively reversed these impairments, particularly at higher doses, indicating its potential neuroprotective, analgesic, antidepressant, and energy-restoring properties. Collectively, the findings highlight the multifaceted therapeutic potential of EPE in combating both metabolic and neurological complications associated with excessive fructose consumption. These results support further exploration of EPE as a natural intervention for managing metabolic syndrome and its related behavioral dysfunctions.

ABBREVIATIONS

MS: Metabolic Syndrome; **EPE:** *Passiflora edulis* Extract; **HOMA-IR:** Homeostatic Model Assessment for Insulin Resistance; **SEM:** Standard Error of the Mean; **ANOVA:** Analysis of Variance; **ELISA:** Enzyme-Linked Immunosorbent Assay; **RPM:** Revolutions per minute; **°C:** Degrees Celsius; **hr:** Hour; **min:** Minutes; **kg:** Kilogram; **mg:** Milligram; **g:** Gram; **mL:** Milliliter; **µL:** Microliter; **n:** Sample size; **p:** Probability value.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Patel KP, Maheshwari RA, Solanki N, Kakadiya J. Modulation of Glucose Homeostasis and Behavioral Parameters by *Passiflora edulis* in a Rodent Model of Metabolic Syndrome Induced by High Fructose Intake. Pharmacog Res. 2025;17(4):1298-302.