EVALUACTION OF *FICUS RACEMOSA* LEAVES EXTRACT EFFECT ON HIGH FRUCTOSE INDUCED INSULINE RESISTANCE ON EXPERIMENTAL ANIMALS

R. P. Babhulkar[1], D. D. Bandawane*, P. K. Hajare[2], A. V. Yalsangi[3]

Department of Pharmacology, P. E. S. Modern College of Pharmacy, Nigdi, Pune-44 Maharashtra, India.

Contact details of Corresponding authors

Dr. Deepti D. Bandawane
HOD & Professor,
Department of Pharmacology, P.E.S. Modern College of Pharmacy, Nigdi, Pune-44 Maharashtra, India.

1. Rasika P. Babhulkar

Department of Pharmacology, P.E.S. Modern College of Pharmacy, Nigdi, Pune-44 Maharashtra, India.

2. Pratiksha K. Hajare

Assistant Professor

Department of Pharmacology, P.E.S. Modern College of Pharmacy, Nigdi, Pune-44 Maharashtra, India.

3. Arpita V. Yalsangi

Department of Pharmacology, P.E.S. Modern College of Pharmacy, Nigdi, Pune-44 Maharashtra, India.

Keywords: - Insulin resistance, High fructose diet, *Ficus racemosa*, Metabolic syndrome.

ABSTRACT:

Background: Reduced sensitivity of body tissues to insulin causes insulin resistance, which impairs the regulation of downstream metabolic pathways and raises blood glucose levels. It has been demonstrated that high fructose diets induce insulin resistance in rats, which lowers insulin sensitivity overall and in the liver in particular. Plant-derived formulations have become more well-liked in the quest for efficient therapies due to their capacity to address a wide range of illnesses. Ficus racemosa, a member of the Moraceae family, is one such plant

that has long been used to treat diabetes and its aftereffects. The study goal is to assess the possible protective role of *Ficus racemosa* against insulin resistance through various analysis.

Methods: In this study, an animal model of insulin resistance caused by a high-fructose diet is used to assess the insulin-resistant action of Ficus racemosa extract using multiple assessment parameters. The animals used in the experiment were given the extract orally. These techniques include measuring serum insulin and glucose levels, analysing the lipid profile, measuring oxidative enzymes, measuring inflammatory markers, and histopathological examination of liver sections. The collective analysis of these analysis sheds light on the effects of Ficus racemosa extract on metabolic parameters associated with insulin resistance.

Results: Findings of this study provide that *Ficus racemosa* has possibly effective in ameliorating the fructose diet-induced insulin resistance. Assessment of serum glucose and insulin levels, lipid profile analysis, and measurement of oxidative enzymes and TNF- α gives positive results. A significant effect of *Ficus racemosa* extract was found for hyperinsulinemia, hyperglycaemia, dyslipidaemia, inflammation and oxidative damage. Additionally, the histopathological examination of liver sections provides visual insights into the structural changes that may occur as a result of the treatment.

Conclusions: This study demonstrates the beneficial effects of extracts of *Ficus racemosa* on insulin resistance in rats fed a high-fructose diet. To completely comprehend the processes underlying these reported benefits and to confirm Ficus racemosa extract's potential as a therapeutic alternative for controlling insulin resistance and its related problems, more study and research are necessary.

Key Words: Insulin resistance, High fructose diet, *Ficus racemosa*, Metabolic syndrome.

1 INTRODUCTION

Insulin resistance is a state in which the body's cells lose their sensitivity to the effects of insulin. As a result, insulin is less able to efficiently regulate other cellular functions, including glucose metabolism, which raises blood glucose levels. Insulin resistance impacts not only glucose homeostasis but also other metabolic pathways such as protein synthesis and lipid metabolism. It may be linked to a number of harmful health outcomes, including a higher chance of type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD) [1,2].

Insulin resistance is associated with both environmental and genetic factors. Dietary composition is a crucial environmental component[3]. The consumption of soft drinks and other high-fructose beverages has surged in recent years, leading to an increase in fructose intake. Research conducted on rats has indicated that an excessive consumption of fructose results in a reduction of insulin sensitivity in the liver and other peripheral organs [2,4]. Higher amounts of nonesterified fatty acids (NEFA), reduced levels of leptin production, and decreased insulin secretion are the outcomes of fructose consumption. Fructose also promotes the production of very-low-density lipoprotein (VLDL) triglycerides in the liver, which exacerbates hypertriglyceridemia. These alterations result in elevated body weight and blood

cholesterol levels. A vicious cycle including low insulin sensitivity, poor glucose metabolism, and increased triglycerides culminates in insulin resistance [5].

Ficus racemosa, a member of the Moraceae family, is also referred to as gular or umbar. F. racemosa is widely grown throughout India and is said to have numerous therapeutic uses. Every part of this plant, including the leaves, fruits, bark, latex, and root sap, has therapeutic value in India's traditional medical system [6]. Many advantageous pharmacological benefits have been demonstrated by it, including antihyperglycemic [7,8], anti-inflammatory [9,10], wound healing [11] and in vitro antioxidative [12] activities. However, no scientific studies have reported for insulin resistance effects of *Ficus racemosa*. The present work was therefore to evaluate its protective effect on insulin resistance in high fructose diet induced model in albino rats.

2 MATERIALS AND METHOD

2.1 Collection and authentication of plant

The leaves of *Ficus racemosa* were collected from Akurdi, Pune-Maharashtra state, India in the month of November 2023. Plant was identified and authenticated by Dr. Randive S. D. and Dr. M. N. Jagtap, Botanist, Herbarium and e herbarium, Department of botany and research center, Solapur. Voucher specimen 6:570 (1847,wfo-0000417298)

2.2 Preparation of extracts

The leaves of *Ficus racemosa* were dried in the shade under normal environmental condition. The completely dried leaves were powdered with an electric grinder and used for the extraction. The leaf powder was subjected to cold maceration using solvents 90% ethanol for 7 days to obtain ethanolic extract. The solvent was filtered using filter paper (Whatman No A-1). Filtrate was collected in tray and evaporated on a rota evaporator at 200 C to obtain a yield of 10.88% w/w. The obtained ethanolic extract of *Ficus racemosa* was preserved in the refrigerator till further use.

2.3 Preparation of fructose diet

Insulin resistance was induced in experimental animals by using high fructose diet. Initially, the rats were divided randomly into two groups first group received normal feed and another group was feed with the fructose-enriched diet for 8 weeks. The composition of the diet is given below in Table 1

Ingredients	**Quantity(per1000gm)**
Fructose	660
Casein	100
Lard	80
Zinc carbonate	0.04
Cellulose	150
Mineral mix	5.0
Vitamin mix	5.0

Table 1: Composition of high fructose diet

2.4 Experimental animals and protocol

Male wistar rats (180–100 g) were purchase from Crystal Biological Solutions, Pune. The study protocol was approved by the Institutional Animal Ethical Committee (IAEC) of the Modern College of Pharmacy in accordance with the regulations of CPCSEA (MCP/IAEC/11/2022).

3.5 Experimental design

A total of 30 rats (6 normal; 24 disease control) were divided into five different groups consisting of six animals in each group as follows.

Group 1: Normal control rats receiving normal diet.
Group 2: High fructose diet receiving group.
Group 3: High fructose diet with 10 mg/kg of Pioglitazone.
Group 4: High fructose diet with 100 mg/kg of EEFR.
Group 5: High fructose diet with 200 mg/kg of EEFR.

The EEFR and pioglitazone were administered orally once daily for 2 weeks using an oral feeding needle. Rats were tested for blood glucose levels at day 0 and then day 42 to check for the induction of insulin resistance.

2.6 Parameters studied

Body weight (g), blood glucose levels (mg/dl), serum cholesterol levels (mg/dl), serum triglyceride (mg/dl), HDL (mg/dl), LDL (mg/dl),VLDL(mg/dl) were measured on initial, 42 and 42th day of experiment. The Serum insulin levels (mU/L), antioxidants such as catalase (CAT), super oxide dismutase (SOD) were determined, Serum level of TNF-a was evaluated by ELISA kits, histopathology of liver were detected in samples taken on 56th day of experiment. The serum glucose was estimated using commercially available glucometer (Accu check, Germany). Serum cholesterol, serum triglyceride, HDL, LDL,VLDL were determined by autoanalyzer (Erba Mannheim test kits).

2.7 Statistical analysis

The different values determined were compared with each other and the comparison was made by using a statistical test. One-way analysis of variance (ANOVA), followed by Dunnet's test and Tukey's test for multiple comparisons was performed for all the raw data recorded during the study using GraphPad Prism Version 10 software. Values were represented as mean ± SEM and $p<0.05$ was considered statistically significant.

3 RESULTS

3.1 Body weight

The diseased group exhibited significant weight gain at day 42 as compared with normal groups. At day 56 pioglitazone and EEFR groups caused significant weight loss as comparison to diseased group.

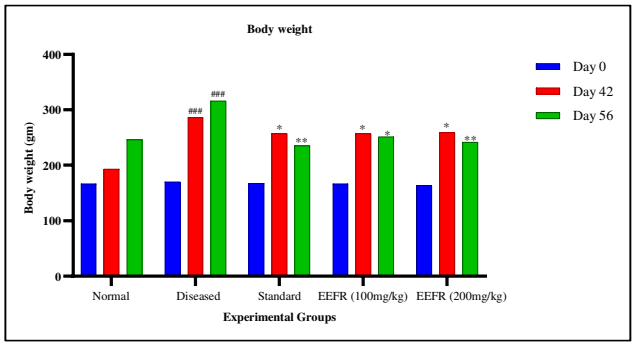

Fig 1: Effect of EEFR on body weight in high fructose-induced insulin-resistant rats. EEFR- ethanolic extract of Ficus racemosa leaves. Data are expressed as mean ± S.E.M. (n=6). ###p < 0.001, as compared to Normal control; **p < 0.05, ***p < 0.001 as compared to Diseased control. Data was analyzed by one-way Analysis of Variance (ANOVA) followed by Tukey's multiple test for comparison.

3.2 Liver weight

Liver weight in the disease group was significantly increased as compared to a normal group. A significant decrease was found in the liver weight of the group treated with pioglitazone and EEFR at doses of 100 mg/kg and 200 mg/kg in comparison with the disease control group.

Groups	**Liver Weight (Day 56)**
NC	10.8 ± 0.8
DC	$13.98 \pm 0.65^{###}$
DC + Pioglitazone	$11.17 \pm 0.22^{***}$
DC + EEFR 100 mg/kg	$12.9 \pm 0.11^{**}$
DC + EEFR 200 mg/kg	$11.25 \pm 0.4^{***}$

Table 2: Effect of EEFR on liver weight in high fructose-induced insulin-resistant rats. NC- normal control; DC- disease control; EEFR- ethanolic extract of *Ficus racemosa* leaves. Data are expressed as mean ± S.E.M. (n=6). ###p < 0.001, as compared to NC; **p < 0.05, ***p < 0.001 as compared to DC. Data was analysed by one-way Analysis of Variance (ANOVA) followed by Dunnet's multiple test for comparison.

3.3 Blood glucose

The diseased group exhibited significant increase fasting blood glucose at day 42 as compared with the normal group. At day 56, pioglitazone and EEFR group showed significant decrease of fasting blood glucose comparison to disease control.

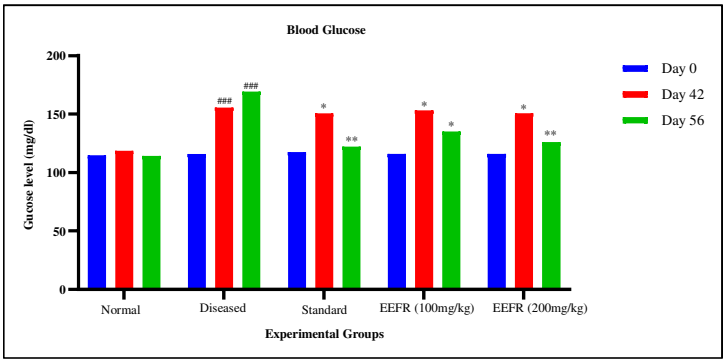

Fig 2: Effect of EEFR on Glucose in high fructose-induced insulin-resistant rats. EEFR- ethanolic extract of *Ficus racemosa* leaves. Data are expressed as mean ± S.E.M. (n=6). ###p < 0.001, as compared to Normal control; **p < 0.05, ***p < 0.001 as compared to Diseased control. Data was analysed by one-way Analysis of Variance (ANOVA) followed by Tukey's multiple test for comparison.

3.4 Serum Insulin and HOMA-IR

There was a significant increase in serum insulin levels and HOMA-IR in the diseased group as compared to the normal group. A significant decrease was found in the serum insulin level HOMA-IR of the group treated with pioglitazone and EEFR groups in comparison with the disease group.

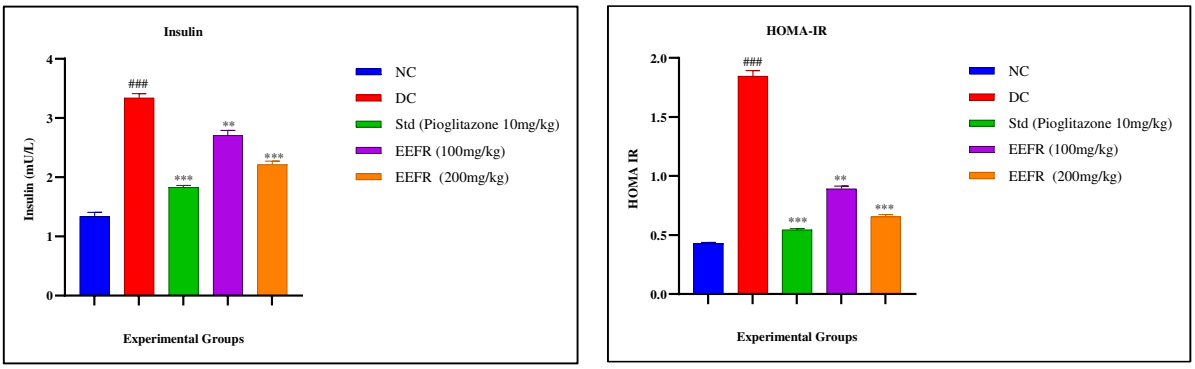

Fig 3: Effect of EEFR on Insulin and HOMA-IR in high fructose-induced insulin-resistant rats. NC- normal control; DC- disease control; EEFR- ethanolic extract of *Ficus racemosa* leaves. Data are expressed as mean ± S.E.M. (n=6). ###p < 0.001, as compared to NC; **p < 0.05, ***p < 0.001 as compared to DC. Data was analysed by one-way Analysis of Variance (ANOVA) followed by Dunnet's multiple test for comparison.

3.6 Lipid profile

Lipid profiles which include TG, TC, HDL, LDL, VLDL and FFA. Serum triglyceride, total cholesterol, LDL and VLDL level in the disease group was significantly increased as compared to a normal group. A significant decreased was found in the Serum triglyceride, total cholesterol, LDL and VLDL level of the group treated with pioglitazone and EEFR at both doses (100 and 200 mg/kg) in comparison with the disease group.

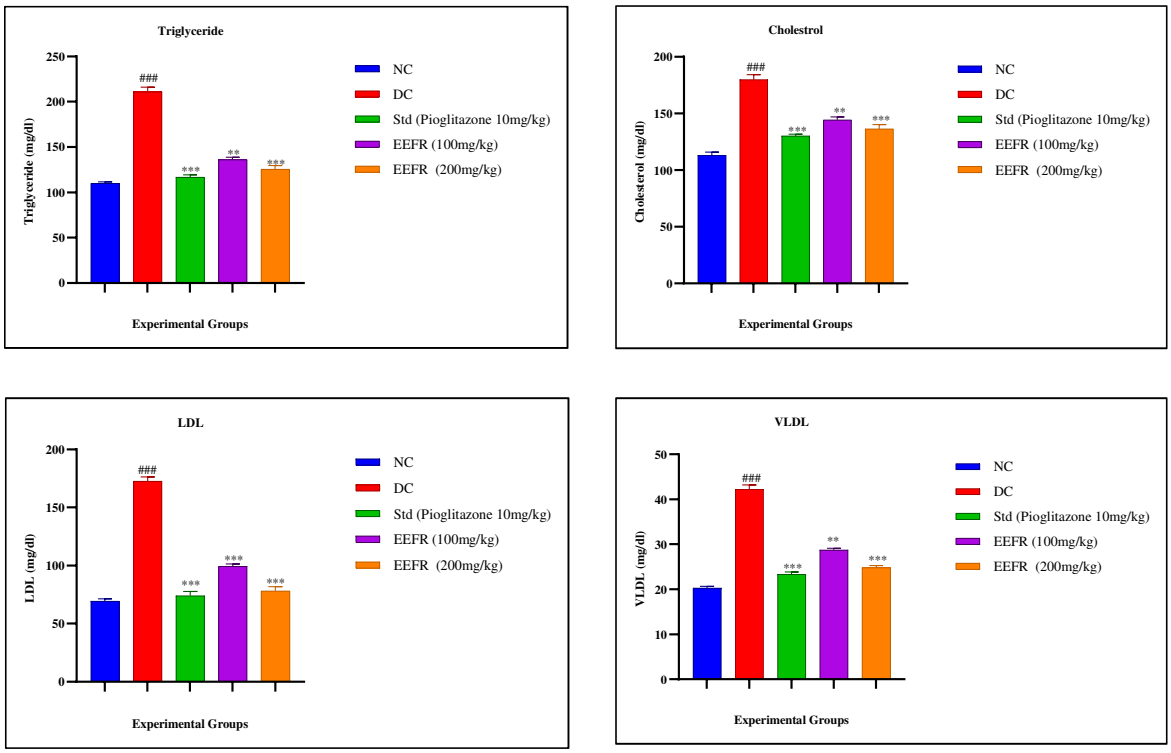

Fig 4: Effect of EEFR on Serum triglyceride, total cholesterol, LDL and VLDL level in high fructose-induced insulin-resistant rats. NC- normal control; DC- disease control; EEFR- ethanolic extract of *Ficus racemosa* leaves. Data are expressed as mean ± S.E.M. (n=6). ###p < 0.001, as compared to NC; **p < 0.05, ***p < 0.001 as compared to DC. Data was analysed by one-way Analysis of Variance (ANOVA) followed by Dunnet's multiple test for comparison.

HDL level in the disease group was significantly decreased as compared to a normal group and significantly increased in pioglitazone and EEFR groups in comparison with the disease group. This indicating the preventive role of *Ficus racemosa* and Pioglitazone against high fructose diet-induced alteration in lipid profile.

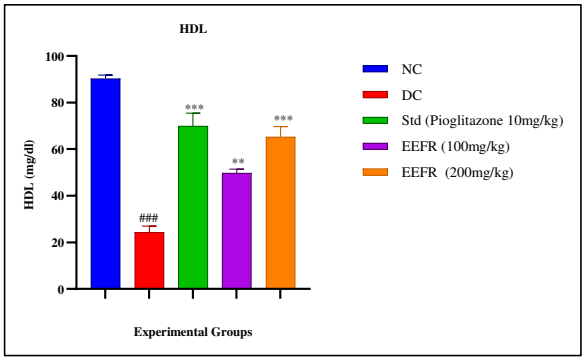

Fig 5: Effect of EEFR on HDL in high fructose-induced insulin-resistant rats. NC- normal control; DC- disease control; EEFR- ethanolic extract of *Ficus racemosa* leaves. Data are expressed as mean ± S.E.M. (n=6). ###p < 0.001, as compared to NC; **p < 0.05, ***p < 0.001 as compared to DC. Data was analysed by one-way Analysis of Variance (ANOVA) followed by Dunnet's multiple test for comparison.

3.7 TNF- α

TNF- α in the disease group was significantly increased as compared to a normal group. A significant decrease was found in the TNF- α of the group treated with pioglitazone and EEFR group in comparison with the disease control group.

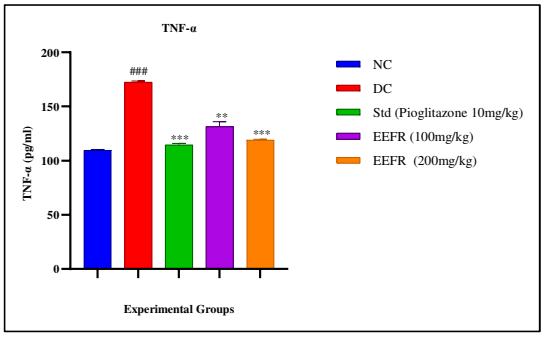

Fig 6: Effect of EEFR on TNF α in high fructose-induced insulin-resistant rats. NC- normal control; DC- disease control; EEFR- ethanolic extract of *Ficus racemosa* leaves. Data are expressed as mean ± S.E.M. (n=6). ###p < 0.001, as compared to NC; **p < 0.05, ***p < 0.001 as compared to DC. Data was analysed by one-way Analysis of Variance (ANOVA) followed by Dunnet's multiple test for comparison

3.8 Oxidative enzymes

Superoxide dismutase: SOD level in the disease group was significantly decreased as compared to a normal group. A significant decrease was found in the SOD level of the group treated with pioglitazone and EEFR groups in comparison with the disease group.

Catalase: catalase level in the disease group was significantly decreased as compared to a normal group. A significant decrease was found in the catalase level of the group treated with pioglitazone and EEFR group in comparison with the disease group.

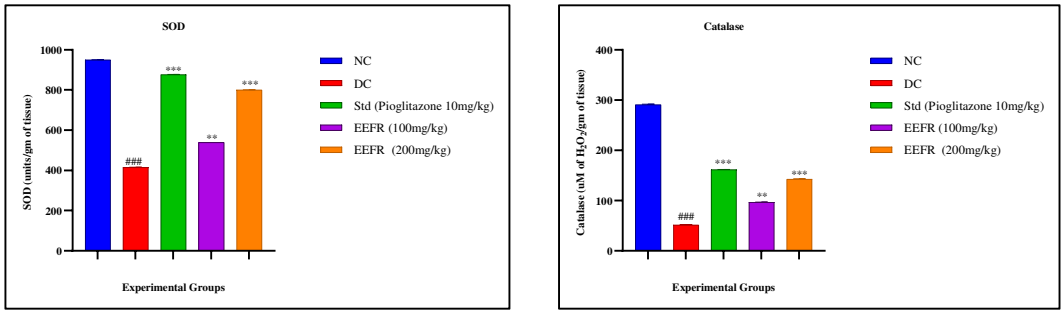

Fig 7: Effect of EEFR on SOD and catalase in high fructose-induced insulin-resistant rats. NC- normal control; DC- disease control; EEFR- ethanolic extract of *Ficus racemosa* leaves. Data are expressed as mean ± S.E.M. (n=6). ###p < 0.001, as compared to NC; **p < 0.05, ***p < 0.001 as compared to DC. Data was analysed by one-way Analysis of Variance (ANOVA) followed by Dunnet's multiple test for comparison.

3.9 Histopathology of Liver

The treatment with high fructose produced histopathological alterations like showing necrosis, vacuolation and extreme fatty changes in the liver of HF group rats indicating

severe damage to the liver tissue. These alterations were markedly ameliorated by treatment with pioglitazone (10mg/kg), EEFR (100 and 200 mg/kg) slight and significant improvement in histological structure.

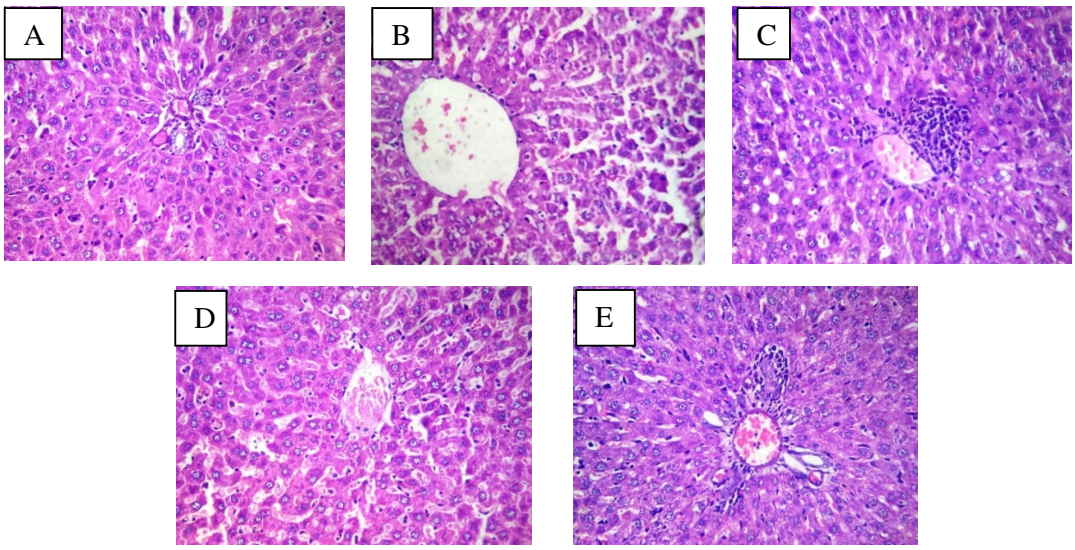

Fig 8: Photomicrographs of histopathology sections of rat liver of different experimental groups. H&E staining of liver sections was performed. (A) Normal histological structure of rat liver showing systematically arranged hepatocytes (B) Necrosis, vacuolation, and extreme fatty changes in the liver of high fructose-induced insulin-resistant rats (C) Treatment with pioglitazone (10 mg/kg) for 2 weeks reduced the fatty changes to some extent in the liver of high fructose-induced insulin resistant rats (D) Oral administration of EEFR 100 mg/kg for 2 weeks in rats showed slight improvement in histological structure (E) Treatment with EEFR 200 mg/kg for 2 weeks showed significant decrease in fatty changes in high fructose-induced insulin resistant rat liver histology.

4 DISCUSSION

Insulin plays a critical role in maintaining homeostasis and regulating glucose metabolism in the human body. It influences not just glucose regulation but also protein and fat metabolism, cell division, and growth. Anomalies in insulin action can lead to insulin resistance, a condition characterized by a reduction in the cellular sensitivity to insulin [13]. Insulin resistance has consequences that go beyond certain metabolic illnesses. Insulin resistance plays a major role in the development of several metabolic diseases, including polycystic ovary syndrome (PCOS), obesity, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and cardiovascular disease. Insulin resistance and the health risks it poses are largely caused by factors like genetic predisposition, sedentary lifestyle, and obesity, especially visceral fat buildup [14–16]. High-fructose diets have been shown in recent research to worsen insulin resistance. For example, major metabolic disturbances such as fasting hyperglycaemia (high blood sugar), hypertriglyceridemia (high triglycerides), hyperinsulinemia (high insulin levels), and hypercholesterolemia (high cholesterol levels) were observed in rats fed a high-fructose diet for 56 days. These modifications point to a weakened anti-inflammatory and antioxidant response, which accelerates the onset of insulin resistance [17]. It has been suggested that this model be used to evaluate the therapeutic effectiveness of medications that are expected to affect insulin sensitivity, such as insulin sensitizers. Therefore, this model is selected to study efficacy of *Ficus racemosa* extract in improving insulin resistance.

It has been demonstrated that long-term fructose consumption has a substantial effect on body weight and metabolic health. Rats fed a high-fructose diet showed a consistent increase

in body weight from the first day to the 42th day in trials with rats. Nevertheless, this weight gain was stopped following therapy, showing that intervention is still possible even in the face of higher energy intake. Fructose has impacts that go beyond weight gain. Throughout the course of the investigation, the rats in these experiments also showed increased levels of insulin, triglycerides, and fasting blood glucose. These metabolic abnormalities became noticeable by day 28, and by days 42 and 56 of fructose eating, they had become more severe. This pattern suggests that long-term fructose consumption can cause insulin resistance, which in turn can cause hyperglycaemia (high blood sugar) and hyperinsulinemia (high insulin levels) [18]. The liver is the only organ that can metabolize fructose. When fructose enters the liver, it disrupts normal hepatic carbohydrate metabolism. This leads to two main effects: disruptions in glucose metabolism and glucose uptake pathways, and a marked increase in the rate of de novo lipogenesis and TG synthesis. This increase is caused by the high flux of glycerol and acyl portions of TG molecules that come from fructose catabolism [19]. The induction of insulin resistance that is frequently seen with high fructose feeding in both human and animal models appear to be caused by these metabolic disruptions. A significant metabolic dyslipidaemia is frequently observed in fructose-induced insulin resistance states, and it seems to be caused by the overproduction of atherogenic lipoprotein particles in the intestine and liver[20]. Our study found that *Ficus racemosa* is effective in dyslipidaemia, EEFR 200mg/kg regulate the lipid levels more significantly.

Consuming large amounts of fructose can have a number of detrimental impacts on health, such as increased intestinal permeability and pro-inflammatory cytokines. These alterations exacerbate metabolic problems and liver damage by causing inflammatory reactions and fat buildup in the liver [21]. An inflammatory chain reaction can be started by consuming too much fructose. Widespread inflammation is encouraged by pro-inflammatory cytokines, particularly in the liver. Toxins can also reach the bloodstream due to increased intestinal permeability, which exacerbates the inflammatory response. Thankfully, therapies appear to have potential in lowering these inflammatory indicators [22]. When compared to untreated groups, the levels of inflammation in the treated groups dropped, indicating that treatments may be able to lessen the negative consequences of excessive fructose intake and improve liver function. The necessity to address high fructose consumption in our diets is highlighted by these findings. Proactive steps to lessen the effects of fructose can be guided by knowledge of the inflammatory pathways it triggers. Effective anti-inflammatory therapies are essential for averting long-term issues linked to high fructose consumption. This study found that EEFR 100mg/kg and 200mg/kg both reduces TNF- α level, show that 200mg/kg *Ficus racemosa* extract more effective in inflammation.

Diets high in fructose over an extended period of time can lead to an excess of reactive oxygen species (ROS) production. As a result, oxidative stress is generated and insulin resistance is mediated [23]. Furthermore, an increase in the accumulation of reactive oxygen species (ROS) within cells directly initiates the activation of serine/threonine kinase cascades, which include nuclear factor-kappa B and c-Jun N-terminal kinase. These cascades then phosphorylate a variety of targets, including the insulin receptor and insulin receptor substrate (IRS) proteins [24]. Impaired glucose uptake in muscle, liver, and adipose tissues results from increased serine phosphorylation of IRS, which directly reduces its capacity to undergo tyrosine phosphorylation and speeds up the breakdown of IRS-1 [24]. One of the key causes of increased ROS and lipid peroxidation, which lowers the level of antioxidant defence in different tissues, is fructose-induced hyperglycaemia [25]. According to the current research, EEFR inhibits hyperglycaemia, hyperinsulinemia, and body weight increase. Furthermore, in rats with insulin resistance, EEFR significantly reduces the

impairment of insulin-stimulated glucose elimination. Lipid peroxidation is reduced and hepatic antioxidant enzyme protection is aided by EEFR.

All rat exhibited notable alterations in histological analysis of the livers as a result of high fructose ingestion. The sick group showed significant damage, with hepatocytes displaying centrilobular degeneration and inflammatory cells mildly infiltrating certain areas. As a result, the parenchymatous sinusoids' structure became disordered, indicating severe liver failure [26]. Rat liver tissues treated with Std-Pioglitazone (10 mg/kg) on the other hand showed a more typical architecture, with only mild to negligible degeneration and healthy branching and anastomosing cords of hepatocytes radiating from the central vein. Compared to the Std-Pioglitazone-treated group, the liver structure of the EEFR treatment at 200 mg/kg was improved and more like that of the group receiving 100 mg/kg of EEFR. This implies that Ficus Racemosa extract at greater dosages might be more successful in reducing the negative consequences of a diet high in fructose. Due to their antioxidant qualities, the active ingredients in Ficus racemosa extract may enhance insulin sensitivity, reduce insulin resistance, and raise the activity of antioxidant enzymes.

4 CONCLUTION

In conclusion, this study demonstrates the beneficial effects of *Ficus racemosa* extract on insulin resistance. The findings suggest that the extract may have a protective role against insulin resistance, as evidenced by improvements in serum glucose and insulin levels, lipid profile, and oxidative enzymes, TNF- α and histopathological characteristics. The observed Protective effect may arise from various active compounds in the extract, contributing to its effectiveness in managing insulin resistance. However, further research is necessary to find out the specific mechanisms for the beneficial effects. These findings suggest that *Ficus racemosa* extract could be a valuable addition to dietary strategies aimed at preventing and managing insulin resistance. Further research and investigations are warranted to fully understand the mechanisms underlying these observed effects and to validate the potential of *Ficus racemosa* extract as a therapeutic option for managing insulin resistance and its associated complications.

5 REFERENCES

[1] Thongnak L, Chatsudthipong V, Kongkaew A, Lungkaphin A. Effects of dapagliflozin and statins attenuate renal injury and liver steatosis in high-fat/high-fructose diet-induced insulin resistant rats. Toxicol Appl Pharmacol 2020;396. https://doi.org/10.1016/j.taap.2020.114997.

[2] Chandrasekaran P, Weiskirchen R. Cellular and Molecular Mechanisms of Insulin Resistance. Curr Tissue Microenviron Rep 2024. https://doi.org/10.1007/s43152-024-00056-3.

[3] Thresher JS, Podolin DA, Wei Y, Mazzeo RS, Pagliassotti MJ. Comparison of the effects of sucrose and fructose on insulin action and glucose tolerance. Am J Physiol Regul Integr Comp Physiol 2000;279:1334–40.

https://doi.org/10.1152/AJPREGU.2000.279.4.R1334/ASSET/IMAGES/LARGE/H61000196002.JPEG.

[4] Basciano H, Federico L, Adeli K. Fructose, insulin resistance, and metabolic dyslipidemia. Nutr Metab (Lond) 2005;2. https://doi.org/10.1186/1743-7075-2-5.

[5] Mlinar B, Marc J, Pfeifer M. Molecular Mechanisms of Insulin Resistance, Obesity and Metabolic Syndrome. Biochem Med (Zagreb) 2006:8–24. https://doi.org/10.11613/bm.2006.003.

[6] Sharma H, Pathak R, Jain S, Bhandari M, Mishra R, Reena K, et al. JPTCP (213-227) Ficus Racemosa L: A Review On Its Important Medicinal Uses. Phytochemicals And Biological Activities 2023;30:213–27. https://doi.org/10.47750/jptcp.2023.30.17.018.

[7] Vikas V. Patil NGSRBPRYCVRP. JOURNAL OF NATURAL REMEDIES. 2010.

[8] Sethuraman J, Nehru H, Shanmugam K, Balakrishnan P. EVALUATION OF POTENT PHYTOCHEMICALS AND ANTIDIABETIC ACTIVITY OF FICUS RACEMOSA LINN. World J Pharm Res 2017;6. https://doi.org/10.20959/wjpr201715-10140.

[9] Mandal S, Maity T, Das J, Saba B, of MP-J, 2000 undefined. Anti-inflammatory evaluation of Ficus racemosa Linn. leaf extract. Elsevier n.d.

[10] Patil V, Patil VR. Evaluation of anti-inflammatory activity of Ficus carica Linn. leaves. Indian J Nat Prod Resour 2011;2:151–5.

[11] Bakoriya R, Thomas T, Soni KK. WOUND HEALING ACTIVITIES OF FICUS RACEMOSA LEAVES ETHANOLIC EXTRACT ON EXCISION WOUND MODEL OF WISTAR ALBINO RATS. Int J Pharm Sci Res 2015;6:2631–5. https://doi.org/10.13040/IJPSR.0975-8232.6(6).2631-35.

[12] Yadav S, Gupta V, Gopalakrishnan A, Ram Verma M, Supriya Yadav C. Antioxidant activity analysis of Ficus racemosa leaf extract. ~ 1443 ~ Journal of Entomology and Zoology Studies 2019;7:1443–6.

[13] Khalilov R, Abdullayeva S. MECHANISMS OF INSULIN ACTION AND INSULIN RESISTANCE. vol. 8. 2023.

[14] Leavens KF, Birnbaum MJ. Insulin signaling to hepatic lipid metabolism in health and disease. Crit Rev Biochem Mol Biol 2011;46:200–15. https://doi.org/10.3109/10409238.2011.562481.

[15] Nogueira JP, Cusi K. Role of insulin resistance in the development of nonalcoholic fatty liver disease in people with type 2 diabetes: From bench to patient care. Diabetes Spectrum 2024;37:20–8. https://doi.org/10.2337/dsi23-0013.

[16] Kosmas CE, Bousvarou MD, Kostara CE, Papakonstantinou EJ, Salamou E, Guzman E. Insulin resistance and cardiovascular disease. Journal of International Medical Research 2023;51. https://doi.org/10.1177/03000605231164548.

[17] Tobey TA, Mondon CE, Zavaroni I, Reaven GM. Mechanism of insulin resistance in fructose-fed rats. Metabolism 1982;31:608–12. https://doi.org/10.1016/0026-0495(82)90100-7.

[18] Tobey TA, Mondon CE, Zavaroni I, Reaven GM. Mechanism of insulin resistance in fructose-fed rats. Metabolism 1982;31:608–12. https://doi.org/10.1016/0026-0495(82)90100-7.

[19] Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. Hypertension 1987;10:512–6. https://doi.org/10.1161/01.HYP.10.5.512.

[20] Catena C, Giacchetti G, Novello M, Colussi G, Cavarape A, Sechi LA. Cellular mechanisms of insulin resistance in rats with Fructose-Induced hypertension: Am J Hypertens 2003;16:973–8. https://doi.org/10.1016/S0895-7061(03)01002-1.

[21] Castro MC, Massa ML, Arbeláez LG, Schinella G, Gagliardino JJ, Francini F. Fructose-induced inflammation, insulin resistance and oxidative stress: A liver pathological triad effectively disrupted by lipoic acid. Life Sci 2015;137:1–6. https://doi.org/10.1016/j.lfs.2015.07.010.

[22] Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne) 2013;4. https://doi.org/10.3389/fendo.2013.00071.

[23] Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature 2006 440:7086 2006;440:944–8. https://doi.org/10.1038/nature04634.

[24] Evans JL, Maddux BA, Goldfine ID. The Molecular Basis for Oxidative Stress-Induced Insulin Resistance. Https://HomeLiebertpubCom/Ars 2005;7:1040–52. https://doi.org/10.1089/ARS.2005.7.1040.

[25] Reddy SS, Ramatholisamma P, Karuna R, Saralakumari D. Preventive effect of Tinospora cordifolia against high-fructose diet-induced insulin resistance and oxidative stress in male Wistar rats. Food and Chemical Toxicology 2009;47:2224–9. https://doi.org/10.1016/J.FCT.2009.06.008.

[26] Jayakumar V, Ahmed SSSJ, Ebenezar KK. Multivariate analysis and molecular interaction of curcumin with PPARγ in high fructose diet induced insulin resistance in rats. Springerplus 2016;5. https://doi.org/10.1186/s40064-016-3364-1.