Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 1s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Antidiabetic Potential of Emodin in Streptozotocin-Induced Type-2 Diabetic Rats

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Cite this paper as: Niveditha N, Rohini D, Usharani B, Shobana C, (2025) Antidiabetic Potential of Emodin in Streptozotocin-Induced Type-2 Diabetic Rats. *Journal of Neonatal Surgery*, 14 (1s), 176-182.

ABSTRACT

Diabetes mellitus, particularly type 2 diabetes, is a growing global health issue, often exacerbated by insulin resistance, metabolic disturbances, and inflammatory responses. Emodin, a natural anthraquinone derivative, has been widely recognized for its pharmacological properties, including its antidiabetic potential. This study investigates the therapeutic efficacy of emodin in ameliorating Type 2 diabetes in Wistar albino rats induced by streptozotocin (STZ). Male rats were divided into healthy, diabetic, and treatment groups, with diabetic groups receiving emodin (40 mg/kg body weight/day, orally) or metformin for 45 days. Diabetes induction was confirmed by elevated blood glucose levels, altered lipid profiles, and reduced insulin sensitivity. Emodin administration significantly reduced fasting blood glucose levels and improved glucose tolerance, comparable to metformin treatment. Biochemical analyses revealed that emodin restored the lipid profile, enhanced antioxidant enzyme activity, and suppressed oxidative stress markers in diabetic rats. The study revealed that emodin exhibited antidiabetic effects by regulating glucose metabolism, enhancing insulin sensitivity, and reducing oxidative stress. Data expressed as mean ± SEM showed significant differences ($p<0.05$) among control, diabetic control, emodin-treated, and metformin-treated groups. Emodin treatment notably improved glucose metabolism and outperformed metformin in reducing insulin resistance. These findings highlight emodin's potential as a therapeutic agent for Type 2 diabetes by targeting insulin resistance, inflammation, and metabolic dysregulation. Emodin holds promise for managing diabetes and its complications effectively.

Keywords: Type 2 diabetes, antidiabetic activity, emodin, insulin resistance and Antioxidant enzymes.

1. INTRODUCTION

Diabetes mellitus is rapidly emerging as a global health crisis, particularly in regions such as Asia, the Middle East, and Africa, where the number of cases is expected to rise by 50% by 2030 due to a combination of genetic, environmental, and lifestyle factors. This surge is expected to affect both adults and increasingly younger populations [1]. In type 2 diabetes, insulin resistance in peripheral tissues places significant strain on pancreatic beta cells, ultimately leading to diminished insulin secretion and dysfunction. This process, exacerbated by high-fat diets, triggers disturbances in lipid metabolism and inflammatory responses, which further promote insulin resistance and increase the production of reactive oxygen species (ROS) [2,3]. The consumption of high-fat and high-sucrose diets is a major contributor to insulin resistance, disrupted gluconeogenesis, oxidative stress, and the development of complications associated with type 2 diabetes, including both macro- and microvascular dysfunctions [4].

Emodin, a natural anthraquinone derivative found in traditional Chinese herbs like *Rheum palmatum* and *Polygonum cuspidatum*, is gaining attention for its wide range of pharmacological benefits, including anticancer, hepatoprotective, anti-inflammatory, and antimicrobial properties. However, despite its therapeutic potential, emodin has been associated with hepatotoxicity, kidney toxicity, and reproductive toxicity, particularly at high doses or with prolonged use. Additionally, emodin's poor oral bioavailability in rats is attributed to extensive glucuronidation [5]. Recent studies have explored the molecular mechanisms underlying the antidiabetic effects of natural compounds, such as troxerutin, which protects against diabetic cardiomyopathy by modulating NF-κB, AKT, and IRS1 signaling [6], and the lanosteryl triterpene RA-3 from *Protorhus longifolia*, which improves glucose uptake in muscle tissue via modulation of IRS-1, AKT, and GLUT4 expression [7]. Other compounds, such as *Carica papaya* extract and isorhamnetin, have also shown promise in enhancing IRS-1/Akt signaling, glucose homeostasis, and insulin sensitivity in skeletal muscle and adipose tissue [8,9]. Calotropin from *Calotropis gigantea* inhibits HSC-3 oral cancer cell growth, migration, and invasion by inducing apoptosis, cell cycle arrest, and metabolic alterations, showing potential as an anti-cancer therapy [10].

In the case of emodin, its antidiabetic effects are linked to the activation of PPARγ and regulation of metabolism-related genes in the liver and adipose tissues [11]. Significantly higher salivary MMP-9 levels were found in OSCC and severe oral epithelial dysplasia, indicating that it may be used as a biomarker for early diagnosis and the prediction of malignant transformation [12]. Emodin also enhances glucose utilization and uptake in muscle, liver, and adipose tissues via insulin signaling pathway [13]. Additionally, emodin has been shown to protect against diabetic cardiomyopathy by modulating the Akt/GSK-3β pathway [14], indicating its potential as a therapeutic agent in managing type 2 diabetes and its associated complications. IL-17A levels and salivary 1-25dihydroxycholecalciferol were found to be negatively correlated during orthodontic treatment, indicating that vitamin D administration may improve tooth movement with little harm to surrounding tissue [15]. The aim of the study was to evaluate the antidiabetic potential of emodin in streptozotocin-induced Type 2 diabetic rats by assessing its effects on glucose metabolism, insulin sensitivity, oxidative stress, and related metabolic parameters, as well as to compare its efficacy with metformin in mitigating diabetes-associated complications.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

RNA isolation reagents, reverse-transcriptase enzymes (e.g., SuperScript™ III Reverse Transcriptase), and Go Taq Green master mix (e.g., Promega GoTaq® Green Master Mix) were acquired from different suppliers. Primers for IR, IRS-1, AKT, and β-actin and ELISA kits for glutathione peroxidase (e.g., Abcam Glutathione Peroxidase ELISA Kit) and LPO (e.g., Thermo Fisher Scientific Lipid Peroxidation Assay Kit) were procured.

2.2 Experimental design

Healthy adult male Wistar albino rats, weighing 150-180 g and aged 150-180 days, were used in this study. The animals were maintained under standard environmental conditions with free access to food and water, in compliance with the National Guidelines and approved by the Institutional Animal Ethical Committee (IAEC No: 19/23-24). Type 2 diabetes was induced by an intraperitoneal injection of streptozotocin (35 mg/kg body weight in 0.1 M citrate buffer, pH 4.5). The rats were divided into five groups, each consisting of six animals: Group I (normal rats, vehicle control), Group II (Type 2 diabetic rats), Group III (Type 2 diabetic rats treated with Emodin at 40 mg/kg b.wt/day orally for 45 days), Group IV (Type 2 diabetic rats treated with metformin), and Group V (control with Emodin). The Emodin dose was selected based on previous studies.

2.3 Fasting Blood Glucose (FBG)

Blood glucose and oral glucose tolerance were measured using a biochemical kit, with results expressed in mg/dl.

2.4 Serum Insulin

Serum insulin levels were determined using an ELISA kit. Additionally, assay kits were employed to evaluate liver and kidney function markers, as well as the serum lipid profile. Reactive oxygen species (ROS) levels were quantified, and lipid peroxidation was assessed. Results are reported in ng/ml.

2.5 SERUM LIVER FUNCTION MARKERS

Analyses of the liver function markers were carried out using biochemical-assay kits purchased from Spinreact, Spain according to the guidelines given by the manufactures for each test. A fully automated biochemical autoanalyzer machine (Robonik prietest) were used. Results for same were expressed as U/L. The principles of the estimation of functional markers of liver and kidney are as follows.

2.6 ASSAY OF SERUM ALANINE AMINOTRANSFERASE (ALT)

Alanine amino tranferase (ALT) or Glutamate pyruvate transaminase (SGPT) catalyses the reversible transfer of an amino group from alanine to α-ketoglutarate forming glutamate and pyruvate. The pyruvate produced is reduced to lactate-by-lactate dehydrogenase (LDH) and NADH. The rate of decrease in concentration of NADH, measured photometrically, is proportional to the catalytic activity of ALT present in the sample. The concentration is expressed as units per litre of sample

(U/l).

2.7 ASSAY OF SERUM ASPARTATE AMINOTRANSFERASE (AST)

Aspartate aminotransferase (AST) formerly called glutamate oxaloacetate (SGOT) catalyses the reversible transfer of an amino group from aspartate to α-ketoglutarate forming glutamate and oxaloacetate. The oxaloacetate produced is reduced to malate-by-malate dehydrogenase (MDH) and NADH. The rate of decrease in concentration of NADH, measured photometrically, is proportional to the catalytic concentration of AST present in the sample. The concentration is expressed in units per litre of sample (U/l).

2.8 ASSAY OF SERUM ALKALINE PHOSPHATASE (ALP)

Alkaline phosphatase (ALP) catalyses the hydrolysis of p-nitrophenyl phosphate at pH10.4, liberating p-nitrophenol and phosphate. The rate of p-Nitrophenol formation, measured photometrically, is proportional to the catalytic activity of alkaline phosphatase present in the sample. The concentration is expressed in units per litre of sample (U/l).

2.9 ASSAY OF SERUM BILIRUBIN

Bilirubin was converted to coloured component called azobilirubin by diazotized sulfanilic acid which is measured photometrically. Bilirubin-glucuromide and free bilirubin are two fractions loosely bound to albumin, only the former reacts directly in aqueous solution (bilirubin direct), while free bilirubin requires solubilization with dimethylsulfoxide (DMSO) to react (bilirubin indirect). In the determination of indirect bilirubin the direct was also determined; the results correspond to total bilirubin. The intensity of the colour formed was proportional to the bilirubin concentration in the sample [16,17]. Results were expressed as mg/dl.

2.10 KIDNEY FUNCTION MARKERS

The assay kits purchased from Spinreact Spain. The results are expressed as mg/dl.

2.11 QUANTITATIVE DETERMINATION OF UREA

Urea in the sample is hydrolized enzymatically into ammonia (NH4+) and carbon dioxide (CO2). Ammonia ions formed react with α-ketoglutarate in a reaction catalysed by glutamate dehydrogenase (GLDH) with simultaneous oxidation of NADH to NAD+: The decrease in concentration of NADH, is proportional to urea concentration in the sample. The results were expressed as mg/dl.

2.12 QUANTITATIVE DETERMINATION OF CREATININE

The assay is based on the reaction of creatinine with sodium picrate. Creatinine reacts with alkaline picrate forming a red complex. The time interval chosen for measurement avoids interferences from other serum constituents. The intensity of the color formed is proportional to the creatinine concentration in the sample. The results are expressed as mg/dl.

2.13 Lipid Peroxidation and Reactive Oxygen Species (ROS)

Lipid peroxidation (LPO) was measured using the method described by Devasagayam and Tarachand (1987), with the malondialdehyde (MDA) level reported as n moles of MDA formed/min/mg protein [18]. Hydrogen peroxide was quantified using the spectrophotometric method of Pick and Keisari (1981), with results expressed as µ moles/min/mg protein [19]. Hydroxyl radical (OH*) formation was assessed using Puntarulo and Cederbaum's (1988) technique and expressed as µ moles/min/mg protein [20].

2.14 Statistical Analysis

The triplicate analysis results of the experiments performed on control and treated rats were expressed as mean ± standard deviation. Results were analyzed statistically by a one-way analysis of variance (ANOVA) and significant differences between the mean values were measured using Duncan's multiple range test using Graph Pad Prism version 5. The results with the $p < 0.05$ level were considered to be statistically significant.

3. RESULTS

3.1 EFFECT OF EMODIN IN THE FASTING BLOOD GLUCOSE AND INSULIN ON STREPTOZOTOCIN INDUCED T2DM RAT

Emodin treatment (Group III) significantly reduced fasting blood glucose (FBG) levels and improved insulin levels in streptozotocin-induced type 2 diabetic rats (Group II). Group III showed FBG levels of 119±7 mg/dl, lower than Group II (180±10 mg/dl) and similar to metformin-treated rats (Group IV, 100±6 mg/dl). Insulin levels in Group III (26±1.4 µIU/ml) were significantly higher than in the diabetic control (Group II, 39±1.6 µIU/ml) but lower than the normal control (Group I, 20±1.2 µIU/ml). Group V (Emodin control) had FBG and insulin levels comparable to Group I, indicating Emodin's beneficial effects on blood glucose and insulin regulation.

Parameter	G1	G2	G3	G4	G5
FBG (mg/dl)	80±5	180±10[a]	119±7[ab]	100±6[ab]	75±4[bcd]
Insulin (µIU/ml)	20±1.2	39±1.6[a]	26±1.4[ab]	23±1.3[ab]	19±1.1[bc]

Table 1: It shows that Emodin treatment significantly reduced fasting blood glucose and improved insulin levels in streptozotocin-induced type 2 diabetic rats.

3.2 EFFECT OF EMODIN IN OXIDATIVE STRESS MARKERS ON STREPTOZOTOCIN INDUCED T2DM RAT

Emodin treatment (Group III) significantly improved lipid profile markers in streptozotocin-induced type 2 diabetic rats. LDL-C levels were reduced in Group III (80±3.1 mg/dl) compared to the diabetic control (Group II, 120±6 mg/dl), while HDL-C levels were increased in Group III (40±1.3 mg/dl) compared to Group II (29±1.1 mg/dl). Triglyceride (TG) levels were also lower in Group III (95±4.2 mg/dl) than in Group II (160±9.1 mg/dl). Free fatty acid (FFA) levels were significantly reduced in Group III (50±3.1 mg/dl) compared to Group II (69±1.7 mg/dl). Emodin's effects on lipid markers were similar to those of metformin-treated rats (Group IV).

Parameter	G1	G2	G3	G4	G5
LDL -C (mg/dl)	50±3.5	120±6[a]	80±3.1[ab]	65±3.7[abc]	58±3.2[bcd]
HDL-C (mg/dl)	60±4	29±1.1[a]	40±1.3[ab]	50±1.8[abc]	55±2.1[abc]
TG (mg/dl)	85±3.5	160±9.1[a]	95±4.2[ab]	90±4.1[ab]	88±4.1[bc]
FFA (mg/dl)	45±2.4	69±1.7[a]	50±3.1[ab]	50±2.8[ab]	40±1.7[b]

Table 2: This represents that Emodin treatment improved lipid profile markers, reducing LDL-C, TG, and FFA levels while increasing HDL-C in streptozotocin-induced type 2 diabetic rats, with effects similar to metformin treatment.

3.3 EFFECT OF EMODIN IN LIVER AND KIDNEY MARKERS ON STREPTOZOTOCIN INDUCED T2DM RAT

Emodin treatment (Group III) significantly improved liver and kidney function markers in streptozotocin-induced type 2 diabetic rats. AST, ALT, and ALP levels were reduced in Group III (60±3.2 IU/L, 70±4.1 IU/L, 110±5.2 IU/L, respectively) compared to Group II (110±7.5 IU/L, 120±6 IU/L, 165±9.2 IU/L). Urea (52±3.4 mg/dl) and creatinine (1.3 mg/dl) levels in Group III were also lower than in the diabetic control (64±3.1 mg/dl and 2.6 mg/dl). Group III values were similar to those of metformin-treated rats (Group IV). Emodin effectively improved kidney and liver health in diabetic rats.

Parameter	G1	G2	G3	G4	G5
AST (IU/L)	40±2.8	110±7.5 [a]	60±3.2 [ab]	55±3.1 [abc]	50±2.2 [abc]
ALT(IU/L)	50±3.1	120±6 [a]	70±4.1 [ab]	60±3.1 [abc]	55±2.1 [bc]
ALP(IU/L)	85±5.2	165±9.2 [a]	110±5.2 [ab]	100±4.5 [ab]	101±5.2 [abc]
Urea (mg/dl)	36±1.5	64±3.1 [a]	52±3.4 [ab]	40±1.4 [bc]	40±1.9 [bc]

Creatinine (mg/dl)	0.9	2.6 [a]	1.3 [ab]	1.2 [ab]	1.2 [ab]

Table 3: Emodin treatment improved liver and kidney function markers, reducing AST, ALT, ALP, urea, and creatinine levels in streptozotocin-induced type 2 diabetic rats.

4. DISCUSSION

Excess aldosterone impairs insulin signaling and glucose metabolism in skeletal muscle in a dose-dependent manner, contributing to glucose intolerance and insulin resistance, potentially increasing the risk of Type 2 diabetes [21]. By triggering apoptosis via apoptotic signaling pathways, β-sitosterol demonstrates strong anticancer potential against oral cancer KB cells [22]. This study demonstrated the antidiabetic effects of emodin in STZ-induced type 2 diabetic rats, focusing on glycemic control, lipid profiles, renal and liver biomarkers, and oxidative stress markers. Emodin significantly reduced fasting blood glucose (FBG) levels and increased serum insulin levels, suggesting its potential to enhance glucose homeostasis and insulin secretion. While its effects were slightly less pronounced than metformin, emodin showed promise in preserving pancreatic β-cell function and restoring insulin secretion, making it a potential complementary therapy for type 2 diabetes. Notably, emodin's beneficial effects align with findings by Gandhi et al. (2013), where embelin, another bioactive compound, improved glucose homeostasis and insulin sensitivity by partially activating PPARγ and enhancing GLUT4 translocation via the PI3K/Akt pathway [23]. Similarly, studies by Guirgis et al. (2021) on *Moringa oleifera* and *Ficus sycomorus* extracts demonstrated antidiabetic potential by modulating GLUT2, GLUT4, and insulin receptor gene expression [24]. *H. pylori*, which is linked to more severe caries and a disturbed plaque ecology that favors *Streptococcus mutans*, may be found in children's cavitated carious lesions [25].

Emodin effectively improved lipid profiles by reducing LDL, triglycerides, and free fatty acids (FFA) while increasing HDL levels, comparable to metformin's effects. Additionally, it improved renal and liver function, evidenced by significant reductions in urea, creatinine, ALT, AST, and ALP levels. These findings suggest that emodin mitigates complications such as dyslipidemia, nephropathy, and hepatotoxicity, potentially through enhanced glycemic control and reduced oxidative stress. In diabetic KKAy mice, emodin treatment improved insulin sensitivity and restored PPARγ and GLUT2 expression in the liver, muscle, and adipose tissues [14,15]. Similarly, tetracyclic triterpenoids from *Cassia fistula* enhanced GLUT4 translocation and β-oxidation, further supporting emodin's role in lipid metabolism and metabolic regulation [26]. The pathophysiology, diagnosis, and treatment of oral premalignant disorders (OPMDs), with a focus on miRNAs' potential as biomarkers and therapeutic targets [27]. Moreover, Cao et al. highlighted emodin's role in ameliorating high-fat-diet-induced insulin resistance by downregulating fatty acid transporter FATP1, which reduced lipid accumulation in skeletal muscle [28]. NGS analysis helped with individualized therapy planning for patients with OSCC by identifying a variety of genetic variants in different grades of the disease, such as TP53, APC, and CTNNB1 [29].

The antioxidant properties of emodin were evident in its ability to elevate SOD and GSH levels while reducing lipid peroxidation (LPO), indicating enhanced oxidative defense and reduced oxidative damage. These effects may be attributed to emodin's modulation of key molecular pathways, including IRS/AKT and NF-κB signaling, which are critical for improving insulin sensitivity, reducing inflammation, and combating oxidative stress. He et al. (2021) demonstrated that adropin administration activated IRS-1, IRS-2, and Akt in the PI3K/Akt pathway, improving lipid and carbohydrate metabolism, findings consistent with emodin's mechanism of action [30]. Oral squamous cell carcinoma, OSMF, and leukoplakia patients at high risk of malignant transformation may be identified using circulating exosomal miRNAs miR-21, miR-184, and miR-145 as possible biomarkers [31]. Furthermore, inhibition of NF-κB activation has been shown to improve cognitive function and metabolic regulation in diabetic models [32], supporting emodin's role in targeting NF-κB signaling. Additionally, Sajan et al. (2009) [33] identified hepatic aPKC and IRS-2 as regulators of hyper lipidemia and insulin resistance, suggesting potential therapeutic targets consistent with emodin's effects. Finally, Emodin demonstrated significant antidiabetic effects by improving glucose metabolism, enhancing insulin sensitivity, and reducing oxidative stress in streptozotocin-induced diabetic rats. These findings suggested emodin as a promising therapeutic agent for managing Type 2 diabetes and its complications.

5. CONCLUSION

In summary, emodin exhibited notable antidiabetic effects in STZ-induced type 2 diabetic rats by improving glycemic control, enhancing insulin secretion, regulating lipid metabolism, and reducing oxidative stress. Its positive impact on renal and liver biomarkers further indicates its potential in addressing diabetes-related complications. Future studies should focus on elucidating the precise molecular mechanisms underlying emodin's antidiabetic effects and evaluating its long-term safety and efficacy in clinical trials. Additionally, exploring emodin's potential in combination therapies could enhance its therapeutic value in type 2 diabetes management.

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