RESEARCH PAPER

Hypoglycemic Potential Of Acalypha Indica In Streptozotocin-Induced Type 2 Diabetic Rats

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Abstract

Background: Type 2 diabetes mellitus (t2dm) is a chronic endocrine-metabolic pathology marked by sustained hyperglycemia, impaired insulin signaling at peripheral target tissues, and progressive deterioration of pancreatic β-cell secretory function and mass. The increasing burden of diabetes and the limitations of conventional pharmacotherapy have prompted investigations into plant-based therapeutic agents. Acalypha indica, a medicinally rich herb belonging to the family euphorbiaceae, has been traditionally employed in ayurvedic and ethnomedicinal practice for the therapeutic intervention of various ailments, including metabolic complications. However, its molecular and biochemical mechanisms of antidiabetic action remain insufficiently elucidated.

Aim: This study aimed to evaluate the anti-hyperglycemic and broader metabolic effects of acalypha indica ethanolic extract at three dose levels (100, 200, and 400 mg/kg b.w.) in streptozotocin (stz)-induced type 2 diabetic wistar rats. Assessments encompassed fasting blood glucose, serum insulin, insulin resistance index (homa-ir), oral glucose and insulin tolerance, hepatic and renal function biomarkers, and serum lipid profiles, with metformin (50 mg/kg) serving as the pharmacological reference.

Results: Treatment with acalypha indica produced significant, dose-dependent reductions in fasting blood glucose and concomitant restoration of serum insulin levels in all treated groups. Homa-ir values were markedly decreased, confirming improved insulin sensitivity. Oftt and itt analyses demonstrated enhanced glucose clearance and augmented insulin responsiveness in treated animals. Hepatic enzyme markers (ast, alt, alp) and total bilirubin, as well as renal parameters (urea, creatinine, uric acid) and lipid profiles (total cholesterol, triglycerides, ldl-cholesterol), were all significantly ameliorated, while hdl-cholesterol was restored toward physiological levels. The highest tested concentration consistently produced efficacy comparable to metformin treated group.

Conclusion: Acalypha indica demonstrates significant antidiabetic, insulin-sensitizing, hepatoprotective, nephroprotective, and hypolipidemic activities in stz-induced type 2 diabetic rats. These findings provide compelling scientific support for its traditional use in metabolic disease management and underscore the need for further mechanistic, phytochemical, and clinical investigations to advance its therapeutic development.

Keywords: Hypoglycemia, Insulin Resistance, Streptozotocin, Type 2 Diabetes, Antidiabetic Activity, Acalypha Indica.

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INTRODUCTION

Diabetes mellitus (DM) has increasingly emerged as a globally rising non-communicable endocrine metabolic pathology of the 21st century and represents a formidable challenge to healthcare systems worldwide. As per IDF data, diabetes impacted over 629 million adults in 2025, and projections indicate this figure will rise to approximately 853 million by 2050 if prevailing trends continue (1). Global Burden of Disease analyses further underscore this trajectory: in 2021 alone, T2DM accounted for 97.1% of all diabetes-related deaths, with age-standardized mortality rising by nearly 10% since 1990, with the most pronounced escalation observed in low and low-middle socioeconomic regions attributable to demographic expansion and ongoing epidemiological transition (2,3). T2DM accounts for nearly 90–95% of all diagnosed diabetes cases, making it by far the predominant subtype, and current estimates indicate it affects approximately one in nine adults globally, with annual direct healthcare costs exceeding one trillion US dollars (4,5).

The pathogenesis of T2DM is multifaceted, encompassing a progressive crosstalk among peripheral insulin resistance and an insufficient pancreatic β-cell secretory response. In its early stages, compensatory hyperinsulinemia can maintain near-normal glycemia; however, as beta-cell dysfunction advances, overt hyperglycemia ensues (6). At the cellular level, IR is mediated by impaired IRS1 phosphorylation, dysregulation of the PI3K/Akt signaling cascade, and aberrant activation of pro-inflammatory kinases including JNK and IKKβ (7). Concurrently, aberrant lipid accumulation within hepatic and skeletal muscle tissues, augmented circulating non-esterified fatty acid concentrations and chronic low-grade systemic inflammation collectively perpetuate insulin resistance and accelerate β-cell exhaustion (8). Hyperglycemia, once established, activates a nexus of pathological cascades including the polyol pathway, advanced glycation end-product (AGE) formation, protein kinase C (PKC) activation, and reactive oxygen species (ROS) overproduction that collectively precipitate the spectrum of diabetic complications (9). Beta-cell dysfunction itself is further compounded by glucotoxicity, lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, and the inflammatory cytokine milieu (8,10).

Chronic hyperglycemia in T2DM culminates in both microvascular and macrovascular complications that substantially impair quality of life and increase premature mortality. Microvascular sequelae encompass diabetic retinopathy, nephropathy and peripheral neuropathy, whereas macrovascular sequelae comprise cerebrovascular disease, coronary artery disease, and peripheral arterial disease (11). Dyslipidemia characterized by increased triglycerides, LDL, and declined HDL is a cardinal metabolic feature of T2DM arising from IR-driven upregulation of hepatic VLDL secretion, enhanced adipose tissue lipolysis, and impaired lipoprotein lipase activity. Hepatic dysfunction, notably manifesting as non-alcoholic fatty liver disease (NAFLD) and elevated transaminase activities, is also highly prevalent due to insulin resistance-driven hepatic lipid accumulation and oxidative stress (12). These multisystem consequences of T2DM underscore the imperative for therapeutic strategies addressing not merely glycemia but the broader metabolic milieu.

Current pharmacological management of T2DM employs a range of agents, including biguanides (metformin), sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonists, and insulin preparations (13,14). While these drugs are generally efficacious in reducing blood glucose, each class carries significant limitations. metformin, the established first-line agent, is associated with gastrointestinal intolerance and is contraindicated in significant renal impairment. Sulfonylureas carry risks of hypoglycemia and weight gain; thiazolidinediones may cause fluid retention and

increase fracture risk; and newer agents, though generally better tolerated, remain prohibitively expensive and inaccessible to the majority of patients in developing nations (13,15,16). Moreover, the progressive nature of beta-cell failure means that monotherapy frequently becomes insufficient over time, necessitating combination regimens with compounding side-effect profiles. These unmet clinical needs have renewed scientific interest in plant-derived therapeutics as safer, multi-target, and cost-effective adjuncts or alternatives.

Traditional systems of medicine, including Ayurveda, Siddha, and Unani, have long employed plant-based remedies for the management of diabetes, many of which have received experimental scientific validation (17,18). These plants harbour rich repositories of bioactive phytoconstituents flavonoids, alkaloids, terpenoids, tannins, and saponins known to modulate multiple biochemical pathways implicated in glycemic equilibrium (19,20). In particular, flavonoids have garnered considerable attention as antidiabetic candidates, acting through AMPK activation, GLUT4 translocation, α-glucosidase and α-amylase inhibition, and suppression of chronic low-grade inflammation (21,22). Among these botanicals, *Acalypha indica* Linn. (family Euphorbiaceae), vernacularly designated as 'Indian Acalypha' or 'Kuppaimeni' in Tamil, is a widely distributed tropical and subtropical herb with an established ethnomedicinal history. Pharmacological investigations have documented its antioxidant, anti-inflammatory, antimicrobial, and wound-healing properties (23,24). Phytochemical profiling has identified alkaloids, coumarins, flavonoids, phenols, saponins, tannins and volatile fatty acids as major bioactive constituents (24). Preliminary in vitro studies have reported alpha-glucosidase inhibitory and antioxidant activities in stem extracts, with in vivo investigations further confirming postprandial antihyperglycemic and hepatoprotective effects (25). Despite these promising preliminary reports, comprehensive, dose-dependent in vivo investigations evaluating the insulin-sensitizing, hepatoprotective, nephroprotective, and hypolipidemic effects of *Acalypha indica* alongside its antidiabetic activity in a well-characterized T2DM model remain lacking. The current investigation was formulated to systematically bridge this knowledge gap.

MATERIALS AND METHODS

Chemicals

The chemicals and reagents employed in this investigation were procured from recognized suppliers to ensure quality and reproducibility. General biochemical reagents were sourced from Krishgen Biosystems (Mumbai, India) and Sigma-Aldrich (St. Louis, MO, USA). Streptozotocin (STZ) was purchased from Sigma-Aldrich (St. Louis, MO, USA) and dissolved freshly in 0.1 M citrate buffer (pH 4.5) immediately before use. Biochemical assay kits for liver function tests were obtained from ERBA Diagnostics, while kidney function test kits were from Agappe Diagnostics. Insulin ELISA kits were procured from commercial sources validated for rat serum insulin quantification.

Experimental animals

Adult male albino Wistar rats (Rattus norvegicus) aged 150–180 days and weighing 180–220 g, were obtained from the Central Animal Facility. They were maintained per National Guidelines and Protocols, sanctioned by the Institutional Animal Ethics Committee (IAEC): BRULAC/SDCH/SIMATS/IAEC/03-2025/08. The experimental animals were housed in sterile polypropylene cages at the BRULAC, SDC facility under regulated ambient conditions encompassing temperature (21 ± 2°C), relative humidity (65 ± 5%), and a 12-hour light/dark photoperiod. All animals had access to a commercially formulated standard pellet chow (Lipton India, Mumbai, India) and fresh drinking water throughout the experimental duration. All experimental procedures were conducted with strict adherence to ethical guidelines to minimize animal discomfort.

T2DM induction in experimental animals

Streptozotocin (36mg/kg b.w.) prepared freshly in 0.1M sodium citrate buffer (pH 4.5), was administered intraperitoneally once to induce diabetes. Following 72 hours of fasting blood glucose levels were assessed, and rats with glycemic index ≥ 200 mg/dl were confirmed diabetic.

Study design

For the present investigation, the doses of *Acalypha indica* were determined using the existing literature evidences. The rats were allocated into six experimental groups, each comprising six animals as outlined below: Group I – Normal control rats receiving vehicle alone, Group II – T2DM rats induced

by STZ, Group III – T2DM rats treated with *Acalypha indica* (100mg/kg b.w) for 45 days, Group IV – T2DM rats administered *Acalypha indica* (200mg/kg b.w) for 45 days, Group V – T2DM rats given *Acalypha indica* (400mg/kg b.w) for 45 days, Group VI – T2DM rats treated with standard metformin (50mg/kg b.w) for 45 days. Following treatment completion, rats underwent overnight fasting prior to anaesthesia which is induced with ketamine-xylazine combination, and subsequently euthanised by cervical decapitation. Blood was obtained via retro-orbital venous plexus puncture, and serum was isolated by centrifugation and presereved at −80 °C until further analysis. Gastrocnemius muscle was rapidly dissected and used for further experimental assays.

Fasting blood glucose

Following overnight fasting, blood was sampled from each rat's teil vein to assess glucose levels. Measurements were performed with On-Call Plus test strips (ACON Laboratories Inc., USA), reported as mg/dl.

Serum Insulin

Serum insulin levels were quantified using Crystal Chem Inc.'s ultrasensitive rat insulin ELISA kit (Illinois, USA). The assay's detection range spanned 0.1–64 ng/ml, with 100% cross-reactivity of the insulin antibody to rat insulin. The intra-assay coefficient of variation was 10%, while the inter-assay coefficient of variation was 10%. The results were expressed in nanograms per millilitre (ng/ml). Insulin levels were used in conjunction with fasting blood glucose to calculate the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index.

HOMA-IR

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was computed from fasting blood glucose and fasting serum insulin values using the formula described by Matthews et al. (1985): HOMA-IR = [Fasting Blood Glucose (mmol/L) × Fasting Serum Insulin (μIU/mL)] / 22.5. Higher HOMA-IR values are indicative of greater insulin resistance, and the index was used to compare the degree of peripheral and hepatic insulin resistance across experimental groups.

Oral glucose tolerance test (OGTT)

All rats were subjected to an oral glucose tolerance test (OGTT) two days before sacrifice. All animals were fasted overnight and then administered an oral glucose load (10ml/kg b.w. of 50% w/v glucose solution). Blood was initially collected from the retro-orbital sinus using heparinized microhematocrit capillary tubes for the estimation of blood glucose and fasting serum insulin. At subsequent time points of 0, 60, 120 and 180 minutes after glucose administration, blood samples were obtained from the tail tip, and a drop of blood was directly applied to the end of the test strips. Blood glucose values were displayed on the glucometer and expressed in mg/dl.

Insulin tolerance test

The insulin tolerance test was performed in accordance with the method described by Bruning et al. (1998) to assess in vivo insulin sensitivity. Following a 4-hour fast, baseline blood glucose (0 min) was measured. Each rat then received a single intraperitoneal injection of regular human insulin at 0.75 IU/kg body weight. Blood glucose levels were subsequently assessed at 15, 30, 45, and 60 minutes post-insulin injection. The rate of blood glucose reduction was computed as an indicator of insulin-stimulated glucose disposal and expressed in mg/dL at respective time points.

Liver function tests

Hepatic function was assessed by determining the serum activities of AST, ALT and ALP using commercially available ERBA biochemical kits, following the manufacturer's recommended protocols. Enzymatic activities were measured on a semi-automated analyzer and expressed in International Units per Liter (IU/L). Total bilirubin levels were also estimated using the diazo method and expressed in mg/dl.

Kidney function tests

Renal function was evaluated by estimating serum levels of urea, creatinine, and uric acid using Agappe diagnostic kits according to the kit protocol. Serum urea was determined by the urease-Berthelot method, creatinine by the Jaffe's kinetic method, and uric acid by the uricase-peroxidase enzymatic method. All values were measured on a semi-automated analyzer and expressed in mg/dl.

Lipid profile

TC, HDL, LDL, and TG levels in serum were quantified with ERBA kits according to instructions, expressed as mg/dl.

Statistical analysis

All experimental data are expressed as Mean ± SEM (n = 6 per group). Statistical analyses were conducted using GraphPad Prism (version 8.2). Inter-group statistical comparisons were done using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. Differences between groups were considered statistically significant at a p-value less than 0.05 ($p < 0.05$).

RESULTS

Effect of *Acalypha indica* on FBG and serum insulin

Diabetic rats (Group II) demonstrated a marked and sustained elevation in FBG levels relative to healthy control animals (Group I), confirming successful induction of experimental T2DM. Treatment with *Acalypha indica* for 45 days elicited substantial dose-responsive decline in FBG levels across Groups III, IV, and V. The 400 mg/kg dose group (Group V) exhibited the most pronounced glycemic reduction, approaching levels observed in the metformin-treated group (Group VI) (figure 1a). The lowest dose (100 mg/kg) produced a moderate but statistically significant reduction in blood glucose, while the intermediate dose (200 mg/kg) produced an intermediate effect, consistent with a dose-response relationship. Concomitantly, serum insulin levels were substantially reduced in the diabetic group relative to normal controls, reflecting partial β-cell destruction and impaired insulin secretion. Following treatment with *Acalypha indica*, serum insulin levels were significantly restored in a dose-responsive fashion. The high dose (400 mg/kg) yielded insulin levels most comparable to the standard metformin group, suggesting either enhanced insulin secretion from residual beta cells, reduced peripheral insulin degradation, or improved beta-cell regeneration (figure 1b).

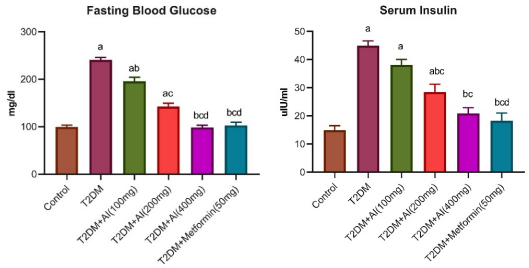

Figure 1a & b: Represents the influence of *Acalypha indica* on (a) FBG and (b) serum insulin levels of experimental animals.

Effect of *Acalypha indica* on HOMA-IR of experimental animals

HOMA-IR values were significantly elevated in the diabetic group relative to healthy control rats, confirming the presence of profound insulin resistance in the experimental model. All three doses of *Acalypha indica* treatment significantly reduced HOMA-IR values relative to the diabetic control, with the 400 mg/kg group exhibiting HOMA-IR values statistically comparable to those of metformin-treated animals (Table 1). The progressive reduction in HOMA-IR across the dose groups underscores the insulin-sensitizing capacity of *Acalypha indica*, likely mediated through upregulation of insulin signaling components in skeletal muscle and adipose tissue.

Groups	HOMA-IR
Control	3.7 ± 0.2
T2DM	26.3 ± 0.7^{a}
T2DM+AI (100mg)	18.3 ± 1.5^{ab}
T2DM+AI (200mg)	10.0 ± 1.3^{abc}
T2DM+AI (400mg)	5.0 ± 0.4^{bcd}
T2DM+Metformin (50mg)	4.6 ± 1.0^{bcd}

Table 1: Represents the effect of *Acalypha indica* on HOMA-IR. Results indicated as Mean±SEM and $p<0.05$ is considered as statistically significant.

Oral glucose tolerance test

In the OGTT, diabetic rats (Group II) exhibited markedly impaired glucose tolerance, with blood glucose levels remaining significantly elevated at all time points (0, 60, 120, and 180 min) following the oral glucose challenge relative to healthy controls, a hallmark of T2DM pathophysiology. Treatment with *Acalypha indica* at all three doses resulted in significantly enhanced glucose clearance, as demonstrated by decreased glycemia excursions and reduced area under the curve (AUC). The 400 mg/kg dose produced glucose tolerance profiles closely mirroring those of the metformin group, with blood glucose returning toward fasting levels by the 180-minute time point (Table 2). These data indicate that *Acalypha indica* improves both peripheral glucose uptake and hepatic glucose regulation following a glucose load, potentially through inhibition of intestinal carbohydrate-digesting enzymes.

Groups/Duration	0 hr	1 hr	2 hrs	3 hrs
Control	99.25 ± 4.3	266.5 ± 3.9	177.25 ± 5.6	124 ± 3.4
T2DM	241 ± 5.2[a]	707.8 ± 8.1[a]	570.5 ± 8.0[a]	488.75 ± 12.3[a]
T2DM+AI (100mg)	195.75 ± 8.7[ab]	551.3 ± 8.7[ab]	415.25 ± 4.8[ab]	237 ± 4.4[ab]
T2DM+AI (200mg)	142.25 ± 7.4[abc]	518.5 ± 4.2a[bc]	316.5 ± 5.2[abc]	140.75 ± 4.3[abc]
T2DM+AI (400mg)	98.5 ± 4.7[bcd]	488.0 ± 5.2[abcd]	240 ± 3.9[abcd]	121 ± 5.9[abcd]
T2DM+Metformin (50mg)	102.75 ± 6.6[bcd]	569.3 ± 3.5[abde]	307 ± 6.5[abce]	167 ± 5.9[bcde]

Table 2: Influence of *Acalypha indica* on glucose tolerance of experimental animals.

Insulin tolerance test

The ITT revealed pronounced insulin resistance in STZ-diabetic control animals, as reflected by a blunted decline in blood glucose following insulin administration at all measured time points (15, 30, 45, and 60 min). In contrast, normal control rats exhibited a typical hypoglycemic response to exogenous insulin. Treatment with *Acalypha indica* significantly improved insulin sensitivity in a dose-responsive fashion, with the high dose (400 mg/kg) producing an insulin responsiveness profile most similar to the metformin reference group (Table 3). These results corroborate the HOMA-IR data and collectively affirm that *Acalypha indica* potentiates insulin-stimulated glucose disposal in peripheral tissues, particularly skeletal muscle.

Groups / Duration	0 min	15 mins	30 mins	45 mins	60 mins
Control	80.44 ± 4.2	81.75 ± 5.1	74.75 ± 5.4	74.40 ± 5.0	67 ± 5.8
T2DM	193.83 ± 5.2[a]	181.75 ± 9.5[a]	173.25 ± 7.6[a]	154.75 ± 7.8[a]	157.5 ± 9.4[a]
T2DM+AI (100mg)	158.33 ± 8.7[ab]	159.75 ± 6.8[a]	149.75 ± 6.3[a]	141.77 ± 10.8[ab]	119.75 ± 13.0[ab]
T2DM+AI (200mg)	115.27 ± 7.4[abc]	109.25 ± 8.4[abc]	101.36 ± 8.8[abc]	100.5 ± 9.0[abc]	88.25 ± 8.4[b]
T2DM+AI (400mg)	79.73 ± 4.7[bcd]	79.0 ± 7.5[bcd]	72.78 ± 4.9[bcd]	69.75 ± 6.3[bcd]	61.5 ± 6.2[bc]
T2DM+Metformin (50mg)	83.52 ± 6.6[bcd]	86.25 ± 4.1[bcd]	76.44 ± 5.2[bcd]	74.5 ± 7.0[bcd]	65.75 ± 8.3[bcd]

Table 3: Represents the insulin tolerance of experimental animals during different time intervals.

Liver function markers

Diabetic control rats exhibited significantly elevated serum levels of AST, ALT, ALP, and total bilirubin compared to normal controls, indicative of hepatocellular injury and biliary dysfunction secondary to chronic hyperglycemia and associated oxidative stress, a well-documented consequence of experimental diabetes. Treatment with *Acalypha indica* induced a marked dose-related decline in all hepatic enzyme markers. At the 400 mg/kg dose, AST, ALT, and ALP enzymes showed restoration relative to substantially normalized values, comparable to the metformin-treated group. Total bilirubin levels were similarly reduced following *Acalypha indica* treatment. These hepatoprotective effects may be attributed to the antioxidant and anti-inflammatory phytoconstituents present in the extract, such as flavonoids and phenolic acids, which scavenge reactive oxygen species and inhibit pro-inflammatory cytokine production in the liver. Results are shown in Figure 2a–d.

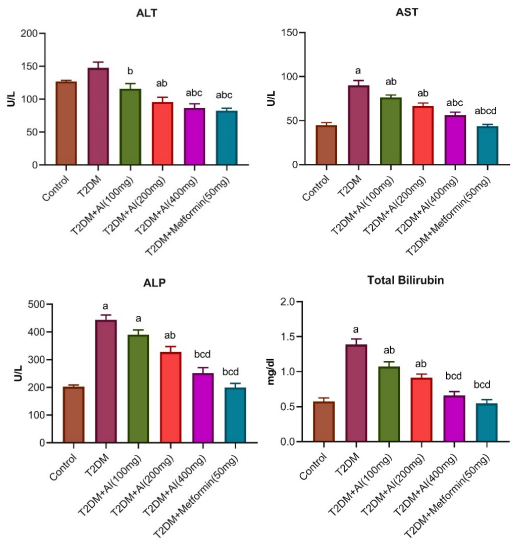

Figure 2 a-d: Effect of *Acalypha indica* on liver marker enzymes and total bilirubin levels of the diabetic rats

Effect on renal function markers

STZ-induced diabetic control rats demonstrated significantly elevated serum urea, creatinine, and uric acid levels relative to normal controls, reflecting diabetic nephropathy characterized by reduced glomerular filtration rate, increased protein catabolism, and impaired tubular secretion. Treatment with *Acalypha indica* at all doses significantly ameliorated these renal parameters, with the 400 mg/kg dose producing the most notable nephroprotective effect. The reduction in serum creatinine and urea suggests improved glomerular function and decreased nitrogenous waste accumulation, while the lowering of uric acid levels may reflect diminished purine catabolism. The results of renal function assessment are presented in Figure 3a–c.

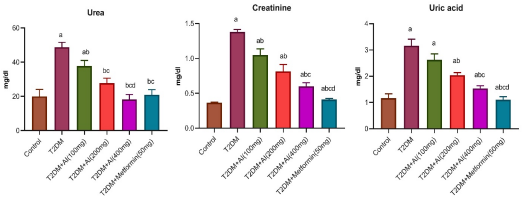

Figure 3 a-c: Effect of *Acalypha indica* on renal function markers of streptotozotocin induced diabetic rats (a) urea (b) creatinine (c) uric acid

Effect on serum lipid profile

The lipid profiles of STZ-induced diabetic control rats were markedly deranged compared to normal controls, manifesting as elevated serum levels of TC, TG, LDL, with a concomitant decline in HDL. Administration of *Acalypha indica* significantly corrected these lipid abnormalities in a dose-dependent manner. TC, TG, LDL levels were substantially declined, whereas HDL levels were significantly elevated toward normal values across all treated groups. The 400 mg/kg treatment group achieved lipid parameters closely approximating those of the metformin reference group. These findings are demonstrated the hypolipidemic activity of *Acalypha indica*. Lipid profile results are depicted in Figure 4a–d.

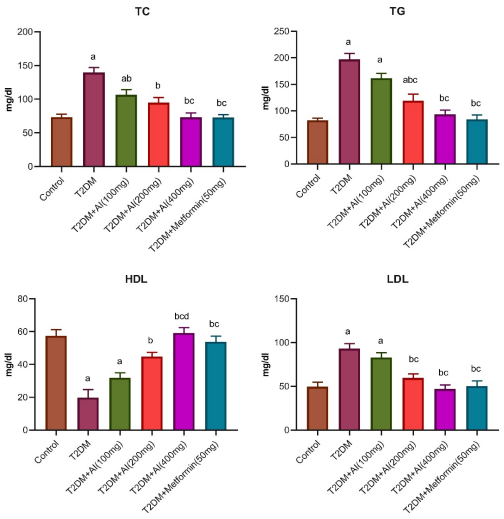

Figure 4 a-d: Impact of *Acalypha indica* on serum lipid profile of streptotozotocin induced diabetic rats (a) total cholesterol (b) triglyceride (c) HDL (d) LDL

DISCUSSION

The present investigation provides the first comprehensive, dose-dependent in vivo assessment of the antidiabetic and metabolic effects of *Acalypha indica* in the low-dose STZ (35 mg/kg) rat model of T2DM a well-validated experimental paradigm that recapitulates partial beta-cell dysfunction, peripheral insulin resistance, and chronic hyperglycemia closely analogous to clinical T2DM (26,27). Our results collectively demonstrate that *Acalypha indica* exerts significant antidiabetic, insulin-sensitizing, hepatoprotective, nephroprotective, and hypolipidemic activities in a consistent, dose-dependent fashion, with the highest dose (400 mg/kg) producing effects comparable to the standard antidiabetic drug metformin across all parameters evaluated.

The concentration dependent progressive decline in FBG concomitant with serum insulin restoration in

Acalypha indica-treated rats can be attributed to several complementary mechanisms. First, the extract may stimulate residual pancreatic β-cell function and augment endogenous insulin secretion, as evidenced by the parallel elevation of serum insulin in treated groups (23,28). Second, phytoconstituents present in *Acalypha indica* particularly flavonoids, tannins, and phenolic acids identified in comprehensive phytochemical reviews of the plant are well-established inhibitors of intestinal α-glucosidase and α-amylase, key catalysts of dietary carbohydrate catabolism and postprandial glucose absorption (29,30). By retarding glucose absorption at the gut level, these phytoconstituents can substantially attenuate postprandial hyperglycemia, as corroborated by the improved OGTT profiles observed in the present study (table 2). Third, flavonoids and terpenoids within the extract may augment peripheral glucose utilization by promoting redistribution of GLUT4 from intracellular stores to the periphery of skeletal muscle and adipose tissue through PI3K/Akt axis and AMPK-dependent signaling, a process critically impaired in diabetes (21,22). These multi-mechanistic actions likely act synergistically to produce the observed improvements in both fasting and postprandial glycemic control (figure 1).

The marked improvements in HOMA-IR and ITT profiles collectively confirm that *Acalypha indica* possesses clinically meaningful insulin-sensitizing properties. Insulin resistance in T2DM is fundamentally driven by defects in IRS-1 phosphorylation, impaired PI3K/Akt signaling, and enhanced serine phosphorylation of IRS-1 mediated by pro-inflammatory kinases including JNK and IKKβ (7). The flavonoid-rich phytochemical profile of *Acalypha indica* positions it well to address these defects: polyphenols have been shown to suppress chronic low-grade inflammation by suppressing NF-κB and reducing circulating TNF-α, IL-1β, and IL-6, while simultaneously activating AMPK that mimics key molecular actions of metformin by suppressing hepatic gluconeogenesis, enhancing fatty acid oxidation, and promoting GLUT4-mediated peripheral glucose uptake (22,31). The close parallels in HOMA-IR and ITT outcomes between the 400 mg/kg *Acalypha indica* group and the metformin reference (table 1 & 3) strongly suggest a mechanistic overlap involving AMPK activation and downstream insulin sensitization, a hypothesis deserving targeted molecular investigation in future studies.

The hepatoprotective effects of *Acalypha indica*, evidenced by significant dose-dependent normalization of serum AST, ALT, ALP, and total bilirubin, are particularly noteworthy from a clinical perspective (figure 2a-d). Hepatic enzyme elevations in STZ-diabetic rats arise from oxidative stress-driven mitochondrial dysfunction, lipid peroxidation, and pro-inflammatory cytokine-mediated hepatocyte injury all consequences of chronic hyperglycaemia (9,12). The antioxidant-rich phytochemical composition of *Acalypha indica* including its flavonoids, phenolic acids, and hydrolysable tannins is well-equipped to counter these pathological processes through direct scavenging of ROS, sequestration of pro-oxidative transition metals, and upregulation of enzymic antioxidants including SOD, CAT, and GPx (24,33). Obtained results were fully consonant with earlier reports documenting hepatoprotective activity of *Acalypha indica* and related species against oxidative hepatic challenge (34), and extend this evidence base into the context of diabetic hepatopathy.

Diabetic nephropathy (DN), resulting from sustained hyperglycaemia-induced activation of the polyol pathway, AGE accumulation, PKC activation, and oxidative stress-driven glomerular hyperfiltration injury, is one of the most serious and prevalent complications of T2DM (11). The significant amelioration of serum urea, creatinine, and uric acid levels in *Acalypha indica*-treated animals in the present study indicates mitigation of these pathological mechanisms and preservation of both glomerular and tubular function (figure 3a-c). These nephroprotective effects align mechanistically with those reported for other polyphenol-rich plant extracts that attenuate DN through activation of the Nrf2/ARE antioxidant pathway, suppression of NF-κB-mediated renal inflammation, and reduction of TGF-β1-driven fibrosis (35). The reduction in serum uric acid observed here is additionally significant, as hyperuricemia is recognized as an independent predictor of cardiometabolic disease, endothelial dysfunction, and progression of renal impairment in individuals with diabetes (36).

The significant hypolipidemic effects of *Acalypha indica* manifesting as reductions in cholesterol, triglyceride, LDL, and elevation of HDL reflect modulation of multiple lipid metabolic pathways deranged in T2DM (figure 4a-d). Insulin resistance drives hepatic VLDL overproduction, impairs lipoprotein lipase activity, and elevates non-esterified fatty acid (NEFA) flux, collectively producing the

characteristic T2DM dyslipidemic pattern (36). Flavonoids within *Acalypha indica* may act through inhibition of HMG-CoA reductase, the rate-limiting enzyme of hepatic cholesterol biosynthesis; activation of PPARα to enhance fatty acid beta-oxidation; inhibition of pancreatic lipase to reduce dietary fat absorption; and upregulation of LDL receptor expression (18,19). Correction of the dyslipidemic profile is of particular clinical significance given that dyslipidemia substantially amplifies the already elevated cardiovascular risk inherent to the diabetic state.

The consistent dose-response relationship observed across all parameters evaluated with the 400 mg/kg dose has potential impact most comparable to metformin suggests that the bioactive constituents of *Acalypha indica* act in a concentration-dependent manner on their respective molecular targets. This is consistent with recent comprehensive phytochemical reviews documenting quantitative correlations between flavonoid and phenolic acid content and antidiabetic bioactivity in related species (23,24). Future experiments are warranted to fractionate extract via bioassays, thereby characterizing the individual efficacious constituents responsible for each observed activity, molecular docking and enzyme inhibition assays to elucidate binding mechanisms at key therapeutic targets (alpha-glucosidase, DPP-4, AMPK, PPARγ, and the insulin receptor), and transcriptomic or proteomic profiling to map the signaling networks modulated by the extract in insulin target tissues (19,20). Long-term subchronic and chronic toxicity evaluations will be essential before clinical development, as will standardized clinical trials in human subjects to validate the translational relevance of these preclinical findings.

CONCLUSION

Current research investigation reveals that the ethanolic extract of *Acalypha indica* exerts significant antidiabetic, insulin-sensitizing, hepatoprotective, nephroprotective, and hypolipidemic effects in the streptozotocin-induced diabetic animals. A 45-day oral administration of *Acalypha indica* at doses of 100, 200, and 400 mg/kg b.w. produced dose-dependent improvements in FBG, serum insulin, HOMA-IR, OGT, and insulin sensitivity. Concomitant amelioration of liver enzyme markers, renal function parameters, and dyslipidemia further underscores the broad-spectrum metabolic benefits of this herbal extract. The highest dose (400 mg/kg) demonstrated efficacy comparable to the standard antidiabetic drug metformin, highlighting its therapeutic potential. These findings yield a strong experimental basis for backing the ethnopharmacological role of *Acalypha indica* in diabetes management and related metabolic complications. Future investigations should focus on isolating and characterizing the active phytoconstituents, elucidating their molecular mechanisms of action, and conducting long-term safety evaluations to facilitate the development of *Acalypha indica*-derived therapeutics for clinical use.

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