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Amelioration of Diabetic Dyslipidaemia by an Aqueous Extract of *Tremella fuciformis* in Streptozotocin-Induced Diabetic Mice#

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Abstract

Diabetic dyslipidaemia is a major contributor to cardiovascular risk in insulin-deficient states. This study evaluated the hypolipidemic activity of an aqueous extract of Tremella fuciformis (AETF) in streptozotocin (STZ)-induced diabetic mice. Male BALB/c mice were rendered diabetic by a single intraperitoneal injection of STZ at a dose of 60 mg/kg body weight. Hyperglycaemic animals exhibiting fasting blood glucose levels ≥250 mg/dL were selected and administered AETF orally at doses of 50 and 100 mg/kg body weight per day for 28 consecutive days. Serum lipid parameters were quantified using enzymatic colourimetric assays. The STZ administration induced significant dyslipidaemia, characterised by elevated triglycerides, total cholesterol, LDL-C, and VLDL-C, along with reduced HDL-C, compared with normal controls ($p < 0.0001$). AETF administration significantly improved all lipid parameters in a dose-dependent manner, with the 100 mg/kg dose demonstrating greater reductions in atherogenic lipoproteins and restoration of HDL-C relative to diabetic controls. These findings indicate that AETF effectively ameliorates diabetes-associated dyslipidaemia and restores lipoprotein balance, supporting its potential as a functional adjunct for mitigating cardiometabolic risk associated with diabetes.

Keywords: *Tremella fuciformis*, diabetic dyslipidaemia, streptozotocin, serum lipid profile, hypolipidemic activity

Diabetes mellitus is a rapidly escalating metabolic disorder affecting more than 400 million individuals worldwide and remains a principal driver of cardiovascular morbidity and mortality (Lu et al*.,* 2024). Although chronic hyperglycemia defines the disease, dyslipidemia constitutes a major determinant of diabetic complications and atherosclerotic progression. Diabetic dyslipidemia is typified by elevated triglycerides (TG), increased low-density lipoprotein cholesterol (LDL-C), reduced high-density lipoprotein cholesterol (HDL-C), and enhanced atherogenic lipoprotein remodelling (Ormazabal et al., 2018; Grundy et al., 2005). Importantly, lipid abnormalities often persist despite glycemic control,

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underscoring the need for therapeutic strategies specifically targeting metabolic lipid derangements (Chew et *al.,*2025). The pathogenesis of diabetic dyslipidemia is mechanistically rooted in insulin resistance and hepatic metabolic reprogramming. Impaired insulin signalling through the PI3K/Akt pathway diminishes suppression of hepatic gluconeogenesis while paradoxically maintaining activation of lipogenic transcription factors such as sterol regulatory element-binding protein-1c (SREBP-1c) (Sakurai et al*.,* 2021). This selective insulin resistance enhances de novo lipogenesis (DNL), triglyceride synthesis, and very-low-density lipoprotein (VLDL) overproduction (Ginsberg*,* 2000). Simultaneously, elevated circulating free fatty acids derived from dysfunctional adipose tissue further amplify hepatic lipid influx and lipotoxicity (Roy et al*.,* 2023*;* Meerarani et al*.,* 2006). Mitochondrial dysfunction exacerbates this imbalance by impairing β-oxidation and increasing reactive oxygen species (ROS) generation, thereby reinforcing lipid accumulation and insulin signalling defects (Kim et al*.,* 2008).

Streptozotocin (STZ)-induced diabetes is a well-established experimental model for investigating these metabolic disturbances due to its reproducible induction of β-cell destruction and sustained hyperglycemia (Marino et al*.,* 2023). STZ, a nitrosourea compound derived from *Streptomyces achromogenes*, selectively targets pancreatic β-cells via DNA alkylation, PARP activation, and oxidative stress, resulting in insulin deficiency (Marino et al., 2023). Beyond hyperglycemia, STZ-induced diabetes is consistently accompanied by marked dyslipidemia, including hypertriglyceridemia, elevated LDL-C, reduced HDL-C, and hepatic steatosis (Liu et al., 2019). Mechanistically, hyperglycemia-driven activation of SREBP-1c and carbohydrate-responsive element-binding protein (ChREBP) promotes expression of lipogenic enzymes such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), thereby enhancing triglyceride synthesis and VLDL assembly (Sakurai *et al.,* 2021*;* Liu *et al.,* 2019). Concurrent suppression of peroxisome proliferator-activated receptor-α (PPAR-α) and carnitine palmitoyl transferase-1 (CPT-1) impairs fatty acid β-oxidation, favouring lipid accumulation (Liu et al., 2019). A critical regulatory node in this metabolic network is AMP-activated protein kinase (AMPK), a master energy sensor that suppresses lipogenesis and promotes fatty acid oxidation. Reduced AMPK phosphorylation has been documented in STZ-induced diabetic models, contributing to unchecked SREBP-1c activation and dyslipidemia (Liu et al., 2019). Oxidative stress further aggravates these abnormalities by promoting lipid peroxidation, activating pro-inflammatory signalling pathways, and impairing insulin receptor substrate (IRS)-mediated signalling cascades *(*Wani et al., 2026*;* Paneni *et al.,* 2013*;* Varghese et al., 2018*).* Collectively, these converging mechanisms establish a pathological axis linking hyperglycemia, oxidative stress, impaired AMPK signalling, and hepatic lipid overproduction. Current pharmacological interventions, including metformin and PPAR agonists, partially improve diabetic dyslipidemia through AMPK activation and metabolic remodelling (Han et al., 2021*;* Meerarani et al., 2006). However, long-term safety concerns and incomplete metabolic correction necessitate exploration of multi-targeted natural interventions. Bioactive compounds derived from medicinal plants and edible mushrooms have demonstrated promising hypolipidemic and antioxidant properties in STZ-induced diabetic models, often mediated through AMPK activation, suppression of lipogenic pathways, and restoration of redox balance (Lin et al., 2017*;* Kahksha et al., 2023*;* Huang et al., 2023)

Tremella fuciformis, an edible medicinal mushroom, has attracted growing interest owing to its reported antioxidative and metabolic regulatory properties. While previous investigations have highlighted its potential glycemic benefits, its role in modulating diabetic dyslipidemia and associated lipid parameters remains insufficiently characterised in experimental STZ models. Therefore, the present study was designed to investigate the hypolipidemic effect of polysaccharide-rich aqueous extract of *Tremella fuciformis* in streptozotocin-induced diabetic BALB/c mice through estimation of serum lipid profile parameters.

Materials and Methods

Collection and Preparation of Edible Mushroom Extract

The dried fruiting bodies of *Tremella fuciformis* were acquired from Biobrite Agro Solutions located in Shirol, Kolhapur, Maharashtra, India. They were subsequently pulverised and subjected to aqueous extraction using distilled water at a ratio of 1:10 (w/v), employing a boiling process at 100°C for 2 hours. Following filtration to eliminate insoluble residues, the resulting extract was concentrated under reduced pressure utilising a rotary evaporator. Subsequently, crude polysaccharides were precipitated by adding three times the volume of 95% ethanol, followed by a 24-hour incubation period at 4°C. The ensuing precipitate was harvested via centrifugation, vacuum-lyophilised, and utilised as the polysaccharide-enriched aqueous extract of *Tremella fuciformis* (AETF). This AETF was orally administered once daily for a duration of 28 consecutive days to streptozotocin-induced diabetic BALB/c mice at varying doses of 50 and 100 mg/kg body weight *(*Chen*,* 2010*;* Sun et al*.,* 2010*;* Li et al., 2025*).*

Experimental Animals

Male BALB/c mice, aged 5-6 weeks and weighing 20-25 g, were housed in polypropylene cages under specific environmental conditions: temperature (24-30 °C), relative humidity (50-60%), and a 12-hour light/12-hour dark cycle, following standard laboratory animal care protocols. The mice had ad libitum access to a commercial pellet diet and water. All procedures were conducted in

accordance with CPCSEA guidelines (Reg. No. 1809/Rebis/Rel/15/CPCSEA), approved under reference No. Ph.D./SVU/RAC/0106220378, with support from the Department of Veterinary Biochemistry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir (SKUAST-K), and the Department of Zoology, Government Degree College Baramulla (Autonomous), Jammu & Kashmir.

Induction of Diabetes

Diabetes was experimentally induced in mice through a single intraperitoneal injection of streptozotocin (STZ) obtained from Sisco Research Laboratories, Mumbai. The STZ was freshly dissolved in 0.1 M citrate buffer at a pH of 4.5 and administered at a dosage of 60 mg/kg body weight. Before inducing diabetes, the mice were acclimatised to standard laboratory conditions and fed a basal pellet diet for seven days. Following STZ injection, fasting blood glucose levels were assessed after 72 hours using blood samples from the tail vein, analysed with glucose test strips and a handheld glucometer (AccuChek). Mice with fasting blood glucose levels exceeding 250 mg/dL were identified as diabetic and included in subsequent experimental procedures, as per established protocols for STZ-induced diabetes models (Zangeneh et al., 2018; Hagh-Nazari et al., 2017).

Experimental Design

After three days of intraperitoneal administration of streptozotocin and confirmation of diabetes induction, the mice were randomly allocated into four groups, each comprising six animals:

Group I: Normal Healthy Control mice, received citrate buffer (i.p as vehicle control).

Group II: Diabetic control mice received a single dose of STZ (60mg/kg bw, i.p.).

Group III: Treated Diabetic mice received the AETF at 50 mg/kg/bw/day through oral gavage.

Group IV: Treated Diabetic mice received the AETF at 100 mg/kg/bw/day through oral gavage.

Blood Sample Collection and Estimation of Serum Lipid Parameters

After 28 days of treatment, mice were fasted overnight (12 h) and sacrificed by cervical dislocation. Blood was collected by cardiac puncture into plain tubes, allowed to clot, and centrifuged at 3000 rpm (≈1500 × g) for 15 min to obtain serum. Serum total cholesterol (TC) and triglycerides (TG) were estimated using commercially available enzymatic colourimetric kits (Erba Mannheim, Germany) based on the CHOD-PAP and GPO-PAP methods, respectively (Allain *et al.,* 1974; McGowan *et al.,* 1983). HDL-cholesterol (HDL-C) was determined using a direct homogeneous enzymatic assay (Erba Mannheim, Germany) (Warnick *et al.,* 2001). LDL-cholesterol (LDL-C) and VLDL-cholesterol (VLDL-C) were calculated using the Friedewald formula (Friedewald *et al.,* 1972).

Statistical Analysis

All data are presented as mean ± SEM (n = 6 per group). Statistical analyses were performed using GraphPad Prism version 11.0 (GraphPad Software, USA). Data were assessed for normality and homogeneity of variance before analysis. Intergroup differences were analysed using one-way analysis of variance (ANOVA), followed by Dunnett's post hoc test to compare treatment groups with the diabetic control group. A value of $p < 0.05$ was considered statistically significant.

Results and discussion

Effect of AETF on Serum Triglycerides and Total Cholesterol

Streptozotocin (STZ) induction resulted in significant elevations in serum triglyceride (TG) and total cholesterol (TC) levels compared with normal controls ($p < 0.0001$), confirming the successful establishment of diabetic dyslipidaemia. As shown in Fig. 1, serum TG levels increased to 201.5 mg/dL in diabetic mice compared with 94.52 mg/dL in the control group. Similarly, TC levels increased to 203.6 mg/dL relative to 121.6 mg/dL in normal mice, as illustrated in Fig. 2. Oral administration of the polysaccharide-enriched aqueous extract of *Tremella fuciformis* (AETF) for 28 days significantly ameliorated these alterations ($p < 0.0001$ vs. diabetic control). TG levels declined to 174.5 mg/dL and 145.6 mg/dL at 50 mg/kg and 100 mg/kg, respectively, as shown in Fig. 1, while TC levels decreased to 185.5 mg/dL and 165.5 mg/dL at the corresponding doses, as illustrated in Fig. 2. The greater reduction observed at 100 mg/kg indicates a dose-dependent hypolipidemic effect.

These findings demonstrate that AETF effectively mitigates hypertriglyceridemia and hypercholesterolemia associated with STZ-induced diabetes. Insulin deficiency resulting from STZ-mediated β-cell destruction promotes enhanced adipose lipolysis and increased hepatic free fatty acid influx, thereby stimulating hepatic lipid synthesis and secretion of triglyceride-rich lipoproteins. This metabolic shift activates lipogenic transcription factors such as sterol regulatory element-binding protein-1c (SREBP-1c), which subsequently upregulate HMG-CoA reductase (HMGCR), fatty acid synthase (FAS), and acetyl-CoA carboxylase (ACC), leading to increased hepatic triglyceride synthesis and VLDL production (Ding et al., 2016). The lipid abnormalities observed in untreated diabetic mice in the present investigation are therefore consistent with this well-established metabolic cascade.

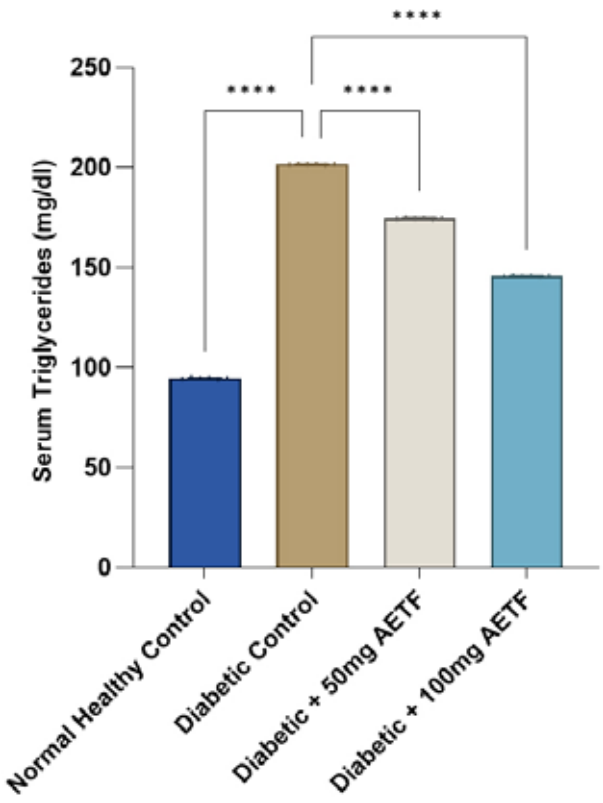

Fig.1: Serum triglyceride levels in normal control, diabetic control, and AETF-treated diabetic BALB/c mice receiving 50 and 100 mg/kg bw for 28 days.

Data are expressed as mean ± SEM (n = 6). **p < 0.0001 vs. diabetic control.

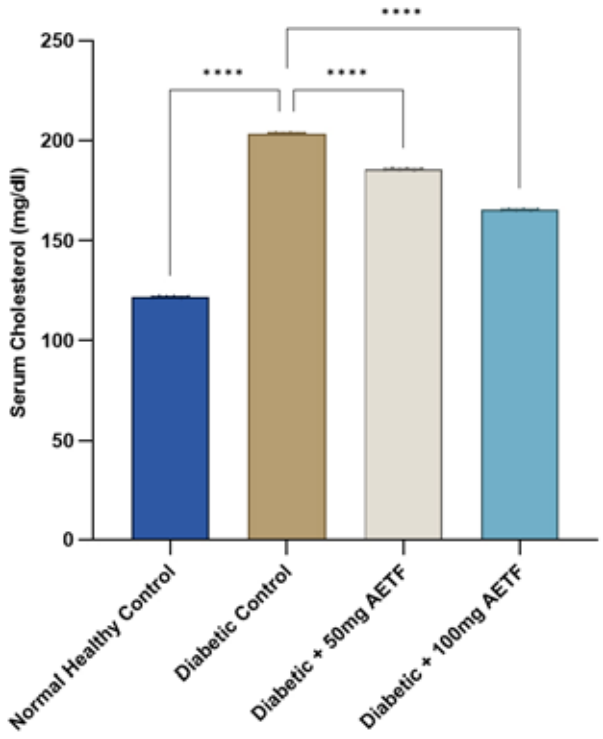

Fig.2: Serum total cholesterol levels in normal control, diabetic control, and AETF-treated diabetic mice receiving 50 and 100 mg/kg bw for 28 days.

Data are expressed as mean ± SEM (n = 6). **p < 0.0001 vs. diabetic control.

The reductions in TG and TC following AETF treatment may be attributed to the ability of *T. fuciformis* polysaccharides to modulate hepatic lipid metabolism. Tremella-derived polysaccharides have been reported to suppress the expression of SREBP, HMGCR, FAS, and ACC while attenuating oxidative and inflammatory mediators involved in metabolic dysfunction (Khan et al., 2022). In addition, dietary polysaccharides have been shown to suppress lipogenic gene networks and enhance cholesterol catabolism through activation of cholesterol 7α-hydroxylase (CYP7A1), a key enzyme in bile acid synthesis (Ganesan & Xu, 2019). Such suppression of hepatic lipid biosynthesis provides mechanistic support for the reductions in TG and TC observed in the treated groups.

Activation of AMP-activated protein kinase (AMPK) may further contribute to the lipid-modulating effects of Tremella polysaccharides. Tremella polysaccharides have been shown to enhance AMPK phosphorylation and upregulate peroxisome proliferator-activated receptor-α (PPARα), promoting fatty acid oxidation while suppressing SREBP-mediated lipogenesis (Song et al., 2025). Similar AMPK-dependent lipid improvements have been documented in STZ-induced models treated with *Clitocybe nuda* (Shih et al., 2014) and in studies demonstrating PPARα-mediated fatty acid oxidation induced by *Hericium erinaceus* (Hiwatashi et al., 2010). Collectively, these findings suggest that activation of the AMPK–PPARα signalling axis may play a central role in mediating the triglyceride-lowering effects observed following AETF administration.

Intestinal lipid regulation may also contribute to the hypocholesterolemic activity of *T. fuciformis*. Uronic acid-rich *Tremella* polysaccharides reduce serum cholesterol by interfering with micelle formation and enhancing faecal lipid excretion (Chiu et al., 2022). Moreover, *Tremella*-derived dietary fibres bind bile acids and improve circulating lipid profiles (Zhang et al., 2023). Comparable cholesterol-lowering effects have been reported in related species such as *Tremella aurantia* (Kiho et al., 2001) and *Tremella aurantialba* (Zhang et al., 2009; Yan et al., 2022), suggesting conserved lipid-regulatory properties within the *Tremella* genus.

Effect of AETF on Serum LDL-C and VLDL-C

The STZ administration also resulted in significant elevations in circulating atherogenic lipoproteins compared with normal healthy controls ($p < 0.0001$). As shown in Fig. 3, serum LDL-C concentrations increased to 124.8 mg/dL in diabetic mice compared with 45.25 mg/dL in healthy controls. Similarly, VLDL-C levels increased to 40.30 mg/dL relative to 18.90 mg/dL in normal mice, as illustrated in

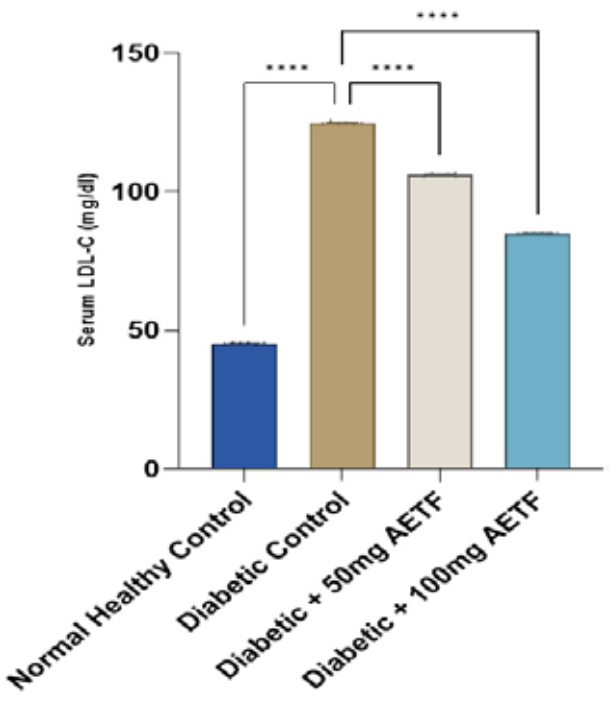

Fig.3: Serum LDL-C concentrations in normal control, diabetic control, and AETF-treated diabetic mice administered 50 and 100 mg/kg bw for 28 days.

Data are presented as mean ± SEM (n = 6). **p < 0.0001 vs. diabetic control.

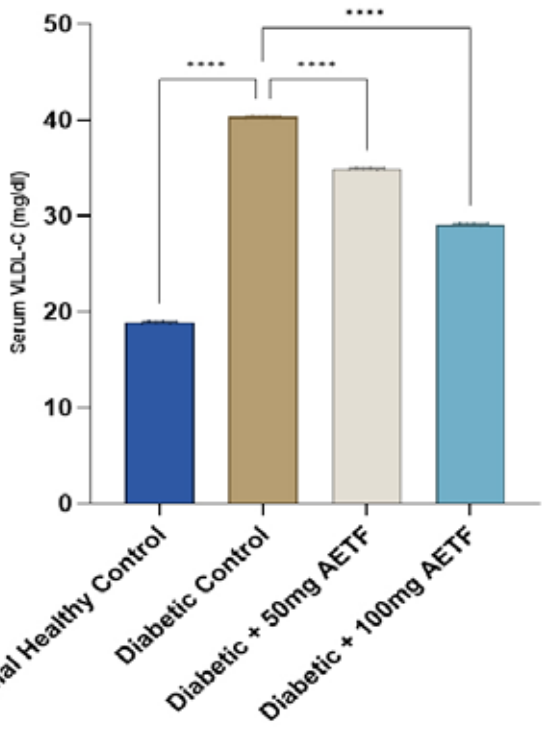

Fig.4: Serum VLDL-C concentrations in normal control, diabetic control, and AETF-treated diabetic mice administered 50 and 100 mg/kg bw for 28 days.

Data are presented as mean ± SEM (n = 6). **p < 0.0001 vs. diabetic control.

Fig. 4. Oral administration of AETF for 28 days significantly reduced both LDL-C and VLDL-C levels relative to diabetic controls ($p < 0.0001$). LDL-C declined to 106.1 mg/dL and 84.93 mg/dL at 50 mg/kg and 100 mg/kg, respectively, as shown in Fig. 3, while VLDL-C decreased to 34.90 mg/dL and 29.12 mg/dL at the corresponding doses, as illustrated in Fig. 4. The greater reduction observed at 100 mg/kg indicates a dose-dependent attenuation of the atherogenic lipoprotein profile. Elevated LDL-C and VLDL-C represent key features of diabetic dyslipidaemia and significantly contribute to cardiovascular risk in diabetic states (Nabi *et al*., 2013; Siddiqui *et al*., 2022; Ansari *et al*., 2024). Increased hepatic VLDL production driven by insulin deficiency and excessive free fatty acid influx subsequently results in elevated circulating LDL-C following lipoprotein metabolism. The pronounced elevations observed in untreated diabetic mice therefore reflect the characteristic atherogenic lipid profile associated with insulin-deficient conditions.

The ability of AETF to significantly reduce LDL-C and VLDL-C may be attributed to coordinated modulation of hepatic lipid synthesis and fatty acid oxidation. Activation of the AMPK–PPARα pathway enhances mitochondrial β-oxidation of fatty acids, thereby reducing substrate availability for triglyceride and VLDL synthesis (Song et al., 2025). Concurrent suppression of SREBP-mediated lipogenic pathways further limits hepatic lipoprotein overproduction (Khan et al., 2022). Together, these mechanisms provide a mechanistic basis for the reductions in circulating atherogenic lipoproteins observed in the present study. Oxidative stress and chronic inflammation also exacerbate diabetic dyslipidaemia by promoting LDL oxidation and impairing lipoprotein metabolism. Mushroom-derived polysaccharides enhance endogenous antioxidant defences (Arunachalam et al., 2022; Luo et al., 2023), while *T. fuciformis* suppresses NF-κB–mediated inflammatory signalling and vascular lipid accumulation (Dong et al., 2024). These antioxidant and anti-inflammatory effects may therefore contribute to improved lipoprotein stability and reduced atherogenic burden following AETF treatment.

Effect of AETF on Serum HDL-Cholesterol

The STZ administration resulted in a significant reduction in serum HDL-C levels compared with normal control mice ($p < 0.0001$). As illustrated in Fig. 5, HDL-C concentrations declined to 38.47 mg/dL in diabetic mice relative to 57.40 mg/dL in normal controls. Oral administration of AETF for 28 days significantly restored HDL-C levels compared with diabetic controls ($p < 0.0001$). HDL-C concentrations increased to 44.45 mg/dL and 51.48 mg/dL at 50 mg/kg and 100 mg/kg, respectively, as shown in Fig. 5, indicating a dose-dependent improvement in the anti-atherogenic lipoprotein profile.

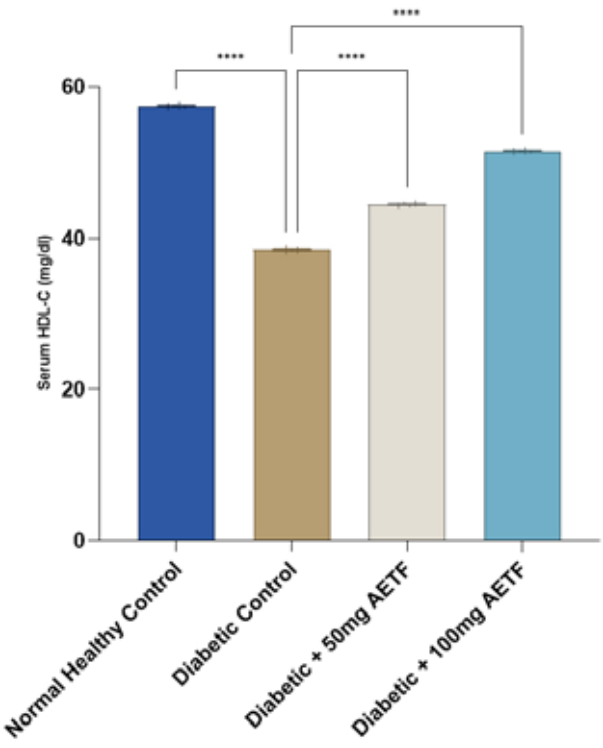

Fig.5: Serum HDL-C levels in normal control, diabetic control, and AETF-treated diabetic mice receiving 50 and 100 mg/kg bw for 28 days.

Data are expressed as mean ± SEM (n = 6). **p < 0.0001 vs. diabetic control.

Reduced HDL-C is a defining feature of diabetic dyslipidaemia and contributes to impaired reverse cholesterol transport and elevated cardiovascular risk. Oxidative stress and inflammatory processes associated with diabetes can impair HDL synthesis and functionality while simultaneously promoting LDL oxidation (Cheng et al., 2017). The restoration of HDL-C observed following AETF treatment, therefore, suggests improved lipoprotein homeostasis and cholesterol transport. Emerging evidence further implicates gut microbiota modulation in Tremella-mediated lipid regulation. Tremella polysaccharides remodel microbial composition and enhance metabolic pathways associated with lipid homeostasis in combined high-fat diet and STZ models (Xu et al., 2024). As fermentable substrates, these polysaccharides influence short-chain fatty acid production and systemic metabolic signalling (Pi et al., 2024; He et al., 2022), potentially reinforcing hepatic and intestinal lipid regulation.

Comparable hypolipidemic effects across mushroom species, including *Pleurotus tuberregium* (Huang et al., 2012), *Fomitopsis pinicola* (Zahid et al., 2020), zinc-enriched *Pleurotus djamor* (Zhang et al., 2015), and *Grifola frondosa* (Ding et al., 2016), further highlight the conserved metabolic regulatory potential of polysaccharide-rich fungal interventions.

Collectively, the hypolipidemic efficacy of AETF in STZ-induced diabetic mice appears to arise from coordinated suppression of hepatic lipogenesis, activation of AMPK–PPARα signalling, enhancement of fatty acid oxidation, promotion of cholesterol elimination, attenuation of oxidative and inflammatory stress, and microbiota-mediated metabolic modulation. These integrated mechanisms plausibly explain the significant normalisation of TC, TG, LDL-C, VLDL-C, and HDL-C observed in the present study. Although molecular markers were not directly assessed, the convergence of mechanistic evidence from complementary models strongly supports the therapeutic relevance of *Tremella fuciformis* as a functional nutraceutical candidate for ameliorating diabetes-associated dyslipidaemia. Future investigations incorporating transcriptomic, proteomic, and metabolomic profiling will be essential to confirm pathway-specific effects and further advance its translational potential toward cardiometabolic disease prevention.

Conclusion

The present study demonstrated that the polysaccharide-enriched aqueous extract of *Tremella fuciformis* exerted a significant hypolipidemic effect in streptozotocin-induced diabetic mice. AETF administration produced a clear dose-dependent improvement in the lipid profile, characterised by reductions in serum triglycerides, total cholesterol, LDL-C, and VLDL-C, along with restoration of HDL-C levels. This coordinated modulation of both atherogenic and protective lipoprotein fractions reflects a substantial correction of diabetes-associated dyslipidaemia and suggests an overall improvement in lipid homeostasis under hyperglycaemic conditions. These findings provide compelling preclinical evidence for the lipid-regulatory capacity of *Tremella fuciformis and* underscore its potential relevance as a natural metabolic modulator. However, further studies are warranted to elucidate the molecular pathways underlying its lipid-regulatory effects and to define its therapeutic scope in metabolic disorders.

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Conflict of interest

The authors declare no conflict of interest with respect to this article.

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