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Research Article

Antidiabetic and haematoprotective effects of an aqueous extract of *Tremella fuciformis* in streptozotocin-induced diabetic mice

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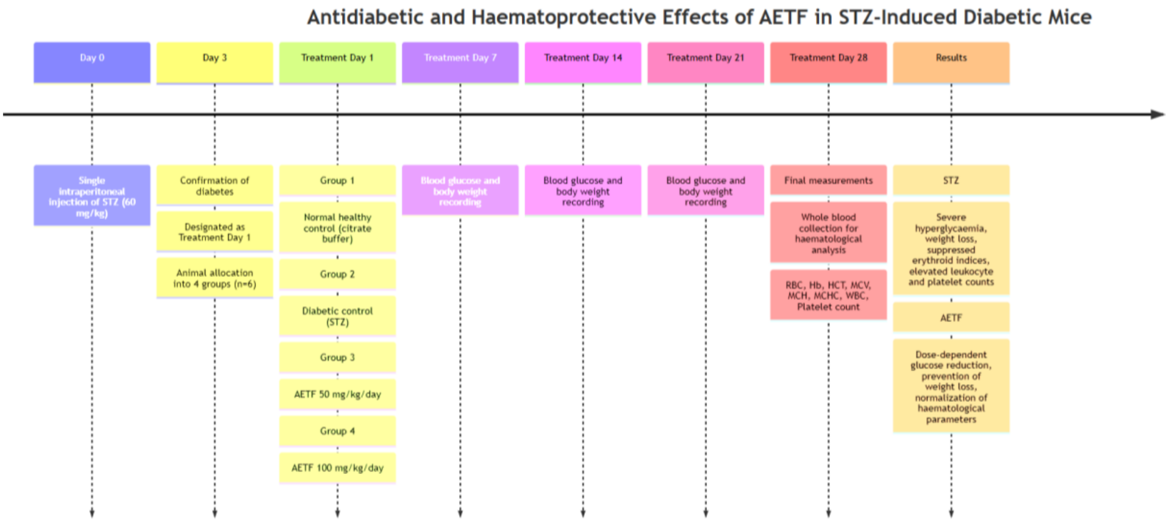
Abstract

Diabetes mellitus is a chronic metabolic disorder characterised by persistent hyperglycaemia, oxidative stress, body-weight loss, and haematological dysfunction. This study investigated the antidiabetic and haematoprotective potential of a polysaccharide-rich aqueous extract of *Tremella fuciformis* (AETF) in streptozotocin-induced diabetic BALB/c mice. Diabetes was induced by a single intraperitoneal injection of streptozotocin at a dose of 60 mg/kg bw, followed by oral administration of AETF at 50 and 100 mg per kilogram body weight for 28 days. Fasting blood glucose, body weight, and haematological parameters were evaluated across normal healthy control, diabetic control, and AETF-treated groups. STZ-induced diabetes resulted in marked hyperglycaemia, significant body-weight loss, reductions in RBC, Hb, HCT, and MCHC, and elevations in WBC, platelet count, MCV, and MCH, indicating substantial metabolic and haematological disturbances. AETF treatment significantly reduced fasting blood glucose levels, attenuated diabetes-associated weight loss, and ameliorated haematological abnormalities in a dose-dependent manner. The observed benefits are consistent with previously reported biological activities of *Tremella fuciformis* polysaccharides, including enhanced glucose utilisation, improved insulin responsiveness, attenuation of oxidative stress, and modulation of key metabolic pathways such as AMPK and PPAR-mediated signalling. Collectively, these findings demonstrate that polysaccharide-rich AETF exerts coordinated antidiabetic and haematoprotective effects in streptozotocin-induced diabetic mice, highlighting *Tremella fuciformis* as a promising functional dietary adjunct for mitigating metabolic and haematological complications associated with diabetes mellitus.

Keywords: Antidiabetic, haematoprotective, hyperglycaemia, Streptozotocin, *Tremella fuciformis,* BALB/c mice

Graphical Abstract



1. Introduction

Diabetes mellitus represents one of the most pressing global health challenges of the twenty-first century and is characterised by chronic hyperglycaemia arising from defects in insulin secretion, insulin action, or both, leading to profound disturbances in carbohydrate, lipid, and protein metabolism[1]. Beyond glycaemic dysregulation, diabetes involves a complex interplay of oxidative stress, inflammatory signalling, and metabolic imbalance that progressively drives multi-organ complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease[2-5]. In addition to these metabolic consequences, diabetes profoundly disrupts haematological homeostasis by altering erythrocyte membrane integrity and deformability, reducing oxygen-transport capacity, increasing blood viscosity, and compromising immune competence[3]. Accordingly, blood parameters including erythroid indices, total white blood cell (WBC) counts, and platelet counts serve as critical diagnostic and prognostic indicators in diabetes mellitus[6]. Chronic hyperglycaemia induces sustained metabolic stress that alters red blood cell (RBC) morphology, membrane stability, enzymatic activity, and rheological properties, resulting in impaired oxygen delivery and accelerated erythrocyte clearance, thereby contributing to anaemia and microvascular dysfunction in diabetic states[7]. Alterations in total WBC counts reflect diabetes-associated immune and inflammatory dysregulation driven by chronic low-grade inflammation and oxidative stress[8], while changes in platelet counts indicate endothelial dysfunction and increased vascular risk[9]. Collectively, these haematological abnormalities provide mechanistic insight into the development and progression of diabetes-associated complications.

Streptozotocin (STZ) remains the most widely used agent for experimental diabetes induction owing to its selective uptake into pancreatic β-cells via the GLUT2 transporter and its ability to trigger DNA alkylation, excessive activation of poly (ADP-ribose) polymerase, oxidative and nitrosative stress, and subsequent β-cell destruction[10-12]. Consequently, diabetic animals develop sustained hyperglycaemia, polyuria, polydipsia, progressive weight loss, and elevations in glycosylated serum proteins and haemoglobin A1c, closely recapitulating key metabolic and biochemical features of human diabetes and providing a robust platform for therapeutic evaluation[2,13]. In streptozotocin-induced diabetic mice, persistent hyperglycaemia is accompanied by pronounced haematological dysregulation, including significant reductions in RBC count, haemoglobin concentration, and haematocrit, along with alterations in erythrocyte indices such as mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH)[11]. Concurrent disturbances in total WBC and platelet counts further indicate systemic inflammatory activation and vascular perturbations in the diabetic state[11,12]. Notably, the magnitude of haematological disruption correlates closely with the degree of hyperglycaemia, underscoring the central role of glucose homeostasis in maintaining haematological integrity[11]. The limitations and adverse effects associated with conventional antidiabetic therapies have intensified the search for safer, multitarget natural interventions[1]. In this context, edible and medicinal mushrooms have attracted increasing scientific interest owing to their abundance of bioactive compounds, particularly polysaccharides such as β-glucans, which exhibit antioxidant, anti-inflammatory, immunomodulatory, hypoglycaemic, and hypolipidemic activities[14]. Among medicinal mushrooms, *Tremella fuciformis* has emerged as a promising functional food due to its reported antioxidant and cytoprotective properties[15], suppression of inflammatory signalling[16], and antidiabetic potential demonstrated in preclinical models[3]. These biological attributes suggest a plausible capacity to improve glycaemic regulation while simultaneously mitigating diabetes-associated haematological disturbances. However, systematic evaluation of the effects of *T. fuciformis* on blood glucose regulation and haematological indices in validated diabetic models remains limited. Therefore, the present study was designed to investigate the antidiabetic and haematoprotective effects of polysaccharide-rich aqueous extract of *Tremella fuciformis* in streptozotocin-induced diabetic BALB/c mice by evaluating its ability to modulate blood glucose levels and restore diabetes-associated alterations in body weight, haemoglobin concentration, erythrocyte indices, and total leukocyte and platelet count profiles.

2. MATERIALS AND METHODS

2.1 Collection and Preparation of Edible Mushroom Aqueous Extract

Dried fruiting bodies of *Tremella fuciformis* were obtained from Biobrite Agro Solutions, Shirol, Kolhapur, Maharashtra, India, and were pulverised and extracted with distilled water (1:10, w/v) by boiling at 100 °C for 2 h. The extract was filtered to remove insoluble debris and concentrated under reduced pressure using a rotary evaporator. Crude polysaccharides were precipitated by the addition of three volumes of 95% ethanol and incubated at 4 °C for 24 h. The precipitate was collected by centrifugation, vacuum-lyophilised, and used as the polysaccharide-rich aqueous extract of *Tremella fuciformis*, which was administered orally once daily for 28 consecutive days to streptozotocin-induced diabetic mice at doses of 50 and 100 mg/kg body weight[17-19].

2.2 Experimental Animals

Male BALB/c mice (5-6 weeks old), weighing 20-25 g, were housed in polypropylene cages under controlled environmental conditions, with temperature maintained at 24-30 °C, relative humidity at 50-60%, and a 12 h light/12 h dark cycle, in accordance with standard laboratory animal care guidelines[20]. The animals had free access to a commercial pellet diet and water ad libitum. All experimental procedures were conducted in accordance with CPCSEA guidelines (Reg. No. 1809/Rebis/Rel/15/CPCSEA) and approved under reference No. Ph.D./SVU/RAC/0106220378, with experimental 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.

2.3 Induction of Diabetes

Experimental diabetes was induced in mice by a single intraperitoneal injection of streptozotocin (STZ; Sisco Research Laboratories, Mumbai), freshly dissolved in 0.1 M citrate buffer (pH 4.5), at a dose of 60 mg/kg body weight. Before diabetes induction, the animals were acclimatised to standard laboratory conditions and adapted to the basal pellet diet for one week. After 72 h of STZ administration, fasting blood glucose levels were measured using blood samples obtained from the tail vein with glucose test strips and a handheld glucometer (AccuChek). Mice exhibiting fasting blood glucose levels exceeding 250 mg/dL were considered diabetic and selected for further experimental procedures, in accordance with previously established protocols for STZ-induced diabetic murine models [21-22].

2.4 Experimental design

After three days of Streptozotocin intraperitoneal injection and establishment of the diabetic mice model, the mice were randomly divided into four groups with 6 mice in each group:

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

2.5 Monitoring of Fasting Blood Glucose and Body Weight

Fasting blood glucose levels and Body weight were recorded at baseline (Day 1) and subsequently on days 7, 14, 21, and 28 throughout the experimental period. Body weight was measured using a calibrated digital balance. For fasting blood glucose estimation, animals were fasted overnight, and capillary blood samples were obtained from the tail vein using sterile lancets. Blood glucose concentrations were measured immediately using a portable handheld glucometer (AccuChek).

2.6 Blood Collection and Determination of Haematological Parameters

At the end of the 28-day treatment period, all animals were sacrificed by Cervical Dislocation and Whole blood was collected immediately by cardiac puncture and transferred into EDTA-coated tubes for haematological analysis. Haematological parameters were analysed using an automated haematology analyser [Humma Count 5D] in accordance with the manufacturer's instructions. The evaluated indices included Red blood cell (RBC) count, Haemoglobin (Hb) concentration, Haematocrit (HCT), Mean corpuscular volume (MCV), Mean corpuscular haemoglobin (MCH), Mean corpuscular haemoglobin concentration (MCHC), Total white blood cell count (WBC) and Platelet count.

2.7 Statistical Analysis

All data are expressed as mean ± SEM (n = 6). Statistical analyses were performed using GraphPad Prism version 11.0 (GraphPad Software, USA). Fasting blood glucose and body weight were analysed using two-way ANOVA with time and treatment as factors, followed by Dunnett's multiple comparison test against the diabetic control group. Haematological parameters (Hb, HCT, RBC, WBC), erythrocyte indices (MCV, MCH, MCHC), and platelet counts were analysed using one-way ANOVA followed by Dunnett's test. A p-value < 0.05 was considered statistically significant.

3. RESULTS

3.1 Effect of AETF on Fasting Blood Glucose Level

Fasting blood glucose levels were monitored on Days 1, 7, 14, 21, and 28 to evaluate the antidiabetic effect of the polysaccharide-rich aqueous extract of *Tremella fuciformis* in streptozotocin-induced diabetic mice. No appreciable fluctuations were observed in the normal control group throughout the experimental period. In contrast, diabetic control mice maintained markedly elevated fasting blood glucose levels, reaching 421.5 mg/dL by Day 28. Treatment with AETF produced a progressive, dose-dependent reduction in glucose levels over time, with levels declining to 240.5 mg/dL and 205.3 mg/dL in the 50 and 100 mg/kg groups, respectively, by Day 28. The reduction was more pronounced at the higher dose, indicating a significant antidiabetic effect of AETF ($p < 0.0001$), as illustrated in **Fig. 1A.**

3.2 Effect of AETF on Body Weight

Body weight was recorded on Days 1, 7, 14, 21, and 28 to assess the effect of AETF on diabetes-associated weight alterations. Diabetic control mice exhibited a progressive decline in body weight compared with normal healthy controls during the experimental period. In contrast, treatment with polysaccharide-rich AETF attenuated diabetes-induced weight loss and gradually restored body weight over time. By Day 28, body weight increased to 24.35 g and 25.50 g in mice treated with 50 and 100 mg/kg AETF, respectively, compared with 17.15 g in diabetic controls. The improvement was more pronounced at the higher dose, indicating a significant protective effect of AETF against diabetes-associated body weight loss ($p < 0.0001$), as illustrated in **Fig. 1B.**

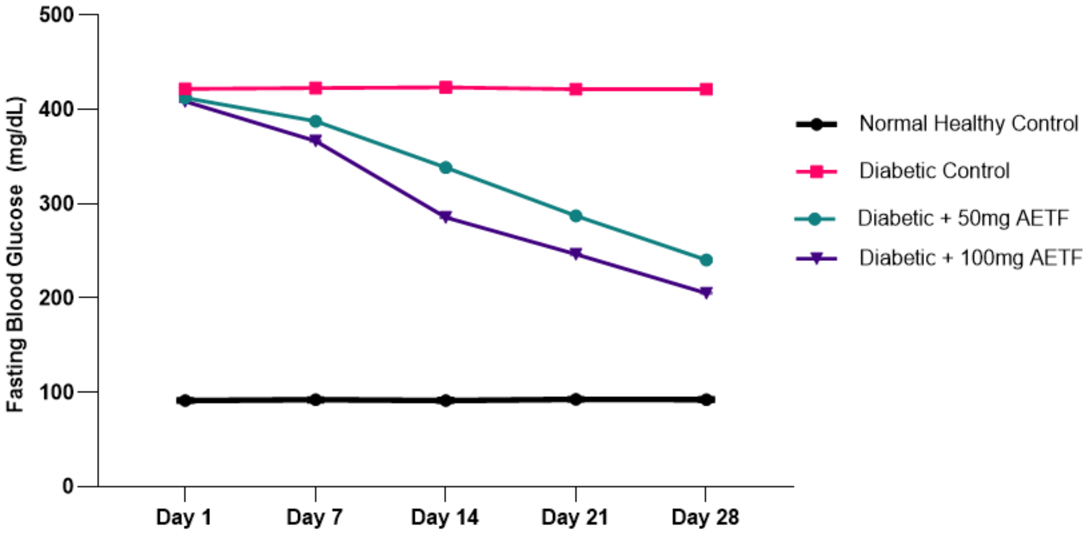


Fig. 1 (A)

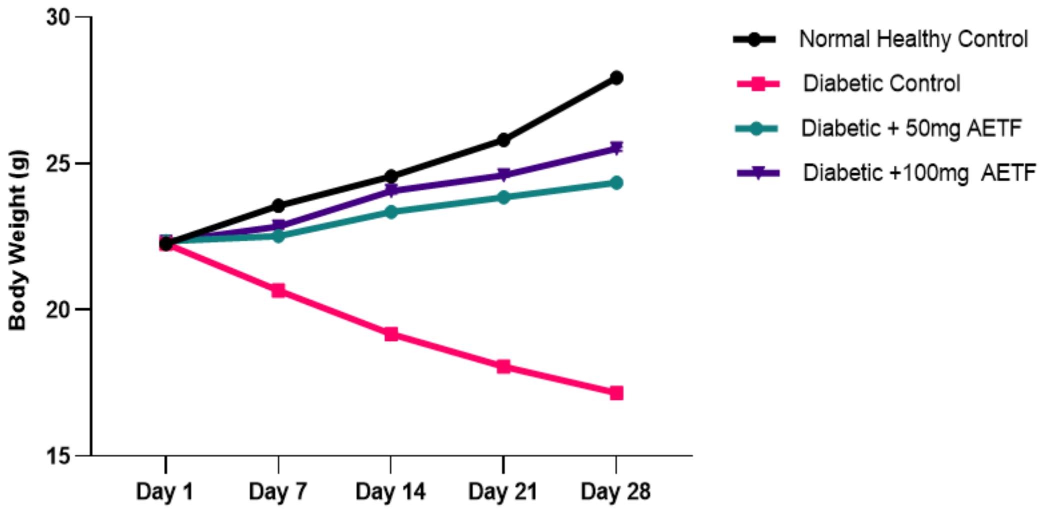


Fig.1 (B)

*Figure 1: Effect of polysaccharide-rich aqueous extract of Tremella fuciformis on fasting blood glucose and body weight in streptozotocin-induced diabetic BALB/c mice. (A) Fasting blood glucose levels and (B) body weight were recorded on Days 1, 7, 14, 21, and 28 in normal healthy control, diabetic control, and diabetic mice treated with AETF at 50 and 100 mg/kg body weight, respectively. Values are expressed as mean ± SEM (n = 6). ****p < 0.0001 vs diabetic control.*

3.3 Effect of AETF on Haematological Parameters

Relative to the normal healthy control group, streptozotocin-induced diabetic mice exhibited significant alterations in haematological parameters. The diabetic control group showed a marked reduction in erythrocytic parameters, including red blood cell (RBC) count, haemoglobin (Hb) concentration, haematocrit (HCT), and mean corpuscular haemoglobin concentration (MCHC), accompanied by significant elevations in total white blood cell (WBC) count, platelet count, mean corpuscular volume (MCV), and mean corpuscular haemoglobin (MCH) ($p < 0.0001$). Administration of the polysaccharide-rich aqueous extract of *Tremella fuciformis* at doses of 50 mg/kg and 100 mg/kg body weight significantly ameliorated these diabetes-associated haematological disturbances. Treatment with AETF significantly increased Hb, HCT, RBC, and MCHC levels, while markedly reducing elevated WBC, platelet, MCV, and MCH values compared with the diabetic control group ($p < 0.0001$). Furthermore, the 100 mg/kg dose showed a more pronounced restorative effect, with most parameters moving closer to those observed in the healthy control group, although complete normalisation was not achieved. These changes are illustrated in **Fig. 2 (A-D)** for Hb, RBC, WBC, and HCT, and **Fig. 3 (A-D)** for MCH, MCHC, MCV, and platelet counts.

4. DISCUSSION

The present study demonstrated that oral administration of the polysaccharide-rich aqueous extract of *Tremella fuciformis* significantly ameliorated hyperglycaemia, attenuated diabetes-associated body-weight loss, and restored haematological derangements in streptozotocin (STZ)-induced diabetic BALB/c mice, indicating a coordinated antidiabetic and haematoprotective action rather than merely an isolated glucose-lowering effect.

STZ-induced diabetes is a well-established experimental model characterised by selective pancreatic β-cell destruction following GLUT2-mediated uptake of STZ. Its nitrosourea moiety induces DNA alkylation, excessive generation of reactive oxygen and nitrogen species, activation of poly(ADP-ribose) polymerase, depletion of intracellular NAD^+, and subsequent β-cell apoptosis and necrosis, resulting in severe and sustained insulin deficiency[2,23]. The resulting metabolic milieu is dominated by persistent fasting hyperglycaemia due to unrestrained hepatic gluconeogenesis, impaired peripheral glucose uptake, enhanced oxidative stress, and chronic inflammatory activation, all of which collectively contribute to profound catabolic weight loss and systemic haematological dysfunction[24].

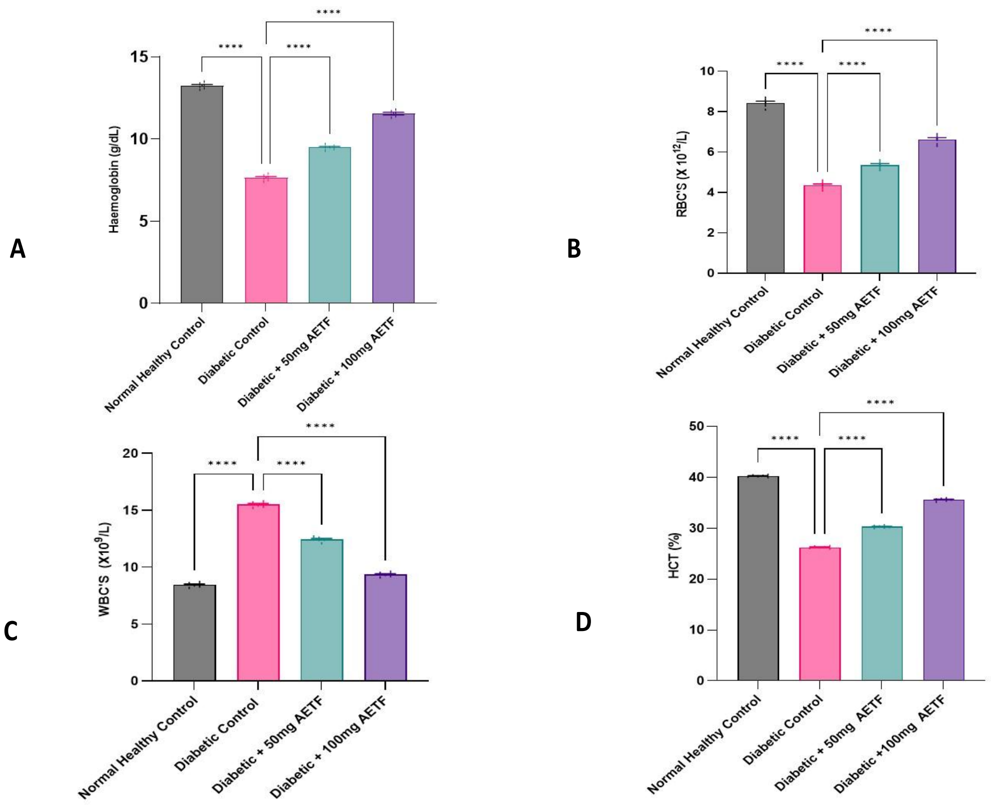


*Figure 2: Effect of polysaccharide-rich aqueous extract of Tremella fuciformis on haematological parameters in streptozotocin-induced diabetic mice. Bar graphs showing Hb (A), RBC (B), WBC (C), and HCT (D) levels in the Normal Healthy Control, Diabetic Control, Diabetic + 50 mg AETF, and Diabetic + 100 mg AETF groups. Data are presented as mean ± SEM (n = 6). **p < 0.0001 vs diabetic control.*

In agreement with the established pathophysiology of diabetes mellitus, untreated streptozotocin-induced diabetic mice in the present study exhibited progressive hyperglycaemia, marked loss of body weight, and significant reductions in erythrocytic parameters, including red blood cell (RBC) count, haemoglobin concentration, haematocrit, and mean corpuscular haemoglobin concentration. These alterations were accompanied by significant elevations in total white blood cell count, platelet count, mean corpuscular volume, and mean corpuscular haemoglobin, reflecting diabetes-associated haematological disturbances. Treatment with AETF markedly reversed these abnormalities, restoring erythrocytic indices while reducing elevated leukocyte and platelet counts, thereby indicating improvement in systemic metabolic and haematological homeostasis. The antihyperglycemic effect observed with AETF is strongly supported by in vivo evidence demonstrating that *Tremella fuciformis* polysaccharides consistently improve glucose metabolism across diabetic models[25]. Oral administration of *Tremella fuciformis* polysaccharides (100 mg/kg) significantly reduced fasting blood glucose and triglyceride levels, enhanced antioxidant capacity, preserved pancreatic β-cell structure, and alleviated diabetes-associated emaciation in high-fat-diet and STZ-induced diabetic mice, with transcriptomic enrichment of insulin signalling, AMPK activation, and glucose-metabolic pathways[26]. Similarly, exopolysaccharides derived from *Tremella fuciformis* mycelial cultures markedly reduced plasma glucose levels and improved glucose tolerance in ob/ob mice through enhanced insulin sensitivity and PPAR-γ-mediated metabolic regulation[27]. These convergent findings provide strong biological plausibility for the sustained reduction in fasting blood glucose observed following AETF administration in the present study.

Preservation of body weight in AETF-treated diabetic mice further reflects improved metabolic efficiency and attenuation of diabetes-induced catabolic stress. Diabetes-associated weight loss is primarily attributed to impaired glucose utilisation, exaggerated proteolysis, and lipolysis secondary to insulin deficiency and oxidative stress[28-30]. Stabilisation of body weight has been consistently reported in diabetic rodents treated with *Tremella fuciformis* polysaccharides, where improved glycaemic control and lipid metabolism coincided with attenuation of emaciation[26]. Comparable weight-protective effects have also been observed in STZ-induced diabetic BALB/c mice treated with antioxidant-rich plant extracts, such as *Mespilus germanica*, where normalisation of body weight closely paralleled reductions in hyperglycaemia and oxidative stress[31]. These observations collectively indicate that the weight-preserving effect of AETF is secondary to restoration of metabolic homeostasis rather than a direct anabolic action.

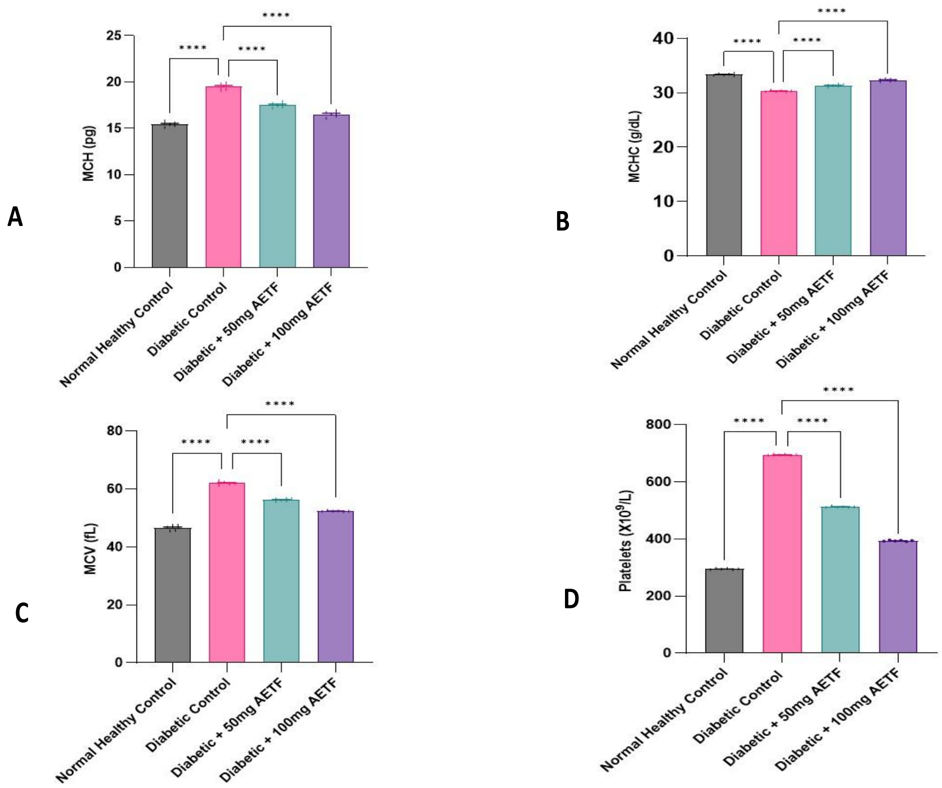


*Figure 3: Effect of polysaccharide-rich aqueous extract of Tremella fuciformis on erythrocyte indices and platelet count in streptozotocin-induced diabetic mice. Bar graphs showing MCH (A), MCHC (B), MCV (C), and platelet count (D) in the Normal Healthy Control, Diabetic Control, Diabetic + 50 mg AETF, and Diabetic + 100 mg AETF groups. Data are presented as mean ± SEM (n = 6). **p < 0.0001 vs diabetic control.*

A particularly important outcome of the present study is the restoration of haematological parameters following treatment with the polysaccharide-rich aqueous extract of *Tremella fuciformis*. Diabetes-associated anaemia and haematological dysfunction are known to arise from multiple pathological mechanisms, including oxidative damage to erythrocyte membranes, accumulation of advanced glycation end products, impaired erythropoiesis, shortened erythrocyte lifespan, chronic inflammation, and reduced renal erythropoietin production[32,33]. In agreement with previous reports, untreated streptozotocin-induced diabetic mice exhibited pronounced haematological alterations, characterised by significant reductions in red blood cell count, haemoglobin concentration, and haematocrit, accompanied by leucocytosis and thrombocytosis[21,34,35]. These findings reflect the systemic inflammatory and oxidative stress responses commonly associated with diabetic pathology. Notably, alterations in erythrocyte indices such as mean corpuscular volume and mean corpuscular haemoglobin were also observed, suggesting structural and functional changes in erythrocytes under hyperglycaemic conditions. Treatment with AETF significantly ameliorated these abnormalities and restored haematological parameters toward normal physiological levels, indicating a clear haematoprotective effect. Supporting this observation, polysaccharides derived from medicinal mushrooms, including *Cordyceps militaris*, have been reported to suppress lipid peroxidation, enhance endogenous antioxidant defence systems, improve glucose homeostasis, and normalise haematological indices in streptozotocin-induced diabetic mice[36]. Collectively, these findings suggest that the beneficial effects of AETF may be largely attributed to its antioxidative and cytoprotective properties, which mitigate oxidative stress and contribute to the correction of diabetes-induced erythroid and inflammatory haematological disturbances.

The mechanistic basis of these *in vivo* effects is reinforced by in vitro evidence demonstrating direct metabolic actions of *T. fuciformis* polysaccharides. The *Tremella*-derived polysaccharide PTP-3a significantly enhanced glucose consumption, increased intracellular glycogen accumulation, and stimulated key glycolytic enzymes, including hexokinase and pyruvate kinase, in palmitic-acid-treated HepG2 cells via activation of the AMPK signalling pathway, while concurrently suppressing lipogenic and insulin-resistance-associated proteins such as SREBP-1c, FAS, ACC, and SOCS3[37]. In addition, *Tremella* polysaccharides have been shown to delay starch digestion and limit intestinal glucose absorption by inhibiting α-glucosidase activity and reducing glucose transport via SGLT1, thereby decreasing glucose availability and postprandial glycaemic excursions[38]. These complementary cellular mechanisms provide strong molecular support for the sustained antihyperglycemic and systemic stabilising effects observed *in vivo*.

5. CONCLUSION

The present investigation provides experimental evidence that the polysaccharide-rich aqueous extract of *Tremella fuciformis* exerts notable antidiabetic and haematoprotective effects in streptozotocin-induced diabetic BALB/c mice. AETF administration significantly attenuated persistent hyperglycaemia, mitigated diabetes-associated body-weight decline, and effectively corrected haematological perturbations, including alterations in erythrocyte indices, leukocyte counts, and platelet levels. These findings indicate a coordinated restoration of metabolic equilibrium and haematological integrity under diabetic stress. The observed protective responses are consistent with the established biological properties of *Tremella*-derived polysaccharides, which have been reported to enhance glucose utilisation, improve insulin responsiveness, and suppress oxidative and inflammatory cascades. Such integrated physiological effects provide mechanistic support for the sustained antihyperglycemic and systemic stabilising actions observed *in vivo*. Collectively, the study highlights *Tremella fuciformis* as a promising natural candidate for mitigating metabolic and haematological complications associated with diabetes mellitus. Further mechanistic and translational investigations are warranted to substantiate its therapeutic potential.

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Author Contributions: **Zahid Ahmad Wani**: Conceptualisation, Methodology, Investigation, Data analysis, and Manuscript drafting. **Asvene Kumar Sharma and Yaqoob Lone**: Supervision, Data interpretation, Experimental guidance, and Critical revision of the manuscript. **Showkeen Muzamil**: Manuscript editing and Experimental support. **Rayees Ahmad Naik**: Data visualisation and Data curation.

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

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