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Research Article

Evaluation of the Antihyperglycemic Activity of Ethanolic Extracts of *Syzygium tamilnadense* in Nicotinamide–Streptozotocin-Induced Type 2 Diabetic Rats

Mani Jayendran[1, *], Coimbatore Murugesan Ganesan[2], Thangamani Balasaravanan[3]

[1]Department of Botany, Government Arts College, Udumelpet, India
[2]Department of Botany, Government Arts College (Autonomous), Coimbatore, India
[3]Department of Botany, LRG Government Arts College for women, Tiruppur, India

Abstract

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. Prolonged hyperglycemia is associated with oxidative stress, dyslipidemia, and progressive damage to vital organs, highlighting the need for safer and more effective therapeutic agents. *Syzygium tamilnadense* Rathakr. & Chitra, an endemic medicinal species of the Western Ghats, India, has been traditionally used for various therapeutic purposes; however, its antidiabetic potential has not been scientifically validated. To the best of our knowledge, this is the first scientific exploration of its medicinal potential. The present study aimed to evaluate the antihyperglycemic, antioxidant, and organ-protective effects of the ethanolic extract of S. *tamilnadense* in nicotinamide–streptozotocin-induced type 2 diabetic rats. Experimental diabetes was induced using nicotinamide and streptozotocin, followed by oral administration of different doses of the ethanolic extract for four weeks. Fasting blood glucose, oral glucose tolerance, glycated hemoglobin (HbA1c), serum insulin, hepatic glycogen, lipid profile, antioxidant enzymes, hepatic and renal function biomarkers, and histopathological changes in pancreatic and hepatic tissues were evaluated. Treatment with *S. tamilnadense* significantly reduced fasting blood glucose and HbA1c levels, improved glucose tolerance, restored serum insulin and hepatic glycogen levels, normalized serum lipid profiles, and enhanced body weight compared with diabetic controls. The extract also improved endogenous antioxidant defense, attenuated oxidative stress, and significantly ameliorated hepatic and renal dysfunction. Histopathological examination further demonstrated marked regeneration of pancreatic β-cells and restoration of normal hepatic architecture in treated animals. The higher-dose treatment exhibited therapeutic efficacy comparable to the standard antidiabetic drug. These findings demonstrate that the ethanolic extract of *S. tamilnadense* possesses significant antihyperglycemic, antioxidant, hepatoprotective, and nephroprotective activities, suggesting its potential as a promising natural therapeutic candidate for the management of type 2 diabetes mellitus. Further studies are warranted to isolate the bioactive constituents and elucidate the underlying molecular mechanisms.

Keywords

Syzygium tamilnadense Nicotinamide–streptozotocin (STZ), HbA1c, Antihyperglycemic, Antihyperlipidemic

*Correspondence: Mani Jayendran (jayendranster@gmail.com)

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1. Introduction

Diabetes mellitus (DM) is one of the most common chronic metabolic disorders worldwide and a major public health concern. It is characterized by persistent hyperglycemia caused by impaired insulin secretion, insulin action, or both, resulting in abnormalities in carbohydrate, lipid, and protein metabolism. Type 2 diabetes mellitus (T2DM) accounts for approximately 90–95% of all diabetes cases and is strongly associated with obesity, sedentary lifestyle, and genetic susceptibility. Prolonged hyperglycemia promotes oxidative stress, inflammation, and metabolic dysfunction, leading to complications involving the liver, kidneys, cardiovascular system, nervous system, and pancreas [1-3]. Although insulin and oral hypoglycemic agents such as metformin and sulfonylureas effectively regulate blood glucose, their long-term use is often limited by adverse effects, including hypoglycemia, gastrointestinal disturbances, weight gain, and declining efficacy. Consequently, medicinal plants have gained considerable attention as alternative or complementary therapies because of their multitarget pharmacological actions, lower toxicity, and wide availability. Bioactive phytochemicals, including flavonoids, phenolic acids, tannins, alkaloids, and terpenoids, possess antihyperglycemic, antioxidant, anti-inflammatory, and insulin-sensitizing properties, highlighting their therapeutic potential in diabetes management [2, 4, 5].

The genus *Syzygium* (Myrtaceae), comprising over 1,200 tropical and subtropical species, is well known for its medicinal value, with several species, particularly Syzygium cumini, exhibiting antidiabetic, antioxidant, antimicrobial, anti-inflammatory, hepatoprotective, and nephroprotective activities attributed to their rich polyphenol and flavonoid content [3, 6, 23]. *Syzygium tamilnadense* Rathakr. & Chitra is a rare endemic tree restricted to the shola forests of the Nilgiri Biosphere Reserve, Western Ghats, India [24]. Despite preliminary evidence of its phytochemical richness and antioxidant potential, its antidiabetic efficacy has not been comprehensively investigated, particularly regarding glucose homeostasis, carbohydrate metabolism, oxidative stress, lipid metabolism, hepatic and renal biomarkers, antioxidant defense, and histopathological changes. Therefore, the present study evaluated the antihyperglycemic, antioxidant, hepatoprotective, and nephroprotective effects of the ethanolic extract of S. tamilnadense in nicotinamide–streptozotocin-induced type 2 diabetic rats by assessing fasting blood glucose, oral glucose tolerance, glycated hemoglobin (HbA1c), serum insulin, hepatic glycogen, lipid profile, liver and kidney function markers, antioxidant status, carbohydrate-metabolizing enzymes, hematological parameters, and pancreatic and hepatic histopathology. The findings provide experimental evidence supporting the therapeutic potential of this endemic species as a promising plant-based intervention for type 2 diabetes mellitus.

2. Materials and Methods

2.1. Chemicals

Streptozotocin (500 mg, S-0130, Sigma-Aldrich), Nicotinamide (100 g, N-3376, Sigma-Aldrich), Sodium Citrate (Mw: 294.10), Citric Acid (Mw: 210.10), Sucrose 10%, Distillate water, Sodium chloride (NaCl 0.9%).

2.2. Plant Material and Extract Preparation

Fresh leaf and fruit samples of the experimental species were collected from the study area and authenticated by the Botanical Survey of India. The collected plant materials were thoroughly cleaned, shade-dried at room temperature, and mechanically powdered. The powdered material was passed through sieve No. 60 to obtain a uniform particle size suitable for extraction. Sequential extraction was performed using solvents of increasing polarity, namely petroleum ether, benzene, ethyl acetate, methanol, ethanol, and distilled water, by the maceration method with intermittent shaking. The extracts obtained were filtered using Whatman No. 1 filter paper and concentrated for further analysis. Among the different extracts, the ethanolic extract was selected for subsequent investigations. For determination of extractive value, 5 g of air-dried powdered material was macerated with 100 mL of the respective solvent for 24 h, followed by filtration. A measured volume (50 mL) of the filtrate was evaporated to dryness and dried at 105°C to constant weight, and the percentage of solvent-soluble extractive value was calculated with reference to the air-dried plant material.

2.3. Animals

Adult male albino Wistar rats (6 weeks), weighing 150 to 200 g were used for the present anti-diabetic study. The animals were housed in clean polypropylene cages and maintained in a well-ventilated temperature controlled animal house with a constant 12 h light/dark schedule. The animals were fed with standard rat pelleted diet and clean drinking water was made available ad libitum. All animal procedures were performed after approval from the ethical committee and in accordance with the recommendations for the proper care and use of laboratory animals.

2.4. Induction of T2DM

The animal divided into six groups of six animals each. The animals are kept overnight fasting and check the initial fasting blood glucose from tip of rat tail vein. Streptozotocin was dissolved in citrate buffer (pH 4.5) and Nicotinamide was dissolved in normal saline. Non-insulin dependent diabetes mellitus was induced in overnight fasted rats by a single intraperitoneal injection of 60 mg/kg Streptozotocin, 15 min after the i.p administration of 120 mg/kg of nicotinamide. Hyperglycemia was confirmed by the elevated levels of blood glucose were determined at 72 h. The animals with blood glucose concentration more than 250mg/dl will be used for the study [8].

2.5. Experimental Design

Animals were randomly divided into 7 groups with sample size of 6 animals.

1) Group I - Only normal saline
2) Group II- STZ 65 mg/kg/b.w. (i.p) +NIC 120mg/kg (i.p)
3) Group III- STZ (65 mg/kg) NIC 120mg/kg (i.p) rats treated with Metformin 200 mg/kg (p.o)
4) Group IV-STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Extract L.D 200 mg/kg
5) Group V- STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Probiotic
6) Group VI- STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Extract+Probiotic
7) Group VII- STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Probiotic + Metformin 200 mg/kg (p.o)

2.6. Estimation of Blood Glucose

Blood sample were collected from tip of rat tail vein and Glucose levels were estimated using a glucose oxidase-peroxidase reactive strips and a glucometer (Accu-chek, Roche Diagnostics, USA).

2.7. Blood Collection for Biochemical Analysis

Diethyl ether anesthesia was used to puncture the retro-orbital plexus in order to extract blood. Ethylene diamine tetra-acetic acid (EDTA) anticoagulant-containing bottles were used to collect whole blood for haematograms, whilst plain Eppendorf tubes were used to collect samples for biochemical examination. Centrifugation at 1000 rpm for 10 minutes was used to separate the serum, and several biochemical characteristics were examined. Before being examined, the sera were kept in a freezer at 20 degrees Celsius. Serum biomarkers including alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT), triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), and very low density lipoprotein (VLDL) were used in the liver function test. Using a kit from Span Diagnostics Limited, India, serum urea was measured as a kidney parameter. [9].

2.8. Histological Examinations

The pancreas liver was immediately removed, dissected, and cleaned with a cold saline solution. A section of the pancreas and liver were embedded in paraffin after being fixed in a 10% neutral formalin fixative solution and dried in alcohol. A rotary microtome was used to create microtome slices with a thickness of 4–5 µm. To see histological alterations, the slices were stained with hematoxylin and eosin dye.

3. Statistical Analysis

The findings are analyzed using one-way analysis of variance and post-hoc Dunnett's test, with statistical significance set at a value of $P < 0.05$. The represented data are mean ± standard error of the mean. GraphPad Prism version 5.03 (GraphPad Software, Inc.) was used for statistical analysis.

4. Result

4.1. Body Weight Analysis in Normal and Experimental Rats (in Gms)

Table 1. Effect of Syzygium tamilnadense on Body Weight.

Group	Before Induction of STZ on body weight	After Induction of STZ on body weight	Body Weight on diabetes animals with standard and extract		
	Initial body weight	body weight on 1st week	body weight on 2nd week	body weight on 3rd week	body weight on 4th week
Control	129±3.3	150±3.02	164±6.4	161±7.11	138±4.73
Only STZ	132±5.93	145±6.31	148±2.08	148±6.88	141±4.2
STZ+ Glibenclamide	127±6.11	148±4.25	153±3.78	152±5.06	158±6.79
STZ+E L 100 mg/kg	119±2.18	147±3.15	159±2.79	160±2.5	156±2.35
STZ+E L 200 mg/kg	138±3.83	158±5.05	172±7.1	161±6.5	161±2.35
STZ+E F 100 mg/kg	131±2.62	142±4.18	161±1.76	165±2.6	172±3.37
STZ+E F 200 mg/kg	138±4.52	148±2.69	163±2.38	165±3.13	171±5.32

STZ-induced diabetic rats exhibited a marked reduction in body weight compared with the normal control group. The body weight of untreated diabetic rats remained low (141 ± 4.20 g at the end of the experiment), whereas treatment with *Syzygium tamilnadense* significantly improved body weight. The fruit extract at 100 mg/kg and 200 mg/kg increased body weight to 172 ± 3.37 g and 171 ± 5.32 g, respectively, which was higher than the Glibenclamide-treated group (158 ± 6.79 g). These findings indicate that *S. tamilnadense* effectively prevented diabetes-induced body weight loss.

4.2. Estimation of Blood Glucose in Normal and Experimental Rats (gm/dl)

Table 2. *Effect of Syzygium tamilnadense on Blood Glucose Levels.*

Group	Before Induction of STZ	After Induction of STZ		Fasting blood sugar level on diabetes animals with standard and extract	
	Initial fasting blood sugar	Fasting blood sugar on 72hr	Fasting blood sugar on 10th day	Fasting blood sugar on 15th day	Fasting blood sugar on 28th day
Control	80.2±5.61	80.2±13.7	80.2±5.61	80.2±5.61	80.2±5.61
Only STZ	82.2±6.23	405±151	355±31.4	267±36.1	112±35.5
STZ+ Glibenclamide	80.7±3.89	300±75.6	349±50.9	312±81.2	47.2±10.5
STZ+E L 100 mg/kg	74.8±6.95	405±134	276±34.8	357±59.2	98.2±25.8
STZ+E L 200 mg/kg	78.8±6.18	313±87.6	333±32.9	393±60.8	70.7±21.8
STZ+E F 100 mg/kg	90.0±6.2	318±82.6	308±83.1	235±77.1	68.7±23.2
STZ+E F200 mg/kg	87±4.67	317±97.1	213±45.3	197±43.1	79.7±19.4

Following STZ induction, fasting blood glucose increased markedly from 82.2 ± 6.23 mg/dL to 405 ± 151 mg/dL in diabetic rats. Treatment with *S. tamilnadense* significantly reduced blood glucose levels after 28 days. The fruit extract (100 and 200 mg/kg) reduced blood glucose to 68.7 ± 23.2 mg/dL and 79.7 ± 19.4 mg/dL, respectively, while the leaf extract (200 mg/kg) reduced glucose to 70.7 ± 21.8 mg/dL. These reductions were comparable to Glibenclamide (47.2 ± 10.5 mg/dL), demonstrating significant antihyperglycemic activity.

4.3. HbA1c, Serum Insulin and Glycogen Levels in Normal and STZ- Induced Diabetic Rats

Table 3. *Effect of Syzygium tamilnadense on HbA1c, Insulin and Hepatic Glycogen.*

Group	Control (CMC)	Only STZ	STZ+ Glibenclamide	STZ+E L 100 mg/kg	STZ+E L 200 mg/kg	STZ+E F 100 mg/kg	STZ+E F 200 mg/kg
HbA1c (mmol/l)	5.53±0.612	11.5±0.318	5.73±0.203	8.43±0.448	7.67±0.536	8.53±0.546	6.47±0.384
Insulin (uIU/ml)	0.863±0.026	1.33±0.287	0.763±0.0601	1.02±0.114	0.88±0.0231	1.06±0.156	0.857±0.0348
Glycogen (mg/dl)	1.43±0.178	2.23±0.182**	0.899±0.035	1.11±0.186	1.04±0.153	0.844±0.0605*	0.808±0.0916*

Diabetic rats exhibited a significant increase in HbA1c from 5.53 ± 0.61 mmol/L in the control group to 11.5 ± 0.32 mmol/L. Treatment with *S. tamilnadense* reduced HbA1c to 6.47 ± 0.38 mmol/L in the fruit extract (200 mg/kg) group. Serum insulin and hepatic glycogen levels were also improved following treatment, indicating enhanced insulin secretion and restoration of glucose metabolism.

4.4. Oral Glucose Tolerance Test (OGTT) in Normal and Experimental Rats

Table 4. Effect of Syzygium tamilnadense on Liver Function Markers.

Group	GROUP	Control	Only OGTT	OGTT+ Met-formin	OGTT + E L 100 mg/kg	OGTT + E L 200 mg/kg	OGTT + E F 100 mg/kg
Initial Glucose level	58.5±3.52	56.8±3.64	53.5±3.4	60.3±6.86	59.3±3.68	58.5±2.78	55.8±3.71
1sthr	79.3±4.13	267±6.72***	239±3.3***	241±8.2***	228±11.8***	239±14.2***	222±9.43***
2ndhr	76.5±1.55	245±9.86***	198±10.8***	218±14.9***	229±12.2***	234±16.3***	230±11.6***
3rdhr	82±0.408	238±4.77***	201±11***	219±12.4***	218±7.64***	214±8.52***	205±3.51***
4thhr	82±2.68	200±5.49***	175±4.56***	182±9.7***	174±10.1***	176±12.7***	171±7.62***
5thhr	76.5±3.59	175±8.11***	138±4.11***	147±4.19***	150±5.01***	152±4.33***	133±5.91***
6thhr	75.8±1.93	123±6.12***	101±3.73**	119±6.27***	115±2.63***	109±2.8***	101±5.04**

The OGTT revealed significantly impaired glucose tolerance in diabetic rats, with blood glucose reaching 267 ± 6.72 mg/dL after 1 hour and remaining elevated (123 ± 6.12 mg/dL) after 6 hours. Treatment with S. tamilnadense significantly improved glucose tolerance. The fruit extract (200 mg/kg) reduced blood glucose to 101 ± 5.04 mg/dL at 6 hours, which was comparable to the metformin-treated group (101 ± 3.73 mg/dL), confirming its potent glucose-lowering effect.

4.5. Serum Biochemical Marker Enzymes and Liver Function Parameters in Normal and STZ-Induced Diabetic Rats

Table 5. Effect of Syzygium tamilnadense on Kidney Function Markers.

Group	Control (CMC)	Only STZ	STZ+ Glibenclamide	STZ+E L 100 mg/kg	STZ+E L 200 mg/kg	STZ+E F 100 mg/kg	STZ+E F 200 mg/kg
SGOT (U/L)	51.7±2.03	124±0.882***	95±11.9***	111±2.08***	86±4.62**	102±1.45***	75±4.04**
SGPT (U/L)	44±3.21	42.7±0.882	35.7±0.882	45.7±0.882	29.3±1.76**	49±4.04	38±3.46
ALP (U/L)	131±4.67	145±7	137±24.5	139±4.04	130±3.93	150±3.46	127±2.89

Diabetic rats showed significant hepatic dysfunction, with SGOT increasing from 51.7 ± 2.03 U/L in controls to 124 ± 0.88 U/L. Administration of *S. tamilnadense* significantly reduced SGOT levels, particularly with the fruit extract (200 mg/kg), which lowered SGOT to 75 ± 4.04 U/L. Similarly, SGPT and ALP values approached normal levels following treatment, confirming the hepatoprotective effect of the extract.

4.6. Kidney Function Markers in STZ-Induced Diabetic Rats

Table 6. Effect of Syzygium tamilnadense on Serum Lipid Profile.

Group	Control (CMC)	Only STZ	STZ+ Glibenclamide	STZ+E L 100 mg/kg	STZ+E L 200 mg/kg	STZ+E F 100 mg/kg	STZ+E F 200 mg/kg
Urea (mg/dl)	41±1.53	86.7±9.96***	40±0.577	73.3±3.53**	69±7.1*	42.3±2.03	36±3.46

Group	Control (CMC)	Only STZ	STZ+ Glibenclamide	STZ+E L 100 mg/kg	STZ+E L 200 mg/kg	STZ+E F 100 mg/kg	STZ+E F 200 mg/kg
Uric acid (mg/dl)	0.567±0.0882	1.73±0.12**	0.767±0.0882	1.53±0.176**	0.933±0.285	0.9±0.208	0.8±0.153
Creatinine (mg/dl)	0.6333±0.1453	1.833±0.03333**	0.5333±0.08819	1.6±0.2309*	1.233±0.318	0.8667±0.3283	0.7333±0.08819

STZ-induced diabetes significantly increased serum urea, uric acid, and creatinine levels. Serum urea increased from 41 ± 1.53 mg/dL in controls to 86.7 ± 9.96 mg/dL in diabetic rats, while creatinine increased from 0.63 ± 0.15 mg/dL to 1.83 ± 0.03 mg/dL. Treatment with the fruit extract (200 mg/kg) reduced urea to 36 ± 3.46 mg/dL and creatinine to 0.73 ± 0.09 mg/dL, indicating marked nephroprotective activity.

4.7. Lipid Profile in STZ-Induced Diabetic Rats

Table 7. Effect of Syzygium tamilnadense on Haematological Parameters.

Group	Control (CMC)	Only STZ	STZ+ Glibenclamide	STZ+E L 100 mg/kg	STZ+E L 200 mg/kg	STZ+E F 100 mg/kg	STZ+E F 200 mg/kg
Total Cholesterol (mg/dl)	48.9±3.29	57.7±3.99	38±0.837	54.2±3.01	47.6±4.86	45.2±2.31	42.2±1.76
Triglycerides (TG) (mg/dl)	53.2±4.79	100±0.924***	71.7±1.1	86.4±6.38**	55.8±7.57	83.7±3.41**	55.4±6.09
HDL- Cholesterol (mg/dl)	8.53±0.664	11.5±0.318*	7.4±0.981	8.43±0.448	8±0.862	8.1±0.493	7.73±0.203

Diabetic rats developed dyslipidemia, as evidenced by elevated total cholesterol (57.7 ± 3.99 mg/dL) and triglycerides (100 ± 0.92 mg/dL) compared with the control group (48.9 ± 3.29 mg/dL and 53.2 ± 4.79 mg/dL, respectively). Treatment with S. tamilnadense significantly reduced serum cholesterol and triglycerides. The fruit extract (200 mg/kg) reduced total cholesterol to 42.2 ± 1.76 mg/dL and triglycerides to 55.4 ± 6.09 mg/dL, indicating improved lipid metabolism.

4.8. Hematological Parameters in Normal and STZ-Induced Diabetic Rats

Table 8. Effect of Syzygium tamilnadense on Oxidative Stress and Antioxidant Status.

Group	Control (CMC)	Only STZ	STZ+ Glibenclamide	STZ+E L 100 mg/kg	STZ+E L 200 mg/kg	STZ+E F 100 mg/kg	STZ+E F 200 mg/kg
RBC ($\times 10^6/\mu L$)	5.67±0.167	5.48±0.15	5.16±0.0173	5.73±0.101	6.24±0.0722	5.62±0.259	5.35±0.232
WBC ($\times 10^3/\mu L$)	10.8±0.346	11.3±0.26	13.2±0.549*	13.6±0**	13.5±0.924*	11±0.491	13.1±0.521*
Total Haemoglobin (g/dl)	13.1±0.145	12.6±0.606	10.8±0.203*	13.1±0.0577	13.8±0.145	12.4±0.328	11.9±0.994
Polymorphs (%)	7.67±0.882	6±0.577	6.67±2.03	10±1.15	7±1.15	5±1.15	4.33±1.86
Lymphocytes (%)	85.7±2.6	90±1.15	87±2.31	79±0.577	85.7±1.45	88.3±3.18	86.3±1.45

Diabetic rats exhibited alterations in hematological parameters, including reduced hemoglobin (12.6 ± 0.61 g/dL) compared with the control group (13.1 ± 0.15 g/dL). Treatment with *S. tamilnadense* improved hemoglobin concentration, reaching 13.8 ± 0.15 g/dL in the leaf extract (200 mg/kg) group. The extract also normalized leukocyte counts and differential leukocyte profiles, indicating improvement in overall physiological status.

4.9. Antioxidant Parameters in Normal and STZ-Induced Experimental Rats

Table 9. Effect of Syzygium tamilnadense on Carbohydrate Metabolic Enzymes.

Group	Control (CMC)	Only STZ	STZ+ Glibenclamide	STZ+E L 100 mg/kg	STZ+E L 200 mg/kg	STZ+E F 100 mg/kg	STZ+E F 200 mg/kg
Total Protein (mg/dl)	0.791 ± 0.407	1.05 ± 0.194	0.229 ± 0.00318	0.9623 ± 0.2399	0.513 ± 0.227	0.447 ± 0.116	0.313 ± 0.057
SOD (unit/min/Mg protein)	0.146 ± 0.0142	0.4 ± 0.045***	0.109 ± 0.00289	0.205 ± 0.0323	0.181 ± 0.00664	0.166 ± 0.0512	0.124 ± 0.0166
Catalysis (µmole h202/min/mg protein)	0.3 ± 0.0157	0.9 ± 0.114***	0.116 ± 0.0234	0.746 ± 0.0303**	0.363 ± 0.0121	0.307 ± 0.147	0.238 ± 0.0307
GPX (µmoles of glutathione oxidized/min/mg protein)	0.039 ± 0.008544	0.2213 ± 0.03262***	0.05167 ± 0.03982	0.1577 ± 0.007796**	0.142 ± 0.003464*	0.117 ± 0.008185	0.075 ± 0.006928
GSH (µg/mg protein)	0.179 ± 0.00733	0.469 ± 0.0661***	0.0827 ± 0.0367	0.326 ± 0.0468	0.273 ± 0.0367	0.163 ± 0.0347	0.146 ± 0.00611
LPO (nmol of MDA /mg protein)	0.0757 ± 0.0012	0.148 ± 0.00866***	0.07 ± 0.00451	0.103 ± 0.00968*	0.0873 ± 0.00145	0.083 ± 0.00866	0.0807 ± 0.00426

STZ-induced diabetes caused marked oxidative stress, reflected by increased lipid peroxidation (LPO) from 0.0757 ± 0.0012 to 0.148 ± 0.0087 nmol MDA/mg protein. Treatment with *S. tamilnadense* significantly reduced LPO to 0.0807 ± 0.0043 nmol MDA/mg protein in the fruit extract (200 mg/kg) group. In addition, antioxidant enzyme activities, including SOD, catalase, GPx, and GSH, were markedly improved, demonstrating potent antioxidant activity.

4.10. Carbohydrate Metabolic Enzymes in Normal and STZ-Induced Diabetic Rats

Table 10. Effect of Syzygium tamilnadense on Oral Glucose Tolerance.

Group	Control (CMC)	Only STZ	STZ+ Glibenclamide	STZ+E L 100 mg/kg	STZ+E L 200 mg/kg	STZ+E F 100 mg/kg	STZ+E F 200 mg/kg
Glucokinase (unit/min/mg protein)	0.875 ± 0.032	0.913 ± 0.0358	0.493 ± 0.0917**	0.664 ± 0.000882	0.467 ± 0.0607***	0.45 ± 0.064***	0.424 ± 0.0502***
Hexokinase (unit/min/mg protein)	1.3 ± 0.00866	0.591 ± 0.153	0.524 ± 0.0242	0.647 ± 0.136	0.585 ± 0.0285	0.578 ± 0.041	0.53 ± 0.0876
Glucose-6- Phosphatase (nmoles of piliberated /min/mg protein)	0.1187 ± 0.01157	0.242 ± 0.02859***	0.182 ± 0.01179	0.1823 ± 0.01068	0.1543 ± 0.01495	0.172 ± 0.008888	0.1503 ± 0.01313
Fructose 1-6- Di Phosphatase (nmoles of piliberated /min/mg protein)	0.503 ± 0.0429	0.737 ± 0.112	0.488 ± 0.0987	0.465 ± 0.0616	0.426 ± 0.0303	0.362 ± 0.0549	0.26 ± 0.0485

Diabetes significantly altered the activities of carbohydrate metabolic enzymes. Glucose-6-phosphatase activity increased from 0.1187 ± 0.0116 in controls to 0.242 ± 0.0286 nmol/min/mg protein in diabetic rats, while hexokinase activity decreased from 1.30 ± 0.0087 to 0.591 ± 0.153 unit/min/mg protein. Treatment with *S. tamilnadense* restored these enzyme activities toward normal values, indicating improved glucose utilization and reduced hepatic glucose production.

Statistical comparison (Tables 1-10): Each group (n=6),

each value represents Mean ± SEM. One way ANOVA, followed by Dunnett comparison was performed. *(***P<0.001)* control group was compared with Only STZ group-II. *(***P<0.001-**P<0.01, *P<0.05)* treated groups III, IV, V, VI and VII was compared with group I.

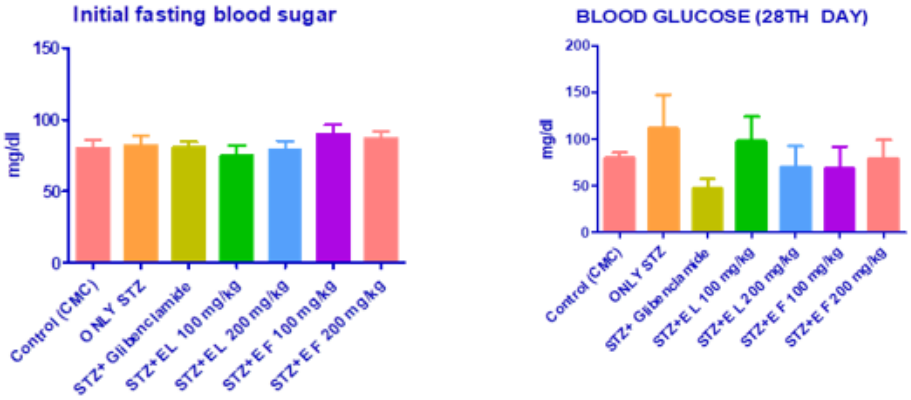

Figure 1. *Body Weight Analysis of Normal and Experimental Rats (g).*

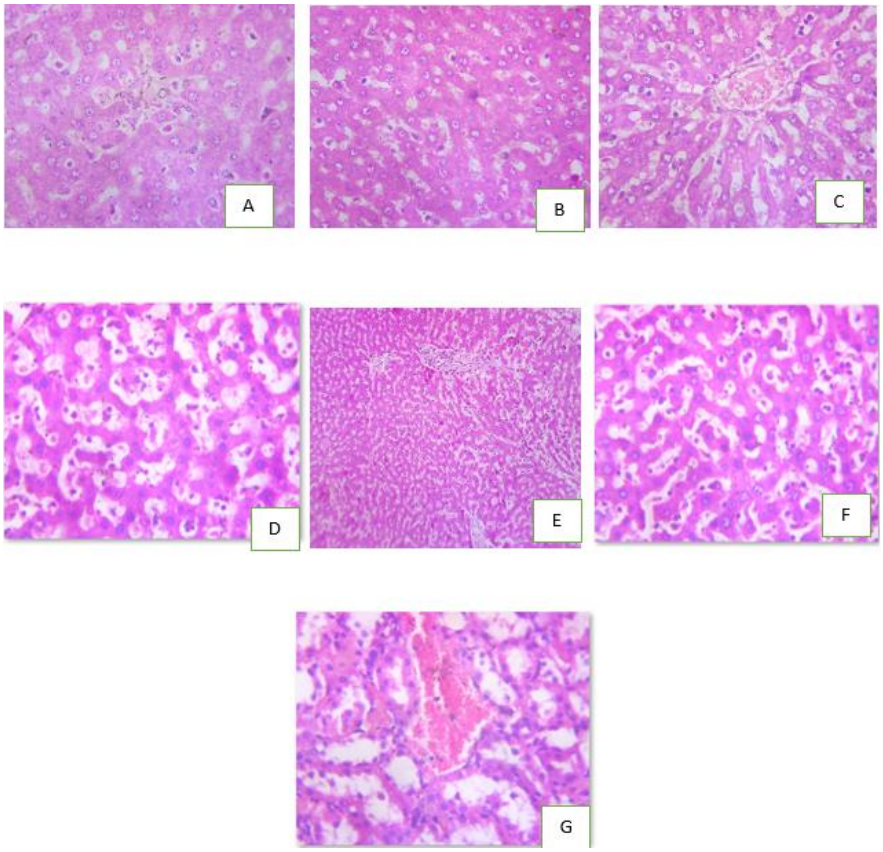

Figure 2. *Liver Histopathological Examination.*

A - Only normal saline
B - STZ 65 mg/kg/b.w. (i.p) +NIC 120mg/kg (i.p)
C – STZ (65 mg/kg) NIC 120mg/kg (i.p) rats treated with Metformin 200 mg/kg (p.o)
D - STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Extract L.D 200 mg/kg
E - STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Probiotic
F - STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Extract+Probiotic
G - STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Probiotic + Metformin 200 mg/kg (p.o)

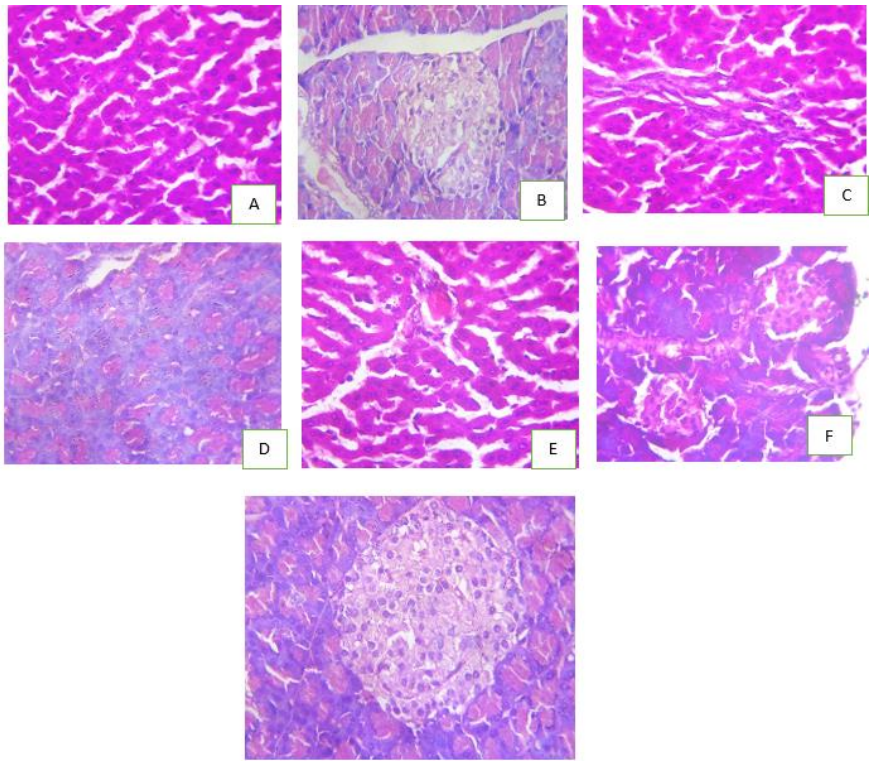

Figure 3. *Pancreas Histopathological Examination.*

A - Only normal saline
B - STZ 65 mg/kg/b.w. (i.p) +NIC 120mg/kg (i.p)
C – STZ (65 mg/kg) NIC 120mg/kg (i.p) rats treated with Metformin 200 mg/kg (p.o)
D - STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Extract L.D 200 mg/kg
E - STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Probiotic
F - STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Extract+Probiotic
G - STZ (65 mg/kg) +NIC 120mg/kg (i.p) rats treated with Probiotic + Metformin 200 mg/kg (p.o)

5. Discussion

As presented in Tables 1-10, the ethanolic extract of *Syzygium tamilnadense* significantly ameliorated diabetes-induced metabolic disturbances in nicotinamide–streptozotocin (NA-STZ)-induced type 2 diabetic rats. This experimental model, characterized by partial pancreatic β-cell destruction and insulin resistance, closely mimics human type 2 diabetes and produced marked hyperglycaemias, impaired glucose tolerance, reduced body weight, elevated glycated haemoglobin (HbA1c), altered insulin secretion, depleted hepatic glycogen, and disrupted carbohydrate-metabolizing enzymes [10, 11]. Untreated diabetic rats showed significant body weight loss (141 ± 4.20 g), whereas treatment with S. tamilnadense restored body weight to 172 ± 3.37 g and 171 ± 5.32 g at fruit extract doses of 100 and 200 mg/kg, respectively, exceeding Glibenclamide (158 ± 6.79 g). Fasting blood glucose increased from 82.2 ± 6.23 mg/dL to 405 ± 151 mg/dL in diabetic rats but declined to 68.7 ± 23.2, 79.7 ± 19.4, and 70.7 ± 21.8 mg/dL following treatment with fruit (100 and 200 mg/kg) and leaf (200 mg/kg) extracts, respectively, comparable to Glibenclamide (47.2 ± 10.5 mg/dL). HbA1c decreased from 11.5 ± 0.32 to 6.47 ± 0.38 mmol/L after fruit extract (200 mg/kg) treatment, with concurrent restoration of serum insulin and hepatic glycogen levels, indicating improved β-cell function and glucose metabolism [5-8]. The oral glucose tolerance test demonstrated improved glucose homeostasis, with blood glucose decreasing from 267 ± 6.72 mg/dL at 1 h to 101 ± 5.04 mg/dL at 6 h in the fruit extract (200 mg/kg) group, comparable to metformin (101 ± 3.73 mg/dL) [2, 9]. Consistent with previous reports on antioxidant-mediated antidiabetic effects of medicinal plants [16-22], *S. tamilnadense* also normalized glucose-6-phosphatase activity (0.242 ± 0.0286 to near normal from the diabetic value) and restored hexokinase activity (0.591 ± 0.153 unit/min/mg protein toward the control value of 1.30 ± 0.0087 unit/min/mg protein), indicating enhanced glycolysis, reduced hepatic gluconeogenesis, improved insulin sensitivity, and better peripheral glucose utilization [18-22].

In addition to its antihyperglycemic effects, *S. tamilnadense* exhibited significant hepatoprotective, nephroprotective, hypolipidemic, and hepatoprotective activities (Tables 4-7). Diabetes-induced hepatic injury, reflected by elevated SGOT (51.7 ± 2.03 to 124 ± 0.88 U/L), was significantly attenuated by the fruit extract (200 mg/kg), reducing SGOT to 75 ± 4.04

U/L, while SGPT and ALP also approached normal levels, indicating restoration of hepatic function [10-12]. Renal dysfunction, evidenced by increased serum urea (41 ± 1.53 to 86.7 ± 9.96 mg/dL) and creatinine (0.63 ± 0.15 to 1.83 ± 0.03 mg/dL), was significantly improved following fruit extract treatment, reducing these values to 36 ± 3.46 mg/dL and 0.73 ± 0.09 mg/dL, respectively [10, 11]. The extract also corrected diabetes-associated dyslipidaemia by reducing total cholesterol from 57.7 ± 3.99 to 42.2 ± 1.76 mg/dL and triglycerides from 100 ± 0.92 to 55.4 ± 6.09 mg/dL, suggesting improved lipid metabolism and insulin sensitivity [3, 6, 13]. Furthermore, reduced haemoglobin levels in diabetic rats (12.6 ± 0.61 g/dL) were restored to 13.8 ± 0.15 g/dL by the leaf extract (200 mg/kg), accompanied by normalization of leukocyte profiles, indicating recovery of haematological homeostasis and reduced oxidative damage [14, 15]. Collectively, these findings demonstrate that *S. tamilnadense* exerts multifunctional antidiabetic effects by improving glycemic control, regulating carbohydrate metabolism, and protecting against hepatic, renal, lipid metabolic, and haematological complications, supporting its potential as a promising natural therapeutic agent for type 2 diabetes mellitus.

6. Conclusion

The present study demonstrates that *Syzygium tamilnadense* possesses significant antidiabetic activity in nicotinamide–streptozotocin-induced type 2 diabetic rats. The extract effectively improved glycemic control by reducing blood glucose and HbA1c levels, enhancing insulin secretion, restoring body weight, improving glucose tolerance, normalizing lipid metabolism, and protecting hepatic and renal functions. It also alleviated oxidative stress and promoted pancreatic β-cell and liver tissue recovery. Overall, these findings suggest that *S. tamilnadense* is a promising natural therapeutic candidate for the management of type 2 diabetes mellitus and its associated complications.

Abbreviations

ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ALT	Alanine Transaminase
DM	Diabetes Mellitus
EDTA	Ethylene Diamine Tetra Acetic Acid
HbA1c	Haemoglobin A1c
HDL	High Density Lipoprotein
NIC	Nicotinamide
OGTT	Oral Glucose Tolerance Test
TG	Triglycerides
TC	Total Cholesterol
VLDL	Very Low Density Lipoprotein
NA-STZ	Nicotinamide–Streptozotocin
STZ	Streptozotocin

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Author Contributions

Mani Jayendran: Conceptualization, Software, Writing – original draft

Coimbatore Murugesan Ganesan: Investigation, Validation, Writing – review & editing

Thangamani Balasaravanan: Data curation, Project administration, Resources

Data Availability Statement

The data generated and/or analysed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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