RESEARCH PAPER

Effect Of Seendhil Polyherbal Formulation In Attenuating Type-2 Diabetes In Stz-Induced Experimental Rats

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Abstract

Background: Type 2 diabetes mellitus (t2dm) is a chronic metabolic disorder associated with hyperglycemia, insulin resistance, dyslipidemia, and oxidative stress, leading to multi-organ complications. Polyherbal formulations from traditional medicine are gaining attention due to their multi-target therapeutic potential and minimal side effects.

Aim: To evaluate the antidiabetic, antihyperlipidemic, and antioxidant effects of seendhil polyherbal formulation (sph) in streptozotocin (stz)-induced type 2 diabetic rats.

Methods: Thirty-two male wistar rats were divided into four groups: control, diabetic control, sph-treated (500 mg/kg), and metformin-treated (50 mg/kg). Diabetes was induced using a high-fat diet combined with stz injection. After 30 days of treatment, biochemical parameters including lipid profile, liver and renal markers, oxidative stress indices, and antioxidant enzyme activities were assessed. Statistical analysis was performed using one-way anova followed by duncan's multiple comparison test.

Results: Diabetic rats showed significant dyslipidemia, elevated liver enzymes (alt, ast, alp), renal dysfunction markers (urea, creatinine), and increased oxidative stress markers (lpo, mda), along with reduced antioxidant enzymes (sod, cat, gpx, gst). Sph treatment significantly improved lipid profile by reducing total cholesterol, triglycerides, ldl-c, and free fatty acids while increasing hdl-c. It also restored liver and kidney function markers to near-normal levels. Furthermore, sph markedly decreased oxidative stress and enhanced antioxidant defense systems.

Conclusion: Seendhil polyherbal formulation exhibits significant antidiabetic, hepatoprotective, nephroprotective, and antioxidant effects in experimental t2dm, supporting its potential as a safe and effective alternative therapy.

Effect of Seendhil polyherbal formulation in attenuating type-2 diabetes in STZ-induced experimental rats

Keywords: Type 2 Diabetes Mellitus, Seendhil, Polyherbal Formulation, Streptozotocin, Dyslipidemia, Oxidative Stress, Antioxidant Enzymes.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both, and is associated with long-term complications affecting the eyes, kidneys, nerves, and cardiovascular system (1). Among its various forms, type 2 diabetes mellitus (T2DM) accounts for approximately 90–95% of all cases and is primarily driven by insulin resistance and progressive pancreatic β-cell dysfunction. The global burden of diabetes has escalated dramatically, with recent estimates from the Global Burden of Disease Study 2021 reporting over 529 million prevalent cases worldwide and projecting continued increases, particularly in low- and middle-income countries such as India (2). Similarly, epidemiological analyses indicate that approximately 462 million individuals were affected globally in 2017, corresponding to 6.28% of the world's population, with projections reaching 7,079 cases per 100,000 population by 2030 (3).

The pathogenesis of T2DM is multifactorial and involves interconnected mechanisms, including oxidative stress, chronic low-grade inflammation, and impaired insulin signaling. Excessive production of reactive oxygen species (ROS) plays a central role in the development of insulin resistance and β-cell dysfunction by disrupting cellular homeostasis and activating pro-inflammatory mediators such as nuclear factor-κB (NF-κB), p38 mitogen-activated protein kinase, and stress-activated protein kinases (4). Chronic oxidative stress, exacerbated by hyperglycemia and dyslipidemia, is particularly detrimental to pancreatic β-cells, which possess relatively low levels of antioxidant defense enzymes. This leads to impaired glucose-stimulated insulin secretion and ultimately contributes to the progression of T2DM (5). Furthermore, nutrient overload enhances mitochondrial ROS generation, activating intracellular stress pathways that induce β-cell dysfunction and peripheral insulin resistance (6).

In addition, defects in key components of the insulin signaling cascade including phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), and 3-phosphoinositide-dependent protein kinase 1 (PDK1) lead to reduced translocation of glucose transporter 4 (GLUT4) to the plasma membrane, thereby impairing glucose uptake in peripheral tissues (7,8). Under insulin-resistant conditions, stress kinases such as c-Jun N-terminal kinase (JNK) and p70S6K further inhibit insulin signaling by reducing insulin receptor substrate (IRS) phosphorylation, thereby perpetuating hyperglycemia (8). Experimental animal models are essential for understanding disease mechanisms and evaluating therapeutic interventions for T2DM. Among these, the combination of a high-fat diet (HFD) and low-dose streptozotocin (STZ) is widely recognized as a clinically relevant model, as it integrates peripheral insulin resistance with partial pancreatic β-cell damage, closely mimicking the metabolic characteristics of human T2DM (9). In this model, HFD feeding induces dyslipidemia, hyperinsulinemia, and insulin resistance, while subsequent administration of low-dose STZ causes selective β-cell toxicity via DNA alkylation and oxidative stress, resulting in moderate hyperglycemia without complete insulin deficiency (10). This combined model is considered a cost-effective and physiologically relevant platform for screening antidiabetic agents (11). Despite the availability of several pharmacological therapies including metformin, sulfonylureas, and insulin their long-term use is often associated with adverse effects, limited efficacy, and economic burden. Consequently, increasing attention has been directed toward alternative therapeutic strategies, particularly those based on medicinal plants, which offer multi-targeted pharmacological effects with relatively fewer side effects.

Traditional systems of medicine, such as Siddha and Ayurveda, emphasize the use of polyherbal formulations that exert synergistic therapeutic actions to restore metabolic homeostasis. Previous studies have demonstrated that polyherbal formulations containing medicinal plants such as *Gymnema sylvestre*, *Tinospora cordifolia*, *Syzygium cumini*, *Momordica charantia*, and *Curcuma longa* significantly reduce fasting blood glucose levels and

improve lipid profiles in diabetic animal models, with efficacy comparable to standard drugs like glibenclamide (12). Moreover, such formulations often exhibit superior antidiabetic and antihyperlipidemic effects compared to individual plant extracts, likely due to synergistic interactions among diverse phytoconstituents, including flavonoids, phenolic compounds, gymnemic acids, and alkaloids (13). Seendhil polyherbal formulation is a traditional Siddha preparation composed of medicinal plants such as *Tinospora cordifolia*, *Terminalia chebula*, *Curcuma longa*, and *Gymnema sylvestre*, all of which are well documented for their antidiabetic, antioxidant, and anti-inflammatory properties. These phytoconstituents exert their therapeutic effects through multiple mechanisms, including enhancement of insulin secretion, improvement of insulin sensitivity, inhibition of carbohydrate-digesting enzymes, and reduction of oxidative stress (14,15). However, despite substantial evidence supporting the individual antidiabetic effects of these medicinal plants, the combined efficacy and mechanistic basis of action of Seendhil polyherbal formulation remain insufficiently explored. Therefore, the present study aims to evaluate the therapeutic potential of Seendhil polyherbal formulation in attenuating T2DM using a high-fat diet and streptozotocin-induced experimental rat model. The study further focuses on assessing glycemic control, biochemical parameters, and metabolic alterations, thereby providing scientific validation for its traditional use and exploring its potential as a safe and effective alternative strategy for diabetes management.

MATERIALS AND METHODS

Reagents & Chemicals

The experiments involved chemicals and reagents are of analytical and molecular biology grade, which were obtained at BDH Laboratory Supplies (Poole, UK); Loba Chemie (Mumbai, India); TCI Chemicals (Tokyo, Japan); VWR International (Radnor, PA, USA); Fisher Scientific (Pittsburgh, PA, USA); and Carl Roth GmbH (Karlsruhe, Germany).

Poly herbal preparation

A polyherbal Siddha formulation known as Seendhil that is traditionally applied to manage diabetes mellitus and other chronic conditions of the body. This preparation is composed of a combination of ten different herbs, with (*Tinospora cordifolia*), Kadukkai thol (*Terminalia chebula*), Nellikkai vattral (*Ribes uvacrispa*), Kariveppillai elai (*Murraya koenigii*), Vilvam (*Aegle marmelos*), Manjal (*Curcuma longa*), Vendhayam (*Trigonella foenum-graecum*), Kovai elai (*Coccinia grandis*), Sirukurinjaan elai (*Gymnema sylvestre*), Maramanjal (*Berberis aristata*). To prepare, the chosen parts of the plants are acquired in the nearby markets, washed, and allowed to dry in the shade of the atmosphere in seven days. Once completely dry, a mechanical grinder is used to grind each plant material into fine powder and they are then sieved in order to obtain uniformly sized particles and then mixed in equal proportions to obtain the final polyherbal blend. The formulations are stored as representative samples of the formulation in the National Institute of Siddha, Department of Medicinal Botany, Chennai, India.

Animals

Thirty-two adult male Wistar rats were housed under controlled laboratory conditions and randomly divided into four groups (n=8), following IAEC-approved protocols. Type 2 diabetes was induced using a 30-day high-fat diet combined with a single intraperitoneal injection of streptozotocin (35 mg/kg body weight). The experimental groups included normal control, diabetic control, polyherbal-treated (300 mg/kg twice daily), and metformin-treated (50 mg/kg once daily) rats for 30 days.

Serum lipid profile

Serum cholesterol (CHO), triglyceride (TG), low-density lipo- proteins (LDL), High-density lipoproteins (HDL), and free fatty acid (FFA) were assessed with help of assay kits purchased from Spinreact, Spain. Results for same were marked as mg/dl.

Liver function markers

To assess liver integrity and functions, serum levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) will be determined. Blood will be taken via retro-orbital puncture into plain tubes, and serum separated by clotting. Serum will be analyzed according to protocols for commercially available biochemical assay kits (Spinreact, Spain) under manufacturer specification. Enzyme activities will be determined utilising a semi-automatic biochemistry analyzer system. Data will be presented in standard units (U/L) and all measurements performed in triplicate for accuracy and reliability.

Renal functional markers

Kidney functional markers (urea and creatinine) were measured using biochemical-assay kits procured from Spinreact, Spain. Results for same were expressed as U/L.

Oxidative stress and antioxidant enzymes

The production of hydroxyl radicals (OH*) and lipid peroxidation (LPO) were determined using the procedures outlined by Devasagayam and Tarachand (1987) and Puntarulo and Cederbaum (1988), respectively (16,17). The results were expressed in terms of nanomoles of malondialdehyde (MDA) formed per minute per milligram of protein for LPO, and micromoles per minute per milligram of protein for OH*. Superoxide dismutase (SOD) activity was evaluated using the method of Marklund and Marklund (1974), catalase (CAT) activity was measured following Sinha (1972) procedure, and glutathione peroxidase (GPx) activity was determined according to Rotruck et al. (1973) (18-20). The activities of SOD, CAT, and GPx were quantified as units per milligram of protein.

Statistical Analysis

The data was statistically assessed using one-way analysis of variance and Duncan's multiple comparison test utilizing computerized software (SPSS 7.5 using Windows student version) to determine the significance of difference between the control and treatment groups. The experiment was conducted with a significance criterion of $p<0.05$.

RESULTS

Effect of Seenthil on Biochemical parameters

Diabetic (DM) rats exhibited significant dyslipidemia compared to the control group, as evidenced by elevated levels of total cholesterol (TC), triglycerides (TG), free fatty acids (FFA), and low-density lipoprotein cholesterol (LDL-C), along with a marked reduction in high-density lipoprotein cholesterol (HDL-C). TC levels were significantly increased in the DM group (150 ± 6 mg/dL) compared to control (50 ± 1 mg/dL), while TG levels rose to 169 ± 6 mg/dL from 90 ± 3 mg/dL in control animals. Similarly, FFA and LDL-C levels were elevated to 200 ± 6 mg/dL and 75 ± 2 mg/dL, respectively, compared to control values of 70 ± 3 mg/dL and 30 ± 1 mg/dL. In contrast, HDL-C levels were significantly decreased in diabetic rats (50 ± 1 mg/dL) compared to control (121 ± 6 mg/dL), confirming severe lipid metabolic disturbances associated with diabetes. Treatment with Seenthil polyherbal formulation (SPH, 500 mg/kg) significantly improved all biochemical parameters. TC, TG, FFA, and LDL-C levels were reduced to 90 ± 3 mg/dL, 116 ± 3 mg/dL, 170 ± 7 mg/dL, and 40 ± 1 mg/dL, respectively, while HDL-C levels were restored to 101 ± 5 mg/dL. These effects were comparable to metformin-treated rats (TC: 67 ± 3.6 mg/dL; TG: 105 ± 5.3 mg/dL; FFA: 89 ± 4.1 mg/dL; LDL-C: 32 ± 1.4 mg/dL; HDL-C: 117 ± 5.9 mg/dL). Notably, the Control + SPH group maintained near-normal lipid levels, indicating the safety of SPH. Overall, SPH effectively ameliorated diabetes-induced dyslipidemia and improved lipid homeostasis.

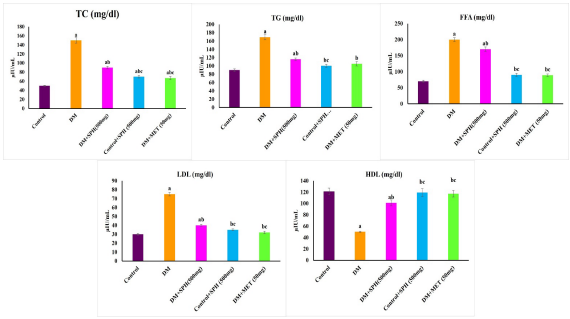

Figure 1: Effect of Seenthil polyherbal formulation (SPH) on serum biochemical parameters including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and free fatty acids (FFA) in experimental groups of type 2 diabetic rats. Values are expressed as mean ± SEM (n = 6). Statistical significance is indicated by different superscripts (*a, b, c*) where *a* denotes comparison with control group, *b* denotes comparison with diabetic (DM) group, and *c* denotes comparison with SPH-treated group at $p < 0.05$.

Effect of Seenthil on Liver and Kidney function

Liver markers

Liver function markers were significantly elevated in diabetic (DM) rats, indicating diabetes-induced hepatic dysfunction. The levels of alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were markedly increased in the DM group (ALP: 179 ± 7 U/L; AST: 119 ± 5 U/L; ALT: 170 ± 6 U/L) compared to control animals (ALP: 111 ± 4 U/L; AST: 60 ± 2 U/L; ALT: 90 ± 4 U/L). Treatment with Seenthil polyherbal formulation (SPH, 500 mg/kg) significantly reduced these elevated enzyme levels (ALP: 117 ± 5 U/L; AST: 80 ± 3 U/L; ALT: 110 ± 6 U/L), indicating restoration of normal liver function. These effects were comparable to those observed with metformin

treatment, suggesting that SPH exerts notable hepatoprotective activity in diabetic conditions.

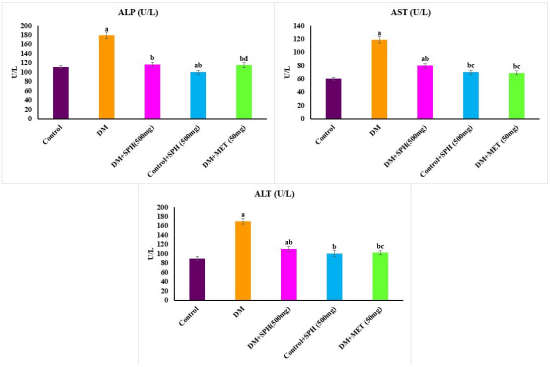

Figure 2: Effect of SPH on liver function markers including alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in experimental groups of type 2 diabetic rats. Values are expressed as mean ± SEM (n = 6). Superscripts (*a, b, c*) indicate statistically significant differences at $p < 0.05$.

Renal Markers

Diabetic (DM) rats exhibited significant impairment in renal function, as evidenced by elevated levels of serum creatinine, urea, and blood urea nitrogen (BUN). The levels of these markers were markedly increased in the DM group (creatinine: 2.9 ± 0.07 mg/dL; urea: 69 ± 2 mg/dL; BUN: 1.0 ± 0.001 mmol/dL) compared to the control group, indicating diabetes-induced renal dysfunction. Treatment with Seenthil polyherbal formulation (SPH, 500 mg/kg) significantly reduced the elevated renal markers (creatinine: 1.2 ± 0.07 mg/dL; urea: 45 ± 2 mg/dL; BUN: 0.4 ± 0.01 mmol/dL), demonstrating a protective effect against kidney damage. Similar improvements were observed in the metformin-treated group, with values approaching normal levels. Overall, SPH exhibited notable nephroprotective activity in diabetic rats.

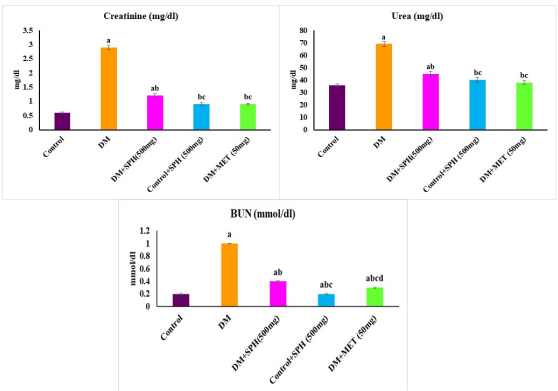

Figure 3: Effect of SPH on renal function markers including creatinine, urea, and blood urea nitrogen (BUN) in experimental groups. Values are expressed as mean ± SEM (n = 6). Statistical significance is indicated by a, b, c at $p < 0.05$.

Effect of Seenthil on Oxidative Stress Markers

Diabetic rats exhibited a significant increase in oxidative stress markers, indicating enhanced lipid peroxidation and cellular damage. The levels of lipid peroxidation (LPO) and malondialdehyde (MDA) were markedly elevated in the DM group (LPO: 29 ± 1 ng/mL; MDA: 120 ± 6 ng/mL) compared to the control group (LPO: 10 ± 0.5 ng/mL; MDA: 40 ± 1 ng/mL). Treatment with Seenthil polyherbal formulation (SPH, 500 mg/kg) significantly reduced these elevated oxidative stress markers (LPO: 12 ± 0.7 ng/mL; MDA: 70 ± 4 ng/mL), indicating a strong protective effect against oxidative damage. Similar improvements were observed in the metformin-treated group, demonstrating comparable antioxidant activity. Overall, SPH effectively attenuated diabetes-induced oxidative stress.

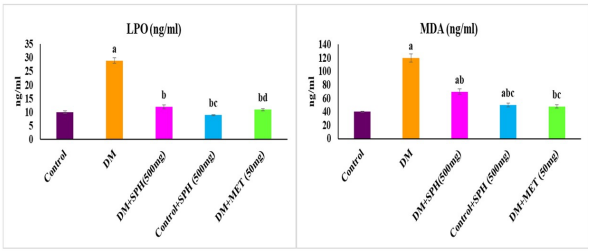

Figure 4: Effect of SPH on oxidative stress markers including lipid peroxidation (LPO) and malondialdehyde (MDA) levels in experimental groups. Values are expressed as mean ± SEM (n = 6). Different superscripts (a, b, c) denote significant differences at $p < 0.05$.

Antioxidant Enzymes

Diabetic (DM) rats exhibited a significant reduction in antioxidant enzyme activities, indicating impaired endogenous defense against oxidative stress. The levels of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST) were markedly decreased in the DM group (SOD: 0.6 ± 0.04 ng/mL; CAT: 0.25 ± 0.01 ng/mL; GPx: 7 ± 0.04 pmol/L; GST: 9 ± 0.4 pg/mL) compared to the control group. Treatment with Seenthil polyherbal formulation (SPH, 500 mg/kg) significantly restored the activities of these antioxidant enzymes (SOD: 1.6 ± 0.04 ng/mL; CAT: 1.8 ± 0.02 ng/mL; GPx: 14 ± 0.7 pmol/L; GST: 13 ± 0.2 pg/mL),

indicating enhanced antioxidant defense. Comparable improvements were observed with metformin treatment, although SPH showed slightly better restoration for certain enzymes. Additionally, the Control + SPH group maintained normal enzyme levels, confirming the safety of the formulation. Overall, SPH demonstrated a strong antioxidative effect in diabetic conditions.

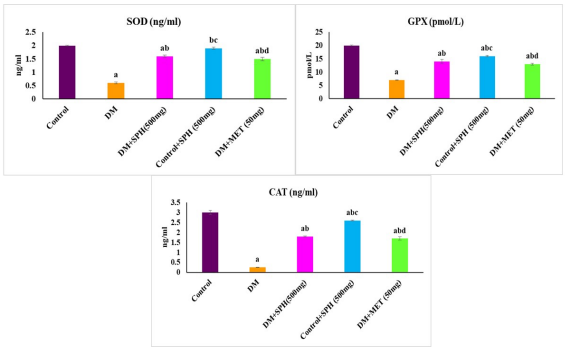

Figure 5: Effect of SPH on antioxidant enzyme activities including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST) in experimental groups. Values are expressed as mean ± SEM (n = 6). Superscripts (a, b, c) indicate statistically significant differences at $p < 0.05$.

DISCUSSION

The present study evaluated the therapeutic efficacy of Seenthil polyherbal formulation (SPH, 500 mg/kg) in streptozotocin (STZ)-induced type 2 diabetic rats and demonstrated its ability to ameliorate multiple metabolic and organ dysfunctions associated with diabetes. The diabetic group exhibited marked hyperglycemia along with elevated serum insulin levels, indicating the development of insulin resistance. Treatment with SPH significantly reduced fasting blood glucose and normalized insulin levels, suggesting improved peripheral insulin sensitivity rather than excessive stimulation of insulin secretion. Importantly, the absence of hypoglycemic effects in normoglycemic animals confirms the safety and glucose-dependent action of the formulation. These findings are supported by earlier reports indicating that *Tinospora cordifolia* enhances glucose uptake and GLUT4 translocation while modulating PPARα and PPARγ pathways, thereby improving insulin sensitivity and glucose homeostasis (21,22). In addition, *Gymnema sylvestre* has been reported to promote β-cell regeneration and improve glycemic control, further contributing to the antihyperglycemic effect observed in the present study (23,24).

Diabetes-induced dyslipidemia was clearly evident in the untreated group, with significant elevations in total cholesterol, triglycerides, free fatty acids, and LDL-C, along with reduced HDL-C levels. These alterations reflect impaired lipid metabolism due to insulin resistance, increased lipolysis, and enhanced hepatic lipogenesis. SPH treatment effectively corrected these lipid abnormalities, bringing the parameters closer to normal levels, comparable to metformin. The hypolipidemic effect of SPH may be attributed to the synergistic action of its phytoconstituents. Curcumin from *Curcuma longa* is known to regulate lipid metabolism through its antioxidant and anti-inflammatory properties, improving both glycemic and lipid profiles (25,26). Similarly, *Gymnema sylvestre* has been shown to normalize lipid parameters in diabetic conditions (27). The combined action of these components likely contributes to the overall improvement in lipid homeostasis observed in SPH-treated animals.

Hepatic dysfunction, a common complication of diabetes, was evident from the elevated levels of liver enzymes such as ALP, AST, and ALT in diabetic rats. These increases are indicative of hepatocellular damage caused by oxidative stress, glucotoxicity, and lipid accumulation. SPH treatment significantly reduced these enzyme levels, suggesting restoration of liver function and membrane integrity. Similar hepatoprotective effects have been reported for *Tinospora cordifolia* and *Curcuma longa*, which possess antioxidant and anti-inflammatory properties that protect hepatocytes from damage (28,29). The observed effects in this study are therefore consistent with the known pharmacological activities of the formulation's constituents. Renal dysfunction was also observed in diabetic animals, as indicated by elevated creatinine, urea, and BUN levels, reflecting early diabetic nephropathy. SPH treatment significantly reduced these markers, demonstrating its nephroprotective potential. These improvements may be attributed to the ability of SPH to attenuate hyperglycemia-induced oxidative stress and inflammation, which are key drivers of renal damage in diabetes. Previous studies have shown that gymnemic acid and curcumin can improve renal function by reducing oxidative stress and modulating inflammatory pathways (30,31). The present findings align with these reports and further support the protective role of SPH against diabetic complications.

Oxidative stress plays a central role in the pathogenesis of diabetes and its complications. In this study, diabetic rats exhibited significantly increased levels of lipid peroxidation markers such as LPO and MDA, along with a marked reduction in antioxidant enzymes including SOD, CAT, GPx, and GST. These changes indicate excessive reactive oxygen species (ROS) production and compromised antioxidant defense. SPH treatment effectively reduced oxidative stress markers and restored antioxidant enzyme activities, highlighting its strong antioxidant potential. This effect is consistent with previous studies demonstrating that *Tinospora cordifolia* and *Curcuma longa* enhance antioxidant defenses and reduce oxidative damage in diabetic models (32,33). The restoration of antioxidant balance is particularly important, as oxidative stress contributes to insulin resistance, β-cell dysfunction, and tissue injury. The overall findings of this study emphasize the multi-target therapeutic potential of SPH in managing type 2 diabetes. Unlike single-compound therapies, polyherbal formulations act through multiple pathways, simultaneously addressing hyperglycemia, dyslipidemia, oxidative stress, and organ damage. This synergistic action aligns with traditional Siddha medicine principles, where combinations of herbs are used to restore systemic balance. The comparable efficacy of SPH with metformin further strengthens its potential as an alternative or adjunct therapy.

CONCLUSION

The present study demonstrates that Seenthil polyherbal formulation (SPH, 500 mg/kg) exerts significant antidiabetic activity in streptozotocin-induced type 2 diabetic rats by effectively reducing hyperglycemia, improving insulin sensitivity, correcting dyslipidemia, and providing hepatoprotective, nephroprotective, and antioxidant effects. These findings highlight the multi-target therapeutic potential of SPH, likely due to the synergistic action of its bioactive phytoconstituents, supporting its traditional use in diabetes management. However, the study is limited by the lack of histopathological validation, absence of detailed molecular mechanism analysis, use of a single dose regimen, and lack of formulation standardization. Therefore, future research should focus on tissue-level investigations, elucidation of underlying signaling pathways such as PI3K/Akt and AMPK, dose optimization studies, phytochemical standardization, and long-term clinical trials to confirm the efficacy and safety of SPH for translational application in human diabetes management.

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