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Investigation Of The Antidiabetic Potential Of A Polyherbal Formulation In Streptozotocin-Induced Diabetic Rats

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Abstract: *Hyperglycemia due to decreased insulin production or insulin action, or both, characterizes diabetes mellitus, a chronic metabolic condition. The use of polyherbal formulations has recently garnered interest as a potential alternative to traditional methods of diabetes treatment because to their synergistic effects and lower toxicity. A new polyherbal formulation of carefully chosen medicinal herbs with a history of usage in diabetes treatment is the subject of this investigation into its antidiabetic properties. The polyherbal formulation was tested on diabetic Wistar rats that had been induced with streptozotocin (STZ). Animals were chosen for the investigation if their fasting blood glucose levels were greater than 250 mg/dL, and diabetes was induced by injecting 55 mg/kg of STZ intraperitoneally. Over the course of 28 days, the diabetic rats were given varying dosages of the polyherbal formulation orally. Blood sugar levels, insulin levels, lipid profiles, and indicators of oxidative stress were among the standard biochemical measures assessed. Additionally, pancreatic tissue was examined histopathologically. In comparison to diabetic control rats, the polyherbal formulation considerably decreased FBG levels and improved serum insulin levels ($p < 0.05$). In addition to reducing oxidative stress and normalizing lipid profile parameters, the formulation treatment also increased activity of antioxidant enzymes like catalase and superoxide dismutase (SOD) and decreased malondialdehyde (MDA) levels. Researchers found that the treated groups' pancreatic islet architecture had been restored by histopathological investigation. The polyherbal formulation probably has antioxidant and pancreatic β-cell protecting actions, since it showed considerable antidiabetic activity in rats with diabetes induced by STZ. These results provide credence to the idea that the formulation could be useful as an auxiliary treatment in the treatment of diabetes mellitus.*

Keywords: *Polyherbal formulation, antidiabetic activity, streptozotocin, oxidative stress, insulin, histopathology*

INTRODUCTION:

Hyperglycemia, caused by either decreased insulin production or insulin action, or both, characterizes diabetes mellitus (DM), a complicated and chronic metabolic condition. As one of the most common endocrine diseases globally, it remains a major issue in terms of public health. The International Diabetes Federation (IDF) estimates that there were 537 million adults living with diabetes worldwide in 2021. If present trends persist, this number is projected to increase to 643 million by 2030 and 783 million by 2045 [1]. Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and relative insulin insufficiency, while type 1 diabetes mellitus (T1DM) is marked by the autoimmune destruction of pancreatic β-cells [2].

Insulin, sulfonylureas, biguanides, and DPP-4 inhibitors are diabetic medications that help manage blood sugar levels; nevertheless, they are not without side effects, including hypoglycemia, gastrointestinal problems, and organ toxicity in the long run [3]. Moreover, the gradual decrease in β-cell function over time may not be sufficiently addressed by these medications. Therefore, there is a rising need to find

natural, complementary, or alternative treatment medicines that can manage blood sugar levels for the long term with few side effects [4].

Ayurveda, Unani, and TCM are just a few examples of the long-established medical systems that rely heavily on herbal remedies. The traditional usage of more than 1,200 plant species for the treatment of diabetes, either singly or in conjunction with other methods, dates back thousands of years [5]. Because many therapeutic plants contain several bioactive phytoconstituents, which can have additive, synergistic, or potentiating effects, polyherbal preparations have attracted a lot of interest. Insulin secretion, glucose uptake, oxidative stress, and lipid metabolism are some of the pathophysiological pathways that these formulations are thought to target [6, 7].

Clinical and preclinical studies have confirmed the antioxidant and antidiabetic effects of various medicinal plants, including Momordica charantia, Gymnema sylvestre, Trigonella foenum-graecum, Withania somnifera, and Tinospora cordifolia [8–10]. Researchers have found that the flavonoids, alkaloids, saponins, and phenolic chemicals found in these plants may have effects on glucose metabolism, insulin sensitivity, pancreatic β-cell regeneration, and free radical scavenging [11, 12].

One of the most common ways to produce experimental diabetes in animal models, particularly for investigating the effectiveness of antidiabetic drugs, is with streptozotocin (STZ), a nitrosourea derivative that targets pancreatic β-cells specifically [13]. The pathophysiology hallmarks of human diabetes mellitus are mimicked in STZ-induced diabetic rats, which show typical hyperglycemia, hypoinsulinemia, oxidative stress, and pancreatic tissue destruction [14].

This is why we're doing this research: to find out whether a new polyherbal formulation with medicinal plants that have been shown effective against diabetes can be effective. Histopathological alterations in pancreatic tissue, oxidative stress markers, fasting blood glucose, insulin levels, lipid profiles, and STZ-induced diabetic mice were used to evaluate the formulation. This project seeks to lay the groundwork for the creation of safe and effective polyherbal medicines for the control of diabetes and to offer scientific evidence in support of the traditional usage of these plants.

2. MATERIAL AND METHODS:

2.1. Plant Materials and Preparation of Polyherbal Formulation

This study focused on medicinal herbs that have been found to have antidiabetic effects. Gymnema sylvestre (Asclepiadaceae), Momordica charantia (Cucurbitaceae), and Trigonella foenum-graecum (Fabaceae) were obtained from a registered herbal source and verified by a botanist from the Department of Pharmacognosy. The raw materials were dried and validated. Gymnema sylvestre leaves, Momordica charantia fruits, and Trigonella foenum-graecum seeds were all washed, dried in the shade, and ground into a coarse powder. After being measured out in equal parts, the powders were hydroalcoholically extracted with 70% ethanol for 8 hours in a Soxhlet apparatus [15]. A semisolid mass was obtained by filtering the extracts, then concentrating them using a rotary evaporator at reduced pressure, and finally drying them under vacuum. Before use, the polyherbal formulation was kept at 4°C after being made by mixing several plant extracts in a 1:1:1 ratio.

2.2. Chemicals and Reagents

We got streptozotocin (STZ) from Sigma-Aldrich in St. Louis, MO, USA. Sanofi India Ltd. of Mumbai, India supplied the glibenclamide, while Merck Life Science Pvt. Ltd. of Mumbai, India supplied all the other analytical-grade chemicals and reagents [16].

2.3. Experimental Animals

The rats were collected at the Central Animal House; they were adult male Wistar albinos weighing 180-220 g. The animals were kept in a typical laboratory setting with a temperature of 22 ± 2°C and a 12-hour light/dark cycle. They were given free access to water and a regular pellet meal. The research followed all regulations set out by the Indian government's Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) [17], and the IAEC gave its stamp of approval to the experiment's protocol.

2.4. Induction of Diabetes

A single intraperitoneal injection of 55 mg/kg body weight of streptozotocin (STZ) caused type 1-like diabetes in rats that had fasted overnight. Solubilizing STZ in cold citrate buffer (0.1 M, pH 4.5) just

before delivery ensures its stability and efficacy. The injection was given using a 1 mL insulin syringe in an aseptic environment [18]. For the next 24 hours after STZ was given, the animals were given water with a 5% glucose solution to avoid hypoglycemia caused by the fast breakdown of pancreatic β-cells. A glucometer (Accu-Chek Active, Roche Diagnostics, Mannheim, Germany) was used to monitor fasting blood glucose (FBG) levels 72 hours after an injection of STZ. Following an overnight fast, blood samples were obtained from the tail vein of every rat. Diabetic rats were included in the trial for further experimentation if their FBG levels were 250 mg/dL or higher. The successful development of diabetes was confirmed by the characteristic hyperglycemia symptoms, including polyuria, polydipsia, and weight loss, which were observed in these diabetic rats [19].

2.5. Experimental Design

As shown below, the rats were randomly assigned to one of five groups, with a total of twenty-six animals per group. Oral administration of 0.5% carboxymethylcellulose (CMC) was the sole intervention in Group I (Normal Control). Participants in Group II (Diabetic Control) were given 0.5% CMC orally after being given streptozotocin (STZ) to induce diabetes. Diabetic rats given 5 mg/kg of glibenclamide orally daily made up Group III, which was called the Standard Treatment. Diabetes rats with an oral dose of 200 mg/kg/day of the polyherbal formulation made up Group IV (PHF Low Dose). Diabetic rats administered an oral dose of 400 mg/kg/day of the polyherbal formulation made up Group V, also known as PHF High Dose. For 28 days in a row, the treatment was maintained. Researchers tracked participants' weight and fasting blood glucose levels every week for the course of the trial [20].

2.6. Biochemical Estimations

All rats were put to sleep with a light ether anesthetic after fasting overnight at the end of the 28-day treatment period. A capillary tube was used to draw blood samples from every animal through the retro-orbital plexus. The serum, which was utilized for biochemical tests, was separated from the collected blood by centrifuging it at 3000 rpm for 15 minutes [21]. A digital glucometer (Accu-Chek Active, Roche Diagnostics) was used to assess fasting blood glucose (FBG) levels. We followed the manufacturer's instructions to estimate serum insulin levels using a commercially available rat-specific ELISA kit. We used conventional diagnostic kits from Erba or Agappe Diagnostics to examine the lipid profile, which includes total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) [8]. After being homogenized, the removed pancreatic tissues were washed with ice-cold saline to evaluate oxidative stress indicators. Utilizing conventional spectrophotometric techniques, the tissue homogenates were examined for malondialdehyde (MDA) levels, superoxide dismutase (SOD) activity, and catalase (CAT) activity [22].

2.7. Histopathological Studies

Humane cervical dislocation was used to sacrifice the animals after blood collection. To maintain tissue architecture, the pancreas was meticulously removed, cleaned with normal saline, and then fixed in 10% neutral buffered formalin for one to two days. Afterwards, the tissues that had been fixed underwent a sequence of procedures to remove excess water and debris. They were subsequently immersed in paraffin wax and cut into 5 µm sections using a microtome. In order to make the histological inspection easier, the tissue sections were placed on glass slides and stained with hematoxylin and eosin (H&E). The structural integrity of the pancreatic tissue was evaluated by examining the stained sections under a light microscope. The architecture of the islets of Langerhans and the preservation of β-cells were given special focus [23].

2.8. Statistical Analysis

The means and standard deviations (SD) of all quantitative data were used for expression. To analyze the differences across the groups, we used one-way analysis of variance (ANOVA). For multiple comparisons, we used Tukey's post hoc test. Version 9.5.1 of GraphPad Prism, developed and published by GraphPad Software, Inc. of San Diego, CA, USA, was used to conduct the analysis. For statistical purposes, a p-value below 0.05 was deemed significant [24].

3. RESULTS:

3.1. Effect of Polyherbal Formulation on Fasting Blood Glucose Levels

Those with diabetes had far higher fasting blood glucose (FBG) levels than those without the disease. Over the course of 28 days, rats treated with the polyherbal formulation (PHF) at doses ranging from 200 mg/kg to 400 mg/kg showed a substantial and dose-dependent decrease in FBG levels. The effectiveness of glibenclamide was found to be similar to that of the high-dose PHF group.

Table 1: Fasting Blood Glucose Levels (mg/dL) at Different Time Points

Group	Day 0	Day 7	Day 14	Day 21	Day 28
Normal Control	89.2 ± 4.3	88.5 ± 5.1	90.4 ± 4.7	87.9 ± 3.8	89.1 ± 4.2
Diabetic Control	88.7 ± 3.9	318.4 ± 12.7	332.2 ± 14.3	341.6 ± 15.9	350.7 ± 18.1
Glibenclamide (5 mg/kg)	90.1 ± 4.1	278.9 ± 11.6	216.2 ± 9.8	145.4 ± 7.5	108.3 ± 6.9
PHF 200 mg/kg	89.6 ± 4.0	295.1 ± 13.2	252.6 ± 10.9	189.8 ± 8.7	145.2 ± 6.3
PHF 400 mg/kg	90.3 ± 4.2	288.3 ± 12.4	215.7 ± 11.1	148.5 ± 7.9	110.4 ± 6.6

Values expressed as mean ± SD, n = 6. Statistical significance: $p < 0.05$ vs diabetic control group.

3.2. Effect on Body Weight

One of the most important physiological markers for assessing metabolic abnormalities caused by diabetes is body weight. Compared to the normal control group, the diabetic control rats lost weight significantly and steadily over the course of the 28-day investigation. It is well-documented that insulin shortage causes this weight loss by increasing proteolysis and lipolysis, which in turn breaks down muscle and fat cells to meet the body's energy demands when glucose is not used effectively. Alternatively, diabetic rats showed a considerable improvement in their weight loss after receiving treatment with glibenclamide and the polyherbal formulation (PHF) at doses of 200 and 400 mg/kg, respectively. Body weight was most dramatically improved in the PHF group (400 mg/kg) compared to the other treatment groups, and it was very close to the values seen in the glibenclamide group. This maintenance or improvement in body weight indicates better glucose regulation and less catabolic processes, which could be because insulin levels are restored and glucose uptake is improved. The herbs that make up PHF work together to stabilize weight because they influence glucose metabolism, make insulin more sensitive, and boost β-cell function.

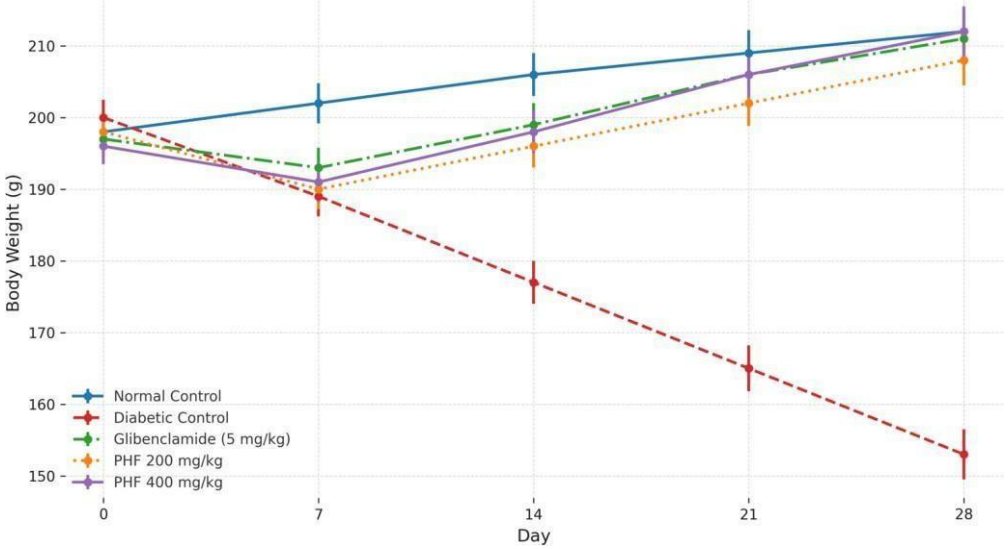

Figure 1: Changes in Body Weight Over 28 Days

3.3. Effect on Serum Insulin Levels

Reflecting the β-cell damage produced by streptozotocin (STZ), the diabetes control group exhibited significantly lower serum insulin levels in comparison to the normal control group. STZ causes β-cell necrosis by targeting pancreatic β-cells specifically through absorption through the GLUT2 transporter, which in turn causes DNA alkylation, oxidative stress, and finally β-cell death. This leads to a significant decrease in the body's natural production of insulin, which in turn causes metabolic abnormalities and prolonged high blood sugar. Alternatively, blood insulin levels were significantly and dose-dependently restored in rats given with the polyherbal formulation (PHF). With insulin levels almost matching those in the group treated with glibenclamide, the higher dosage of PHF (400 mg/kg) proved to be the most

beneficial. The improvement in insulin production and secretion could be due to the polyherbal formulation either promoting β-cell regeneration or enhancing residual β-cell activity. It is possible that the insulin-enhancing effects of PHF are due to the beneficial interactions between the herbs that make it up. The regeneration effects on β-cells and stimulation of insulin release have been linked to Gymnema sylvestre. Trigonella foenum-graecum improves insulin sensitivity and glucose-dependent insulin production, while Momordica charantia mimics insulin. The observed improvement in serum insulin levels was probably due to the combined activity of these plants. These results indicate that the polyherbal combination has a dual action: reducing glucose levels and perhaps helping diabetics maintain or restore pancreatic β-cell mass.

Table 2: Serum Insulin Levels (μIU/mL) at Day 28

Group	Insulin Level (μIU/mL)
Normal Control	15.8 ± 1.2
Diabetic Control	6.4 ± 0.9
Glibenclamide	13.7 ± 1.0
PHF 200 mg/kg	10.9 ± 1.1
PHF 400 mg/kg	13.2 ± 0.8

3.4. Effect on Lipid Profile

High levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) and decreased levels of high-density lipoprotein (HDL) are common in people with diabetes mellitus, a condition known as dyslipidemia. Cardiovascular problems are more likely to develop in diabetics when these abnormalities are present. Significant changes in lipid indices, indicative of normal diabetic dyslipidemia, were observed in the present study's diabetic control rats. Lipid profiles were significantly improved after treatment with the polyherbal formulation (PHF). There was a rise in HDL levels and a decrease in TC, TG, LDL, and VLDL in both groups who were treated with PHF. The PHF group that received 400 mg/kg was more severely affected; their lipid values were similar to those of the control and glibenclamide groups. The hypolipidemic effect that has been noted could be because the herbs included in this formulation contain phytoconstituents, which include dietary fibers, flavonoids, and saponins. By increasing bile acid excretion, decreasing lipid absorption, and increasing lipoprotein clearance from circulation, these chemicals are recognized to influence lipid metabolism.

Table 3: Serum Lipid Profile at Day 28 (mg/dL)

Parameter	Normal Control	Diabetic Control	Glibenclamide	PHF 200 mg/kg	PHF 400 mg/kg
TC	92.3 ± 3.8	163.4 ± 5.7	104.1 ± 4.2	115.6 ± 4.7	101.3 ± 3.6
TG	78.5 ± 3.2	148.7 ± 5.2	89.2 ± 3.9	95.1 ± 4.1	85.6 ± 3.2
HDL	45.7 ± 2.1	26.3 ± 1.7	40.4 ± 2.0	37.6 ± 1.9	41.2 ± 2.2
LDL	28.6 ± 1.9	104.3 ± 4.9	46.1 ± 2.4	58.3 ± 2.8	43.2 ± 2.1
VLDL	15.7 ± 1.1	29.7 ± 1.8	17.8 ± 1.0	19.0 ± 1.2	17.1 ± 0.9

3.5. Effect on Oxidative Stress Markers

In the development and advancement of diabetes mellitus and its consequences, oxidative stress is an essential factor. Pancreatic β-cells are extremely susceptible to damage by streptozotocin (STZ) because they do not have strong antioxidant defense systems. This leads to the development of diabetes. High levels of malondialdehyde (MDA), an important indicator of lipid peroxidation, were found in the pancreatic tissues of diabetic control rats in this investigation, suggesting increased oxidative damage. Concurrently, there was a marked decline in levels of catalase (CAT) and superoxide dismutase (SOD), two essential antioxidant enzymes, suggesting compromised antioxidant defenses. Reduced malondialdehyde (MDA) levels and restored SOD and CAT activity demonstrated that treatment with the polyherbal formulation (PHF) significantly reduced oxidative stress. Dosage determined the magnitude of these effects; the 400 mg/kg PHF group outperformed the 200 mg/kg group and was as effective as the gold standard medicine glibenclamide. Gymnema sylvestre, Momordica charantia, and Trigonella foenum-graecum are the plants that make up PHF, and their high flavonoid, polyphenol, and alkaloid content is what gives it its antioxidant action. The oxidative damage in diabetic tissues can be

reduced by these phytochemicals because of their ability to scavenge free radicals, chelate metal ions, and upregulate endogenous antioxidant enzymes.

Table 4: Oxidative Stress Parameters in Pancreas

Parameter	Normal Control	Diabetic Control	Glibenclamide	PHF 200 mg/kg	PHF 400 mg/kg
MDA (nmol/mg protein)	1.2 ± 0.1	3.9 ± 0.2	1.5 ± 0.1	1.8 ± 0.2	1.4 ± 0.1
SOD (U/mg protein)	8.3 ± 0.5	4.1 ± 0.3	7.6 ± 0.4	6.5 ± 0.4	7.4 ± 0.3
CAT (U/mg protein)	6.9 ± 0.4	3.0 ± 0.2	6.2 ± 0.3	5.4 ± 0.3	6.1 ± 0.4

3.6. Histopathological Findings

The study's biochemical and functional findings were corroborated by the morphological data supplied by the histopathological examination of pancreatic tissues. The histological structure of the pancreas seemed unaltered in the control group that had normal exocrine tissue and clearly characterized, densely packed islets of Langerhans. On the other hand, the diabetic control group's pancreatic sections showed a plethora of pathological alterations, such as cytoplasmic vacuolation, decreased cellular density, disrupted endocrine architecture, and significant islet of Langerhans degeneration and shrinking. The results validate the cellular level onset of diabetes and are in line with STZ-induced selective β-cell cytotoxicity. Islet size and cellular organization were moderately restored after glibenclamide treatment, suggesting that the drug partially retained islet structure and cellular integrity. Likewise, histological improvement was dose-dependent in rats treated with the polyherbal formulation (PHF) at 200 mg/kg and 400 mg/kg, respectively. The groups that received modest doses of PHF demonstrated some regeneration of islet cells and less vacuolization, but the groups that received high doses of PHF (400 mg/kg) showed significant preservation of islet morphology, similar to the normal control group. According to these findings, the polyherbal mixture might have cytoprotective or regenerative abilities that encourage the survival or neogenesis of β-cells. The treatment groups' lower fasting blood glucose and higher serum insulin levels are supported by the improvement in islet architecture.

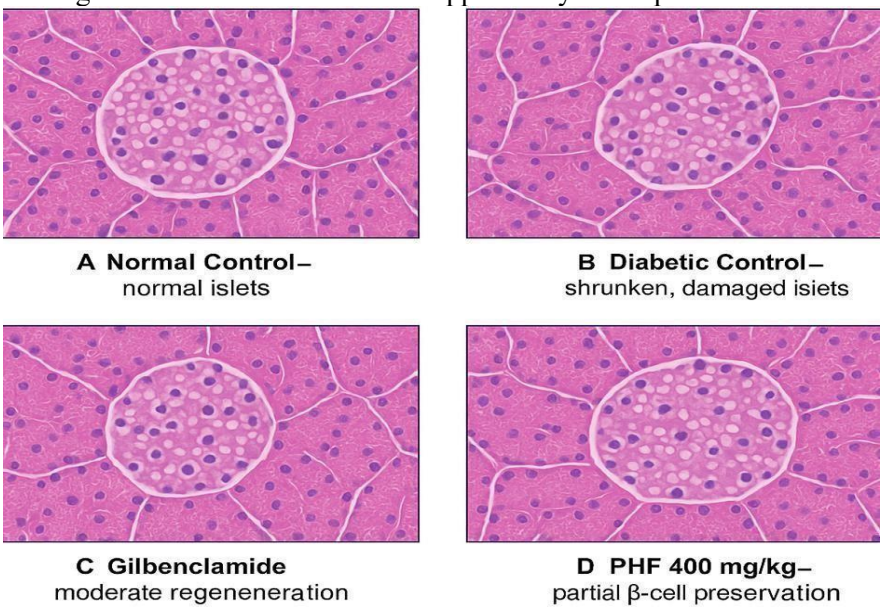

Figure 2: Histopathological Images of Pancreas (H&E stain, 40× magnification); A: Normal Control – normal islets; B: Diabetic Control – shrunken, damaged islets; C: Glibenclamide – moderate regeneration; D: PHF 200 mg/kg – partial β-cell preservation and E: PHF 400 mg/kg – improved architecture close to normal

DISCUSSION:

In rats that were induced with diabetes by streptozotocin (STZ), the antidiabetic potential of a polyherbal formulation (PHF) containing Gymnema sylvestre, Momordica charantia, and Trigonella foenum-

graecum was examined in this work. These results show that PHF dose-dependently reduced hyperglycemia, improved lipid metabolism, increased antioxidant defense, and conserved pancreatic architecture. It has been observed in mouse models of type 1 diabetes that STZ causes insulin insufficiency and hyperglycemia by specifically destroying pancreatic β-cells [25]. Consistent with previous findings, untreated diabetic rats shown histological damage to the pancreatic islets, decreased body weight, and markedly elevated fasting blood glucose (FBG) levels after receiving STZ injections. A typical sulfonylurea antidiabetic drug, glibenclamide, is effective at lowering FBG levels; the 400 mg/kg dose of PHF was just as effective.

It is the synergistic action of the herbs that gives PHF its hypoglycemic effect. It has been shown that Gymnema sylvestre can improve insulin secretion and encourage the regeneration of β-cells [26]. Momordica charantia aids peripheral tissue glucose absorption and has insulin-like characteristics [27]. The high fiber and saponin content of Trigonella foenum-graecum causes it to control glucose metabolism and postpone the absorption of glucose in the intestines [28]. Treatment groups' restored insulin levels and better glycemic control were likely due, in part, to the synergistic effects of these phytochemicals. An elevated total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) level and a decreased high-density lipoprotein (HDL) level describe dyslipidemia, a typical diabetic consequence. Treatment with PHF substantially restored the normal lipid profile in this research of diabetic rats. Previous research has shown that the individual herbs utilized in the formulation have lipid-lowering capabilities, which is supported by this hypolipidemic effect [29].

The pathophysiology of diabetes problems is influenced by oxidative stress, which is caused by an excess of reactive oxygen species (ROS) and impaired antioxidant defenses [30-35]. Control rats with diabetes showed signs of increased lipid peroxidation and oxidative stress, as indicated by elevated malondialdehyde (MDA) levels and decreased superoxide dismutase (SOD) and catalase (CAT) activities. Treatment with PHF considerably undiminished these alterations, suggesting that it possesses antioxidant properties. The selected plants contain phytochemicals with a well-documented ability to scavenge reactive oxygen species (ROS) [36-39]. These phytochemicals include flavonoids, tannins, and alkaloids. The histopathological study provided additional evidence that PHF protected pancreatic tissue. Treatment with PHF, especially at the high dose, retained the shape and mass of the islets and β-cells, suggesting that it may reduce the pancreatic damage caused by STZ, even though the diabetic control rats had significant islet degeneration and vacuolization. Taken together, the data point to the polyherbal formulation's potential for enhancing glycemic control, resolving dyslipidemia, decreasing oxidative stress, and maintaining pancreatic architecture as valuable tools in the therapy of diabetes. The combination therapeutic effects provided by the formulation's bioactive components seem to outweigh those of individual plant extracts [40-41].

CONCLUSION:

The results of this study show that rats induced with diabetes by streptozotocin can be effectively treated with a polyherbal formulation that includes Gymnema sylvestre, Momordica charantia, and Trigonella foenum-graecum. Fasting blood glucose levels were lowered, insulin concentration in the serum was improved, dyslipidemia was rectified, and antioxidant defense mechanisms were boosted by the formulation. Histopathological examination further verified that the formulation had a protective impact on the architecture of pancreatic β-cells. The combined extracts attack many pathophysiological elements of diabetes, which likely explains the reported therapeutic potential. The phytoconstituents in them work synergistically. These findings provide credence to the long-standing practice of using these plants as medicine to control diabetes, and they raise the possibility that the polyherbal formulation might be an effective supplementary or replacement treatment for type 2 diabetes. In order to support and expand upon these findings, additional research on bioactive molecule isolation, pharmacokinetic characterization, and clinical validation is necessary.

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Nil
Conflict of interest:

None

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