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THERAPEUTIC POTENTIAL OF A PLANT-BASED NUTRACEUTICAL FORMULATION IN SUPPORTING B-CELL FUNCTION AND REGENERATIVE CAPACITY FOR DIABETES MANAGEMENT

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ABSTARCT

Introduction: Diabetes mellitus (DM) is characterized by progressive pancreatic β-cell deterioration and chronic inflammation, affecting over 536.6 million adults globally. While conventional treatments exist, they often present limitations including inadequate β-cell protection and potential toxicities. This study evaluated the therapeutic potential of a Instanema in supporting β-cell function and regenerative capacity and maintaining normal blood glucose level. **Materials and Methods:** The study utilized STZ-induced diabetic Wistar rats (n=10/group) divided into four groups: normal control, diabetic control, glibenclamide (10 mg/kg), and Instanema (250 mg/kg). The 28-day treatment protocol assessed fasting blood glucose, insulin levels, inflammatory markers (IFN-γ, IL-1β, IL-6), and pancreatic histopathology. **Results:** Instanema treatment significantly reduced fasting blood glucose from 384.30 mg/dL to 160.71 mg/dL and improved insulin levels (1.80 ng/mL vs. 0.42 ng/mL in diabetic controls). The formulation demonstrated marked anti-inflammatory effects, reducing elevated levels of IFN-γ, IL-1β, and IL-6 towards normal ranges. Histopathological analysis revealed notable preservation of pancreatic islet architecture and reduced inflammatory damage in treated specimens, suggesting potential regenerative capabilities. **Conclusion:** Instanema demonstrates promising therapeutic potential in diabetes management through multiple mechanisms, including glycaemic control, anti-inflammatory effects, and β-cell protection. The formulation's ability to promote β-cell regeneration while managing inflammation and hyperglycaemia warrants further clinical investigation.

KEYWORDS: Diabetes mellitus, Insulin, Blood Glucose, Fenugreek, Jamunbeej, Vijaysar.

INTRODUCTION

A class of metabolic illnesses known as diabetes mellitus is defined by persistently high blood sugar levels brought on by deficiencies in either insulin secretion, insulin action, or both.[1] This condition is characterized by progressive deterioration of pancreatic β-cells, leading to decreased insulin production and chronic inflammation, which further contributes to retinopathy, nephropathy, neuropathy, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease.[2]

According to estimates, the prevalence of diabetes among adults aged 20 to 79 worldwide in 2021 was 10.5% (536.6 million), and it was projected to reach 12.2% (783.2 million) by 2045. The predicted cost of treating diabetes worldwide was 966 billion USD in 2021, and by 2045, it is expected to reach 1,054 billion USD.[3] With an expected 74.2 million cases in 2021, India has the second-highest global incidence of type 2 diabetes. Estimates indicate that by 2045, the number of cases among individuals aged 20 to 79 years will have significantly increased to 124.9 million. Over 90% of cases of diabetes globally are caused by this form of diabetes, making it the most common.[4]

Diabetes mellitus manifests itself in three main forms: The body's incapacity to produce adequate insulin is the cause of type 1 diabetes. "Juvenile diabetes" or "insulin-dependent diabetes mellitus" (IDDM).[5] T2DM progression is marked by chronic inflammation and oxidative stress that contribute to β-cell dysfunction, making it a "silent disease" that causes significant organ damage as it advances gradually without early symptoms. Its increasing incidence is linked to food habits, lifestyle modifications, and urbanization.[6] Important risk factors include smoking, dyslipidaemia, hypertension, family history, obesity, physical inactivity, and quantity and quality of sleep, all of which can impact β-cell function and inflammatory status.[7]

Effective lifestyle modifications and the use of prescription medications are combined in the management of type 2 diabetes.[8] Conventional treatments include PPARγ agonists for improving insulin sensitivity, biguanides for reducing hepatic glucose production, α-glucosidase inhibitors for decreasing glucose absorption, and sulfonylureas for enhancing insulin secretion.[9] However, these medications often present limitations including weight gain, hypoglycaemia, inadequate β-cell protection, and potential organ toxicities. Despite advances in anti-diabetic medications, preserving β-cell function and preventing long-term complications remain significant challenges.[9,10]

According to the World Health Organization (WHO), adjuvant therapy based on vitamins and medicinal herbs offers promising alternatives for managing type 2 diabetes, particularly in protecting and regenerating β-cells. Traditional medicine systems have utilized these natural compounds for centuries, with scientific evidence now supporting their roles in glucose regulation, β-cell protection, and anti-inflammatory effects. While numerous conventional medications exist, their side effects and high costs have driven interest in herbal alternatives. The traditional medical system of Ayurveda has long employed herbs like Gymnema sylvestre and Syzygium cumini for their anti-diabetic properties. These plants contain diverse phytochemicals including alkaloids, flavonoids, phenols, and terpenoids that demonstrate multiple beneficial effects on glucose metabolism and β-cell function.

Nutritional formulations have emerged as promising treatment for both monotherapy and adjuvant therapy in experimental diabetes management, showing potential in reducing blood glucose levels, improving insulin sensitivity, and mitigating diabetic complications in animal models. To evaluate the safety and effectiveness of a novel nutritional

formulation, we conducted a study using STZ-induced diabetic Wistar rats as an established experimental model for investigating anti-diabetic interventions. Investigational Product contains Gudmur, Fenugreek, Jamunbeej, Vijaysar etc.

METHODOLOGY

Material and Method

The rats were housed in animal house facility with adequate environmental conditions of temperature 20 + 3°C and relative humidity 30-70 %. The 12-hour light and 12-hour dark cycle was maintained manually throughout study. Each day floor of the experimental room was cleaned and mopped twice with disinfectant solution. Glibenclamide (GLB) is evaluated for sugar and insulin only as it has no role in other parameters.[11] Rats were acclimatized for a period of seven days and observed for general health before the commencement of the experiment.

10 animals in each group: G1 Normal control (0.25% Na-CMC)- 10 ml/kg, p.o.; G2 Disease control (0.25% Na-CMC)- 10 ml/kg, p.o.; G3 Glibenclamide (GLB)-10 mg/kg, p.o.; G4 Instanema tab (test compound)- 250 Mg/kg, p.o.

Induction of Diabetes

The diabetes was induced in the rats according to the modified protocol of Furman (2015). Single dose of Streptozotocin (STZ) (70mpk; i.p.) was used to induce diabetes in the Wistar rats. Animals was fast for 10- 12 h before the Streptozotocin (STZ) injection. Freshly prepared, filtered (0.2-micron filter), ice chilled 100mM sodium citrate buffer (pH 4.5) was used as solvent. Different aliquots of STZ was prepared and kept in ice bath. The required quantity of ice chilled sodium citrate buffer was added to each STZ aliquot, vortexed for 0.5-1 min and injected intraperitoneal to each animal. The dose volume of 10mL/kg was kept constant for all the animals. Diabetes was recognized by symptoms like polydipsia and polyuria along with analysis of fasting blood glucose levels after 48 h of STZ administration. However, stable hyperglycaemia (fasting blood glucose >200mg/dL) was observed after 4 days of STZ injection.[12,13]

Anti-Diabetic and Beta Cell Regeneration Effect

The treatment of vehicle or test or GLB was continued for the next 28 days to assess sub-acute anti-diabetic potential. Fasting blood glucose levels was monitored weekly once throughout the experiment. Altogether the rats were kept at daily observation for the clinical signs and/or mortality if any. Bodyweight, Feed-water consumption was calculated on every day till end of the experiment. Interleukin-6, Interleukin-1β and Interferon-γ was also analysis from blood serum after 28 days of treatment in rats. At the end of 28 days, entirely the animals were anaesthetized, and blood was withdrawn. Serum was separated and processed for insulin analysis. Further, animal was humanely sacrifice and organs such as liver, kidney(s) and pancreas were isolated for histopathology analysis.

Observations

Individual body weights of animal were recorded prior to dosing on every day and continue till end of experiment i.e., Day 28. Feed consumption of animal was calculated on everyday till end of experiment. Water consumption of animal was calculated on everyday till end of experiment. Fasting Blood glucose level was monitored weekly once throughout the experiment. All the animals were observed daily for the clinical signs and/or mortality, if any.

Histopathological Observations

Liver, kidney and pancreas were divided out, excised and rinsed in cold saline solution. A portion of each tissue were fixed in 10% neutral buffered formalin. After fixation, tissues were processed to dehydrated in ascending grades of alcohol, clearing in xylene and fixed in paraffin; solid sections of 3-5µm thickness were analysis by using a microtome. The sections were stained with haematoxylin-eosin and histological observations were made using microscope. Blinded evaluations of coded slides were performed by veterinary pathologist to avoid bias in experiment. Images of the histological slides were took using Olympus Magnus Microscope camera and managed by Olympus Mag Vision Image analysis software. For Pancreas, Regeneration (cytoplasmic vacuolation of exocrine and endocrine pancreas-- Islet of Langerhans) Necrosis of exocrine, endocrine pancreas and surrounding adipose tissues, Atrophy, Hyperplasia of exocrine and endocrine pancreas, any other lesion(s) was observed.

Statistical Analysis

The facts and numbers were stated as Mean±SD for each group. The Statistical analysis was made by using GraphPad Prism version 7.0 software. The test called one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison t-test was considered to calculated statistical difference. Values of $p<0.05$ was measured statistically significant.

RESULTS

Effect of Instanema on Fasting Blood Sugar

In the normal control group, the mean fasting blood sugar levels remained relatively stable, increasing from 118.23 mg/dL at baseline to 129.36 mg/dL after 28 days. The diabetic control group displayed significantly elevated fasting blood sugar levels, starting at 349.12 mg/dL and decreasing to 308.3 mg/dL over the 28-day period. Treatment with the reference drug glibenclamide (GLB) led to a marked reduction in fasting blood sugar, from an initial 399.73 mg/dL to 145.85 mg/dL after 28 days. The test compound, Instanema, also demonstrated a notable glucose-lowering effect. Fasting blood sugar levels decreased from 384.30 mg/dL at baseline to 160.71 mg/dL by the end of the 28-day treatment period (Table 1).

These results indicate that the test compound, Instanema, was able to significantly reduce fasting blood sugar levels in the diabetic animal model, with an effect comparable to that of the reference drug glibenclamide.

Table 1: Assessment of fasting blood sugar (mg/dL).

Groups	Fasting Blood Sugar (mg/dL)	
	Initial (Mean±SD)	After 28 days (Mean±SD)
Normal control	118.23 ±6.45	129.36 ±10.74
Diabetics control	349.12 ±44.37	308.3 ±88.45
Glibenclamide (GLB)	399.73 ±38.87	145.85 ±18.97
Instanema (test) 250 mg	384.30 ±44.84	160.71 ±22.69

Effect of Instanema on Fasting insulin level

The normal control group had a mean fasting insulin level of 0.62 ng/mL. The diabetic control group showed a lower fasting insulin level of 0.42 ng/mL. The group treated with the reference drug glibenclamide (GLB) had a significantly higher fasting insulin level of 3.42 ng/mL compared to the diabetic controls. The group treated with the test compound Instanema at 250 mg had a fasting insulin level of 1.80 ng/mL, which was higher than the diabetic controls but lower than the GLB group (Table 2).

Table 2: Assessment of fasting insulin level (ng/dL).

Groups	Fasting insulin level (ng/mL) After 28 days (Mean±SD)
Normal control	0.62 ±0.06
Diabetics control	0.42 ±0.02
Glibenclamide (GLB)	3.42 ±0.84
Instanema (test) 250 mg	1.80 ±0.44

Effect of Instanema on Level of inflammatory mediators (IFN-y, IL1β, IL 6)

The data shows that the diabetic control group had significantly elevated levels of all three inflammatory markers compared to the normal control group. Treatment with the test compound Instanema at 250 mg reduced the levels of IFN-γ, IL-1β, and IL-6 towards normal levels, suggesting an anti-inflammatory effect (Table 3).

Table 3: Assessment of fasting insulin level (ng/dL).

Groups	Interferon-gamma (IFN-y) pg/ml	Interleukin 1Beta (IL1β) pg/ml	Interlukin-6 (IL 6) pg/ml
Normal control	52.50±3.56	157.42 ±10.84	1.78 ±0.04
Diabetics control	90.58 ±11.20	390.41 ±22.14	12.72 ±1.36
Instanema (test) 250 mg	61.85±4.88	165.96 ±14.77	7.14 ±1.43

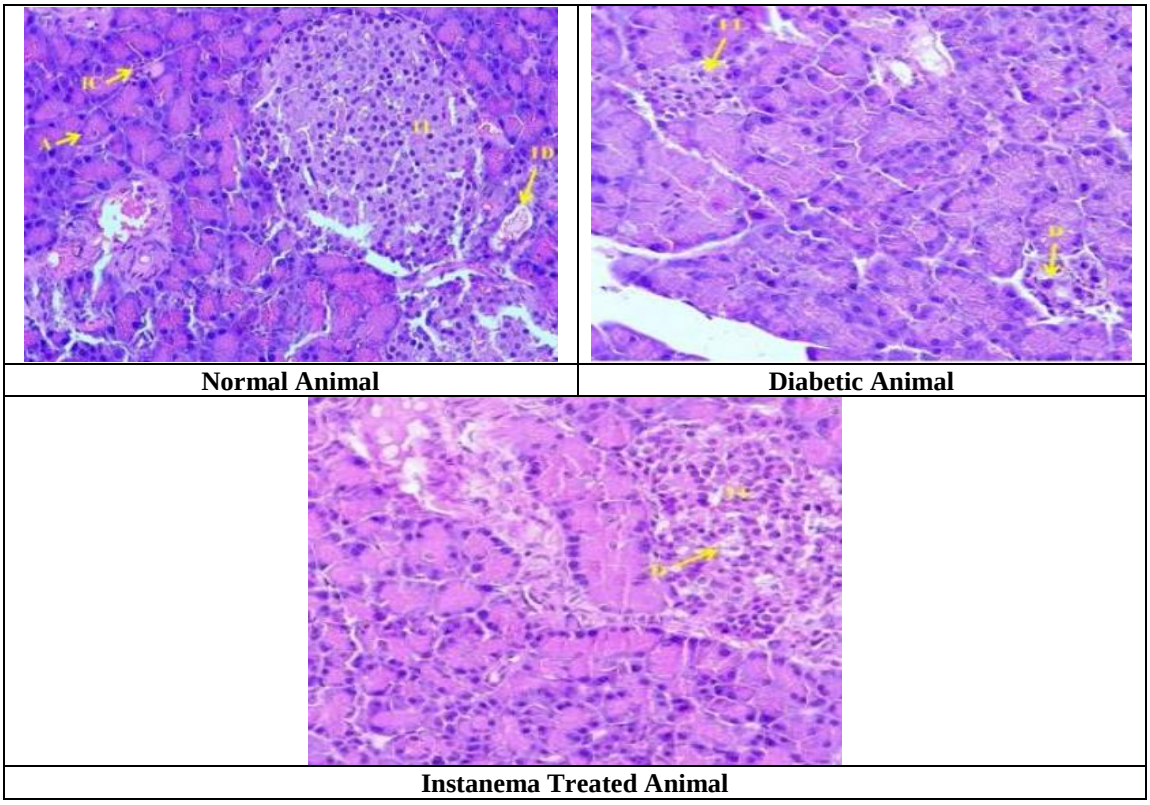
Histopathological Analysis

Microscopic evaluation of pancreatic tissue from diabetic rats revealed substantial structural alterations characterized by pronounced islet deterioration, widespread inflammatory infiltrates, and extensive beta cell damage. The pancreatic architecture showed marked disruption, evidenced by severe vacuolar degeneration within islets and compromised cellular organization. Notably, both alpha and beta cell populations displayed abnormal distribution patterns, with distinctive beta cell aggregation and prominent nuclear deterioration indicating cellular death within islet structures.

Analysis of pancreatic sections aligned with established pathological patterns documented in diabetic models, particularly regarding the widespread reduction in islet density and pronounced cellular degeneration. Our microscopic observations confirmed significant islet depletion in diabetic animals when compared to normal controls, demonstrating consistent pathological progression.

Examination of Instanema-treated specimens revealed notable preservation of pancreatic morphology compared to untreated diabetic controls, with increased islet density and improved structural integrity. Detailed histological assessment demonstrated that while diabetic induction triggered substantial inflammatory reactions and degenerative changes in control animals, these pathological alterations appeared significantly moderated in treated specimens, suggesting protective effects of the intervention.

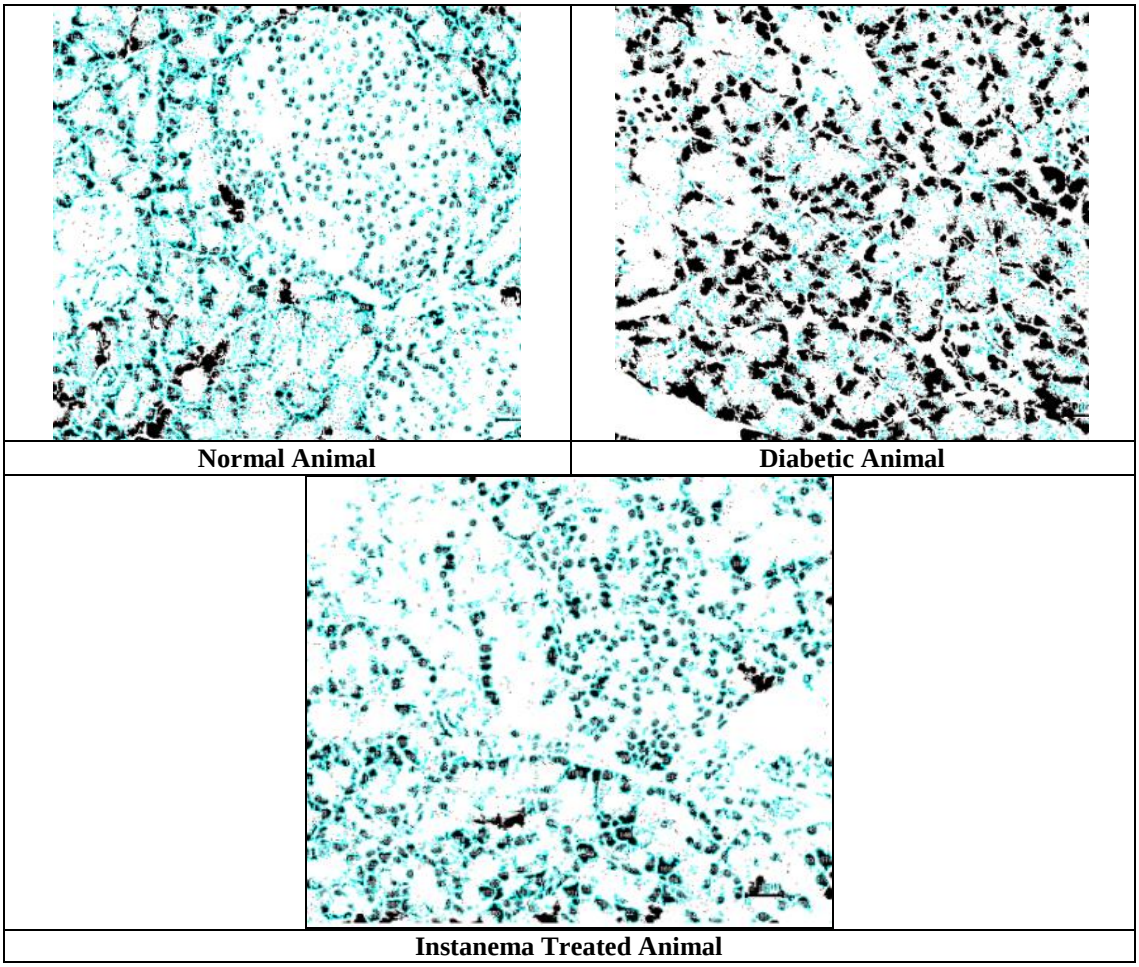
The therapeutic intervention demonstrated remarkable efficacy in preserving islet architecture and reducing inflammatory damage. This protective effect was evidenced by enhanced islet preservation and reduced degenerative changes in treated animals, suggesting potential regenerative capabilities of the compound on pancreatic tissue. The observed improvements indicate direct therapeutic action on islet cell populations, potentially supporting both protective and regenerative mechanisms in pancreatic tissue maintenance (Figure 1 & 2).



Normal Animal | Diabetic Animal

Instanema Treated Animal

Figure 1: Histopathology images of pancreas.



Normal Animal | Diabetic Animal

Instanema Treated Animal

Figure 2: Histopathology images of pancreas as per IMAGE-J software.

DISCUSSION

The present investigation demonstrates the remarkable therapeutic potential of a novel polyherbal formulation in managing diabetes mellitus through multiple mechanisms. Our findings reveal significant improvements in glycaemic control coupled with notable anti-inflammatory and β-cell protective effects, supported by recent scientific literature on individual components.

The marked reduction in fasting blood glucose levels (384.30 mg/dL to 160.71 mg/dL) over the 28-day treatment period approaches the efficacy of standard medications, suggesting potent anti-hyperglycaemic activity. This effect can be primarily attributed to *Gymnema sylvestre*, which recent studies have shown enhances insulin secretion through β-cell regeneration and improved membrane permeability.[14] Furthermore, gymnemic acids have demonstrated ability to suppress intestinal glucose absorption while enhancing peripheral glucose uptake.[15]

The significant improvement in fasting insulin levels (1.80 ng/mL vs. 0.42 ng/mL in diabetic controls) aligns with contemporary research on *Pterocarpus marsupium's* insulinotropic properties. Recent investigations have revealed that P. marsupium flavonoids enhance insulin secretion through K+-ATP channel-dependent pathways in pancreatic β-cells.[16] Additionally, *Trigonella foenum-graecum* compounds have shown enhanced insulin sensitivity through AMPK and PPARγ pathway activation.[17]

A notable finding was the formulation's pronounced anti-inflammatory effect, evidenced by significant reductions in inflammatory markers. This action can be attributed to *Curcuma longa* and *Withania somnifera* components. Current research demonstrates that curcumin from C. longa effectively inhibits NF-κB signaling and reduces pro-inflammatory cytokine production under diabetic conditions.[18] Similarly, withanolides from *W. somnifera* have shown potent anti-inflammatory properties through NLRP3 inflammasome modulation.[19]

The histopathological findings provide compelling evidence of β-cell protective and regenerative capabilities. The observed preservation of islet architecture correlates with recent studies on *Syzygium cumini's* protective effects, particularly through Nrf2/HO-1 pathway activation.[20] The inclusion of Vitamin D3 may enhance this protection, as recent meta-analyses have shown its role in improving β-cell function and reducing inflammation in type 2 diabetes.[21]

The incorporation of Trikatu may enhance the bioavailability of other active compounds, as recent pharmacokinetic studies have demonstrated piperine's ability to enhance phytochemical absorption through P-glycoprotein inhibition.[22] This multi-targeted approach is particularly relevant given our current understanding of diabetes pathogenesis, addressing hyperglycemia, inflammation, and β-cell dysfunction simultaneously.

While our findings are promising, certain limitations should be acknowledged. The 28-day study duration, while sufficient for acute effects, may not fully reflect long-term outcomes. Additionally, while the STZ-induced diabetic model is well-established, it may not completely mirror human type 2 diabetes pathophysiology.

Future research should include Long-term safety and efficacy studies. Investigation of specific molecular mechanisms through genomic and proteomic analyses. Evaluation of potential interactions with conventional anti-diabetic medications. Assessment of effects on diabetes-related complications.

CONCLUSION

Instanema demonstrates promising potential as a comprehensive therapeutic approach for diabetes management, supported by both traditional wisdom and modern scientific evidence. The formulation's multi-modal mechanism of action, particularly its ability to promote β-cell regeneration while managing inflammation and hyperglycemia, warrants further investigation in clinical settings.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

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