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ORIGINAL ARTICLE

PIRIBEDIL, A DOPAMINE AGONIST MODULATE GLYCEMIC CONTROL IN DIABETIC RAT MODEL

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ABSTRACT

Background: Diabetes mellitus is a metabolic syndrome presenting with multiple pathologies. Numerous regimens of antidiabetic drugs are in practice. Bromocriptine, a dopamine agonist, is approved by the FDA for the management of hyperglycemia. Piribedil is a piperazine derivative. It has been authorized by the European Union for the treatment of depression, Parkinson's disease, and restless leg syndrome. The objectives of this study were to investigate piribedil for treatment of hyperglycemia in diabetic rat model.

Materials & Methods: This in-vivo experimental study was duly approved by the Faculty Research Board and was conducted in Pharmacology Department, Azra Naheed Medical College, Lahore. Diabetes was induced by alloxan (150 mg/kg) intraperitoneal injection in Sprague–Dawley rats. The animals were divided into normal control, diseased control, positive control (glimepiride 0.1 mg/kg), piribedil low dose (25 mg/kg), piribedil medium dose (50 mg/kg), and piribedil high dose (75 mg/kg). Treatment was given for 2 weeks. The body weights, and fasting blood glucose levels were monitored weekly. The animals were euthanized, and blood samples were drawn through cardiac puncture. Plasma insulin levels were determined using rat ELISA kits.

Results: Piribedil significantly reduced blood glucose levels as compared to the diabetic group in a dose dependent manner. Additionally, serum insulin levels were significantly increased in all treatment groups ($P<0.05$). All treatment groups experienced a post-treatment reduction in HOMA-IR with glimepiride (3.52 ± 0.41) and high-dose piribedil (3.60 ± 0.27), showing the most substantial improvement. High dose piribedil and glimepiride groups demonstrated QUICKI values (0.316 ± 0.003) & (0.317 ± 0.005) respectively, comparable to the normal control (0.326 ± 0.003), indicating improved insulin sensitivity.

Conclusion: Piribedil operates by reducing fasting blood glucose levels and enhancing insulin production. These findings imply that piribedil may play a role in combating hyperglycemia.

KEY WORDS: Alloxan; Diabetes mellitus; Dopamine agonists; Insulin; Piribedil.

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INTRODUCTION

Diabetes mellitus (DM) is a persistent metabolic condition, identified by increased blood glucose levels, stemming from either a lack of insulin production or the body's poor utilization of glucose.[1] Globally, the prevalence has risen to 14% in individuals aged 20–79 years.[2] Type II diabetes mellitus (T2DM) is a more prevalent form of the disease, characterized by insulin resistance and a progressive deterioration in beta-cell function. Although it generally manifests later in life, genetic predispositions can also influence its emergence.[3] Managing T2DM presents a significant therapeutic challenge, as insufficient glycemic control leads to accelerated disease progression. Although a variety of pharmacological agents are available, current statistics reveal a significant percentage of diabetic adults who do not achieve the recommended HbA1c targets.[4]

There is a complex relationship between DM and impaired cognitive functions, Alzheimer's disease, anxiety, and depression. It is suggested that central dopaminergic pathways are significantly dysregulated in DM, leading to deficits in social recognition memory.[5] Insulin and dopamine have a reciprocal regulation relationship in the brain and gut. Dopamine regulates glucose and insulin sensitivity.

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Conversely, insulin is mainly known for its role in the metabolism of glucose, but it also plays a role in brain neuromodulation, implying that the activity of one may influence the other.[6] Dopamine agonists are pharmaceutical agents that replicate the effects of dopamine by binding to and activating dopamine receptors in the brain. They are commonly used in the treatment of hyperprolactinemia.[7] Bromocriptine, a D2 agonist, originally used for Parkinson's disease (PD) has been approved for the treatment of DM because of its potential to lower weight and FBGLs, with improved insulin sensitivity.[8]

Piribedil (PB) is the first and unique non-ergoline derivative among the first generation of Data Research Associates and acts as a specific partial agonist at D2/D3 receptors, which enhances dopaminergic transmission without leading to an overactivation of D2/D3 receptors. PB has unique pharmacodynamic profiles with alpha-2 adrenoreceptor antagonistic effects. As a result, it boosts dopaminergic and adrenergic transmission, which may improve motor function, cognition, mood, and reduce daytime drowsiness.[9] It is often preferred due to a reduced risk of pulmonary, retroperitoneal, and valvular fibrosis.

Recent studies have explored the repurposing of pharmacological agents that target dopamine, serotonin, and other receptors as potential supplementary therapies to improve glycemic control and reduce the burden of the disease. The objective of this study were to determine the effect of piribedil on fasting blood glucose levels in alloxan-induced diabetic rats.

MATERIALS AND METHODS

It was an in-vivo experimental study which was carried out at Superior University Lahore in the Pharmacology Department, Azra Naheed Medical College, from November 2023 to April 2024. The research proposal was approved by the Faculty Research Board vide letter number FRB/BMS/02/014/2023. Animals were purchased from the University of Health Sciences, Lahore. Purposive sampling was used to select 36 adult healthy male Sprague Dawley rats, weighing 180-225 grams. Sample size was calculated through power analysis. The study adhered to the ethical principles for animal research outlined in the WMA Declaration of Helsinki (2008). [10]

Animals were kept under controlled room temperature (22-24°C), humidity (45-65%), and natural light/dark cycle for one week to acclimatize to the environment. They were fed on standard chow and water ad libitum. Alloxan monohydrate was dissolved in 0.9% ice-cold saline. The animals were fasted overnight, and 150mg/kg alloxan was given through the intraperitoneal route. The animals were closely observed and 5% dextrose water was given for 24 hours. Fasting blood glucose level (FBGL) was measured after 72 hours. The animals showing FBGL ≥ 200 mg/dl were labeled as diabetics. The 30 diabetic animals were randomly divided by balloting method into 5 groups.[11]

The normal control (NC) group received a single intraperitoneal injection of 0.9% saline and 1 mL of drinking water daily by gavage for two weeks. The diabetic control (DC) only received 1ml of distilled water by gavage. Positive control (PC) received glimepiride 0.1 mg/kg orally. Piribedil was administered orally, in low dose (LPB) 25mg/kg, medium dose (MPB) 50mg/kg, and high dose (HPB) 75mg/kg, by gavage for 14 days to the diabetic animals.

Body weights of the experimental animals were measured on day 0, 7, and 14th day of treatment. Blood samples were collected from the tail vein, and FBGL was determined pre-experiment, and at 7th day of treatment by glucometer (Freestyle Optimum Neo). On day 14, the overnight fasting animals were anesthetized, and blood samples were taken by cardiac puncture. Blood was collected in a vial and allowed to clot for ½ an hour. Blood samples were centrifuged at 4500 rpm at 4°C for 15 min (DM0412 centrifuge machine, DLAB Scientific, China). The separated serum was stored at -20°C. Insulin levels were measured by the rat ELISA kit. (INS BT-LAB kit Cat. No.E0707Ra.)

Homeostasis Model Assessment Insulin Resistance (HOMA-IR), β-cell function (HOMA-B), and Quantitative Insulin Sensitivity Check Index (QUICKI) were calculated using standard formulae. [12] Statistical Package for Social Sciences version 23 (SPSS 23) was used for statistical analysis. To evaluate the quantitative differences between the experimental groups, One-way ANOVA, and post-hoc Tukey's tests were applied to observe the significance at threshold of P-value ≤0.05.

RESULTS

The mean pre-experimental body weights range from 196.83 ± 11.77 to 201.83± 12.37 grams. The reduction in mean body weights of the diabetic control (DC) was 171± 14.02 and 158.5 ±19.99. The glimepiride control (GC) group presented an increase in body weight from 201.83 ± 12.37, 229.67± 12.6, and 254±15.67 correspondingly, on day 0, 7th, and 14th day (table-1). After seven days of treatment, groups LPB, MPB, and HPB recorded mean weights of 204.83 ± 21.40 g, 225.16 ± 6.79 g, and 231.83 ± 8.20 g, respectively. The remaining groups; LPB, MPB, and HPB demonstrated weight gain, with mean ± SD values of 254.00 ± 15.67 g, 219.33 ± 21.16 g, 257.50 ± 12.14 g, and 262.67 ± 12.32 g, respectively. The diabetic control DC, LPB presented significantly lower body weights compared to group NC, while groups GC and HPB had significantly higher body weights, indicating a weight-restorative effect of glimepiride and high-dose piribedil ($P<0.05$), table-1. Results are expressed as Mean ± S.D. Significant difference from group-1 (NC) is denoted as *, while

significant difference from group-2 (DC) is denoted as # (p-value <0.05).

Pre-experiment FBGL, mean ± SD was 106.83 + 7.62 mg/dl. The diabetic groups II-VI exhibited significant hyperglycemia 302.66 ± 40.71 to 316.83 ± 48.36 mg/dl (P<0.05). On the 7th day, NC and the DC groups did not show any significant change in FBGL levels. The GC group presented significantly lower FBGLs. Whereas, piribedil-treated groups (LPB, MPB, and HPB) demonstrated a dose-dependent improvement in FBGLs. On day 14, Group NC continued to exhibit normoglycemia, and the DC group had persistent hyperglycemia (311.16 + 45.91mg/dl). The glimepiride group (GC) presented a significant reduction in FBGLs as compared to day zero (P<0.05) Figure 1. The piribedil LPB, MPB, and HPB groups demonstrated a dose-dependent reduction of FBGLs. The HPB (75mg/kg) and GC (1 mg/kg) had maximum reduction in FBGLs as compared to day zero and day seven.

Results are expressed as Mean ± S.D. Significant difference from group-1 (NC) is denoted as *, while significant difference from group-2 (DC) is denoted as # (p-value <0.05). In group I (NC) the mean ±SD insulin level was 10.84 ± 0.15miU/L, while the diabetic group (DC) showed a significant reduction in insulin 6.52 ±0.22miU/L (P<0.05). The treatment with glimepiride significantly raised serum insulin levels to 11.66 ±0.35miU/L. There was a dose-dependent enhancement among piribedil groups (LPB, MPB, and HPB), which exhibited serum insulin levels 9.29 ± 0.40 mIU/L, 9.19 ± 0.38mIU/L, and 10.54 ±0.47 mIU/L, respectively. Figure 2. Results are expressed as Mean ± S.D. Significant difference from group-1 (NC) is denoted as *, while significant difference from group-2 (DC) is denoted as # (p-value <0.05).

The normal control group recorded the highest HOMA-B values, which showed normal β-cell activity, while the diabetes control group presented much lower values, indicating a decline in insulin secretion. Although the LPB and MPB had a moderate impact, the HPB (51.26 ± 9.36) and glimepiride-treated animals (73.37 ± 14.16) presented significantly boosted β-cell activity (P<0.05), Table 3.

HOMA-IR, a metric for insulin resistance, was greater in the DC than in the NC group. All groups experienced a reduction in HOMA-IR at the end of drug therapy. The HPB (3.60 ± 0.27) and GC (3.52 ± 0.41) groups presented substantial improvement at the end of drug therapy. Insulin sensitivity was assessed through QUICKI values, which were lowest in the diabetes control group and improved as treatment progressed. Both high-dose piribedil (0.316 ± 0.003) and glimepiride (0.317 ± 0.005) demonstrated results comparable to the normal control (0.326 ± 0.003), indicating improved insulin sensitivity (Table 3). Results are expressed as Mean ± S.D. Significant difference from group-1 (NC) is denoted as *, while significant difference from group-2 (DC) is denoted as # (p-value <0.05).

Table1. Pre and post-body weights of diabetic animals treated with piribedil

Groups (n=6)	**Body weight (grams) Mean ± S.D.**		
	Day-0	**Day-7**	**Day-14**
Group I (NC)	196.83 ±11.77	225.17 ±13.64	258.83 ±23.96
Group-II (DC)	197.5 ±15.43	171 ±14.02 *	158.5 ±19.99 *
Group-III (GC)	201.83 ±12.37	229.67 ±12.6 #	254 ±15.67 #
Group-IV (LPB)	198.33 ±9.91	204.83 ±21.40 *	219.33 ±21.16 *
Group-V (MPB)	201.33 ±11.03	225.16 ±6.79 #	257.50 ±12.14 *#
Group-VI (HPB)	197.83 ±8.68	231.83 ±8.20 #	262.66 ±12.32 #

Where: NC= Normal control, DC= Disease control, GC= Glimepiride control (0.1 mg/kg), LPB= Low dose piribedil (25 mg/kg), MPB= Medium dose piribedil (50mg/kg), HPB= High dose piribedil (75mg/kg).

Table 2. The effect of piribedil on fasting blood glucose levels in diabetic rats

Groups	Fasting blood glucose levels mg/dl. (n=6)		
	Day-0	Day-7	Day-14
Group-I (NC)	106.83 ±7.62	107.00 ±7.87	106.66 ±7.00
Group-II (DC)	315.16 ± 34.49*	312.83 ±37.55*	311.16 ±45.91*
Group-III (GC)	316.83 ± 48.36*	135.66 ±23.78#	122.16 ±12.31#
Group-IV (LPB)	302.66 ± 40.71*	210.33 ±19.27*#	191.00 ±11.83*#
Group-V (MPB)	305.16 ± 35.38*	167.83 ±22.59*#	166.83 ±19.10#
Group-VI (HPB)	297.50 ± 38.31*	158.83 ±22.04#	138.66 ±11.30#

Where: Results are expressed as Mean ± S.D. Significant difference from group-1 (NC) is denoted as *, while significant difference from group-2 (DC) is denoted as # (p-value <0.05).

Table 3. Distribution of HOMA-B, HOMA-IR & QUICKI in the diabetic animals

Groups	HOMA-B	HO-MA-IR	QUICKI
Group- (NC)	91.24 ±13.85	2.85 ±0.17	0.326 ±0.003
Group-II (DC)	9.73 ±1.79 *	5.00 ±0.66 *	0.302 ±0.005*
Group-III (GC)	73.37 ±14.16 #	3.52 ±0.41 #	0.317 ±0.005#
Group-IV (LPB)	26.32 ±2.5 *#	4.38 ±0.32 *#	0.307 ±0.003*
Group-V (MPB)	32.62 ±5.14 *#	3.79 ±0.47 *#	0.314 ±0.005*#
Group-VI (HPB)	51.26 ±9.36 #	3.60 ±0.27 #	0.316 ±0.003#

Results are expressed as Mean ± S.D. Significant difference from group-1 (NC) is denoted as *, while significant difference from group-2 (DC) is denoted as # (p-value <0.05).

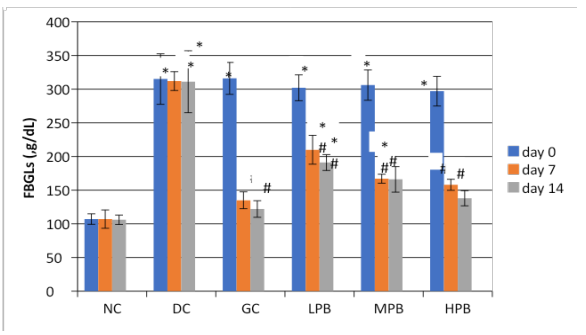

Figure 1. Dose-dependent effect of piribedil on fasting blood glucose levels in diabetic rats

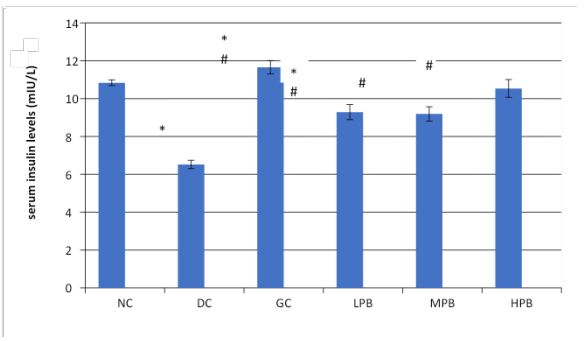

Figure 2: Effect of piribedil on serum insulin levels in alloxan-induced diabetic rats (n=6)

DISCUSSION

Drug repurposing, often referred to as drug reprofiling, is a method that focuses on the analysis of already existing medications that were created for a particular condition to determine their possible effectiveness against different diseases. Piribedil has a strong preference for D3 receptors, with much higher affinity than for D2.[13] Prior studies have demonstrated the significant potential of the various dopamine agonists as antidiabetics.[14] These findings suggest that they may have multiple target actions in regulating blood glucose levels, and constituents may work synergistically. The objective of this project was to evaluate the blood glucose-lowering and body weight modulating effect of piribedil in diabetic rats.

In our study, despite no change in food consumption, diabetic control animals exhibited a weight reduction of 24% and 38% by day 7 and 14, respectively. In contrast, the groups treated with piribedil demonstrated a dose-dependent increase in the body weight: LPB resulted in gains of 18% and 28%, MPB in 25% and 39% and HPB in 30% and 40% on days 7 and 14. Animals receiving glimepiride had weight increases of 25% and 40% during this study period. These results support earlier findings that alloxan induces weight loss, while glimepiride significantly reverses this effect over time.[15] Overall, piribedil resulted in a dose-dependent increase in the body weight among diabetic rats, although the effect was less pronounced than that of glimepiride, suggesting that both medications counteract weight loss associated with diabetes, with glimepiride being more effective.

According to a previous study, Sprague Dawley rats have a fasting normal blood glucose level below 170 mg/dL. The diabetic control group displayed persistently high FBGLs, confirming chronic hyperglycemia. Our results show that administration of piribedil is associated with lower blood glucose levels in a diabetic rat model: the LPB decreased FBGLs by 32%, the MPB enhanced glycemic control by 45%, and the HPB achieved a 50% reduction. The HPB and PC resulted in FBGL reduction 50% and 60% respectively. In previous studies, glimepiride led to a 50% reduction in FBGLs in streptozocin-induced diabetic rats, while our animal model showed a 60% reduction, possibly due to differences in the induction method or animal strain.

While glimepiride increases insulin secretion, piribedil may lower glucose levels through dopaminergic modulation, potentially improving insulin sensitivity or glucose metabolism. Although the antidiabetic effects of piribedil have not been previously reported, related dopamine agonists like bromocriptine have demonstrated glycemic improvements in T2DM patients, suggesting a class effect that warrants further exploration.[16]

All the treatment groups presented with significantly raised plasma insulin levels as compared to the DC group ($p<0.001$). Piribedil showed a dose-dependent increase (30–40%) in serum insulin. These findings are consistent with earlier findings of another dopamine agonist, bromocriptine, which likewise raised insulin and decreased glucose in animal models.[17] A significant 90% decrease in HOMA-β within the diabetic control group highlighted severe β-cell impairment, corroborating earlier research conducted on alloxan-induced diabetic rats.

Animals treated with glimepiride exhibited the most substantial enhancement, demonstrating an 80% increase in HOMA-β, which indicates a robust recovery of insulin secretion. This finding is consistent with research indicating that glimepiride positively affects both HOMA-IR and HOMA-β, especially when used in conjunction with metformin.[18] The groups treated with piribedil displayed improvements that were dependent on dosage. Comparable enhancements have been observed with dopamine agonists such as bromocriptine and cabergoline.[19]

Piribedil has numerous effects on dopamine-associated cerebral functioning. Its broad range of effects suggest a multifaceted impact on brain function. The neuronal projection patterns may be involved in achieving the specific therapeutic target in T2DM. Piribedil has no direct antidiabetic effect through D2 and D3 receptors in pancreatic β-cells. Piribedil juxtaposed with circuitry and neuronal cells coordination in the hypothalamus for regulation of blood glucose is vital, hence deeper understanding of dopamine agonists could play a role in diabetes.

Our study has numerous limitations, particularly time and financial resources. The measurement of glycated hemoglobin (HbA1c) was not carried out which is typically measured after every 3-6 months for individuals with diabetes mellitus. We observed the effects of piribedil for 2 weeks. Histopathology of the pancreas to determine beta cell mass and the inflammatory changes or cell death were not performed. Therefore, further studies are recommended to explore the role of piribedil on the hormones and glucose-sensing systems of the brain.

Conclusion: Piribedil improves pancreatic functions. It operates by reducing fasting blood glucose levels and enhancing insulin production. Furthermore, the marked reduction in HOMA-IR and the improvement in QUICKI values, particularly at higher doses, suggest enhanced insulin sensitivity. These results support the potential role of piribedil as an adjunct or alternative therapeutic option for the management of hyperglycemia.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	TS, NSA
Acquisition, Analysis or Interpretation of Data:	TS, NSA, AI, MZAK, BS, RK
Manuscript Writing & Approval:	TS, NSA, AI, MZAK, BS, RK

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.