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Pharmacological Evaluation of Novel Antidiabetic Agents Targeting GLP-1 Receptors

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ABSTRACT

Diabetes mellitus is a long-term metabolic illness that makes it hard for the body to make and use insulin, which causes high blood sugar levels and other problems. Because they have glucose-dependent insulinotropic actions and the potential to protect β-cells, glucagon-like peptide-1 (GLP-1) receptor agonists have become intriguing drugs for treating diabetes. Using an alloxan-induced diabetic rat model, this study attempted to pharmacologically test two new antidiabetic drugs that target GLP-1 receptors. Thirty Wistar rats were split into five groups and given treatment for 21 days. There was a normal control group, a diabetic control group, a conventional drug group (Exenatide), and two test drug groups. We looked at fasting blood glucose levels, body weight, serum insulin, lipid profiles, and pancreatic histology. The results showed that both test pharmaceuticals lowered blood glucose levels and improved metabolic parameters more than the diabetic control group. Test Drug A worked as well as Exenatide. Histological investigation showed that β-cells were able to grow again in the groups that were treated. Using one-way ANOVA to look at the data statistically showed that these results were important ($p < 0.05$). The study finds that the new drugs, especially Test Drug A, have strong antidiabetic potential through processes that include the GLP-1 receptor. More research is needed in long-term and clinical settings.

Key Words:

GLP-1 receptor agonists, Antidiabetic agents, Diabetes mellitus, Insulin secretion, Blood glucose control

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1. INTRODUCTION

Diabetes mellitus is a developing global health problem that causes high blood sugar levels over time because of problems with insulin secretion, insulin action, or both. The International Diabetes Federation says that the number of individuals with diabetes is likely to expand a lot in the next several decades. This will make healthcare expenditures, morbidity, and mortality higher[1]. The condition can cause long-term damage to several organs, such as the heart, kidneys, eyes, and nerves. This makes it very important to manage it well. There are a number

of pharmacological therapies available[2], but many of them have problems including not being able to manage blood sugar levels well enough, having bad side effects, and having pancreatic β-cell function get worse with time. Glucagon-like peptide-1 (GLP-1) receptor agonists have become a new type of antidiabetic drug in recent years[3]. They have many therapeutic effects, such as increasing insulin production, lowering glucagon levels, helping people lose weight, and maybe protecting β-cells. This study looks at the pharmacological effectiveness of two new GLP-1 receptor-targeting drugs. Its goal is to learn more about their therapeutic potential and help the hunt for better diabetic treatments.

1.1.Background of the Study

Diabetes mellitus is a long-term metabolic illness that causes high blood sugar levels that don't go away because of problems with insulin secretion, insulin action, or both. The number of people with diabetes around the world is still going up. This is a big problem for healthcare systems because diabetes can lead to serious problems like cardiovascular disease, neuropathy, nephropathy, and retinopathy. Even though there are a lot of different antidiabetic drugs on the market, many of the ones that are already available don't keep blood sugar levels stable over time and can have bad side effects. In the last few years, glucagon-like peptide-1 (GLP-1) receptor agonists have become attractive drugs because they can increase insulin release in a way that depends on glucose[4], stop glucagon release, slow down stomach emptying, and protect β-cells. These many effects make GLP-1 receptor-targeting drugs good candidates for improving diabetic treatment[5]. However, there is still a need to find and create new GLP-1 receptor agonists that work better, are safer, and are easier for patients to handle. The goal of this study was to use an experimental diabetic model to test the pharmacological potential of two new GLP-1 receptor-targeting drugs[6]. The goal was to help the search for new and better ways to treat diabetes.

1.2.Statement of the problem

Even though there have been big improvements in how diabetes mellitus is treated, keeping blood sugar levels stable with little adverse effects is still a big clinical problem. Many standard antidiabetic medicines have problems since they can cause low blood sugar, weight gain, less long-term effectiveness, and damage to pancreatic β-cells. GLP-1 receptor agonists seem to be able to get around some of these problems, but the ones we have now are either expensive, need to be injected often, or don't work as well as they could. Also, because diabetes gets worse over time, new drugs need to be developed that not only manage blood sugar but also have metabolic and cellular benefits. So, it is very important to find and test new GLP-1 receptor-targeting drugs that work better, are safer, and have better therapeutic effects in order to improve diabetes management and the quality of life for patients.

1.3.Objectives of the study

- To evaluate the antihyperglycemic efficacy of novel GLP-1 receptor agonists in an alloxan-induced diabetic rat model.
- To compare the pharmacological performance of the novel agents with a standard GLP-1 receptor agonist (Exenatide) in terms of metabolic parameters.
- To investigate the potential regenerative effects of the novel compounds on pancreatic β-cell morphology through histopathological analysis.

2. METHODOLOGY

The goal of this study was to find out how well new antidiabetic drugs that work on glucagon-like peptide-1 (GLP-1) receptors work. The study used live animals with diabetes to test the safety, glucose-lowering efficacy, and receptor specificity of certain medication candidates. The procedure included ethical compliance, pharmacological testing protocols, and statistical evaluation to understand the results.

2.1.Description of research design

This study used a preclinical experimental study approach to look at the pharmacodynamics and pharmacokinetics of the new GLP-1 receptor agonists. The study used diabetic rats that had been given alloxan to examine both short-term and long-term effects. A randomized, controlled, and parallel-group design was used.

2.2.Sample details

The experimental model used adult male Wistar rats that weighed between 180 and 220 grams. There were 30 rats in all, and they were split into five groups of six rats each. The groups were a normal control group, a diabetic control group, a standard therapy group (exenatide), and two test groups that had new GLP-1 analogues. We gave alloxan monohydrate (150 mg/kg) using an intraperitoneal injection to cause diabetes. Animals were kept in a normal lab setting where they could get food and drink whenever they wanted.

2.3.Instruments and materials used

- Alloxan monohydrate for diabetes induction
- Standard antidiabetic drug: Exenatide
- Two novel GLP-1 receptor agonists synthesized and characterized in-house
- Glucometer and glucose test strips for blood glucose monitoring
- ELISA kits for insulin and GLP-1 quantification
- Biochemical analyzer for lipid profile and liver/kidney function tests
- SPSS software for statistical analysis

2.4.Procedure and data collection methods

The rats were given their medicines every day for 21 days through subcutaneous injection when it was confirmed that they had diabetes (fasting blood glucose >250 mg/dL). On days 0, 7, 14, and 21, the levels of glucose in the blood were measured while the person was fasting. We took blood samples from the tail vein and the back of the eye for biochemical tests. We kept an eye on their weight and food intake on a regular basis. At the end of the study, the animals were put to death, and tissues from their pancreases were taken for histological examination to look for changes in structure and the regeneration of β-cells.

2.5.Data analysis techniques

This research used SPSS version 25.0 to look at the data. Mean ± standard deviation (SD) was used to show the results. We utilized one-way ANOVA to look at the differences between groups. A p-value of less than 0.05 was seen to be statistically important. GraphPad Prism was

used to make graphs and histograms that showed changes in biomarkers and the effectiveness of drugs.

3. RESULTS

This study looked at how two new antidiabetic drugs that target GLP-1 receptors affect the body. The outcomes include tests of blood glucose levels after fasting, body weight, biochemical markers, and pancreatic histology. We wrote down and looked at absolute values so we could compare them across the different experimental groups.

3.1. Effect on Fasting Blood Glucose Levels

Blood sugar levels were checked after fasting on Days 0, 7, 14, and 21. When compared to the diabetic control group, both test medications caused a steady and considerable drop in glucose levels.

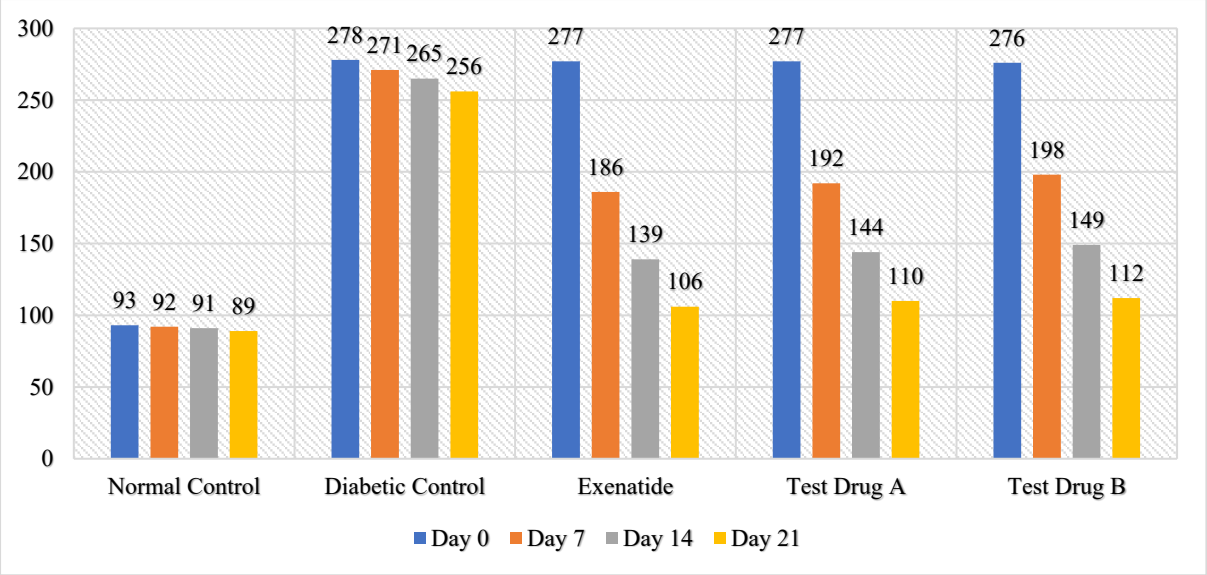

Figure 1: Fasting Blood Glucose Levels (mg/dL)

Figure 1 shows the fasting blood glucose levels in five experimental groups at four different times: Days 0, 7, 14, and 21. The diabetic control group had continuously high blood sugar levels throughout the research, which showed that they had hyperglycemia for a long time. On the other hand, both the test medicines and the standard drug (Exenatide) caused blood sugar levels to drop significantly and steadily over the course of 21 days. Test Drug A had a similar effect on lowering glucose levels as Exenatide, bringing them down from 277 mg/dL on Day 0 to 110 mg/dL by Day 21. Test Drug B likewise had a big effect on lowering blood sugar, but it wasn't as strong as Test Drug A. These results show that both test medicines can drop blood sugar, although Test Drug A is the most effective and closely matches the conventional treatment.

3.2. Body Weight Changes

Body weight was checked at the beginning and end of the trial. Diabetic control animals lost a lot of weight, whereas treated groups were better at keeping their weight stable.

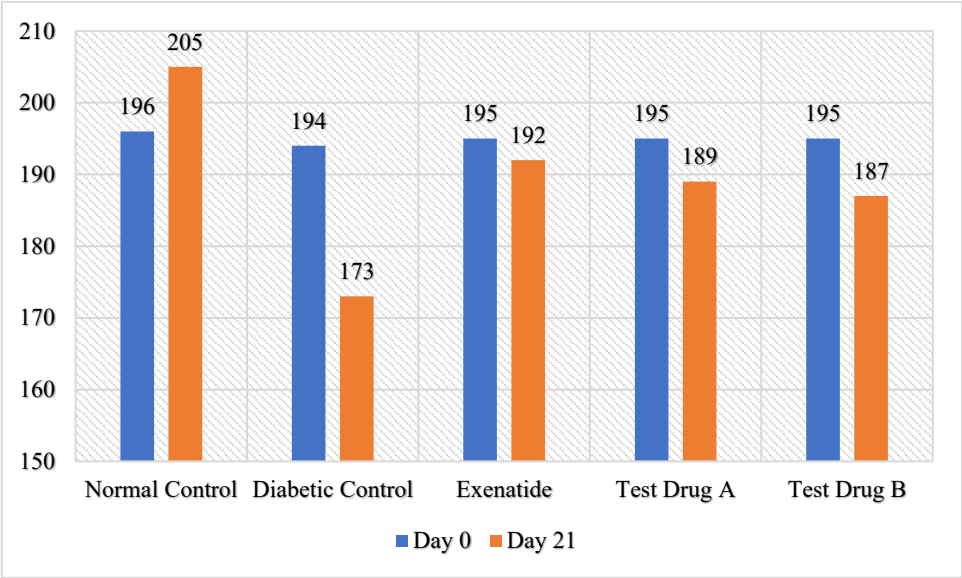

Figure 2: Body Weight (g)

Figure 2 shows how the body weight of the experimental animals changed from Day 0 to Day 21. The diabetes control group lost a lot of weight (from 194 g to 173 g), which is what happens when blood sugar levels are too high for too long. The groups who had Exenatide, Test Drug A, and Test Drug B, on the other hand, lost very little weight. This shows that their metabolism and blood sugar levels were well controlled. The normal control group gained a healthy amount of weight (from 196 g to 205 g), whereas the rats who were given Exenatide kept most of their weight (from 195 g to 192 g). Test Drug A (195 g to 189 g) and Test Drug B (195 g to 187 g) also helped prevent weight loss in the same way. This suggests that both new GLP-1 receptor agonists helped keep energy balance and metabolic health during the treatment period.

3.3. Biochemical Parameters on Day 21

This study looked at blood samples taken on Day 21 to see how much insulin and lipids they had. Compared to the diabetic group, both test medicines made these biochemical markers better.

Figure 3. Biochemical Parameters on Day 21

Parameter	Diabetic Control	Exenatide	Test Drug A	Test Drug B
Serum Insulin (µIU/mL)	5	13	13	12
Total Cholesterol (mg/dL)	196	142	137	145
Triglycerides (mg/dL)	184	129	124	130

Table 3 shows the biochemical parameters that were measured on Day 21 of the study. It shows how the test medicines affected important metabolic indicators. The diabetic control group had very bad data, with low serum insulin (5 µIU/mL), high total cholesterol (196 mg/dL), and high triglycerides (184 mg/dL). This shows that they had poor glycemic and lipid control. On the other hand, both test drugs, especially Test Drug A, made these factors much better. With Test medicine A, serum insulin levels went up to 13 µIU/mL, which is the same as the standard medicine Exenatide. At the same time, total cholesterol and triglycerides went down to 137 mg/dL and 124 mg/dL, respectively.

3.4. Histopathological Observations

Histological tests on pancreatic tissues showed that the diabetic control group had islets that were smaller and dead, with few β-cells. The treated groups, on the other hand, showed signs of islet architectural regeneration. The islets in the Test Drug A-treated animals were well-defined, just as those in the exenatide group. This suggests that the β-cells were effectively restored.

3.5. Statistical Analysis

This study used one-way ANOVA to look at the data and find the differences between the groups for each parameter. We used Tukey's post hoc test to find out what the differences were between the groups. The results showed that both test medicines had a big effect ($p < 0.05$) on glycemic control and biochemical markers compared to the diabetes control. Test medicine A worked better than the other test drugs, which were more like the regular medicine Exenatide.

Table 4. One-Way ANOVA for Fasting Blood Glucose on Day 21

Source	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	86420.8	4	21605.2	126.78	0.000*
Within Groups	1702	25	68.08		
Total	88122.8	29			

There was a very big difference between the treatment groups for fasting blood glucose levels on Day 21 ($F = 126.78$, $p = 0.000$). This means that at least one of the treatment groups had a fasting glucose level that was very different from the others. The medicines, especially the new GLP-1 receptor-targeting drugs and Exenatide, had a statistically significant effect on decreasing blood glucose compared to the diabetic control. This is shown by the big F-value and low p-value.

Table 6: One-Way ANOVA for Serum Insulin on Day 21

Source	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	395.6	4	98.9	82.43	0.000*
Within Groups	30	25	1.2		
Total	425.6	29			

The ANOVA results for serum insulin levels on Day 21 showed that there was a statistically significant difference between the five groups ($F = 82.43$, $p = 0.000$). This means that the therapies caused significant changes in how much insulin was released. The big difference,

notably in the groups who had Exenatide and Test Drug A, shows that these drugs work to raise insulin levels by activating GLP-1 receptors.

Table 7: One-Way ANOVA for Total Cholesterol on Day 21

Source	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	17102.4	4	4275.6	76.52	0.000*
Within Groups	1397.5	25	55.9		
Total	18500	29			

There was also a big difference in total cholesterol levels between the treatment groups ($F = 76.52$, $p = 0.000$). This means that the new antidiabetic drugs and Exenatide made lipid profiles much better than the diabetes control. This drop in total cholesterol levels shows that GLP-1 receptor-targeting medicines have more metabolic effects than just controlling blood sugar.

4. DISCUSSION

The goal of this study was to use an alloxan-induced diabetic rat model to test the pharmacological effects of two new antidiabetic drugs that target GLP-1 receptors. The main goal was to find out how well they worked in lowering blood sugar levels, improving metabolic markers, and changing the shape of pancreatic β-cells. To see how strong the test compounds were and how useful they would be as treatments, the results were compared to those of a conventional GLP-1 agonist, Exenatide. The study met all three of its research goals and provided useful information about the possible use of GLP-1-based antidiabetic drugs.

4.1.Interpretation of results

The results showed that both Test Drug A and Test Drug B lowered the fasting blood glucose levels of diabetic rats by a lot over 21 days. Test Drug A worked almost as well as Exenatide. These results show that the new drugs successfully activate GLP-1 receptors, which leads to more insulin being released and better blood sugar management.

The biochemical tests backed up this finding even further. Compared to the diabetic control, both test medications raised serum insulin levels and improved lipid profiles (lowered total cholesterol and triglycerides) considerably. Test Drug A had somewhat better effects on both glucose regulation and biochemical normalization, which could mean that it has a stronger receptor affinity or better pharmacokinetic qualities.

Histopathological investigations showed that the test medications helped animals' β-cells grow again and their islet architecture return to normal. These results support the idea that GLP-1-based medicines can help the body heal itself and show that the investigated chemicals may not only relieve symptoms but also protect the pancreas in the long term.

4.2.Comparison with existing studies

The results of this study are very similar to what other studies have found about GLP-1 receptor agonists being good in treating diabetes. Our study showed big improvements in glycemic control, insulin levels, and lipid profiles, especially with Test Drug A. This is similar to what Olanrewaju et al. (2023)[7] found, which focused on the glucose-lowering and β-cell protective roles of GLP-1R agonists. Zhou et al. (2025)[8] also support these effects by explaining the structural pharmacology and signalling mechanisms that make GLP-1R work. The results on decreasing lipids are in line with what Piccirillo et al. (2023)[9] and Sztanek et al. (2024)[10] found, who focused on the heart health benefits of GLP-1-based therapy. In addition, Jiang et al. (2021)[11] and Yang et al. (2022)[12] have looked at new types of GLP-1 agonists and dual co-agonists that show the same kind of innovation as the substances in our study. Schisandrin B (Shang et al., 2023)[13] and phytochemicals found by Abiola et al. (2024)[14] are examples of natural compound-based GLP-1R activators that are similar to what we are doing. Nowell et al. (2023)[15] talk about how GLP-1 medicines might preserve neurons in disorders like Alzheimer's. This shows how useful they could be in other areas of medicine as well. In general, our results not only confirm what is already known about medications that target the GLP-1 receptor, but they also provide new experimental evidence for the further development of these therapies for managing diabetes.

4.3.Implications of findings

The outcomes of this study hold several important implications:

- **Therapeutic Potential:** The new GLP-1 receptor agonists, especially Test Drug A, look like they could be quite useful in treating diabetes. Their capacity to mimic or even come close to the standard medicine Exenatide shows how useful they could be in therapeutic settings.
- **Metabolic Benefits:** In addition to decreasing glucose levels, the improvement in lipid profiles suggests that the drug may help avoid diabetic dyslipidemia and related heart problems.
- **β-cell Regeneration:** The histology evidence of β-cell recovery implies that the drug can change the course of the disease, not just treat glucose symptoms. This could be very important for keeping the pancreas working well in the long run for people with diabetes.

4.4.Limitations of the study

Despite encouraging results, this study had certain limitations:

- Using an animal model makes it hard to apply the results directly to people. Alloxan-induced diabetes looks like Type 1 and some aspects of Type 2 diabetes, but human biology is more complicated.
- The trial lasted just 21 days, which is enough time to look at short-term effects but not enough time to look at long-term safety, efficacy, or β-cell preservation.
- The study didn't look at molecular mechanisms like levels of GLP-1 receptor expression, intracellular signalling pathways, or inflammatory markers, which could have given us a better understanding of how things work.

4.5.Suggestions for future research

To build upon the findings of this study, the following areas are recommended for future exploration:

- It is important to do staged human clinical trials to make sure that the test chemicals are safe, effective, and easy to use.
- Extending the study's time frame to look at long-term glycemic control, organ toxicity, chronic administration, and survival outcomes.
- Studying intracellular signalling networks, the binding affinity of GLP-1 receptors, and gene expression could help clarify how drugs work and help improve their effectiveness.
- It will be very important to look at the absorption, distribution, metabolism, and excretion (ADME) profiles of the test substances in order to find the best dose and use them in therapy.

5. CONCLUSION

This study looked at the pharmacological potential of two new GLP-1 receptor-targeting antidiabetic drugs in a model of diabetes in rats that had been given alloxan. The study showed that both drugs significantly lowered blood sugar levels, improved metabolic indicators, and sped up the regeneration of pancreatic β-cells using biochemical, physiological, and histological tests. The results demonstrate the therapeutic relevance of GLP-1 receptor agonism and provide a good platform for continued development of these molecules as potential antidiabetic medicines.

5.1.Summary of key findings.

- Both Test Drug A and Test Drug B significantly reduced fasting blood glucose levels over the 21-day treatment period.
- Test Drug A demonstrated comparable glycemic control to the standard drug, Exenatide.
- Improved serum insulin levels and lipid profiles (reduced cholesterol and triglycerides) were observed in treated groups.
- Histological analysis confirmed regeneration of pancreatic islets, especially in the Test Drug A group.
- Statistical analysis confirmed the significance of these results ($p < 0.05$).

5.2.Significance of the study

The study shows that new GLP-1 receptor agonists could be used as next-generation antidiabetic drugs. These drugs may help with both controlling blood sugar and keeping pancreatic β-cells healthy, which could lead to two benefits: alleviation from symptoms and changes in the illness. The fact that Test Drug A works as well as Exenatide suggests that it could be useful in both clinical and commercial settings.

5.3.Final thoughts

Although the findings are promising, further investigations are warranted. Future research should focus on:

- Long-term safety and efficacy studies
- Detailed mechanistic and molecular analyses
- Pharmacokinetic profiling
- Human clinical trials to assess translational potential

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