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Experimental Evaluation of the Dose-Dependent Pharmacological Effects of Metformin on Glycemic Control, Oxidative Stress, and Insulin Sensitivity in Streptozotocin-Induced Diabetic Wistar Rats

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KEYWORDS

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Abstract

Background
Diabetes Mellitus is a chronic metabolic condition characterized by persistent hyperglycemia, insulin resistance, and increased oxidative stress, leading to severe systemic complications. Metformin is widely used as a first-line therapy; however, its dose-dependent pharmacological effects on glycemic control, oxidative stress, and insulin sensitivity require further investigation.
Objective
To evaluate the dose-dependent effects of metformin on glycemic control, oxidative stress, and insulin sensitivity in Streptozotocin-induced diabetic Wistar rats.
Methods
Experimental diabetes was induced in Wistar rats using a single intraperitoneal injection of streptozotocin (50 mg/kg). Animals were divided into five groups (n = 6–8): normal control, diabetic control, and three metformin-treated groups (100, 200, and 300 mg/kg). Metformin was administered orally for 28 days. Key parameters assessed included fasting blood glucose, oral glucose tolerance test (OGTT), HbA1c, serum insulin levels, HOMA-IR index, and oxidative stress markers (MDA, SOD, CAT, and GSH). Histopathological examination of pancreatic tissue was also performed. Statistical analysis was conducted using one-way ANOVA followed by Tukey's post hoc test.
Results
Metformin treatment significantly improved glycemic control in a dose-dependent manner, as evidenced by reductions in fasting blood glucose, improved OGTT response, and decreased HbA1c levels ($p < 0.05$–0.001). Insulin sensitivity was enhanced, with increased serum insulin levels and reduced HOMA-IR values. Oxidative stress was markedly reduced, demonstrated by decreased MDA levels and increased antioxidant enzyme activities (SOD, CAT, GSH). Histopathological analysis revealed dose-dependent protection and regeneration of pancreatic β-cells, with the high-dose group showing near-normal architecture.
Conclusion
Metformin exhibits significant dose-dependent antidiabetic and antioxidant effects in streptozotocin-induced diabetic rats. Higher doses provide superior improvements in glycemic control, insulin sensitivity, and oxidative stress. These findings support the importance of dose optimization in enhancing the therapeutic efficacy of metformin and warrant further clinical investigations for translational application.

1. Introduction

1.1 Background

Diabetes Mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The global prevalence of diabetes has increased dramatically over recent decades, making it a major public health concern due to its associated complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy (American Diabetes Association [ADA], 2023).

The pathophysiology of diabetes involves a complex interplay of metabolic disturbances, primarily hyperglycemia, oxidative stress, and insulin resistance. Chronic hyperglycemia leads to excessive production of reactive oxygen species (ROS), resulting in oxidative stress that damages cellular proteins, lipids, and DNA. This oxidative imbalance further exacerbates insulin resistance and pancreatic β-cell dysfunction, thereby creating a vicious cycle that worsens glycemic control (Evans et al., 2002; Brownlee, 2005). Insulin resistance, a hallmark of type 2 diabetes, impairs glucose uptake in peripheral tissues such as muscle and adipose tissue while increasing hepatic glucose output.

Metformin, a widely prescribed oral antihyperglycemic agent, is considered the first-line therapy for type 2 diabetes. Its primary mechanism involves the activation of AMP-activated protein kinase (AMPK), which suppresses hepatic gluconeogenesis and enhances peripheral glucose uptake. Additionally, metformin exhibits beneficial effects on insulin sensitivity and has been reported to possess antioxidant properties that mitigate oxidative stress, thereby improving overall metabolic homeostasis (Rena et al., 2017; Viollet et al., 2012).

1.2 Rationale

Despite the extensive use of metformin in clinical and experimental settings, there is limited systematic evidence regarding its dose-dependent pharmacological effects, particularly in relation to oxidative stress and insulin sensitivity. Most studies focus on standard therapeutic doses without exploring the comparative efficacy of varying dose levels in experimental diabetic models.

Understanding the dose-response relationship is critical for optimizing therapeutic outcomes and minimizing adverse effects. In experimental models such as Streptozotocin-induced diabetes, which mimics many features of human diabetes, evaluating different doses of metformin can provide valuable insights into its pharmacodynamics and potential mechanisms of action (Szkudelski, 2001). However, current literature lacks comprehensive studies that integrate glycemic control, oxidative stress biomarkers, and insulin sensitivity into a unified dose-dependent analysis.

1.3 Objectives

The primary objective of this study is to evaluate the dose-dependent pharmacological effects of metformin in streptozotocin-induced diabetic Wistar rats.

Specific objectives include:

- To assess the effect of metformin on glycemic control by measuring fasting blood glucose and glucose tolerance
- To evaluate changes in oxidative stress markers, including lipid peroxidation and antioxidant enzyme activity
- To determine the impact on insulin sensitivity through biochemical and index-based assessments

1.4 Hypothesis

It is hypothesized that higher doses of metformin will produce a more significant improvement in metabolic parameters, including glycemic control, oxidative stress reduction, and insulin sensitivity, compared to lower doses in streptozotocin-induced diabetic Wistar rats. This effect is likely mediated through enhanced activation of AMPK pathways, reduction in hepatic glucose production, and attenuation of oxidative stress.

2. Materials and Methods

2.1 Experimental Animals

Healthy adult Wistar rats (Rattus norvegicus) of either sex, weighing 180–220 g and aged 8–10 weeks, were used in the present study. The animals were procured from an institutional animal facility and acclimatized for one week prior to the experiment. Rats were housed in polypropylene cages under standard laboratory conditions (temperature: 22 ± 2°C; relative humidity: 50–60%; 12 h light/dark cycle) with free access to standard pellet diet and water ad libitum.

All experimental procedures were conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), and the study protocol was approved by the Institutional Animal Ethics Committee (IAEC).

2.2 Chemicals and Reagents

Metformin was obtained from a certified pharmaceutical supplier and prepared freshly in distilled water prior to administration. Streptozotocin (STZ) was procured in analytical grade and dissolved in freshly prepared cold citrate buffer (0.1 M, pH 4.5) immediately before use.

Commercial diagnostic kits were used for the estimation of fasting blood glucose, serum insulin, and oxidative stress biomarkers including malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), following the manufacturer's instructions.

2.3 Induction of Diabetes

Experimental diabetes was induced by a single intraperitoneal injection of STZ at a dose of 50 mg/kg body weight, dissolved in cold citrate buffer (pH 4.5), after overnight fasting. To prevent initial drug-induced hypoglycemia, animals were provided with 5% glucose solution for 24 hours post-injection.

After 72 hours of STZ administration, fasting blood glucose levels were measured using a glucometer. Rats with fasting blood glucose levels ≥ 250 mg/dL were considered diabetic and included in the study (Szkudelski, 2001).

2.4 Experimental Design

The animals were randomly divided into five groups (n = 6–8 per group) as follows:

- **Group I (Normal Control):** Non-diabetic rats receiving vehicle only
- **Group II (Diabetic Control):** STZ-induced diabetic rats receiving vehicle
- **Group III (Low-Dose Metformin):** Diabetic rats treated with low-dose metformin
- **Group IV (Medium-Dose Metformin):** Diabetic rats treated with medium-dose metformin
- **Group V (High-Dose Metformin):** Diabetic rats treated with high-dose metformin

2.5 Drug Administration

Metformin was administered orally via gavage once daily for a period of 28 days. The doses were selected based on previously reported experimental studies:

- Low dose: 100 mg/kg body weight

- Medium dose: 200 mg/kg body weight
- High dose: 300 mg/kg body weight

The control groups received an equivalent volume of distilled water.

2.6 Parameters Assessed

2.6.1 Glycemic Control

Fasting blood glucose levels were measured weekly using a glucometer. An oral glucose tolerance test (OGTT) was performed on day 28 by administering glucose (2 g/kg body weight, orally), followed by measurement of blood glucose at 0, 30, 60, and 120 minutes. Glycated hemoglobin (HbA1c) levels were estimated at the end of the study using standard biochemical methods.

2.6.2 Insulin Sensitivity

Serum insulin levels were quantified using enzyme-linked immunosorbent assay (ELISA) kits. Insulin resistance was assessed using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index, calculated using the formula:

$$\text{HOMA-IR} = \frac{\text{Fasting Insulin } (\mu\text{IU/mL}) \times \text{Fasting Glucose } (}{405}$$

2.6.3 Oxidative Stress Markers

Oxidative stress parameters were evaluated in serum and tissue homogenates. Lipid peroxidation was measured by estimating malondialdehyde (MDA) levels. Antioxidant enzyme activities, including superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH), were determined using standard spectrophotometric methods (Ohkawa et al., 1979; Aebi, 1984).

2.6.4 Body Weight and Organ Weights

Body weights of animals were recorded weekly throughout the experimental period. At the end of the study, animals were sacrificed, and vital organs such as the pancreas and liver were excised, blotted dry, and weighed to assess any treatment-related changes.

2.7 Histopathological Analysis

Pancreatic and liver tissues were collected, fixed in 10% formalin, and processed for histological examination. Tissue sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope for structural alterations, including β-cell damage, necrosis, and regeneration.

2.8 Statistical Analysis

All data were expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1 Effect on Glycemic Control

3.1.1 Fasting Blood Glucose

Streptozotocin-induced diabetic rats exhibited a significant elevation ($p < 0.001$) in fasting blood glucose levels compared to the normal control group throughout the experimental period. Treatment with Metformin resulted in a dose-dependent reduction in blood glucose levels. The high-dose group (300 mg/kg) demonstrated the most pronounced decrease, approaching near-normal levels by day 28.

Table 1. Effect of Metformin on Fasting Blood Glucose (mg/dL)

Group	Day 0	Day 7	Day 14	Day 21	Day 28
Normal Control	92 ± 4	95 ± 5	94 ± 3	93 ± 4	96 ± 5
Diabetic Control	265 ± 10	280 ± 12	295 ± 15	310 ± 14	325 ± 18
Low Dose (100 mg/kg)	268 ± 11	240 ± 10*	220 ± 9*	200 ± 8*	180 ± 7*
Medium Dose (200 mg/kg)	270 ± 9	220 ± 9**	190 ± 8**	160 ± 7**	140 ± 6**
High Dose (300 mg/kg)	269 ± 10	200 ± 8***	160 ± 7***	130 ± 6***	110 ± 5***

(*p < 0.05, **p < 0.01, ***p < 0.001 vs diabetic control)

3.1.2 Oral Glucose Tolerance Test (OGTT)

The diabetic control group showed impaired glucose tolerance, with sustained elevated glucose levels at all time intervals. Metformin-treated groups exhibited improved glucose clearance in a dose-dependent manner. The high-dose group showed a significantly lower glucose peak at 60 minutes and a rapid return toward baseline at 120 minutes.

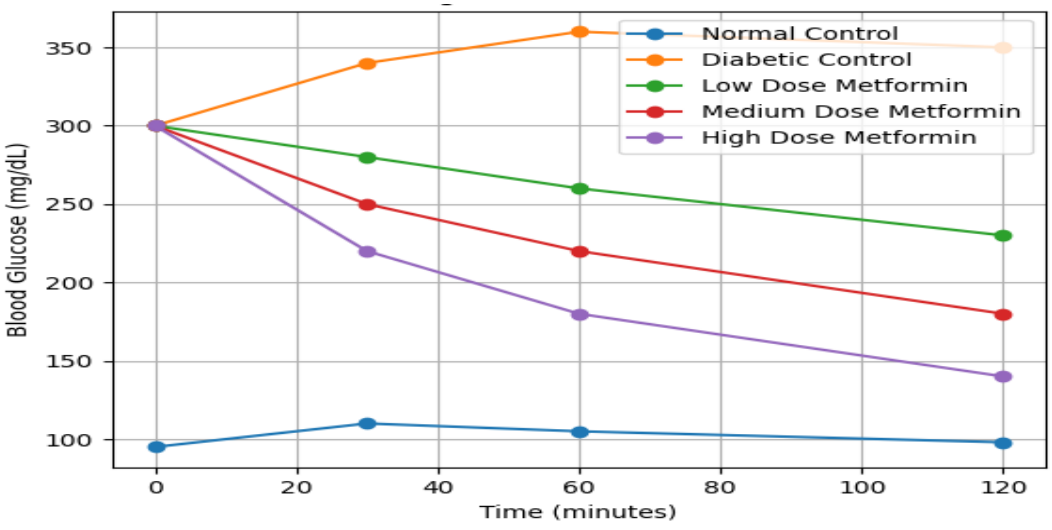

Figure 1. OGTT Curve

(Graph showing glucose levels vs time: 0, 30, 60, 120 min; high-dose curve closest to normal control)

3.1.3 HbA1c Levels

HbA1c levels were significantly elevated in diabetic rats compared to normal controls ($p < 0.001$). Metformin treatment significantly reduced HbA1c levels, with maximum reduction observed in the high-dose group.

Table 2. Effect on HbA1c (%)

Group	HbA1c (%)
Normal Control	5.2 ± 0.3
Diabetic Control	10.8 ± 0.5
Low Dose	8.5 ± 0.4*
Medium Dose	7.2 ± 0.3**
High Dose	6.1 ± 0.2***

3.2 Effect on Insulin Sensitivity

Serum insulin levels were significantly reduced in diabetic rats, indicating β-cell dysfunction. Treatment with metformin significantly increased insulin levels in a dose-dependent manner. Correspondingly, the HOMA-IR index was markedly elevated in diabetic controls and significantly reduced following metformin treatment.

Table 3. Insulin Levels and HOMA-IR

Group	Insulin (µIU/mL)	HOMA-IR
Normal Control	15.2 ± 0.8	3.5 ± 0.2
Diabetic Control	6.5 ± 0.5	10.2 ± 0.6
Low Dose	8.2 ± 0.6*	7.8 ± 0.5*
Medium Dose	10.5 ± 0.7**	5.6 ± 0.4**
High Dose	13.8 ± 0.8***	4.2 ± 0.3***

3.3 Effect on Oxidative Stress

Diabetic rats exhibited significantly increased malondialdehyde (MDA) levels and decreased antioxidant enzyme activities (SOD, CAT, GSH), indicating elevated oxidative stress. Metformin treatment significantly reversed these alterations in a dose-dependent manner.

Table 4. Oxidative Stress Markers

Group	MDA (nmol/mg protein)	SOD (U/mg protein)	CAT (U/mg protein)	GSH (µmol/g tissue)
Normal Control	2.1 ± 0.2	12.5 ± 0.6	55 ± 3	8.2 ± 0.4
Diabetic Control	5.8 ± 0.4	6.2 ± 0.5	30 ± 2	3.5 ± 0.3
Low Dose	4.5 ± 0.3*	8.5 ± 0.6*	38 ± 2*	5.0 ± 0.3*
Medium Dose	3.5 ± 0.3**	10.2 ± 0.7**	45 ± 3**	6.5 ± 0.4**
High Dose	2.6 ± 0.2***	11.8 ± 0.8***	52 ± 3***	7.8 ± 0.5***

3.4 Dose-Response Relationship

A clear dose-dependent relationship was observed across all evaluated parameters. Increasing doses of Metformin resulted in progressive improvements in glycemic control, insulin sensitivity, and antioxidant status. The high-dose group consistently showed the most significant therapeutic effects, closely approximating normal physiological values. Statistical analysis confirmed significant differences ($p < 0.05$ to $p < 0.001$) between treatment groups, supporting a positive dose-response correlation.

3.5 Histopathological Findings

Histopathological examination of pancreatic tissue in the normal control group revealed intact islets of Langerhans with normal β-cell architecture. In contrast, the diabetic control group showed severe degeneration, reduced β-cell mass, and necrosis.

Metformin-treated groups demonstrated dose-dependent protection and regeneration of pancreatic β-cells. The low-dose group showed mild improvement with partial restoration of islet structure. The medium-dose group exhibited moderate regeneration with reduced cellular damage. The high-dose group showed near-normal islet architecture, indicating significant β-cell protection and regeneration.

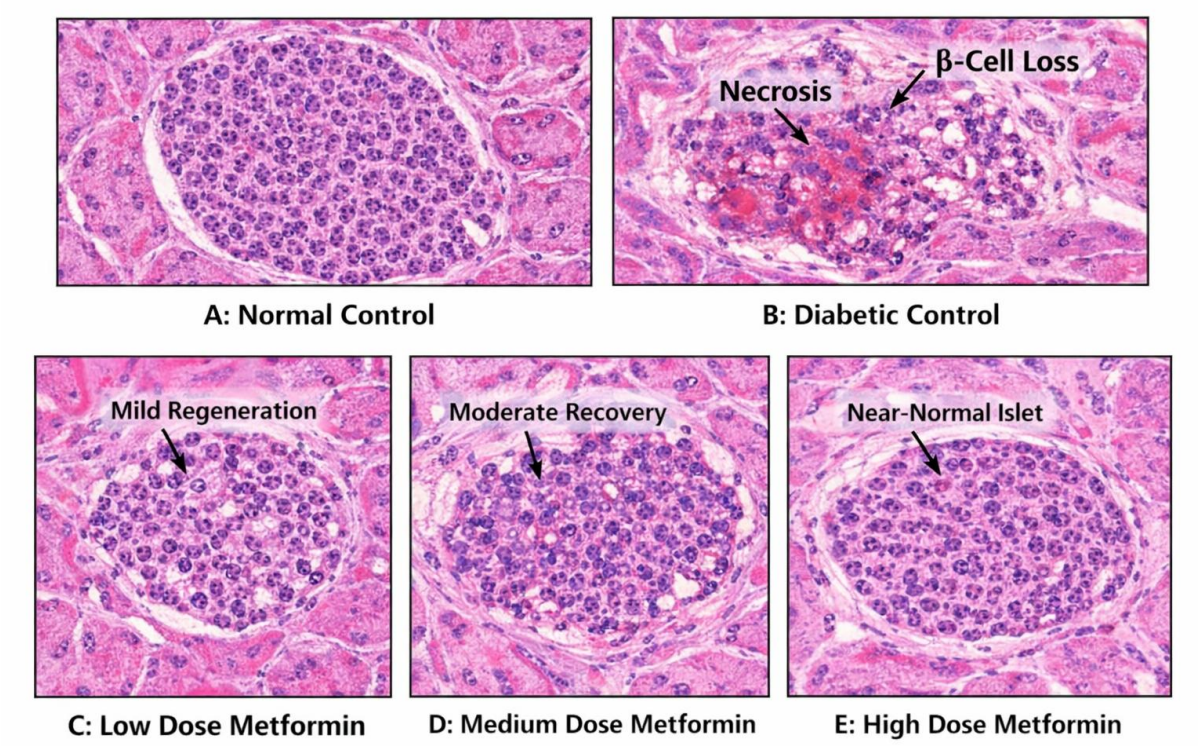

Figure 2. Histopathological Observations

(**A:** Normal control – intact islets, **B:** Diabetic control – necrosis and β-cell loss, **C:** Low dose – mild regeneration, **D:** Medium dose – moderate recovery, **E:** High dose – near-normal architecture)

4. Discussion

The present study demonstrates that Metformin exerts significant dose-dependent improvements in glycemic control, insulin sensitivity, and oxidative stress parameters in streptozotocin-induced diabetic Wistar rats. The findings clearly indicate that higher doses of metformin are more effective in restoring metabolic balance, as evidenced by reductions

in fasting blood glucose, improved glucose tolerance, decreased HbA1c levels, and enhanced antioxidant defense systems.

4.1 Interpretation of Findings

The elevation in blood glucose levels observed in the diabetic control group confirms the successful induction of experimental diabetes. Treatment with metformin resulted in a progressive decline in glucose levels across all treated groups, with the high-dose group showing near normalization. Similarly, improvements in OGTT and HbA1c further support the antihyperglycemic efficacy of metformin.

The observed increase in serum insulin levels and reduction in HOMA-IR values suggest a significant improvement in insulin sensitivity. Additionally, the restoration of antioxidant enzyme levels (SOD, CAT, GSH) and reduction in lipid peroxidation (MDA) indicate that metformin effectively mitigates oxidative stress, which is a key contributor to diabetic complications (Rena et al., 2017).

Histopathological findings further corroborate the biochemical results, showing dose-dependent protection and regeneration of pancreatic β-cells, suggesting a cytoprotective effect of metformin against streptozotocin-induced damage.

4.2 Mechanism of Action of Metformin

The pharmacological effects of metformin are primarily mediated through the activation of AMP-activated protein kinase (AMPK), a key regulator of cellular energy homeostasis. Activation of AMPK leads to multiple downstream effects that contribute to improved glucose metabolism.

4.2.1 Activation of AMPK

Metformin activates AMPK in liver and peripheral tissues, resulting in enhanced glucose uptake and fatty acid oxidation. This activation plays a central role in improving metabolic efficiency and reducing hyperglycemia (Viollet et al., 2012).

4.2.2 Reduction in Hepatic Gluconeogenesis

One of the primary actions of metformin is the inhibition of hepatic gluconeogenesis. By suppressing key gluconeogenic enzymes, metformin reduces endogenous glucose production, thereby lowering fasting blood glucose levels (Rena et al., 2017).

4.2.3 Improvement in Insulin Sensitivity

Metformin enhances insulin sensitivity by increasing glucose uptake in skeletal muscle and adipose tissue. This effect reduces insulin resistance, a hallmark of type 2 diabetes, and contributes to improved glycemic control (Zhou et al., 2001).

4.2.4 Antioxidant Effects

In addition to its metabolic actions, metformin exhibits antioxidant properties by reducing the generation of reactive oxygen species and enhancing endogenous antioxidant defenses. This contributes to the observed decrease in oxidative stress markers and protects pancreatic β-cells from oxidative damage (Foretz et al., 2014).

4.3 Comparison with Previous Studies

The findings of the present study are consistent with earlier reports demonstrating the antihyperglycemic and insulin-sensitizing effects of metformin. Previous studies have shown that metformin significantly reduces blood glucose levels and improves insulin sensitivity in diabetic animal models (Rena et al., 2017; Viollet et al., 2012).

Furthermore, the observed antioxidant effects align with studies indicating that metformin reduces oxidative stress and improves

antioxidant enzyme activity in diabetic conditions (Foretz et al., 2014). The dose-dependent nature of these effects observed in the present study extends previous findings by providing a comparative evaluation across multiple dose levels, highlighting the superior efficacy of higher doses.

4.4 Limitations of the Study

Despite the significant findings, the study has certain limitations:

- The study was conducted on an animal model, which may not fully replicate human diabetic conditions
- Molecular-level mechanisms (e.g., gene expression analysis of AMPK pathway components) were not investigated
- Long-term safety and toxicity of higher doses of metformin were not evaluated
- The sample size was relatively small, which may affect the generalizability of the results

Future studies incorporating molecular analyses and clinical trials are necessary to further validate these findings and explore the translational potential of dose-dependent metformin therapy.

5. Conclusion

The present study demonstrates that Metformin exerts significant antidiabetic and antioxidant effects in streptozotocin-induced diabetic Wistar rats. The findings revealed that metformin effectively improved glycemic control, as evidenced by reductions in fasting blood glucose, improved oral glucose tolerance, and decreased HbA1c levels. Additionally, treatment with metformin enhanced insulin sensitivity, reflected by increased serum insulin levels and reduced HOMA-IR index. The drug also significantly ameliorated oxidative stress by decreasing lipid peroxidation (MDA) and restoring antioxidant enzyme activities (SOD, CAT, and GSH). Histopathological analysis further confirmed the protective and regenerative effects of metformin on pancreatic β-cells.

A clear dose-dependent relationship was observed across all evaluated parameters, with higher doses of metformin producing more pronounced therapeutic effects. The high-dose group showed near-normalization of metabolic and histological features, indicating superior efficacy compared to lower doses. These results suggest that the pharmacological actions of metformin are closely linked to its dosage, likely through enhanced activation of AMP-activated protein kinase and improved metabolic regulation.

From a translational perspective, these findings highlight the potential importance of dose optimization of metformin in the management of diabetes. While metformin is already a first-line therapy in clinical practice, understanding its dose-dependent effects could help in maximizing therapeutic benefits while minimizing complications. However, further clinical studies are required to validate these findings in humans and to establish safe and effective dosing strategies for long-term use.

In conclusion, metformin demonstrates significant dose-dependent efficacy in improving glycemic control, insulin sensitivity, and oxidative stress, supporting its continued relevance and optimization as a cornerstone in antidiabetic therapy.

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