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# Modulation of insulin secretion and lipid profiles through glutamate dehydrogenase activators in diabetic rabbits

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## ABSTRACT

Diabetes mellitus is a prevalent metabolic disorder characterized by impaired insulin secretion and aberrant lipid metabolism. Targeting glutamate dehydrogenase (GDH) activators has emerged as a potential therapeutic strategy in managing diabetes. This study aims to investigate the effects of GDH activators on insulin secretion and lipid profiles in diabetic rabbits. Utilizing Streptozotocin (STZ) to induce diabetes in male New Zealand White rabbits, the impacts of three different GDH activators—Metformin, Epigallocatechin Gallate (EGCG), and Leucine—were examined. The subjects were categorized into five groups, including a diabetic control, a sham group, and three treatment groups administered with Metformin (5 mg $kg^{-1}$), EGCG (15 mg $kg^{-1}$), and Leucine (15 mg $kg^{-1}$), respectively. The study reveals significant modulations in insulin and lipid profiles due to these treatments. In the Metformin-treated group, blood glucose levels significantly decreased during the second ($p < 0.001$) and third ($p<0.01$) weeks. The EGCG group exhibited a significant increase in insulin levels ($p < 0.001$), but no notable change in blood glucose. Conversely, the Leucine group showed an increase in triglyceride levels ($p < 0.05$) and a significant decrease in blood glucose levels ($p < 0.01$). Additionally, Metformin led to a substantial reduction in triglycerides ($p < 0.001$), while EGCG and Leucine were effective in lowering LDL levels ($p < 0.01$). Cholesterol and HDL levels remained relatively unchanged across all groups. These findings suggest that GDH activators, i.e., Metformin, EGCG, and Leucine, significantly impact insulin secretion and lipid metabolism, offering novel insights into diabetes management. This study not only demonstrates the therapeutic potential of these agents, but also emphasizes the importance of GDH pathways in diabetes research, providing a foundation for future investigations into metabolic regulation and treatment.

**Keywords:** Amino acids, Enzymes, Hormones, Diabetes.
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## INTRODUCTION

Diabetes is a complex and chronic disease characterized primarily by elevated blood glucose levels. This elevation is often a result of insufficient insulin production or the body's inability to effectively use insulin. Without proper insulin function, glucose accumulates in the blood, leading to hyperglycemia (Mukhtar *et al.* 2020; Aziz Mahdi Al-badry 2022; Humaidan Al-Moussawi 2022). Diabetes not only affects blood glucose levels but also has a significant impact on various lipid components in the blood. People with diabetes commonly experience altered lipid metabolism, leading to changes in serum levels of triglycerides, cholesterol, and lipoproteins (Li *et al.* 2020). An increase in triglycerides and cholesterol is often observed in diabetic individuals (Poznyak *et al.* 2020). High levels of triglycerides can contribute to the hardening and narrowing of arteries, increasing the risk of heart disease and stroke (Alexopoulos *et al.* 2019). Cholesterol is essential for building cells and producing hormones, but excessive levels can lead to similar cardiovascular risks (Perego *et al.* 2019). Lipoproteins are particles that transport fats like cholesterol and triglycerides in the bloodstream. There are different types of lipoproteins, including Low-Density Lipoprotein (LDL) and Very Low-Density Lipoprotein (VLDL), both of which tend to be elevated in diabetes (Davidson & Shah 2019; Rizvi *et al.* 2021). LDL is often referred to as "bad" cholesterol because it can lead to plaque buildup in arteries. VLDL primarily carries triglycerides and can contribute to atherosclerosis, a condition characterized by the hardening of arteries. Conversely, High-Density Lipoprotein (HDL) levels often decrease in individuals with diabetes. HDL is known as "good" cholesterol because it helps remove other forms of cholesterol from the bloodstream, thereby reducing the risk of heart disease. The reduction in HDL levels in diabetic patients further exacerbates their risk of cardiovascular complications (Cochran *et al.* 2021). As our understanding of this disease expands, it becomes imperative to discover potent compounds that can effectively treat diabetes and its complications while minimizing side effects. The treatment of diabetes mellitus primarily involves the administration of insulin and hypoglycemic agents. While effective in managing blood sugar levels, these treatments come with various side effects. The use of insulin, for example, can lead to increased fat deposits and tissue degeneration at the injection site. Additionally, both insulin and hypoglycemic agents carry the risk of inducing hypoglycemic shock, a condition where blood sugar levels fall dangerously low (Dubey *et al.* 2020; Wondmkun 2020). Another significant limitation of these treatments is their inability to substantially influence the long-term complications of diabetes (Cloete 2021; Rohm *et al.* 2022). Intraperitoneal Streptozotocin (STZ) is a compound that is instrumental in diabetes research, as it can induce specific cellular responses (Mitchelson *et al.* 2021). STZ, primarily through its alkylation of DNA, specifically targets pancreatic β-cells, leading to their destruction and, consequently, the onset of insulin-dependent diabetes mellitus. This cytotoxic effect is linked to the generation of nitric oxide and reactive oxygen species, exacerbating oxidative stress within the cells. This increase in oxidative stress, particularly in the pancreatic islets, leads to cell necrosis, mirroring the pathophysiological mechanisms observed in both type I and type II diabetes (Wang *et al.* 2019).

The presence of STZ intensifies oxidative stress reactions and plays a pivotal role in the development of diabetes and its related microvascular complications, underscoring the significance of oxidative stress in the progression of the disease ( Park *et al.* 2019; Li *et al.* 2021;). In conditions marked by elevated insulin (hyperinsulinemia) and ammonia levels (hyperammonemia), often stemming from a dominant genetic mutation, the critical function of glutamate dehydrogenase (GDH) is highlighted (Bian *et al.* 2022). This enzyme's role becomes especially prominent when it's inhibited by adenosine triphosphate (ATP) and guanosine triphosphate (GTP), both key energy-transferring molecules in cells (Zeng & Sang 2023). Research involving transgenic mice, which show lower blood sugar levels (hypoglycemia) due to increased insulin production compared to typical mice, further illuminates GDH's essential part in regulating insulin (Petraki *et al.* 2019). This indicates that agents influencing GDH activity could potentially manage diabetes effectively. Notably, GDH inhibitors like Epigallocatechin Gallate (EGCG) that also positively influences insulin sensitivity and glucose metabolism through its antioxidant properties (Casanova *et al.* 2019; Chang *et al.* 2022), and Metformin, recognized for its ability to improve insulin sensitivity and lower blood glucose levels, and characterized by its biguanide structure which contributes to its antihyperglycemic properties (Sainero-Alcolado *et al.* 2022), exemplify such agents. Leucine, an amino acid, significantly influences the activity of GDH in pancreatic β-cells. It functions as an allosteric activator of GDH, enhancing the enzyme's activity, which is pivotal in the oxidative deamination of glutamate to α-ketoglutarate. This reaction is a critical step in the tricarboxylic acid cycle, leading to an increase in ATP levels within the β-cells. The rise in ATP subsequently triggers the closing of ATP-sensitive potassium channels and the opening of voltage-dependent calcium channels. As a result, calcium influx occurs in the β-cells, ultimately stimulating the

release of insulin (Losada-Barragán 2021). This complex interplay of biochemical reactions, regulated by molecules like Leucine, is central to understanding the intricate mechanisms underlying diabetes, a disease with a largely elusive etiology. In light of this, developing accurate laboratory models for studying diabetes is of paramount importance. To induce diabetes in lab animals, various chemical compounds are employed, with STZ being the most prevalent (Akinlade *et al.* 2021; Furman 2021). This approach helps in understanding the complex interactions and mechanisms underlying diabetes. In this study, we explore the impacts of consuming specific compounds, namely Metformin, EGCG, and Leucine, on various physiological parameters in male rabbits with STZ-induced diabetes. Our focus is to assess how these substances influence insulin secretion, blood glucose levels, lipid profiles, and other related factors in this animal model. This approach aims to provide a deeper understanding of the potential therapeutic effects of these compounds in the context of diabetes management. In order to provide a clear and concise overview of the complex nature of diabetes, its impact on lipid metabolism, and the various therapeutic strategies, a comprehensive mind map has been developed. Fig. 1, visually encapsulates the key aspects of the disease, including its characteristics, the alterations in lipid profiles commonly observed in diabetic patients, and the current approaches to treatment and research:


**Fig. 1.** Comprehensive overview of diabetes pathophysiology, lipid impact, and therapeutic approaches.

## MATERIAL AND METHODS

In this research, specific pathogen-free (SPF) male New Zealand White rabbits aged between 10-12 weeks, exhibiting an average mass of 2.98 ± 0.29 kg, were subjected to an acclimatization period under meticulously controlled environmental parameters, with a consistent ambient temperature maintained at 24 ± 1 °C. Subsequently, these animals were methodically segregated into five distinct groups, each comprising six specimens. To precipitate diabetic conditions within the experimental groups, an intraperitoneal administration of STZ was employed, with each dosage quantified at 100 mg $kg^{-1}$. The group designated as the diabetic control was provided a normative diet comprising standard food and water. In contrast, the diabetic sham group was supplemented with corn oil in addition to their regular diet. One experimental subset, termed diabetic experimental group 1, was subjected to treatment involving Metformin, formulated at a concentration of 5 mg $kg^{-1}$ and solubilized in 0.5cc of corn oil. In a divergent approach, diabetic experimental group 2 received a preparation of Epigallocatechin gallate (EGCG), at a concentration of 15 mg $kg^{-1}$, also dissolved in 0.5cc of corn oil. Lastly, diabetic experimental group 3 was administered L-Leucine, with the dosage set at 15 mg $kg^{-1}$, similarly incorporated in a 0.5cc corn oil medium. This treatment regimen was diligently continued for a duration of one month, employing the method of gavage. Parallel to this, the non-diabetic control, sham, and experimental groups were subjected to identical treatments in terms of both the substances used and their dosages. In the execution of the gavage procedure, the apparatus comprised a needle affixed to an insulin syringe, through which the specified solution was administered to the subject animal. This entailed grasping the skin at the posterior cervical and

auricular regions to maintain the animal in an upright posture, facilitating direct delivery of the solution into the esophagus via the needle. Concurrently, throughout the duration of the treatment, volumetric assessments of water intake and urine output were meticulously conducted and documented utilizing a metabolic cage. Additionally, glycemic monitoring was performed on a weekly basis. This necessitated the secure placement of the animal within a specially designed rabbit restrainer to ensure accurate blood glucose measurements. A blood glucometer (AccuChek, Roche Diabetes Care, Inc., Indianapolis, IN, USA) was utilized to ascertain the concentration of blood clots. Subsequent to the conclusion of the treatment phase, cardiac puncture was performed on the rabbits to extract blood samples. These samples were then analyzed for insulin levels using ELISA kits (Crystal Chem). Additionally, lipid profiles, encompassing cholesterol, triglycerides, LDL, and HDL, were quantified using corresponding diagnostic kits. The data underwent rigorous statistical analysis employing one-way ANOVA and Tukey's post hoc test. Subsequent findings are delineated as the mean ± standard error. For inferential statistical determination, a threshold of $P < 0.05$ was established as the criterion of significance.

**RESULTS**

In this part of the study, comprehensive results and insights are detailed for both non-diabetic and diabetic groups. The process began with the evaluation of glucose levels, followed by the analysis of changes in water consumption, urinary excretion, and blood insulin concentrations in the test animals. In the comparative analysis of blood serum glucose level variations, it was found that non-diabetic experimental groups 1 and 3 exhibited no significant deviations ($p < 0.05$) compared to the baseline (sham) group throughout the duration of the treatment. Contrastingly, a significant rise in glucose levels was noted in the non-diabetic experimental group 2 ($p < 0.05$) in week 4 (Fig. 2). Upon analyzing the fluctuations in blood glucose concentrations within diabetic experimental group 1 across the second and third weeks of treatment, the data revealed substantial reductions in glucose levels ($p < 0.001$ and $p < 0.01$, respectively) when contrasted with the sham group. Similarly, diabetic experimental group 3 exhibited a significant reduction in blood glucose concentrations ($p < 0.01$) relative to the sham group. Contrarily, the diabetic experimental group 2 failed to demonstrate a statistically significant alteration in blood glucose levels ($p < 0.05$) in comparison to the sham group (Fig. 3). The observed groups exhibited no significant alterations in blood glucose levels throughout the treatment duration, as evidenced by statistical insignificance ($p < 0.05$) when juxtaposed with the sham group. Notably, solely the non-diabetic experimental group 2, treated with EGCG, demonstrated a statistically significant elevation in blood glucose, reaching a threshold of $p < 0.05$. It is observed that diabetic experimental group 1, treated with Metformin, exhibited a marked decline in blood glucose levels during the second ($p < 0.001$) and third ($p < 0.01$) weeks of treatment, a change which is statistically significant when compared to the sham group. Similarly, diabetic experimental group 3, receiving Leucine, demonstrated a statistically significant reduction in blood glucose levels in the third week ($p < 0.01$) relative to the sham group. However, diabetic experimental group 2, treated with EGCG, did not exhibit any statistically significant alterations in blood glucose levels when compared to the sham group. Upon conducting a comparative analysis of water intake and urine output in non-diabetic experimental groups 1 and 3, it was observed that the water consumption in non-diabetic group 1 exhibited a statistically significant reduction ($p < 0.05$) when juxtaposed with the sham group. Conversely, the water consumption and urine output in non-diabetic group 3 did not demonstrate any significant alterations ($p < 0.05$). In contrast, when evaluating the variations in water consumption and urine volume in diabetic experimental groups 1, 2, and 3, it was discerned that all diabetic cohorts experienced a substantial decline in both water intake and urine output ($p < 0.001$), as compared to the sham group (Fig. 4). It is observed that the water consumption in the non-diabetic experimental group 1, treated with Metformin, exhibits a statistically significant reduction ($p < 0.05$) when contrasted with the sham group. Conversely, the water intake of the non-diabetic experimental group 3, administered with Leucine, does not demonstrate any significant alterations, paralleled by an absence of significant variations in their urine output ($p < 0.05$). A significant decline in both water and urine consumption was observed across all diabetic experimental groups (1, 2 and 3), exhibiting statistically significant differences when compared with the sham group ($p < 0.001$). Subsequent analyses focused on the insulin levels in the rabbits. These were assessed by comparing insulin levels in non-diabetic experimental groups (1, 2, and 3) with those in the non-diabetic sham group, and similarly, comparing diabetic experimental groups (1, 2, and 3) with the diabetic sham group (Fig. 5a). A noteworthy finding was the marked elevation of insulin levels in diabetic experimental group 2 relative to its corresponding sham group ($p < 0.001$), a phenomenon not mirrored in groups 1 and 3, where insulin levels remained statistically

unchanged. A significant increase was exclusively observed in the EGCG diabetes group in comparison to the sham baseline ($p < 0.001$).

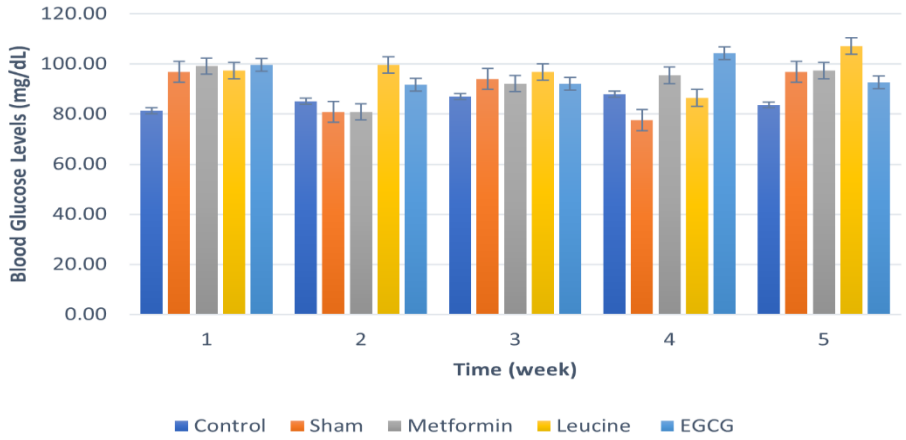



**Fig. 2.** Comparison of blood glucose levels in non-diabetic experimental groups 1, 2, and 3 with the sham group.

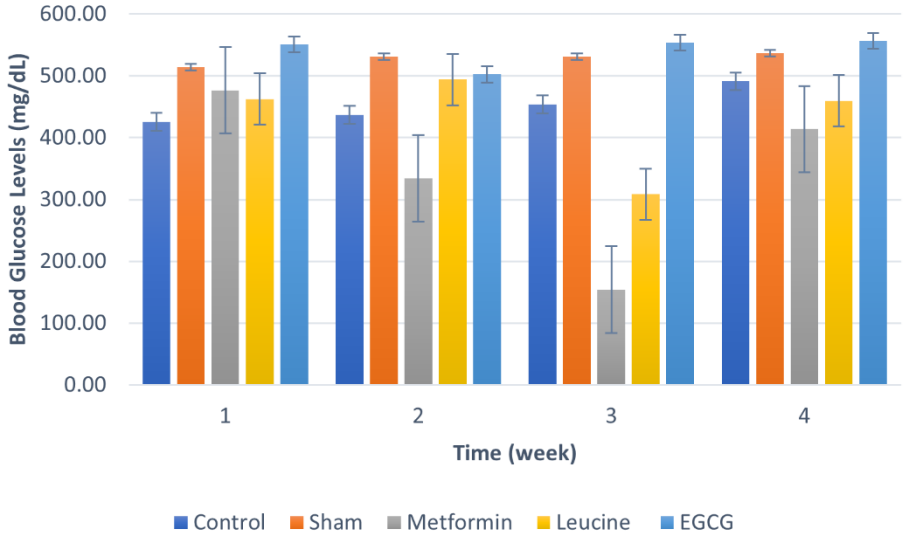
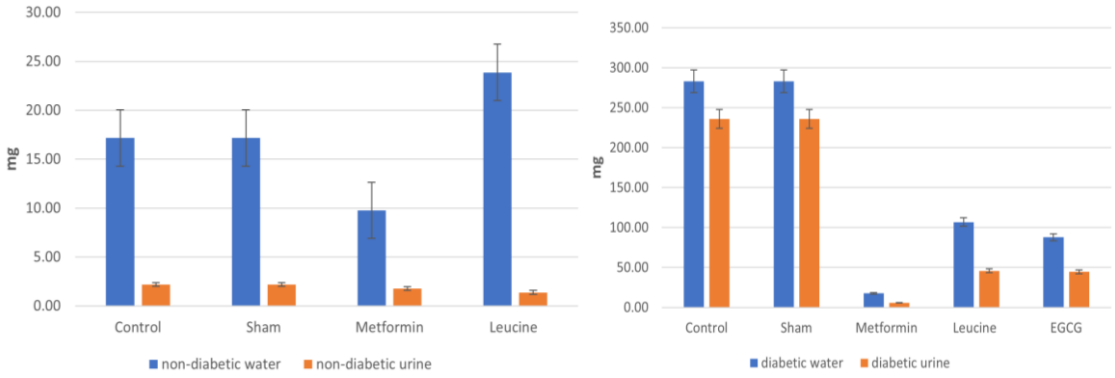



**Fig. 3.** Comparison of blood glucose levels in diabetic experimental groups 1, 2 and 3 with the sham group.




(a) (b)

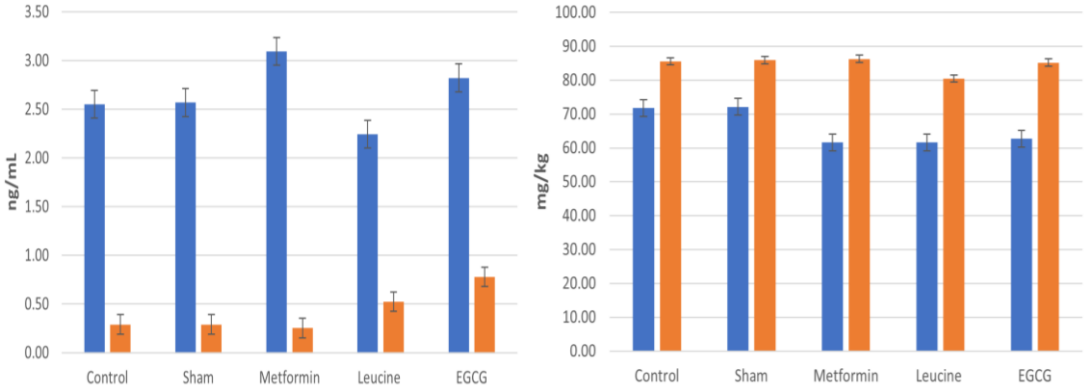
**Fig. 4.** Comparison of water and urine changes with the sham group: **(a)** non-diabetic experimental groups 1 and 3; **(b)** diabetic experimental groups 1, 2 and 3.

Upon examining lipid alterations across the groups under investigation, it was discerned that the administered compounds did not manifest any significant impact on the levels of cholesterol (Fig. 5b) and HDL (Fig. 5c). Contrarily, in the diabetic experimental group 1, a significant reduction in cholesterol levels was noted ($p < 0.001$).

Similarly, in the diabetic experimental group 2, a marked decrease in LDL was observed ( $p < 0.01$; Fig. 5d). However, in the diabetes experimental group 3, despite the recorded decline in LDL levels ($p < 0.01$), there was an observed augmentation in triglyceride levels ($p < 0.05$; Fig. 5e). Diabetic experimental group 2 (EGCG) and diabetic experimental group 3 (Leucine) show a significant decrease in the level ($p < 0.01$) of blood LDL, compared to the sham group. The diabetic experimental group 1 (Metformin) exhibits a statistically significant decrease in triglyceride levels ($p < 0.001$) compared to the sham group. Furthermore, the diabetic experimental group 3 (Leucine), demonstrated a significant increase in triglyceride levels ($p < 0.05$) relative to the sham group during the third week of observation.

## DISCUSSION

The findings of this study on the effects of GDH activators, namely Metformin, EGCG, and Leucine, on insulin secretion and lipid profiles in diabetic rabbits offer novel insights into the management of diabetes. Our results align with and extend the current understanding of GDH activators in diabetes treatment, as indicated in the literature. Our study observed a significant decrease in blood glucose levels in the Metformin-treated group, consistent with established research (Sainero-Alcolado *et al.* 2022). Notably, we also recorded a substantial reduction in triglycerides. This dual effect of Metformin corroborates with findings by Dubey *et al.* (2020), highlighting its potential in managing both hyperglycemia and dyslipidemia in diabetic conditions. The EGCG group exhibited a significant increase in insulin levels without notable change in blood glucose. This is in line with studies by Chang *et al.* (2022), indicating EGCG's influence on insulin sensitivity and glucose metabolism. The lack of significant change in glucose levels, despite increased insulin, might suggest a complex interaction within diabetic physiology, warranting further investigation. The Leucine group demonstrated a decrease in blood glucose and an increase in triglyceride levels. This aligns partially with Losada-Barragán (2021), who discussed Leucine's role in stimulating insulin release. However, the increase in triglycerides presents a contrasting effect, which might be attributed to the varied metabolic pathways influenced by Leucine. The augmentation of insulin levels by EGCG and Leucine mirrors studies on GDH pathways' role in insulin regulation (Bian *et al.* 2022). However, the differential impact on blood glucose levels highlights the intricacy of metabolic responses in diabetic models. The effects on lipid profiles, especially LDL levels by EGCG and Leucine, offer a new perspective compared to traditional therapies. While our findings on cholesterol and HDL remained relatively unchanged, studies by Cochran *et al.* (2021) suggest potential long-term effects on these parameters. The differential efficacies of Metformin, EGCG, and Leucine in modulating insulin and lipid profiles underscore the need for a personalized approach in diabetes management, as indicated in recent diabetes research trends (Rohm *et al.* 2022). The varying responses to different GDH activators emphasize the importance of personalized medicine in diabetes care, considering individual metabolic profiles.




**(a)** **(b)**

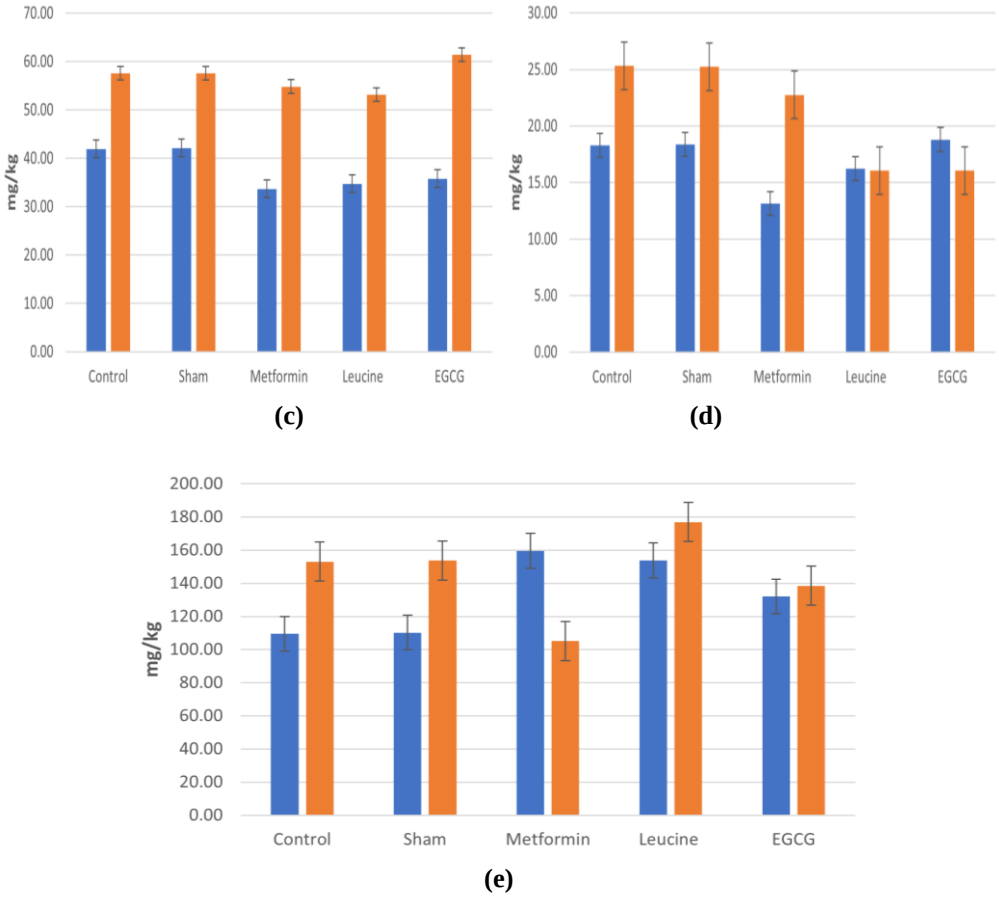



**Fig. 5.** Comparative evaluation of biochemical parameters in rabbit populations: a detailed assessment of **(a)** insulin; **(b)** cholesterol; **(c)** HDL; **(d)** LDL; **(e)** triglyceride levels in non-diabetic (blue) and diabetic (orange) subjects across experimental groups 1, 2, and 3 in relation to their respective sham groups.

Further studies are necessary to elucidate the precise mechanisms through which these compounds modulate insulin and lipid metabolism, especially in the context of different diabetic states. Longitudinal studies are required to assess the long-term implications and safety profiles of these GDH activators, especially regarding their effects on lipid metabolism and cardiovascular risk factors in diabetics.

In conclusion, this study contributes to the expanding landscape of diabetes treatment by exploring the effects of GDH activators. While our findings reinforce some aspects of existing literature, they also raise new questions about the complex interplay of metabolic pathways in diabetes, paving the way for future research and therapeutic advancements.

## CONCLUSION

This study has provided significant insights into the role of glutamate dehydrogenase (GDH) activators in modulating insulin secretion and lipid profiles in a diabetic rabbit model. Our investigation focused on three GDH activators: Metformin, Epigallocatechin Gallate (EGCG), and Leucine, each demonstrating distinct effects on the metabolic parameters of diabetic rabbits.

### Key Findings

1. Metformin showed a pronounced reduction in blood glucose and triglyceride levels, reinforcing its role in the management of hyperglycemia and dyslipidemia.
2. EGCG led to increased insulin levels, indicating its potential in enhancing insulin sensitivity, although it did not significantly alter blood glucose levels.
3. Leucine resulted in decreased blood glucose but increased triglyceride levels, suggesting a complex metabolic influence that needs further exploration.

**Implications for Diabetes Management**

- The differential responses to these GDH activators highlight the potential for personalized treatment strategies in diabetes care.
- Understanding the specific pathways and mechanisms through which these compounds exert their effects is critical for developing targeted therapies.
- The effects observed on lipid profiles, particularly with Metformin and Leucine, suggest broader implications for cardiovascular health in diabetic patients.

**Limitations and Future Directions**

- While our study provides valuable data, it is limited to a rabbit model of diabetes. Human clinical trials are essential to validate these findings.
- Long-term studies are needed to assess the safety and efficacy of these treatments over extended periods.
- Further research should also explore the interactions between these GDH activators and other metabolic pathways, particularly in relation to cardiovascular risk factors.
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**Final Thoughts**

This research contributes to the understanding of GDH activators as potential therapeutic agents in diabetes management. The findings underscore the complexity of diabetes as a metabolic disorder and the need for a multifaceted approach in its treatment. We hope that this study will pave the way for more personalized and effective strategies in combating diabetes and its complications.

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