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Peer Review

Review of: "Evaluation of Antidiabetic Potential of Gymnema Sylvestre and Metformin Combination in Streptozotocin-Induced Diabetic Rats"

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The research article titled "Evaluation of Antidiabetic Potential of Gymnema Sylvestre and Metformin Combination in Streptozotocin-Induced Diabetic Rats" presents a well-structured and scientifically sound preclinical investigation.

The study aims to evaluate and compare the antidiabetic potential of Gymnema sylvestre, metformin, and their combination — a timely and relevant topic considering the growing interest in complementary therapies for T2DM.

Use of the high-fat diet + STZ-induced diabetic rat model is appropriate and widely accepted for mimicking T2DM in humans.

Proper grouping (control, diabetic control, Met, GS, Met+GS) with randomization is well-executed.

Well-Defined Interventions: Dosage selection and routes of administration are justified based on prior studies.

A duration of 4 weeks is reasonable for observing biochemical and physiological changes.

Comprehensive Parameters: Measurement of FBG, HbA1c, creatinine, cholesterol, and weight provides a multidimensional view of antidiabetic and systemic effects.

Statistical Analysis: Use of two-way ANOVA with Tukey's post hoc test and reporting of p-values (<0.05) is appropriate and strengthens the conclusions.

Tables and figures are clearly laid out with consistent results across replicates.

The results are reported in a way that matches the objectives and leads logically into the discussion.

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Areas for Improvement:

Literature Context:

The introduction could provide more comparative context with previous studies evaluating metformin-herb combinations.

Discussion Depth:

While the discussion summarizes the findings well, it could benefit from deeper mechanistic insights, especially regarding why metformin outperforms GS and the biological basis for potential synergy.

Standardization of Herbal Extract:

There is no mention of the standardization or specific active components (e.g., gymnemic acids) in the Gymnema extract. This would be crucial for reproducibility and future clinical translation.

Sample Size Justification:

Although n=6 per group is standard in preclinical work, a power analysis or justification of sample size would improve methodological transparency.

Language and Editing:

Minor grammatical errors and typos, and occasional formatting inconsistencies, reduce the polish of the manuscript.

1. Strengthen the Introduction with Specific Prior Studies

The current introduction mentions the relevance of combining Gymnema sylvestre (GS) and metformin but lacks depth in citing key previous works. You could enhance the rationale for your study by referencing and briefly analyzing the following:

Patel, K., Gadewar, M., & Tripathi, R. (2012). Pharmacological and analytical aspects of gymnemic acid: a concise report. Asian Pacific Journal of Tropical Disease, 2(5), 414-416.

Patel, K., Gadewar, M., Tripathi, R., Prasad, S. K., & Patel, D. K. (2012). A review on medicinal importance, pharmacological activity and bioanalytical aspects of beta-carboline alkaloid “Harmine”. Asian Pacific journal of tropical biomedicine, 2(8), 660-664.

Subramoniam, A. (2016). Plants with anti-diabetes mellitus properties. CRC Press.

Janapati, Y. K., Junapudi, S., & Dachani, S. R. (2021). Optimization of diabetes by herbal medicine. Technol Innov Manag Rev, 6, 1-18.

These examples can bolster your argument that GS is not only a traditional antidiabetic herb but has demonstrated complementarity with metformin in prior models — justifying your combination approach.

2. Add Mechanistic Insights or Hypotheses for the Synergy

While your results clearly show that the combination group (Met+GS) improved glycemic markers more than GS alone, the mechanistic rationale for this synergy is not explored in the discussion. Below are some biological mechanisms that could be incorporated to deepen the scientific insight:

Complementary Pathways Hypothesis

Metformin acts primarily by inhibiting hepatic gluconeogenesis via AMPK activation, which increases insulin sensitivity and glucose uptake in peripheral tissues.

Gymnemic acids in GS are believed to:

Promote pancreatic β-cell regeneration and insulin secretion

Inhibit intestinal glucose absorption by occupying sweet taste receptors

Reduce oxidative stress and inflammation, contributing to insulin action.

Hypothesis: The synergy may result from dual pathway modulation: metformin improves insulin sensitivity (input-side), while GS enhances insulin secretion and reduces glucose influx (output-side).

Antioxidant + Metabolic Effects

Oxidative stress plays a key role in insulin resistance and β-cell dysfunction. GS has antioxidant and anti-inflammatory activity, which may complement metformin's metabolic effects, leading to better preservation of pancreatic function.

Potential Gene Expression Modulation

There's emerging evidence that herbal constituents like those in GS may influence the expression of glucose transporter proteins (GLUT4), insulin receptor substrates (IRS-1/2), and SIRT1 — all of which are also modulated by metformin.

Suggestion: Add a sentence such as:

"Future studies should investigate whether the observed synergy stems from complementary

modulation of insulin signaling and glucose transporter gene expression by metformin and Gymnema sylvestre, respectively."

3. Suggested Edits for Discussion

You could add the following section or integrate these points into the existing discussion:

The enhanced antidiabetic effects observed in the metformin-GS combination group may be attributed to a complementary mechanism. While metformin acts via AMPK activation to suppress hepatic gluconeogenesis and improve peripheral glucose uptake, GS may stimulate pancreatic insulin secretion, inhibit intestinal glucose absorption, and exert antioxidative effects. This dual action could explain the greater reduction in fasting blood glucose, cholesterol, and HbA1c levels seen in the combination group compared to GS alone.

Declarations

Potential competing interests: No potential competing interests to declare.