

Peer Review

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

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This study investigates the antidiabetic efficacy of *Gymnema sylvestre* (GS) and metformin, both individually and in combination, using a high-fat diet (HFD) and streptozotocin (STZ)-induced rat model of Type 2 Diabetes Mellitus (T2DM). Given the increasing global prevalence of T2DM and the ongoing need for improved management strategies with enhanced efficacy and fewer side effects, this research addresses a highly relevant and important public health challenge. The exploration of a traditional medicinal plant alongside a conventional first-line drug holds significant potential for integrative therapeutic approaches. A key strength of this study lies in its well-established animal model for T2DM. The use of a high-fat diet followed by low-dose streptozotocin effectively mimics the dual pathophysiological defects seen in human T2DM, encompassing both insulin resistance and pancreatic β -cell dysfunction. This robust model provides a suitable and reliable platform for assessing the efficacy of potential antidiabetic agents, thereby increasing the translatability of the findings to the human condition. The study's systematic evaluation of key biochemical and physiological parameters is another notable strength. By meticulously monitoring fasting blood glucose (FBG), total cholesterol, serum creatinine, and HbA1c over the treatment period, the authors provide a comprehensive picture of the metabolic changes induced by the interventions. The clear presentation of results in Table 2 and the accompanying figures effectively illustrates the treatment effects and allows for straightforward interpretation of the data. The findings regarding metformin's efficacy are consistent with established literature, reinforcing its role as a potent antidiabetic agent that improves glycemic control, lipid profiles, and renal function. This serves as a strong internal control for the study, validating the experimental setup and the responsiveness of the chosen animal model to a known therapeutic. The confirmation of

metformin's pronounced effects adds confidence to the comparative analysis with *Gymnema sylvestre*. The investigation of *Gymnema sylvestre* is particularly valuable, shedding light on the antidiabetic properties of this traditional Indian medicinal plant. While its glucose-lowering effect was more modest than metformin, the observation that it contributes to glycemic regulation and improves other metabolic parameters supports its historical use in Ayurvedic practice and suggests its potential as a complementary therapy. This highlights the ongoing importance of exploring natural compounds for their therapeutic potential. The inclusion of a combination therapy group (Metformin + GS) is a thoughtful aspect of the study design. This allows for an assessment of potential additive or synergistic interactions between the conventional drug and the herbal extract. Although the study concluded an additive rather than synergistic effect, this finding is important for guiding future research and clinical applications. Understanding the nature of such interactions is crucial for developing effective integrative treatment strategies. However, the study also presents several opportunities for improvement that, if addressed, could significantly enhance its scientific rigor and clinical relevance. A primary limitation is the relatively short 28-day treatment period. While this duration may be sufficient for initial efficacy screening, it is often inadequate for evaluating the long-term effectiveness, safety, or potential toxicity of chronic interventions for a progressive disease like T2DM. Longer-term studies are essential to understand sustained effects and potential adverse outcomes. The modest sample size ($n = 6$ per group) is another significant limitation. While the authors acknowledge this, it is crucial to emphasize that such a sample size may restrict the statistical power of the study, potentially leading to an inability to detect true differences or limiting the generalizability of the findings. Future studies should consider larger sample sizes to enhance the robustness and reliability of the statistical analyses. A notable absence in the methodological approach is the lack of functional evaluations such as oral glucose tolerance tests (OGTT) and insulin tolerance tests (ITT). These tests are critical for providing a more comprehensive understanding of glucose metabolism, insulin sensitivity, and β -cell function. Their inclusion would have provided more detailed insights into how each treatment, particularly the combination, influences the underlying mechanisms of glucose homeostasis beyond just fasting blood glucose and HbA1c levels. Furthermore, the study did not delve into the biological processes driving insulin resistance, such as insulin receptor signaling or GLUT4 expression. The exclusion of histopathological examinations of the pancreas, liver, and kidneys also restricts the morphological confirmation of biochemical results and limits the ability to assess potential organ-specific protective or adverse effects. Incorporating these mechanistic and histological analyses would provide a deeper understanding of the treatments' modes of action and their impact on target organs. In conclusion, this study provides valuable preliminary evidence

for the antidiabetic effects of *Gymnema sylvestre* and metformin in a relevant animal model of T2DM. Its strengths lie in the appropriate disease model and the comprehensive measurement of key metabolic parameters. However, to translate these promising findings into clinically meaningful insights, future research should prioritize longer treatment durations, larger sample sizes, the incorporation of functional metabolic tests, investigation into molecular mechanisms, and histopathological evaluations. These enhancements would contribute significantly to a more complete understanding of *Gymnema sylvestre*'s potential role as an adjunct therapy in the complex management of Type 2 Diabetes Mellitus.

Declarations

Potential competing interests: No potential competing interests to declare.