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Peer Review

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

Jonas Michel Wolf[1]

1. Hospital Moinhos de Vento, Porto Alegre, Brazil

This study investigates the antidiabetic potential of a combination therapy involving *Gymnema sylvestre* (G. sylvestre) and metformin in a streptozotocin (STZ)-induced rat model of Type 2 Diabetes Mellitus (T2DM). Given the rising global prevalence of T2DM and the continuous search for improved therapeutic strategies with fewer side effects, this research addresses a highly relevant public health concern. The exploration of a natural product in combination with a well-established conventional antidiabetic drug is a promising avenue for integrative medicine.A key strength of this study lies in its well-structured experimental design for inducing T2DM. The use of a high-fat diet (HFD) followed by low-dose STZ administration accurately mimics the dual pathophysiological mechanisms of human T2DM: insulin resistance and partial pancreatic β-cell dysfunction. This model provides a more relevant and robust platform for evaluating antidiabetic agents compared to models relying solely on high-dose STZ, which primarily induces Type 1 diabetes.The study clearly defined and measured a comprehensive set of key metabolic and renal parameters, including fasting blood glucose (FBG), total cholesterol, serum creatinine, and HbA1c. These are crucial indicators for assessing glycemic control, lipid metabolism, and renal function in diabetes. The consistent and significant improvements observed across these parameters in the treatment groups, especially with metformin, strongly support the efficacy of the interventions.The inclusion of both individual treatments (metformin alone and G. sylvestre alone) and their combination allows for a direct comparison of their effects. This approach helps to elucidate whether G. sylvestre has independent antidiabetic properties and, more importantly, whether its combination with metformin yields additive or synergistic benefits. The finding that the combination provides additional benefits over G. sylvestre alone is a valuable insight for potential adjunctive

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therapies.Furthermore, the use of two-way ANOVA followed by Tukey's post-hoc test for statistical analysis is appropriate for this experimental design, allowing for the assessment of differences between multiple treatment groups across time points. This robust statistical approach enhances the reliability of the reported findings regarding treatment efficacy. The clear presentation of results in tables and figures, along with statistical annotations, aids in the interpretation of the data.However, several significant opportunities for improvement exist that, if addressed, could substantially enhance the scientific rigor, mechanistic understanding, and translational potential of this research. A primary limitation, acknowledged by the authors, is the small sample size of n=6 rats per group. This small number significantly limits the statistical power of the study and the generalizability of the findings, making it difficult to draw definitive conclusions about the efficacy and interactions of the treatments. Future studies should aim for larger sample sizes to ensure more robust and reproducible results.The 28-day treatment duration, while providing initial insights, may not be sufficient to fully assess the long-term safety, sustained efficacy, or the progression of diabetic complications. T2DM is a chronic disease, and a longer study period would offer more comprehensive data on the durability of the antidiabetic effects and potential long-term benefits or adverse effects of the combination therapy.A critical omission is the lack of functional assessments such as oral glucose tolerance tests (OGTT) and insulin tolerance tests (ITT). These tests are essential for a deeper understanding of how the treatments affect glucose metabolism, insulin sensitivity, and pancreatic beta-cell function, which are core pathophysiological aspects of T2DM. Their inclusion would provide mechanistic insights beyond just fasting blood glucose and HbA1c levels.Another significant opportunity for improvement is the absence of histological analysis of key metabolic organs, particularly the pancreas, liver, and kidneys. Histopathological examination would allow for the correlation of observed biochemical changes with structural alterations, such as pancreatic islet integrity, insulin granule content, hepatic steatosis, or renal damage. This would provide direct evidence of the protective or restorative effects of the treatments on these target organs.Finally, the study acknowledges the lack of phytochemical profiling of the *Gymnema sylvestre* extract. Identifying and quantifying the active compounds (e.g., specific gymnemic acids) would be crucial for standardizing the extract, understanding its precise mechanisms of action, and ensuring reproducibility in future research. Investigating molecular mechanisms, such as insulin signaling pathways (e.g., GLUT4 translocation, IRS-1 phosphorylation), would also provide valuable mechanistic depth.In conclusion, this study provides valuable preliminary data on the antidiabetic potential of *Gymnema sylvestre* as an adjunct to metformin in a relevant animal model of T2DM. Its strengths lie in the appropriate T2DM induction model and comprehensive metabolic parameter assessment. However, to truly advance the understanding and

translational potential of this combination therapy, future research must address the limitations regarding sample size, study duration, inclusion of functional and histological assessments, and detailed phytochemical and mechanistic investigations. Such comprehensive studies are essential before considering clinical translation.

Declarations

Potential competing interests: No potential competing interests to declare.