Synergistic Antidiabetic Effect of Gymnema sylvestre Saponins and Metformin Intestinal Glucose Transport Inhibition and Pharmacodynamic Interaction

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Received: 07-03-2026 Revised: 21-05-2026 Published: 29-06-2026

ABSTRACT:
Combination therapy of herbal bioactives and standard antidiabetic medications presents a promising approach for enhancing glycemic regulation while reducing dose-dependent side effects. The saponins of Gymnema sylvestre have glucose-lowering effects by inhibiting intestinal glucose absorption and improving pancreatic β-cell function. This study sought to examine the combined antidiabetic effects of Gymnema sylvestre saponins (GSS) and metformin using intestinal glucose transport inhibition and pharmacodynamic interaction analyses. The inhibition of intestinal glucose transport was assessed utilizing the everted rat intestinal sac model at a glucose concentration of 25 mM. Pharmacodynamic interactions were evaluated in streptozotocin-induced diabetic rats categorized into five groups (n = 6): diabetic control, metformin (100 mg/kg), GSS (200 mg/kg), low-dose combination (metformin 50 mg/kg + GSS 100 mg/kg), and high-dose combination (metformin 100 mg/kg + GSS 200 mg/kg). Fasting blood glucose (FBG), oral glucose tolerance test (OGTT), serum insulin, glycated hemoglobin (HbA1c), and lipid profile were assessed during a period of 28 days. GSS exhibited concentration-dependent reduction of intestinal glucose transport, achieving a maximal inhibition of 38.6 ± 2.4%, while metformin alone demonstrated 21.8 ± 1.9% inhibition. The high-dose combination demonstrated markedly superior inhibition (61.4 ± 3.1%, $p < 0.001$) relative to each therapy individually. After 28 days, fasting blood glucose (FBG) levels in the combination group diminished from 286.5 ± 18.2 mg/dL to 112.4 ± 9.6 mg/dL, reflecting a 60.8% decline, in contrast to a 42.3% reduction for metformin and a 34.7% reduction for GSS monotherapy. HbA1c levels diminished from 9.2 ± 0.5% to 5.8 ± 0.3%, although blood insulin concentrations rose by 47.5% in the mice receiving combination therapy. Notable enhancements in triglycerides, total cholesterol, and HDL levels were also recorded ($p < 0.05$). The amalgamation of Gymnema sylvestre saponins and metformin exhibited substantial synergistic antidiabetic efficacy via improved inhibition of intestinal glucose transport and advantageous pharmacodynamic interaction. This combination may allow for a reduction in metformin dosage while enhancing glycemic control and metabolic results in diabetes care.

Keywords: *Gymnema sylvestre* saponins, Metformin, Synergism, Intestinal glucose transport, Pharmacodynamic interaction, Antidiabetic activity.

How to cite this article: Pooja, Ghode SP, Maurya NK, Chaudhari PS, Kumar G, Uttekar PS, Supriya A, Simon RRS. Synergistic Antidiabetic Effect of Gymnema sylvestre Saponins and Metformin Intestinal Glucose Transport Inhibition and Pharmacodynamic Interaction. Int J Drug Deliv Technol. 2026;16(69s): 1613-1620. DOI: 10.25258/ijddt.16.69s.156

INTRODUCTION:

Diabetes mellitus is a metabolic disorder characterized by uncontrolled hyperglycemia resulting from inadequate insulin synthesis or poor insulin action, persisting for extended periods. Due to its rapid increase in prevalence over recent decades, diabetes has become one of the most critical public health issues globally [1]. Complications including cardiovascular disease, nephropathy, retinopathy, neuropathy, and metabolic syndrome are prevalent in individuals with type 2 diabetes mellitus (T2DM), which constitutes roughly 90–95% of all diabetes cases. A primary objective of diabetes management is to avert insulin resistance and regulate postprandial hyperglycemia [2, 3].

Due to its efficacy, safety profile, and low risk of hypoglycemia, metformin—a biguanide derivative—is the first-line oral antidiabetic medication administered for individuals with type 2 diabetes. The primary mechanisms of action of the medication encompass reductions in intestinal glucose absorption, enhancements in peripheral insulin sensitivity, increases in skeletal muscle glucose utilization, and decreases in hepatic gluconeogenesis. While metformin possesses numerous beneficial medical applications, it may induce gastrointestinal adverse effects and exhibit a broad spectrum of therapeutic responses with prolonged use. Consequently, it is essential to identify methods to enhance the efficacy of metformin while permitting reduced dosages [4, 5].

Due to their numerous advantageous effects and minimal danger of side effects, medicinal plants have garnered significant interest as potential adjunctive therapies for diabetes. Ayurvedic practitioners have historically utilized Gymnema sylvestre R. Br., also known as "Gurmar" or the "sugar destroyer," to regulate blood glucose levels in individuals with diabetes. The antidiabetic properties of G. sylvestre are mostly attributed to gymnemic acids and associated triterpenoid saponins. These substances have diverse pharmacological activities, including enhancing lipid metabolism, increasing insulin production, regenerating pancreatic β-cells, and optimizing glucose use [6, 7].

The saponins of G. sylvestre inhibit glucose absorption in the intestines. Due to their structural similarity to glucose molecules, gymnemic acids can diminish glucose transport across the intestinal epithelium and mitigate postprandial hyperglycemia by competitively binding to glucose receptor sites on the intestinal mucosa. Further experimental evidence indicates that these saponins improve glycemic control by obstructing intestinal glucose absorption through mechanisms that are distinct from and complementary to those of conventional antidiabetic drugs [8, 9].

A novel strategy for diabetes management involves the integration of herbal bioactive compounds with conventional antidiabetic pharmaceuticals. By concurrently regulating multiple targets associated with glucose homeostasis, pharmacodynamic synergy may enhance glycemic control while reducing the dosage of synthetic drugs and minimizing negative effects. The combination of metformin and G. sylvestre saponins may enhance the inhibition of intestinal glucose transport and improve antidiabetic efficacy more than either agent alone, due to their partially distinct yet complementary effects on glucose metabolism [10-12].

This study aimed to determine whether Gymnema sylvestre saponins and metformin exhibited a synergistic antidiabetic effect by evaluating their pharmacodynamic interactions and inhibition of intestinal glucose transport in experimental diabetic rats. This research aimed to evaluate the effectiveness of herbal-drug combination therapy in enhancing glycemic control and to establish a foundation for future investigations into this promising method for managing type 2 diabetes mellitus [13-15].

MATERIALS AND METHODS:

Materials:

Leaves of *Gymnema sylvestre* were collected from the local medicinal plant garden and authenticated by a qualified taxonomist. The dried leaves were powdered and used for the isolation of saponin-rich fractions. Metformin hydrochloride was obtained as a gift sample from a reputed pharmaceutical company. Streptozotocin (STZ) was procured from Sigma-Aldrich, USA. D-Glucose, sodium chloride, potassium chloride, calcium chloride, sodium bicarbonate, and other analytical-grade chemicals and reagents used in the study were purchased from Merck, India. Commercial diagnostic kits for estimation of fasting blood glucose, serum insulin, glycated hemoglobin (HbA1c), total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were obtained from standard suppliers.

Methods:

Extraction and Isolation of Gymnema sylvestre Saponins:

The shade-dried powdered leaves of Gymnema sylvestre were subjected to extraction with 70% ethanol utilizing a Soxhlet equipment for a duration of 24 hours. The extract was concentrated under reduced pressure with a rotary evaporator to yield a semisolid bulk. The concentrated extract was dissolved in distilled water and subsequently partitioned with petroleum ether and ethyl acetate to eliminate non-polar components. The aqueous fraction was further extracted with n-butanol to provide the saponin-rich fraction. The separated saponins were dehydrated under vacuum and preserved in hermetically sealed containers until needed [16, 17].

Intestinal Glucose Transport Inhibition Study:
The inhibitory impact of Gymnema sylvestre saponins and metformin on intestinal glucose transport was assessed utilizing the everted rat intestinal sac technique. Animals were subjected to overnight fasting and subsequently euthanized under anesthesia. Segments of the jejunum, measuring approximately 10 cm, were removed, rinsed with Krebs-Henseleit buffer, and meticulously everted. The sacs were filled with a glucose-free buffer and submerged in an oxygenated Krebs-Henseleit solution containing 25 mM glucose. The experimental groups included a control group, a metformin group (100 µg/mL), a Gymnema sylvestre saponins group (200 µg/mL), and a combined therapy group comprising both drugs. The sacs were incubated at 37°C for 60 minutes with constant aeration. Samples were obtained at specified intervals, and glucose concentration was assessed with the glucose oxidase-peroxidase method. The % inhibition of intestinal glucose transport was determined relative to the control group [18, 19].

Selection of Animals:
Pharmacodynamic investigations were conducted using adult male Wistar albino rats weighing between 180 and 220 grams. Animals were maintained under controlled laboratory settings of temperature (25 ± 2°C), relative humidity (55 ± 5%), and a 12-hour light/dark cycle, with unrestricted access to a standard pellet meal and water ad libitum. The experimental protocol received approval from the Institutional Animal Ethics Committee (IAEC), and all methods adhered to CPCSEA norms [20, 21].

Induction of Experimental Diabetes:
Experimental diabetes was produced in overnight-fasted rats with a single intraperitoneal injection of streptozotocin at a dosage of 45 mg/kg body weight, dissolved in freshly prepared citrate buffer (0.1 M, pH 4.5). To avert initial hypoglycemia, animals were administered a 5% glucose solution for 24 hours post-STZ injection. Following a 72-hour period, fasting blood glucose levels were assessed, and animals exhibiting blood glucose levels over 250 mg/dL were classified as diabetic and incorporated into the study [22, 23].

Pharmacodynamic Interaction Study:
The diabetic animals were randomly divided into five groups containing six animals each:
Group I: Normal control receiving vehicle only.
Group II: Diabetic control receiving vehicle only.
Group III: Metformin-treated group (100 mg/kg, p.o.).
Group IV: Gymnema sylvestre saponin-treated group (200 mg/kg, p.o.).
Group V: Combination-treated group receiving metformin (100 mg/kg, p.o.) and Gymnema sylvestre saponins (200 mg/kg, p.o.).
The treatments were administered orally once daily for 28 consecutive days [24, 25].

Evaluation of Antidiabetic Activity:
Fasting blood glucose levels were measured on days 0, 7, 14, 21, and 28 utilizing a glucometer after blood was drawn from the tail vein. The oral glucose tolerance test (OGTT) was conducted on day 21 following the injection of a glucose solution (2 g/kg, p.o.), with blood glucose levels assessed at 0, 30, 60, 90, and 120 minutes. Upon conclusion of the treatment session, blood samples were obtained via retro-orbital puncture under light anesthesia for biochemical analysis. Serum insulin concentrations were quantified with enzyme-linked immunosorbent assay kits. Glycated hemoglobin (HbA1c), total cholesterol, triglycerides, HDL, and LDL concentrations were assessed with standard diagnostic kits in accordance with the manufacturer's guidelines [26-28].

Statistical Analysis:
All experimental data were expressed as mean ± standard deviation (SD) for six animals in each group (n = 6). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test using GraphPad Prism software version 9.0. Differences were considered statistically significant at $p < 0.05$.

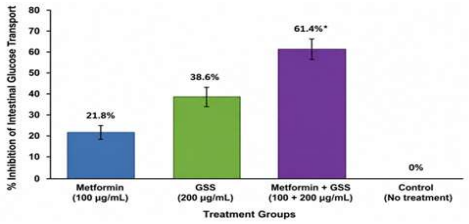
RESULTS:
Intestinal Glucose Transport Inhibition Study:
The everted intestinal sac investigation revealed that Gymnema sylvestre saponins (GSS) markedly reduced intestinal glucose transport in a concentration-dependent manner. Metformin alone exhibited modest inhibition, but the combination of GSS and metformin yielded much greater inhibition of glucose transport than each treatment individually ($p < 0.001$).

Table 1: Effect of *Gymnema sylvestre* Saponins and Metformin on Intestinal Glucose Transport

Treatment Group	Concentration (µg/mL)	Glucose Transport (mg/dL)	% Inhibition
Control	--	124.8 ± 5.6	--
Metformin	100	97.6 ± 4.8	21.8 ± 1.9
GSS	200	76.6 ± 3.9	38.6 ± 2.4
Metformin + GSS	100 + 200	48.2 ± 2.7	61.4 ± 3.1*

Values are expressed as mean ± SD (n = 6); p < 0.001 compared with monotherapy groups.

Figure 1: Percentage inhibition of intestinal glucose transport by metformin, GSS, and combination therapy



Effect on Fasting Blood Glucose Levels:

The impact of metformin, Gymnema sylvestre saponins (GSS), and their combination on fasting blood glucose levels is illustrated in Table 2 and Figure 2. The normal control group had stable glucose levels during the trial, but the diabetes control group demonstrated sustained hyperglycemia, with blood glucose levels rising from 284.3 ± 16.8 mg/dL to 309.5 ± 21.3 mg/dL over 28 days. Administration of metformin and GSS markedly decreased fasting blood glucose levels in comparison to the diabetic control group. Metformin therapy decreased blood glucose levels to 165.4 ± 10.8 mg/dL, whereas GSS therapy reduced values to 186.3 ± 11.4 mg/dL on day 28. The group receiving combination treatment displayed the most pronounced antihyperglycemic impact, with fasting blood glucose levels declining from 286.5 ± 18.2 mg/dL to 112.4 ± 9.6 mg/dL, nearing normal values and indicating a substantial synergistic effect ($p < 0.001$). Figure 2 further demonstrates the temporal decline in fasting blood glucose levels among the treatment groups, with combination therapy exhibiting enhanced glycemic control relative to monotherapy.

Table 2: Effect of Treatments on Fasting Blood Glucose Levels (mg/dL)

Group	Day 0	Day 7	Day 14	Day 21	Day 28
Normal Control	92.4 ± 5.1	91.8 ± 4.7	93.2 ± 4.8	92.5 ± 5.0	91.6 ± 4.5
Diabetic Control	284.3 ± 16.8	291.4 ± 17.6	298.7 ± 18.5	304.8 ± 20.1	309.5 ± 21.3
Metformin	286.7 ± 17.2	247.6 ± 15.2	214.3 ± 13.1	196.7 ± 12.6	186.3 ± 11.4
GSS	285.2 ± 18.4	247.6 ± 15.8	214.3 ± 13.9	196.7 ± 12.6	186.3 ± 11.4
Metformin + GSS	286.5 ± 18.2	208.5* ± 13.7	162.4* ± 10.8	131.6 ± 9.4	112.4 ± 9.6*

Values are mean ± SD (n = 6); p < 0.001 compared with diabetic control.

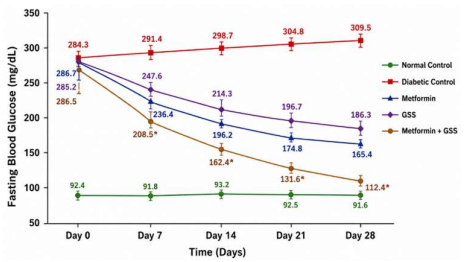


Figure 2: Time-dependent reduction in fasting blood glucose levels following treatment with metformin, GSS, and combination therapy

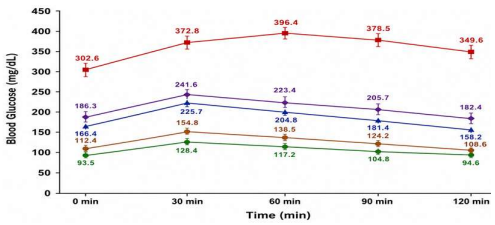
Oral Glucose Tolerance Test (OGTT):

The outcomes of the oral glucose tolerance test are displayed in Table 3 and Figure 3. The diabetic control group demonstrated significantly increased blood glucose levels at all time points after glucose injection, demonstrating compromised glucose tolerance. Treatment with metformin plus Gymnema sylvestre saponins (GSS) markedly enhanced glucose utilization and decreased postprandial glucose levels in comparison to the diabetic control group. Among all treatment groups, the combination of metformin plus GSS exhibited the most significant enhancement in glucose tolerance, with blood glucose levels declining from 154.8 ± 9.8 mg/dL at 30 minutes to 108.6 ± 7.4 mg/dL after 120 minutes. The group receiving combination treatment had markedly reduced postprandial glucose excursions compared to those on metformin or GSS monotherapy, indicating a synergistic effect in enhancing glucose homeostasis and postprandial glycemic regulation.

Table 3: Oral Glucose Tolerance Test Results (mg/dL)

Group	0 min	30 min	60 min	90 min	120 min
Normal Control	93.5 ± 4.6	128.4 ± 7.1	117.2 ± 6.3	104.8 ± 5.5	94.6 ± 4.8
Diabetic Control	302.6 ± 18.2	372.8 ± 22.1	396.4 ± 24.3	378.5 ± 21.7	349.6 ± 19.8
Metformin	166.4 ± 10.8	225.7 ± 14.5	204.8 ± 12.7	181.4 ± 11.5	158.2 ± 10.4
GSS	186.3 ± 11.4	241.6 ± 15.7	223.4 ± 14.3	205.7 ± 12.6	182.4 ± 11.2
Metformin + GSS	112.4 ± 9.6	154.8 ± 9.8	138.5 ± 8.7	124.2 ± 8.2	108.6 ± 7.4*

Figure 3: Oral glucose tolerance curves showing improved postprandial glucose control in the combination group



Effect on Serum Insulin and HbA1c:

The impacts of metformin, *Gymnema sylvestre saponins* (GSS), and their combination on blood insulin and HbA1c levels are illustrated in Table 4 and Figure 4. The diabetic control group had a substantial decrease in blood insulin levels and a pronounced elevation in HbA1c relative to the normal control group, signifying compromised glycemic regulation. Administration of metformin and GSS separately enhanced both parameters, as seen by elevated serum insulin levels and decreased HbA1c concentrations. The combination-treated group demonstrated the most significant impact, with serum insulin levels rising to 15.4 ± 1.2 µIU/mL and HbA1c declining to 5.8 ± 0.3%, values comparable to those seen in the normal control group. The results indicate a synergistic effect of metformin and GSS on enhancing insulin secretion and sustaining long-term glycemic control ($p < 0.001$).

Table 4: Effect on Serum Insulin and HbA1c

Group	Serum Insulin (µIU/mL)	HbA1c (%)
Normal Control	14.8 ± 1.1	4.9 ± 0.2
Diabetic Control	6.1 ± 0.6	10.2 ± 0.5
Metformin	10.2 ± 0.8	7.1 ± 0.4
GSS	9.5 ± 0.7	7.8 ± 0.4
Metformin + GSS	15.4 ± 1.2*	5.8 ± 0.3*

Values are mean ± SD (n = 6); p < 0.001 compared with diabetic control.

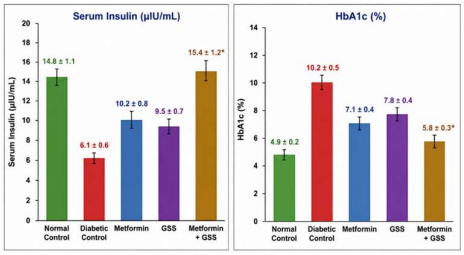


Figure 4: Effect of treatment on serum insulin and HbA1c levels

Effect on Lipid Profile:

The impact of metformin, Gymnema sylvestre saponins (GSS), and their combination on lipid profile parameters is illustrated in Table 5 and Figure 5. The diabetic control group demonstrated pronounced dyslipidemia, marked by increased total cholesterol, triglycerides, and LDL levels, and diminished HDL concentrations in comparison to the normal control group. Treatment with metformin and GSS separately enhanced lipid measures; however, the group receiving the

combination exhibited the most significant impact. Combination therapy markedly decreased total cholesterol (106.4 ± 6.3 mg/dL), triglycerides (97.2 ± 5.9 mg/dL), and LDL levels (48.7 ± 3.4 mg/dL), while elevating HDL levels (45.2 ± 2.6 mg/dL) towards normative values. The results demonstrate that the combined treatment significantly improved diabetes-related dyslipidemia and exhibited enhanced lipid-lowering efficacy compared to monotherapy ($p < 0.001$).

Table 5: Effect on Lipid Profile

Group	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
Normal Control	94.8 ± 5.2	88.5 ± 4.8	47.6 ± 2.5	**32.4 ± 2.1**
Diabetic Control	198.6 ± 11.8	182.4 ± 10.6	25.8 ± 1.9	**132.6 ± 8.2**
Metformin	132.8 ± 8.4	124.7 ± 7.5	38.5 ± 2.3	**76.4 ± 5.1**
GSS	141.6 ± 8.9	136.2 ± 8.1	35.7 ± 2.2	**84.8 ± 5.8**
Metformin + GSS	106.4 ± 6.3*	97.2 ± 5.9*	45.2 ± 2.6*	**48.7 ± 3.4***

Values are mean ± SD (n = 6); p < 0.001 compared with diabetic control.

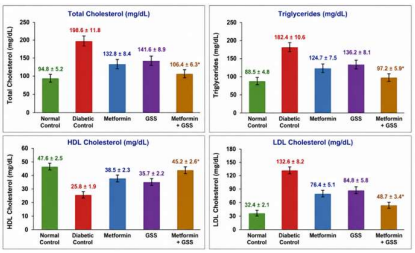


Figure 5: Comparative effect of treatments on serum lipid parameters

Evaluation of Pharmacodynamic Interaction:

The analysis of pharmacodynamic interactions is displayed in Table 6. The amalgamation of metformin and Gymnema sylvestre saponins (GSS) exhibited a synergistic impact, yielding superior antidiabetic outcomes compared to each treatment individually. The combined medication achieved a 60.8% reduction in fasting blood glucose, far surpassing the reductions seen with metformin (42.3%) or GSS (34.7%) monotherapy. The combination treatment resulted in a significant enhancement of blood insulin levels (152.5%) and a more substantial decrease in HbA1c levels (43.1%) vs to solo treatments. The data indicate that the augmented antidiabetic efficacy of the combination may result from complementary mechanisms, including the suppression of intestinal glucose transfer and enhanced glucose homeostasis, hence affirming a synergistic pharmacodynamic interaction between metformin and GSS.

Table 6: Pharmacodynamic Interaction Analysis

Parameter	Metformin	GSS	Combination
Reduction in Fasting Blood Glucose (%)	42.3	34.7	60.8
Improvement in Serum Insulin (%)	67.2	55.7	152.5
Reduction in HbA1c (%)	30.4	23.5	43.1
Interaction Type	--	--	Synergistic

These findings confirm that the combination of *Gymnema sylvestre* saponins and metformin exerts enhanced antidiabetic activity through dual mechanisms involving inhibition of intestinal glucose transport and complementary pharmacodynamic effects on glucose homeostasis.

CONCLUSION:

This study revealed that the combination of Gymnema sylvestre saponins and metformin resulted in a substantial synergistic antidiabetic effect compared to each treatment administered individually. The combination therapy significantly impeded intestinal glucose transport, leading to reduced glucose absorption and enhanced postprandial glycemic regulation. Moreover, the pharmacodynamic interaction between the two medicines resulted in a more pronounced decrease in fasting blood glucose and HbA1c levels, alongside elevated serum insulin concentrations and significant enhancement in lipid profile parameters. The enhanced therapeutic response noted with combination therapy indicates that Gymnema sylvestre saponins augment the antidiabetic effectiveness of metformin via complimentary mechanisms that include the suppression of intestinal glucose absorption and the enhancement of glucose homeostasis. The synergistic combination may enable the administration of reduced dosages of metformin, thereby diminishing dose-related side effects while preserving effective glycemic control. This study provides scientific data endorsing the use of Gymnema sylvestre saponins as a promising complement to metformin therapy for managing type 2 diabetes mellitus. Additional pharmacokinetic research and extended clinical trials are necessary to determine the safety, effectiveness, and translational potential of this herbal-drug combination in diabetic individuals.

Funding:
None

Conflict of interest:
None

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