Research Article

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

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This study evaluated the antidiabetic effects of Gymnemasylvestre and metformin, alone and in combination, in a rat model of type 2 diabetes mellitus (T2DM) induced by high-fat diet (HFD) and streptozotocin (STZ). Thirty male Sprague Dawley rats (150 ± 20 g) were housed under standard conditions and acclimatized before being randomly assigned to five groups: normal control, diabetic control, metformin-treated, Gymnemasylvestretreated, and a combination therapy group. T2DM was induced by feeding the rats an HFD for 21 days to promote insulin resistance, followed by two intraperitoneal injections of STZ at a dose of 25 mg/kg body weight in 0.1 mM citrate buffer (pH 4.5), administered five days apart. Rats with fasting blood glucose (FBG) ≥250 mg/dl were considered diabetic and included in the treatment phase.

After 4 weeks of treatment, all therapy groups showed significant improvements in biochemical markers compared to diabetic controls. Metformin and combination therapy significantly reduced FBG, cholesterol, creatinine, and HbA1c levels ($p<0.05$). Although Gymnemasylvestre alone demonstrated a modest glucose-lowering effect, its impact was significantly enhanced when combined with metformin. Metformin alone, however, showed superior efficacy in improving glycemic control and renal function markers compared to the herbal extract. Body weight gain was reduced in diabetic controls and improved across treatment groups.

These findings suggest that while Gymnemasylvestre has antidiabetic potential, its combination with metformin may enhance treatment outcomes. However, metformin remains the more potent agent in regulating glucose metabolism in STZ-induced diabetic rats.

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia due to impaired insulin secretion, insulin action, or both. It is a major global health concern, with increasing prevalence and complications such as cardiovascular disease, neuropathy, and nephropathy[1] Type I diabetes, an autoimmune condition, is typically associated with the destruction of pancreatic beta cells, leading to insufficient insulin production. Type II diabetes, on the other hand, is characterized by insulin resistance and impaired insulin secretion. The treatment of diabetes primarily involves the use of oral antidiabetic agents such as metformin, which enhances insulin sensitivity, and insulin therapy for type I diabetes. However, the need for better management strategies persists, especially with regard to reducing side effects and improving therapeutic outcomes[2]

Gymnemasylvestre, an Indian medicinal plant, has long been known to have anti-diabetic qualities. Gymnemasylvestre active substances, such as gymnemic acids, have been demonstrated to have considerable blood glucose-lowering potential[3]Gymnema has been shown to increase insulin production, improve glucose utilization, and reduce intestinal glucose absorption. It has also shown anti-inflammatory and antioxidant properties, which might help manage diabetes-related problems[4]

Metformin, a biguanide, is a first-line oral antidiabetic medication often used to treat type II diabetes. It primarily operates by decreasing hepatic glucose synthesis, boosting peripheral glucose absorption, and enhancing insulin sensitivity[5] Metformin has been shown to be useful in managing hyperglycemia and reducing diabetic complications. However, long-term usage may cause gastrointestinal adverse effects and lactic acidosis, making the quest for alternative therapies even more important[6]

The combination of Gymnemasylvestre and metformin shows promise for improving diabetes treatment[7]Gymnema's potential to enhance insulin secretion and sensitivity, along with metformin's involvement in regulating glucose metabolism, implies that their combined usage may have a greater effect on blood glucose management than monotherapy[8] Furthermore, combining herbal therapies with conventional medications can reduce negative effects while increasing therapeutic efficacy.

Streptozotocin (STZ) is a powerful molecule that preferentially damages pancreatic beta cells, causing insulin insufficiency and hyperglycemia, making it a popular chemical for inducing diabetes in laboratory animals[9] The STZ-induced diabetes rat model is widely used to evaluate new anti-diabetic

treatments. In this regard, assessing the combined antidiabetic ability of Gymnemasylvestre and metformin in STZ-induced diabetic rats should offer useful information on the advantages of such a combination for diabetes therapy[9] This study will look at how Gymnemasylvestre and metformin improve blood glucose management, insulin sensitivity, and pancreatic function in a diabetic rat model[10]

Material and Method

The study was conducted in the Laboratory of Central Animal Facility and Department of Pharmacology, Maulana Azad Medical College (MAMC), New Delhi after the approval of the Institutional Animal Ethical Committee (IAEC). The experiment was conducted after obtaining clearance from the Animal Ethics Committee of MAMC, New Delhi vide letter no. IAEC/MAMC/CAF/2023/03 dated 28-04-2023.

Drugs, Chemicals, and Supplements

Streptozotocin (STZ), a chemical powder supplied in a 500 mg vial, was obtained from Sisco-Research Laboratories Pvt. Ltd. (Mumbai, India).

GymnemaSylvestre Leaf Extract, a chemical powder supplied in 100g, was obtained from Arjuna Natural Pvt. Ltd. (Kerala, India).

High Fat Diet (HFD), composed of 60% fat, 20% protein, and 20% carbohydrates, was obtained from KaryomePvt. Ltd. (Mysuru, India).

Metformin, in the form of OKAMET 500 mg tab, was purchased from Cipla Ltd. (Haridwar, India).

Citric acid, sodium citrate, and sodium carboxymethyl cellulose (Na-CMC) were obtained from Sigma-Aldrich Company (St. Louis, MO, USA). Citric acid and sodium citrate were used for the preparation of the citrate buffer.

Animals

Thirty male Sprague Dawley rats, aged 6-8 weeks and weighing 150 ± 20 grammes, were selected from the Central Animal Facility at Maulana Azad Medical College (MAMC), Delhi. The rats were housed in groups of three per cage, using standard-sized cages under standard laboratory conditions. These conditions included a temperature of 25 ± 5°C, a humidity of 55 ± 10%, and a 12-hour light and dark cycle. Throughout the study, all animals were provided with their respective diets: a normal pellet diet for the

control group and a high-fat diet (HFD) for the experimental group. Water was provided ad libitum. Before commencing the treatment, the animals were allowed to acclimatise to their new environment for 7 days. The rats were randomly divided into five groups, with their tails marked with numbers, and the grouping was done by a computer-generated randomization method.

Phase 1: Induction of Type 2 Diabetes Mellitus (T2DM)

The fat-fed/STZ rat model for the induction of T2DM was used according to a previous study[11] T2DM was induced in rats using a high-fat diet combined with low-dose STZ injections.

Rats were fed high-fat diet ad libitum for 21 days to induce insulin resistance. During the feeding period, the weight of the rats was measured weekly to ensure weight gain.

After 21 days, rats received two intraperitoneal injections of freshly prepared STZ at a dose of 25 mg/kg body weight in citrate buffer (0.1 mM, PH = 4.5), with a 5-day interval between injections[12]

Three days after the second STZ injection, the fasting blood glucose level of each rat was recorded in a tail-vein blood sample using a Mylife pure X glucometer (YpsomedPvt. Ltd., New Delhi, India). Rats with fasting blood glucose levels of 250 mg/dl or higher were considered to have developed T2DM and were included in phase 2 of the study[11]

Phase 2: Drug administration

Diabetic rats were randomly divided into four groups of six rats each. Nondiabetic rats were kept in the normal control group.

Group 1: Normal control rats were given normal saline (10 ml/kg) via oral gavage for 4 weeks. Group 2: Untreated diabetic rats received normal saline (10 ml/kg) via oral gavage for 4 weeks.

Group 3: Metformin-treated diabetic rats were treated with metformin (200 mg/kg) via oral gavage for 4 weeks.

Group 4: GymnemaSylvestre-treated diabetic rats were treated with GymnemaSylvestre (600 mg/kg) via oral gavage for 4 weeks.

Group 5: Both combined-treated diabetic rats received both metformin (200 mg/kg) and GymnemaSylvestre (600 mg/kg) via oral gavage for 4 weeks.

According to the literature, the doses of GymnemaSylvestre (600 mg/kg) were based on a previous study[13] Metformin (200 mg/kg) was calculated using the human equivalent dose method[14] Normal

saline (10 ml/kg) was used as the vehicle. The high-fat diet (HFD) consisted of 60% fat, 20% carbohydrate, and 20% protein. The STZ dose (25 mg/kg) was also taken from previous studies[15][16]

Blood Sampling

The rats were anesthetized with ketamine (80 mg/kg) and xylazine (100 mg/kg) in combination. The rat was placed on the operation table, and with a capillary tube (both ends open) 75 mm in diameter, the blood was collected from the retro-orbital sinus route (0.4-0.5 ml) in microcentrifuge tubes. 0,7 and 28th day for FBG level and 0 and 28th day for HbA1c, serum creatinine, and total cholesterol. Blood samples were centrifuged at 7000 g for 15 min at 4 °C to obtain the plasma, which will be stored at -80 °C until analysis with the Semi-Auto Biochemistry Analyzer(Rapid Diagnostic Pvt. Ltd., New Delhi, India)

Statistical analysis

The values obtained were expressed as mean ± SD for each group. Statistical comparison among different groups was evaluated using a two-way analysis of variance (ANOVA) and post hoc Tukey's Honest Significant Difference (HSD) test. Calculations were done with SPSS software version 20.0 (Chicago, Illinois). Statistical significance was defined as *p*-value less than 0.05.

Result

Group	Weight (gm)		FBG (mg/dl)
	Baseline	Pre-treatment (Day 0)	Pre-treatment (Day 0)
NC	163.16 ± 9.95	265.83 ± 21.77	101.16 ± 12.78
DC	163.16 ± 6.64	302.83 ± 56.02	476.00 ± 80.88*
Met	158.16 ± 5.38	235.50 ± 22.98	461.50 ± 13.50*
GS	154.66 ± 4.84	269.50 ± 32.77	448.66 ± 10.26*
Met+GS	156.00 ± 6.54	280.16 ± 24.01	436.33 ± 27.78*

Table 1. Induction of diabetes

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Values are mean ± SEM, n= 6 in each group

**P<0.05, compared to normal control group (NC)*

Inference:-

In this study, we examined variations in weight across various groups of rats that were administered various treatments. Over a period of three weeks, the animals were given a high-fat diet. This signified the beginning of the therapy.

All groups started with comparable weights, as evidenced by the absence of statistically significant differences in baseline weights (p-values > 0.05) in all comparisons with the NC group. (Table 1)

On Day 0 (pre-treatment), all comparisons with p-values > 0.05 indicate no statistically significant change in weight across the groups compared to the NC group. (Table 2). Compared to the normal control group, the Met group weighed less but gained weight by the conclusion of the study (Day 28), suggesting statistically significant weight differences (increase) between the DC and Met groups. High-fat diets (HFDs) contribute to the development of diabetes in animal models by increasing insulin resistance, which happens when the body's reaction to circulating insulin is reduced.

At pre-treatment (Day 0), i.e., before administration of the oral dose, significantly higher average glucose levels were found in all treatment groups compared to NC group 0.001 (p<0.05). (Table 1)

On Day 0, compared to NC, rats with fasting blood glucose levels of >250 mg/dl were classified as having T2DM and were enrolled in the experiment.

Group	Weight (gm)	FBG (mg/dl)		Cholesterol (g/L)		Creatinine (mg/dl)		Hb1Ac (g/L)	
	Day 28	Day 7	Day 28	Day 0	Day 28	Day 0	Day 28	Day 0	Day 28
DC	293.0 ±	445.66 ±	401.33 ±	351.6 ±	345.14±	2.05 ±	1.85±	10.55 ±	9.95 ±
	33.41	51.74	24.548	75.99	70.77	0.47	0.04	0.57	0.49
Met	389.8 ±	409.66 ±	122.50 ±	331.6 ±	106.49 ±	1.85 ±	0.44 ±	10.65 ±	5.82 ±
	19.53*	8.16*	6.15*	10.06	2.73*	0.76	0.03*	0.11	0.15*
GS	393.0 ±	423.83 ±	296.33 ±	323.9 ±	293.43 ±	1.77 ±	0.69 ±	10.62 ±	8.24 ±
	30.21*	13.61	8.26*†	16.91	3.29*†	0.89	0.04*†	0.27	0.13*†
Met+	421.8 ±	395.83 ±	176.50 ±	315.7 ±	208.99 ±	1.74 ±	0.54 ±	10.65 ±	7.26 ±
GS	27.96*†	10.88*†	9.20*†	14.53	1.18†	0.12	0.02*†	0.70	0.09*†

Table 2. Drug administration

Values are mean ± SEM, n= 6 in each group

**P<0.05, compared to diabetes control group (DC)*

† P<0.05, compared to the standard (Metformin) group

Inference:-

At the end of the trial (Day 28), weight, fasting blood glucose, cholesterol, creatinine, and Hb1Ac levels were significantly different in all groups (Met, GS, and Met+GS) compared to the DC group by 0.001 ($p<0.05$).

On Day 7, there were significant differences in fasting blood glucose levels between the DC group and the Met group p-values of 0.030 ($p<0.05$) and between the DC group and the Met+GS group p-values of 0.004 ($p<0.05$), as well as between the Met group and the Met+GS group p-values of 0.030 ($p<0.05$). There were no significant differences between the DC group and the GS group, with p-values of 0.132 ($p > 0.05$). (Table 2)

In terms of reducing fasting blood glucose, cholesterol, creatinine, and HbA1c levels on Day 28, Metformin performs better than Gymnemasylvestre and the combination group of Metformin and Gymnemasylvestre

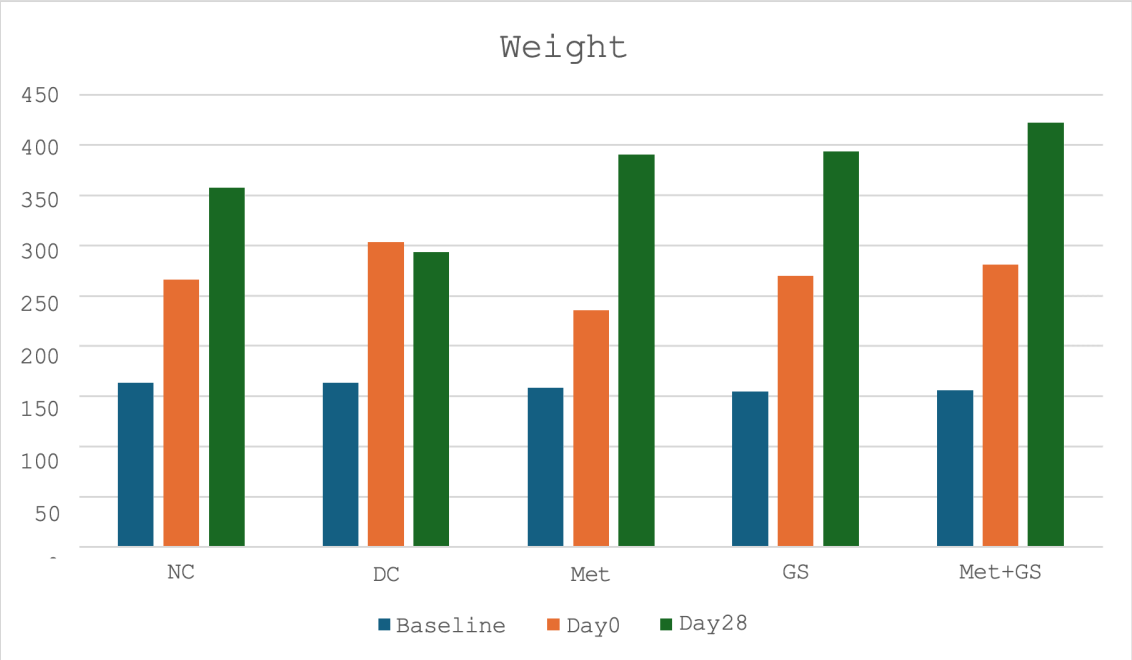

Figure 1. Body weight (gm) at baseline, day 0, and day 28

All groups started with comparable weights, as evidenced by the absence of statistically significant differences in baseline weights (p-values > 0.05) in all comparisons with the NC group. (Table 1, Fig. 1)

On Day 0 (pre-treatment), all comparisons with p-values > 0.05 indicate no statistically significant change in weight across the groups compared to the NC group. (Table 2, Figure 4)

The p-values for all comparisons are 0.001, indicating statistically significant differences in weight between DC and other groups on Day 28. The normal control group, which received a normal pellet diet, had significantly lower weights compared to the other groups, which received HFD/STZ.

Compared to the normal control group, the DC group weighed less because those who are untreated may have metabolic dysregulation that causes weight changes. Weight can be impacted by diabetes-related hormonal imbalances, insulin resistance, and elevated blood glucose levels. (Table 2, Fig. 1)

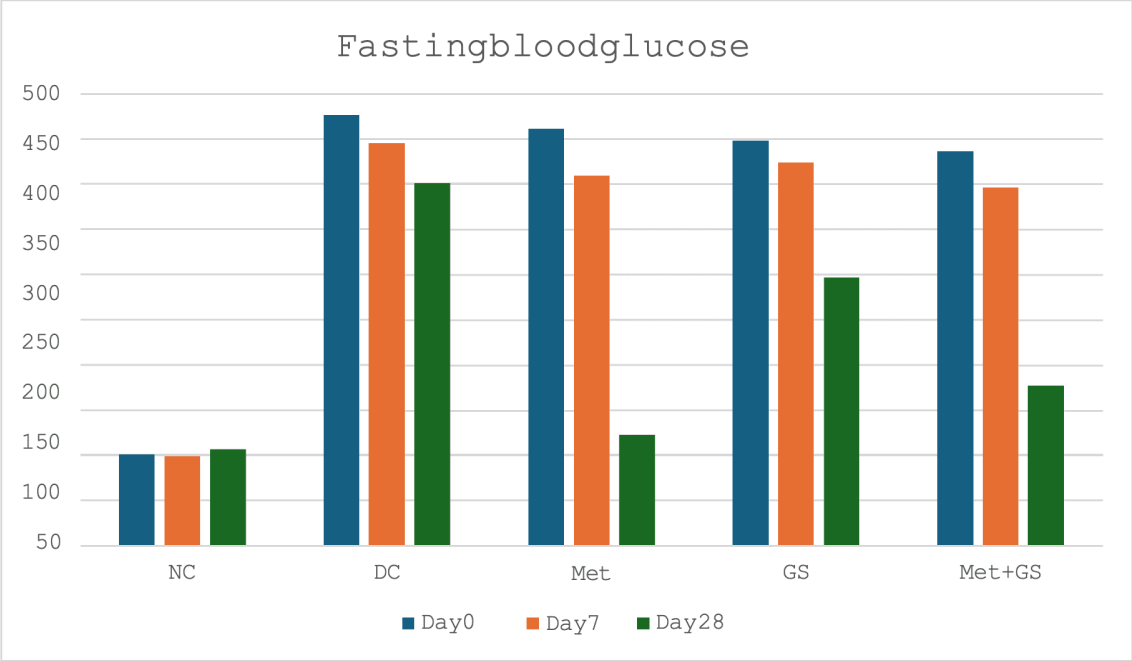

Figure 2. Fasting blood glucose (mg/dl) on day 0, 7, and 28

At pre-treatment (Day 0), i.e., before administration of the oral dose, glucose levels were significantly higher in all treatment groups after the induction of diabetes, compared to the NC group 0.001 ($p<0.05$), whereas a significant difference was seen between the NC and other treatment groups. (Table 1)

On Day 0, compared to NC, rats with fasting blood glucose levels of >250 mg/dl were classified as having T2DM and were enrolled in the experiment.

By Day 7, the DC group displayed the highest mean fasting blood glucose level at 445.66 ±51.74. There were significant differences between the DC group and the Met group p-values of 0.030 ($p<0.05$) and between the DC group and the Met+GS group p-values of 0.004 ($p<0.05$), as well as between the Met group and the Met+GS group p-values of 0.030 ($p<0.05$). There were no significant differences between the DC group and the GS group, with p-values of 0.132 ($p > 0.05$). (Table 2, Fig. 2)

All comparisons had p-values of 0.001, demonstrating statistically significant differences (reductions) in fasting blood glucose between DC and the other groups on Day 28. Using two- way RM ANOVA, inter-group comparisons at different time points showed that the Met, GS, and Met+GS groups had significantly decreased levels of fasting blood glucose at the end of the study compared to the DC group.

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The statistical analysis revealed significant differences between the Met and Met+GS groups with p-values of 0.01 ($p<0.05$), as well as between the Met and GS groups. (Table 2, Fig. 2)

In a comparison of changes in glucose levels from pre-treatment to the end of the study between groups, all groups showed significant changes (reductions) in glucose compared to the DC group. Using a two-way RM ANOVA, there was a relatively greater reduction in glucose levels from pre-treatment to the end of the study in the Met (122.50 ± 6.15) group compared to the Met+GS (176.50 ± 9.20) group and the GS (296.33 ± 8.26) group. (Table 2, Fig. 2)

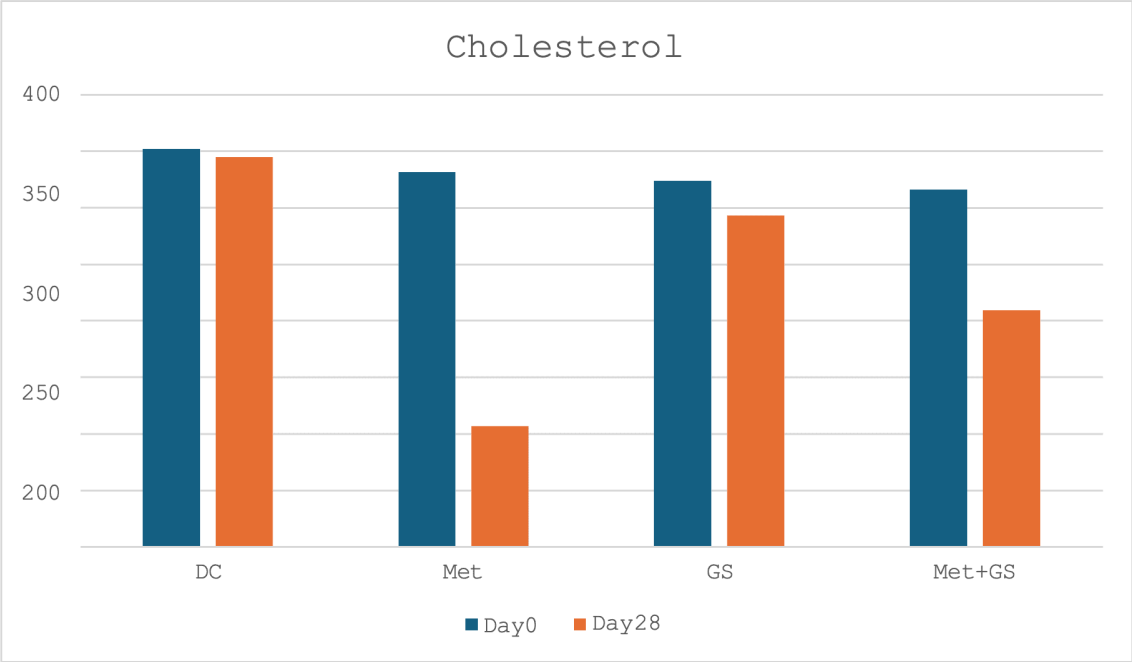

Figure 3. Cholesterol (g/L) at day 0 and day 28

All comparisons had p-values of 0.001, demonstrating statistically significant differences (reductions) in total serum cholesterol between DC and the other groups on Day 28. Using two-way RM ANOVA, inter-group comparisons at different time points showed that the Met, GS, and Met+GS groups had significantly decreased levels of total serum cholesterol at the end of the study compared to the DC group.

The statistical analysis revealed significant differences between the Met and Met+GS groups with p-values of 0.01 ($p<0.05$), as well as between the Met and GS groups (Table 2, Fig. 3)

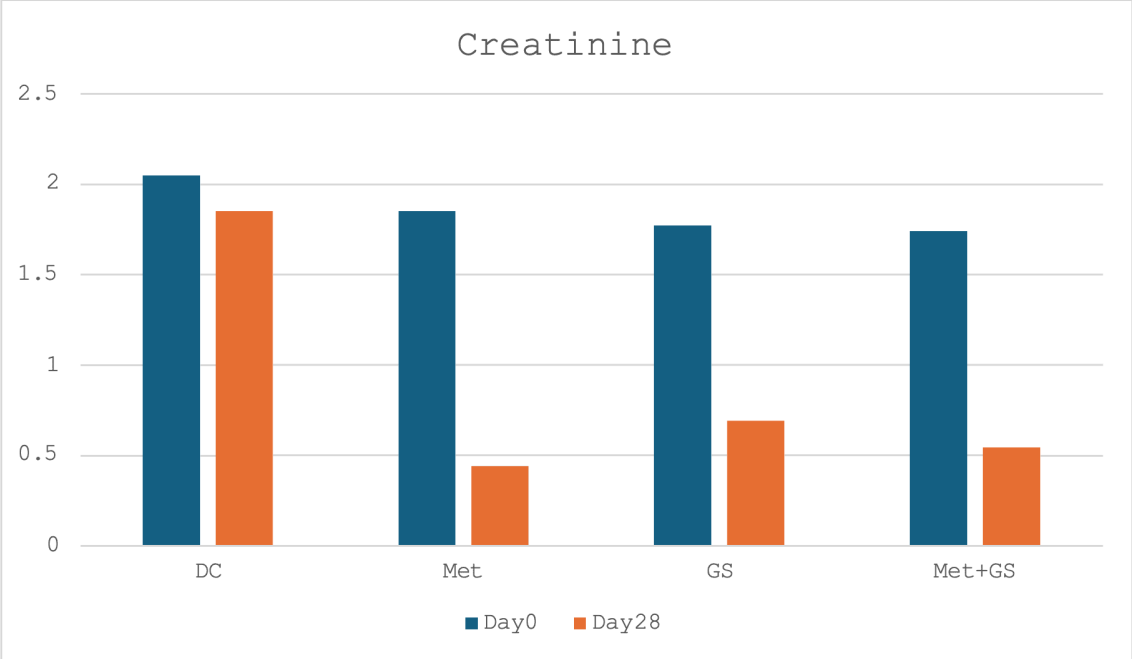

Figure 4. Creatinine (mg/dl) at day 0 and day 28

All comparisons had p-values of 0.001, demonstrating statistically significant differences (reductions) in serum creatinine between DC and the other groups on Day 28. Using two-way RM ANOVA, inter-group comparisons at different time points showed that the Met, GS, and Met+GS groups had significantly decreased levels of serum creatinine at the end of the study compared to the DC group.

The statistical analysis revealed significant differences between the Met and Met+GS groups with p-values of 0.01 ($p<0.05$), as well as between the Met and GS groups. (Table 2, Fig. 4)

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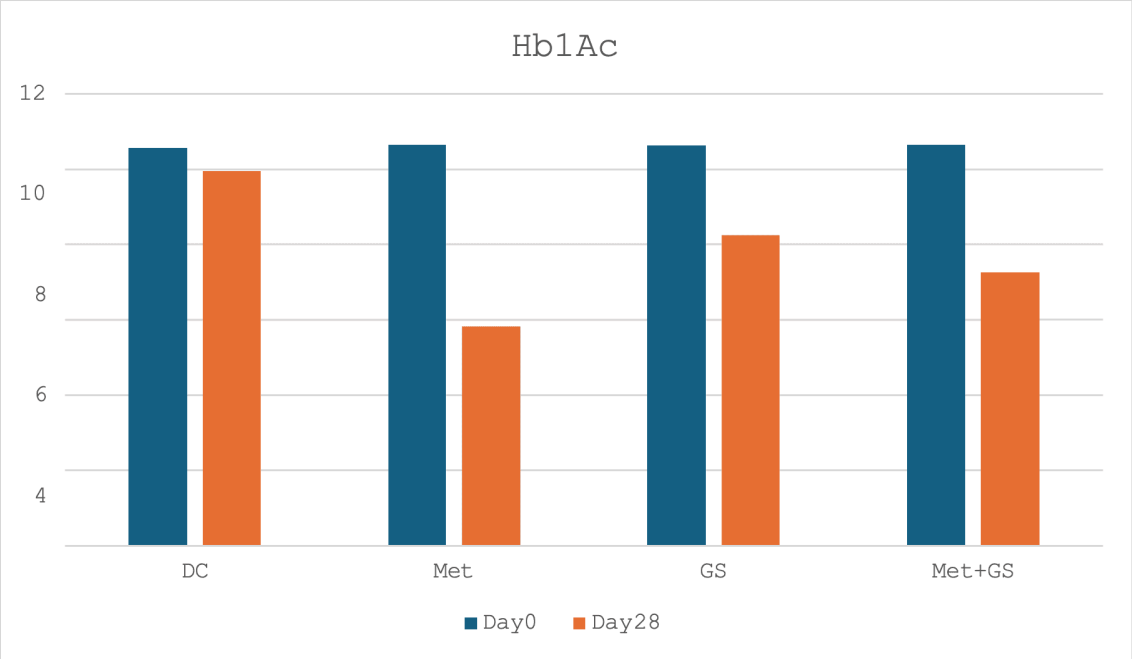

Figure 5. Hb1Ac (g/L) at day 0 and day 28

All comparisons had p-values of 0.001, demonstrating statistically significant differences (reductions) in HbA1c between DC and the other groups on Day 28. Using two-way RM ANOVA, inter-group comparisons at different time points showed that the Met, GS, and Met+GS groups had significantly decreased levels of HbA1c at the end of the study compared to the DC group.

The statistical analysis revealed significant differences between the Met and Met+GS groups with p-values of 0.01 ($p<0.05$), as well as between the Met and GS groups. (Table 2, Fig. 5)

Discussion

Diabetes mellitus (DM) is a chronic condition marked by high blood glucose levels, which result from insulin resistance, insulin deficiency, or both.[17] The prevalence of DM is rising worldwide, presenting a major public health issue. There are two main types of diabetes: type 1 (T1DM) and type 2 (T2DM). T1DM is an autoimmune condition that destroys insulin-producing beta cells in the pancreas, leading to absolute insulin deficiency. This type typically appears in childhood and requires lifelong insulin therapy. In contrast, T2DM is primarily caused by insulin resistance, where cells become less responsive to insulin, and is often linked to factors such as poor diet, lack of exercise, and obesity.[18] T2DM is more common globally and is closely tied to increasing rates of obesity and aging populations. The

management of T2DM involves a combination of lifestyle changes, including dietary adjustments, regular exercise, and medications aimed at enhancing insulin sensitivity or secretion. In some cases, insulin therapy may be required as the disease progresses. Preventing and managing T2DM involves promoting healthy living and early detection.[19]

Metformin is the first-line treatment for T2DM due to its effectiveness, safety, and affordability. It works by reducing glucose production in the liver and improving insulin sensitivity. Despite being well-tolerated, it can occasionally cause side effects.[20] Traditional remedies, such as Gymnemasylvestre, are being studied for their potential to lower blood glucose and complement standard treatments like metformin. Gymnemasylvestre is believed to possess antidiabetic properties, and its combination with metformin is being explored to improve overall treatment outcomes.[21]

Animal models are often used to study T2DM, with high-fat diets (HFDs) and streptozotocin (STZ) used to induce diabetes. HFDs promote insulin resistance, while STZ induces beta-cell dysfunction and insulin deficiency.[22] These models help replicate human T2DM, allowing researchers to study disease mechanisms and evaluate potential treatments. Inflammation and oxidative stress in the pancreas are key factors in the development of insulin resistance and beta-cell dysfunction in these models. By using HFD and STZ together, researchers can simulate both insulin resistance and beta-cell failure, mirroring the metabolic disturbances seen in human T2DM.[23]

The effects of treatments such as metformin and Gymnemasylvestre were tested in animal models. Significant reductions in body weight and blood glucose levels were observed in all treatment groups compared to diabetic controls, with metformin showing the most effective results.[24] Similarly, serum cholesterol levels were significantly reduced in all treatment groups, with metformin being more effective than Gymnemasylvestre in lowering cholesterol. These findings support the potential of combining Gymnemasylvestre with metformin for enhanced therapeutic outcomes in T2DM. [25]Gymnemasylvestre's mechanism includes inhibition of glucose absorption and stimulation of insulin secretion, while metformin primarily works by reducing hepatic glucose production and enhancing insulin sensitivity.[26]

Both treatments demonstrated antidiabetic effects, with metformin proving superior in terms of glucose and cholesterol reduction. These results underscore the importance of both pharmacological and traditional treatments in managing T2DM.[27]

Conclusion

The study demonstrated that Metformin, Gymnemasylvestre, and their combination effectively reduced fasting blood glucose, total serum cholesterol, serum creatinine, and HbA1c levels in STZ-induced diabetic rats. However, Metformin showed superior efficacy, significantly improving key diabetes markers and serum creatinine, indicating better kidney function benefits. While Gymnemasylvestre provided some positive effects, its impact was less pronounced compared to Metformin. Metformin's enhanced insulin sensitivity and glucose production reduction likely contributed to its consistent and potent results. These findings emphasize Metformin's greater efficacy in managing type 2 diabetes and related biochemical parameters in experimental models.

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Declarations

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