Alqalam Journal of Medical and Applied Sciences. 2026;9(11):3834-3839
https://doi.org/10.54361/ajmas.261140

Original article

Comparative Effect of Cinnamon, Glimepiride, and Their Combination on Glycated Hemoglobin in a High-Fat Diet/Alloxan-Induced Type 2 Diabetic Mouse Model

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Abstract
Cinnamon has been reported to improve glycemic control, but its effect relative to standard sulfonylurea therapy is unclear. This study compared cinnamon, glimepiride, and their combination on glycated hemoglobin (HbA1c) in experimental type 2 diabetes mellitus (T2DM). T2DM was induced in mice by a high-fat diet for 2 weeks followed by a single dose of alloxan. Animals [n = 6 per group] were divided into five groups: control, untreated T2DM, cinnamon, glimepiride, and cinnamon plus glimepiride. Treatments were given for 4 weeks, after which HbA1c was measured. Data were checked for normality and homogeneity of variance and analyzed by one-way ANOVA with Tukey's post hoc test. HbA1c was markedly higher in the T2DM group (8.00 ± 0.14) than in controls (4.82 ± 0.72; $p < 0.001$). Cinnamon, glimepiride, and the combination significantly reduced HbA1c relative to untreated T2DM (6.10±0.37, 6.30±0.29, and 6.12±0.33, respectively; $p < 0.001$), although values remained above controls ($p < 0.001$). No significant differences were found among the three treated groups (Cinnamon vs glimepiride, $p \geq 0.85$; cinnamon vs combination $p \geq 0.99$; glimepiride vs combination $p \geq 0.9029$). Cinnamon lowered HbA1c to a degree comparable to glimepiride, and the combination gave no significant additional benefit. Larger and longer studies are needed to confirm these findings.
Keywords. Cinnamon, Glimepiride, HbA1c, Type 2 Diabetes Mellitus.

Introduction

Type 2 diabetes mellitus has become one of the most critical metabolic diseases worldwide, with global prevalence estimated at 537 million adults in 2021 and projected to rise substantially over the coming decades [1,2]. T2DM is characterized by insulin resistance and sustained hyperglycemia that progressively damages multiple organ systems, particularly the small blood vessels [3]. Chronic hyperglycemia is therefore recognized as a defining and clinically important feature of the disease, and a growing body of evidence indicates that improved glycemic control can reduce the development and progression of diabetic complications [4]. Because a single blood-glucose reading reflects glycemic status only at one moment, it cannot capture this cumulative exposure. Glycated hemoglobin [HbA1c], by contrast, reflects average plasma glucose over roughly the preceding eight to twelve weeks and can be measured at any time without fasting, making it the most widely accepted and reliable outcome measure for evaluating long-term glycemic control [4,5]. This integrated, time-averaged property makes HbA1c—rather than an isolated glucose measurement—the more appropriate endpoint for evaluating a glucose-lowering intervention.

Glimepiride is a second-generation sulfonylurea used clinically to lower blood glucose in patients with T2DM. It acts primarily by binding to the sulfonylurea receptor 1 (SUR1) on ATP-sensitive potassium (K-ATP) channels of pancreatic beta cells, closing these channels and depolarizing the cell membrane; this depolarization opens voltage-dependent calcium channels, and the resulting rise in intracellular calcium triggers exocytosis of insulin-containing granules, releasing insulin into the bloodstream [6,7]. Through this well-characterized insulinotropic mechanism, glimepiride has long been established as an effective oral antidiabetic agent, making it a suitable positive pharmacological reference against which the glucose-lowering effect of cinnamon can be evaluated.

Alongside pharmacological agents, cinnamon has been investigated as a potential natural, plant-derived intervention for glucose regulation. Research has suggested that cinnamon may have potentially useful pharmacological effects relevant to diabetes [8], and experimental work suggests it can influence glucose metabolism and insulin sensitivity; animal studies, for instance, have found cinnamon to act as an insulin sensitizer, an effect proposed to involve enhanced translocation of the GLUT4 glucose transporter and consequently increased glucose uptake and utilization [9]. However, findings across human studies have not been consistent: some studies report that cinnamon does not improve glycemic control in patients with type 2 or type 1 diabetes, whereas studies in people with prediabetes, insulin resistance, or metabolic syndrome have shown improvements in glycemic control and insulin sensitivity [8]. More recent syntheses echo this uncertainty, noting that although numerous studies report beneficial metabolic outcomes with cinnamon supplementation, findings across trials remain inconsistent [10]. Given this variability, and because cinnamon has not been established as an antidiabetic drug in the way glimepiride has, its glucose-lowering potential relative to an established pharmacological treatment requires further direct experimental investigation.

Despite growing interest in cinnamon as an adjunct or alternative approach to glycemic management, most existing evidence compares cinnamon to placebo or examines short-term fasting glucose changes, rather than benchmarking its effect against an established antidiabetic drug using a longer-term, integrated measure of glycemic control such as HbA1c. This gap limits conclusions about how cinnamon's efficacy compares with standard pharmacological therapy

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Received*: 14-09-2026 -* ***Accepted****: 11-11-2026 -* ***Published****: 18-11-2026*

over a clinically meaningful timeframe. Therefore, the present study was designed to compare the effect of cinnamon supplementation with glimepiride and their combination on HbA1c levels across the study groups.

Materials and Methods

Materials

Drugs and chemicals

- Alloxan monohydrate [Alfa Aesar, UK]. .
- Glimepiride [Amaryl] [Sanofi Arabia -Egypt].

Animals

Mice were obtained from the animal unit of the Faculty of Medicine, University of Benghazi, and housed in the care of the laboratory. All experiments in this study were done according to the ethics guidelines of the University of Benghazi. A total of 30 adult male albino mice weighing 20- 25 g were housed under regulated standard environmental conditions (25±1°C, 50±2% humidity), with 12-hour light/dark cycles, and allowed free access to commercial mice chow and tap water ad libitum.

Experimental Protocol.

The Mice were randomly divided into five groups [n=6 mice/group]. The control group (G1) was fed a normal diet. The remaining mice were fed a high-fat diet for two weeks [11]. The high-fat diet (HFD) employed was adapted from Abd-Eldaim's study [12,13], with some modifications. (Table 1) describes the chemical composition of the HFD. A single dose of Alloxan was administered intraperitoneally (180 mg/ kg body weight) to animals fasted for 12 h, and the control animals received only vehicle [14]. After 3-7 days, blood glucose was measured to confirm the establishment of diabetes.

Preparation of Cinnamon Extract

Fifty grams (50 g) of ground cinnamon were added to 500 mL of distilled water that had been brought to a boil. The mixture was then allowed to cool to room temperature. The resulting cinnamon extract was stored in a refrigerator throughout the treatment period [15].

Experimental Design and Grouping

Mice in the T2DM group (G2) did not receive any intervention. Mice in the Cin-treated group (G3) received cinnamon (0.5 mg/kg/day, PO) concurrently for 28 days. Mice in the Gilm-treated group (G4) received Glimepiride (0.5 mg/kg/day, PO) concurrently for 28 days [16]. Mice in the Cin- Glim group (G5) received the same doses of cinnamon and glimepiride for 28 days.

Blood Collection

Animals were euthanized with a high dose of urethane (1.5 mg/kg, i.p.) [17]. Blood samples were obtained for fasting blood glucose and HbA1c measurements.

Results

The mean HbA1c value was 4.82 ± 0.72 in the control group, 8.00 ± 0.14 in the T2DM group, 6.10 ± 0.37 in the Cin-treated group, 6.30 ± 0.29 in the Glim-treated group, and 6.12 ± 0.33 in the Cin–Glim group. The T2DM group had the highest HbA1c value, whereas the control group had the lowest (Figure 1).

Compared with the control group, the T2DM group had a significantly higher HbA1c value (8.00 ± 0.14 vs. 4.82 ± 0.72; $p<0.001$) (Figure 1). The relative ratio of HbA1c was 0.69 ± 0.28 for T2DM, and the comparison was significant ($p<0.001$) (Figure 2, Panel A). The Cin-treated group had a significantly different HbA1c value (6.10 ± 0.37 vs. 4.82 ± 0.72; $p<0.001$) (Figure 1), although its HbA1c ratio relative to control was not significant (0.29 ± 0.17; $p=0.192$) (Figure 2, Panel A). Similarly, the Glim-treated group had a significantly different HbA1c value from control (6.30 ± 0.29 vs. 4.82 ± 0.72; $p<0.001$) (Figure 1), and its ratio relative to control was also significantly higher (0.33 ± 0.18; $p=0.026$) (Figure 2, Panel A). The Cin–Glim group differed significantly from control in HbA1c value (6.12 ± 0.33 vs. 4.82 ± 0.72; $p<0.001$) (Figure 1), and its ratio relative to control was not significant (0.29 ± 0.18; $p=0.192$) (Figure 2, Panel A).

Compared with the T2DM group, the Cin-treated group had a significantly lower HbA1c value (6.10 ± 0.37 vs. 8.00 ± 0.14; $p<0.001$) (Figure 1). The mean HbA1c ratio relative to T2DM was 0.24 ± 0.04. This relative reduction was not significant ($p=0.0619$); however, it approached the significant threshold (Figure 2, Panel B). The Glim-treated group also had a significantly lower HbA1c value than T2DM (6.30 ± 0.29 vs. 8.00 ± 0.14; $p<0.001$) (Figure 1), while its ratio relative to T2DM was 0.21 ± 0.03 and was not significant ($p=0.9198$) (Figure 2, Panel B). The Cin–Glim group had a significantly lower HbA1c value than T2DM (6.12 ± 0.33 vs. 8.00 ± 0.14; $p<0.001$) (Figure 1); however, its ratio relative to T2DM was 0.24 ± 0.03 and was not significant ($p=0.0583$) but approached the significance threshold (Figure 2, Panel B).Compared with the Cin-treated group, the Glim-treated group had a slightly higher mean HbA1c value (6.30 ± 0.29 vs. 6.10 ± 0.37), but this difference was not significant ($p=0.8524$) (Figure 1). The mean HbA1c ratio relative to Cin-treated was 0.03 ± 0.02, and this relative ratio was also not significant ($p=0.3448$) (Figure 3, Panel A). The Cin–Glim group had a mean HbA1c value of 6.12 ±

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Received*: 14-09-2026 -* ***Accepted****: 11-11-2026 -* ***Published****: 18-11-2026*

0.33 compared with 6.10 ± 0.37 in the Cin-treated group; this difference was not significant (p>0.9999) (Figure 1). The corresponding ratio (0.00 ± 0.02) was also not significant (p>0.9999) (Figure 3, Panel A). Compared with the Glim-treated group, the Cin–Glim group had a lower mean HbA1c value (6.12 ± 0.33 vs. 6.30 ± 0.29), but the difference was not significant (p=0.9029) (Figure 1). The mean HbA1c ratio relative to the Glim-treated group was 0.03 ± 0.02, and this comparison was also not significant (p=0.4756) (Figure 3, Panel B).

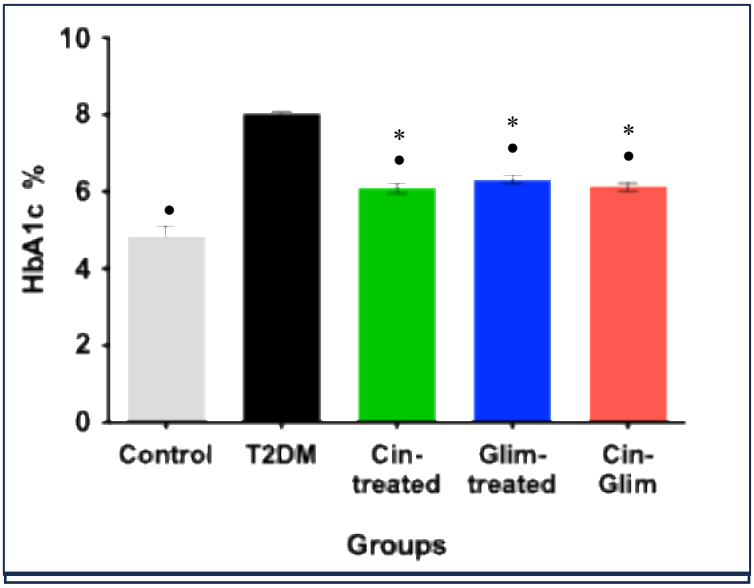


Figure 1. Bar charts showing the effect of Cinnamon, glimepiride, and their combination on HbA1c value [%] in male albino mice of different groups.

T2DM: Type 2 Diabetes Mellitus; Cin: Cinnamon; Glim: glimepiride.
Results were presented as Mean ± SEM. n = 6 mice.
Significant [p<0.001] differences in HbA1c compared to the control group.
Significant (p<0.001) differences in HbA1c compared to the T2DM group.

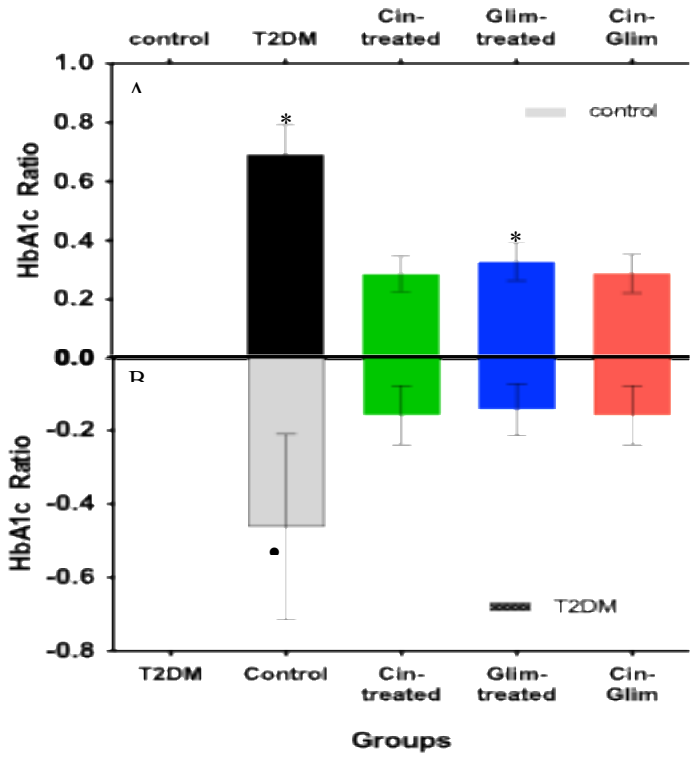


Figure 2. Bar charts showing the effect of Cinnamon, glimepiride, and their combination on the relative HbA1c ratios in male albino mice of different groups.

T2DM: Type 2 Diabetes Mellitus; Cin: Cinnamon; Glim: glimepiride.
Panel A: HbA1c rate compared with Control; Panel B: HbA1c rate compared with T2DM.
Results were presented as Mean ± SEM. n = 6 mice.
Significant [p<0.001] increase in HbA1c rate compared to the control group.
Significant [p<0.001] difference in HbA1c rate comparedto the DM group.

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Received*: 14-09-2026 -* ***Accepted****: 11-11-2026 -* ***Published****: 18-11-2026*

https://doi.org/10.54361/ajmas.261140

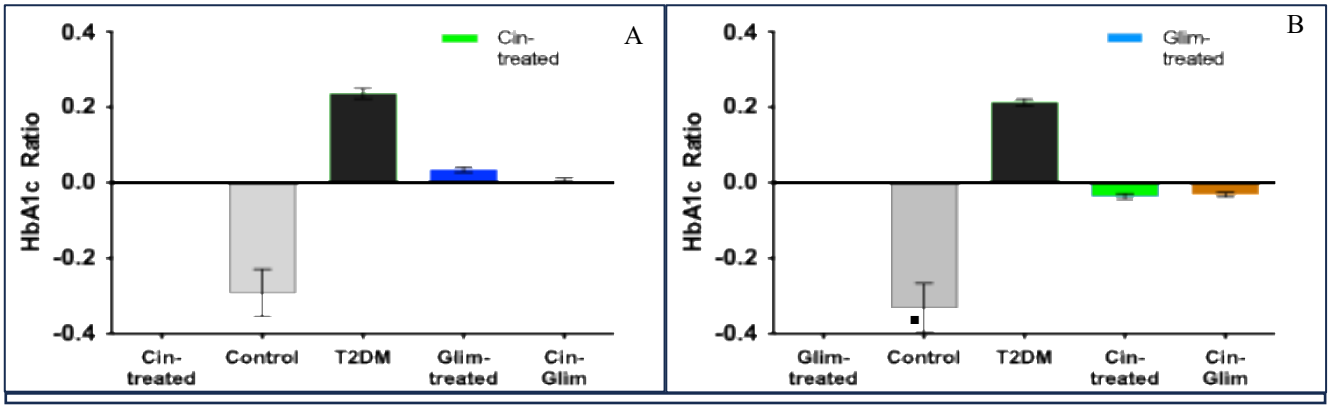


Figure 3. Bar charts showing the effect of Cinnamon, glimepiride, and their combination on the relative HbA1c ratios in male albino mice of different groups.

T2DM: Type2 Diabetes Mellitus; Cin: Cinnamon; Glim: glimepiride.
Panel A: HbA1c relative ratio compared with Control.
Panel B: HbA1c relative ratio compared with T2DM.
Results were presented as Mean ± SEM. n = 6 mice.
Significant [p<0.001] increase in HbA1c relative ratio compared to the Glim-treated group.

We conclude that the T2DM group had the highest HbA1c value and differed significantly from the control and all treatment groups. Although the Cin-treated, Glim-treated, and Cin–Glim groups had significantly lower absolute HbA1c values than the T2DM group, their relative HbA1c ratios did not differ significantly from T2DM. No significant differences were observed among the three treatment groups in either absolute HbA1c values or relative ratios. Therefore, the results demonstrate improved HbA1c values in the treatment groups compared with T2DM, but do not demonstrate a statistically significant superiority of cinnamon, glimepiride, or their combination over one another.

Table 1. Compositions of the standard and high-fat diets

Diet content	Standard diet		HFD	
	Energy Kcal/100 g	%	Energy Kcal/100 g	%
Protein	96.14	25.3	62	12
Fat	49.4	13	303.5	57
Carbohydrates	228	60	161.5	30.5
Fiber	6.46	1.7	3	0.5
Total	380	100	530	100

Discussion

The control group showed substantially lower HbA1c than the T2DM group, and this difference was statistically significant in both the direct comparison and the analysis relative to control. This finding confirms marked deterioration of glycaemic control in the diabetic group and is consistent with experimental diabetes studies in which untreated diabetic animals develop persistent hyperglycaemia and increased HbA1c compared with non-diabetic controls [18].

In comparison with the control group, the Cin-treated group showed increased HbA1c, and the direct comparison was significant; however, the relative analysis did not show a significant difference. This finding indicates that cinnamon treatment did not restore HbA1c to the control level. It is partly inconsistent with reports describing modest HbA1c-lowering effects of cinnamon [19-21], but it agrees with reviews describing inconsistent or limited effects that may depend on cinnamon species, preparation, dose, treatment duration, and baseline glycaemia [22,23]. The Glim-treated group also had increased HbA1c compared with the control group, and both direct and relative comparisons were significant. Although glimepiride improved glycaemic control compared with diabetes, HbA1c did not return to the control level. This finding is consistent with clinical studies showing that glimepiride lowers HbA1c without necessarily restoring values to those of non-diabetic individuals [24,25]. Similarly, the Cin–Glim group had increased HbA1c compared with the control group in the direct analysis, whereas the relative analysis was not significant. These findings suggest incomplete normalization after combined treatment and are compatible with reports that cinnamon may be useful as an adjunct but does not consistently produce an additional effect beyond standard therapy [23,26].

Compared with the T2DM group, the Cin-treated group showed significantly decreased HbA1c, indicating improved glycaemic status. However, the relative analysis did not show a significant difference. The reduction in HbA1c is consistent with studies reporting potential glucose-lowering effects of cinnamon, although the absence of significance in the relative analysis agrees with systematic reviews describing a modest and variable effect on HbA1c [19, 20, 27]. The Glim-treated group also showed significantly decreased HbA1c compared with T2DM, while the relative analysis was not significant. This result agrees with the established glucose-lowering effect of glimepiride and with clinical studies

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Received: *14-09-2026 -* ***Accepted:*** *11-11-2026 -* ***Published:*** *18-11-2026*

demonstrating improved HbA1c following glimepiride treatment [24]. The Cin–Glim group similarly showed significantly decreased HbA1c compared with T2DM, but its relative analysis was not significant. This finding indicates an improvement in the absolute HbA1c value but does not demonstrate a statistically significant relative improvement. It is consistent with the concept that cinnamon may act as an adjunct to conventional treatment, while the additional benefit of combining it with standard therapy remains uncertain [23,26].

The Cin-treated and Glim-treated groups showed no significant difference in HbA1c, and their relative comparison was also nonsignificant. These findings suggest that the two monotherapies produced broadly comparable HbA1c outcomes in the present experiment. This result is compatible with the variable literature on cinnamon, in which its effect may be modest and not clearly different from active glucose-lowering treatment in some studies [22, 23]. The Cin-treated and Cin–Glim groups also showed no significant difference in HbA1c or in the relative analysis. Therefore, adding glimepiride to the Cin-treated regimen did not produce a statistically detectable additional HbA1c improvement. This finding does not support the expectation that combination treatment necessarily provides greater benefit, although the result may have been influenced by treatment duration, variability, sample size, dose, or residual beta-cell function. It is compatible with evidence that the additional effect of cinnamon alongside established therapy is not consistently demonstrated [26].

The Glim-treated and Cin–Glim groups did not differ significantly in HbA1c, and the relative comparison was also nonsignificant. Although the combined-treatment group showed a numerically lower HbA1c, the difference did not demonstrate statistical superiority. This finding is consistent with the mixed evidence regarding cinnamon supplementation and with reviews reporting that its effect on HbA1c is generally modest and variable [20,22,23]. The result also suggests that adding cinnamon to glimepiride did not provide a clearly greater effect than glimepiride alone under the conditions of this experiment.

Overall, diabetes induction produced a marked increase in HbA1c, whereas cinnamon, glimepiride, and the combined treatment were associated with improved HbA1c compared with untreated T2DM. Nevertheless, the relative analyses did not consistently confirm these differences, and no significant differences were found among the treatment groups. Therefore, the findings support an improvement in glycaemic status following treatment but do not demonstrate that cinnamon was superior to glimepiride or that the combined treatment provided an additional statistically significant benefit. The results should be interpreted in view of the variability of cinnamon preparations and the experimental conditions.

Ethical Approval

The study was approved by the University of Bengazi Ethics Committee.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

No external funding was received for this study.

Author Contributions

- Huda MG: Conceptualization, Methodology, Data curation, Formal analysis, Writing – review & editing, Supervision
- Nouh MH: Conceptualization, Methodology, Data curation, Review & editing, Supervision
- Nadeen AA: - Methodology, Data curation.

Acknowledgments

The authors thank the technical staff of the departments of pharmacology and of the animal housing.

AI Use Disclosure

No generative artificial intelligence tools were used in the preparation of this manuscript.

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Received*: 14-09-2026 -* ***Accepted****: 11-11-2026 -* ***Published****: 18-11-2026*