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Rosuvastatin and RM-1 polyphenol effects on insulin resistance, coagulation, and platelet aggregation in diabetic rats

Siroj S Khodjiyev [1*], Guli M Raimova [1], Muhammadqodir Musajonugli Ortiqov [1], Islom B Qozoqov [1], Jobir I Dedaboyev [1], Nozimjon N Khoshimov [1], Qobil E Nasirov [1], Alisher A Mukhtorov [2], Nazifa R Achilova [3], Lola S Sadilloyeva [4]

[1] Institute of Biophysics and Biochemistry, National University of Uzbekistan named after Mirzo Ulugbek, Tashkent, UZBEKISTAN
[2] National University of Uzbekistan named after Mirzo Ulugbek, Tashkent, UZBEKISTAN
[3] Department of Biology, Faculty of Natural Sciences and Medicine, Navoi State University, Navoi, UZBEKISTAN
[4] Department of Natural and Technical Sciences, Navoi Innovations University, Navoi, UZBEKISTAN
***Corresponding Author:** sirojxodjiyev807@gmail.com

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ABSTRACT

Background: Type 2 diabetes mellitus is associated with disturbances in carbohydrate and lipid metabolism as well as hemostasis, including hyperfibrinogenemia and enhanced platelet aggregation. Statins, while cardioprotective, may impair insulin secretion and increase insulin resistance (IR).

Aim: To evaluate the effects of rosuvastatin alone and in combination with RM-1 polyphenol on IR, lipid and hepatic parameters, coagulation, plasma fibrinogen, and platelet aggregation in a high-fat diet/streptozotocin-induced rat model of type 2 diabetes.

Methods: Forty male Wistar rats (280-320 g) were divided into four groups (n = 10 each): intact, diabetic control, diabetic + rosuvastatin (10 mg/kg/day), and diabetic + rosuvastatin + RM-1 (10 mg/kg/day each), treated orally for 4 weeks.

Results: Diabetic rats showed marked hyperglycemia, dyslipidemia, elevated liver enzymes, hyperinsulinemia with increased HOMA-IR, shortened APTT and PT, hyperfibrinogenemia (4.4 vs 2.1 g/L in intact rats), and enhanced platelet aggregation. Rosuvastatin partially corrected these parameters; the rosuvastatin + RM-1 combination produced the most consistent improvement, approaching intact-group values, and also improved ALT, AST, low-density lipoprotein, and HDL beyond rosuvastatin alone. Effects on triglycerides and total cholesterol were less uniform.

Conclusion: RM-1 polyphenol enhances the corrective effect of rosuvastatin on diabetes-induced glycemic and hemostatic disturbances, supporting its potential as an adjunct therapy.

Keywords: experimental diabetes, streptozotocin, rosuvastatin, RM-1 polyphenol, insulin resistance, HOMA-IR, fibrinogen, platelet aggregation

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by severe, disabling complications that can result in loss of working capacity and premature death. The key pathogenic mechanisms underlying T2DM are insulin resistance (IR) and progressive dysfunction of pancreatic β-cells, both of which impair the regulatory effects of insulin on glucose, protein, and lipid metabolism.

Statins, particularly rosuvastatin, are widely used lipid-lowering agents for the prevention and treatment of cardiovascular disease. Rosuvastatin selectively inhibits HMG-CoA reductase, thereby reducing total cholesterol and low-density lipoprotein (LDL) levels. However, several clinical studies and meta-analyses have shown that statins, including rosuvastatin, may increase the risk of new-onset diabetes by reducing insulin secretion and worsening IR [1-3].

Although the diabetogenic effect of statins is well established epidemiologically, its molecular basis has only recently been elucidated [4]. Statins inhibit HMG-CoA reductase, blocking the mevalonate pathway and reducing downstream isoprenoid synthesis, which impairs post-translational modification of G-proteins required for insulin granule exocytosis. In pancreatic β-cells, simvastatin directly inhibits L-type Ca^{2+} channels independent of its cholesterol-lowering action [5, 6], while impaired mitochondrial ATP production further disrupts closure of ATP-sensitive potassium (K-ATP) channels—both essential steps in glucose-stimulated insulin secretion. Statins may also suppress GLUT-2 and GLUT-4 transporter expression, impairing both β-cell glucose sensing and peripheral glucose uptake, and may promote hepatic

gluconeogenesis by upregulating phosphoenolpyruvate carboxykinase and glucose-6-phosphatase [4]. This diabetogenic effect appears more pronounced with simvastatin, rosuvastatin, and atorvastatin than with pravastatin [4, 7].

Polyphenols are a widely distributed class of biologically active plant compounds with antioxidant, anti-inflammatory, and antiplatelet properties, mediated in part through inhibition of cyclooxygenase and lipoxygenase pathways and modulation of arachidonic acid metabolism [8]. Prior studies from our group have further shown that polyphenols and related polysaccharide-based compounds can correct hemostatic system disturbances across a range of pathological rat models, including diabetes, Alzheimer's disease, attention-deficit hyperactivity disorder, hypothyroidism, and thromboplastin-induced thrombosis [9-14].

RM-1 is a polyphenol fraction isolated from the aerial parts of Tamarix ramosissima (Tamaricaceae). The plant material was extracted with chloroform to remove non-polar constituents, followed by extraction with an EtOH-H_2O mixture (8:2, v/v); the resulting aqueous residue was successively partitioned with diethyl ether, ethyl acetate, and n-butanol, and the ethyl acetate fraction was further purified to yield a flavonoid- and phenolic acid-enriched fraction. High-performance liquid chromatography analysis using authentic reference standards identified quercetin-3-O-glucuronide, apigenin, luteolin-7-O-glucoside, and gallic acid as the major constituents of RM-1. Compounds isolated from T. ramosissima have been reported in the literature to possess antioxidant, antibacterial, antifungal, anti-inflammatory, and antidiabetic properties.

The scientific novelty of this study lies in evaluating, for the first time, the combined effects of rosuvastatin and RM-1 polyphenol on IR, coagulation, and platelet aggregation in a streptozotocin-induced experimental diabetic rat model.

MATERIALS AND METHODS

The study was conducted on 40 male Wistar rats weighing 280-320 g, randomly allocated into four groups of 10 animals each. Animals were maintained under standard vivarium conditions with free access to food and water. All experimental procedures involving animals were approved by the Bioethics Committee of the Institute of Biophysics and Biochemistry, National University of Uzbekistan named after Mirzo Ulugbek (Chair: G. M. Artykbaeva), in accordance with the institutional Regulation on Biomedical Experiments and the Use of Laboratory Animals, based on the Declaration of Helsinki, the ARRIVE guidelines, and Directive 2010/63/EU of the European Parliament and the Council on the protection of animals used for scientific purposes.

T2DM was modeled by feeding animals a high-fat diet (55% of calories derived from fat) for 28 days, followed by a single intraperitoneal injection of streptozotocin (STZ, 35 mg/kg), dissolved in 0.1 M citrate buffer (pH 4.5). This combined high-fat diet/low-to-moderate-dose STZ protocol is a well-established method for modeling the IR and relative insulin deficiency characteristic of T2DM in rats, in contrast to high-dose STZ alone, which more closely models insulin-deficient (type 1-like) diabetes [15]. Blood glucose was measured 72 hours after the STZ injection; animals were considered diabetic if fasting glucose exceeded 11.1 mmol/L, the standard diagnostic threshold for diabetes.

Animals were divided into the following groups: group 1 (intact)—healthy rats injected with physiological saline (n = 10); group 2 (STZ-diabetic)—untreated diabetic rats (n = 10); group 3 (diabetic + rosuvastatin)—diabetic rats treated with oral rosuvastatin 10 mg/kg daily for 4 weeks (n = 10); group 4 (diabetic + rosuvastatin + RM-1)—diabetic rats treated with oral rosuvastatin 10 mg/kg plus RM-1 polyphenol 10 mg/kg daily for 4 weeks (n = 10).

The RM-1 dose (10 mg/kg) was selected based on the established antidiabetic and antioxidant dose range reported in the literature for its major constituent flavonoids. Quercetin and related flavonoids (e.g., apigenin), the principal constituents identified in RM-1, have demonstrated antidiabetic and antioxidant efficacy in streptozotocin-induced diabetic rat models across a dose range of approximately 10-100 mg/kg, with 10 mg/kg previously reported as an effective dose for quercetin in this model. RM-1 was therefore administered at the conservative lower end of this established dose range.

At the end of the 4-week treatment period, blood samples were collected from all animals in all four groups in the morning, at the same time of day, following a standardized 12-hour fasting period, in order to minimize diurnal and postprandial variability in the measured metabolic and hemostatic parameters. At the end of the treatment period, animals were anesthetized by ether inhalation and euthanized by decapitation, in accordance with the institutional Bioethics Committee guidelines; trunk blood was collected immediately following decapitation. Biochemical parameters—glucose (mmol/L), total protein (g/dL), alanine and aspartate aminotransferases (ALT, AST; U/L), total cholesterol (mmol/L), triglycerides (mmol/L), LDL and HDL cholesterol (mmol/L)—were determined using Cypress Diagnostica (Belgium) test kits on a CYANSmart semi-automatic biochemical analyzer. Insulin levels were measured using a Humans Reader HS biochemical device. IR was calculated using the HOMA-IR formula: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L) / 22.5 [16].

Coagulation parameters—activated partial thromboplastin time (APTT) and prothrombin time (PT)—were determined using CYANCoag (Belgium) reagent kits on a single-channel coagulometer (CYANCoag, Belgium, model CY003, SN: 5400439). Plasma fibrinogen concentration was determined using the CYANSmart coagulation analyzer (Cypress Diagnostica, Belgium). Platelet aggregation was assessed turbidimetrically using an aggregation analyzer (model AT-2), based on the classical optical aggregometry principle [17], using adrenaline, ADP, and collagen as inducers, with aggregation recorded over a 5-minute interval.

Statistical analysis was performed using student's t-test and one-way ANOVA followed by Tukey's HSD post-hoc test for pairwise comparisons. Data are presented as mean (M) ± standard deviation (SD). The value of $p < 0.05$ was considered statistically significant.

Group size (n = 10 rats/group) was selected to ensure a high level of reliability and is consistent with the design previously used in a comparable HFD/STZ-induced type 2 diabetes rat model [18]. A post-hoc power analysis performed on the primary outcome measures (HOMA-IR, plasma fibrinogen, APTT, PT) confirmed that, given the observed effect sizes (Cohen's d = 3.6-21.9), the statistical power achieved with n =

Table 1. Baseline (pre-induction) laboratory values in intact rats prior to random allocation to experimental groups

Parameter	Intact (n=10), pre-induction baseline
Glucose, mmol/L	3.9 ± 0.2
Insulin, µU/ml	7.5 ± 0.4
HOMA-IR	1.30 ± 0.04
Total cholesterol, mmol/L	1.6 ± 0.1
LDL, mmol/L	0.62 ± 0.04
HDL, mmol/L	0.74 ± 0.04
Triglycerides, mmol/L	0.78 ± 0.04
ALT, U/L	46.8 ± 1.9
AST, U/L	145.2 ± 4.3
Total protein, g/L	51.4 ± 1.8

Note. Values are represented as M ± SD

10/group exceeded 0.999 (α = 0.05), indicating that the chosen sample size was more than adequate to detect the observed between-group differences in these parameters.

RESULTS

Baseline Characteristics

Prior to diabetes induction and random allocation to experimental groups, baseline metabolic and biochemical values were recorded in all 40 rats (**Table 1**). These pre-induction values were comparable across the animals that were subsequently assigned to each of the four groups, confirming that the groups did not differ at baseline and that the between-group differences reported below arose from diabetes induction and treatment rather than pre-existing variability.

Biochemical Parameters

Table 2 summarizes glucose, total protein, triglycerides, liver enzymes, and lipid profile across the four experimental groups.

Diabetic rats showed a 3.0-fold increase in glucose relative to intact animals (12.50 ± 0.46 vs. 4.10 ± 0.18 mmol/L, p < 0.001). Rosuvastatin reduced glucose to 9.80 ± 0.35 mmol/L (p < 0.001 vs diabetic), while the rosuvastatin + RM-1 combination reduced it further to 6.20 ± 0.25 mmol/L (p < 0.001 vs both diabetic and rosuvastatin-alone groups), approaching the intact value most closely among the treatment groups, though the difference from intact remained significant (p < 0.001).

Total protein was significantly higher in diabetic rats than in intact rats (60.10 ± 0.89 vs. 53.40 ± 1.09 g/dL, p < 0.001). Both treatment groups differed significantly from the diabetic group and from each other (p < 0.001); the rosuvastatin + RM-1 group (43.22 ± 0.77 g/dL) fell below the intact level, while rosuvastatin alone (51.20 ± 0.85 g/dL) was closer to it.

Triglycerides were significantly higher in diabetic rats than in intact rats (1.110 ± 0.037 vs. 0.852 ± 0.027 mmol/L, p < 0.001). Both treatment groups fell significantly below the intact value (p < 0.001 for each vs intact). Notably, rosuvastatin alone (0.280 ± 0.018 mmol/L) and rosuvastatin + RM-1 (0.301 ± 0.017 mmol/L) did not differ significantly from each other (p = 0.28), indicating that RM-1 did not measurably alter rosuvastatin's triglyceride-lowering effect, which itself markedly overshot the intact range.

ALT activity increased approximately 3-fold in diabetic rats relative to intact animals (148.10 ± 3.66 vs. 49.40 ± 1.70 U/L, p < 0.001), and AST increased significantly (196.90 ± 3.73 vs. 151.40 ± 2.90 U/L, p < 0.001). Rosuvastatin monotherapy reduced ALT to 17.70 ± 0.93 U/L—significantly below the intact value (p < 0.001)—whereas the rosuvastatin + RM-1 combination resulted in an ALT of 47.00 ± 1.61 U/L that was not significantly different from intact (p = 0.09), indicating a statistically complete normalization of ALT with combination therapy. For AST, rosuvastatin reduced the value to 125.00 ± 2.53 U/L (significantly below intact, p < 0.001) while rosuvastatin + RM-1 resulted in 163.00 ± 3.01 U/L, closer to but still significantly above the intact value (p < 0.001).

Total cholesterol was significantly higher in diabetic rats than in intact rats (3.55 ± 0.18 vs. 1.80 ± 0.11 mmol/L, p < 0.001). Rosuvastatin reduced cholesterol to 1.20 ± 0.08 mmol/L (significantly below intact, p < 0.001), while rosuvastatin + RM-1 resulted in 2.60 ± 0.15 mmol/L (significantly above intact, p < 0.001); the two treatment groups also differed significantly from each other (p < 0.001).

LDL was markedly elevated in diabetic rats relative to intact animals (2.20 ± 0.14 vs. 0.69 ± 0.02 mmol/L, p < 0.001). Rosuvastatin significantly reduced LDL to 1.10 ± 0.03 mmol/L (p < 0.001 vs. diabetic), and the rosuvastatin + RM-1 combination reduced it further to 0.91 ± 0.02 mmol/L (p < 0.001 vs both diabetic and rosuvastatin-alone groups), approaching but not fully reaching the intact value (p < 0.001 vs intact).

HDL was significantly elevated in diabetic rats relative to intact animals (1.50 ± 0.05 vs. 0.84 ± 0.02 mmol/L, p < 0.001). Rosuvastatin monotherapy reduced HDL to 1.10 ± 0.03 mmol/L (significantly different from both diabetic and intact, p < 0.001 for each), while the rosuvastatin + RM-1 combination reduced it further to 0.82 ± 0.02 mmol/L—not significantly different from the intact value (p = 0.70), indicating full statistical normalization of HDL with combination therapy.

Overall, the rosuvastatin + RM-1 combination showed a consistent, statistically supported improvement over rosuvastatin alone for glucose, total protein, ALT, AST, LDL, and HDL, in each case moving significantly closer to (and, for ALT and HDL, statistically indistinguishable from) the intact value. Two exceptions were noted: for triglycerides, rosuvastatin

Table 2. Summary of glucose, total protein, triglycerides, liver enzymes, and lipid profile across the four experimental groups

Parameter	Intact (n = 10)	Diabetic (n = 10)	Diabetic+rosuvastatin (n = 10)	Diabetic+rosuvastatin+RM-1 (n = 10)	p
Glucose, mmol/L	4.10 ± 0.18	12.50 ± 0.46	9.80 ± 0.35	6.20 ± 0.25	< 0.001
Total protein, g/dL	53.40 ± 1.09	60.10 ± 0.89	51.20 ± 0.85	43.22 ± 0.77	< 0.001
Triglycerides, mmol/L	0.852 ± 0.027	1.110 ± 0.037	0.280 ± 0.018	0.301 ± 0.017	< 0.001
ALT, U/L	49.40 ± 1.70	148.10 ± 3.66	17.70 ± 0.93	47.00 ± 1.61	< 0.001
AST, U/L	151.40 ± 2.90	196.90 ± 3.73	125.00 ± 2.53	163.00 ± 3.01	< 0.001
Total cholesterol, mmol/L	1.80 ± 0.11	3.55 ± 0.18	1.20 ± 0.08	2.60 ± 0.15	< 0.001
LDL, mmol/L	0.69 ± 0.02	2.20 ± 0.14	1.10 ± 0.03	0.91 ± 0.02	< 0.001
HDL, mmol/L	0.84 ± 0.02	1.50 ± 0.05	1.10 ± 0.03	0.82 ± 0.02	< 0.001

Note. Values are represented as M ± SD; One-way ANOVA was significant (p < 0.001) for all parameters; Tukey's HSD was used for pairwise post-hoc comparisons (see text for specific pairwise p-values)

Table 3. Insulin and insulin resistance (HOMA-IR)

Parameter	Intact (n = 10)	Diabetic (n = 10)	Diabetic+rosuvastatin (n = 10)	Diabetic+rosuvastatin+RM-1 (n = 10)	p
Insulin, µU/mL	8.00 ± 0.26	19.40 ± 0.58	16.30 ± 0.48	13.30 ± 0.37	< 0.001
HOMA-IR	1.45 ± 0.04	10.80 ± 0.39	7.09 ± 0.18	3.66 ± 0.13	< 0.001

Note. Values are represented as M ± SD & all pairwise Tukey post-hoc comparisons were statistically significant (p < 0.001)

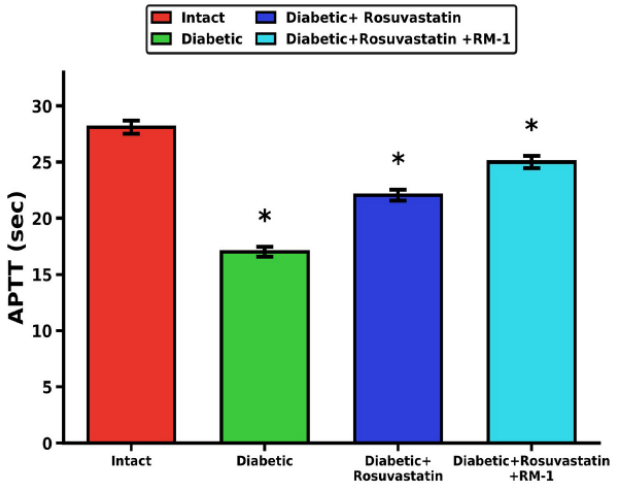

Figure 1. Activated partial thromboplastin time (APTT, sec) across groups (*p < 0.05 vs. intact group) (created by the authors using GraphPad Prism based on the study's own experimental data)

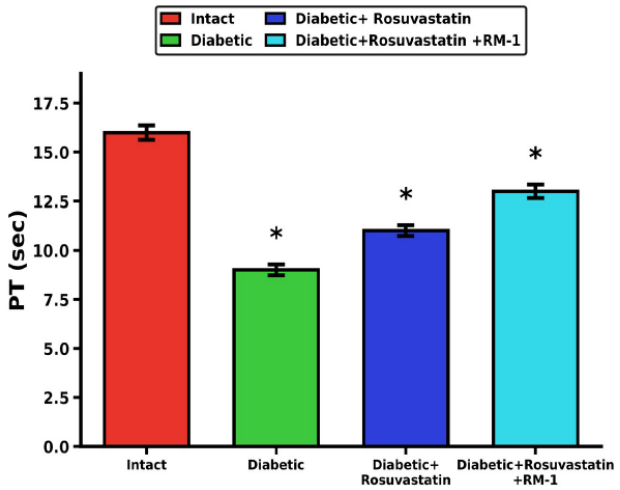

Figure 2. Prothrombin time (PT, sec) across groups (*p < 0.05 vs. intact group) (created by the authors using GraphPad Prism based on the study's own experimental data)

alone and rosuvastatin + RM-1 did not differ significantly from each other (p = 0.28), and both overshot below the intact range; for total cholesterol, rosuvastatin + RM-1 resulted in a significantly higher value than rosuvastatin alone, moving further from the value seen with rosuvastatin monotherapy, though still intermediate between the diabetic and intact groups. These two exceptions are discussed further in **Table 3**.

Diabetic rats exhibited compensatory hyperinsulinemia, with insulin levels significantly higher than intact animals (19.40 ± 0.58 vs. 8.00 ± 0.26 µU/mL, p < 0.001). Rosuvastatin significantly reduced insulin to 16.30 ± 0.48 µU/mL (p < 0.001 vs diabetic), while the rosuvastatin + RM-1 combination reduced it further to 13.30 ± 0.37 µU/mL (p < 0.001 vs both diabetic and rosuvastatin-alone groups)—the closest of the treatment groups to the intact value, though the difference from intact remained significant (p < 0.001).

HOMA-IR, reflecting IR, was markedly elevated in diabetic rats (10.80 ± 0.39) compared with intact animals (1.45 ± 0.04, p < 0.001), indicating severe IR. Rosuvastatin significantly reduced HOMA-IR to 7.09 ± 0.18 (p < 0.001 vs diabetic), while rosuvastatin + RM-1 produced a significantly greater reduction, to 3.66 ± 0.13 (p < 0.001 vs both diabetic and rosuvastatin-alone groups)—the closest approach to the intact value among all treatment groups, though still significantly different from it (p < 0.001).

Coagulation Parameters (APTT and PT)

APTT was shortest in diabetic rats (17.00 ± 0.45 sec) compared with intact animals (28.10 ± 0.59 sec, p < 0.001), indicating a hypercoagulable state (**Figure 1**). Rosuvastatin treatment significantly lengthened APTT to 22.04 ± 0.49 sec (p < 0.001 vs diabetic), but this remained significantly below the intact value (p < 0.001). The rosuvastatin + RM-1 combination lengthened APTT further, to 25.00 ± 0.53 sec (p < 0.001 vs both diabetic and rosuvastatin-alone groups), producing the greatest reduction in hypercoagulability among treatment groups and the closest approach to the intact value, though still significantly different from it (p < 0.001).

PT showed a parallel pattern: it was shortest in diabetic rats (9.00 ± 0.28 sec) compared with intact animals (16.00 ± 0.37 sec, p < 0.001) (**Figure 2**). Rosuvastatin significantly lengthened PT to 11.00 ± 0.28 sec (p < 0.001 vs diabetic), while rosuvastatin + RM-1 produced a significantly greater lengthening, to 13.00 ± 0.35 sec (p < 0.001 vs. both diabetic and rosuvastatin-alone groups), approaching but not reaching the intact level (p < 0.001 vs intact).

Plasma Fibrinogen

Plasma fibrinogen was significantly higher in diabetic rats than in intact animals (4.40 ± 0.20 vs. 2.10 ± 0.15 g/L, p < 0.001), consistent with a hypergemostatic, procoagulant state (**Figure 3**). Rosuvastatin monotherapy significantly reduced fibrinogen to 3.30 ± 0.15 g/L (p < 0.001 vs diabetic), though this remained significantly above the intact value (p < 0.001). The rosuvastatin + RM-1 combination produced a further significant reduction, to 2.78 ± 0.14 g/L (p < 0.001 vs both diabetic and rosuvastatin-alone groups), the closest approach to the intact value among the treatment groups, though still significantly different from it (p < 0.001).

Platelet Aggregation

Platelet aggregation was recorded over 5 minutes, spontaneously and following induction with adrenaline, ADP, and collagen, across the intact, diabetic, diabetic + rosuvastatin, and diabetic + rosuvastatin + RM-1 groups.

At the 5-minute endpoint, spontaneous platelet aggregation in diabetic rats (15.90 ± 3.60%) was numerically more than 3-fold higher than intact animals (4.54 ± 0.32%), but this difference did not reach statistical significance after correction for multiple comparisons (Tukey HSD, p = 0.23),

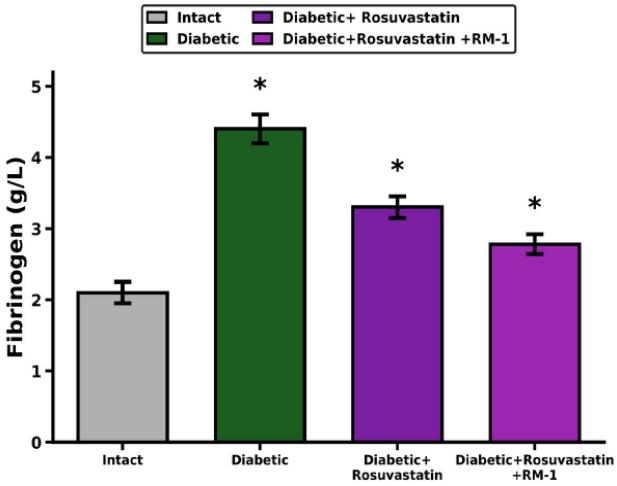

Figure 3. Plasma fibrinogen (g/L) across groups (*p < 0.05 vs. intact group) (created by the authors using GraphPad Prism based on the study's own experimental data)

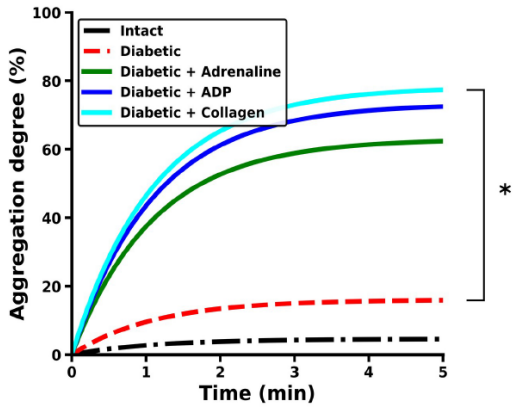

Figure 4. Platelet aggregation (%) over 5 minutes—Intact vs. untreated diabetic group, spontaneous and induced by adrenaline, ADP, and collagen (*p < 0.05 vs. intact group) (created by the authors using GraphPad Prism based on the study's own experimental data)

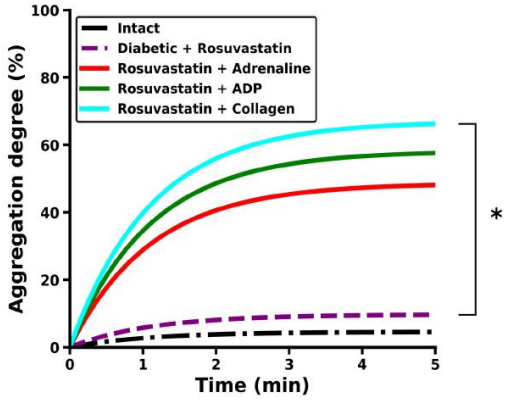

Figure 5. Platelet aggregation (%) over 5 minutes—Diabetic + rosuvastatin group, spontaneous and induced by adrenaline, ADP, and collagen (*p < 0.05 vs. intact group) (created by the authors using GraphPad Prism based on the study's own experimental data)

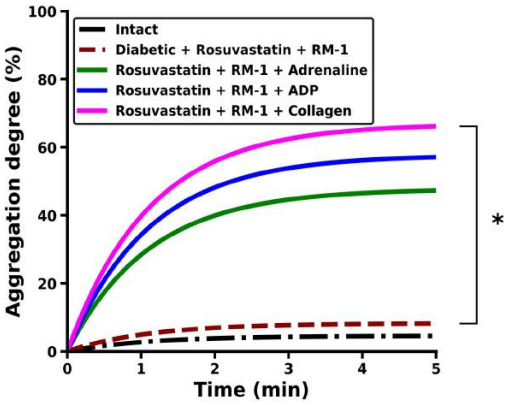

Figure 6. Platelet aggregation (%) over 5 minutes—Diabetic + rosuvastatin + RM-1 group, spontaneous and induced by adrenaline, ADP, and collagen (*p < 0.05 vs. intact group) (created by the authors using GraphPad Prism based on the study's own experimental data)

reflecting the wide inter-animal variability of spontaneous aggregation in the diabetic group.

In contrast, all three induced-aggregation conditions differed significantly from both the intact and spontaneous-diabetic groups ($p < 0.001$): adrenaline-induced aggregation reached 62.40 ± 15.24%, ADP-induced aggregation reached 72.50 ± 15.66%, and collagen-induced aggregation reached 77.40 ± 15.28% (**Figure 4**). Pairwise differences among the three inducers themselves did not reach significance (adrenaline vs. ADP, $p = 0.34$; ADP vs collagen, $p = 0.89$; adrenaline vs. collagen, $p = 0.06$), indicating a similar order of magnitude of platelet activation across agonists in diabetic rats, despite the numerically graded pattern (adrenaline < ADP < collagen).

Rosuvastatin monotherapy reduced spontaneous aggregation at 5 minutes to 9.60 ± 3.33%; as with the untreated diabetic group, this did not differ significantly from the intact value ($p = 0.47$), again reflecting high inter-animal variability in spontaneous aggregation. Induced aggregation, however, remained significantly elevated above intact in all three conditions ($p < 0.001$): adrenaline-induced aggregation was 48.10 ± 8.05%, ADP-induced was 57.60 ± 8.40%, and collagen-induced was 66.30 ± 9.26%—each significantly lower than the corresponding untreated diabetic value (adrenaline: $p < 0.001$; ADP: $p < 0.001$; collagen: $p < 0.001$, unpaired comparisons across blocks) but not normalized to intact levels (**Figure 5**).

The rosuvastatin + RM-1 combination produced the most consistent reduction across all measures. Spontaneous aggregation at 5 minutes was 8.20 ± 2.63%, numerically the closest of all treatment groups to the intact value (4.54 ± 0.32%) and, as in the other two groups, this difference did not reach statistical significance ($p = 0.67$). Induced aggregation, however, was significantly reduced beyond both the untreated diabetic and rosuvastatin-alone groups while still remaining significantly elevated above intact ($p < 0.001$ for all three inducers vs intact): adrenaline-induced aggregation was 47.30 ± 7.02%, ADP-induced was 57.10 ± 7.59%, and collagen-induced was 66.20 ± 8.53% (**Figure 6**).

Across all three induced-aggregation conditions (adrenaline, ADP, collagen) in all three treatment blocks, a consistent and statistically robust gradient was observed: diabetic → diabetic + rosuvastatin → diabetic + rosuvastatin + RM-1, with aggregation activity progressively approaching, though not fully reaching, intact-group values ($p < 0.001$ for each group vs intact, in each block). Spontaneous aggregation

showed the same numerical gradient (15.90% → 9.60% → 8.20%, vs 4.54% in intact) across all three blocks, but in no block did this reach statistical significance against intact ($p = 0.23$, $p = 0.47$, and $p = 0.67$, respectively), reflecting consistently high inter-animal variability in unstimulated platelet activity across all groups studied. This pattern—robust significance for agonist-induced aggregation alongside non-significant spontaneous aggregation—was reproducible across all three independently analyzed treatment blocks, suggesting it reflects a genuine feature of this experimental system rather than a chance finding in any single group; a larger sample size would nonetheless improve power to detect a possible true difference in spontaneous aggregation.

DISCUSSION

The present findings confirm that streptozotocin-induced diabetes produces a broadly procoagulant, hyperaggregable hemostatic state alongside marked IR, consistent with previous reports linking hyperglycemia to endothelial dysfunction and platelet hyperreactivity [19]. The magnitude of IR observed here (7.4-fold increase in HOMA-IR) indicates a severe metabolic disturbance in this model.

Rosuvastatin monotherapy produced only partial correction of glycemic, coagulation, fibrinogen, and platelet parameters, consistent with the growing body of evidence that statins—including rosuvastatin—can themselves impair insulin secretion and worsen insulin sensitivity through mevalonate-pathway-dependent mechanisms affecting β-cell K-ATP and L-type Ca^{2+} channel function [4-6, 20]. This may explain why rosuvastatin alone did not fully normalize glucose, insulin, or HOMA-IR in the present study, despite its established lipid-lowering efficacy.

The addition of RM-1 polyphenol to rosuvastatin produced a consistently greater corrective effect than rosuvastatin alone on glucose, insulin, HOMA-IR, fibrinogen, coagulation times, and platelet aggregation—the parameters most directly relevant to the diabetic hypercoagulable and insulin-resistant state. Under physiological conditions, insulin itself exerts an antiaggregatory effect on platelets via hybrid insulin/IGF-1 receptor signaling [21] and modulation of platelet calcium metabolism [22], an effect that is attenuated in insulin-resistant and diabetic states [23]; the greater reduction in platelet aggregation observed with rosuvastatin + RM-1 may therefore partly reflect the improved insulin sensitivity in this group. The pronounced response to collagen relative to adrenaline and ADP across all groups is consistent with the central role of the glycoprotein VI (GPVI) receptor in collagen-induced platelet activation and thrombus formation [24-26]. This is also consistent with the known antioxidant and anti-inflammatory properties of polyphenols [8], which may counteract statin-associated mitochondrial and oxidative stress in β-cells and reduce platelet membrane oxidative damage and arachidonic acid pathway activation.

The rosuvastatin + RM-1 combination also produced a significantly greater corrective effect than rosuvastatin alone on total protein, ALT, AST, LDL, and HDL, with HDL and ALT reaching values statistically indistinguishable from intact animals—indicating that RM-1's benefit extends beyond glycemic and hemostatic parameters to much of the lipid and hepatic profile as well. Two exceptions were noted. Triglycerides were reduced similarly by rosuvastatin alone and by the combination (no significant difference between them, $p = 0.28$), with both overshooting below the intact range—suggesting that rosuvastatin's triglyceride-lowering action at this dose is not further modified by RM-1 and may itself exceed the degree of correction needed. Total cholesterol, in contrast, was significantly higher with the combination than with rosuvastatin alone, moving further from (rather than toward) the value achieved by monotherapy, though still intermediate between the diabetic and intact groups; this may reflect a specific interaction between RM-1 and hepatic cholesterol synthesis or clearance pathways that is not shared with LDL and HDL handling, and warrants targeted follow-up (e.g., assessment of hepatic HMG-CoA reductase activity and lipoprotein turnover) before firm conclusions are drawn.

One limitation should be noted: the mechanism of RM-1 polyphenol's action was not directly assessed biochemically (e.g., oxidative stress markers and inflammatory cytokines) and remains inferential.

A further limitation of this study is the absence of an RM-1-only treatment group; consequently, the independent contribution of RM-1 to the observed metabolic and hemostatic improvements could not be isolated from the effects of rosuvastatin. Future studies incorporating a standalone RM-1 arm are needed to clarify whether RM-1 acts independently, synergistically, or only in combination with statin therapy.

CONCLUSION

Streptozotocin-induced diabetic rats developed pronounced disturbances in glycemic control, lipid metabolism, hepatic enzymes, insulin sensitivity, coagulation, plasma fibrinogen, and platelet aggregation. Rosuvastatin monotherapy partially corrected these disturbances but did not normalize any parameter to intact-group levels. The combination of rosuvastatin with RM-1 polyphenol produced a more consistent corrective effect than rosuvastatin alone on glycemic, insulin-resistance, and hemostatic parameters specifically, approaching but not fully reaching physiological values; its effect on lipid profile and hepatic enzymes was less uniform and, for some parameters, did not follow the same pattern. These findings support the potential of RM-1 polyphenol as an adjunct to statin therapy for mitigating diabetes-associated IR and hemostatic complications, while highlighting the need for further study of its effects on lipid metabolism and for confirmation of statistical significance.

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Ethical statement: This study was conducted in accordance with the institutional Regulation on Biomedical Experiments and the Use of Laboratory Animals of the Institute of Biophysics and Biochemistry, National University of Uzbekistan named after Mirzo Ulugbek, approved by the Institute Director on 17 February 2026. This regulation is based on the Declaration of Helsinki, the ARRIVE guidelines, and Directive 2010/63/EU of the European Parliament and the Council on the protection of animals used for scientific purposes. Ethical oversight was provided by the Institute's Bioethics Committee (Chair: G. M. Artykbaeva). A separate study-specific approval code was not issued, as this institutional regulation serves as the governing ethical

framework for all animal research conducted at the Institute; the full regulation document is uploaded as the Ethics Committee Approval Form accompanying this submission.

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