

Concurrently Administered Rutin and Vitamin E Mitigate Diabetes-driven Pathological Mechanisms and Enhance Memory

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A Multi-targeted Therapeutic Approach of Combating Diabetic-induced Memory Decline and Improving Quality of Life with Rutin and Vitamin E!!!

Introduction

Background: Poor glycemic control, altered insulin signaling, oxidative stress, inflammation, and synaptic dysfunction contribute to memory loss in type 2 diabetes mellitus (T2DM), which affects the quality of life of the diabetic individual (Pugazhenthil et al., 2017; Silverman et al., 2022). Previous experimental evidence has shown that individually administered rutin or vitamin E (VE) demonstrated antihyperglycemic and memory-enhancing activities (Tuzcu and Baydas, 2006; Hasanein et al., 2020). However, the concurrent administration of these drugs in mitigating the complex pathological mechanisms in T2DM still remains underexplored.

Aim: Investigate how concurrent administration of rutin and VE ameliorated diabetes-induced memory loss and their underlying mechanisms

Methods

Animal grouping:

Fifty male Wistar rats (n = 10) were randomly placed into five groups as shown below:

Group 1: distilled water only (DW) (Control)

Group 2: (diabetes group – 10 mL/kg) HFD + STZ (35 mg/kg) (HS).

Group 3: HS+ Rutin (Rt) (50 mg/kg) + Vitamin E (VE) (200 mg/kg)

Group 4: HS+ Rt (100 mg/kg) + VE (200 mg/kg)

Group 5: HS + Dz (25 mg/kg)

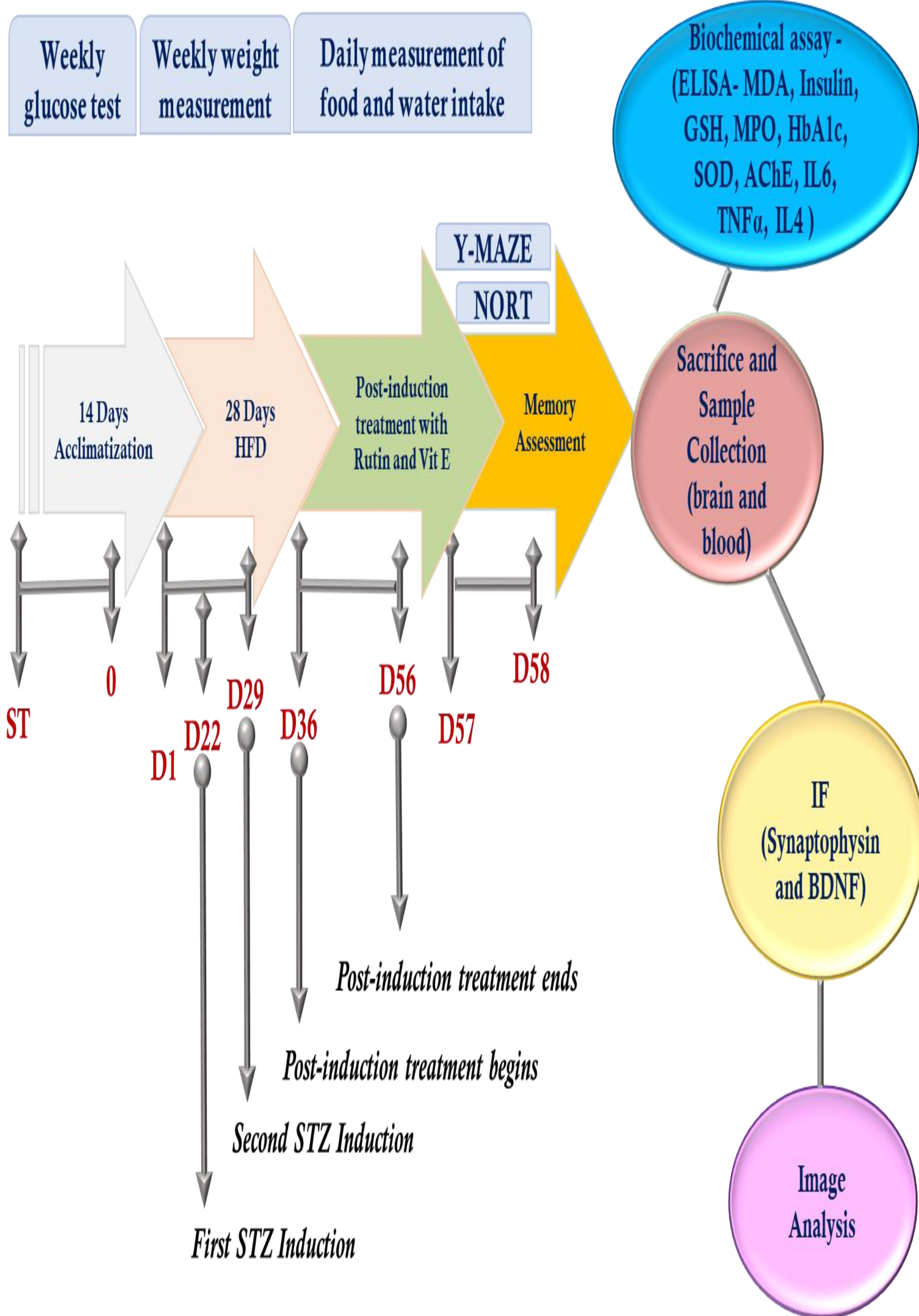


Figure 1: Experimental flow chart

ABBREVIATIONS: **HFD:** High-fat diet; **STZ:** Streptozotocin; **Dz:** Donepezil; **HS:** High-fat diet and streptozotocin; **DW:** Distilled water; **BDNF:** Brain-derived neurotrophic factor; **Rt:** Rutin; **VE:** Vitamin E; **TNFα:** Tumor necrosis alpha; **IL-6:** Interleukin-6; **IL-4:** Interleukin -4; **MDA:** Malondialdehyde; **SOD:** Superoxide dismutase; **MPO:** Myeloperoxidase; **GSH:** Reduced glutathione; **HbA1c:** Glycosylated hemoglobin; **AChE:** Acetylcholinesterase enzyme

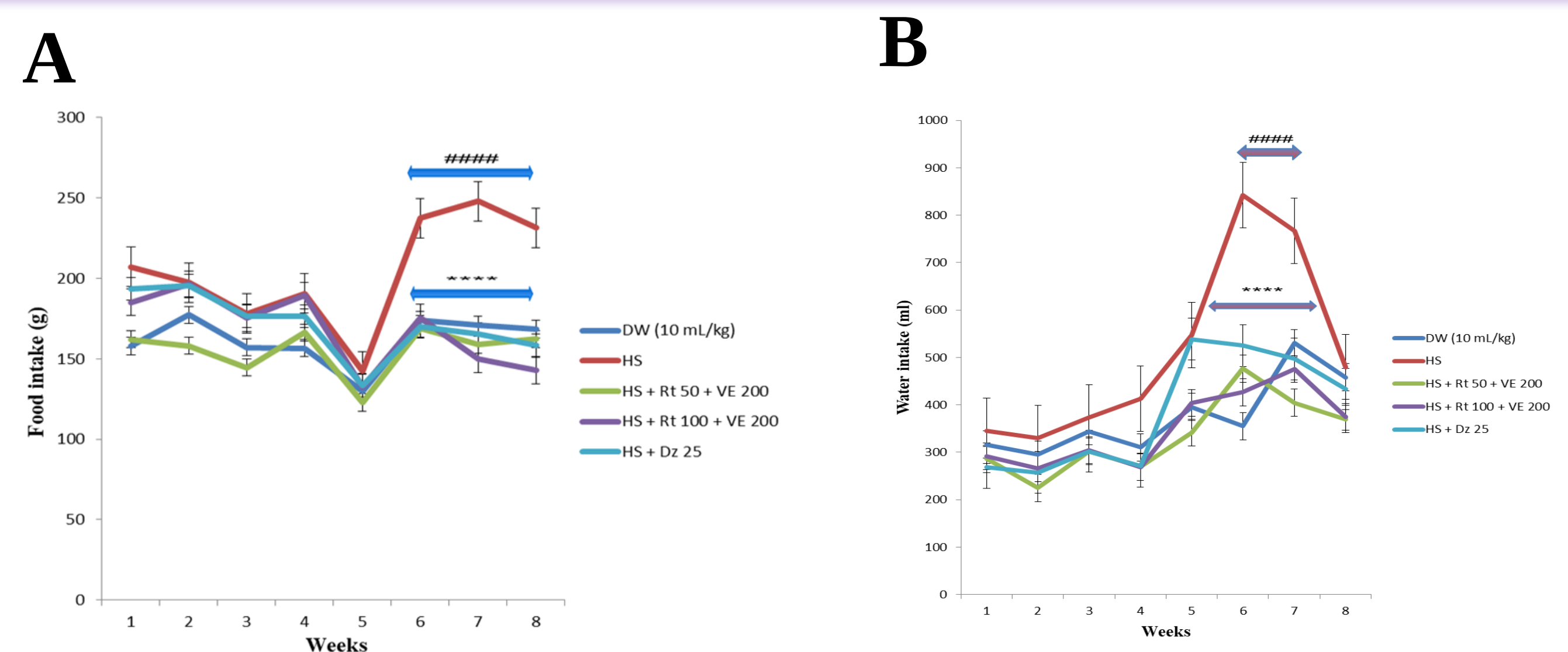


Figure 2: Effect of a 21-day concurrent administration of rutin and vitamin E on weekly food and water intake by type 2 diabetic rats. (A) Food intake. (B) Water intake. Data are represented as mean ± SEM, n=10 per group. #####P<0.0001 vs DW; ***P<0.0001 vs HS.

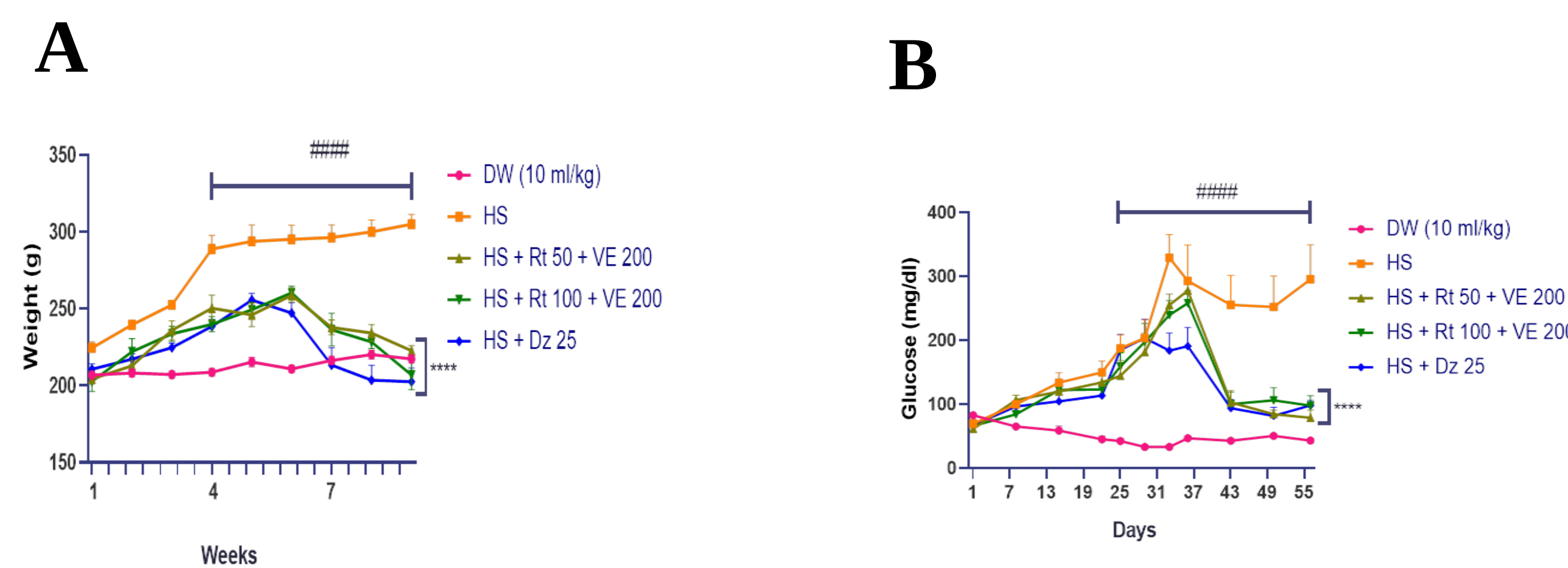


Figure 3: Effect of concurrent administration of rutin and vitamin E for 21 days on the weight and glucose levels of type 2 diabetic rats. (A) Weight of rats. (B) Glucose levels of rats. Data are represented as mean ± SEM, n =10 per group. #####P<0.0001 vs DW; ****P<0.0001 vs HS.

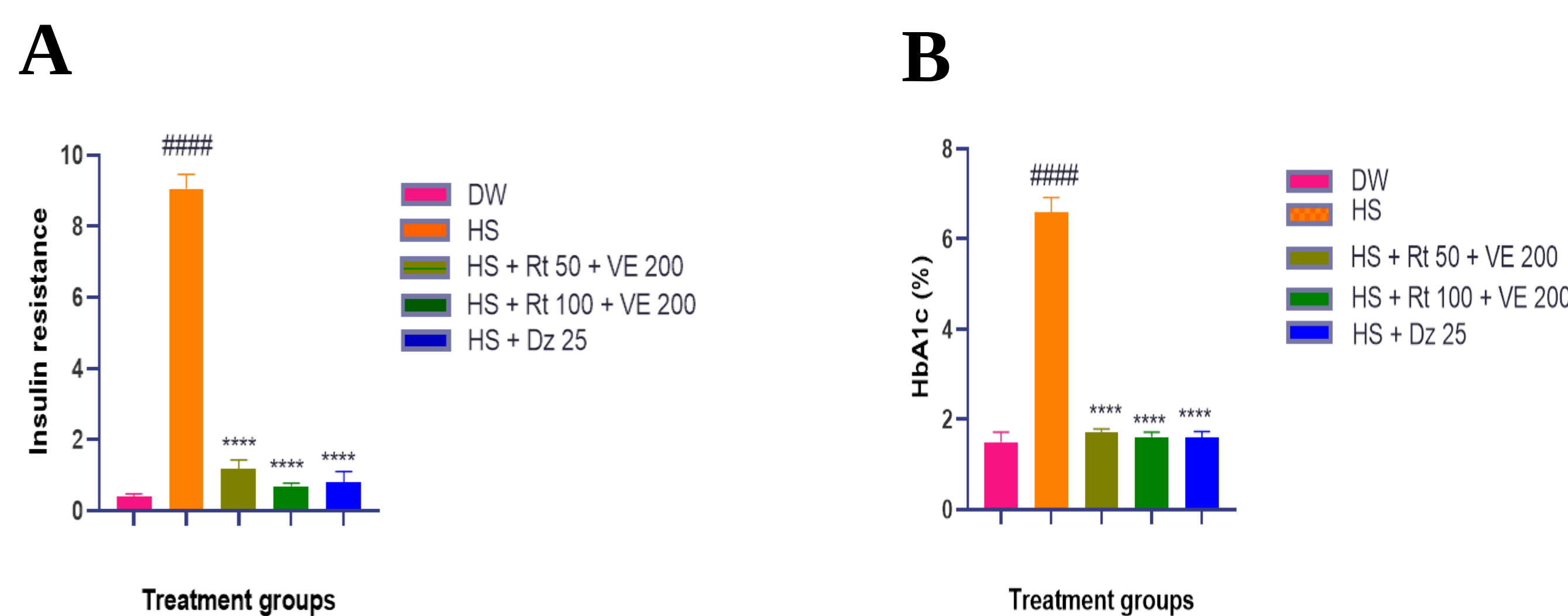


Figure 4: Effect of concurrent administration of rutin and vitamin E for 21 days on insulin resistance and glycosylated hemoglobin levels in type 2 diabetic rats. (A) Insulin resistance (B) Glycosylated hemoglobin. Data are expressed as mean ± SEM, n = 3 per group. #####P<0.0001 vs DW; ****P<0.0001 vs HS; Glycosylated hemoglobin.

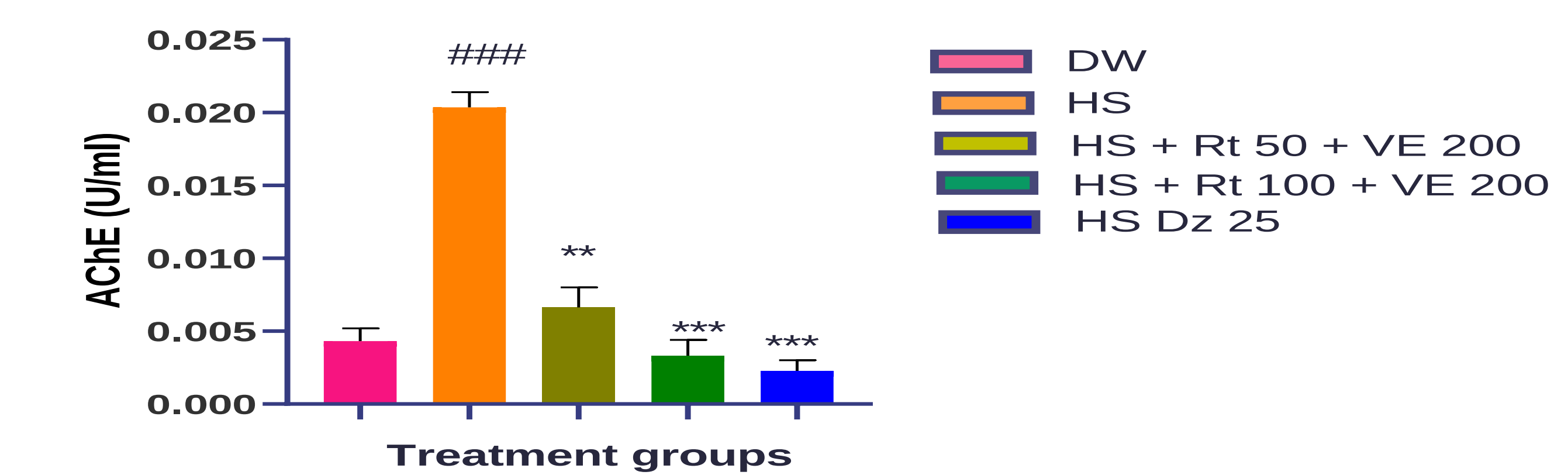


Figure 5: Effect of concurrent administration of rutin and vitamin E on acetylcholinesterase enzyme levels in diabetic rats. Data are expressed as mean ± SEM, n = 3. #####P<0.001 vs DW; **P<0.01 vs HS; ***P<0.001 vs HS.

Table 1: The lipid profile of type 2 diabetic rats concurrently administered rutin and vitamin E for 21 consecutive days:				
Treatment groups	CHOL (mmol/L)	TRIG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
DW (ml/kg)	1.11 ± 0.28	0.17 ± 0.09	3.40 ± 0.28	0.22 ± 0.02
HS	3.88 ± 0.38 ^a	4.31 ± 0.28 ^c	0.80 ± 0.07 ^c	2.65 ± 0.16 ^c
HS + Rt 50 + VE 200	2.57 ± 0.54	3.63 ± 0.45	1.14 ± 0.18	2.41 ± 0.07
HS + Rt 100 + VE 200	0.77 ± 0.35 ^b	0.18 ± 0.13 ^c	2.86 ± 0.04 ^c	0.13 ± 0.02 ^c
HS + Dz 25	0.71 ± 0.17 ^b	0.73 ± 0.19 ^c	3.12 ± 0.09 ^c	0.46 ± 0.10 ^c

Data are expressed as mean ± SEM, n = 3 per group. ####P<0.001 vs DW; **P<0.01 vs HS; ***P<0.001 vs HS.

Results

Table 2: The effect of concurrent administration of rutin and vitamin E on brain oxidative stress markers and inflammatory cytokines in type 2 diabetic rats

Biochemical Parameters	DW (ml/kg)	HS	HS + Rt 50 + VE 200	HS + Rt 100 + VE 200	HS + Dz 25
Oxidative stress biomarkers					
MDA (mmol/mg)	2.57 ± 0.40	7.11 ± 0.24 ^b	2.87 ± 0.35 ^b	1.84 ± 0.47 ^b	0.23 ± 0.45 ^b
MPO (U/mg)	0.00 ± 0.00	0.14 ± 0.01 ^c	0.01 ± 0.01 ^c	0.01 ± 0.00 ^c	0.01 ± 0.00 ^c
SOD (U/mg)	1.98 ± 0.08	0.27 ± 0.17 ^c	1.89 ± 0.04 ^c	1.71 ± 0.11 ^b	1.43 ± 0.26 ^b
GSH (µM/mg)	0.30 ± 0.02	0.16 ± 0.02 ^b	0.31 ± 0.02 ^b	0.44 ± 0.02 ^c	0.26 ± 0.01 ^a
Inflammatory cytokines (pg/ml)					
TNFα	305.9 ± 40.49	946.7 ± 15.56 ^c	285.0 ± 20.69 ^c	280.0 ± 49.98 ^c	210.0 ± 14.95 ^d
IL-6	17.79 ± 2.63	37.17 ± 1.16 ^b	20.52 ± 2.76 ^a	19.99 ± 0.94 ^b	14.55 ± 1.72 ^b
IL-4	142.5 ± 3.73	25.03 ± 3.06 ^c	155.0 ± 10.19 ^c	152.7 ± 5.48 ^c	143.3 ± 11.73 ^c

Data are represented as mean ± SEM, n=10 per group. ^bP<0.01 vs DW; ^cP<0.001 vs DW; ^aP<0.05 vs HS; ^bP<0.01 vs HS; ^cP<0.001 vs HS. .

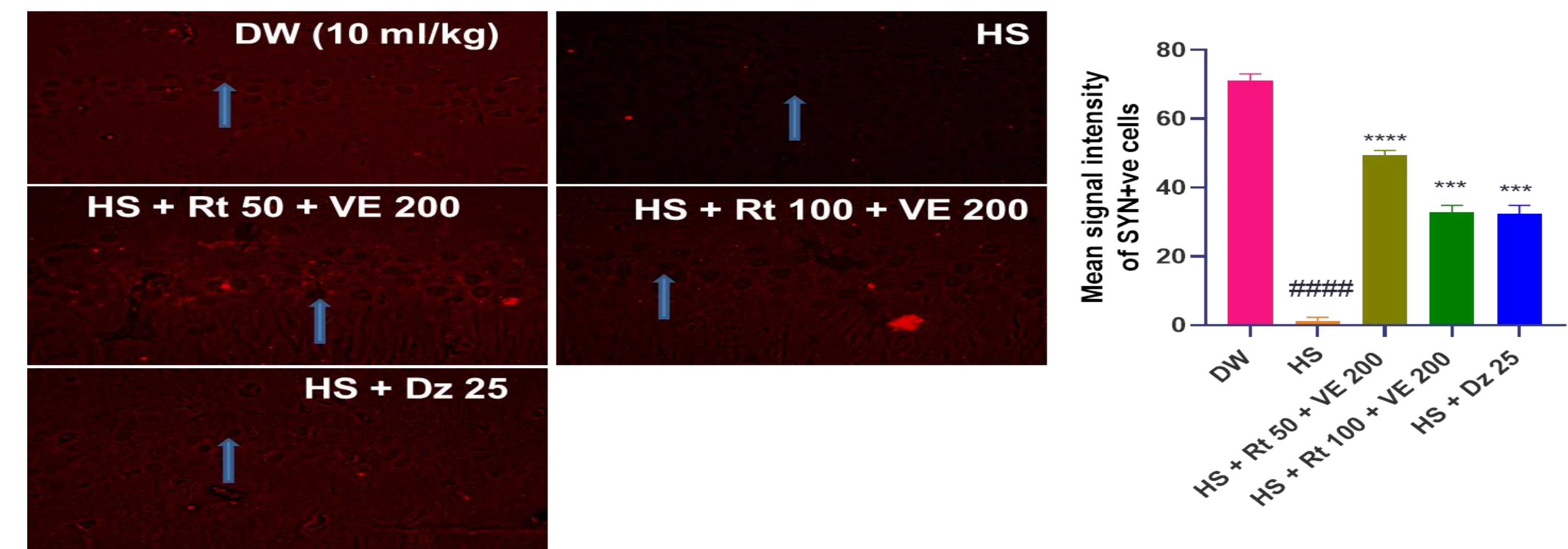


Figure 6: Effect of concurrent administration of rutin and vitamin E on the expression and signal intensity of synaptophysin immunopositive cells of the cornu ammonis 1 (CA1) of type 2 diabetic rats. #####P<0.0001 vs DW; ***P<0.001 vs HS; ****P<0.0001 vs HS; Magnification x400. IMAGE J Software

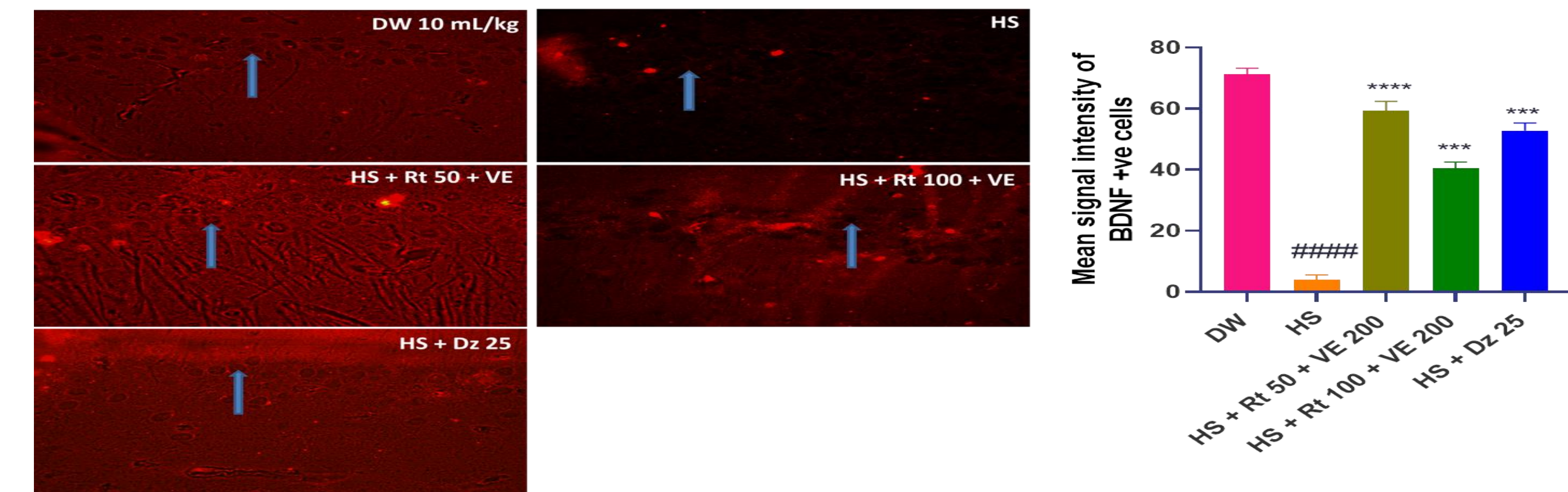


Figure 7: Effect of concurrent administration of rutin and vitamin E on the expression and signal intensity of brain-derived neurotrophic factor (BDNF) immunopositive cells of the cornu ammonis 1 (CA1) of type 2 diabetic rats. #####P<0.0001 vs DW; ***P<0.001 vs HS; ****P<0.0001 vs HS; Magnification x400. IMAGE J Software

Conclusion

- ❖ Concurrently administered rutin and VE improved glycemic control and insulin sensitivity, reversed inflammation, oxidative stress, and synaptic dysfunction and upregulated brain neurotrophins to improve diabetes-induced memory loss in diabetic rats.
- ❖ This therapeutic strategy may help T2DM patients manage memory impairment and improve their quality of life.

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