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Impact of *Citrullus colocynthis* on BDNF Levels and Lipid Profiles in Rats with Type 1 Diabetes Induced by STZ

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Abstract

Background: Type 1 diabetes (T1D) affects a variety of pathways that can contribute to diabetic neuropathy, such as oxidative stress, neuroinflammation, and autophagy. One neurogenesis factor that is thought to play a part in memory and Alzheimer's disease is the brain-derived neurotrophic factor (BDNF). The current study sought to evaluate the effects of *Citrullus colocynthis* seeds on lipid profiles, oxidative status, BDNF level, glycemic control, and antioxidant defenses in rats with T1D mellitus.

Methods: Forty-two male Wistar rats (3–4 months of age and 200–250 g in weight) were evaluated. The rats were randomly assigned to three groups: control, diabetes, and diabetes + drug. The extract of *C. colocynthis* was given to the diabetic rats by gavage. The tests for oxidants and antioxidants included malondialdehyde (MDA), total antioxidant capacity (TAC), paraoxonase1 (PON1), nitric oxide (NO), superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and protein carbonyl (PC). The status of the lipid profile was measured by evaluating high-density lipoprotein (HDL), cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). The ELISA technique was used to measure hippocampal BDNF. The student's and paired *t* tests and one-way ANOVA were conducted using SPSS software version 22 for data analysis.

Results: *Citrullus colocynthis* prescription in the diabetes + drug group significantly decreased PC ($P<0.05$), MDA ($P<0.05$), and NO ($P<0.05$). It also elevated SOD ($P<0.001$), GPx ($P<0.001$), CAT ($P<0.05$), and PON1 ($P<0.05$) activities and TAC ($P<0.001$), BDNF ($P<0.001$), and insulin levels ($P<0.001$). Improved lipid profile, HOMA-IR ($P<0.001$), HOMA-B ($P<0.01$), and QUICKI ($P<0.001$) were observed compared to the diabetes group.

Conclusion: This research revealed that administering 200 mg/kg *C. colocynthis* once daily for 40 days can enhance the BDNF levels in the hippocampus, lessen metabolic problems and oxidative stress, and increase antioxidant defenses.

Keywords: *Citrullus colocynthis*, Diabetes, Hippocampal BDNF, Oxidant and antioxidant system, Lipid profile

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Introduction

Hyperglycemia, arising from a defect in insulin secretion or insulin resistance, is the etiology of type 1 diabetes (T1D), a chronic illness. In 2017, there were 425 million cases of diabetes mellitus worldwide; there will probably be 629 million instances by 2045 (1). Diabetes, with a prevalence of 1 in every 11 people across the world, is an emerging 21st-century pandemic (2). Complications can result from persistent hyperglycemia in young people and adults and can affect the retina, heart, kidneys, peripheral nerves, and, more recently, the brain (3). Hyperglycemia affects various pathways that can contribute to diabetic neuropathy, such as oxidative stress, neuroinflammation, and autophagy (4,5). Oxidative stress occurs when the reactive oxygen species (ROS) generation overcomes the scavenging capacities of antioxidants. The genetic absence of antioxidant enzymes and environmental factors such as viral infections can mediate such cases (6). One well-established factor contributing to the onset, progression, and consequences of diabetic mellitus (DM) is oxidative stress. Disturbance of the physiological free radical homeostasis has been linked to beta-cell dysfunction (7). The overproduction of free radicals in type 1 diabetes mellitus (T1DM) may destroy biomolecules, including lipids, proteins, and DNA, and trigger initial β-cell harm (8). There is mounting evidence that excessive accumulation of ROS/RNS from free fatty acids (FFA) and high blood sugar levels might seriously impair pancreatic β-cell function, mainly because antioxidant defenses are being depleted (catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) (1). According to studies, compared to age-matched controls, prediabetic and T1DM patients have poorer overall blood antioxidant levels assessed through urate, vitamin C, and plasma antioxidant concentrations (9-12).

The central nervous system's survival-promoting

protein, brain-derived neurotrophic factor (BDNF), regulates synaptic development and neuronal survival (13). Tropomyosin receptor kinase B (TrkB), broadly expressed in the mammalian brain, is the transmembrane protein receptor for BDNF. For the synaptic plasticity of adults and memory, foundation is vital, as are both BDNF and TrkB (14). It is reported that systemic BDNF injections in obese mouse models ameliorate blood glucose levels and relieve fasting hyperglycemia (15). Reduced BDNF expression has been observed in type 1 and type 2 diabetic rat hippocampi (4). Also, children with T1DM performed worse neurocognitively than children without the condition, according to Chen et al, and their serum levels of BDNF were lower (16).

Some non-pharmacological therapeutic approaches to treating diabetes are diet, exercise, and weight loss. Drugs such as tolbutamide, metformin, and glyburide are used in pharmacological treatment. Another approach to curing diabetes is gene therapy. Using herbal medicine is the final way to cure diabetes (17). *Citrullus colocynthis* belongs to the Cucurbitaceae family. The seeds of *C. colocynthis*

are less expensive and more available when grown for food. In Europe, Asia, and Africa, *C. colocynthis* is an annual plant. *C. colocynthis* generates substantial quantities of antioxidant phenolic compounds and flavonoids (18). The seeds have medicinal properties, including soothing, antioxidant, and anti-inflammatory effects (19). In an investigation, researchers monitored the methanolic extract of *C. colocynthis*. to determine this compound's free-radical-scavenging ability. *C. colocynthis* extract has demonstrated optimum free-radical scavenging and antioxidant capabilities at 2500 mg/mL (20).

In vitro testing of *C. colocynthis* extract activity on plasma glucose levels indicated that *C. colocynthis* inhibits glucosidase and boosts the insulin-triggered movement of the glucose transporter (GLUT4) from internal storage areas to the plasma membrane, thereby enhancing insulin-stimulated glucose uptake (21).

Following a phytochemical examination of *C. colocynthis* seed extracts, it was concluded that flavonoids, which are plant chemical components, act as antioxidants. This study aimed to examine how the *C. colocynthis* aqueous seed extract affects glycemic and BDNF levels, oxidative status, antioxidant defenses, and lipid profiles in rats with T1D.

Methods

Preparation of crude extract

Ripe but dry *C. colocynthis* fruit was picked up during the summer from the Saleh Abad region in Ilam Province in western Iran, and the seeds were manually removed and dried for 72 hours. Then, 100 g of seeds were heated to 80 °C in 1 L of distilled water for 2 hours in a water bath after they were blended and ground with a mixer. After collecting the supernatant, Whatman No. 1 filter paper was utilized to filter the mixture. After each filtration, this process was repeated, and the solvent was renewed every time. The vacuum-filtered extract was concentrated at 80 °C by a rotary evaporator to speed up the freeze-drying process (Freeze-dryer Alpha 1-2 LDplus, Germany). A prior study used the preparative HPLC method to identify the bioactive compounds and phytochemical analysis of *C. colocynthis* extract. The results identified the main compounds of *C. colocynthis* as rutin hydrate, ferulic acid, chlorogenic acid, gallic acid, chicoric acid, vanillic acid, and quercetin (22).

Animals

All experimental procedures have received approval from the Ethics Committee of Kerman University of Medical Sciences (ethics code IR.KMU.REC.1398.127). Efforts were made to provide the animals with maximum comfort throughout the investigation. Male Wistar rats aged 3–4 months and weighing 200–250 g were utilized in the present investigation. Three groups of animals ($n = 7$) were kept in cages with unlimited water and food access. Their environment was climate-controlled (23 ± 1 °C) with a 12-hour cycle of light and darkness (lights on from 07:00–19:00). Twenty-one intact rats were divided into three subgroups by randomization: control (healthy rats that were not subjected to any treatment), diabetes (rats that were administered streptozotocin [STZ] and then received saline as *C. colocynthis* solvent), and diabetes + drug (diabetic rats that were given oral *C. colocynthis* extract). Serum and hippocampal samples were taken for analysis after the animals were killed by injection with a fatal dose of xylazine and ketamine. Because the animals were diabetic, the cages were cleaned daily, and the rats were given adequate access to water and food.

T1D induction

Following an overnight fast (8 hours), the experimental diabetic type was developed. One STZ dosage was used to cause severe diabetes (50 mg/kg of body weight(. It was prepared in a sodium citrate buffer with a pH of 4.5 and was administered intraperitoneally using an insulin syringe (23,24). Four days after injection, significant diabetes symptoms such as polyuria, polydipsia, weight loss, and high fasting blood glucose (FBS) presented, and the rats were considered diabetic rats. The forty-day course of treatment began on the fifteenth day following the introduction of diabetes.

Drug administration

Treatment with *C. colocynthis* began fifteen days after the STZ injection. For 40 days, 200 mg/kg of the oral aqueous extract of *C. colocynthis* was administered daily (17, 22).

Biochemical parameters

In a typical laboratory scenario, the autoanalyzer (Selectra-

XL, Vital Science; Netherlands) analyzed triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-c) (Pars Azmoon, Tehran, Iran) using conventional kits. Cholesterol from low-density lipoproteins (LDL-c) was determined by applying the Friedewald formula.

$$[\mathrm{LDL-C}] = [\mathrm{TC}] - \mathrm{HDL-C}] - \left(\frac{[\mathrm{TAG}]}{5}\right)$$

$$[\mathrm{VLDL-C}] = \frac{[\mathrm{TAG}]}{5}$$

Also, the values of paraoxonase1 (PON1) (arylesterase activity) (25), malondialdehyde (MDA) (TBARS method) (26), total antioxidant capacity (TAC) (FRAP method) (27), SOD3 activity (28), GPX3 activity (29), CAT (Sinha method) (30), protein carbonyl (PC) (31) and Nitrite (Griess method) (32) were measured using spectrophotometry and related kits. BDNF concentration in the hippocampus was measured using an ELISA kit.

Body weight and FBS measurements

FBS and body weight were assessed before receiving the STZ injection, fourteen days following the STZ injection, and twenty and forty days following the beginning of treatment. Blood samples taken from the tail vein were examined for FBS using a glucometer.

Evaluation of HOMA-IR, HOMA-B, and QUICKI

The function of pancreatic β-cells and insulin resistance (IR) were assessed through homeostasis model assessment (HOMA). The following formula was used to determine the HOMA-IR and HOMA-B scores: HOMA-IR = [(fasting glucose (mmol/L) × fasting insulin (μU/mL)) / 22.5]. HOMA β-cell = [(20 × fasting insulin (μU/mL)) / (fasting glucose (mmol/L) – 3.5). Fasting insulin and blood glucose levels were used in the Quantitative Insulin Sensitivity Check Index (QUICKI) calculation: QUICKI = 1 / [log (fasting insulin) + 1 / log (fasting glucose)] (33).

Data analysis

The Kolmogorov-Smirnov test was utilized to determine if the data were distributed normally. One-way ANOVA was utilized to assess all the data from the oxidants, antioxidants, lipid profiles, and metabolic and BDNF evaluations. Tukey's post hoc test was utilized to determine whether the groups' differences were statistically significant. A paired *t* test was conducted to examine the body weight and FBS levels recorded before and following the onset of diabetes. Repeated measures tests analyzed data on body weight and FBS. The data were expressed as mean ± standard error of the mean (SEM), and statistical significance was established when the *P* value was less than 0.05.

Results

Effects of C. colocynthis on diabetic rat blood oxidant indices levels

Our research showed that diabetes considerably increased PC (Figure 1A, $P < 0.01$), MDA (Figure 1B, $P < 0.001$), and nitric oxide (NO) (Figure 1C, $P < 0.01$) in the control group. Conversely, administration of *C. colocynthis* dramatically decreased PC (Figure 1A, $P < 0.05$), MDA (Figure 1B, $P < 0.05$), and NO (Figure 1C, $P < 0.05$) compared to the diabetes group.

Effects of C. colocynthis on diabetic rat blood antioxidant index levels

According to our findings, diabetes significantly reduced GPx (Figure 2A, $P < 0.001$), SOD (Figure 2B, $P < 0.001$), catalase (Figure 2C, $P < 0.05$), TAC (Figure 2D, $P < 0.001$), and PON 1 (Figure 2E, $P < 0.001$) compared to the healthy group. As opposed to the diabetes group, *C. colocynthis* remarkably enhanced GPx (Figure 2A, $P < 0.001$), SOD (Figure 2B, $P < 0.001$), catalase (Figure 2C, $P < 0.05$), TAC (Figure 2D, $P < 0.001$), and PON 1 (Figure 2E, $P < 0.05$).

Effects of C. colocynthis on diabetic Rats' serum lipid profile indices

Our research showed that, compared to the control group, diabetes considerably raised TG (Figure 3A, $P < 0.001$), cholesterol (Figure 3B, $P < 0.001$), LDL (Figure 3C, $P < 0.001$), and VLDL (Figure 3D, $P < 0.001$). Administration of *C. colocynthis* considerably reduced TG (Figure 3A, $P < 0.01$), cholesterol (Figure 3B, $P < 0.001$), LDL (Figure 3C, $P < 0.001$), and VLDL (Figure 3D, $P < 0.001$) compared to the diabetes group. Additionally, our findings showed that diabetes dramatically reduced HDL (Figure 3E, $P < 0.001$) and TP (Figure 3F, $P < 0.01$),

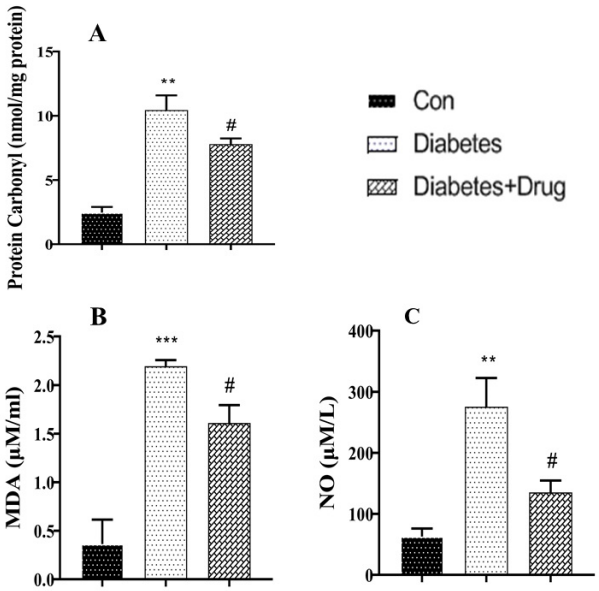

Figure 1. The impact of diabetes and the administration of *Citrullus colocynthis* on serum oxidants levels. Mean ± SEM, (**) $P < 0.01$ vs control. (***) $P < 0.001$ vs control. (#) $P < 0.05$ vs diabetes

while compared to the diabetic group, *C. colocynthis* administration significantly improved HDL (Figure 3E, $P<0.001$) and TP (Figure 3F, $P<0.05$).

Effects of C. colocynthis on diabetic rat hippocampal BDNF concentration

According to our findings, diabetes considerably reduced

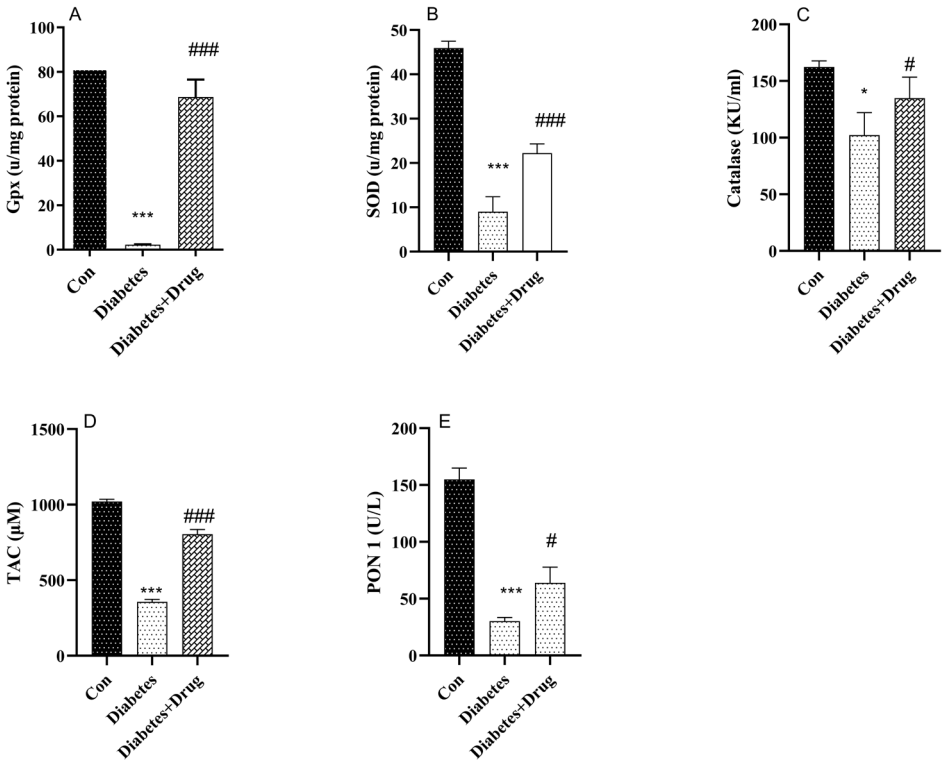

Figure 2. The impact of diabetes and the administration of *Citrullus colocynthis* on serum antioxidant levels. Mean ± SEM, (*) $P<0.05$ vs control. (***) $P<0.001$ vs control. (#) $P<0.05$ vs diabetes. (###) $P<0.001$ vs diabetes

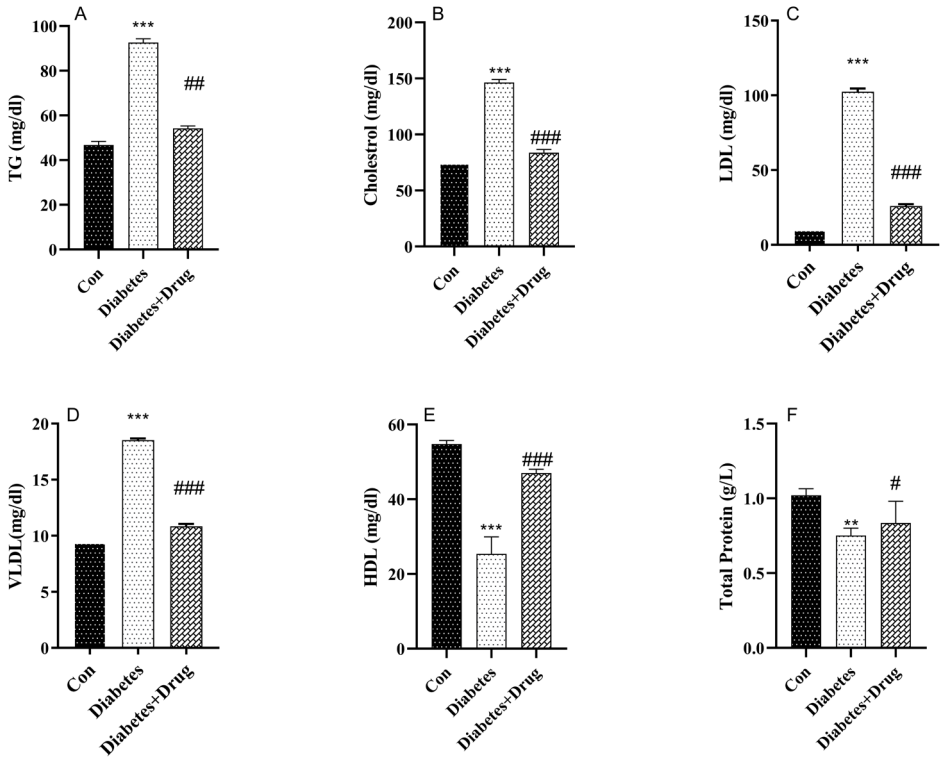

Figure 3. The impact of diabetes and the administration of *Citrullus colocynthis* on serum lipid profile. Mean ± SEM, (**) $P<0.01$ vs control. (***) $P<0.001$ vs control. (#) $P<0.05$ vs diabetes. (##) $P<0.01$ vs diabetes. (###) $P<0.001$ vs diabetes

BDNF levels in the hippocampus (Figure 4A, $P<0.001$) compared to the control group. At the same time, *C. colocynthis* therapy remarkably boosted BDNF levels compared to the diabetes group (Figure 4A, $P<0.001$). Our findings showed that the diabetic group's insulin levels were significantly lower than the control group's (Figure 4B, $P<0.001$), and *C. colocynthis* raised the insulin levels (Figure 4B, $P<0.001$).

Effects of C. colocynthis on diabetic rat HOMA-IR, HOMA-B, and QUICKI

According to the analysis, the diabetic group's HOMA-IR was higher than that of the control group (Figure 5A, $P<0.001$), but it was lower in the treatment group (Figure 5A, $P<0.001$). However, HOMA-B and QUICKI were reduced in diabetic rats compared to healthy rats (HOMA-B: Figure 5B, $P<0.001$; QUICKI: Figure 5C, $P<0.001$). These indices increased in treated diabetic rats (HOMA-B: Figure 5B, $P<0.01$; QUICKI: Figure 5C, $P<0.001$).

Effects of C. colocynthis on diabetic rat body weight

In the current study, 14 days following the injection of STZ, the body weights of the diabetic rats in both the diabetes and diabetes + drug groups (before the beginning of treatment) were considerably lower than before the injection (Figure 6A; $P<0.01$, $n=14$). Additionally, the study of body weight after the beginning of treatment showed that in the diabetes + drug group, *C. colocynthis* administration for twenty and forty days significantly raised body weight compared to before beginning the treatment (Figure 6B; $P<0.01$ for 20- and 40-day treatment, $n=7$). There were no notable differences between the treatment and control groups (Figure 6B).

Effects of C. colocynthis on diabetic rat FBS

Our findings demonstrated that diabetic rats in the diabetes and diabetes + drug groups (before initiation of treatment) had significantly higher FBS fourteen days following injection of STZ in contrast to baseline (Figure 7A; $P<0.001$, $n=14$) (Paired *t*-test was done for this analysis). Furthermore, the assessment of FBS following the initiation of therapy showed that in the diabetes + drug group, *C. colocynthis* administration for twenty and forty days significantly reduced FBS compared to before beginning the treatment (Figure 7B; $P<0.01$ for twenty days therapy and $P<0.001$ for forty days therapy, $n=7$). The treated groups did not significantly vary from one another or from the control group (For this analysis, repeated measures were used).

Discussion

Our findings revealed that T1D increased the levels of oxidant agents, such as MDA, PC, and NO, and decreased the levels of antioxidant agents, such as GPx, SOD, TAC, and PON1, in the serum and the BDNF level in the hippocampus. *C. colocynthis* was able to reverse these changes. *C. colocynthis* improved the circumstances following diabetes. Also, our data showed that diabetes impaired lipid profile status while *C. colocynthis*

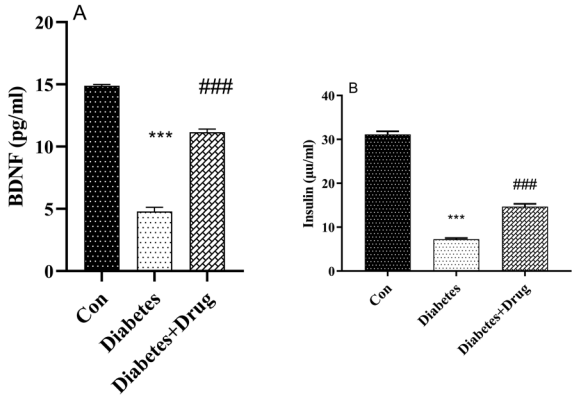

Figure 4. The effects of diabetes on hippocampus BDNF and blood insulin levels when *Citrullus colocynthis* is administered. Mean ± SEM, (***) $P<0.001$ vs control. (###) $P<0.001$ vs diabetes

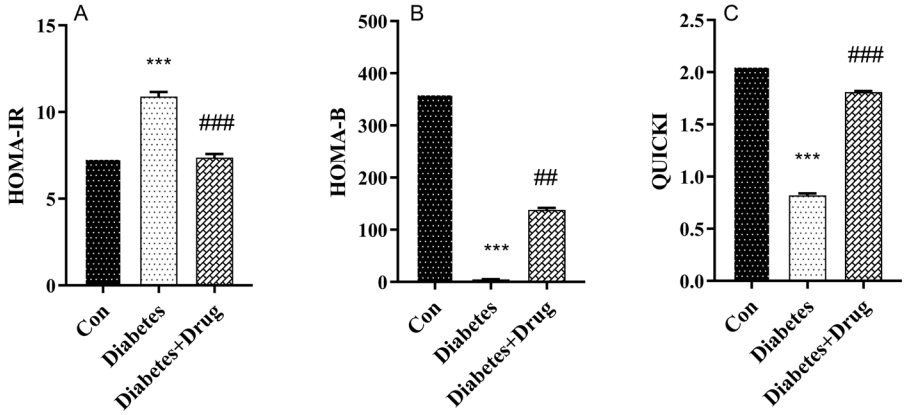

Figure 5. The impact of diabetes and the administration of *Citrullus colocynthis* on HOMA-IR, HOMA-B, and QUICKI. Mean ± SEM, (***) $P<0.001$ vs control. (##) $P<0.01$ vs diabetes. (###) $P<0.001$ vs diabetes

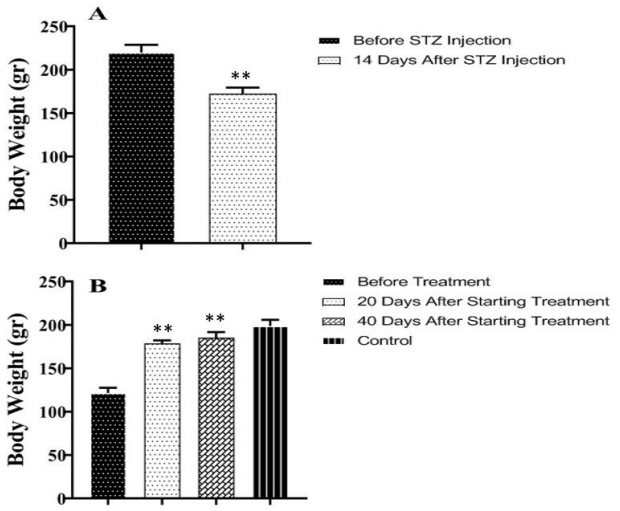

Figure 6. The impact of diabetes and the administration of *Citrullus colocynthis* on body weight at different times. Mean ± SEM, (**) $P < 0.01$ vs Before STZ injection in Figure 7A and before starting the treatment in Figure 6B

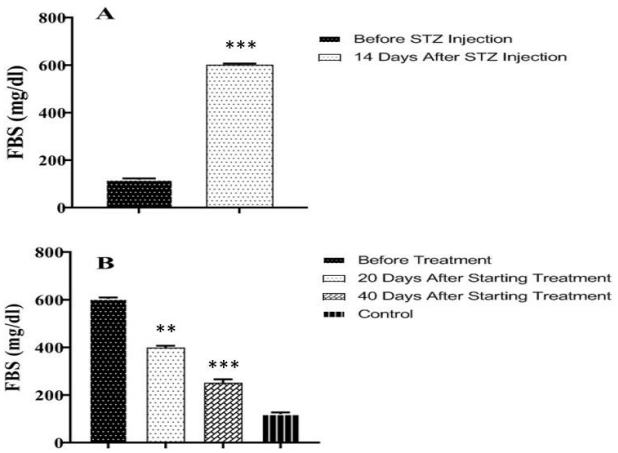

Figure 7. The impact of diabetes and the administration of *Citrullus colocynthis* on FBS at different times. Mean ± SEM, (***) $P < 0.001$ vs Before STZ injection in Figure 7A. (**) $P < 0.01$ and (***) $P < 0.001$ vs before starting treatment in Figure 7B

ameliorated this status.

ROS, which are produced by hyperglycemia, harm cells in several ways. The secondary problems of diabetes mellitus ultimately arise from cell damage (34). Regarding type 2 diabetes, oxidative stress is believed to be important in the advancement of vascular problems (35). Increased synthesis of ROS by antioxidants like CAT, SOD, and GPx could be the reason for the elevated ROS levels observed in diabetes. Variations in these enzyme levels make the tissues vulnerable to oxidative stress and play a role in the emergence of diabetes-associated problems (36). Alzheimer's disease, Parkinson's disease, memory impairment, depression, and stroke are the nervous system problems that can develop due to diabetes and be triggered by oxidative stress (37).

Studies have shown that diabetes can increase animal-related oxidative factors such as MDA, NO, and PC (38). Numerous studies have also shown that diabetes reduces antioxidant factors such as SOD, GPx (39), PON1 (40), TAC, and CAT (41). Our results also revealed that oxidant factor levels increased and antioxidant parameters were reduced in rats with diabetes compared to healthy rats. The study showed the antioxidant effects of *C. colocynthis* seeds, and one study confirmed our findings (42). Comparably, Abbas et al showed the benefits of the antioxidant colocynth seed in raising antioxidant agents and lowering oxidative stress marker concentrations in laying hens (43).

Diabetes patients who experience lipid abnormalities—often referred to as "diabetic dyslipidemia"—are frequently identified by high T-Chol, TG, low HDL-C, and increased levels of small dense LDL particles. LDL-C readings could be slightly elevated or normal. Diabetes patients frequently experience lipid problems (17). It has been shown that diabetes increases TG, cholesterol, and LDL; on the other hand, it can decrease HDL and total protein (44). Our results also showed that diabetes disturbs the lipid profile balance. In addition, we assessed the effect of *C. colocynthis* on lipid profile and found that it significantly lowered TG, TC, and HDL levels compared with the diabetes group. Similarly, Fouzi et al showed *C. colocynthis* L. hypolipidemic impacts in the liver injury model of rats with a decrease in cholesterol and triglyceride levels (45). Therefore, our findings were consistent with these studies' findings.

HOMA is a technique for measuring insulin resistance and beta-cell activity (46). HOMA-IR, HOMA-B, and QUICKI are the indices for evaluating insulin resistance, β-cells function, and insulin sensitivity, respectively. It has been revealed that insulin HOMA-IR is high in diabetic rats and patients, while QUICKI and HOMA-B are low (47). Our findings also confirm these results. Based on the findings from this study, *C. colocynthis* improved the level of HOMA-IR, QUICKI, and HOMA-B. However, Ahangarpour et al observed no notable differences in the QUICKI, HOMA-IR, and DI indices compared to their values before treatment (48). They attributed racial differences to the lack of a relationship between HOMA-IR with glucose disposal rate and fasting insulin levels.

Impairments of brain function and psychological illnesses are substantially more common in people with diabetes. BDNF is one of several neurotrophic factors that protect neuronal tissue and enhance central nervous system performance. Insulin resistance appears to affect and be linked to BDNF's amount and role in diabetes (49). Since the brain is primarily a glucose-dependent organ, hyperglycemia can disrupt neuronal glucose transport and metabolism, increasing free radical generation and reducing BDNF production (50). Decreased BDNF levels may be a factor in diabetes-related memory loss and cognitive impairment. Reduced BDNF expression is likely to be the primary mechanism for decreased neuroprotection. A deficiency in neurotrophins such as

BDNF is considered one of the main contributing factors in the neuropathies brought on by diabetes (51). It has been reported that the level and expression of BDNF in the animal's serum and hippocampi were diminished (52). In our previous research at the behavioral level, we revealed that diabetes causes the animals to malfunction in the Morris Water maze test, which is a hippocampal-dependent test (23). It has been shown that changes in the hippocampus occur following diabetes, which is reflected in hippocampal-related behavioral tests and may be related to BDNF levels. In this study, our findings showed that *C. colocynthis* seeds positively affect reduced BDNF levels. No study has been observed on the impacts of this plant on BDNF levels in the hippocampus, and this study seems to be new in this regard.

It is essential to assess this study for both its strengths and weaknesses. One limitation inherent in this type of research is the challenge of pinpointing the precise causes behind correlations and statistical significance; we can merely recognize their existence. The results highlight a significant demand for research aimed at uncovering cause-and-effect relationships. Notably, a key strength of this study lies in its comprehensive comparison of data concerning classification and the assessment of parameters related to disease in every stage. Another benefit is adding a control group to the investigation, which enabled a reliable and valid comparative analysis.

Conclusion

Overall, our results revealed that STZ-induced diabetes may compromise hippocampal BDNF expression. Nevertheless, the prescription of *C. colocynthis* demonstrated the ability to enhance this reduction over 40 days, leading to systemic therapeutic effects such as decreased FBS levels, increased serum insulin secretion, reduction of LDL, VLDL, TG, and cholesterol, and increase of HDL, reduction of oxidative stress and enhancement of antioxidant defenses.

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Authors' Contribution

Conceptualization: Mohammad Amin Rajizadeh.
Investigation: Mohammad Reza Ashrafi.
Methodology: Mohammad Amin Rajizadeh.
Supervision: Fouzieh Salimi.
Writing–original draft: Mohammad Amin Rajizadeh.

Competing Interests

We confirm that there are no known conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

Ethical Approval

Throughout the investigation, we strived to keep the animals as comfortable as possible (ethics code: IR.KMU.REC.1398.127).

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