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Original Research Article

The hepatoprotective impacts of *Citrullus colocynthis* seeds extract on type 1 diabetes-induced liver inflammation and oxidative stress in rats: The role of nrf2/keap1 pathway

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Abstract

Objective: Type 1 Diabetes (T1D) induces several consequences including hepatic damage resulting from oxidative stress and inflammation. The Nrf2/Keap1 pathway is crucial in oxidative stress signaling, and its modifications significantly influence health and illness. In this study, rats with T1D were used to test *Citrullus colocynthis* (CC) ability to reduce oxidative stress and inflammation in the diabetic liver.

Materials and Methods: Twenty-one male Wistar rats were assessed. Three groups—control (healthy rats), diabetes (received STZ), and diabetes with drug—were allocated at random to the rats. The CC fruits extract was administered to diabetic rats via gavage for 40 days. Oxidative stress indicators, including malondialdehyde (MDA), total antioxidant capacity (TAC), and superoxide dismutase (SOD), were determined. The ELISA method quantified liver cytokines, whereas western blotting evaluated the Nrf2/Keap1 pathway.

Results: The administration of CC in the Diabetes+Drug group dramatically reduced MDA levels while enhancing SOD activity and TAC levels in the liver. Following CC administration, Tumor necrosis factor alpha (TNF-α) levels decreased while rats with diabetes had higher amounts of interleukine-10 (IL-10) in their liver tissue. The CC administration could regulate the Nrf2/Keap1 pathway.

Conclusion: This study concluded that a daily administration of 200 mg/kg CC for 40 days can enhance liver function in diabetic subjects by controlling the Nrf2/Keap1 pathway and reducing oxidative stress and inflammation.

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Introduction

The principal symptom of diabetes mellitus (DM), a widespread disease, is hyperglycemia brought on by a dysfunction in the action, secretion, or both of insulin. According to estimates from the international diabetes federation (IDF), 415 million people worldwide received a diabetes diagnosis in 2015; by 2040, that number is predicted to climb to 642 million (Patil et al. 2023; Rajizadeh et al. 2023c). DM causes progressive damage to the liver and other internal tissues (Loria et al. 2013; Rajizadeh et al. 2023a). Both types of diabetes are associated with hepatopathy and Non-alcoholic fatty liver disease (NAFLD) (Khoramipour et al. 2023). Increased oxidative damage combined with an abnormal inflammatory response is the underlying mechanism of hyperglycemia-mediated liver damage. (Mohamed et al. 2016).

Nuclear factor erythroid-2–related factor-2 (Nrf2) is an essential transcription factor identified initially as a main regulator of the antioxidant response and drug or xenobiotic detoxification while now, iron, lipid, and carbohydrate metabolism, DNA repair, and proteasomal and autophagic function for which it is recognized as a regulator. There is genetic and pharmacological evidence that Nrf2 plays a significant role in mediating the onset of diabetic complications, and it is implicated in the prevention or promotion of the various types of diabetes (Dodson et al. 2022). Several pharmacological therapies have been demonstrated to activate Nrf2 to protect against type 1 traits. For example, injection of the Nrf2 inducers or cinnamaldehyde dramatically reduced both diabetic wound healing and nephropathy in Nrf2+/+ mice treated with streptozotocin (STZ) (Long et al. 2016; Zheng et al. 2011). In an STZ model of type 1 diabetes, fenofibrate and minocycline have also been demonstrated to improve diabetic nephropathy (DN) in an Nrf2-dependent manner (Cheng et al. 2016; Shahzad et al. 2016).

Nrf2 and Keap1 (Kelch-like ECH-associated protein 1) have a close relationship. Keap1 is an adapter protein for ubiquitin E3 ligase based on cullin3. When the ubiquitin-proteasome pathway is not activated, Keap1 promotes ubiquitination and degradation, which suppresses Nrf2 signaling (Baird and Yamamoto 2020). After oxidative stress, Nrf2 separates from Keap1. Encoding antioxidant enzymes such as glutathione S-transferase, heme oxygenase-1 (HO1), NADPH quinone oxidoreductase (NQO1), superoxide dismutase (SOD), catalase (CAT), and γ-glutamylcysteine synthetase, it enters the nucleus and attaches itself to antioxidant-responsive elements (AREs) in the nucleus. This lowers the risk of diabetes and its consequences by increasing the expression of these genes, which in turn contribute to detoxification, antioxidation, and anti-inflammation (Kaspar et al. 2009; Ngo and Duennwald 2022). Additionally, an essential component of the pathogenesis of type 1 diabetes (T1D) is inflammation and is the cause of its consequences (Clark et al. 2017).

Herbal medicine is one of the essential and common approaches for treating the maladies (Esmaeilpour et al. 2023; Rajizadeh et al. 2023d; Rajizadeh et al. 2024b). *Citrullus colocynthis* (CC), commonly referred to as bitter cucumber or apple, is a well-known plant in the Cucurbitaceae family with anti-diabetic properties. Africa and Asia are the plant natural regions. Its pulp contains the phytochemical elements pectin, colocynthetin, colocynthin, and gum; its seeds include fixed oils and albuminoids. Because of these factors, it may be an effective therapeutic herb (Pravin et al. 2013).

None of the literature review studies reported on the anti-diabetic potential of CC seeds based on the Nrf2/Keap1 pathway. Therefore, the purpose of this study is to investigate how an aqueous extract of CC seeds affects hepatic

inflammation and the Nrf2/Keap1 pathway in streptozotocin-induced diabetic rats.

Materials and Methods

Animals and grouping

Male Wistar rats weighing 200–250 g and 3–4 months old were utilized in research. The animals were prepared at the Kerman University of Medical Sciences (KUMS). The KUMS ethics committee gave its approval to all procedures (IR.KMU.AEC.1402.101). Food and water were freely available to the animals in their enclosures. They were housed in a climate-controlled environment (23 ± 1°C) with a 12-hr light-dark cycle (lights on from 7:00 to 19:00). Three subgroups were randomly created from 21 intact rats (n=7): 1. Control (or CTL , healthy rats), 2. Diabetes (or Db , The rats received STZ), and 3. Diabetes+Drug (or Db+C , The diabetic rats received oral CC extract). Treatment with CC began fifteen days after the STZ injection. Every day for 40 days, 200 mg/kg of the aqueous extract of CC was administered orally (Kalva et al. 2018). Animals were sacrificed after treatment, and liver samples were obtained for analysis.

Induction of diabetes

After an overnight fast (8 hr), the experimental diabetes model was developed. One STZ dosage was used to cause severe diabetes (50 mg/kg body weight); this group is referred to as having "Diabetes". Using an insulin syringe, STZ was delivered intraperitoneally after being prepared in a sodium citrate buffer at pH 4.5 (Kumarappan and Mandal 2008). Four days after injection, significant signs of diabetes, like frequent urination, were observed; nevertheless, fasting blood glucose must be measured after 15 days to confirm that the condition is diabetes. The forty-day course of treatment began on the fifteenth day following the introduction of diabetes. In rats, a blood glucose level of greater than 300 mg/dl is regarded as an indication that diabetes has been induced.

Body weight and fasting blood glucose (FBS) measurements

Before STZ injection, 14 days following STZ injection, 20 days following treatment, and 40 days following treatment, FBS and body weight were assessed. Analysis was done on blood samples taken from the tail vein for FBS using a glucometer.

Preparation of crude extract

Fresh or ripe but dry CC fruit was picked up during the summer from the Saleh Abad region in the province of Ilam in western Iran, and the seeds were manually removed and dried for 72 hr. A liter of distilled water and two hours were spent heating 100 g of seeds to 80°C in a water bath after they were blended and ground with a mixer. After recovering the supernatant, Whatman No. 1 filter paper was used to filter the mixture. After each filtration, this process was repeated numerous times while the solvent was renewed. A rotary evaporator concentrated the vacuum-filtered extract at 80°C to speed up freeze-drying process (Freeze-dryer Alpha 1-2 LDplus, Germany). In a prior study, the bioactive substances of CC extract were detected using the preparative HPLC method. The results showed that rutin hydrate, ferulic acid, chlorogenic acid, gallic acid, chicoric acid, vanillic acid, and quercetin are the main compounds of CC (Afshari et al. 2021).

Biochemical evaluations

After performing all protocols, high doses of xylazine (50 mg/kg) and ketamine (100 mg/kg) were administered to the animals before they were slaughtered. Their liver and blood samples were taken, and after sonication and homogenization, The homogeneous samples underwent centrifugation for 15 min at 3000 rpm to separate the supernatant. The level of SOD, MDA, and TAC in the supernatant was

measured by related kits (Navand Salamat Co). The levels of TNFα (Cat number: DY510-05) and IL10 (Cat number: DY522-05) were measured by related ELISA kits. Also, ELISA kits were used to measure insulin levels in accordance with the manufacturer's recommendations (Rat ELISA Kit, Eastbiopharm).

Western blotting

Protease inhibitors were added to ice-cold RIPA buffer (1:10 w/v) to homogenize the liver tissue. At 4°C, the homogenate was centrifuged for 15 min at 12,000 rpm. The resultant supernatant was then collected. The bicinchoninic acid assay was used to measure the protein content. 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was used to separate equal amounts of isolated proteins, which were then deposited onto PVDF membranes. Overnight at 4°C, the membranes were blocked using 5% non-fat milk in TBST buffer. The membranes were then treated for one hour at room temperature with primary antibodies specific to β-actin (sc-517582), Keap1 (sc-365626), and Nrf2 (sc-365949). Following TBST washing, membranes were incubated for one hour at room temperature with secondary antibodies (sc-516102 and sc-2357, 1:10,000) coupled to horseradish peroxidase (HRP). Following TBST washing, membranes were examined for protein bands using an ECL kit (Bio-Rad, USA). ImageJ analysis software was used to quantify the bands that were found. The internal reference was β-actin (Bejeshk et al. 2023b; Bejeshk et al. 2024; Joukar et al. 2024; Rajizadeh et al. 2023b).

Data analysis

All data were evaluated using a two-way ANOVA. When there were statistically significant differences between the groups, Tukey's post hoc multiple comparison test was utilized to find those differences. A paired t-test was used to examine the body weight and FBS measurements made before and after the onset of diabetes. The results of the repeated measurement test were used to investigate the body weight and FBS measurement data after therapy. When the data is reported as means ± standard error of the means, $p<0.05$ was deemed statistically significant. The Shpiro-Wilk test was used to determine whether the data were normal.

Results

The effects of CC on oxidative stress in liver tissue following diabetes

Our findings displayed that the levels of MDA rose ($p<0.01$), and TAC levels and SOD activity ($p<0.05$) decreased in diabetic animals compared to the healthy animals.

Administration of CC could significantly reduce MDA ($p<0.01$) and increase TAC ($p<0.05$) and SOD activity ($p<0.05$) compared to the diabetic animals (Figure 1).

The effects of CC on inflammation in liver tissue following diabetes

Diabetes results in increased inflammation in liver tissue through increasing TNFα ($p<0.01$) and decreasing IL10 ($p<0.001$) compared to the healthy rats significantly. CC could significantly reduce TNFα ($p<0.05$) and increase IL10 ($p<0.01$) compared to the diabetic animals (Figure 2).

The effects of CC on Nrf2/Keap1 pathway in liver tissue following diabetes

Our findings revealed that the Nrf2 expression in diabetic animals was significantly reduced compared to the healthy animals ($p<0.01$) while CC could increase the Nrf2 expression compared to the diabetes group ($p<0.01$). Conversely, diabetes led to elevation of Keap1 expression ($p<0.01$), while CC could reduce the expression of Keap1 ($p<0.01$) (Figure 3).

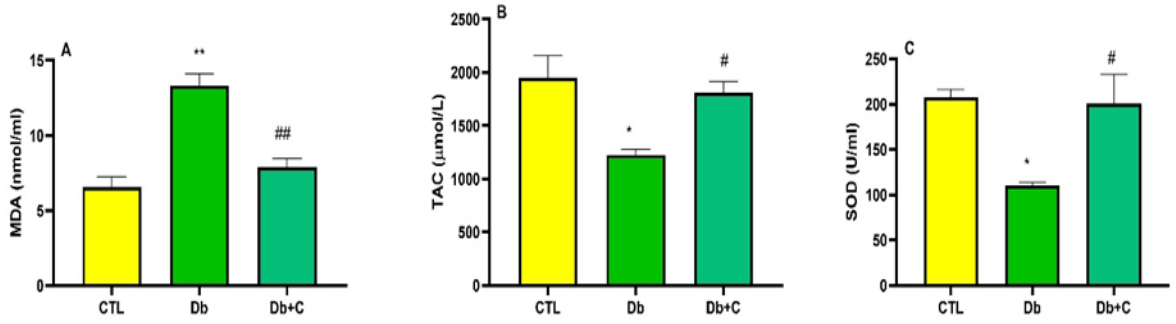

Figure 1. The effects of CC on oxidative stress parameters in liver tissue of diabetic rats. Two-way ANOVA was used for analysis of data. Data are presented as Mean ± SEM. **p<0.01 and *p<0.05 vs CTL group. #p<0.0 and ##p<0.01 vs Db group. Seven rats in each group were included in these experiments.

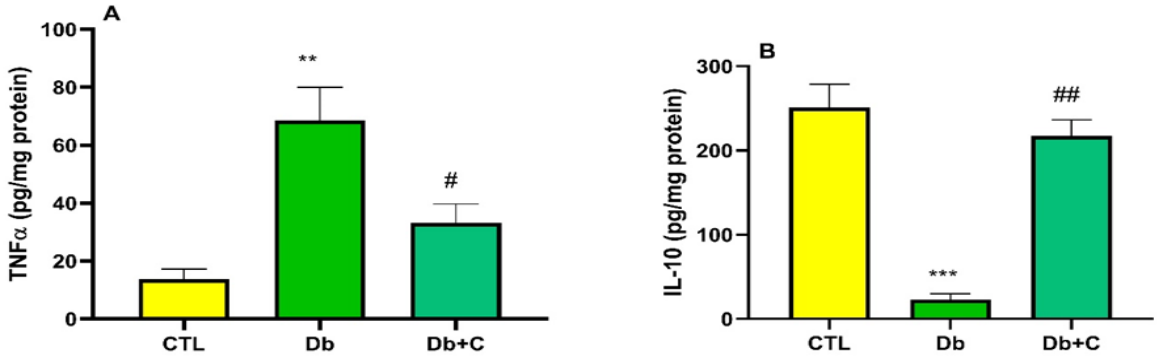

Figure 2. The effects of CC on inflammatory cytokines in liver tissue of diabetic rats. Two-way ANOVA was used for analysis of data. Data are presented as Mean±SEM.**p<0.01 and ***p<0.001 vs CTL group. #p<0.05 and ##p<0.01 vs Db group. Seven rats in each group were included in these experiments.

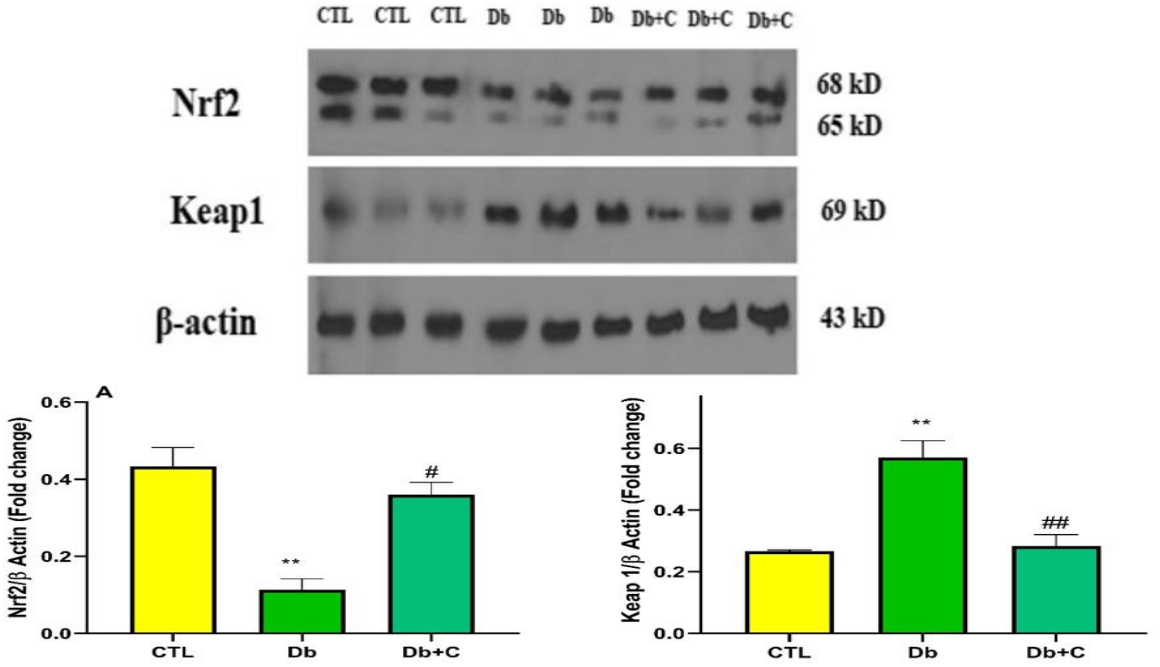

Figure 3. The effects of CC on Nrf2/Keap1 pathway in liver tissue of diabetic rats. Two-way ANOVA was used for analysis of data. Data are presented as Mean±SEM.**p<0.01 vs CTL group. #p<0.05 and ##p<0.01 vs Db group. Seven rats in each group were included in these experiments.

Impacts of CC on diabetic rats' serum insulin level

Our findings demonstrated that compared to the control group, the diabetes group's insulin level was much lower ($p<0.001$), while CC could raise insulin levels ($p<0.001$) (Figure 4).

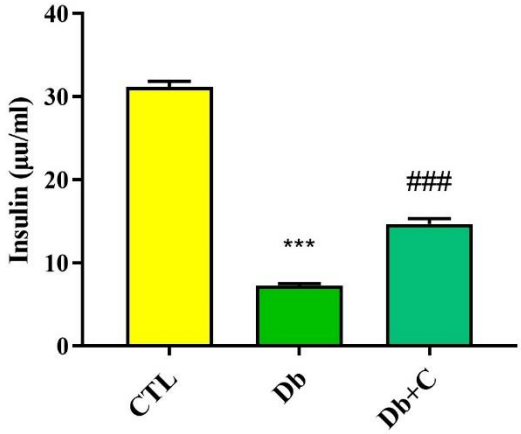

Figure 4. The effects of CC on Insulin level on serum of diabetic rats. Two-way ANOVA was used for analysis of data. Data are presented as Mean±SEM.***p<0.001 vs CTL group. ###p<0.001 vs Db group. Seven rats in each group were included in these experiments.

Impacts of CC on diabetic rats' fasting blood glucose (FBS)

Our results showed that 14 days after STZ injection, the FBS of diabetic rats in the Db and Db+C (before treatment commencement) groups was considerably greater than baseline ($p<0.001$) (Figure 5). Additionally, FBS measurement following treatment commencement revealed that CC administration for 20 and 40 days considerably reduced FBS in the Db+C group compared to pre-treatment levels ($p<0.01$ for 20 days treatment and $p<0.001$ for 40 days treatment). No appreciable difference was seen between the treatment and control groups (multiple measurements were conducted for this analysis) (Figure 5).

Effects of CC on diabetic rats' body weight

The diabetic rats in the Db and Db+C groups in the current study had significantly lower body weights than the animals before the injection 14 days after receiving the STZ injection ($p<0.01$) (Figure 6). In the Db+C group, body weight increased considerably after 20 and 40 days of CC administration as compared to prior therapy ($p<0.01$ for 20- and 40-day treatment), according to the analysis of body weight after treatment. The treatment and control groups did not vary in any noticeable way (Figure 6).

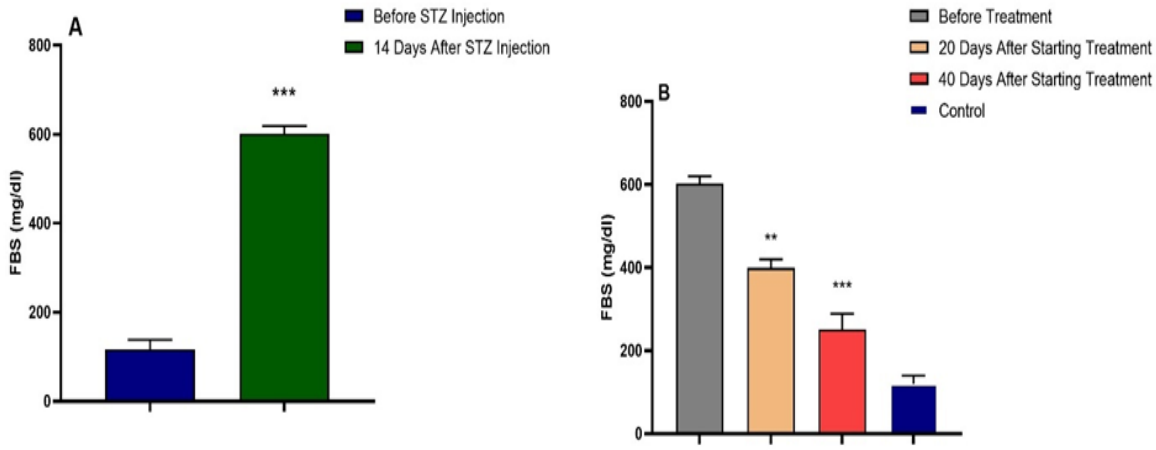

Figure 5. The effects of CC on fasting blood sugar at different times. Two-way ANOVA was used for analysis of data in panel B and paired t-test was used for analysis of the data in panel A. Data are presented as Mean±SEM.**p<0.01 & ***p<0.001 vs before STZ injection (A) and before treatment (B). Seven rats in each group were included in these experiments.

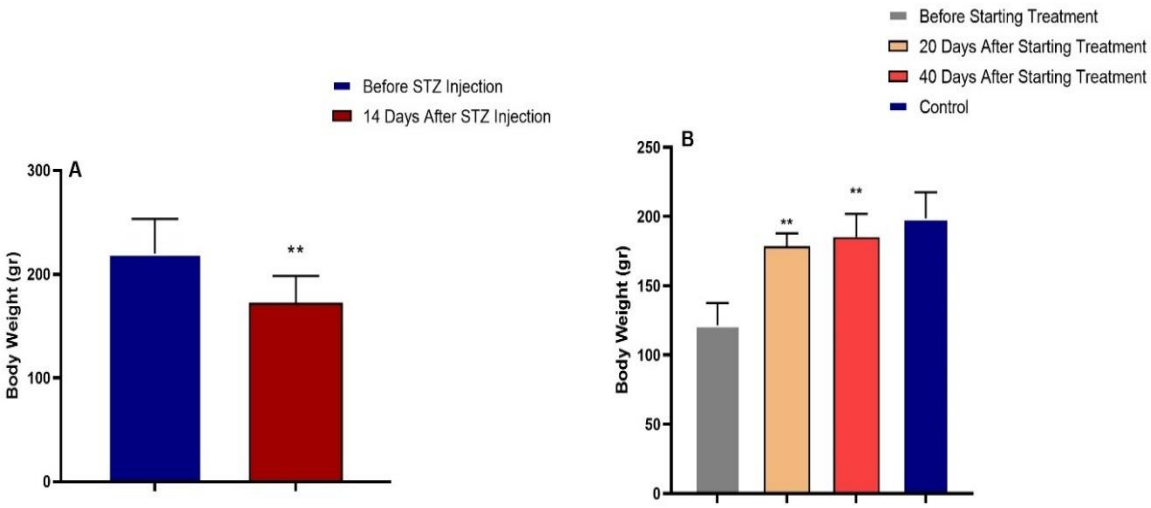

Figure 6. The effects of CC on body weight at different times. Two-way ANOVA was used for analysis of data in panel B and paired t-test was used for analysis of the data in panel A. Data are presented as Mean±SEM.**p<0.01 vs before STZ injection (A) and before treatment (B). Seven rats in each group were included in these experiments.

Discussion

This research aimed to investigate the effects of CC on inflammatory and oxidative consequences following T1D in rats' liver tissue. Our findings revealed that CC could diminish inflammation and oxidative stress in the liver tissue of diabetic rats.

The pathophysiology of several diabetes problems is significantly influenced by oxidative stress (Ceriello 2000). There is strong evidence that blood sugar levels above normal levels, play a role in the antioxidant system's decline and, therefore, enhances oxidative stress in diabetic patients (Hernández-Marco et al. 2009; Saberi et al. 2024; Zimmerman and Flores 2009). Many investigations showed that T1D increased oxidant parameters such as MDA (Behrouj et al. 2019; Chang et al. 2012) and total oxidant status (TOS) (Behrouj et al. 2019) and decreased antioxidant indices such as TAC (Behrouj et al. 2019; Boarescu et al. 2022) , SOD (Xie et al. 2018) ,glutathione peroxidase (GPX) (Manna et al. 2010) and catalase (Manna et al. 2010) in the liver tissue of rodents. Consistent with these investigations, our results showed that T1D increased MDA level and reduced TAC level and SOD activity in rat liver tissue.

On the other hand, the Keap1/Nrf2 signaling pathway has an crucial role in modulating oxidative stress, and its inhibition in T1D can enhance disease progression (Lou et al. 2021). It has been proven that in insulin-sensitive tissues, the antioxidant involvement of the Keap1/Nrf2 pathway is essential for sustaining glucose metabolism through the release of insulin and the consumption of glucose (Uruno et al. 2015). Additionally, in the liver of diabetic rats, oxidative stress events including elevated ROS generation and downregulation of the Nrf2/Keap1 pathway, can activate NF-κB and enhance the release of inflammatory cytokines (Al-Amarat et al. 2021).

Our results demonstrated that by reducing MDA, raising TAC and SOD, and altering the Nrf2/Keap1 pathway, CC seeds might reduce oxidative stress in the liver of diabetic rats.

Vakiloddin et al. provided evidence of the hepatoprotective and antioxidant properties of CC fruits in the context of paracetamol-induced hepatotoxicity (Vakiloddin et al. 2015). It has been shown

that the CC pulp had effects of antioxidants in diabetic rats' livers through reducing MDA and increasing catalase (Ostovan et al. 2014). Through raising SOD and GPX, one study showed that CC fruit may have protective benefits on kidney tissues and functioning after diabetic nephropathy (Abd El-Baky and Amin 2011). Our previous study revealed that CC seeds could reduce oxidative stress in diabetic lung (Bejeshk et al. 2023a). Ostovan et al disclosed that CC pulp could diminish oxidative stress in the testis and epididymis of diabetic rats (Ostovan et al. 2017).

Nuclear factor κB (NF-κB), which is in charge of producing proinflammatory cytokines, can be activated by hyperglycemia and oxidative stress (Cheng et al. 2008; Joukar et al. 2024; Rajizadeh et al. 2024a). So, an important factor in T1D-induced liver damage is inflammation (Mohamed et al. 2016).

Our observations also showed that the TNFα level (a proinflammatory cytokine) increased and the IL10 level (an anti-inflammatory cytokine) decreased following T1D in liver tissue.

In our previous study, we showed that by lowering TNFα and IL6 and increasing IL10 in the lung tissue of diabetic rats, CC exhibited an anti-inflammatory impact (Bejeshk et al. 2023a). The role of CC in reducing inflammatory agents in osteoarthritis was reported by Akhzari et al (Akhzari et al. 2015). The inhibitory role of CC on TNFα and IL-6 gene expression was shown in diabetic mice (Sanadgol et al. 2011).

Previous research showed that by strengthening antioxidant defenses and lowering the expression of the lipogenesis gene, Nrf2 activation reduces alcohol-induced oxidative stress and the accumulation of free fatty acids in the liver (Wu et al. 2012). The p62-Keap1-Nrf2 antioxidant pathway was shown by Shen et al. to be mostly active during the early stages of acetaminophen hepatotoxicity, possibly acting as a buffer against acetaminophen-induced acute liver injury (Shen et al. 2018). Previous studies show that Nrf2 helps reduce the inflammatory response that NF-κB causes in a variety of impairments (Bellezza et al. 2010; Tu et al. 2019). Lipopolysaccharide-induced Rac1 stimulates NF-κB to support Nrf2, which raises the expression of HO-1. Following this, in order to prevent NF-κB activation, HO-1 decreases NF-κB inflammatory activity and moves the cells into a more reductive environment (Bellezza et al. 2012; Tu et al. 2019).

Hence, based on our findings, CC could modulate the Nrf2/Keap1 pathway. Given the association between this pathway and inflammation, the anti-oxidative and anti-inflammatory effects of CC in liver tissue are justifiable.

In conclusion, it seems that CC seeds extract decreases inflammation and oxidative stress in the liver tissue of diabetic rats. We believe that the modulatory effects of CC on Nrf2/Keap1 pathway are one of the feasible mechanisms for reducing oxidative stress and inflammation in liver tissue and regulating blood glucose levels.

Acknowledgment

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Conflicts of interest

The authors declare there is no conflict of interest.

Funding

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Ethical Considerations

The KUMS' Institutional Animal Care and Use Committee approved the procedures (Ethical code: IR.KMU.AEC.1402.101).

Code of Ethics

IR.KMU.AEC.1402.101

Authors' Contributions

Mohammad Amin Rajizadeh: Methodology, Investigation. Fouzieh Salimi: Methodology, Conceptualization, Supervision

Data availability statement

The data will be available on reasonable request.

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