Trop J Nat Prod Res, January 2026; 10(1): 6869 – 6875
ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

The Effect of *Crataegus monogyna* Fruit Polyphenol Fraction on Fructose-Induced Blood Glucose Level *In Vivo*: Biochemical Analysis and Temporal Monitoring of Body Weights

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ARTICLE INFO

Article history:
Received 29 June 2025
Revised 23 December 2025
Accepted 30 December 2025
Published online 01 February 2026

ABSTRACT

Diabetes mellitus is a chronic metabolic disorder with a rapidly increasing global prevalence, necessitating the exploration of effective natural treatments. This study assessed the antidiabetic and antidiabetogenic effects of the polyphenol extract of *Crataegus monogyna* in a fructose-induced diabetes model in healthy male rats. Thirty rats were divided into five groups (n = 6 per group). The control group received distilled water, while group 2 received fructose (20 g/kg). Group 3 received fructose (20 g/kg) for 60 days, followed by treatment with the polyphenol extract (150 mg/kg). Group 4 received the polyphenol extract for 60 days before fructose administration, and group 5 received the extract throughout the 110-day study period. Blood glucose and body weight were monitored every 10 days. At the end of the study, biochemical parameters were analyzed. Fructose significantly increased blood glucose and creatinine levels and altered body weight ($p < 0.05$). Treatment with the polyphenol extract mitigated these effects, especially in groups 4 and 5. These findings suggest that the polyphenol extract of *Crataegus monogyna* possesses both preventive (antidiabetogenic) and therapeutic (antidiabetic) properties against fructose-induced diabetes, supporting its potential as a natural treatment option.

Keywords: *Crataegus monogyna*, Antidiabetic, Antidiabetogenic, Fructose, Polyphenol extract.

Introduction

The World Health Organisation defines diabetes as a metabolic disease with multiple etiologies, characterized by anomalies in the metabolism of proteins, lipids, and carbohydrates, resulting from issues with the release of certain chemicals, as well as chronically elevated blood sugar levels and/or insulin function, referred to as insulin resistance.[1,2,3] Free radicals are released into the body's cells when a person has diabetes. One way the disease might worsen is through oxidative stress, an imbalance caused by these radicals attacking the body.[4] Following diabetes, there are imperfections in cognitive function and whole-body efficiency, as evidenced by our earlier work in rats and other findings from human and animal investigations.[5] The body, therefore, has natural defences, including antioxidants, to combat this condition. The diet plays a key role in the prognosis. Furthermore, it is known that vegetables are potential providers of antioxidants.[6]

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Citation: Soulo N, Lahmass I, Tahiri NE, El khomsi M, Lyoussi B, Benziane-Ouaritini Z. The Effect of *Crataegus monogyna* fruit polyphenol fraction on fructose-induced blood glucose level *in vivo*: Biochemical Analysis and Temporal monitoring of Body weights. Trop J Nat Prod Res. 2025; 10(1): 6869 – 6875 https://doi.org/10.26538/tjnpr/v10i1.58

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Plant extracts have been shown in numerous studies to be effective at scavenging free radicals; their antioxidant properties may help prevent diabetes. Numerous medications are antidiabetic and hypolipidemic, but adverse side effects are significant issues. Therefore, more potent hypolipidemic and antidiabetic medications are required. Plant-based medicines may cure type 1 or type 2 diabetes.[7] Diabetes mellitus can be prevented and treated with the use of traditional medications, which are an excellent alternative therapy.[8] These herbal remedies are less expensive to use and offer antidiabetic benefits that are on par with those of prescription medications.[9]

One of the oldest and most regularly used medicinal plants, one-seeded hawthorn or *Crataegus monogyna*, is well-known in Asia and is widely used in China.[10] It is also commonly prescribed in central Europe. Approximately 280 species are found worldwide, and they can spread as trees or shrubs. Temperate regions of Europe, North America, North Africa, India, China, and Western Asia are home to this plant.[11] Research on the HPLC-UV analysis of the C. monogyna aqueous extract revealed the presence of rutin and ascorbic acid, tannic acid, rosmarinic acid, gallic acid, catechin, caffeic acid, and coumaric acid.[12] Another study found isovanillic acid and apigenin in the methanolic extract of *C. monogyna* from Spain. Additionally, flavonoids include kaempferol, arbutin, rutin, hesperetin, and quercitrin.[12] This study aimed to investigate the possible impact of hawthorn polyphenol extract on blood glucose levels and serum lipid profiles in treating fructose-induced diabetic rats.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Materials and Methods

Plant material and botanical identification

Crataegus monogyna (CM) fruit samples were collected in October 2022 from the Ain Chkef forest, situated in the Fez-Meknes region (33.9636° N, 5.0208° W, 499m). Prof. Hamid Khamar, a botanist, verified the harvested plant's botanical identity. The National Herbarium and Scientific Institute of Rabat received a voucher with the number RAB114863, and *Crataegus monogyna* Jacq was accepted as the botanical name. The plant sample was then allowed to dry at room temperature, and the dry material was ground to a fine powder.

Polyphenolic fraction's preparation

The plant material (100 g) was extracted with 300 mL of methanol (x3) for three hours at 50 °C. The three macerates were combined, then dissolved in 0.5 L of distilled water and evaporated. The sample was then extracted by partitioning in 200 mL of hexane and 200 mL of chloroform. The aqueous phase was then extracted with 200 mL of ethyl acetate x 3. The extracts were evaporated under reduced pressure at 40°C using a rotary evaporator to obtain the Polyphenol extract (P.E). The sample was redissolved in 300 mL of water, and the residue was freeze-dried to give a 5.9% final polyphenol yield [13].

Animals

Wistar male adult rats weighing between 247 and 250 g were obtained from the USMBA's Faculty of Sciences Dhar El Mahraz's Animal house in Fez, Morocco. Every ethical guideline was rigorously adhered to. The animals were kept in a controlled environment with a temperature of 24 ± 1°C and a 12-hour light-dark cycle (12 L/12 D) to acclimatize for seven days, which helped them successfully adapt to their new surroundings. They were handled with great care to ensure their comfort and Wellbeing, and they had unlimited access to food and tap water. The study design and method followed the institutional animal protection committee guidelines for the use of experimental animals, with ethical approval registration number L.20.

Experimental design

Five groups of six animals each, each with an identical number and weight, were randomly selected from among the animals. All animals received treatment by oral gavage every day at a dose of 10 mL/kg for 110 days. Rats in group 1 (normal group), received distilled water; in group 2 (fructose group) received fructose (20 g/kg) exclusively during the entire treatment period; rats in group 3 (fructose-polyphenol group) received fructose (20 g/kg) for 60 days and then polyphenol (150 mg/kg) until the last day of treatment; and rats in group 4 (polyphenol-fructose group) received polyphenol (150 mg/kg) for 60 days before receiving fructose (20 g/kg) until the day of treatment and group 5 (polyphenol group), rats received just polyphenol (150 mg/kg) during the period of treatment. Over the period of the 110-day experiment, blood glucose levels were measured once every 10 days from the tip of the tail using a portable glucometer (URIGHT Blood Glucose Monitoring Device - TD-4277 / COMPLETE Kit). Rats were fasted for 12 hours before the blood samples were taken taken from their tail veins. Body weight measurements were recorded at 10-day intervals throughout the experimental period. On the day of necropsy, blood samples were collected via retro-orbital bleeding under light anesthesia. The collected blood was immediately transferred into heparinized tubes to prevent coagulation. Subsequently, plasma was separated and used for the determination of biochemical parameters, including alanine transaminase (ALT), aspartate aminotransferase (AST), urea, and creatinine (CREA).

Statistical Analysis

All experimental data are presented as the mean ± standard deviation (SD) derived from six biological replicates. Statistical analysis was carried out using GraphPad Prism 8 software. Initially, a one-way analysis of variance (ANOVA) was applied to assess the overall differences between the control and experimental groups. Following a significant ANOVA result, Tukey's test was used to identify specific differences between groups. Statistical significance was defined at a threshold of $p < 0.05$.

Results and Discussion

This current study investigated the influence of polyphenol content in *Crataegus monogyna* fruit on the body weights and blood glucose levels of fructose-induced diabetic rats. Results of the investigation show that body weights were affected by fructose and polyphenol treatments in comparison to the water control group (Figure 1). The fructose group weighed more than the control group at the end of the test, with noticeable differences. However, in rats fed fructose, as well as in animals provided a supplemented diet, polyphenols were able to significantly decrease body weight. The water consumption and urine production of both normal and diabetic rats after a 60-day treatment period are illustrated in Figure 2. When compared to the normal group, the untreated diabetic rats significantly increased their water consumption and urine elimination ($p<0.0001$ and $p<0.001$, respectively). The water intake ($p<0.0001$) and urine elimination ($p<0.001$) were significantly reduced by the polyphenol extracts. The glucose levels in normal and diabetic animals are summarized in Figure 3. In contrast to the normal rats, the diabetic rats showed significant ($p<0.001$) hyperglycemia. When compared to the diabetic rats that were not treated, the polyphenol extracts reduced the diabetic rats' blood glucose levels after 60 days (Figure 3). The fructose-treated group showed a substantial drop in relative brain weight and a significant rise in liver weight and relative weight (Table 1). Relative weights were considerably higher in the fructose+polyphenol and polyphenol+fructose groups, and the same outcomes were observed in the kidney weight group treated with polyphenol+fructose. Additionally, the group that received fructose treatment had a considerably lower relative kidney weight. The pancreas weight and relative pancreas weight did not vary across the entire cohort. Following 110 days of fructose and polyphenol treatment, a significant difference in plasma glucose was observed between the control group and the group that received 20 g of fructose (Figure 4). Also, there was a significant difference between the groups that received distilled water as the control, 20 g of fructose plus 150 mg of polyphenol (group 3), 150 mg of polyphenol plus 20 g of fructose (group 4), and 150 mg of polyphenol (group 5). There was a notable difference in plasma glucose levels between groups 1 and 2, as well as between groups 2 and 4.

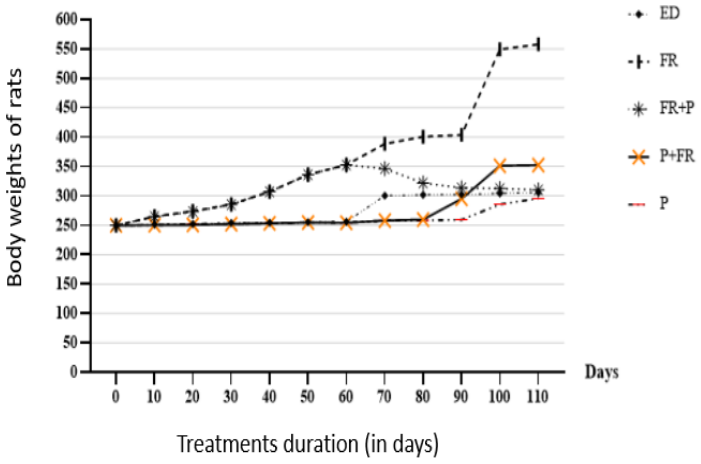

Figure 1: weights of Wistar rats after 110 days of oral fructose and polyphenol administration. ED: rats given distilled water; FR: rats given 20 g/kg of fructose; FR + P: rats given 20 g/kg of fructose + 150 mg/kg of polyphenol; P+ FR: rats given 150 mg/kg of polyphenol + 20 g/kg of fructose; and P: rats given 150 mg/kg of polyphenol.

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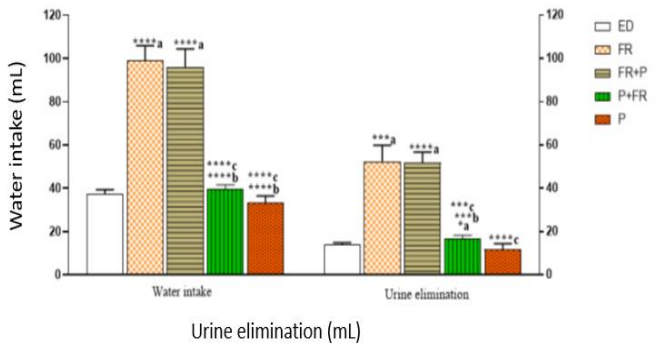

Figure 2: Effect of fructose and polyphenol on water intake and urine elimination. ED: rats given distilled water; FR: rats given 20 g/kg of fructose; FR + P: rats given 20 g/kg of fructose + 150 mg/kg of polyphenol; P+ FR: rats given 150 mg/kg of polyphenol + 20 g/kg of fructose; and P: rats given 150 mg/kg of polyphenol. Note: a: comparison of every group with the group that received distilled water. The FR group is compared to every other group in b, while FR+ P and P + FR is compared in c.** p<0.01, *** p<0.001, **** p<0.0001, * p<0.05, and ** p<0.01, respectively. The data are displayed as mean ± SD and represent the means of six replicates (n = 6).

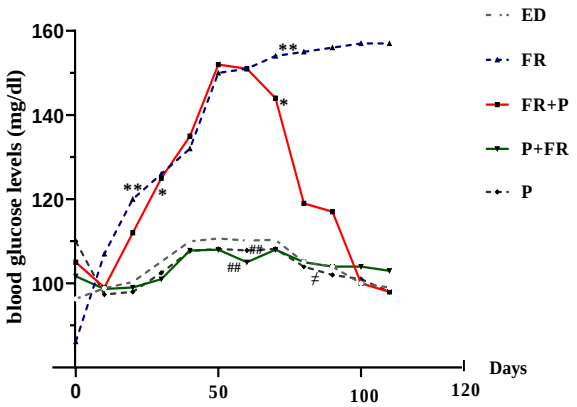

Figure 3: Variations in blood glucose levels during the 110-day study. ED: rats given distilled water; FR: rats given 20 g/kg of fructose; FR + P: rats given 20 g/kg of fructose + 150 mg/kg of polyphenol; P+ FR: rats given 150 mg/kg of polyphenol + 20 g/kg of fructose; and P: rats given 150 mg/kg of polyphenol. Note: *comparison between distilled water group and all groups. #: comparison between fructose group and all groups, ≠: comparison between fructose +polyphenol and polyphenol + fructose. * p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001. Data are the means of six replicates (n = 6) and presented as mean ± SD.

Table 1: Weight of the organs of Wistar rats that were sacrificed on day 110 after receiving fructose and polyphenol subchronic treatment.

Parameters	Distilled Water	Polyphenol	Fructose	Fructose +Polyphenol	Polyphenol+Fructose
Body weight (g)	305.67±2.809	295.74±19.288	557.67±9.268	310.04±0 .952	352.35±0.417
Brain weight (g)	2.965±0.053	2.847±0.173	2.942±0.092	2.850±0.169	2.998±0.004
Liver weight (g)	6.42±0.243	6.45±0.117 *** b	9.29±0.502 **** a	7.87±0.596 * a	6.93±0.605 * b
Kidney weight (g)	2.432±0.144	2.213±0.351	2.662±0.365	1.820±0.412 * a	1.987±0.109 * a
Pancrea weight (g)	1.543±0.394	1.508±0.369	1.938±0.479	1.225±0.505	1.683±0.354
Brain relative weight (g/100 g BW)	0.970±0.013	0.945±0.050 **** b	0.528±0.019 **** a	0.919±0.056 *** b	0.851±0.002 **** a **** b
Liver relative weight (g/100 g BW)	2.10±0 .089	2.19±0.171 **	1.67±0.080 **** a	2.54±0.188 * a ** b	1.97±0.172 ** c
Kidney relative weight (g/100 g BW)	2.432±0.144	2.213±0.351 *b	2.662±0.365 *** a	1.820±0.412 * a	1.987±0.109 **a
Pancreas relative weight (g/100 g BW)	0.505±0.129	0.517±0.153	0.347±0.081	0.395±0.163	0.478±0.101

a: comparison of all groups with the distilled water group. Comparisons between the fructose group and all other groups are shown in b and fructose+polyphenol and polyphenol+fructose, respectively, in c. ** p<0.01, *** p<0.001, **** p<0.0001, * p<0.05, and ** p<0.01, respectively. The data are shown as mean ± SD and represent the means of three replicates (n = 6).

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

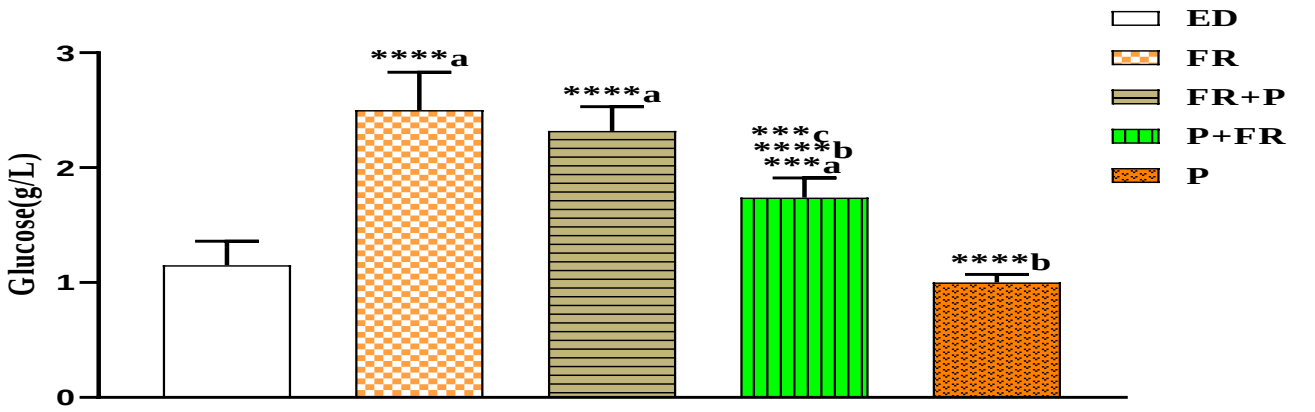

Figure 4: Polyphenols and fructose's effects on plasma glucose levels. ED: rats given distilled water; FR: rats given 20 g/kg of fructose; FR + P: rats given 20 g/kg of fructose + 150 mg/kg of polyphenol; P+ FR: rats given 150 mg/kg of polyphenol + 20 g/kg of fructose; and P: rats given 150 mg/kg of polyphenol. Note: a: comparison of every group with the group that received distilled water. The FR group is compared to every other group in b, while FR+ P and P + FR is compared in c.** p<0.01, *** p<0.001, **** p<0.0001, * p<0.05, and ** p<0.01, respectively. The data are displayed as mean ± SD and represent the means of six replicates (n = 6).

Plasma levels of creatinine and urea in each group of normal and diabetic animals on day 110 are shown in Figure 5 (A and B). Rats with untreated diabetes had greater plasma levels of urea and creatinine (p<0.0001) than the normal group. After being treated with polyphenol extracts, plasma creatinine significantly decreased (p<0.0001). Rats administered fructose plus polyphenol and polyphenol + fructose also showed significant (p<0.0001) decreases in their plasma levels of urea and creatinine (Figure 5A and B). Plasma ezymes, ALT, and AST values for each group of normal and experimental animals are illustrated in Figure 6 (A and B). The plasma ALT and AST levels of fructose-diabetic rats were considerably higher (p<0.0001) than those of the normal control group. The administration of polyphenol extracts resulted in a significant decrease in plasma ALT (p<0.0001) and plasma AST (p<0.0001). Triglyceride (A) and total cholesterol (B) plasma levels in each group of normal and experimental animals are presented in Figure 7(A and B). Rats with fructose-induced diabetes had significantly higher levels of triglycerides and plasma cholesterol (p<0.0001) than the control group, which were significantly reduced (p<0.0001) after the polyphenol extracts were administered. The data from our study indicate that polyphenol extracts significantly reduced body weight and provided protective effects against increases in blood glucose, plasma triglycerides, total cholesterol, urea, creatinine, AST, ALT, water intake, urine output, and blood glucose levels in diabetic rats. A notable rise in both final body weight and blood glucose levels was observed after 110 days of fructose administration. These changes were accompanied by alterations in the weights of the liver, kidneys, brain, and pancreas, which varied in proportion to overall body weight. However, as shown in Table 1, the relative organ weights remained unaffected by polyphenol extract treatment. Chronic fructose exposure notably decreased the relative weights of the liver, kidneys, and brain. Furthermore, the current study confirmed that daily fructose administration over 110 days significantly elevated serum glucose concentrations compared to control animals. These results are consistent with previous findings by Ferreira-Santos, who also reported significantly higher serum glucose levels in fructose-treated rats. [14] Our results also demonstrated that the polyphenol extract and its main active component effectively reduced serum glucose levels. The antioxidant potential of *Crataegus monogyna*'s active compound may help restore insulin secretion, thereby offering protection against diabetes-related complications. [15]Several studies have shown that the administration of 20% fructose leads to a significant increase in blood pressure. Additionally, other findings indicate that diets in which fructose accounts for 60% of total caloric intake can cause elevated blood pressure, increased plasma triglycerides, promote insulin resistance, and contribute to the development of metabolic syndrome. [16] In support of these findings, Badalova *et al*. (2025) emphasized the role of dyslipidemia in the development of diabetic angiopathies and highlighted the corrective potential of *Crataegus* extracts.[17] Recent studies also show that SMV treatment significantly improves hepatic and serum lipid profiles, including triglycerides, total cholesterol, AST, ALT, and HDL cholesterol in models of obesity induced by a high-fat diet (HFD) in both rats and mice. These findings further underline the strong association between type 2 diabetes and obesity. [18]

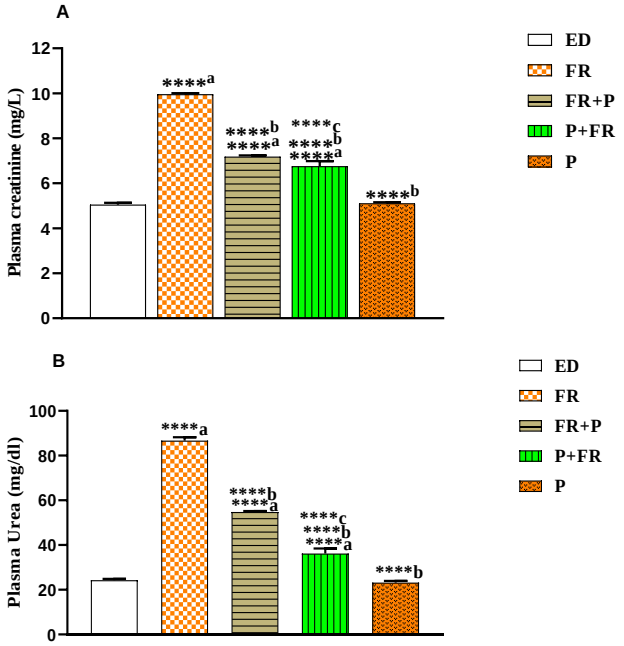

Figure 5: Impact of fructose and polyphenol on urea (B) and creatinine (A) plasma levels. ED: rats given distilled water; FR: rats given 20 g/kg of fructose; FR + P: rats given 20 g/kg of fructose + 150 mg/kg of polyphenol; P+ FR: rats given 150 mg/kg of polyphenol + 20 g/kg of fructose; and P: rats given 150 mg/kg of polyphenol. Note: a: comparison of every group with the group that received distilled water. The FR group is compared to every other group in b, while FR+ P and P + FR is compared in c.** p<0.01, *** p<0.001, **** p<0.0001, * p<0.05, and ** p<0.01, respectively. The data are displayed as mean ± SD and represent the means of six replicates (n = 6).

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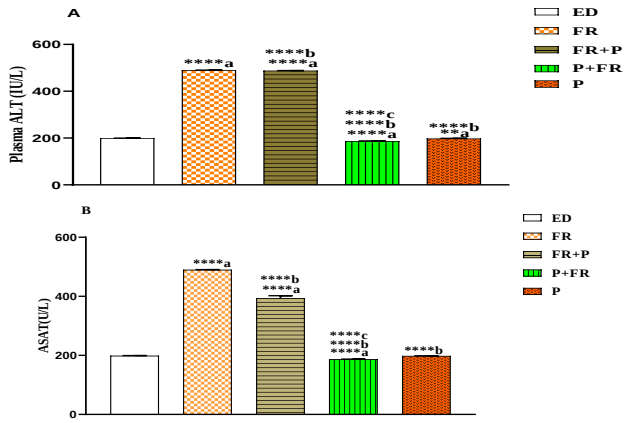

Figure 6: Impact of fructose and polyphenol on ALT (A) and AST (B) plasma levels. ED: rats given distilled water; FR: rats given 20 g/kg of fructose; FR + P: rats given 20 g/kg of fructose + 150 mg/kg of polyphenol; P+ FR: rats given 150 mg/kg of polyphenol + 20 g/kg of fructose; and P: rats given 150 mg/kg of polyphenol. Note: a: comparison of every group with the group that received distilled water. The FR group is compared to every other group in b, while FR+ P and P + FR is compared in c.** p<0.01, *** p<0.001, **** p<0.0001, * p<0.05, and ** p<0.01, respectively. The data are displayed as mean ± SD and represent the means of six replicates (n = 6).

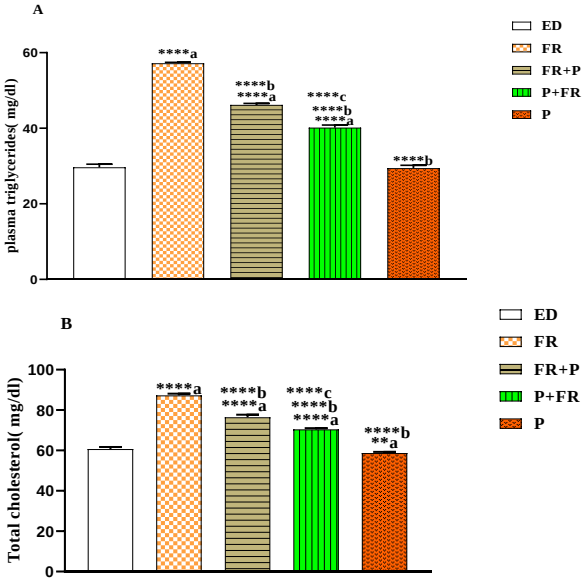

Figure 7: Effect of fructose and polyphenol on plasma levels of triglycerides (A) and total cholesterol (B). ED: rats given distilled water; FR: rats given 20 g/kg of fructose; FR + P: rats given 20 g/kg of fructose + 150 mg/kg of polyphenol; P+ FR: rats given 150 mg/kg of polyphenol + 20 g/kg of fructose; and P: rats given 150 mg/kg of polyphenol. Note: a: comparison of every group with the group that received distilled water. The FR group is compared to every other group in b, while FR+ P and P + FR is compared in c.** p<0.01, *** p<0.001, **** p<0.0001, * p<0.05, and ** p<0.01, respectively. The data are displayed as mean ± SD and represent the means of six replicates (n = 6).

Aqueous extracts of *C. monogyna* have also been shown to significantly enhance glucose tolerance by minimizing postprandial blood glucose spikes following carbohydrate-rich meals. This improvement is believed to result from enhanced glucose utilization by peripheral tissues. Additionally, various studies have reported that these extracts may stimulate insulin production by the pancreas and/or reduce glucose absorption in the intestine. [19] Another study conducted in 2020 investigated the hepatoprotective potential of aqueous extracts from *C. monogyna* fruits and leaves, native to northern Algeria, in a model of copper sulfate-induced hepatotoxicity. A protective effect was observed in mice when hydroethanolic extracts were administered at doses of 300 mg/kg and 1000 mg/kg alongside 1000 mg/kg of acetaminophen. [20] Similarly, Elango *et al*. demonstrated that a 100 mg/kg dose of ethanolic *C. monogyna* extract, administered over 15 days, produced immunomodulatory effects in a rat model of stroke. [20] The reduction in brain apoptosis observed during reperfusion has been attributed to multiple factors, including increased expression of Bcl-xL, phosphorylation of STAT3, a rise in regulatory T cell (Treg) numbers, suppression of activated inflammatory cells due to elevated IL-10 and Foxp3-positive Tregs, and reduced pro-inflammatory responses following ischemia-reperfusion injury. [21] The antioxidant capacity of *Crataegus* has been validated through water-based infusions made from its leaves and unripe fruits. These infusions displayed substantial free radical scavenging activity and effectively inhibited *β*-carotene oxidation and lipid peroxidation in rat liver tissue. [22] Phenolic compounds play a key role in reducing oxidative stress and hyperlipidemia by enhancing the activity of antioxidant enzymes and limiting free radical formation. [23] In a related study, seven potent phenolic compounds found in hawthorn fruit, hyperoside, isoquercitrin, epicatechin, quercetin, rutin, chlorogenic acid, and protocatechuic acid, were shown to strongly inhibit LDL oxidation, emphasizing the significance of the phenol-rich phase in the fruit. [24] Dyslipidemia presents differently in type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D is commonly associated with normal HDL-C and LDL-C levels but elevated triglycerides, whereas T2D typically features low HDL-C, normal LDL-C, and high triglyceride levels. [25] One of the most prevalent symptoms of T2D is weight gain, especially in the context of poor glycemic control. Consistent with the known relationship between T2D and obesity, continuous administration of 10% D-glucose in another study led to a significant increase in both body weight gain and final body weight compared to the control group. In contrast, T1D is often characterized by a reduction in body weight. [25]

Conclusions

The findings of our investigation demonstrate the possible use of *C. monogyna* polyphenol extract as a protective antidiabetogenic and antidiabetic treatment for conditions brought on by high fructose dosages. Actually, taking this extract lowers creatinine and blood sugar levels. Future studies should focus on clarifying the mechanisms behind the effects observed and improving treatment approaches in order to enhance the comprehension and applicability of these findings. In order to confirm or refute the possible application of the compounds isolated from *C. monogyna* for cellular and molecular therapeutic approaches in the future, additional clinical testing is also necessary. *C. monogyna* may therefore be considered a beneficial treatment for diabetes mellitus.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The authors gratefully acknowledge Prof. Hamid Khamar (Botany Department) for the taxonomic verification of the collected plant material. A voucher specimen (No. RAB114863) was prepared and deposited at the National Herbarium and Scientific Institute of Rabat, where it has been officially accepted under the botanical name *Crataegus monogyna* Jacq.

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ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

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