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Effect of Crataegus extract supplementation on diabetes induced memory deficits and serum biochemical parameters in male rats

Amin Pirmoghani[a,b], Iraj Salehi[a,c], Shirin Moradkhani[d], Seyed Asaad Karimi[a,c,*], Sakineh Salehi[e]

[a] Neurophysiology Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[b] Student Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran
[c] Department of Neuroscience, School of Science and Advanced Technologies in Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[d] Medicinal Plants and Natural Products Research Center, Department of Pharmacognosy and Pharmaceutical Biotechnology, School of pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran
[e] Department of Physiology and Neurophysiology Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

This study was undertaken to investigate the Crataegus extract (CE) eff ;ects on diabetes-induced memory deficit in passive avoidance learning (PAL), blood glucose, and lipid profile panel. Male Wistar rats were divided into five groups: **Control** (CTRL); **Diabetic** (DM); and **Diabetic animals treated** with three doses of CE (100, 300 and 1000 mg/kg) (DM + CE). Streptozotocin (STZ)-induced diabetic rats (50 mg/kg, ip) were orally administrated with CE once a day for 2 weeks. After 2 weeks, PAL task was used to evaluate the passive avoidance learning and memory. At the end of experiment, the level of plasma glucose, triglycerides (TG), cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were determined. Our results showed that the step-through latency (STLr) in diabetic animals was less than the control group ($P = 0.0009$). Crataegus (300 mg) increased STLr in diabetic animals ($P = 0.0418$). Diabetic animals spent more time in the dark compartment (TDC) ($P = 0.0009$). Crataegus (300 and 1000 mg) decreased TDC in diabetic animals ($P = 0.0175$). Crataegus (100 and 300 mg) decreased blood glucose in diabetic animals ($P < 0.001$). TG and Cholesterol concentration increased in diabetic animals in comparison with control ($P < 0.05$). CE (100 and 300 mg) reduced the cholesterol concentration in diabetic animals ($P < 0.001$). There was no significant difference in the case of LDL among the experimental groups ($P > 0.05$). CE (1000 mg) increased HDL in diabetic animals ($P < 0.05$). Our findings demonstrated that CE had the hypolipidemic and hypoglycemic effects and lead to memory improvement in STZ-induced diabetes.

1. Introduction

Diabetes mellitus (DM) is a complex and heterogeneous metabolic disorder that can exert harmful effects on multiple organs in the body and especially on the central nervous system (CNS). DM is characterized by high blood glucose levels and dysfunctional glucose and lipid metabolism that result from insufficient and defective insulin secretion, insulin resistance, or both (Association, 2016). In addition to the relation of impaired glucose homeostasis with vision loss, neuropathy, cardiovascular disease, and metabolic diseases, DM is associated with cognitive decline (Omidi et al., 2019a; Chaytor et al., 2019) and is a risk factor for the development of Alzheimer's disease and dementia (Salas and De Strooper, 2019; Fiore et al., 2019). Observations from our previous work in rats (Omidi et al., 2019b) and others findings from human and rodent studies demonstrate deficits in cognitive function and whole-body efficiency following diabetes (Chaytor et al., 2019; Novak et al., 2018; Baydas et al., 2003). Passive avoidance learning (PAL) and memory impairments also occur in streptozotocin (STZ)-induced diabetic rats (Baydas et al., 2003). Also, deficits in cognitive function has been observed in middle-aged adults with Type I or Type II diabetes mellitus (Croxson and Jagger, 1995; Kalmijn et al., 1995). Diabetes related neurodegeneration is contributed to the development of diabetes-mediated cognitive dysfunction (Kodl and Seaquist, 2008).

There are many antidiabetics and hypolipidemic drugs, but unfavorable side eff ;ects are serious problems. Therefore, there is a need for more eff ;ective antidiabetic and hypolipidemic agents. Plant therapeutic agents may provide a cure for type 1 or 2 diabetes. Traditional drugs are a remarkable alternative treatment that may be prescribed to prevent and treat DM (Xie et al., 2011). These herbal plants have antidiabetic effects comparable to conventional drugs and are consumed

* Corresponding author at: Department of Neuroscience, School of Medicine, Hamadan University of Medical Sciences, Postal Code: 65178/518, Hamadan, Iran.
E-mail addresses: a.karimi@umsha.ac.ir, asaskarimi@sbmu.ac.ir (S.A. Karimi).

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at a lower cost.

Crataegus species (Hawthorn) have been used traditionally to treat cardiovascular diseases and is traditionally used to aid digestion. In addition, this plant is prescribed for the treatment of hyperlipidemia and hawthorn administration has antidiabetic and hypolipidemic effects (Xie et al., 2012; Shih et al., 2013).

Moreover, it is well known that Crataegus species have antioxidative activities (Dolatkhani and Jameie, 2015).

Crataegus extracts (CE) are generally rich in triterpenes, procyanidins, flavonoids and glycosides, which are shown to be the main ingredients responsible for the biological effects of Crataegus (Melikoğlu et al., 2004).

Consequently, the beneficial effects of Crataegus might provide a reliable protection against the memory impairment in diabetes. Previous studies showed the effect of the CE on diabetic animals. But it is unknown whether CE can protect against diabetes induced passive avoidance learning and memory impairment in male rat. Based on this point, we propose that CE administration may restore the diabetes-induced behavioral changes in male rats. To prove our hypotheses, we employed a diabetic rat model to evaluate the effects CE on behavioral and biochemical alterations in rats. Therefore, the specific aims of this study were to examine the potential effect of Crataegus extract treatment on passive avoidance learning, blood glucose level and serum lipid profile in streptozotocin (STZ)-induced diabetic rats.

2. Materials and methods

2.1. Ethics statement

All experimental procedures using rats were conducted in accordance with the animal care and use guidelines approved by the institutional ethics committee at Hamadan University of Medical Sciences and were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (Care, Animals, and Resources, 1985). All efforts were made to minimize suffering. The operations that could cause pain and distress were performed in another room in the absence of other animals.

2.2. Animals and experimental design

Male Wistar rats of 3 months old obtained from Pasteur Institute of Tehran, Iran. The animals were housed in an air-conditioned room at 22 ± 2 °C with a 12-h light/dark cycle. The animals were kept in cages with 2–3 rats in each cage. Standard animal chow and water were freely available. After one week of adaptation, subjects were randomly divided into five groups: **Control** (CTRL); **Diabetic** (DM); and **Diabetic animals treated** with three doses of Crataegus extract (100, 300 and 1000 mg/kg) (DM + CE). The number of animals in each experimental group was 6-8. All the rats had free access to the food and tap water. Administrations of saline or extract were done by 14 days (daily) gavage. Extract of Crataegus or vehicle were administered orally by gastric intubation using a syringe once daily at 08:00 a.m. Experimental design and schedule of passive avoidance learning (PAL) test is shown in Fig. 1.

2.3. Induction of diabetes

Diabetes was induced by intraperitoneal injection of 50 mg/kg STZ (Sigma, St. Louis, MO, USA), which was dissolved in freshly prepared 0.05 M citrate buffer, pH 4.5, immediately before injection (Moradkhani et al., 2015). Blood glucose concentrations were monitored once per week. A minimum blood glucose level greater than 250 mg/dl and the presence of urinary glucose were used as criteria for identification of diabetic rats. Age-matched, vehicle-treated rats were used as controls.

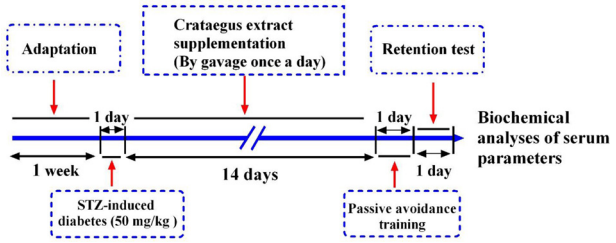

Fig. 1. Experimental design and schedule of PAL test. After one week of adaptation, Extract of Crataegus was administered intragastrically by gavage once a day for 14 days. After 14 days, Passive Avoidance Learning (PAL) task was used to evaluate the passive learning and memory in rats.

2.4. Collection and preparation of herbal sample

The berries of Crataegus were collected from Sanandaj city; Kurdistan, Iran and identified at the Botanic Institute of this University. A voucher specimen was deposited in the Department of Pharmacognosy and Biotechnology, School of Pharmacy, Hamadan University of Medical Sciences. The fresh pulp of the fruits was dried at 40 °C with air circulation and crushed, and absolute water was added. This mixture was allowed to stand for 72 h at 4 °C. The extract was then centrifuged and the resulting supernatant was filtered. The filtered extract was then concentrated to dryness in a rotary evaporator under reduced pressure at a constant temperature of 40 °C. The resulting extract was stored in a refrigerator. The extracts were redissolved in their solvents before each individual experiment (Zarrinkalam et al., 2018b). Major components in Crataegus are phenolic and flavonoids which were measured by colorimetric assay.

2.5. Determination of total phenolic

The total phenolic content of extract was measured according to the formerly published method with using Folin-Ciocalteu reaction. Briefly, 1 mg of extract was dissolved in 2.8 mL of deionized water, 2 mL of Na_2CO_3 (2%), and 0.1 mL of 50% Folin–Ciocalteau reagent. afterward, the tube was incubated for 30 min at room temperature and absorbance of the sample was measured at 750 nm against blank. Finally, total phenolic content was calculated equivalents of gallic acid (GAE) per gram of extract.

2.6. Determination of total flavonoids

Total flavonoids were measured by colorimetric assay using aluminum chloride according to the formerly published method. Briefly, 1.0 mg/mL of extract was mixed with and 2.8 mL of deionized water, 1.5 mL of 95% alcohol, 0.1 mL of 10% $AlCl_3$ and 0.1 mL of 1 M CH_3COOK. Mixture then incubated at room temperature for 40 min and measured at 415 nm against a blank (deionized water). Flavonoid content was calculated as mg equivalents of quercetin per gram of extract.

2.7. HMG-CoA reductase activity

For measurement of HMG-CoA reductase activity, 50 µg of extract was used for the determination of enzyme activity using HMG-CoA reductase assay kit (Sigma-Aldrich Co.). HMG-CoA reductase inhibitory activity was calculated by following formula:

$$\text{Inhibition}\% = \frac{\Delta\,\text{Absorbance control} - \Delta\,\text{Absorbance test}}{\Delta\,\text{Absorbance control}} \times 100$$

2.8. Biochemical analyses of serum parameters

At the end of the study, animals were anesthetized with urethane (ethyl carbamate, 1.8 g/kg; i.p.). Blood samples were taken from the portal vein and centrifuged at 3000 rpm for 10 min at 4 C. We assayed triglycerides (TG) and cholesterol from the plasma samples. Total cholesterol was measured using cholesterol esterase/ cholesterol oxidase/peroxidase reactions. A triglyceride assay was performed using lipase/glycerol kinase/glycerolphosphate oxidase/peroxidase reactions. All lipid assays were carried out using colorimetric methods (Pars Azmun kits, Iran). All biomarker assays were carried out on a UV–Visible spectrophotometer (Spectronic Genesys 2; Spectronic Instruments, USA) (Karimi et al., 2015; Goodarzi et al., 2007). Serum random blood glucose concentration was measured by the glucose oxidase method (Pars Azmoon kits, Iran); intra- and interassay coefficients of variation were 2.5 and 6.1%, respectively (Gheibi et al., 2018).

2.9. Passive avoidance learning (PAL) test

2.9.1. Passive avoidance apparatus

We used the step-through apparatus to estimate passive avoidance learning and memory (Komatsu et al., 2008; Kohara et al., 2014; Komaki et al., 2015). The step-through passive avoidance apparatus consisted of a lighted chamber (20 cm × 20 cm × 30 cm) made of transparent plastic and a dark chamber whose walls were made of dark opaque plastic (20 cm × 20 cm × 30 cm). The floor of both chambers was made of stainless steel rods (3 mm diameter) spaced 1 cm apart. The floor of the dark chamber could be electrified using a shock generator (Behbood Pardaz Co. Iran). A rectangular opening (6 cm × 8 cm) was located between the two chambers and could be closed by an opaque guillotine door.

2.9.2. Passive avoidance training (acquisition)

First, all experimental groups were given two trials to habituate them to the apparatus. For these trials, the rats were placed in a lighted compartment of the apparatus facing away from the door and 5 s later the guillotine door was raised. The rat has a natural preference for the dark environment. Upon the rat entering the dark compartment, the door was closed and after 30 s the rats were taken from the dark compartment and placed in their home cage. The habituation trial was repeated after 30 min and followed after the same interval by the first acquisition trial. The entrance latency to the dark compartment (step-through latency, STLa) was recorded when the animal had placed all four paws in the dark compartment. After the animal had spontaneously entered the dark compartment, the guillotine door was lowered and an electrical shock (50-Hz square wave, 1 mA for 1.5 s) was applied. After 30 s, the rat was returned to its home cage. Then after 2 min, the procedure was repeated. The rat received a foot-shock each time it reentered the dark and had placed all four paws in the dark compartment. Training was terminated when the rat remained in the light compartment for 120 consecutive seconds. The number of trials (entries into the dark chamber) (NTa) was recorded.

2.9.3. Retention test

The retention test was performed 24 h after the PAL acquisition trial (Komaki et al., 2015; Karimi et al., 2018). The rats were placed in the lighted chamber as in PAL training and 5 s later, the guillotine door was raised, and the entrance latency to the dark compartment in the retention test (step-through latency, STLr) and time spent into the dark compartment (TDC) were recorded for up to 300 s. If the rat did not enter the dark compartment within 300 s, the retention test was terminated and a ceiling score of 300 s was assigned. The animal behavior in passive avoidance recording was recorded manually by a professional researcher.

2.10. Statistical analysis

All data were presented as mean ± SEM. Statistical analyses were performed using GraphPad Prism (v. 6.0; GraphPad Software, Inc, La Jolla, CA) software. The distribution of data was normal when examined using Kolmogorov-Simonov test. One-way ANOVA followed by the Tukey's test, and two-tailed unpaired Student's *t*-test were used for multiple comparisons. A probability of 0.05 was considered as the criterion for significance.

3. Results

3.1. Total phenolics and flavonoids as well as enzyme activity

Total phenolic and flavonoid contents of extract were 2018 ± 20.50 and 850 ± 18 mg/100 g extract respectively. In this experiment extract showed 4% inhibitory on HMG-CoA reductase activity when compared with atorvastatin.

3.2. Effects of diabetes and Crataegus on random blood glucose

Streptozotocin injection resulted in a diabetic syndrome verified by the presence of polydypsia, polyuria and hyperglycemia in the diabetic animals. Mean **random blood glucose** level in the diabetic group was significantly higher than the control group after STZ injection [$F(4, 17) = 131.9$, $P < 0.0001$, One-way ANOVA], and blood glucose levels in the diabetic group remained significantly elevated (Fig. 2). There was a significant difference in the blood glucose among the experimental groups of rats. Specifically, Crataegus (100 and 300 mg) decreased blood glucose in diabetic animals ($P < 0.001$). The results are summarized in Fig. 2.

3.3. Effects of diabetes and Crataegus on lipid profile of animals

There was significant difference in the TG among the experimental groups of rats [$F(4, 17) = 11.91$, $P < 0.0001$, one-way ANOVA, Fig. 3a]. TG increased in Diabetic animals in comparison with control animals ($P < 0.05$). Surprisingly, Crataegus (1000 mg) increased TG in diabetic animals ($P < 0.01$). We performed the multiple *t*-test analysis in the case of Cholesterol. There was a significant difference in the Cholesterol concentration between the control and diabetic animals ($t_8 = 8.432$, $P < 0.0001$, Fig. 3b). The Cholesterol concentration in

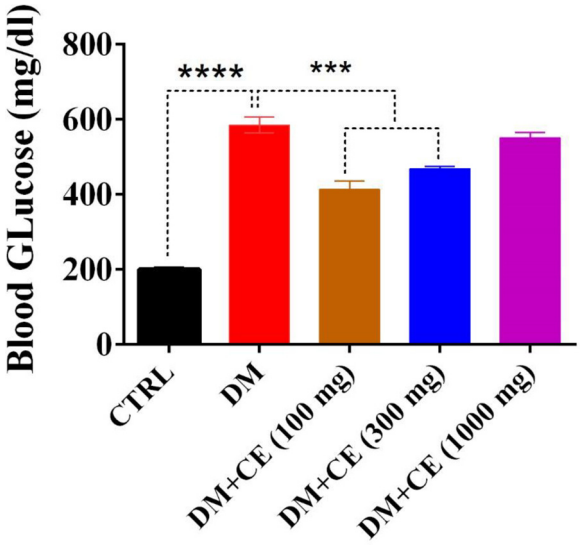

Fig. 2. Effect of Crataegus on random blood levels of glucose. Each column and bar represents mean ± S.E.M. **** $P < 0.0001$, *** $P < 0.001$.

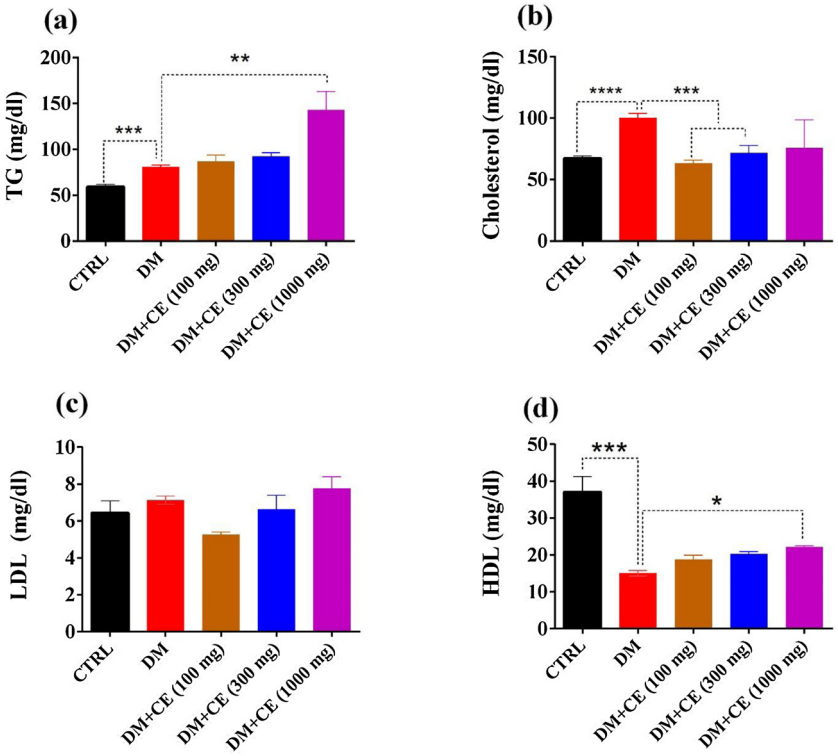

Fig. 3. Effect of Crataegus on serum levels of TG (a), cholesterol (b), LDL (c) and HDL (d). Each column and bar represents mean ± S.E.M. ****P < 0.0001, ***P < 0. 001, **P < 0. 01, *P < 0. 05.

control rats was 67.17 ± 2.182 mg/dl, (n = 7), which was significantly elevated to 100.3 ± 3.568 mg/dl (n = 8) in diabetic animals (Fig. 3b). Doses of 100 and 300 mg of Crataegus reduced the cholesterol concentration in diabetic animals (P < 0.001, Fig. 3b). There was no significant difference in the case of LDL among the experimental groups of rats [F (4, 16) = 2.463, P = 0.0872, one-way ANOVA, Fig. 3c]. HDL decreased in diabetic animals in comparison with control animals [F (4, 16) = 10.58, P = 0.0002, Fig. 3d]. Crataegus (1000 mg) increased HDL in diabetic animals (P < 0.05, Fig. 3d). The results are summarized in Fig. 3.

3.4. Effects of diabetes and Crataegus on the PAL acquisition

There was no significant difference in the Step-through latency (STLa) among the experimental groups of rats in the acquisition trial (before receiving the electrical shock) [F (4, 26) = 0.7649, P = 0.5577, One-way ANOVA, Fig. 4a). This result indicates that the exploratory behavior of the different groups of rats in the dark did not differ. An addition, there was no significant difference in the number of trials (entries into the dark chamber) (NTa) among the experimental groups of rats in the acquisition trial [F (4, 18) = 1.050, P = 0.4094, One-way ANOVA, Fig. 4b).

3.5. Effects of diabetes and Crataegus on the PAL retention

The retention test was conducted 24 h after the training. It revealed a significant difference in the STLr among the groups [F (4, 20) = 9.726, P = 0.0002, One-way ANOVA, Fig. 5a]. Specifically, the STLr in diabetic animals was significantly less than the control group (P = 0.0009). Crataegus (300 mg) increased STLr in diabetic animals (P = 0.0418, Fig. 5a).

In addition, there was also a statistically significant difference in TDC between experimental animals [F (4, 16) = 7.154, P = 0.0017, One-way ANOVA, Fig. 5b]. Diabetic animals spent more time in the dark compartment in comparison with control animals (P = 0.0009, Fig. 5b). Crataegus (300 and 1000 mg) decreased TDC in diabetic animals (P = 0.0175, Fig. 5b). All results are summarized in Fig. 5.

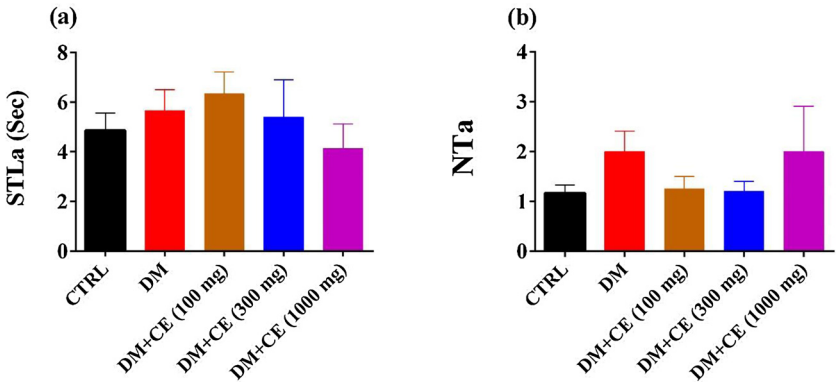

Fig. 4. Effects of diabetes and Crataegus on the step-through latency in the acquisition trial (STLa) (a), number of trials to acquisition (NTa) (b) of passive avoidance learning (PAL) task in all experimental groups. There was no significant difference in the STLa among the experimental groups of rats. Data presented as means ± S.E.M.

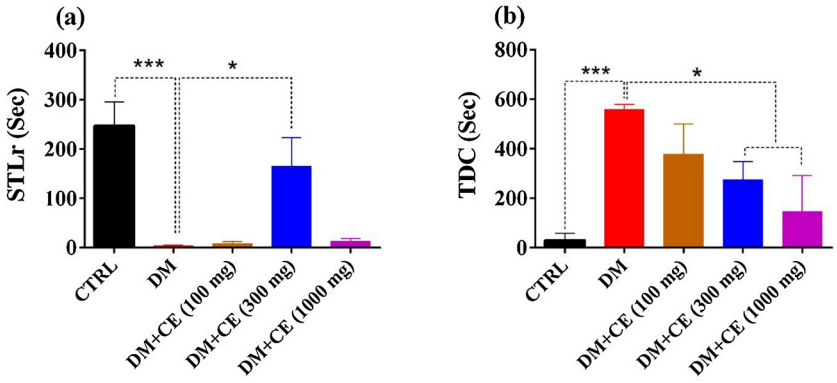

Fig. 5. Effect of diabetes and Crataegus on the step-through latency in the retention trial (STLr) (a), the time spent in the dark compartment in the retention trial (TDC) (b), which was carried out 24 h after acquisition trial of passive avoidance learning (PAL) task in all experimental groups. Data presented as means ± S.E.M. ***P < 0.001, **P < 0.01 and *P < 05.

4. Discussion

This study was firstly undertaken to investigate the eff ;ects of the Crataegus extract on blood glucose level, lipid profile and diabetes-induced memory deficit in passive avoidance learning (PAL) in STZ-induced diabetic rats.

The results demonstrate that both STZ-induced diabetes and Crataegus extract supplementation have significant effects that both altered cognitive performance, as measured by the PAL task. The increase in STLr and decrease in TDC during the retention test demonstrates facilitatory effects on memory retention (Komaki et al., 2015; Karimi et al., 2019). The principal findings of this study are: STZ-induced diabetes reduced PAL, whereas Crataegus extract supplementation significantly improved PAL. Supplementation with a Crataegus extract improves learning. Furthermore, the Crataegus extract did not affect STLa, suggesting that the passive avoidance learning improvement is not caused by locomotion improvement.

Streptozotocin injection resulted in a diabetic syndrome verified by the presence of polydypsia, polyuria and hyperglycemia in the diabetic animals. Blood glucose level in the diabetic animals was higher than the control group. Crataegus (100 and 300 mg) decreased blood glucose in diabetic animals. Obesity-related parameters such as blood TG and cholesterol were increased in the serum of diabetic rats. Surprisingly, Crataegus (1000 mg) increased TG in diabetic animals. Crataegus (100 and 300 mg) reduced the cholesterol concentration in diabetic animals. There was no significant difference in the case of LDL among the experimental groups. HDL decreased in diabetic animals and Crataegus (1000 mg) increased HDL in diabetic animals. There is no established ideal dose of Crataegus. But Trials have evaluated dosages ranging from 160 to 1800 mg/day standardized extracts in divided doses over 2 to 24 weeks (Schlegelmilch and Heywood, 1994). Minimum effective doses are suggested to be standardized extract 100 (Shatoor, 2011) and 300 mg (Schlegelmilch and Heywood, 1994) daily. Crataegus is reportedly toxic in high doses; low doses of Crataegus usually lack adverse effects. Based on these reports and the results of our study, it can be concluded that Crataegus extract at the dose of 1200 mg is toxic. (at least for glucose, TG and cholesterol) parameters. Based on our results, Crataegus (100 and 300 mg) decreased blood glucose in diabetic animals. In general, it can be concluded that the Crataegus has clear hypoglycemic effect but it should be further investigated to find the most ideal dose.

Our observations showed that high doses of Crataegus extract (300 and 1000 mg) improved PAL and decreased TDC in diabetic animals. Özgür et al examined CNS effects of Crataegus extract on exploratory behavior, spontaneous locomotor activity, motor coordination, and nociception perception of mice by using different experimental models (Can et al., 2010). Their results suggest a significant and dose-dependent decreases in spontaneous locomotor activities and exploratory behaviors of animals suggested CNS depressant activities of extract. Also, a dose-dependent analgesic activities were seen at 100–1000 mg/kg doses of extract. Based on these observations, it can be concluded that even high doses of the extract are not toxic to brain function. In our study and the study of Özgür et al. (Can et al., 2010) no animal died by administration of Crataegus extract, even at the highest dose of 1000 mg/kg.

Impairment of learning and memory have been reported in both type 1 and type 2 diabetes. Adverse effects of DM on cognitive performances have been noticed for a long time (Saedi et al., 2016; Chaytor et al., 2019). In addition, DM is an essential risk factor for subsequent Alzheimer's disease (Vijayakumar et al., 2012).

As we mentioned in the introduction section, the antioxidant property of Crataegus extract has been reported (Dolatkhani and Jameie, 2015). Also, DM leading to oxidative damage to cellular components by rising free radical formation and decreasing antioxidant capacity (Bashan et al., 2009). Deficiency of antioxidant capacity and oxidative stress caused by free radical generation and lipid peroxidation plays a significant role in pathogenesis of cognitive decline (Berr et al., 2000; Hajjar et al., 2018). It seems that Crataegus induced memory improvement in diabetic animals is contributed to antioxidant property of Crataegus.

Consistent with our observation, Saoudi et al. by using open field and elevated plus maze tests indicated the beneficial effects of Crataegus extract on neurobehavioral deficits and brain tissue damages induced by an insecticide mixture of deltamethrin and chlorpyrifos in adult Wistar rats (Saoudi et al., 2019). Also, Ranjbar et al. demonstrated the lowering effects of Crataegus oxyacantha extract on oxidative stress biomarkers in ischemia reperfusion–induced oxidative stress in diabetic rats (Ranjbar et al., 2018). Moreover, it has been demonstrated that extracts of the Crataegus possess considerable antioxidant potential because they inhibited oxidation of β-carotene and 2,2-azobis(2-amidino-propan) dihydrochloride (AAPH)-induced plasma oxidation (Ljubuncic et al., 2005). Consistent with our result, Zarrinkalam et al. demonstrated that the resistance training and hawthorn extract ameliorate cognitive deficits in streptozotocin-induced diabetic rats (Zarrinkalam et al., 2018a).

According to the study of Fanet et al., Hawthorn Flavonoids affect lipid metabolism by regulating lipoprotein lipase (LPL) expression (Fan et al., 2006). Previous studies also have reported a pharmacological lipid lowering efficacies of Crataegus (Jurikova et al., 2012). Additionally, it has been demonstrated that Crataegus alone and in combination with simvastatin displayed a considerable lipid lowering efficiency in hyperlipidemic albino rats (Kausar et al., 2011). These remarkable effects can be correlated to the effect of the main combinations identified in the Crataegus extract. In addition, it has been shown that in high cholesterol diet fed rats Hawthorn major compounds, inhibiting synergistically 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and cholesterol absorption could manifest substantial hypolipidemic benefits (Al-Hallaq et al., 2012; Zhang et al., 2002; Huang et al., 2010).

We showed that Crataegus extract (100 and 300 mg) decreased

blood glucose in diabetic animals. Moreover, it has been shown that flavonoids are one of the major ingredients of Crataegus extract (Melikoğlu et al., 2004). It has been demonstrated that flavonoids act as an alpha-amylase inhibitor and exhibit glycemic control in STZ-induced rat model of type I DM and have beneficial eff ;ects on dyslipidemia in diabetic rats (Najafian et al., 2010).

Proposed the possible mechanism by which flavonoids show these therapeutic properties are upregulation of hepatic superoxide dismutase activity, reduction of hepatic malondialdehyde content, downregulation of hepatic CYP2E1 expression, increase of glucose transporter 4 (GLUT-4) expression, and upregulation of hepatic/adipocyte peroxisome proliferator-activated receptor gamma (PPARγ) expression (JIANG et al., 2012; Jung et al., 2006).

Additionally, flavonoids suppress hepatic HMG-CoA reductase and acyl CoA: cholesterol acyltransferase (ACAT) activities with increased fecal cholesterol and lead to decreased plasma and hepatic cholesterol levels (Jung et al., 2006). It has been reported that hawthorn increases insulin sensitivity associated with the phosphorylation and activation of AMP-activated protein kinase (AMPK). Furthermore, AMPK activation leads to reduce hepatic glucose production, resulting in reduced glucose level in high fat-fed mice (Shih et al., 2013).

Cui et al. demonstrated the synergic antidiabetic effects of Astragalus polysaccharides (APS) combined with Crataegus flavonoids via rehabilitation of islet cell function by upregulating pancreatic and duodenal homeobox-1 (PDX-1) expression and promoting the metabolism of liver glucose via the promotion of adenosine 5′-monophosphate-activated protein kinase (AMPK) phosphorylation (Cui et al., 2016). In addition, they reported that Crataegus decrease the mRNA expression levels of inflammatory factors, including interleukin 6 (IL-6,) and tumor necrosis factor-α (TNF-α) in the pancreatic tissues and concluded that fasting blood glucose lowering effects of Crataegus are mediated by its anti-inflammatory effects (Cui et al., 2016).

5. Conclusion

Briefly, present findings indicate that STZ-induced diabetes causes learning and memory deficits in rats. In conclusion, based on above-mentioned complications and our knowledge, Crataegus extract may have a therapeutic role via its antioxidant potential, anti-inflammatory, hypolipidemic and hypoglycemic effects. Our findings demonstrated that hawthorn had the therapeutic potential for the protection against diabetes and Crataegus extract lead to memory improvement in STZ-induced diabetes.

Conflict of interest

None. We confirm that the authors do not have any conflict of interest with this publication.

Acknowledgments

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