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Original Article

Ameliorative effect of cranberry on erectile function in diabetic rats

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ABSTRACT

Background and Aims: Cranberry products are beneficial in erectile dysfunction (ED). Therefore, we assessed the impact of Cranberry fruit extract (Cranberry-E) on *in vivo* erectile response and *in vitro* relaxant responses in the corpus cavernosum (CC).

Methods: Rats (n=10) were divided into control and diabetic groups. In vivo erectile function was measured following intracavernosal injection of Cranberry-E. The relaxation responses to Cranberry-E were obtained after pre-contraction with phenylephrine (Phe, 10 μM) and KCl (60 mM). Cranberry-E caused relaxant responses in the incubation with nitric oxide synthase (NOS) blocker (L-NAME, 100 μM) and soluble guanylate cyclase (sGC) blocker (ODQ, 30 μM), and relaxation responses of cavernosal tissue were calculated before and after the incubation with Cranberry-E.

Results: Erectile responses were significantly reduced in diabetic animals as compared to controls ($p<0.001$), which was normalized after the intracavernous administration of Cranberry-E. There was no difference in the relaxation responses to Cranberry-E between the control and diabetic groups. Cranberry-E induced the relaxation of cavernosal tissue, which remained unaltered in the presence of L-NAME and ODQ. Relaxation responses to Cranberry decreased after KCl-induced precontraction ($p<0.001$). The relaxation of cavernosal tissue increased after Cranberry-E incubation.

Conclusion: Cranberry-E improved diabetes-induced ED and induced relaxation of cavernosal tissue via a nitric oxide-independent mechanism. Thus, cranberry consumption is likely to be effective as a potential strategy to prevent diabetes-induced ED.

Keywords: Cranberry-E, Corpus cavernosum, diabetes, erectile function, ericaceae, *Vaccinium oxycoccos* L.

INTRODUCTION

Diabetes is a significant reason for erectile dysfunction (ED), negatively affecting quality of life (Mazzilli et al., 2015). ED is observed at a younger age and more frequently in the diabetic population compared to the general population (Johannes et al., 2000). Multifactorial mechanisms play a role in diabetic ED with a weak response to oral phosphodiesterase type 5 (PDE-5) inhibitors (Ruan et al., 2016). Plant and plant-derived drugs have long been investigated in treating ED patients (Shin et al., 2015; Stasiak, Zarlok, & Tomaszewski, 2016). The widespread plant-based options for ED are *Epimedium sagitatum, Pausynstalia yohimbe, Eurycoma longifolia, Panax ginseng, Tribulus terrestris*, and *Gingko biloba* (Karakaya et al., 2019; Shin et al., 2015; Petre et al., 2023). Alternative or complementary therapies for diabetic ED may be referred to as herbal medicines or phytomedicines.

Plant-based compounds can help to treat or prevent atherosclerosis, hypertension, cancer, and infectious diseases (such as gastric mucosa, urinary tract, and oral cavity infections) through their potential activities regarding antioxidant properties (Liska, Kern, & Maki, 2016; Olas, 2017; Vidlar et al., 2010). The berry fruits of the Ericaceae family represent essential sources of active compounds, for instance, proanthocyanidins, anthocyanins, phenolic acids, terpenes, and flavonoids (Blumberg et al., 2013). Earlier data have shown that the fruits have strong antioxidant properties and include exotic flavors (Jeszka-Skowron, Zgola-Grzeskowiak, Stanisz, & Waskiewicz, 2017; Skrovankova, Sumczynski, Mlcek, Jurikova, & Sochor, 2015). The *Vaccinium* genus includes more than 450 species in Europe, Central America, North America, Japan, Africa, Asia, and Madagascar. The most popular of these species are cranberry (*Vaccinium macrocarpon* Aiton, *Vaccinium oxycoccos* L.), bilberry (*Vaccinuim myrtillus*), blueberry (*Vaccinium angustifolium* Aiton, *Vaccinium ashei*, *Vaccinium corymbosum* L.), lingonberry (*Vaccinium vitis*) and huckleberry (*Vaccinium ovatum, Vaccinium parvifolium*). European cranberry, *Vaccinium oxycoccos* also known as “small cranberry” or “bog

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cranberry", is found in Europe, Asia, and North America (Jurikova, Skrovankova, Mlcek, Balla, & Snopek, 2018). The polyphenol-rich extract from cranberry is a potentially powerful tool to protect against obesity-induced metabolic disorders in obese mice (Anhe et al., 2015). In addition, Cranberry fruit extract (Cranberry-E) has been traditionally used to treat bladder and kidney ailments (Mojaverrostami, Bojnordi, Ghasemi-Kasman, Ebrahimzadeh, & Hamidabadi, 2018). It is the most popular herbal medicine for urinary tract infections (UTI) in the United States (Bukhari et al., 2015; Rossi, Porta, & Canovi, 2010; Yarnell, 2002). Furthermore, a prospective clinical study has shown the beneficial effects of a mix of cranberry, soy germ, pumpkin seed extract, and isoflavonoids on lower urinary tract symptoms and erectile function (Nemr et al., 2020).

In the present study, we evaluated the potential favorable effects of Cranberry-E on streptozotocin (STZ)-induced diabetic ED and in vitro relaxation responses in the penile tissue.

MATERIALS AND METHODS

Sample preparation

The sample was supplied from Spring Valley®, a dietary supplement for Urinary Tract Health. Each capsule (highly concentrated) contained 500 mg of cranberry fruit extract (*Vaccinium oxycoccos* L., European cranberry, small cranberry) that was dissolved in water (10 mL) and applied to the tissues. The stock solution concentration was 50 mg/mL.

The induction of diabetes

Sprague-Dawley rats (n=10) were divided into two groups: control and diabetic rats. In a temperature-controlled room (22±1°C), the rats were held in individual cages with food and water *ad libitum*. Diabetes was induced by a single intraperitoneal injection with STZ (50 mg/kg, i.p.) in a citrate buffer (pH:5.5). Seventy-two hours after the STZ injection, diabetes was confirmed by the assessment of blood glucose levels higher than 250 mg/dL with a glucometer (Roche Diagnostics, Indianapolis, IN). The experimental animal procedure was accepted by the Institutional Animal Care and Use Committee of Ankara University (2019-12-117).

In vivo assessment of erectile function

Eight weeks after the induction of diabetes, the intracavernosal pressure (ICP, mmHg) and the main arterial pressure (MAP, mmHg) were estimated using polyethylene-50 tubing for cannulation of the crura and carotid artery in anesthetized rats. The right crura were cannulated to measure ICP using the transducer (Statham, CA, USA) with a data acquisition system (Biopac MP 100 System). After the determination of the cavernous nerve (CN) and the major right pelvic ganglion, the CN was induced (2.5, 5, and 7.5 V, 15 Hz, 30-s pulse width) with a stainless-steel bipolar hook electrode and a square pulse stimulator (Grass Instruments, MA, USA). The measurements were repeated after intracavernosal administration of Cranberry-E (5mg/mL) in the control and diabetic rats. A rest period of 5 min. before each measurement was given in order to allow a return to baseline (Onder et al., 2019; Karakaya et al., 2019; Yilmaz et al., 2014).

In vitro organ bath studies

Following the *in vivo* studies, isolated corpus cavernosum (CC) strips (1 × 1 × 8 mm) were transferred in an organ bath under an initial isometric tension (1 g) within Krebs solution with a mixture of O_2/CO_2 (95% / 5%). The CC strips were equilibrated for 1 hour, and the solution was changed every 15 minutes. All changes in tension were recorded using an isometric force transducer connected to a computer-based data acquisition system (Biopac Systems). Cranberry-E-induced relaxant responses were obtained after precontraction with phenylephrine (Phe, 10 μM) and KCl (60 mM) (Onder et al., 2019; Salahdeen, Idowu, Yemitan, Murtala, & Alada, 2015). After precontraction with Phe (10 μM), Cranberry-E-induced relaxant responses were obtained before and after the incubation (20 min) with nitric oxide synthase (NOS) blocker, L-N(G)- nitroarginine methyl ester (L-NAME, 100 μM); soluble guanylate cyclase (sGC) blocker, 1H-[1,2,4]-oxadiazolo[4,3-a] quinoxaline-1-one (ODQ, 30 μM).

In the second series of trials, acetylcholine (ACh, 10 μM), electrical field stimulation (EFS, duration: 15 seconds, amplitude: 40 V, frequency: 10 Hz, pulse width: 5 ms) and sodium nitroprusside (SNP, 0.01 μM)-induced relaxation responses were measured before and after the incubation (20 min) with Cranberry-E (1,2 mg/mL).

Chemicals and reagents

All drugs were purchased from Sigma Chemical Co. (St. Louis, MO, USA).

Statistical analysis

All measurements were displayed as mean±standard error of the mean (SEM). Statistical differences were determined by one-way analysis of variance (ANOVA) with repeated measures followed by a Bonferroni post-test performed using Prism 4 (GraphPad Software, La Jolla, CA, USA). A p-value < 0.05 was considered to be significant.

RESULTS

Body weight and blood glucose levels in animals

The body weight in the diabetic animals declined compared to the controls (Figure 1). The blood glucose level in the diabetic rats was significantly greater than in the controls (Figure 1).

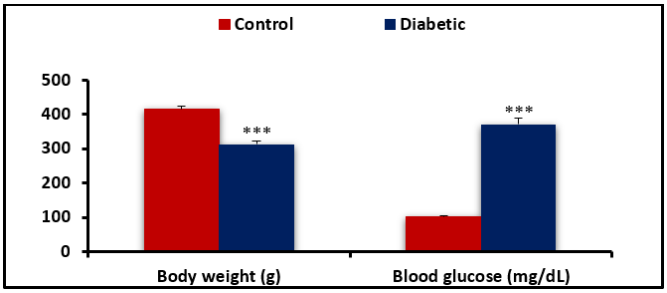

Figure 1. Body weight and blood glucose levels in the groups. Results displayed the mean ± SEM of 4-5 observations. ***p<.001 vs. controls.

Effects of intracavernosal Cranberry-E on *in vivo* erectile functions

Figure 2 shows ICP/MAP (A) and total ICP (B) values in the control and diabetic rats. *In vivo* erectile responses in the diabetic animals were less than in the controls (P<.001), which improved following intracavernosal injection of Cranberry-E (5 mg/mL) (Figure 2). Furthermore, erectile responses in the control rats increased after injection of Cranberry-E, except at 7.5V (Figure 2).

Relaxant responses of the CC strips

The maximum relaxation to Cranberry-E in the control rats was 74.4 ± 3.6%, which was not different for diabetic rats (73.3 ± 2.3%; Figure 3).

The relaxant responses to Cranberry-E were not altered after incubating with the NOS inhibitor, L-NAME (61.0 ± 5.0%, Figure 4A). In addition, ODQ (65.0 ± 4.0%) did not change the relaxation responses (Figure 4A). Cranberry-E caused 10% relaxation in the CC obtained from the control rats at 2.4 mg/mL (P <.001) after pre-contraction with KCl, which was 85% lower than after pre-contraction with Phe (Figure 4B).

The relaxant response to EFS at 10 Hz in the CC obtained from the control rats was significantly increased after incubating Cranberry-E at 1.2 mg/mL (P< .01, Figure 5). The relaxant response to ACh at 10 μM in the controls was raised in the presence of Cranberry-E at 1.2 mg/mL (P <.01, Figure 5). The relaxant response to SNP was enhanced after incubating with Cranberry-E at 1.2 mg/mL (P <.01, Figure 5).

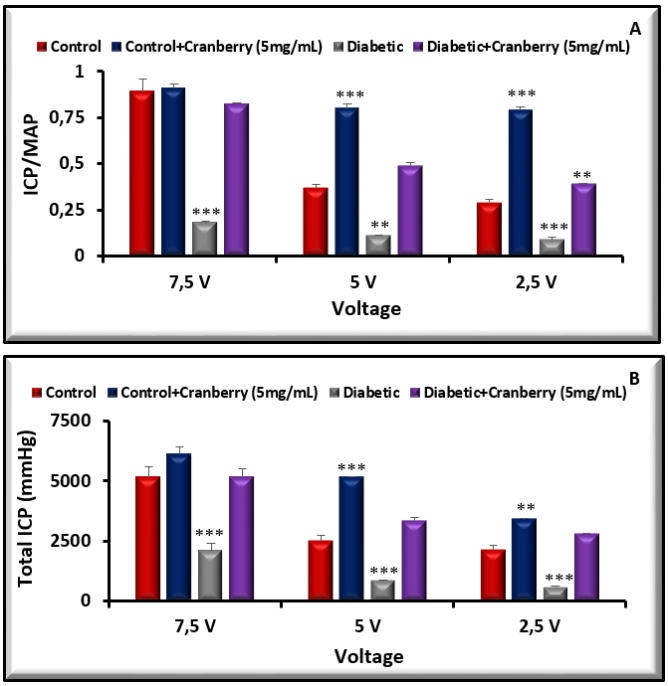

Figure 2. *In vivo* intracavernosal effect of Cranberry-E on ICP/MAP and Total ICP values in control and diabetic rats. Results displayed the mean ± SEM of 4-5 observations. **p<.01, ***p<.001 vs. corresponding controls.

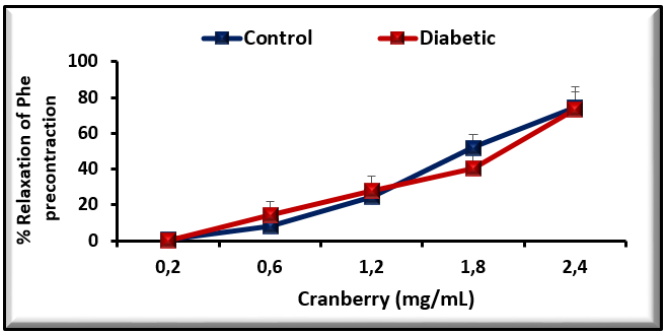

Figure 3. Concentration-response curves to Cranberry-E (0.2-2.4 mg/mL) after pre-contraction with Phe (10^{-5} M) in the control and diabetic rat CC. Data represent the mean ± SEM of 4-5 observations.

DISCUSSION

The present results exhibit that (a) Cranberry-E increases erectile function in control and diabetic rats; (b) Cranberry-E induces relaxant responses in the CC from both groups; (c) Cranberry-E-caused relaxant response is independent of NO pathway while it is likely to depend on K+ channels; (d) the relaxant responses in CC from the control animals were considerably increased after incubation with Cranberry-E.

In the present study, ICP/MAP and total ICP values in diabetic rats were diminished. Both groups' erectile responses dramatically increased after receiving cranberry intracavernosal injections. Also, we showed an increased neurogenic relaxant response in the CC from controls after cranberry incuba-

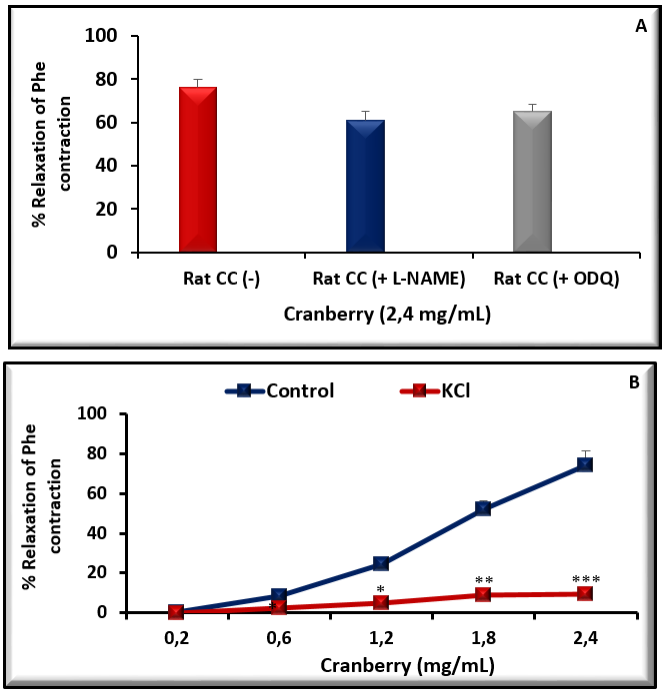

Figure 4. The bar graph shows relaxation responses to Cranberry-E at 2.4 mg/mL incubation with L-NAME (100 µM) and ODQ (30 µM) in control rat CC. Concentration-response curves to Cranberry-E (0.2-2.4 mg/mL) after pre-contraction with KCl (60mM, B) in relaxation in the CC obtained from the control rats. Data represent the mean ± SEM of 4-5 observations. *p<.05, **p<.01, ***p<.001 vs. controls.

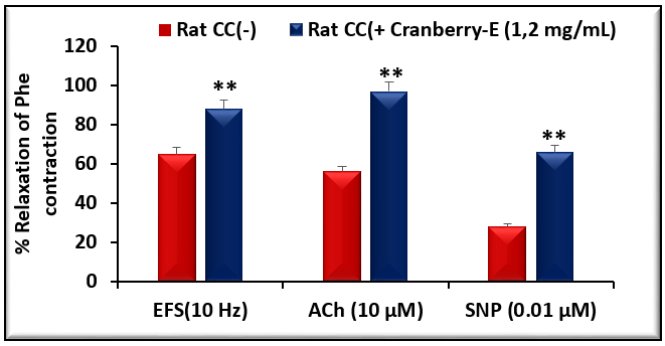

Figure 5. The bar graph shows relaxation responses to EFS (10Hz), ACh (10μM) and SNP (0.01 μM) in the absence and presence of Cranberry-E 1.2 mg/mL in the CC obtained from the control rats. Data represent the mean ± SEM of 4-5 observations. **p<.01, vs. controls.

tion. In addition, Cranberry-E relaxed both control and diabetic CC following Phe, α1-adrenergic receptor agonist-induced pre-contraction. There are no earlier studies that assess the effects of Cranberry-E on erectile function. An earlier prospective multi-center study revealed that cranberry was administered for three months and was beneficial to erectile function in men (Nemr et al., 2020). Cranberries are a rich source of polyphenols such as proanthocyanidins, phenolic acids, flavonoids and anthocyanins with antioxidant properties (Nemzer, Al-Taher, Yashin, Revelsky, & Yashin, 2022). Previous clinical trials displayed that the consumption of cranberry considerably decreased glycated hemoglobin and fasting blood glucose levels. Cranberry consumption also changed oxidative stress and proinflammatory markers in patients with diabetes and obesity (Delpino, Figueiredo, Goncalves da Silva, & Flores, 2022; Hsia, Zhang, Beyl, Greenway, & Khoo, 2020). Furthermore, Shukitt-Hale et al. demonstrated that 16 weeks of cranberry supplementation improved motor functions, neural function, and neuroprotective responses in aged rats (Shukitt-Hale et al., 2005). According to the available research, cranberries can treat oxidative stress from hyperglycemia, reducing diabetes-related ED.

The current results show that cranberry caused relaxation independent of the NO-cGMP pathway. The relaxing mechanism of cranberries in the cavernosal smooth muscle has not been studied previously. However, a conflicting result indicated that cranberry juice induced vasodilation in rat aorta, and the relaxant response was inhibited after incubating with L-NAME (Maher, Mataczynski, Stefaniak, & Wilson, 2000). In our study, pre-contraction of the cavernosal tissues with 60 mmol KCl significantly decreased cranberry-induced relaxations compared to pre-contraction with Phe. The contraction induced by KCl is generated due to membrane depolarization (Ebeigbe & Aloamaka, 1987). Our findings show that high K+ concentration inhibited the relaxation response induced by cranberry in rat cavernosal tissue suggesting that K+ conductance channels are probably responsible for this reduction. Based on the current result, understanding the relaxant mechanisms of cranberry in the penile erection mechanism is necessary for additional research.

Our findings show that Cranberry-E incubation boosted the isolated CC from the control group's endothelium-dependent ACh and endothelium-independent SNP relaxant responses. Additionally, in the porcine coronary artery, juice from various berries can cause endothelium-dependent relaxations involving endothelium-derived NO and endothelium-derived hyperpolarizing factors (Auger et al., 2011). Similarly, earlier data demonstrated that Cranberry juice enhanced endothelium-dependent relaxation in the aorta from ovariectomized rats via repairing endothelial NO synthase (Yung et al., 2013).

CONCLUSION

According to the present research, cranberries may have an impact on diabetes-related ED that is independent of the NO/sGC/cGMP pathway. Additionally, our *in vivo* and *in vitro* investigations suggest that consuming Cranberry-E may be appropriate and result in an alluring novel technique for avoiding and treating ED in diabetic male patients.

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