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ARTICLE

Restorative effects of red onion (*Allium cepa* L.) juice on erectile function after-treatment with 5α-reductase inhibitor in rats

Didem Yilmaz-Oral[1] · Alev Onder[2] · Ecem Kaya-Sezginer[3] · Cetin Volkan Oztekin[4] · Murat Zor[5] · Serap Gur[6]

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Abstract

Benign prostatic hyperplasia (BPH) is one of the most prevalent conditions among aged men. The use of 5α-reductase inhibitors (5-ARIs) to treat BPH was linked to erectile dysfunction (ED). Many medicinal plants and secondary metabolites are used in the management of ED. Onion (*Allium cepa* L.) is an economically affordable vegetable with vital phytochemicals and biological functions. The study aimed to identify the beneficial effects of onion juice on dutasteride (a 5-ARI)-induced ED. Rats were divided into two groups ($n = 5$ per group): control and dutasteride-treated rats (0.5 mg/kg/day). Dutasteride was administered in drinking water for 12 weeks. Experiments were performed at the end of the 12th week. In vivo erectile responses were measured before and after intracavernosal injection of onion. Relaxant responses to onion juice were examined in the corpus cavernosum (CC). Acetylcholine (ACh)-, electrical field stimulation (EFS)-, sodium nitroprusside (SNP)-induced relaxation responses in CC tissues were evaluated in the absence and presence of onion juice. Total intracavernosal pressure (ICP) and ICP/ mean arterial pressure were significantly reduced in dutasteride-treated rats (1881.14 ± 249.72 mmHg, $P < 0.001$;0.26 ± 0.03, $P < 0.01$) as compared to control rats (4542.60 ± 429.19 mmHg, 0.51 ± 0.05), which was normalized after the intracavernous administration of onion (3288.60 ± 185.45 mmHg, 0.58 ± 0.04). Onion markedly induced relaxant responses in control (72.5 ± 4.7) and dutasteride-treated (66.5 ± 2.7) groups after precontraction with phenylephrine. Relaxation responses to onion were partially inhibited after precontraction with KCl (32.5 ± 3.1, $P < 0.001$). The relaxant responses to ACh (14.9 ± 4.2, $P < 0.01$) were diminished in dutasteride-treated CC) compared to control CC (59.8 ± 3.4), which was enhanced after the incubation with onion (36.6 ± 4.8). There were no differences in relaxation response to SNP among all groups. However, relaxation response to SNP was reduced in dutasteride-treated CC at 1 μM ($P < 0.05$) and 10 μM dosages ($P < 0.001$), which was partially increased after the incubation with onion at 10 μM dosage ($P < 0.01$). The presence of onion did not change the reduction in EFS-caused relaxation in the dutasteride-treated group. The current data suggest that red onion juice has a restorative effect on erectile function and endothelium-dependent relaxation response following the treatment of dutasteride.

Introduction

Benign prostatic hyperplasia (BPH) is a common problem that influences 75% of males over 50 years of age [1, 2]. Lower urinary tract symptoms (LUTS) are mostly associated with BPH, which is related to a decline in the quality of life [3].

The 5α-reductase inhibitors (5-ARIs) such as dutasteride are frequently prescribed for patients with BPH [4, 5]. Dutasteride inhibits two isoforms of 5-AR enzymes which convert testosterone to dihydrotestosterone (DHT) [6]. It is known that a decrease in DHT levels is related to prostatic volume reduction [7]. However, it is reported by controlled studies and meta-analyses that 5-ARIs cause sexual adverse effects, including erectile dysfunction (ED) [8–10]. Previous studies indicated that the treatment with dutasteride caused

✉ Serap Gur
serapgur@ankara.edu.tr

1 Department of Pharmacology, Faculty of Pharmacy, Cukurova University, Adana, Turkey

2 Department of Pharmacognosy, Faculty of Pharmacy, Ankara University, Ankara, Turkey

3 Department of Biochemistry, Faculty of Pharmacy, Ankara University, Ankara, Turkey

4 Department of Urology, Faculty of Medicine, University of Kyrenia, Girne-TRNC, Mersin 10, Turkey

5 Department of Pharmacognosy, Faculty of Pharmacy, Lokman Hekim University, Ankara, Turkey

6 Department of Pharmacology, Faculty of Pharmacy, Ankara University, Ankara, Turkey

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persistent and irreversible ED in rats, even after discontinuation of dutasteride [11, 12]. On the contrary, herbal formulations or plant-based non-nutritive compounds are being popularized globally for BPH treatment [13]. Milder side effects of phytotherapeutic supplements and adverse effects of pharmacological therapy were reported [14]. In the USA and Europe, ~50% of patients with BPH use phytotherapeutic drugs alone or with pharmacologic drugs to treat BPH [15, 16]. Phytotherapeutic supplements, including Serenoa repens, Pygeum africanum, Cinnamomi cortex, Asteris Radix et Rhizoma, and Pao Pereira Extract have been evaluated as complementary treatments for the management of BPH in preclinical and clinical trials [17–21]. Thus, phytotherapeutic supplements may alternatively be an essential approach in the treatment of BPH as well as BPH-induced ED.

Allium genus from the Amaryllidaceae family includes ~500–660 species originally native to central Asia, Africa, and South America [22]. In ancient medical texts, it was mentioned as the oldest cultivated plant in the world for its therapeutic benefits, cited by the Roman naturalist Pliny, the Elder in his "Historia Naturalis" [22, 23]. It is also an essential food in the traditional diet used for many aims, such as nutrition, flavoring, condiment, and the treatment of many diseases [24]. Among the onion species, red onion (*Allium cepa* L.), includes polyphenols, flavonoids (quercetin and kaempferol) [25], tannins [26], and anthocyanins [27]. In addition, red onion has critical positive effects on oxidative stress-related diseases due to potent antioxidant activity [25, 28]. Furthermore, a previous study demonstrated that methanolic extract of red onion had a protective effect on atypical prostatic hyperplasia in rats via anti-inflammatory and immunomodulatory effects [29]. On the other hand, quercetin showed a synergistic effect with finasteride to decrease prostate weight via a cell cycle deregulation, which may be androgen-independent [30]. Moreover, medieval Persian practitioners suggested that foods with well-balanced diet help heal ED, including *Allium cepa* L [31]. Previous studies indicated that fresh onion juice and onion bulb ethyl acetate extract ameliorated sexual behavior in paroxetine-induced sexual dysfunction in male rats via enhancing serum testosterone levels [32, 33]. FRS 1000, a beverage containing flavonoids extracted from onion peel, inhibited the activity of phosphodiesterase 5 A (PDE5A) enzyme in in vitro enzyme assay [34]. In this study, we aimed to investigate the effects of fresh red onion juice on ED after 12 weeks of dutasteride treatment.

Materials and methods

Collection and preparation of onion juice

Red onions (*Allium cepa* L) were purchased from a domestic market in Turkey. The sample was used directly in its fresh form. The red onion juice was obtained after removing the onion peels. The juice of *Allium cepa* has been prepared by the grating of onion (173.94 g), then by filtering the shredded portion. 30.5 mL of the onion juices represented 30.92 g of onion.

Animal studies

Adult male Sprague-Dawley rats (10 weeks old, average weight: 334.2 g) were obtained from Bilkent University, Department of Molecular Biology and Genetics (Ankara, Turkey) and divided into 2 groups. Group 1: control ($n = 5$) and group 2: 12wk dutasteride ($n = 5$). Dutasteride was delivered to the rats in drinking water (0.5 mg/rat/day). The in vivo studies were executed at the end of the 12th week. All study protocol was approved by the Ethics Committee of Ankara University (approval no: 2018–22-139). Rats were housed in separate cages and provided with food and water ad libitum in a temperature-controlled room (22 ± 1 °C) that was artificially lit from 7:00 a.m. to 7:00 p.m. daily. The weights of all animals were measured using a precision scale. Prostate tissues of all rats were excised and weighted by an electronic scale.

In vivo evaluation of erectile response

After 12 weeks of dutasteride treatment, intracavernosal pressure (ICP) was measured in anesthetized rats (ketamine/xylazine [100/10 mg/kg], i.p.) [35]. The polyethylene-50 tubing was inserted into the carotid artery to determine to mean arterial pressure (MAP) with a transducer (Statham, Oxnard, CA) and a data acquisition system (Biopac MP 100 System, Santa Barbara, CA). The right crura of the penis was cannulated with a 25-G needle filled with 250 U/mL heparin and connected to the PE-50 tubing and a pressure transducer to measure ICP. Intracavernosal injection of onion juice was performed using the heparin-filled 25-G needle placed in the right crura. 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) using a stainless steel bipolar hook electrode and a square pulse stimulator (Grass Instruments, Quincy, MA). The assessments were repeated following intracavernosal administration of onion juice in dutasteride-treated rats. All injections were administered in a total volume of 200 µL, and a washout period of 15–30 min was observed between injections.

In vitro studies

After in vivo experiments, anesthetized rats were euthanized by cardiac exsanguination under anesthesia.

Isolated cavernosal strips (1 × 1 × 8 mm) were located in an organ bath (20 ml) including Krebs solution (NaCl: 118.1, KCl: 4.7, NaHCO3: 25.0, MgSO4: 1.0, CaCl2: 2.5, KH2PO4: 1.0, and glucose: 11.1 mM, pH: 7.4, 37 °C) and constantly bubbled with a mixture of O_2/CO_2 (95 % /5 %). Electrical field stimulation (EFS, duration: 15 seconds, amplitude: 40 V, frequency: 1–20 Hz, pulse width: 5 ms) of nerves was performed via platinum electrodes, placed on either side of the corpus cavernosum (CC) strip. All tension changes were recorded with an isometric force transducer connected to a PC-based data acquisition system (Biopac System, St. Barbara, CA, USA) [36]. Following the equilibration period (1 h), concentration-response curves to onion juice (25–500 µL) were obtained after precontraction with Phe (10 µM) and KCl (60 mM) in CC strips in the first series of experiments.

In the second series of experiments, acetylcholine (ACh, 10^{-8}-10^{-3} M), EFS (1- 20 Hz) and sodium nitroprusside (SNP, 10^{-8}-10^{-4} M)-induced relaxation responses were evoked after precontraction of CC strips in the presence or absence of onion juice (100 µL).

Data analysis

All results have been displayed as mean ± SEM. Statistical differences were evaluated via one-way analysis of variance (ANOVA) and Bonferroni post hoc test (GraphPad Software, La Jolla, CA, USA). A p-value less than 0.05 was regarded as statistically significant.

Results

Body and prostate weight in rats

The body weight in dutasteride treated rats (480.6 ± 19.6 g) was not altered when compared with controls (418.3 ± 13.6 g). Prostate weight in the dutasteride treatment group (0.68 ± 0.02 g, $P < 0.01$) was considerably lower than in controls (1.01 ± 0.05 g).

Effects of intracavernosal onion administration on in vivo erectile responses

Erectile responses were reduced in dutasteride treated rats ($P < 0.001$; Fig. 1A, B). Following intracavernosal onion injection, an increase in the ICP/MAP and the total ICP values was observed in rats treated with dutasteride (Fig. 1A, B). Surprisingly, the ICP/MAP levels at 5 V (Fig. 1A) but not total ICP (Fig. 1B) were significantly increased following intracavernosal injection of onion ($P < 0.01$, Fig. 1A, B).

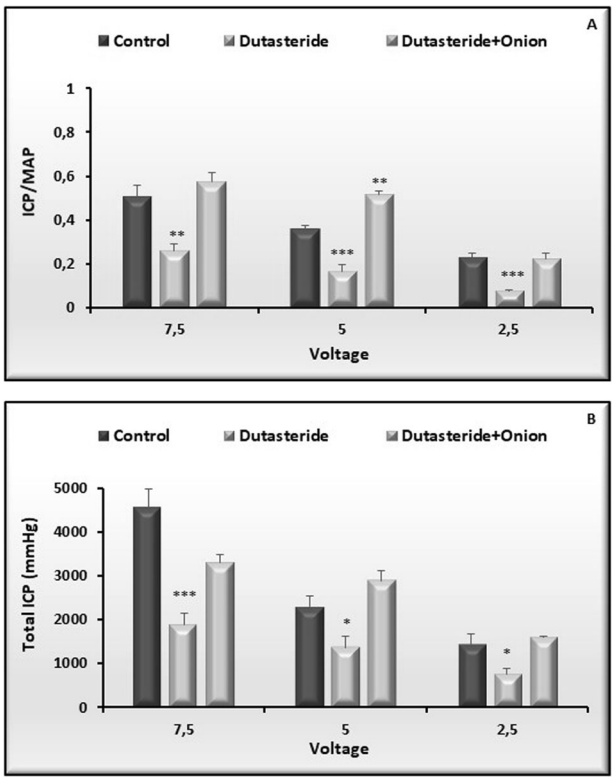

Fig. 1 In vivo intracavernosal effect of onion on the erectile response. A the ratio of ICP to MAP and **B** total ICP after cavernosal nerve stimulation in control and dutasteride treated rats. Data represent the mean ± SEM of 5 observations. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs control value.

In vitro relaxant responses in isolated penile tissues

The maximum relaxant response to onion in isolated cavernosal tissue obtained from control rats was 72.5 ± 4.7%, which was not altered in CC from dutasteride-treated rats (66.5 ± 2.5 %, Fig. 2A). Onion induced 32.6 ± 3.1 % ($P < 0.001$) relaxation following KCl-caused pre-contraction, which was 55% less than following Phe-caused pre-contraction (Fig. 2B).

The endothelium-dependent relaxation response to ACh in dutasteride-treated rats was lower than in controls ($P < 0.01$), which was enhanced in the presence of onion (100 µL), except at 1 µM ($P < 0.05$) and 10 µM dosages ($P < 0.01$, Fig. 3A).

The relaxant response to EFS was significantly reduced in dutasteride treated rats ($P < 0.01$, Fig. 3B). There were no differences in EFS-caused relaxation responses between the absence and presence of onion (Fig. 3B).

There were not any differences in the maximum relaxation responses to SNP among all groups (Fig. 3C). However, relaxation response to SNP was decreased in dutasteride-treated cavernosal tissue at 1 µM ($P < 0.05$) and 10 µM dosages ($P < 0.001$, Fig. 3C). In addition, the

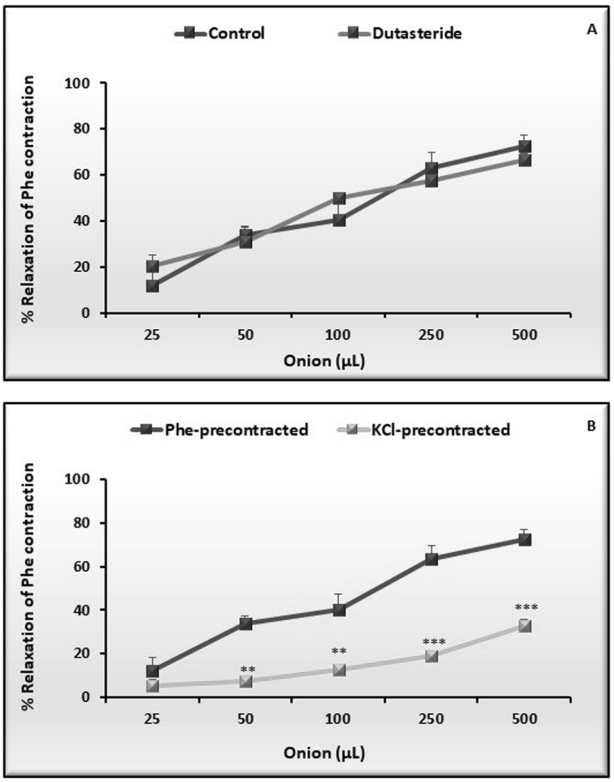

Fig. 2 Dose-response relaxation curves to onion in the CC. Concentration-response curves for onion after precontraction with Phe (**A**) and KCl (**B**). Data represent the mean ± SEM of 5 observations. $^{**}P < 0.01$, $^{***}P < 0.001$ vs control value.

incubation with onion partially improved at 10 µM dosage ($P < 0.01$, Fig. 3C).

Discussion

To our knowledge, this is the first study to examine the effects of *Allium cepa* L. (Red onion juice) on erectile function in dutasteride-treated rats. Onion juice induced a remarkable relaxation response in the CC obtained from all groups. In addition, the neurogenic, endothelium-dependent and -independent relaxant responses in CC from dutasteride treated rats were significantly decreased, and importantly, the endothelium-dependent and independent relaxation responses but not nitrergic responses were improved after the incubation with onion.

Our data showed that dutasteride treatment for 12 weeks reduced in vivo erectile response of rats. Similarly, previous data showed a reduction of erectile responses after 4 and 8 weeks of dutasteride treatment compared to control rats [11, 12, 37]. Furthermore, this decrease did not improve after the washout period [11, 12]. Interestingly, erectile responses (ICP/MAP and total ICP) in the presence of intracavernosal onion were enhanced in the dutasteride-treated group. There are no previous data regarding the effects of onion on erectile function. Besides, earlier studies showed that oral treatment with fresh *Allium cepa* L. juice improved sexual behavior and enhanced serum testosterone levels in paroxetine-treated rats [33]. Furthermore, in paroxetine-treated male rats, the treatment with onion bulb ethyl acetate extract recovered sexual behavior [32]. It is in fact that onions include a complex of sulfur compounds [38]. Therefore, in a previous report, Valle et al. implied that onions are likely to be a natural source of hydrogen sulfide (H_2S) that is a gasotransmitter like nitric oxide (NO) and induces relaxation in cavernosal tissue [38]. In our recent research, the combination treatment with H_2S donor and PDE5 inhibitor had positive impacts on erectile function via the improvement of ischemia-caused morphological and functional penile changes in the obstruction [39]. We suggested that H_2S and NO are likely to have a synergistic role in the modulation of erectile function and may have beneficial effects on clinical outcomes in men with ED and BPH/LUTS [39]. In another study, Lines et al. showed the inhibition of PDE5A enzyme by FRS 1000, an extract of onion peel [34]. This inhibitory effect of onion can be related to its sulfur-containing compounds. Previous studies demonstrated a similar inhibitor effect of H_2S donors on PDE5 enzyme in aorta smooth muscle and endothelial cells [40, 41]. These data may contribute to further research on the usage of onion as a food and/or dietary supplement in order to ameliorate erectile function in traditional medicine.

We showed that onion remarkably relaxed control and dutasteride treated rat CC in a dose-dependent manner after pre-contraction with Phe. In the present study, onion induced 33% relaxation in the isolated CC following KCl pre-contraction. The maximum relaxant response to onion after KCl pre-contraction was lower than that after Phe pre-contraction. The contractile response to KCl is created as a result of membrane depolarization [42]. According to our data, high K^+ inhibited onion-caused relaxant responses in rat CC, suggesting the decrease in onion-induced relaxation may be mediated via K^+ conductance channels. In addition, previous data showed a reduction in onion peel hydroalcoholic extract-induced relaxation in rat thoracic aorta after KCl-caused pre-contraction [43]. Furthermore, a substitute of quercetin, that is one of the major constituents in onion caused vasorelaxations in rat resistance arteries via K^+ channel opening in smooth muscle cells [44]. We suggest that the underlying mechanism of onion in smooth muscle relaxation may be mediated through activating K^+ channels. In a previous publication, H_2S affects several signaling pathways such as K_{ATP}, T-type Ca^{2+} [45], L-type Ca^{2+} [46], transient receptor potential ankyrin-1 channels [47, 48]. Based on previous studies, understanding the relaxant

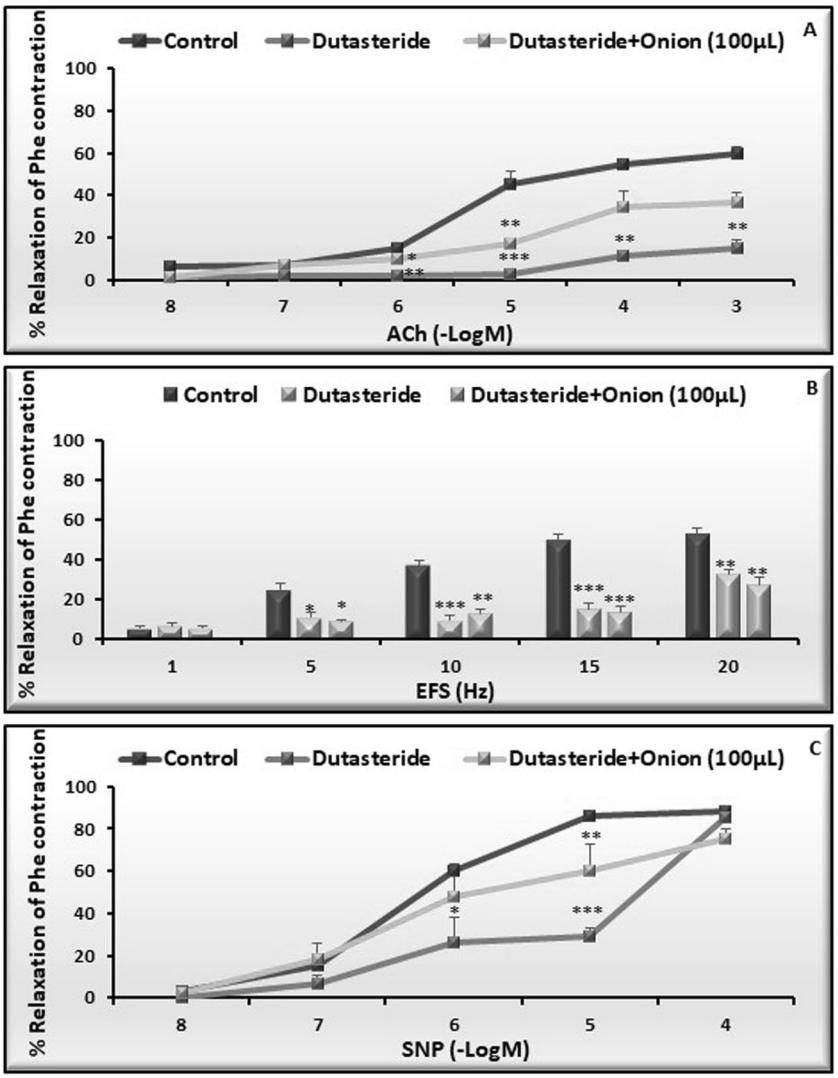

Fig. 3 Dose-response relaxation curves in the absence or presence of onion. Concentration-response curves to ACh (10^{-8}-10^{-3}M), (**A**), EFS (1–20 Hz), (**B**), and SNP (10^{-8}-10^{-4}M), (**C**) in the absence or presence of red onion (100 µL). Data represent mean ± SEM of 5 observations. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs control value.

mechanisms of onion in cavernosal tissue is required in further investigations.

In cavernosal tissues from dutasteride treated rats, endothelium-dependent relaxation response to ACh, endothelium-independent relaxation response to SNP as well as neurogenic relaxant response to EFS were markedly reduced as compared to untreated-control rats. Also, a reduction in endothelial and neurogenic relaxant responses in isolated CC after dutasteride treatment was shown in previous studies [12, 37]. According to our data, the incubation with onion enhanced ACh and SNP-induced relaxation responses in the isolated CC from the dutasteride treatment group, but not EFS-induced relaxation response. The onion-induced vasodilator responses may have multiple mechanisms. A previous study showed that Welsh onion extract caused the endothelium-dependent vasodilation in rat aorta via NO and cyclic guanosine monophosphate (cGMP) [49]. However, González-Peña et al. demonstrated that onion (*Allium cepa* L.) diet improved endothelial vasorelaxation in a NO/cGMP-independent manner since onion diet did not increase SNP-induced relaxation in mesenteric arteries from high-cholesterol enriched diet-fed rat [50]. Furthermore, quercetin treatment enhanced ACh-caused relaxation response in aorta from hypertensive rats, but not SNP-caused relaxation [51]. Also, treatment with quercetin decreased acetylcholinesterase and oxidative stress in penile tissues obtained from paroxetine-treated rats [52]. The incubation with quercetin markedly attenuated high glucose-induced deficits in ACh- and EFS-caused relaxation responses in mice CC [53]. On the other hand, quercetin did not change ACh-, EFS- and SNP-induced relaxations in control mice cavernosal tissues [54]. The beneficial effect of onion juice on erectile function in rats after treatment with dutasteride is likely to associate with improved endothelial function.

Among the species of onions, the red onion is an important one because of its abundance in several activated

phytomolecules such as polyphenols, flavonoids, flavonol [26, 55]. Various preclinical studies exhibited that treatment with oral onion juice or its extracts achieved therapeutic effects on sexual function [32, 33] and prostate weight in rats with atypical prostatic hyperplasia [29]. In addition, a previous clinical study showed that onion extract treatment (30 mg/kg, orally) had a positive effect on testosterone levels in healthy men [56]. In light of these data, onion dietary supplement most probably has beneficial effects on erectile function and BPH. In addition to these results, onion juice inhibited CYP3A4 enzyme activity [57] which is responsible for the metabolism of dutasteride [58] and the deactivation of testosterone [59]. However, the net effect of red onion extract supplementation on the efficacy of 5 ARIs in BPH treatment is yet to be understood, as CYP3A4 inhibition may theoretically cause increases in activity of both 5 ARIs and testosterone, which have potentially opposing effects. Moreover, it should be kept in mind that 5ARIs exert their therapeutic activity by minimizing the levels of DHT, not testosterone. Taking these results together, research on the physiological effects of red onion in BPH patients treated with 5ARIs is warranted to understand the overall impact of CYP3A4 inhibition on activities of 5ARIs and testosterone, and the resulting clinical outcome.

The current study also showed the potential of red onion juice to improve ED associated with 5-ARI treatment. The red onion juice increased erectile responses and caused the relaxation of the CC in dutasteride treated rats. Further studies are required to examine the restorative potential of the active constituents of red onion.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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