



# Oral Testofen, L-Citrulline, Resveratrol, and Caffeine Supplement Drink Improves Sexual Function in Men with Phosphodiesterase 5 Inhibitors: Randomized, Double-Blind, Placebo-Controlled Crossover Pilot Study

Masato Shirai<sup>1</sup>, Yuto Miyoshi<sup>1,2</sup>, Taiki Ogasa<sup>1,2</sup>, Miho Miyoshi<sup>1,2</sup>, Keisuke Ishikawa<sup>1,2</sup>,  
Ippei Hiramatsu<sup>1,2</sup>, Yuka Uesaka<sup>1</sup>, Taiji Nozaki<sup>1</sup>, Taro Koyama<sup>3</sup>, Akira Tsujimura<sup>1</sup>

<sup>1</sup>Department of Urology, Juntendo University Urayasu Hospital, Chiba, <sup>2</sup>Department of Urology, Juntendo University, Graduate School of Medicine, <sup>3</sup>D Clinic Tokyo Men's, Tokyo, Japan

**Purpose:** Sexuality is very important for men's health. Currently, phosphodiesterase type 5 inhibitors (PDE5i) remain the first-line therapy for erectile dysfunction, and no other oral drugs or drinks are approved and used clinically to treat male libido or orgasm dysfunction. In reference to a pharmaceutical dosage document, growing health consciousness is said to have boosted yearly sales of supplement drinks to more than 170 billion yen (1.58 billion US dollars) in Japan. We have created a supplement drink comprised of testofen, L-citrulline, resveratrol, and caffeine. We hypothesized that our supplement drink would be effective for men with sexual dysfunction, and especially libido dysfunction.

**Materials and Methods:** In this study, men with sexual dysfunction received a placebo drink for 14 days or our supplement drink (testofen, 600 mg/d; L-citrulline, 800 mg/d; resveratrol, 300 mg/d; and caffeine, 40 mg/d) for another 14 days separated by a 7-day washout period. Patients continued on-demand use of PDE5i. The International Index of Erectile Function (IIEF) score and adverse events were assessed.

**Results:** Twenty patients aged 30–47 years old were enrolled in and concluded the study with no adverse events experienced. The IIEF domains of desire frequency, erection frequency, erection firmness, erection confidence, intercourse satisfaction, ejaculation frequency, orgasm frequency, and overall satisfaction were significantly improved with our supplement drink.

**Conclusions:** This is the first study to show that our supplement drink may not only be effective for erection but also for libido, orgasm, and ejaculation.

**Keywords:** Caffeine; Citrulline; Resveratrol; Sexual dysfunction, physiological; Trigonella

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**Correspondence to:** Akira Tsujimura  <https://orcid.org/0000-0002-3821-5184>

Department of Urology, Juntendo University Urayasu Hospital, 2-1-1 Tomioka, Urayasu, Chiba 279-0021, Japan.

**Tel:** +81-47-353-3111, **Fax:** +81-47-353-6511, **E-mail:** [atsujimu@juntendo.ac.jp](mailto:atsujimu@juntendo.ac.jp)

## INTRODUCTION

Sexuality is very important for men's health [1]. Men with erectile dysfunction (ED) report low rates of quality of life [1]. Thus, treatment for ED is very important for improved quality of life. Libido dysfunction and orgasmic dysfunction are also important aspects of men's quality of life. In general, treatment for male libido dysfunction or orgasmic dysfunction is challenging. In the treatment of female libido dysfunction, flibanserin is the only approved oral drug [2]. Testosterone replacement therapy (TRT) is the only approved medical treatment that improves libido in hypogonadal men with sexual dysfunction [3]. However, men with sexual dysfunction and normal testosterone levels should not be offered TRT [4]. Additionally, in the treatment of male libido or orgasm dysfunction, no oral drugs or drinks are approved and used clinically. Currently, vacuum erection devices, intracavernous injections, and surgical penile prosthesis implantation are appropriate treatments for ED [5] if phosphodiesterase type 5 inhibitors (PDE5i) are not effective. However, as very few Japanese patients choose these therapies [6], it is extremely important that sexual function be improved by oral administration of effective agents.

Testofen is a specialized extract from *Trigonella foenum-graecum* seeds that reduces age-related symptoms in healthy aging males [7]. Significant androgenic activity in men is achieved with Testofen supplementation [8] through its increase of testosterone and free testosterone levels [9].

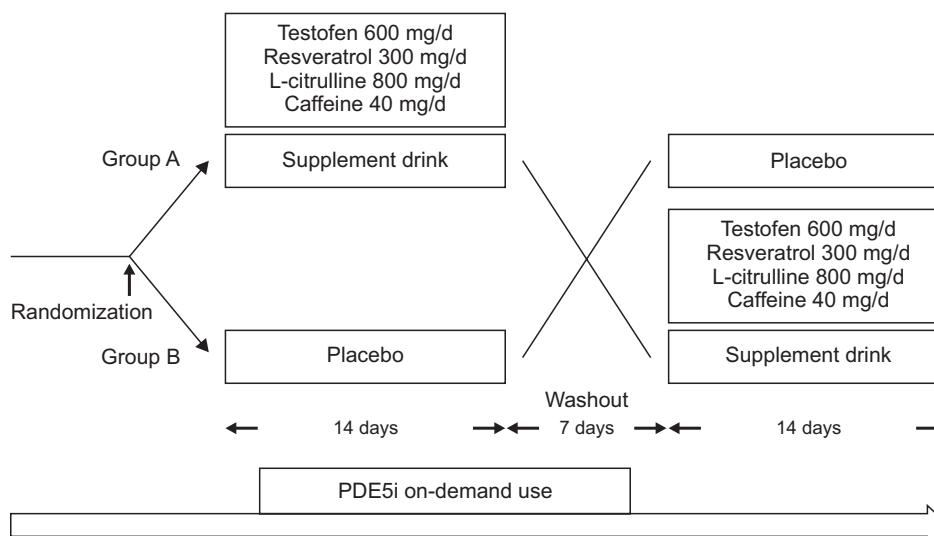
Caffeine is an alkaloid present in the everyday diet,

such as coffee and tea. It is a nonselective phosphodiesterase inhibitor that raises the levels of intracellular cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate [10]. Caffeine improved sexual function in animal studies [11], but few such studies have been fully performed on humans with sexual dysfunction.

We showed that combination therapy with an L-citrulline and resveratrol capsule with on-demand use of PDE5i is effective in ED patients [12]. In reference to a pharmaceutical dosage document, growing health consciousness is said to have boosted yearly sales of supplement drinks to more than 170 billion yen (1.58 billion US dollars) in Japan [13]. We have created a supplement drink containing testofen, L-citrulline, resveratrol, and caffeine. We hypothesized that our supplement drink would be effective for patients with sexual dysfunction and especially libido dysfunction. Therefore, we investigated the efficacy of our supplement drink in improving male sexual function.

## MATERIALS AND METHODS

We recruited 20 patients who visited our clinics specializing in sexual function to participate in this randomized, double-blind, placebo-controlled crossover pilot study. Men with sexual dysfunction (International Index of Erectile Function [IIEF]-Erectile Function score <25 and IIEF-11 (desire frequency) and IIEF-12 (desire level) scores of <3) despite their on-demand use of PDE5i received a placebo drink for 14 days or our supplement drink (testofen 600 mg/d, L-citrulline 800



**Fig. 1.** Study protocol. Men with sexual dysfunction drank a placebo drink for 14 days or the active drink for another 14 days followed by a 7-day washout period before crossover to the other drink. The patients continued their on-demand use of phosphodiesterase type 5 inhibitors (PDE5i) throughout the study. Group A: received supplementation first, Group B: received placebo first.

mg/d, resveratrol 300 mg/d, and caffeine 40 mg/d) for another 14 days, separated by a 7-day washout period. The patients continued their on-demand use of PDE5i (Fig. 1). The 50-mL supplement drink or 50-mL placebo drink was drunk once daily after a meal. The patients were randomly divided into two groups (A group, men receiving the supplement drink first; and B group, men receiving the placebo first). Randomization was centralized at Juntendo University Urayasu Hospital and performed by a simple randomization method using a computed random number table. The supplement and placebo drinks were prepared by Angfa, Inc. (Tokyo, Japan).

The testofen, L-citrulline, resveratrol, and caffeine at the above-mentioned doses were mixed with diluting water and a sweetener, a flavoring agent, and a stabilizing agent. The four active agents were not added to the placebo drink. The exclusion criteria in this study were patients who underwent radical prostatectomy and those allergic to chickpeas.

We evaluated sexual function with the IIEF and erection hardness score (EHS). Both measures have been validated as tools for the assessment of sexual function [14,15]. Japanese versions of both questionnaires have been validated [6]. The self-reported questionnaires were collected from the participants in the clinic. Because our supplement drink was commercially prepared, a medical doctor evaluated all patients to assess their medical condition and adverse events without performing blood tests.

### 1. Main outcome measures

The main outcome measures were improvement of the IIEF total score and libido (IIEF-11 [desire frequency] score and IIEF-12 [desire level] score).

### 2. Secondary outcome measures

The secondary outcome measures were improvement of erection (IIEF-1, -2, -3, -4, -5, and -15), orgasm (IIEF-9 and -10), intercourse satisfaction (IIEF-6, -7, and -8), and overall satisfaction (IIEF-13 and -14).

### 3. Ethics statement and informed consent

The study protocol complied with Good Clinical Practices, the Declaration of Helsinki (2013), and applicable Institutional Review Board regulations. The protocol was registered in the University Hospital Medical Information-Clinical Trials Registration (UMIN number:

UMIN000028816). The Institutional Review Board of the Juntendo University Urayasu Hospital approved the protocol (approval number: 30-007). Informed consent was obtained from the study participants prior to beginning any of the study-related procedures or medications.

### 4. Statistical analysis

Data are presented as the mean±standard error. A repeated measure analysis of variance was used to determine statistical significance. A p-value of <0.05 was considered to indicate statistical significance. Statistical analysis was performed with IBM SPSS Statistics for Macintosh, Japanese ver. 25 (IBM Japan, Tokyo, Japan).

## RESULTS

Twenty men aged 30–47 years (40.0±1.3 years) were enrolled in the study and began treatment (Table 1), and all 20 men completed the study without experiencing any adverse events (group A, n=10; group B, n=10). The number of men with ED overlap using on-demand PDE5i included 17 men using sildenafil, 7 men using tadalafil, and 2 men using vardenafil (Table 1). None of the men with ED used tadalafil once daily for lower urinary tract symptoms (LUTS).

The mean IIEF total score of the men taking our supplement drink was significantly greater than the baseline score and that of the men taking the placebo drink (p<0.001, p=0.025, respectively) (Table 2).

In the domains of IIEF-1, -2, -7, -9, -10, -13, and -15, the mean scores with our supplement drink increased significantly compared with those at baseline and with

Table 1. Patient demographics at baseline

Variable	Group A (n=10)	Group B (n=10)	p-value
Age (y)	40.40±1.89	39.60±1.83	0.77
IIEF total	19.10±1.94	21.20±1.32	0.83
EHS	2.00±0.15	2.40±0.27	0.21
Duration of ED (mo)	14.68±7.54	49.79±17.67	0.14
On-demand PDE5i (S/T/V)	8/2/0	9/5/2	-

Values are presented as mean±standard error or number only. Group A: received supplementation first, Group B: received placebo first, IIEF: International Index of Erectile Function, EHS: erection hardness score, ED: erectile dysfunction, PDE5i: phosphodiesterase type 5 inhibitor, S: sildenafil, T: tadalafil, V: vardenafil.

**Table 2.** Assessment of the IIEF domains in baseline, placebo, and supplement drink groups

Variable	Baseline	Placebo	Supplement drink
IIEF total	20.15±1.17	38.40±3.16 <sup>a</sup>	46.05±3.37 <sup>a,b</sup>
IIEF-EF	7.75±0.65	16.10±1.62 <sup>a</sup>	19.65±1.77 <sup>a,b</sup>
IIEF-IS	2.40±0.44	5.90±0.67 <sup>a</sup>	7.50±0.69 <sup>a,b</sup>
IIEF-OF	3.75±0.48	5.60±0.60 <sup>a</sup>	7.25±0.60 <sup>a,b</sup>
IIEF-SD	3.70±0.27	5.35±0.38 <sup>a</sup>	5.55±0.38 <sup>a</sup>
IIEF-OS	2.55±0.24	5.45±0.28 <sup>a</sup>	6.10±0.36 <sup>a</sup>
SHIM	5.60±0.41	13.05±1.35 <sup>a</sup>	16.25±1.51 <sup>a,b</sup>
EHS	2.20±0.16	2.80±0.16 <sup>a</sup>	3.00±0.15 <sup>a</sup>

Values are presented as mean±standard error.

IIEF: International Index of Erectile Function, IIEF-EF: IIEF-Erectile Function, IIEF-IS: IIEF-Intercourse Satisfaction, IIEF-OF: IIEF-Orgasmic Function, IIEF-SD: IIEF-Sexual Desire, IIEF-OS: IIEF-Overall Satisfaction, SHIM: Sexual Health Inventory for Men, EHS: erection hardness score.

<sup>a</sup>p<0.05 compared with baseline. <sup>b</sup>p<0.05 compared with placebo.

the placebo drink (Table 3). In the domains of IIEF-3, -6, and, -11, the mean scores of our supplement drink increased significantly compared with the baseline scores, whereas they did not increase significantly compared with baseline scores for the placebo drink (Table 3).

The mean EHS of the men taking our supplement drink was significantly greater than the baseline score (p=0.001), as was the mean EHS of the men taking the placebo (p=0.002). However, the change between the EHS with our supplement drink and that with the placebo was not significantly different (p=0.157) (Table 2).

## DISCUSSION

We investigated the efficacy of a supplement drink containing testosterone, L-citrulline, resveratrol, and caffeine in improving sexual function, especially libido, in men with sexual dysfunction. The present study revealed significant improvement in the IIEF-total score; the frequency of desire, erection, intercourse, orgasm, and ejaculation; erection firmness, erection confidence, penetration ability, intercourse satisfaction, and overall satisfaction. The results clearly showed that our supplement drink can rescue libido and erectile, orgasmic, and ejaculatory function in patients taking PDE5i. This is the first study to show that our supplement drink may be effective in improving libido, erection, orgasm, and ejaculation.

Our previous study using L-citrulline and transres-

**Table 3.** Assessment of the IIEF domains in baseline, placebo, and supplement drink groups

Variable	Baseline	Placebo	Supplement drink
IIEF-1	1.60±0.23	2.75±0.30 <sup>a</sup>	3.35±0.28 <sup>a,b</sup>
IIEF-2	1.80±0.20	2.70±0.33 <sup>a</sup>	3.40±0.33 <sup>a,b</sup>
IIEF-3	1.25±0.26	2.60±0.35	3.20±0.36 <sup>a</sup>
IIEF-4	0.80±0.16	2.60±0.34 <sup>a</sup>	3.20±0.36 <sup>a</sup>
IIEF-5	0.80±0.16	2.85±0.35 <sup>a</sup>	3.45±0.36 <sup>a</sup>
IIEF-6	0.80±0.16	1.25±0.16	1.55±0.20 <sup>a</sup>
IIEF-7	0.70±0.13	2.30±0.33 <sup>a</sup>	3.15±0.36 <sup>a,b</sup>
IIEF-8	0.90±0.18	2.35±0.26 <sup>a</sup>	2.80±0.28 <sup>a</sup>
IIEF-9	2.00±0.25	3.00±0.31 <sup>a</sup>	3.85±0.28 <sup>a,b</sup>
IIEF-10	1.75±0.24	2.60±0.30 <sup>a</sup>	3.40±0.34 <sup>a,b</sup>
IIEF-11	1.80±0.16	2.65±0.24	2.75±0.25 <sup>a</sup>
IIEF-12	1.90±0.14	2.70±0.16 <sup>a</sup>	2.80±0.16 <sup>a</sup>
IIEF-13	1.20±0.12	2.70±0.15 <sup>a</sup>	3.10±0.19 <sup>a,b</sup>
IIEF-14	1.35±0.13	2.75±0.14 <sup>a</sup>	3.00±0.18 <sup>a</sup>
IIEF-15	1.50±0.17	2.60±0.20 <sup>a</sup>	3.05±0.24 <sup>a,b</sup>

Values are presented as mean±standard error.

IIEF: International Index of Erectile Function.

<sup>a</sup>p<0.05 compared with baseline. <sup>b</sup>p<0.05 compared with placebo.

veratrol revealed significant improvements in the Sexual Health Inventory for Men-total score, confidence in and firmness of erection, and intercourse satisfaction. Maintenance frequency and ability were also improved after the supplementation although not significantly. Our previous combination therapy might have been more effective in improving confidence and satisfaction [12]. However, the present study revealed reproducible results of the use of resveratrol and L-citrulline for ED patients with PDE5i.

A previous study using testosterone at 600 mg/d reported significant improvements in sexual cognition, arousal, and behavior, and in orgasm in healthy aging males and also showed that sexual satisfaction was associated with better quality of life [16]. However, in another previous study also using testosterone at the same dose, there were no changes in sexual cognition, sexual behavior, or orgasm in healthy aging males [7]. We speculated that the results of the present study showed greater effect than those of this previous study because the present study included men with low libido. Potential mechanisms of testosterone include a possible increase in serum testosterone, increased testicular sensitivity to luteinizing hormone, and increased synthesis of testosterone or a reduction in testosterone catabolism [7].

Oral L-citrulline supplementation increases the serum level of L-arginine and nitric oxide production

[17]. L-citrulline improved intracavernous and mean arterial pressures, the ratio of smooth muscle to collagen, and serum levels of nitrogen oxides in an animal ED model [18]. One clinical study reported significant improvement in EHS from 3 to 4 in 50% of men when they took L-citrulline and a significant increase in the mean number of intercourses per month compared with baseline,  $2.3 \pm 1.37$  versus  $1.37 \pm 0.93$  [19].

Resveratrol increases endothelial nitric oxide synthase expression [20] and improves endothelial function by activation of sirtuin 1, which then promotes endothelium-dependent vascular relaxation [21]. Resveratrol could potentially be an effective treatment to prevent atherosclerotic change, increase blood testosterone, and provide a relaxing effect in the corpus cavernosum, as observed in hypercholesterolemic rabbits [22]. Resveratrol also elevated the intracellular cGMP level in the human corpus cavernosum smooth muscle cells [23]. Combination treatment with resveratrol and PDE5i had a synergistic effect in improving erectile function in rat model of ED [23].

Maintenance frequency, maintenance ability, intercourse enjoyment, desire level, and relationship satisfaction were all improved significantly after the supplement drink compared with baseline. However, these factors also improved significantly after the placebo drink compared with baseline, and the difference between the two drinks was not significant. In a previous randomized placebo-controlled study, the greatest placebo response occurred in participants younger than 45 years old [24]. Notable placebo effects have been reported in various therapeutic areas, especially in clinical investigations using patient-reported outcome measures [25]. We speculated that the placebo effects were as high as or beyond our expectation because the participants of the present study were young men with a mean age of 40.0 years old.

The applied dose of testosterone in the present study was 600 mg/d. The safety of testosterone was assessed by oral toxicity studies using acute (2,500 mg/kg for 14 days) and subchronic (1,000 mg/kg for 90 days) administration [26]. Previous studies reported that testosterone administered at a dose of 600 mg/d is safe and effective in healthy aging males [7,16]. Thus, we used 600 mg of testosterone in the supplement drink.

The applied dose of L-citrulline in the present and previous studies was 800 mg/d. At the time of these studies, this was the highest dose available in Japan

(Kyowa Hakko Bio, Ibaragi, Japan). The safety of L-citrulline has been evaluated in patients (1.5 g/d) and rats (approximately 2 g/d) with ED [18,19]. No side effects have been reported following the administration of citrulline as an oral supplement at doses up to 15 g [27].

The applied dose of resveratrol in the present study was 300 mg/d, the same as that used in our previous study in which we calculated a dose of 5 mg/kg in both human and rat studies [12,23]. We also evaluated its safety in patients and rats with ED [23]. Another previous study reported gastrointestinal side effects in a large number of participants taking resveratrol doses of 2,500 mg/d or more, indicating that doses at or above this level may not be tolerated chronically, and that a dose of 450 mg/d can be considered safe for a 60-kg individual [28]. We considered the dose administered in our study to be safe and effective.

The applied dose of caffeine in the present study was 40 mg/d. Consumption of caffeine in healthy adults up to 400 mg/d is not associated with overt, adverse cardiovascular effects, reproductive and developmental effects, other acute effects, or bone status [29]. Additionally, we used the 40-mg dose of caffeine in the supplement drink to prevent insomnia.

Despite being a prospective, placebo-controlled study, the present study has some limitations. First, this two-institution study with a small sample size was short, lasting only 5 weeks. We will be planning a longer-duration study that includes more institutions. Second, this study excluded ED patients taking tadalafil once daily for LUTS, which is an effective and well-tolerated medical treatment for patients with these conditions [30]. Daily use of PDE5i may be more effective in treating ED treatment combined with testosterone, L-citrullines, resveratrol, and caffeine. Third, information on patient comorbidities that might affect sexual function, such as diabetes and neurologic disease was lacking. Fourth, we did not have data on the use of our supplement drink alone, not in combination with PDE5i. Fifth, we did not measure hormonal levels before and after treatment. We will be planning a study that includes such data. Sixth, the participants of the present study were young men. We could not recruit a different participant cohort, which might have been able to minimize the placebo effect.



## CONCLUSIONS

This is the first study to show that our supplement drink may not only be effective for erection treatment in men with ED along with the added on-demand use of PDE5i but also effective in improving libido, orgasm, and ejaculation. The present results showed that our supplement drink may be a possible treatment option for these patients.

## Conflict of Interest

The authors have nothing to disclose.

## Author Contribution

Conceptualization: MS, AT. Data curation: MS, TK, AT. Formal analysis: MS, AT. Funding acquisition: MS, AT. Investigation: MS, AT. Methodology: MS, AT. Project administration: MS, AT. Resources: MS, AT. Software: MS, AT. Supervision: YM, TO, MM, KI, IH, YU, TN, TK. Validation: MS, AT. Visualization: MS, AT. Writing – original draft: MS, AT. Writing – review & editing: MS, AT.

## Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at <https://doi.org/10.7910/DVN/T5URB6>.

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