

ORIGINAL ARTICLE

Efficacy and safety of pomegranate juice on improvement of erectile dysfunction in male patients with mild to moderate erectile dysfunction: a randomized, placebo-controlled, double-blind, crossover study

CP Forest¹, H Padma-Nathan¹ and HR Liker²

¹The Male Clinic, Beverly Hills, CA, USA and ²David Geffen School of Medicine at University of California, Los Angeles, CA, USA

This randomized-controlled trial examined the efficacy of wonderful variety pomegranate juice versus placebo in improving erections in 53 completed subjects with mild to moderate erectile dysfunction. The crossover design consisted of two 4-week treatment periods separated by a 2-week washout. Efficacy was assessed using International Index of Erectile Function (IIEF) and Global Assessment Questionnaires (GAQ). Of the 42 subjects who demonstrated improvement in GAQ scores after beverage consumption, 25 reported improvement after drinking pomegranate juice. Further, 17 subjects showed preference of one beverage to the other. Subjects were more likely to have improved scores when pomegranate juice was consumed ($P=0.058$). Although overall statistical significance was not achieved, this pilot study suggests the possibility that larger cohorts and longer treatment periods may achieve statistical significance.

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Introduction

Pomegranate juice (POM) a potent antioxidant, enhances endothelial nitric oxide (NO) levels and directly impacts atherosclerotic changes associated with erectile dysfunction (ED). The juice from pomegranates contains potent polyphenolic flavonoid antioxidants known as anthocyanins. Studies demonstrate that POM has more polyphenol antioxidants than any other fruit juice tested for antioxidant activity. It has also been demonstrated to have greater antioxidant activity than green tea or wine. POM contains approximately 1.5% flavonoids, polyphenols, pectin and ascorbic acid by weight.¹

Antioxidants, such as those in POM, enhance the bioavailability of NO and offer protection against

atherosclerosis.¹ Recent laboratory tests revealed that POM consumption in atherosclerotic apolipoprotein E-deficient mice reduced the size of atherosclerotic lesions by 44% and decreased low-density lipoprotein (LDL) susceptibility to aggregation and retention in humans.² The protective effects of NO on atherosclerosis and oxidative destruction are attributed to its ability to prevent adhesion and aggregation of blood cells and platelets, inhibit vascular smooth muscle cell proliferation, and prevent oxidation of LDL cholesterol.² LDL cholesterol that has been oxidized is much more likely to become arterial plaque, therefore, by reducing LDL oxidation in mice, POM reduces arterial plaque. One study in humans demonstrated that POM consumption significantly reduced common carotid intima-media thickness associated with carotid artery stenosis, along with concomitant lowering of blood pressure and inhibition of lipid peroxidation in serum and in LDL.³

Because erectile tumescence and rigidity require significant dilatation of the penile arteries, NO deficiency may manifest itself as ED, the first clinical manifestation of atherosclerotic disease.^{4,5}

Correspondence: Dr CP Forest, The Male Clinic, 9100 Wilshire Blvd., Suite 350, East Tower, Beverly Hills, CA 90212, USA.

E-mail: cforest@usc.edu

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Owing to its effect on NO, antioxidants may play a role in smooth muscle relaxation as well. Studies demonstrate that POM, improves erectile function and decreases fibrosis in animal models.⁶ POM, with its inherent antioxidant properties, has potential benefit for ED due to its ability to decrease fibrosis, increase NO bioavailability and reduce atherosclerotic plaque.

This randomized-controlled trial explores the clinical efficacy of POM for the management of ED. The primary hypothesis is that treatment of ED patients with POM Wonderful POM would produce statistically significant positive Global Assessment Questionnaire (GAQ) scores when compared to placebo-controlled patients. The GAQ elicits the patient's self-evaluation of study beverage effect on erectile activity during that period. The secondary hypothesis is that treatment of ED patients with POM Wonderful POM would produce changes in the erectile function domain of the International Index of Erectile Function (IIEF) as well as the remaining IIEF domains (intercourse satisfaction, overall satisfaction, orgasm and desire domains) when these values are compared with baseline and between the two treatment groups. The IIEF is a validated questionnaire whose erectile function domain score has been demonstrated to correlate with ED intensity.^{7,8} Other domains of the IIEF were evaluated as secondary end points.

Materials and methods

Study design and entrance criteria

This randomized, double-blind, placebo-controlled clinical trial utilized a crossover design to compare the efficacy of POM to placebo. Sixty sexually active, healthy males aged 21–70 years with a history of ED for at least 3 months duration were recruited at a single site. To qualify, subjects were required to have mild to moderate ED as indicated by an erectile function domain score of 17–25 on the IIEF Questionnaire.⁸ Inclusion criteria included being in a stable, monogamous relationship with a consenting female partner and being willing to attempt sexual intercourse on at least one occasion per week during each study period. Subjects were excluded from entrance into the study for the following reasons: ED caused by untreated endocrine disease, significant penile pathology, clinically significant hepatic, renal or neurological disease, a recent history of myocardial infarction, diabetes mellitus or an HbA1c ≥ 7.0 , history of prostate cancer or prostate surgery other than a transurethral resection of the prostate, a history of alcoholism within the previous 2 years, or the current consumption of three or more alcoholic drinks per day. Any subject currently on ED therapy (prescription medications, over-the-counter

medications, herbal preparations or medical devices) was required to discontinue therapy during the screening period and for the duration of the study.

Study event timeline

The study was designed to incorporate a screening period for verification of eligibility followed by two 28-day treatment periods and a 14-day washout after period 1. At visit 1, before all screening procedures, the subject completed the IRB approved informed consent process. A general medical and ED history was obtained, a physical exam and laboratory evaluations were performed, and the IIEF questionnaire was administered. Once it was determined that a subject met inclusion criteria for entrance into the study, he was scheduled to return for randomization.

At visit 2, immediately before randomization, the subject was dosed with a sample containing 4 ounces of each beverage to verify tolerance. The subject was subsequently randomized to either placebo juice or POM for period 1. Subjects were instructed to consume the entire 8 ounces of beverage on a daily basis with their evening meal or shortly after. The quantity of beverage required was based upon human research, which indicated that 1.5 mmol of total polyphenols is the optimal dose per day.² At the end of 28 days of daily consumption the subject returned for visit 3, where the GAQ and IIEF were administered to assess the effect of the period 1 study beverage on the subject's erectile function. A 2-week washout period ensued during which time the subject did not consume any study beverage nor utilize any treatment for ED. The subject was provided with the opposite study beverage during study period 2 as per the crossover design of the study. Upon completion of 28 days of consumption of the study beverage, the subject returned for his final visit, where GAQ and IIEF questionnaires were administered again to assess the study beverage effect during the second study period.

Results

Of the 74 subjects who entered the screening process, 61 were enrolled and 53 completed the study. Subjects with mild to moderate ED were randomized into two cohorts, 31 subjects in cohort 1 and 30 in cohort 2. During period 1, subjects in cohort 1 received the study beverage while those in cohort 2 received placebo. Beverage assignments were reversed during period 2 per crossover design. At least 87% of subjects in each cohort consumed the study beverage a minimum of 21 days during each 28-day study period. Four subjects in cohort 1

and three subjects in cohort 2 were lost to follow-up; one subject discontinued for reasons not related to the study. The mean age for each cohort was 46 years old (46.39 in cohort 1; 45.97 in cohort 2) and the mean IIEF score was 21 (20.84 in cohort 1; 20.73 in cohort 2). No serious adverse events occurred during the study and no subjects discontinued due to adverse events. The most commonly reported adverse events were upper respiratory infections and pharyngitis (8% for POM; 4% for placebo). The following adverse events were reported while on POM: diarrhea (2%), flatulence (2%), hyperlipidemia (2%), nasal congestion (2%) and hypertension (2%). One patient (2%) reported anxiety while on placebo.

Of the 55 subjects who drank the placebo beverage, 53 also drank POM. A total of 42 subjects demonstrated improvement in GAQ score after beverage consumption, 25 after drinking POM. In total, 17 subjects showed preference of one beverage to the other in GAQ scores. Of the 17 subjects, 8 from cohort 1 and 5 from cohort 2 preferred POM to placebo while 2 subjects from each cohort preferred placebo to POM. It was observed that subjects were more likely to have improved scores if they drank POM ($P=0.058$). It was noted that a higher proportion of subjects showed improved GAQ scores in cohort 1 (56 and 33%) than in cohort 2 (38 and 29%). Beverage preferred statistical analyses were performed for the overall beverage comparisons without controlling for age group. They utilized the Mainland-Gart test for phase or beverage preference, considering both cohort and period. Beverage preferred is defined as POM when the

GAQ response was improved following the POM beverage phase, but not after placebo beverage phase and similarly for placebo (Table 1). Subjects with missing or the same response for both phases were not considered to have a preference (Table 2).

Secondary efficacy end points did not reach clinical significance. The mean \pm s.d. of change from baseline in IIEF erectile function domain score was -0.13 ± 6.08 for POM and -0.02 ± 5.04 for placebo ($P=0.72$). The mean \pm s.d. of change from baseline in IIEF of other domains was 1.40 ± 7.88 for POM and 1.64 ± 6.88 for placebo.

Discussion

Endothelial dysfunction has been closely associated with atherosclerotic disease and compromises the availability of NO in the penile tissues necessary to cause smooth muscle relaxation and the resultant tumescence and rigidity. Increasing the availability of endothelium-derived NO is believed to increase ultimately erectile response. PDE5 inhibitors, first-line therapy for ED, prevent the breakdown of cyclic GMP (cGMP) while appearing to facilitate local NO release in the tissues with resultant erectile response. POM has been demonstrated to contain the highest potency of antioxidants when compared to other beverages, enhancing the action of NO by vascular endothelial cells. This study explored whether the known antioxidant activity of POM translates into clinical efficacy in healthy male subjects with mild or mild-to-moderate ED.

This study observed trends toward increased erectile function based on self-administered questionnaires, although overall statistical significance was not achieved ($P=0.058$). Cohort 1 subjects performed differently from cohort 2 even though they shared similar demographic and baseline characteristics (except remaining IIEF domain score). Why subjects from cohort 1 were more likely to have improved GAQ scores is unclear.

While improved scores on GAQ approached statistical significance, the scores on the IIEF questionnaire did not. It is important to note that the GAQ is an assessment of the final result of 4 weeks of beverage consumption, while the IIEF

Table 1 Subjects demonstrating improvement in GAQ scores^a

Cohort (sequence)	POM	Placebo
1. (POM-Placebo)	15 (56%)	9 (33%)
2. (Placebo-POM)	10 (38%)	8 (29%)
Total	25 (47%)	17 (31%)

Abbreviations: GAQ, Global Assessment Questionnaire; POM, pomegranate juice.

^aA total of 55 subjects drank Placebo; 53 of them drank POM.

Table 2 Compliance data for consumption of study beverage

		Cohort 1 (n = 31)		Cohort 2 (n = 30)	
		Period 1	Period 2	Period 1	Period 2
Number of study beverages consumed	Mean \pm s.d.	32.3 \pm 3.8	34.5 \pm 8.5	32.4 \pm 2.9	32.5 \pm 3.5
Number of subjects consuming at least 21 bottles of study beverage	n (%)	27 (87%)	27 (87%)	28 (93%)	26 (87%)
Number of subjects consuming 8–20 bottles of study beverage	n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of subjects consuming <8 bottles of study beverage	n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of subjects with missing beverage consumption data	n (%)	4 (13%)	4 (13%)	2 (7%)	4 (13%)

takes into consideration all sexual activity during the previous 4 weeks. If the POM required as much as 2 weeks of consumption before demonstrating a response based upon recent studies,² then the IIEF would not be as sensitive to recognizing an improvement in erectile function as the GAQ. The use of a subject sexual encounter diary would have been useful in this situation to demonstrate if there was progressive improvement in erectile function during each treatment period.

The limitations of this pilot study include cohort size, treatment period duration, and compliance issues. Considering that the *P*-value nearly achieved statistical significance (0.058) for those who preferred POM, it is possible that statistical significance could have been achieved with either larger cohorts of subjects or extended treatment periods. It was proposed at the onset of the study that the clinical effect of POM on ED could be observed as quickly as within a week, yet this may not have been long enough time to allow for a clinical response. Extended treatment periods could provide the time necessary to observe improved clinical response and thus improved GAQ and IIEF scores. Study visit compliance among many subjects was difficult and required multiple telephone contacts to insure maintenance of visits within windows. This was anticipated since compliance issues are common in clinical trials involving young healthy men (study mean age of 46). This is largely related to the commitment and activity levels in this age group. A potential limitation of the study is that POM has a distinct appearance and taste. This was minimized for the study by taste and color matching the placebo beverage as well as providing a 2-week washout so that it would be difficult for subjects to discern any subtle difference in taste or appearance between the study beverages. To minimize bias, patients were asked not to attempt to speculate which month's beverage had the active ingredient.

Although the results of this pilot study did not achieve statistical significance, a trend was demonstrated toward benefit of erectile function in men with mild and mild-to-moderate ED based upon results from self-administered GAQ. Modifying the design of the study to incorporate a larger cohort of subjects and longer treatment periods could possibly demonstrate statistical significance. As a power-

ful antioxidant, enhancing the actions of NO in vascular endothelial cells, POM has great potential in the management of ED. Of interest would be the use of this POM in conjunction with medications that depend heavily on NO activity such as PDE5 inhibitors.⁹ Further studies are warranted to clarify the efficacy and clinical role of POM on male ED.

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