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Effects of Pumpkin Seed in Men with Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia in the One-Year, Randomized, Placebo-Controlled GRANU Study

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Key Words
Benign prostatic hyperplasia · *Cucurbita pepo* · International Prostate Symptom Score · Lower urinary tract symptoms · Pumpkin seed · Quality of life

Abstract
Introduction: The German Research Activities on Natural Urologicals (GRANU) study was a randomized, partially blinded, placebo-controlled, parallel-group trial that investigated the efficacy of pumpkin seed in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH/LUTS). ***Subjects and Methods:*** A total of 1,431 men (50–80 years) with BPH/LUTS were randomly assigned to either pumpkin seed (5 g b.i.d.), capsules with pumpkin seed extract (500 mg b.i.d.) or matching placebo. The primary response criterion was a decrease in International Prostate Symptom Score (IPSS) of ≥5 points from baseline after 12 months. Secondary outcome measures included IPSS-related quality of life, IPSS single items and diary-recorded nocturia. ***Results:*** After 12 months, the response rate (intention-to-treat/last-observation-carried-forward approach) did not differ between pumpkin seed extract and placebo. In the case of pumpkin seed (responders: 58.5%), the difference compared with placebo (responders: 47.3%) was descriptively significant. The study products were well tolerated. Overall, in men with BPH, 12 months of treatment with pumpkin seed led to a clinically relevant reduction in IPSS compared with placebo. ***Conclusion:*** In order to fully justify a recommendation for the use of pumpkin seed to treat moderate LUTS, these findings need to be substantiated in a confirmatory study or systematic review.

Introduction

Pumpkin seed has long been used to treat micturition disorders and has found a place in the medical treatment of lower urinary tract symptoms due to benign prostatic hyperplasia (BPH/LUTS) over the past decades [1–3]. The improvement of LUTS in men with BPH was confirmed in clinical practice [4, 5].

The seed contains fatty acids (≤64% linoleic acid), specific delta-7-sterols, tocopherols and micronutrients [6]. The sterol fraction of pumpkin seed includes the wide-

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spread delta-5-sterols, but the main fraction consists of delta-7-sterols, which are claimed to account for the therapeutic effects and have not been found in other sterol-containing plant extracts used in BPH treatment. According to recent analyses, consistently high amounts of delta-7-sterols were only detected in preparations manufactured from medicinal pumpkin seed [7].

The oral administration of high doses of pumpkin seeds and pumpkin seed oil reduced prostate weight in experimental animal models of prostate growth [3, 8–10]. The injection of pumpkin seed oil caused reproducible effects on urodynamic parameters in rabbits [11]. Prostatic inflammation has been shown to aggravate LUTS [12]. Therefore, anti-inflammatory effects of pumpkin seed oil as observed in the rat arthritis model [13] may also contribute to clinical improvement. To our knowledge, pumpkin seed extract is the first herbal preparation ever verified in accordance with the clinical research criteria of the International Consultation on BPH [14]. A 1-year-long, placebo-controlled study including 465 patients and using the International Prostate Symptom Score (IPSS) as the primary endpoint demonstrated statistically significant improvements compared with placebo. The pumpkin seed extract used is therefore recommended by the author for the treatment of BPH/LUTS of mild-to-moderate severity [15].

The German Research Activities on Natural Urologicals (GRANU) study was planned in consultation with the German Federal Institute for Drugs and Medical Devices to demonstrate the efficacy of pumpkin seed in men with BPH/LUTS. In accordance with the criteria of the International Consultation on BPH, a placebo-controlled design was considered the most suitable, since considerable symptomatic improvement had been demonstrated with placebo. Therefore, the present three-armed study compared pumpkin seed and pumpkin seed extract with placebo in parallel groups.

Subjects and Methods

The study was performed by German urologists in private practice in accordance with good clinical practice and the Declaration of Helsinki. The study protocol was approved by the responsible ethics committee and the Federal Institute for Drugs and Medical Devices (BfArM). All patients gave written informed consent.

Participants

Men between 50 and 80 years old with BPH/LUTS for ≥6 months were recruited if they had either never received any treatment (phytotherapeutic agents, α-adrenergic blocking agents and 5-α-reductase inhibitors) or had stopped such treatment ≥6 months prior to enrolment. Patients eligible for randomization had an IPSS ≥13 and ≤19, IPSS-related quality of life (QoL) ≥3, diary-recorded nocturia ≥2 times and peak urinary flow rate (Q_{max}) ≤12 ml/s (voided volume: ≥150 ml).

Exclusion criteria were prostate volume >40 ml or post-void residual volume (PVR) >100 ml. Further exclusion criteria and prohibited concomitant medications followed the recommendations of the International Consultation on BPH [14–16]. As anti-inflammatory mechanisms are postulated for herbal substances, concomitant use of NSAIDs was also prohibited.

Study Medication

Active medications were purified pumpkin seed (brand name: GRANU FINK® Kürbiskerne) or pumpkin seed extract (500 mg each capsule; former brand name: PROSTA FINK® FORTE 500 mg; current name: GRANU FINK Prosta forte 500 mg); both are registered medicinal products in Germany and manufactured from medicinal pumpkin seed (GRANU FINK Arzneikürbis), a special, company-owned, registered cultivar of *Cucurbita pepo* L. convar. citrullinina GREB. var. styriaca GREB. Extraction with ethanol 92% (w/w) gives a semisolid extract with a drug-extract ratio of 15–25:1. The total daily dose was 10 g pumpkin seed (2 × 5 g) or 2 capsules with pumpkin seed extract. The patients took the study medication in the morning and the evening.

Randomization and Treatment

After a 1-month run-in period without treatment, eligible patients were assigned to receive either pumpkin seed or pumpkin seed extract or placebo (1:1:1). The contract statistician had generated the block randomization schedule (stratified by site) using SAS PROC PLAN. The block size was not stated in the protocol. To ensure allocation concealment, the sealed randomization envelopes were not opened before the moment of assignment.

Study Procedure

At the screening visit, the patients underwent a physical examination as well as laboratory tests including prostate-specific antigen (PSA), uroflowmetry and sonographic measurements of prostate volume and PVR. Concomitant diseases and medications were recorded, and the IPSS and IPSS-related QoL were assessed. Potentially suitable patients were given a micturition diary to assess nocturia and asked to return after 1 month. At the baseline visit, the patients returned the micturition diary and completed the IPSS questionnaire including IPSS-related QoL. The investigator reviewed the inclusion and exclusion criteria and assigned eligible patients to one of the three treatment groups by opening the randomization envelopes in ascending order. Four post-randomization visits were scheduled after 3, 6, 9 and 12 months to assess IPSS, QoL and diary-recorded nocturia. At all visits, blood pressure, concomitant medications and adverse events were recorded. At the final visit, all the examinations and tests performed at screening were repeated.

Outcomes

The primary endpoint was the response rate defined as the proportion of patients with a decrease of ≥5 points on the IPSS after 12 months of treatment. Secondary outcomes included changes in IPSS (total score and 7 single items), nocturia and IPSS-related QoL. Safety and tolerability were assessed by laboratory tests, urological examinations and the evaluation of adverse events.

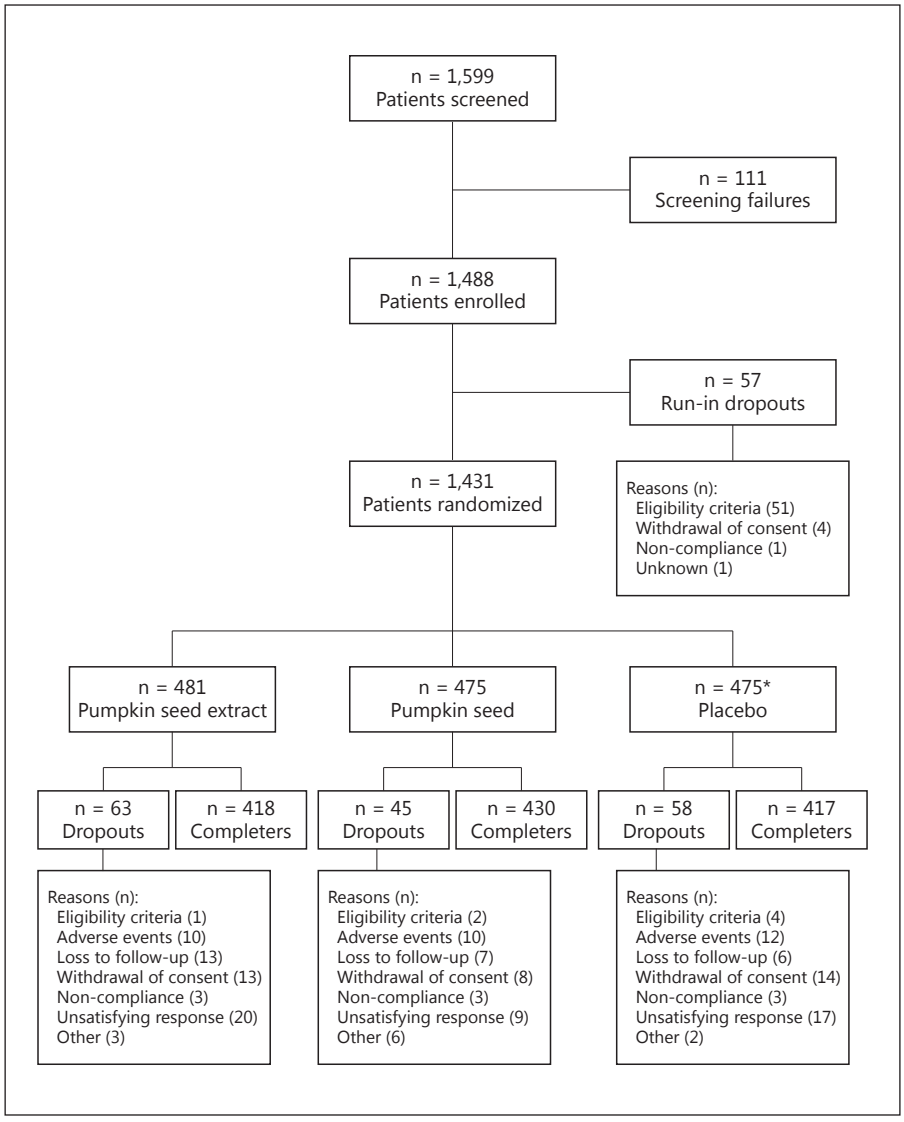

Fig. 1. Subject disposition. * One patient was randomized to the placebo group but did not take any medication and therefore was excluded from the ITT population.

Sample Size Calculation

Based on a two-sided α-level of 0.05, a power of 90% and the assumption of a 10% difference in response rate compared with placebo, 1,590 men were to be randomized, and in order to account for a run-in dropout rate of up to 10%, a total of 1,770 patients were to be screened. To control for multiplicity, a hierarchical testing procedure was set up for the primary efficacy endpoint. In this procedure, placebo was to be compared firstly with pumpkin seed extract and subsequently (only if statistical significance was demonstrated at this level) with pumpkin seed.

Statistical Analysis

All data analyses were performed in accordance with a statistical analysis plan pre-established before enrolment. All the staff involved in study analyses (data managers and statisticians) was unaware of the treatment assignment and the randomized sequence list. Study centres with a low number of enrolled patients were pooled before unblinding. SAS software (German version 9.2) was used for analysis.

The primary analysis was performed according to the intention-to-treat (ITT) principle using the last-observation-carried-forward (LOCF) approach. The ITT population was defined as all the patients who took at least 1 dose of the study medication. All analyses were repeated for the PP population. An independent, blinded, third-party review committee was responsible for patients' allocation to the PP set.

Response rates and 95% CI according to Clopper-Pearson were estimated. The proportion of responders was compared across the treatment groups using the Cochran-Mantel-Haenszel procedure complemented by the Breslow-Day test to estimate site-by-treatment interactions. Confirmatory and descriptive analyses were performed. In the hierarchical confirmatory strategy for the primary efficacy endpoint, the effect of pumpkin seed extract versus placebo was tested first because the pumpkin seed

Table 1. Demographic characteristics and outcome measures at baseline (ITT set)

Parameter	Pumpkin seed extract (n = 481)	Pumpkin seed (n = 475)	Placebo (n = 474)
Age			
Observations, n	481	475	474
Mean ± SD, years	65.2±6.9	65.2±7.0	65.5±6.8
Median (range), years	66.0 (45.0–80.0)	66.0 (50.0–80.0)	66.0 (47.0–82.0)
IPSS total[a]			
Observations, n	471	470	467
Mean ± SD	16.0±2.1	16.0±2.1	16.1±1.9
Median (range)	16.0 (5.0–22.0)	16.0 (12.0–31.0)	16.0 (11.0–23.0)
IPSS-QoL			
Observations, n	472	466	469
Mean ± SD	3.5±0.7	3.5±0.7	3.5±0.7
Median (range)	3.0 (0.0–6.0)	3.0 (2.0–6.0)	3.0 (2.0–6.0)
Nocturia[b]			
Observations, n	481	474	472
Mean ± SD	2.6±0.8	2.6±0.8	2.7±0.8
Median (range)	2.0 (0.0–6.0)	2.0 (1.0–6.0)	3.0 (0.0–6.0)
Duration of symptoms			
Observations, n	312	315	320
Mean ± SD, years	4.4±3.5	4.0±3.5	4.5±3.3
Median (range), years	3.2 (0.2–15.0)	2.6 (0.5–16.1)	3.7 (0.0–17.7)
Prostate size			
Observations, n	468	467	468
Mean ± SD, cm^3	29.0±7.7	28.6±7.3	28.0±7.3
Median (range), cm^3	30 (10–52)	30 (10–45)	30 (10–53)
PVR			
Observations, n	479	475	473
Mean ± SD, ml	33.5±28.3	33.0±26.8	34.8±27.9
Median (range), ml	30 (0–100)	30 (0–100)	30 (0–100)
Uroflow: Q_{max}			
Observations, n	475	473	473
Mean ± SD, ml/s	9.5±2.4	9.6±1.9	9.8±2.6
Median (range), ml/s	10 (2–36)	10 (4–16)	10 (4–27)
Uroflow: volume			
Observations, n	476	473	473
Mean ± SD, ml	237±91	237±96	235±89
Median (range), ml	206 (16–724)	210 (21–793)	208 (32–648)

[a] Homogeneity of IPSS across the groups was assessed by use of the Kruskal-Wallis test; p = 0.216. [b] Nocturia: mean values over 3 nights recorded by micturition diary before the baseline visit.

extract was given in a double-blinded manner. The subsequent comparison of pumpkin seed with placebo was to be carried out only if the first comparison had demonstrated efficacy. The purpose of this strategy was, firstly, to strengthen the credibility of the results for the comparison between placebo and pumpkin seed, which could not be blinded, and, secondly, to reduce the overall study sample size.

In the case of secondary outcomes, laboratory tests and urological examinations, descriptive statistical parameters of absolute and relative differences compared with baseline were calculated for each treatment group. Safety and tolerability were evaluated on the basis of reported adverse events.

Results

A total of 267 study centres were initiated, and between July 2005 and June 2008, a total of 158 study sites screened 1,599 patients for eligibility. Of these, 1,431 were randomly assigned to one of the three treatment groups (fig. 1). Their baseline characteristics are shown in table 1. There were no differences between the groups in terms of treatment duration or dropout rate (p = 0.181; Fisher's exact test). The PP set consisted of 908 patients (table 2).

Table 2. Major protocol violations with a frequency ≥3.0% in all randomized patients

	Pumpkin seed extract (n = 481; ITT)	Pumpkin seed (n = 475; ITT)	Placebo (n = 475; ITT)
Patients excluded from PP analysis	174 (36.2)	184 (38.7)	165 (34.7)
Non-compliance	27 (5.6)	81 (17.1)	28 (5.9)
Deviation from treatment schedule at visit 6[a]	39 (8.1)	26 (5.5)	37 (7.8)
Withdrawal for non-medicinal reasons	33 (6.9)	26 (5.5)	29 (6.1)
Randomization error	30 (6.2)	26 (5.5)	27 (5.7)
Absence of any IPSS value after baseline	28 (5.8)	21 (4.4)	16 (3.4)
Prohibited concomitant medication	24 (5.0)	15 (3.2)	17 (3.6)
Diseases likely to affect micturition	13 (2.7)	13 (2.7)	18 (3.8)

Values denote numbers with percentages in parentheses. Multiple options were possible per patient.
[a] After 12 months of treatment.

Table 3. OR analyses of IPSS response rates (LOCF: ITT and PP) after 12 months of treatment

Compared groups	OR		p value	
	value	95% CI[a]	M-H χ^2 test	B-D test[b]
ITT (LOCF) analysis				
Placebo vs. PS extract[c]	1.06	0.82–1.37	0.65	0.68
Placebo vs. PS[c]	0.65	0.50–0.84	<0.01[d]	0.33
PS vs. PS extract	1.64	1.26–2.12	<0.01[e]	0.35
PP (LOCF) analysis				
Placebo vs. PS extract	0.94	0.69–1.29	0.72[e]	0.22
Placebo vs. PS	0.68	0.49–0.93	0.02[e]	0.34
PS vs. PS extract	1.40	1.01–1.93	0.04[e]	0.09

B-D = Breslow-Day; M-H = Mantel-Haenszel; PS = pumpkin seed.
[a] CI were estimated according to Clopper-Pearson. [b] The homogeneity of the OR across the sites was estimated by means of the Breslow-Day test with the Tyrone correction (α-level, $p < 0.1$). [c] These comparisons belong to the primary confirmatory hierarchical test procedure. [d] As the analysis was performed in 2 steps, the results of step 2 are interpreted descriptively as a consequence of the non-significant result of step 1 (placebo vs. PS extract). [e] Descriptive p values.

Primary Outcome

In the ITT cohort (LOCF), the response rate did not differ significantly between the double-blinded groups but was significantly (about 10%) higher in the pumpkin seed group (tables 3, 4). This statistical significance is descriptive only, as the confirmatory statistical testing strategy was stopped after the non-significant result for the comparison between pumpkin seed extract and placebo. The IPSS response rate as observed increased by 6% during treatment with pumpkin seed extract (for placebo: 2% relative change to ITT-LOCF; table 4, fig. 2).

Secondary Outcomes

The mean IPSS decreased continuously in all groups from month 3 onwards (fig. 2, table 5). After the 1-year treatment period, the mean differences compared with baseline for the ITT-LOCF population were –5.4 ± 5.1, –4.2 ± 5.4 and –4.0 ± 5.5 with pumpkin seed, pumpkin seed extract and placebo, respectively. For the PP population, the differences were –5.5 ± 5.2 (pumpkin seed), –4.6 ± 5.6 (pumpkin seed extract) and –4.2 ± 5.6 (placebo).

At the study end, only 10.2% of the patients treated with pumpkin seed reported a worsening of their symp-

Table 4. IPSS response rates after 12 months of treatment (visit 6)

Treatment group	IPSS response rate					
	ITT population			PP population		
	total, n	n (%)	95% CI	total, n	n (%)	95% CI
Pumpkin seed extract						
Visit 6 (as observed)	396	195 (49.2)	44.2–54.3	289	151 (52.2)	46.3–58.1
Visit 6 (LOCF)	471	218 (46.3)	41.7–50.9	307	155 (50.5)	44.8–56.2
Pumpkin seed						
Visit 6 (as observed)	422	259 (61.4)	56.5–66.0	280	166 (59.3)	53.3–65.1
Visit 6 (LOCF)	470	275 (58.5)	53.9–63.0	291	171 (58.8)	52.9–64.5
Placebo						
Visit 6 (as observed)	402	203 (50.5)	45.5–55.5	289	144 (49.8)	43.9–55.7
Visit 6 (LOCF)	467	223 (47.8)	43.1–52.4	310	152 (49.0)	43.3–54.7

CI were estimated according to Clopper-Pearson.

Table 5. IPSS data for all study visits

Treatment group	Total IPSS					
	ITT population			PP population		
	total, n	mean ± SD	median	total, n	mean ± SD	median
Pumpkin seed extract						
Visit 1 (screening)	474	15.8±1.9	16.0	305	15.8±1.9	16.0
Visit 2 (baseline)	471	16.0±2.1	16.0	307	16.0±1.8	16.0
Visit 3 (3 months)	455	12.8±4.6	13.0	302	12.9±4.5	13.0
Visit 4 (6 months)	442	11.9±4.9	12.0	301	11.9±4.6	12.0
Visit 5 (9 months)	428	11.8±5.2	12.0	294	11.7±5.0	12.0
Visit 6 (12 months)[a]	404	11.4±5.5	11.0	289	11.2±5.5	11.0
Visit 6 (LOCF)	480	11.7±5.5	12.0	307	11.4±5.5	11.0
Pumpkin seed						
Visit 1 (screening)	471	15.9±1.8	16.0	290	15.9±1.8	16.0
Visit 2 (baseline)	470	16.0±2.1	16.0	291	15.9±1.8	16.0
Visit 3 (3 months)	449	12.3±4.6	12.0	286	12.4±4.6	13.0
Visit 4 (6 months)	446	11.1±4.7	11.0	286	11.2±4.8	11.0
Visit 5 (9 months)	434	10.5±4.8	10.0	284	10.4±4.6	10.0
Visit 6 (12 months)[a]	425	10.2±5.1	10.0	280	10.3±5.1	10.0
Visit 6 (LOCF)	475	10.6±5.2	10.0	291	10.4±5.2	10.0
Placebo						
Visit 1 (screening)	471	16.1±1.9	16.0	310	16.0±1.8	16.0
Visit 2 (baseline)	467	16.1±1.9	16.0	310	16.1±1.8	16.0
Visit 3 (3 months)	461	13.2±4.7	13.0	308	13.1±4.6	13.0
Visit 4 (6 months)	440	12.3±5.0	12.0	304	12.1±5.1	12.0
Visit 5 (9 months)	425	12.0±5.3	12.0	299	11.8±5.4	12.0
Visit 6 (12 months)[a]	407	11.7±5.4	11.0	289	11.7±5.5	11.0
Visit 6 (LOCF)	474	12.1±5.6	12.0	310	11.9±5.7	11.0

[a] As observed.

Table 6. Proportion of patients with improvement, no change or worsening of the IPSS compared with baseline and cumulative frequency of IPSS decrease from baseline after 12 months of treatment

	Pumpkin seed extract		Pumpkin seed		Placebo	
	ITT (n = 471)	PP (n = 307)	ITT (n = 471)	PP (n = 291)	ITT (n = 471)	PP (n = 310)
Any improvement (≥1 point)	362 (76.9)	248 (80.8)	382 (81.3)	239 (82.1)	349 (74.7)	235 (75.8)
No change	37 (7.9)	12 (3.9)	40 (8.5)	18 (6.2)	26 (5.6)	14 (4.5)
Worsening	72 (15.3)	47 (15.3)	48 (10.2)	34 (11.7)	92 (19.7)	61 (19.7)
IPSS decrease by						
≥9 points	109 (23.1)	74 (24.1)	141 (30.0)	92 (31.6)	107 (22.9)	78 (25.2)
≥7 points	159 (33.8)	166 (37.8)	221 (47.0)	136 (46.7)	164 (35.1)	118 (38.1)
≥5 points (responders[a])	218 (46.3)	155 (50.5)	275 (58.5)	171 (58.8)	223 (47.8)	152 (49.0)
≥3 points	291 (61.8)	204 (66.4)	328 (69.8)	205 (70.4)	286 (61.2)	195 (62.9)

Values denote numbers of patients with percentages in parentheses.
[a] p values are presented in table 3.

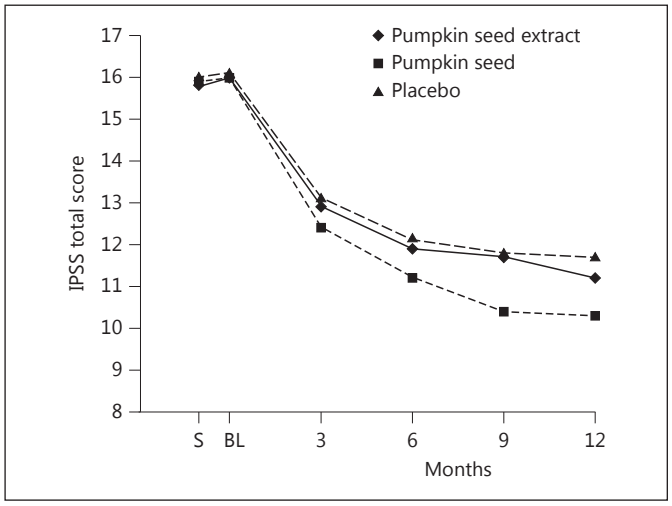

Fig. 2. Mean IPSS total scores during randomized treatment over 12 months. PP analysis set as observed. S = Screening visit; BL = baseline, 1 month after screening.

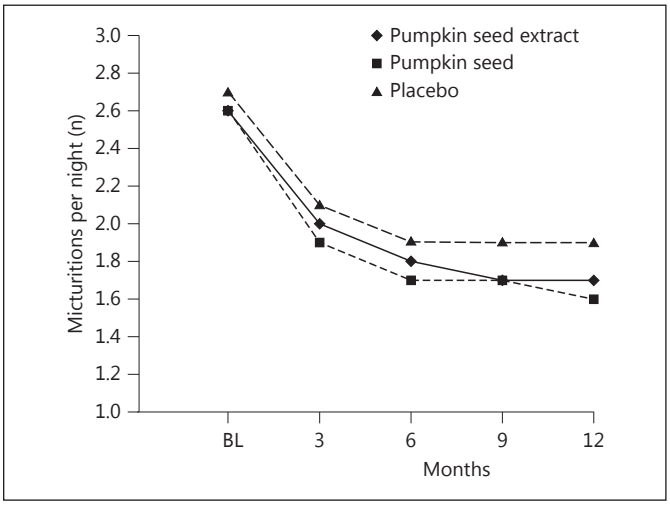

Fig. 3. Mean values for nocturia according to diary before baseline and at post-randomization visits over 12 months (ITT set). For each patient the mean value over 3 nights was calculated. Mean differences ± SD from baseline after 12 months: –1.0 ± 0.9 (pumpkin seed), –0.9 ± 0.9 (pumpkin seed extract) and –0.8 ± 1.0 (placebo). BL = Baseline.

toms (15.3 and 19.7% with pumpkin seed extract and placebo, respectively) (table 6). After 12 months, all individual symptoms had improved in all groups, and in the pumpkin seed group, the relief of urgency, incomplete emptying and weak stream by 1.0, 0.9 and 0.9 points, respectively, accounted for most of the total IPSS change from baseline.

The mean values for diary-recorded nocturia and IPSS-related QoL decreased continuously over time in all study groups. At the study end, the mean decrease in nocturia from baseline was 1.0, 0.9 and 0.8 with pumpkin seed, pumpkin seed extract and placebo, respectively (fig. 3). QoL improved, on average, by 36.0, 33.4 and 29.2% with pumpkin seed, pumpkin seed extract and placebo, respectively (fig. 4).

Safety and Tolerability

On average, the Q_{max} increased by 4.3, 3.6 and 3.6 ml/s (means of relative differences: 49.1, 45.1 and 41.7%) with pumpkin seed, pumpkin seed extract and placebo, respectively (table 7). As expected, there was no clinically

Table 7. Results of urological examinations and serum PSA levels at the screening and the final visit (after 12 months or at the time of last observation for dropout patients) for the safety population

Parameter	Pumpkin seed extract		Pumpkin seed		Placebo	
	n	mean ± SD (median)	n	mean ± SD (median)	n	mean ± SD (median)
Uroflow Q_{max}, ml/s						
Visit 1 (screening)	475	9.5±2.4 (10.0)	473	9.6±1.9 (10.0)	474	9.8±2.6 (10.0)
Visit 6 (final)	408	13.3±6.5 (12.0)	412	13.8±6.9 (12.0)	406	13.3±6.5 (12.0)
Difference[a]	406	3.6±6.3 (2.6)	412	4.3±6.8 (3.0)	406	3.6±6.4 (2.0)
Voided volume, ml						
Visit 1 (screening)	476	237±91 (206)	473	237±96 (210)	474	235±89 (208)
Visit 6 (final)	408	230±122 (209)	412	234±135 (208)	406	242±143 (209)
Difference[a]	406	−7±131 (−3)	412	−4±138 (−10)	406	4±148 (−2)
Prostate size, ml						
Visit 1 (screening)	468	29.0±7.7 (30.0)	467	28.6±7.3 (30.0)	469	29.1±7.4 (30.0)
Visit 6 (final)	417	31.2±11.8 (30.0)	424	31.3±11.5 (30.0)	416	31.4±12.2 (30.0)
Difference[a]	410	2.3±9.7 (1.0)	420	2.7±8.8 (1.0)	413	2.6±10.2 (2.0)
PVR, ml						
Visit 1 (screening)	479	33.5±28.3 (30.0)	475	33.0±26.8 (30.0)	474	34.8±27.9 (30.0)
Visit 6 (final)	421	31.9±38.2 (25.0)	432	30.6±34.6 (22.0)	420	35.0±40.8 (27.0)
Difference[a]	421	−1.8±41.2 (0.0)	432	−2.4±35.7 (0.0)	420	1.2±41.1 (0.0)
PSA, ng/ml						
Visit 1 (screening)	481	1.7±1.5 (1.3)	474	1.8±1.6 (1.3)	474	1.9±1.6 (1.3)
Visit 6 (final)	421	1.9±1.7 (1.3)	433	2.0±1.9 (1.4)	428	2.0±1.8 (1.4)
Difference[a]	421	0.1±1.1 (0.0)	433	0.2±1.0 (0.1)	428	0.2±0.9 (0.1)

[a] Individual difference = value at visit 6 – value at visit 1.

significant change in mean prostate volume in any of the groups. No relevant changes in PVR or PSA levels were observed (table 7).

Of the 1,431 patients, 284 (19.1%) reported at least one adverse event without relevant differences between the groups in distribution by system organ classes. Only 2.2% of the patients discontinued the study due to adverse events. Serious events, all of them to be expected in this age group and not related to the study medication, occurred in 67 patients (4.5%). Blood pressure, heart rate and safety laboratory results showed only marginal variations.

Only 13 non-serious adverse events, most of them gastrointestinal disorders, were judged by the investigators to be possibly drug related. These events were reported by 8 patients, of whom 3, 2 and 3 had been treated with pumpkin seed, pumpkin seed extract and placebo, respectively. Of these patients, 1 in the pumpkin seed group and 1 in the placebo group discontinued the study.

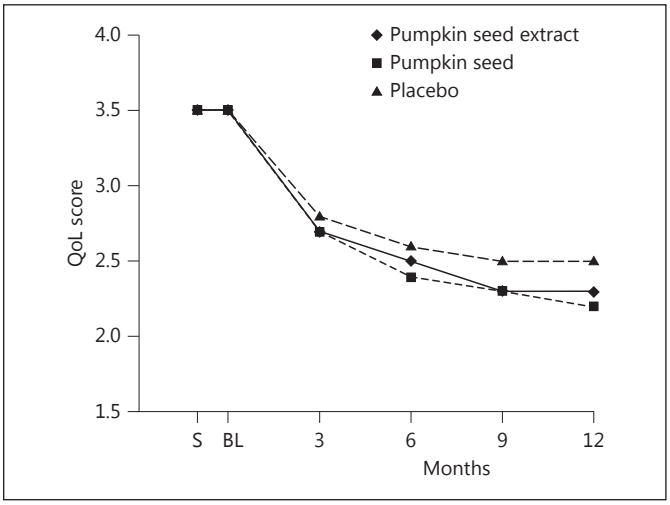

Fig. 4. Mean IPSS-related QoL (ITT set). Scores range from 0 = 'delighted' to 6 = 'terrible'. Mean differences ± SD from baseline after 12 months: −1.3 ± 1.1 (pumpkin seed), −1.2 ± 1.2 (pumpkin seed extract) and −1.0 ± 1.2 (placebo). S = Screening visit; BL = baseline, 1 month after screening.

Discussion

Recent studies comparing herbal preparations with synthetic drugs have been barely accepted by the scientific community due to the lack of a placebo control and/or inadequate power [16, 17]. In this specific three-armed trial, we presented a design to compare the efficacy of unprocessed pumpkin seed with that of placebo treatment. The randomization procedure resulted in well-balanced baseline characteristics between the groups. The patients had ≥13 IPSS points and their QoL score was ≥3; therefore, they had symptoms bothersome enough to seek treatment. The responders had an IPSS improvement by ≥5 points, and so they unequivocally experienced a clinically significant symptom relief. According to previous symptom evaluations, a minimum improvement of 3 points is necessary for a patient to perceive a clinical benefit [18, 19].

The inclusion criteria were strictly in accordance with the recommendations of the International Consultation on BPH (IPSS ≥13, QoL ≥3 and Q_{max} ≤12 ml/s) [14]. As this study was placebo controlled, the ethics committee tightened these selection criteria by limiting IPSS to 19 points, prostate volume to 40 ml and PVR to 100 ml. In addition, a number of eligible patients did not accept placebo treatment. Patient recruitment therefore progressed with difficulties, and only 60% of the initiated study sites were able to identify eligible patients.

A total of 1,431 patients, equivalent to 90% of the calculated sample size, were eventually randomized. The scale of this study is similar to that of well-conducted trials on BPH with synthetic drugs [20]. It easily exceeds that of controlled studies of herbal products in general, and in particular those with a 1-year treatment duration in men suffering from BPH/LUTS [16, 21].

Relief of symptoms was observed in all treatment groups, and similar response rates were found for pumpkin seed extract and placebo in the ITT set. However, the increased response to the extract observed in the PP analysis could indicate pharmacologic effects, since protocol violations that could have diminished the response had been excluded from that set.

Among the patients who received pumpkin seed, the response rate after 12 months was about 60%. This exceeded the response to either form of capsule treatment by 10%. The descriptive intergroup comparisons showed statistically significant differences.

Differences in cultivation and manufacturing processes mean that these results cannot be extrapolated to pumpkin seed preparations in general. Further investigation of the components that contribute to the pharmacologic actions of the drug might explain possible differences in action between unprocessed pumpkin seed and the extract.

The possible contribution made by the patients' perception of the open-label treatment cannot fully explain the improvement in symptoms that was observed with pumpkin seed, since the observed effects are quite striking compared with those seen with any other conservative treatment of BPH/LUTS. Nearly 70% of the patients experienced a decrease of ≥3 points on the IPSS, and nearly 60% of the patients reported a decrease of ≥5 points. This response exceeds the rate of 43% reported by patients treated with herbal medicines in real-life practice in the TRIUMPH study [22]. The average IPSS reduction of 5.8 points that was achieved with pumpkin seed in the present study exceeds the placebo result by 1.4 points, whereas in studies of other herbal preparations, only a 1-point difference from placebo was observed [16, 23]. The post-/pre-treatment ratio of 0.66 for the IPSS in the pumpkin seed group represents a fair response and almost reaches the level of 0.6 indicating a good response according to the efficacy grading of the International Consultation on BPH [24].

The decrease in IPSS was accompanied by a continuous improvement in QoL score compared with baseline. As it is assumed that QoL might be less responsive than the IPSS, this observation is noteworthy. As irritative symptoms, which are the most prevalent LUTS in men [25], are more likely to affect QoL, the reduction in nocturia could account for a large part of this effect [26, 27]. With pumpkin seed, a good response was also observed for urgency.

Consistent with previous observations, the incidence of drug-related adverse events was very low. No serious adverse events were attributed to the study medications. The PSA levels were not influenced.

Conclusion

This partially double-blinded, randomized study over 12 months compared pumpkin seed extract and pumpkin seed with placebo. The sample size of 1,431 randomized patients with BPH/LUTS by far exceeds the usual scale of controlled studies conducted on herbal and chemical drugs.

The findings of this study add to the evidence that treatment with pumpkin seed results in a substantial improvement in BPH/LUTS. The observed symptom relief

is accompanied by a clinically significant improvement in IPSS-related QoL. The numerical improvements in IPSS-related QoL and nocturia compared with baseline were greater in the pumpkin seed groups than in the placebo group. Q_{max} increased in all groups.

Both pumpkin seed medications showed an excellent safety profile consistent with previous observations. Only 8 patients (0.6%) reported treatment-emergent adverse events which were classified as possibly drug related. The objective of the treatment of uncomplicated BPH is to improve QoL by relieving the associated LUTS. The effects seen in this study with pumpkin seed suggest it could be recommended for patients with mild-to-moderate symptoms. However, this needs to be further substantiated in a confirmatory study or systematic review.

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