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Pelvic Pain

A Pollen Extract (Cernilton) in Patients with Inflammatory Chronic Prostatitis–Chronic Pelvic Pain Syndrome: A Multicentre, Randomised, Prospective, Double-Blind, Placebo-Controlled Phase 3 Study

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Abstract

Background: National Institutes of Health (NIH) category III prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a prevalent condition for which no standardised treatment exists.
Objectives: To assess the safety and efficacy of a standardised pollen extract in men with inflammatory CP/CPPS.
Design, setting, and participants: We conducted a multicentre, prospective, randomised, double-blind, placebo-controlled phase 3 study comparing the pollen extract (Cernilton) to placebo in men with CP/CPPS (NIH IIIA) attending urologic centres.
Intervention: Participants were randomised to receive oral capsules of the pollen extract (two capsules q8 h) or placebo for 12 wk.
Measurements: The primary endpoint of the study was symptomatic improvement in the pain domain of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). Participants were evaluated using the NIH-CPSI individual domains and total score, the number of leukocytes in post–prostatic massage urine (VB3), the International Prostate Symptom Score (IPSS), and the sexuality domain of a life satisfaction questionnaire at baseline and after 6 and 12 wk.
Results and limitations: In the intention-to-treat analysis, 139 men were randomly allocated to the pollen extract ($n = 70$) or placebo ($n = 69$). The individual domains *pain* ($p = 0.0086$) and *quality of life* (QoL; $p = 0.0250$) as well as the total NIH-CPSI score ($p = 0.0126$) were significantly improved after 12 wk of treatment with pollen extract compared to placebo. Response, defined as a decrease of the NIH-CPSI total score by at least 25% or at least 6 points, was seen in the pollen extract versus placebo group in 70.6% and 50.0% ($p = 0.0141$), respectively. Adverse events were minor in all patients studied.
Conclusions: Compared to placebo, the pollen extract significantly improved total symptoms, pain, and QoL in patients with inflammatory CP/CPPS without severe side-effects.

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1. Introduction

Prostatitis syndrome is characterised by genitourinary pain and lower urinary tract symptoms (LUTS) [1]. The prevalence of symptoms suggestive of prostatitis ranges between 2.2% and 13.8% according to different studies [2]. National Institutes of Health (NIH) category III prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most frequent subtype, with a heterogeneous and mainly unknown aetiology. Classification of prostatitis syndrome is based on the clinical presentation of the patient, the presence or absence of white blood cells in the expressed prostatic secretion (EPS), post–prostatic massage urine (VB3) or seminal plasma, and the presence or absence of bacteria in the EPS or VB3 [1]. In the NIH classification bacterial prostatitis (acute and chronic) is distinguished from inflammatory and noninflammatory CP/CPPS [3].

Evidence-based treatment of CP/CPPS has been difficult because of the heterogeneous patient population in this syndrome. Even the seemingly proven use of α-blocker therapy in naïve patients [2] is now in dispute [4]. Phytotherapeutic agents such as pollen extract, quercetin, or saw palmetto are widely used with variable success [5,6] but have only rarely been evaluated in suitable clinical trials.

The pollen extract Cernilton contains 63 mg of the defined pollen extract fractions Cernitin T60 (water-soluble fraction) and Cernitin GBX (fat-soluble fraction). These fractions contain carbohydrates, fat, amino acids, vitamins, and minerals and have been used for treatment of benign prostatic hyperplasia [7] and prostatitis [5,8]. Experimental data in nonbacterial prostatitis in rats showed that Cernitin GBX protects mainly acinar epithelial cells and inhibits stromal proliferation in association with an enhanced apoptosis mediated by Cernitin T60 [9]. In a further study, a dose-dependent anti-inflammatory action in nonbacterial prostatitis in rats was noted, leading to decreased levels of interleukin-1β, interleukin-6, and tumour necrosis factor α, which decreases glandular inflammation and might be responsible for the decrease in proliferation and increase of apoptosis seen in the prostate [10]. A further in vitro study found an inhibition of the arachidonic acid cascade [11]; another possible effect on the prostate is via the androgen metabolism [12]. In three noncomparative clinical studies in 90, 24, and 15 patients with CP/CPPS treated with pollen extract, improvement of symptoms was noted in 78%, 63%, and 86%, respectively [5,8,13]. To our knowledge, however, no placebo-controlled study comparing pollen extract has been performed so far. This investigator-initiated (W.W.) study was designed to ascertain the safety and efficacy of pollen extract versus placebo in a clearly defined population of men diagnosed with inflammatory CP/CPPS.

2. Patients and methods

2.1. Study design

This double-blind, prospective, randomised, placebo-controlled, multicentre, clinical phase 3 study was conducted according to Good Clinical Practice (GCP) in 34 German urologic centres to ascertain the safety and efficacy of 12-wk pollen extract versus placebo in men diagnosed with inflammatory CP/CPPS. The study protocol was approved by the ethical committee of the Justus-Liebig-University, Giessen, Germany. The design of the study was in accordance with the guidelines for clinical trials in CP/CPPS described by the NIH Chronic Prostatitis Collaborative Research Network [14].

Inclusion criteria were (1) men between 18 and 65 yr of age with symptoms of pelvic pain for at least 3 mo during the 6 mo before study entry, (2) a score in the *pain* domain of the German-validated version of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) [15] of ≥7, and (3) leukocytes of ≥10 in VB3 (field of vision: ×400). Exclusion criteria were (1) urinary tract infection; (2) acute bacterial or chronic bacterial prostatitis at study entry (bacteriuria ≥104 colony-forming units (CFU)/ml in mid-stream urine (VB2) or ≥103 CFU/ml in VB3); (3) history of urethritis, with discharge 4 wk prior to study entry; (4) a history of epididymitis or sexually transmitted disease (STD); (5) residual urine volume >50 ml resulting from bladder outlet obstruction (BOO); (6) indication for or history of prostate surgery, including prostate biopsy; (7) history of urogenital cancer; (8) treatment with phytotherapeutic agents, α-blocker agents, or antimicrobial substances with prostatic penetration 4 wk prior to study entry; and (9) treatment with agents influencing intraprostatic hormone metabolism 6 mo prior to study entry. The above-listed substances were not allowed during the full study course, nor were any other accompanying treatments that could influence the study aims.

2.2. Study procedure

At the start of the 1-wk screening phase, after giving written informed consent, patients were evaluated using a detailed medical history, including German-validated versions of the NIH-CPSI [15], the International Prostate Symptom Score (IPSS) [16], and the *sexuality* domain of a life satisfaction questionnaire [17,18], as well as a physical examination, including prostate, external genitalia, vital parameters, routine laboratory tests, measurement of residual urine volume by ultrasound, and a standardised four-glass test localisation study [19]. Patients included in the screening phase were pretreated with azithromycin (250 mg q6h) for 1 d to eliminate atypical pathogens.

After 1 wk, the inclusion criteria were rechecked, and patients were included in the treatment phase when both conditions—*pain* domain of NIH-CPSI ≥7 and leukocytes ≥10 in VB3—were fulfilled. Patients were then allocated to receive either pollen extract (two capsules q8h, with the active substance consisting of 60 mg Cernitin T60 and 3 mg Cernitin GBX) or placebo (two capsules q8h, with identical capsulation and weight only containing the inactive substances in proportional doses as compared with the pollen extract) in a randomised order. Randomisation was carried out in blocks ($n = 4$) within the centre using a random number generator. The study medication was manufactured in accordance with the random scheme and Good Manufacturing Practice (GMP) and was labelled in accordance with regional law (AMG). The investigators were instructed to use the study drug in ascendant order of random numbers available in the respective trial centre.

NIH-CPSI (0–43) with its subscales (*pain* domain [0–21], *micturition* domain [0–10], and *quality of life* [QoL] domain [0–12]), IPSS (0–35), the *sexuality* domain of a life satisfaction questionnaire (0–42), a standard urologic examination, and the four-glass test were carried out at weeks 0 (before start of study drug), 6, and 12 (end of study drug). Residual urine was measured at weeks 0 and 12. At week 12 or at premature study end, a global assessment of the efficacy of treatment defined by five items (very good, good, moderate, bad, very bad) was collected from the patient and the corresponding physician.

Adverse events were documented during the whole course of study. Tolerability was assessed at study end by patient and physician using a scale with four items (very good, good, moderate, bad).

2.3. Statistical analysis and assessments

The primary target of the study was symptomatic improvement in the *pain* domain of the NIH-CPSI. This parameter had to be evaluated one sided in a statistical design according to Bauer and Köhne [20] with two sample size adaptive interim analyses. Secondary outcomes included symptomatic improvement of the NIH-CPSI total score and the *micturition* and *QoL* domains of the NIH-CPSI questionnaire as well as a decrease in the number of leukocytes in VB3. Further explorative outcome criteria were changes in the IPSS, the *sexuality* domain of the life satisfaction questionnaire, residual urine volume, and safety of the study drug. Additionally, qualitative efficacy parameters based on NIH-CPSI—namely, improvement of NIH-CPSI summary score by $\geq$ 25% and improvement of NIH-CPSI summary score by at least 6 points—were introduced as recommended by Nickel et al [21].

Usual methods of two-group comparisons were employed: student *t* test, Wilcoxon rank sum test, χ^2 test, and analysis of covariance with baseline values as covariates. The sample size estimation was based on a treatment difference of at least 3 $\pm$ 7 score points, a power of 1-β = 0.8, and a significance level of α = 0.025 one sided. At least 87 patients should be enrolled in each trial group. Using a three-stage adaptive procedure according to Bauer and Köhne [20], superiority of pollen extract versus placebo could be demonstrated with 70 (active) and 69 (placebo) patients.

3. Results

3.1. Disposition of patients

Thirty-seven of 176 screened patients were not included into the intention to treat (ITT) set of this trial (12 screening failures, 9 treatment failures [wrong allocation of trial drug], 4 GCP failures within one centre [cessation of the trial, no open access to study data], and 12 early drop-outs [no data postrandomisation] were identified). The analyses were carried out in the ITT (pollen extract: n = 70; placebo: n = 69) and in the per protocol (PP) population (pollen extract: n = 51; placebo: n = 60). Exclusions from the PP analysis were predominantly justified by bacterial infections at baseline, violations of the inclusion criteria regarding pain and leukocytes in VB3, and premature trial termination not due to efficacy reasons (Fig. 1).

3.2. Baseline characteristics

During the screening period between week −1 and week 0 (pretreatment with azithromycin), a slight improvement of

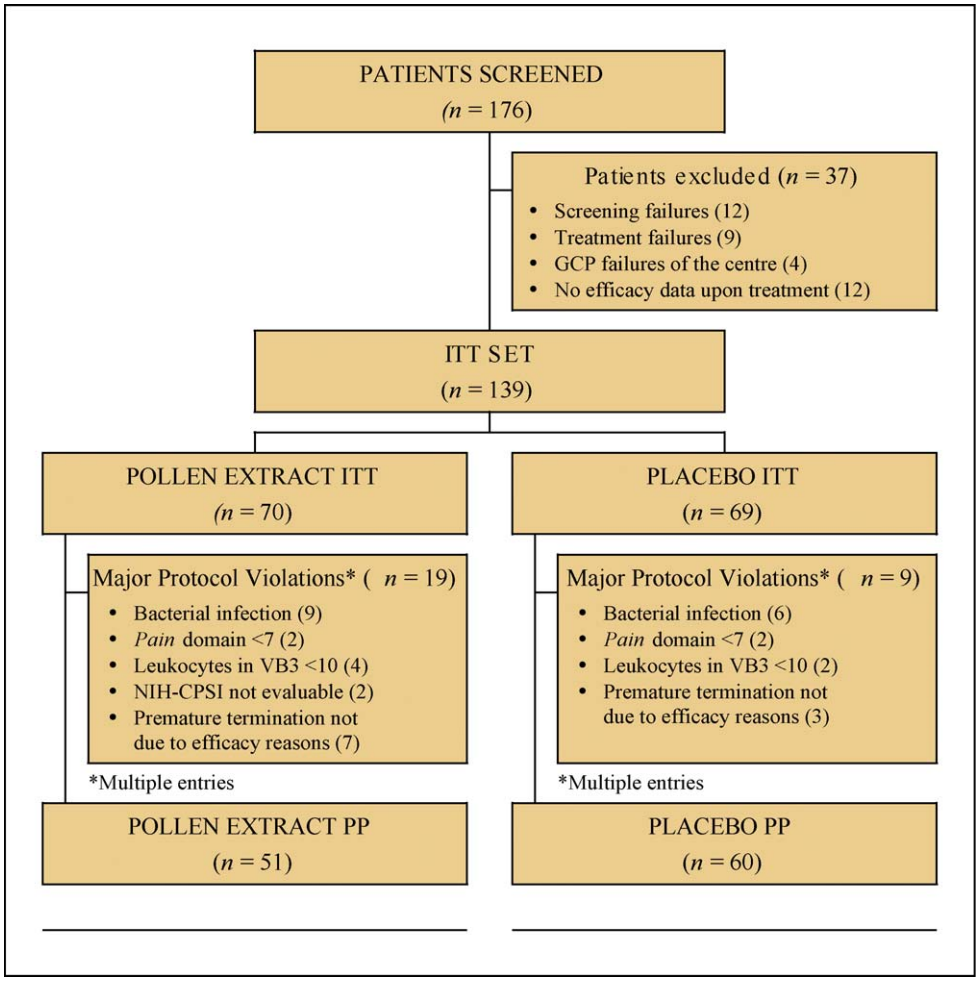

Fig. 1 – Disposition of patients.
GCP = Good Clinical Practice; ITT = intention to treat; VB3 = post–prostatic massage urine; NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index; PP = per protocol.

Table 1 – Baseline characteristics and clinical parameters at week 0*

Parameters	Pollen extract (*N* = 70)	Placebo (*N* = 69)	Overall (*N* = 139)
Patient age, yr (range)	39.7 ± 7.2 (20–54)	39.3 ± 9.1 (18–63)	39.5 ± 8.1 (18–63)
Height, cm	180 ± 8	178 ± 7	179 ± 7
Weight, kg	82.7 ± 12.2	81.2 ± 11.8	81.9 ± 12.0
Duration of disease, yr	4.4 ± 5.2	4.9 ± 6.2	4.6 ± 5.7
Duration of current symptoms, mo	7.6 ± 10.7	9.0 ± 16.0	8.3 ± 13.6
Prior medication† (%)	29 (41%)	32 (46%)	61 (44%)
NIH-CPSI	19.3 ± 5.1	20.3 ± 5.2	19.8 ± 5.2
Pain domain	10.0 ± 2.4	10.2 ± 2.6	10.1 ± 2.5
Micturition domain	2.8 ± 2.3	3.5 ± 2.5	3.2 ± 2.4
QoL domain	6.5 ± 2.5	6.7 ± 2.2	6.6 ± 2.4
IPSS	7.3 ± 5.3	8.5 ± 6.4	7.9 ± 5.9
Sexuality domain of life satisfaction questionnaire	2.2 ± 1.2	2.3 ± 1.1	2.3 ± 1.1
Leukocytes (field of vision: × 400) in VB3	17.7 ± 11.9	15.7 ± 6.4	16.7 ± 9.5
Residual urine volume, ml‡	11.9 ± 13.9	10.8 ± 12.3	11.4 ± 13.1

NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index; QoL = quality of life; IPSS = International Prostate Symptom Score; VB3 = post–prostatic massage urine; SD = standard deviation.

* Plus–minus values are means plus or minus SD. For NIH-CPSI, higher scores indicate more severe symptoms. The following score ranges are used: total score 0–43, *pain* score 0–21, *urinary* score 0–10, *QoL* score 0–12. For IPSS, higher scores indicate more severe symptoms on micturition; score range is 0–35. For the sexuality domain of the life satisfaction questionnaire, the score range is 1–7, and a lower score indicates less sexual satisfaction.

† Analgesics, antiphlogistics, antibiotics, anticholinergics, phytotherapeutics, α-blockers (median duration since last intake: 21 wk; minimum: 5 wk; maximum: 302 wk).

‡ Measurement at week −1.

the clinical signs was observed: The mean scores of NIH-CPSI decreased from 21.0 ± 5.0 to 19.8 ± 5.2, of IPSS from 8.5 ± 6.0 to 7.9 ± 5.9, of the *sexuality* domain of the life satisfaction questionnaire from 2.4 ± 1.2 to 2.3 ± 1.1, and of leukocytes in VB3 from 18.0 ± 9.8 to 16.7 ± 9.5. Baseline demographic characteristics and clinical parameters at week 0 are listed in Table 1. There were no significant differences between the two groups at the start of the double-blind treatment.

Localisation and circumstances of pain at baseline were indicated as (1) pain in the lower abdomen (71%); (2) pain in the perineum (64%); (3) pain in the testicles (55%); (4) pain in the tip of the penis (46%); (5) painful ejaculation (55%); (6) and painful micturition (46%).

3.3. *Primary analysis*

Using the preplanned primary outcome analysis procedure, a significant superiority of pollen extract versus placebo could be established at the third step ($p = 0.0080$). The rest of the results section show the overall findings in the total study population without consideration for the preplanned sequential construction analysis plan.

3.4. *Changes from baseline in the National Institutes of Health Chronic Prostatitis Symptom Index*

After 12 wk of treatment, the mean changes (plus or minus standard error [SE]) from baseline in the *pain* domain of the NIH-CPSI were −4.50 ± 0.42 in the pollen extract and −2.92 ± 0.42 in the placebo group. The higher improvement in the pollen extract group compared to placebo was statistically significant (ITT: −1.58 ± 0.59, $p = 0.0086$; Table 2). In the PP set, the treatment difference amounted to −2.14 ± 0.63 ($p = 0.0009$; Fig. 2).

The mean NIH-CPSI total score decreased from 19.18 to 11.72 in the pollen extract group and from 20.31 to 14.94 in the placebo group. There was a significantly higher baseline-adjusted improvement in the pollen extract group (−7.66 ± 0.70) compared to placebo (ITT: −5.16 ± 0.70, $p = 0.0126$; Table 2). In the PP set, the treatment difference was −3.95 ± 1.06 ($p = 0.0003$; Fig. 2). A definite improvement over baseline can be determined by a 25% decrease of the NIH-CPSI total score [21]. There was a significantly greater percentage of patients in the pollen extract group who demonstrated 25% improvement compared to the placebo group (ITT: 69.1% vs 48.5%, $p = 0.0147$; Table 2). Analysis of the percentage of patients who demonstrated a six-point decrease from baseline in the total score yielded a similar conclusion (ITT: 61.8% vs 42.6%, $p = 0.0256$; Table 2).

The *micturition* domain of the NIH-CPSI improved in both groups. A slightly higher improvement in the pollen extract group compared to placebo was not statistically significant (ITT: $p = 0.5469$; PP: $p = 0.1173$; Table 2).

The mean *QoL* domain of the NIH-CPSI decreased from 6.44 to 4.26 in the pollen extract group and from 6.68 to 5.28 in the placebo group. The baseline-adjusted improvement was significantly higher in the pollen extract group (−2.23 ± 0.27) compared to placebo (ITT: −1.35 ± 0.27, $p = 0.0250$; Table 2). In the PP set, the treatment difference was −1.50 ± 0.41 ($p = 0.0005$; Table 2).

3.5. *Changes from baseline in International Prostate Symptom Score*

The mean IPSS improved in both groups. A tendency in favour of pollen extract was statistically significant in the PP set only (ITT: $p = 0.0711$; PP: −1.53 ± 0.74, $p = 0.0418$; Table 2).

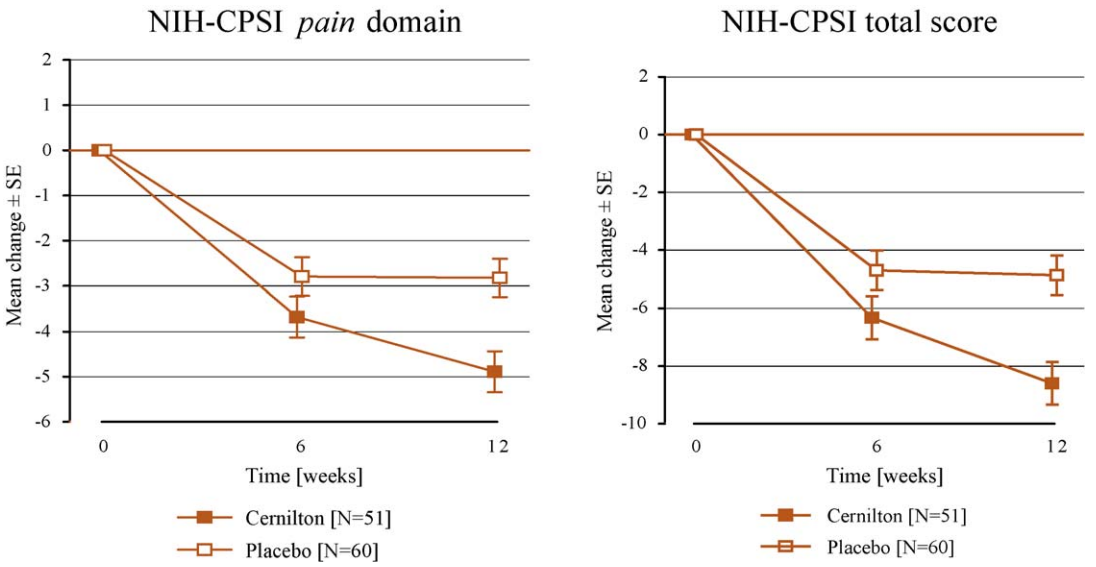

Fig. 2 – Mean change (plus or minus standard error [SE]) from baseline in the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) *pain* domain and in the NIH-CPSI total score after 6 and 12 wk of treatment with pollen extract (Cernilton group) or placebo (per-protocol group).

3.6. *Changes from baseline in the sexuality domain of the life satisfaction questionnaire*

The mean *sexuality* domain of the life satisfaction questionnaire decreased in both groups. A slightly higher improvement in the pollen extract group compared to placebo was not statistically significant (ITT: $p = 0.2964$; PP: $p = 0.4658$; Table 2).

3.7. *Changes from baseline in leukocytes in post–prostatic massage urine*

The mean changes from baseline in the number of leukocytes per field of vision were 5.0 in the pollen extract group and 3.0 in the placebo group. The Hodges–Lehmann estimate of the shift parameter from placebo to pollen extract was 2.0 (ITT: $p = 0.1243$; Table 2). In the PP set, the

Table 2 – Efficacy outcomes at week 12 in the intention to treat (ITT) and per protocol (PP) sets*

Parameter			Pollen extract		Placebo		Treatment difference	
NIH-CPSI	• *Pain* domain	ITT	68	−4.50 ± 0.42	69	−2.92 ± 0.42	−1.58 ± 0.59	$p = 0.0086$
	N, adj. mean ± SE	PP	51	−4.93 ± 0.46	60	−2.79 ± 0.43	−2.14 ± 0.63	$p = 0.0009$
	• *Micturition* domain	ITT	68	−1.02 ± 0.19	69	−0.86 ± 0.19	−0.17 ± 0.27	$p = 0.5469$
	N, adj. mean ± SE	PP	51	−1.27 ± 0.21	60	−0.82 ± 0.19	−0.46 ± 0.29	$p = 0.1173$
	• *QoL* domain	ITT	68	−2.23 ± 0.27	68	−1.35 ± 0.27	−0.88 ± 0.39	$p = 0.0250$
	N, adj. mean ± SE	PP	51	−2.62 ± 0.30	59	−1.12 ± 0.28	−1.50 ± 0.41	$p = 0.0005$
	• Total score	ITT	68	−7.66 ± 0.70	68	−5.16 ± 0.70	−2.49 ± 0.99	$p = 0.0126$
	N, adj. mean ± SEM	PP	51	−8.72 ± 0.77	59	−4.77 ± 0.72	−3.95 ± 1.06	$p = 0.0003$
	• 25% decrease in NIH-CPSI	ITT	68	69.1%	68	48.5%	–	$p = 0.0147$
	N, %	PP	51	76.5%	59	47.5%	–	$p = 0.0019$
	• Six-point decrease in NIH-CPSI	ITT	68	61.8%	68	42.6%		$p = 0.0256$
	N, %	PP	51	66.7%	59	40.7%	–	$p = 0.0065$
IPSS		ITT	69	−2.29 ± 0.44	69	−1.15 ± 0.44	−1.14 ± 0.63	$p = 0.0711$
N, adj. mean ± SE		PP	51	−2.52 ± 0.54	60	−0.99 ± 0.50	−1.53 ± 0.74	$p = 0.0418$
Sexuality domain of life satisfaction questionnaire		ITT	69	−0.30 ± 0.09	68	−0.17 ± 0.09	−0.13 ± 0.13	$p = 0.2964$
N, adj. mean ± SE		PP	51	−0.25 ± 0.10	59	−0.15 ± 0.09	−0.10 ± 0.14	$p = 0.4658$
Leukocytes in VB3		ITT	70	−5.0	69	−3.0	−2.0†	$p = 0.1243$‡
N, median		PP	51	−7.0	60	−4.5	−3.0†	$p = 0.0876$‡

NIH-CPSI = National Institutes of Health-Chronic Prostatitis Symptom Score; adj. = adjusted; SE = standard error; QoL = quality of life; IPSS = International Prostate Symptom Score; SEM = standard error of the mean; VB3 = post–prostatic massage urine.

* For the NIH-CPSI, higher scores indicate more severe symptoms; for the *QoL* domain, higher scores indicate a more negative effect; for the IPSS, higher scores indicate more severe symptoms; for the *sexuality* domain of the life satisfaction questionnaire, a lower score indicates less sexual satisfaction.

† Hodges–Lehmann estimate of shift parameters.

‡ Exact Mann-Whitney test.

Table 3 – Assessment of efficacy and tolerability

Set	Parameter		Pollen extract	Placebo
Efficacy				
ITT	Patient assessment, no. (%)	Good to very good	44 (62.9%)	28 (41.8%)
	($p = 0.0136$)	Very bad to moderate	26 (37.1%)	39 (58.2%)
		Missing values	–	2
	Investigator assessment, no. (%)	Good to very good	48 (69.6%)	39 (58.2%)
	($p = 0.1679$)	Very bad to moderate	21 (30.4%)	28 (41.8%)
		Missing values	1	2
PP	Patient assessment, no. (%)	Good to very good	35 (68.6%)	22 (36.7%)
	($p = 0.0008$)	Very bad to moderate	16 (31.4%)	38 (63.3%)
	Investigator assessment, no. (%)	Good to very good	38 (74.5%)	32 (53.3%)
	($p = 0.0212$)	Very bad to moderate	13 (25.5%)	28 (46.7%)
Tolerability				
ITT	Patient assessment, no. (%)	Very good	51 (72.9%)	49 (73.1%)
	($p = 0.7513$)	Good	15 (21.4%)	16 (23.9%)
		Moderate	3 (4.3%)	2 (3.0%)
		Bad	1 (1.4%)	–
		Missing values	–	2
ITT	Investigator assessment, no. (%)	Very good	52 (74.3%)	50 (74.6%)
	($p = 0.2122$)	Good	15 (21.4%)	17 (25.4%)
		Moderate	3 (4.3%)	–
		Bad	–	–
		Missing values	–	2

ITT = intention to treat; PP = per protocol.

shift amounted to −3.0 ($p = 0.0876$; Table 2); neither change was significant.

3.8. Changes from baseline in residual urine volume

Residual urine volume was ≤50 ml in all patients at any time measured, and there was no significant change from baseline or difference between groups.

3.9. Assessment of efficacy

The global assessment of efficacy by the patient showed significantly higher rates of *very good* or *good* results in the pollen extract group (ITT: 62.9%; PP: 68.6%) as compared to placebo (ITT: 41.8%; PP: 36.7%; Table 3). Regarding the global assessment of efficacy by the physician, a significant treatment difference was seen in the PP set only (pollen extract 74.5%; placebo: 53.3%; Table 3).

3.10. Adverse events, physical examination, safety laboratory

Adverse events were reported in 12.9% of patients for pollen extract and 14.5% of patients for placebo ($p = 0.7790$). No statistically significant differences were seen between groups on the level of MedDRA System Organ Class. No or an unlikely causal relationship with study medication was noted in the majority of events. In only two patients—both treated with pollen extract—adverse events possibly attributable to study drug were documented: mild gastrointestinal disorders that caused a short treatment interruption and moderate pain (not otherwise specified) that caused discontinuation of treatment. Serious adverse events were reported in three patients in the pollen extract group and in two patients in the placebo group. All serious adverse events were hospitalisations resulting from concomitant illnesses and not attributed to study drug administration. Physical examinations, including vital signs, and the laboratory examinations showed no relevant changes from baseline.

3.11. Assessment of tolerability

In both study groups, the tolerability was rated *very good* in >70% of patients (Table 3).

4. Discussion

Although antibiotic treatment is the standard treatment for chronic bacterial prostatitis [22], there is no standard treatment of CP/CPPS to date [23,24]. Even the evidence to recommend α-blocker therapies [2] is now in dispute [4]. Apart from that, a variety of other treatment options are reported, such as antibiotics, anti-inflammatory agents, phytotherapeutics, and various other modalities [5,8,21,25–29]. All treatment modalities, however, showed rather limited effects on the symptoms experienced in CP/CPPS, of which pain and dysfunctional voiding cause the greatest morbidity and a poor QoL [30]. Given the lack of proven efficacy of conventional therapies, alternative treatment options are urgently needed. Additionally, long-term treatment is usually conducted for CP/CPPS patients. Therefore, phytotherapeutics— amongst which are pollen extract, quercetin, saw palmetto, or terpenes—are an interesting option because of their generally low side-effects; however, few have been subjected to scientific scrutiny and prospective controlled clinical trials [8,26–28].

Cernilton, a standardised pollen extract mixture, has been used for treatment of CP/CPPS for almost 20 yr [8,13]. The exact mechanism of action is largely unknown; however, an anti-inflammatory potential associated with

cyclo-oxygenase and lipoxygenase inhibition is discussed and substantiated by in vitro experiments [9–11] and could be beneficial for patients with CP/CPPS [31].

This study is the first to compare pollen extract to placebo in a large, clearly defined patient cohort. The study focused on inflammatory CP/CPPS (NIH category IIIA), because elevated numbers of leukocytes in VB3 are indicative of an inflammatory prostatitis syndrome [32] and therefore defines a clear study cohort. To exclude possible contamination of this study cohort by infection with atypical pathogens, a 1-wk run-in phase, during which all patients were treated with azithromycin, was introduced before assessment of baseline and start of study drug medication. To exclude patients with LUTS resulting from BOO, patients with elevated residual urine (>50 ml) were also excluded.

Both study groups experienced progressive improvement in symptoms over 12 wk as measured by the NIH-CPSI total score and the subdomains *pain, micturition,* and *QoL*. However, the pollen extract group has significantly more improvement for the NIH-CPSI total score and the subdomains *pain* and *QoL* than did the placebo group. Interestingly, the differences between the two groups became significant after the sixth week (Fig. 2), suggesting that a long treatment period is required in this condition. Clinically significant improvement, as defined by a 25% (or six-point) improvement of the NIH-CPSI total score and a three-point improvement in the *pain* subdomain, was only seen in the pollen extract group, not in the placebo group (Table 2). The *micturition* subdomain of the NIH-CPSI did not reveal any significant difference concerning the improvement between the treatment groups, probably because symptoms in the *micturition* domain were generally low, which was also substantiated by the rather low symptoms in the IPSS (Table 2). The same holds true for the *sexuality* domain of the life satisfaction questionnaire. The global assessment on the efficacy of the treatment by the patient also exhibited a significantly better improvement for pollen extract compared to placebo.

Interestingly, the leukocytes in VB3 also showed a decrease in both arms. The meaning of cellular markers of inflammation in prostate secretions or VB3 in patients with CP/CPPS is still unclear, although the improvement of symptoms in this study was accompanied by a reduction of leukocytes in VB3. However, as there was no significant difference between the two groups, leukocytes cannot be correlated with clinical success in this study.

The pollen extract was generally well tolerated over the full study period.

5. Conclusions

This placebo-controlled study showed that 12 wk of pollen extract in men diagnosed with inflammatory CP/CPPS (NIH category IIIA) resulted in a significantly higher symptom improvement compared to placebo and was well tolerated. This symptom improvement was mainly the result of a significant response in the pain symptomatology, which consequently led to a significant improvement in the total NIH-CPSI score and the *QoL* subdomain but not in the *micturition* subdomain. Pollen extract can therefore be recommended for patients with CP/CPPS in the dosage and duration studied.

Author contributions: Florian M.E. Wagenlehner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wagenlehner, Weidner.
Acquisition of data: Wagenlehner, Ludwig, Schneider, Weidner.
Analysis and interpretation of data: Wagenlehner, Schnitker, Brähler.
Drafting of the manuscript: Wagenlehner.
Critical revision of the manuscript for important intellectual content: Wagenlehner, Weidner.
Statistical analysis: Schnitker.
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