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A phase II randomised double-blind placebo-controlled clinical trial investigating the efficacy and safety of ProstateEZE Max: A herbal medicine preparation for the management of symptoms of benign prostatic hypertrophy

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Benign prostate hypertrophy;
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Summary
Objective: The aim of the clinical trial was to evaluate the efficacy and safety of ProstateEZE Max, an orally dosed herbal preparation containing *Cucurbita pepo*, *Epilobium parviflorum*, lycopene, *Pygeum africanum* and *Serenoa repens* in the management of symptoms of medically diagnosed benign prostate hypertrophy (BPH).
Design: This was a short-term phase II randomized double-blind placebo controlled clinical trial.
Setting: The trial was conducted on 57 otherwise healthy males aged 40—80 years that presented with medically diagnosed BPH.
Intervention: The trial participants were assigned to receive 3 months of treatment (1 capsule per day) with either the herbal preparation ($n = 32$) or a matched placebo capsule ($n = 25$).
Outcome measures: The primary outcome measure was the international prostate specific score (IPSS) measured at baseline, 1, 2 and 3 months. The secondary outcomes were the specific questions of the IPSS and day-time and night-time urinary frequency.
Results: There was a significant reduction in IPSS total median score in the active group of 36% as compared to 8% for the placebo group, during the 3-months intervention ($p < 0.05$). The day-time urinary frequency in the active group also showed a significant reduction over the 3-months intervention (7.0—5.9 times per day, a reduction of 15.6% compared to no significant reduction change for the placebo group (6.2—6.3 times per day) ($p < 0.03$). The night-time urinary frequency was also significantly reduced in the active group (2.9—1.8, 39.3% compared to placebo (2.8—2.6 times, 7%) ($p < 0.004$).

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Conclusion: The herbal preparation (ProstateEZE Max) was shown to be well tolerated and have a significant positive effect on physical symptoms of BPH when taken over 3 months, a clinically significant outcome in otherwise healthy men.

Introduction

Benign prostatic hyperplasia (BPH) (also known as hypertrophy) is the non-malignant enlargement of the prostate gland characterized by the proliferation of both the stromal and epithelial elements within the periurethral and transition zone of the prostate, resulting in obstructive and irritative symptoms of the lower urinary tract in men.[1–3] BPH is present in more than 50% of men aged over 60 years with 15% to 30% of these men reporting lower urinary tract symptoms (LUTS). However, not all symptoms are caused by the hyperplasia, and many are attributable to various types of dysfunction of smooth muscle (detrusor) in the bladder.[4] Clinical evaluation for BPH includes the presence of LUTS such as hesitancy in initiation of micturition, straining, weak force of stream, stopping and re-starting or interruption of the stream, a feeling of incomplete voiding, terminal dribbling, dysuria (painful urination) and increased nocturia (night-time urination).[3,5] However, it is reported that up to one third of men with low flow rates do not have bladder outflow obstruction but have detrusor underactivity that results in reduced stream.[3,6]

Although nearly all men develop histological BPH, the degree of prostatic enlargement resulting from hyperplasia is highly variable.[1] Frequency of symptoms and prostate enlargement naturally increases with age. At 30 years of age, the prostate weighs approximately 20 g and remains so unless BPH develops. By 40 years, hyperplasia is present in 8% of men, increasing to 60% in their seventies and 90% in those aged over 80 years.[4,7,8] About 25% of men experience moderate to severe LUTS, which greatly affects their quality of life and potential risk of complications such as recurrent urinary tract infections, bladder calculi (stones) and haematuria (blood in urine).[4,9]

The management of BPH is typically multi-modal comprising pharmacotherapy, herbal medicines, life-style modifications and in severe cases, surgery. Pharmacotherapy treatment utilises α1-adrenergic receptor antagonists and 5α-reductase inhibitors. These α1 agonists block the α1adrenoreceptors at the bladder neck and in prostatic smooth muscle causing muscle relaxation, however, about 15% of patients have mild side-effects such as headache, dizziness, drowsiness, postural hypotension, and rarely syncope (<1%).[4] The 5α-reductase inhibitors have anti-androgenic activity by suppressing the formation of dihydrotestosterone from testosterone. Dihydrotestosterone is ten times more active than testosterone and plays a central role in the development of the prostate, but the biochemical factors underlying prostate enlargement remain unclear.[4,5,10] Adverse effects associated with 5α-reductase inhibitors (i.e. finasteride) include ejaculatory dysfunction, loss of libido and impotence.[4,11]

Over the last two decades there has been a strong interest in the use of herbal medicine extracts to treat BPH, and these have included *Seronoa repens* (Saw Palmetto), *Equisitum* (Field or Common Horsetail) and *Epilobium* (Fireweed).[12–14] In Europe, particularly Germany, Austria, Italy and France, phytotherapy is often the first line treatment administered for the management of symptoms of BPH.[14] The earliest commonly prescribed botanical extracts were derived from *S. repens*[15] and *Epilobium parviflorum*. The German commission E monograph also provides documentation on the traditional use of the oil from *Cucurbita pepo* (Pumpkin seed) for the treatment of prostate enlargement in Europe.[16] In Africa, *Pygeum africanum* (African prune tree) was used traditionally to treat bladder problems and *Old man's disease* before being introduced to Western medicine.[17] The benefits of lycopene in prostate health have had a more recent history. Early epidemiological studies reported that diets rich in tomato (*Solanum lycopersicum*) were correlated with a lower incidence of prostate cancer.[18,19] There is now a growing body of clinical evidence attributing these benefits for treatment of prostate problems to the lycopene content of the fruit.[20]

This study was designed to evaluate the effect of an herbal preparation (ProstateEZE Max) containing *C. pepo*, *E. parviflorum*, lycopene, *P. africanum* and *Serenoa repens* for the management of LUTS symptoms in men medically diagnosed with BPH.

Materials and methods

Recruitment and randomization: The participants were recruited through local media advertising and clinical trial databases. Participants that met the inclusion criteria were healthy males aged between 40 and 80 years of age with medically diagnosed (histologically) BPH, having a minimum score of 8 on the international prostate symptom score (IPSS) questionnaire.

Potential participants were excluded if they had used a pharmaceutical or natural therapy for BPH or other urological symptoms within the last 30 days. Men were ineligible if they had recently started a bladder-training program; had urogenital surgery within the last 6 months; had bladder biopsy and/or cystoscopy and biopsy within the past 30 days; had an indwelling catheter or practiced self-catheterisation. Men were also ineligible if they had been medically diagnosed with chronic persistent local pathology (i.e. interstitial cystitis, bladder stones), were receiving/prescribed anticoagulation therapy; had been diagnosed with severe renal and/or hepatic insufficiency; and had been diagnosed with genital anatomical deformities. Men were also ineligible to participate if they had uncontrolled diabetes mellitus, a history of spinal cord injury, an uncontrolled psychiatric disorder and/or abnormal secondary sexual characteristics, had diagnosed prostatic cancer, had current or a history of chronic alcohol and/or illicit drug abuse, or had participated in any other clinical trial during last 30 days.