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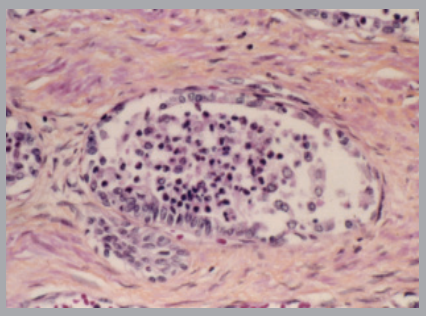

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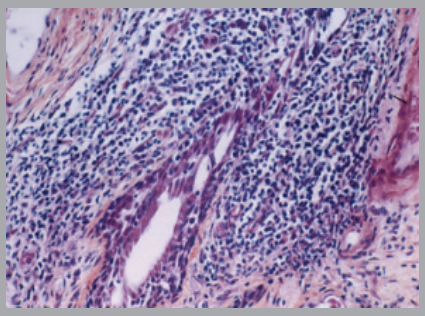

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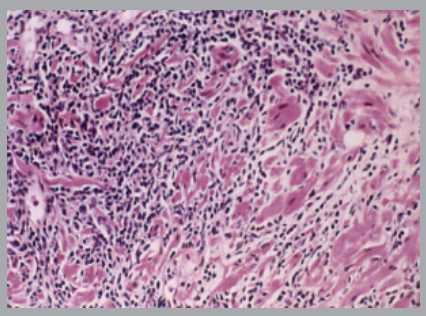

Stromal inflammation

Inflammation and Prostatic Diseases: From Bench to Bedside

From a Satellite Symposium to the 30th European Association of Urology Annual Congress

20-24 March 2015, Madrid, Spain

Guest Editor:
Javier Burgos, Madrid, Spain

Cover images, from left to right

Prostatic glandular inflammation, periglandular inflammation, stromal inflammation

Cover images courtesy of Professor J. Curtis Nickel.

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Sponsored by Pierre Fabre Médicament.

The papers in this supplement were peer reviewed by two independent reviewers

CONTENTS

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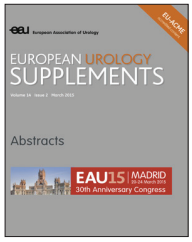

European Association of Urology

Editorial

Inflammation and Prostatic Diseases: From Bench to Bedside

Javier Burgos[a,*]

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Benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) is the most commonly diagnosed urologic disease in older men. BPH is characterised by enlargement of the prostate gland due to age-related progressive proliferation of stromal and glandular prostatic cells [1,2]. The overall prevalence of BPH in the male population is reported to be >70% at age 60 yr and >90% at age 70 yr [3,4]. Histologically confirmed prostatic inflammation is a common finding in biopsy and surgical specimens from elderly male patients with BPH and is reportedly present in 43–77% of samples [5–7]. Due to increased longevity of the male population and more thorough clinical investigation (earlier consultations and screening programmes), the BPH diagnosis is becoming increasingly common [8].

Although BPH aetiology remains somewhat uncertain, a number of factors are known to be involved in its pathogenesis. BPH is clearly associated with the ageing process. Other risk factors include hormonal alterations (presence of testicular androgens), a proinflammatory environment (insulin resistance, secondary hyperinsulinaemia, and the metabolic syndrome), increased sympathetic nerve activity, and local (prostatic) inflammation. A review was performed recently by Gandaglia et al [9]. In particular, and in relation to the theme of this symposium, the role of chronic prostatic inflammation has generated much interest in the past decade [2,9–11]. Patients with BPH and chronic inflammation have larger prostate volumes, are predisposed to more severe LUTS, are more likely to develop acute urinary retention, and have a poorer response to conventional medical therapy than patients without inflammation [2,9,11]. Although histologic evaluation for prostatic inflammation would be the ideal confirmatory diagnostic procedure, it can be performed only in patients who have undergone biopsy for suspected prostate cancer. Other predictors of chronic inflammation investigated have included prostatic calcifications, prostate volume, LUTS severity, symptoms, poor response to medical treatment, and urine and serum biomarkers [9,12].

Biomarkers represent a potentially interesting noninvasive alternative to biopsy for detecting chronic prostatic inflammation. Prostate tissue often contains increased inflammatory infiltrates, including T cells and macrophages [11,13]. Cytokines are key mediators of inflammation and may play an important role in the initiation and progression of BPH. Proinflammatory cytokines with potential application as predictive biomarkers for BPH include interleukin-8 in seminal plasma; monocyte chemotactic protein 1 in prostatic secretions; and urinary biomarkers CCR7, CTLA4, ICOS, and CD40LG. Each of these urinary biomarkers has been shown to be upregulated at the messenger RNA level in patients with chronic prostatic inflammation [12]. Recently, Engelhardt and colleagues found a high incidence of prostatic calcification in patients with obstructive BPH; the chronic inflammatory reaction of the prostate gland appeared to be triggered by the cytokine-induced inflammatory effect of tumour necrosis factor α [14]. The pivotal role played by chronic prostatic inflammation in the pathogenesis and progression of symptomatic BPH suggests potential benefits with use of novel anti-inflammatory medical therapies in this clinical setting.

At the European Association of Urology (EAU) congress in 2013, evidence was reviewed implicating inflammation as a largely neglected factor in BPH and LUTS [15]. In the current communication series, recent evidence pertaining to BPH pathophysiology was evaluated with a focus on the role of prostatic inflammation in the development and progression of BPH [16]. Key clinical findings from the REDUCE and MTOPS studies were reviewed [17], and the potential for new treatments with anti-inflammatory activity in the prostate was discussed. There is evidence of clinical benefit with agents that inhibit cyclooxygenase (COX) in the arachidonic acid cascade (eg, nonsteroidal anti-inflammatory drugs and COX-2 inhibitors), although their use may be limited by safety issues.

In 2013, the role of the phytotherapeutic agent *Serenoa repens* was reviewed with a focus on its anti-inflammatory

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effects [18,19]. At that juncture, the PERMIN study had just commenced. PERMIN was a randomised controlled trial comparing hexanic extract of *Serenoa repens* (Permixon; Pierre Fabre Medicament, Castres, France) with tamsulosin in patients with moderate to severe BPH-related LUTS; full results have recently been published [20]. At the EAU 2015 congress, some key findings from PERMIN were presented and interpreted for their clinical relevance [21].

Many brands of *Serenoa repens* produced from different botanical sources and using a variety of extraction procedures are available worldwide. Although the hexanic lipidosterolic extract is the most widely researched product, it is useful to know whether other brands are comparable in terms of efficacy and safety [22]. The European Medicines Agency recently concluded that available evidence for the hexane extract supported its use as "a well-established medicinal product with recognised efficacy and acceptable safety," whereas data for the two other main extracts (ethanolic and supercritical CO_2 extracts) did not support such a conclusion [23].

Finally, a large body of evidence supports the concept that prostatic inflammation plays a key role in the pathogenesis and progression of BPH. This has opened the gateway to new avenues of treatment based on targeting inflammatory mediators. *Serenoa repens* has exhibited anti-inflammatory effects in pharmacologic studies, and the hexanic extract has now produced positive results in a well-controlled clinical trial. Future studies are expected to confirm these positive clinical findings.

Conflicts of interest

Javier Burgos has received fees for serving as a speaker and/or consultant for Astellas, Janssen, Pierre Fabre, and Sanofi within the past 3 yr.

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Inflammation in the Pathophysiology of Benign Prostatic Hypertrophy

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Article info

Keywords:
Benign prostatic hyperplasia
Inflammation
Pathogenesis

Abstract

Context: Benign prostatic hyperplasia (BPH) is classically understood to be a disturbance in prostate homeostasis, but the underlying questions of how and why this disturbance occurs have yet to be answered definitively. An increasing body of evidence points to inflammation as a central component of the pathogenic process of BPH.

Objective: To review recent evidence regarding the association between histologic prostatic inflammation and the development and progression of BPH.

Evidence acquisition: This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed.

Evidence synthesis: Evidence from a canine model of BPH and human prostate tissue has confirmed the presence of inflammation as a component of BPH. Pronounced inflammation was observed in dogs with hormonally induced prostatic hyperplasia. Longitudinal biopsy indicated that the cell-mediated and humoral immune response was preceded by hyperplasia. In surgically treated human BPH specimens, high-level inflammation was significantly associated with prostate enlargement and symptom evolution. Current opinion is that chronic inflammation and endocrine changes lead to disturbed homeostasis and tissue damage or, alternatively, that abnormal stem cell expansion and disturbed homeostasis lead to chronic inflammation and endocrine changes. Either way, a "vicious cycle" is initiated that leads to hyperplasia with fibrosis and changes in prostate tissue composition.

Conclusions: Increased insight into BPH pathogenesis indicates that restoring tissue endocrine metabolism and reducing chronic inflammation are prostate-specific targets for the treatment of BPH.

Patient summary: Increasing insight into benign prostatic hyperplasia (BPH) pathogenesis indicates that restoring tissue endocrine metabolism and reducing chronic inflammation are prostate-specific targets for treatment of BPH.

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1. Introduction

Benign prostatic hyperplasia (BPH) is the most common urologic disease in elderly men, with an estimated prevalence of >70% at age 60 yr and >90% at age 70 yr [1,2]. BPH is a histologic diagnosis characterised by hyperproliferation of stromal and glandular cells in the transition zone and periurethral areas of the prostate gland [2,3]. The condition is often expressed clinically in the form of lower urinary tract symptoms (LUTS) [3,4]. Although several theories have been proposed to explain the progressive hyperplastic processes underlying BPH, the exact pathogenesis is not yet fully understood. Over the past decade in particular, accumulating evidence has suggested that inflammation contributes to the development and progression of prostatic hyperplasia [5]. In this review, some earlier aetiological theories are revisited, and evidence for inflammation as a central component of BPH pathogenesis is examined.

2. Evidence acquisition

This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed. The article is complemented by relevant related literature identified on PubMed and by hand searches of key references.

3. Evidence synthesis

3.1. Classical understanding of benign prostatic hyperplasia aetiology

Over the years, the classical understanding of BPH aetiology has centred around three main theories: the dihydrotestosterone (DHT) hypothesis, the embryonic reawakening theory, and the stem cell theory. Although each theory is not without some merit, none has been able to define the aetiologic trigger events responsible for progressive prostatic enlargement.

In the early 1980s, the prevailing assumption was that BPH resulted from an increased concentration of DHT, the most powerful androgen driving differentiation and growth in the early adult male. Although this hypothesis was ultimately proved incorrect, as DHT concentrations in prostate tissue actually decrease with age, 5α-reductase inhibitors were developed to treat BPH and continue to be prescribed with some success. Lending further support against the DHT hypothesis was the knowledge that DHT drives differentiation, not proliferation, in the prostate gland of an adult male. A defining event in the aging prostate gland is the increased ratio between prostatic oestradiol and DHT [6], which results in imbalance or disbalance in endocrine homeostasis.

During ontogenesis, epithelial buds arising from the urogenital sinus penetrate the surrounding mesenchyme and branch into the ductal system to form the primordium of the transition zone. After birth, prostatic morphogenesis reverts to the embryonic state [7]. According to the embryonic reawakening theory, the embryonic potential to drive prostate morphogenesis is reawoken in adulthood. Although plausible, this theory simply redefines the question, as it fails to identify factors or mechanisms responsible for the reawakening.

The stem cell theory is arguably the most complex of the various hypotheses and is intertwined with embryonic reawakening. The morphogenic potential of the entire prostate epithelium is known to reside within a small fraction of adult stem cells [8]. In BPH, it is proposed that epithelial growth results from alterations in stem cell properties which give rise to a clonal expansion of cell populations that develop into exocrine basal and luminal cells and neuroendocrine epithelial cells [9]. Branching morphogenesis increases glandular structures, leading to prostatic enlargement. As with embryonic reawakening, however, this theory fails to identify the factors or mechanisms that underlie the "derailment" of stem cell expansion.

Although the classical model of BPH can be described in general terms as a disturbance in prostate homeostasis, the real question is why and how this disturbance occurs. The current understanding is that prostatic inflammation is either an initiating or a promoting event, but either way, the presence of inflammation explains many of the uncertainties in BPH models developed to date.

3.2. The role of inflammation in prostate abnormalities

Mahapokai and colleagues investigated the immune response in hormonally induced prostatic hyperplasia in the dog (the best-described model for human BPH identified to date) [10] and followed the process sequentially by biopsy [11]. Marked infiltration with immune effector cells was observed. The majority of inflammatory cells (>80%) in the mononuclear infiltrates were T lymphocytes. B lymphocytes were found mainly in areas with marked follicular formation and diffuse infiltration, and macrophages were found primarily in areas with atrophic and cystic changes with and without inflammation. Longitudinal biopsy indicated that the cell-mediated and humoral immune response was preceded by hyperplasia. In brief, hormonal disbalance as a primary event led to pronounced inflammation, and the processes appeared to work in concert. Regardless of whether inflammation was a cause, a consequence, or a crucial promoting factor in the prostatic enlargement and BPH progression observed in this model, it was a conspicuous component of the process.

Although human samples are typically more representative of a given disease than animal models, in the case of BPH, human specimens provide a single snapshot rather than longitudinal evaluation of the process over time. Notwithstanding this limitation, Robert and colleagues examined a large cohort of surgically treated BPH specimens to evaluate inflammation intensity and to investigate the relationship between inflammation and LUTS [12]. A total of 227 prostatectomy specimens were used to build a tissue microarray of four spots per patient. A control tissue microarray was constructed using normal prostatic tissue samples from 10 donors after death. The inflammation score was determined on the basis of six cytologic parameters

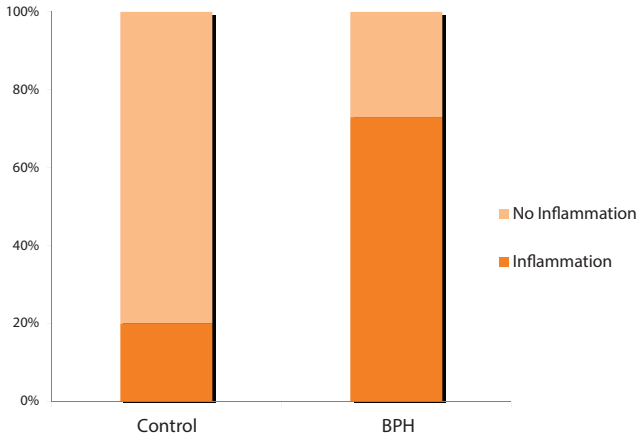

Fig. 1 – Incidence of prostatic inflammation in prostatectomy specimens from controls (donors after death) and patients with symptomatic benign prostatic hyperplasia [12]. BPH = benign prostatic hyperplasia.

(lymphocytes, macrophages, polynuclear leukocyte infiltrates, glandular atrophy, glandular destruction, and tissue fibrosis) and five immunohistochemistry markers: CD3 antibody for T lymphocytes, CD4 antibody for T4, CD8 antibody for T8, CD20 antibody for B lymphocytes, and CD163 antibody for macrophages. The median inflammation level was used to divide patients into two groups (high and low levels).

A significant increase in inflammatory processes was observed, with good correlation between cytology and immunohistochemistry (r = 0.772; p < 0.0001). Significant prostatic inflammation was recorded in 73% of surgically treated BPH specimens versus 20% of specimens from donors after death (Fig. 1). A high level of inflammation was associated significantly with greater prostate volume (104 vs 90 g; p = 0.002) and a higher mean International Prostate Symptom Score (21.2 vs 12.8; p = 0.02). No differences were observed between high- and low-level inflammation groups for age, prostate-specific antigen level, or uroflowmetry. The inflammatory infiltrate consisted of 37.4% macrophages, 37% T lymphocytes (two-thirds T8 and one-third T4), and 12.9% B lymphocytes. Although an inflammation diagnosis was considered feasible on biopsy cores using either cytologic or immunohistochemical techniques, for clinical purposes, the author identified the need for less invasive diagnostic methods such as biomarkers [13].

The presence of inflammation as a component of BPH has been confirmed in both a canine model and human prostate tissue. Clinical questions that arise are whether inflammation is a key factor in BPH progression and/or a potential actionable target for BPH therapy.

Known causes of inflammation include infectious agents, cell trauma due to oxidative stress, hypoxia, autoimmunity, and endocrine changes. Aging-related visceral fat accumulation may initiate or contribute to inflammation through the secretion of inflammatory adipokines [14]. In the case of BPH pathogenesis, the current hypothesis is that, whether cause or consequence, chronic inflammation is likely to be part of a domino effect (Fig. 2). Chronic inflammation and endocrine changes lead to disturbed homeostasis and tissue damage that, in turn, lead to compensatory cellular proliferation.

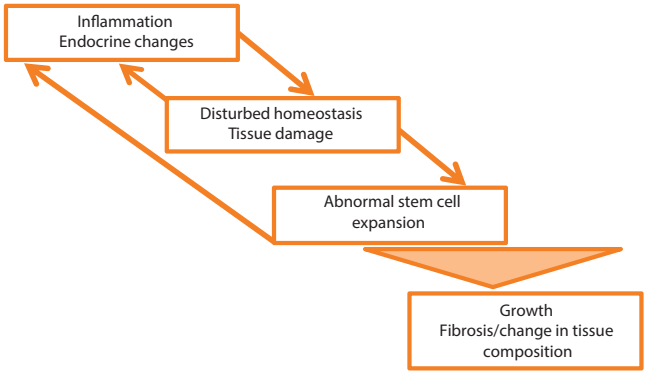

Fig. 2 – Proposed mechanism for the aetiology of benign prostatic hyperplasia. Inflammation is part of a "vicious cycle" of glandular changes that lead to alterations in prostate tissue volume and architecture.

Alternatively, it is possible that abnormal stem cell expansion and disturbed homeostasis lead to chronic inflammation and endocrine changes. Either way, a vicious cycle is initiated that leads to hyperplasia along with fibrosis and changes in tissue composition. Although the hypothesis requires confirmation, it already provides an interesting and testable model about the role of inflammation in the development and progression of BPH.

4. Conclusions

Current understanding of BPH aetiology suggests that gradual endocrine changes and chronic inflammation disturb prostate homeostasis, particularly the interaction between stroma and epithelium; the stroma harbours the infectious components. Glandular changes lead to alterations in tissue architecture and often volume. Consequently, restoring tissue endocrine metabolism and reducing chronic inflammation are prostate-specific targets for the treatment of BPH. As knowledge of the disease processes steadily improves, it is becoming increasingly clear that BPH is much more than an enlarged prostate.

Conflicts of Interest

The author has nothing to disclose.

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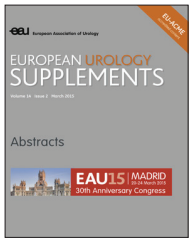

European Association of Urology

Role of Prostatic Inflammation in the Clinical Presentation of Benign Prostatic Hyperplasia

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Article info

Keywords:
Inflammation
Benign prostatic hyperplasia
Lower urinary tract symptoms
Metabolic syndrome

Abstract

Context: Although it was hypothesised >20 yr ago that prostatic inflammation could influence clinical presentation and possibly surgical outcome in patients with benign prostatic hyperplasia (BPH)-related lower urinary tract symptoms (LUTS), only more recently has compelling substantiating evidence become available.
Objective: To review the evidence for the role of inflammation in the clinical presentation and treatment of BPH/LUTS.
Evidence acquisition: This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed.
Evidence synthesis: Studies such as the large-scale Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial and others have clearly demonstrated the association between the presence and/or degree of histologic inflammation and its impact on parameters such as prostate volume, voiding LUTS, and type of surgery required to treat BPH. Prostatic inflammation has been shown to increase by threefold the risk for acute urinary retention, an end point in the natural progression of BPH. Inflammation has been proposed as the common thread between the metabolic syndrome and BPH/LUTS, which frequently co-exist, and offers new therapeutic targets for medical treatment. Motivated patients can undertake lifestyle modifications (eg, weight, diet, exercise) to potentially prevent the need for surgery. Selective cyclooxygenase-2 inhibition appears promising as a therapeutic approach for inflammation, but its suitability for long-term use in the BPH population is limited by safety concerns.
Conclusions: Greater understanding of the relationship between inflammation and the clinical presentation of BPH/LUTS provides an opportunity to effect clinical changes to improve treatment outcomes.
Patient summary: An increased understanding of the role of prostatic inflammation in the pathogenesis, symptomatology, and progression of benign prostatic hyperplasia (BPH) is likely to change the treatment paradigm for BPH.

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1. Introduction

Although it was hypothesised >20 yr ago that prostatic inflammation could influence clinical presentation and possibly surgical outcome in patients treated for symptomatic benign prostatic hyperplasia (BPH) [1], substantiating evidence was scarce. Since then, evidence has steadily accumulated that points to the role of inflammation in the pathogenesis and progression of BPH and its relationship to lower urinary tract symptoms (LUTS). The current challenge is to apply this knowledge to effect clinical changes that will improve treatment outcomes. This review examined evidence for the role of inflammation in the clinical presentation of BPH-related LUTS (BPH/LUTS).

2. Evidence acquisition

This article is based primarily on material presented at a satellite symposium entitled "Inflammation and Prostatic Diseases: From Bench to Bedside", held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed. The article is complemented by relevant related literature identified on PubMed and by hand searches of key references.

3. Evidence synthesis

3.1. The role of inflammation in lower urinary tract symptoms due to benign prostatic hyperplasia and progression

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) clinical trial provided a unique opportunity to examine longitudinally the effects of prostatic inflammation on patient outcomes. In this international multicentre study, >8000 men aged 50–75 yr with elevated prostate-specific antigen (PSA) levels but negative prostate biopsy (6–12 cores) were randomised to receive dutasteride or placebo for up to 4 yr [2]. At baseline, the type and severity of prostatic inflammation were documented to determine whether inflammation might predict outcomes such as prostate cancer, BPH/LUTS, or progression over the 4-yr study period. Inflammation was described by type (acute or chronic) and graded on a modified four-point scale (none = 0, mild = 1, moderate = 2, marked = 3) based on inflammatory cell density and extent of tissue involvement [3]. LUTS were assessed using the International Prostate Symptom Score (IPSS).

Data were available for 8224 men [4]. At baseline, 77.4% of patients had chronic inflammation, which was of a mainly mild (89.0% of cases) or moderate (10.7%) grade. Acute prostatic inflammation was present in 15.4% of patients and was mainly mild (97.9%). No inflammation was present on biopsy in 21.8% of patients. Compared with the group with no inflammation, the group with grade 1, 2, or 3 chronic inflammation had a slightly but significantly higher mean total IPSS (8.8 vs 8.2; $p < 0.0001$). There was no association between acute inflammation and LUTS. Although the correlation between average chronic inflammation and total IPSS was weak (r = 0.057; $p < 0.0001$), possibly because of study entry criteria which selected older men and excluded men with clinical prostatitis or severe LUTS, the results nonetheless suggested involvement of inflammation in the pathogenesis of BPH and provided first evidence of the relationship between the degree of chronic inflammation and the degree of BPH/LUTS. The findings were subsequently corroborated in a study of patients with a more advanced disease course.

Robert and colleagues examined the relationship between inflammation intensity and clinical outcomes in 282 patients who had undergone surgery for complicated and/or symptomatic BPH [5]. Prostatectomy specimens were used to build a tissue microarray (four spots per patient) and prostatic inflammation was graded using a combination of cytologic parameters and immunohistochemical markers. Patients were separated into two groups based on the median inflammation score. Compared with patients with low-grade inflammation, patients with high-grade inflammation had a significantly higher IPSS (21.2 vs 12.8; $p = 0.02$) and significantly greater prostate volume (104 vs 90 g; $p = 0.01$). Patients with high-grade versus low-grade inflammation were also more likely to have undergone open prostatectomy (62% vs 43%), which, in itself, is an indication of greater prostatic volume [6].

The association between the intensity of histologic inflammation and BPH parameters of prostate volume, IPSS, and surgery type reported by Robert et al [5,6] raised the question of whether histologic inflammation influences BPH outcomes. This question was possibly best addressed by the randomised, double-blind, placebo-controlled Medical Therapy of Prostatic Symptoms (MTOPS) study, which examined the long-term effects of doxazosin and finasteride, alone or in combination, on the clinical progression of BPH [7]. Of 3047 men with symptomatic BPH recruited into the study, 1056 had randomly undergone sextant prostate biopsy at baseline. Histologic inflammation was documented in 46.5% of this subset and was mainly chronic (93% of cases); the remaining patients showed no evidence of inflammation. Depending on the presence or absence of inflammation, clinically significant differences in BPH progression were observed [8]. Among patients with biopsy who had been treated with placebo (ie, outcomes were not confounded by active treatment), the proportions with clinical progression, increased American Urology Association symptom scores, and need for invasive therapy were consistently greater in the group with inflammation versus the group without, although the differences were not statistically significant (Fig. 1). The most notable finding, and notwithstanding the limited sample size, was the difference in the proportion of patients who developed acute urinary retention (AUR) between those with and without inflammation (5.6% vs 0%; $p = 0.003$) (Fig. 1). In other words, after 4 yr of observation, every case of AUR that occurred in the placebo group involved a patient with histologic evidence of inflammation at baseline; therefore, inflammation was shown to be a strong predictor of BPH progression.

The association between inflammation and AUR was corroborated in other studies published after the MTOPS study. Tuncel and colleagues investigated the role of inflammation in the aetiology of urinary retention in 98 consecutive patients requiring surgery for urinary

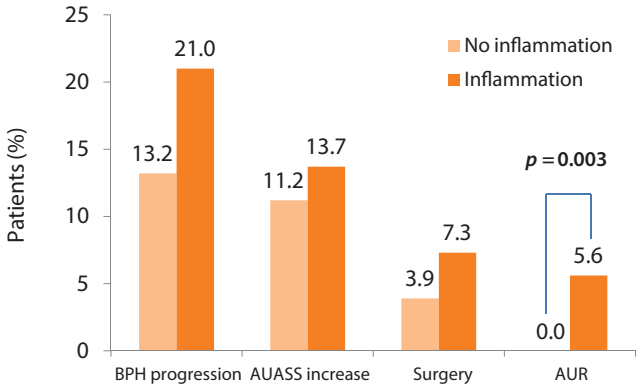

Fig. 1 – Impact of inflammation on benign prostatic hyperplasia outcomes in placebo-treated patients in the Medical Therapy of Prostatic Symptoms (MTOPS) study [8]. AUASS = American Urological Association symptom score; AUR = acute urinary retention; BPH = benign prostatic hyperplasia.

symptoms [9]. Among patients who underwent transurethral resection of the prostate (TURP), the prevalence of prostatic inflammation was significantly higher in those with AUR versus LUTS (54.7% vs 28.9%; p = 0.01) and the risk of AUR was threefold higher in patients with prostatic inflammation (95% confidence interval [CI], 1.28–7.15; p = 0.01). In a larger study, Mishra and coworkers showed clearly that prostatic inflammation was associated with a higher risk for AUR [10]. Among 374 evaluable patients treated with TURP at a single institution, chronic intraprostatic inflammation was found in 70% of men with AUR compared with 45% of patients with LUTS (p < 0.001). Elsewhere, Kwon and colleagues reported on the effect that chronic intraprostatic inflammation had on response to medical treatment for BPH [11]. The study enrolled 82 patients with BPH who underwent prostate biopsy. The extent of chronic prostatic inflammation was classified initially into four grades, then categorised into two groups: low grade and high grade. BPH outcomes were evaluated at baseline and after 1, 3, 6, and 12 mo of medical therapy with α-blockers and 5α-reductase inhibitors. Although between-group differences were not statistically significant, there was a trend towards greater and longer-lasting improvements in IPSS in the group with low-grade inflammation. Moreover, whereas no patient in the low-grade inflammation group underwent surgery during the course of the study, four patients in the high-grade inflammation group required TURP for either AUR or insufficient therapeutic response. Collectively, the results lend support to an association between prostatic inflammation in BPH progression.

Numerous studies have reported a strong independent association between components of the metabolic syndrome and BPH/LUTS [12]. Given the association between the metabolic syndrome and various inflammatory biomarkers [13], inflammation has been proposed as the link between the two conditions. The correlation between the severity of preoperative BPH/LUTS and features of the metabolic syndrome was examined retrospectively using specimens from 271 consecutive men treated with simple prostatectomy [14]. Nearly one-third of the sample (n = 86) had the metabolic syndrome, based on international criteria for the presence of at least three of the following five characteristics: elevated blood pressure, elevated triglyceride levels, lowered high-density lipoprotein cholesterol (HDL-C) levels, elevated fasting glucose, and central obesity [15]. Among the entire population, a direct correlation was observed between prostate volume (r = 0.151; p = 0.023) and prostate diameter (r = 0.267; p < 0.0001) and the number of positive components of the metabolic syndrome. In particular, patients with three or more parameters (ie, those who met the criteria for metabolic syndrome) had, on average, a prostate volume >60 ml and an anteroposterior diameter >45 mm. A correlation was also observed between the pathologic characterisation of the surgical specimen and clinical symptoms, with an inflammatory score of *severe* corresponding with a mean IPSS of 22.46 (an IPSS score ≥20 indicates severe LUTS). After adjusting for age, logistic regression analysis identified low HDL-C and elevated triglyceride levels, in particular, as putative predictors of a higher score for inflammatory infiltrates [16]. It appears increasingly certain that other diseases associated with metabolic syndrome and its risk factors are also associated, via inflammation, with the pathogenesis, clinical implications, and progression of BPH/LUTS (Fig. 2) [17].

3.2. *Impact of inflammation on treatment considerations*

Evidence that inflammation contributes to BPH pathogenesis, is associated with symptoms, and is at least partly responsible for progression underpinned the reasoning that targeting inflammation would have a positive impact on BPH. Although there are no large-scale studies published to date to confirm this hypothesis, evidence from a few small studies suggests that reduction of inflammation provides clinical benefits. Given the known overexpression of cyclooxygenase (COX)-2 in prostatic smooth muscle cells [18,19], selective COX-2 inhibition was a natural target.

In a single-centre unblinded trial from Italy, 46 consecutive men with BPH and LUTS were randomised to receive finasteride 5 mg/d monotherapy or finasteride 5 mg/d plus rofecoxib 25 mg/d for 24 wk [20]. Improvement in total IPSS was more rapid in patients treated with the finasteride/COX-2 inhibitor combination, particularly during the first 3 mo of treatment (Fig. 3). The rofecoxib-induced reduction in inflammation appeared to have a more immediate effect on clinical symptoms, and this persisted until the effects of finasteride began to predominate.

In a separate group of 57 patients with BPH-related LUTS, the combination of doxazosin 4 mg and tenoxicam 20 mg for 6 wk improved the Overactive Bladder Symptom Score by nearly twofold compared with doxazosin alone (8.7 vs 4.8; p = 0.009), yielding significant improvement in both voiding and storage symptoms [21].

Finally, in a prospective, randomised, double-blind study involving 80 men with BPH/LUTS, treatment with celecoxib 100 mg for 1 mo reduced the number of nocturia episodes from baseline by one-half (5.2 vs 2.5; p < 0.0001), whereas placebo had no effect (5.3 vs 5.1; p = 0.98) [22].

Despite such evidence of benefit, caution is advised when using nonsteroidal anti-inflammatory drugs (NSAIDS) and COX-2 inhibitors in patients with BPH/LUTS, as the long-term effects are unknown. Valuable lessons were learnt from the Adenomatous Polyp Prevention on Vioxx (APPROVe)

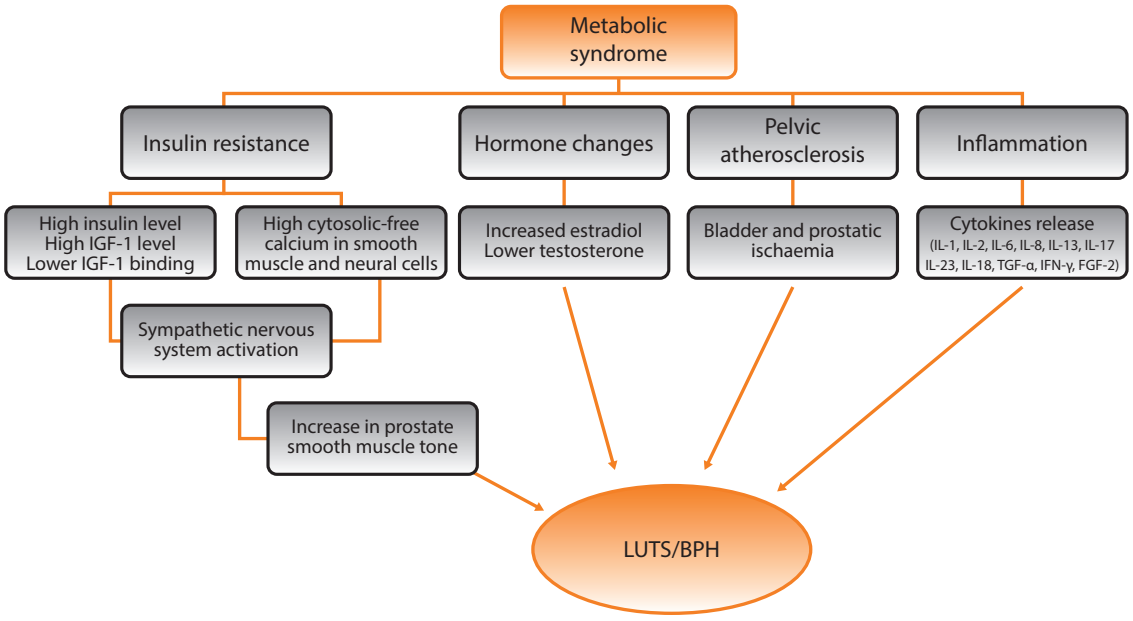

Fig. 2 – A proposed link between chronic inflammation and metabolic syndrome and the relationship to benign prostatic hyperplasia-related lower urinary tract symptoms. Reproduced with permission from Elsevier [17]. BPH = benign prostatic hyperplasia; FGF = fibroblast growth factor; IFN = interferon; IGF = insulin-like growth factor; IL = interleukin; LUTS = lower urinary tract symptoms; TGF = tumour growth factor.

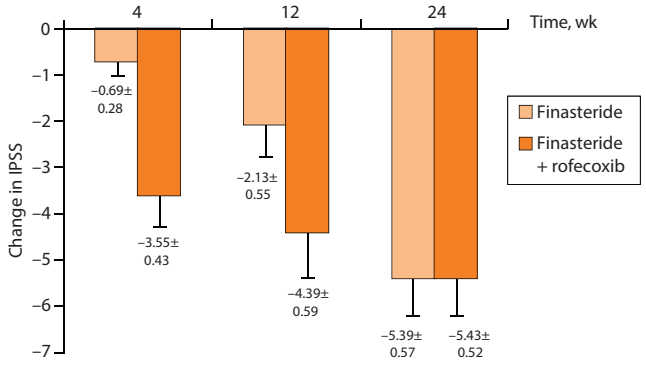

Fig. 3 – Change in the International Prostate Symptom Score in patients with benign prostatic hyperplasia and lower urinary tract symptoms treated with either finasteride 5 mg/d monotherapy or finasteride 5 mg/d plus rofecoxib 25 mg/d for 24 wk. Reproduced with permission from Elsevier [20]. IPSS = International Prostate Symptom Score.

study in which rofecoxib was compared with placebo for the prevention of colon cancer in at-risk patients [23]. A confirmed increase in the cardiovascular event rate (relative risk: 1.92; 95% CI, 1.19–3.11; p = 0.008) after 18 mo of treatment led to early termination of the study and eventual removal of rofecoxib from the market.

4. Conclusions

Evidence for the role of inflammation in BPH has several important implications for clinicians in everyday practice. As histologic inflammation appears to be a key component associated with the pathogenesis, symptomatology, and progression of BPH, knowledge of its type and severity is useful clinically. Inflammation has predictive value for BPH/LUTS and, in certain situations, can be used to guide treatment decisions. The association between metabolic syndrome and increased risk for BPH/LUTS and BPH progression provides opportunity to intervene at the clinical level (eg, weight, diet, exercise) to possibly prevent the need for surgery. Motivated patients can assume a high level of personal responsibility to reduce their individual risk factors for BPH. On the basis of accumulating evidence linking inflammation to BPH risk factors (eg, metabolic syndrome, diabetes, age) and BPH progression, an anti-inflammatory treatment strategy might be considered in selected men with evidence of or risk for inflammation who may benefit from nighttime treatment with an NSAID to reduce nocturia episodes.

Looking ahead, it seems clear that a urine or serum biomarker for prostatic inflammation would serve not only as a valuable noninvasive investigative tool but possibly also as a predictor of response to long-term anti-inflammatory therapy [24]. In light of mounting evidence for the link between chronic inflammation and development and progression of BPH, safe anti-inflammatory strategies may be the next frontier on the BPH management algorithm.

Conflicts of interest

J.C. Nickel has received support as a consultant/lecturer and/or for scientific studies and trials from Allergan, Aquinox, Astellas, Auxillium, Eli Lilly, Farr Labs, Ferring, Pierre Fabre, Pfizer, Taris Biomedical, and Tribute.

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Acknowledgments

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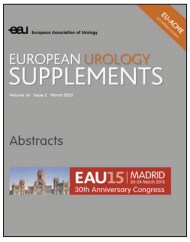

European Association of Urology

How to Choose the Right *Serenoa repens* Extract

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Article info

Keywords:
Benign prostatic hyperplasia
Herbal medicines
Serenoa repens
Standardisation

Abstract

Context: Herbal medicines are complex mixtures of various compounds. Standardisation is essential to ensure a consistent biological effect.
Objective: This article reviews findings related to herbal medicines with a specific focus on *Serenoa repens*, which is available in a number of different forms.
Evidence acquisition: This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and benign prostatic hyperplasia (BPH) were reviewed.
Evidence synthesis: A review of the available literature indicated that many natural products are being used in therapeutic settings such as cardiology, neurology, oncology, psychology, and urology. The need to standardise these products to ensure a consistent clinical effect is a prerequisite for good medical practice. In the case of *Serenoa repens*, which is used in the symptomatic treatment of BPH, best evidence has been published for the n-hexane lipidosterolic extract of the dwarf American palm.
Conclusions: This literature review highlighted the variability in the composition of the various brands of *Serenoa repens*. *Serenoa repens* hexanic extract is considered by the European Medicines Agency to be a "well-established medical use product" for symptomatic treatment of BPH.
Patient summary: Standardisation of herbal medicines is essential to ensure a consistent level of clinical activity and safety. In the case of *Serenoa repens,* the n-hexane lipidosterolic extract is the only formulation currently considered by the European Medicines Agency to be a "well-established medical use product."

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1. Introduction

Herbs and other botanical sources of medicines have been used to treat human ailments for >5000 yr [1]. Botanical drugs, as defined by the US Food and Drug Administration, can contain ingredients from a number of sources such as fresh or dried plants, plant parts, and isolated or combined components of plant origin, including algae and fungi [2]. In Europe, herbal medicines are defined as any medicinal product exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations or one or more such herbal substances in combination with one or more such herbal preparations. The various challenges physicians face when ascertaining the potential uses and

benefits of herbal medicines can be summed up in a few questions:

- What is the extract?
- What is it used for?
- What is the evidence for its efficacy and safety?
- Who would benefit from using it, and, conversely, who should not receive it?
- Does it have a proven place in therapy?
- Does it provide good value for cost?

Some issues associated with the use of herbal medicines include lack of quality control and standardisation; adulteration with other plants, pharmaceutical drugs, and/or heavy metals; inappropriate use; and adverse effects [1–5]. The perception that botanical products are safe because they are natural appears to be based on their traditional usage as folk remedies rather than on any formal clinical evaluation to confirm safety and tolerability [3]. Although more adverse effects are reported for conventional medicines than for herbal products, this may be explained in part by the under-reporting of herbal toxicity [1]. Herbal medicines are complex mixtures of chemicals contained within different parts of plant material. Scientists face a major challenge in standardising the final product so as to deliver a formulation with a consistent chemical profile that produces a consistent level of biological activity [2,3,5]. As noted by Liu and Wang, a long history of use, often with good evidence of efficacy, does not negate the need to validate natural products in terms of their biological authentication, chemical characterisation, process development (extraction and standardisation), safety, and efficacy before they can be accepted into mainstream medical practice [2].

Many products have achieved these standards, and the number of natural remedies, particularly from botanical sources, is increasing steadily in many therapeutic areas. Examples include cardiovascular diseases (*Digitalis purpurea, Achillea millefolium*), constipation (*Cassia acutifolia*, senna), depression (St. John's wort), some cancers (docetaxel, paclitaxel, vinca alkaloids), and pain and spasticity (*Cannabis sativa*) [1,4,6–8]. The use of herbal medicines is also becoming more widely established in urologic disorders such as benign prostatic hyperplasia (BPH) to minimise lower urinary tract symptoms (LUTS) [9]. In particular, extracts of the American dwarf palm (*Serenoa repens,* saw palmetto) have been widely used in this setting in Europe and the United States [4].

The aim of this review was to compare a number of commercially available brands of *Serenoa repens*, which are produced using different extraction processes, to assess whether they are consistent in terms of their composition and constituents and their biological activity.

2. Evidence acquisition

This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH are reviewed. The article is complemented by relevant related literature identified on PubMed and by hand searches of key references.

3. Evidence synthesis

3.1. *Serenoa repens*

Serenoa repens is a phytopharmaceutical listed as a traditional medicinal product in the European Union herbal monographs for symptomatic treatment of BPH [10]. The dosage is 160 mg twice daily. There are numerous branded *Serenoa repens* products, and they differ both qualitatively and quantitatively because of differences in the source of the biological product and variations in the process used to extract the active ingredients. Hexanic, ethanolic, and supercritical CO_2 extracts of *Serenoa repens* are all commercially available in some markets in the European Union, but few clinical data are available for some products. Furthermore, a number of modern extraction techniques such as microwave-assisted, ultrasound-assisted, enzyme-assisted, and pressurised liquid or fluid extraction methods have been developed [11]; however, these techniques have not yet been applied to the extraction of *Serenoa repens*. The lipidosterolic extract of *Serenoa repens* obtained by solvent (hexane) extraction is the most widely studied product in clinical and experimental trials and forms the basis of this review. Future trials should explore the possible clinical profiles of plant extracts obtained using the various extraction processes [11].

3.2. *Composition of different brands of Serenoa repens*

Despite being used widely for many years in numerous countries worldwide, the mechanism of action and the role of particular constituents of *Serenoa repens* are poorly understood. Studies attributing clinical benefits to any particular component of *Serenoa repens* are lacking, but pharmacologic experiments have identified the following properties: inhibition of 5α-reductase, modulation of androgen-receptor binding, inhibition of α-receptor binding, inhibition of eicosanoid synthesis, spasmolytic activity, and anti-inflammatory effects [4,10,12–17]; however, activity of the different extracts can vary, possibly due to compositional differences such as variation in the levels of free fatty acids. An understanding of the composition of different brands of *Serenoa repens* is essential to ascertaining whether they are likely to be bioequivalent. To this end, Habib and Wyllie compared 14 brands of *Serenoa repens* obtained from France (n = 1), Germany (n = 7), Italy (n = 3), and the United States (n = 3) [4]. The analysis highlighted significant variations in composition among the different brands (Table 1). In particular, the concentration of free fatty acids, which have been suggested as the main active ingredients of *Serenoa repens*, ranged between 40.7% (Solaray; Neutraceutical Corp, Park City, UT, USA) and 80.7% (Permixon; Pierre Fabre, Castres, France). Notably, the proportion of individual free fatty acids was found to be similar for all products tested, with lauric and oleic acids present at the highest concentrations in each sample assayed [4]. The study also highlighted potential discrepancies between the stated and actual doses of commercially available preparations due to differences in plant source, extraction process, and formulation with bioactive adjuvants.

Table 1 – Composition of 14 different brands of *Serenoa repens*

Product	FFA (mean %)	Methyl and ethyl esters (mean %)	Long-chain esters (mean %)	Glycerides (mean %)	Unsaponified matter (mean %)
Permixon	80.7	2.5	1.36	6.8	2.27
Prosteren	74.0	3.7	1.3	10.8	2.37
Saba	70.25	2.85	1.2	14.4	2.15
Rilaprost	68.8	2.4	1.0	21.43	1.87
Prostess	68.4	9.5	1.2	10.6	2.6
Sita	62.9	9.35	1.3	13.45	2.2
Quanterra prostate	63.1	6.3	1.03	19.55	1.9
Ratiopharm uno	62.3	4.25	0.9	24.25	1.6
Talso uno	61.4	4.4	0.8	25.3	1.8
Prostamol uno	59.3	12.6	0.97	15.37	2.4
Prostagutt uno	59.2	9.25	0.85	19.7	2.0
Strogen uno	54.8	6.6	1.2	27.1	2.4
Prosta-urgenine	54.05	16.7	0.7	16.55	2.2
Solaray	40.7	1.5	0.9	52.15	1.6

Adapted from [4] with permission from Macmillan Publishers Ltd. FFA = free fatty acid.

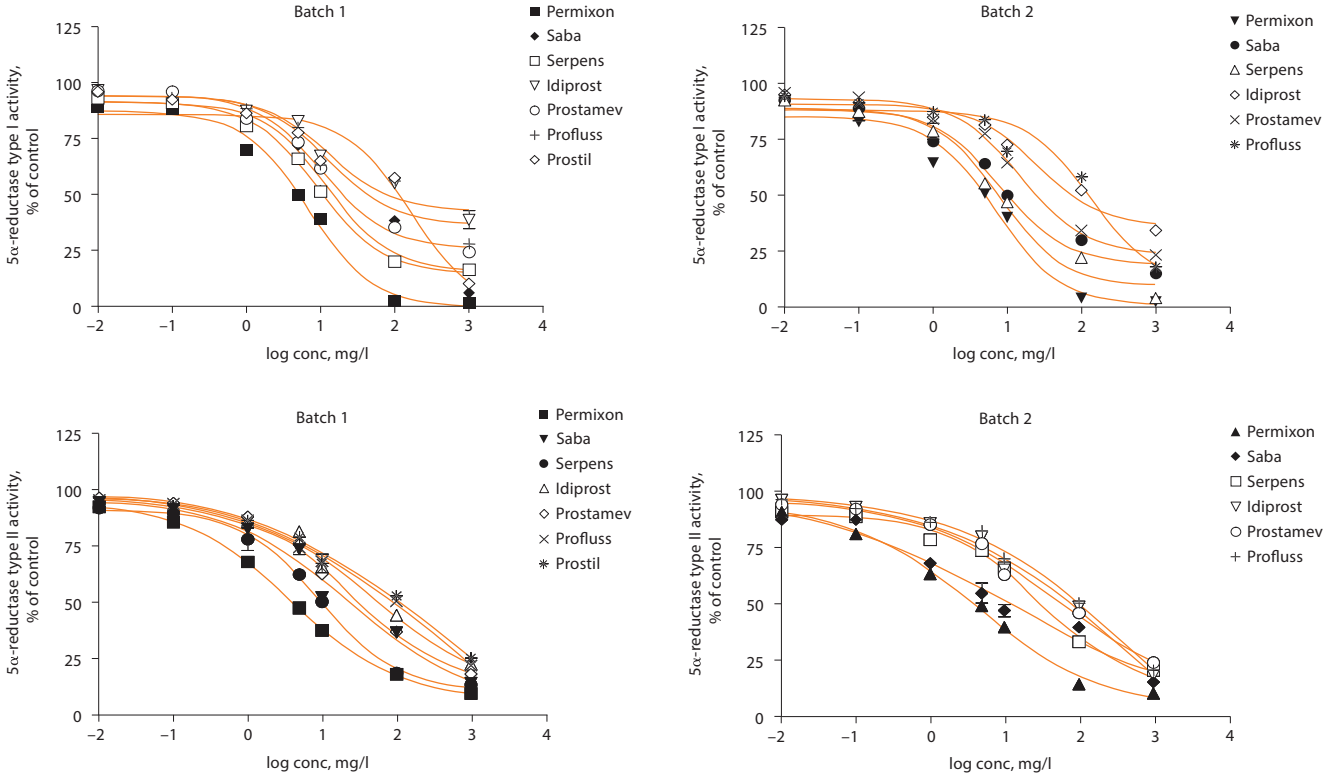

Fig. 1 – Inhibition of 5α-reductase by various extracts of *Serenoa repens*. Enzyme activity is expressed as a percentage of the control (conversion of 1 μM of testosterone in the absence of inhibitors is defined as 100% activity). Reproduced with permission from Karger Publishers [17]. conc = concentration.

3.3. Comparison of the activity of different brands of Serenoa repens

In light of the different compositions of the various brands of *Serenoa repens*, a number of studies have been performed to investigate their biological activity. In 2008, our group evaluated seven brands of *Serenoa repens* available in Italy using a 5α-reductase activity assay involving epithelial and fibroblast cells cocultured for 10 d [17]. All extracts tested inhibited both isoforms of 5α-reductase (Fig. 1), although there was marked variation in potency between the different extracts and between different batches of the same extracts. This is highlighted in the half maximal inhibitory concentrations, with Permixon being the most active inhibitor of both isoforms of 5α-reductase and Prostil (isoform I) and Profluss (isoform II) being the least active inhibitors (Table 2). More recently, we repeated this study by comparing the potency of lipidosterolic extracts from 10 different brands of *Serenoa repens* from a number of different countries including Argentina, China, France, Mexico, Panama, Poland, Russia,

Table 2 – Activity of *Serenoa repens* extracts on inhibition of 5α-reductase types I and II (half maximal inhibitory concentration in micrograms per millilitre)

Extract	5α-reductase type I	5α-reductase type II
Permixon batch 1	6.836	3.841
Permixon batch 2	6.979	4.313
Saba batch 1	12.54	23.40
Saba batch 2	8.170	23.02
Serpens batch 1	9.132	9.237
Serpens batch 2	7.934	25.37
Idiprost batch 1	12.63	45.47
Idiprost batch 2	25.50	471.5
Prostamev batch 1	10.77	22.99
Prostamev batch 2	15.07	48.45
Profluss batch 1	12.95	908.4
Profluss batch 2	132.4	347.2
Prostil batch 1	161.4	513.1

Adapted from [17] with permission from Karger Publishers.

and Thailand [12]. All extracts inhibited 5α-reductase I and II isoenzymes and fibroblast proliferation (after induction by human fibroblast growth factor), but there were marked differences between the various brands, with Permixon being the most potent. Figure 2 shows the inhibitory effects of the various products for 5α-reductase I; Permixon was the most active extract in this model ($p < 0.05–0.001$). The qualitative and quantitative variation in bioactivity among the products tested is almost certainly related to differences in the levels of active constituents. This was highlighted by Raynaud and colleagues in a study that measured inhibition of 5α-reductase I and II by the free fatty acid ingredients of Permixon [18]. The long-chain unsaturated fatty acids oleic and linoleic acid (two-thirds of total Permixon composition) were active against 5α-reductase I and, to a lesser extent, against 5α-reductase II. Saturated lauric acid was active against both isoforms of 5α-reductase, whereas myristic acid was active against 5α-reductase II. Palmitic and stearic acids, esterified fatty acids, alcohols, and sterols were inactive against both isoforms of 5α-reductase. Although *Serenoa repens* exhibited some α_1-adrenoceptor activity in vitro, at therapeutic doses it did not antagonise the α_1-adrenoceptors in humans [19].

3.4. *Serenoa repens* in the treatment of benign prostatic hyperplasia

The prostatic inflammation observed in patients with BPH is associated with cytokine release, which creates a proinflammatory environment and a state of relative hypoxia due to the increased oxygen demand of proliferating cells [20]. Cytokines and growth factors released from inflammatory cells may interact not only with immune effectors but also with stromal and epithelial cells. In turn, epithelial cells have been shown to release inflammatory mediators [21]. Latil and colleagues compared the anti-inflammatory effects of the hexanic lipidosterolic extract of *Serenoa repens* (Permixon) with that of the supercritical CO_2 extract using cultured human prostate and vascular cell lines [16]. The hexanic

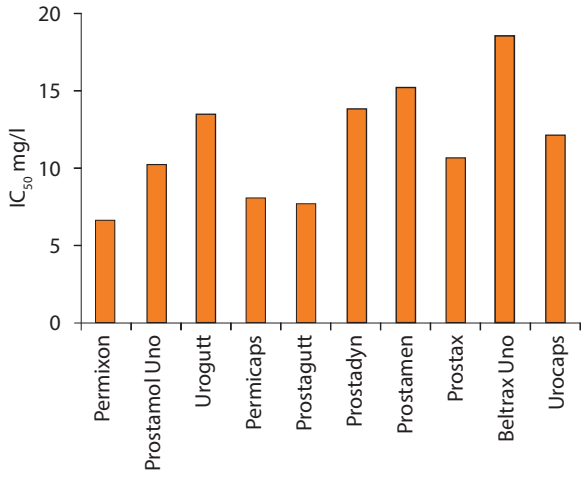

Fig. 2 – Half maximal inhibitory concentration values for inhibition of 5α-reductase I by 10 extracts of *Serenoa repens* [12]. IC_{50} = half maximal inhibitory concentration.

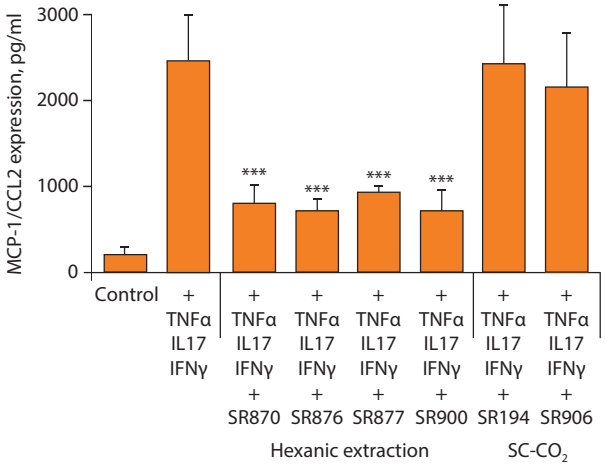

Fig. 3 – Effects of different extracts of *Serenoa repens* on monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL-2) protein expression in prostate myofibroblastic cells. Batches 870, 876, 877, and 900 were obtained by hexanic extraction (Permixon), and batches 194 and 906 were obtained by supercritical CO_2 extraction. Data presented as mean plus SD (bar). *** $p < 0.001$. Reproduced with permission from John Wiley and Sons, Inc. [16]. IFNγ = interferon γ; IL17 = interleukin 17; SC = supercritical; SR = *Serenoa repens*; TNFα = tumour necrosis factor α.

extract inhibited the early steps of leukocyte infiltration in vitro by downregulating monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 (MCP-1/CCL-2) and vascular cell adhesion protein-1 (VCAM-1) expression. It also inhibited tumour necrosis factor α–induced MCP-1/CCL-2 secretion by human vascular cells and surface VCAM-1 protein expression in a concentration-dependent manner. Under proinflammatory conditions, the hexanic extract of *Serenoa repens* produced maximal inhibition of MCP-1/CCL-2 protein expression, whereas the supercritical CO_2 extract did not significantly inhibit MCP-1/CCL-2 expression (Fig. 3).

Experimental findings support the potential of *Serenoa repens* in BPH, and various mechanisms of action have been postulated. These include inhibition of 5α-reductase activity, modulation of androgen-receptor binding, inhibition of α-receptor binding, inhibition of eicosanoid synthesis, and spasmolytic and anti-inflammatory effects. The activity

Table 3 – Outcome of studies of *Serenoa repens* ranked by type of extract (only extracts on the European market)

Type of extract	Outcome	Reference
Ethanolic extract	Negative (PL-controlled)	[22]
Hexane extract	Equivalence (T, SR, T+SR)	[23]
	Positive (Meta-analysis: N=17)	[24]
	Equivalence (T)	[25]
	Equivalence (T, T+SR)	[26]
	Equivalence (F)	[27]
	Positive (PL-controlled)	[28]
	Negative (PL-controlled)	[29]
	Positive (PL-controlled)	[30]
	Positive (PL-controlled)	[31]
	Positive (PL-controlled)	[32]
	Positive (PL-controlled)	[33]
	Positive (PL-controlled)	[34]
Supercritical CO_2	Positive (PL-controlled)	[35]

Adapted from [10] by permission from the European Medicines Agency.
F = finasteride; N = number of studies; PL = placebo; SR = *Serenoa repens*; T = tamsulosin.

level may differ from one extract to another, probably due to the fatty acid content, which can influence the clinical efficacy of the different available brands [10]. In a recent monograph of *Serenoa repens* published by the European Medicines Agency (EMA), it was concluded that available evidence for the hexane extract (Permixon) supported its use as a "well-established medicinal product with recognised efficacy and acceptable safety," whereas data for the ethanolic and supercritical CO_2 extracts were insufficient to support such a conclusion [10,22–35] (Table 3). By contrast, a recent Cochrane systematic review in which data for the various brands of *Serenoa repens* were combined reported no improvement in LUTS compared with placebo, although the authors were uncertain whether this conclusion could be extrapolated to proprietary products such as Permixon [36]. The EMA suggested that the methodology of the review was flawed, given the compositional differences of the various brands included in the analysis [10]. A review of the evidence cited on PubMed found that 51 of the 81 (63%) clinical trials of *Serenoa repens* involved the hexanic extract (Permixon).

4. Conclusions

A review of current best evidence in the literature enabled a number of general recommendations to be made regarding herbal medicines. Quality assurance is a key consideration. It is important to use herbal medicines produced by larger companies because these are more likely to be of higher quality and to have been rigorously tested (to protect the company's reputation). Standardising herbal medicines to contain specific amounts of active constituent is very important. Finally, the safety profile of herbal products needs to be clearly defined, including the potential for drug–drug interactions, because the products are not always as innocuous as might be perceived.

Serenoa repens is an example of an herbal medicine that highlights some general concerns in the area. Many different brands of *Serenoa repens* are available, and at least three different extraction processes are used to produce the active medicine (hexanic, ethanolic, and supercritical CO_2 extraction). There are marked differences among extracts in terms of their pharmacological activity and clinical efficacy. At the present time, the EMA supports the use of only the mostly widely studied product, the hexanic lipidosterolic extract, which includes products such as Permixon.

Conflicts of interest

F. Scaglione has received fees for serving as a speaker and/or consultant for Astellas, Bayer, MSD, and Sanofi-Aventis within the past 3 yr.

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Appendix A

Manufacturers for the various *Serenoa repens* products mentioned in this article:
Beltrax Uno (Belierda, Argentina)
Idiprost (IdiPharma, Italy)
Permicaps (Bago, Argentina)
Permixon (Pierre Fabre Médicament, France),
Profluss (KonPharma, Italy)
Prostadyn (Dr Dunner, China)
Prostagutt (Schwabe Pharma, Russia)
Prostagutt uno (Willmar Schwabe, Germany)
Prostamen (Ancalmo, Panama)
Prostamev (Farmaceutica MEV, Italy)
Prostamol Uno (Berlin Chemie, Poland)
Prostamol uno (Berlin-Chemie, Germany)
Prosta-urgenine (Hoyer-Madaus, Germany)
ProstaX (Interfarma corporation, Panama)
Prosteren (Sirton Pharmaceuticals, Italy)
Prostess (TAD Pharmazeutisches Werk, Germany)
Prostil (AccaPharma, Italy)
Quanterra prostate (Warner-Lambert, NJ, USA)
Ratiopharm uno (Ratiopharm, Germany)
Rilaprost (Guidotti, Italy)
Saba (Lampugnani Farmaceutici, Italy)
Saba (Lampugnani, Italy)
Serpens(Lisapharma, Italy)
Sita (Hoyer-Madaus, Germany)
Solaray (Nutraceutical Corporation, UT, USA)
Strogen uno (Strathmann, Germany)
Talso uno (Sanofi Winthrop, PA, USA).
Urocaps (Division Fitoterapeitica, Mexico)
Urogutt (Farmasa Schwabe, Thailand)

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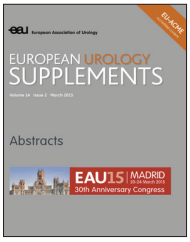

European Association of Urology

Comparison of the Effects of Hexanic Extract of *Serenoa repens* (Permixon) and Tamsulosin on Inflammatory Biomarkers in the Treatment of Benign Prostatic Hyperplasia-Related Lower Urinary Tract Symptoms

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Article info

Keywords:
Benign prostatic hyperplasia
Inflammatory biomarkers
Lower urinary tract symptoms
Permixon
Tamsulosin

Abstract

Context: Chronic prostatic inflammation appears to have a key role in the pathogenesis and progression of benign prostatic hyperplasia (BPH). The PERMIN study compared the effects of hexanic extract of *Serenoa repens* (Permixon; Pierre Fabre, Castres, France) and tamsulosin on inflammation-related biomarkers secreted in urine of patients with BPH-related lower urinary tract symptoms (LUTS).
Objective: To review key features of the PERMIN study as they relate to treatment effects on the messenger RNA expression of selected inflammation-related genes and proteins.
Evidence acquisition: This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed.
Evidence synthesis: Permixon showed a more pronounced effect than tamsulosin on selected inflammation-related genes and proteins. Among the 15 most frequently expressed genes in patients at baseline, 73% were favourably affected by Permixon versus 27% with tamsulosin, as indicated by the combination of downregulation and fewer upregulation effects. Expression of inflammatory proteins (CCL2/MCP-1, CXCL10/IP-10, macrophage migration inhibitory factor [MIF]) was downregulated in a higher percentage of patients and upregulated in a lower percentage of patients treated with Permixon compared with tamsulosin. Greater International Prostate Symptom Score improvement was observed in Permixon-treated patients with versus without baseline MIF overexpression (−6.4 vs −4.5).
Conclusions: Downregulation of inflammation-related genes and proteins by Permixon brought meaningful symptomatic improvement in patients with moderate to severe LUTS. Patients with high chronic prostatic inflammation may benefit from early treatment with Permixon.
Patient summary: Downregulation of inflammation-related genes and proteins by *Serenoa repens* (Permixon) was associated with meaningful symptomatic improvement in patients with moderate to severe lower urinary tract symptoms. Patients with high chronic prostatic inflammation may benefit from early treatment with Permixon.

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1. Introduction

The transcriptome of the aging prostate stroma is characterised by upregulation of numerous genes that encode secreted inflammatory mediators shown to stimulate prostatic cell growth [1]. As such, prostatic inflammation has been proposed as an appropriate target for medical treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) [2]. In the 20 yr since the anti-inflammatory activity of hexanic extract of *Serenoa repens* (Permixon; Pierre Fabre, Castres, France) was first reported [3], a considerable body of in vitro and in vivo evidence has accumulated that demonstrates inhibition by Permixon of inflammatory cells (macrophages, T lymphocytes, B lymphocytes) [4,5] and a wide variety of inflammatory mediators and proteins [3,5–9] as well as deregulation of numerous genes known to play key roles in the proliferative, apoptotic, and inflammatory pathways of BPH [10]. Nevertheless, evidence of its anti-inflammatory activity at the clinical level was lacking.

PERMIN was a randomised clinical trial designed specifically to investigate the anti-inflammatory activity of therapy intended for the treatment of BPH-related LUTS [11]. Based on our work at the University of Bordeaux and other published articles [9,10,12–20], the 29 most significant inflammation markers in BPH were identified and selected for investigation (Table 1). To better understand the mechanisms behind the anti-inflammatory effects of Permixon, tamsulosin was selected as the comparator because of its frequent prescription, well-established mechanism of action, and absence of any known anti-inflammatory activity. The PERMIN study has recently been reported in full [11]. This review examines some key features of the study and provides a clinical interpretation of the comparative effects of Permixon and tamsulosin on inflammatory markers in men with BPH-related LUTS.

2. Evidence acquisition

This article is based primarily on material presented at a satellite symposium entitled, "Inflammation and Prostatic Diseases: From Bench to Bedside," held during the 2015 annual meeting of the European Association of Urology in Madrid, Spain. Current data regarding the link between inflammation and BPH were reviewed. The article is complemented by relevant related literature identified on PubMed and by hand searches of key references.

3. Evidence synthesis

3.1. PERMIN study: patients and methods

PERMIN was a multicentre, exploratory, double-blind, randomised, phase 4 study designed to compare the effects of Permixon and the α_{1a}-adrenergic receptor antagonist tamsulosin on inflammatory biomarkers secreted in the urine of patients with BPH-related LUTS. To monitor inflammatory status, a noninvasive method was used that allowed for collection of prostatic epithelial cells desquaming in the lumen of glands and seminal plasma fluid after digital rectal examination. As the methods are detailed in the original article [11], only a brief summary is provided in this report.

Table 1 – Selected inflammation-related genes [9–19]

IL-1β	*PLA2G2A*	*CTLA4*	*ALOX5*	*CAT*	*NFKB1*
IL-6	*CXCL10*	*FGF-2*	*ICOS*	*CCL5*	*PTGES2*
IL-8	*CCL2/MPC-1*	*CXCL6*	*SELP*	*HIF1A*	*PTGES3*
IL-15	*CD40LG*	*ALOX15*	*STAT3*	*LTC4S*	*PTGS2*
IL-17	*CCR7*	*ALOX15B*	*PTPRC*	*MIF*	

Patients eligible for inclusion were men aged 45–85 yr with a minimum 12-mo history of bothersome LUTS related to BPH. Specific criteria were International Prostate Symptom Score (IPSS) ≥12, prostatic volume ≥30 ml, maximal urinary flow rate (Q_{max}) of 5–15 ml/s for a voided volume 150–500 ml, serum total prostate-specific antigen (PSA) ≤4 ng/ml or ≤10 ng/ml with a ratio free to total PSA ≥25% or a negative prostate biopsy.

Initial screening was followed by a 28-d washout/run-in phase and further patient selection (Fig. 1). Eligible patients were randomised at a 1:1 ratio to receive Permixon 160 mg twice daily or extended-release tamsulosin 0.4 mg once daily for 90 d. Four visits were planned for each participant: selection visit, baseline visit (day 1), first assessment visit (day 30), and end-of-study visit (day 90).

The primary end point was the change from baseline to study end in messenger RNA (mRNA) expression of the selected BPH inflammation markers (Table 1). Downregulation and upregulation of gene expression were considered to have occurred when a change of twofold or more from baseline was observed. Secondary end points were the change from baseline to study end in mRNA expression of selected proteins and the clinical efficacy of medical treatments based on patients' prostatic inflammation status (change in IPSS) from day 1 to days 30 and 90.

3.2. PERMIN study: results

The PERMIN study took place between June 2012 and October 2013 at 42 centres across France, Italy, Portugal, and Spain. Of 323 patients screened, 303 patients were selected and 206 patients were randomised to treatment, 102 to Permixon and 104 to tamsulosin (101 were treated). Main reasons for noninclusion were failure to meet entrance criteria (n = 64), particularly with regard to Q_{max}, and patient's decision not to participate (n = 22). Nineteen patients withdrew from Permixon for reasons of safety (n = 7), efficacy (n = 2), safety and efficacy (n = 1), or other (n = 9). Eighteen patients withdrew from tamsulosin for reasons of safety (n = 3), efficacy (n = 2), or other (n = 13).

Groups were well matched at baseline for demographic and clinical characteristics (Table 2). Similar to the population in the Combination of Avodart and Tamsulosin (CombAT) study [21], PERMIN patients had moderate to severe BPH-related LUTS.

3.2.1. Primary end point

3.2.1.1. Change in messenger RNA expression of inflammation-related genes

Twenty-six of the 29 selected inflammation-related genes were detected in at least one patient. From baseline to

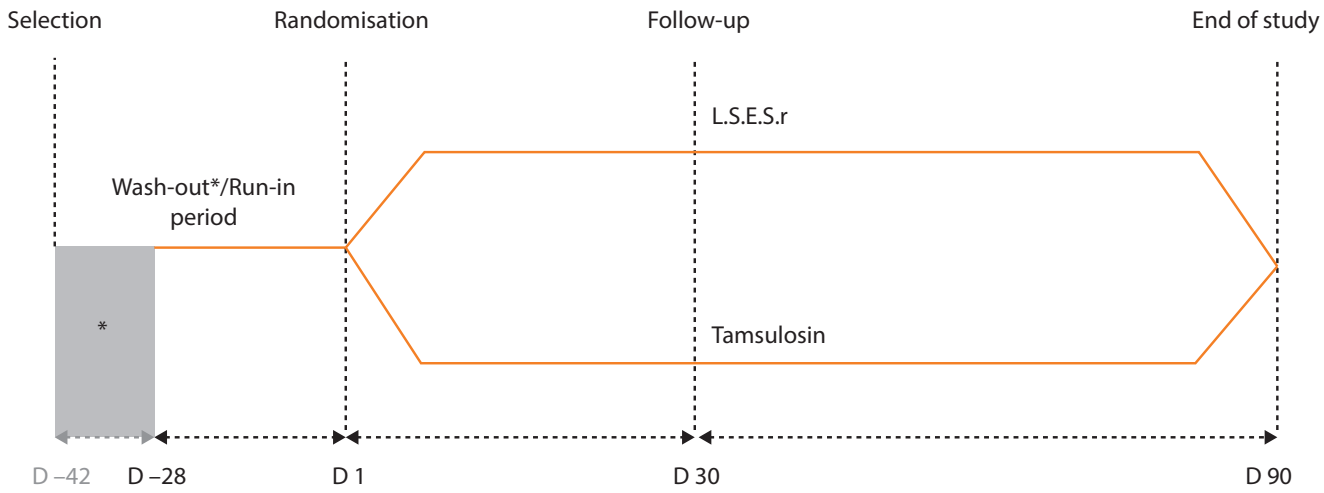

Fig. 1 – PERMIN study design. * Optional 2-wk washout period. D = day; L.S.E.r = lipidosterolic hexanic extract of *Serenoa repens* (Permixon); V = visit.

Table 2 – Baseline characteristics of patients in the PERMIN study

Parameter	Permixon (n = 102)	Tamsulosin (n = 101)
Age, years	65.4 (7.8)	66.1 (7.6)
IPSS	17.7 (4.4)	16.8 (4.5)
IPSS question 8	3.9 (0.9)	3.8 (0.9)
MSF4 score	7.4 (4.5)	6.9 (4.5)
Q_{max}, ml/s	10.88 (2.69)	10.60 (3.03)
Transrectal prostate volume, ml	48.82 (20.80)	46.29 (13.88)
Suprapubic postvoid residual volume, ml	53.82 (57.07)	42.04 (47.61)

All values are means (SD). IPSS = International Prostate Symptom Score; IPSS question 8 = patient's perceived quality of life; MSF4 score = Male Sexual Function 4-item questionnaire; Q_{max} = maximal urinary flow rate; SD = standard deviation.
Adapted with permission from Wiley-Blackwell [11].

study end, mean mRNA expression was reduced in 65.4% of genes in Permixon-treated patients and in 46.2% of genes in tamsulosin-treated patients, for a difference of 19.2% in favour of Permixon. With respect to the 15 most frequently expressed genes at baseline (*ALOX5, ALOX15B, CAT, CCL2, HIF1A, IL1B, IL8, MIF, NFKB1, PLA2G2A, PTGES2, PTGES3, PTGS2, PTPRC* and *STAT3*), mean mRNA expression was reduced in 80% of genes in Permixon-treated patients and in 33% of genes in tamsulosin-treated patients, for a difference of 47% in favour of Permixon. Analyses of the cumulative favourable effect per gene, defined as a combination of more downregulation and less upregulation, indicated a favourable effect on 73% of genes after Permixon treatment versus 27% of genes after tamsulosin treatment (Fig. 2).

3.2.2. *Secondary end points*

3.2.2.1. *Change in protein expression*

Three of the 10 selected proteins were detected in urine: monocyte chemoattractant protein-1 (CCL2/MCP-1); CXCL10/IP-10, a chemoattractant for human monocytes and T cells; and macrophage migration inhibitory factor (MIF). For CCL2/MCP-1, the proportion of patients showing expression in urine samples from baseline to study end decreased from 54.8% to 35.6% with Permixon (−19.2%) and increased from 46.5% to 47.9% with tamsulosin (+1.4%). For CXCL10/IP-10, the proportion of patients showing expression in urine samples from baseline to study end decreased from 74.0% to 63.0% with Permixon (−11.0%) and increased from 64.8% to 67.6% with tamsulosin (+2.8%). MIF was expressed in all urine samples at baseline and at study end. MIF expression was downregulated in a higher proportion (42.5% vs 23.9%) and upregulated in a lower proportion (43.8% vs 66.2%) of patients treated with Permixon compared with tamsulosin ($p = 0.007$).

3.2.2.2. *Change in International Prostate Symptom Score*

From baseline to study end, IPSS was reduced by 4.5 points with Permixon (from 17.7 to 13.2) and by 6.3 points with tamsulosin (from 16.6 to 10.3). Among Permixon-treated patients, those with greater baseline MIF expression had more pronounced symptomatic improvement (mean IPSS change) than those without MIF overexpression (Fig. 3).

3.2.3. *Safety*

Permixon and tamsulosin had similar safety profiles. Treatment-emergent adverse events (TEAEs) were reported in 10.8% of Permixon-treated patients and in 8.9% of tamsulosin-treated patients. No related TEAE occurred at a frequency >1% in the Permixon group, whereas ejaculation failure, retrograde ejaculation, and asthenia were each reported in 2% of patients treated with tamsulosin.

4. Discussion

The PERMIN study is unique in that it was designed specifically to assess, in a noninvasive manner, the anti-inflammatory effects of medical treatments on BPH-related LUTS. The anti-inflammatory activity of Permixon was greater than that of tamsulosin across all primary and secondary end points. A decrease in mean mRNA expression of detected BPH inflammation markers was observed in 65% of patients in the Permixon group versus 46% of patients in the tamsulosin group. Among the 15 most frequently

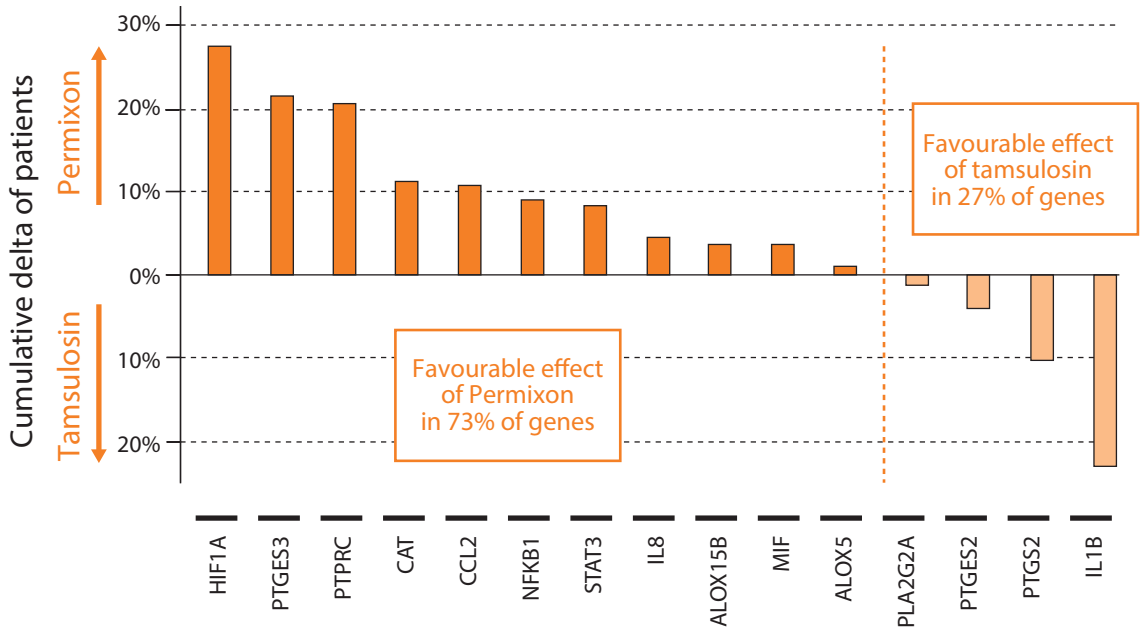

Fig. 2 – Cumulative effect of Permixon and tamsulosin on messenger RNA expression of inflammation-related genes at end of treatment (day 90). The global favourable effect corresponded to the sum of the delta of patients between treatment groups for the combination of more downregulation and fewer upregulation effects. Reproduced with permission from Wiley-Blackwell [11].

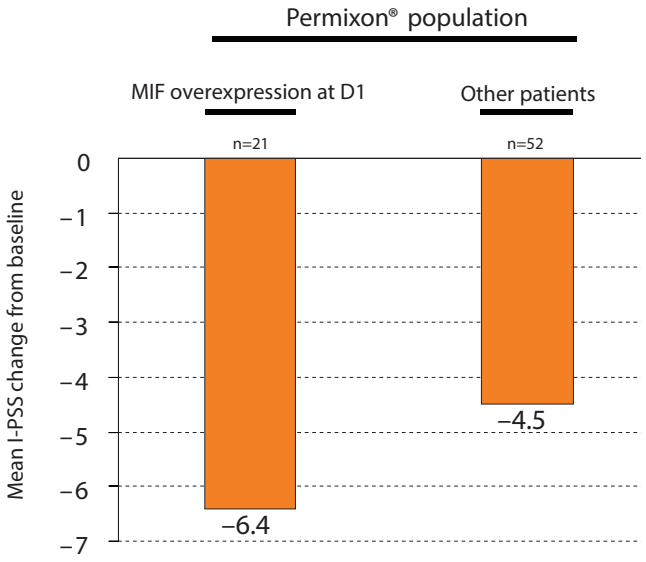

Fig. 3 – Change in the International Prostate Symptom Score from baseline to study end in Permixon-treated patients according to expression of macrophage migration inhibitory factor at baseline. Adapted with permission from Wiley-Blackwell [11]. D1 = baseline; IPSS = International Prostate Symptom Score; MIF = macrophage migration inhibitory factor.

expressed markers, Permixon had a cumulative favourable effect (more downregulation and less upregulation) on 73% of genes compared with 27% for tamsulosin.

Permixon, but not tamsulosin, decreased the proportion of patients expressing CCL2/MCP-1 and CXCL10/IP-10 proteins between baseline and study end. Between-treatment differences in MIF expression were statistically significant: MIF expression was downregulated in more patients (42.5% vs 23.9%) and upregulated in fewer patients (43.8% vs 66.2%) treated with Permixon than tamsulosin (p = 0.007). Given its role as a key player in immune response regulation with an influence on prostatic cell growth, targeting MIF may be a rational approach from clinical and therapeutic perspectives. Symptomatic improvement of LUTS was considerably more pronounced in Permixon-treated patients with than without MIF overexpression at baseline, suggesting that early treatment with Permixon may prevent unfavourable clinical evolution. Moreover, the ubiquity of MIF expression in urine samples at baseline and study end suggests that it may be a candidate biomarker to assess chronic prostatic inflammation.

The greater efficiency of Permixon in the subset of patients with MIF overexpression may be explained by benchside observations. Immunohistochemistry studies in prostate tissue samples of patients undergoing surgery for BPH have shown greater MIF expression in BPH lesions than in adjacent normal area [22]. In vitro, MIF has been shown to upregulate BPH epithelial cell line proliferation through a process involving cyclooxygenase-2 and p53 signalling [22].

The inclusion criteria of the PERMIN study also provide clues when interpreting the results for clinical practice. Eligibility was restricted to patients with moderate to severe LUTS and a high “bother” score, in contrast to other studies of plant extracts in which populations were generally limited to patients with mild to moderate symptoms. The mean improvement of 4.5 points in IPSS in Permixon-treated patients was thus a clinically meaningful result in a therapeutically challenging population.

Permixon is the only medical treatment for BPH-related LUTS with anti-inflammatory activity demonstrated in vitro, in vivo, and now in a randomised clinical trial. The favourable effect of tamsulosin observed on some genes and/or patients in the PERMIN study can likely be explained by the relief of urinary obstruction associated with effective α-blocker therapy.

5. Conclusions

Downregulation of inflammation-related genes and proteins by Permixon was associated with meaningful symptomatic improvement in patients with moderate to severe BPH-related LUTS. The greater degree of improvement in IPSS with Permixon in patients with higher baseline MIF protein expression suggests that patients with higher chronic prostatic inflammation and greater MIF overexpression may benefit most from this treatment.

Conflicts of interest

G.Y. Robert has received honoraria as a consultant and speaker from Pierre Fabre Médicament.

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