Serenoa repens extract in the treatment of benign prostatic hyperplasia

Petrisor Geavlete, Razvan Multescu and Bogdan Geavlete

Ther Adv Urol
(2011) 3(4) 193–198
DOI: 10.1177/1756287211418725

***Abstract*:** We are experiencing a revival of interest in phytotherapeutic agents, both in Europe and North America, especially as a consequence of patients' dissatisfaction with the adverse effects of the medical alternatives. One of the most frequently prescribed and studied such agents is *Serenoa repens* extract, derived from the berry of the dwarf palm tree. We aimed to review the most important published data regarding this type of treatment for benign prostatic hyperplasia. A review of the existing articles regarding the use of *Serenoa repens* extracts for benign prostatic hyperplasia was performed. The articles were analysed with regard to their relevance, scientific value and the size of the evaluated series. Multiple mechanisms of action have been attributed to this extract, including antiandrogenic action, an anti-inflammatory/anti-oedematous effect, prolactin signal modulation, and an antiproliferative effect exerted through the inhibition of growth factors. Regarding efficacy, European Association of Urology guidelines state that *Serenoa repens* extracts significantly reduce nocturia in comparison with placebo. However, the guideline committee is unable to make specific recommendations about phytotherapy of male lower urinary tract symptoms owing to the heterogeneity of the products and the methodological problems associated with meta-analyses. Most of the published trials regarding *Serenoa repens* phytotherapy demonstrate a significant improvement of urinary status and a favourable safety profile. Also, some authors have credited it with giving a significant improvement in erectile function and decreasing complications following transurethral resection of the prostate, especially bleeding. The results of phytotherapy with *Serenoa repens* extracts are very promising. More high-quality, randomized, placebo-controlled studies are required in order to demonstrate without doubt the true therapeutic value of these products. Particular attention must be focused on differentiating between registered preparations, which are regulated as drugs, and those considered to be food supplements.

***Keywords*:** benign prostatic hyperplasia, lower urinary tract symptoms, phytotherapy, *Serenoa repens*

Introduction

Although the real incidence of benign prostatic hyperplasia (BPH) is difficult to assess, this pathological entity is widespread in the elderly male population [Oelke *et al*. 2011]. Nowadays, medical therapy tends to replace the surgical approach in a significant number of cases. Phytotherapeutic agents, α1-blockers and 5α-reductase inhibitors are the three main alternatives that may replace surgery in a selected subpopulation of cases.

After an initial period in which phytotherapy was the only viable medical therapy, the development of synthetic molecules such as α1-blockers and 5α-reductase inhibitors seemed to offer the ideal BPH treatment. However, we are now experiencing a revival of interest in phytotherapeutic agents, both in Europe and North America, especially as a consequence of patients' dissatisfaction with the the adverse effects of the medical alternatives [Debruyne *et al*. 2004b; Carraro *et al*. 1996].

Correspondence to:
Petrisor Geavlete, MD, PhD
Department of Urology, 'Saint John' Emergency Clinical Hospital, Vitan Barzesti 13, 042122 Bucharest, Romania
geavlete@gmail.com

Razvan Multescu, MD, PhD
Bogdan Geavlete, MD, PhD
Department of Urology, 'Saint John' Emergency Clinical Hospital, Vitan Barzesti 13, 042122 Bucharest, Romania

The most frequently prescribed and studied agent is the *Serenoa repens* extract, derived from the berry of the dwarf palm tree. A large number of papers have evaluated its efficacy in controlling BPH-related lower urinary tract symptoms (LUTS). However, many studies are limited by short-term follow up, a low number of patients, the absence of a placebo arm, or lack of standardized instruments to evaluate efficacy [Giannakopoulos *et al*. 2002; Gerber *et al*. 2001; Marks *et al*. 2000; Bauer *et al*. 1999]. Controversies still remain regarding its mechanisms of action and its real therapeutic value. The main question that has to be answered is: 'Are *Serenoa repens* extracts effective drugs for BPH treatment or do they provide just a placebo effect?' The main reasons for the persistence of this scepticism are the inconsistent outcomes from existing placebo-controlled trials and the insufficient number of long-term treatment studies [Tacklind *et al*. 2009].

Nowadays, more than 100 products containing *Serenoa repens* extract are available on the market worldwide, some registered as drugs and others as food supplements.

History

Serenoa repens originated in the swamps of the south-eastern coast of the USA (South Carolina, Florida, Alabama and inland as far as Texas). The first use of the extract is attributed to the Native Americans, for genitourinary disturbances [Murray and Pizzorno, 1994]. In the 1870s, the berries started to be investigated for their medicinal properties. Multiple effects were reported, both digestive (stimulating appetite and providing nutrition) and reproductive (increasing the size and secreting ability of the mammary glands, decreasing ovarian and uterine irritability, relieving dysmenorrhoea, ameliorating ovarian dysfunction, decreasing prostate enlargement etc.). In the era of synthetic pharmaceuticals, *Serenoa repens*, like many other phytotherapeutic alternatives, was initially disregarded, only to be rediscovered when the mirage of the perfect BPH drug faded [Buck, 2004].

Extraction technique

The fruits of *Serenoa repens* are dark purple to black berries that grow in clusters and ripen from October to December. The source of the extract is the ripe, partially dried berries. Various extraction methods are used by different manufacturers, and for this reason it is probable that one product is not equivalent to another. The lipidosterolic extract of *Serenoa repens* (Permixon) was the first to be more rigorously evaluated, and in recent years new studies have emerged regarding the ethanolic extract (Prostamol Uno) [Sinescu *et al*. 2011; Pais, 2010; Alyaev *et al*. 2007; Breza *et al*. 2005].

A steam hydrodistillate of *Serenoa repens* has also been reported. Chemical analysis of the resulting product identified 144 steam-volatile components, including about 100 structures that have not so far been described as constituents of these fruits [Rösler *et al*. 2009]. However, no clear data are available regarding the advantages of one method of extraction or another.

Mechanisms of action

A literature search reveals a significant number of studies addressing the subject of the mechanisms of action of *Serenoa repens*. Several have been proposed, including antiandrogenic action, an anti-inflammatory effect and an antiproliferative proapoptotic effect mediated through the inhibition of growth factors. However, the precise mechanisms of action are still to be described. In this regard, extrapolating the results of *in vitro* laboratory studies to the complex human situation requires caution and supplementary scientific evidence [Buck, 2004].

In vitro studies have emphasized dose-dependent inhibition of intracellular binding of dihydrotestosterone to cytosolic and nuclear receptors by the liposterolic extract of *Serenoa repens* in foreskin cell cultures [Sultan *et al*.1984]. Bayne and colleagues, in a trial using cocultures of epithelial and fibroblast cell suspensions, demonstrated that a *Serenoa repens* extract significantly inhibited both type I and II isoenzymes of 5α-reductase [Bayne *et al*. 1998]. However, variability of this effect was shown when evaluating various extracts on the market. All tested extracts inhibited both isoforms of 5α-reductase, but their potency appeared to be very different, probably owing to qualitative and quantitative inequities in the active ingredients [Scaglione *et al*. 2008].

The anti-inflammatory and anti-oedematous effects of *Serenoa repens* have also been demonstrated, the extract being an *in vitro* dual inhibitor of the cyclooxygenase and 5-lipoxygenase pathways [Breu *et al*. 1992; Tarayre *et al*. 1983].

Another mechanism of action attributed to *Serenoa repens* extract is the modulation of apoptosis via growth factors: it reverses the apoptosis/proliferation ratio seen in BPH tissue [Vacherot *et al.* 2000; Di Silverio *et al.* 1998].

Phytotherapy also seems to be able to modulate the prolactin signal transduction pathways, as well as to block the effect of prolactin on protein kinase C-dependent phosphorylation of a potassium channel [Van Coppenolle *et al.* 2000; Vacher *et al.* 1995].

These multiple synergistic mechanisms of action are explained by the fact that plant extracts are composites of several different molecules. Unfortunately, most of the studies researching these parameters are performed *in vitro*, the exact *in vivo* mechanisms still having to be described. Moreover, not all the studies agree about the effects of the *Serenoa repens* extract. Some authors challenge the ability of phytotherapy to promote apoptosis in BPH tissues or to inhibit 5α-reductase in a manner comparable to that of finasteride [Hill and Kyprianou, 2004].

Treatment of lower urinary tract symptoms

A large number of papers have evaluated *Serenoa repens* extracts in the treatment of BPH-related LUTS. However, many physicians remain sceptical regarding its true therapeutic value.

Phytotherapy was recently added to the European Association of Urology guidelines. Clear data that *Serenoa repens* extracts significantly reduce nocturia by comparison with placebo are cited. However, the guideline committee states that it is still unable to make specific recommendations about phytotherapy for male LUTS owing to the heterogeneity of the products and the methodological problems associated with meta-analyses [Oelke *et al.* 2011].

Under these circumstances, a number of more strictly conducted trials have been performed in recent years. Many of the existing papers cover only a short-term follow up of 1–6 months [Willetts *et al.* 2003; Descotes *et al.* 1995]. More recently, a few studies included a long-term follow up [Pytel *et al.* 2002]. One of them is FLUX, an observational, multicentre clinical trial that aimed to determine the effect of the daily intake of 320 mg *Serenoa repens* extract (Prostamol Uno) over a 24-month period [Sinescu *et al.* 2011].

Most of the short-, medium- and long-term studies showed statistically significant improvement in total international prostate symptom score (IPSS) during 6, 12 or 24 months of follow up [Debruyne *et al.* 2004a; Gerber *et al.* 2001]. When the irritative and obstructive IPSS subscores were separately evaluated, a decrease in both was seen [Sinescu *et al.* 2011; Debruyne *et al.* 2004a]. This combined action of *Serenoa repens* extract may offer at least a theoretical advantage over α-blocking therapy.

Regarding the quality-of-life score, although some studies reported only a limited improvement at 6 months [Gerber *et al.* 2001], others described a significant decrease between 9 and 24 months [Sinescu *et al.* 2011]. It is not completely clear whether the study period is the only parameter explaining this difference, or there are some other issues involved.

Although improvement in symptoms seems to be consistent throughout the existing studies, the effects on relevant urodynamic parameters tend to vary more widely. Some of the papers describe insignificant improvements of the maximum urinary flow [Debruyne *et al.* 2004a], while others record a statistically significant (but always linear) increase during a long-term treatment.

Studies comparing *Serenoa repens* extracts with tamsulosin underline the equivalence of the two drugs in alleviating BPH-induced LUTS symptoms. A combination of the two drugs showed no additional benefits [Hizli and Uygur, 2007].

The main issue regarding phytotherapy with *Serenoa repens* extract is that many of the existing placebo-controlled studies are not consistent in showing a significant superiority over placebo [Bent *et al.* 2006; Marks *et al.* 2000; Bauer *et al.* 1999]. The problem was recently raised in a meta-analysis, although the evaluation included studies of various durations as well as some on mixed herbal drugs consisting not only of *Serenoa repens* extract [Tacklind *et al.* 2009].

Nowadays, some studies with high scientific value are producing more and more valuable data. The TRIUMPH study, from six European countries, demonstrated that monotherapy with either α1-blockers, 5α-reductase inhibitors or *Serenoa repens*/*Pygeum africanus* extracts improves urinary status by comparison with 'watchful waiting' [Hutchison *et al.* 2007]. The PERMAL

randomized study reported slight superiority of *Serenoa repens* lipidosterolic extract (Permixon) over tamsulosin 0.4 mg/day in reducing LUTS in severe BPH patients after 3 months and up to 12 months of treatment [Debruyne *et al.* 2004a]. The FLUX study emphasized significant improvements in IPSS, quality of life and maximum urinary flow following Prostamol Uno treatment during a long-term follow up (24 months). This trial had no placebo arm, owing to concerns that the long-term lack of treatment in some patients would be unethical [Sinescu *et al.* 2011].

Erectile function

Some studies have described a significant improvement in the International Index of Erectile Function score following treatment with *Serenoa repens* extracts. If we take into consideration that retrograde ejaculation and reduced ejaculate volume related to α-blockers, and erectile dysfunction and decreased libido related to 5α-reductase inhibitors are frequently associated with dissatisfaction in medically treated BPH patients, *Serenoa repens* extract may become a viable alternative in selected cases [Giuliano, 2006; Zlotta *et al.* 2005; Debruyne *et al.* 2004a; Carraro *et al.* 1996].

Impact on the outcome of surgical treatment

The preoperative use of *Serenoa repens* extracts has been advocated for its ability to increase the efficacy of transurethral resection of the prostate (TURP) and to decrease the surgically related complications, in particular, bleeding [Pecoraro *et al.* 2004]. This aspect has been confirmed by other trials. The duration of surgery, overall intraoperative complications, transfusion needs, catheterization time and changes in haemodynamic parameters were significantly more favourable in the preoperatively treated study group [Anceschi *et al.* 2010].

This idea is, however, contested by some authors, who did not find any reduction of intraoperative bleeding after treatment with either *Serenoa repens* extract or dutasteride [Tuncel *et al.* 2009]. However, there are more published articles that support the fact that phytotherapy has a role in decreasing TURP-related morbidity than those disputing it.

Safety issues

Owing to the long-term nature of the therapy, safety aspects of the drug are of extreme importance. Most of the studies (including those that were long term) describe the satisfactory safety profile of *Serenoa repens* extracts [Agbabiaka *et al.* 2009; Vinarov *et al.* 2009; Avins *et al.* 2008]. A systematic review of the literature, including 26 randomized controlled trials, four nonrandomized controlled trials, six uncontrolled trials and four case reports suggested that adverse events associated with the use of *Serenoa repens* are mild and similar to those seen in the placebo series of patients. The most frequently reported adverse events are abdominal pain, diarrhoea, nausea, fatigue, headache, decreased libido, and rhinitis. More serious adverse events, such as death and cerebral haemorrhage, are extremely rarely reported. Moreover, in these patients even the causality between the adverse event and the treatment is questionable. Furthermore, no drug interactions were reported [Agbabiaka *et al.* 2009].

Conclusion

Despite the large volume of information regarding the *in vitro* effects of *Serenoa repens* extracts, the *in vivo* method of action is still to be clarified.

Analysis of the existing clinical database indicates that extracts of *Serenoa repens* may be considered a viable first-line therapy for treating LUTS. They offer significant improvements of urinary status while having a favourable safety profile.

However, the existing herbal formulations are extremely heterogeneous and thus difficult to assess in meta-analysis. More randomized, placebo-controlled, long-term trials are needed in order to eliminate all scepticism related to the use of phytotherapeutic agents in BPH-related LUTS patients. Particular attention must be focused on differentiating between registered preparations, which are regulated as drugs, and those considered to be food supplements.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

Agbabiaka, T.B., Pittler, M.H., Wider, B. and Ernst, E. (2009) *Serenoa repens* (saw palmetto): a systematic review of adverse events. *Drug Saf* 32: 637–647.

Alyaev, Y.G., Apolikhin, O.I., Mazo, E.B., Vinarov, A.Z., Lokshin, K.L., Medvedev, A.A. *et al.* (2007) First results of a clinical trial of the efficacy and safety of Prostamol® Uno in patients with the early signs of prostatic hyperplasia. *Eff Pharmacother Urol* 8: 11.

Anceschi, R., Bisi, M., Ghidini, N., Ferrari, G. and Ferrari, P. (2010) *Serenoa repens* (Permixon®) reduces intra- and postoperative complications of surgical treatments of benign prostatic hyperplasia. *Minerva Urol Nefrol* 62: 219–223.

Avins, A.L., Bent, S., Staccone, S., Badua, E., Padula, A., Goldberg, H. *et al.* (2008) A detailed safety assessment of a saw palmetto extract. *Complement Ther Med* 16: 147–154.

Bauer, H.W., Casarosa, C., Cosci, M., Fratta, M. and Blessmann, G. (1999) Saw palmetto fruit extract for treatment of benign prostatic hyperplasia. Results of a placebo-controlled double-blind study. *MMW Fortschr Med* 141: 62.

Bayne, C.W., Donnelly, F., Chapman, K., Bollina, P., Buck, C. and Habib, F. (1998) A novel coculture model for benign prostatic hyperplasia expressing both isoforms of 5 alpha-reductase. *J Clin Endocrinol Metab* 83: 206.

Bent, S., Kane, C., Shinohara, K., Neuhaus, J., Hudes, E.S., Goldberg, H. *et al.* (2006) Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 354: 557–566.

Breu, W., Hagenlocher, M., Redl, K., Tittel, G., Stadler, F. and Wagner, H. (1992) Anti-inflammatory activity of sabal fruit extracts prepared with supercritical carbon dioxide. In vitro antagonists of cyclooxygenase and 5-lipoxygenase metabolism. *Arzneimittelforschung* 42: 547–551.

Breza, J., Kliment, J., Valansky, L. and Capova, G. (2005) Phytotherapy of symptomatic benign prostatic hyperplasia using alcohol extract of *Serenoa repens* fruit (Prostamol Uno). *Urologia* 11: 6–10.

Buck, A.C. (2004) Is there a scientific basis for the therapeutic effects of *Serenoa repens* in benign prostatic hyperplasia? Mechanisms of action. *J Urol* 172: 1792–1799.

Carraro, J.C., Raynaud, J.P., Koch, G., Chisholm, G.D., Di Silverio, F., Teillac, P. *et al.* (1996) Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate* 29: 231–240.

Debruyne, F., Boyle, P., Calais Da Silva, F., Gillenwater, J.G., Hamdy, F.C., Perrin, P. *et al.* (2004a) Evaluation of the clinical benefit of Permixon and tamsulosin in severe BPH patients – PERMAL study subset analysis. *Eur Urol* 45: 773–779.

Debruyne, F., Boyle, P., Calais da Silva, F., Gillenwater, J.G., Hamdy, F.C., Perrin, P. *et al.* (2004b) Evaluation of the clinical benefit of Permixon and tamsulosin in severe BPH patients – PERMAL study subset analysis. *Prog Urol* 14: 326–331.

Descotes, J.L., Rambeaud, J.J., Deschaseau, P. and Faure, G. (1995) Placebo-controlled evaluation of the efficacy and tolerability of Permixon in benign prostatic hyperplasia after exclusion of placebo responders. *Clin Drug Invest* 9: 291–297.

Di Silverio, F., Monti, S., Sciarra, A., Varasano, P.A., Martini, C., Lanzara, S. *et al.* (1998) Effects of long-term treatment with *Serenoa repens* (Permixon) on the concentrations and regional distribution of androgens and epidermal growth factor in benign prostatic hyperplasia. *Prostate* 37: 77–83.

Gerber, G.S., Kuznetsov, D., Johnson, B.C. and Burstein, J.D. (2001) Randomized, double-blind, placebo-controlled trial of saw palmetto in men with lower urinary tract symptoms. *Urology* 58: 960–964.

Giannakopoulos, X., Baltogiannis, D., Giannakis, D., Tasos, A., Sofikitis, N., Charalabopoulos, K. *et al.* (2002) The lipidosterolic extract of *Serenoa repens* in the treatment of benign prostatic hyperplasia: a comparison of two dosage regimens. *Adv Ther* 19: 285–296.

Giuliano, F. (2006) Impact of medical treatments for benign prostatic hyperplasia on sexual function. *BJU Int* 97: 34–38.

Hill, B. and Kyprianou, N. (2004) Effect of Permixon on human prostate cell growth: lack of apoptotic action. *Prostate* 61: 73–80.

Hizli, F. and Uygur, M.C. (2007) A prospective study of the efficacy of *Serenoa repens*, tamsulosin, and *Serenoa repens* plus tamsulosin treatment for patients with benign prostate hyperplasia. *Int Urol Nephrol* 39: 879–886.

Hutchison, A., Farmer, R., Verhamme, K., Berges, R. and Navarrete, R.V. (2007) The efficacy of drugs for the treatment of LUTS/BPH, a study in 6 European countries. *Eur Urol* 51: 207–215.

Marks, L.S., Partin, A.W., Epstein, J.I., Tyler, V.E., Simon, I., Macairan, M.L. *et al.* (2000) Effects of a saw palmetto herbal blend in men with symptomatic benign prostatic hyperplasia. *J Urol* 163: 1451–1456.

Murray, M.T. and Pizzorno, J. (1994) Encyclopedia of Natural Medicine, John Bastyr University Publishing: Seattle, WA.

Oelke, M., Bachmann, A., Descazeaud, A., Emberton, M., Gravas, S., Michel, M.C. *et al.* (2011) Guidelines on the treatment of non-neurogenic male LUTS. EAU online Guidelines. Available at: http://www.uroweb.org/gls/pdf/12_Male_LUTS.pdf

Pais, P. (2010) Potency of a novel saw palmetto ethanol extract, SPET-085, for inhibition of 5alpha-reductase II. *Adv Ther* 27: 555–563.

Pecoraro, S., Annecchiarico, A., Gambardella, M.C. and Sepe, G. (2004) Efficacy of pretreatment

with *Serenoa repens* on bleeding associated with transurethral resection of prostate. *Minerva Urol Nefrol* 56: 73–78.

Pytel, Y.A., Vinarov, A., Lopatkin, N., Sivkov, A., Gorilovsky, L. and Raynaud, J.P. (2002) Long-term clinical and biologic effects of the lipidosterolic extract of *Serenoa repens* in patients with symptomatic benign prostatic hyperplasia. *Adv Ther* 19: 297–306.

Rösler, T.W., Matusch, R., Weber, B. and Schwarze, B. (2009) Analysis of the hydrodistillate from the fruits of *Serenoa repens*. *Planta Med* 75: 184–186.

Scaglione, F., Lucini, V., Pannacci, M., Caronno, A. and Leone, C. (2008) Comparison of the potency of different brands of *Serenoa repens* extract on 5alpha-reductase types I and II in prostatic co-cultured epithelial and fibroblast cells. *Pharmacology* 82: 270–275.

Sinescu, I., Geavlete, P., Multescu, R., Gangu, C., Miclea, F., Coman, I. *et al.* (2011) Long-term efficacy of *Serenoa repens* treatment in patients with mild and moderate symptomatic benign prostatic hyperplasia. *Urol Int* 86: 284–289.

Sultan, C., Terraza, A., Devillier, C., Carilla, E., Briley, M., Loire, C. *et al.* (1984) Inhibition of androgen metabolism and binding by a liposterolic extract of *Serenoa repens* B in human foreskin fibroblasts. *J Steroid Biochem* 20: 515.

Tacklind, J., MacDonald, R., Rutks, I. and Wilt, T.J. (2009) *Serenoa repens* for benign prostatic hyperplasia. *Cochrane Database Syst Rev* 15: CD001423.

Tarayre, J.P., Delhon, A., Lauressergues, H., Stenger, A., Barbara, M., Bru, M. *et al.* (1983) Anti-edematous action of a hexane extract of the stone fruit of *Serenoa repens* Bartr. *Ann Pharm Fr* 41: 559–570.

Tuncel, A., Ener, K., Han, O., Nalcacioglu, V., Aydin, O., Seckin, S. *et al.* (2009) Effects of short-term dutasteride and *Serenoa repens* on perioperative bleeding and microvessel density in patients undergoing transurethral resection of the prostate. *Scand J Urol Nephrol* 43: 377–382.

Vacher, P., Prevarskaya, N., Skyrma, R., Audy, M.C., Vacher, A.M., Odessa, M.F. *et al.* (1995) The lipidosterolic extract from *Serenoa repens* interferes with prolactin receptor signal transduction. *J Biomed Sci* 2: 357.

Vacherot, F., Azzouz, M., Gil-Diez-De-Medina, S., Colombel, M., De LaTaille, A., Lefrere Belda, M.-A. *et al.* (2000) Induction of apoptosis and inhibition of cell proliferation by the lipido-sterolic extract of *Serenoa repens* (LSESr, Permixon®) in benign prostatic hyperplasia. *Prostate* 45: 259.

Van Coppenolle, F., Le Bourhis, X., Carpentier, F., Delaby, G., Cousse, H., Raynaud, J.P. *et al.* (2000) Pharmacological effects of the lipidosterolic extract of *Serenoa repens* (Permixon) on rat prostate hyperplasia induced by hyperprolactinaemia: comparison with finasteride. *Prostate* 43: 49.

Vinarov, A.Z., Aliaev, Iu.G. and Lokshin, K.L. (2009) Safety of continuous (more than 1 year) intake of *Serenoa repens* extract by patients with prostatic adenoma. *Urologiia* 1: 84–87.

Willetts, K.E., Clements, M.S., Champion, S., Ehsman, S. and Eden, J.A. (2003) *Serenoa repens* extract for benign prostate hyperplasia: a randomized controlled trial. *BJU Int* 92: 267–270.

Zlotta, A.R., Teillac, P., Raynaud, J.P. and Schulman, C.C. (2005) Evaluation of male sexual function in patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) treated with a phytotherapeutic agent (Permixon), tamsulosin or finasteride. *Eur Urol* 48: 269–276.