Serenoa Repens in the hands of the modern urologist

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Abstract

**Background:** Benign Prostatic Hyperplasia (BPH) is a non-malignant enlargement of the prostate gland that affects around 50% of men between the ages of 50 and 60 years old. The application of Serenoa Repens in the treatment of the symptoms of stage I & II BPH is a therapeutic option that is present in the urologist’s agenda for nearly three decades. The purpose of this work is the complete evaluation of existing literature on Serenoa Repens (in-vitro experiments, clinical trials and institutional monographs), summing up clinical trial references in an appendix and raising the necessary issues as far as raw material quality is concerned, providing a good point of reference to the contemporary urologist.

**Methods:** A complete review of the available literature on the effect of the lipidosterolic extract of Serenoa Repens in Benign Prostatic Hyperplasia was conducted. Studies were collected via Pubmed.org, and an analytical appendix was formed, providing the full spectrum of available data.

**Results:** There are contradictions in the available literature, especially between the results of 1984 to 2014 clinical trials and the available monographs. Contemporary clinical trial publications don’t make any reference to the specifications prescribed by European Pharmacopoieia, which are the only quality markers available.

**Conclusion:** Future research should focus on and take into account the specifications available in European Pharmacopoieia concerning the content and method of production, providing thorough quantitative analysis of the contents of the extract used in trials.

Introduction

The application of Serenoa Repens (Saw Palmetto) in the treatment of the symptoms of stage I & II Benign Prostatic Hyperplasia (BPH) is a therapeutic option that is present in the urologist’s agenda for nearly three decades. The beneficial contribution of the herb in alleviating Lower Urinary Tract Symptoms and improving patient’s quality of life is clearly reflected in the commercial figures of those thirty last years. Sereneoa Repens has established its position as one of the most commercial phytotherapeutic ingredients for BPH in Western markets, and especially in the United States and Germany.

Citation


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In parallel lines with the commercial consolidation of Serenoa Repens in the markets, extensive research has taken place, focusing on the clinical and biochemical potency of the plant’s extract. As a result, a wide range of published in vitro and clinical research, focusing on the lipidosterolic extract of Serenoa Repens is available. In our days, over a century after Serenoa Repens was registered as a medicine in United States Pharmacopoieia (1906), new published work keeps emerging and added for evaluation by the professional practitioner.

The purpose of this work is to evaluate existing literature, (in vitro experiments, clinical trials and institutional monographs), sum up clinical trial references in an appendix and raise the necessary issues as far as raw material quality is concerned, providing a good point of reference to the contemporary urologist.

Materials & Methods
The available literature on the lipidosterolic extract of Serenoa Repens is quite extensive, especially when compared to the literature referring to other phytotherapeutic ingredients. Our team contacted a literature search in pubmed.org using “Saw Palmetto” “Serenoa Repens” “Sabal Serrulata” “Benign Prostatic Hyperplasia” and “Lower Urinary Tract Symptoms” “Clinical Trial” as mesh terms. Further search was conducted on the studies performing in-vitro tests on the mechanism of action of Serenoa Repens. pubmed.org was used as a search engine, using “Serenoa Repens”, “Saw Palmetto”, “Sabal Serrulata”, “Prostate”, “Benign Prostatic Hyperplasia”, “in vitro”, “anti-inflammatory” as mesh terms. The monographs from certain institutions were collected through accessing the respective web-sites (European Medicines Agency, American Botanic Council, World Health Organization).

Finally, information was gathered through our authorized access to the European Pharmacopoieia ver. 8.0

Results

Mechanism of Action
The mechanism of action of Serenoa Repens lipidosterolic extract is not yet clearly defined. However, an important part of the literature evaluates the chemical ingredients included in the extract as inhibitors of the activity of the enzyme 5-a reductase. The enzyme 5-a reductase is a basic modulator of the conversion of testosterone to dihydrotestosterone (DHT), an enzyme associated with the overgrowth of the prostate’s epithelial cells. At the same time, anti-inflammatory activity is achieved through the inhibition of inflammatory mediators, and the apoptotic processes in prostate’s cells are modulated. Both have been attributed by specific studies to different compounds of the plant’s extract. However, the mechanism of action is yet to be thoroughly and fully specified.

Safety Profile
The majority of the literature converges on the fact that the treatment with Serenoa Repens is a safe choice for patients. All studies, review papers and monographs claim that Serenoa Repens is safe without any side effects resulting from long term use. The safety profile of Serenoa Repens is mentioned in the American Botanic Council’s Clinical Guide to Herbs as being better than that of Finasteride. Serenoa Repens is not associated with side-effects such as erectile dysfunction, ejaculation problems and negative effects on libido.

From the urologist’s perspective, Serenoa Repens appears to be a safe choice in special patients’ cases. For example, it is widely known that the use of medicines acting at a-adrenergic receptors increases the chances for orthostatic hypotension. Furthermore, older patients already being treated for hypertension and cardiac arrhythmias using b-adrenergic receptor antagonists, are already under greater danger of orthostatic hypotension. In such cases, preparations with Serenoa Repens have the obvious advantage of avoiding side effects that are dangerous for older people.

Monographs
Official monographs approve the application of Serenoa Repens for the relief of BPH symptoms. The American Botanic Council, an institution that translated the monographs of German Commission E in the early 90’s, reports that 17 out of 19 studies evaluated for the «ABC clinical guide to Herbs» showed positive results. The World Health Organization (p. 288, WHO monographs on selected medicinal plants, vol 2) included the treatment of LUTS in people with BPH stage I & II in

Key words
Serenoa Repens; Saw Palmetto; Benign Prostatic Hyperplasia
its monograph for Serenoa Repens under the section “Uses Supported By Clinical Data”. Along similar lines, the Committee on Herbal Medicinal Products of the European Union, defines as a therapeutic indication in the respective Herbal Monograph, the “Symptomatic treatment of benign prostatic hyperplasia” (well established use) and the “Traditional medicinal product for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia, after serious conditions have been excluded by a doctor” (Traditional Use).

**Clinical Trials**

The evaluated clinical studies included open label or placebo controlled studies, comparison of Serenoa Repens with pharmaceutical preparations (e.g Tamsulosin, Finasteride), studies on combinations of Serenoa Repens with other herbal material, as well as studies that compare different daily dosage and administration patterns of the plant’s extracts.

Inspite of the monographs’ positive assessment on Serenoa Repens, there still is no definite verdict that can be deducted from the available clinical literature. From 22 studies, dating from 1984 to 2014, the results are ambiguous and contradictory. In addition, two meta-analyses from 2004 and 2009 (the last one was updated in 2012) that analyze an important part of the aforementioned studies (as well as some studies that were not available in English and were excluded from our search), they draw a non-positive conclusion on the effectiveness of Serenoa Repens in the treatment of BPH. The studies that were gathered are cited in the special appendix at the end of this article. A stand-alone 30 page appendix that collects and compares the results of those trials, is available upon request by e-mail info@synapse.com.gr.

The important question upon the contradictory results and the quality of available studies is being propped by the European Urological Association. In the institute’s directions of 2009, “Guidelines on Benign Prostatic Hyperplasia” the contradictory issue is being noted, and the question of the extract’s standardization is being officially raised. As far as our literature research work is concerned, we came upon the definite conclusion that little information is given on the chemical composition of the extract or, quite often, the extraction method of the preparation used is not even mentioned.

**Discussion**

The results of our literature research led us to look further into the quality markers of the extract. The World Health Organization (p. 288 of respective monograph) defines the free fatty acids and the respective ethyl-esters as main chemically active constituents. As mentioned before, similar references exist in certain in-vitro studies. In complete accordance, the monograph from the Committee on Herbal Medicinal Products (published in 2014), defines the pharmaceutical form by referring to the respective paragraph of European Pharmacopoeia. The specification of the extract’s composition according to European Pharmacopoeia (2014, p. 1377) is described in the definition of Sabalis Serrulatae extractum. The minimum content per anydrous extract is the following

Similarly, the American Botanic Council (Commission E’s Monograph) defines in the «ABC clinical guide to Herbs» under «Dosage & Administration» the «administration of 320 mg/day of soft native extract containing approximately 85% - 95% fatty acids». The achievement of a therapeutically beneficial composition can be firmly related with the method of extraction. The European Pharmacopoeia specifies the use of ethanol (min 90 % v/v), supercritical CO₂ or mixture of n-hexane and methylpentanes) as extraction solvents. Similar specifications are found in the Commission E monograph, where the amount suggested as a daily dosage is defined as «320 mg lipophilic ingredients extracted with lipophilic solvents (hexane or ethanol 90 percent v/v)».

Therefore, taking the previous specifications under consideration, we can safely state that most studies provided generic or inadequate descriptions of the preparations used with regards to the free fatty acid and phytosterol percentage of the extract. Furthermore, no study gave extra information on the pivotal aspect of the preparation’s lauric acid content that would show compliance with the European Pharmacopoeia recommendation.

This lack of standardization is an issue that directly affects the commercial side of Serenoa Repens. The lack of correspondence in between the aforementioned specifications and the actual content of commercial products is an issue that has been evaluated by certain publications. Indicatively, in a study published in the Journal of Urology (2002), three out of the six preparations that were analyzed in the study contained less...
than 25% of the labelled free fatty acid value, while in a study published in the Journal of Pharmacy and Pharmacology (2013), 35% out of the 46 preparations analyzed contained less than 70% in fatty acids. Furthermore, another British study published in Prostate Cancer and Prostatic Diseases in 2004, evaluated the concentration in free fatty acids, methyl esters and glycerides in 14 preparations with Serenoa Repens. The results of this study clearly show the big fluctuation existing in between the preparations, something that content can be variable in between different batches of the same product and have an effect in the potency/effectiveness of the preparation. The aforementioned study concluded that the samples that were produced with similar methods of extraction were closer in terms of composition and couldn’t be statistically distinguished.

**Conclusion**

Serenoa repens has been used for decades as a supplement for the relief of LUTS associated with BPH. The benefit of the use of Serenoa Repens however remains unverified, due to the great limitations of available research. Furthermore, the use of Serenoa Repens is considered to be safe, with very few ADRs reported in the literature. It is crucial that future research should focus on and take into account the specifications available in European Pharmacopoeia concerning the content and method of production. We clearly suggest that all new published studies should provide thorough quantitative analysis of the contents of the Serenoa Repens preparations used in the trials. Furthermore, we clearly suggest that studies that are actually clinical trials of commercial preparations should strictly use preparations from the same batch, providing the preparation's content of fatty acids, lauric acid and sterols, prioritizing scientific investigation over the commercial aspect of their work.

From the urologist's perspective, the knowledge of the specifications and the continuous update on modern literature is important, and this work lists a great part of available literature. Ultimately, the urologist is the one that has got the absolute priority in evaluating the effectiveness of certain preparations, through his own experience and his accumulated knowledge as a therapist.

**Conflicts of interest**

Both authors are employed at Synapse Hellenic Pharmaceuticals & Services, a company that markets a product containing Serenoa Repens (Prostanoa Rx®).
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## Clinical Trial Appendix 1984 - 2014

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