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File: ■ Saw Palmetto (*Serenoa repens*, Arecaceae)
■ Benign Prostatic Hyperplasia
■ Extraction Methods

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RE: Impact of Extraction Techniques on the Profiles and Efficacy of Saw Palmetto Used to Treat Urinary Tract Symptoms

De Monte C, Carradori S, Granese A, Di Pierro GB, Leonardo C, De Nunzio C. Modern extraction techniques and their impact on the pharmacological profile of *Serenoa repens* extracts for the treatment of lower urinary tract symptoms. *BMC Urol*. August 11, 2014;14:63. doi: 10.1186/1471-2490-14-63.

Symptomatic benign prostatic hyperplasia (BPH), the most common urologic disorder among elderly men, rises in prevalence with increasing age, and affects about 25% of men in their 50s (50% of those in their 80s). Slow-progressing BPH may cause bladder prostatic obstruction (BPO) and lower urinary tract symptoms (LUTS). To manage LUTS, it is desirable to keep symptoms from worsening by limiting disease progression. Treatment options include α1-adrenoceptor antagonists, 5α-reductase inhibitors, anti-cholinergic agents, phosphodiesterase 5 inhibitors, and plant extracts (PEs). The first two may contribute to sexual dysfunctions. Although use of PEs is rising, especially noted in Belgium, Hungary, Poland, and France, the European Association of Urology cannot recommend specific products for LUTS-BPH due to product heterogeneity and subsequent methodological problems in meta-analysis.

The most popular PEs for BPH are from saw palmetto (*Serenoa repens*, Arecaceae), with constituents found to inhibit 5α-reductase and exert pro-apoptotic, anti-estrogenic, and anti-inflammatory effects. As in many plants, amounts of therapeutic compounds in saw palmetto are low. Exhaustive extraction provides maximum amounts. Extraction processes should be reproducible, time-saving, and eco-friendly. Thermolability is an issue with many phytochemicals; hence, extraction temperatures and other conditions should be optimized. Qualitative and quantitative variances among BPH saw palmetto products are caused in part by different extractive processes used in manufacturing and may affect clinical results. This study aimed to evaluate available evidence on extraction methods and possible clinical implications for saw palmetto products.

Although pharmacological profiles for saw palmetto's active compounds are not yet fully described, standard reference materials (SRMs) for some dietary supplements, prepared by the National Institutes of Health's Office of Dietary Supplements, the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research, and the National Institute of Standards and Technology (NIST), include two saw palmetto SRMs. SRM

3250 is ground saw palmetto fruit. SRM 3251 is a supercritical CO_2 saw palmetto extract (SPE). Each has certified concentration values (CCVs) for specific phytosterols and fatty acids, free or as triglycerides; these are higher in SRM 3251. SRM 3251 also has CCVs for β-carotene and its isomers and for γ- and δ-tocopherol. The authors extracted SRM 3250 with several extracts under various conditions, finding that for pressurized fluid extraction (PFE), the choice of solvent, extraction temperature, and extraction pressure had little effect on the composition of extracted fractions; for Soxhlet extraction, solvent choice was of little importance but extraction time (at least 40 hours) was critical for efficiency. Fatty acids as triglycerides were six to 25 times higher in SRM 3251 than any SRM 3250 extract. Concentration of each fatty acid triglyceride was generally higher than its corresponding free fatty acid extract in either SRM. SRM 3250 had about one-sixth of the linoleic and α-linolenic acid as SRM 3251; the latter has one of the highest concentrations of linoleic acid triglycerides of any SRM, including fish oil, and the highest of α-linolenic acid.

In a database search, the authors found 12 studies of ten SPE products made with four extraction methods (for two products, extraction method was not reported), reviewing them for information about bioactive compounds and clinical effects. Two products were multi-herbal. Studies are not described in detail and were not evaluated for quality, and it is unclear whether all products have been fully characterized. Only one study directly compared pharmacological profiles associated with different extraction methods — a hexanic SPE product inhibited MCP-1/CCL2 messenger RNA (mRNA) expression in a concentration-dependent manner not seen in an SPE made with supercritical CO_2 extraction using batches of the same plant. Studies differed markedly in product or extract type, design, and results reported, making comparison difficult. One study compared a product's activity in rats with a bovine prostate peptide complex. While each showed benefits, response to the SPE product was more targeted. Research on several products is either ongoing or promising and suggestive of follow-up studies.

The authors describe extraction techniques that could be used to boost concentrations of active compounds in SPEs; most have apparently not been used nor evaluated for clinical performance. These include microwave-assisted extractions of several types, ultrasonic-assisted extraction, ionic liquid extraction, and enzyme-assisted extraction. Pressurized liquid/fluid extraction – a novel, eco-friendly method of phytochemical extraction – is mentioned, but the authors do not state whether it has been used for SPEs or for any of the products discussed. On the other hand, one of those products is made with an oily extract; this technique is not discussed. Of eight products reporting extraction method used, six used solvents, with five of those using ethanol at different concentrations and one using hexane; two used supercritical CO_2.

While it may be possible, as these authors have attempted, to compare different plant extracts, link different levels of bioactive compounds in different extracts to specific effects, and eventually standardize therapeutic compounds to best address specific conditions, the research base for this effort does not yet exist for SPEs.

—Mariann Garner-Wizard

Peer Review Comments:
The validity of the reviewed results on the product PC-SPES, a blend of eight herbs, is questionable. Firstly, the original experiments were performed using a 70% ethanol extract of PC-SPES, where the authors claimed this process isolated saw palmetto from the eight-herb mixture,[1] which is physically impossible and not supported by any

chemical analysis. Secondly, batches of PC-SPES had been found to contain pharmaceutical adulterations, and the product was recalled by the FDA in 2002.[2] However, PC-SPES may still be sold in other countries such as China where the original study was performed in 2007.

References

[1]Yang Y, Ikezoe T, Zheng Z, Taguchi H, Koeffler HP, Zhu WG. Saw palmetto induces growth arrest and apoptosis of androgen-dependent prostate cancer LNCaP cells via inactivation of STAT 3 and androgen receptor signaling. *Int J Oncol*. 2007;31(3):593-600.

[2]National Cancer Institute. PC-SPES – for health professionals (PDQ®). Bethesda, MD: National Cancer Institute. http://www.cancer.gov/cancertopics/pdq/cam/pc-spes/HealthProfessional/page1. Updated May 22, 2015. Accessed June 18, 2015.

Referenced article can be accessed at http://www.biomedcentral.com/1471-2490/14/63.