valensa

USPlus® Saw Palmetto

USPlus® Saw Palmetto Extract:
The Best Quality, Highest Purity and Value You Can Trust

Quality, purity and value. It is hard to achieve all three in the same product. Often you can get quality and purity, but not value. Or, you get value, but inferior quality or less of the active ingredient, so purity is sacrificed. Rarely do quality, purity, and value relate to the same product proposition. Even more difficult is to deliver a commercial product that has quality, purity and value, *and* adds trust to the equation. But that is what USPlus® saw palmetto extract offers to our customers: a high quality saw palmetto extract, delivering standardized potency and purity, for a value proposition for prostate health – all in a product that is US Pharmacopeia (USP)-verified, adding trust to the fundamental aspects of quality, potency and consistency offered by USPlus®.

Trust Starts with Supply Chain Mastery

Serenoa repens (Sabal serrulata), commonly known as saw palmetto, is a small palm, growing 7 to 10 feet tall, native to parts of the southeastern United States, but primarily found in Florida[1]. It is an interesting fact that *Serenoa repens* cannot be found outside this limited geographic region - Europe, Asia, and the rest of the world that use saw palmetto berries must source from Florida to obtain this valuable botanical.

With the limited geographic growing area for *Serenoa repens*, sustainability of supply and responsible sourcing are critically important. Because delivering consistent quality is important for Valensa's USPlus® saw palmetto extract, the company has implemented a comprehensive supply chain program, GEMS, that begins with responsible sourcing and a focus on berry quality, and is managed all the way from harvesting to final extract.

GEMS
HARVESTING A BETTER FUTURE

GEMS is anchored by four supply chain pillars:

- TRACEABILITY
- SUSTAINABILITY
- PURITY
- RESPONSIBILITY

Measures are in place at each step of the supply chain to allow Valensa to consistently and reliably deliver quality and potency in USPlus® saw palmetto extract, from harvest to final production. The fruit of the saw palmetto plant are berries that develop and ripen from green to deep purple over the course of the spring to early fall. As the berries ripen, they develop the phytonutrient profile that makes them an important natural botanical for prostate health[2]. A quality extract from ripe saw palmetto berries contains predominantly fatty acids, with a large proportion of

free fatty acids, as well as fatty alcohols and phytosterols. The lipid profile for saw palmetto is unique compared to extracts from other plant, vegetable, animal or nut oils[3], but attempts are often made to try to mimic the lipid composition. Only a true, quality saw palmetto extract can support prostate health.

Trust Comes from Green Extraction Technology

Starting with ripe saw palmetto berries sourced responsibly from nature, it is only logical that Valensa would want to continue the commitment to nature and the environment by using a green extraction technology to capture the valuable lipid compounds that make saw palmetto important for prostate health. Rather than using chemical solvents like hexane, Valensa deploys a patented Deep Extract® Supercritical CO_2 ($SCCO_2$) process to extract the bioactive lipids from the saw palmetto fruit. With this green extraction technology platform Valensa can obtain the highest quality extract, consistently achieving 85-95% total fatty acids[4] without the use of strong solvents. The high level of total fatty acids and the lipid fraction composition is directly related to the maturity of the berry and the extraction technology used. For example, low pressure carbon dioxide extraction technology does not efficiently pull the sterols and carotenoids from the mature berry, but ultrahigh pressure supercritical carbon dioxide extraction does[5] (Figure 1).

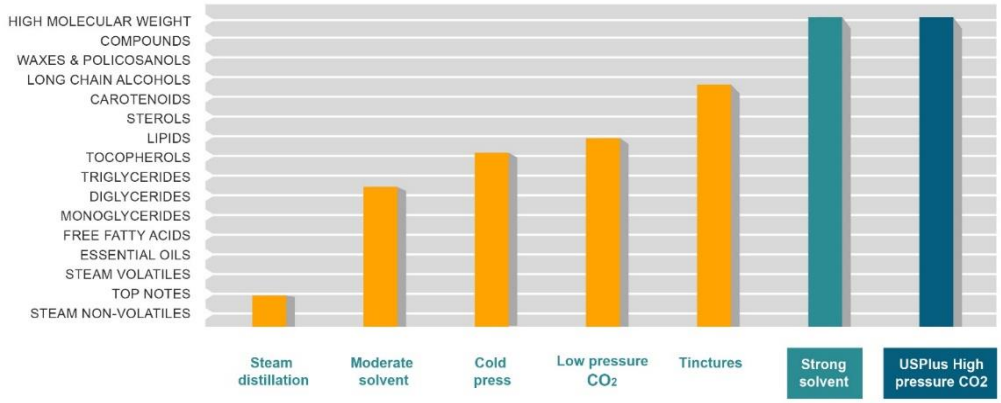


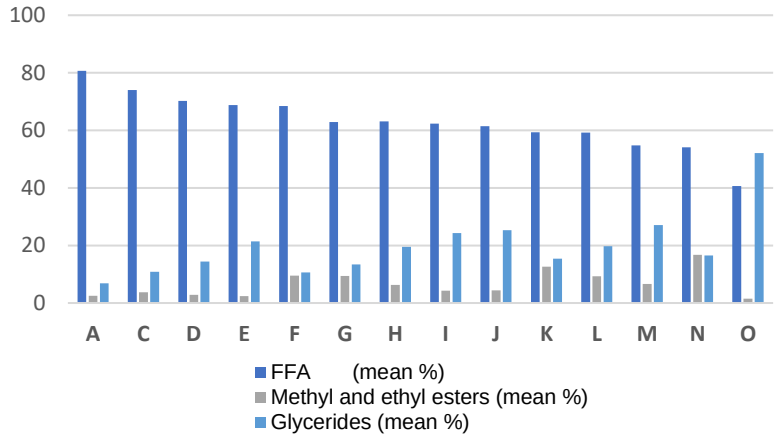
Figure 1. *A comparison of the actives extracted by various extraction methods. The deepest extracts are obtained by strong solvents (hexanes) or high-pressure supercritical CO_2 extraction[5].*

In 2014, De Monte et al. provided a review of extraction techniques used for 12 different brands of *Serenoa repens* (saw palmetto) and the impact on the presence of key beneficial components: free fatty acids, esterified fatty acids and other compounds such as phytosterols[6]. In his publication, De Monte reported that the supercritical carbon dioxide extraction method is non-toxic, non-flammable, and leaves no residue or impact on the environment (eco-friendly) unlike solvent extraction techniques. In addition, supercritical carbon dioxide extraction draws out an important lipid profile of bioactive phytonutrients from the saw palmetto berry to achieve beneficial amounts of actives[7].

In addition to the types of lipid components extracted from the saw palmetto berry, the composition within the lipid fraction can vary widely in commercial saw palmetto products[8-11]. In Figure 2 below, the variability in free fatty acids (FFA), methyl and ethyl esters, and

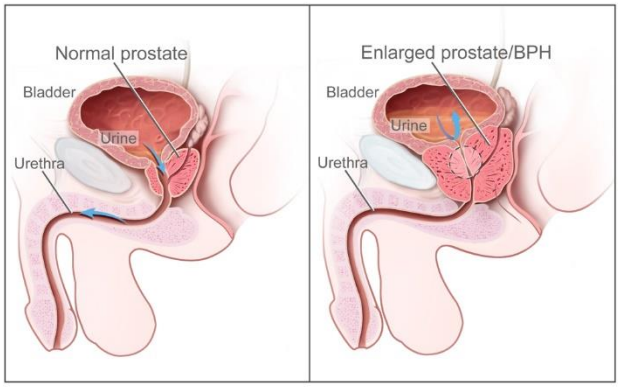
glyceride content in 14 commercial saw palmetto extracts is represented. In this study by Habib and Wyllie[12], the level of free fatty acids as a percentage of total fatty acids ranged from 80% to as low as 40%. The authors noted that hexane extraction technology tended to give a high content of free fatty acids (variable A, Permixon®, the hexane lipid extract of saw palmetto)[12], but $SCCO_2$ can also produce a high content of total fatty acids and a fatty acid profile needed to support prostate health. Importantly, fatty acids are the most predominant compounds in lipid extracts from saw palmetto[13] and are therefore considered to be the main biologically important components of saw palmetto products.

Figure 2. Commercial Products Vary Widely in Their Lipid Composition[10]



Trust Comes from Understanding the Science

BPH is the non-malignant enlargement of the prostate gland, a common occurrence in older men which can cause lower urinary tract symptoms[14]. Approximately 50% of men 51 to 60 years of age suffer from BPH, and over 80% of men over 80 years of age suffer from an enlarged prostate and experience lower urinary tract symptoms.

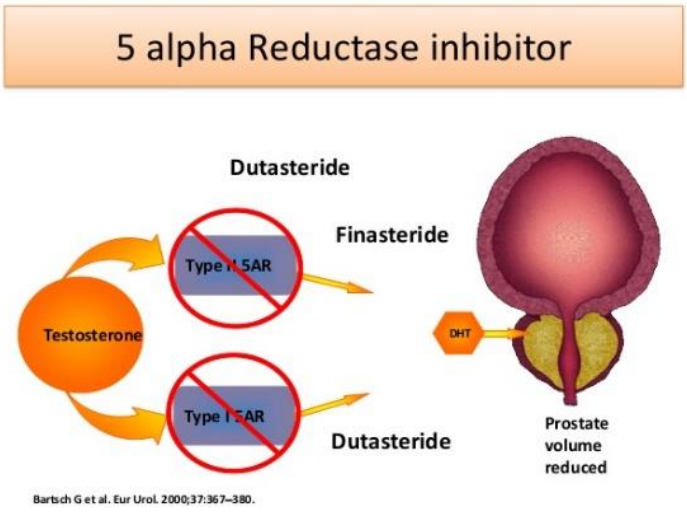


An enlarged prostate can impede the flow of urine from the bladder and cause urine retention, leading to the need to urinate frequently during the day and night. Standard of care in the US and Europe[8] is for men with mild to moderate symptoms associated with BPH to enter a "watchful waiting" phase to monitor the course of the condition, during which time the physician observes the symptoms to check if they are stable or progressing from moderate to more severe. Lifestyle modifications, such as alcohol consumption and caffeine intake, are also suggested[9]. If BPH is progressive, physicians recommend one of three options: medication, in-office BPH therapy, or surgery[9]. Men who remain stable with mild to moderate symptoms often remain in the watchful waiting phase. It is during this early stage of BPH symptoms when phytotherapies have been found to play a role in prostate health.

As noted before and in the literature, a key natural phytonutrient for prostate health is the lipidosterolic extract from ripe saw palmetto berries that is rich in key lipid compounds and free fatty acids. For decades in Europe, the hexane-extract product, Permixon®, has been approved as an herbal medicine for use in mild to moderate BPH[8,10], and has been clinically established for efficacy in treatment of lower urinary tract symptoms associated with BPH[8,11,15].

5α-reductase and Development of BPH

Testosterone and dihydrotestosterone (DHT) are two important male hormones. Testosterone is less potent than DHT, which is specifically important for the biological development and maturation of male sex organs, and for the development and maintenance of the prostate gland and seminal vesicles. The enzyme 5α-reductase, or 5αR, irreversibly catalyzes the formation of DHT from testosterone in certain tissues, including the prostate gland, seminal vesicles, epididymites, skin, hair follicles, liver and brain[16,17]. Circulating levels of DHT are approximately one-tenth the concentration of testosterone, but DHT levels can be up to 10 times those of testosterone in tissues with high 5αR expression, such as in the prostate gland and in hair follicles[18,19]. Both testosterone and DHT bind to the androgen receptor, but DHT is more potent because it has a higher affinity for the receptor[17]. The reduction of testosterone to DHT correlates with enlargement of the prostate gland, and development of lower urinary tract symptoms, such as an increase in urine retention, difficulty starting urination, and the increased frequency or need to urinate[17]. Also, male pattern hair loss is caused by an overproduction of 5αR enzyme and elevated levels of DHT in the hair follicles, which interferes with the cycle of scalp hair growth. In the presence of increased levels of DHT in hair follicles, the natural hair cycle is interrupted and newly produced hairs are miniaturized rather than achieving full growth[20,21]. Thus, compounds with the ability to inhibit 5αR and the conversion of testosterone to DHT could play a role in minimizing hair loss and prostate enlargement in men[20,22-24].

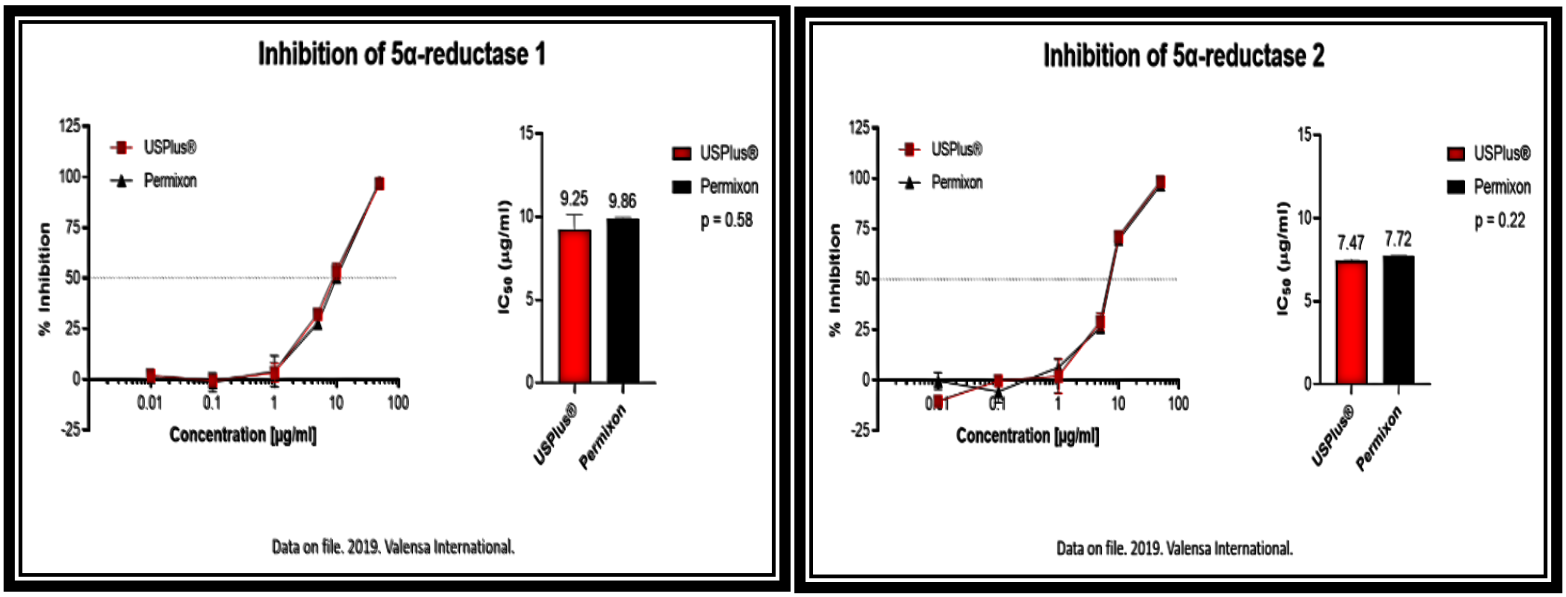


In human tissue, there are two main isoforms of the 5α-reductase enzyme expressed, Type 1 and Type 2[25,26], 5αR1 and 5αR2, respectively. Both types are found throughout the body, and predominantly expressed in skin, scalp and follicles and in prostate tissue[25,27-28]. The pharmacological agents dutasteride and finasteride are known to inhibit 5αR2, and dutasteride also inhibits 5αR1 (see the graphic representation from Bartsch et al.[24], above). Fatty acids also can have anti-androgenic activity[29].

The literature has reported that the hexanic lipidosterolic extract of saw palmetto, Permixon®, an herbal medicine in Europe, acts to prevent the conversion of testosterone to DHT[26]. Published studies have noted that it is the fatty acids in a quality *Serenoa repens* extract that are responsible for the potent inhibitory activity against the 5αR enzymes[13,29,31-34]. The other constituents in saw palmetto extract have little to no effect on 5αR activity[32-35]. Because the lipid profile of the supercritical CO_2 extract of saw palmetto from Valensa, USPlus®, is very similar to Permixon®, USPlus® should also be able to inhibit 5αR enzyme activity.

In an experiment conducted at a contract research organization in Europe, standardized cell culture assays were used to determine the inhibitory activity of USPlus® on both 5αR1 and 5αR2, with Permixon® as a comparator, and dutasteride and finasteride as positive controls in the 5αR1 and 5αR2 assays, respectively[36]. The data (below) indicate that USPlus® is very effective in inhibiting both 5αR1 and 5αR2 enzyme activity, with virtually identical activity to the reference comparator, Permixon®[36].

Figure 3. Inhibitory activity by USPlus® on 5α-reductase 1 and 2



Trust Is Delivered by Quality, Potency, and USP-Verified Certification

The fatty acid profile of saw palmetto extracts have been shown to vary widely[12,37-39]. And, so the quality of commercial saw palmetto products also varies. Variability in product quality can be due to extraction of the lipid fraction from unripe berries; use of ground dried berry powder rather than the lipid extract; or, even adulteration. Because the specific ratio of lauric acid to other fatty acids is very distinctive for saw palmetto, this can be used as a fingerprint to confirm identity. The percentage of total fatty acids alone does not guarantee that a product labeled as saw palmetto is in fact a quality product (Table 1). Instead, it is important to look at the fatty acid ratios and levels, as well as the

Table 1. Fingerprint of Quality Saw Palmetto Extract			
Parameter	USP Monograph	Valensa USPlus®	Imported Extract
Lauric Acid Ratio Identification			
Capric	9 – 16	10	16
Caproic	9 – 40	13	124
Caprylic	8.5 – 17.5	12	11
Linoleic	4 – 8	7	5.6
Linolenic	35 – 60	38	19
Myristic	2.2 – 2.8	2.6	3.2
Oleic	0.60 – 1.15	0.9	1.1
Palmitic	2.8 – 3.9	3.4	3.1
Stearic	13 – 20	16	14
Total Fatty Acids	min. 80%	90%	91%
Free Fatty Acids	-	71%	23%
Phytosterols	min. 0.2%	0.34%	0.30%
Fatty Alcohols	min. 0.15%	0.23%	0.001%
Peroxide Value	-	0.6	6.5

level of free fatty acids, phytosterols and fatty alcohols to confirm a true, quality saw palmetto product. The lipid profile is an important characteristic of a saw palmetto product needed to support prostate health and management of LUTS in men with mild to moderate BPH[40-42].

In the United States, the US Pharmacopeia (USP) is an important independent organization which has established a monograph for saw palmetto extract. The monograph provides strict standards for the extract phytochemical composition to ensure authenticity[40]. There is a minimum for total fatty acids, sterol content and β-sitosterol level specified. In addition to the total fatty acid concentration, USP has defined the fatty acid profile identity fingerprint for a quality saw palmetto extract, representing the specific ratio of each fatty acid to lauric acid. This further enhances the rigor of the monograph standard to verify quality and identify, and detect adulteration.

To further enhance the value proposition for USPlus®, Valensa committed to third party audit and verification of the integrity, quality and identity of its saw palmetto extract under the US Pharmacopeia Dietary Ingredient Verification Program (DIVP). This rigorous process subjected Valensa's manufacturing operations and quality systems to a thorough review and inspection, and verification by a third-party laboratory of the quality, potency and purity of USPlus® saw palmetto extract. Valensa International is the first company in the world to have a saw palmetto extract successfully complete the USP DIVP process. This recognition for USPlus® is an accomplishment that acknowledges Valensa International's commitment to berry sourcing and extraction in a quality and consistent way, in compliance with USP's officially recognized requirements and standards. USP-verified status recognizes USPlus® as a quality dietary ingredient our partners' can trust.

Over 25 clinical research trials, including 15 randomized controlled trials and twelve observational studies, have successfully documented the value proposition for a quality saw palmetto extract in prostate health and LUTS associated with BPH. The recommended clinically efficacious dose of USP-compliant saw palmetto extract is 320 mg per day. When a man in the "watchful waiting" phase of urinary tract symptom-progression is looking for a saw palmetto product that delivers quality, purity

and value that can be trusted, he should look no further than USPlus®, the first USP-Verified saw palmetto extract. Consumers should be aware that taking crushed dried saw palmetto berry powder supplements have not been established to provide any clinical efficacy or benefit. For a trusted solution, choose USPlus®. When Quality, Consistency, Potency and Value are important, you can trust Valensa's USPlus® saw palmetto extract.

References

1. University of Florida's Institute of Food and Agricultural Sciences. http://gardeningsolutions.ifas.ufl.edu/plants/trees-and-shrubs/palms-and-cycads/saw-palmetto.html
2. Gerber, G.S., D. Kuznetsov, B.C. Johnson, and J.D. Burstein, Randomized, double-blind, placebo-controlled trial of saw palmetto in men with lower urinary tract symptoms. *Urol.* 2001; 58(6): 960-964; discussion 964-965.
3. Schantz M.M., et al., Development of saw palmetto (*Serenoa repens*) fruit and extract standard reference materials. *Anal Bioanal Chem*. 2008; 392:427–438.
4. Valensa International data on file.
5. Valensa International data on file.
6. De Monte, C., et al., Modern extraction techniques and their impact on the pharmacological profile of *Serenoa repens* extracts for the treatment of lower urinary tract symptoms, *BMC Urol,* 2014; 14: 63-73.
7. Suzuki, M., et al., Pharmacological effects of saw palmetto extract in the lower urinary tract, *Acta Pharmacol Sin,* 2009; 30 (3): 271-281.
8. Gravas, S. et al., EAU Guidelines on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO). *Eur Assoc Urol.* 2016; pp 456 – 509.
9. Wu, Y., et al., Guidelines for the Treatment of Benign Prostatic Hyperplasia. *US Pharm.* 2016; 41(8): 36 – 40.
10. Sakalis, V., et al., Medical treatment of nocturia in men with lower urinary tract symptoms: systematic review by the European Association of Urology Guidelines Panel for male lower urinary tract symptoms. *Eur Urol.* 2017; 72: 757-769.
11. Vela-Navarrete, R., et al., Efficacy and safety of a hexanic extract of *Serenoa repens* (Permixon®) for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH): systematic review and meta-analysis of randomized controlled trials and observational studies. *BJU Int* 2018; 10.1111/bju.14362
12. Habib, F. K. and M.G. Wyllie, Not all brands are created equal: a comparison of selected components of different brands of *Serenoa repens* extract. *Prostate Cancer Prostatic Dis.* 2004; 7(3): 195-200
13. Raynaud, J.P., H. Cousse, and P.M. Martin, Inhibition of type 1 and type 2 5alpha-reductase activity by free fatty acids, active ingredients of Permixon. *J Steroid Biochem Mol Biol*, 2002. 82(2-3): p. 233-9.
14. Parsons, J.K., Benign Prostatic Hyperplasia and Male Lower Urinary Tract Symptoms: Epidemiology and Risk Factors. *Curr Bladder Dysfunct Rep,* 2010; 5(4): 212–218.

15. Novara, G., et al., Efficacy and safety of hexanic lipidosterolic extract of *Serenoa repens* (Permixon®) in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: systematic review and meta-analysis of randomized controlled trials, *Eur Urol Focus,* 2016; 2(5): 553-561.
16. Marks, L.S., 5α-Reductase: history and clinical importance, *Rev Urol,* 2004; 6 (Suppl 9): S11-21.
17. Roehrborn, C.G., Pathology of benign prostatic hyperplasia, *Int J Impot Res*, 2008; 20 Suppl 3: p. S11-18.
18. Governa, P., et al., Hypothesis on Serenoa repens (Bartram) small extract inhibition of prostatic 5alpha-reductase through an in silico approach on 5beta-reductase x-ray structure. *Peer J,* 2016; 4: p.e2698.
19. Renehan, A., Hormones, growth factors and tumor growth. Hay, I.A. and J.A. Wass (Eds.) *Clinical Endocrine Oncology*. 26 Jan 2009. John Wiley & Sons.
20. Urysiak-Czubatka, I., M.L. Kmieć and G. Broniarczyk-Dyla, Assessment of the usefulness of dihydrotestosterone in the diagnostics of patients with androgenetic alopecia, *Postepy Dermatol Alergol,* 2014 Aug; 31(4) 207-15.
21. Messenger, A. Male androgenetic alopecia. Blume-Peytavi, U. D.A. Whiting and R.M. Trüeb (Eds.), *Hair Growth Disorders,* 26 Jun 2008. Springer Science & Business Media. pp. 160-170.
22. Bruchovski, N., et al., Characterization of 5α-reductase gene expression in stroma and epithelium of human prostate. *J Steroid Biochem Mol Biol,* 1996; 59: 397-404.
23. Azzouni, F. and J. Mohler, Role of 5α-reductase inhibitors in benign prostatic diseases. *Prostate Cancer Prostatic Dis,* 2012; 15 (3): 222–230.
24. Bartsch, G., R.J. Rittmaster and H. Klocker, Dihydrotestosterone and the concept of 5alpha-reductase inhibition in human benign prostatic hyperplasia, *Eur Urol*, 2000 Apr;37(4): 367-380.
25. Iehlé, C., et al., Human prostate steroid 5 alpha-reductase isoforms – a comparative study of selective inhibitors, *J Steroid Biochem Mol Biol,* 1995 Sep; 54(5-6): 273-9.
26. Bayne, C.W., F. Donnelly, M. Ross and F.K. Habib. *Serenoa repens* (Permixon®): a 5α-reductase Types I and II inhibitor – new evidence in the coculture model of BPH, *Prostate* 1999; 40: 232-41.
27. Goldenberg, L. et al., The role of 5-alpha reductase inhibitors in prostate physiology: Is there an additional advantage to inhibition of type 1 isoenzyme? *Can Urol Assoc J,* 2009; 3 (3 Suppl 2): S109-14.
28. Shirakawa, T., et al., Messenger RNA levels and enzyme activities of 5 alpha-reductase types 1 and 2 in human benign prostatic hyperplasia (BPH) tissue. *Prostate* 2004; 58: 33-40.
29. Liu, J., K. Shimizu, and R. Kondo, Anti-androgenic activity of fatty acids. *Chem Biodivers*, 2009. 6(4): p. 503-12.
30. Abe, M., et al., Pharmacologically relevant receptor binding characteristics and 5alpha-reductase inhibitory activity of free Fatty acids contained in saw palmetto extract. *Biol Pharm Bull*, 2009. 32(4): p. 646-50.

31. Niederprum, H.J., et al., Inhibition of steroid 5 alpha-reductase activity by aliphatic fatty acids. Candidates for chemoprevention of prostate cancer. *Ann N Y Acad Sci*, 1995. 768: p. 227-30.
32. Niederprum, H.J., H.U. Schweikert, and K.S. Zanker, Testosterone 5alpha-reductase inhibition by free fatty acids from Sabal serrulata fruits. *Phytomedicine*, 1994. 1(2): p. 127-33.
33. Weisser, H., et al., Effects of the sabal serrulata extract IDS 89 and its subfractions on 5 alpha-reductase activity in human benign prostatic hyperplasia. *Prostate*, 1996. 28(5): p. 300-6.
34. Liang, T. and S. Liao, Inhibition of steroid 5 alpha-reductase by specific aliphatic unsaturated fatty acids. *Biochem J*, 1992. 285 (Pt 2): p. 557-62.
35. Cabeza, M., et al., Effect of beta-sitosterol as inhibitor of 5 alpha-reductase in hamster prostate. *Proc West Pharmacol Soc*, 2003. 46: p. 153-5.
36. Valensa International data on file.
37. Booker, A., et al., A phytochemical comparison of saw palmetto products using gas chromatography and (1) H nuclear magnetic resonance spectroscopy metabolomic profiling. *J Pharm Pharmacol*, 2014. 66(6): p. 811-22.
38. Feifer, A.H., N.E. Fleshner, and L. Klotz, Analytical accuracy and reliability of commonly used nutritional supplements in prostate disease. *J Urol*, 2002. 168(1): p. 150-4; discussion 154.
39. de Combarieu, E., et al., Metabolomics study of Saw palmetto extracts based on 1H NMR spectroscopy. *Fitoterapia*, 2015. 102: p. 56-60.
40. Saw Palmetto Extract Monograph (USP40). 2017, United States Pharmacopeia.
41. European Union herbal monograph on Serenoa repens (W. Bartram) Small, fructus. 2015, European Medicines Agency.
42. Fructus Serenoae Repentis monograph. World Health Organization.