Egypt. J. Chem. **Vol. 68,** No. 8 pp. 665 - 688 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Serenoa repens: A Phytochemical and Pharmacological Review

Aya M. Taha[a], Mona M. Hashem*[a], Enas H. Abdelrahman[a], Camilia G. Michel[a]

[a]*Department of Pharmacognosy, Faculty of Pharmacy, Cairo University,Kasr El-Aini Street, Cairo 11562, Egypt*

Abstract

Background: Thedried ripe fruit of *Serenoa repens* (W. Bartram) Small (Arecaceae) is traditionally used for urinary tract disorders, infertility, and prostate hyperplasia in men and for hormonal disturbances and infertility in women.

Aim: This paper aims to introduce a collective overview of *S. repens* research regarding its ethnopharmacological uses, chemical constituents, pharmacological effects, and toxicity. This was performed to identify the research gaps in current studies on *S. repens* and suggest potential avenues for further investigation.

Method: A review of the literature on *S. repens* was conducted from inception to December 2023. The data was acquired through Egyptian Knowledge Bank (EKB), Scopus, Web of Science, Google Scholar, PubMed, and Elsevier databases. Furthermore, a bibliometric analysis of research output on *S. repens* was conducted until December 2023 using the Scopus database. Data was analyzed, and VOSviewer software was used to visualize the relationships between authors, countries, and keywords in the retrieved documents.

Results:*S. repens* is reported to exhibit anti-androgenic, anti-inflammatory, antioxidant, anti-proliferative, and apoptotic activities, thereby alleviating symptoms associated with benign prostate hyperplasia (BPH) and chronic prostatitis. Phytosterols (mainly *β*-sitosterol) and fatty acids (predominantly lauric and oleic acid) were regarded as the chief active constituents responsible for such activities.

Conclusions: Based on this review, using *S. repens* extract in BPH management has been the focal point over the last few years. Recently, interest has been raised in other androgen-related conditions, such as androgenetic alopecia, yet these uses are still under investigation. To maximize the medicinal uses of *S. repens*, we suggest that more research to be performed to unveil new phytochemicals and their biological activities.

Keywords: *Serenoa repens;* saw palmetto; fatty acids; phtosterols; anti-androgenic; Benign prostatic hyperplasia.

1. Introduction

Serenoa repens (W. Bartram) Small, commonly known as saw palmetto, is the sole representative of the genus *Serenoa* (Family Arecaceae) [1]. It is endemic to the swamps of the southeastern United States, including South Carolina, Alabama, Georgia, Mississippi, and the Florida peninsula [2]. The leaves are fan-shaped, borne on slender petioles lined with short, recurved, sharp, saw-like spines [3]. The fruit is a drupe with a fleshy mesocarp, which turns bluish-black when fully ripe [4].

Historically, the plant has been widely used for centuries and provided food and habitat for many species of wildlife [5]. Among Southeastern American tribes, the plant held significant cultural value. Its leaves and fibers were used to craft baskets, fans, dolls, fish drags, rope, wax, roof thatch, brushes, and camp bedding [6]. The fruits have been recognized for their high nutritional value, served as a food source, either raw or cooked. Regular consumption of the fruits was thought to promote better digestion, enhance strength, and support healthy weight gain. Additionally, the seeds are edible and can be ground into flour [7], [8].

The therapeutic benefits of *S. repens* fruits have been documented since the 19th century. Its introduction to the medical practice dates back to 1877, credited to J. R. Read, M.D., and Abraham A. Solomons [9]. By 1898, eclectic medicine practitioners Felter and Lloyd recommended *S. repens* for treating various ailments, describing it as a nerve sedative, expectorant, and nutritive tonic. It was also used for digestive health and reproductive disorders. Hale (1898) detailed various preparations, including fruit tinctures, oils, suppositories, and crushed seeds, highlighting their benefits in prostate hyperplasia and other conditions [8].

Currently, *S. repens* fruits lipophilic extract is one of the most popular natural remedies for managing Benign prostatic hyperplasia (BPH) associated with lower urinary tract symptoms (LUTS). Many regulatory agencies haveapproved the use of *S. repens* fruits *n*-hexane extract. It was approved by the German Commission E for the treatment of BPH in stages I and II [10], and included in the European Medicines Agency (EMA) report as an official herbal medicine for BPH management associated with LUTS [11]. By 2021, a recommendation for using *S. repens* fruits *n*-hexane extract for the management of non-neurogenic male LUTS added to the European Association of Urology (EAU) guidelines to be the first phyto-therapeutic agent recommended by EAU guidelines [12].

Serenoa repens fruits *n*-hexane extract contains mainly fatty acids and phytosterols [13], which have been reported to possess various *in vitro* and *in vivo* pharmacological activities. It was reported to exert anti-androgenic activity *via* the

*Corresponding author e-mail: mona.hashem@pharma.cu.edu.eg.; (Mona M. Hashem).
Receive Date: 07 December 2024, Revise Date: 16 December 2024, Accept Date: 29 December 2024
DOI: 10.21608/ejchem.2024.342554.10943

inhibition of 5α-reductase enzyme, both types 1 and 2 [14], [15], the enzyme responsible for the conversion of testosterone into 5α-dihydro testosterone (DHT), which is more potent than testosterone and is thought to be implicated in the development of BPH. It was also reported to suppress many inflammatory mediators [16]**,** possess antioxidant [17]**,** apoptotic [18], anti-proliferative [19], spasmolytic [20] and anti-oedemic activities [21], which makes it beneficial for the treatment of BPH and other androgen-related conditions.

Clinical studies assessed the activity of *S. repens* in treating BPH and reported the different adverse drug reactions, such as nausea, diarrhea, fatigue, stomach upset, and headache. In the assessment of the tolerability of *S. repens*n-hexane extract, it was found to be better tolerated than α-blockers such as tamsulosin[22], [23]and other 5α-reductase inhibitors [22]**.** However, variations in the content and activity of pharmaceutical products derived from *S. repens* are observed in the market, likely due to differences in extraction methods; studies suggest that *n*-hexane, supercritical CO_2, and ethanol extraction technologies of *S. repens* fruits lead to different fatty acid and phytonutrient profiles [24].

2. Bibliometric overview of *Serenoa repens* research

To identify the research gaps and trends in *S. repens* research and identify future research directions, a bibliometric study of literature published on the plant was conducted using Scopus database (Elsevier, Netherlands) from 1954 to 2023.

Data extraction and preprocessing: Publications were retrieved from the Scopus database (Elsevier, Netherlands) using the search terms "*S. repens*" OR "Saw palmetto" OR "*Sabal serrulate*". The end date of the search was December 31, 2023.

Data analysis: The retrieved studies were analyzed based on publication year and journals. VOSviewer version 1.6.20 was used to analyze and visualize the relations between keywords, authors, and countries through network visualization. The items are represented as circles that differ in size according to their weight, colors represent clusters of related items, and links are represented by lines connecting the items.

Results: The Scopus search retrieved 915 documents published from 1954 to 2023. Analysis of the data showed that most of these documents were original research articles (70.6%), followed by reviews (16.6%) and a miscellaneous group (12.8%) comprising book chapters, notes, short surveys, letters, conference papers, editorials, erratums, and reports.

Distribution in terms of publications per year and journals

The data were analyzed for annual output. The total number of publications over the period 1954-1996 was relevantly low, with an average of 4.1 publications per year. A remarkable increase in the number of publications was observed from 1997, as manifested by doubling the number of publications compared to the previous year. Furthermore, the number of publications continued to increase until 2023 with fluctuation; the highest number was recorded in 2012 (42 publications) **(Fig. 1).**

Table 1 presents a curated list of high-productivity journals in the field of *S. repens* research. A comprehensive search of the Scopus database identified 155 journals publishing research articles on *S. repens* across various scientific disciplines from 1954 to 2023. This table focuses on prominent journals with a minimum publication threshold of 10 articles. The Journal of Urology is the leading publication venue with 23 documented outputs on *S. repens*.

Table 1: Top-performing journals with a minimum of ten articles on *Serenoa repens* spanning 1954 to 2023

Journal	No. of publications	IF
Journal Of Urology	23	6.6
Urology	18	2.1
Prostate	16	2.8
Urologia	16	0.8
Archivio Italiano Di Urologia E Andrologia	13	1.4
BJU International	10	4.5
Current Urology Reports	10	2.6
European Urology	10	23.4

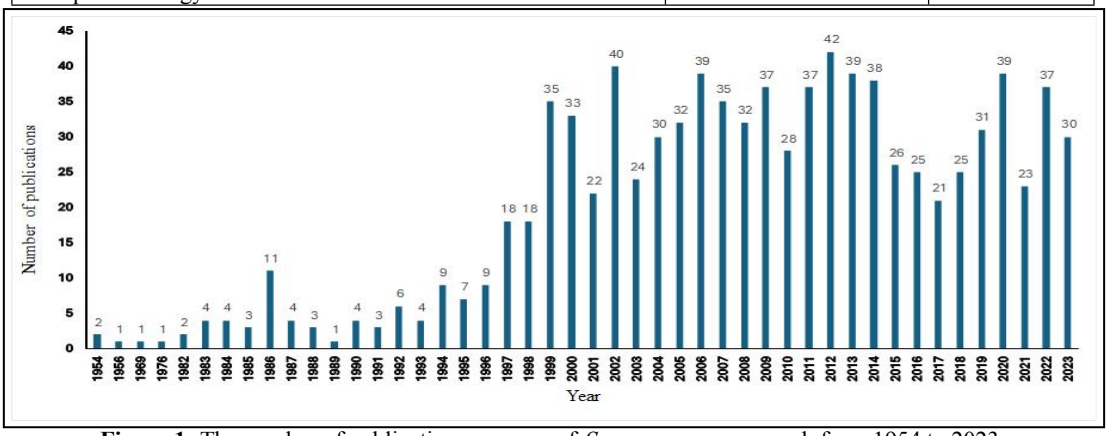


Figure 1: The number of publications per year of *Serenoa repens* research from 1954 to 2023.

Keywords analysis

The most common keywords found in *S. repens* articles were identified through keywords co-occurrence map **(Fig. 2).** Only the terms that occurred at least 5 times in the publications were visualized. Out of the 1722 keywords, 80 met the eligibility criteria, and 3 of them were manually removed for similarity (BPH, benign prostatic hyperplasia, and benign prostatic hyperplasia (bph)) and replaced by (Benign prostatic hyperplasia).

According to the map, seven clusters are generated. Three clusters (2,3,5) demonstrate the research on bioactivity assessment of *S. repens* concerning BPH. Cluster (1) contains such keywords as "androgenetic alopecia", "toxicity", "tolerability", and "side effects". Cluster (4) contains keywords such as "garlic", "ginseng", and "alternative medicine". Cluster (6) comprises terms related to environmental sciences "fire", "Florida", and "Arecaceae" and Cluster (7) contains keywords such as "lycopene" and "selenium" which are used frequently in combinations with *S. repens*. Considering these findings, another search using the search terms "Saw palmetto" or "*Serenoa repens*" and bph or "Benign prostatic hyperplasia" or luts or "lower urinary tract" was conducted; the search identified 377 publications, accounting for 41.2% of all included publications. **Fig. 3** presents a bibliometric analysis visualizing keywords categorized by their average publication year. A color gradient denotes publication time, with blue signifying the earliest publications and yellow representing the most recent ones. The analysis reveals a historical focus on the utility of *S. repens* for BPH management. However, there is a recent upsurge in research interest exploring *S. repens* extract for treating other conditions, such as androgenetic alopecia.

Country Analysis

Fig. 4 shows countries' contribution towards *S. repens* research with 10 publications or more. The United States of America (USA) is the key contributor, with 340 publications. Further analysis of the USA publications revealed that 76.5% of the publications are original articles, and 49.2% of these articles are involved in the fields of agricultural and environmental sciences. This high percentage indicates the importance of *S. repens* as a native plant in the USA. The rest of the publications focused on botanical, phytochemical, toxicological, ethnopharmacological, and clinical information.

The network of country co-authorship map **(Fig. 5)** shows collaborative linkages between countries contributing towards *S. repens* research. In this plot, countries are linked by their cumulative co-authorship, and the size of a node indicates total collaborative strength.

From the plot, five collaborative clusters are visible, as indicated by the different colors (Fig. 5). The first cluster (red) comprised China, Japan, South Korea, India, Turkey, Egypt, Ukraine, Pakistan, Saudi Arabia, and South Korea; the second cluster (green) included United States, Australia, Brazil, Canada, Czech Republic, New Zealand, Portugal, Russian Federation, South Africa; the third cluster (blue) included Italy, Greece, Slovakia, Slovenia, Switzerland; the fourth cluster (yellow) included Germany, United Kingdom, Austria, Spain, and the fifth cluster (purple) included France, Belgium, Netherlands.

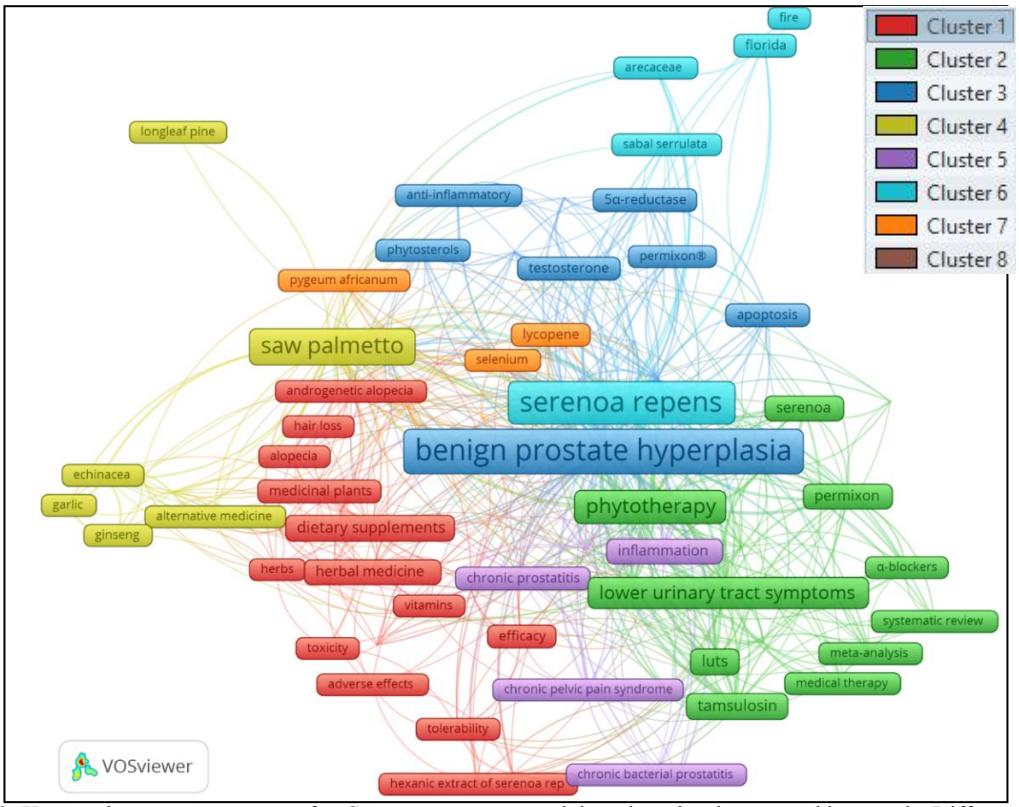


Figure 2: Keyword co-occurrence map for *Serenoa repens* research based on the abstract and keywords. Different colors represent different clusters of related keywords.

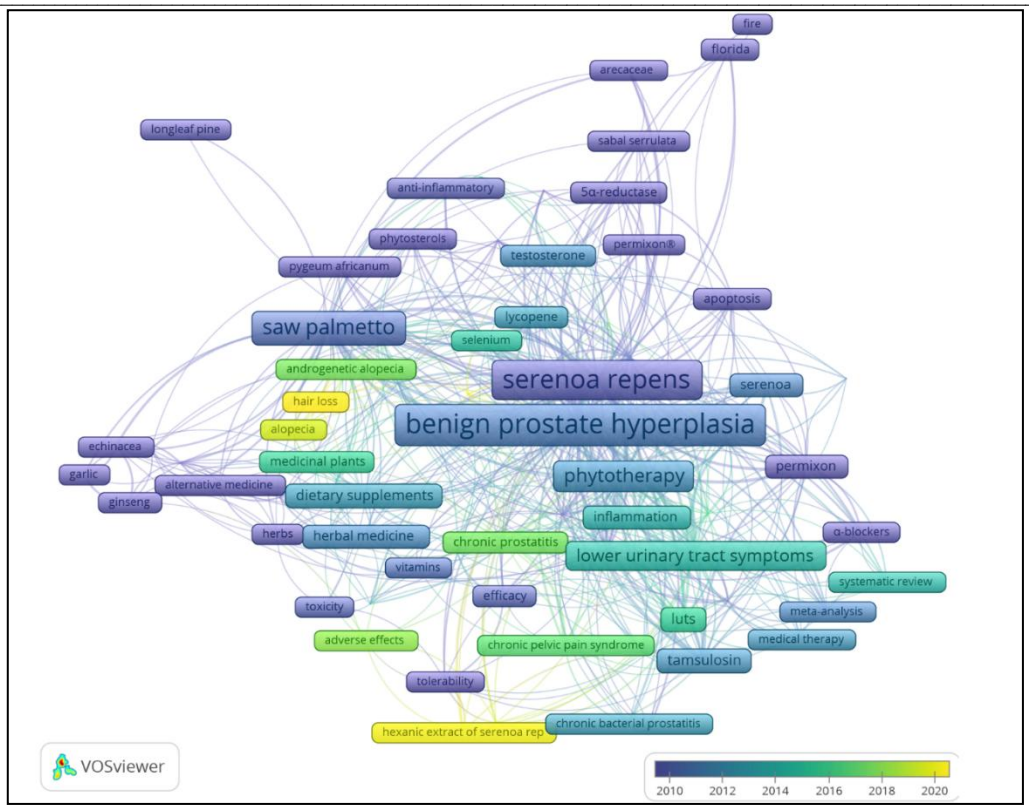


Figure 3: Keyword co-occurrence map for *Serenoa repens* research by the average of publication year (blue: earlier, yellow: later).

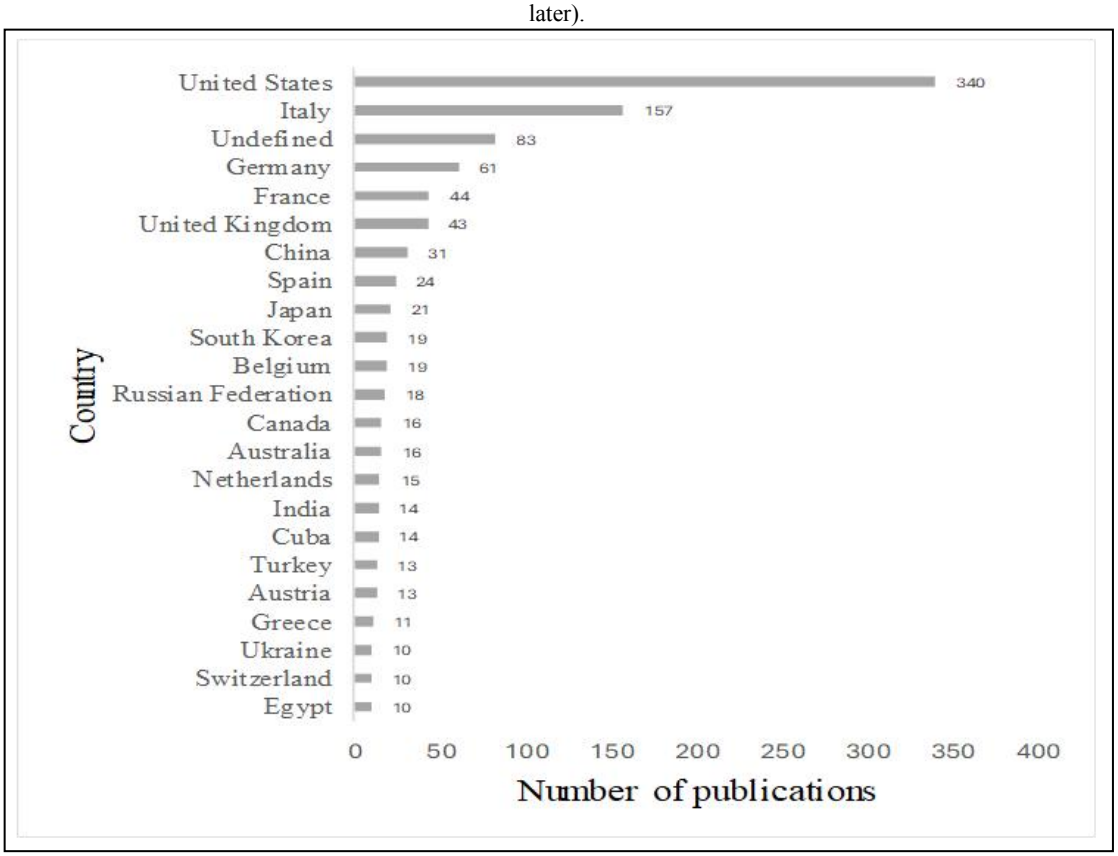


Figure 4: Most productive countries towards *Serenoa repens* research (minimum of 10 publications included).

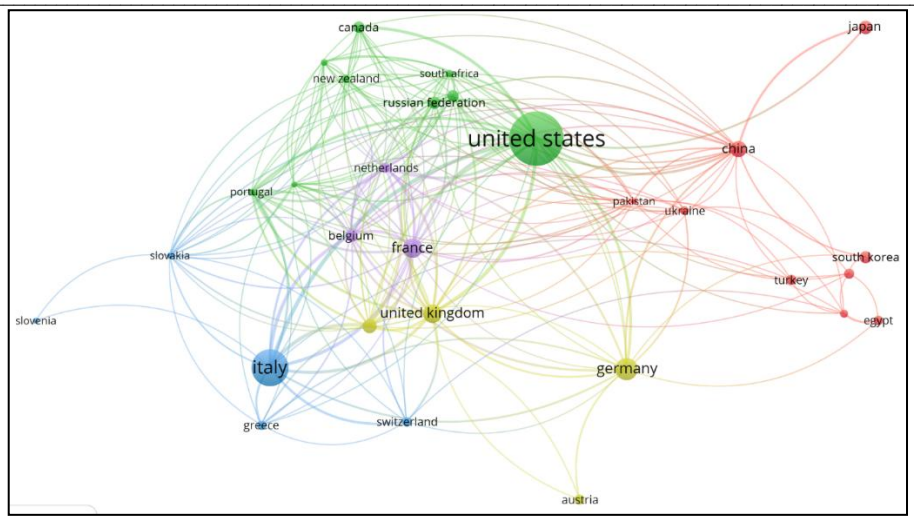


Figure 5: Network-country map for S. repens research (countries had at least 5 publications) from 1995 to 2023.

3. Botanical aspects

Taxonomy

Serenoa repens is the only member of the genus Serenoa (Family Arecaceae, subfamily Coryphoideae, tribe Coryphae, and subtribe Livistoninae) [1].

Scientific name

Serenoa repens (W. Bartram) Small.

Synonyms

Sabal serrulata (Michx.) Nutt. ex Schult. f., *Serenoa serrulata* (Michx.) Hook. f. ex B.D. Jacks [25].

Common/English names

Saw palmetto, Serenoa, American dwarf palm tree, Cabbage palm [25].

Geographic distribution

S. repens is endemic to the Southeastern United States, ranging from South Carolina, Alabama, Georgia, and Mississippi to Southeastern Louisiana, encompassing the Florida peninsula [2].

Botanical description

S. repens, commonly known as saw palmetto, exhibits a dimorphic growth habit, manifesting as either a low-growing shrub or, less frequently, a small tree [4]. Stems are subterranean or prostrate and surface creeping, rarely erect, covered with persistent leaf sheaths. Axillary buds develop as either reproductive branches (inflorescences) or vegetative branches (suckers) [26]. Numerous green palmate leaves emerge from the stems' terminal buds [3]. The leaves are fan-shaped up to one meter wide with 15 to 30 divisions that are roundish in outline and are borne on slender petioles lined with short recurved sharp spines, from which saw palmetto acquired its common name [1]. The inflorescences, of a paniculate form, arise from the base of the leaves and bear small flowers. Each flower has a tubular, three-lobed calyx (1–2 mm long) and a cream-colored, three-lobed corolla (3–5 mm long), with six stamens, a tricarpellate ovary, and a single style. Upon fertilization, only one carpel develops into a drupaceous fruit with a thin endocarp. The drupes ripen in September and October, transitioning from green to black, and represent the plant's reproductive and medicinally valuable component. The roots are mycorrhizal, enabling it to grow on low-nutrient soil [27]. **Fig. 6-8** show some of the morphological features of *S. repens*.

Figure 6: *Serenoa repens* dried fruits. X=1.

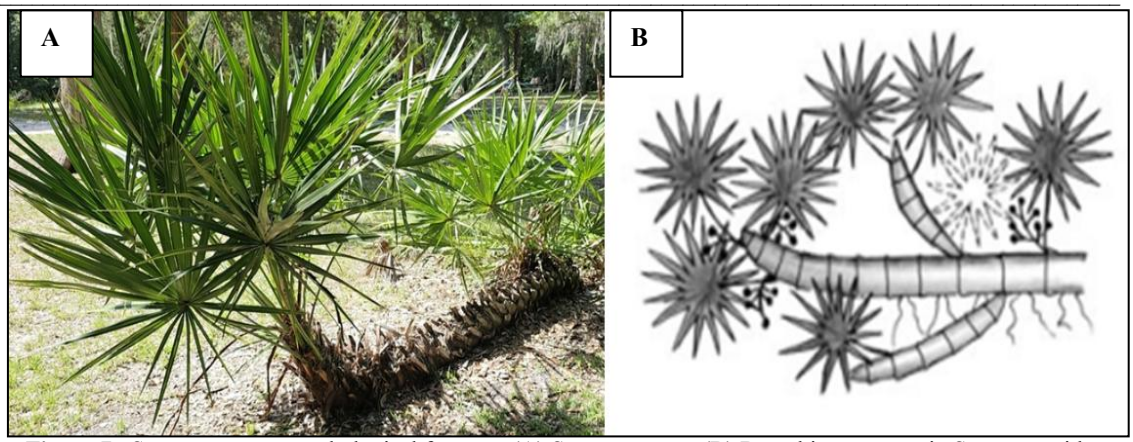


Figure 7: *Serenoa repens* morphological features, (A) S. repens stem, (B) Branching patterns in S. repens, either inflorescences or vegetative shoots along a mostly prostrate stem (Drawn by Marion Ruff Sheehan.

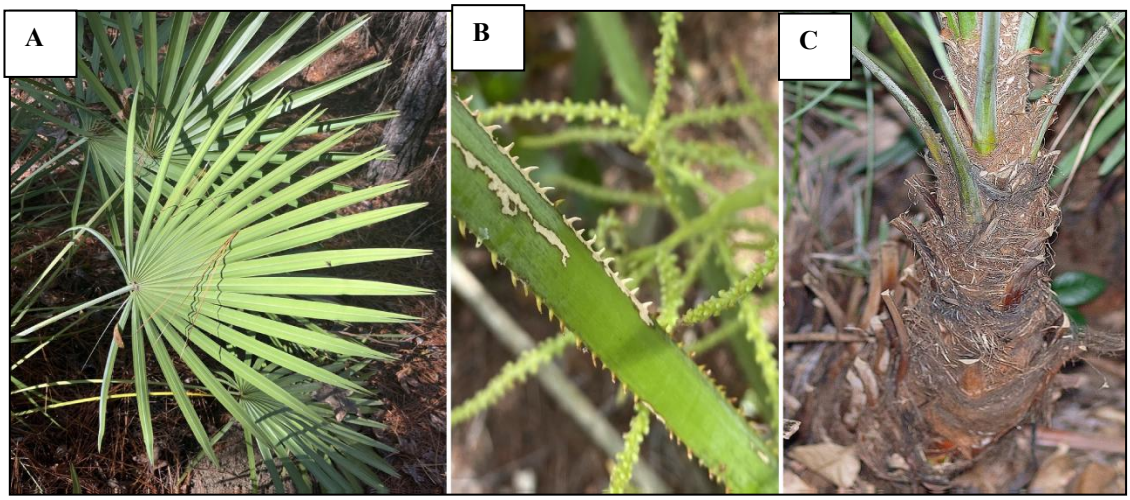


Figure 8: *Serenoa repens* morphological features. (A) S. repens palmate leaf, (B) S. repens petiole with short sharp spines, (C) S. repens leaf sheaths expand into a rough mat of dark brown fibers (iNaturalist. available from https://www.inaturalist.org. Accessed [14/1/2024]).

4. Phytochemistry

The ripe fruit of *S. repens* is the most used part for the treatment of many disorders; it consists mainly of 15-20% lipids, primarily free fatty acids, fatty acid esters, triglycerides, fatty alcohols, and sterols [13], [24], [28], with the highest content of lauric and oleic acid [29].

Phytosterols and fatty acids have been the focus of phytochemical studies, and biological activities have been mainly ascribed to these compounds.

The fruits are also rich in phenolic acids and flavonoids [30]–[32]. Different solvents (ethanol, methanol, acetone, and water) were tested for phenolic acid and flavonoid extraction. The lowest content was shown when extracted by distilled water, while the highest content was recorded in the case of extraction using acetone [31].

Tables2-5 show the chemical structure of major identified compounds of *Serenoa repens* fruits.

Minor components

Minor components such as *β*-carotene, tocopherols [33], hydrocarbons and volatile compounds [34], monoacylglycerides such as 1-monolaurin and 1-monomyristin[35]and chalcanonol glycoside dimer [36], were reported. The hydrophilic subfraction of the fruit contains carbohydrates, amino acids, and polysaccharides such as galactose, arabinose, and uronic acid[37], [38].The literature has also reported terpenoids such as farnesol, phytol, geranylgeraniol lupeol, and polyprenols [25].

5. Traditional uses

Serenoa repens has been widely used traditionally to address reproductive issues in both sexes. In men, it was used to promote urination, serve as a urinary tract antiseptic, and as an aphrodisiac in erectile dysfunction [39]. It was also used for the management of prostate hypertrophy and male infertility [40]. For women, traditional practices involved promoting breast enlargement, treating infertility, and addressing hormonal disturbances. The fruits have also been used to treat respiratory disorders such as colds, coughs, chronic bronchitis, and asthma. They also treat indigestion and diabetes [6], [25]. Furthermore, owing to their rich nutritional content, they have been characterized as anabolic and beneficial for weight gain [25].

Table 2: Structures of fatty acids and fatty alcohols identified in the fruits of *Serenoa repens.*

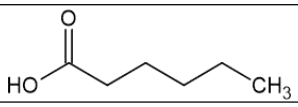
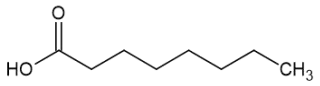
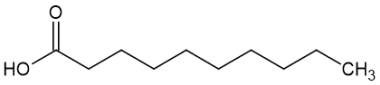
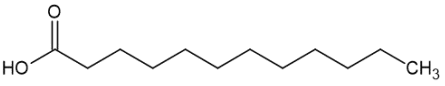
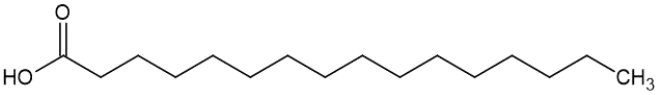
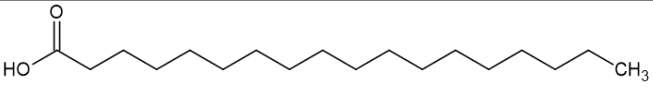
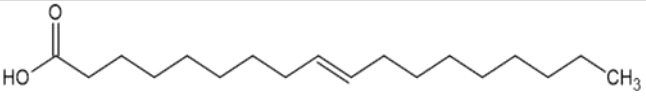
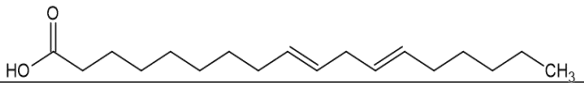
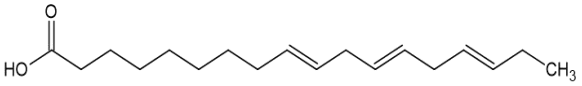
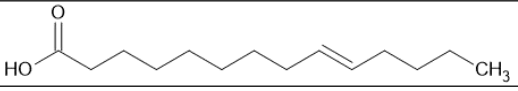
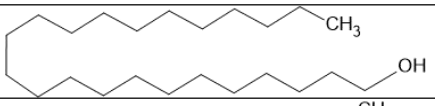
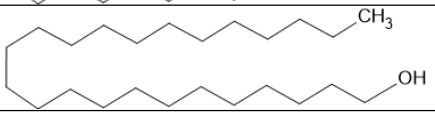
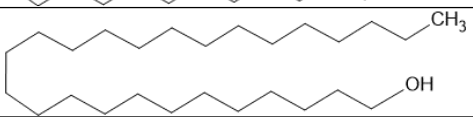
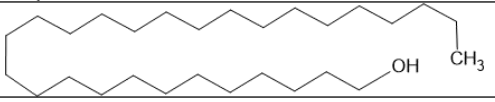
Common name	Molecular fomula	Structure	Reference
Staurated fatty acids			
Caproic acid	$C_6H_{12}O_2$ (6:0)		[24], [28], [146], [147]
Caprylic acid	$C_8H_{16}O_2$ (8:0)		
Capric acid	$C_{10}H_{20}O_2$ (10:0)		
Lauric acid	$C_{12}H_{24}O_2$ (12:0)		
Palmitic acid	$C_{16}H_{32}O_2$ (16:0)		
Stearic acid	$C_{18}H_{36}O_2$ (18:0)		
Unsaturated fatty acids			
Oleic acid	$C_{18}H_{34}O_2$ ($18:1\Delta^9$)		
Linoleic acid	$C_{18}H_{32}O_2$ ($18:2\Delta^{9,12}$)		[24], [28], [146], [147]
Linolenic acid	$C_{18}H_{30}O_2$ ($18:3\Delta^{9,12,15}$)		
Myristoleic acid	$C_{14}H_{26}O_2$ ($14:1\Delta^9$)		[148]
Fatty alcohols			
Tricosanol	$C_{23}H_{48}O$		[13]
Tetracosanol	$C_{24}H_{50}O$		
Hexacosanol	$C_{26}H_{54}O$		
Octacosanol	$C_{28}H_{58}O$		

Table 3: Structures of sterols identified in the fruits of *Serenoa repens.*

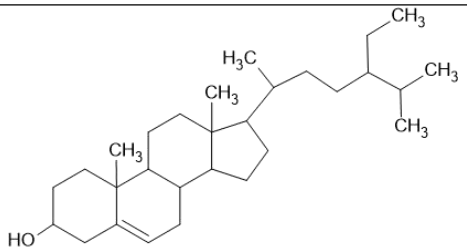
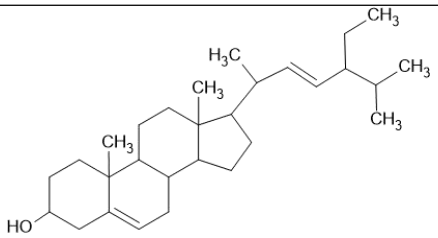
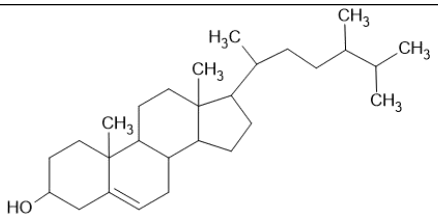
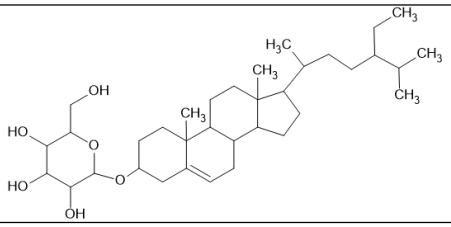
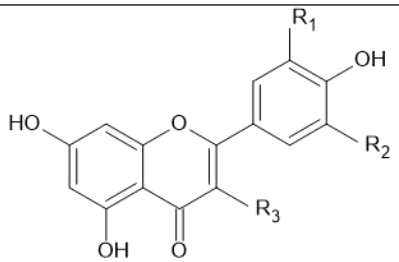
Sterol	Structure	Reference
β-sitosterol		[13], [24]
Stigmasterol		
Campesterol		
β-sitosterol-3-*O*-glucoside		[36]

Table 4: Structures of flavonoids identified in the fruits of *Serenoa repens.*

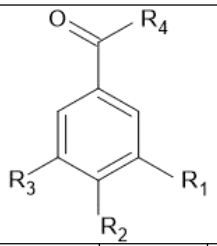
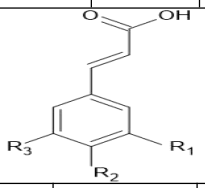
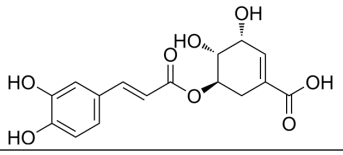
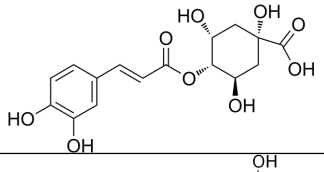
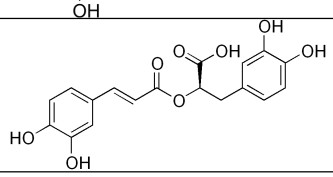
Compound				
Flavonol and glycosides	**R1**	**R2**	**R3**	**Reference**
Quercetin 3-*O*-neohesperidoside	H	OH	ONeo	[30]–[32]
Isoquercetin	H	OH	OGlu	
Myricetin	OH	OH	OH	
Isorhamentin	H	OCH_3	OH	
Isorhamnetin-3-*O*-rutinoside	H	OCH_3	ORut	
Rutin	H	OH	ORut	
Astragaline	H	H	OGlu	

Neo:neohespridoside, **Glu**: glucose, **Rut**: rutinoside

6. Pharmacological studies

6.1. Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS)

Table 5: Structures of phenolic acids identified in the fruits of Serenoa repens.

Compound					
Benzoic acid derivatives	**R1**	**R2**	**R3**	**R4**	**Reference**
p-Hydroxybenzoic acid	H	OH	H	OH	[30]–[32]
Gallic acid	OH	OH	OH	OH	
Syringic acid	OCH_3	OH	OCH_3	OH	
Protocatechuic acid	OH	OH	H	OH	
Veratric acid	OCH_3	OCH_3	H	OH	
Vanillic acid	H	OH	OCH_3	OH	
3-Methoxybenzoic acid (*syn.*: *m*-Anisic)	OCH_3	H	H	OH	
4-Methoxybenzoic acid (*syn.*: *p*-Anisic)	H	OCH_3	H	OH	
6'-*O*-(4-Hydroxybenzoyl)-*β*-glucose	H	OH	H	OGlu	
6'-*O*-(3,4-Dihydroxybenzoyl)-*β*-glucose	OH	OH	H	OGlu	
4-Hydroxybenzaldehyde	H	OH	H	H	
Compound					
Cinnamic acid derivatives	**R1**	**R2**	**R3**		**Reference**
p-Coumaric acid	H	OH	H		[30]–[32]
Ferulic acid	OCH_3	OH	H		
Caffeic acid	H	OH	OH		
5-*O*-Caffeoylshikimic acid					
4-*O*-Caffeylquinic acid(Chlorogenic acid)					
Rosmarinic acid					

As discussed by previous review articles [2], [40]–[43]. ***In vitro* and *in vivo*** studies have extensively explored the effects of *S. repens* lipophilic extract on benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS), highlighting its potential as a therapeutic agent. The benefits of *S. repens* in BPH treatment are primarily attributed to its anti-androgenic properties.*S. repens* fruits lipophilic extract was found to exhibit a dual inhibitory activity for 5*α*-reductase isoenzymes 1 and 2, in comparison to finasteride, which selectively inhibits the type 2 isoform *in vitro*[14], [15], [44]–

[49].The enzyme 5*α*-reductase converts testosterone into dihydrotestosterone (DHT), a potent androgen receptor ligand [50]**,** implicated in the pathogenesis and progression of BPH, prostate cancer, androgenetic alopecia, hirsutism, and acne [51]**.** Notably, *S. repens* fruits *n*-hexane extract does not affect serum levels of prostate-specific antigen (PSA), an essential marker for prostate cancer diagnosis [14], [44].*S. repens* fruits lipophilic extract was also found to inhibit the binding of DHT to its receptor in cultured human foreskin fibroblasts[45][1]**.**

An ***in vivo*** study by **Talpur *et al.*, (2003)**demonstrated that *S. repens*, in both extract and whole berry forms, reduced **androgen-induced prostate hyperplasia** through 5α-reductase inhibition and androgen metabolism modulation [52]. The reduction in prostate size was comparable to the control group and not significantly different from finasteride treatment. Furthermore, *S. repens* fruits extract decreased prostate tumor progression and prostate DHT concentrations in **transgenic adenocarcinoma of the mouse prostate (TRAMP)** mice model [53] and inhibited prostate growth in a **hyperprolactinemia-induced prostate hyperplasia** model [54].

Multiple studies suggest that *S. repens* fatty acids are responsible for its ability to inhibit 5*α*-reductase enzyme. However, the specific fatty acid(s) purported to be responsible for this inhibition differs between publications. The major constituents of *S. repens* lipophilic extract—lauric acid, oleic acid, myristic acid, and linoleic acid—showed more potent inhibitory properties to 5α-reductase than many other types of fatty acids and are considered among the most therapeutically relevant fatty acids to the proposed mechanism of action of *S. repens* lipophilic extract[29], [55].Studies have provided evidence that prostate cells preferentially absorb free fatty acids, including those in *S. repens* extract[56], [57], which can alter nuclear membrane fluidity, inducing conformational changes in 5α-reductase that disrupt testosterone conversion to DHT[58]**.** Additionally, phytosterols such as campesterol, stigmasterol, and *β*-sitosterol have been shown to inhibit 5α-reductase in hamster prostate tissue and reduce prostate cancer cell growth [59]–[61]**,** as well as BPH symptoms in men.

Beyond its anti-androgenic effects, *S. repens* fruits lipophilic extract exhibits anti-inflammatory properties by targeting key enzymes and chemokines involved in inflammation. Prostatic inflammation is increasingly recognized as a contributor to BPH pathogenesis, where inflammatory cytokines and growth factors create a pro-inflammatory environment that supports abnormal epithelial and stromal cell proliferation [62]**.*In vitro*** studies have demonstrated the anti-inflammatory properties of *S. repens* lipophilic extract through downregulation of the pro-inflammatory genes, including interleukin (IL)-6, chemokine ligand (CCL)-5, CCL-2, cyclooxygenase (COX)-1, COX-2, and inducible nitric oxide synthase (iNOS) in benign prostate cell lines or primary cultures [19], [41], [63]**.** The *n*-hexane extract, in particular, has been shown to inhibit monocyte chemoattractant protein-1 (MCP-1/CCL2) expression, whereas the supercritical CO_2 extract did not significantly impact this marker [63]**.** Additionally, *S. repensn*-hexane extract interferes with the arachidonic acid cascade by inhibiting the synthesis of 5-lipoxygenase metabolites [64]**.**

Serenoa repens fruits lipophilic extract also promotes prostate health by **inducingapoptosis and inhibiting cell proliferation**. After reaching adult size, the prostate maintains homeostasis through a balance of cell proliferation and apoptosis, and disruptions in this balance are implicated in BPH [65]. Several ***in vitro*** studies confirm that *S. repens* lipophilic extract exerts pro-apoptotic effects, with or without additional anti-proliferative activity, on prostate cancer cells [19], [58], [61], [66]–[72] *via* different mechanisms of action (discussed in **Table 6**).

Additionally, *S. repens* extract interacts with receptors in the lower urinary tract, which may explain its spasmolytic effects and improvement of LUTS [29], [73]–[76]. Some studies further suggest that *S. repens* extract exerts a direct spasmolytic effect on human prostate and bladder smooth muscles [20], [77].

The hexane extract has also demonstrated *in vivo* antioxidant activity in a testosterone-induced prostatic hyperplasia model. Administration of 25 mg/kg/day of *S. repens* lipophilic extract for four weeks modulated oxidative stress markers by reducing nitric oxide (NO) and malondialdehyde while increasing glutathione, superoxide dismutase (SOD), and catalase levels [17].

6.2. Androgenetic alopecia

As discussed by [78]–[80] in their reviews, *S. repens* fruit extract has gained popularity as a natural, safe hair care remedy for androgenetic alopecia. Its efficacy is primarily attributed to its antiandrogenic properties and ability to inhibit the 5-α-reductase enzyme, which converts testosterone to dihydrotestosterone (DHT)—a key factor in hair loss [81]. Excess DHT shortens the anagen phase and prolongs the telogen phase, leading to hair thinning and loss [82].

While FDA-approved treatments such as finasteride and minoxidil are commonly used for androgenetic alopecia, they are associated with various side effects [83], [84]. This has led to increased interest in *S. repens* as a potential natural alternative. *In vitro* studies on human keratinocytes and dermal papilla cells have demonstrated that lipophilic extracts of *S. repens* inhibit 5-α-reductase activity, reduce inflammation—alone or in combination with other anti-inflammatory agents—and protect the vascular endothelium by preventing lipid peroxidation [85]–[88]. Beyond oral supplements, *S. repens* extract is also incorporated into various hair care products, including shampoos, conditioners, hair masks, and scalp treatments. These topical formulations offer a potentially safer approach by targeting hair loss locally without disrupting systemic hormonal balance [78].

6.3. Polycystic ovary syndrome

PCOS is a heterogeneous endocrine disorder characterized by elevated levels of male androgens, insulin resistance, anovulation, infertility, acne, and hirsutism [89]. Studies showed elevation in androgen production rate and increased 5-α-reductase activity in PCOS patients, alongside with Increased 5-α-reductase activity in specific tissues such as the skin, where it has been associated with hirsutism, and acne [90]. *S. repens* fruits is an ingredient of PCOS traditional recipes most

probably due to its antiandrogenic activity that eases polycystic ovarian symptoms [91]. An *in vivo* animal study investigated the effects of *S. repens* on PCOS and showed significant improvement in both metabolic and histological parameters of the treated animals [92]. The potential of *S. repens* for managing acne and hirsutism has also been explored in clinical trials. A Yousefi et al. (2009) evaluated the efficacy of a cream containing *S. repens* fruit extract applied twice daily for two months in 31 women with idiopathic facial hirsutism. The study reported a statistically significant decline in hair counts (29%) in hair count after two months. However, further research is needed to confirm its effectiveness and safety [93], [94]. Similarly, Dobrev (2007) assessed a day cream containing *S. repens* lipophilic extract, along with sesame seed extract, argan oil, and 0.1% vitamin B6, for its effects on oily skin. After four weeks of twice-daily application, participants experienced a 20% decrease in sebum levels and a 42% reduction in the area covered by oily spots [95], [96].

6.4. Anti-bacterial and Anti-fungal activity

Barakat *et al.* (2020b) evaluated the antimicrobial and anti-fungal potential of ***S. repens*** fruits **acetone phenolic-rich extract*in vitro***. Their findings demonstrated that the extract exhibited potent inhibitory activity against a panel of four pathogenic bacteria, encompassing both Gram-positive *(Staphylococcus aureus* and *Bacillus subtilis)* and Gram-negative *(Escherichia coli* and *Pseudomonas aeruginosa)* species. The minimum inhibitory concentration (MIC) values ranged from 1.5 to 2.1 mg/mL, comparable to **augmentin,** which had an MIC value of 1.6 to 2.2 mg/mL [31].

***Serenoa repens* acetone extract** anti-fungal efficacy was tested against five fungal strains: *Fusarium proliferatum, Penicillum verrucosum, Aspergillus westerdijkae, Aspergillus carbonarius and Aspergillus ochraceus.* The acetone extract exhibited a potent inhibitory effect surpassing that of **econazole**, with MIC values ranging from 1.7 to 2.7. while econazole exhibited MIC values of 2.5 to 3.1 mg/mL [31].

Likewise, **El-Hawary *et al.,* (2016)** investigated the antimicrobial activity of the **essential oil of *S. repens* fruits** and showed positive results [97]. Additionally, *S. repens* lipophilic extract and fatty acids (lauric acid and myristic acid) demonstrated anti-biofilm formation activity against various microbes ***in vitro***[98]**.**

6.5. Anti-cancer activity

The pro-apoptotic activity of *S. repens* extract was evaluated ***in vitro*** in **human glioma cell lines**, a type of central nervous system tumor. The extract triggered the apoptosis by inhibiting the PI3K/Akt signaling pathway [99]**. Additionally,** *S. repens* ethanolic extract induced a dose-dependent antiproliferative effect on different human malignant cells, including **breast MCF-7** cell lines [100]**.**

6.6. Anti-diabetic activity

One study aimed to assess the role of ***S. repens* fruits acetone phenolic-rich extracts** in modulating **diabetic complications and oxidative stress*in vivo*in streptozotocin-induced diabetic rats.***S. repens* acetone extract demonstrated significant anti-diabetic effects by inhibiting α-amylase activity, lowering blood glucose levels, and protecting against diabetes-related complications. It effectively inhibited both microbial and pancreatic α-amylase enzymes, with IC_{50} values of 0.68 µg GAE/ml and 10.08 µg GAE/ml, respectively, showing comparable inhibition to acarbose, a pharmaceutical α-amylase inhibitor (IC_{50} were expressed as gallic acid equivalent (GAE)). *S. repens* acetone extract was administered at 60 mg GAE/kg/day until day 17 of the study, increasing to 90 mg GAE/kg/day from day 17 to day 24, leading to a 54% reduction in blood glucose after 7 days and 63.2% by Day 24, with a dose-dependent effect. Additionally, *S. repens* treatment helped maintain body weight, preventing diabetes-induced weight loss. Histopathological analysis revealed that *S. repens* extract preserved pancreatic *β*-cell integrity, reduced kidney and liver damage, and restored normal tissue architecture. Furthermore, *S. repens* enhanced antioxidant defense by increasing the activities of catalase, glutathione-S-transferase, glutathione reductase, and glutathione peroxidase, counteracting oxidative stress and inhibiting inducible nitric oxide synthase. These findings suggest that *S. repens* extract could serve as a natural therapeutic option for managing diabetes and its complications through α-amylase inhibition, glucose regulation, tissue protection, and oxidative stress modulation [101]**.**

7. Clinical studies

7. 1. Clinical trials for management of BPH& LUTS

Many clinical trials have evaluated the effectiveness of *S. repens* fruits lipophilic extract in managing BPH. However, systematic reviews and meta-analyses [2], [43], [102] have analyzed these data and showed mixed results.

A Cochrane systematic review conducted in 2009, with an updated version published in 2012, concluded that treatment with *S. repens* fruits lipophilic extract for more than six months did not improve the symptoms of LUTS consistent with BPH. In addition, in males with LUTS associated with BPH, *S. repens* fruits extract at twice or triple doses did not enhance urinary flow measures or reduce prostate size [103], [104].

Two other systematic reviews and meta-analyses by **Novara *et al.*, 2016**[105]and **Vela-Navarrete *et al.*, 2018**[106] assessed the clinical studies of *S. repens* fruits ***n*-hexane extract** and showed positive results comparable to the placebo. **Novara *et al.*2016** reported that *S. repens* fruits ***n*-hexane** extract demonstrated a statistically significant decrease in nocturnal urination frequency and a concomitant increase in maximum urinary flow rate compared to placebo. Additionally, results suggested that the extract possessed efficacy in alleviating LUTS symptoms to a similar degree as tamsulosin. **Vela-Navarrete *et al.,* 2018**further emphasized the good tolerability and long-term effectiveness of a standardized *n*-hexane extract of *S. repens*for treating LUTS/BPH. Their meta-analysis concluded that *S. repens* extract significantly reduced nocturia and improved peak urinary flow rate compared to the placebo. These findings align with a previous meta-analysis by **Boyle *et al.* (2004)** [107], which reported that permixon® (*S. repens n*-hexane extract product) significantly improved peak flow rate, reduced nocturia compared to placebo, and resulted in a 5-point decrease in the international prostate symptom score.

In 2021, **Strum** published a systematic review of three parts. The author evaluated all the clinical studies of *S. repensversus* LUTS included in four publications: the European Scientific Cooperative on Phytotherapy (ESCOP) 2003 monograph [108], the 2012 Cochrane meta-analysis conducted by **Tacklind *et al.*** [104]**,** the 2014 European Medicines Agency monograph [11], and the 2014 guidelines of the American Urology Association [109]. The analysis included **36**

clinical studies. In these studies, 15 studies were conducted on *S. repens*-hexane extract products, 11 studies used ethanolic extract products, and the remaining 10 used supercritical CO_2 extract products.

Out of the total studies, **33 studies showed positive results** (15 studies involved *n*-hexane extract products, 11 studies involved supercritical CO_2 extract products and seven involved ethanolic extract products)**, while three studies gave negative results**: **Willetts *et al.* (2003)** [110] (used a supercritical CO_2 extract product); **Bent *et al.* (2006)** [111] (used a supercritical CO_2 extract product**)** and **Barry *et al.* (2011)** [112] (used ethanolic extract product)**(Strum, 2021).**

7.1.1. Placebo-controlled studies:

Several studies showed the beneficial effect of *S. repens* extract in managing BPH against a placebo. 160 mg of *S. repens* extract twice daily for one to six months was superior to the placebo in terms of effects on urinary frequency and peak urinary flow rate[113]–[120], while two studies conducted in the US failed to show a benefit for *S. repens* extract versus placebo [111], [112]**.**

7.1.2. Comparative studies with tamsulosin (α-blocker):

Many studies investigated the comparative efficacy of *S. repens*and tamsulosin in treating BPH following at least a six-month treatment cycle [22], [121]–[123]**.**The analysis of these studies revealed comparable effectiveness between *S. repens*and tamsulosin for BPH symptoms after at least 6 months of treatment **.**

In 2020, **Alcaraz *et al.*** published a follow-up to their 2016 study, further investigating the comparative efficacy of tamsulosin, *n*-hexane extract of *S. repens* (HESr), and their combination in the management of moderate to severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). A total of 709 participants were enrolled in the study. Participants were assigned to receive either tamsulosin (0.4 mg/day), permixon (320 mg/day), or a combination of both for a treatment duration of 6 months. After 6 months, the combination arm results were statistically superior in relation to International Prostate Symptom Score (IPSS), quality of life, and BPH Impact Index (BII) at *p*-values of 0.002, 0.001, and 0.007, respectively [124]**.**

7.1.3. Non-comparative studies [125]–[127]*:*

Pytel *et al.* (2002)[126] conducted a long-term open study for 2 years. One hundred fifty-five men with clinically diagnosed BPH and complaints of prostatic symptoms for more than 6 months were enrolled in the study, with a mean age of 65 years. All the subjects were treated with *S. repens* 160 mg twice daily for 24 months. At 6, 12, 18, and 24 months, IPSS, quality of life, and sexual function scores were recorded, and urodynamics and biological values were measured. Relative to the baseline, the IPSS decreased progressively over the 24 months of treatment, and a statistically significant improvement in quality of life was observed. Urodynamic results showed a significant improvement in the urine flow rate (Qmax) compared with baseline, an increase in voiding volume, and a reduction in prostate volume, and this reduction was maintained throughout the study**.**

7.2. Clinical trials in androgenetic alopecia

As discussed in previous reviews [79]. Several clinical trials have evaluated the efficacy of *S. repens,* when taken solely or combined with other treatments, in improving the symptoms of androgenetic alopecia **(Table 8).**

7.3. Clinical trials in hirsutism and acne

The potential of *S. repens* for managing acne and hirsutism has been explored in clinical trials. **Yousefi *et al.* (2009)** [93] evaluated the efficacy of a cream containing *S. repens* fruit extract applied twice daily for two months in 31 women with idiopathic facial hirsutism. The study reported a statistically significant decline in hair count (29%) after two months. However, further research is needed to confirm its effectiveness and safety [94]**.** Similarly, **Dobrev (2007)** [95] assessed a day cream containing *S. repens* lipophilic extract, along with sesame seed extract, argan oil, and 0.1% vitamin B6, for its effects on oily skin. After four weeks of twice-daily application, participants experienced a 20% decrease in sebum levels and a 42% reduction in the area covered by oily spots [95], [96]**.**

8. Lack of standardization may affect the extract quality

Herbal medicines suffer from a lack of standardization parameters, which may affect the quality, safety, and efficacy of herbal medicines. Research proved significant differences between different *S. repens* marketed products in terms of content and efficacy[128]–[133]**.**These differences may refer to variations in the extraction method. **Habib and Wyllie (2004)** [130]analyzed fourteen *S. repens* marketed European products; the results showed significant differences between different brands. The mean proportion of free fatty acids ranged from 80.7 to 40.7%, methyl and ethyl ester content ranged from 16.7 to 1.5%, while long chain ester ranged from 1.36 to 0.7%. **Penugonda and Lindshield (2013)** [131] analyzed twenty commercial *S. repens* supplements in different forms: liquid, tincture, powders, and dried berries, regarding the content of fatty acids and phytosterols. The study revealed significant differences between the products and the different supplements' forms. The liquid supplements recorded significantly higher ($p < 0.05$) concentrations of total fatty acids, individual fatty acids, total phytosterols and *β*-sitosterol than other supplement forms, followed by powder, dried berry, and tincture supplements, respectively.

Another study compared the effect of different marketed extracts of *S. repens* to inhibit the two isoforms of the 5-alpha reductase in a co-culture of human prostatic fibroblast and epithelial cells. The results revealed significant differences between both brands and batches **(Scaglione *et al.*, 2008)** [132]**.**

Table 6: Reported biological activities for *Serenoa repens* fruits lipophilic extract in BPH.

Assay	Cell line	Activity	Reference
Anti-androgenic activity			
5-alpha reductase I & II inhibition assay	*In vitro* (prostatic epithelial and fibroblast cells)	Different commercial products of *Serenoa repens* inhibited 5α-reductase isoenzymes I and II, but significant differences in the results were observed.	[116]
5-alpha reductase I & II inhibition assay	*In vitro* (human prostate cancer cells)	Authors found that 10 µg/ml LSESr inhibited the activities of both isoenzymes (5α-R-I, 72% decrease, and 5α-R-II, 76% decrease). In contrast, 5 nM of finasteride inhibited 5α-R-II (83% reduction) compared to LSESr and did not affect the 5α-R-I activity of cells.	[17]
5-alpha reductase I & II inhibition assay	*In vitro* (human prostate cancer cells)	LSESr inhibits both 5α-reductase isoenzymes I and II without interfering with PSA secretion.	[58], [60]
5-alpha reductase inhibition assay	*In vitro* (prostatic tissue)	320 mg/day of LSESr for 3 months induces a 50% reduction of DHT in BPH tissues with respect to the control group, associated with a 125% increase in testosterone level.	[59]
5-alpha reductase inhibition assay	*In vitro*	The LSESr effect is due to a modification of the nuclear membrane environment of 5α-reductase by the lipid component of *Serenoa repens*.	[117]
DHT receptor inhibition assay	*In vitro* (Cultured foreskin fibroblasts)	In human foreskin fibroblasts, 7.14 U/ml and 28.6 U/ml LSESr inhibited DHT binding to androgenic receptors by 50% and 70%, respectively.	[60]
Anti-inflammatory activity			
RT-qPCR gene expression array	*In vivo* mouse model	A daily dose of 100 mg/kg of LSESr for 28 days down-regulates the prostate pro-inflammatory cytokine profile, with a significant reduction of CCR7, CXCL6, IL-6, and IL-17 expression.	[118]
RT-PCR	*In vitro*	Permixon down-regulates the inflammation-related genes (IL-6, CCL-5, CCL-2, COX-2, and iNOS).	[22]
RT-qPCR gene expression array	*In vitro* (prostatic hyperplasia epithelial and stromal cells)	LSESr down-regulates pro-inflammatory markers.	[68]
RT-QPCR – ELISA assay	*In vitro* (human prostate cells)	LSESr down-regulates pro-inflammatory markers (MCP-1/CCL2 and VCAM-1) expression.	[19]
5-lipoxygenase metabolites inhibition assay	*In vitro*	LSESr inhibited in a dose-dependent relationship the synthesis of 5-lipoxygenase metabolites.	[65]
Apoptosis, immunofluorescence assay – cell viability assay.	*In vitro* (prostatic cancer cells).	Permixon reduces cell proliferation and increases the apoptotic activity by an increase in the activity of caspase-3.	[22]
Proliferation MTT assay.	In vitro (BPH1 human prostate epithelial cells, (PrSF primary stromal fibroblasts).	Dose-dependent cytotoxic effect. The estimated 50% lethal concentration (LC50) was 60 µg/mL for BPH1 cells and 50 µg/mL for PrSF.	[68]
Receptor binding assay	*In vitro*	Competitive inhibition of epidermal growth factor (EGF) receptor, and thus inhibit proliferation.	[119]
Cell proliferation assay by cell counting-apoptosis assay by FACScan and morphological analysis.	*In vitro* (PC3 prostate cancer cells).	LSESr induces apoptosis and inhibits the proliferation of PC3 cells by causing complex changes in cell membrane organization and fluidity of prostate cancer cells that have progressed to hormone-independent status.	[120]
Apoptosis assay by Western blot.	*In vivo* (open, multicenter pilot study)	Permixon (marketed product of saw palmetto fruit hexane extract) increased molecular markers involved in the apoptotic process (Bax-to-Bcl-2 expression ratio) and caspase-3 activity.	[21]
Apoptosis and proliferation assay	*In vitro* (P69 prostate epithelial cell line).	LSESr suppresses growth and induces apoptosis by inhibiting IGF-I signaling.	[121]
Immunohistochemistry, proliferation assay – Apoptosis assay by In Situ End Labeling.	*In vitro* (prostate epithelium and stroma cells)	Induce induction of apoptosis and inhibition of cell proliferation.	[69]
Proliferation assay	*In vitro*	LSES inhibits the proliferation of prostate epithelial cells induced by growth factors.	[122]
Other activities			
Antioxidant activity	*In vitro*	25 mg/kg/day for 4 weeks of LSESr affected markers of oxidative stress (decrease nitric oxide (NO) and malondialdehyde and increased glutathione,	[20]

		superoxide dismutase (SOD) and catalase).	
Spasmolytic activity	*In vitro* (human prostate and detrusor tissues).	Recently, the spasmolytic effect of LSESr was evaluated using different contractile agonists on human prostate and detrusor tissues. The results showed concentration-dependent inhibition of smooth muscle contractions. LSESr inhibited α1-adrenergic and thromboxane-induced contractions in prostate tissues, and methacholine and thromboxane-induced contractions in detrusor tissues, while the neurogenic contractions were inhibited in both tissues.	[23]
	In vitro	Gutierrez *et al.* (1996) suggested the spasmolytic effects of *S. repens* total fruit extract and saponifiable fraction on noradrenaline-induced contractions of rat aorta, potassium chloride-induced contractions of rat uterus, and acetylcholine-induced contractions of the urinary bladder.	[123]
Receptor inhibition activity radioligand binding assay	*In vitro*	Saw palmetto extract Inhibits the function of vanilloid receptors on bladder afferent nerves that transmit the sensation of the desire to void to the brain.	[124]
	In vitro	*S. repens* fruit extract and isolated free fatty acids from *S. repens* fruits exhibited non-competitive inhibitory activity to alpha-1 adrenoceptor, muscarinic, and 1,4 dihydro pyridine receptors. According to IC_{50} values, the binding activity of saw palmetto extract for muscarinic receptors was four times greater than that for alpha 1-adrenergic receptors, while the free fatty acids (oleic acid, myristic acid, and linoleic acid) exhibited higher affinity towards each receptor than saw palmetto supercritical CO_2 extract.	[32], [125], [128]
Anti-oedemic activity	*In vitro*	The hexane extract is a dual inhibitor of the cyclooxygenase and 5-lipoxygenase pathways	[24]
Anti-bacterial activity	Gram positive *(Staphylococcus aureus* and *Bacillus subtilis)* and Gram negative *(Escherichia coli* and *Pseudomonas aeruginosa).*	Saw palmetto acetone extract inhibited bacterial growth, with MIC values ranging from 1.5 to 2.1mg/ mL, compared to Augmentin, which had MIC values ranging from 1.6 to 2.2 mg/mL.	[73]
Anti-fungal activity	*Fusarium proliferatum*, *Penicillum verrucosum*, *Aspergillus westerdijkae*, *Aspergillus carbonarius* and *Aspergillus ochraceus.*	The acetone extract of saw palmetto showed a potent inhibitory effect compared to Econazole, with MIC values ranging from 1.7–2.7 and 2.5–3.1 mg/mL, respectively.	[73]

5α-R: 5 alpha-reductase, HESr: *n*-hexane extract of *S. repens*, TRAMP: transgenic adenocarcinoma of the mouse prostate model, DHT: dihydrotestosterone, BPH: benign prostatic hyperplasia, PSA: Prostate-Specific Antigen, Permixon: marketed product of *S. repens n*-hexane extract, LNCaP: Lymph Node Carcinoma of the Prostate and refers to anandrogen-sensitive human prostate cancer cell line**,** PC3: Prostate Cancer-3 and refers to an androgen-independent human prostate cancer cell line.

***In vitro* effects unless otherwise specified.**

LSESr: lipidosterolic extract of *Serenoa repens*; 5α-R: 5α-reductase; PSA: prostate-specific antigen; DHT: di hydro testosterone; BPH: benign prostate hyperplasia

LNCaP: Lymph Node Carcinoma of the Prostate and refers to an androgen-sensitive human prostate cancer cell line**,** PC3: Prostate Cancer-3 and refers to an androgen-independent human prostate cancer cell line, HESr: hexane extract of *S. repens.*

Table 7: Reported biological activities for *Serenoa repens* fruits lipophilic extract in androgenetic alopecia.

Assay	Cell line	Activity	Reference
Anti- androgenic activity			
5 alpha reductase II inhibition assay.	*In vitro* (Dermal papilla cells).	LSESr significantly prevented 5-α reductase II expression.	[70]
Anti-inflammatory activity			
Genes expression assay.	*In vitro* (Human keratinocyte cells).	LSESr combined with Carnitine and Thioctic Acid suppressed lipopolysaccharide-activated gene expression of chemokines, including CCL 17, CXCL 6, and LTB (4).	[66]
Anti-apoptotic activity			
Western blot assay	*In vitro*	LSESr suppresses the apoptotic biomarkers (TGF-β2 expression, cleaved caspase 3, and Bax/Bcl2 ratio), suggesting that LSESr induces hair regeneration by activating TGF-β and the mitochondrial signaling pathway.	[129]
Other activities			
Cell viability assay	*In vitro* (Human follicle dermal papilla cells, human microvascular endothelial cells).	LSESr promotes the proliferation of human microvascular endothelial cells and human follicular dermal papilla cells.	[70]
Antioxidant activity assay	*In vitro* (Human follicle dermal papilla cells, human microvascular endothelial cells).	Protect the vascular endothelium from oxidative stress.	[70]
Cell viability assay	*In vitro* (human keratinocyte cells).	Increase the proliferation of human keratinocyte cells.	[129]

Table 8: Clinical trials of *Serenoa repens* in androgenetic alopecia.

Ref.	Patients	Intervention	Treatment	Outcome
[151]	80 subjects (30 women).	Double-blind, randomized, placebo-controlled study for 6 months.	Forty subjects receivedoral supplement containing L-Cystine, *S. repens*, *Cucurbita pepo, Pygeum africanum,* and vitamins, while the other 40 received placebo.	Hair density increased by 9.9 hairs/cm^2 after 3 months and 12.3 hairs/cm^2 after 6 months in the oral supplement group.
[152]	80 subjects (males and females aged 18–50 years).	Double-blind, placebo-controlled for 16 weeks.	Subjects were divided into four groups (n=20): • Oral formulation of standardized *S. repens* oil. • Placebo oral group. • Topical formulation of standardized *S. repens* oil. • Placebo topical group.	In the oral treatment group, hair shedding decreased by 24.74% after 8 weeks and 29% after 16 weeks ($p<0.001$). The topical group showed a 12.08% reduction after 8 weeks and 22.19% after 16 weeks ($p<0.05$).
[153]	60 males.	Open-label study for 6 months.	Topical treatment of combination therapy twice daily.	Significant increase in hair growth and reduced shedding after 8 weeks of use. No side effects.
[154]	40 females.	Double-blinded placebo-controlled study for 6 months.	Group 1 received a women's oral herbal supplement containing standardized ingredients, including *S. repens.* Group 2 received a placebo.	Significant increase in terminal, vellus, and total hair counts for the supplement group.
[155]		Case report	Oral herbal supplement contains standardized ingredients, including *S. repens.*	Subjective improvement in hair growth and temple area coverage; also decreased shedding.
[88]	30 subjects (15 males and 15 females).	Non-comparative, for 6 months.	A combination therapy containing 300 mg of several nutritional ingredients, including *S. repens.*	Improvement of hair density and new hair growth, improvement of vascularization, and reduction of greasiness at the follicle level.

[156]	52 males (20–50 years).	Non-comparative for 24-week period	Topical treatment of combination therapy.	Significant increase in the number of total hair.
[157]	40 post-menopausal women.	Placebo-controlled trial.	Two capsules containing lipophilic extract of *S. repens and Pygeium africanum.*	Statistically significant increase in the percentage of anagen hair, decrease in telogen hair and increase in the hair resistance to traction.
[158]	A 67 years old patient suffering from telogen effluvium.	Case report	An oral supplement containing amino acids (L-cystine and L-methionine), vitamin E, iron, and extract of *S. repens.*Two tablets per day.	Increased anagen hairs on trichoscopy.
[159]	100 males.	Comparative study for 24 months.	One group received 320 mg *S. repens*, while the other received 1 mg finasteride.	38% against 68% improvement respectively.
[160]	26 males (23 to 64 years).	Placebo-Controlled Trial.	Soft gel supplement twice daily. It contains 50 mg β-sitosterol and 200 mg saw palmetto extract.	60% of the active group rated it as improved.
[161]	60 subjects (women and men) between 21 and 38 years, affected by androgenetic alopecia.	Double-blind, placebo-controlled, for 50 weeks.	• Twelve received active lotion (contains *S. repens*) • Twelve received placebo lotion. • Twelve received a diet supplement (active) containing gelatin-cystine. 4 pills per day. • Twelve received diet supplements (placebo). • Twelve received active lotion and diet supplements.	Subjects who used the lotion only recorded an increase in hair mass from 20 to 30% and an increase in hair number from 17 to 27% compared to the placebo. With the diet supplement, a further increase of 50% ($p<0.005$).

9. Tolerability and side effects

Numerous systematic reviews and meta-analyses have been conducted to assess the safety and tolerability of *S. repens* extract. **Agbabiaka *et al.*, (2009)**conducted a systematic review of the adverse effects of *S. repens* and concluded that *S. repens* extract is typically well-tolerated, with rare side effects. Across 14 randomized controlled and placebo-controlled trials, various adverse events were documented in 4.6% of the total patient population. These reported adverse events encompassed symptoms such as nausea, diarrhea, fatigue, depression, gastrointestinal discomfort, headache, cold symptoms, and urinary issues [134]. Supporting these findings, two large-scale clinical trials**, the STEP study (2016) and the CAMUS study (2013),** further evaluated the safety of *S. repens* lipophilic extract. A total of 594 male patients involved in these studies were randomized to a standardized extract of *S. repens* fruits group or placebo group for 12months and 18 months, respectively. The findings indicated no significant differences in the occurrence of severe or non-severe adverse events between the *S. repens* and placebo groups. Additionally, no indications of toxicity were observed at dosages up to three times the standard clinical dose (960 mg daily). Furthermore, *S. repens* was reported to be better tolerated than α-blockers and other 5α-reductase inhibitors [22], [135]**.**

Concerns about *S. repens*' potential effects on male sexual function have also been investigated. **Paulis *et al.*, (2021)**conducted a systematic review and meta-analysis to evaluate whether *S. repens* extract negatively impacts male sexual function. The study analyzed 20 clinical trials comparing *S. repens* with placebo, tamsulosin, and other BPH treatments. The findings indicated no significant difference in sexual dysfunction between *S. repens* and placebo, as well as no significant difference between *S. repens* and tamsulosin, suggesting that *S. repens* does not negatively impact male sexual function [136].

In 2023, an assessment of the pharmacovigilance and phytovigilance records was published concerning medications and dietary supplements containing *S. repens*. The analysis, which involved 1810 cases, indicated that *S. repens* products are generally well-tolerated, with over 50% of the suspected adverse reactions classified as non-severe. However, 26.2% of the reports were classified as severe suspected adverse reactions. These severe reactions included instances of melanoma, cardiovascular events, elective orthopedic surgery, acute urinary retention, and gastrointestinal bleeding.Notably, in over 30% of cases, details regarding the outcomes of the suspected adverse reactions were either unreported or unknown [137]**.**

Despite the overall safety profile of *S. repens*, the pharmacoviglance reported few cases of more serious adverse effects following the use of *S. repens* supplements. Instances of liver damage and pancreatitis have been linked to *S. repens* use [138]–[141]**.** A case reported for an 11-year-old girl presented with hot flashes that appeared after taking a dietary supplement containing *S. repens* for two months to treat telogen effluvium. The hot flashes disappeared after the discontinuation of the treatment. This case raised awareness about the safety of *S. repens* extract in children. Another case was reported for fixed

drug eruption to *S. repens* in a 61-year-old male; the patient suffered from two episodes of eruption after taking *S. repens* supplement for the treatment of BPH. The first episode occurred three days after taking the saw palmetto supplement and cleared up a week after stopping the medication with residual hyperpigmentation. The second episode occurred six months later, a few hours after reusing *S. repens*[142]**.** On the other hand, a case reported for erectile dysfunction in a 49-year-old patient received a high dose (400 to 800 mg/day) of *S. repens* supplement for one year for treatment of LUTS [143]**.**

10. Drug interactions

There is a possible interaction between *S. repens* and specific drugs. For example, taking *S. repens* along with acetylsalicylic acid or warfarin may raise the risk of bleeding[144], [145]**.**

Conclusion

S. repens is one of the most prominently marketed medicinal plants for benign prostatic hyperplasia treatment. Explorations into the phytochemistry of this plant have resulted in the identification of components, including fatty acids and phytosterols, that potentially contribute to its therapeutic effects. The widespread utilization of *S. repens* in traditional medicine is supported by scientific research showcasing various biological properties such as anti-androgenic, anti-inflammatory, and antioxidant effects. Analyses of clinical trials involving *S. repens* have indicated promising long-term efficacy and the potential to mitigate BPH-related complications. Nonetheless, further research is essential to assess its efficacy in addressing other androgen-related conditions.

Declarations

- **Ethics approval and consent to participate**

Not applicable.

- **Competing interests**

The authors declare that they have no competing interests.

- **Availability of data and materials**

Not applicable.

References

[1] **Hicklin, B.C.B. and J.R.,** 1998. " Uses of Saw Palmetto (*Serenoa repens*, Arecaceae) in Florida", *Economic Botany*.52, 381-393. https://doi.org/10.1007/BF02862068

[2] **Geavlete, P., Multescu, R., Geavlete, B.,** 2011. "*Serenoa repens* extract in the treatment of benign prostatic hyperplasia". *Ther. Adv. Urol.* 3(4), 193–198. https://doi.org/10.1177/1756287211418725

[3] **Francis, J.K.,** 2004. "Wildland Shrubs of the United States and Its Territories: Thamnic Descriptions, Volume 1". *The U.S. Department of Agriculture, Forest Service, International Institute of Tropical Forestry operates in cooperation with the University of Puerto Rico, Río Piedras, PR, 00936-4984.* 1,704-707. https://doi.org/10.2737/IITF-GTR-26

[4] **Ross, I.A.,** 2005. "Medicinal Plants of the World, Volume 3. Chemical Constituents, Traditional and Modern Medicinal Uses*". Humana Totowa, NJ.* 461-478. https://doi.org/10.1007/978-1-59259-887-8

[5] **Abrahamson, W.G.,** 1984. "Species Responses to Fire on the Florida Lake Wales Ridge". *Am. J. Bot.* 71(1), 35–43. https://doi.org/10.2307/2443621

[6] **Oakes, T.,** 2012. "Plant Guide Saw Palmetto *Serenoa repens* (Bartram) Small Plant Symbol = SERE2". *Contributed by: United state Department of Agriculture. National Plants Data Team, Davis, California and the Mississippi Choctaw Tribal Field Office Choctaw, Mississippi.*

[7] **Bown, D.,** 1995. "Encyclopedia of herbs & their uses". 1st American edition. *Dorling Kindersley ; Distributed by Houghton Mifflin*. p. 352.

[8] **Hale, E.M.,** 1898. "Saw palmetto (*Sabal serrulata*, *Serenoa serrulata*): Its history, botany, chemistry, pharmacology, provings, clinical experience and therapeutic applications". *Boericke et Tafel.* 103 pages.

[9] **Tyler, V.E.,** 1998. "Importance of European Phytomedicinals in the American Market: An Overview". *American Chemical Society*, pp. 1–2. https://doi.org/doi:10.1021/bk-1998-0691.ch001

[10] **Nathan, M., Scholten, R.,** 1999. "The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines". Ann. Intern. Med. 130(5), 459. https://doi.org/10.7326/0003-4819-130-5-199903020-00024

[11] **Laekeman, G., Vlietinck, A.,** 2016. "Assessment report on *Serenoa repens* (W. Bartram) small fructus". (Vol. 44, pp. 1–85). *Committee on Herbal Medicinal Products*. Reference Number: EMA/HMPC/280079/2013

[12] **Gravas, S., Cornu, J.N., Gacci, M., Gratzke, C., Herrmann, T.R.W., Mamoulakis, C., Rieken, M., Speakman, M.J., Tikkinen, K.A.O., Karavitakis, M.,** 2020. "Management of nonneurogenic male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)". *EAU guidelines.* 67,1099-1109.

[13] **Chua, T., Eise, N.T., Simpson, J.S., Ventura, S.,** 2014. "Pharmacological characterization and chemical fractionation of a liposterolic extract of saw palmetto (*Serenoa repens*): Effects on rat prostate contractility". *J. Ethnopharmacol.* 152(2), 283–291. https://doi.org/10.1016/j.jep.2013.12.030

[14] **Habib, F.K., Ross, M., Ho, C.K.H., Lyons, V., Chapman, K.,** 2005. "*Serenoa repens* (Permixon®) inhibits the 5α-reductase activity of human prostate cancer cell lines without interfering with PSA expression". *Int. J. Cancer* 114(2), 190–194. https://doi.org/10.1002/ijc.20701

[15] **Cartwright, E.J., Dohnalek, M.H., Hill, W.S.,** 2023. "Lipid Profile and 5α-Reductase Inhibition Activity of Proprietary Ultrahigh-Pressure Supercritical Carbon Dioxide and Hexane Saw Palmetto Extracts". *Uro. 3*(1), 27-39

https://doi.org/10.3390/uro3010005

[16] **Bernichtein, S., Pigat, N., Camparo, P., Latil, A., Viltard, M., Friedlander, G., Goffin, V.,** 2015. "Anti-inflammatory properties of Lipidosterolic extract of *Serenoa repens* (Permixon®) in a mouse model of prostate hyperplasia". *Prostate* 75(7), 706–722. https://doi.org/10.1002/pros.22953

[17] **Colado-Velázquez, J., Mailloux-Salinas, P., Medina-Contreras, J., Cruz-Robles, D., Bravo, G.,** 2015. "Effect of *Serenoa repens* on oxidative stress, inflammatory and growth factors in obese wistar rats with benign prostatic hyperplasia". *Phyther. Res.* 29(10), 1525–1531. https://doi.org/10.1002/ptr.5406

[18] **Vela-Navarrete, R., Escribano-Burgos, M., López Farré, A., García-Cardoso, J., Manzarbeitia, F., Carrasco, C.,** 2005. "*Serenoa repens* treatment modifies Bax/Bcl-2 index expression and Caspase-3 activity in prostatic tissue from patients with benign prostatic hyperplasia". *J. Urol.* 173, 507–510. https://doi.org/10.1097/01.ju.0000150533.94952.25

[19] **Silvestri, I., Cattarino, S., Aglianò, A., Nicolazzo, C., Scarpa, S., Salciccia, S., Frati, L., Gentile, V., Sciarra, A.,** 2013. "Effect of *Serenoa repens* (Permixon®) on the expression of inflammation-related genes: Analysis in primary cell cultures of human prostate carcinoma". *J. Inflamm. (United Kingdom)* 10. https://doi.org/10.1186/1476-9255-10-11

[20] **Tamalunas, A., Wendt, A., Springer, F., Vigodski, V., Ciotkowska, A., Rutz, B., Wang, R., Huang, R., Liu, Y., Schulz, H., Ledderose, S., Kolben, T., Magistro, G., Stief, C.G., Hennenberg, M.,** 2022. "Permixon®, hexane-extracted *Serenoa repens*, inhibits human prostate and bladder smooth muscle contraction and exerts growth-related functions in human prostate stromal cells". *Life Sci.* 308. https://doi.org/10.1016/j.lfs.2022.120931

[21] **Tarayre, J.P., Delhon, A., Lauressergues, H., Stenger, A., Barbara, M., Bru, M., Villanova, G., Caillol, V., Aliaga, M.,** 1983. "Anti-edematous action of a hexane extract of the stone fruit of *Serenoa repens* Bartr". *Ann. Pharm. Fr.* 41, 559–570.

[22] **Alcaraz, A., Carballido-Rodríguez, J., Unda-Urzaiz, M., Medina-López, R., Ruiz-Cerdá, J.L., Rodríguez-Rubio, F., García-Rojo, D., Brenes-Bermúdez, F.J., Cózar-Olmo, J.M., Baena-González, V., Manasanch, J.,** 2016. "Quality of life in patients with lower urinary tract symptoms associated with BPH: change over time in real-life practice according to treatment--the QUALIPROST study". *Int. Urol. Nephrol.* 48, 645–656. https://doi.org/10.1007/s11255-015-1206-7

[23] **de la Taille, A., Bardin, L., Castagné, C., Auges, M., Capronnier, O., Chalret du Rieu, Q.,** 2020. "Alpha-bloquants ou phytothérapie en traitement de première intention des SBAU/HBP en médecine générale : l'étude non interventionnelle PERSAT". *Progrès en Urol.* 30(10), 522–531. https://doi.org/10.1016/J.PUROL.2020.07.001

[24] **Marti, G., Joulia, P., Amiel, A., Fabre, B., David, B., Fabre, N., Fiorini-Puybaret, C.,** 2019. "Comparison of the Phytochemical Composition of Serenoa repens Extracts by a Multiplexed Metabolomic Approach". *Molecules* 24(12). https://doi.org/10.3390/molecules24122208

[25] **Lim, T.K.,** 2012. "Edible medicinal and non-medicinal plants", 1st ed, Vol. 1, Fruits. *Springer Dordrecht, Canberra, Australia.*

[26] **Dransfield, J., Uhl, N.W., Asmussen, C.B., Baker, W.J., Harley, M.M., Lewis, C.E.,** 2008. "Genera palmarum-the evolution and classification of the palms". *Royal Botanic Gardens, Kew.* 274-276.https://doi.org/10.34885/92

[27] **Fisher, J., Jayachandran, K.,** 1999. "Root structure and arbuscular mycorrhizal colonization of the palm *Serenoa repens* under field conditions". *Plant Soil* 217, 229–241. https://doi.org/10.1023/A:1004576001334

[28] **Schantz, M.M., Bedner, M., Long, S.E., Molloy, J.L., Murphy, K.E., Porter, B.J., Putzbach, K., Rimmer, C.A., Sander, L.C., Sharpless, K.E., Thomas, J.B., Wise, S.A., Wood, L.J., Yen, J.H., Yarita, T., NguyenPho, A., Sorenson, W.R., Betz, J.M.,** 2008. "Development of saw palmetto (*Serenoa repens*) fruit and extract standard reference materials". *Anal. Bioanal. Chem.* 392, 427–438. https://doi.org/10.1007/s00216-008-2297-0

[29] **Abe, M., Ito, Y., Suzuki, A., Onoue, S., Noguchi, H., Yamada, S.,** 2009. "Isolation and pharmacological characterization of fatty acids from saw palmetto extract". *Anal. Sci. Int. J. Japan Soc. Anal. Chem.* 25, 553–557. https://doi.org/10.2116/analsci.25.553

[30] **Olennikov, D.N., Zilfikarov, I.N., Khodakova, S.E.,** 2013. "Phenolic compounds from *Serenoa repens* fruit". *Chem. Nat. Compd.* 49, 526–529. https://doi.org/10.1007/s10600-013-0659-0

[31] **Barakat, A.Z., Hamed, A.R., Bassuiny, R.I., Abdel-Aty, A.M., Mohamed, S.A.,** 2020b. "Date palm and saw palmetto seeds functional properties: antioxidant, anti-inflammatory and antimicrobial activities". *J. Food Meas. Charact.* 14, 1064–1072. https://doi.org/10.1007/s11694-019-00356-5

[32] **Mando, H., Hassan, A., Moussa, N.,** 2022. "Flavonoids in benign prostate hypertrophy: Identification in herbal preparations and molecular docking approach". *Biointerface Res. Appl. Chem.* 12, 8307–8323. https://doi.org/10.33263/BRIAC126.83078323

[33] **M. Bedner, M. M. Schantz, L. C. Sander, and K. E. Sharpless**, 2008 "Development of liquid chromatographic methods for the determination of phytosterols in Standard Reference Materials containing saw palmetto," *J. Chromatogr. A*, vol. 1192, no. 1, pp. 74–80, doi: 10.1016/j.chroma.2008.03.020.

[34] **Rösler, T.W., Matusch, R., Weber, B., Schwarze, B.,** 2009. "Analysis of the hydrodistillate from the fruits of *Serenoa repens*". *Planta Med.*https://doi.org/10.1055/s-0028-1088392

[35] **Shimada, H., Tyler, V.E., McLaughlin, J.L.,** 1997. "Biologically Active Acylglycerides from the Berries of Saw-Palmetto (*Serenoa repens*)". *J. Nat. Prod.* 60, 417–418. https://doi.org/10.1021/np960552o

[36] **Abdel Bar, F.M.,** 2015. "New chalcanonol glycoside from the seeds of saw palmetto: antiproliferative and antioxidant effects". *Nat. Prod. Res.* 29(10), 926–932. https://doi.org/10.1080/14786419.2014.960413

[37] **Wagner, H., Flachsbarth, H., Vogel, G.,** 1981. "A New Antiphlogistic Principle from Sabal serrulata, II". *Planta Med.* 41, 252–258. https://doi.org/10.1055/s-2007-971711

[38] **Weisser, H., Tunn, S., Behnke, B., Krieg, M.,** 1996. "Effects of the sabal serrulata extract IDS 89 and its

subfractions on 5 alpha-reductase activity in human benign prostatic hyperplasia". *Prostate* 28, 300–306. https://doi.org/10.1002/(SICI)1097-0045(199605)28:5<300::AID-PROS5>3.0.CO;2-F

[39] **Abdolmleki, A., Iqbal, M., Akram, M., Laila, U., Rashid, A., Zainab, R., Khalil, M., Alinia-Ahandani, E., Iftikhar, M., Shahid, N., Bankole, M., Kayode, A., Fethi, A., Ozdemir, G., Sołowski, E., Alinia-Ahandani, M., Altable, B., Adetuyi, N., Akhter, N., Jammu, A.,** 2023. "A review on phytotherapy of saw palmetto for reproduction". *Int. Arch. Integr. Med.* 10(9), 19–26.

[40] **Tracy, T.S.,** 2007. "Saw Palmetto. In: Tracy, T.S., Kingston, R.L. (eds) Herbal Products. Forensic Science and Medicine". *Humana Press, Totowa*, NJ, pp. 165–175. https://doi.org/10.1007/978-1-59745-383-7_10

[41] **Suzuki, M., Ito, Y., Fujino, T., Abe, M., Umegaki, K., Onoue, S., Noguchi, H., Yamada, S.,** 2009. "Pharmacological effects of saw palmetto extract in the lower urinary tract". *Acta Pharmacol. Sin.* 30, 227–281. https://doi.org/10.1038/aps.2009.1

[42] **Kwon, Y.,** 2019. "Use of saw palmetto (*Serenoa repens*) extract for benign prostatic hyperplasia". *Food Sci. Biotechnol.* 28, 1599–1606. https://doi.org/10.1007/s10068-019-00605-9

[43] **Blair, H.A.,** 2022. "Hexanic Extract of *Serenoa repens* (Permixon(®)): A Review in Symptomatic Benign Prostatic Hyperplasia". *Drugs Aging* 39, 235–243. https://doi.org/10.1007/s40266-022-00924-3

[44] **Bayne, C.W., Donnelly, F., Ross, M., Habib, F.K.,** 1999. "*Serenoa repens* (Permixon®): A 5α-reductase types I and II inhibitor - New evidence in a coculture model of BPH". *Prostate* 40(4), 232–241. https://doi.org/10.1002/(SICI)1097-0045(19990901)40:4<232::AID-PROS4>3.0.CO;2-0

[45] **Sultan, C., Terraza, A., Devillier, C., Carilla~, E., Briley~, M., Loire, C., Descomps, B.,** 1984. Inhibition of androgen metabolism and binding by a liposterolic extract of "*Serenoa repens* B" in human foreskin fibroblasts", *J. steroid Eiochem.* 20(1). https://doi.org/10.1016/0022-4731(84)90264-4

[46] **Di Silverio, F., Monti, S., Sciarra, A., Varasano, P.A., Martini, C., Lanzara, S., D'Eramo, G., Di Nicola, S., Toscano, V.,** 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(2), 77–83. https://doi.org/10.1002/(SICI)1097-0045(19981001)37:2<77::AID-PROS3>3.0.CO;2-I

[47] **Anderson, M.L.,** 2005. "A preliminary investigation of the enzymatic inhibition of 5alpha-reduction and growth of prostatic carcinoma cell line LNCap-FGC by natural astaxanthin and Saw Palmetto lipid extract in vitro". *J. Herb. Pharmacother.* 5(1), 17–26. https://doi.org/10.1080/J157v05n01_03

[48] **Buonocore, D., Verri, M., Cattaneo, L., Arnica, S., Ghitti, M., Dossena, M.,** 2018. "*Serenoa repens* extracts: *In vitro* study of the 5α-reductase activity in a co-culture model for Benign Prostatic Hyperplasia". Arch. *Ital. di Urol. Androl.* 90(3), 199–202. https://doi.org/10.4081/aiua.2018.3.199

[49] **Liang, T., Liao, S.,** 1992. "Inhibition of steroid 5x-reductase by specific aliphatic unsaturated fatty acids", *Biochem. J.* 285 ,557-62.

[50] **Wang, K., Fan, D.D., Jin, S., Xing, N.Z., Niu, Y.N.,** 2014. "Differential expression of 5-alpha reductase isozymes in the prostate and its clinical implications". *Asian J. Androl.* https://doi.org/10.4103/1008-682X.123664

[51] **Cilotti, A., Danza, G., Serio, M., 2001**. "Clinical application of 5alpha-reductase inhibitors". *J. Endocrinol. Invest.* 24, 199–203. https://doi.org/10.1007/BF03343844

[52] **Talpur, N., Echard, B., Bagchi, D., Bagchi, M., Preuss, H.G.,** 2003. "Comparison of Saw Palmetto (extract and whole berry) and Cernitin on prostate growth in rats". *Mol. Cell.Biochem.* 250, 21–26. https://doi.org/10.1023/a:1024988929454

[53] **Wadsworth, T.L., Worstell, T.R., Greenberg, N.M., Roselli, C.E.,** 2007. "Effects of dietary saw palmetto on the prostate of transgenic adenocarcinoma of the mouse prostate model (TRAMP)". *Prostate* 67, 661–673. https://doi.org/10.1002/pros.20552

[54] **Van Coppenolle, F., Le Bourhis, X., Carpentier, F., Delaby, G., Cousse, H., Raynaud, J.P., Dupouy, J.P., Prevarskaya, N.,** 2000. "Pharmacological effects of the lipidosterolic extract of *Serenoa repens* (Permixon®) on rat prostate hyperplasia induced by hyperprolactinemia: Comparison with finasteride". *Prostate* 43, 49–58. https://doi.org/10.1002/(SICI)1097-0045(20000401)43:1<49::AID-PROS7>3.0.CO;2-J

[55] **Raynaud, J.-P., Cousse, H., Martin, P.-M.,** 2002. "Inhibition of type 1 and type 2 5α-reductase activity by free fatty acids, active ingredients of Permixon®". *J. Steroid Biochem. Mol. Biol.* 82, 233–239. https://doi.org/10.1016/S0960-0760(02)00187-5

[56] **Pinthus, J.H., Lu, J., Bidaisee, L.A., Lin, H., Bryskine, I., Gupta, R.S., Singh, G.,** 2007. "Androgen-dependent regulation of medium and long chain fatty acids uptake in prostate cancer". *Prostate* 67(12), 1330–1338. https://doi: 10.1002/pros.20609.

[57] **Liu, Y., Zuckier, L.S., Ghesani, N. V,** 2010. "Dominant uptake of fatty acid over glucose by prostate cells: a potential new diagnostic and therapeutic approach". *Anticancer Res.* 30, 369–374.

[58] **Petrangeli, E., Lenti, L., Buchetti, B., Chinzari, P., Sale, P., Salvatori, L., Ravenna, L., Lococo, E., Morgante, E., Russo, A., Frati, L., Di Silverio, F., Russo, M.A.,** 2009. "Lipido-sterolic extract of *Serenoa repens* (LSESr, Permixon®) treatment affects human prostate cancer cell membrane organization". *J. Cell. Physiol.* 219, 69–76. https://doi.org/10.1002/jcp.21648

[59] **von Holtz, R.L., Fink, C.S., Awad, A.B.,** 1998. "β-sitosterol activates the sphingomyelin cycle and induces apoptosis in LNCaP human prostate cancer cells". *Nutrition and Cancer*, 32(1), 8–12. https://doi.org/10.1080/01635589809514709

[60] **Awad, A.B., Fink, C.S., Williams, H., Kim, U.,** 2001. "*In vitro* and *in vivo* (SCID mice) effects of phytosterols on the growth and dissemination of human prostate cancer PC-3 cells". *Eur. J. Cancer Prev.* 10(6), 507–513. https://doi.org/10.1097/00008469-200112000-00005

[61] **Scholtysek, C., Krukiewicz, A.A., Alonso, J.-L., Sharma, K.P., Sharma, P.C., Goldmann, W.H.,** 2009. "Characterizing components of the Saw Palmetto Berry Extract (SPBE) on prostate cancer cell growth and traction". *Biochem. Biophys. Res. Commun.* 379, 795–798. https://doi.org/10.1016/j.bbrc.2008.11.114

[62] **De Nunzio, C., Salonia, A., Gacci, M., Ficarra, V.,** 2020. "Inflammation is a target of medical treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia". *World J. Urol.* 38, 2771–2779. https://doi.org/10.1007/s00345-020-03106-1

[63] **Latil, A., Libon, C., Templier, M., Junquero, D., Lantoine-Adam, F., Nguyen, T.,** 2012. "Hexanic lipidosterolic extract of *Serenoa repens* inhibits the expression of two key inflammatory mediators, MCP-1/CCL2 and VCAM-1, in vitro". *BJU Int.* 110. https://doi.org/10.1111/j.1464-410X.2012.11144.x

[64] **Paubert-Braquet, M., Mencia Huerta, J.-M., Cousse, H., Braquet, P.,** 1997. "Effect of the lipidic lipidosterolic extract of *Serenoa repens* (Permixon on the ionophore A23187.stimulated production of leukotriene B 4 (LTB4) from human polymorphonuclear neutrophils", *Prostaglandins, Leukotrienes and Essential Fatty Acids.*57(3):299-304. https://doi: 10.1016/s0952-3278(97)90548-2.

[65] **Novara, G., Galfano, A., Berto, R.B., Ficarra, V., Navarrete, R.V., Artibani, W.,** 2006. "Inflammation, apoptosis, and BPH: What is the evidence?" *Eur. Urol.* Suppl. 5, 401–409. https://doi.org/10.1016/j.eursup.2006.02.003

[66] **Sirab, N., Robert, G., Fasolo, V., Descazeaud, A., Vacherot, F., De La Taille, A., Terry, S.,** 2013. "Lipidosterolic extract of *Serenoa repens* modulates the expression of inflammation related-genes in benign prostatic hyperplasia epithelial and stromal cells". *Int. J. Mol. Sci.* 14, 14301–14320. https://doi.org/10.3390/ijms140714301

[67] **Vacherot, F., Azzouz, M., Gil-Diez-de-Medina, S., Colombel, M., De La Taille, A., Belda, M.A.L., Abbou, C.C., Raynaud, J.P., Chopin, D.K.,** 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, 259–266. https://doi.org/10.1002/1097-0045(20001101)45:3<259::AID-PROS9>3.0.CO;2-G

[68] **Opoku-Acheampong, A.B., Penugonda, K., Lindshield, B.L.,** 2016. "Effect of Saw Palmetto Supplements on Androgen-Sensitive LNCaP Human Prostate Cancer Cell Number and Syrian Hamster Flank Organ Growth". *Evid. Based. Complement. Alternat. Med.* 8135135. https://doi.org/10.1155/2016/8135135

[69] **Iglesias-Gato, D., Carsten, T., Vesterlund, M., Pousette, A., Schoop, R., Norstedt, G.,** 2012. "Androgen-independent effects of *Serenoa repens* extract (Prostasan ®) on prostatic epithelial cell proliferation and inflammation". *Phyther. Res.* 26(2), 259–264. https://doi.org/10.1002/ptr.3537

[70] **Wadsworth, T.L., Carroll, J.M., Mallinson, R.A., Roberts, C.T., Roselli, C.E.,** 2004. "Saw palmetto extract suppresses insulin-like growth factor-I signaling and induces stress-activated protein kinase/c-Jun N-terminal kinase phosphorylation in human prostate epithelial cells". *Endocrinology* 145, 3205–3214. https://doi.org/10.1210/en.2003-1716

[71] **Goldmann, W.H., Sharma, A.L., Currier, S.J., Johnston, P.D., Rana, A., Sharma, C.P.,** 2001. "Saw palmetto berry extract inhibits cell growth and Cox-2 expression in prostatic cancer cells". *Cell Biol. Int.* 25(11), 1117–1124. https://doi.org/10.1006/cbir.2001.0779

[72] **Paubert-Braquet, M., Cousse, H., Raynaud, J.-P., Mencia-Huerta, J.M., Braquet, P.,** 1998. "Basic Science Effect of the Lipidosterolic Extract of *Serenoa repens* (Permixon ®) and Its Major Components on Basic Fibroblast Growth Factor-Induced Proliferation of Cultures of Human Prostate Biopsies Effect of LSESr on Human Prostate Cell Cultures". *Eur Urol.* 33(3): 340-7. https://doi: 10.1159/000019570.

[73] **Goepel, M., Hecker, U., Krege, S., Rübben, H., Michel, M.C.,** 1999. "Saw palmetto extracts potently and noncompetitively inhibit human α1- adrenoceptors *in vitro*". *Prostate* 38(3), 208–215. https://doi.org/10.1002/(SICI)1097-0045(19990215)38:3<208::AID-PROS5>3.0.CO;2-4

[74] **Oki, T., Suzuki, M., Nishioka, Y., Yasuda, A., Umegaki, K., Yamada, S.,** 2005. "Effects of saw palmetto extract on micturition reflex of rats and its autonomic receptor binding activity". *J. Urol.* 173, 1395–1399. https://doi.org/10.1097/01.ju.0000146273.26591.f5

[75] **Suzuki, M., Oki, T., Sugiyama, T., Umegaki, K., Uchida, S., Yamada, S.,** 2007. "Muscarinic and alpha 1-adrenergic receptor binding characteristics of saw palmetto extract in rat lower urinary tract". *Urology* 69, 1216–1220. https://doi.org/10.1016/j.urology.2007.02.038

[76] **Yamada, S., Kato, Y.,** 2022. "Effects of saw palmetto extract on the vanilloid receptor TRPV1". *LUTS Low. Urin. Tract Symptoms* 14(2), 117–121. https://doi.org/10.1111/luts.12413

[77] **Gutierrez, M., Garcia De Bow, M.J., Cantabrana, B., Hidalgo, A., De Farmacologfa, L., De Medicina, D., Memcina, D.E., Jult^n Claverfa S/N, C./,** 1996. "Mechanisms involved in the spasmolytic effect of extracts from *Sabal serrulata* fruit on smooth muscle", *Gen. Pharmac.*27(1):171-6. doi: 10.1016/0306-3623(95)00094-1.

[78] **Igielska-Kalwat, J., Kalwat, J.I.,** 2019. "The Use of *Serenoa Repens* (Saw Palmetto) in Hair Care Products". *Biomed. J. Sci. Tech. Res.* 13(1). https://doi.org/10.26717/BJSTR.2019.13.002348

[79] **Evron, E., Juhasz, M., Babadjouni, A., Mesinkovska, N.A.,** 2020. "Natural Hair Supplement: Friend or Foe? Saw Palmetto, a Systematic Review in Alopecia". *Ski. appendage Disord.* 6(6), 329–337. https://doi.org/10.1159/000509905

[80] **Chatterjee, S., Agrawala, S.,** 2003. "Saw palmetto (*Serenoa repens*) in androgenic alopecia An effective phytotherapy". 2(6) 302-305.

[81] **Piwecki, M., Urban, A., Pełszyńska, J.,** 2023. "The role of 5-α-reductase inhibition in supressing progression of male androgenetic alopecia − a postulate for further studies on possible application of saw palmetto extracts". *Ann. Acad. Medicae Silesiensis* 77, 190–196. https://doi.org/10.18794/aams/165996

[82] **Dhariwala, M.Y., Ravikumar, P.,** 2019. "An overview of herbal alternatives in androgenetic alopecia". *J. Cosmet. Dermatol.* 18(4), 966-975. https://doi.org/10.1111/jocd.12930

[83] **Levy, L.L., Emer, J.J.,** 2013. "Female pattern alopecia: Current perspectives". *Int. J. Womens. Health.* 29,541-56. https://doi.org/10.2147/IJWH.S49337

[84] **Padois, K., Cantiéni, C., Bertholle, V., Bardel, C., Pirot, F., Falson, F.,** 2011. "Solid lipid nanoparticles suspension versus commercial solutions for dermal delivery of minoxidil". *Int. J. Pharm.* 416, 300–304. https://doi.org/10.1016/j.ijpharm.2011.06.014

[85] **Zhu, H.-L., Gao, Y.-H., Yang, J.-Q., Li, J.-B., Gao, J.,** 2018. "*Serenoa repens* extracts promote hair regeneration and repair of hair loss mouse models by activating TGF-β and mitochondrial signaling pathway". *Eur. Rev. Med. Pharmacol. Sci.* 22(12), 4000–4008. https://doi.org/10.26355/eurrev_201806_15285

[86] **Marcovici, G., Chittur, S., Parr, B.,** 2011. "Inhibition of inflammatory gene expression in keratinocytes using a composition containing carnitine, thioctic acid and saw palmetto extract. Evidence-based Complement". *Altern. Med.* https://doi.org/10.1093/ecam/nep102

[87] **Bassino, E., Gasparri, F., Munaron, L.,** 2019. "*Serenoa repens* and N-acetyl glucosamine/milk proteins complex differentially affect the paracrine communication between endothelial and follicle dermal papilla cells". *J. Cell. Physiol.* 234(5), 7320–7329. https://doi.org/10.1002/jcp.27491

[88] **Zanzottera, F., Bizzaro, G., Michelotti, A., Nobile, V.,** 2017. "Efficacy of a Nutritional Supplement, Standardized in Fatty Acids and Phytosterols, on Hair Loss and Hair Health in both Women and Men". *J. Cosmetol Trichology* 03(2), 1000121. https://doi.org/10.4172/2471-9323.1000121

[89] **Nagarathna, P.K.M., Rajan, P.R., Koneri, R.,** 2013. "A detailed study on poly cystic ovarian syndrome and it's treatment with natural products". *Int. J. Toxicol. Pharmacol. Res.* 5(4):109-120.

[90] **Vassiliadi, D.A., Barber, T.M., Hughes, B.A., McCarthy, M.I., Wass, J.A.H., Franks, S., Nightingale, P., Tomlinson, J.W., Arlt, W., Stewart, P.M.,** 2009. "Increased 5 alpha-reductase activity and adrenocortical drive in women with polycystic ovary syndrome". *J. Clin. Endocrinol. Metab.* 94, 3558–3566. https://doi.org/10.1210/jc.2009-0837

[91] **Zeng, L.-H., Rana, S., Hussain, L., Asif, M., Mehmood, M.H., Imran, I., Younas, A., Mahdy, A., Al-Joufi, F.A., Abed, S.N.,** 2022. "Polycystic Ovary Syndrome: A Disorder of Reproductive Age, Its Pathogenesis, and a Discussion on the Emerging Role of Herbal Remedies". *Front. Pharmacol.* 13, 874914. https://doi.org/10.3389/fphar.2022.874914

[92] **Kumar, V.S., KP, S.G.,** 2022. "Effects of Saw-Palmetto (*Serenoa repens*) in Letrazole Induced Poly Cystic Ovarian Syndrome in Female Albino Wistar Rats". *Int. J. Med. Res. Heal. Sci.* 11(8): 1-12.

[93] **Yousefi, M., Barikbin, B., Givrad, S., Moravej, H., Khoushnoudi, R.,** 2009. The effectiveness of the extract of *Serenoa repens* (saw palmetto) in idiopathic facial hirsutism (letter to editor). *Iranian Journal of Dermatology*, 12(4), 139.

[94] **Ghanbarian, R., Ranjbai, M., Babaeian, M., Mazaheri, M.,** 2024. "A Narrative Review of Herbal Remedies for Managing Hirsutism". *Int. J. Prev. Med.* 15, 17. https://doi.org/10.4103/ijpvm.ijpvm_62_23

[95] **Dobrev, H.,** 2007. "Clinical and instrumental study of the efficacy of a new sebum control cream". *JCD.* 6(2), 113–118. https://doi.org/10.1111/j.1473-2165.2007.00306.x

[96] **Reddy, V., Bubna, A., Veeraraghavan, M., Rangarajan, S.,** 2017. "Saw palmetto extract: A dermatologist's perspective". *Indian J. Drugs Dermatology* 3, 11. https://doi.org/10.4103/ijdd.ijdd_45_16

[97] **El-Hawary, S.S., Mohammedb, R., AbouZidb, S.F., Hassanb, H.M., Lithyc, N.M.,** 2016. "DNA Fingerprinting, Chemical Composition and Antimicrobial Activity of the Essential Oil isolated from the Fruits of *Serenoa repens* W. Bartram". *J. Biol. Agric. Healthc.* 6(12).

[98] **Kim, Y.-G., Lee, J.-H., Park, S., Kim, S., Lee, J.,** 2022. "Inhibition of polymicrobial biofilm formation by saw palmetto oil, lauric acid and myristic acid". *Microb. Biotechnol.* 15, 590–602. https://doi.org/10.1111/1751-7915.13864

[99] **Yang, Y., Hui, L., Yuqin, C., Jie, L., Shuai, H., Tiezhu, Z., Wei, W.,** 2014. "Effect of saw palmetto extract on PI3K cell signaling transduction in human glioma". *Exp. Ther. Med.* 8, 563–566. https://doi.org/10.3892/etm.2014.1756

[100] **Hostanska, K., Suter, A., Melzer, J., Saller, R.,** 2007. "Evaluation of cell death caused by an ethanolic extract of *Serenoae repentis* fructus (Prostasan) on human carcinoma cell lines". *Anticancer Res.* 27, 873–881.

[101] **Barakat, A.Z., Bassuiny, R.I., Abdel-Aty, A.M., Mohamed, S.A**., 2020a. "Diabetic complications and oxidative stress: The role of phenolic-rich extracts of saw palmetto and date palm seeds". *J. Food Biochem.* 44:e13416. https://doi.org/10.1111/jfbc.13416

[102] **Strum, S.,** 2021. "*Serenoa Repens* (Saw Palmetto) for Lower Urinary Tract Symptoms (LUTS): The Evidence for Efficacy and Safety of Lipidosterolic Extracts. Part I". *Uro 1*, 139–154. https://doi.org/10.3390/uro1030016

[103] **Tacklind, J., MacDonald, R., Rutks, I., Wilt, T.J.,** 2009. "*Serenoa repens* for benign prostatic hyperplasia". *Cochrane database Syst. Rev.* CD001423. https://doi.org/10.1002/14651858.CD001423.pub2

[104] **Tacklind, J., Macdonald, R., Rutks, I., Stanke, J.U., Wilt, T.J.,** 2012. "*Serenoa repens* for benign prostatic hyperplasia". *Cochrane database Syst. Rev.* 12, CD001423. https://doi.org/10.1002/14651858.CD001423.pub3

[105] **Novara, G., Giannarini, G., Alcaraz, A., Cózar-Olmo, J.-M., Descazeaud, A., Montorsi, F., Ficarra, V.,** 2016. "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* 2(5), 553–561. https://doi.org/10.1016/j.euf.2016.04.002

[106] **Vela-Navarrete, R., Alcaraz, A., Rodríguez-Antolín, A., Miñana López, B., Fernández-Gómez, J.M., Angulo, J.C., Castro Díaz, D., Romero-Otero, J., Brenes, F.J., Carballido, J., Molero García, J.M., Fernández-Pro Ledesma, A., Cózar Olmos, J.M., Manasanch Dalmau, J., Subirana Cachinero, I., Herdman, M., Ficarra, V.,** 2018. "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 randomised controlled trials and observational studies". *BJU Int.* 122, 1049–1065. https://doi.org/10.1111/bju.14362

[107] **Boyle, P., Robertson, C., Lowe, F., Roehrborn, C.,** 2004. "Updated meta-analysis of clinical trials of *Serenoa repens* extract in the treatment of symptomatic benign prostatic hyperplasia". *BJU Int.* 93(6), 751–756. https://doi.org/10.1111/j.1464-410X.2003.04735.x

[108] **European Scientific Cooperative on Phytotherapy (ESCOP).,**2003. "*Serenoae repentis Fructus* (Sabal Fructus) Saw Palmetto Fruit monograph. ESCOP Monographs: The Scientific Foundation for Herbal Medicinal Products, 2nd ed.". *George Thieme Verlag: New York, NY, USA*. https://books.google.com.eg/books?id=_ONsAAAAMAAJ

[109] **McVary, K.T., Roehrborn, C.G., Avins, A.L., Barry, M.J., Bruskewitz, R.C., Donnell, R.F., Foster, H.E.J., Gonzalez, C.M., Kaplan, S.A., Penson, D.F., Ulchaker, J.C., Wei, J.T.,** 2011. "Update on AUA guideline on the management of benign prostatic hyperplasia". *J. Urol.* 185, 1793–1803. https://doi.org/10.1016/j.juro.2011.01.074

[110] **Willetts, K.E., Clements, M.S., Champion, S., Ehsman, S., Eden, J.A.,** 2003. "*Serenoa repens* extract for benign prostate hyperplasia: a randomized controlled trial". *BJU Int.* 92, 267–270. https://doi.org/10.1046/j.1464-410X.2003.04316.x

[111] **Bent, S., Kane, C., Shinohara, K., Neuhaus, J., Hudes, E.S., Goldberg, H., Avins, A.L.,** 2006. "Saw Palmetto for Benign Prostatic Hyperplasia". *N. Engl. J. Med.* 354(6), 557–566. https://doi.org/10.1056/NEJMoa053085

[112] **Barry, M.J., Meleth, S., Lee, J.Y., Kreder, K.J., Avins, A.L., Nickel, J.C., Roehrborn, C.G., Crawford, E.D., Foster, H.E.J., Kaplan, S.A., McCullough, A., Andriole, G.L., Naslund, M.J., Williams, O.D., Kusek, J.W., Meyers, C.M., Betz, J.M., Cantor, A., McVary, K.T.,** 2011. "Effect of increasing doses of saw palmetto extract on lower urinary tract symptoms: a randomized trial". *JAMA.* 306(12), 1344–1351. https://doi.org/10.1001/jama.2011.1364

[113] **Champault, G., Patel, J.C., Bonnard, A.M.,** 1984. "A double-blind trial of an extract of the plant *Serenoa repens* in benign prostatic hyperplasia". *Br. J. Clin. Pharmacol.* 18(3), 461–462. https://doi.org/10.1111/j.1365-2125.1984.tb02491.x

[114] **J. Cuckier, J. Ducassu, and M. Le Guillou**, "Permixon versus placebo: results of a multicentre study," *CR Ther Pharmacol Clin*, vol. 4, pp. 15–21, 1985.

[115] **Descotes, J.L., Rambeaud, J.J., Deschaseaux, P., Faure, G.,** 1995. "Placebo-Controlled Evaluation of the Efficacy and Tolerability of Permixon® in Benign Prostatic Hyperplasia after Exclusion of Placebo Responders". *Clin. Drug Investig.* 9, 291–297. https://doi.org/10.2165/00044011-199509050-00007

[116] **Ye, Z., Huang, J., Zhou, L., Chen, S., Wang, Z.Z., Ma, L., Wang, D., Wang, G., Wang, S., Liang, C., Qiu, S., Gu, X., Liu, J., Weng, Z., Wu, C., Wei, Q., Xie, L., Wu, W., Cheng, Y., Hu, J., Wang, Z.Z., Zeng, X.,** 2019. "Efficacy and Safety of *Serenoa repens* Extract Among Patients with Benign Prostatic Hyperplasia in China: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial". *Urology* 129, 172–179. https://doi.org/10.1016/j.urology.2019.02.030

[117] **Braeckman, J., Bruhwyler, J., Vandekerckhove, K., Geczy A. Z. VUB, Laarbeeklaan 103, 1090 Brussels (Belgium)), J. (Department of U.,** 1997. "Efficacy and safety of the extract of *Serenoa repens* in the treatment of benign prostatic hyperplasia: therapeutic equivalence between twice and once daily dosage forms". *Phyther. Res. (United Kingdom).*11, 558–563.

[118] **Ishii, I., Wada, T., Takara, T.,** 2020. "Effects of saw palmetto fruit extract intake on improving urination issues in Japanese men: A randomized, double-blind, parallel-group, placebo-controlled study". *Food Sci. Nutr.* 8(8), 4017–4026. https://doi.org/10.1002/fsn3.1654

[119] **Yamada, S., Shirai, M., Ono, K., Kageyama, S.,** 2022. "Beneficial Effects of Saw Palmetto Fruit Extract on Urinary Symptoms in Japanese Female Subjects by a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study". *Nutrients* 14. https://doi.org/10.3390/nu14061190

[120] **Kimura, M., Ishii, I., Baba, A., Takara, T.,** 2024. "Beneficial effects of saw palmetto (*Serenoa repens*) fruit extract on the urinary symptoms of healthy Japanese adults with possible lower urinary tract symptoms: A randomized, double-blind, placebo-controlled study". *Nutr. Health* 0(0). https://doi.org/10.1177/02601060241265389

[121] **Debruyne, F., Koch, G., Boyle, P., Da Silva, F.C., Gillenwater, J.G., Hamdy, F.C., Perrin, P., Teillac, P., Vela-Navarrete, R., Raynaud, J.-P.,** 2002. "Comparison of a Phytotherapeutic Agent (Permixon) with an α-Blocker (Tamsulosin) in the Treatment of Benign Prostatic Hyperplasia: A 1-Year Randomized International Study". *Eur. Urol.* 41(5), 497–507. https://doi.org/10.1016/S0302-2838(02)00066-0

[122] **Argirović, A., Argirović, D.**, 2013. "Does the addition of *Serenoa repens* to tamsulosin improve its therapeutical efficacy in benign prostatic hyperplasia?" *Vojnosanit. Pregl.* 70(12), 1091–1096. https://doi.org/10.2298/vsp110620029a

[123] **Hızlı, F., 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. https://doi.org/10.1007/s11255-006-9106-5

[124] **Alcaraz, A., Rodríguez-Antolín, A., Carballido-Rodríguez, J., Castro-Díaz, D., Esteban-Fuertes, M., Cózar-Olmo, J.M., Ficarra, V., Medina-López, R., Fernández-Gómez, J.M., Angulo, J.C., Medina-Polo, J., Brenes-Bermúdez, F.J., Molero-García, J.M., Fernández-Pro-Ledesma, A., Manasanch, J.,The Qualiprost Study Group, O.B.O.,** 2020. "Clinical Benefit of Tamsulosin and the Hexanic Extract of *Serenoa repens*, in Combination or as Monotherapy, in Patients with Moderate/Severe LUTS-BPH: A Subset Analysis of the QUALIPROST Study". *J. Clin. Med.* 9(9):2909. https://doi.org/10.3390/jcm9092909

[125] **Winograd, J., Lama, J., Codelia-Anjum, A., Bhojani, N., Elterman, D.S., Zorn, K.C., Margolis, E., Brahmbhatt, J., Gonzalez, R., Chughtai, B.,** 2024. "Measuring the efficacy of *Serenoa repens* (USPlus) extract with mobile uroflowmetry". *Can. J. Urol.* 31(16), 12053–12059.

[126] **Pytel, Y.A., Vinarov, A., Lopatkin, N., Sivkov, A., Gorilovsky, L., 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. https://doi.org/10.1007/BF02853175

[127] **Ju, X., Gu, X., Zhang, Z., Wei, Z., Xu, Z., Miao, H., Zhou, W., Xu, R., Cheng, B., Ma, J., Niu, T., Qu, P., Xue, B., Zhang, W.,** 2015. "Efficacy and safety of Saw Palmetto Extract Capsules in the treatment of benign prostatic hyperplasia". *Zhonghua nan ke xue = National journal of andrology* 21, 1098–1101. http://europepmc.org/abstract/MED/26817302

[128] **Sorenson, W.R., Sullivan, D.,** 2006. "Determination of campesterol, stigmasterol, and beta-sitosterol in saw palmetto rawmaterials and dietary supplements by gas chromatography: single-laboratory validation". *J. AOAC Int.* 89, 22–34.

[129] **Sorenson, W.R., Sullivan, D.,** 2007. "Determination of campesterol, stigmasterol, and beta-sitosterol in saw palmetto raw materials and dietary supplements by gas chromatography: collaborative study". *J. AOAC Int.* 90, 670–678.

[130] **Habib, F.K., Wyllie, M.G.,** 2004. "Not all brands are created equal: a comparison of selected components of different brands of Serenoa repens extract". *Prostate Cancer Prostatic Dis.* 7, 195–200. https://doi.org/10.1038/sj.pcan.4500746

[131] **Penugonda, K., Lindshield, B.L.,** 2013. "Fatty acid and phytosterol content of commercial saw palmetto supplements". *Nutrients* 5, 3617–3633. https://doi.org/10.3390/nu5093617

[132] **Scaglione, F., Lucini, V., Pannacci, M., Caronno, A., 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. https://doi.org/10.1159/000161128

[133] **Chughtai, B., Bhojani, N., Zorn, K.C., Elterman, D.,** 2023. "Variability of Commercial Saw Palmetto–Based Supplements for the Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms". *JU Open Plus* 1(8):e00037. https://doi.org/10.1097/JU9.0000000000000040

[134] **Agbabiaka, T.B., Pittler, M.H., Wider, B., Ernst, E.,** 2009. "*Serenoa repens* (saw palmetto): a systematic review of adverse events". *Drug Saf.* 32, 637–647. https://doi.org/10.2165/00002018-200932080-00003

[135] **Avins, A.L., Lee, J.Y., Meyers, C.M., Barry, M.J.,** 2013. "Safety and toxicity of saw palmetto in the CAMUS trial". *J. Urol.* 189, 1415–1420. https://doi.org/10.1016/j.juro.2012.10.002

[136] **Paulis, G., Paulis, A., Perletti, G.,** 2021. "*Serenoa repens* and its effects on male sexual function. A systematic review and meta-analysis of clinical trials". *Archivio Italiano Di Urologia E Andrologia* 93(4), 475–480. https://doi.org/10.4081/aiua.2021.4.475

[137] **Crescioli, G., Maggini, V., Raschi, E., Gonella, L.A., Luxi, N., Ippoliti, I., Di Giovanni, V., Bonaiuti, R., Firenzuoli, N., Gallo, E., Menniti-Ippolito, F., Moretti, U., Trifirò, G., Vannacci, A., Firenzuoli, F., Lombardi, N.,** 2023. "Suspected adverse reactions to medications and food supplements containing Serenoa repens: A worldwide analysis of pharmacovigilance and phytovigilance spontaneous reports". *Phytother. Res.* 37(11), 5289–5299. https://doi.org/10.1002/ptr.7960

[138] **Lapi, F., Gallo, E., Giocaliere, E., Vietri, M., Baronti, R., Pieraccini, G., Tafi, A., Menniti-Ippolito, F., Mugelli, A., Firenzuoli, F., Vannacci, A.,** 2010. "Acute liver damage due to *Serenoa repens*: a case report". *Br. J. Clin. Pharmacol.* 69(5), 558–560. https://doi.org/10.1111/j.1365-2125.2010.03618.x

[139] **Bruminhent, J., Carrera, P., Li, Z., Amankona, R., Roberts, I.M.,** 2011. "Acute pancreatitis with saw palmetto use: a case report." *J. Med. Case Rep.* 5, 414. https://doi.org/10.1186/1752-1947-5-414

[140] **Wargo, K.A., Allman, E., Ibrahim, F.,** 2010. "A possible case of saw palmetto-induced pancreatitis". *South. Med. J.* 103, 683–685. https://doi.org/10.1097/SMJ.0b013e3181e1e3ee

[141] **Wargo, K.A., Allman, E., Ibrahim, F.,** 2010. "A possible case of saw palmetto-induced pancreatitis". *South. Med. J.* 103, 683–685. https://doi.org/10.1097/SMJ.0b013e3181e1e3ee

[142] **Gammoudi, R., Ameur, K., Ouni, B., Mokni, S., Aounallah, A., Boussoffara, L., Nejet, G., Belajouza, C., Sriha, B., Ben Salem, C., Denguezli, M.,** 2020. "Fixed drug eruption to *Serenoa repens*: First case report and consideration of the use of herbal medicine". *Dermatol. Ther.* 33,14247-3. https://doi.org/10.1111/dth.14247

[143] **Gallo, E., Maggini, V., Lombardi, N., Crescioli, G., Sivelli, F., Vannacci, A., Firenzuoli, F.,** 2022. "*Serenoa repens* induced erectile dysfunction: Underdiagnosis and phytovigilance". *Br. J. Clin. Pharmacol.* 88(5), 2441-2443. https://doi.org/10.1111/bcp.15129

[144] **Bressler, R.,** 2005. "Herb-drug interactions. Interactions between saw palmetto and prescription medications". *Geriatrics* 60(11), 32,34.

[145] **Wang, C.-Z., Moss, J., Yuan, C.-S.,** 2015. "Commonly Used Dietary Supplements on Coagulation Function during Surgery". *Med. (Basel, Switzerland)* 2, 157–185. https://doi.org/10.3390/medicines2030157

[146] **Priestap, H.A., Quirke, J.M.E., Houle, P., Bennett, B.C.,** 2011. "Fatty acid composition of fruits of two forms *of Serenoa repens". Chem. Nat. Compd.* 47, 511. https://doi.org/10.1007/s10600-011-9983-4

[147] **Ganzera, M., Croom, E.M., Khan, I.A.,** 1999. "Determination of the Fatty Acid content of pumpkin seed, pygeum, and saw palmetto". *J. Med. Food* 2(1), 21–27. https://doi.org/10.1089/jmf.1999.2.21

[148] **Iguchi, K., Okumura, N., Usui, S., Sajiki, H., Hirota, K., Hirano, K.,** 2001. "Myristoleic acid, a cytotoxic component in the extract from *Serenoa repens*, induces apoptosis and necrosis in human prostatic LNCaP cells". *Prostate* 47(1), 59–65. https://doi.org/10.1002/pros.1047

[149] **Scaglione, F., Lucini, V., Pannacci, M., Dugnani, S., Leone, C.,** 2012. "Comparison of the potency of 10 different brands of *Serenoa repens* extracts". *Eur. Rev. Med. Pharmacol. Sci.* 16, 569–574.

[150] **Baron, A., Mancini, M., Caldwell, E., Cabrelle, A., Bernardi, P., Pagano, F**., 2009. "*Serenoa repens* extract targets mitochondria and activates the intrinsic apoptotic pathway in human prostate cancer cells". *BJU Int.* 103, 1275–1283. https://doi.org/10.1111/j.1464-410X.2008.08266.x

[151] **Piquero-Casals, J., Saceda Corralo, D., Aladren, S., Bustos, J., Fernández-Botello, A., Navasa, A., Logusso, G., Jourdan, E., Mir-Bonafé, J., Morgado-Carrasco, D.,** 2024. "Oral Supplementation with L-Cystine, *Serenoa repens,*

Cucurbita pepo, and Pygeum africanum in Chronic Telogen Effluvium and Androgenetic Alopecia: A Double-Blind, Placebo-Controlled, Randomized Clinical Study". *Ski. Appendage Disord.* https://doi.org/10.1159/000540081

[152] **Sudeep, H. V, Rashmi, S., Jestin, T. V, Richards, A., Gouthamchandra, K., Shyamprasad, K.,** 2023. "Oral and Topical Administration of a Standardized Saw Palmetto Oil Reduces Hair Fall and Improves the Hair Growth in Androgenetic Alopecia Subjects – A 16-Week Randomized, Placebo-Controlled Study". *Clin. Cosmet. Investig. Dermatol.* 16, 3251–3266. https://doi.org/10.2147/CCID.S435795

[153] **Rapaport, J., Sadgrove, N.J., Arruda, S., Swearingen, A., Abidi, Z., Sadick, N.,** 2023. "Real-World, Open-Label Study of the Efficacy and Safety of a Novel Serum in Androgenetic Alopecia". *J. Drugs Dermatol.* 22, 559–564. https://doi.org/10.36849/JDD.7403

[154] **Ablon, G., Kogan, S.,** 2018. "A Six-Month, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of a Nutraceutical Supplement for Promoting Hair Growth in Women With Self-Perceived Thinning Hair". *J. Drugs Dermatol.* 17(5), 558–565.

[155] **Farris, P.K., Rogers, N., McMichael, A., Kogan, S.,** 2017. "A novel multi-targeting approach to treating hair loss, using standardized nutraceuticals". *J Drugs Dermatol* 16(11), s141–s148.

[156] **Wessagowit, V., Tangjaturonrusamee, C., Kootiratrakarn, T., Bunnag, T., Pimonrat, T., Muangdang, N., Pichai, P.,** 2016. "Treatment of male androgenetic alopecia with topical products containing *Serenoa repens* extract. Australas". *J. Dermatol.* 57, e76-82. https://doi.org/10.1111/ajd.12352

[157] **Borrás, J., Piqué, N., Nieto, C., González, J., Maria Borrás, J., Piqué, N., Nieto, C., González, J.,** 2016. "Efficacy and safety of a dietary supplement containing a lipid co-extract from *Serenoa repens* and *Pygeum africanum* for the treatment of androgenetic alopecia (AGA) in women. Results of a randomized, double-blind, placebo-controlled clinical trial". *Más dermatología.* 25, 5–14. https://doi.org/10.5538/1887-5181.2016.25.5

[158] **Pezza, M., Carlomagno, V., Casucci, G.,** 2014. "Telogen effluvium treated with *Serenoa repens* supplement". *Senses Sci.* 9(4) 1668-1679. https://doi.org/10.14616/sands-2014-1-4143

[159] **Rossp, A., Marp, E., Scarn02, M., Garellil, V., Maxiai, C., Scalp, E., Iorioi, A., Carlesim03, M., Rossi, A., Mari, E., Scarno, M., Garelli, V., Maxia, C., Scali, E., Iorio, A., Carlesimo, M.,** 2012. "Comparitive effectiveness of finasteride vs *Serenoa repens* in male androgenetic alopecia: a two-year study". *International journal of immunopathology and pharmacology. England.* https://doi.org/10.1177/039463201202500435

[160] **Prager, N., Bickett, K., French, N., Marcovici, G.,** 2002. "A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the treatment of androgenetic alopecia". *J. Altern. Complement. Med.* 8, 143–152. https://doi.org/10.1089/acm.2002.8.143

[161] **Morganti, P., Fabrizi, G., James, B., Bruno, C.,** 1998. "Effect of gelatin-cystine ano *Serenoa repens* extract on free radicals level and hair growth". *J Appl Cosmetol* 16, 57–64.