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A Review on *Serenoa serrulata*: A Potential Medicinal Plant for Prostatic Diseases

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ABSTRACT

Background: Prostatic diseases which include prostatitis, benign prostatic hyperplasia (BPH) and prostate cancer are the benign or malignant disorders that affect the prostate. Phytotherapies have been adopted as the alternative treatment/ management option especially for BPH since the current modern methods of treatment presents a lot of adverse effects.

Methodology: The literature was searched using different databases including Medline/PubMed, Cochrane library, Scopus, Proquest library, Embase, EBooks and Google Scholar for relevant records for a period from 1988 to 2021 to identify all the published articles of *S. serrulata* regarding treatment of prostatic diseases. The key search terms were *Serenoa serrulata,* S. repens, Saw palmetto, Prostate cancer treatment with *Serenoa serrulata,* treatment of Benign Prostatic Hyperplasia with *Serenoa serrulata,* phytochemicals of *Serenoa serrulata,* ethnobotanical uses of *Serenoa serrulata,* toxicity of *Serenoa serrulata,* pharmacological activities of *Serenoa serrulata* and also traditional management and treatment of prostatic diseases using *Serenoa serrulata* and also clinical trials on treatment of prostatic diseases with *Serenoa serrulata.* The retrieved articles were reviewed, synthesized and analyzed qualitatively. The reference list of the retrieved articles was also reviewed and synthesized. The original research articles which reported an investigation of *S. serrulata* of any study design, original published research articles, any time of publication and grey literature (conference papers, reported articles, academic thesis) were included. The articles whose full texts were not freely available by the time of search and those without clear information about methodology and study design were excluded.

Results: This review reported that *Serenoa serrulata* belonging to the *Arecaceae* family commonly known as saw palmetto is used traditionally for treating prostatic disease conditions and other infertility conditions in both men and women. Phytochemical screening of hexanic and ethanolic extracts of *S. serrulata* comprised of free fatty acids and phytosterols which together contribute to their antiprostatic activities. These extracts of *S. serrulata* exhibited antiandrogenic, anti-inflammatory and anti-proliferative activities through inhibition of both isoenzymes 5**α**- reductase and inhibition of binding of dihydrotestosterone (DHT) to the cytosolic androgen receptors. This is a similar mechanism exhibited by finasteride and Tamsulosin both antiprostatic conventional drugs though the plant phytochemicals do not interfere with PSA secretion. *S. serrulata* has also been reported to be non-toxic in both non-clinical and clinical trial studies. The medicinal plants reported by this review to be used in combination include; stinging nettle (*Urtica dioca*), *Zingiber officinalis*, *Echinacea angustifolia* and pumpkin (*Cucurbita pepo*). The antiprostatic conventional drugs reported include Finasteride and Tamsulosin.

Conclusion and Recommendation: The results showed that *S. serrulata* is effective in treating prostatic diseases. The potency and safety are improved when used in combination with *Urtica dioca, Cucurbita pepo, Zingiber officinalis* and *Echinacea angustifolia* as compared with anti-prostatic conventional drugs Finasteride and Tamsulosin alone. The plant combination has also been shown to have improvement in the quality of life and as well enhancing the synergy of Finasteride and Tamsulon and

their adverse effects. Effective medicinal plant combinations should be formulated into products and integrated into the usual treatment for prostatic diseases.

Key words: Prostatic diseases, Prostate Cancer, Benign Prostatic Hyperplasia, prostate tumors, Phytotherapy, anti-prostatic drugs, *Serenoa serrulata*, ethnobotanical, phytochemical, toxicity and pharmacological.

INTRODUCTION

Prostatic diseases are the benign or malignant disorders affecting the prostate. Common examples of prostatic diseases include Prostatitis, Benign Prostatic Hyperplasia (BPH) and Prostate cancer.[1] Prostatitis is an inflammatory disease mainly caused by infections or related health conditions affecting mainly younger and middle aged men characterised by symptoms of pain and discomfort around the anus, scrotum and the area in between.[1] This mainly occurs in men younger than 35 years. Benign Prostatic Hyperplasia (BPH), a non-cancerous growth of the prostate is so common in older men over the age of 60 years causing an enlargement of the prostate. Statistics show that 92% of men from the age of 31 to 40 years do not have symptoms of BPH and this increases with age to only 10% not showing symptoms of BPH from the age of 60 years and above.[2,3] This non-cancerous growth is mainly caused by proliferation of the stroma and epithelia cells of the prostate. However, it is a slow progressing and non-cancerous condition leading to an impediment of the urethra causing difficulty in urination. The treatment goal of BPH has always been to relieve irritative (urgency, frequency and nocturia) and obstructive (weak stream, hesitancy, intermittency and incomplete emptying) symptoms.[4] Prostate Cancer (PC), a slow growing cancer that occurs in the prostate is the second most common malignancy in adult male over the age of 65 worldwide.[4]. This slow growing cancer accounts for 7.1% of all cancers in men with about 1,276,106 new cases annually.[5,6] Though with variations in the statistics among countries and continents.[6] This is a fatal disease which grows slowly and do not spread beyond the prostate, however some are aggressive and spread quickly to other areas of the body.[1] Prostate cancer and Benign Prostatic Hyperplasia whose pathogenesis and progression are due to inflammation are chronic prostatic diseases with a long period of development and progression. The factors minimising cell apoptosis and stimulating proliferation create an imbalance existing
effects. The prostatic diseases could also co-exist with other health conditions, commonly referred to as comorbid.[2] Examples of comorbid diseases include diabetes, high blood pressure, cancer etc. Combinatory therapies also could indirectly have effect on the between prostate cell growth and apoptosis.[7] Prostate cancer and Benign Prostatic Hyperplasia are also found to form in different areas of the prostate with only 20% coexisting in the same zone.8 There is no clear molecular and genetic relationship between PC and BPH and they present 2 distinctive pathogenic pathways. Neither PC nor BPH is a single disease; both are hormonal dependent.[9] However, both PC and BPH if left untreated develop disease progression since they are progressive diseases.

The current method of treatment for both PC and BPH include modification in lifestyle especially avoiding consumption of highly protein animal related diet, smoking cigarettes and drinking alcohol; device and surgical therapies; pharmaceutical and phytotherapeutic therapies.[4,10, 11] These methods of treatment have a lot of adverse effects, however, some prove to be less effective. Phytotherapeutic agents have been most commonly used because of their proven potency, availability, cheap and present few or no adverse effects.

Serenoa serrulata (Hook. F.) Michx (syn. S repens [Bartram]) (*Arecaceae*) is one of the most common phytotherapies used for treatment or management of prostatic diseases. The safety and efficacy of the extracts of *S. serrulata* have been proven both in vitrally and in vivally. This highly rich anti-prostatic plant possesses an inhibitory effect of the 5-α reductase enzyme, anti-androgenic and estrogenic effect.[12] However, the anti-prostatic activity of *S. serrulata* have been proven with mixed reports with some manuscripts reporting that its extracts have no significant therapeutic effects even at high dose.[13]

The used of combination therapies are now days on the rise. Combination therapies are commonly preferred to aid in the reduction of the amount of dose of the drugs used, improving on the therapeutic effect of drugs by improving on the activity of the other, minimising the risk of adverse effects as well as provide synergistic

comorbid conditions thus supporting their potency.[2] The most commonly used combination therapies are between phytotherapies and modern therapy.

Medicinal plants are used in third world countries for management or treatment of various health conditions including cancer because of their availability or being cheap. Some of these medicinal plants have shown their potency either singly or in combination. *S. serrulata* is one of those medicinal plants highly used for prostatic diseases either singly or in combination with other medicinal plants or even with anti-prostatic conventional drugs. However, there are few reports especially on their combinatory use. Therefore, this review synthesised information on *S. serrulata's* botany, phytochemistry, pharmacology as well as it's used in combination with other medicinal plants and anti-prostatic conventional drugs either clinically or non-clinically.

METHODS

Literature Review

The literature was searched from different databases including Medline/PubMed, Cochrane library, Scopus, Proquest library, Embase, EBooks and Google Scholar for relevant records for a period ranging from 1988 to 2021 to identify all published articles on *S. serrulata* regarding treatment of prostatic diseases. The key search terms were *Serenoa serrulata*, *S. repens*, *Saw palmetto*, Prostate cancer treatment with *Serenoa serrulata*, treatment of Benign Prostatic Hyperplasia with *Serenoa serrulata*, phytochemicals of *Serenoa serrulata*, ethno botanical uses of *Serenoa serrulata*, toxicity of *Serenoa serrulata*, pharmacological activities of *Serenoa serrulata*, traditional management and treatment of prostatic diseases using *Serenoa serrulata* and also clinical trials on treatment of prostatic diseases with *Serenoa serrulata*. The retrieved articles were reviewed, synthesised and then quantitatively analysed. The reference list of the retrieved articles was also reviewed and synthesised. The original research articles which reported an investigation of *S. serrulata* of any study design, original published research articles, any time of publication and grey literature (conference papers, reported articles, academic thesis) were included. The articles whose full text were not freely available by the time of search and those without clear information about methodology and study were excluded.

RESULTS

A total of 220 articles were obtained from multiple databases. After a thorough review, a total of 80 articles were excluded because they were not related to the subject matter, 40 articles did not have freely available full text, 35 articles did not have clear research design and methodology and thus 65 were reviewed for this article.

Botany and Description of Serenoa Serrulata.

Serenoa serrulata (Hook.F.) Michx (syn. S repens [Bartram]) (*Arecaceae*) commonly known as *saw palmetto*, *sabal*, America dwarf palm tree, cabbage palm, fan palm, scrub palm is a rhizomatous plant with fan-shaped leaves and fragrant creamy flowers bearing ovoid blue-black fruits. This medicinal plant is native to South-eastern United States and grows between 3 and 6 feet in height, reaching up to 15 feet. This highly rich medicinal plant grows in sandy soil, producing fruits throughout summer.[9] The fruit is bluish-black when fully ripe with a distinct sweet aroma, peculiar with a taste that is slightly soapy and acrid.[9] The classification of *S. serrulata* is shown in ***Table 1***.

TABLE 1: Classification of *Serenoa serrulata* (Hook. F.) Michx.

Family;	***Arecaceae***
Genus;	*Serenoa*
Species;	*S. serrulata* (Michx) G. Nicholson
Scientific name (s);	*Serenoa serrulata* (Michx) G. Nicholson
Synonym (s);	*Brahea serrulata*, *Chamaerops serrulata* Michx, *Corypha repens*, *Sabal serrulata*, *Sabal serrulatum*, *Serenoa repens* (W. Bartram) Small, *Serenoa serrulata* (Michx) G. Nicholson
Common name (s);	American dwarf palm tree, Cabbage palm, Dwarf palmetto, Fan palm, *Fructus Serenoae Repentis*, *Sabal fructus*, *Sabal palm*, *Saw palmetto*, *Saw palmetto berry*, *Scrub palm*, *Scrub palmetto*, *Serenoa*

Habit;	Shrub tree
Habitat;	Flatwoods, Scrub, Swamps, acidic to alkaline sandy soil
Propagation;	Seeds

Ethnobotanical uses of S. serrulata

S. serrulata is used traditionally in several forms as medicine for many ailments, mostly for treating benign enlargement of the prostate.[12] The use of *S. serrulata* can be traced back to the 18th century when it was first introduced into the Western medicine practice for prostate related health conditions and other urologic conditions.[12] It's other uses include; treatment of enlarged prostate, cystitis, gonorrhoea and irritation of the mucous membranes.[12] Apart from its medicinal uses, some communities use the fruits of *S. serrulata* as food for nourishment.[14] The fruits of *S. serrulata* provide it's medicinal properties. These fruits can be used as herbal tea to treat benign enlargement of the prostate, frequent urinary tract infections, enhancing hair growth, reducing cancer cell growth, boosting sexual drive and sperm production in men as well as reducing on the frequent or excessive night urination caused by the inflammation of the bladder or prostate.[15] It's fruits are also commonly used traditionally as treatment for infertility and underdeveloped breasts in women, increasing lactation and mitigating painful menstruation cycles.[9,12]

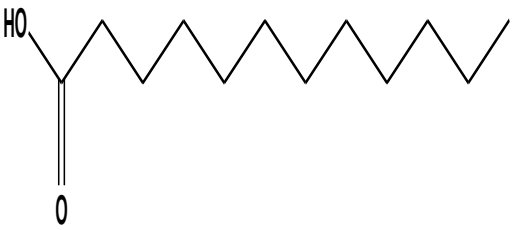
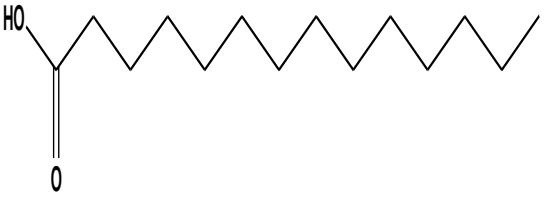
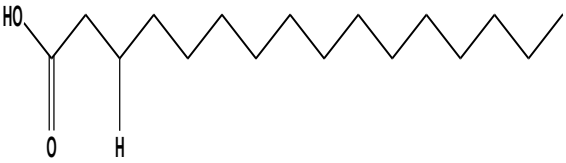
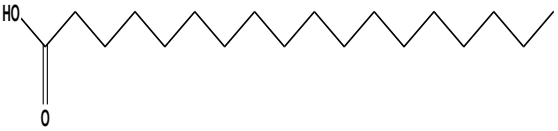
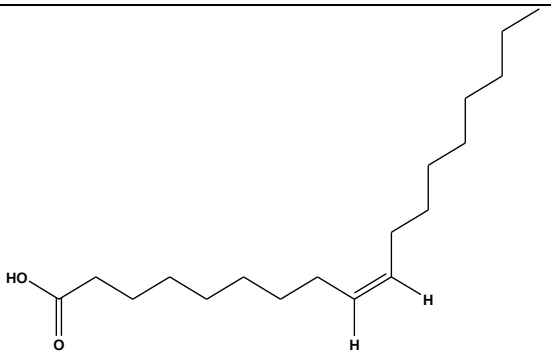
Phytochemicals of Serenoa Serrulata and their activities against Prostatic Diseases

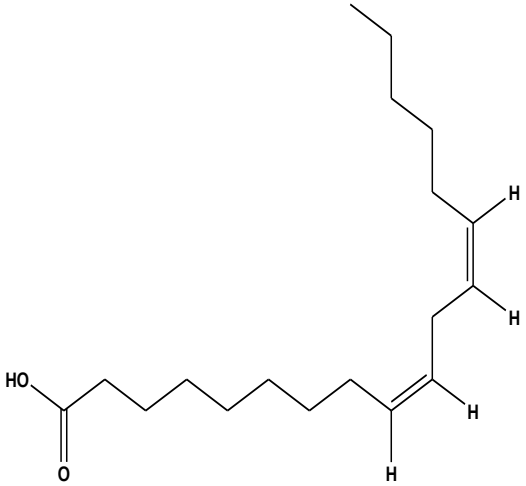
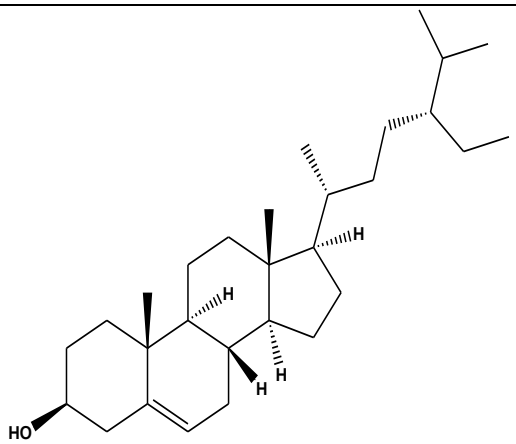
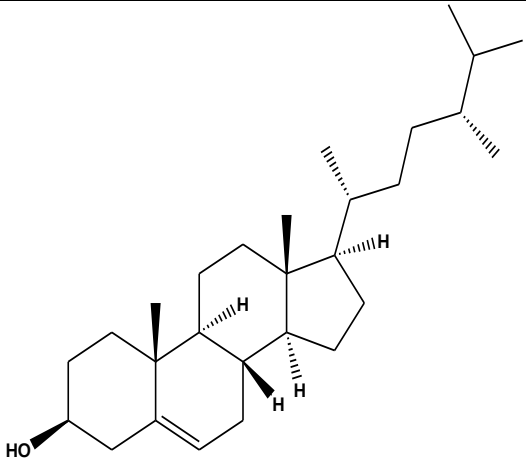
Phytochemicals are biologically active compounds or substances that are produced by plants, the phytochemicals give the plants their therapeutic activities. These chemicals are mainly extracted from the plant material by different solvents depending on the nature of their polarity. Examples of active compounds in the plant extracts include Alkaloids, Fatty acids, Sterols, Steroids, Coumarins, Flavonoids, Anthocyanin, Anthracenoside etc. These phytochemicals have been reported to have anticancer, anti-malarial, anti-bacterial, anti-fungal activities etc. and most of the pharmaceutical drugs in use are derived directly or indirectly from these compounds.

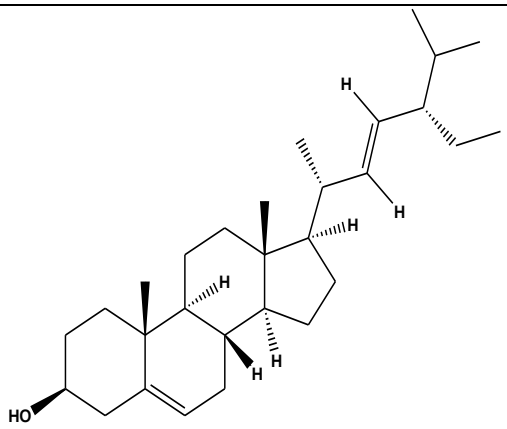
S. serrulata is one of the medicinal plants whose berries have been reported to be rich in a number of phytochemicals as shown in ***Table 2***. Phytochemical screening of *S. serrulata* have shown presence of fatty acids, phytosterols and other bioactive components which together contribute to the pharmacological activities of this medicinal plant.[9,16] The most commonly screened extracts of *Serenoa serrulata* (Hook. F.) Michx are the hexanic, ethanolic and the supercritical fluid carbondioxide.[9,16] Phytochemical screening of *S. serrulata* (Hook. F.) Michx showed that it contains high amounts of free saturated and unsaturated short chained fatty acids and their esters; phytosterols, triglycerides, aliphatic alcohols and various polyprenic acids.[9,16] The potent phytochemicals of *Serenoa serrulata* (Hook. F.) Michx, are best extracted with ethanol 90%, hexane and supercritical carbondioxide.[9] The fatty acids from *S. serrulata* include Lauric acid, oleic acid, Myristic acid and palmitic acid; of which Lauric and oleic acid are the majority and the phytosterols include β-sitosterol, campesterol, stigmasterol and cycloartenol; of which β-sitosterol has the highest content.[9] The fatty acids and phytosterols are collectively responsible for the reduction of the amount of dihydrotestosterone (an active form of testosterone), by blocking conversion of testosterone to dihydrotestosterone and inhibiting the actions of inflammatory substance by suppressing the production of prostaglandins resulting into the prevention of the swelling of the prostate, thus playing an important role in the management and treatment of prostate diseases.[13,17,18] *S. serrulata* is postulated to work by reducing androgenic activity through inhibition of 5-α reductase I & II and inhibition of binding of dihydrotestosterone (DHT) to the cytosolic androgen receptors. *S. serrulata* also has anti-inflammatory activity, anti-proliferative activity and also binds to the receptors existing in the lower urinary tract.[19,20] The fatty acids are known for inhibiting 5-α reductase only while the phytosterols inhibit 5-α reductase, reduces
prostate tumour growth and ameliorate BPH symptoms however, none of the phytochemicals of *S. serrulata* is effective alone. [13,17,21,22]

Interestingly, some conventional anti-prostatic drugs also act by inhibiting conversion of testosterone to dihydrotestosterone through inhibition of 5-alpha reductase but some do not inhibit both type 1 and 2 isoenzymes of 5-alpha reductase.[23] A major undoing is that alpha blockers and 5-alpha reductase inhibitors are associated with major adverse effects like retrograde ejaculation and erectile dysfunction.[24, 25] (***Table 2***).

TABLE 2: Phytochemicals of *S.serrulata* and their activities.

Bioactive component	Group	Structure	Activity	Reference
Laurate (Lauric acid).	saturated medium-chain fatty acid.		-inhibition of isoenzymes (5α-reductase 1 and 2). -inhibition of prostate enlargement. -reduction in prostate weight. -decreases inflammation of the prostate.	[28, 49, 50]
Myristate (myristic acid)	saturated medium-chain fatty acid.		-inhibition of prostate enlargement. -reduction in prostate weight. -decreases inflammation of the prostate.	[13, 49,50]
Palmitate (palmitic acid).	fatty acid		-decreases inflammation of the prostate.	[13]
Stearate (stearic acid).	fatty acid		-decreases inflammation of the prostate.	[13]
Oleate (oleic acid).	fatty acid		-inhibition of 5α- reductase 1. -decreases inflammation of the prostate.	[13,28, 51, 52]

Linoleate (linoleic acid).	fatty acid		-inhibition of isoenzymes (5α-reductase 1 and 2). -decreases inflammation of the prostate.	13, 28, 51, 52,
Beta-Sitosterol.	Phytosterol		-inhibit 5α-reductase. -inhibit prostate cancer cell/growth, BPH symptoms.	9,53,54,55,56
Campesterol	Phytosterol		-inhibit 5α-reductase. -inhibit prostate cancer cell/growth, BPH symptoms.	18,53,54,55,56

Stigmasterol	Phytosterol		-inhibit 5α-reductase. -inhibit prostate cancer cell/growth, BPH symptoms.	[18,53,55,56,57]

Pharmacological activity of *Serenoa serrulata* (Hook. F.) Michx. *Serenoa serrulata* (Hook. F.) Michx have been reported to elicit its anti-prostatic effects through anti-androgenic, anti-inflammatory and pro-apoptotic, anti-edematous and anti-cancer activities.[19,20,26] These activities are attributed to the presence of the free fatty acids and the phytosterols.[9,16,27]

A study by Bayne et al., reported that phytosterols of *S. serrulata* inhibit both forms of 5-alpha reductase type 1 and 2 iso-enzymes[19] resulting in an anti-androgenic effect. Most of the synthetic drugs for prostate cancer like Finasteride and Furosteride inhibit only type 2 isoforms.[28] Finasteride is only a competitive inhibitor of type 2 5-alpha reductase[26] while *S. serrulata* (Hook. F.) Michx, inhibits both forms of 5-alpha reductase (1&2) and as well ensures greater control of the activity of the enzyme in the gland.[19] Dutasteride, a synthetic drug is an inhibitor of both type 1 & 2 5-alpha reductase[28] just like the phytosterol of *S. serrulata* (Hook.F.) Michx. However, *S. serrulata* (Hook. F.) Michx, does not only inhibit type 1& 2 5-alpha reductase, an ant androgenic effect2[6] but also inhibits the binding of dihydrotestosterone (DHT) to the cytosolic androgen receptors. *S. serrulata* (Hook. F.) Michx, does not interfere with the cellular capacity of the prostate to secrete Prostate Specific Antigen (PSA) in vitro and in vivo[19]. This offers far much better therapeutic advantage over the other conventional 5 alpha reductase inhibitors since continuous screening and monitoring of the tumour progression in prostate cancer can be carried out through continuous measurement of PSA levels.

An in vivo study conducted using wistar rats in 2000 found out that the phytosterols of *S. serrulata* inhibits both androgenic and prolactin in lateral prostate hyperplasia.[29] The inhibition of prolactin and growth factor induces cell proliferation. A double blind placebo-controlled clinical study conducted using *S. serrulata* was also found to greatly lower the oestrogen receptors in the nuclear.[30] *S. serrulata* administered orally daily in an in vivo experiment using mouse model produced a significant potent anti-inflammatory activity.[31]

The phytochemicals of this plant just like other anti-prostatic conventional drugs do not interfere with cellular capacity of the prostate in secreting Prostate Specific Antigen (PSA), making it beneficial for continuous screening and monitoring of the tumour progression in prostate cancer by continuous measurement of PSA.[19] The activities exhibited by these phytochemicals support the potential activity of this plant extract in the management and treatment of prostatic diseases.[21, 13, 22, 17]

Summary of Studies Showing Effects of S. Serrulata on Prostatic Diseases

Inhibition of Isoenzymes 1& 2 Alpha Reductase

A study conducted by Iehle, C. et al., in 1995 described the independent expression of the type 1 and 2 isoforms of human 5-α reductase and compared the effects of finasteride, turosteride, 4-MA and lipido-sterol extract of S. repens. The study found out that finasteride and furosteride inhibited type 2 isoforms only but the lipido-sterol extract of S. repens inhibited both type 1 and 2 iso-enzymes.[28]

Inhibition of Prolactin and Growth Factor Induced Cell Proliferation

It has been established that prolactin and androgens influence the growth and development of prostate gland naturally.[29] In a study conducted by Van Coppenolle et al., in 2000 using wistar rats to compare

the effects of lipidosterolic extract of S. repens and finasteride both of which are 5-α reductase inhibitors, the lipidosterolic extract of S. repens was found to inhibit both androgenic and prolactin in lateral prostate hyperplasia while the finasteride only inhibited the effect of androgens on prostate enlargement.[29]

Antiestrogen Effects

A double blind placebo-controlled clinical study conducted by Silverio, F. et al., in 1992 using 35 BPH patients who had never been on any treatment, showed that the estrogen receptors in the nuclear were significantly lowered in groups treated with the extracts of S. repens than those which were not treated with *S. repens*.[32]

Anti-inflammatory effects

In an in vivo experiment conducted by Bernichtein, S. et al., in 1995 using unique pro-inflammatory mouse model of prostate hyperplasia with Permixon- a hexanic lipidosterolic extract of S. repens orally administered daily at a dose of 100mg/kg for 28 days, there was a significant potent anti-inflammatory activity in the group that were given the extract when compared to the group that were not.[31]

Toxicity of Serenoa Serrulata

There are a number of preparations from dried berries of *S. serrulata* in the market. The most commonly available, used and highly investigated remedy, clinically and non-clinically with most published reports on the toxicity profile of *S. serrulata* is Permixon (French Producer Pierre Fabre Medicament).[33] Permixon is a hexane lipidosterolic extract of the berries of *S. serrulata*.[33] The adverse effects of extracts of berries of *S. serrulata* are abdominal pain, diarrheal, nausea, fatigue, headache, rhinitis and decreased libido which are all mild, infrequent and reversible.[21,13, 22, 17] A clinical trial study conducted in 1997 on 132 patients suffering from Benign prostatic hyperplasia to determine the efficacy and safety of 2 dosage forms (160 mg b.i.d and 320 mg o.d) of the extract of *Serenoa* repens concluded that the extracts of the 2 dosage forms were safe and efficacious.[34] Meanwhile in an in vitro study to investigate the hepatotoxicity potential of saw palmetto in rats' liver function, it was reported that the extracts of saw palmetto exhibited no toxic effect on the laboratory animal.[35] Furthermore, an in vivo experiment to assess the tolerability and toxicity of lipidosterolic extract of America dwarf palm *Serenoa* repens in wistar rats concluded that there was no toxicological effect of the preparations in the experimental animals.[33]

Combination of *S. Serrulata* with other Medicinal Plants for the Treatment/Management of Prostatic Diseases

Combination therapy is an important treatment modality in many disease settings including cancer, cardio-vascular disease and infectious diseases.[36] Poly-herbal formulation is a common practice for exploiting the advantage of synergistic interaction for enhanced therapeutic efficacy.[36] Many chronic conditions have been treated with combination therapy for many years based on the phenomenon of resistance.[37] Resistance arises when an organism gains the ability to resist a drug which initially effectively slowed the growth or even killed the target organism. Treatment with a combined therapy reduces the chance of resistance especially if the 2 drugs have different mechanisms of reducing the organism's normal functions.[38] Combining drugs enhance the efficacy, minimises the adverse effects of drugs, improved therapeutic value, dose and toxicity reduction as well as to minimising or delaying the induction of drug resistance. Toxicity reduction and resistance minimisation benefits could also be the outcomes of synergism.[38,36,39] The 2 drug combinations might have effect on either one another or on the organism.

When drugs are combined, there are 3 possible effects: First is they act independently of one another, Secondly they increase each other's effect; this could happen because they affect the body in the same way or because one drug increases the concentration of the other in the body and thirdly, they decrease each other's intended effects; this could occur when one drug blocks or prevents another drug from working (combination-drugs).[36,39]

Phytotherapies comprise of many active constituents which enhance their activity synergistically. The effects of many constituents found in herbal medicinal products and their extracts are mainly explained by the term synergy and polyvalence especially when it is difficult to distinguish the active ingredient.[39] Drug synergy occurs when drugs interact in ways that enhance or magnify one or more effects or side effects of the drugs.[39] Synergy is used in a positive sense, that is, an increase in effect greater than that predicted. However, an unexpected decrease in activity referred to as negative synergy or antagonism may occur particularly in interactions between some modern medicines and herbal products.[39,40] Synergy often occurs when an extract of a plant gives a greater or

safer response than an equivalent dose of the compound considered to be the active one.[41,42] The choice of treatment or management methods of prostatic diseases have always been the use of a combination of therapies to prevent the spread to other places. The treatment modalities are radical prostatectomy for the localised tumours, radical radiotherapy and androgen deprivation therapy for non-confined tumours.[43,44] The presence of comorbidities which are highly prevalent among these patients are also some of the factors for the combination therapies. Comorbidities which contribute to the increase in mortality rates among the prostatic patients need to be managed through combination therapies because monotherapies treat or manage only one condition and yet a factor contributing to the death of the patient could be from the comorbidities.[45]

The rationale for combinatory treatment is to use drugs that work by different mechanism thus decreasing the possibility of building resistance. When drugs with different effects are combined, each drug can be used at its optimal dose without intolerable side effects. A combinatory treatment also reduces disease symptoms and prolongs life. Combination therapy can be between modern therapies, modern therapy with phytotherapy or between phytotherapies only. In this review, the combinatory therapies showed a better synergy, improvement in the quality of life and as well reduction in the adverse effects especially of the conventional drugs. The conventional drugs used in combination with *S. serrulata* in studies reported in this review include Finasteride and Tamsulosin while the medicinal plants reported include Stinging Nettle (*Urtica dioca*), *Zingiber officinalis*, *Echinacea angustifolia* and Pumpkin (*Cucurbita pepo*). The isolated compounds reported include β-sitosterol, Vitamin E, lycopene and Selenium; the extract of pollen grain- Cernitin. Finasteride is an anti-prostatic conventional drug which acts by inhibiting type 2 5-α reductase, a similar mechanism exhibited by *S. serrulata*, however, *S. serrulata* inhibits both type 1 and 2 isoforms of 5-α reductase; a mechanism which complements the other. The summary of studies showing combination between phytotherapies alone and then phytotherapies with conventional drug is shown in ***Table 2***. The combinatory therapy has exhibited high efficacy on prostatitis diseases as compared to monotherapies. This is shown in the ***Table 3***. The synergistic effect shown by the combinations as presented in ***Table 3*** proved to be better than the conventional monotherapy alone.

TABLE 3: Combination of *S. serrulata* with other medicinal plants

Study design	Combination	Prostatic disease	Observations	Conclusion	References
Randomized-controlled - double blind-placebo	-Cernitin (collection of pollens) -Saw palmetto (*S. serrulata* or *S. repens*) -Beta Sitosterol -Vitamin E (antioxidant)	-BPH	- the combination exhibited a decreased in the overall symptoms of BPH like Nocturia and frequency of urination. - the monotherapies exhibited very small change in the PSA measurement, maximal and average urinary flow rates and residual volume which was not significant.	-There was a general improvement in the symptoms of BPH with the combination compared to the monotherapy and the placebo.	58

			-The combination test group had no adverse effect.		
In vivo study	-Saw palmetto (extract and whole berry) -Cernitin	-Prostate growth	-The prostate size Reduced in all the treatment to the same size as the non-castrated rat. -the body weight reduced in all the treatment group too.	-significant reduction in the prostate size in all the treatment. -combination of Saw palmetto and Cernitin influences prostatic hyperplasia through the effects on androgen metabolism.	59
Randomized, double blind, placebo controlled trials clinical study	-Pumpkin seed oil -Saw palmetto oil	-BPH	-There was a little Improvement of Quality of Life in the saw palmetto oil group but much higher in the combination group within a short period of about 6months. -The PSA level was reduced in the saw palmetto oil group after 3 months. -All the group treatment had no improvement in prostate volume. -Maximal urinary flow rate had great improvement in saw palmetto and pumpkin seed oil group.	-Combination of saw palmetto and pumpkin seed oil had an insignificant improvement in all the parameters though its effect was higher symptomatically. -The combination was clinically safe. -Recommends the used of the combination for BPH.	60
Randomized double blinded clinical study	-*Serenoa repens* -Lycopene and selenium -Tamsulosin	-BPH -LUTS	-Much higher significant improvement in the combination therapy. -Increase in Qmax. -Changes in IPSS and Qmax was greater for the combination than	-Combination was more effective than single therapies in improving IPSS and increasing Qmax in patients with LUTS.	61

			for the monotherapies.		
Randomized double blind clinical study	-Tamsulosin (alpha blockers) or Finasteride (5alpha reductase inhibitor) -*Sabal repens* -*Urtica dioca*	-BPH (Nocturia in men with LUTS)	-There was a significant decreased in nocturnal voiding frequency by the plant combinations compared to Placebo and Tamsulosin or Finasteride. -A high decreased in total IPSS with plant combination than with the Placebo.	-The combination had a Significantly higher improvement in all the parameters than the Placebo.	54
Clinical trial	-Tamsulosin -*Serenoa repens*	-BPH	-The combination of Tamsulosin and *S. repens* had a great reduction in IPSS compared to the monotherapies. -The combination also exhibited Significantly higher improvement in the storage symptoms. -There was an insignificant improvement in the Voiding score, LUTS related QoL, Qmax, PVR, PSA and prostate volume by the combination. -The combination however showed some adverse effects like ejaculatory disorders, postural hypotension, dizziness,	-The combination of *Serenoa repens* and Tamsulosin had greater effect than the Tamsulosin alone and as well it reduced the BPH symptoms in patients within 6 to 12 months.	62

			headache, gastrointestinal disorders, rhinitis, fatigue, and Asthenia.		
Randomized double blind multi centre clinical trial	-*Sabal repens* -*Urtica dioca* -*Finasteride*	-Prostate volume	-Both the combined phytotherapies and Finasteride exhibited no statistically significant difference in the Maxima urinary flow. -The combination and Finasteride showed no statistical Improvement in the international prostate symptoms score. -The combination presented better results for voiding symptoms in the patients with prostate than finasteride. -More adverse effects cases were reported by the patients using Finasteride but minor effects reported by the group using plant therapy.	-The plant combination and Finasteride exhibited the same therapeutic effect on the prostate volume however, the phytotherapy had better tolerability than Finasteride with less or no adverse effects compared to Finasteride.	63
In vitro	-*Saw palmetto* -*Astaxanthin*	-BPH -Prostate cancer	-Astaxanthin had a greater inhibition of 5alpha reductase. -Combination had even much higher inhibition of the enzyme. -Reduction in prostatic carcinoma cells by the monotherapies and was much	-much increase in testosterone level by the combination. -the combination therapy was more effective in stopping the growth of cancer cells than the monotherapies.	64

			greater by the inhibition.		
Randomized study	-*Zingiber officinalis* -*Saw palmetto* -*Echinacea angustifolia*	-BPH	-the plant combination had a significant regression of urogenital symptoms in both men and women than each plant extract. -the combination as well exhibited reduction of inflammation in prostatism and pelvic pain.	-there was a high synergy exhibited by the combination compared to the individual plant.	65

DISCUSSION

Prostatic diseases include prostate cancer, prostatitis and benign prostatic hyperplasia. Prostate cancer and Benign Prostatic Hyperplasia are still common condition affecting men especially of older age while prostatitis affect men as young as 35 years mainly due to infections. There are quite a number of treatment options being used and most of them present adverse effects while others are not very effective even at higher doses which are not pleasant to the end user.[46] Medicinal plants have been used for decades for treatment or management of different ailments including prostatic diseases.[47] One of the medicinal plants used for treatment or management of prostatic diseases is *S. serrulata*. Both clinical and non-clinical studies have proven the used of *S. serrulata* either singly or in combination with anti-prostatic conventional drugs or with other medicinal plants.

The phytochemical and the pharmacological results for the investigation of *S. serrulata* as an antiprostatic remedy is in agreement with the ethnobotanical claims as shown *in* ***Tables 1*** and ***2***. The plant toxicity profile is also in agreement with its ethnobotanical claims. This medicinal plant when used in combination is proven to enhance its activity. ***Table 3***, further points out the synergistic effect of the combination of *S. serrulata* with other medicinal plants and even with conventional drug presenting minimal or no adverse effect compared to the conventional drugs Tamsulosin or Finasteride used alone. This study found out that the medicinal plants which are used in combination with *S. serrulata* include; *Urtica dioca, Cucurbita pepo, Zingiber officinalis* and *Echinacea angustifolia* and then the anti-prostatic conventional drugs include; Finasteride and Tamsulosin. This finding could also explain the variations in efficacy reported by some studies during the determination of the anti-prostatic activities of *S. serrulata*.[8] The review also noted that most of these studies were clinical, few were *in vivo* and the review didn't come across any *in vitro* study.

CONCLUSION AND RECOMMENDATION

This review has shown that *S. serrulata* is used as a remedy for different ailments but most commonly used for prostatic diseases with less or no adverse toxic effects. This medicinal plant has also shown a great potential when used as an anti-prostatic remedy when used in combination. *S. serrulata* has vital phytochemicals with promising pharmacological activities which could be developed into well standardised drugs either as a single plant or in their combinations with other medicinal plants. There is however need to investigate further their effects and safety on prostatic conditions when used in combination with other medicinal plants which might not have been mentioned here but have been reported to have anti-prostatic activities.

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