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Research Article

INDIAN HERBS THAT ACT AS 5-ALPHA REDUCTASE INHIBITORS

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ABSTRACT

Traditional medicine has remained a pillar component in healthcare systems of resource poor economies. Drugs like *Prunus africana, Serenoa repens* (Saw palmetto) and *Saxifraga stolonifera* etc.have been used traditionally and in modern medicines in the management of Benign prostatic hyperplasia (BPH) .BPH is an age dependent condition that affects old men. The condition is associated with symptoms like frequency in urination, hesistancy, nocturia, weak urine stream and sexual dysfunction. Thus there is , need for update of the medications of the disease. To avoid these adverse effects People prefer to go for phytotherapy for the management of BPH so this review provides information of herbal drugs which act as 5AR inhibitors, these are the enzymes responsible for converting testosterone to dihydrotestosterone (DHT), which is important for the progression of benign prostatic hyperplasia.

Keywords: Benign prostatic hyperplasia, 5AR inhibitors, Herbal Drugs, Saw palmetto.

INTRODUCTION

 5α -reductases (5AR) are the enzymes responsible for converting testosterone to dihydrotestosterone (DHT), which is important for the progression of benign prostatic hyperplasia (BPH). BPH is a common and progressive condition that could impair one's quality of life and affects men in an agedependent manner; more than 50% of men over the age of 50 and close to 90% of men over 80 years old are affected¹. It is characterized by various lower urinary tract symptoms, including decreased urinary stream, incomplete voiding, urinary frequency and hesitancy². By blocking the enzyme, 5AR inhibitors decrease the serum concentration of DHT, inhibiting prostatic growth³ and decreasing disease progression².

The mechanism of 5α-RI is complex but involves the binding of NADPH to the enzyme followed by the substrate. The $\Delta^{4,5}$ bond is broken and a hydride anion is transferred from NADPH directly to the C-5 carbon on the α face followed by a proton attacking the C-4 carbon on the β face leading to the formation of the product that subsequently leaves the enzyme-NADP⁺ complex. NADP⁺ departs last and the enzyme becomes free for further catalysis cycles. Based on this, the mechanism of inhibition of 5α -R isozymes is divided into three types⁴:

- Competitive with the cofactor (NADPH) and substrate (bi-substrate inhibitors): the inhibitor binds the free enzyme.
- Competitive with the substrate: the inhibitor binds the enzyme-NADPH complex.
- Uncompetitive with the enzyme-NADP⁺ complex: the inhibitor binds the enzyme-NADP⁺ complex after the product leaves⁵.

1.2 Medicinal Use

- Benign prostatic hyperplasia
- Prostate cancer
- Androgenic alopecia in both men and women
- Lower Urinary Tract Symptoms
- 5-aris are also sometimes employed as supplementary antiandrogens in hormone replacement therapy for trans women⁶.

1. Herbal Drugs

Traditional medicine has remained a pillar component in healthcare systems of resource poor economies. Their upsurge in use is dependent in long term clinical experience. A

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growing body of scientific evidence also supports that complementary and alternative health care practices that improves the health and well-being of patients. Drugs like *Prunus africana, Serenoa repens* (Saw palmetto) and *Saxifraga stolonifera* etc.have been used traditionally and in modern medicines in the management of BPH also below mention herbal drugs are used as 5α -reductase inhibitors⁷.

1. Saw Palmetto (Serenoa repens)⁸



Fig. 1: saw palmetto

Saw palmetto is one of the herbs that block DHT and has been studied extensively. Of particular interest to researchers is the presence of a specific plant sterol found in this herb called beta-sitosterol. The anti-androgen effects of this substance are directly related to the inhibition of an enzyme called 5-alpha-reductase type II, which is required by the body to convert testosterone into DHT in the prostate. The July 10, 2010, issue of Advances in Therapy featured an article reporting that low concentrations of a saw palmetto ethanol extract dubbed SPET-085 was as effective at inhibiting 5-alpha-reductase type II as finasteride, the standard prescription drug used to counter DHT conversion9.Research shows that saw palmetto inhibits testosterone from binding to and stimulating prostate cells, which reduces the multiplication of prostatic cells and prostatic enlargement. Other treatments for BPH, alpha blockers and 5-alphareductase inhibitors cause sexual dysfunctions themselves — while saw palmetto is a natural supplement that doesn't have a long list of side effects. That makes it one of the best sources

to increase testosterone naturally and improve prostate health the natural way.

A systematic literature review of 11 studies identified saw palmetto supplements as one of the five commonly used forms of alternative medicine by men with prostate cancer.

Saw palmetto supplements work as 5-alpha reductase inhibitors — meaning they slow down the conversion of testosterone to DHT by blocking the enzyme and preventing its formation. According to research, DHT is responsible for prostate enlargement, which may be a cause of prostate cancer.

Saw palmetto, on the other hand, can also inhibit DHT and help with urinary problems from BPH, such as trouble urinating and leaking urine, plus it regulates your testosterone levels, helps with libido and works as a natural remedy for impotence.Studies have also found that saw palmetto inhibits the growth of prostatic cancer cells and may destroy dangerous cells. A study conducted at the Department of Biochemistry and Molecular Biology in Beijing found that saw palmetto induced growth arrest of prostate cancer LNCaP, DU145 and PC3 cells and downregulated DHT, the hormone that leads to prostate enlargement¹⁰. Saw Palmetto inhibited both isozymes (5 α -reductase 1 and 2) in a noncompetitive manner¹¹⁻¹³ whereas finasteride inhibited only 5α -reductase 2 in a competitive manner¹⁴. Among the many components of Saw palmetto, lauric acid and linoleic acid showed inhibition of both isozymes, oleic acid was active only against 5α -reductase 1 and myristic acid was active only against 5α -reductase 2. However, palmitic acid, stearic acid, esterifies fatty acids, sterols, and alcohols were inactive against both¹⁵.

Saw palmetto inhibited [3H]dihydrotestosterone from binding to its receptor. The affinity of Saw palmetto was higher for cytosol receptors than for nuclear receptors. Competitive interference with the binding of [3H]methyltrienolone to cytosolic androgen receptors was also shown in rat prostate cells¹⁶.



Fig. 2: Mechanisms of pharmacological action of saw palmetto extracts (SPE). They include antiandrogenic effects, such as inhibition of 5α-reductase I and II and inhibition of binding of dihydrotestosterone (DHT) to the cytosolic androgen receptors¹⁷.



Fig. 3: Nettle root

Nettle root (Urtica dioica) is right up there, almost as useful as saw palmetto when it comes to BPH. Nettle root does appear to have some 5ar inhibiting activity, but we also note that it lowers sex hormone binding globulin and aromatase enzyme. These in turn mean that you have more free testosterone and less estrogen. More specifically with the prostate, nettle root has been shown to improve urine flow, reduce frequency, and allow for more complete evacuation¹⁸. Buhner states that "61-83% of 5492 men who used 1200 mg of nettle root daily for 3-4 months saw a reduction in BPH symptoms¹⁹. A combo of nettle root and saw palmetto, in a double-blind placebo-controlled study, found a reduction in symptoms and size of the prostate. It performed as well as the drug finasteride, but with far fewer side effects²⁰.

Clinical studies have confirmed stinging nettle's benefit to men in reducing symptoms of benign prostatic hyperplasia noncancerous (a enlargement of the prostate gland). A concentrated root extract of nettle is sometimes combined with saw palmetto (Serenoa repens) and the bark of the pygeum evergreen tree (Pygeum africanum) to treat the early stages of the disease. The herbal combination helps to increase the urinary volume and maximize the rate of urine flow. German research suggests that active ingredients in the nettle root may prostate reduce swelling. Again, since androgenetic alopecia is caused by the same factors (DHT) as prostatic hyperplasia⁹.

3. Green Tea (Camellia sinensis)⁸



Fig. 4: Green tea

Green tea may also have an important antiandrogen effect because it contains epigallocatechins, which inhibit the 5-alphareductase conversion of normal testosterone into DHT. As previously noted, this antiandrogen mechanism may help to reduce the risk of BPH, acne, and baldness. As yet, no randomized controlled trials of green tea for these androgen dependent conditions have been conducted²¹.

Research indicates that epigallocatechin-3-Gallate, or EGCG, one of the active constituents of green tea, also blocks the formation of DHT. A team of scientists from Harvard Medical School reported in the February 2003 issue of The Journal of Nutrition that green tea significantly reduced DHT and testosterone concentration in the blood. In another study published in The Prostate in 2009, British researchers found that EGCG decreased cell proliferation in prostate cancer cells by inhibiting DHT and promoting apoptosis, or cell death⁹.

4. Black cohosh (Actaea racemosa)^{6,8}



Fig. 5: black cohosh

Black cohosh (Actaea racemosa) is a plant of the buttercup family. Extracts from these plants are thought to possess analgesic, sedative, and antiinflammatory properties. Black cohosh preparations (tinctures or tablets of dried materials) are used to treat symptoms associated with menopause, such as hot flashes, although the efficacy has been questioned²² The inhibitory effects of black cohosh extracts (Cimicifuga syn. Actaea racemosaL.) on the proliferation of human breast cancer cells has been reported recently²³ and Hostsanka. et al²⁴ have examined the plant's effects on prostate cancer, another androgen hormone-dependent, epidemiologically important tumor. In that study, the inhibitory effect of an isopropanolic extract of black cohosh (iCR) on cell growth in androgen-sensitive LNCaP and androgeninsensitive PC-3 and DU 145 prostate cancer cells was investigated.

The authors found that regardless of hormone sensitivity, the growth of prostate cancer cells was significantly and dose-dependently down regulated by iCR. At a concentration between 37.1 and 62.7 μ g/ml, iCR caused 50% cell growth inhibition in all cell lines after 72h. Increases in the levels of the apoptosis-related M30 antigen of approximately 1.8-, 5.9-, and 5.3-fold over untreated controls were observed in black cohosh-treated PC-3, DU 145, and LNCaP cells, respectively, with the induction of apoptosis being dose and time dependent.

Black cohosh extract was therefore shown to kill both androgen-responsive and non-responsive human prostate cancer cells by induction of apoptosis and activation of caspases. This finding suggested that the cells' hormone responsive status was not a major determinant of the response to the iCR, and indicated that the extract may represent a novel therapeutic approach for the treatment of prostate cancer²¹.

5. Pygeum (*Prunus africanum, Pygeum africanum*) /Red stinkwood



Prunus africana is an evergreen tree with shining foliage, greenish or white flowers a height of more than 40 meters and a stem diameter of up to 1 meter²⁵. The species is geographically widespread in African mountains at altitudes above 1500 meters. Prunus africana bark extracts are used to make capsules for benign prostatic hyperplasia a condition common in aging men. Traditionally, the bark is powdered and drunk as a tea for inflammation, genito-urinary complaints, kidney disease, malaria, allergies, fever and stomachache. A patent for use of the bark extracts for the treatment of benign prostate hyperplasia was issued in 1966²⁶ Initially, the therapeutic effects of *Prunus africana* were attributed to ßsitosterol, and its glycoside and to ndocosanol²⁷. This finding is unlikely to be true given the low amounts of n-docosanol in Prunus africana extracts and high levels of triterpenes and sterols²⁸. The therapeutic effects of *Prunus* africana bark extracts are now believed to be as a result of a pharmacological combination whereby several compounds act synergistically thus counteracting the functional and biochemical changes that characterize BPH²⁶. The pharmacologically active compounds in the bark extract include pentacyclic triterpenes, phytosterols and ferulic acid esters of long chain unsaturated fatty acids. Two new compounds have been identified: 4-O-ß-D-glucopyranosyl-(7,8)-dimethoxyisolariciresinol²⁹ and 24-Otrans-ferulyl-2", 3"-dihydroxy-urs-12-en-28-oic acid³⁰.

6. Black pepper (Piper nigrum)



Fig. 7: Black pepper

Previously we reported that Piper nigrum leaf extract showed a potent stimulation effect on melanogenesis and that (-)-cubebin (1) and (-)-3,4-dimethoxy-3,4-desmethylenedioxycubebin² were isolated as active constituents. As a part of our continuous studies on Piper species for the development of cosmetic hair-care agents, testosterone 5alpha-reductase inhibitory activity of aqueous ethanolic extracts obtained from several different parts of six Piper species, namely Piper nigrum, P. methysticum, P. betle, P. kadsura, P. longum, and P. cubeba, were examined. Among them, the extracts of P. nigrum leaf, P. nigrum fruit and P. cubeba fruit showed potent inhibitory activity³¹.

7. Reishi Mushroom (Ganoderma lucidum)



Fig. 8: Reishi mushroom

Ganoderma Lucidum 5-alpha possesses reductase inhibitors, able to attenuate the conversion of testosterone to dihvdrotestosterone (DHT)32 Reishi was measured, along with 18 other medicinal and edible mushrooms including lion's mane, shiitake, white button, oyster, maitake and others. This was to investigate possible treating benign properties in prostatic hyperplasia (BPH) and prostate cancer.



Fig. 9: 5-alpha reductase inhibitory activity(%)

In castrated rats it was shown to significantly inhibit the testosterone-induced growth of the ventral prostate. This was done both with methanol and ethanol extracts, which functioned virtually the same³³. In this study they stated:

"These results suggest that the suppression effect of prostatic growth by Ganoderma lucidum might come in part from its ability to act as an inhibitor of 5alpha-reductase."

Much research was later done to find what constituents in reishi specifically were responsible for this action.

The components that appear to exert this action are thought to be in the triterpenoid fraction, most specifically ganoderols B and F. This is important in that this is pulled out more in alcohol (ethanol) extractions than water extractions³⁴.

While significant, it is weak 5alpha-reductase inhibitory activity and binding to androgen receptors. Ganoderol B also showed an ability to down-regulate androgen receptor activity and prostate specific antigen (PSA)³⁵.

Based on this research, a human study was launched. A total of 88 men with lower urinary tract symptoms were split into a reishi extract (6 mg once per day) group and those taking a placebo for twelve weeks of treatment. In the end the reishi group was found to have improved the men's International Prostate Symptom Score, without any significant side effects. This was done without altering testosterone levels³⁶.

8. Soya (Glycine max)



Fig. 10: Soyabeen

Soy, a member of the pea family, has been a fixture in Asian diets for thousands of years, according to the National Center for Complementary and Alternative Medicine, or NCCAM. High-protein seeds from the soy plant contain estrogen-like compounds called isoflavones -- and according to Dr. Ray Sahelian, soy also contains a molecule that prohibits the formation of DHT, which is thought to benefit prostate cancer. Preventive Medicine and Nutrition reports that an analysis of 14 studies published in the "American Journal of Clinical Nutrition" determined that soy reduced prostate cancer by as much as 26 percent⁹.

9. Curcumin (*Curcuma longa*)



Fig. 11: curcumin

It is known that curcumin behaves as a natural 5- α reductase (5AR) inhibitor, and this activity was exploited in a multicenter, randomized, double-blind, placebo-controlled study which tested the efficacy of 5% hexane extract of Curcuma aeruginosa when added to 5% minoxidil, the combination inducing slowed hair loss and increased hair growth³⁷. Curcumin may also possess inhibitory actions against 5-alpha reductase. the enzyme that converts testosterone into the more potent androgen DHT. The IC₅₀value is reportedly between5-10uM³⁸. Protective effects on the testes have also been noted with curcumin in regards to alcohol, where curcumin (80mg/kg bodyweight) was able to preserve testicle structure and testosterone levels despite alcohol consumption,³⁹ most likely though preventing the oxidation of ethanol to acetylaldehyde.[40] Other compounds that damage the testicles and reduce testosterone, but are protected against by curcumin, include excessive chromium levels⁴¹ and cadmium⁴².

10. Pumpkin seeds



Fig. 12: pumpkin seed

Eating raw pumpkin seeds is an old-fashioned remedy for the prevention of benign prostatic hyperplasia. In Europe, the German E Commission, a regulatory agency similar to the U.S. Federal Drug Administration, has approved the use of pumpkin seed and pumpkin seed oil for the treatment of prostate disorders. According to the "Physicians' Desk Reference for Herbal Medicines," the DHT-blocking effects of pumpkin seed stem from the presence of unusual amino acids such as cucurbitin, as well as several plant steroids, particularly delta-7sterols⁹.

11.Giant Dodder (Cucuta reflexa)



Fig. 13: giant dodder

According to a study published in the Sept. 7, 2008, issue of the Journal of Cosmetic Dermatology, this botanical also blocks DHT by inhibiting 5-alpha-reductase type II, at least in cultured skin cells. The study authors reported that DHT conversion was prevented when giant dodder extract was added to culture dishes containing skin cells taken from mice with testosterone-induced alopecia⁹.

Giant Dodder is one of the most effective natural DHT blockers. the most common herbs used to inhibit DHT production are green tea, saw palmetto, pumpkin seed, and giant dodder. Giant Dodder is an herb that had been used in the ancient Indian system Ayurveda to fight hair loss. Giant Dodder contains anti-androgen properties. It was found Giant Dodder contains compounds that are able to inhibit 5-alpha-reductase type II³⁷.

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