Urinary Tract Infections & Treatment

Chapter 3

5-Alpha reductase inhibitors in the management of benign prostatic hyperplasia : A rationale

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1. Introduction

Benign Prostatic hyperplasia and its clinical manifestation as lower urinary tract symptoms is a major health concern for aging men. Prevalence increases with age, affecting about 60% of men aged over 50 years, and 80% by the age of 80 years. Nearly all men will develop microscopic BPH by the age of 90 [1]. Despite the high prevalence of BPH in aged men population, the disease pathogenesis is far from complete understanding. It is the non-malignant enlargement of the prostate gland caused by increase in the number of stromal and epithelial cells, resulting in obstruction of the proximal urethra, thus causes urinary flow disturbances. Although many men with mild to moderate symptoms do well without therapy, others have gradually increasing symptoms and require medical therapy or surgery. BPH is a rarely fatal but if left untreated, chronic obstructions can lead to the back up of urine into the ureters and compromises kidney function, thus serious life threatening complications such as acute urinary retention may arises [2].

2. Prostate gland: An androgen dependent organ

The prostate is a walnut–sized gland, located between the bladder and the rectum and forms part of the male reproductive system. It is a heterogeneous organ consisting of central peripheral and transition zone and is composed of three different types of cells: glandular epithelial cells, smooth muscle cells and stromal cells (Figure 1). The area of the prostate that wraps around the urethra is called the transition zone [3].
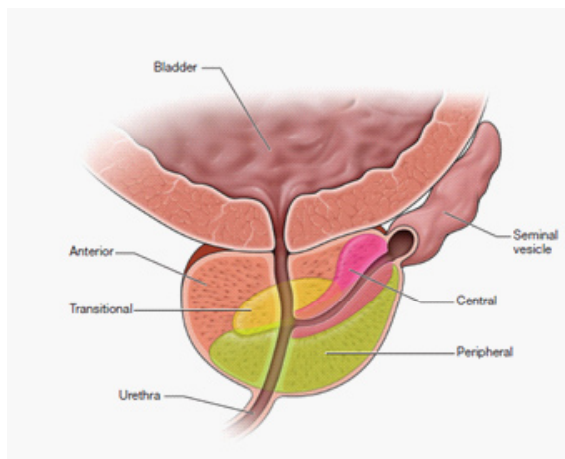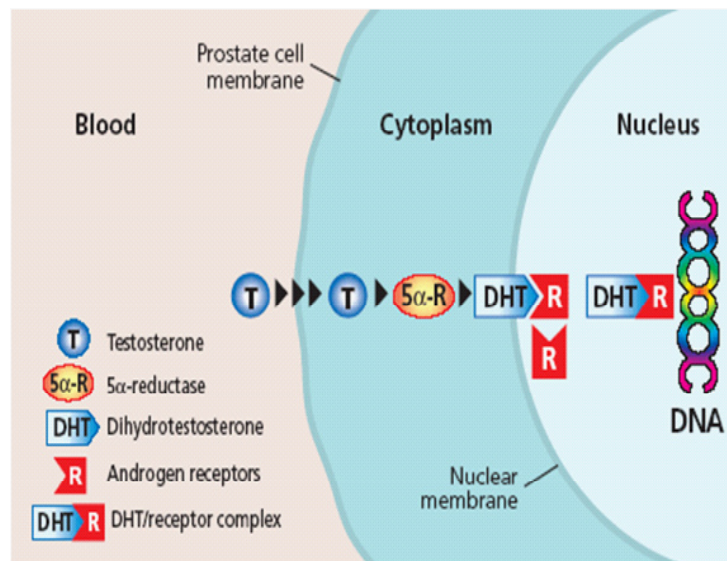
Figure 1

The prostate undergoes many changes during the course of man's life. At the time of birth, prostate is about the size of a pea and grows only slightly until puberty, then it begins to enlarge rapidly attaining normal adult size and shape. Normal growth, development and maintenance of the prostate is dependent on the testicular androgens. Testicular androgen production is controlled by the hypothalamus and the pituitary gland (Figure 2) [4].
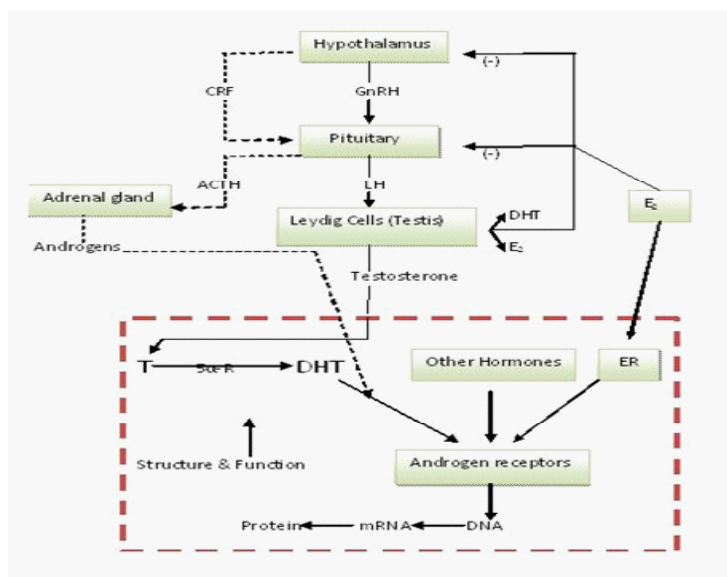
Figure 2

More than 98% of all testosterone in the prostate is of testicular origin and others 5-10% is being produced by adrenal gland. Testosterone (T) is a major androgen in adult male and its bioavailability is linked to the prostate development, differentiation. Serum T level rises dramatically in males between the 10-20 years of age and pronounced exponential growth of the prostate is controlled by the balanced agonist and antagonist abililties of androgens to stimulate cell proliferation and to inhibit the rate of cell death in prostate tissue. After the age of 20 years, and under the continuing presence of T, the healthy prostate achieves a steady state of self renewal and maintenance [5].

Within the prostate, the unbound T diffuses into prostate cell, where most of it is converted to dihydrotestosterone (DHT) by the NADPH dependent enzyme 5α-reductase. In prostate dihydrotestosterone binds to cytosol androgen receptor protein (AR) and DHT-AR complex enters the nucleus, where it stimulates the RNA synthesis after interacting with DNA binding sites (Figure 3) [6].
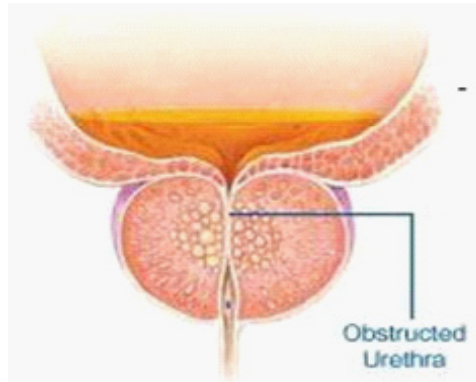

Figure 3

T in serum has approximately 10 times the concentration of DHT, but in the prostate gland, the ratio is more or less reverse with lesser binding affinity to the androgen receptor than that of DHT. The physiological role of T and DHT is quite different. In the embryo, T stimulates the transformation of Wollffian ducts in epididymis, differential ducts and seminal vesicle and activates the expression of 5α-reductase with the subsequent production of DHT. DHT which in turn is determinant for the sexual differentiation of male foetus organ with the formation of external genitilia, urethera and prostate in the embryo. After the puberty, T determines the modification of external genitilia, increase of muscle mass, deeping of voice, spermatogenesis, sexual potency and male sexual behavior in males and the DHT formation is related with the increase of body hair, facial hair and the enlargement of prostate [7]. Thus DHT remains at high levels in the prostate through out life, without the age related decline seen in circulating testosterone. It has been well postulated by Burckovsky and Wilson that testosterone acted as prohormone and dihydrotestosterone was the main active hormone in androgen sensitive tissue [8].

3. Benign prostatic hyperplasia

The gland generally remains stable until about the mid forties. In males over the age of 50, the prostate begins to enlarge gaining through a process of multiplication called benign prostatic hyperplasia. The prevalence of BPH increases with increasing age affecting up to 40% of men after age 60, and nearly all men will develop microscopic BPH by the age of 90 [1]. BPH is characterized by increase in both glandular and fibromuscular tissue, with periurethral and transition zones of the prostate. BPH is considered a stromal disease since the ratio

of stroma to epithelium increase from 2:1 to in normal prostate to 5:1 in BPH. Initial BPH manifests as microscopic nodules in them, and then progressive nodular proliferation leads to bladder outlet obstructions or Lower urinary tract symptoms (LUTS) [9]. In many cases, such symptoms occur when the dense capsule surrounding the enlarging prostate prevents it from further expansion outward, forcing the prostate to press against the urethra, thus partially blocking urine flow (Figure 4).

Figure 4

This obstruction, in turn, causes bladder irritation and contraction, even for small amount of urine. Eventually the bladder weakens and does not completely empty through urination. Benign prostatic hyperplasia can affect urination in a number of ways. Symptoms are often classified as either obstructive or irritative (Figure 5) [10].
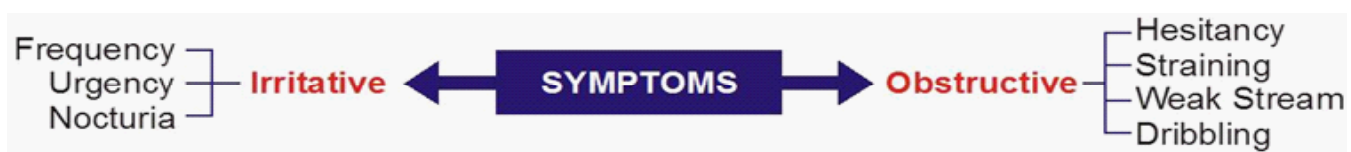
Figure 5

Acute urinary retention, kidney failure and bladder stones, some of the serious complications may be precipitated by prolonged attempts to retain urine. BPH may also be described as quality of life disorder, affecting man's ability to initiate or terminate urine flow stream (the symptoms interfere with the normal activities) and reduces the feeling of well being [2].

4. Management

The causes of benign prostatic hyperplasia are not fully known, but the overgrowth which occurs in both smooth muscle tissue and glandular epithelial tissue, is attributed to number of different causes: aging, late activation of cell growth, genetic factors and hormonal changes. The management of symptomatic BPH has changed significantly over the last decade in response to the availability of number of therapeutic approaches to BPH. The specific approach used to treat BPH depends upon number of factors like age, prostrate size, weight, prostate specific antigen level and severity of the symptoms [Figure 2] [11,12].

The options are:

- A wait and watch approach (watchful waiting)
- Surgical treatment
- Phytotherapy
- Pharmacological treatment

4.1 Watchful waiting

Watchful waiting is suitable for men with mild to moderate uncomplicated LUTS (causing no serious health threat) or with low levels of bothersome symptoms. It is generally considered as the first tier in the therapeutic cascade. Regular check up is recommended along with continual education and conditions will progress to AUC and complications such as renal insufficiency and stones, if left untreated. Further optimization can be achieved by including certain lifestyle changes as recommended in EAU guidelines [13-15].

4.2 Surgical treatment

Surgical interventions are recommended for patients with bothersome LUTS, patients refractory to other medical management and for those who have developed AUR or other BPH related complications like renal insufficiency, recurrent urinary tract infections (UTI's), persistent gross hematuria [16].

In early 1900s, the gold standard for the surgical treatment was achieved by removal of obstructing tissue i.e. open prostatectomy [17], which was later on replaced by trans uretheral resection of prostate (TURP). Significant improvement in LUTS has been observed by resecting an average gland weighing around 30g. Though urologist compare the other therapeutic measures with surgical hallmark i.e TURP, but it carry the risks of excessive bleeding and longer hospital stay [18]. Another less invasive technique Transuretheral Incision of Prostate (TUIP) with similar improvements in symptoms is recommended for prostate gland weighing <25g, but its long term effectiveness is yet to be determined [19]. Transurethral vaporisation (TUVP), an electrosurgical modification of the TURP and TUIP technique is reserved particularly for patients with bleeding disorders and a small prostate [20].

Low level radiofrequency (microwave) i.e. low range transurethral microwave therapy (TUMT) found applications in the management of BPH by by raising the temperature of prostate cells thus specific necrosis of obstructive tissue without affecting normal cells [17,21]. Another simple, safe and relatively inexpensive technique to deliver high frequency radio waves to produce localized necrotic lesions in hyperplastic tissue of small sized gland is Transurethral needle ablation (TUNA). Its a method of choice over TURP in younger men wishing to preserve sexual function, as it poses a low or no risk for incontinence and impotence [22,23].

Laser vaporization or prostectomy, uses four types of lasers, namely neodymium: yttrium-aluminium-garnet (Nd: YAG) laser, potassium titanyl phosphate (KTP) diode laser and holmium YAG laser (Ho:YAG), capable to generates light at different wavelength that causes irreversible cellular damage, followed by their coagulation necrosis and ultimately vaporization of tissues. It has been found to be safe and effective technique with significant improvement in urinary flow rates and symptoms, and has become increasingly widespread form of MIT to treat LUTS. Short operative time, minimal blood loss and fluid absorption, decrease hospital stay, impotence rates and bladder neck contractures are few of the advantages of laser prostatectomy over the TURP and other conventional techniques [24-26]. And evolution in holium laser prostatectomy i.e. Holmium laser enucleating of the prostate (HoLEP) with the potential to be useful for all sizes of the prostate at considerable faster rate than TURP with less side effects is finding its ways as a new gold standard for treatment of BPH.

The primary goal of the treatment for BPH is to improve urinary flow and to reduce symptoms and use of the herbal products with fewer side effects has been found to be the reasonable approach for many men with patients.

4.3 Phytotherapy

Drugs derived from plants have a long tradition in the treatment of BPH and was first described in Egypt in the 15th century BC. Phytotherapeutic products are the extracts derived from the roots, seeds, bark, or fruits of the various plants used. The use of plant-derived compounds with protective or disease-preventive properties for urinary symptoms with BPH has gained widespread interest, probably due to perceived reduction in side effects, and contribution of additional factors that they are natural products, thus presumed to be safe, easy to obtain (no prescription necessary), avoid prostate surgery and their long term usage can prevent PCa [27,28].

Table 1 present the list of common phytotherapies for BPH, African plum (Pygeum africanum), rye pollen (Secale cereale), purple cone flower (Echinacea purpurea), pumpkin seeds (Cucurbita pepo), saw palmetto berry extract (Serenoa repens), South African star grass (Hypoxis rooperi), and stinging nettle (Urtica dioica) etc [29,30]. The proposed active components of these preparations include fatty acids, flavonoids, lectins , phytosterols, plant oils, phytoestrogens, terpenoids, and polysaccharides etc. [31]; however, the mechanisms of action of these agents are in general, poorly understood. Not surprisingly, they are purported to be similar to those of available pharmacotherapies, although this similarity has not been clearly demonstrated.

Table 1

Plant	Common Name	Main chemical constituents
Aframomum melegueta	Grains of paradise Alligator pepper	Alkaloids, Glycosides, Sterols, Tannins, Flavonoids, Resins
Agathosma betulina	Buchu	Volatile oils, Flavonoids
Brassica rapa	Field mustard	Polyphenolic compounds, Hydroxycinnamic Derivatives, Flavonols
camellia sinensis	Green tea	catechins, flavonols
Clinicifugar racemosa	Black cohosh, Black snake root, Fairy candle	Triterpine glycosides, polyphenols, Protocatechuic acids
Cocos nucifera	Coconut oil	Lauric acid, Myristic acid
Cucurbita pepo	Pumpkin seed	Alpha-tocoferols, β-sitosterols
Echinacea purpurea	Purple cone flower	Phytosterols, Phenolic compounds Polysaccharides, Caffeic acid derivatives
Epilobium parviflorum	Willow herb	Macrocyclic Tannins, Sterols, Triterpenes
Ganoderma lucidum	Shelf mushroom, Bracket fungi	Triterpenoids, Polysaccharides
Hypoxis rooperi	South African star grass	Rooperol, Sterolin, Monoterpene glycosides, Hypoxoside, β-sitosterol
Lycopersicum esculentum	Tomato	Lycopene(acyclic carotenoid)
Opuntia ficus indica	Cactus pear, Spineless cactus	Betacyanins(Betanin)
Piper nigrum	Black pepper	Piperine, Palmitic acid
Pinus	Pine tree	Abietic acid, Neobietic acid, Pimaric acid
Phelloden dron	Cork tree	Phytoestrogens
Polygonum multiflorum	Knotweed, knotgrass	Emodin, alizarin, Stillbene glycosides
Pygeum africanum	Red stinkwood	Sitosterols, Pentacyclic triterpenes, oleanotic acid, Ursolic acid
Roystonea regia	Cubal royal palm	Oleic acid, Lauric acid, Palmitic acid, Myristic acid
Rehmannia glutinosa	Chinese foxglove	Iridoids, Norcarotenoids, Phenethyl alcohol, Glycosides, Cyclopentanoid monoterpenes
Serenoa repens	Saw palmetto	Sitosterols, Stigmasterols, Lupeol, Lupenone

Table 2

S. No	List of various possible/proposed mechanisms of actions of different phytochemicals useful in treatment of BPH
1	Inhibition of 5α-reductase
2	Anti-inflammatory
3	Interference with growth factors
4	antiandrogenic
5	estrogenic
6	Inhibition of aromatase
7	Decrease sex hormone-binding globulin
8	Alteration of cholesterol mechanism
9	Action on α-adrenergic receptors
10	Free radical scavenger
11	Alteration of lipid peroxidation
12	Modulation of prolaction-induced prostatic growth
13	Protection bladder and detrusor function

These purported mechanisms of action include aromatase, or growth factors; antiandrogenic/antiestrogenic, antiinflammatory, or antiedematous effects; protection of detrusor function or preservation of detrusor compliance; decrease of sex hormone-binding globulin; effects as free radical scavengers; reduction of urethral resistance; alpha-adrenergic receptor antagonism and inhibition of 5-alpha-reductase, as shown in Table 2 [31].

In different regions and culture combination products (plant extracts) in addition to mono preparations (single plant only) of herbal plants with an attempt to provide enhanced efficacy, to improve marketability, are also available. Some of these includes Himplasia Chinese Zi-Shen pill (ZSPE), PC-SPES, Prostagutt forte, Bodyprost, Eviprostat, Prostate EZE Max [32,33]. When used in combination, due to presence of multiple components in the herbal products, the effects arising from herb-herb or herb-drug interactions are often unpredictable and complicated, but the most desirable or intended interactions are the one which results in additional therapeutic benefit.

Though the phytotherapies have a long history of use and availability of these products in health food stores especially in European and Asian cultures, traditional pharmacies, and super-as well as at numerous web sites on the internet has contributed to their usage and reflected the demand for these phytotherapeutic agents. But the US health care professionals as well as the Food and Drug Administration (FDA) are little reluctant to advocate their use, primarily because their purported efficacy and safety have not been substantiated by randomized, double-blind, placebo-controlled studies. Most of the studies are open-label, retrospective studies with no placebo control or poorly conducted placebo-controlled studies with in-

conclusive and often conflicting data. Further there are no standards regarding composition of available products, their dosage i.e., the amount and quality of active ingredients varies greatly among manufacturers and sometimes among batches of a product from the same manufacturer. Also most of the preclinical studies have been performed in vitro with supratherapeutic doses and therefore do not accurately reflect biological activity [34].

5. 5α-Reductase inhibitors (androgen deprivation therapy): A rationale

Widely accepted hypothesis male hormones (Androgens)/ Dihydrotestosterone (DHT) hypothesis postulates that BPH occurs following an age related changes in prostate androgen metabolism which favours the accumulation of DHT. DHT stimulates cell growth in the tissues that lines the prostate gland and a major cause of the rapid prostate enlargement. Further role of dihydrotestosterone was discovered through male pseudohermaphroditism. In this genetic disorder the biochemical cause is complete or partial 5α-reductase deficiency, accompanied by low level of DHT, produces several of feature at critical juncture in foetal and postnatal development. Male with this condition show ambiguous external genitilia at-birth, often raised as girls, little facial hairs as adults, no temporal receding hairline, small prostate no acne and normal libido. Female with 5α-reductase deficiency appears to have no clinical symptoms. On the other hand formation of dihydrotestosterone is also related with development of several endocrine diseases such as male pattern baldness, acne, alopecia in men, hirusitism in women, prostatic carcinoma and benign prostatic hyperplasia. The concentration of dihydrotestosterone is 2.5 fold higher than in normal prostate [35].

5α-Reductase is a membrane bound enzyme responsible for the conversion of testicular testosterone into dihydrotestosterone. Thus 5α-reductase dictates the cellular availability of dihydrotestosterone to prostatic epithelial cells and consequently modulate its growth (Figure 6).
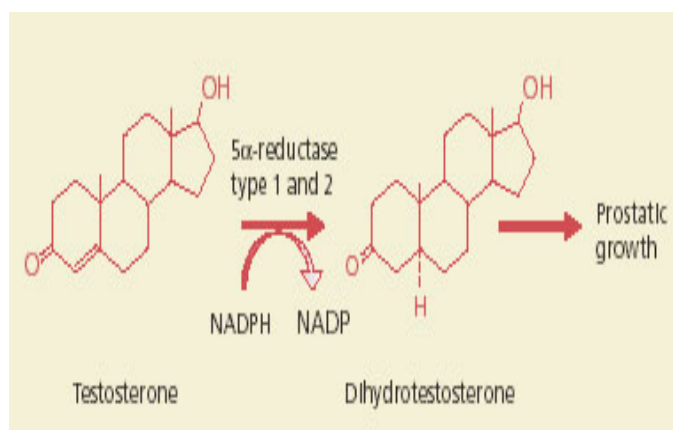
Figure 6

Therefore, inhibitors of androgen action by 5α-reductase is a logical treatment of 5 α-reductase activity disorder i.e. benign prostatic hyperplasia. These agents suppress the dihydrotestosterone concentration by blocking the enzyme, resulting in shrinkage in the size of

prostate, increased peak urinary flow rates and ultimately providing relief from the symptoms related to the static mechanical obstruction caused by BPH. Further, the rationale for use of 5 α-reductase inhibitors is rooted in the observation that these are more specific to DHT androgens action without affecting / lowering testosterone level, thus capable of decreasing long term side effect of castration due to loss of testosterone without compromising the efficacy of hormonal therapy [36].

6. Isozyme of 5α-reductase

Two isozymes of 5α-reductase (5α-reductase type 1 and 5α-reductase type 2) have been cloned, expressed and characterized based on differences in their chromosomal localization, tissue expression pattern and biochemical properties (Table 1). The type 2 isozyme is found predominant in the prostate, genital skin, seminal vesicle, epididymis and liver and have been found to be essential for differentiation of male external genitilia during foetal life, as its deficiency in gene leads to the male pseudohermaphroditisms [37].

Table 1: Comparison of biochemical properties of 5α-reductase isozymes

	Type 1	Type 2
Gene structure	5 exons, 5 introns	5 exons, 4 introns
Gene, chromosome location	SRD5A1, 5p15	SRD5A2, 2p23
Size	259 amino acids, Mr=29, 462	254 amino acids, Mr=28, 398
Tissue distribution	Liver, nongenital skin, prostate, brain	Prostate, epididymis, seminal vesicle, genital skin, uterus, liver, breast, hair follicle, placenta, brain
pH optima	Neutral to basic	Acidic or neutral
Prostate level	Low	High
Substrate (T) affinity	Km = 1-5 μM	Km = 0.004-1 μM
Activity in 5α-reducatse deficiency	Normal	Mutated

The type 1 is not the major species expressed in the prostate and exhibit micromolar affinities for steroidal substrate i.e. testosterone. These two isoforms have optimal activity at different pH range as type 1 is active at alkaline pH of 8.5 while type 2 is active at pH 4.7- 5.5.
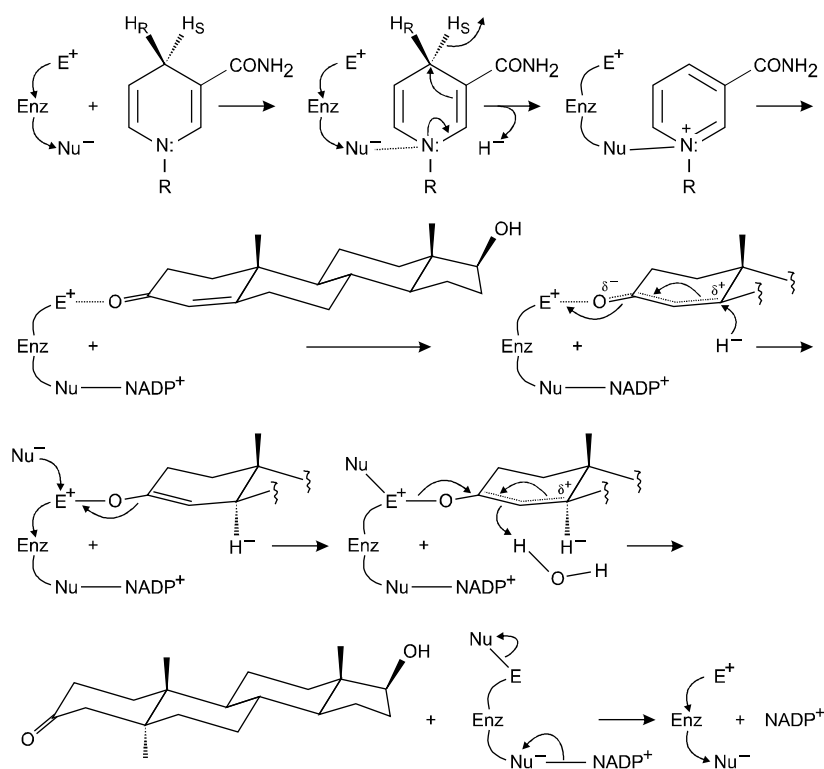
7. Mechanism of action of 5α-reductase

Steroidal 5α-reductase catalyzes the irreversible conversion of 4-en-3-oxo-steroid (testosterone) to the corresponding 5α-H-3-oxo-steroid (dihydrotestosterone and the chemical and kinetic mechanisms of this conversion have been investigated.

7.1 Chemical mechanism

The proposed chemical mechanism of T reduction to DHT by 5α-reductase catalysis (Figure 7), based on the known regio and stereoselectivity of the reduction, involves the formation of binary complex between the enzyme and NADPH, followed by formation of ternary complex with the substrate [37].

Once this complex is formed, the activation of the enone system by a strong interaction with an electrophilic residue (E^+ = proton, positively charged group, proton donor) present in the active site give the delocalized carbocation which is reduced selectively at C-5, on the α-face, by a direct hydride transfer from NADPH, leading to the formation of the enolate of DHT . This intermediate, which is presumably coordinated with $NADP^+$ on the α- face, is attacked by a proton on the β -face at C-4 giving the ternary complex E-$NADP^+$–DHT. Then the departure of DHT gives the binary $NADP^+$-enzyme complex and finally the release of $NADP^+$ leaves the enzyme free for further catalytic cycles.

Figure 7: Chemical Mechanism of action of 5α-Reductase.

7.2 Kinetic mechanism

The kinetic mechanism of T reduction is presented in the Figure 8. It involves the formation of complex between enzyme and NADPH, followed by complex with substarte testosterone [38].
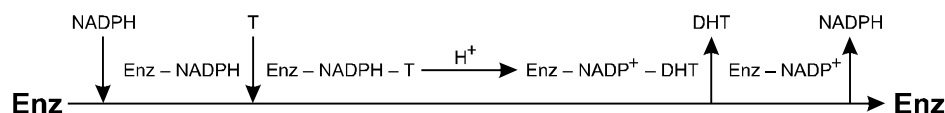
Figure 8

8. Classification of 5α-reductase inhibitors

The control of the biological action of single steroid dihydrotestosterone, through the inhibition of specific enzyme 5α-reductase involved in its synthesis and metabolism, without significant change in the overall profile of other hormone (T) has been a major theme in the design of 5α-reductase inhibitors, mimicking the electronic and steric properties of the enolate. The identification of two isozymes of 5α-reductase, their relative role in physiological and pathological developments of benign prostatic hyperplasia has opened the door for more specific and selective inhibitors of this enzyme. Broadly 5α-reductase inhibitors can be divided into two major groups a) Transition state analogues b) Mechanism based inhibitors [39].

8.1 Transition state analogues

Based on chemical mechanism of 5α-reductase, two possible transition states (Figure 9) have been postulated. The 'substrate like' transition state in which the C-5 has not yet changed it sp²-hybridization where the structure of C-3, C-4, and C-5 are similar to those of intermediate carbonation, and the 'product like' TS in which C-5 has assumed, the final sp³ hybridization and structure of C-3, C-4 and C-5 are similar to those of enol form of DHT .
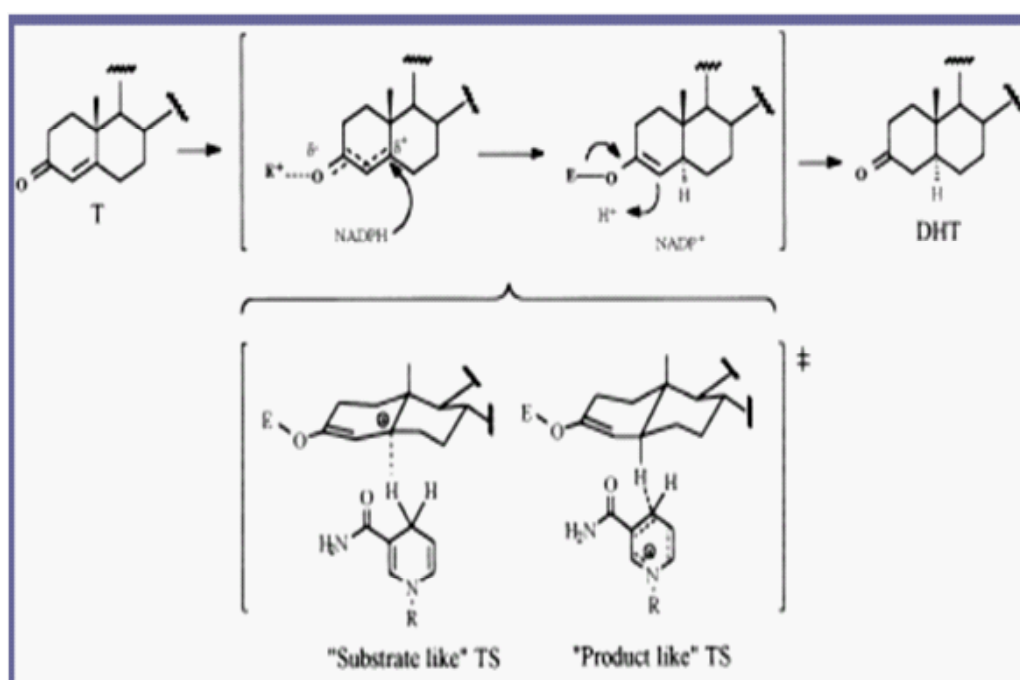

Figure 9

The concept of transition state analogue states that the enzyme binding, and so inhibition could be greater for molecules being mimic of the transition of the enzymatic process. Generally both these type of inhibitors are competitive versus to testosterone.

8.2 Mechanism based analogues

According to the kinetic mechanism of testosterone reduction to dihydrotestosterone, three different types of inhibitors could be conceived:

a)   Type A : Inhibitors compete with cofactor NADPH and the substrate testosterone i.e. bisubstrate.

b)   Type B : Compounds that bind reversibly to NADPH-enzyme complex by competitive with natural substrate testosterone i.e. competitive inhibitors and fail to turn over rapidly.

c)   Type C : Inhibitor fitting the enzyme- NADP complex should be uncompetitive versus the substrates.

Hundreds of steroidal and non-steroidal inhibitors ranging from classical, reversible and irreversible inhibitors, and transition state analogues to mechanism-based analogues have been synthesized during last two decades. The azasteroid series first disclosed by Merck in early 1980's to mimic the putative enzyme bound enolate intermediate by incorporating sp2-hybridized center at C-3 and C-4[262] gained widespread publicity. These inhibitors like the substrate can strongly interact with the enzyme at the active site and on other hand unlike the substrate cannot be further reduced to 5α-metabolites, thus have been shown to possess *in vivo* inhibitory activity and resulted into first clinically approved 5α-reductase inhibitor (Finatseride).

9. Drugs available in the market

9.1 Finasteride

Finasteride (MK-906) synthesized in 1984, is chemically 17β-(N-tert-butyl-carbamoyl)-4-aza-5α-androst-1-en-3-one. It was the first 5α-reductase inhibitor approved in U.S. in 1992 for the treatment of BPH. Finasteride is a competitive inhibitor of 5α-reductase type 2 with 10 fold high affinity than type 1 and forms a stable complex with enzyme. It has been reported that in non-comparative clinical trials, at clinical doses of 5mg/day in human, it decreases the prostate DHT level by 70%, thus resulting in decreased prostate volume or size and improved urinary flow rate [40,41].
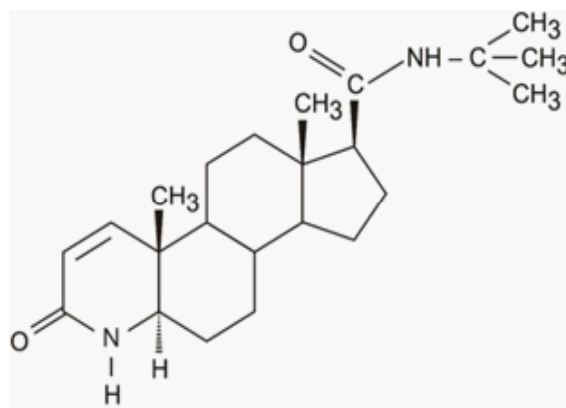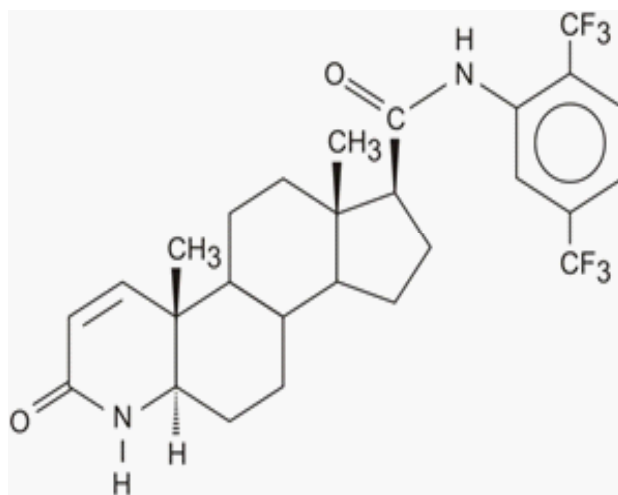

Finasteride

It has neither androgenic, antiandrogenic, other hormone related properties, nor it interferes with the binding of testosterone or dihydrotestosterone to the androgen receptor. The

investigators found significant improvement in finasteride treated groups in term of increased flow rates and decreased prostate specific antigen level. The most commonly reported side effects on finasteride long term usage are decreased libido, ejaculatory dysfunction or impotence while some of the patients showed rashes and breast enlargement.

Further number of investigators hypothesized that a dual inhibition of both isozymes would lead to greater reduction of both plasma and prostatic dihydrotestosterone, therefore, greater clinical efficacy. Variation of C-17 amide substituent on the optimal 4-aza-3-oxo-androstane skeleton was of particular interest in the search of potent dual azasteroid inhibitor and resulted into the development of first dual reductase inhibitor (Dutasteride)

9.2 Dutasteride

Dutasteride belongs to class of 4-aza-steroids and chemical name is 17β- N- {2, 5- bis (trifluoromethyl) phenyl)}-3- oxo- 4-aza- 5α- androst- 1- ene- 17- carboxamide. It was approved by U.S. FDA in 2002, for the symptomatic treatment of BPH. Unlike finasteride , dutasteride has been reported to be a non selective competitive inhibitor of both 5α-reductase type 1 and 5α-reductase type 2 isozymes. In contrast to Finasteride, in chronic therapy with Dutasteride at clinical dose of 0.5mg/day it has been shown to decrease DHT levels >90% by forming a stable complex with a slow rate of dissociation constant [42,43].

Dutasteride

Dutasteride was found to improve urinary flow rate, decrease the risk of acute urinary retention and need for surgery by reducing the size of enlarged prostate. Improved efficacy of dutasteride (0.5mg/day) over finasteride (5mg/day) in terms of symptom score, maximal urinary flow rate and quality of life has been reported in recently published article by Kumar et al.

Short-Term comparative clinical efficacy of these 5ARIs was established in double-blind, active-controlled trials (Enlarged Prostate International Comparative Study) in 1630

patients with symptoms of BPH and enlarged prostate glands duly examined by digital rectal exam. Pateints were randomized to finasteride 5 mg daily (n = 817) and dutasteride 0.5 mg daily (n = 813) for a period of 12 months. Results of comparative dose- ranging trial of finasteride and dutasteride in phase II, double-blind, clearly demonstrated that serum DHT suppression was significantly greater with dutasteride (0.5 mg daily) than with finasteride (5 mg daily). The mean reduction in baseline DHT concentration in patients receiving finasteride 5 mg daily was $70.8 \pm 18.3\%$, and for patients receiving 0.5 mg dutasteride daily was $94.7 \pm 3.3\%$ respectively ($P <.001$). These trials also demonstrated that 5AR inhibition results in reduction in baseline prostate volume, improvement of urinary flow rate, and reduction in symptoms compared with placebo in patients with BPH [44].

American Urological Association (AUA) in its meeting held in 2004, decided to conduct prospective and consecutive studies in order to evaluate the onset of symptom and relief with finasteride versus dutasteride in 120 BPH patients each for a period of 3-month. 23% of patients (n=28) experienced improvement with significant reduction in AUA symptoms of patients treated with finasteride, but even greater reductions in symptoms score of AUA symptoms with 43% improvement was observed in patients n=52 received dutasteride. Unfortunately, firm conclusions couldn't be drawn from this study because it was not a randomized or controlled study and it only examined for a short period of 3 months [45].

BPH has been established a gradually progressive disease. Thus to establish long-term efficacy and safety of finasteride and dutasteride, a non comparative study (Proscar Long-Term Efficacy and Safety Study (PLESS) was conducted as a first long-term, placebo-controlled trials [46]. In PLESS, 3040 men with symptomatic BPH and large prostates were randomized to receive finasteride (n = 1524) or placebo (n = 1516) for 4 years. Finasteride treatment resulted in significant improvement in symptom scores and decreased prostate volume in the first year in comparison to placebo group with gradual increase in prostate volume . Also the risk of undergoing BPH-related surgery was reduced by 55% after 4 years in the finasteride group compared with placebo. The pivotal data from the evaluation of the efficacy and safety of dutasteride consisted of a pooled analysis of identical randomized, double-blind, placebo-controlled, parallel-group clinical trials , similar to those of the PLESS trial with finasteride . Differences in trial design included a larger number of patients in dutasteride trials (n = 4325) and the fact that the patients received double-blind therapy for only 2 years, as compared to 4 years in PLESS. Significant reduction in the symptoms score and reduction in the prostate volume was observed in the dutasteride group compared with placebo group after 2 years. Also after 2 years, dutasteride therapy reduced the risk of BPH-related surgery by 48% and AUR by 57% compared with placebo [44].

In both the finasteride and dutasteride trials, most frequent drug-related adverse events were sexual in nature that included impotence, decreased libido, decreased volume of ejacula-

tion, and ejaculatory disorders as well as breast tenderness and/or enlargement gynaecomastia, in the 5ARI groups than in the placebo groups. At 2 years, dutasteride therapy reduced the risk of BPH-related surgery by 48% and AUR by 57% compared with placebo. Although fewer drug-related sexual adverse events occurred in patients who received dutasteride than finasteride (17% of the dutasteride group compared with 20% of the finasteride treated patients), there were no substantial differences between the 2 drugs and appeared to have similar safety profile [47].

10. Conclusion

Finasteride and Dutasteride by blocking the conversion of testosterone to dihydrotestosterone in males provide the relieve from urinary tract symptoms. These drugs are better for men with significantly enlarged prostates. In addition to relieving symptoms, they increase urinary flow, shrink the prostate size and even prevent infections or acute urinary retentions . However, patients may have to take these drugs for up to 6-12 months to achieve full benefits. But these benefits come with a high risk of harmful side effects including cardiovascular problems, erectile dysfunction, depression and elevated risks for high-grade prostate cancer . More research is needed to maximize the effectiveness of such medical therapy for BPH. Given the mounting evidence on side effects, it is possible that the benefits of treating BPH with 5-alpha-reductase inhibitors may not outweigh the potential harms.

11. References

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984; 132: 474-9.

2. Roehrborn CG. Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: results of a 2-year placebo-controlled study. BJU Int. 2006; 97: 7.

3. Kenny B, Ballard S, Blagg J, Fox DJ. Pharmacological options in the treatment of benign prostatic hyperplasia. Med. Chem. 1997; 40: 1293.

4. Thomas R J, Bilal C, Steven A K. Testosterone and benign prostatic hyperplasia. Asian J Androl. 2015; 17(2): 212.

5. Trachtenberg J, Hicks LL, Walsh PC. Androgen- and estrogen-receptor content in spontaneous and experimentally induced canine prostatic hyperplasia J. Clin. Invest. 1980; 65: 1051.

6. Blohm TR, Laughlin ME, Benson HD, Johnston JO, Wright CL, Schatzman GL, Weintraub P M. Pharmacological induction of 5 alpha-reductase deficiency in the rat: separation of testosterone-mediated and 5 alpha-dihydrotestosterone-mediated effects. Endocrinology 1986; 119: 959.

7. Quemener E, Amet Y, di Stefano S, Fournier G, Floch HH, Abalain JH. Purification of testosterone 5 alpha-reductase from human prostate by a four-step chromatographic procedure. Steroids 1994; 59: 712.

8. Bruchovsky N, Wilson JD. The conversion of testosterone to 5-alpha-androstan-17-beta-ol-3-one by rat prostate in vivo and in vitro. J. Biol. Chem 1968; 243:, 2012.

9. Thorpe A, Neal D. Benign prostatic hyperplasia Lancet 2003; 361: 1359.

10. Djavan B, Remzi M, Erne B, Marberger M. The pathophysiology of benign prostatic hyperplasia. Drugs of Today 2002; 38 : 867.

11. Cristoni A, Di Pierro F, Bombardelli E. Botanical Derivatives for the Prostate. Fitoterapia, 2000; 71(1): 21.

12. Russell DW, Wilson JD. Steroid 5 Alpha-Reductase: Two Genes/two Enzymes. Annu. Rev. Biochem. 1994; 63: 25.

13. Rosette J DeLa, Alivizatos G, Madersbacher S, Rioja Sanz C, Nordling J, Emberton M. Guidelines On Benign Prostatic Hyperplasia. European Assoc Urol., 2002: 5.

14. Griffiths DJ. Pressure-Flow Studies of Micturition. Urol. Clin. North. Am., 1996; 23 (2): 279.

15. Eri LM, Tveter KJ. Treatment of Benign Prostatic Hyperplasia. A Pharmacoeconomic Perspective. Drugs Aging. 1997 ; 10 (2): 107.

16. Orandi A. Transurethral Resection versus Transurethral Incision of the Prostate. Urol. Clin. Am., 1990; 17 (3): 601.

17. Garg G, Singh D, Saraf S. Management of benign prostate hyperplasia: An overview of α-adrenergic antagonist. Biol Pharm Bull. 2006; 29:1554.

18. Blohm TR, Laughlin ME, Benson HD, Johnston JO, Wright CL, Schatzman GL. Pharmacological induction of 5-alpha reductase deiciency in rats: Separation of testosterone-mediated and 5- alpha- dihydrotestosterone- mediated effects. Endocrinology 1986; 119: 959.

19. Reid P, Kantoff P, Oh W. Antiandrogens in prostate cancer. Invest New Drug. 1999; 17: 271.

20. Wolf H, Madson PO. Treatment of benign prostatic hypertrophy with progestational agents: A preliminary report. J Urol. 1968; 99: 980.

21. Mearini L, Massimo P. Transrectal high-intensity focused ultrasound for the treatment of prostate cancer: Past, present and future. Indian J Urol., 2010; 26: 4.

22. Griesinger G. Felberbaum R, Diedrich K. GnRH-antagonists in reproductive medicine. Arch Gynecol Obstet., 2005; 273: 71.

23. Scott WW, Wade JC. Medical treatment of benign nodular prostatic hyperplasia with cyproterone acetate. J Urol. 1969; 101: 81.

24. Berardinelli F, Hinh P, Wang R. Minimally Invasive Surgery in the Management of Benign Prostatic Hyperplasia. Minerva. Urol. Nefrol., 2009; 61 (3): 269.

25. Handratta VD, Vasaitis TS, Njar VC, Gediya LK, Kataria R, Chopra P. Novel C-17-heteroaryl steroidal CYP17 inhibitors/antiandrogens: Synthesis, in vitro biological activity, pharmacokinetics and antitumor activity in the LAPC4 human prostate cancer xenograft model. J Med Chem, 2005; 48: 2972.

26. Ai N, De Lisle RK, Yu SJ, Welsh WJ. Computational model for predicting the binding afinity of ligands for the wild type androgen receptor and a mutated variant associated with human prostate cancer. Chem Res Toxicol., 2003; 16: 1652.

27. Lowe FC, Ku JC. Phytotherapy in Treatment of Benign Prostatic Hyperplasia: A Critical Review. Urology, 1996;, 48 (1): 12–20.

28. [54] Marwick C. Growing Use of Medicinal Botanicals Forces Assessment by Drug Regulators. J. Am. Med. Assoc. 1995; 273 (8): 607.

29. Gerber GS. Phytotherapy for Benign Prostatic Hyperplasia. Curr. Urol. Rep., 2002; 3 (4): 285–291.

30. Lowe FC, Ku JC. Phytotherapy in Treatment of Benign Prostatic Hyperplasia: A Critical Review. Urology 1996; 48

(1): 12.

31. Sae Wooong Kim, Phytotherapy : emerging therapeutic options in urologic disease; Transl Androl Urol 2012; 1(3):181.

32. Che CT, Wang ZJ, Chow MS, Lam CW. Herb-Herb Combination for Therapeutic Enhancement and Advancement: Theory, Practice and Future Perspectives. Molecules, 2013; 18(5): 5125.

33. Sökeland, J. Combined Sabal and Urtica Extract Compared with Finasteride in Men with Benign Prostatic Hyperplasia: Analysis of Prostate Volume and Therapeutic Outcome. BJU Int., 2000; 86 (4): 439.

34. Wilt TJ, Ishani A, Rutks I, MacDonald R. Phytotherapy for Benign Prostatic Hyperplasia. Public Health Nutr. 2000; 3 (4): 459

35. Walsh PC, Madden JD, Harrod MJ, Goldstein JL, MacDonald PC, Wilson JD. Familial incomplete male pseudohermaphroditism, type 2. Decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. N. Engl. J. Med. 1974; 291: 944.

36. Faragalla J, Bremner J, Brown D, Griffith R, Heaton A. Comparative pharmacophore development for inhibitors of human and rat 5-alpha-reductaseJ. Mol. Graph. Model. 2003; 22: 83.

37. Labrie F, Sugimoto Y, Luu-The V, Simard J, Lachance Y, Bachvarov D, Leblanc, G, Durocher F, Paquet N. Structure of human type II 5 alpha-reductase gene Endocrinology 1992; 131: 1571.

38. Abell AD, Henderson BR. Steroidal and Non Steroidal inhibitors of 5-alpha reductase Curr. Med. Chem 1995, 2, 583.

39. Bull HG, Garcia–Calvo M, Andersson S, Baginsky WF, Chan HK, Ellsworth DE, Milles RR, Stearns RA. Mechanism-Based Inhibition of Human Steroid 5α-Reductase by Finasteride: Enzyme-Catalyzed Formation of NADP−Dihydrofinasteride, a Potent Bisubstrate Analog Inhibitor. J. Amer. Chem. Soc. 1996; 118: 2359

40. Tian G, Mook RA, Moss ML, Frye SV. Mechanism of time-dependent inhibition of 5 alpha-reductase by delta 1-4-azasteroids: Toward perfection of rates of time-dependent inhibition by using ligand-binding energies. Biochemistry 1995; 34: 13453.

41. Kumar VL, Wahane VD. Current status of 5α-reductase inhibitors in the treatment of benign hyperplasia of prostate. Indian J Med Sci 2008; 62: 167-75

42. Marihart S, Harik M, Djavan B. Dutasteride: A review of current data on a novel dual inhibitor of 5-alpha reductase. Rev Urol 2005; 7: 203.

43. Miller J, Tarter TH. Update on the use of dutasteride in the management of benign prostatic hypertrophy. Clin Interv Aging 2007; 2: 99.

44. Nickel Curtis J, Comparison of clinical trials with Finasteride and Dutasteride, Reviews in Urol. 2004; S38 6: SUPPL. 9.

45. Hagerty JA, Ginsberg PC, Metro MJ, Harkaway RC. A prospective, comparative study of the onset of symptomatic benefit of dutasteride ver-sus finasteride in men with benign prostatic hyperplasia in clinical practice. J Urol. 2004; 171:356.

46. McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia N Engl J Med. 1998; 338: 557.

47. Bullock TL, Andriole GL. Emerging drug therapies for benign prostatic hyperplasia. Expert Opin Emerg Drugs 2006; 11: 111.