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Research Article

Effect of enalapril and losartan on testosterone induced benign prostatic hyperplasia in rats

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ABSTRACT

The aim of the present investigation is to establish the therapeutic potential of drugs affecting Renin Angiotensin System (RAS) on Testosterone induced benign prostatic hyperplasia (BPH) in rats. We investigated whether RAS affecting drugs modulate on testosterone induced BPH in Rats. Animals were distributed in 5 groups (6 rats each). Group 1 receives only vehicles. Four other groups injected with Testosterone (3mg/kg, SC) to induce BPH, Group 2 was model group, Group 3 animals were treated with Enalapril (10mg/kg, IP), Group 4 animals were treated with Losartan (10mg/kg, IP), Group 5 animals were treated with Finasteride (5mg/kg, IP). The drugs were administered once a day for 21 days consecutively. Body weights were recorded before and after treatment. On 22nd day, blood samples were collected from the Retro-orbital plexus, centrifuged to obtain serum for determination of various parameters like Serum Testosterone level, Serum Prostate Specific Antigen, Serum Prostatic Acid Phosphatase, Serum Lactate Dehydrogenase. Then animals were sacrificed, prostates were weighed and histopathological studies of prostate were carried out. Effect of Enalapril and Losartan on contractility were examined on preparations of the isolated rat prostate gland. Enalapril and Losartan treatment showed significant inhibition of prostate enlargement, prevent the reduction in Serum Testosterone levels, reduced the level of Serum Prostate Specific Antigen, reduced the level of Serum Prostatic Acid Phosphatase, protection of histoarchitecture of prostate when compared with model group. These results suggest that Enalapril and Losartan has a definite inhibitory effect on BPH and might be an alternative medicine for treatment of human BPH.

Keywords: Benign Prostatic Hyperplasia; Renin Angiotensin System; Serum Testosterone; Serum Prostate Specific Antigen; Serum Prostatic Acid Phosphatase.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a progressive condition characterized by prostate enlargement accompanied by lower urinary tract symptoms (LUTS) (Parsons, Kashefi, 2008. Roehrborn, Siami, Barkin, 2009) Benign prostatic hyperplasia arises in the periurethral and transition zones of the prostatic gland and represents an inescapable phenomenon for the ageing male population (Untergasser, Madersbacher, Berger, 2005). Benign prostatic hyperplasia (BPH), a noncancerous enlargement of the prostate gland, makes urination difficult and uncomfortable. The prostate gland found between the bladder (where urine is stored) and the urethra (the tube urine passes through). As the prostate gland expands, it squeezes the urethra or causes the muscles around the urethra to contract, making it difficult to urinate (Untergasser, Madersbacher, Berger, 2005). As men age, the prostate gland slowly grows bigger (or enlarges). As the prostate gets bigger, it may press on the urethra and cause the flow of urine to be slower and less forceful. At that age, in the ninth decade-BPH was found in 88% of histological samples. 20% of males in their 60s, 43% in their 80s (Madsen, Bruskewitz, 1995).

Despite methodological differences, some conclusions can be drawn:

(1) Mild urinary symptoms are very common among men aged 50 years and older.

(2) The same symptoms can cause different troublesome and daily living interference (Holman, Wisniewski, Semmens, 1999).

The currently used drugs for the treatment of this disease in modern medicine are:-

(A) α-adrenergic antagonists [Phenoxybenzamine, Prazosin, Terazosin, doxazosin, Tamsulosin], 5-α Reductase Inhibitors [Finasteride, Dutasteride].

(B) Also Different Surgical treatments:- Transurethral resection of the prostate (TURP), Transurethral incision of the prostate (TUIP), Open prostatectomy,

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The use of microwave energy, Termed transurethral microwave therapy (TUMT), Transurethral needle ablation of the prostate (TUNA), High-intensity focused ultrasound (HIFU), Water-induced thermotherapy, Mechanical approaches are available.

The Renin Angiotensin System (RAS) is present in the human prostate. Angiotensin-II enhances noradrenaline release from sympathetic nerves of the rat prostate via a novel angiotensin receptor**.** Angiotensin-converting enzyme (ACE) degrades vasodilator kinins and generates angiotensin-II (Ang-II), which is a major effector peptide of the RAS. The physiological role of ACE in the prostate is not well understood. ACE synthesis by the prostate has been reported and the AT-1 receptor subtype is the predominant Ang-II prostatic receptor (Isaacs, Coffey, 1987. Krieg, Weisser, 1995. Liu, Huang, 2007. Thompson, Yang, 2000). The hyperactivity of local tissue RAS is thought to be involved in the pathophysiology of BPH and overactivated RAS possibly stimulates cellular growth and increases smooth muscle tone, thus affecting both dynamic and somatic component of BPH (Isaacs, Coffey, 1987).

The aim of the present investigation is to establish the therapeutic potential of drugs affecting Renin Angiotensin System (RAS) on Testosterone induced Benign prostatic hyperplasia (BPH) in rats.

The objectives of the present investigations are:

1. To evaluate the efficacy of drugs affecting RAS in the BPH.

2. To investigate the probable mechanism of action of drugs affecting RAS for the treatment of BPH.

MATERIALS AND METHODS

The protocol of this experiment was approved by our institutional animal ethical committee as per the guidance of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), (Protocol No. CPCSEA/IAEC/ARCP/2011-2012/03).

Drugs**:** Enalapril, Losartan, Finasteride, Testosterone were procured from Sun Pharma, Vapi.

Animals**:** Male albino rats of wistar strain were procured from JRF, Vapi, weighing 200-300gm were used. Animals were fed a standard laboratory diet and water *ad libitum*. They were housed in the departmental animal house and exposed to natural cycles of light and dark.

Experimental Design

The effect of drugs were studied on healthy male rats fed on commercial pellet diet and water *ad libitum*. The animals were divided into 5 groups each containing 6 rats.

Group I Received Normal Saline.

Group II Received Testosterone propionate (3mg/kg, SC) (Veeresh Babu, 2010).

Group III Received Testosterone propionate (3mg/kg, SC) and treated with Enalapril (10mg/kg, i.p) (Tourandokht, Mehrdad, 2004).

Group IV Received Testosterone propionate (3mg/kg, SC) and treated with Losartan (10mg/kg, i.p) (Vincent, Frédéric, 2002).

Group V Received Testosterone propionate (3mg/kg, SC) and treated with Finasteride (5mg/kg, i.p). (Veeresh Babu, 2010)

Testosterone propionate and treatment were given daily single dose for 21 days.

Animals were weighed before initiation and after completion of the experiment.

Twenty-four hours after the last administration and an overnight fasting, blood samples were collected from the Retro-orbital plexus, centrifuged to obtain serum for determination of various parameters.

Serum Prostate Specific Antigen were measured by chemiluminescence technique.

Serum Testosterone were measured by commercial ELISA kit (AB Diachem).

Serum Prostatic Acid Phosphatase were measured by spectrometric kit (Accurex biomedical).

Serum Lactate Dehydrogenase were measured by spectrometric kit (Accurex biomedical).

Then Rats were killed and prostates were removed, weighed and histopathological studies of prostates were done. Also Dose response curve of normal prostates were taken on student physiograph.

Statistical analysis

Data were expressed as mean±SEM. Statistical analysis is done by one-way ANOVA followed by tukey's test. Data were considered statistically significant at a $P < 0.05$.

There were no significant differences ($P>0.05$) in body weights of rats before and after treatments among the groups.

Testosterone significantly elevated ($P<0.001$) the prostate weights/body weights ratio in model group when compared with control rats. Compared with model group, significant reduced ($P<0.001$) the elevated prostate weight/body weight ratio was found by Enalapril and Losartan in testosterone treated rats.

In model group, significantly reduction ($P<0.05$) in Serum Testosterone level when compared with control rats. But significant elevation ($P<0.001$) of Serum Testosterone level was found by Enalapril and there was

Table 1: Effect of Enalapril and Losartan on Body weight, Prostate weight/Body weight ratio, Serum Testosterone

Treatment	Body weight(g)		PW/BW ratio	S.Testosterone (ng/ml)
	Before	After		
Normal Saline (Control)	275.8 ± 5.54	304.2 ± 7.12	0.0146 ± 0.0002	54.0 ± 2.082
TESTO (3mg/kg,SC) (Model)	253.3 ± 7.71	285.0 ± 9.12	0.0276 ± 0.0002$^{\#}$	38.0 ± 2.082$^{\#\#}$
TESTO (3mg/kg,SC) + ENL(10mg/kg,IP)	275.8 ± 4.72	300.0 ± 4.47	0.0156 ± 0.0002*	65.33 ± 10.68*
TESTO (3mg/kg,SC) + LSR(10mg/kg,IP)	271.1 ± 7.92	302.5 ± 8.92	0.0150 ± 0.0003*	32.67 ± 2.96
TESTO (3mg/kg,SC) + FNST(5mg/kg,IP)	273.3 ± 5.42	293.3 ± 5.57	0.0148 ± 0.0003*	58.33 ± 11.92**

TESTO:Testosterone Propionate; ENL:Enalapril; LSR:Losartan; FNST:Finasteride; PW/BW:Prostate weight/Body weight; SC:Subcutaneous; IP:Intraperitoneal; Each value expressed as mean ± S.E.M. Data were analyzed by one way analysis of variance followed by Tukey's test (n=6). $^{\#}$P<0.001,$^{\#\#}$P<0.01, when compared with control. * P<0.001, ** P<0.05, when compared with Model group.

Table 2: Effect of Enalapril and Losartan on Serum Prostate Specific Antigen, Serum Prostatic Acid Phosphatase, Serum Lactate Dehydrogenase

Treatment	S.PSA (ng/ml)	S.PAP (IU/L)	S.LDH (IU/L)
Normal Saline (Control)	1.4 ± 0.060	1.73 ± 0.051	3702 ± 61.71
TESTO (3mg/kg,SC) (Model)	6.1 ± 0.106$^{\#}$	4.55 ± 0.093$^{\#}$	3600 ± 44.80
TESTO (3mg/kg,SC) + ENL(10mg/kg,IP)	4.2 ± 0.094*	3.26 ± 0.046*	3292 ± 123.6
TESTO (3mg/kg,SC) + LSR(10mg/kg,IP)	3.6 ± 0.077*	2.56 ± 0.040*	3559 ± 52.18
TESTO (3mg/kg,SC) + FNST(5mg/kg,IP)	2.5 ± 0.066*	2.18 ± 0.039*	3363 ± 71.91

TESTO:Testosterone Propionate; ENL:Enalapril; LSR:Losartan; FNST:Finasteride; S.PSA:Serum Prostate Specific Antigen; S.LDH:Serum Lactate Dehydrogenase; S.PAP:Serum Prostatic Acid Phosphatase;; SC:Subcutaneous; IP:Intraperitoneal; Each value expressed as mean ± S.E.M. Data were analyzed by one way analysis of variance followed by Tukey's test (n=6). $^{\#}$P<0.001,$^{\#\#}$P<0.01, when compared with control. * P<0.001, ** P<0.05, when compared with Model group.

no significant (P>0.05) change in Serum Testosterone level by Losartan.

Testosterone significantly elevated (P<0.001) the Serum Prostate Specific Antigen (PSA) level when compared with control rats. But significantly prevent (P<0.001) the elevation in Serum Prostate Specific Antigen (PSA) level was found by Enalapril and Losartan in testosterone treated rats.

Testosterone significantly elevated (P<0.001) the Serum Prostatic Acid Phosphatase (PAP) level when compared with control rats. But significantly prevent (P<0.001) the elevation in Serum Prostatic Acid Phosphatase (PAP) level was found by Enalapril and Losartan in testosterone treated rats.

There were no significant differences (P>0.05) in Serum Lactate Dehydrogenase (LDH) level of rats after the treatment among the groups.

There was no change in the histoarchitecture of prostate gland in normal control group. The tissues were tightly packed, epithelium was cuboidal and regular in size. The prostate gland is surrounded by capsule; a thick layer of involuntary muscles with distinct nucleus and normal sarcoplasmic texture was visible. In model group, there was disruption in the histoarchitecture of the prostate tissue. The amount of connective tissue was well marked increased and more fibrotic tissues were found in model group. The tubules became wider compared with the control. The walls of tubules were thickened and every tubule almost had developed large involutions projecting into the lumen, reducing the volume of the lumen compared with the control. Enalapril, Losartan and Finasteride treatments showed mild glandular hyperplasia. No stromal appearance was found in drug treated group.

Dose response curve

The contraction of prostates were induced by Noradrenaline. But Enalapril and Losartan were not inhibited the contraction of prostates induced by Noradrenaline.

DISCUSSION

In the present study, we were checked the efficacy of Enalapril and Losartan on testosterone induced Benign Prostatic Hyperplasia. Treatment with Enalapril and Losartan for 21 days significantly inhibited the development of testosterone induced Benign Prostatic Hyperplasia, which was evidenced by reduction in elevated levels of prostate weight and prostate weight to body weight ratio, Serum Prostate Specific Antigen (PSA), Serum Prostatic Acid Phosphatase (PAP) and prevent the reduction in Serum Testosterone level and histo-pathological alterations.

The cellular availability of sufficient amounts of dihydrotestosterone is thought to be a prerequisite for the normal growth and function of the prostate. Moreover, the development of benign prostatic hyperplasia

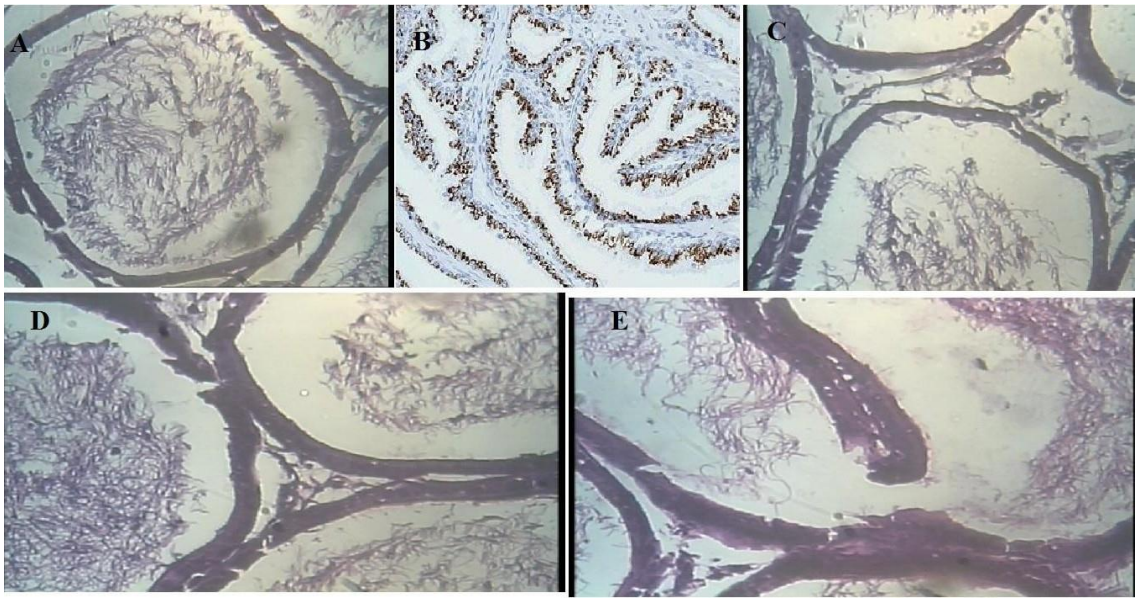

Figure 1: Effect of Enalapril and Losartan on Histopathology of Prostate

A:(Control):Normal saline; B:(Model): Testosterone(3mg/kg); C: Testosterone(3mg/kg)+Enalapril(10mg/kg); D: Testosterone(3mg/kg)+Losartan(10mg/kg); E: Testosterone(3mg/kg)+Finasteride(5mg/kg).

seems to be a pathobiological process that is at least in part dependent on dihydrotestosterone (Krieg, Weisser, 1995). The model rats exhibited enlargement of prostate as a consequence of progressive hyperplasia of glandular and stromal tissues around urethra, clearly confirmed the influence of androgen on prostate growth due to increased amount of dihydrotestosterone from testosterone by 5-α-reductase enzyme (Zu-Yue, Hong-Yan, 1999).

Since previous studies have shown that Prostate Weight gain induced by testosterone in rats is accompanied by histological changes indicative of BPH (Mitra, Sundaram, 1999). Although the effect of treatment on prostate weight gain was evident, that should be related to body weight changes; therefore the prostate weight to body weight ratio has been used as the main marker for the treatment. The treatment Enalapril and Losartan did not significantly affect body weight, but the effect was prominent on prostate weight to body weight ratio by inhibiting the growth of prostatic cells (Veeresh Babu, 2010).

Testosterone is converted to the more potent dihydrotestosterone by the enzyme 5-α-reductase present in prostate homogenates (Dhanotiya, Chauhan, 2009). Increased levels of unchanged Serum testosterone level, suggested the inhibition of enzyme action by the treatment. Therefore, more testosterone remained unchanged. An increased production of dihydrotestosterone and decreased Serum Testosterone results in the development of Benign Prostatic Hyperplasia (McCollen, 1992). The results of the present investigations suggested that Enalapril inhibit prostatic hyperplasia induced with an exogenous supply of testosterone in a rat model.

Prostate specific antigen (PSA) is a protein produced by the cells of the prostate gland. When prostatic gland is disrupted, Serum Prostate Specific Antigen will 'leak' into the circulation. PSA serum levels are abnormally elevated in patients with prostate cancer, benign prostatic hypertrophy (BPH) and patients with prostate inflammatory conditions. If a decrease in PSA levels is observed, it can be considered that the test sample having protective effect on hypertrophy of the prostate induced by testosterone (Nahata, Dixit, 2011). Testosterone treatment increased the PSA levels which is an indication of hyperplasia, whereas finasteride reduced the PSA levels significantly suggesting its protective effects. Enalapril and Losartan significantly reduced the PSA levels which are an indication of their efficacy in the treatment of prostatic hyperplasia.

In cases where cellular masses of prostates are more, it secretes more Serum Prostatic Acid Phosphatase (PAP) and Lactate Dehydrogenase (LDH). Treatment with Enalapril and Losartan prevent the elevation of PAP level by preventing the increases in prostatic cellular mass. However, Treatment with Enalapril and Losartan did not show any significant effect in the levels of LDH (stanford.edu).

The development of BPH is associated with the enhanced proliferation and suppressed apoptosis of prostatic cells. There was no change in the histoarchitecture of prostate gland in normal control group. The tissues were tightly packed; epithelium was cuboidal and regular in size. In model group, there was disruption in the histoarchitecture of the prostate tissue. The amount of connective tissue was well marked increased and more fibrotic tissues were found in model group. Enalapril and Losartan treatments showed mild glandular hyperplasia markedly reduced

the density of the prostatic epithelial compartment. No stromal appearance was found in drug treated group.

Dose response curve of Prostates were investigated whether Enalapril and Losartan were able to inhibit prostatic smooth muscle contractility in healthy rat prostate. But Enalapril and Losartan did not shows any inhibition in contractility of prostates induced by Noradrenaline.

Previous findings suggest that Angiotensin Converting Enzyme may have an important neuro-modulatory role on sympathetic transmission in the prostate by regulating the synthesis of Ang II, which have demonstrable effects on transmitter NA release in the rat prostate. Although Angiotensin Converting Enzyme inhibition may suppress local Ang II-mediated effects on sympathetic transmission in the prostate (Fabiani, Sourial, 2001).

The findings of the previous study provide direct evidence that Ang II enhances NA release from sympathetic nerves of the rat prostate. These suggest that a tissue based Renin Angiotensin System is indeed and functionally active in the rat prostate and capable of generating Ang II locally. These establish a novel functional role for the Renin Angiotensin System in the modulation of sympathetic transmission in the prostate, which may have important implications for the understanding of the pathophysiology of BPH. Increased local sympathetic activity is a characteristic feature of BPH and represents a target for drug treatment with α_1-adrenoceptor blockers. It is possible; therefore, that hyperactivity of the local Renin Angiotensin System resulting in increased tissue concentrations of Ang II may represent an important factor in the pathophysiology of BPH by enhancing local sympathetic activity in the prostate. The exogenous and locally generated Ang II facilitates the release of NA from sympathetic nerves of the rat prostate by a prejunctional mechanism. The receptor subtype mediating the effects of Ang II on sympathetic transmission in the rat prostate is unclear, but may involve a novel functional Ang II receptor distinct from the cloned AT1a, AT1b or AT2. These novel data provide direct evidence in support of a functional role for the local Renin Angiotensin System in modulating sympathetic activity in the prostate, which may have important implications for the pathophysiology of BPH (Fabiani, Sourial, 2001).

The AT1 receptors are concentrated around the periurethral region of the human prostate suggests that Ang II may be involved in modulating smooth muscle tone and growth and, hence, control of micturition. It is possible therefore that Ang II may promote cellular growth and enhance sympathetic tone in the prostate, two major factors that contribute to the pathophysiology and symptomatology of BPH (Madsen, 1995).

Previous paper reports the first demonstration of the distribution and binding properties of Ang II receptors in normal and hyperplastic human prostates are highly concentrated around the periurethral region, and are localized to stromal smooth muscle (Dinh, Frauman, 2001). Angiotensin Converting Enzyme's highest activity was found in benign prostatic hyperplasia. Normal prostate and prostatic adenocarcinoma has a much lower activity (Marc, Van Sande, 1985).

In the present study, treatment with Enalapril and Losartan for 21 days significantly inhibited the development of testosterone induced Benign Prostatic Hyperplasia. The preventive effect is may be due to their inhibitory effect on Renin Angiotensin System. Viz by inhibiting Noradrenaline release or inducing the apoptosis of prostate epithelium and increase the TGFβ1 expression in rats (Wei Yu, Ya-Yuan, 2007). Further experimental studies should confirm the present results before deciding whether they are meaningful enough to be explored in men with Benign Prostatic Hyperplasia.

CONCLUSION

In the present study, treatment with Enalapril and Losartan for 21 days significantly inhibited the development of testosterone induced Benign Prostatic Hyperplasia. The preventive effect is may be due to their inhibitory effect on Renin Angiotensin System. Viz by inhibiting Noradrenaline release or inducing the apoptosis of prostate epithelium and increase the TGFβ1 expression in rats (Wei Yu, Ya-Yuan, 2007). Further experimental studies should confirm the present results before deciding whether they are meaningful enough to be explored in men with Benign Prostatic Hyperplasia.

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REFERENCES

Brandli A, Simpson J. Isoflavones isolated from red clover (Trifolium pratense) inhibit smooth muscle contraction of the isolated rat prostate gland. Phyto. 2010, 17, 895-901.

Dhanotiya R, Chauhan N. Effect of Citrullus colocynthis Schard. on testosterone induced benign prostatic hyperplasia. J. Compl. Integr. Med. 2009, 10, 1553-1557.

Dinh D, Frauman A. Identification, Distribution, and Expression of Angiotensin II Receptors in the Normal Human Prostate and Benign Prostatic Hyperplasia. J endocrinol. 2001, 142, 3, 1349-1356.

Fabiani M, Sourial M. Angiotensin II enhances noradrenaline release from sympathetic nerves of the rat

prostate via a novel angiotensin receptor: implications for the pathophysiology of benign prostatic hyperplasia. J Endocrinol. 2001, 171, 97–108.

Holman C, Wisniewski Z, Semmens J, Rouse I, Bass A. Mortality and prostate cancer risk in 19, 598 men after surgery for benign prostatic hyperplasia. BJU Int. 1999, 84, 37-42.

Isaacs J, Coffey D. Etiology and disease process of benign prostatic hyperplasia. Prostate, 1987, 2, 33–50.

Krieg M, Weisser H, Tunn S. Potential activities of androgen metabolizing enzymes in human prostate. J. Steroid. Biochem. Mol. Biol. 1995, 53, 395–400.

Liu C, Huang S, Li W. Relationship between serum testosterone and measures of benign prostatic hyperplasia in aging men. Urol. 2007, 70, 677–680.

Madsen F, Bruskewitz R. Benign prostatic hyperplasia: pathophysiology and pharmacological treatment. Curr Opin Nephrol Hypertens. 1995, 4, 455–459.

Marc E, Van Sande, Simon L. Scharpé. Distribution of angiotensin converting enzyme in human tissues. Clinica Chimica Acta. 1985, 30, 255-260.

McCollen J, Wilson J, George F, Geller J., Pappas F., Stoner E. Finasteride an inhibitor of 5 alpha-reductase, suppresses prostatic dihydrotestosterone in men with benign prostatic hyperplasia. J. Clin. Endocrinol. Metab. 1992, 74, 505–508.

Mitra S, Sundaram R, Mohan A. Protective effect of Prostane in experimental prostatic hyperplasia in rats. Asian J. Androl. 1999, 1, 175–179.

Nahata A, Dixit V. Sphaeranthus indicus Attenuates Testosterone induced Prostatic Hypertrophy in Albino Rats. Phytother. Res. 2011, 25, 1839–1848.

Parsons J, Kashefi C. Physical activity, benign prostatic hyperplasia, and lower urinary tract symptoms. Eur Urol. 2008, 53, 1228–1235.

Roehrborn C, Siami P, Barkin J. The influence of baseline parameters on changes in international prostate symptom score with dutasteride, tamsulosin, and combination therapy among men with symptomatic benign prostatic hyperplasia and an enlarged prostate: 2-year data from the Comb AT study. Eur Urol. 2009, 55, 461–471.

Thompson T, Yang G. Regulation of apoptosis in prostatic disease. Prostate Suppl. 2000, 9, 25–28.

Tourandokht B, Mehrdad R, Alireza I. Protective effect of enalapril on vascular reactivity of the rat aorta. Vasc Pharmacol, 2004, 40 (6), 301-307.

Untergasser G, Madersbacher S, Berger P. Benign prostatic hyperplasia: age-related tissue-remodeling. Exp Gerontol. 2005, 40, 121–128.

Veeresh Babu S, Veeresh B, Patil A. Lauric acid and myristic acid prevent testosterone induced prostatic hyperplasia in rats. Eur J Pharmacol, 2010, 626, 262–265.

Vincent C, Frédéric M, Nary V. Hemodynamic and antifibrotic effects of losartan in rats with liver fibrosis and/or portal hypertension. J Hepat. 2002, 37 (6), 773-780.

Wei Yu, Ya-Yuan Zhao. Angiotension II receptor 1 blocker modifies the expression of apoptosis-related proteins and transforming growth factor ß1 in prostate tissue of spontaneously hypertensive rats. Int. BJU. 2007, 100, 1161-1165.

Zu-Yue S, Hong-Yan W. The mechanism of epristeride against benign prostatic hyperplasia. Eur. J. Pharmacol. 1999, 371, 227-233.