PHARMACODYNAMIC INTERACTION BETWEENTAMSULOSIN AND FINASTERIDE TREATMENT ON INDUCED BENIGN PROSTATE HYPERPLASIA IN MICE BY USING CHOA-TALALAY METHOD

[1]SHUKUR M.YASEEN, [2]FIRAS R. AL-SAMARAI, [3]HUDA F. HASAN

[1]Medical Biology and Anatomy Department, Faculty of Medicine, Diyala University, Iraq
[2]Department of Veterinary Public Health, College of Veterinary Medicine, University of Baghdad, Iraq
[3]Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Baghdad, Iraq
E-mail: dr. hudaalqaraghuli@yahoo.com

Abstract - The study was designed to measure the efficacy and interaction type of tamsulosin with finasteride treatment on induced benign prostate hyperplasia (BPH) in mice. (BPH) was induced by subcutaneous injection of testosterone propionate (20 mg/kg) for 30 days. Eighty-five mice were divided into five groups. The first group (G1): twenty-five mice induced BPH treated with tamsulosin orally and divided into five equal subgroups with doses (0.017, 0.052, 0.087, 0. 123, and 0.158) mg/kg. The second group (G2): twenty-five mice induced BPH treated with finasteride orally and divided into five equal subgroups with doses (0.175, 0.527, 0.878, 1.23, and 1.580) mg/kg. third group (G3): twenty five mice induced BPH treated with combination of tamsulosin with finasteride orally, and divided into five equal subgroup with doses (0.0085, 0.0875), (0.026, 0.2635), (0.0435, 0.439) , (0.0615, 0.615) and (0.079 , 0.790) mg/kg respectively. The fourth group (G4): five mice induced BPH and treated with distilled water. In the fifth group (G5): five mice were not inducing BPH and without any treatment. The results showed a gradual significant increase in prostate weight % and prostate index % Inhibitions until reached saturation in the last two doses of tamsulosin, finasteride, and combination groups, the maximum effective dose of tamsulosin and finasteride were (0.156) and (1.495) mg/kg respectively. Moreover, the effective dose of combination tamsulosin and finasteride was computed (0.06876, 0.6876) mg/kg respectively as well as the type of interaction was synergistic and the value of the combination index was 0.046. This study concluded that the combination of tamsulosin with finasteride gave a synergistic effect in BPH treatment by minimizing the side effect of each drug by decreasing the dose of each one.

Keywords - Tamsulosin, Finasteride, Effective Dose, BPH, Mice.

I. INTRODUCTION

Benign prostatic hyperplasia (BPH) is characterized by inflammation, oxidative stress, proliferative and apoptotic changes [1]. Commonly, testicular hormones and aging are two core elements attributed to the genesis and development of BPH. Moreover, pathways of proliferation/apoptosis and inflammation in addition to oxidation/antioxidation are involved in BPH development [2]. Alpha-blockers such as Tamsulosin and 5α-reductase inhibitors such as finasteride is currently used for the medical management of BPH, the effect of tamsulosin treatment commences more rapidly than finasteride [3]. Finasteride is an inhibitor that prevents the conversion of testosterone to DHT and acts to reduce the DHT and testosterone levels, consequently suppressing the hyperplastic growth of the prostate [4]. Finasteride side effects included loss of interest in sex, sexual dysfunction, loss of libido, and reduction of ejaculation [5]. The standard mixture α-blocker and 5ARI for reducing prostate volume and BPH, and the possibility of adapting BPH treatment according to different patient characteristics and expectations using two or more drugs appeared to be a promising pathway in the LUTS / BPH and recommend that taking an alpha-blocker and a 5-alpha-reductase inhibitor simultaneously [6]. The aims of the current study included determining the efficacy and interaction type of tamsulosin with finasteride treatment on induced benign prostate hyperplasia (BPH) in mice.

II. MATERIALS AND METHOD

Experimental design: (BPH) was induced by subcutaneous injection of testosterone propionate (20 mg/kg) for 30 days. Eighty-five mice were divided into five groups according to Kim et al [7]. The first group (G1): twenty-five mice induced BPH treated with tamsulosin orally and divided into five equal subgroups with doses (0.017, 0.052, 0.087, 0. 123, and 0.158) mg/kg. The second group (G2): twenty-five mice induced BPH treated with finasteride orally and divided into five equal subgroups with doses (0.175, 0.527, 0.878, 1.23, and 1.580) mg/kg. third group (G3): twenty five mice induced BPH treated with combination of tamsulosin with finasteride orally, and divided into five equal subgroup with doses (0.0085, 0.0875), (0.026, 0.2635), (0.0435, 0.439) , (0.0615, 0.615) and (0.079 , 0.790) mg/kg respectively. The fourth group (G4): five mice induced BPH and treated with distilled water. In the fifth group (G5): five mice were not inducing BPH and without any treatment. After the end of the experiment, the percentage inhibition of prostate weight and the prostate index was determined according to Cai et al. [1].

Assessment of percentage inhibition of prostate weight and index: The body weight was conducted every week of the experiment. After the end of the experiment's period, mice were anesthetized with Diethyl ether inhalation, Sacrificed, and anatomical process preparation of animals taken please to demonstrate the prostate weight (Pw(and the Prostatic Index (P.I. %) account was calculated as PW/BW ×100%, and the mean P.I. ratio was computed in each group. The percentage of inhibition of P.W. and P.I. was computed as follows: 100–[(T–C) / (B–C) ×100], where the C value is the control group, B is the BPH group, and T is the treatment group [1].

Determination of the Log dose-response curve and effective doses of Tamsulosin and finasteride: After the end of the period of the experiment (30 days), the percentage inhibition of prostate weight and the prostate index were used to determine the log -Dose-response curve, and (MED) maximum effective dose by using a simple line equation and determining R2 to select the appropriate effective dose that given the best results according to Lepak et al., [8].

Determination of the type and effective dose of Combination drugs by combination Index (CI) Equation of Chou-Talalay: The percentage inhibition of prostate index was determined as parameter dependent to determine the effective dose (ED) and type of interaction between tamslosine and finasteride according to ChoaTalalay method, as follows:CI> 1 (Antagonism effect), CI <1 (Synergism effect), and CI= 1 (additive effect), by using computer software (CompySun) for dose-effect analysis based on the "mass-action law". This law describes how a chemical reaction takes place under ideal conditions. Combination Index Equation for two Drugs was estimated as followed: (D)1/(Dx)1+ ((D)2/(Dx)2= CI . Where in the denominators, (Dx)1 are the doses of Drug1 (Tamslosin) alone that inhibits x% (percentage inhibition of prostate weight). Likewise, (Dx)2 is the dose of Drug2 (finasteride) alone that inhibits x%. In the numerators, (D)1 is the portion of Drug1 in combination (D)1 + (D)2 also inhibits x%. Again, likewise (D)2. Thus (D)1 + (D)2 also inhibits x%.[9].

Statistical analysis:The statistical analysis was accomplished for this data of experiment; all analyses were performed using SPSS version 16.0. Values are expressed as Mean ± SE. Differences among treatment group means were tested by analysis of variance and LSD tests. The 0.05 level was considered statistically significant for all tests.

III. RESULTS

Effect of Tamsulosin doses on inhibition of prostate weight% and Inhibition PI %:

The prostate weight% and PI % Inhibition of mice in the Tamsulosin treated group at doses (0.017, 0.052, 0.087, 0.123, and 0. 158) revealed a gradual significant increase (P<0.05) until reached a plateau at doses 0.123 and 0.158 mg/kg in means values (80.145±0.37, 65.85±0.33, and 81.566±0.25, 65.74±0.24,) respectively as in figure (1).

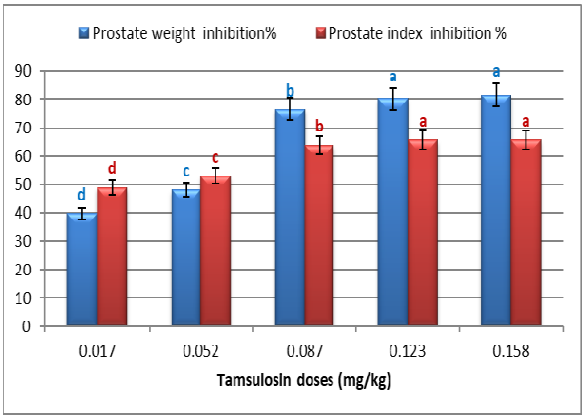


Figure (1): Effect of Tamsulosin doses on inhibition of prostate weight% and Inhibition PI %:

Effect of Finasteride doses on inhibition of prostate weight% and Inhibition PI %:

The prostate weight% and Inhibition PI %of mice in the Finasteride treated group at doses (0.175, 0.527, 0.878, 1.230, and 1. 580) revealed a gradual significant increase (P<0.05) until reached a plateau at doses1.230 and 1.580 mg/kg in means values (62.47±0.35, 68.07±0.16, and 68.67±0.18, 68.39±0.20) respectively as shown in figure (2).

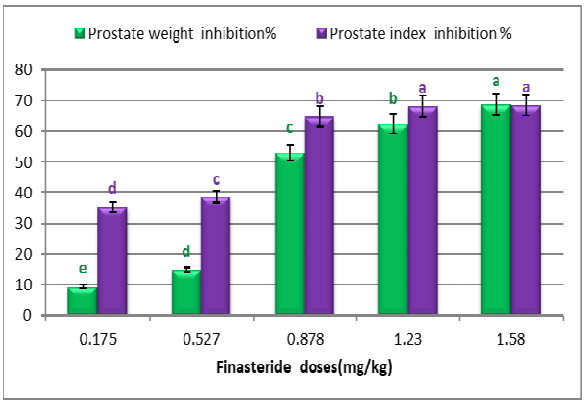


Figure (2): Effect of Finasteride doses on inhibition of prostate weight% and Inhibition PI %:

Effect of Combination of Tamsulosin and Finasteride Inhibition PI %:

The PI %Inhibition of mice treated with Tamsulosin and Finasteride at doses (0.0085, 0.026, 0.0435, 0.0615, 0.079) and (0.0875, 0.2635, 0.439 , 0.615, 0.790) respectively revealed a gradual significant increase (P<0.05) until reached to saturation at doses 0.0615, 0.615 and 0.079 , 0.790 mg/kg respectively in means values (96.38±0.54, 93.67±0.49) respectively (Figure 3).

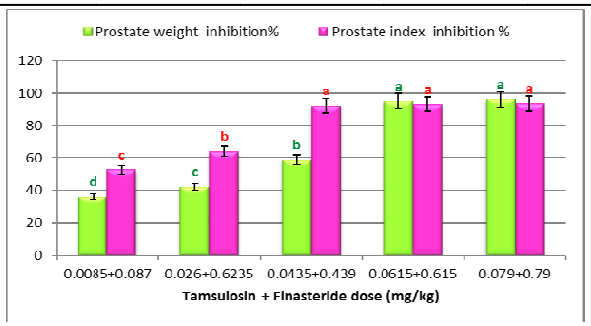


Figure (3): Effect of Combination of Tamsulosin and Finasteride on Inhibition PI %:

Log dose-response curve and effective dose:

The log dose-response curve Inhibition of PI % in groups of mice treated with different doses of Tamsulosin (0.017, 0.052, 0.087, 0.123 and 0.158) and Finasteride (0.175, 0.527, 0.878, 1.23and, 1.58), shown in figures (4 and 5) respectively. In addition, the simple linear equation revealed the Maximum effective dose of Tamsulosin and Finasteride Inhibition PI % were (0.156 and 0.15) mg/kg and (1.495 and 1.73) mg/kg respectively.

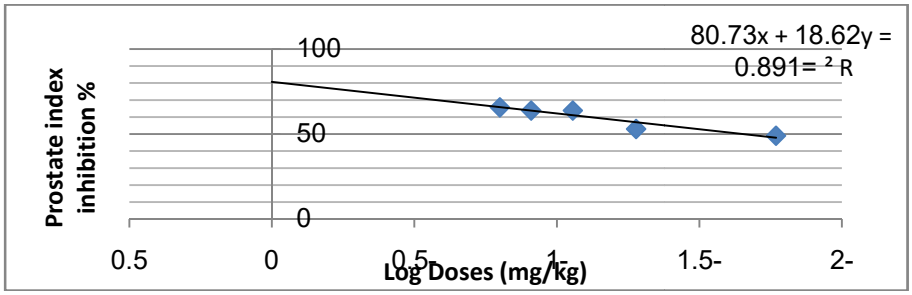


Figure 4: Log dose-response curve of Tamsulosin on PI inhibition% in Induced BPH.

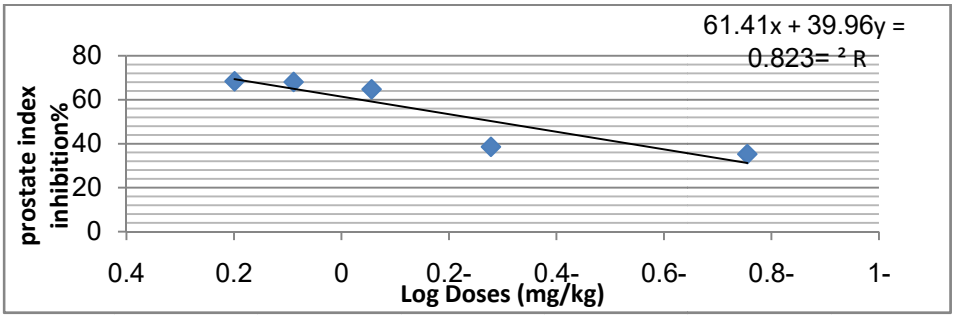


Figure 5: Log dose-response curve of Finasteride on PI inhibition% in Induced BPH.

Estimation of an effective dose of Combination of Tamsulosin and Finasteride on Inhibition PI %:
The effective dose of Combination of Tamsulosin and Finasteride for Inhibition PI % was shown in figures (6 and7). The value of the combination index was 0.04627 and the type of combination was < 1 (Synergism). As well as the Maximum effective doses were (0.06876, 0.6876) mg/kg respectively, depending on the current experiment.

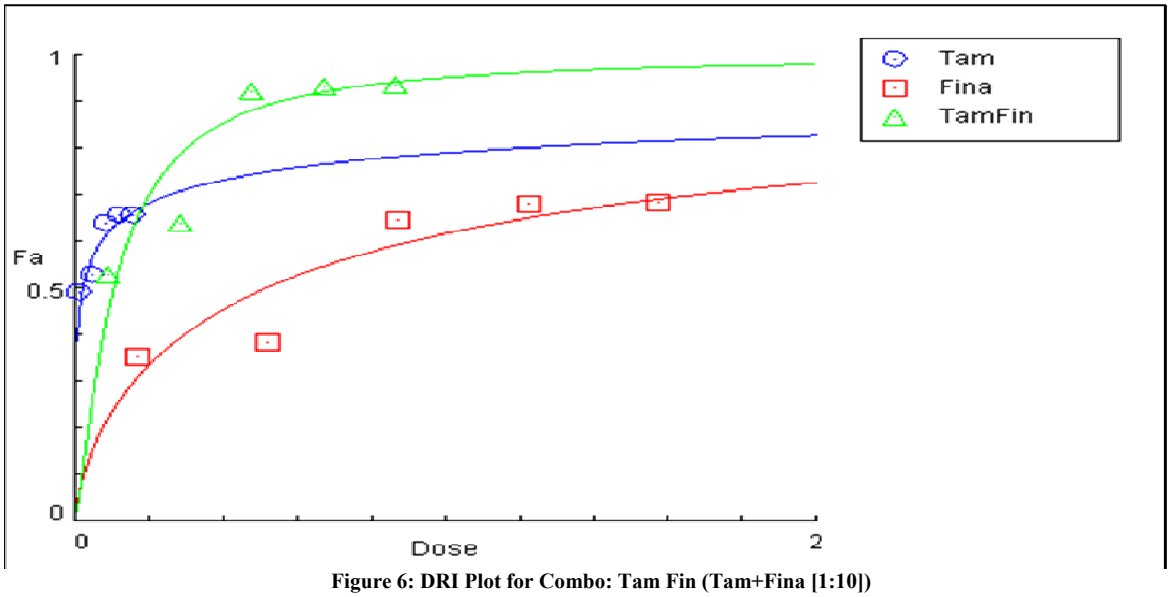


Figure 6: DRI Plot for Combo: Tam Fin (Tam+Fina [1:10])

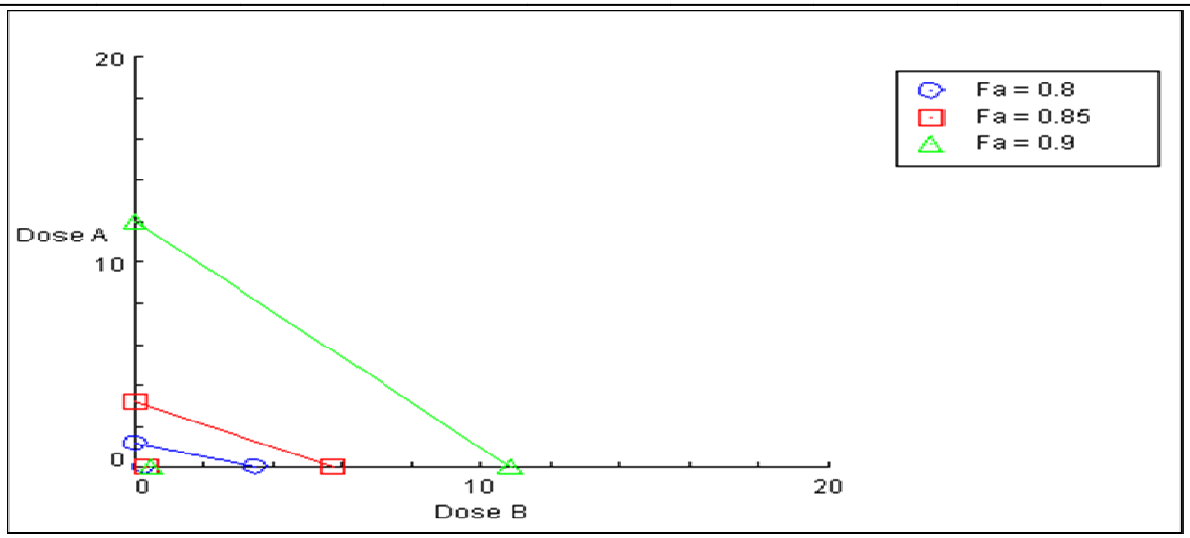


Figure 7 :Isobologram for Combo: Tam Fin (Tam +Fina [1:10]):

IV. DISCUSSION

The development of BPH induced by testosterone propionate leads to a significantly increased prostate weight and prostate index [10]. Testosterone demonstrated that being involved-induced mice caused an abnormal proliferation of epithelial and stromal cells of the prostate. Moreover, resulting in inflammation and enlargement of the prostate, the prostate enlargement caused compressing of the urethra and reduces daily urinary output, and increases prostate weight, the results agreed with results reported by Kim et al., [7] and Dzulsuhaimi et al., [11], which was the enlargement of the organ seen as more of histological diagnosis characterized by proliferation of the cellular stromal and epithelial components? As well as the decrease in body weight may be attributed to a reduction in appetite and food consumed daily, leading to a decrease in body weight, these results were agreed with results reported by Mbaka, et al., [12]. The results of decreased prostate weight and increased body weight in the group treated with Tamsulosin perhaps due to tamsulosin acting blocking nerve ending (alpha receptors), lead to relaxing smooth muscles of the prostate and neck bladder, and then reduced testosterone concentration in the blood by the influence of steroid-forming enzymes in the testes or its inhibitory properties on the adrenergic and serotonin systems involved in steroid formation that lead to reduce the prostate size and increase in PI % inhibition [13]. The increase in PI % inhibition in the group treated with Finasteride may be regarded to Finasteride was reported to decrease the prostate size by inhibiting the formation of the active androgen DHT metabolite from testosterone, these results agreed with results recorded by Wang et al., [15]. While the results of returned prostate weight and body weight in the group treated with a combination drug to normal weights may be due to the combination and synergistic action were more effective and competent than monotherapy in the treatment of BPH. Combination therapy with tamsulosin and finasteride was significantly more effective, in the treatment of BPH compared to tamsulosin alone. Also, these results may be attributed to the ability of finasteride in decreasing the levels of steroid hormones, by inhibition of 5α-reductase activity led to reducing testosterone and DHT levels in the serum and prostate [16]. As well as, combination medicinal therapy may be better than monotherapy from tamsulosin or finasteride alone.

V. CONCLUSION

Tamsulosin treatment was reduced BPH more rapidly than finasteride, and fewer side effects. Combination tamsulosin with finasteride was more effective and competent in the treatment of BPH than only tamsulosin or finasteride alone due to the synergistic action lead to minimize the side effect of each drug by decreasing the dose of each one.

REFERENCES

[1] H. Cai, ZGuowei, Y.Zechen and S. Xuejun Shang. "The Effect of Xialiqi Capsule on Testosterone-Induced Benign Prostatic Hyperplasia in Rats".Evidence-Based Complementary and Alternative Medicine.https://doi.org/10.1155/2018/5367814.2018

[2] X.Yang, Y. Liuliu, X. Chaomei, Y.Chunping and R. JinlanRuan. "AbacopterisPenangiana Exerts Testosterone-Induced Benign Prostatic Hyperplasia Protective Effect through Regulating Inflammatory Responses, Reducing Oxidative Stress and Anti-Proliferative". Journal of Ethnopharmacology 157 105–13. November, 2014.https://doi.org/10.1016/j.jep.2014.09.025.

[3] J. Gilbert, D. Thomas, E. A. Davis; and A.O. Daniel. "An Examination of Treatment Patterns and Costs of Care among Patients with Benign Prostatic Hyperplasia".Am J Manag Care 12: S99–S110.2006.

[4] C. Carson, and R. Roger (2003). The Role of Dihydrotestosterone in Benign Prostatic Hyperplasia.; Urology. Elsevier Inc. https://doi.org/10.1016/S0090-4295(03)00045-1. Cascorbi, Ingolf. "Drug Interactions.DeutschesAerzteblatt Online, August. https://doi.org/10.3238/arztebl.2012.0546.2003.

[5] T. J. Murtola, J. Teemu, L.J. Teuvo, M/Liisa, H.MattiandA.Anssi."Prostate Cancer Risk among Users of Finasteride and Alpha-Blockers - A Population Based Case-Control Study". European Journal of Cancer 43 (4): 775–81.2007.https://doi.org/10.1016/j.ejca.2006.12.001.

[6] D. Nunzio, D.Cosimo, P.Fabrizio, and T. Andrea. "Inflammatory Mediators in the Development and Progression of Benign Prostatic Hyperplasia".Nature Reviews Urology 13 (10).2016.https://doi.org/10.1038/nrurol.2016.168.

[7] S.K. Kim, S. Hosik, J.P.Hae, S.J. Hye, W.K. Sang, C.L.Byung,Y. Jooil et al. "Inhibitory Effect of Curcumin on Testosterone Induced Benign Prostatic Hyperplasia Rat Model. BMC Complementary and Alternative Medicine 15 (1).2015.https://doi.org/10.1186/s12906-015-0825-y.

[8] A.J. Lepak, K. MarchilloK, J. Vanhecker, D.R. Andes. "Posaconazolepharmacodynamic target determination against wild-type and Cyp51mutant isolates of Aspergillusfumigatus in an in vivo model of invasivepulmonaryaspergillosis. Antimicrob.Agents Chemother. 57:579 –585.[2013]

[9] T. Chou and P. Talalay"Qunantitive analysis of dose –effect relationships: The combined effect of multiple drugs or enzyme inhibitors. Advances in Enzyme Reguation. 22:27-55. 1984.

[10] L. Zhang, X. Fan, H.Xie, Q.He, Y.Nie, M. Zhang, andM. Yan."Anti-Inflammatory and Antioxidant Effects of Kelong-Capsule on Testosterone-Induced Benign Prostatic Hyperplasia in Rats". Evidence-Based Complementary and Alternative Medicine Volume 2018, Article ID 5290514, 8 pages.2018.https://doi.org/10.1155/2018/5290514

[11] D. Dzulsuhaimi, N.Fekery, and N. Hashim N." Reproductive Health of Rats with Benign Prostatic Hyperplasia Following Cosmos CaudatusEthanolic Extract Consumption. Journal of Applied Pharmaceutical Science 7 (6): 202–5.2017.https://doi.org/10.7324/JAPS.2017.70630.

[12] G. Mbaka, O. Steve, S. Adeola, and O. Daniel Osiagwu. "Histomorphological Effects of the Oil Extract of SphenocentrumJollyanum Seed on Benign Prostatic Hyperplasia Induced by Exogenous Testosterone and Estradiol in Adult Wistar Rats". Avicenna Journal of Phytomedicine 9 (1): 21–33.2019.https://doi.org/10.22038/ajp.2018.24039.1882

[13] N. Alwachi, and D. Husain D. " Research Article Tamsulosin Hydrochloride (Flomax) Effects on Fertility of Albino Male Mice. International Journal of Recent Scientific Research 5 (2): 326–31. 2014.

[14] X. Wang, W. Yiming, G. Christian, S. Christian, Y. Qingfeng, L.Bingsheng, S. Frank et al. " Ghrelin Aggravates Prostate Enlargement in Rats with Testosterone-Induced Benign Prostatic Hyperplasia, Stromal Cell Proliferation, and Smooth Muscle Contraction in Human Prostate Tissues. Oxidative Medicine and Cellular Longevity.November.2019.https://doi.org/10.1155/2019/4748312.

[15] T. Abdulmaged, J. Hassani, A.Guay, M.Zitzmann, and M. Hansen ." Adverse Side Effects of 5α-Reductase Inhibitors Therapy: Persistent Diminished Libido and Erectile Dysfunction and Depression in a Subset of Patients".The Journal of Sexual Medicine 8 (3). 2011. https://doi.org/10.1111/j.1743-6109.2010.02157.x

★★★